VHIO
VALL D'HEBRON
Institute
of Oncology

SCIENTIFIC REPORT
2017

# The next decade of VHIO's translation toward precision oncology

Centres de recerca de Catalunya

Vall d'Hebron Institute of Oncology (VHIO)
CELLEX CENTER
C/Natzaret, 115 – 117
08035 Barcelona, Spain
Tel. +34 93 254 34 50
www.vhio.net

Direction: Amanda Wren
Design: Parra estudio
Photography: Katherin Wermke

# Index
# Scientific Report


INTRODUCING VHIO

02 Foreword
08 2017: marking the next chapter of VHIO's translational story
18 Scientific Productivity: research articles
19 Selection of some of the most relevant articles by VHIO researchers published in 2017
25 A Golden Decade: reflecting on the past 10 years of VHIO's translational success story

PRECLINICAL RESEARCH

49 From the Director
50 Experimental Therapeutics Group
52 Growth Factors Group
54 Mouse Models of Cancer Therapies Group
56 Tumor Biomarkers Group

TRANSLATIONAL RESEARCH

61 From the Director
62 Gene Expression & Cancer Group
64 Stem Cells & Cancer Group

CLINICAL RESEARCH

69 From the Director
70 Breast Cancer & Melanoma Group
72 Early Clinical Drug Development Group
74 Gastrointestinal & Endocrine Tumors Group
76 Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site Group
78 Gynecological Malignancies Group
80 High Risk & Cancer Prevention Group
82 Oncogenetics Group
84 Oncology Data Science (ODysSey) Group
86 Radiation Oncology Group
88 Thoracic Tumors & Head and Neck Cancer Group

CORE TECHNOLOGIES

92 Cancer Genomics Group
94 Molecular Oncology Group
96 Proteomics Group

VHIO'S TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

100 Clinical Trials Office
102 Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa"
104 Clinical Research Oncology Nurses
106 Clinical Research Oncology Pharmacy Unit

RECENTLY INCORPORATED GROUPS

110 Cellular Plasticity & Cancer Group
112 Experimental Hematology Group
114 Tumor Immunology & Immunotherapy Group
116 Applied Genetics of Metastatic Cancer Group
118 Chromatin Dynamics in Cancer Group
120 Prostate Cancer Translational Research Group
122 Radiomics Group

124 Full listing of articles published by VHIO Investigators in 2017

138 Funding, Consortia & Accreditation

# Foreword

Josep Tabernero
Director, Vall d'Hebron Institute of Oncology (VHIO)

## VHIO in 3 Words: Predictive, Proven & Precise

During the 2017 Congress of the European Society for Medical Oncology (ESMO), themed *Integrating science into oncology for a better patient outcome*, I was honoured to deliver a keynote address tackling the pressing issue of how to cope with escalating healthcare costs in cancer. Framed on the fable of the hare and the tortoise, I concluded that the entire oncology ecosystem should better combine the alacrity of the former and the deliberate progress of the latter to achieve optimal outcomes.

I believe that accelerating our efforts to advance our field must be based on careful, scrupulous evidence-based assessment and proven benefit for patients to ensure the best possible outcomes.

This cross-balance approach, emphasizing realistic yet pioneering strategic direction, has successfully established VHIO as a leading comprehensive cancer center on the global oncology stage. Last year's report celebrated our Institute turning ten. As we embrace the next exciting decade, I want to highlight just some of our many milestones throughout VHIO's brief history (see 'A Golden Decade', pages 25-43).

These important steps have all contributed to firmly positioning VHIO's 3 Ps - Predictive, Proven & Precise – at the core of

our multidisciplinary and translational research model. Following these guiding principles, I highlight below some of the exceptional research advances, contributions and developments that have been driven by out talents and teams throughout 2017.

## The science that shaped our year

As we embark on the next decade of VHIO's purely translational story, I am proud to report that 2017 was a record breaker in both the number and impact of papers published. Last year, 282 scientific articles were published by VHIO researchers as corresponding/senior or co-authors. Many appeared in prestigious international journals, others in more specialized publications, but I have never been prouder of the quality and scope of our research productivity (see pages 124-137).

These papers present myriad contributions to cancer science in preclinical, translational and clinical areas. It is impossible to showcase a representative selection here in my Foreword. That said, I take this opportunity to mention a mere few VHIO 'hot spots' that made the headlines throughout 2017:

### Preclinical predictability

The issue of reproducibility of predictive preclinical science has been widely debated in the literature. 2017 kicked-off with a study (1) first authored by D. Benjamin, Biomedical Ethics Unit/ STREAM, McGill University (Montreal, Canada), claiming that cancer researchers overestimate the reproducibility of their preclinical findings.

Whether one agrees with their arguments or not, we at VHIO strive to deliver the data required to reliably inform the clinical development of innovative agents and approaches before moving to the clinic. Reflective of our expertise in developing and tuning cancer models to identify factors influencing tumor growth, progression and response to therapy, VHIO is a founding member of the EuroPDX Consortium (see page 13).

In a 2017 *Perspectives* article (2) EurOPDX members and co-authors explored the challenges of patient-derived xenografts (PDX), at the vanguard of precision medicine. In their elegant review of where we stand with these models in more faithfully recapitulating the molecular specificities of patient samples, the authors balance preclinical realities with current expectations from the clinical perspective.

Lastly, following their review of using next-generation models to establish the role of the immune system in tumor cell spread and test-bed the increasing portfolio of immunotherapeutics, one major 'take home' touched on the absolute necessity of sharing and exchanging data from various experimental models – a guiding principle that defines both the EurOPDX Consortium and VHIO.

Co-authored by VHIO's Paulo Nuciforo, Principal Investigator of our Molecular Oncology Group, a report (3) led by colleagues at the Dana-Farber Cancer Center, Boston (USA), in collaboration with VHIO researchers and the Medical Oncology and Pathology Departments of our Hospital, headed by myself and Santiago Ramón y Cajal respectively, showed that the colonization of human colorectal cancer (CRC) with *Fusobacterium* and its associated microbiome is found in primary tumors and persists in liver metastases.

Supporting the hypothesis that *Fusobacterium* travels with primary cancer cells as part of metastatic tissue colonization, findings also revealed that it survives through the multiple generation of PDX and that treating mice bearing bacterium-positive models with metronidazole significantly decreases tumor growth. These observations suggest that this bacterium is more than a mere bystander of tumorigenesis. It could in fact be a driver of metastases and selective antimicrobial therapy could therefore represent important weaponry for the treatment of patients with *Fusobacterium*-associated CRC.

Worthy of mention here is that VHIO's robust preclinical and translational research of excellence also spurred the creation of two successful spin-offs in 2014, both of which continue to go from strength to strength (see page 15).

### Championing combinations to improve response and halt metastatic spread

In an open access article (4), findings reported by a purely VHIO *tour de force*, first authored by Alex Martínez, Medical Oncologist and Clinical Investigator of VHIO's Thoracic Tumors & Head and Neck Cancer Group, directed by Enriqueta Felip, identified a novel and more effective therapeutic strategy to combat acquired resistance to third-generation epidermal growth factor tyrosine kinase inhibitor (EGFR-TKIs), osimertinib, in the treatment of metastatic non-small cell lung cancer (NSCLC).

Using a patient-derived orthopatic xenograft model, the team successfully characterized the role of MET gene amplification and signalling as a mechanism of resistance to osimertinib and showed the superior efficacy of pairing the EGFR inhibitor afatinib with a c-MET inhibitor, capmatinib. Further studies will explore the EGFR-TKI-MET inhibitor combination as a novel therapy, as well as consider the addition of immunotherapy for the earlier treatment of patients.

Presented for the first time during ESMO's 2017 Congress, Cristina Saura, Principal Investigator of VHIO's Breast Cancer Group, delivered results from the LORELEI phase II study. Assessing the efficacy of adding taselisib to letrozole before surgery for the treatment of patients with operable early estrogen receptor-positive and HER2-negative breast cancer, this study is the first to demonstrate a marked increase in response to treatment with a PI3K-selective inhibitor.

Carried out in collaboration with academic partners including the Breast International Group (BIG), SOLTI Breast Cancer Research Group, and the Austrian Breast & Colorectal Cancer Study Group (ABCSG), this research showed that taselisib and letrozole prior to surgery significantly improved outcomes for these patients compared to treatment with letrozole alone.

Results from another study (5), timed to coincide with this year's Annual Meeting of the American Association for Cancer Research (AACR), showed the promise of combining encorafenib with cetuximab, with or without alpelisib as a strategy against metastatic BRAF-mutant metastatic colorectal cancer (mCRC).

Both pairings demonstrated efficacy and acceptable safety profiles, with similar overall response rates: 19% in the dual and 18% in the triple combination group. In our efforts to suppress MAPK signalling and halt tumor growth in this difficult-to-treat population, these findings promise a new therapeutic avenue towards improving outcomes for patients.

## VHIO's pursuit of new emerging research areas

In last year's Scientific Report I hailed the arrival of Sandra Peiró, Principal Investigator of VHIO's Chromatin Dynamics in Cancer Group, and Leticia de Mattos-Arruda, Junior Principal Investigator of Applied Genetics of Metastatic Cancer.

Throughout 2017, Sandra has successfully consolidated her lab. Her group elucidates the epigenetic mechanisms controlling the expression of genes during tumor progression, with special emphasis on the role of the primary structure of chromatin fiber, as determined by histone tail modification, and the 3D chromatin structure implicated in transcription regulation. By identifying the molecular mechanisms of chromatin conformation changes in tumor cells they strive to unveil potentially druggable proteins.

Leticia's research centers on integrating multi-omics data towards better understanding of tumor heterogeneity and the role of the immune system within and between tumors. She also focuses on identifying novel biomarkers to guide the selection of anti-cancer therapies based on the specificities of individual patients and advance insights into differential clinical responses in individuals with metastatic breast cancer.

At the end of 2017 we also warmly welcomed two new talents to VHIO whom we have lured from London:

Raquel Perez-Lopez moved to VHIO in October from the Institute of Cancer Research - Royal Marsden Hospital, where she conducted her PhD under the supervision of Johann de Bono, to head up our newly established Radiomics Group.

As Principal Investigator, Raquel's research will center on functional CT and MRI techniques such as perfusion, diffusion and spectroscopy, to better identify the histological and molecular characteristics of tumors. Her group will seek to optimize drug development by more effectively characterizing the antitumor effect of novel agents including immunotherapies, identify those patients who are most likely to benefit from these therapies, and further enforce our translational research programs in genomics, predictive science, and biomarkers of response and resistance.

Raquel has already established interdisciplinary collaborations with various VHIO groups, and soon she will welcome an MR researcher for novel imaging biomarker development and an MSc student and clinical research fellow on her team.

Also joining us from the same institution (and mentorship) is Joaquin Mateo, as Principal Investigator of our recently created Prostate Cancer Translational Research Group.

He will lead research aimed at translating prostate cancer genotypes into phenotypes and a clinically-relevant classification of the disease, and will also build a precision medicine core for prostate cancer patients. He has already recruited three group members to join us early next in 2018, and, together with our Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site Group, led by Joan Carles, has launched a program to prospectively acquire samples from metastatic lesions and circulating biomarkers from patients with metastatic prostate cancer treated at our hospital, the Vall d'Hebron University Hospital (HUVH).

These important additions will fortify VHIO as it continues to more swiftly translate cancer discovery into clinical benefit. To discover more about our recently incorporated groups I invite you to browse pages 110-123 of this report.

## Potentiating novel immune agents as mono therapy or in combination

It's not so long ago that immunotherapy featured in my Foreword as "emerging" or even promising but not as proven. At the close of 2017, *Nature* published its annual cherry-pick of *bright spots* [6] in science. The selection included the first approval of CAR-T cell therapy involving the genetic engineering of a patient's immune cells to target and attack tumors. The US Food and Drug Administration approved it for the use in children and young adults with a type of acute leukaemia.

Despite safety concerns regarding this treatment, we are seeing how the efficacy of novel immunotherapeutics is increasingly reported as proven, as opposed to merely promising, across different tumor types either as mono therapy or in combination. While the advent of immune-based therapies must be celebrated, their power and potential continues to vary immensely in patients. This is because some tumors manage to block the immune system defence or even sneakily slip past undetected.

Looking ahead, much research needs to center on better predicting response to these therapies in individual patients and thus further validate precision medicine in oncology. Only then can we reasonably expect to extend immunotherapies to more tumor types, as well as continue to combine powerful immunotherapeutics with the current cornerstones of cancer – chemotherapy, surgery and radiation. We will also need to better understand the cellular and molecular mechanisms modulating immune response as well as learn from the outcomes of current and future trials.

Announced in December, VHIO and the BBVA Foundation paired in collaboration with the Memorial Sloan Kettering Cancer Cancer Center – MSKCC (New York) to pioneer a Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI). Building on the successes of a previous joint project to implement a tumor biomarkers research program, CAIMI represents an important forward step in advancing agents that inhibit checkpoint regulation of the immune system, better understanding mechanisms of resistance and response to these therapies, and prioritizing the early development of those drugs showing most promise.

This project will combine the expertise of VHIO's Elena Garralda (PI of VHIO's Early Clinical Drug Development and Executive Director of our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa"), who will head up CAIMI's clinical research, Alena Gros (PI, VHIO's Tumor Immunology and Immunotherapy Group), who will take the lead on translational research, and Ana Vivancos(PI of our Cancer Genomics Group), who directs our internationally recognized pre-screening platform. In collaboration with our MSKCC colleagues, VHIO will co-found six translational projects linked to the early clinical development phases of immunotherapy.

Elsewhere, also reflective of VHIO's efforts aimed at accelerating immunotherapies including atezolizumab, nivolumab and pembrolizumab, results from two VHIO-led studies were selected for prestigious oral presentations during the 2017 Annual Meeting of the American Society of Clinical Oncology (ASCO).

Enriqueta Felip revealed results from an early phase I multi-center trial designed to analyze the safety and dose escalation of the combination of ceritinib with PD-1 inhibitor nivolumab in patients with advanced ALK+ non-small-cell lung cancer.

While findings showed that ceritinib paired with nivolumab as active in these patients, considerable toxicity was observed, calling for adjustments of the protocol on the administration of this particular combination with an alternative dosage regimen in trials to follow.

During the meeting, I presented results from two early phase studies exploring the preliminary therapeutic activity and safety of the novel carcinoembryonic antigen (CEA) T-cell bispecific antibody, either as monotherapy or in combination with PD-L1 inhibitor atezolizumab in patients with mCRC.

We reported that when CEA is administered as monotherapy, an initial response is noted, yet, at the same time, it starts to express PD-1 /PD-L1 rendering the immune system dormant, leading to disease progression. When this agent is delivered in combination with the PD-1 /PD-L1 inhibitor however, there is a rating of 82% in response and stabilization of disease.

Ongoing studies will continue to validate this combinatorial approach, but these initial findings certainly show promise in boosting the immune system to mount an effective antitumor response against mCRC.

## Big Data-derived insights and the pan-omic exploration of solid tumors

An additional framework agreement between VHIO and MSKCC, renewed this year, is the Obra Social "la Caixa" 2nd International Program for Cancer Research and Education. This 3-year project will include several initiatives focused on the pan-omic exploration (genomics and radiomics) of solid tumors, with particular emphasis on Big Data. More specifically, with José Baselga, Physician-in-Chief at MSKCC and myself as co-PIs (in collaboration with Maurizio Scaltriti, MSKCC, and VHIO's Rodrigo Dienstmann, Ana Vivancos, Joaquin Mateo and Raquel Perez-Lopez) we will conduct research on the impact of gene mutations in DNA damage repair and metastatic prostate cancer, together with data mining to reveal new molecular genetic determinants of sensitivity to targeted therapy in solid cancers.

Talking of Big Data, VHIO also leads efforts to report, interpret and exchange meaningful mass data. Our Oncology Data Science (ODysSey) Group directed by Rodrigo Dienstmann, facilitates data exchange among a wide range of experts for the review of patient medical histories and cancer molecular profiles in order to guide treatment decisions.

As a partner of the EU Horizon 2020-funded MedBioinformatics, Rodrigo's group has been extensively involved in the development of integrative bioinformatics tools to analyze the huge amount of data and knowledge generated in healthcare and biomedical research in order to advance translational research. Furthermore, important advances in datamining and interpretation of somatic gene alterations with a therapeutic impact in cancer have spurred the development of the publicly available Cancer bioMarkers database, which has become a reference for clinical investigators across the globe.

Rodrigo's group, in collaboration with our Molecular Oncology and Cancer Genomics labs, led by Paolo Nuciforo and Ana Vivancos respectively, continues to focus on the multi-molecular approach to developing novel anti-cancer therapies based on established subtypes. As a result of our expertise in cancer classification, this year we published a review article (7) underlining the challenges and opportunities ahead in putting the brakes on the molecular culprits that drive tumor initiation, development and growth in each individual consensus molecular subtype of colorectal cancer.

Representing an important forward step in this direction, as this Report goes to print, I am proud to announce that VHIO has been accepted as a new participant in the AACR international data-sharing initiative known as AACR Project Genomics Evidence Neoplasia Information Exchange (GENIE), launched back in 2015.

It's not just about consensus in the subtyping, it's also about harmonizing the same language in oncology, precisely speaking! Aimed at resolving certain ambiguity arising within the oncology community concerning terminology entering the cancer lexicon, ESMO's *Precision Medicine Glossary* (8) incorporates 43 selected terms that, upon consensus, were grouped across 5 main categories: mechanism of decision, characteristics of molecular alterations, tumor characteristics, clinical trials & statistics, and new research tools. Also tackling the 'which is best' debate on precision as opposed to personalized, this glossary is a useful tool to improve communication and thus further spur collaborative research of excellence.

## Liquid biopsy: better guiding treatment decisions for our patients

Since VHIO incorporated in-house BEAMing liquid biopsy RAS biomarker technology in 2015, the first academic test center to do so, we have made significant progress in validating and developing liquid biopsy and Droplet Digital PCR Bio-Rad technologies for the more effective, less invasive 'policing' of cancer over time, in real time.

As a direct reflection of our expertise in developing this approach at clinical level, driven in collaboration with our Cancer Genomics Group, VHIO counted two out of the five projects selected under the TRANSCAN Joint Translational Call on *Minimally and non-invasive methods for early detection and/or progression of cancer.*

Awarded by the Spanish Association against Cancer (AECC) and the Institute of Health Carlos III (ISCIII) through the ERA-NET TRANSCAN-2 program funded by EU's Horizon 2020, the first of VHIO's two TRANSCANs, led by Enriqueta Felip, Principal Investigator of our VHIO's Thoracic Tumors & Head and Neck Cancer Group, will establish non-invasive prognostic markers for resected early stage non-small cell lung cancer (NSCLC) by assessing the role of circulating and exosomal miRNAs and free circulating DNA (fcDNA).

The second, directed by Elena Élez, Medical Oncologist and Clinical Investigator of VHIO's Gastrointestinal & Endocrine Tumors Group, focuses on the early detection of relapse in advanced colon cancer patients by longitudinally following a personalized molecular signature by liquid biopsy. This proof-of-concept, prospective and multi-center study seeks to evaluate the clinical feasibility of tracking tumor progression by dynamically detecting a molecular signature from a blood test. As an innovative approach for the early detection of disease relapse, this project represents an important next step in more accurately monitoring cancer's next moves.

## Task-forcing team science

VHIO's expert and interdisciplinary taskforces comprise comprehensive teams of oncologists, pathologists, other MD disciplines, preclinical and translational researchers, research nurses, data curators and miners as well as study coordinators, among others.

Currently counting seven groups covering colorectal, breast, lung, gynecologic, prostate, melanoma tumor types as well as immunotherapy, our taskforces regularly convene to synergize efforts, boost collaborations among groups and between specialists, and continuously revise respective circuits and ethics toward advancing cancer science and medicine.

In line with recommendations outlined in our Scientific Advisory Board's 2017 Report, and to complement and expand our priority research areas, we will seek to further develop and functionalize our appointed taskforces as well as strengthen our shared and standard operating procedures.

## Picking up the prizes and A-grade accreditation

In recognition of VHIO's efforts aimed at rendering cancer medicines more precise and our contribution to the Spanish National Health System, we received *Gaceta Médica*'s 2017 Best-in-Class Prize for R&D in oncology.

Based on our ability to advance cancer discovery through the integration of translational science and clinical research, this wonderful accolade also recognizes the work performed at the hub of VHIO's early drug development program led by Elena Garralda, our Research Unit for Molecular Therapies of Cancer (UITM) – "la Caixa" (pages 102-103).

More specifically, the Unit's broad portfolio of promising novel anti-cancer therapies continues to grow each year with special focus on first-in-human studies, novel combinations, and best-in-class compounds. Since its inauguration in 2010, the UITM, previously coordinated by Jordi Rodón and now under the direction of Elena, has established itself as one of the few comprehensive facilities in Europe to up the tempo in transforming latest discovery into benefits for our patients.

Launched this year, the European Alliance for Personalised Medicine's (EAPM) Health Innovation Five 'HI-5' Award for the *Best EU-based hospital for integrating personalised cancer medicines* was presented to VHIO in recognition of our capacity to swiftly integrate and transform precision medicine against cancer.

At the core of everything we do, our rapid translation of cancer discovery into benefits for patients is only possible thanks to VHIO's multidisciplinary teams composed of research talents, top drawer clinical investigators, leading physicians, expert oncology care providers at our Hospital's Medical Oncology Department, in collaboration with other healthcare professionals across the Vall d'Hebron Barcelona Hospital Campus (pages 10-11).

Additionally in 2017, VHIO underwent evaluation for accreditation of the CERCA Institute of Research Centres of Catalonia (*Institució CERCA – Centres de Recerca de Catalunya*) for the period 2013 – 2016. In recognition of VHIO's progress, performance in knowledge transfer activities and management of excellence, VHIO was awarded with the maximum qualification of an A grading.

## The Last Word

*"People do not decide to become extraordinary, they decide to accomplish extraordinary things."*

- Sir Edmund Hillary, Explorer (1919–2008)

As VHIO's Director, I am honored and privileged to lead and work with our many research talents and dedicated healthcare professionals in oncology. Without our multidisciplinary teams, cross-border collaborations and partnerships, and the passion and drive that unite us all in our ambition to solve cancer sooner, our Institute would cease to exist.

That same sustained devotion and belief is also shared in equal measure by our wonderful institutional supporters – the *Generalitat de Catalunya, Fundació Privada CELLEX, FERO Fundación de Investigación Oncológica, Fundació Bancària "la Caixa", Fundación BBVA*, as well as VHIO's many other supporters, funding entities and agencies (see pages 138-139).

We can and will only continue to accelerate our pace in advancing more precise, effective and targeted therapies against cancer through the public funding we receive, as well as the generous support from private institutions, companies and individuals, all of whom share the same intense desire as we do: to reduce the devastating burden that this disease has on society.

In 2015 there were an estimated 17.5 million cancer cases globally, with 8.7 million deaths. Cases are forecast to soar by 75% over the next 20 years. Added to this alarming picture, spending on cancer medicines totaled $107 billion worldwide in 2015 and is projected to exceed $150 billion by 2020 (9). This tremendous socioeconomic burden on healthcare systems across the globe can no longer be sustained anywhere – irrespective of national cancer plans, allocated resources or corresponding treasury.

Driving advances in cancer discovery and translating these insights into improved outcomes for patients as quickly as possible must therefore be a top priority for the entire oncology ecosystem as well as the public at large, globally.

As I close this Foreword and consider the many vital contributions that VHIO's teams make to cancer science and medicine, I am proud to report that we are getting smarter and moving faster in our quest to combat cancer.

Building on the progress made over VHIO's first decade, we are more committed than ever to expanding our efforts in breadth, depth, and scope – faithful to VHIO's 3 established principles: Predictive, Proven & Precise.

As VHIO evolves in tune with the current era of precision medicine, we can and will do better.

Josep Tabernero
Director, Vall d'Hebron Institute of Oncology (VHIO)

## References:

1. Benjamin D, Mandel DR, Kimmelman J. Can cancer researchers accurately judge whether preclinical reports will reproduce? *PLoS Biol.* 2017 Jun 29;15(6):e2002212.
2. Byrne AT, Alférez DG, Amant F, Annibali D, Arribas J, Biankin AV, Bruna A, Budinská E, Caldas C, Chang DK, Clarke RB, Clevers H, Coukos G, Dangles-Marie V, Eckhardt SG, Gonzalez-Suarez E, Hermans E, Hidalgo M, Jarzabek MA, de Jong S, Jonkers J, Kemper K, Lanfrancone L, Mælandsmo GM, Marangoni E, Marine JC, Medico E, Norum JH, Palmer HG, Peeper DS, Pelicci PG, Piris-Gimenez A, Roman-Roman S, Rueda OM, Seoane J, Serra V, Soucek L, Vanhecke D, Villanueva A, Vinolo E, Bertotti A, Trusolino L. Interrogating open issues in cancer precision medicine with patient-derived xenografts. *Nat Rev Cancer.* 2017 Apr;17(4):254-268.
3. Bullman S, Pedamallu CS, Sicinska E, Clancy TE, Zhang X, Cai D, Neuberg D, Huang K, Guevara F, Nelson T, Chipashvili O, Hagan T, Walker M, Ramachandran A, Diosdado B, Serna G, Mulet N, Landolfi S, Ramon Y Cajal S, Fasani R, Aguirre AJ, Ng K, Élez E, Ogino S, Tabernero J, Fuchs CS, Hahn WC, Nuciforo P, Meyerson M. Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer. *Science.* 2017 Dec 15;358(6369):1443-1448.
4. Martinez-Marti A, Felip E, Matito J, Mereu E, Navarro A, Cedrés S, Pardo N, Martinez de Castro A, Remon J, Miquel JM, Guillaumet-Adkins A, Nadal E, Rodriguez-Esteban G, Arqués O, Fasani R, Nuciforo P, Heyn H, Villanueva A, Palmer HG, Vivancos A. Dual *MET* and *ERBB* inhibition overcomes intratumor plasticity in osimertinib-resistant-advanced non-small-cell lung cancer (NSCLC). *Ann Oncol.* 2017 Oct 1;28(10):2451-2457.
5. van Geel RM, Tabernero J, Elez E, Bendell JC, Spreafico A, Schuler M, Yoshino T, Delord JP, Yamada Y, Lolkema M, Faris JE, Eskens FA, Sharma S, Yaeger R, Lenz HJ, Wainberg ZA, Avsar E, Chatterjee A, Jaeger S, Tan E, Maharry K, Demuth T, Schellens JHM. A phase Ib dose-escalation study of encorafenib and cetuximab with or without alpelisib in metastatic BRAF-mutant colorectal cancer. 2017. *Cancer Discov.* 7: 610-619.
6. Callaway E, Castelvecchi D, Cyranoski D, Gibney E, Ledford H, Lee JJ, Morello L, Phillips N, Schiermeier Q, Tollefson J, Van Noorden R, Witze A. 2017 in news: The science events that shaped the year. *Nature.* 2017 Dec 21;552(7685):304-307.
7. Dienstmann R, Vermeulen L, Guinney J, Kopetz S, Tejpar S, Tabernero J. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. *Nat Rev Cancer.* 2017;7(2):79-92.
8. Yates LR, Seoane J, Le Tourneau C, Siu LL, Marais R, Michiels S, Soria JC, Campbell P, Normanno N, Scarpa A, Reis-Filho JS, Rodon J, Swanton C, Andre F. The European Society for Medical Oncology (ESMO) Precision Medicine Glossary. *Ann Oncol.* 2018 Jan 1;29(1):30-35. (13 November, epub ahead of print).
9. IMS Institute for Healthcare Informatics. Global Oncology Trend Report: A Review of 2015 and Outlook to 2020. June 2016.

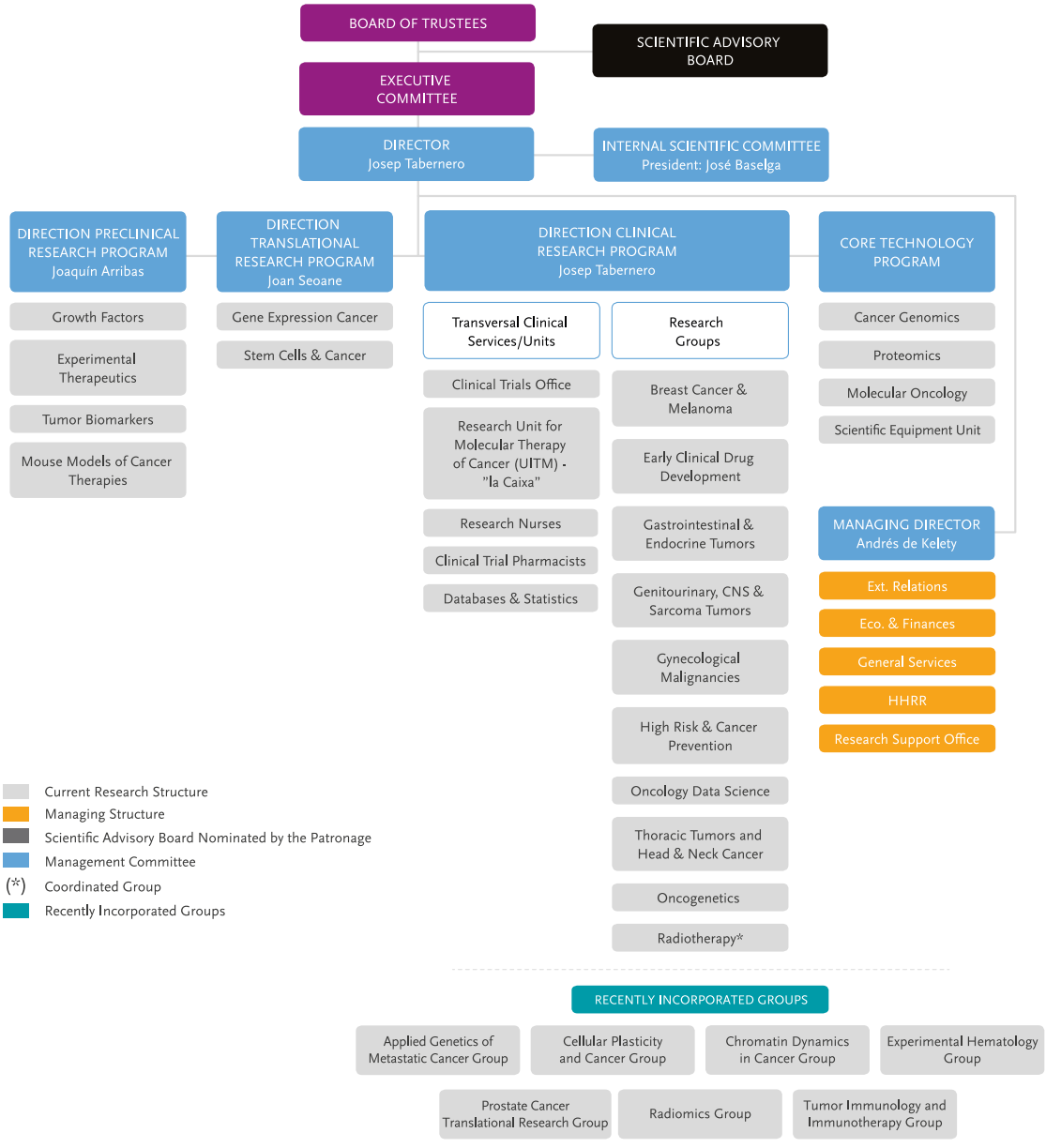
# 2017: marking the next chapter of VHIO's translational story

## Who we are and what we do

### VHIO's Organigram 2017

In order to translate cancer discovery into real benefit for an increasing number patients, VHIO has, for the last decade, adopted a purely translational, multidisciplinary research model. Organized into four main programs – Preclinical, Translational, Clinical, and Core Technologies, our research focuses on understanding the fundamental biology of human cancer, from cellular and molecular biology and genetics through to therapeutics.

Its optimal organizational structure allows VHIO talents to continue to both anticipate and tackle the many unresolved questions in ultimately outsmarting the multifaceted, heterogeneous and complex disease that is cancer:

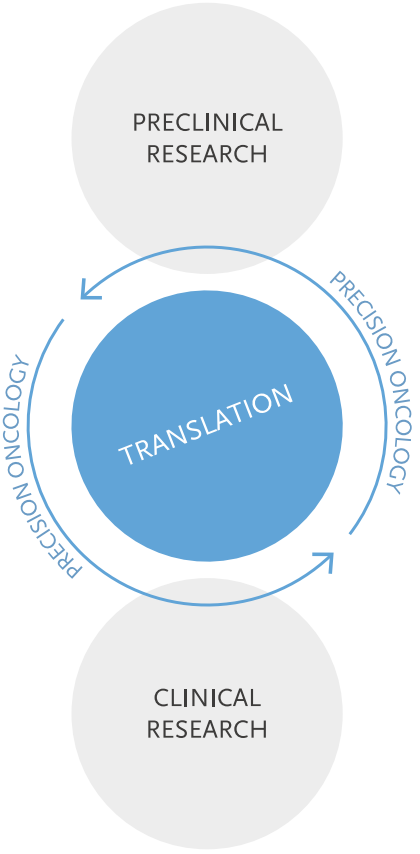


# VHIO's translation toward precision oncology: a little more on how we did it in 2017

Under the leadership of Josep Tabernero, the Vall d'Hebron Institute of Oncology (VHIO), created by José Baselga in 2006, has established itself as a comprehensive cancer centre of proven excellence internationally. It is thanks to exceptional directorship and VHIO's optimal organizational structure based on a purely multidisciplinary and translational model that VHIO talents continue to anticipate and tackle the many unresolved questions in combatting this multifaceted and heterogeneous disease.

Located within the Vall d'Hebron Barcelona Hospital Campus, our researchers closely collaborate and interact with Vall d'Hebron University Hospital physician-scientists. Translational science and clinical research are therefore tightly connected which promotes superb interaction and teamwork which, in turn, accelerates the bench-bedside-bed cycle of knowledge. This privileged environment affords VHIO direct access to patients as well as the entire spectrum of oncology professionals who care for them, and a second-to-none appreciation of how cancer science can translate into more powerful, targeted treatments and better practice for the care of patients.

VHIO's pioneering model and programs, coupled with its belief in combining strengths through cross-border collaborations, continue to spur advances in reversing cancer resistance, halting metastatic spread, and more effectively treating even the most undruggable tumor types.



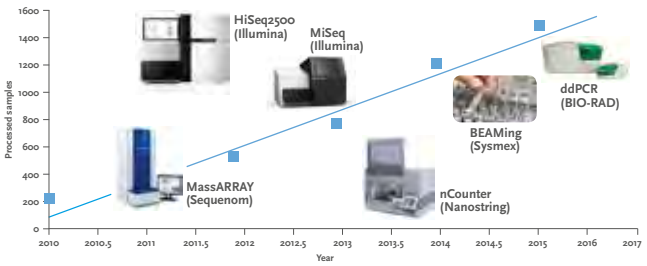

## Principal areas of cancer research at VHIO: a snapshot

- Preclinical humanized models (PDXs – Avatars – and Organoids).
- Mechanisms of sensitivity, and primary and acquired resistance.
- Molecular and clinical Big Data to characterize subtypes of diseases.
- Early drug development.
- Clinical trials with innovative agents (phase I & II) and first-in-human studies.

## Prowess in prescreening and oncogenomics

At the core of VHIO's research activities lies our suite of cutting-edge core technology platforms which allow our expert teams to apply next-generation whole-genome sequencing for precision oncology as well as develop and improve existing applications to drive faster results.

By sequencing panels of genes or entire genomes in cancer patients, we are now better equipped than ever before to identify specific molecular risk factors and better predict the potential efficacy of specific agents matched to the specificities of individual patients. VHIO's Cancer Genomics Group headed by Ana Vivancos, serves as a Core Technology laboratory to bridge the preclinical and clinical levels of cancer discovery.




Technologies in Cancer Genomics: an ongoing revolution.

Our state-of-the-art enabling technologies include an n-counter Nanostring platform, BEAMing Sysmex, and Droplet Digital PCR (ddPCR) Bio-Rad Technology, Miseq and HiSeq2500, Illumina.Two of these tests are based on NGS: an Amplicon-seq approach to sequence 70 genes (Illumina), as well as a 400-gene capture panel, and two are based on nCounter (Nanostring): a gene fusion panel (with the capacity of detecting over 100 recurrent gene fusions) and a Copy Number Alteration panel (detecting 59 genes).

As a reflection of high quality testing on patient samples, VHIO is increasingly approached by the pharmaceutical industry and other research entities as either the selected

Central Lab of choice, or as their preferred service provider and advisor.

VHIO's Prescreening Program, pioneered by VHIO's Cancer Genomics and Molecular Oncology Groups (led by Ana Vivancos and Paolo Nuciforo respectively), performs molecular profiling in over 1500 patients per year as candidates for enrolment in early phase clinical trials carried out at our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", directed by Elena Garralda.

Suitability for enrolment in a given trial is evaluated based on the genomic or pathologic profile of individual patients. Our capacity to more precisely match individual patients with a particular clinical study represents a significant forward step in delivering on the true promise of personalized treatment and care in oncology.

By bringing more detailed prognostics directly to the clinical setting, and further developing and validating the next generation of tests, VHIO also continues to significantly contribute to better guided treatment decisions as well as improved outcomes for patients.

As a reflection of our dedication to excellence and quality services we provide, we continue to successfully undergo ISO 15189 accreditation and are now focused on transferring some of our technologies.

## VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa": the hub of VHIO's early clinical drug development

Obra Social "la Caixa"

VHIO continues to establish itself as a leading reference in progressing drug development and targeted therapies against cancer. Since its inauguration in 2010, the UITM (pages 102-103), under the direction of Josep Tabernero and now coordinated by Elena Garralda as Executive Director, has rapidly become as one of the few comprehensive facilities in Europe to up the tempo in transforming latest discovery into improved outcomes for patients.

It has been able to do so not only through the bridging and tight connectivity between health care professionals, VHIO researchers and clinical investigators, but also by identifying novel predictive markers of response to anti-cancer therapies and markers of primary resistance (de novo) and secondary treatment.

Research at the UITM is driven by Elena's Early Clinical Drug Development Group (pages 72-73), and focuses on the development of novel agents based on the molecular profile of each tumor as well as the optimization of therapies using combinations of new drugs with existing ones.

In 2017, 120 Phase I clinical trials and 17 basket studies were performed at our Unit with a total of 445 patients enrolled. Our Clinical Trials Office (pages 100-101), directed by Gemma Sala and also located in the patient environment of the Vall d'Hebron University Hospital, coordinates a large portfolio of Phase I, Baskets, Phase II & III clinical trials. In 2017 the number of patients included in these trials totaled at 1096 across 355 actively recruiting trials.

Research at our Unit has contributed to the development of several tumor cell targeted agents including trastuzumab, pertuzumab, cetuximab, panitumumab, ramucirumab, trifluridine/tipiracil, gefitinib, osimertinib, ceritinib, crizotinib, loratinib and everolimus, among others. Current focus also centers on accelerating and advancing immunotherapies including atezolizumab, nivolumab and pembrolizumab.

Head of VHIO's Clinical Research Oncology Nurses, Ángeles Peñuelas, pictured here with Supervisory Assistant Juan Manuel García. Our expert nurses are specialized in molecular therapies and are essential members of VHIO's multidisciplinary oncology teams.

VHIO continues to grow its portfolio of studies and fine-tune patient selection criteria and stratification based on intrinsic biological intelligence and a more precise classification of cancers.

Announced last year, an academic Cancer Core Europe Consortium endorsed study, Basket of Baskets (BoB), is a pioneering trial set to integrate molecular prescreening, the development of new diagnostic tests such as circulating DNA, with the testing of targeted therapies in patients who, matched to the molecular alterations detected in their respective tumors, will be most likely to benefit from them.

In 2017 the protocol of it first module supported by a pharmaceutical company has been approved (see Cancer Core Europe, page 13).

## VHIO's direct access to cancer patients: crucial to our purely translational research model

Vall d'Hebron Barcelona Hospital Campus | Vall d'Hebron Hospital | VHIO Vall d'Hebron Institute of Oncology


The Vall d'Hebron University Hospital (HUVH): the largest hospital complex in Catalonia and one of the most important in Spain.

Located within the Vall d'Hebron Barcelona Hospital Campus, which also incorporates a trio of research institutes of international reference; Vall d'Hebron Institute of Research (VHIR), CEMCAT – Multiple Sclerosis Center of Catalonia, and VHIO, the Vall d'Hebron University Hospital (HUVH), affords VHIO direct access to patients as well as the entire spectrum of oncology professionals who care for them.

Organized into multidisciplinary and integrated teams, our researchers closely collaborate and interact with Vall d'Hebron physician-scientists. Translational science and clinical research are therefore tightly connected, accelerating the bench-bedside-bed cycle of knowledge.

## Commandeering research aimed at combating cancer

2017 celebrated a record breaking year in both the number and impact of scientific papers published. 282 scientific articles were published by VHIO researchers as corresponding/senior or co-authors with a cumulative Impact Factor (IF) totalling at 2851.

These figures reflect an increase in scientific productivity as well as the importance of VHIO's research contribution to the oncology field. For the complete list of articles published by VHIO researchers and clinical investigators in 2017 see pages 124-137. To view this year's selection of just some of the most relevant articles by VHIO faculty published in 2017, refer to pages 19-23.

## Hailing the arrival of new VHIO talents

In pursuit of new emerging research areas at VHIO we were fortunate to welcome the following new talents to our Institute throughout 2017:

Throughout this year, Sandra Peiró, PI of our Chromatin Dynamics in Cancer Group, has been busy consolidating her lab. Her group elucidates the epigenetic mechanisms controlling the expression of genes during tumor progression, with special emphasis on the role of the primary structure of chromatin fiber, as determined by histone tail modification, and the 3D chromatin structure implicated in transcription regulation. By identifying the molecular mechanisms of chromatin conformation changes in tumor cells they strive to unveil potentially druggable proteins.

As Junior Principal Investigator of VHIO's Applied Genetics of Metastatic Cancer Group, Leticia de Mattos-Arruda's research centers on integrating multi-omics data towards better understanding of tumor heterogeneity and the role of the immune system within and between tumors. She also focuses on identifying novel biomarkers to guide the selection of anti-cancer therapies based on the specificities of individual patients and advance insights into differential clinical responses in individuals with metastatic breast cancer.

Towards the end of the year a further two Principal Investigators joined VHIO:

Raquel Perez-Lopez moved to VHIO in October from the Institute of Cancer Research - Royal Marsden Hospital, where she conducted her PhD under the supervision of Johann de Bono, to head up our newly established Radiomics Group.

As Principal Investigator, Raquel's research will center on functional CT and MRI techniques such as perfusion, diffusion and spectroscopy, to better identify the histological and molecular characteristics of tumors. Her group will seek to optimize drug development by more effectively characterizing the antitumor effect of novel agents including immunotherapies, identify those patients who are most likely to benefit from these therapies, and further enforce our translational research programs in genomics, predictive science, and biomarkers of response and resistance.

Raquel has already established interdisciplinary collaborations with various VHIO groups, and soon she will welcome an MR researcher for novel imaging biomarker development and an MSc student and clinical research fellow on her team.

Also joining us from the same institution (and mentorship) is Joaquin Mateo, as Principal Investigator of our recently created Prostate Cancer Translational Research Group.

Leading research aimed at translating prostate cancer genotypes into phenotypes and a clinically-relevant classification of the disease, he will also build a precision medicine core for prostate cancer patients. Joaquin has already recruited three group members to join us early in 2018, and, together with our Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site Group, led by Joan Carles, has launched a program to prospectively acquire samples from metastatic lesions and circulating biomarkers from patients with metastatic prostate cancer treated at the Vall d'Hebron University Hospital (HUVH).

Sandra Peiró, Principal Investigator, Chromatin Dynamics in Cancer.

Leticia de Mattos-Arruda, Junior Principal Investigator, Applied Genetics of Metastatic Cancer.

Raquel Perez-Lopez, Principal Investigator, Radiomics.

Joaquin Mateo, Principal Investigator, Prostate Cancer Translational Research.

**For more information about our new and recently incorporated groups** see pages 116-122.

## Liquid biopsy and the less invasive tracking of cancer

Since VHIO incorporated its in-house BEAMing liquid biopsy RAS biomarker technology in 2015, the first academic test center to do so, we have made significant progress in validating and developing liquid biopsy and Droplet Digital PCR Bio-Rad technologies for the more effective, less invasive 'policing' of cancer over time, in real time.

As a direct reflection of our expertise in developing this approach at clinical level, driven in collaboration with our Cancer Genomics Group, VHIO counted two out of the five projects selected under the TRANSCAN Joint Translational Call on *Minimally and non-invasive methods for early detection and/or progression of cancer.*

Awarded by the Spanish Association against Cancer (AECC) and the Institute of Health Carlos III (ISCIII) through the ERA-NET TRANSCAN-2 program funded by EU's Horizon 2020, the first of VHIO's two TRANSCANs, led by Enriqueta Felip, Principal Investigator of our Thoracic Tumors & Head and Neck Cancer Group, will establish non-invasive prognostic markers for resected early stage non-small lung cancer (NSCLC) by assessing the role of circulating and exosomal miRNAs and free circulating DNA (fcDNA).

The second, directed by Elena Élez, Medical Oncologist and Clinical Investigator of VHIO's Gastrointestinal & Endocrine Tumors Group, focuses on the early detection of relapse in advanced colon cancer patients by longitudinally following a personalized molecular signature by liquid biopsy. This proof-of-concept, prospective and multi-center study seeks to evaluate the clinical feasibility of tracking tumor progression by dynamically detecting a molecular signature from a blood test.

To essentially pave the way for projects to come, we are currently setting up our in-house plasma bank, *Seroteca*, to centralise the collection and management of blood samples from all patients participating in research projects at VHIO. This excellent resource will significantly advance the clinical validation of liquid biopsy across tumor types.

## The power of collaboration of excellence: at home and away

### Task-forcing team science

VHIO's expert and interdisciplinary taskforces, coordinated by Alejandro Piris, our Scientific Research Manager, comprise comprehensive teams of oncologists, pathologists, other MD disciplines, preclinical and translational researchers, clinical research nurses, data curators and miners as well as study coordinators, among others.

Currently counting seven groups covering colorectal, breast, lung, gynecologic, prostate, melanoma tumor types as well as immunotherapy, our taskforces regularly convene to synergize efforts, boost collaborations among groups and between specialists, and continuously revise respective circuits and ethics toward advancing cancer science and medicine.

In line with recommendations outlined in our Scientific Advisory Board's 2017 Report, and to complement and expand our priority research areas, we will seek to further develop and functionalize our appointed taskforces as well as strengthen our shared and standard operating procedures.

Meetings of collaborative minds: VHIO's Colorectal Taskforce in action.

### Strategic alliances between public entities across Catalonia

The Oncology Network of Catalonia is a strategic collaboration between two public entities: the Catalan Institute of Health (ICS) and the Catalan Institute of Oncology (ICO).

Scientifically led by Josep Tabernero in his capacity as Head of the Medical Oncology Department of the Vall d'Hebron University Hospital (HUVH), this network combines the expertise and critical mass toward further advancing precision oncology in the treatment and cancer of cancer patients.

This collaboration also represents a hub of research of excellence from within the region and connects renowned institutes that are dedicated to further spurring innovation, cancer discovery and therapeutic advancements.

Its clinical research program incorporates therapies in currently conducted trials and aims to spur competition in the design and initiation of new studies as well as improved molecular diagnostics.

### Updating on VHIO's participation in international consortia of excellence

VHIO believes in combining strengths and overcoming current challenges in oncology in concert, and consequently (co) identifies, develops and cements important partnerships globally. Important updates concerning our participation in existing collaborations are as follows:

Cancer Core Europe (CCE) is a unique partnership aimed at addressing the cancer care cancer research continuum. Launched in the Autumn of 2014, this working consortium represents a critical mass of activity for the successful integration of all cancer care information, clinical research and outcome research.

CCE is led by its six founding partners and European comprehensive cancer centers of excellence: the Gustave Roussy Cancer Campus Grand Paris (Villejuif, France), Cambridge Cancer Centre (Cambridge, UK), Karolinska Institute (Stockholm, Sweden), Netherlands Cancer Institute - NKI (Amsterdam, The Netherlands), National Center for Tumor Diseases - DKFZ-NCT (Heidelberg, Germany), and VHIO.

Recently incorporating The National Cancer Institute of Milan (Italy), CCE promotes the pooling and exchanging of latest research findings, the sharing of platforms and processes, and empowers researchers and clinicians to rapidly exploit this trove of biological insights and clinical data for the benefit of patients.

VHIO has led the design of the Cancer Core Europe's endorsed Basket of Baskets (BoB) trial. This academic study will integrate molecular prescreening, the development of new diagnostic tests such as circulating DNA, with the testing of targeted therapies in populations of patients who, matched to the molecular alterations detected in their respective tumors, will be most likely to benefit from them.

In 2017 the protocol of its first module supported by a pharmaceutical company, Immune-Checkpoint Blockade in Genomically Selected Populations, was approved. Protocol title: *A Modular, Open-label, Phase II, Multicentre Study to Evaluate Targeted Agents in Molecularly Selected Populations With Advanced Solid Tumours*.

The protocol will be sent to the relevant authorities next year and first patient enrolment is envisaged towards the end of 2018.

**www.cancercoreeurope.eu**

As a reflection of our expertise in developing and finely tuning cancer models to identify factors influencing tumor growth, predict cancer progression and response to treatments, VHIO is both founding member and member of the Board of Coordinators for strategic decisions and management of the EuroPDX Consortium – *Translating Knowledge in Oncology*. Established in 2013, it connects 20 institutions across 9 EU countries and the US that are developing PDX cancer models, promotes the sharing and exchange of findings on promising therapeutics, and leads multicenter preclinical studies.

As highlighted in our Director's Foreword this year (page 3), EurOPDX members co-authored an important article* exploring the current challenges of patient-derived xenografts (PDX). The review assessed the progress marked to-date in developing these and other models to more faithfully recapitulate the molecular specificities of patient samples, and balanced preclinical realities with current expectations from the clinical perspective.

Following their review of using next-generation models to establish the role of the immune system in tumor cell spread and test-bed the increasing portfolio of immunotherapeutics, co-authors also stressed the absolute necessity of sharing and exchanging data from various experimental models– a guiding principle that defines both the EurOPDX Consortium and VHIO.

**www.europdx.eu**

*Byrne AT, Alférez DG, Amant F, Annibali D, Arribas J, Biankin AV, Bruna A, Budinská E, Caldas C, Chang DK, Clarke RB, Clevers H, Coukos G, Dangles-Marie V, Eckhardt SG, Gonzalez-Suarez E, Hermans E, Hidalgo M, Jarzabek MA, de Jong S, Jonkers J, Kemper K, Lanfrancone L, Mælandsmo GM, Marangoni E, Marine JC, Medico E, Norum JH, Palmer HG, Peeper DS, Pelicci PG, Piris-Gimenez A, Roman-Roman S, Rueda OM, Seoane J, Serra V, Soucek L, Vanhecke D, Villanueva A, Vinolo E, Bertotti A, Trusolino L. Interrogating open issues in cancer precision medicine with patient-derived xenografts. *Nat Rev Cancer.* 2017 Apr;17(4):254-268.

Spurred by Horizon 2020's European Union funding for Research and Innovation funding, MoTriColor (Molecularly guided Trials with specific treatment strategies in patients with advanced newly molecular defined subtypes of Colorectal cancer), led by VHIO, is powered by a total of eight clinical research centers of excellence, spanning Spain, Italy, The Netherlands and Belgium, as well as the European Organisation for Research and Treatment of Cancer (EORTC), and a diagnostic/prognostic SME.

Dedicated to conducting multi-center early phase clinical trials to establish the anti-tumor activity of novel experimental therapies for patients with metastatic or advanced colorectal cancer, patients will be stratified based on their gene expression profiles according to recently established predictive signatures, and response and resistance to selected therapies will be tracked by liquid biopsy.

This year, prescreening is currently underway and patient enrolment in the three clinical trials commences in 2018.

**www.motricolor.eu**

Initiated in 2010, WIN's Worldwide Innovative Networking (WIN) Consortium in personalized cancer medicine aims at rapidly translating precision cancer medicine discoveries into standards of patient care worldwide. Currently comprising 43 partners including VHIO, this global collaboration strives to up the tempo and reduce the costs of translating novel cancer treatments to the clinic by developing and applying the most promising genomic-based research advances.

Building on the unique, academic and international trial, WINTHER (WIN Therapeutics) selected partners have designed a second WIN trial: Survival Prolongation by Rationale Innovative Genomics (SPRING). Bringing key stakeholders together from industry and academia, this

collaboration will focus on advancing precision medicine against lung cancer.

In 2017 the Consortium received the US Food and Drug Administration's (FDA) approval to start the clinical investigation of a novel therapeutic approach using the combination of three targeted therapies for the first line treatment of patients with advanced non-small cell lung cancer (NSCLC).
**www.winconsortium.org**

**For the full list of VHIO's participation in cross-border international cosortia and other collaborations** see pages 140-143.

## Other partnering opportunities in 2017

### VHIO and the Memorial Sloan Kettering Cancer Center - MSKCC (New York) recently renewed its collaborative framework agreements as follows:

The Obra Social "la Caixa" 2nd International Program for Cancer Research and Education, renewed as a 3-year initiative to consolidate and further pursue the established synergies between VHIO and MSKCC.

This new project will include several initiatives focused on the pan-omic exploration (genomics and radiomics) of solid tumors, with particular emphasis on Big Data. More specifically, with José Baselga, Physician-in-Chief at MSKCC and myself as co-PIs (in collaboration with Maurizio Scaltriti, MSKCC, and VHIO's Rodrigo Dienstmann, Ana Vivancos, Joaquin Mateo and Raquel Perez-Lopez), we will conduct research on the impact of gene mutations in DNA damage repair and metastatic prostate cancer, together with data mining to reveal new molecular genetic determinants of sensitivity to targeted therapy in solid cancers.

VHIO and the BBVA Foundation paired in collaboration with MSKCC to pioneer a Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI). Building on the successes of a previous joint project to implement a tumor biomarkers research program, CAIMI represents an important forward step in advancing agents that inhibit checkpoint regulation of the immune system, better understanding mechanisms of resistance and response to these therapies, and prioritizing the early development of those drugs showing most promise.

This project combines the expertise of VHIO's Elena Garralda (PI of VHIO's Early Clinical Drug Development and Executive Director of our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa"), who heads up CAIMI's clinical research, Alena Gros (PI, VHIO's Tumor Immunology and Immunotherapy Group), who takes the lead on translational research, and Ana Vivancos (PI of our Cancer Genomics Group), who directs our internationally recognized prescreening platform. In collaboration with our MSKCC colleagues, VHIO will co-found six translational projects linked to the early clinical development phases of immunotherapy.

**For additional updates on VHIO's research aimed at advancing novel immune agents either as monotherapy or in combination in 2017 please** see pages 4-5 **of our Director's Foreword.**

## Institutional accolades & accreditation

### "HI-5'd" by the European Alliance for Personalised Medicine for best integrating personalized medicine in oncology

This year's European Alliance for Personalised Medicine (EAPM) Congress: *Personalising Your Health: A Global Imperative,* 27 – 30 November (Belfast, Ireland), celebrated the launch of its Health Innovation Five 'HI-5' Awards. In recognition of VHIO's purely integrative and comprehensive research model that tightly connects cancer discovery with clinical research, our Institute was awarded under the category of *Best EU-based hospital for integrating personalised cancer medicine*.

This coveted prize salutes VHIO's capacity to swiftly integrate and transform precision medicine against cancer.

### 2017 Best-in-Class Prize awarded by *Gaceta Médica*

Also announced in 2017, VHIO was awarded with *Gaceta Médica*'s Best-in-Class Prize for R&D in oncology in recognition of our contribution to the Spanish National Health System.

This accolade recognizes VHIO as a leading comprehensive cancer center of excellence and our capacity for turning cancer discovery into more powerfully tailored treatments and better practice for the care of patients.

Sergi Cuadrado, VHIO's Deputy Managing Director, Josep Tabernero, Director of VHIO, Joan Seoane, Director of Translational Research, Joan Carles, PI, Genitourinary, CNS Tumors & Sarcoma Group, pick up *Gaceta Médica*'s 2017 Best-in-Class Prize.

### Recognition through accreditation

In 2017 VHIO underwent evaluation for accreditation of the CERCA Institute of Research Centres of Catalonia (*Institució CERCA*

– *Centres de Recerca de Catalunya*) for the period 2013 – 2016. In recognition of VHIO's progress, performance in knowledge transfer activities and management of excellence, VHIO was awarded with the maximum qualification of an A grading.

Also reflecting our dedication to excellence and the quality of our services and procedures, our Cancer Genomics and Molecular Groups, led by Ana Vivancos and Paolo Nuciforo respectively, have both received ISO 15189 accreditation for their testing methods and technologies. Similarly, we continue to meet the high standards in quality and procedures in the audit of our clinical trials Units, carried out by the *Generalitat de Catalunya*. Our Research Management is also endorsed by ISO 9001 Certification.

## Translational insights spurring VHIO Spin-Offs

Establishing the role of leukemia inhibitor factor (LIF) as a promoter of cancer progression and the discovery of humanized antibody MSC-1's capacity to effectively target LIF, VHIO's translational research led to the launch of VHIO-born spin-off Mosaic Biomedicals S.L. , and the promise of the accelerated clinical development of MSC-1.

Mosaic Biomedicals, co-founded in 2014 by VHIO's Joan Seoane (Director of our Translational Research Program and ICREA Professor), merged with a Canadian company, Northern Biologics in 2016, and will run a clinical trial across sites at VHIO, Memorial Sloan Kettering Cancer Center (MSKCC) and the Princess Margaret Hospital in early 2018.

In 2017 Mosaic was co-recipient of *CataloniaBio's Biosuccess Award* of the Year for its exceptional entrepreneurship and biobusiness development aimed at advancing healthcare. This year's prize also recognized the aforementioned merger consequent promise of the humanized antibody MSC-1.

Built on research carried out at VHIO to successfully translate Omomyc-based therapy into clinical application, a second VHIO spin-off, Peptomyc S.L., co-founded by VHIO's Laura Soucek in 2014 (PI of our Mouse Models of Cancer Therapies Group, ICREA Professor, and CEO of Peptomyc) centers on developing anti-Myc peptides for the treatment of non-small cell lung cancer, triple negative breast cancer and glioblastoma. The Omomyc cell-penetrating peptide (CPP), proven preclinically, promises to become the first ever clinically viable and direct inhibitor of Myc – a protein implicated in the formation of most tumor types.

In 2017 this spin-off secured 4.2 million euros in a Series A round led by the Barcelona-based venture capital investment firm, Alta Life Sciences. This funding will provide Peptomyc with the necessary capital for the development of clinical trials to test this novel peptide for the inhibition of MYC.

## VHIO-organized events: exchange and debate of latest discovery to spur progress against cancer

VHIO is highly dedicated to organizing events of the highest calibre to provide unparalleled opportunity to present, debate and discuss the very latest in cancer discovery – from the bench to bedside and back. These educational opportunities frequently lead to new and essential research collaborations that continue to accelerate our collective efforts aimed at solving cancer sooner.

### VHIO's *Meet the Editors*

Launched back in 2011 VHIO's *Meet the Editors* series are special sessions providing oncology professionals at research institutes of excellence in Barcelona with unique opportunity to learn more about scientific publishing and 'hot spot' areas of cancer research, as well as put questions and comments directly to editors during the Q&A with the audience.

Over the last few years we have been fortunate to have welcomed Senior Editors of some of the most prestigious publications in oncology and biomedicine including *Nature, Nature Reviews Cancer, Science, The New England Journal of Medicine, Nature Medicine, Cancer Cell, The Lancet Oncology, Cancer Discovery* and *Annals of Oncology.*

As this year's Report goes to print, Barbara Marte, Senior Editor, *Nature,* will return to VHIO for a day with several of our Principal Investigators. We also envisage a VHIO *Meet the Editors* session this year with Kevin Davies, Founding Editor, *Nature Genetics*, former Editor-in-Chief of Cell Press, and Executive Editor of the newly launched, *The CRISPR Journal.*

### Ad-hoc courses, workshops & observerships

Based on specific lines and research areas that continue to position VHIO as a leading international reference, we share our expertise, learn from eminent guest speakers, discuss and debate our latest findings through the organization of VHIO ad-hoc courses and workshops.

1.- Preceptorship in the Management of Advanced Prostate Cancer: Multidisciplinary Approach, 16- 17 March 2017, Coordinator: Joan Carles 2.- Breast Cancer Preceptorship Programme, 13 – 15 September 2017, Coordinator: Cristina Saura 3.- Colorectal and Gynecological Malignancies (RIME), Dates: 15 – 17 November 2017, Coordinator: Elena Élez.

Exchanging latest discovery in cancer science and medicine, VHIO organized and hosted a total of 30 Courses, Workshops, Observerships and Perceptorships in 2017.

Launched in February 2016 by co-Chairs Verónica Rodilla and Jordi Martínez Quintanilla, Post-Doctoral Fellows of VHIO's Growth Factors and Stem Cells & Cancer Groups respectively, our series of *Benchstoming Seminars*

represent an excellent educational opportunity for junior faculty at VHIO to both present and exchange on and around their respective research interests across VHIO's various research programs.

Not only do our young researchers learn more about their other colleagues and research lines, they can also express their ideas surrounding a given topic presented at each seminar. The specially crafted informal format of these meetings favours free thought, flow, and interaction between the speakers and participants.

In 2017, a total of 17 researchers presented, discussed and 'benchstormed' their research areas.

## The welcoming and hosting of other meetings

Our move to VHIO's new premises, the CELLEX Building, back in 2015 has not only provided us with the valuable space through which to our research programs, but also gave us a state-of-the-art auditorium. It is with huge thanks to the CELLEX Foundation that we can now happily and readily review requests received from our project partners as well as leading societies in oncology to host and celebrate their respective scientific meetings and conferences.

As an example, in 2017 we welcomed the EU FP7-supported REQUITE project's 5th annual gathering and 9th anniversary of the Radiogenomics Consortium meeting, 19 – 21 June. This hosting was spurred by VHIO's Orland Díez's and Sara Gutiérrez's (Principal Investigator and Senior Scientist of our Oncogenetics Group, respectively), participation in REQUITE – *Validating predictive models of radiotherapy toxicity to improve quality-of-life and reduce side-effects in cancer survivors.*

Throughout the course of the meeting participants updated on important progress reported from various cross-border studies that are developing and validating statistical models incorporating biomarker to establish the likelihood of adverse side-effects, explored the application of machine learning techniques to radiogenomics, and road-mapped next directions in a session dedicated to future projects.

REQUITE's two-day annual meeting showcased latest developments across its various work packages with up-to-the-minute results from its various studies and trials.

## Coming to VHIO in 2018

An EACR masterclass: *LIF as We Know It: From Basic Science to Clinical Trials.*

Organized by Joan Seoane, Director of Translational Research at VHIO and ICREA Professor, in collaboration with the European Association for Cancer Research (EACR), *LIF as We Know It: From Basic Science to Clinical Trials,* will be coming to VHIO's CELLEX Auditorium, Barcelona, 28 – 29 May 2018, for a bench-bedside and back review of all the very latest insights in the field of LIF.
**www.eacr.org/conference/lif2018.**

## VHIO's public engagement & outreach

VHIO supports and organizes activities to increase public interest in cancer research and promote the important advances reported by our scientists and clinical investigators. These efforts are aimed at patients, youngsters and non-specialized adult audiences to enrich scientific culture as well as promote science as a stimulating career path for young people - the future of our research.

Importantly, some of these initiatives have resulted in considerable funding for research at VHIO. We will continue to identify, lead and participate in all these precious initiatives and launch new ones based on identified opportunities.


In 2017 we celebrated the launch of two new public engagement activities: VHIO's *Running for Research* and our *Schools and Science* Education Program:

VHIO VALL D'HEBRON Institute of Oncology
RUNNING FOR RESEARCH
www.vhio.net

Inspired by Daniel Massó Vallés and Irene Rius, Post-Doctoral Fellow and Graduate Student of VHIO's Mouse Models of Cancer Therapies and Growth Factors Groups, respectively, VHIO's *Running for Research* currently comprises a team of 15 researchers who are participating in several half and full marathons to mix and mingle with the general public and spread the word about who we are, what we do, and promote the value and importance of supporting cancer research.

VHIO runners with our Director, Josep Tabernero.

Our dedicated runners, who officially enter sports events in the name of VHIO, are kitted out with VHIO: *Running for Research* branded baseball caps and t-shirts to increase visibility and trigger conversation with fellow runners and other members of the public present.

VHIO's new education program, *Schools and Science*, welcomed over 50 under-twelves from a local primary school to meet our faculty, tour our laboratories and learn more about cancer biology and research.

VHIO's Violeta Serra, PI of our Experimental Therapeutics Group delivering a junior masterclass at CELLEX on the origins and development of cancer.

The main objectives of this outreach program are to teach young and inquisitive minds about the importance of research in solving cancer sooner, how we at VHIO conduct our investigation, and to hopefully inspire some to ultimately become the next generation of cancer scientists.

During their half day visit our young visitors participated in workshops and hands-on activities led and supervised by VHIO faculty. In view of the tremendous success and excellent feedback received from the students and teachers, we will continue to open our doors to all primary schools who wish to participate in this inspired program, with dates already in the diary for next 2018.

## Continued evolution: VHIO's international and internal scientific communication

VHIO's web portal and content is principally aimed at the multidisciplinary, international oncology community and exists to report on all the latest research, developments and activities of our expanding faculty as well as important outcomes from VHIO's broad range of projects.

VHIO's International Communications, directed by Amanda Wren, is focuses on upgrading and constantly updating our website's content, adding new programs as they launch, and implementing new features aimed at further generating traffic, maintaining and attracting new visitors.

At the end of 2017 we launched our new, fresher look website as we transitioned from our previous content management platform:

www.vhio.net: the face of VHIO and the main way in which we communicate with the international oncology and scientific community.

Our new portal has afforded us more flexibility with exciting opportunities to create interactive content, upload videos, rotating banners, dynamic illustrations and figures to complement the written word.

Launched in December 2017, *Wren's Lens*, our internal monthly newsletter, was devised to update all VHIO faculty on highlights covered in our news and/or media program along with special newsletter extras: *Talent Tidbits*, special features and dates in the diary that might be of interest.

The branding, inspired by our Communication Director's surname, incorporates a silhouette of the Wren species perched on top of a lens accentuating VHIO's logo (not to be mistaken for Twitter's bird!).

Initially intended as an internal publication, upon tracking the 'flight' of this e-publication, we are seeing that external shares are on the up.

**For the extended version of this VHIO Scientific Report 2017, with more information about our PIs, groups, programs and activities we invite you to visit: memorias.vhio.net/2017.**

# Scientific Productivity: research articles

## Articles published in 2017

In 2017, 282 scientific articles (77% Q1) were published by VHIO researchers as corresponding/senior or co-authors with a cumulative Impact Factor (IF) totaling at 2851 and a Median Impact Factor (MIF) of 10,11.

These figures reflect an increase in scientific productivity as well as the importance of VHIO's research and contribution to the oncology field.

Figure I:
Number of articles published by VHIO researchers from 2007 - 2017

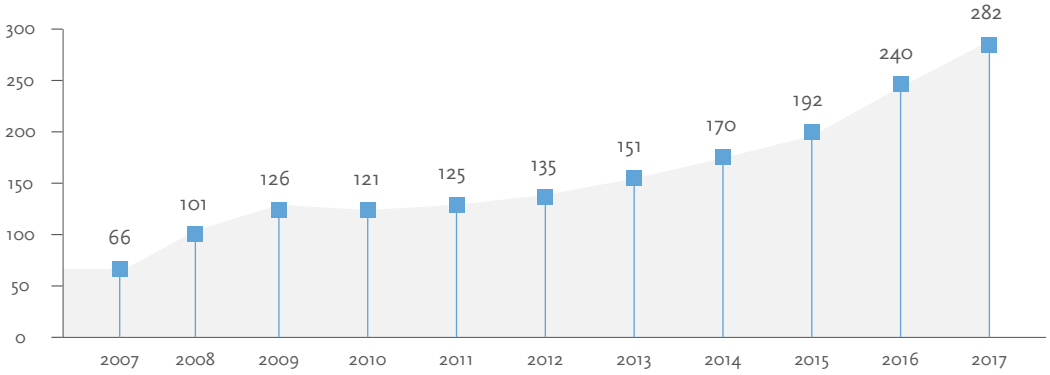
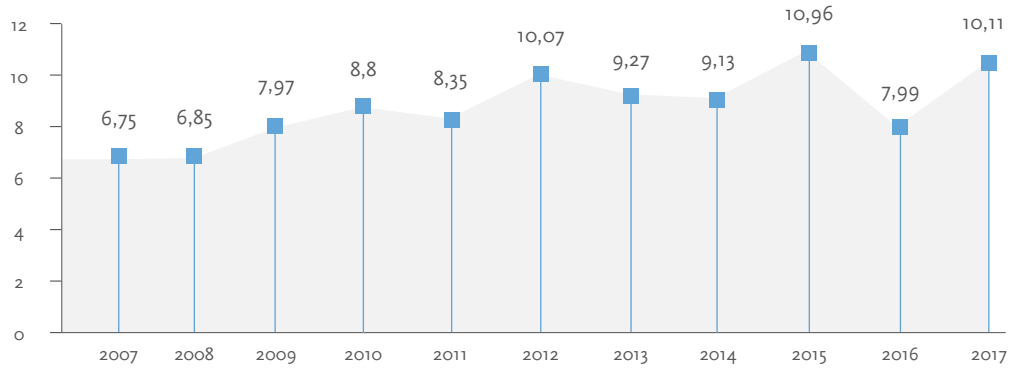



Figure II:
Median Impact Factor of papers published by VHIO faculty from 2007 – 2017




For the complete list of VHIO scientific articles published in 2017 in journals with allocated Impact Factor please see pages 124-137 To view a selection of most relevant articles by VHIO researchers published in 2017 please refer to pages 19-24 of this Scientific Report.

To view our Principal Investigators' selection of a maximum of 4 top papers per group please see respective team pages (sub-section *PI paper pick*). To view each group's full list of publications in 2017, as compiled by our Principal Investigators, visit the extended version of our Scientific Report online at: **http://memorias.vhio.net/2017**

Introducing VHIO

# Selection of some of the most relevant articles by VHIO researchers published in 2017

Below is a selected list of articles published by VHIO researchers in 2017 with respective Impact Factors indicated. For the complete list of VHIO scientific articles published in 2017 in journals with allocated Impact Factor please see pages 124-137 of this Scientific Report.

First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. Carbone DP; Reck M; Paz-Ares L; Creelan B; Horn L; Steins M; Felip E; van den Heuvel MM; Ciuleanu TE; Badin F; Ready N; Hiltermann TJN; Nair S; Juergens R; Peters S; Minenza E; Wrangle JM; Rodriguez-Abreu D; Borghaei H; Blumenschein GR; Villaruz LC; Havel L; Krejci J; Corral Jaime J; Chang H; Geese WJ; Bhagavatheeswaran P; Chen AC; Socinski MA; CheckMate 026 Investigators. 2017. *N Engl J Med.* 376: 2415-2426. IF: 72,406

Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. Peters S; Camidge DR; Shaw AT; Gadgeel S; Ahn JS; Kim DW; Ou SI; Pérol M; Dziadziuszko R; Rosell R; Zeaiter A; Mitry E; Golding S; Balas B; Noe J; Morcos PN; Mok T; ALEX Trial Investigators. 2017. *N Engl J Med.* 377: 829-838. IF: 72,406

Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Tewari KS; Sill MW; Penson RT; Huang H; Ramondetta LM; Landrum LM; Oaknin A; Reid TJ; Leitao MM; Michael HE; DiSaia PJ; Copeland LJ; Creasman WT; Stehman FB; Brady MF; Burger RA; Thigpen JT; Birrer MJ; Waggoner SE; Moore DH; Look KY; Koh WJ; Monk BJ. 2017. *Lancet.* 390: 1654-1663. IF: 47,831

Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Coleman RL; Oza AM; Lorusso D; Aghajanian C; Oaknin A; Dean A; Colombo N; Weberpals JI; Clamp A; Scambia G; Leary A; Holloway RW; Gancedo MA; Fong PC; Goh JC; O'Malley DM; Armstrong DK; Garcia-Donas J; Swisher EM; Floquet A; Konecny GE; McNeish IA; Scott CL; Cameron T; Maloney L; Isaacson J; Goble S; Grace C; Harding TC; Raponi M; Sun J; Lin KK; Giordano H; Ledermann JA; ARIEL3 investigators. 2017. *Lancet.* 390: 1949-1961. IF: 47,831

mTORC1-dependent AMD1 regulation sustains polyamine metabolism in prostate cancer. Zabala-Letona A; Arruabarrena-Aristorena A; Martín-Martín N; Fernandez-Ruiz S; Sutherland JD; Clasquin M; Tomas-Cortazar J; Jimenez J; Torres I; Quang P; Ximenez-Embun P; Bago R; Ugalde-Olano A; Loizaga-Iriarte A; Lacasa-Viscasillas I; Unda M; Torrano V; Cabrera D; van Liempd SM; Cendon Y; Castro E; Murray S; Revandkar A; Alimonti A; Zhang Y; Barnett A; Lein G; Pirman D; Cortazar AR; Arreal L; Prudkin L; Astobiza I; Valcarcel-Jimenez L; Zuñiga-García P; Fernandez-Dominguez I; Piva M; Caro-Maldonado A; Sánchez-Mosquera P; Castillo-Martín M; Serra V; Beraza N; Gentilella A; Thomas G; Azkargorta M; Elortza F; Farràs R; Olmos D; Efeyan A; Anguita J; Muñoz J; Falcón-Pérez JM; Barrio R; Macarulla T; Mato JM; Martinez-Chantar ML; Cordon-Cardo C; Aransay AM; Marks K; Baselga J; Tabernero J; Nuciforo P; Manning BD; Marjon K; Carracedo A. 2017. *Nature.* 547: 109-0. IF: 40,137

CANCER: A precision approach to tumour treatment. Dienstmann R; Tabernero J. 2017. *Nature.* 548: 40-41. IF: 40,137

CANCER: Division hierarchy leads to cell heterogeneity. Seoane J. 2017. *Nature.* 549: 164-166. IF: 40,137

Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. Bullman S; Pedamallu CS; Sicinska E; Clancy TE; Zhang X; Cai D; Neuberg D; Huang K; Guevara F; Nelson T; Chipashvili O; Hagan T; Walker M; Ramachandran A; Diosdado B; Serna G; Mulet N; Landolfi S; Ramon Y Cajal S; Fasani R; Aguirre AJ; Ng K; Élez E; Ogino S; Tabernero J; Fuchs CS; Hahn WC; Nuciforo P; Meyerson M. 2017. *Science.* 358: 1443-0. IF: 37,205

Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. Dienstmann R; Vermeulen L; Guinney J; Kopetz S; Tejpar S; Tabernero J. 2017. *Nat Rev Cancer.* 17: 79-92. IF: 37,147

Interrogating open issues in cancer precision medicine with patient-derived xenografts. Byrne AT; Alférez DG; Amant F; Annibali D; Arribas J; Biankin AV; Bruna A; Budinská E; Caldas C; Chang DK; Clarke RB; Clevers H; Coukos G; Dangles-Marie V; Eckhardt SG; Gonzalez-Suarez E; Hermans E; Hidalgo M; Jarzabek MA; de Jong S; Jonkers J; Kemper K; Lanfrancone L; Mælandsmo GM; Marangoni E; Marine JC; Medico E; Norum JH; Palmer HG; Peeper DS; Pelicci PG; Piris-Gimenez A; Roman-Roman S; Rueda OM; Seoane J; Serra V; Soucek L; Vanhecke D; Villanueva A; Vinolo E; Bertotti A; Trusolino L. 2017. *Nat Rev Cancer.* 17: 254-268. IF: 37,147

Drugging the 'undruggable' cancer targets. Dang CV; Reddy EP; Shokat KM; Soucek L. 2017. *Nat Rev Cancer.* 17: 502-508. IF: 37,147

Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Swisher EM; Lin KK; Oza AM; Scott CL; Giordano H; Sun J; Konecny GE; Coleman RL; Tinker AV; O'Malley DM; Kristeleit RS; Ma L; Bell-McGuinn KM; Brenton JD; Cragun JM; Oaknin A; Ray-Coquard I; Harrell MI; Mann E; Kaufmann SH; Floquet A; Leary A; Harding TC; Goble S; Maloney L; Isaacson J; Allen AR; Rolfe L; Yelensky R; Raponi M; McNeish IA. 2017. *Lancet Oncol.* 18: 75-87. IF: 33,900

HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. Llombart-Cussac A; Cortés J; Paré L; Galván P; Bermejo B; Martínez N; Vidal M; Pernas S; López R; Muñoz M; Nuciforo P; Morales S; Oliveira M; de la Peña L; Peláez A; Prat A. 2017. *Lancet Oncol.* 18: 545-554. IF: 33,900

Maintenance therapy with vinflunine plus best supportive care versus best supportive care alone in patients with advanced urothelial carcinoma with a response after first-line chemotherapy (MAJA; SOGUG 2011/02): a multicentre, randomised, controlled, open-label, phase 2 trial. García-Donas J; Font A; Pérez-Valderrama B; Virizuela JA; Climent MÁ; Hernando-Polo S; Arranz JÁ; Del Mar Llorente M; Lainez N; Villa-Guzmán JC; Mellado B; Del Alba AG; Castellano D; Gallardo E; Anido U; Del Muro XG; Domènech M; Puente J; Morales-Barrera R; Pérez-Gracia JL; Bellmunt J. 2017. *Lancet Oncol.* 18: 672-681. IF: 33,900

Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Baselga J; Im SA; Iwata H; Cortés J; De Laurentiis M; Jiang Z; Arteaga CL; Jonat W; Clemons M; Ito Y; Awada A; Chia S; Jagiello-Gruszfeld A; Pistilli B; Tseng LM; Hurvitz S; Masuda N; Takahashi M; Vuylsteke P; Hachemi S; Dharan B; Di Tomaso E; Urban P; Massacesi C; Campone M. 2017. *Lancet Oncol.* 18: 904-916. IF: 33,900

Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Shaw AT; Kim TM; Crinò L; Gridelli C; Kiura K; Liu G; Novello S; Bearz A; Gautschi O; Mok T; Nishio M; Scagliotti G; Spigel DR; Deudon S; Zheng C; Pantano S; Urban P; Massacesi C; Viraswami-Appanna K; Felip E. 2017. *Lancet Oncol.* 18: 874-886. IF: 33,900

Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Kim SB; Dent R; Im SA; Espié M; Blau S; Tan AR; Isakoff SJ; Oliveira M; Saura C; Wongchenko MJ; Kapp AV; Chan WY; Singel SM; Maslyar DJ; Baselga J; LOTUS

investigators. 2017. *Lancet Oncol.* 18: 1360-1372. IF: 33,900

The Cancer Moonshot from a European perspective. Ciardiello F; Tabernero J. 2017. *Lancet Oncol.* 18: 626-0. IF: 33,900

Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Shaw AT; Felip E; Bauer TM; Besse B; Navarro A; Postel-Vinay S; Gainor JF; Johnson M; Dietrich J; James LP; Clancy JS; Chen J; Martini JF; Abbattista A; Solomon BJ. 2017. *Lancet Oncol.* 18: 1590-1599. IF: 33,900

CIViC is a community knowledgebase for expert crowdsourcing the clinical interpretation of variants in cancer. Griffith M; Spies NC; Krysiak K; McMichael JF; Coffman AC; Danos AM; Ainscough BJ; Ramirez CA; Rieke DT; Kujan L; Barnell EK; Wagner AH; Skidmore ZL; Wollam A; Liu CJ; Jones MR; Bilski RL; Lesurf R; Feng YY; Shah NM; Bonakdar M; Trani L; Matlock M; Ramu A; Campbell KM; Spies GC; Graubert AP; Gangavarapu K; Eldred JM; Larson DE; Walker JR; Good BM; Wu C; Su AI; Dienstmann R; Margolin AA; Tamborero D; Lopez-Bigas N; Jones SJ; Bose R; Spencer DH; Wartman LD; Wilson RK; Mardis ER; Griffith OL. 2017. *Nat Genet.* 49: 170-174. IF: 27,959

Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Phelan CM; Kuchenbaecker KB; Tyrer JP; Kar SP; Lawrenson K; Winham SJ; Dennis J; Pirie A; Riggan MJ; Chornokur G; Earp MA; Lyra PC; Lee JM; Coetzee S; Beesley J; McGuffog L; Soucy P; Dicks E; Lee A; Barrowdale D; Lecarpentier J; Leslie G; Aalfs CM; Aben KKH; Adams M; Adlard J; Andrulis IL; Anton-Culver H; Antonenkova N; AOCS study group; Aravantinos G; Arnold N; Arun BK; Arver B; Azzollini J; Balmaña J; Banerjee SN; Barjhoux L; Barkardottir RB; Bean Y; Beckmann MW; Beeghly-Fadiel A; Benitez J; Bermisheva M; Bernardini MQ; Birrer MJ; Bjorge L; Black A; Blankstein K; Blok MJ; Bodelon C; Bogdanova N; Bojesen A; Bonanni B; Borg Å; Bradbury AR; Brenton JD; Brewer C; Brinton L; Broberg P; Brooks-Wilson A; Bruinsma F; Brunet J; Buecher B; Butzow R; Buys SS; Caldes T; Caligo MA; Campbell I; Cannioto R; Carney ME; Cescon T; Chan SB; Chang-Claude J; Chanock S; Chen XQ; Chiew YE; Chiquette J; Chung WK; Claes KBM; Conner T; Cook LS; Cook J; Cramer DW; Cunningham JM; D'Aloisio AA; Daly MB; Damiola F; Damirovna SD; Dansonka-Mieszkowska A; Dao F; Davidson R; DeFazio A; Delnatte C; Doheny KF; Diez O; Ding YC; Doherty JA; Domchek SM; Dorfling CM; Dörk T; Dossus L; Duran M; Dürst M; Dworniczak B; Eccles D; Edwards T; Eeles R; Eilber U; Ejlertsen B; Ekici AB; Ellis S; Elvira M; EMBRACE Study; et al. 2017. *Nat Genet.* 49: 680-691. IF: 27,959

Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer. Milne RL; Kuchenbaecker KB; Michailidou K; Beesley J; Kar S; Lindström S; Hui S; Lemaçon A; Soucy P; Dennis J; Jiang X; Rostamianfar A; Finucane H; Bolla MK; McGuffog L; Wang Q; Aalfs CM; ABCTB Investigators; Adams M; Adlard J; Agata S; Ahmed S; Ahsan H; Aittomäki K; Al-Ejeh F; Allen J; Ambrosone CB; Amos CI; Andrulis IL; Anton-Culver H; Antonenkova NN; Arndt V; Arnold N; Aronson KJ; Auber B; Auer PL; Ausems MGEM; Azzollini J; Bacot F; Balmaña J; Barile M; Barjhoux L; Barkardottir RB; Barrdahl M; Barnes D; Barrowdale D; Baynes C; Beckmann MW; Benitez J; Bermisheva M; Bernstein L; Bignon YJ; Blazer KR; Blok MJ; Blomqvist C; Blot W; Bobolis K; Boeckx B; Bogdanova NV; Bojesen A; Bojesen SE; Bonanni B; Børresen-Dale AL; Bozsik A; Bradbury AR; Brand JS; Brauch H; Brenner H; Bressac-de Paillerets B; Brewer C; Brinton L; Broberg P; Brooks-Wilson A; Brunet J; Brüning T; Burwinkel B; Buys SS; Byun J; Cai Q; Caldés T; Caligo MA; Campbell I; Canzian F; Caron O; Carracedo A; Carter BD; Castelao JE; Castera L; Caux-Moncoutier V; Chan SB; Chang-Claude J; Chanock SJ; Chen X; Cheng TD; Chiquette J; Christiansen H; Claes KBM; Clarke CL; Conner T; Conroy DM; Cook J; Cordina-Duverger E; Cornelissen S; Coupier I; Cox A; Cox DG; Cross SS; Cuk K; Cunningham JM; Czene K; Daly MB; Damiola F; Darabi H; Davidson R; De Leeneer K; Devilee P; Dicks E; Diez O; Ding YC; Ditsch N; Doheny KF; Domchek SM; Dorfling CM; Dörk T; Dos-Santos-Silva I; Dubois S; Dugué PA; Dumont M; Dunning AM; Durcan L; Dwek M; Dworniczak B; Eccles D; Eeles R; Ehrencrona H; Eilber U; Ejlertsen B; Ekici AB; Eliassen AH; EMBRACE; et al. 2017. *Nat Genet.* 49: 1767-1778. IF: 27,959

Pembrolizumab in patients with extensive-stage small-cell lung cancer: Results from the phase Ib KEYNOTE-028 study. Ott PA; Elez E; Hiret S; Kim DW; Morosky A; Saraf S; Piperdi B; Mehnert JM. 2017. *J Clin Oncol.* 35: 3823-3829. IF: 24,008

Targeting RET in patients with RET-rearranged lung cancers: Results from the global, multicenter RET registry. Gautschi O; Milia J; Filleron T; Wolf J; Carbone DP; Owen D; Camidge R; Narayanan V; Doebele RC; Besse B; Remon-Masip J; Janne PA; Awad MM; Peled N; Byoung CC; Karp DD; Van Den Heuvel M; Wakelee HA; Neal JW; Mok TSK; Yang JCH; Ou SI; Pall G; Froesch P; Zalcman G; Gandara DR; Riess JW; Velcheti V; Zeidler K; Diebold J; Früh M; Michels S; Monnet I; Popat S; Rosell R; Karachaliou, N; Rothschild SI; Shih JY; Warth A; Muley T; Cabillic F; Mazières J; Drilon A. 2017. *J Clin Oncol.* 35: 1403-1410. IF: 24,008

Pertuzumab Use in the Adjuvant Setting: Why Not? Prat A. 2017. *J Clin Oncol.* 35: 1138-0. IF: 24,008

Reply to R.L. Nussbaum et al and J.S. Dolinsky et al. Balmaña J; Nathanson K; Offit K; Robson M; Domchek S. 2017. *J Clin Oncol.* 35: 1262-1263. IF: 24,008

Osimertinib in Pretreated T790M-Positive Advanced Non-Small-Cell Lung Cancer: AURA Study Phase II Extension Component. Yang JC; Ahn MJ; Kim DW; Ramalingam SS; Sequist LV; Su WC; Kim SW; Kim JH; Planchard D; Felip E; Blackhall F; Haggstrom D; Yoh K; Novello S; Gold K; Hirashima T; Lin CC; Mann H; Cantarini M; Ghiorghiu S; Jänne PA. 2017. *J Clin Oncol.* 35: 1288-0. IF: 24,008

New Molecular Assay for the Proliferation Signature in Mantle Cell Lymphoma Applicable to Formalin-Fixed Paraffin-Embedded Biopsies. Scott DW; Abrisqueta P; Wright GW; Slack GW; Mottok A; Villa D; Jares P; Rauert-Wunderlich H; Royo C; Clot G; Pinyol M; Boyle M; Chan FC; Braziel RM; Chan WC; Weisenburger DD; Cook JR; Greiner TC; Fu K; Ott G; Delabie J; Smeland EB; Holte H; Jaffe ES; Steidl C; Connors JM; Gascoyne RD; Rosenwald A; Staudt LM; Campo E; Rimsza LM; Lymphoma/Leukemia Molecular Profiling Project. 2017. *J Clin Oncol.* 35: 1668-1677. IF: 24,008

Prediction of breast and prostate cancer risks in male BRCA1 and BRCA2 mutation carriers using polygenic risk scores. Lecarpentier J; Silvestri V; Kuchenbaecker KB; Barrowdale D; Dennis J; McGuffog L; Soucy P; Leslie G; Rizzolo P; Navazio AS; Valentini V; Zelli V; Lee A; Amin Al Olama A; Tyrer JP; Southey M; John EM; Conner TA; Goldgar DE; Buys SS; Janavicius R; Steele L; Ding YC; Neuhausen SL; Hansen TVO; Osorio A; Weitzel JN; Toss A; Medici V; Cortesi L; Zanna I; Palli D; Radice P; Manoukian S; Peissel B; Azzollini J; Viel A; Cini G; Damante G; Tommasi S; Peterlongo P; Fostira F; Hamann U; Evans DG; Henderson A; Brewer C; Eccles D; Cook J; Ong KR; Walker L; Side LE; Porteous ME; Davidson R; Hodgson S; Frost D; Adlard J; Izatt L; Eeles R; Ellis S; Tischkowitz M; EMBRACE; Godwin AK; Meindl A; Gehrig A; Dworniczak B; Sutter C; Engel C; Niederacher D; Steinemann D; Hahnen E; Hauke J; Rhiem K; Kast K; Arnold N; Ditsch N; Wang-Gohrke S; Wappenschmidt B; Wand D; Lasset C; Stoppa-Lyonnet D; Belotti M; Damiola F; Barjhoux L; Mazoyer S; GEMO Study Collaborators; Van Heetvelde M; Poppe B; De Leeneer K; Claes KBM; de la Hoya M; Garcia-Barberan V; Caldes T; Perez Segura P; Kiiski JI; Aittomäki K; Khan S; Nevanlinna H; van Asperen CJ; HEBON; Vaszko T; Kasler M; Olah E; Balmaña J; Gutiérrez-Enríquez S; Diez O; Teulé A; Izquierdo A; Darder E; Brunet J; et al. 2017. *J Clin Oncol.* 35: 2240-2250. IF: 24,008

Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1–positive endometrial cancer: Results from the KEYNOTE-028 study. Ott PA; Bang YJ; Berton-Rigaud D; Elez E; Pishvaian MJ; Rugo HS; Puzanov I; Mehnert JM; Aung KL; Lopez J; Carrigan M; Saraf S; Chen M; Soria JC. 2017. *J Clin Oncol.* 35: 2535-2541. IF: 24,008

HELOISE: Phase IIIb randomized multicenter study comparing standard-of-care and higher-dose trastuzumab regimens combined with chemotherapy as first-line therapy in patients with human epidermal growth factor receptor 2–positive metastatic gastric or gastroesophageal junction adenocarcinoma. Shah MA; Xu RH; Bang YJ; Hoff PM; Liu T; Herráez-Baranda LA; Xia F; Garg A; Shing M; Tabernero J. 2017. *J Clin Oncol.* 35: 2558-2567. IF: 24,008

Phase II Trial of Atezolizumab As First-Line or Subsequent Therapy for Patients With

Programmed Death-Ligand 1-Selected Advanced Non-Small-Cell Lung Cancer (BIRCH). Peters S; Gettinger S; Johnson ML; Jänne PA; Garassino MC; Christoph D; Toh CK; Rizvi NA; Chaft JE; Carcereny Costa E; Patel JD; Chow LQM; Koczywas M; Ho C; Früh M; van den Heuvel M; Rothenstein J; Reck M; Paz-Ares L; Shepherd FA; Kurata T; Li Z; Qiu J; Kowanetz M; Mocci S; Shankar G; Sandler A; Felip E. 2017. *J Clin Oncol.* 35: 2781-0. IF: 24,008

Treatment Efficacy, Adherence, and Quality of Life Among Women Younger Than 35 Years in the International Breast Cancer Study Group TEXT and SOFT Adjuvant Endocrine Therapy Trials. Saha P; Regan MM; Pagani O; Francis PA; Walley BA; Ribi K; Bernhard J; Luo W; Gómez HL; Burstein HJ; Parmar V; Torres R; Stewart J; Bellet M; Perelló A; Dane F; Moreira A; Vorobiof D; Nottage M; Price KN; Coates AS; Goldhirsch A; Gelber RD; Colleoni M; Fleming GF; SOFT; TEXT Investigators; International Breast Cancer Study Group. 2017. *J Clin Oncol.* 35: 3113-0. IF: 24,008

Phase III study comparing a reduced dose of cabazitaxel (20 mg/m2) and the currently approved dose (25 mg/m2) in postdocetaxel patients with metastatic castration-resistant prostate cancer - PROSELICA. Eisenberger M; Hardy-Bessard AC; Kim CS; Géczi L; Ford D; Mourey L; Carles J; Parente P; Font A; Kacso G; Chadjaa M; Zhang W; Bernard J; de Bono J. 2017. *J Clin Oncol.* 35: 3198-3206. IF: 24,008

Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. Vitolo U; Trnený M; Belada D; Burke JM; Carella AM; Chua N; Abrisqueta P; Demeter J; Flinn I; Hong X; Kim WS; Pinto A; Shi YK; Tatsumi Y; Oestergaard MZ; Wenger M; Fingerle-Rowson G; Catalani O; Nielsen T; Martelli M; Sehn LH. 2017. *J Clin Oncol.* 35: 3529-3537. IF: 24,008

Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). Horn L; Spigel DR; Vokes EE; Holgado E; Ready N; Steins M; Poddubskaya E; Borghaei H; Felip E; Paz-Ares L; Pluzanski A; Reckamp KL; Burgio MA; Kohlhäeufl M; Waterhouse D; Barlesi F; Antonia S; Arrieta O; Fayette J; Crinò L; Rizvi N; Reck M; Hellmann MD; Geese WJ; Li A; Blackwood-Chirchir A; Healey D; Brahmer J; Eberhardt WEE. 2017. *J Clin Oncol.* 35: 3924-0. IF: 24,008

Targeting c-MET in gastrointestinal tumours: Rationale, opportunities and challenges. Bradley CA; Salto-Tellez M; Laurent-Puig P; Bardelli A; Rolfo C; Tabernero J; Khawaja HA; Lawler M; Johnston PG; Van Schaeybroeck S; MErCuRIC consortium. 2017. *Nat Rev Clin Oncol.* 14: 562-576. IF: 20,693

A first-in-human phase I study of the ATP-competitive AKT inhibitor Ipatasertib demonstrates Robust and safe targeting of AKT in patients with solid tumors. Saura C; Roda D; Roselló S; Oliveira M; Macarulla T; Pérez-Fidalgo JA; Morales-Barrera R; Sanchis-García JM; Musib L; Budha N; Zhu J; Nannini M; Chan WY; Sanabria Bohórquez SM; Meng RD; Lin K; Yan Y; Patel P; Baselga J; Tabernero J; Cervantes A. 2017. *Cancer Discov.* 7: 102-113. IF: 20,011

A phase Ib dose-escalation study of encorafenib and cetuximab with or without alpelisib in metastatic BRAF-mutant colorectal cancer. van Geel RM; Tabernero J; Elez E; Bendell JC; Spreafico A; Schuler M; Yoshino T; Delord JP; Yamada Y; Lolkema M; Faris JE; Eskens FA; Sharma S; Yaeger R; Lenz HJ; Wainberg ZA; Avsar E; Chatterjee A; Jaeger S; Tan E; Maharry K; Demuth T; Schellens JH. 2017. *Cancer Discov.* 7: 610-619. IF: 20,011

Improving the armamentarium of PI3K inhibitors with isoform-selective agents: A new light in the darkness. Rodon J; Tabernero J. 2017. *Cancer Discov.* 7: 666-669. IF: 20,011

Erlotinib and bevacizumab in patients with advanced non-small-cell lung cancer and activating EGFR mutations (BELIEF): an international, multicentre, single-arm, phase 2 trial. Rosell R; Dafni U; Felip E; Curioni-Fontecedro A; Gautschi O; Peters S; Massutí B; Palmero R; Aix SP; Carcereny E; Früh M; Pless M; Popat S; Kotsakis A; Cuffe S; Bidoli P; Favaretto A; Froesch P; Reguart N; Puente J; Coate L; Barlesi F; Rauch D; Thomas M; Camps C; Gómez-Codina J; Majem M; Porta R; Shah R; Hanrahan E; Kammler R; Ruepp B; Rabaglio M; Kassapian M; Karachaliou N; Tam R; Shames DS; Molina-Vila MA; Stahel RA; BELIEF collaborative group. 2017. *Lancet Respir Med.* 5: 435-444. IF: 19,287

Increased Risk of Colorectal Cancer in Patients With Multiple Serrated Polyps and Their First-Degree Relatives. Egoavil C; Juarez M; Guarinos C; Rodríguez-Soler M; Hernández-Illán E; Alenda C; Payá A; Castillejo A; Serradesanferm A; Bujanda L; Fernández-Bañares F; Cubiella J; de-Castro L; Guerra A; Aguirre E; Herreros-de-Tejada A; Bessa X; Herráiz M; Marín-Gabriel JC; Balmaña J; Piñol V; Cuatrecasas M; Balaguer F; Castells A; Soto JL; Zapater P; Jover R. 2017. *Gastroenterology.* 153: 106-1122. IF: 18,392

Association of survival benefit with docetaxel in prostate cancer and total number of cycles administered: A post hoc analysis of the Mainsail study. de Morrée ES; Vogelzang NJ; Petrylak DP; Budnik N; Wiechno PJ; Sternberg CN; Doner K; Bellmunt J; Burke JM; Ochoa de Olza M; Choudhury A; Gschwend JE; Kopyltsov E; Flechon A; van As N; Houede N; Barton D; Fandi A; Jungnelius U; Li S; Li JS; de Wit R. 2017. *JAMA Oncol.* 3: 68-75. IF: 16,559

RNA Sequencing to Predict Response to Neoadjuvant Anti-HER2 Therapy A Secondary Analysis of the NeoALTTO Randomized Clinical Trial. Fumagalli, Debora; Venet, David; Ignatiadis, Michail; Azim, Jr., Hatem A.; Maetens, Marion; Rothe, Francoise; Salgado, Roberto; Bradbury, Ian; Pusztai, Lajos; Harbeck, Nadia; Gomez, Henry; Chang, Tsai-Wang; Coccia-Portugal, Maria Antonia; Di Cosimo, Serena; de Azambuja, Evandro; de la Pena, Lorena; Nuciforo, Paolo; Brase, Jan C.; Huober, Jens; Baselga, Jose; Piccart, Martine; Loi, Sherene; Sotiriou, Christos. 2017. *JAMA Oncol.* 3: 227-234. IF: 16,559

Prognostic and Predictive Relevance of Primary Tumor Location in Patients With RAS Wild-Type Metastatic Colorectal Cancer Retrospective Analyses of the CRYSTAL and FIRE-3 Trials. Tejpar, Sabine; Stintzing, Sebastian; Ciardiello, Fortunato; Tabernero, Josep; Van Cutsem, Eric; Beier, Frank; Esser, Regina; Lenz, Heinz-Josef; Heinemann, Volker. 2017. *JAMA Oncol.* 3: 194-201. IF:16,559

Effect of fluorouracil, leucovorin, and oxaliplatin with or without onartuzumab in HER2-negative, MET-positive gastroesophageal adenocarcinoma: The METGastric randomized clinical trial. Shah MA; Bang YJ; Lordick F; Alsina M; Chen M; Hack SP; Bruey JM; Smith D; McCaffery I; Shames DS; Phan S; Cunningham D. 2017. *JAMA Oncol.* 3: 620-627. IF: 16,559

Nomogram-based Prediction of Overall Survival in Patients with Metastatic Urothelial Carcinoma Receiving First-line Platinum-based Chemotherapy: Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC). Necchi A; Sonpavde G; Lo Vullo S; Giardiello D; Bamias A; Crabb SJ; Harshman LC; Bellmunt J; De Giorgi U; Sternberg CN; Cerbone L; Ladoire S; Wong YN; Yu EY; Chowdhury S; Niegisch G; Srinivas S; Vaishampayan UN; Pal SK; Agarwal N; Alva A; Baniel J; Golshayan AR; Morales-Barrera R; Bowles DW; Milowsky MI; Theodore C; Berthold DR; Daugaard G; Sridhar SS; Powles T; Rosenberg JE; Galsky MD; Mariani L; RISC Investigators. 2017. *Eur Urol.* 71: 281-289. IF: 16,265

Prognostic Significance of Venous Thromboembolic Events in Disseminated Germ Cell Cancer Patients. Gonzalez-Billalabeitia E; Castellano D; Sobrevilla N; Guma J; Hervas D; Luengo MI; Aparicio J; Sanchez-Muñoz A; Mellado B; Saenz A; Valverde C; Fernandez A; Margeli M; Duran I; Fernandez S; Sastre J; Ros S; Maroto P; Manneh R; Cerezuela P; Carmona-Bayonas A; Spanish Germ Cell Cancer Group/Grupo Germinal (SGCCG). 2017. *J Natl Cancer Inst.* IF: 12,589

Prognostic Value of BRAF and KRAS Mutations in MSI and MSS Stage III Colon Cancer. Taieb J; Le Malicot K; Shi Q; Penault Lorca F; Bouché O; Tabernero J; Mini E; Goldberg RM; Folprecht G; Luc Van Laethem J; Sargent DJ; Alberts SR; Francois Emile J; Laurent Puig P; Sinicrope FA. 2017. *J Natl Cancer Inst.* IF: 12,589

Evaluation of Polygenic Risk Scores for Breast and Ovarian Cancer Risk Prediction in BRCA1 and BRCA2 Mutation Carriers. Kuchenbaecker KB; McGuffog L; Barrowdale D; Lee A; Soucy P; Dennis J; Domchek SM; Robson M; Spurdle AB; Ramus SJ; Mavaddat N; Terry MB; Neuhausen SL; Schmutzler RK; Simard J; Pharoah PDP; Offit K; Couch FJ; Chenevix-Trench G; Easton DF; Antoniou AC; Lush M; Hamann U; Southey M; John EM; Chung WK; Daly MB; Buys SS; Goldgar DE; Dorfling CM; van Rensburg EJ; Chun Ding Y; Ejlertsen B; Gerdes AM; Hansen TV; Slager S; Hallberg E; Benitez J; Osorio A;

Cohen N; Lawler W; Weitzel JN; Peterlongo P; Pensotti V; Dolcetti R; Barile M; Bonanni B; Azzollini J; Manoukian S; Peissel B; Radice P; Savarese A; Papi L; Giannini G; Fostira F; Konstantopoulou I; Adlard J; Brewer C; Cook J; Davidson R; Eccles D; Eeles R; Ellis S; Frost D; Hodgson S; Izatt L; Lalloo F; Ong KR; Godwin AK; Arnold N; Dworniczak B; Engel C; Gehrig A; Hahnen E; Hauke J; Kast K; Meindl A; Niederacher D; Schmutzler RK; Varon-Mateeva R; Wang-Gohrke S; Wappenschmidt B; Barjhoux L; Collonge-Rame MA; Elan C; Golmard L; GEMO Study Collaborators; EMBRACE; Barouk-Simonet E; Lesueur F; Mazoyer S; Sokolowska J; Stoppa-Lyonnet D; Isaacs C; Claes KBM; Poppe B; de la Hoya M; Garcia-Barberan V; Aittomaki K; Nevanlinna H; Ausems MGEM; de Lange JL; Gomez Garcia EB; Hogervorst FB; HEBON; Kets CM; Meijers-Heijboer HE; Oosterwijk JC; Rookus MA; van Asperen CJ; van den Ouweland AMW; van Doorn HC; van Os TAM; Kwong A; Olah E; Diez O; Brunet J; et al. 2017. *J Natl Cancer Inst.* IF: 12,589

Convergent Akt activation drives acquired EGFR inhibitor resistance in lung cancer. Jacobsen K; Bertran-Alamillo J; Molina MA; Teixidó C; Karachaliou N; Pedersen MH; Castellví J; Garzón M; Codony-Servat C; Codony-Servat J; Giménez-Capitán A; Drozdowskyj A; Viteri S; Larsen MR; Lassen U; Felip E; Bivona TG; Ditzel HJ; Rosell R. 2017. *Nat Commun.* 8: 410-0. IF: 12,124

Modulation of telomere protection by the PI3K/AKT pathway. Méndez-Pertuz M; Martínez P; Blanco-Aparicio C; Gómez-Casero E; Belen García A; Martínez-Torrecuadrada J; Palafox M; Cortés J; Serra V; Pastor J; Blasco MA. 2017. *Nat Commun.* 8: 1278-0. IF: 12,124

Single-cell transcriptome conservation in cryopreserved cells and tissues. Guillaumet-Adkins A; Rodríguez-Esteban G; Mereu E; Mendez-Lago M; Jaitin DA; Villanueva A; Vidal A; Martinez-Marti A; Felip E; Vivancos A; Keren-Shaul H; Heath S; Gut M; Amit I; Gut I; Heyn H. 2017. *Genome Biol.* 18: 45-0. IF: 11,908

An update on the management of sporadic desmoid-type fibromatosis: A European Consensus Initiative between Sarcoma PAtients EuroNet (SPAEN) and European Organization for Research and Treatment of Cancer (EORTC)/Soft Tissue and Bone Sarcoma Group (STBSG). Kasper, B.; Baumgarten, C.; Garcia, J.; Bonvalot, S.; Haas, R.; Haller, F.; Hohenberger, P.; Penel, N.; Messiou, C.; van der Graaf, W.T.; Gronchi, A.; Bauer, S.; Blay, J.Y.; van Coevorden, F.; Dileo, P.; Dürr, H.R.; Fiore, M.; Grünwald, V.; Jones, R.; Judson, I.; Kettelhack, C.; Kopeckova, K.; Lazar, A.; Lindner, L.H.; Martin-Broto, J.; Rutkowski, P.; Stacchiotti, S.; Stoeckle, E.; Valverde, C.; Verhoef, K.; Wardelmann, E.; Wartenberg, M. 2017. *Ann Oncol.* 28: 2399-2408. IF: 11,855

Improving brain penetration of kinase inhibitors in lung cancer patients with oncogene dependency. Remon, J.; Soria, J.C. 2017. *Ann Oncol.* 28: 196-198. IF: 11,855

Research needs in breast cancer. Cardoso F; Harbeck N; Barrios CH; Bergh J; Cortés J; El Saghir N; Francis PA; Hudis CA; Ohno S; Partridge AH; Sledge GW; Smith IE; Gelmon KA. 2017. *Ann Oncol.* 28: 208-217. IF: 11,855

Adherence to capecitabine in preoperative treatment of stage II and III rectal cancer: Do we need to worry? Font R; Espinas JA; Layos L; Martinez Villacampa M; Capdevila J; Tobeña M; Pisa A; Pericay C; Lezcano C; Fort E; Cardona I; Berga N; Solà J; Borras JM. 2017. *Ann Oncol.* 28: 831-835. IF: 11,855

Osimertinib benefit in EGFR-mutant NSCLC patients with T790M-mutation detected by circulating tumour DNA. Remon, J.; Caramella, C.; Jovelet, C.; Lacroix, L.; Lawson, A.; Smalley, S.; Howarth, K.; Gale, D.; Green, E.; Plagnol, V.; Rosenfeld, N.; Planchard, D.; Bluthgen, M.V.; Gazzah, A.; Pannet, C.; Nicotra, C.; Auclin, E.; Soria, J.C.; Besse, B. 2017. *Ann Oncol.* 28: 784-790. IF: 11,855

Pathway level alterations rather than mutations in single genes predict response to HER2-targeted therapies in the neo-ALTTO trial. Shi W; Jiang T; Nuciforo P; Hatzis C; Holmes E; Harbeck N; Sotiriou C; Peña L; Loi S; Rosa DD; Chia S; Wardley A; Ueno T; Rossari J; Eidtmann H; Armour A; Piccart-Gebhart M; Rimm DL; Baselga J; Pusztai L. 2017. *Ann Oncol.* 28: 128-135. IF: 11,855

Incidence and management of diarrhea in patients with HER2-positive breast cancer treated with pertuzumab. Swain SM; Schneeweiss A; Gianni L; Gao JJ; Stein A; Waldron-Lynch M; Heeson S; Beattie MS; Yoo B; Cortes J; Baselga J. 2017. *Ann Oncol.* 28: 761-768. IF: 11,855

Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer: A phase 1 trial. Hui R; Garon EB; Goldman JW; Leighl NB; Hellmann MD; Patnaik A; Gandhi L; Eder JP; Ahn MJ; Horn L; Felip E; Carcereny E; Rangwala R; Lubiniecki GM; Zhang J; Emancipator K; Roach C; Rizvi NA. 2017. *Ann Oncol.* 28: 874-881. IF: 11,855

Adjuvant FOLFOX +/- cetuximab in full RAS and BRAF wildtype stage III colon cancer patients. Taieb J; Balogoun R; Le Malicot K; Tabernero J; Mini E; Folprecht G; Van Laethem JL; Emile JF; Mulot C; Fratté S; Levaché CB; Saban-Roche L; Thaler J; Petersen LN; Bridgewater J; Perkins G; Lepage C; Van Cutsem E; Zaanan A; Laurent-Puig P; for PETACC8 investigators. 2017. *Ann Oncol.* 28: 824-830. IF: 11,855

Prediction of overall survival in stage II and III colon cancer beyond TNM system: a retrospective, pooled biomarker study. Dienstmann, R.; Mason, M. J.; Sinicrope, F. A.; Phipps, A. I.; Tejpar, S.; Nesbakken, A.; Danielsen, S. A.; Sveen, A.; Buchanan, D. D.; Clendenning, M.; Rosty, C.; Bot, B.; Alberts, S. R.; Jessup, J. Milburn; Lothe, R. A.; Delorenzi, M.; Newcomb, P. A.; Sargent, D.; Guinney, J. 2017. *Ann Oncol.* 28: 1023-1031. IF: 11,855

A step towards the harmonization of clinical trials inform consent forms. Remon J; Ferté C. 2017. *Ann Oncol.* 28: 910-912. IF: 11,855

Intratumoral heterogeneity in gastric cancer: a new challenge to face. Alsina M; Gullo I; Carneiro F. 2017. *Ann Oncol.* 28: 912-913. IF: 11,855

A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial. Kulke MH; Ruszniewski P; Van Cutsem E; Lombard-Bohas C; Valle JW; De Herder WW; Pavel M; Degtyarev E; Brase JC; Bubuteishvili-Pacaud L; Voi M; Salazar R; Borbath I; Fazio N; Smith D; Capdevila J; Riechelmann RP; Yao JC. 2017. *Ann Oncol.* 28: 1309-1315. IF: 11,855

Concordance of blood- and tumor-based detection of RAS mutations to guide anti-EGFR therapy in metastatic colorectal cancer. Grasselli J; Elez E; Caratù G; Matito J; Santos C; Macarulla T; Vidal J; Garcia M; Viéitez JM; Paéz D; Falcó E; Lopez Lopez C; Aranda E; Jones F; Sikri V; Nuciforo P; Fasani R; Tabernero J; Montagut C; Azuara D; Dienstmann R; Salazar R; Vivancos A. 2017. *Ann Oncol.* 28: 1294-1301. IF: 11,855

Targeting the fibroblast growth factor receptor 2 in gastric cancer: Promise or pitfall? Hierro C; Alsina M; Sánchez M; Serra V; Rodon J; Tabernero J. 2017. *Ann Oncol.* 28: 1207-1216. IF: 11,855

The search for simplicity: Is this compatible with precision medicine? Nuciforo PG. 2017. *Ann Oncol.* 28: 10-12. IF: 11,855

Phase II randomized study of PM01183 versus topotecan in patients with platinum-resistant/refractory advanced ovarian cancer. Poveda A; Del Campo JM; Ray-Coquard I; Alexandre J; Provansal M; Guerra Alía EM; Casado A; Gonzalez-Martin A; Fernández C; Rodriguez I; Soto A; Kahatt C; Fernández Teruel C; Galmarini CM; Pérez de la Haza A; Bohan P; Berton-Rigaud D. 2017. *Ann Oncol.* 28: 1280-1287. IF: 11,855

A prospective examination of circulating tumor cell profiles in non-small-cell lung cancer molecular subgroups. Lindsay CR; Faugeroux V; Michiels S; Pailler E; Facchinetti F; Ou D; Bluthgen MV; Pannet C; Ngo-Camus M; Bescher G; Caramella C; Billiot F; Remon J; Planchard D; Soria JC; Besse B; Farace F. 2017. *Ann Oncol.* 28: 1523-1531. IF: 11,855

A randomized phase II/III study of cabazitaxel versus vinflunine in metastatic or locally advanced transitional cell carcinoma of the urothelium (SECAVIN). Bellmunt J; Kerst JM; Vázquez F; Morales-Barrera R; Grande E; Medina A; González Graguera MB; Rubio G; Anido U; Fernández Calvo O; González-Billalabeitia E; Van den Eertwegh AJM; Pujol E; Perez-Gracia JL; González Larriba JL; Collado R; Los M; Maciá S; De Wit R; SOGUG and DUOS. 2017. *Ann Oncol.* 28: 1517-1522. IF: 11,855

Professional burnout in European young oncologists: results of the European Society for Medical Oncology (ESMO) Young Oncologists Committee Burnout Survey. Banerjee S; Califano R; Corral J; de Azambuja E; De Mattos-Arruda L; Guarneri V; Hutka M; Jordan K; Martinelli E; Mountzios G; Ozturk MA; Petrova M;

Postel-Vinay S; Preusser M; Qvortrup C; Volkov MNM; Tabernero J; Olmos D; Strijbos MH. 2017. *Ann Oncol.* 28: 1590-1596. IF: 11,855

Reply to the letter to the editor 'Addressing the quality of the ESMO-MCBS' by Del Paggio. Cherny NI; Dafni U; Bogaerts J; Pentheroudakis G; Tabernero J; Zielinski C; de Vries EGE. 2017. *Ann Oncol.* 28: 2031-2032. IF: 11,855

Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Arnold D; Lueza B; Douillard JY; Peeters M; Lenz HJ; Venook A; Heinemann V; Van Cutsem E; Pignon JP; Tabernero J; Cervantes A; Ciardiello F. 2017. *Ann Oncol.* 28: 1713-1729. IF: 11,855

Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: Results from two randomized first-line panitumumab studies. Boeckx N; Koukakis R; Op de Beeck K; Rolfo C; Van Camp G; Siena S; Tabernero J; Douillard JY; André T; Peeters M. 2017. *Ann Oncol.* 28: 1862-1868. IF: 11,855

An antisense oligonucleotide targeting TGF-ß2 inhibits lung metastasis and induces CD86 expression in tumor-associated macrophages. Huber-Ruano I; Raventós C; Cuartas I; Sánchez-Jaro C; Arias A; Parra JL; Wosikowski K; Janicot M; Seoane J. 2017. *Ann Oncol.* 28: 2278-2285. IF: 11,855

A randomized, open-label, multicenter, phase 3 study to compare the efficacy and safety of eribulin to treatment of physician's choice in patients with advanced non-small cell lung cancer. Katakami N; Felip E; Spigel DR; Kim JH; Olivo M; Guo M; Nokihara H; Yang JC; Iannotti N; Satouchi M; Barlesi F. 2017. *Ann Oncol.* 28: 2241-2247. IF: 11,855

Reply to the letter to the editor 'Can we trust burnout research?' by Bianchi et al. Banerjee S; Preusser M; Tabernero J; Strijbos M. 2017. *Ann Oncol.* 28: 2625-2626. IF: 11,855

ESMO-Magnitude of Clinical Benefit Scale version 1.1. Cherny NI; Dafni U; Bogaerts J; Latino NJ; Pentheroudakis G; Douillard JY; Tabernero J; Zielinski C; Piccart MJ; de Vries EGE. 2017. *Ann Oncol.* 28: 2340-2366. IF: 11,855

Dual MET and ERBB inhibition overcomes intratumor plasticity in osimertinib-resistant-advanced non-small-cell lung cancer (NSCLC). Martinez-Marti A; Felip E; Matito J; Mereu E; Navarro A; Cedrés S; Pardo N; Martinez de Castro A; Remon J; Miquel JM; Guillaumet-Adkins A; Nadal E; Rodriguez-Esteban G; Arqués O; Fasani R; Nuciforo P; Heyn H; Villanueva A; Palmer HG; Vivancos A. 2017. *Ann Oncol.* 28: 2451-2457. IF: 11,855

Observation as the initial management strategy in patients with mantle cell lymphoma. Abrisqueta P; Scott DW; Slack GW; Steidl C; Mottok A; Gascoyne RD; Connors JM; Sehn LH; Savage KJ; Gerrie AS; Villa D. 2017. *Ann Oncol.* 28: 2489-2495. IF: 11,855

Reply to the letter to the editor `Including lynch syndrome in personalized prognostication and follow-up of stage II and III colon cancer' by Sciallero et al. Dienstmann R; Guinney J. 2017. *Ann Oncol.* 28: 2889-2890. IF: 11,855

BRAF mutant colorectal cancer: prognosis, treatment, and new perspectives. Sanz-Garcia E; Argiles G; Elez E; Tabernero J. 2017. *Ann Oncol.* 28: 2648-2657. IF: 11,855

Gemcitabine plus sirolimus for relapsed and progressing osteosarcoma patients after standard chemotherapy: a multicenter, single-arm phase II trial of Spanish Group for Research on Sarcoma (GEIS). Martin-Broto J; Redondo A; Valverde C; Vaz MA; Mora J; Garcia Del Muro X; Gutierrez A; Tous C; Carnero A; Marcilla D; Carranza A; Sancho P; Martinez-Trufero J; Diaz-Beveridge R; Cruz J; Encinas V; Taron M; Moura DS; Luna P; Hindi N; Lopez-Pousa A. 2017. *Ann Oncol.* 28: 2994-2999. IF: 11,855

Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab. Arnold D; Fuchs C; Tabernero J; Ohtsu A; Zhu AX; Garon EB; Mackey JR; Paz-Ares L; Baron AD; Okusaka T; Yoshino T; Yoon HH; Das M; Ferry D; Zhang Y; Lin Y; Binder P; Sashegyi A; Chau I. 2017. *Ann Oncol.* 28: 2932-2942. IF: 11,855

Incorporating BEAMing technology as a liquid biopsy into clinical practice for the management of colorectal cancer patients: an expert taskforce review. García-Foncillas J; Alba E; Aranda E; Díaz-Rubio E; López-López R; Tabernero J; Vivancos A. 2017. *Ann Oncol.* 28: 2943-2949. IF: 11,855

DPYD genotype-guided fluoropyrimidines dose: is it ready for prime time? Páez D; Salazar R; Tabernero J. 2017. *Ann Oncol.* 28: 2913-2914. IF: 11,855

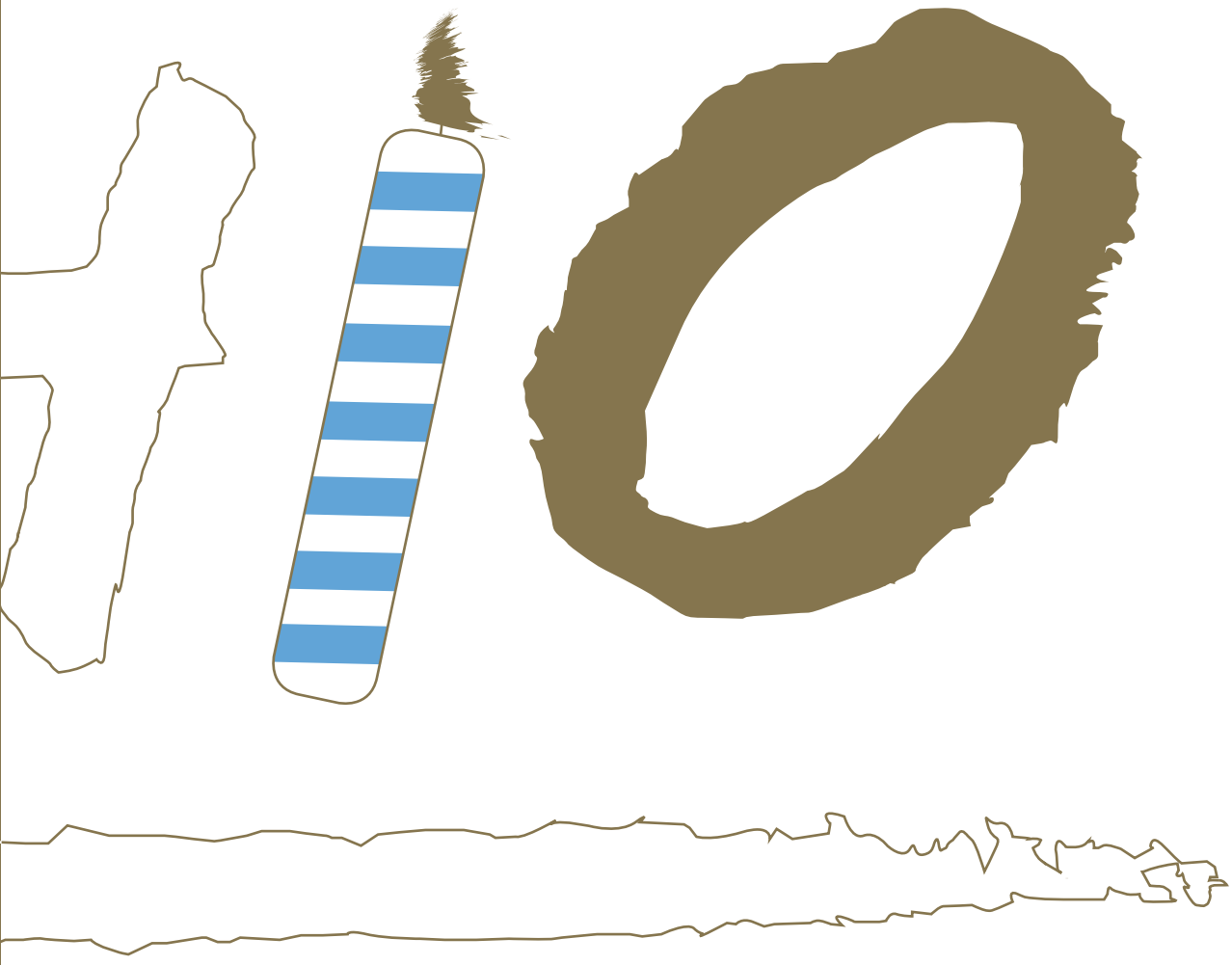
A phase 1b/2b multicenter study of oral panobinostat plus azacitidine in adults with MDS, CMML or AML with ≤ 30% blasts. Garcia-Manero G; Sekeres MA; Egyed M; Breccia M; Graux C; Cavenagh JD; Salman H; Illes A; Fenaux P; DeAngelo DJ; Stauder R; Yee K; Zhu N; Lee JH; Valcarcel D; MacWhannell A; Borbenyi Z; Gazi L; Acharyya S; Ide S; Marker M; Ottmann OG. 2017. *Leukemia.* 31: 2799-2806. IF: 11,702

TALEN/CRISPR-mediated engineering of a promoterless anti-viral RNAi hairpin into an endogenous miRNA locus. Senís E; Mockenhaupt S; Rupp D; Bauer T; Paramasivam N; Knapp B; Gronych J; Grosse S; Windisch MP; Schmidt F; Theis FJ; Eils R; Lichter P; Schlesner M; Bartenschlager R; Grimm D. 2017. *Nucleic Acids Res.* IF: 10,162

Histone H1 depletion triggers an interferon response in cancer cells via activation of heterochromatic repeats. Izquierdo-Bouldstridge A; Bustillos A; Bonet-Costa C; Aribau-Miralbés P; García-Gomis D; Dabad M; Esteve-Codina A; Pascual-Reguant L; Peiró S; Esteller M; Murtha M; Millán-Ariño L; Jordan A. 2017. *Nucleic Acids Res.* 45: 11622-11642. IF: 10,162.

VHIO
VALL D'HEBRON
Institute
of Oncology

# A **Golden Decade**: reflecting on the past 10 years of VHIO's translational success story



# A Golden Decade

## 10 years' translational cancer research: the barometer of VHIO's success

The Vall d'Hebron Institute of Oncology (VHIO) was officially established in 2006 by our former Director, José Baselga, now Physician-in-Chief at the Memorial Sloan Kettering Cancer Center (MSKCC, New York), President of VHIO's Internal Scientific Committee, and Founder and President of the FERO Foundation.

From the outset, José had one pioneering and guiding principle for VHIO: to seamlessly bridge preclinical and clinical research in order to foster a continuous virtuous cycle of knowledge from bench to bedside and back. As evidenced throughout this Scientific Report, this bold approach continues to be at the very core of VHIO's philosophy, passionately pursued by our strong multidisciplinary teams.

Back in 1990: José Baselga in John Mendelsohn's Laboratory, MSKCC, where he pioneered trastuzumab (Herceptin) against HER2 positive breast cancer.

As early as 1990, José was carving out a new paradigm for cancer research through the translational approach – a concept which has only relatively recently been embraced by the professional cancer community. During his time at the prestigious Memorial Sloan Kettering Cancer Center (MSKCC) and Memorial Hospital in New York, he developed and conducted clinical and translational research in parallel – many years before the term 'translational' entered the oncology lexicon.

Specifically, he was responsible for conducting preclinical studies and leading a clinical trial to test the potential therapeutic effects of trastuzumab, a monoclonal antibody anti-HER2.The molecule proved highly efficacious in treating breast cancer patients that overexpressed this receptor and for whom life expectancy was very low at that stage. Numerous patients' lives have since been saved after being treated with this molecule and HER2 positive breast cancer is thankfully no longer as frightening a disease as it used to be.

Returning to the Vall d'Hebron University Hospital (HUVH) in 1996 to lead its then very small Medical Oncology Department, José's vision, work ethic and impeccable commitment to medical oncology quickly lifted the department to new heights. These qualities coupled with his devotion to integrating translational science and clinical research, rapidly established the department as an international reference. José created an environment in which optimal patient care is conciliated with innovative translational research, all in the context of a Public Health System – an exemplary model that has since been adopted and adapted across borders.

Josep Tabernero, Director of VHIO and our Clinical Research Program, with José Baselga and VHIO's two other Program Directors, Joan Seoane – Translational Research (far left), and Joaquín Arribas – Preclinical Research (far right), back in 2013.

This not only extended his translational approach to multidisciplinary teams but also emboldened him to create VHIO, which has over the past decade become a leading comprehensive cancer center of international acclaim. José turned his unique vision into a reality: aided by direct access to patients and his purely translational model VHIO has rapidly gained its rightful place as one of the few cancer institutes to swiftly transform discovery in oncology into benefits for patients.

In 2017: the European Society for Medical Oncology (ESMO) honoured José Baselga with the ESMO Lifetime Achievement Award for his crucial role in breast cancer drug development. His pivotal laboratory and clinical studies have led the approval of trastuzumab, pertuzumab and everolimus, among many other groundbreaking therapies across other tumor types including cetuximab. Photo courtesy of ESMO.

His strategy has been widely adopted as the model of excellence in the current era of precision oncology against this brutal disease that continues to outsmart and evade our most powerful arsenal of anti-cancer weaponry. In short, José's vision establishes him as one of the godfathers of this connective, multidisciplinary approach.

*"Oncology, like no other field, is defined by its collaborative nature and I have been blessed by having worked over the years with wonderful trainees and clinical and laboratory scientists. This award goes to them."* José Baselga, Physician-in-Chief, Memorial Sloan Kettering Cancer Center - MSKCC (New York).

Josep Tabernero, VHIO's Director and current President of the European Society for Medical Oncology (ESMO).

As Director of VHIO and its Clinical Research Program, since 2012 and 2010 respectively, I am privileged to observe the many milestones marked by our Institute, often through combining strengths across borders, that spur our efforts aimed at treating even the most undruggable and resistant tumor types.

Year in, year out, our talented teams continue to report important developments in exposing the many previously hidden cancer drivers, harness vast amounts of data, step up the pace in turning discovery into real benefits for an increasing number of patients, and innovate our research approaches and clinical trial design based on precious insights provided through this translational research.

I would like to close this introduction to *A Golden Decade* by saluting José Baselga, without whom none of VHIO's many achievements and important contributions to solving cancer sooner would have been possible.

Lastly but by no means least, I thank our amazing institutional supporters, our private patrons: the FERO Foundation (*FERO Fundación de Investigación Oncológica*), CELLEX Foundation (*Fundació Privada CELLEX*), "la Caixa" Foundation (*Fundació Bancària "la Caixa"*), BBVA Foundation (*Fundación BBVA*), and the support received from our public patron, the Government of Catalonia (*Generalitat de Catalunya*).

I would also like to express my gratitude to our many other supporters and partners for their continued and devoted belief and backing of our research.

Only with this precious funding can we continue to do what we do best: translate our discoveries in oncology into more precise, individualized treatment and care of patients suffering from cancer.

Josep Tabernero
Director, Vall d'Hebron Institute of Oncology (VHIO)

**For more information about VHIO's purely multidisciplinary and translational model** see pages 8-9.

## Raising the roof in VHIO's ambitions to solve cancer sooner

With VHIO's translational and multidisciplinary model came a strategically devised expansion plan and with it, major reconstruction and the introduction of new facilities, research units and ultimately, an entire new building – quite literally raising the roof in VHIO's ambitions to solve cancer sooner:

Fundació Privada
CELLEX

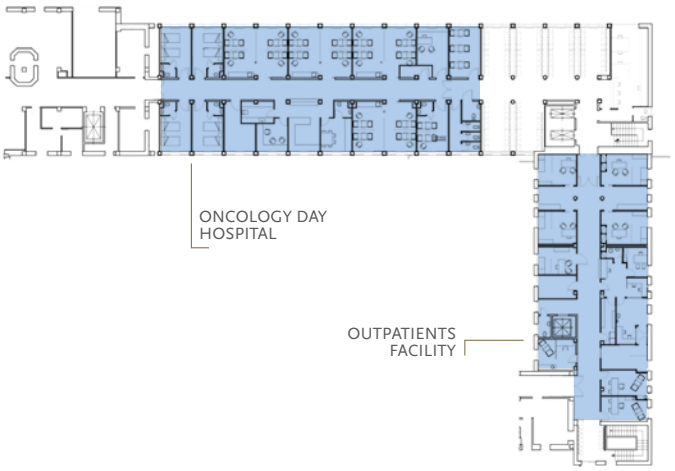
### New facilities and reform rounds to promote multidisciplinary breast cancer of excellence

Further to the completion of a first phase development in 2003, the Vall d'Hebron University Hospital's Oncology Department's Oncology Day Hospital and Outpatients Facility opened its adjoining doors in 2008, with a subsequent and final phase of reforms in 2012.

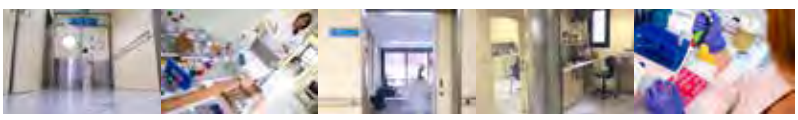
Spanning 988 m², the then new premises was especially designed to connect and link both services along one corridor. Financed entirely by the CELLEX Foundation, this carefully planned expansion and integration of various units and services, resulted in uniting all specialties and disciplines involved in the treatment and care of our patients in the same place and in so doing, promotes the purely translational and multidisciplinary model for which VHIO is famed.

Not only has this essential and complete infrastructural makeover provided the necessary space that was so desperately needed for our patients and our multidisciplinary and transversal oncology teams alike, it has also led to increased efficiency and excellence in the services we provide.

From the initial planning...




... to this in 2008:



## 2008: marking a crucial year of new agreements and an inaugural celebration

The year 2008 laid the very first 'paper' foundations for two major new projects:

First, the agreement was written up and signed between VHIO and the CELLEX Foundation (*Fundació Privada* CELLEX) for the construction of a brand new, state of the art research building to centralize all VHIO's programs, teams and technologies in the same physical space and thus further promote the multidisciplinary and translational two-way interaction and exchange between VHIO's cancer researchers and physician-scientists *en force* (see page 31).

Representing another groundbreaker in VHIO's translational 10 year history was the signing of the agreement for the construction of our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", driven by support received from the "la Caixa" Foundation (*Fundació Bancària "la Caixa"*). This Unit was established to lead early phase clinical trials with novel drugs and therapeutic targets to potentiate the efficacy of anti-cancer therapies and reduce toxicity (see page 30).

### 2008: the inauguration of our internationally renowned Breast Cancer Center

Located on two floors of our Hospital's Maternity and Pediatrics Building, our Breast Cancer Center "*Endavant i de Cara*" (loosely translated as 'upwards, head high'), was financed through a personal donation received from Maria Angels Sanahuja, an ex-patient of José Baselga, in memorium of Roman Sanahuja and Francisca Pons.

Dedicated to advancing the prevention, treatment and care of breast cancer patients by pooling and combining expertise across all specialties in multidisciplinary teams, our Center houses the entire circuit of patient care incorporating all the necessary services and spaces including consultancy rooms, screening facilities and technologies, radiomics, latest diagnostics, and pharmacy.

Inaugurated by Her Majesty the Queen Sofía of Spain, 30 April 2008, the Center was initially directed by José Baselga under the co-leadership of Deputy Director, and former Principal Investigator of VHIO's Breast Cancer and Melanoma Group, Javier Cortés (see 2008 group picture in the photo collage below). This trailblazing tandem quickly established the our Center and its clinical research group as a leading reference in advancing personalized treatment and care against breast cancer.

An inaugural celebration of VHIO's Breast Cancer Center back in 2008.

Our translational and multidisciplinary breast cancer program, spearhead by VHIO's Cristina Saura since 2015, continues to be one of the most active and recognized throughout Europe by significantly advancing novel and more precise anti-cancer therapies to improve outcomes for patients suffering from this disease (see pages 70-71).

Obra Social "la Caixa"

## 2010: VHIO's Research Unit for Molecular Therapies of Cancer (UITM) – "la Caixa" opened its doors to pioneer early drug discovery and clinical studies tailored to the specificities of patients

Knowledge of the molecular biology of cancer has grown exponentially over the last decade and this in turn has meant the identification of a host of therapeutic leads for the development of selective drugs.

Directed by Josep Tabernero, Director of VHIO as well as our Clinical Research Program (pages 68-89), under the former coordination of Jordi Rodón, our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" was inaugurated on 23 June 2010, thanks to the essential support received from the "la Caixa" Foundation (*Fundació Bancària "la Caixa"*), in order to develop novel therapies based on the molecular profile of each tumor and optimize treatment strategies using combinations of new agents with already existing ones (see pages 102-103):

The 2010 inauguration of VHIO's UITM - "la Caixa": an important milestone towards rendering cancer science and medicine more precise.

Research at the Unit has contributed to the development of several tumor cell targeted agents including trastuzumab, pertuzumab, cetuximab, panitumumab, ramucirumab, trifluridine/tipiracil, gefitinib, osimertinib, ceritinib, crizotinib, loratinib and everolimus, among others. Current focus also centers on accelerating and advancing immunotherapies including atezolizumab, nivolumab and pembrolizumab.

Now coordinated by Elena Garralda as UITM's Executive Director, our Unit goes from strength to strength each and every year. It continues to grow its portfolio of studies and fine-tune patient selection criteria and stratification based on intrinsic biological intelligence and a more precise classification of cancers. In 2017, 120 Phase I clinical trials and 17 basket studies were performed at our Unit with a total of 445 patients enrolled.

From this in 2008...

...to this in 2010:

Fundació Privada CELLEX

## 2015: The CELLEX Building

As previously mentioned, the initial agreement paving the way for VHIO's new home was signed by VHIO and the CELLEX Foundation (*Fundació Privada CELLEX*) was formalized in 2008. Under Josep Tabernero's leadership, the construction of the CELLEX building commenced in 2012 and was completed in 2015. Marking a new VHIO chapter, our new premises provided the necessary space and amenities to expand our research activities and further foster the already existing multidisciplinary connectivity and exchange by bringing all VHIO's research teams together under the same roof.

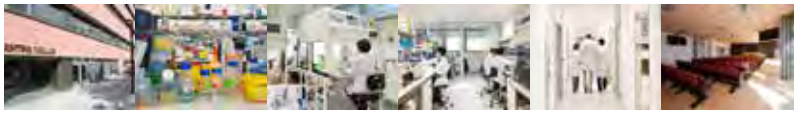
Key to advancing predictive cancer models, and representing the final jewel in the crown of the construction of the CELLEX Building, VHIO's cutting edge Animal Facility opened for business in 2016. Occupying the basement of our building, it serves as a shared facility across the Vall d'Hebron Barcelona Hospital Campus, spans a surface area of 1347 $m^2$, and is equipped with 5500 cages.

Incorporating the latest platforms and technologies for analyzing small animal models of human disease, VHIO's expertise in developing and rendering cancer models including patient derived xenografts (PDX) more precise and predictive, has further expanded thanks to this cutting-edge facility.

Providing the valuable space through which to grow, the CELLEX Building has not only further enhanced collaborations and accelerated our dedicated efforts to combat cancer, it has also allowed us to more hotly pursue new emerging research areas including immunology & immunotherapies, as well as fortify our research structure. In fact, since we occupied our new premises, VHIO's full-time equivalents (FTEs) in research now totals at 254.37 (at the close of 2017 - see page 35).

From this in 2012...

...to this as we moved in, August 2015...



## Potentiating VHIO's programs, groups and technologies

In addition to new buildings and facilities, VHIO's successes marked to-date have only been possible thanks to the tremendous support received from our other two private patrons, the FERO Foundation (*FERO Fundación de Investigación Oncológica*), and the BBVA Foundation (*Fundación BBVA*), as well as the funding it receives from our public patron, the Government of Catalonia (*Generalitat de Catalonia*), international and national competitive grants, private institutions, companies, and individuals (see pages 138-139 for the full listing in 2017).

Generalitat de Catalunya

### Our cherished public patron, the Government of Catalonia: dedicated supporter of cancer science and medicine of excellence

From the very outset, the Government of Catalonia (*Generalitat de Catalonia*) and more specifically, the Catalan Departments of Finance and Health, has been a keen and devoted ambassador of VHIO and our various research programs and projects. As one of our Founding Patrons, it has been institutionally and financially supporting us throughout our Golden Decade and now, beyond, with the Catalan Minister of Health as the President of our Board of Trustees.

VHIO's translational and multidisciplinary approach to cancer research is only possible through the connectivity and tremendous collaboration we have with the entire spectrum of oncology professionals at our hospital, the Vall d'Hebron University Hospital – HUVH (Vall d'Hebron Barcelona Hospital Campus, see pages 10-11), and the rest of the Catalan Public Health System (page 12).

Worthy of special mention, as we reflect on the first ten years of VHIO's relatively short existence, is the pivotal role played by the Catalan Department of Health in integrating VHIO's research activity into the Catalan Health System, representing a remarkable example of how the public and private sectors can successfully collaborate for the benefit of science, patients and society. As an active member of the CERCA Institute of Research Centers of Catalonia (*Institució CERCA – Centres de Recerca de Catalunya*), pages 14-15, this essential collaboration affords us access to the Catalan Research System and the fiscal and legal benefits that this represents.

Last but not least, the financial support provided by the Government of Catalonia has contributed majorly to VHIO's structural overheads, allowing us to center our efforts on our core research activities.

Fundación
de Investigación
Oncológica

## FERO Foundation: faithful promoter of new VHIO talents

The precious support received through FERO over the last decade has enabled science of excellence at VHIO as well as promoted and grown the careers of up-and-coming talents in oncology. Concerning the former, to name but two, the labs of both Josep Villanueva, PI of our Tumor Biomarkers Group, and Laura Soucek, PI of VHIO's Mouse Models of Cancer Therapies Group and ICREA Professor, have significantly been able to grow their groups and advance their pioneering research lines thanks to FERO.

More specifically, Josep, who joined VHIO in 2009 to advance biomarker and drug target discovery toward ultimately enabling a more precise diagnosis and monitoring of cancer therapies, received funding, thanks to FERO, through a donation from the Josep Botet Foundation (*Fundació Josep Botet*), to finance the implementation in 2010 of the LTQ-Orbitrap Velos mass spectrometer.

In 2011 we attracted another new talent, Laura Soucek, who joined us thanks to a FERO start-up grant twinned later that year with a highly coveted FERO Award. This funding, along with support received from other entities, has not only contributed to the growth of her team from two investigators to a total of eleven (2017), but also helped them to pursue and advance research aimed at preclinically validating novel anti-Myc therapies across various tumor types.

Regarding FERO's Annual Award for Translational Research, as a further reflection of VHIO's sustained cancer discovery of excellence, a total of six of our research scientists have been honored with this prize:

Laura Soucek (2011), Héctor G. Palmer (2012), Ibrahim Yasir (2013), César Serrano (2015), Beatriz Morancho (2016), and María Abad (2017).

Importantly as an example this year, funding received from FERO has also financed our recently incorporated Droplet Digital PCR (ddpCR) Bio-Rad Technology platform, and we are already making significant progress in validating and developing this technology for the more effective and less invasive tracking of cancer by liquid biopsy.

Fundación BBVA

## BBVA Foundation: driving powerful and programs to spur VHIO's avant-garde translational research in precision oncology

Combining expertise of VHIO with colleagues at Massachusetts General Hospital Cancer Center – MGHCC (Boston), where José Baselga was at the time Chief of Hematology and Oncology, the BBVA Foundation launched the Tumor Biomarkers Research Program back in 2011.

Under the co-scientific direction of José Baselga and Josep Tabernero, this five-year major framework agreement fueled collaborative science centering on the development of personalized therapies for cancer patients through biomarker research.

As a direct reflection of the importance of this program, only made possible through the essential funding we received from the Foundation, 26 scientific articles generated through this research were published in top-tier journals of excellence. Important findings were also reported as 8 posters during several must-attend international congresses within our field.

(Left) The signing of our 2011 BBVA Foundation framework agreement. (Right) The 2017 launch of our BBVA Foundation framework agreement: the Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI).

VHIO and the BBVA Foundation this year renewed their agreement in collaboration the Memorial Sloan Kettering Cancer Center - MSKCC (New York). Building on the successes of the first program, our Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI), represents an important forward step in advancing agents that inhibit checkpoint regulation of the immune system, better understanding mechanisms of resistance and response to these therapies, and prioritizing the early development of those drugs showing most promise.

Under the superb co-leadership of José Baselga in his current capacity as Physician-in-Chief at MSKCC, and Josep Tabernero, Director of VHIO, this ambitious project counts on the expertise of VHIO's Elena Garralda (PI of VHIO's Early Clinical Drug Development and Executive Director of our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa"), who heads up CAIMI's clinical research, Alena Gros (PI, VHIO's Tumor Immunology and Immunotherapy Group), who takes the lead on translational research, and Ana Vivancos (PI of our Cancer Genomics) who directs our internationally recognized prescreening platform.

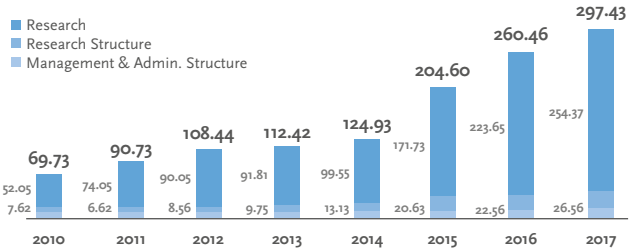
In collaboration with our distinguished MSKCC colleagues, VHIO will co-found six translational projects linked to the early clinical development phases of immunotherapy.

The launch of our 2017 BBVA Foundation framework program.

## Our Golden Decade: a few more must-mentions

It is thanks to all the aforementioned support received from our treasured institutional supporters (page 138), and the critical funding from many other entities (see pages 138-139 for all a full listing in 2017), that we have been able to expand our programs and research lines.

We have also consequently been fortunate enough to grow our teams and personnel based on carefully planned strategic direction. The incorporation of all our new talents at VHIO over the years has enabled us to significantly advance translational science and medicine in oncology on the global stage as well as continue to render cancer treatment and care more precise.




VHIO'S FTEs EVOLUTION (2010-2017)
*VHIO incorporates and additional 61,2 associated MD's FTEs (Oncology & Hematology) contracted by our Hospital

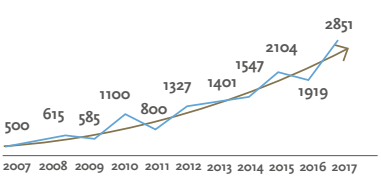
In science and medicine, according to a 2015 UNESCO report, as highlighted in a recent article (Clark J et al. *Lancet*. 2017), women undergraduates outnumber men and yet 72% of the global scientific workforce is male. We at VHIO are pleased to report that 74% of our current entire workforce is female.

While this statistic is certainly something to be celebrated as we continue to uphold and support gender parity, we at VHIO place strict emphasis is placed on contracting the right individual, with the necessary skill set matched to the requirements of a particular position.

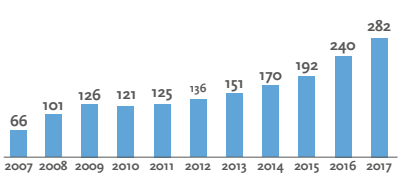
One of our guiding principles is to contract, promote and grow all our talents, totally irrespective of gender. As such, VHIO constantly seeks to strengthen its policies and practices that, in turn, undoubtedly contribute to spurring our research of excellence.

### VHIO discovery aimed at dismantling cancer's armory

Commandeering research aimed at thwarting this disease, our preclinical, translational and clinical investigators continue to report important advances in cancer biology and therapeutic oncology. Since 2007, published papers have increased from 66 to a total of 282 for this year. Similarly, cumulative Impact Factor has progressively risen from 500 back in 2007 to 2851 in 2017:




Cumulative Impact Factor per year (2007-2017).




Number of articles published by VHIO researchers from 2007 – 2017.


In this Report's special *A Golden Decade* chapter, it would have been fitting to have selected a top-10 of papers published throughout VHIO's relatively young history. An impossible task!

We have therefore restricted our pick to 25. These are merely representative examples of the myriad contributions made by VHIO to advancing cancer science and medicine:

Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. Hyman DM, Puzanov I, Subbiah V, Faris JE, Chau I, Blay JY, Wolf J, Raje NS, Diamond EL, Hollebecque A, Gervais R, Elez-Fernandez ME, Italiano A, Hofheinz RD, Hidalgo M, Chan E, Schuler M, Lasserre SF, Makrutzki M, Sirzen F, Veronese ML, Tabernero J, Baselga J. *N Engl J Med.* 2015 Aug 20;373(8):726-36.

—

The consensus molecular subtypes of colorectal cancer. Guinney J, Dienstmann R, Wang X, de Reyniès A, Schlicker A, Soneson C, Marisa L, Roepman P, Nyamundanda G, Angelino P, Bot BM, Morris JS, Simon IM, Gerster S, Fessler E, De Sousa E Melo F, Missiaglia E, Ramay H, Barras D, Homicsko K, Maru D, Manyam GC, Broom B, Boige V, Perez-Villamil B, Laderas T, Salazar R, Gray JW, Hanahan D, Tabernero J, Bernards R, Friend SH, Laurent-Puig P, Medema JP, Sadanandam A, Wessels L, Delorenzi M, Kopetz S, Vermeulen L, Tejpar S. *Nat Med.* 2015 Nov;21(11):1350-6.

—

Analysis of circulating DNA and protein biomarkers to predict the clinical activity of regorafenib and assess prognosis in patients with metastatic colorectal cancer: a retrospective, exploratory analysis of the CORRECT trial. Tabernero J, Lenz HJ, Siena S, Sobrero A, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Yoshino T, Goldberg RM, Sargent DJ, Wagner A, Laurent D, Teufel M, Jeffers M, Grothey A, Van Cutsem E. *Lancet Oncol.* 2015 Aug;16(8):937-48.

—

Clinical response to a lapatinib-based therapy for a Li-Fraumeni syndrome patient with a novel HER2V659E mutation. Serra V, Vivancos A, Puente XS, Felip E, Silberschmidt D, Caratù G, Parra JL, De Mattos-Arruda L, Grueso J, Hernández-Losa J, Arribas J, Prudkin L, Nuciforo P, Scaltriti M, Seoane J, Baselga J. *Cancer Discov.* 2013 Nov;3(11):1238-44.

—

Active CREB1 promotes a malignant TGFβ2 autocrine loop in glioblastoma. Rodón L, Gonzàlez-Juncà A, Inda Mdel M, Sala-Hojman A, Martínez-Sáez E, Seoane J. *Cancer Discov.* 2014 Oct;4(10):1230-41.

—

Effect of p95HER2/611CTF on the response to trastuzumab and chemotherapy. Parra-Palau JL, Morancho B, Peg V, Escorihuela M, Scaltriti M, Vicario R, Zacarias-Fluck M, Pedersen K, Pandiella A, Nuciforo P, Serra V, Cortés J, Baselga J, Perou CM, Prat A, Rubio IT, Arribas J. *J Natl Cancer Inst.* 2014 Sep 24;106(11).

Phase I Dose-Escalation Study of JNJ-42756493, an Oral Pan-Fibroblast Growth Factor Receptor Inhibitor, in Patients With Advanced Solid Tumors. Tabernero J, Bahleda R, Dienstmann R, Infante JR, Mita A, Italiano A, Calvo E, Moreno V, Adamo B, Gazzah A, Zhong B, Platero SJ, Smit JW, Stuyckens K, Chatterjee-Kishore M, Rodon J, Peddareddigari V, Luo FR, Soria JC. *J Clin Oncol.* 2015 Oct 20;33(30):3401-8.

—

Safety and Activity of the First-in-Class Sym004 Anti-EGFR Antibody Mixture in Patients with Refractory Colorectal Cancer. Dienstmann R, Patnaik A, Garcia-Carbonero R, Cervantes A, Benavent M, Roselló S, Tops BB, van der Post RS, Argilés G, Skartved NJ, Hansen UH, Hald R, Pedersen MW, Kragh M, Horak ID, Braun S, Van Cutsem E, Tolcher AW, Tabernero J. *Cancer Discov.* 2015 Jun;5(6):598-609.

—

Cerebrospinal fluid-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma. De Mattos-Arruda L, Mayor R, Ng CK, Weigelt B, Martínez-Ricarte F, Torrejon D, Oliveira M, Arias A, Raventos C, Tang J, Guerini-Rocco E, Martínez-Sáez E, Lois S, Marín O, de la Cruz X, Piscuoglio S, Towers R, Vivancos A, Peg V, Ramon y Cajal S, Carles J, Rodon J, González-Cao M, Tabernero J, Felip E, Sahuquillo J, Berger MF, Cortes J, Reis-Filho JS, Seoane J. *Nat Commun.* 2015 Nov 10;6:8839.

—

Myc inhibition is effective against glioma and reveals a role for Myc in proficient mitosis. Annibali D, Whitfield JR, Favuzzi E, Jauset T, Serrano E, Cuartas I, Redondo-Campos S, Folch G, Gonzàlez-Juncà A, Sodir NM, Massó-Vallés D, Beaulieu ME, Swigart LB, Mc Gee MM, Somma MP, Nasi S, Seoane J, Evan GI, Soucek L. *Nat Commun.* 2014 Aug 18;5:4632.

—

Dual MET and ERBB inhibition overcomes intratumor plasticity in osimertinib-resistant-advanced non-small-cell lung cancer (NSCLC). Martinez-Marti A, Felip E, Matito J, Mereu E, Navarro A, Cedrés S, Pardo N, Martinez de Castro A, Remon J, Miquel JM, Guillaumet-Adkins A, Nadal E, Rodriguez-Esteban G, Arqués O, Fasani R, Nuciforo P, Heyn H, Villanueva A, Palmer HG, Vivancos A. *Ann Oncol.* 2017 Oct 1;28(10):2451-2457.

—

Concordance of blood- and tumor-based detection of RAS mutations to guide anti-EGFR therapy in metastatic colorectal cancer. Grasselli J, Elez E, Caratù G, Matito J, Santos C, Macarulla T, Vidal J,

Garcia M, Viéitez JM, Paéz D, Falcó E, Lopez Lopez C, Aranda E, Jones F, Sikri V, Nuciforo P, Fasani R, Tabernero J, Montagut C, Azuara D, Dienstmann R, Salazar R, Vivancos A. *Ann Oncol.* 2017 Jun 1;28(6):1294-1301.

—

A predictive model of pathological response based on tumor cellularity and tumor-infiltrating lymphocytes (CelTIL) in HER2-positive breast cancer treated with chemo-free dual HER2 blockade. Nuciforo P, Pascual T, Cortés J, Llombart-Cussac A, Fasani R, Paré L, Oliveira M, Galvan P, Martínez N, Bermejo B, Vidal M, Pernas S, López R, Muñoz M, Garau I, Manso L, Alarcón J, Martínez E, Rodrik-Outmezguine V, Brase JC, Villagrasa P, Prat A, Holgado E. *Ann Oncol.* 2017 Oct 12.

—

A First-in-Human Phase I Study of the ATP-Competitive AKT Inhibitor Ipatasertib Demonstrates Robust and Safe Targeting of AKT in Patients with Solid Tumors. Saura C, Roda D, Roselló S, Oliveira M, Macarulla T, Pérez-Fidalgo JA, Morales-Barrera R, Sanchis-García JM, Musib L, Budha N, Zhu J, Nannini M, Chan WY, Sanabria Bohórquez SM, Meng RD, Lin K, Yan Y, Patel P, Baselga J, Tabernero J, Cervantes A. *Cancer Discov.* 2017 Jan;7(1):102-113.

—

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. Baselga, J; Cortes, J; Kim, S-B; Im, S-A; Hegg, R; Im, Y-H; Roman, L; Pedrini, JL; Pienkowski, T; Knott, A; Clark, E; Benyunes, MC.; Ross, G; Swain, SM.; CLEOPATRA Study Group. 2012. *N Engl J Med.* 366: 109-119.

—

Beta-catenin confers resistance to PI3K and AKT inhibitors and subverts FOXO3a to promote metastasis in colon cancer. Tenbaum, Stephan P.; Ordonez-Moran, Pa; Puig, I;Chicote, I; Arques, O;Landolfi, S; Fernandez, Y; Raul Herance, J; Gispert, J D.; Mendizabal, L; Aguilar, S; Ramon y Cajal, S; Schwartz, Jr., S; Vivancos, A; Espin, E; Rojas, S; Baselga, J; Tabernero, J;Munoz, A;Palmer, H G. 2012. *Nat Med.* 18: 892-900.

—

USP15 stabilizes TGF-beta receptor I and promotes oncogenesis through the activation of TGF-beta signaling in glioblastoma. Eichhorn, P J. A.; Rodon, L; Gonzalez-Junca, A; Dirac, A; Gili, M; Martinez-Saez, E; Aura, C; Barba, I; Peg, V; Prat, A;Cuartas, I; Jimenez, J; Garcia-Dorado, D; Sahuquillo, J; Bernards, R; Baselga, J; Seoane, J. 2012. *Nat Med.* 18: 429-492.

—

The landscape of somatic copy-number alteration across human cancers. Beroukhim, R; Mermel, CH.; Porter, D; Wei, G; Raychaudhuri, S; Donovan, J; Barretina, J; Boehm, JS.; Dobson, J; Urashima, M; Mc Henry, K T.; Pinchback, RM.; Ligon, AH.; Cho, YJ; Haery, L; Greulich, H; Reich, M; Winckler, W; Lawrence, M S.; Weir, B A.; Tanaka, K E.; Chiang, Derek Y.; B, Adam J.; Loo, A; Hoffman, C; Prensner, J; Liefeld, T; Gao, Q; Yecies, D; Signoretti, S; Maher, E; Kaye, F J.; Sasaki, H; Tepper, JE.; Fletcher, JA.; Tabernero, J; Baselga, J; Tsao, MS; Demichelis, F; Rubin, M A.; Janne, PA.; Daly, MJ.; Nucera, C; Levine, R L.; Ebert, BL.; Gabriel, S; Rustgi, A K.; Antonescu, C; Ladanyi, M; Letai, A; Garraway, LA.; Loda, M; Beer, D G.; True, L D.; Okamoto, A; Pomeroy, SL.; Singer, S; Golub, TR.; Lander, ES.; Getz, G; Sellers, WR.; Meyerson, M. 2010. *Nature.* 463: 899-905.

TGF-beta Receptor Inhibitors Target the CD44(high)/Id1(high) Glioma-Initiating Cell Population in Human Glioblastoma. Anido, J; Saez-Borderias, A; Gonzalez-Junca, A; Rodon, L; Folch, Gerard; Carmona, MA.; Prieto-Sanchez, RM.; Barba, Ignasi; Martinez-Saez, E; Prudkin, L; Cuartas, I; Raventos, C; Martinez-Ricarte, F; Antonia Poca, M.; Garcia-Dorado, D; Lahn, M M.; Yingling, J M.; Rodon, J;Sahuquillo, J; Baselga, J; Seoane, J. 2010. *Cancer Cell.* 18: 655-668.

—

Phase I Pharmacokinetic and Pharmacodynamic Dose-Escalation Study of RG7160 (GA201), the First Glycoengineered Monoclonal Antibody Against the Epidermal Growth Factor Receptor, in Patients With Advanced Solid Tumors. Paz-Ares, LG; Gomez-Roca C, Delord JP, Cervantes A, Markman B, Corral J, Soria JC, Bergé Y, Roda D, Russell-Yarde F, Hollingsworth S, Baselga J, Umana P, Manenti L, Tabernero J. *J Clin Oncol.* 2010; 29: 3783-3790.

—

CDK8 is a colorectal cancer oncogene that regulates beta-catenin activity. Firestein R, Bass AJ, Kim SY, Dunn IF, Silver SJ, Guney I, Freed E, Ligon AH, Vena N, Ogino S, Chheda MG, Tamayo P, Finn S, Shrestha Y, Boehm JS, Jain S, Bojarski E, Mermel C, Barretina J, Chan JA, Baselga J, Tabernero J, Root DE, Fuchs CS, Loda M, Shivdasani RA, Meyerson M, Hahn WC. *Nature.* 2008 Sep 25;455(7212):547-51.

—

Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamic study in patients with advanced solid tumors. Tabernero J, Rojo F, Calvo E, Burris H, Judson I, Hazell K, Martinelli E, Ramon y Cajal S, Jones S, Vidal L, Shand N, Macarulla T, Ramos FJ, Dimitrijevic S, Zoellner U, Tang P, Stumm M, Lane HA, Lebwohl D, Baselga J. *J Clin Oncol.* 2008 Apr 1;26(10):1603-10.

—

A naturally occurring HER2 carboxy-terminal fragment promotes mammary tumor growth and metastasis. Pedersen K, Angelini PD, Laos S, Bach-Faig A, Cunningham MP, Ferrer-Ramón C, Luque-García A, García-Castillo J, Parra-Palau JL, Scaltriti M, Ramón y Cajal S, Baselga J, Arribas J. *Mol Cell Biol.* 2009 Jun;29(12):3319-31.

TGF-beta increases glioma-initiating cell self-renewal through the induction of LIF in human glioblastoma. Peñuelas S, Anido J, Prieto-Sánchez RM, Folch G, Barba I, Cuartas I, García-Dorado D, Poca MA, Sahuquillo J, Baselga J, Seoane J. *Cancer Cell.* 2009 Apr 7;15(4):315-27.

—

Expression of p95HER2, a truncated form of the HER2 receptor, and response to anti-HER2 therapies in breast cancer. Scaltriti M, Rojo F, Ocaña A, Anido J, Guzman M, Cortes J, Di Cosimo S, Matias-Guiu X, Ramon y Cajal S, Arribas J, Baselga J. *J Natl Cancer Inst.* 2007 Apr 18;99(8):628-38.

# VHIO: empowering predictive cancer science towards rendering cancer therapies more precise

VHIO strives to deliver the predictive data required to reliably inform the clinical development of innovative agents and approaches as well as evidence reproducibility before moving to the clinic:

VHIO has internationally renowned expertise in developing and finely tuning cancer models to identify factors influencing tumor growth, predict cancer progression and response to treatments, with one of the biggest PDX collections in Europe - particularly in breast, glioblastoma and colorectal cancers.

—

Current efforts include more accurately modeling anti-tumor immunotherapy strategies by generating humanized PDX models (Hu PDXs) to validate the efficacy of T-cell bispecific antibodies.

—

Using colorectal cancer PDX, VHIO groups have reported that Wnt inhibitors can overcome β-catenin-induced resistance to PI3K and AKT inhibitors and experimentally showed a rational stratification of patients to be treated with this trio of inhibitors using β-catenin and FOXO3A as predictive biomarkers of response. This marks a significant milestone in ultimately advancing personalized therapy against colorectal cancer.

—

Leadership in the generation of a variety of modelling systems including PDX and Organoids resulted in VHIO participating as a founding member of the EuroPDX Consortium (see page 13 ).

—

One most recent example of VHIO's translational teams bringing discovery to market and clinical practice has been the validation of the RAD51 assay as predictive response biomarker of PARPi-clinical activity with implication beyond BRCA1/2-mutation carriers. This project is now supported by a technology transfer program to bring the RAD51 assay to market.

—

Predictive, translational and robust science of excellence at VHIO has also resulted in two spin-off successes (see page 15).

—

**To discover more about VHIO's Preclinical Research Program directed by Joaquín Arribas, ICREA Professor, see pages 47-57.**

**For developments reported by our Translational Research Program led by Joan Seoane, also an ICREA Professor, see pages 58-65.**

## VHIO's novel programs and approaches in advancing anti-cancer armoury

VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa": the hub of VHIO's early clinical drug development efforts focused on phase I and II trials with innovative agents and first-in-human studies:

Thanks to VHIO's translational vision, scientific framework, and its Prescreening Program, the Unit has established itself as one of the few comprehensive facilities in Europe to rapidly transform discovery into improved outcomes for patients.

—

Based on the idea that each tumor has an independent genetic identity, VHIO clinical scientists aim at potentiating molecular therapies targeting specific oncoproteins and accelerating more effective personalised cancer medicines for patients displaying genetic lesions or pathway dysregulation. One of the team's main objectives is to establish novel predictive markers of response to anti-cancer therapies and identify markers of primary resistance (de novo) and secondary treatment.

—

VHIO has contributed to the development of several tumor cell targeted agents including:

Trastuzumab, pertuzumab, cetuximab, panitumumab, ramucirumab, trifluridine/tipiracil, gefitinib, osimertinib, ceritinib, crizotinib, loratinib and everolimus, among others.

—

VHIO is also accelerating and advancing immunotherapies including atezolizumab, nivolumab and pembrolizumab.

—

VHIO continues to grow its portfolio of studies and fine-tune patient selection criteria and stratification based on intrinsic biological intelligence and a more precise classification of cancers. In 2017, 120 phase I clinical trials and 17 Basket studies were conducted with patient enrolment totaling at 445.

—

We have led the design of Cancer Core Europe Consortium-endorsed Basket of Baskets (BoB) trial. In 2017 the protocol for its first module was approved and first patient enrolment is envisaged towards the end of next year, 2018 (see page 13 for more details).

—

2017 celebrated the renewal of VHIO's framework program supported by the *Fundació Bancària* "la Caixa", in collaboration with the Memorial Sloan Kettering Cancer Center – MSKCC (New York), to further pursue the established synergies between the two (see page 14).

**To read more about VHIO's VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa",** see pages 102-103**.**

**To discover more about VHIO's Clinical Research Program, led by Josep Tabernero, also Director of our Institute,** see pages 66-89**.**

## VHIO: applying and extending immunotherapies to more tumor types

Driven by our Early Clinical Drug Development and Tumor Immunology & Immunotherapy Groups (led by Elena Garralda and Alena Gros repsecitvely), in collaboration with out teams at our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", VHIO advances novel immune agents either as monotherapy or in combination:

Current research at VHIO pairs liquid biopsy with immunotherapy for the evaluation of patients treated with immune checkpoint inhibitors using novel sequencing technologies. Led by Enriqueta Felip (PI of our Thoracic Tumors & Head and Neck Cancer Group), in collaboration with Ana Vivancos (PI of our Cancer Genomics Group), research on the characterization of blood-based tumor-educated platelets for the analysis of these patients may more accurately guide immunotherapeutic strategies for the treatment of non-small cell lung cancer.

–

VHIO reported results from two early phase trials showing that the anti-CEA/CD3 novel bispecific antibody, either as monotherapy or paired with atezolizumab, promises an increased therapeutic efficacy in the treatment of metastatic colorectal cancer. Its effect also proved more potent in combination.

–

UITM's Task Force - incorporating VHIO's scientists and clinical investigators (see pages 66-89 to view our Clinical Research Program led by Josep Tabernero, Director of VHIO) - in early drug development of immunotherapeutics and cell signaling centers on second generation immunotherapies, including new cytokines, immunomodulatory agents and immune checkpoint inhibitors and combinations, as well as translational research in immuno-oncology.

–

Regarding the aforementioned BoB trial (page 13, sub-section 'Cancer Core Europe'), the first module to open will focus on the response of tumors to anti-PDL1 therapy based on mutation load and DNA repair status.

–

Launched by Roche in 2016, the Immunotherapy Centres of Research Excellence (imCORE) Network is a global partnership powered by 25 leading cancer research institutions, including VHIO. This network is driving the application and extension of novel immune-based medicines to more tumor types as well as progressing research into the cellular and molecular mechanisms modulating immune response to cancer.

–

In 2017 VHIO and the BBVA Foundation (*Fundación BBVA*), this year renewed their research program in collaboration the Memorial Sloan Kettering Cancer Center - MSKCC (New York). Building on the successes of the first program, our Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI), represents an important forward step in advancing agents that inhibit checkpoint regulation of the immune system, better understanding mechanisms of resistance and response to these therapies, and prioritizing the early development of those drugs showing most promise (see page 14).

**For more information about our Early Clinical Drug Development and Tumor Immunology & Immunotherapy Groups** see pages 72-73 **and 114-115.**

## VHIO and the power and potential of cancer subtyping

To deliver transformative therapies VHIO validates molecular subclasses of disease and better develops, matches, and measures novel therapies according to the specificities of each molecular subtype:

Led by Rodrigo Dientstmann (PI of our Oncology Data Science - ODysSey - Group), VHIO has co-established a novel classification for colorectal cancer based on genomic and transcriptomic data. We led efforts to establish 4 main molecular subtypes evidenced by consensus. These data promise a more precise prognosis and will better predict response to targeted molecular therapies as well as guide more precise therapeutic strategies.

—

Genomic technologies, cutting-edge platforms, coupled with big data generated by international networks and collaborations, including the Horizon 2020-supported MoTriColor which is led by VHIO (see page 13 for updates in 2017), are enabling us to accelerate the translation of molecular subclasses and biomarkers into benefits at patient level.

—

As a reflection of our expertise, VHIO has just been accepted to participate in the American Association for Cancer Research's (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE).

**For more updates on these important efforts in 2017** see our Oncology Data Science Group on page 84**.**

## Oncogenomics and VHIO's Prescreening Program

VHIO is one of the few centres in Europe to run such a comprehensive prescreening program: molecular profiling in around 1500 patients per year as candidates for enrollment in our Research Unit for Molecular Therapies of Cancer (UTIM) - "la Caixa" early phase trials. This enables VHIO to more precisely match an increasing number of individual patients with a particular study. This program is pioneered by Ana Vivancos in collaboration with Paolo Nuciforo, PIs of our Cancer Genomics and Molecular Oncology Groups, respectively:

Enabling technologies: VHIO applies state-of-the-art technologies for precision oncology and develops existing applications for faster results (n-counter Nanostring platform, BEAMing Sysmex, and Droplet Digital PCR (ddpCR) Bio-Rad Technology, Miseq and HiSeq2500, Illumina).

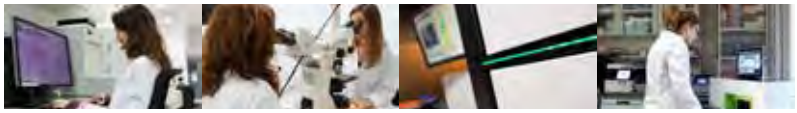
—

Two of these tests are based on NGS: an Amplicon-seq approach to sequence 70 genes (Illumina), as well as a 400-gene capture panel, and two are based on nCounter (Nanostring): a gene fusion panel (with the capacity of detecting over 100 recurrent gene fusions) and a Copy Number Alteration panel (detecting 59 genes).

—

Since we are able to develop and perform high quality testing on patient samples, VHIO is increasingly approached by the pharmaceutical industry and other research entities as either the selected Central Lab of choice, or as their preferred service provider and advisor.

VHIO's main testing methods continue to successfully undergo ISO 15189 accreditation – reflecting excellence and quality.



VHIO's suite of enabling technologies

**For more updates in 2017 see pages 9-10. To find out more about our Cancer Genomics and Molecular Oncology Groups, refer to pages 92-93 and 94-95.**

## The power of collaboration of excellence: at home and away

VHIO believes in combining strengths and overcoming current challenges in concert, and consequently (co) identifies, develops and cements alliances globally. As is widely document throughout this Report, in order to help accelerate efforts aimed at solving cancer sooner, VHIO is called upon to lead and co-participate in many pan-European and international collaborations and consortia of excellence (see pages 140-143).

'At home' to further reinforce VHIO's purely translational and multidisciplinary model, we continue to expand our expert and interdisciplinary taskforces, as well as foster and support strategic alliances between public entities across Catalonia (see page 12).

**For important updates on our various collaborations, consortia and partnerships in 2017 see pages 12-14.**

## VHIO-born entrepreneurship

2014 celebrated the launch of two Spin-Off successes:

VHIO research establishing the role of leukemia inhibitor factor (LIF) as a promoter of cancer progression and the discovery of humanized antibody MSC-1's capacity to effectively target LIF, led to the launch of VHIO-born spin-off Mosaic Biomedicals S.L., and the promise of the accelerated clinical development of MSC-1.

Co-founded by our Director of Translational Research and ICREA Professor, Joan Seoane, Mosaic merged in 2016 with a Canadian company, Northern Biologics, and will run a clinical trial across sites at VHIO, Memorial Sloan Kettering Cancer Center (MSKCC), and the Princess Margaret Hospital in early 2018.

In 2017 the company was co-recipient of *CataloniaBio's Biosuccess Award* of the Year for its exceptional entrepreneurship and biobusiness development aimed at advancing healthcare. This year's prize recognized the aforementioned merger the consequent promise of the humanized antibody MSC-1.

Built on research carried out at VHIO to successfully translate Omomyc-based therapy into clinical application, a second VHIO spin-off, Peptomyc S.L., co-founded by VHIO's Laura Soucek in 2014 (PI of our Mouse Models of Cancer Therapies Group, ICREA Professor, and CEO of this company, centers on developing anti-Myc peptides for the treatment of non-small cell lung cancer, triple negative breast cancer and glioblastoma. The Omomyc cell-penetrating peptide (CPP), proven preclinically, promises to become the first ever clinically viable and direct inhibitor of Myc – a protein implicated in the formation of most tumor types.

In 2017 this spin-off secured 4.2 million euros in a Series A round led by the Barcelona-based venture capital investment firm, Alta Life Sciences. This funding will provide Peptomyc with the necessary capital for the development of clinical trials to test this novel peptide for the inhibition of MYC.

## Recognition through accreditation

In 2017 VHIO underwent evaluation for accreditation of the CERCA Institute of Research Centres of Catalunya (*Institució CERCA – Centres de Recerca de Catalunya*) for the period 2013 – 2016. In recognition of VHIO's progress, performance in knowledge transfer activities and management of excellence, VHIO was awarded with the maximum qualification of an A grading.

Also reflecting our dedication to excellence and the quality of our services and procedures, our Cancer Genomics and Molecular Groups, led by Ana Vivancos and Paolo Nuciforo respectively, have both received ISO 15189 accreditation for their testing methods and technologies. Similarly, we continue to meet the high standards in quality and procedures in the audit of our clinical trials Units, carried out by the *Generalitat de Catalunya*. Our Research Management is also endorsed by ISO 9001 Certification.

**For our Director's selection of updates across all our programs in 2017** see pages 2-7.

## In Memorandum

Dr. Pere Mir
Founder and President, *Fundació Privada CELLEX*
(1919 – 2017)

2017 sadly marked the passing one of the greatest supporters of biomedical research and healthcare across Catalonia, Dr. Pere Mir, Founder and President of the *Fundació Privada Cellex*.

The many initiatives that have been fortunate enough to benefit from Dr. Mir's conviction and thus, funding from CELLEX, include VHIO, the Vall d'Hebron University Hospital, Institute of Photonic Sciences (ICFO), IDIBAPS Institute of the *Hospital Clínic*, other leading hospitals across Catalonia, as well as the *Centro de Formación Interdisciplinaria Superior* (CFIS).

*"I am truly grateful to Dr. Pere Mir for his immeasurable generosity and backing and belief in biomedical research across Catalonia. He was a remarkably kind human being, a true gentleman and scholar. He is sorely missed by us all."*

Josep Tabernero, Director of VHIO.

# Programs

Preclinical Research..... 47

Translational Research ..... 59

Clinical Research ..... 67

Core Technologies ..... 91

VHIO's Transversal Clinical Trials Core Services & Units.... 99

Recently Incorporated VHIO Groups ..... 109

Director, Preclinical Research Program
Joaquín Arribas

# Preclinical Research

FROM THE DIRECTOR ..... 49

THE PI PAGES

Experimental Therapeutics Group ..... 50

Growth Factors Group ..... 52

Mouse Models of Cancer Therapies Group ..... 54

Tumor Biomarkers Group ..... 56

Experimental Therapeutics Group

Growth Factors Group

Mouse Models of Cancer Therapies Group

Tumor Biomarkers Group

# Preclinical Research

Director, Preclinical Research Program

# Joaquín Arribas

"With emphasis on a multidisciplinary and collaborative approach to research, our expert preclinical groups continue to develop, pioneer and finely tune cancer models as critical tools to identify factors that influence tumor growth, predict cancer progression and response to certain treatments. We consequently strive to empower predictive science for the development of the next generation of precise anti-cancer therapies."

Preclinical research at VHIO focuses on establishing how highly aggressive tumors affecting the breast, pancreas, colon, lung, or brain can be treated more precisely and potently. Some of these cancers are highly prevalent and are either ultimately resistant to therapy, having worked for a limited period of time, or lack effective therapeutic avenues, resulting in poor prognosis. Our main goal is to investigate novel anti-cancer treatment approaches for these patients and unmask mechanisms of resistance to the array of currently available cancer medicines.

To deliver on this ambition, VHIO's Mouse Models of Cancer Therapies led by Laura Soucek has developed a novel therapeutic strategy centered on Myc inhibition based on peptides that enter the cell and block this particular oncogene that is activated in the majority of cancers. This novel approach has been recognized through several grants, including those awarded by the European Commission and several national agencies. Of note, the development of the new therapeutic strategy developed by Laura through Peptomyc S.L.- a VHIO-born biopharmaceutical spin-off company that she co-founded in 2014, has been awarded a NEOTEC and an APC grant from the Ministry of Economy, Innovation and Competitiveness. Further, Laura has been selected by EIT Health as Role Model for the project *Empowering Women Entrepreneurship in Health, Innovation and Competitiveness.*

Our Experimental Therapies Group headed by Violeta Serra continues to advance insights into the mechanism of action and resistance to targeted therapy in breast cancer, with special emphasis on the blockade of the PI3K and CDK4/6 to overcome endocrine resistance, as well as treatments targeting FGFR1 and cells with homologous recombination deficiency. Her group has developed a novel organoid culture model that facilitates research into anticancer drug activity as well as a comprehensive collection of breast cancer patient-derived xenografts (PDX) harboring FGFR1/4 amplification or BRCA1/2 mutations. These and similar models have been instrumental to the publication of relevant articles in top-tier journals including *Nature* and *Nature Communications*.

VHIO's Tumor Biomarkers Group led by Josep Villanueva has continued to redirect its main research focus to explore novel mechanisms of tumor progression by non-classical secretion. This switch has attracted funding from the Susan G. Komen Foundation, *Instituto de Salud Carlos III* (Institute of Health Carlos III - ISCIII), as well as the pharmaceutical company Servier. This has led to the recruitment of additional lab members to further expand his group. More specifically, Josep's team has transitioned from studying the cancer secretome following a methodology-driven approach to a more biologically-focused one, where non-classical secretion pathways play an important role. They will consequently continue to extend their studies to characterizing the non-classical secretome linked to tumor invasion and metastasis.

Finally, my own Growth Factors Group has continued to characterize a subtype of breast cancer known as HER2. We have developed a novel therapy to treat these tumors based on the recruitment of cytotoxic lymphocytes by a bispecific antibody. This antibody binds to a tumor specific antigen, p95HER2 and to the CD3 subunit of the T cell receptor. Importantly, to test its efficacy we have implemented humanized mouse models in which we recapitulate the interplay between the tumor and immune system. In addition, using the panel of pancreatic cancer patient-derived xenogratfs generated over the last few years, we have characterized the mechanism of primary resistance to anti-Mek inhibitors. We are currently finalizing our identification of factors that mediate this resistance.

In recognition of our efforts, we continue to receive essential support through international and national competitive grants from the European Commission, Breast Cancer Research Foundation (BCRF), *Instituto de Salud Carlos III*, FERO Foundation, and the Spanish Association Against Cancer (AECC). I am also proud to report that at the beginning of 2017, I was appointed as Scientific Director of CIBERONC - the largest network of cancer research groups in Spain.

In 2017, our groups' findings have been published in several journals of excellence including *Nature, Nature Communications, Nature Reviews in Cancer, Cancer Research, Clinical Cancer Research, Oncogene, Oncotarget, Oncoscience,* among others.

Preclinical Research

# Experimental Therapeutics Group

## Strategic goals:

- Developing predictive biomarkers of PI3K-pathway, CDK4/6, FGFR and PARP inhibitors in ER+ and TN breast cancers.
- Exploring novel treatment combinations for ER+ and TN breast cancers.
- Unveiling novel mechanisms of resistance against targeted therapies in germline BRCA1/2 breast cancer.
- Establishing a patient tumor-derived breast cancer preclinical model to explore hypothesis-based combinatorial therapies.

## Highlights:

- We have established an organoid culture model that enables us to assess the activity of CDK4/6 inhibitors and recapitulates the *in vivo* response (Figure).
- CDK4/6 inhibitor sensitive PDX exhibit pRb expression and loss of p16. We have validated overexpression of cyclin D1/2 as a resistance biomarker.
- We have established that the lack of RAD51 nuclear foci formation, a functional biomarker of homologous recombination deficiency, correlates with PARP inhibitor response in a panel of over 50 PDX and a dozen of clinical samples.
- We have established a panel of 13 BC PDXs harboring FGFR1/4 amplification and another composed of 22 PDXs derived from BRCA1/2 mutation carriers.

Principal Investigator
Violeta Serra

Medical Oncologists
Cristina Cruz
Jordi Rodón

Post-Doctoral Fellows
Albert Gris-Oliver
Alba Llop-Guevara
Marta Palafox

Masters Student
Laia Monserrat

Graduate Students
Marta Castroviejo-Bermejo
Judith Llena
Mònica Sánchez-Guixé

ESMO Translational Research Fellow
Benedetta Pellegrino

Technicians
Judit Grueso
Marta Guzmán
Mireia Parés
Olga Rodríguez

## Summary:

VHIO's Experimental Therapeutics Group conducts bench-to-bedside preclinical research in breast cancer to advance insights into targeted-therapeutics response biomarkers. We have significantly contributed to the field of PI3K inhibitor resistance by firstly evidencing that an adaptive response activating the MEK/ERK pathway through receptor tyrosine kinase upregulation bypasses the PI3K-survival pathway and mediates resistance to PI3K inhibitor. Secondly, we have identified that RSK, a MEK/ERK downstream kinase limits the activity of dual PI3K/mTOR inhibitors partly through the attenuation of apoptotic response and upregulation of protein translation.

Our group has also identified PI3K-pathway activation downstream of PI3K, via upregulation of mTORC1, as a mechanism of resistance to PI3K inhibitors. To advance our understanding of novel therapeutic strategies in breast cancer, we are exploring the mode of action and mechanisms of resistance to CDK4/6 inhibitors (drug combinations with PI3K inhibitors and hormone therapy) in endocrine-resistant breast tumors. Using clinically relevant patient-derived tumor xenografts we have established that loss of G1-cell cycle checkpoint control, such as mutation/loss of RB1 or CCND1-amplification, is associated with lack of response to CDK4/6 blockade in estrogen receptor positive breast cancer PDX. The addition of a PI3Kalpha inhibitor improved and prolonged disease control in all experimental models analyzed.

Encouraged by the early success of DNA damage repair inhibitors in germline BRCA1/2 tumors, we have initiated a project aimed at identifying response biomarkers of PARP inhibitors (PARPi) and DNA binding agents including PM01183, a novel derivative of trabectedine, in homologous recombination repair (HRR) deficient tumors. Our studies underpin the capacity of germline BRCA mutant tumors to recover HR functionality and develop resistance to PARPi. The RAD51 assay can identify which germline BRCA tumors have restored HRR functionality, as well as tumors that are sensitive to PARPi through HRR alterations beyond the germline BRCA condition.

In short, our group has significantly improved the understanding of the mode of action of novel targeted therapies, identified new response biomarkers, and demonstrated the efficacy of hypothesis-based drug combinations.

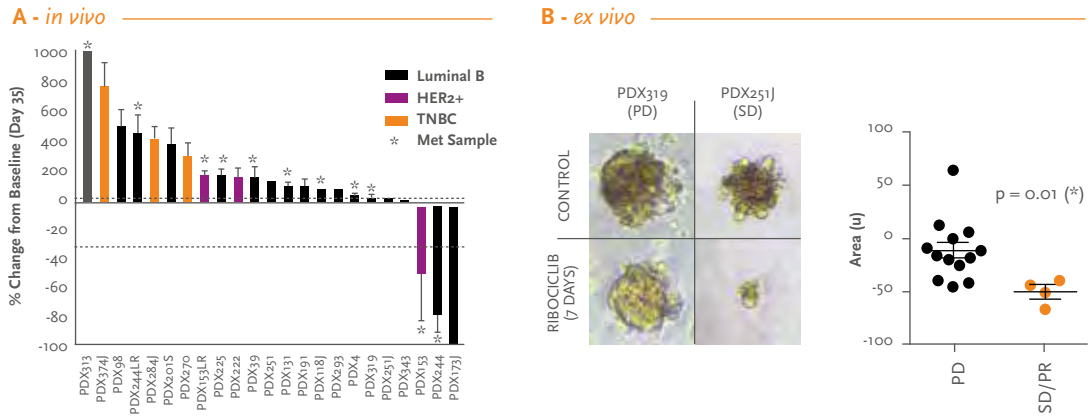



Figure: Antitumor and antiproliferative activity of the CDK4/6 inhibitor ribociclib in patient derived models. A) *In vivo* analysis of tumor growth or regression upon treatment with ribociclib during 35 days (75mg/kg, 6 days/week). B) Analysis of *ex vivo* cultures treated with ribociclib for 7 days and categorized according to the in vivo response shown in panel A.

## PI paper pick:

Méndez-Pertuz M, Martínez P, Blanco-Aparicio C, Gómez-Casero E, Belen García A, Martínez-Torrecuadrada J, Palafox M, Cortés J, Serra V, Pastor J, Blasco MA. Modulation of telomere protection by the PI3K/AKT pathway. *Nat Commun.* 2017 Nov 2;8(1):1278.

Zabala-Letona A, Arruabarrena-Aristorena A, Martín-Martín N, (...), Serra V, (...), Carracedo A. mTORC1-dependent AMD1 regulation sustains polyamine metabolism in prostate cancer. *Nature.* 2017 Jul 6;547(7661):109-113.

Hierro C, Alsina M, Sánchez M, Serra V, Rodon J, Tabernero J. Targeting the fibroblast growth factor receptor 2 in gastric cancer: promise or pitfall? *Ann Oncol.* 2017 Jun 1;28(6):1207-1216.

Byrne AT, Alférez DG, Amant F, Annibali D, Arribas J, Biankin AV, Bruna A, Budinská E, Caldas C, Chang DK, Clarke RB, Clevers H, Coukos G, Dangles-Marie V, Eckhardt SG, Gonzalez-Suarez E, Hermans E, Hidalgo M, Jarzabek MA, de Jong S, Jonkers J, Kemper K, Lanfrancone L, Mælandsmo GM, Marangoni E, Marine JC, Medico E, Norum JH, Palmer HG, Peeper DS, Pelicci PG, Piris-Gimenez A, Roman-Roman S, Rueda OM, Seoane J, Serra V, Soucek L, Vanhecke D, Villanueva A, Vinolo E, Bertotti A, Trusolino L. Interrogating open issues in cancer precision medicine with patient-derived xenografts Interrogating open issues in cancer precision medicine with Patient-Derived Xenografts. *Nat Rev Cancer.* 2017 Apr; 17(4):254-268.

Preclinical Research

# Growth Factors Group

## Strategic goals:

- Development of novel therapeutic strategies for the treatment of HER2-positive tumors and identify mechanisms of resistance to current therapies.
- Preclinical characterization of T cell bispecific antibodies (TCBs) against HER2 positive tumors.
- Characterization of the role of premature senescence in breast cancer progression and treatment.
- To evaluate the activity of novel anti-cancer therapies in our panels of breast and pancreatic cancer patient-derived xenografts.

## Highlights:

- Identification of several novel mechanisms of resistance against anti-HER2 therapies in breast cancer
- Development of our platform of patient-derived models for immuno-oncology.
- Discovery of a mechanism of resistance against targeted therapies in pancreatic cancer.

Principal Investigator
Joaquín Arribas

Scientific Manager
Cristina Bernadó

Medical Oncologist
César Serrano

Post-Doctoral Fellows
Enrique Javier Arenas
Cristina Bernadó
Beatriz Morancho
Mercedes Nadal
Bhavna Rani
Veronica Rodilla

Masters Student
Rita Casas

Graduate Students
Faiz Bilal
Luis Alfonso Garcia
Irene Rius
Junjie Zhang

Technicians
Marta Escorihuela
Antoni Luque
David Olivares
Jordi Rosell
Ismael Varela

## Summary:

During 2017 our group has consolidated and expanded our platform of breast and pancreatic cancer patient-derived experimental models, which is key to unravelling mechanisms of resistance to anti-tumor therapies and developing novel immune-based strategies.

Our breast cancer models have been instrumental in several collaborations. With groups from the *Centro Investigación del Cáncer* (Salamanca, Spain), *Hospital del Mar* (Barcelona, Spain) and the Virginia Commonwealth University (Richmond, USA), we have described three novel mechanisms of resistance to drugs directed against the receptor tyrosine kinase HER2, a potent oncogene overexpressed in ~20 % of breast and gastric cancers (Rios Luci et al. 2017; A Sabbaghi et al. 2017; Floros et al. 2018). These mechanisms will help to refine current therapies against these cancer subtypes as well as generate novel and more effective anti-HER2 therapies.

In collaboration with groups from CABIMER (*Centro Andaluz de Biología Molecular y Medicina Regenerativa* - Andalusian Molecular Biology and Regenerative Medicine Centre, Seville, Spain) we have shown that p95HER2, an overactive fragment of HER2, sensitizes cells to apoptosis. This discovery opens up new avenues in developing novel therapies against p95HER2-positive tumors, which are particularly aggressive (Martín-Pérez, R. et al. 2017).

Finally, in collaboration with colleagues from the *Institut de Recerca Biomédica de Barcelona* (IRBB), our patient-derived models have be used to characterize the mechanism behind metastatic dormancy in breast cancer (Gawrzak, S et al. 2018).

A distinctive feature of our patient-derived experimental platform is that it facilitates the study of the interplay between the immune system and cancer cells. We have implemented co-cultures of lymphocytes and cancer cells donated by the same patients to model anti-tumor immunotherapies, as well as the *humanization* of mice that carry patient-derived tumor grafts with human hematopoietic cells. These models have been used to activate effector lymphocytes with anti-tumor activity by DNA-demethylating drugs (Loo Yau et al. –under review, pre-published in *bioRxiv*, 2017). As a reflection of our expertise in these models, we were invited to write the section on humanized mouse models in a recent and authoritative review on patient-derived xenografts (Byrne et al. 2017).

Regarding our more recent collection of pancreatic patient-derived xenografts, these models have been key to analyzing the efficacy of novel therapies using regimes that most closely resemble the treatments patients have received in the clinic. By adopting this *mouse hospital* concept, we have evidenced that a subset of pancreatic cancers are sensitive to inhibitors of a serine threonine kinase known as Mek; however, after an initial response tumors became resistant due to the proliferation of pre-existing resistant tumor cells (Pedersen et al. 2017).

Our highly collaborative approach has allowed us to participate in several large-scale projects funded by the European Union including EDIReX, an infrastructure for research into patient-derived cancer xenografts, and COLOSSUS, a collaborative project to study colon cancer, in which we will develop humanized mouse models. In addition, we are extremely grateful to both the Spanish Association Against Cancer (AECC), and the Breast Cancer Research Foundation (BCRF), for their continued funding and support.

Lastly, it has been an extremely productive year for the *Centro de Investigación Biomédica en Red* (CIBER-ONC: Center for the Biomedical Research Network in Oncology). This new network is comprised of several of the most active cancer research groups across Spain, including three groups from VHIO.

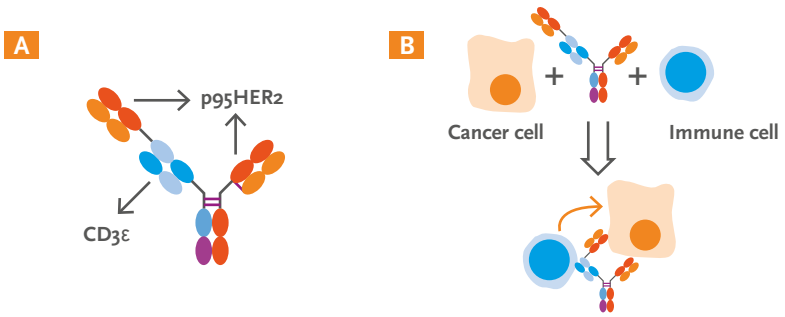



Figure: A) p95HER2-TCB bispecific antibody that binds to bivalently to p95HER2 and monovalently to the CD3ε of the T-Cell receptor. B) Mechanism of action of p95HER2-TCB. The bispecific establishes a contact between cancer cells and lymphocytes inducing the killing of the former by the latter.

## PI paper pick:

Ríos-Luci C, García-Alonso S, Díaz-Rodríguez E, Nadal-Serrano M, Arribas J, Ocaña A, Pandiella A. Resistance to the Antibody-Drug Conjugate T-DM1 Is Based in a Reduction in Lysosomal Proteolytic Activity. *Cancer Res.* 2017 Sep 1;77(17):4639-4651.

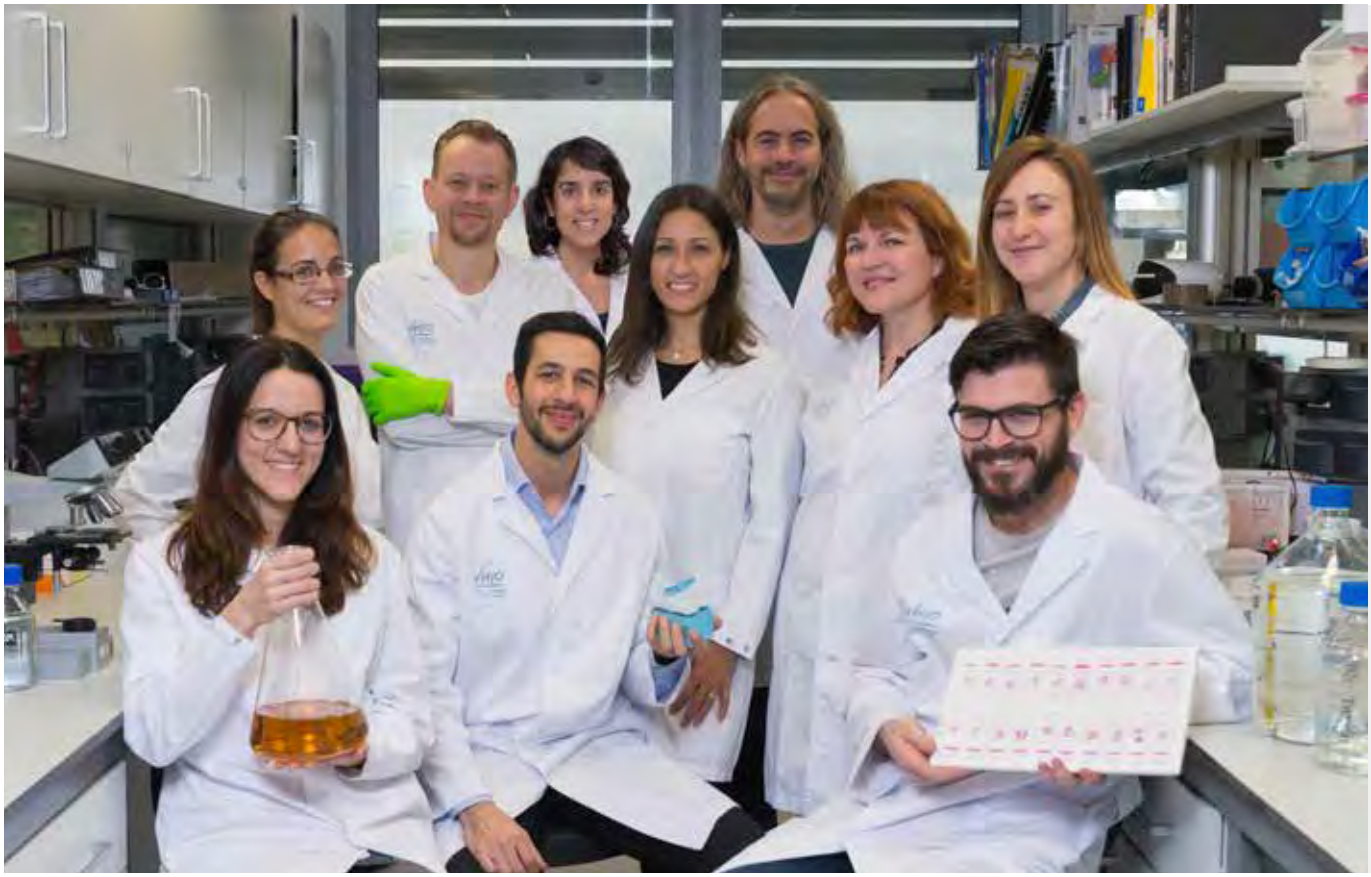
Sabbaghi M, Gil-Gómez G, Guardia C, Servitja S, Arpí O, García-Alonso S, Menendez S, Arumi-Uria M, Serrano L, Salido M, Muntasell A, Martínez-García M, Zazo S, Chamizo C, González-Alonso P, Madoz-Gúrpide J, Eroles P, Arribas J, Tusquets I, Lluch A, Pandiella A, Rojo F, Rovira A, Albanell J. Defective Cyclin B1 Induction in Trastuzumab-emtansine (T-DM1) Acquired Resistance in HER2-positive Breast Cancer. *Clin Cancer Res.* 2017 Nov 15;23(22):7006-7019.

Pedersen K, Bilal F, Bernadó Morales C, Salcedo MT, Macarulla T, Massó-Vallés D, Mohan V, Vivancos A, Carreras MJ, Serres X, Abu-Suboh M, Balsells J, Allende E, Sagi I, Soucek L, Tabernero J, Arribas J. Pancreatic cancer heterogeneity and response to Mek inhibition. *Oncogene.* 2017 Oct 5;36(40):5639-5647.

Byrne AT, Alférez DG, Amant F, Annibali D, Arribas J, Biankin AV, Bruna A, Budinská E, Caldas C, Chang DK, Clarke RB, Clevers H, Coukos G, Dangles-Marie V, Eckhardt SG, Gonzalez-Suarez E, Hermans E, Hidalgo M, Jarzabek MA, de Jong S, Jonkers J, Kemper K, Lanfrancone L, Mælandsmo GM, Marangoni E, Marine JC, Medico E, Norum JH, Palmer HG, Peeper DS, Pelicci PG, Piris-Gimenez A, Roman-Roman S, Rueda OM, Seoane J, Serra V, Soucek L, Vanhecke D, Villanueva A, Vinolo E, Bertotti A, Trusolino L. Interrogating open issues in cancer precision medicine with patient-derived xenografts. *Nat Rev Cancer.* 2017 Apr;17(4):254-268.

Preclinical Research

# Mouse Models of Cancer Therapies Group



## Strategic goals:

- Validation of new Omomyc-based cell penetrating peptides for cancer therapy.
- Preclinical validation of novel anti-Myc therapies in breast, brain, lung, neuroblastoma, melanoma, and multiple myeloma.
- Define the role of Myc in cancer-associated immune tolerance.

## Highlights:

- Invited as a key opinion leader within the field, Laura Soucek was one of the main authors of two high impact reviews published this year in *Nature Reviews Cancer*.
- Daniel Massó-Vallés is the first graduate student in our group to have been awarded a PhD for a project entitled: *Inhibiting Myc and Myc dependent inflammatory response as cancer therapies*. Congratulations Daniel!
- Thanks to another successful year of awards and grants, VHIO's Mouse Models of Cancer Therapies Group has incorporated three new technicians: Virginia Castillo Cano, Génesis Martín Fernández and Meritxel Sánchez Hervás.
- Along with other VHIO peers, Laura Soucek was co-applicant of a successful H2020 INFRAIA 2017 Grant: *EDIReX: EurOPDX Distributed Infrastructure for Research on patient-derived cancer Xenografts*.
- Peptomyc S.L. was awarded a NEOTEC and an APC grant from the Ministry of Economy, Innovation and Competitiveness, with Laura Soucek as Principal Investigator.
- Laura was selected by EIT Health as a Role Model for the project *Empowering Women Entrepreneurship in Health Innovation* (WE Health) aimed at promoting the participation of women in health innovation and entrepreneurship. For more information: http://www.we.eithealth.eu/en/role-models.

Principal Investigator
Laura Soucek

Staff Scientist
Jonathan Whitfield

Post-Doctoral Fellows
Daniel Massó Vallés
Mariano Zacarías-Fluck

Graduate Students
Toni Jauset González
Sandra Martínez Martín

Technicians
Virginia Castillo Cano
Laia Foradada Felíp
Génesis Martín Fernandez
Meritxell Sánchez Hervás
Erika Serrano del Pozo

## Summary:

Our group focuses on the pleiotropic and ubiquitous Myc oncoprotein, whose deregulation is implicated in almost all human cancers. The technical challenges of targeting nuclear transcription factors such as Myc – and the concern regarding potential side effects – had until recently precluded any preclinical validation of Myc inhibition as a possible therapeutic strategy. Over the past few years, we have since demonstrated in several mouse models that Myc inhibition has a dramatic therapeutic impact across several tumor types, with very mild and reversible side effects in normal tissue.

Encouraged by our results in mice, we are now interested in developing viable, non-toxic pharmacological options for Myc targeting in the clinic. To do so, we have created a spin-off company, Peptomyc S.L., for the development of Myc-inhibiting peptides for cancer therapy. We are currently validating our novel therapeutic strategy in notoriously difficult-to-treat cancers that are resistant to standard treatments and in dire need of new therapeutic avenues (i.e. KRAS-driven Non-Small Cell Lung Cancer, glioblastoma, and metastatic triple negative breast cancer).

The Soucek lab has continued to contribute to groundbreaking science at both regional and international levels by publishing in top-tier journals of prestige. This year Laura was invited to contribute as a key opinion leader on advances in drugging "undruggable" targets in cancer treatment for several publications (Dang et al., *Nat Rev Cancer* 2017; Whitfield et al., *Front Cell Dev Biol*, 2017), as well as the power and predictive value of patient-derived xenograft models (PDX) in cancer precision medicine (Byrne et al., *Nat Rev Cancer*, 2017).

Finally, our group has shared its scientific expertise with others resulting in two other important publications in 2017 (Pedersen et al., *Oncogene* 2017; Maltais et al., *PLoS One*, 2017).

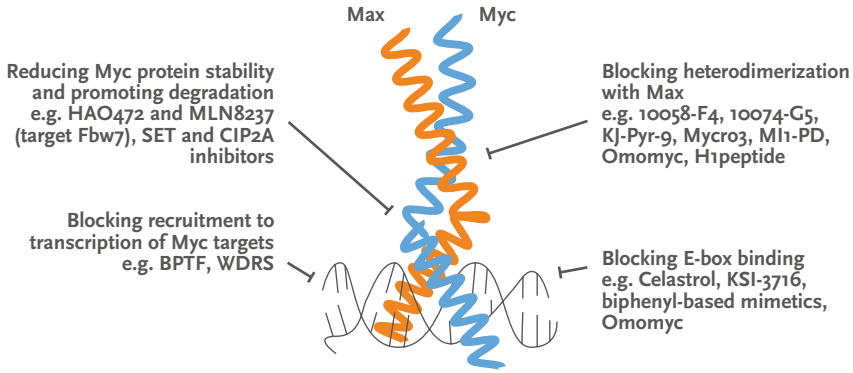



Figure: Adapted from Whitfield JR et al., *Front Cell Dev Biol*., 2017: **Multiple strategies to target Myc: reducing Myc stability and function**. Direct (right side) and indirect (left side) inhibitors are shown related to how they affect Myc's stability or binding to its partners or DNA. Other approaches impede Myc-dependent transcription of target genes. Some examples of each inhibitor strategy are listed. Omomyc functions through at least two of these mechanisms, blocking both Myc/Max heterodimerization and their binding to DNA.

## PI paper pick:

Dang C, Reddy EP, Shokat K, and Soucek L. Drugging the 'undruggable' cancer targets. *Nat Rev Cancer.* 2017 Aug;17(8):502-508.

Pedersen K, Bilal F, Bernadó Morales C, Salcedo MT, Macarulla T, Massó-Vallés D, Mohan V, Vivanco A, Carreras MJ, Serres X, Abu-Suboh M, Balsells J, Allende E, Sagi I, Soucek L, Tabernero J, Arribas J. Pancreatic cancer heterogeneity and response to Mek inhibition. *Oncogene.* 2017 Oct 5;36(40):5639-5647.

Whitfield JR, Beaulieu ME, Soucek L. Strategies to inhibit Myc and their clinical applicability. *Front Cell Dev Biol.* 2017 Feb 23;5:10. eCollection 2017.

Byrne AT, Alférez DG, Amant F, Annibali D, Arribas J, Biankin AV, Bruna A, Budinská E, Caldas C, Chang DK, Clarke RB, Clevers H, Coukos G, Dangles-Marie V, Eckhardt SG, Gonzalez-Suarez E, Hermans E, Hidalgo M, Jarzabek MA, de Jong S, Jonkers J, Kemper K, Lanfrancone L, Mælandsmo GM, Marangoni E, Marine JC, Medico E, Norum JH, Palmer HG, Peeper DS, Pelicci PG, Piris-Gimenez A, Roman-Roman S, Rueda OM, Seoane J, Serra V, Soucek L, Vanhecke D, Villanueva A, Vinolo E, Bertotti A, Trusolino L.. Interrogating open issues in cancer precision medicine using Patient-Derived Xenograft Models. *Nat Rev Cancer.* 2017 Apr;17(4):254-268.

Preclinical Research

# Tumor Biomarkers Group

## Strategic goals:

- The characterization of mechanisms adopted by tumor cells to communicate with their microenvironment during tumorigenesis and targeted drug therapy. This data is then used for biomarker and drug target discovery.
- Characterize the role of extracellular HMGA1 in breast cancer invasion and metastasis.
- Exploit the role of non-classical secretion linked to tumor invasion for the identification of therapeutic targets in breast cancer.

## Highlights:

- This year we have established a role for HMGA1 in the tumor invasion of breast cancer cells.
- We have expanded our studies to delineate the impact of non-classical secretion pathways on the cancer secretome. We have initiated the functional validation of two candidate drug targets non-classically secreted in the tumor invasion of breast cancer.

Principal Investigator
Josep Villanueva

Post-Doctoral Fellows
Juan Manuel Duran
Mercè Juliachs
Olga Méndez
Nathalie Meo-Evoli

Graduate Student
Mireia Pujals

Technicians
Ana Matres
Candida Salvans

## Summary:

Tumor cell communication with its microenvironment performs an important role in tumor initiation and progression. Tumor cells hijack the tumor microenvironment ecosystem via paracrine signaling to promote a pro-oncogenic microenvironment that is crucial for the development of primary and metastatic tumors.

Our main aim is to characterize the mechanisms adopted by cancer cells to communicate amongst themselves as well as with their microenvironment during tumorigenesis. We intend to exploit these findings to advance biomarker and drug target discovery. Our group's working hypothesis is that cellular signaling pathways undergo alteration during the tumorigenesis process and that these changes are translated into differential protein secretion, which can also potentially be used to identify secreted markers. In addition, some of the differentially regulated proteins could be direct extracellular messengers of intracellular signaling pathways contributing to fundamental stages implicated in cancer initiation and progression, thus representing potential therapeutic targets.

The methodological focus of our group centers on profiling the secreted sub-proteome ('secretome') of cells by quantitative mass spectrometry. Most secreted proteins contain a signal peptide that directs their sorting to the extracellular space through the endoplasmic reticulum (ER)–Golgi secretory pathway. One of the most striking observations when secretome profiles are carefully produced and analyzed is that they contain hundreds of theoretical intracellular proteins. Recent reports showing intracellular proteins with alternative extracellular functions suggest that new protein functions associated with alternative subcellular localizations could be relevant in tumorigenesis. In line with this new view, our recent efforts in the context of therapeutics and tumor invasion have led us to hypothesize that the characterization of non-classical protein secretion could lead to novel therapies against cancer.

The cancer secretome contains classical and non-classical secreted proteins that tumor cells use as molecular SMS to communicate to each other and with their microenvironment. Our main goal is to characterize the mechanisms adopted by cancer cells to communicate amongst themselves as well as with their microenvironment during tumorigenesis, and exploit these data to advance biomarker and drug target discovery.

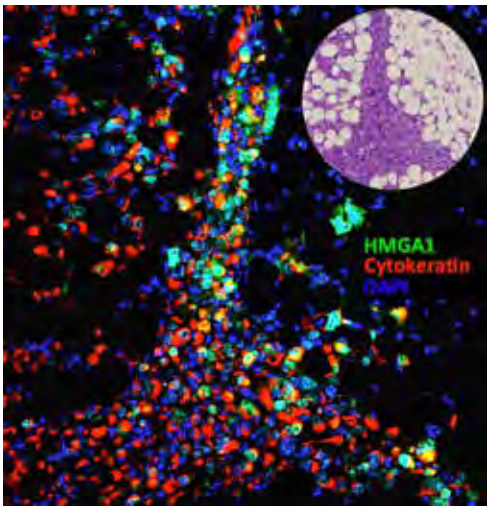



Figure: **The nuclear protein HMGA1 is enriched in the invasive front of primary breast tumors.** Immunofluorescence analysis of HMGA1 in an orthotopic xenograft model of breast cancer. HMGA1 expression (green) increased towards the invasive front. Cytokeratin (red) is used to stain human epithelial cells, and Hoechst to counterstain the nuclei. The inset shows the histology of the tumor tissue.


Director, Translational Research Program
Joan Seoane

# Translational Research

FROM THE DIRECTOR ..... 61

THE PI PAGES

Gene Expression & Cancer Group ..... 62

Stem Cells & Cancer Group ..... 64

Gene Expression &
Cancer Group

Stem Cells &
Cancer Group

# Translational Research

Director, Translational Research Program

# Joan Seoane

"The secret behind the swift translation and application of cancer science and medicine is the two-way collaboration and dialect between researchers and clinical investigators in a multidisciplinary setting. It is thanks to our team science that translational and clinical research at VHIO are tightly connected, enabling us to deliver on the promise of precision medicine for an increasing number of our patients. Rapidly transforming cancer discovery into real benefits can and will only continue to happen through the pooling of expertise from bench to bedside and back."

VHIO's Translational Research Program promotes and accelerates the integration of preclinical and clinical research. By tackling cancer from all angles and establishing synergies between molecular and clinical cancer research, we rapidly translate scientific advances into benefits for our patients.

In our collective battle to solve cancer sooner, one of the major challenges we face is tumor diversity. Cancer is an extremely complex, heterogeneous, fluctuating and 'smart' disease given that tumors are molecularly diverse and evolve over time. Tumors are formed by cells with multifarious states of proliferation, differentiation, motility, and, importantly, varying sensitivity to anti-cancer medicines. Each individual patient consequently has a unique tumor with a particular combination of genomic aberrations that can alter during tumor progression. Patients should therefore be treated with the optimal compound/combination of therapies that more effectively target the specificities of their respective disease.

Selecting the most appropriate treatment depends on the specific molecular taxonomy of a particular tumor at a given time, and the challenge is therefore to identify which treatment should be precisely matched to which patient and in so doing, further advance personalized medicine in oncology. To potentiate cancer therapies through the combination of compounds targeting all cell types within a tumor, we must achieve a deeper understanding of the nature of intratumoral heterogeneity.

Among the different cell types forming intratumoral heterogeneity, some cells with stem cell characteristics have been identified. Known as Cancer-Initiating Cells (CICs), or Cancer Stem Cells (CSCs), they are characterized by their self-renewing capacity, multi-lineage differentiation properties, high oncogenic potential, and ability to replicate the heterogeneity of original human tumors in mouse models. CICs are also responsible for the initiation, recurrence and chemo- and radio-resistance of tumors indicating that more effective therapies could be identified via strategies targeting the stem-cell-like component of tumors. To-date, few pharmacological compounds have proven successful.

To explore the two levels of cancer heterogeneity, we investigate cancer as closely as possible to the actual tumor and generate patient-derived *in vitro* and *in vivo* cancer models. Tumor specimens are obtained shortly upon surgical resection and we study their respective tumor cells and cancer stem cells. We then develop mouse models that recapitulate the characteristics of patients' tumors as faithfully as possible.

Both VHIO's Stem Cells & Cancer Group led by Héctor G. Palmer, and my own Gene Expression & Cancer Group, have developed these models for brain and colon cancer respectively; work which has led to important publications in top-tier journals. Providing optimal therapy tailored to individual patients relies on teamwork, studying cancer as closely as possible to the actual patient, and collectively tackling cancer heterogeneity head-on. VHIO's Translational Research Program is committed to delivering on the promise of precision medicine in oncology by catalyzing the transfer of new insights generated by cancer research into true benefits for patients.

In 2017, Héctor's Group has explored novel strategies to combat slow-cycling cancer-initiating cells and discovered new therapeutic targets that can be used to develop anti-cancer compounds. Moreover, they have identified biomarkers to more precisely stratify patients for enrollment in clinical trials performed at out Hospital, and have shed light on the molecular mechanisms implicated in the Wnt pathway.

My own group has developed novel and barely invasive liquid biopsies to disentangle the complexity and heterogeneity of brain tumors. The analysis of ctDNA in cerebrospinal fluid has opened new avenues for research aimed at achieving a better understanding of central nervous system cancers. We have also generated insights into the TGF-beta pathway as an effective therapeutic target. Finally, we have developed an anti-cancer drug, MSC1, in close collaboration with VHIO spin-off company Mosaic Biomedicals. MSC1, a humanized LIF neutralizing antibody, will be tested in clinical trials in early 2018.

As VHIO embarks on its second decade of *Translation toward precision oncology*, we can rightly expect to mark many more breakthroughs in ultimately improving outcomes for those who matter most – our patients.

Translational Research

# Gene Expression & Cancer Group

## Strategic goals:

- Identify both new therapeutic targets against brain tumors as well as novel biomarkers to more precisely predict response to therapy.
- Study intratumor heterogeneity.
- Investigate the tumor microenvironment.
- Develop methods for non-invasive molecular diagnosis through the study of circulating biomarkers.
- Generate patient-derived mouse models of brain tumors.

## Highlights:

- Translating our discoveries into a clinical trial. Our efforts during 2017 have led to an IND submission, and next year will result in a novel compound for the treatment of cancer patients, designed and developed in our lab with the spin off company derived from our group; Mosaic Biomedicals in partnership with Northern Biologics Inc. (Toronto, Canada).

Principal Investigator
Joan Seoane

Post-Doctoral Fellows
Ester Bonfill
Raffaella Iurlaro
Regina Mayor
Josep Lluis Parra-Palau
Monica Pascual
Ester Planas
Ada Sala

Graduate Student
Ester Arroba

Technicians
Alexandra Arias
Isabel Cuartas
Carolina Raventós
Cristina Sánchez

## Summary:

Our group focuses on the study of brain tumors: primary tumors and brain metastasis. These are some of the most aggressive cancers and advancing progress within this field is consequently crucial.

In brain tumors, as in many other malignancies, evolving heterogeneity represents one of the most important challenges that are currently hampering our efforts aimed at more effectively treating cancer. We are studying genomic heterogeneity at the level of genomic alterations.

Tumors are composed of a mosaic of cell subclones that differ in their genomic alterations. We explore this genomic diversity present in glioblastoma and are analyzing intratumor genomic heterogeneity as it evolves over time in response to therapy. Following Darwinian selection rules, the cellular subclones enriched in response to treatment are those that will confer resistance and facilitate the identification of novel therapeutic targets to counter tumor resistance and relapse.

We have identified some of the candidate genes responsible for disease recurrence and are designing therapeutic approaches to prevent the reappearance of brain tumors. Moreover, in order to track, assess and better understand their evolving genomic heterogeneity, we are studying cell-free circulating tumor DNA in fluids from patients with brain tumors. Tumors shed DNA into the blood stream and the sequencing of this circulating DNA enables the accurate, less invasive molecular characterization of tumors, and these blood-based markers facilitate a more precise diagnosis, monitoring and identification of actionable gene mutations.

Finally, we study the role of the tumor microenvironment which, in the case of brain cancers, plays a critical role in cancer progression. Tackling the tumor microenvironment might be a way of attacking cancer independently of its heterogeneity. By eliminating the niche where cancer resides and thrives should help us to develop more effective anti-cancer compounds.

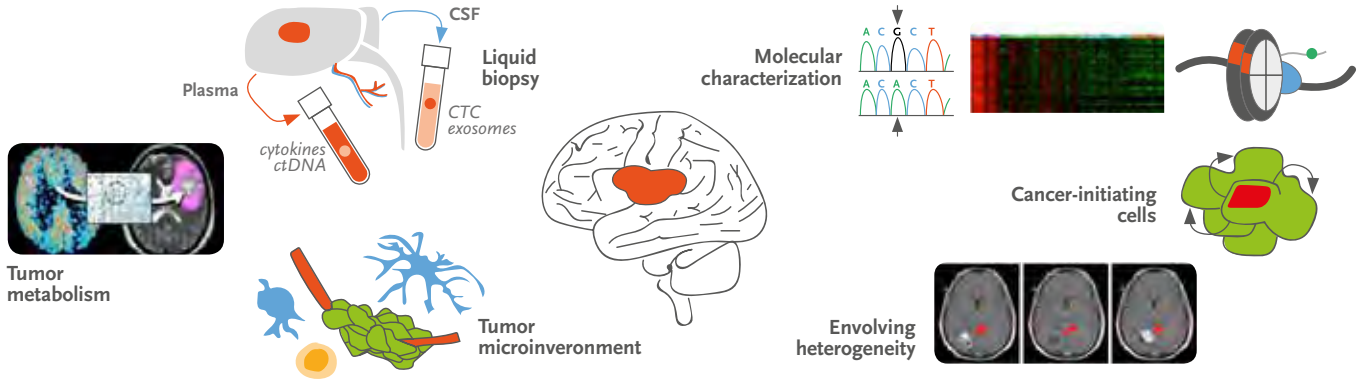



Figure: Studying brain tumors from all angles.

## PI paper pick:

Seoane J. Division hierarchy leads to cell heterogeneity. *Nature*. 2017 Sep 14;549(7671):164-166.

Huber-Ruano I, Raventos C, Cuartas I, Sánchez-Jaro C, Wosikowski K, Janicot M, Seoane J. An Antisense oligonucleotide targeting TGF-β2 inhibits lung metastasis and induces CD86 expression in tumor-associated macrophages. *Ann Oncol*. 2017 Sep 1;28(9):2278-2285

Seoane J, Gomis RR. TGFβ Family Signaling in Tumor Suppression and Cancer Progression. *Cold Spring Harb Perspect Biol*. 2017 Dec 1;9(12).

Byrne AT, Alférez DG, Amant F, Annibali D, Arribas J, Biankin AV, Bruna A, Budinská E, Caldas C, Chang DK, Clarke RB, Clevers H, Coukos G, Dangles-Marie V, Eckhardt SG, Gonzalez-Suarez E, Hermans E, Hidalgo M, Jarzabek MA, de Jong S, Jonkers J, Kemper K, Lanfrancone L, Mælandsmo GM, Marangoni E, Marine JC, Medico E, Norum JH, Palmer HG, Peeper DS, Pelicci PG, Piris-Gimenez A, Roman-Roman S, Rueda OM, Seoane J, Serra V, Soucek L, Vanhecke D, Villanueva A, Vinolo E, Bertotti A, Trusolino L. Interrogating open issues in cancer precision medicine with patient-derived xenografts. *Nat Rev Cancer*. 2017 Apr;17(4):254-268.

Translational Research

# Stem Cells & Cancer Group

## Strategic goals:

- Describe key molecular mechanisms that confer CSC their capacity to self-renew and resist conventional or target-directed therapies.
- Unmask molecular drivers of CSC quiescence, clinical relevance in cancer progression and evaluate their potential inhibition to eradicate CSC.
- Study the efficacy and mechanism of action of new Wnt/ beta-catenin, Notch and EGFR inhibitory drugs for the treatment of CRC, lung or neuroendocrine tumors.
- Identify the genetic determinants of sensitivity or resistance to the novel generation of EGFR, Notch and Wnt/beta-catenin inhibitors.
- Implement predictive biomarkers of response to therapeutic EGFR, Notch and Wnt/ beta-catenin inhibitors and other targeted therapies.
- Expand our collection of PDX models and start working on those derived from other tumor types.

## Highlights:

- We have unmasked the molecular mechanisms governing the delicate link between stemness and quiescence in chemo-resistant colon cancer cells. Many genes and proteins playing a central role in this process are epigenetic chromatin remodelers. Their activity could potentially be inhibited as a new therapeutic approach to eliminating slow-cycling cancer-initiating cells. These molecular mechanisms are common in several solid tumors (CRC, breast, lung, melanoma, glioblastoma).
- Identification of a biomarker and a drug target to identify and eliminate slow-cycling cancer-initiating cells. Both could become essential tools in improving patient survival and reducing disease relapse.
- We have accumulated evidence surrounding the efficacy and mechanisms of action of a novel generation of Wnt/ beta-catenin inhibitory drugs on CRC and identified biomarkers to predict response to these inhibitors.
- We have revealed new molecular mechanisms behind the response of advanced lung cancer patients to novel target-directed therapies.

Principal Investigator
Hector G. Palmer

Post-Doctoral Fellows
Oriol Arqués
Jordi Martínez-Quintanilla
Isabel Puig

Graduate Student
Estefania Cuesta

Technicians
Irene Chicote
Lorena Ramírez

## Summary:

We aim to better understand the molecular mechanisms that confer tumors the capacity to self-renew, resist therapy, relapse and metastasize – all definitive factors in the survival of patients. We are dedicated to studying the consequences of intratumoral cell heterogeneity for tumor evolution and patient survival. Among the various cell populations that construct heterogeneous tumors, Cancer Stem Cells (CSC) are at the apex of a differentiation process within the cancerous tissue -- somewhat reminiscent of the hierarchy present in the normal tissue from which they originate. CSC can also compose the small reservoir of drug-resistant cells that trigger relapse after chemotherapy-induced remission, or give rise to distant metastasis. It is therefore becoming increasingly evident that the failure to eradicate cancer stem cells can promote tumor regrowth.

Our studies mainly focus on colorectal cancer. At molecular level we are analyzing the role of oncogenic pathways controlling the fate of Colon Cancer Stem Cells (CoCSC). RAS/PI3K/AKT, Wnt/beta-catenin and Notch pathways are drivers of cancer stem cell fate and lead to disease progression in many tumor types. Over recent years we have described a novel mechanism of resistance to PI3K and AKT inhibitory drugs conferred by beta-catenin in colorectal cancer. This is of great relevance since many patients in clinical studies do not respond to these therapies, and no molecular explanation behind such resistance had previously been described.

Our findings will facilitate the selection of 'sensitive' patients based on their expression of particular biomarkers predicting drug-response. We are currently focusing on a new generation of EGFR, Wnt/beta-catenin and Notch inhibitors in close collaboration with several major pharmaceutical companies, and have already experimentally evidenced the efficacy and mechanisms of action of these drugs in pre-clinical models of colorectal cancer with patient-derived xenografts. This marks an important milestone within the field; for decades colorectal cancer had been described as a paradigmatic tumor addicted to the oncogenic Wnt/beta-catenin pathway.

We also seek to identify the molecular determinants of response to these anti-cancer therapies that could consequently become robust biomarkers for the selection of 'sensitive' patients as well as better guide the design of future clinical trials. Some of these predictive biomarkers are mutations affecting components of the Wnt/beta-catenin pathway, whose identification can be perfectly standardized in clinical practice for patient selection.

Our collaboration with the Vall d'Hebron University Hospital's Medical Oncology Department, led by Josep Tabernero, as well as partnerships with pharmaceutical companies, will accelerate the translation of our findings into clinical practice, and hopefully revert the long-stalled scenario of CRC drugs.

Our group has developed a collection of PDX models derived from primary tumors or liver metastasis of more than 150 CRC patients. Most recently, we have also generated around 50 clinical trial associated xenografts (CTAX) from patients enrolled in these studies.

During this past year we have also been developing translational research projects focusing on lung cancer, hepatocarcinomas and neuroendocrine tumors. We are generating PDX models, evaluating mechanisms of drug action, treatment resistance and sensitivity to novel therapeutic strategies tested in clinical trials.

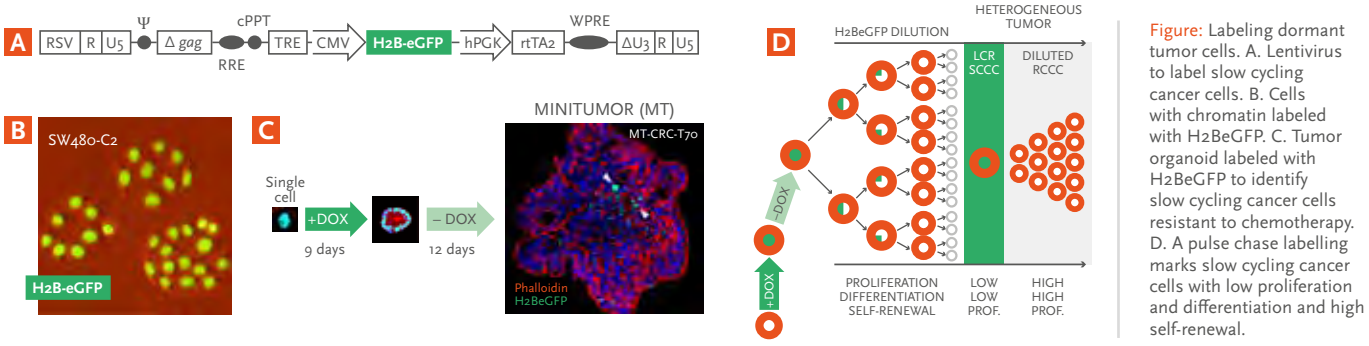



Figure: Labeling dormant tumor cells. A. Lentivirus to label slow cycling cancer cells. B. Cells with chromatin labeled with H2BeGFP. C. Tumor organoid labeled with H2BeGFP to identify slow cycling cancer cells resistant to chemotherapy. D. A pulse chase labelling marks slow cycling cancer cells with low proliferation and differentiation and high self-renewal.

## PI paper pick:

Sveen A, Bruun J, Eide PW, Eilertsen IA, Ramirez L, Murumägi A, Arjama M, Danielsen SA, Kryeziu K, Elez E, Tabernero J, Guinney J, Palmer HG, Nesbakken A, Kallioniemi O, Dienstmann R, Lothe RA. Colorectal Cancer Consensus Molecular Subtypes Translated to Preclinical Models Uncover Potentially Targetable Cancer Cell Dependencies. *Clin Cancer Res.* Epub 2017 Dec 14.

Martinez-Marti A, Felip E, Matito J, Mereu E, Navarro A, Cedrés S, Pardo N, Martinez de Castro A, Remon J, Miquel JM, Guillaumet-Adkins A, Nadal E, Rodriguez-Esteban G, Arqués O, Fasani R, Nuciforo P, Heyn H, Villanueva A, Palmer HG, Vivancos A. Dual MET and ERBB inhibition overcomes intratumor plasticity in osimertinib-resistant-advanced non-small-cell lung cancer (NSCLC). *Ann Oncol.* 2017 Oct 1;28(10):2451-2457.

Byrne AT, Alférez DG, Amant F, Annibali D, Arribas J, Biankin AV, Bruna A, Budinská E, Caldas C, Chang DK, Clarke RB, Clevers H, Coukos G, Dangles-Marie V, Eckhardt SG, Gonzalez-Suarez E, Hermans E, Hidalgo M, Jarzabek MA, de Jong S, Jonkers J, Kemper K, Lanfrancone L, Mælandsmo GM, Marangoni E, Marine JC, Medico E, Norum JH, Palmer HG, Peeper DS, Pelicci PG, Piris-Gimenez A, Roman-Roman S, Rueda OM, Seoane J, Serra V, Soucek L, Vanhecke D, Villanueva A, Vinolo E, Bertotti A, Trusolino L. Interrogating open issues in cancer medicine with patient-derived xenografts. *Nat Rev Cancer.* 2017 Sep 15;17(10):632.

Dienstmann R, Elez E, Argiles G, Matos I, Sanz-Garcia E, Ortiz C, Macarulla T, Capdevila J, Alsina M, Sauri T, Verdaguer H, Vilaro M, Ruiz-Pace F, Viaplana C, Garcia A, Landolfi S, Palmer HG, Nuciforo P, Rodon J, Vivancos A, Tabernero J. Analysis of mutant allele fractions in driver genes in colorectal cancer - biological and clinical insights. *Mol Oncol.* 2017 Sep;11(9):1263-1272.


Director, Clinical Research Program
Josep Tabernero

# Clinical Research

FROM THE DIRECTOR ..... 69

THE PI PAGES

Breast Cancer & Melanoma Group ..... 70

Early Clinical Drug Development Group ..... 72

Gastrointestinal & Endocrine Tumors Group ..... 74

Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site Group ..... 76

Gynecological Malignancies Group ..... 78

High Risk & Cancer Prevention Group ..... 80

Oncogenetics Group ..... 82

Oncology Data Science (ODysSey) Group ..... 84

Radiation Oncology Group ..... 86

Thoracic Tumors & Head and Neck Cancer Group ..... 88

Breast Cancer &
Melanoma Group

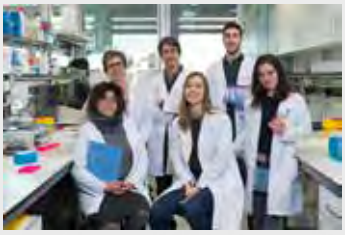
Early Clinical Drug
Development Group

Gastrointestinal &
Endocrine Tumors Group

Genitourinary, CNS Tumors,
Sarcoma & Cancer of Unknown
Primary Site Group

Gynecological
Malignancies Group

High Risk & Cancer
Prevention Group



Oncogenetics Group

Oncology Data Science
(Odyssey) Group

Radiation Oncology
Group

Thoracic Tumors & Head
and Neck Cancer Group

# Clinical Research

Director, Clinical Research Program

# Josep Tabernero

"Our patients and VHIO's multidisciplinary approach to driving advances against cancer are at the center of everything we do. Incorporating exceptionally talented groups and taskforces, VHIO's Clinical Research Program follows three guiding principles, namely, predictive, proven and precise. We develop novel agents and approaches to diagnose cancer earlier and better predict response to therapy in order to deliver optimal and personalized treatments to the right patients at the right time, on time."

VHIO's multidisciplinary and translational approach to research closely connects its researchers with our clinical investigators and in so doing, enables our Program to spearhead cooperative preclinical, early phase studies aimed at developing novel therapeutics, as well as new or redefined prognostic/diagnostic tools to better detect disease, track progression and more accurately predict response to anti-cancer therapies.

We pioneer novel study design including Baskets and first-in-human trials. Concerning the former, our Cancer Core Europe endorsed Basket of Baskets (BoB) trial's protocol of its first module, *Immune-Checkpoint Blockade in Genomically Selected Populations*, was approved this year (page 13). An example of VHIO's contribution to the latter, a study led by Cristina Saura, PI of our Breast Cancer and Melanoma Group (Saura et al. *Cancer Discov*), showed that the potent inhibition of AKT signaling with AKT inhibitor, ipatasertib, was associated with a tolerable safety profile and meaningful disease control in patients with diverse solid tumors who progressed on prior therapies with many of their tumors manifesting activation of AKT. These findings promise new therapeutic opportunity for the treatment of this subpopulation of patients.

We have continued to develop next generation blood-based diagnostics to monitor disease, its respective molecular specificities, and response to novel targeted therapies. More specifically, we continue to employ our in-house BEAMing digital PCR/flow cytometry technology to evaluate patients with metastatic colorectal cancer.

Importantly too, thanks to funding received from the FERO Foundation, we have incorporated our Droplet Digital PCR (ddpCR) Bio-Rad Technology platform which has enabled us to develop panels to detect mutations in *EGFR* in patients with lung cancer and AKT1, *PIK3CA* and *ESR1* in breast cancer patients. We are making significant progress in validating and developing this technology for the more effective, less invasive 'policing' of cancer over time, real time.

As a reflection of our expertise in developing liquid biopsy, in collaboration with our Cancer Genomics Group directed by Ana Vivancos, we counted two projects awarded under the TRANSCAN Joint Translational Call on *Minimally and non-invasive methods for early detection and/or progression of cancer*. The first will establish non-invasive prognostic markers for resected early stage non-small cell lung cancer by assessing the role of circulating and exosomal miRNAs and free circulating DNA (fcDNA). The second will focus on the early detection of relapse in advanced colon cancer patients by longitudinally following a personalized signature by liquid biopsy (see page 12).

Cancer immunotherapy continues to show much promise as a firm contender in dismantling cancer's armory. We at VHIO are dedicated to potentiating novel immune agents as mono therapy or in combination as well as accelerating insights into the cellular and molecular mechanisms modulating immune response.

We have launched our Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI) supported by the BBVA Foundation, in collaboration with colleagues at the Memorial Sloan Kettering Cancer Center – MSKCC (New York). As a renewal of our framework agreement, CAIMI aims to advance agents that inhibit checkpoint regulation of the immune system, establish the mechanisms of resistance and response to these therapies, and prioritize the early development of those agents showing most promise (page 14). In partnership with MSKCC, we will co-found and develop six translational projects linked to the early clinical development phases of immunotherapy.

This year also celebrated the renewal of our Obra Social "la Caixa" International Program for Cancer Research and Education. This initiative will further pursue the established synergies between VHIO and MSKCC, and spur the development of several new research lines including the pan-omic exploration (genomics and radiomics) of solid tumors with particular emphasis on Big Data. We will explore the impact of gene mutations in DNA damage repair and metastatic prostate cancer together with data mining to expose the molecular genetic determinants of sensitivity to targeted therapies in solid cancers (page 14).

Talking of Big Data, as a result of our leading research in cancer classification performed by our Oncology Data Science (ODysSey) Group, led by Rodrigo Dienstmann, we published a review article (Dienstmann et al. *Nat Rev Cancer*, 2017), underlining the challenges and opportunities ahead in putting the brakes on the molecular culprits that drive tumor initiation, development and growth in each established individual consensus molecular subtype of colorectal cancer. As this Report goes to print I am pleased to announce that VHIO has been accepted to participate in AACR's Project Genomics Evidence Neoplasia Information Exchange (GENIE).

To better understand how major molecular alterations support the irrepressible growth of tumors, findings from a muli-center study (Zabala-Letona et al. *Nature*. 2017) led by colleagues at CIC bioGune (Bizkaia, the Basque Country), in collaboration with VHIO groups and several others, including MSKCC, revealed a mechanism through which prostate cancer produces metabolites essential for tumor biology to thrive. Evidencing that mTORC1-dependent AMD1 regulation sustains polyamine metabolism in this tumor type, this study supports the metabolic characterisation of cancer as an innovative approach to identify new ways to effectively treat disease.

We also advance cancer discovery and therapeutics in partnership through various international consortia and networks of excellence (pages 140-143). In colorectal cancer, we coordinate the EU H2020 funded MoTriColor Consortium which focuses on validating three novel therapeutic approaches linked to three gene expression signatures. In 2017, we initiated the prescreening of patients from the different clinical sites and next year we will start enrolling patients in the three MoTriColor clinical trials.

'At home', combining expertise with several other leading research centers across Catalonia, we are now participating in the pilot testing of the implementation and application of comprehensive genomics to clinical decision making in the treatment and care of our patients. Led by Elías Campo (Pi i Sunyer Biomedical Research Institute – IDIBAPS, and *Hospital Clínic*), with myself as PI, this project is supported by the Catalan Strategic Plan for Health Research and Innovation (PERIS) to promote people centered health research.

I believe in forging closer collaborations with other specialties and engaging the entire oncology ecosystem. Only by considering and responding to the needs of all stakeholders in oncology including patients and their families, researchers, payers, regulators, the policymakers, and industry, will we accelerate our dedicated efforts aimed at solving cancer sooner.

We can and will do better.

Clinical Research

# Breast Cancer & Melanoma Group


## Strategic goals:

- Optimize therapies with the introduction of novel anti-cancer therapies and addition of rational combinations to overcome mechanisms of resistance.
- Incorporate proteomics, genomics, and circulating tumor cell platforms in translational research to advance insights into tumor biology.
- Apply preclinical, predictive data to help guide innovative clinical trial design in advanced disease.
- Participate in clinical studies and projects for the collection of clinical and biological data from patients in order to ultimately improve outcomes.

## Highlights:

- We have published practice-changing data in the field of adjuvant and metastatic breast cancer.
- Thanks to our collaboration with various clinical departments at the Vall d'Hebron University Hospital (HUVH), our group has become one of the most active in neoadjuvant and metastatic breast cancer studies worldwide, set firmly within the context of translational research.
- VHIO has established itself as a reference center in developing patient-derived xenografts (PDX) and we are currently expanding our collection of these models. We are also consolidating our cfDNA program for genotyping in breast cancer.
- In melanoma, our group is one of the largest networks in Spain and across Europe, and one of the most active in metastatic and adjuvant studies in melanoma. Each trial is tightly connected with the corresponding translational research led by VHIO.

Principal Investigator
Cristina Saura

Associate Translational Investigators
Javier Cortés
Isabel Rubio

Medical Oncologists and Clinical Fellows
Miriam Arumí
Analía Azaro
Judith Balmaña
Meritxell Bellet
Marta Capelan
Cristina Cruz
Santiago Ignacio Escrivà
Laia Garrigós
Patricia Gómez
Eva Muñoz
Mafalda Oliveira
Carolina Ortiz
Beatriz Rojas
Esther Zamora

Clinical Nurse Specialist
Anna Suñol

Nutritionist
Nuria Durán

## Summary:

Our Breast Cancer & Melanoma Group is one of the most active and renowned in Europe. In 2017 our group published a total of 29 papers with a cumulative Impact Factor (IF) of 287,28. We are not only committed to participating in clinical trials, but also lead many of them; reflected by our representation on several Steering Committees. We apply translational data to help both guide and accelerate the clinical development of anti-cancer compounds.

Our key areas of interest include:

**HER-positive disease:** we continue to participate in major trials testing novel therapies, and recruit patients in clinical studies with the most promising agents including neratinib, margetuximab, tucatinib, SYD985, DS8201 and MCLA128. We also treat patients in combination therapy trials that are designed to overcome mechanisms of resistance such as trastuzumab plus palbociclib or abemaciclib. In collaboration with VHIO's Growth Factors Group, led by Joaquín Arribas, we continue to explore cancer drug resistance to these therapies.

**Discovery of novel mechanisms of resistance:** In close collaboration with VHIO's Experimental Therapeutics Group, headed by Violeta Serra, we have developed several PDX models to advance insights into the mechanisms of resistance in breast cancer that may be overcome by treatment with PI3K inhibitors. Our group has established expertise in triple negative breast cancer and *BRCA* tumors thanks to our broad program focused on the evaluation of immunotherapies and various PARP inhibitors in the clinic combined with translational research of excellence in both areas. In hormone receptor-positive disease we are leading different trials using the most novel compounds (PI3K-AKT-mTOR, CDK4/6 inhibitors and BET inhibitors), and have observed encouraging activity of neratinib in tumors harboring HER2 mutations.

**New compounds:** an emerging group of drugs known as immunoconjugates are undoubtedly here to stay. Their innovative design makes them extremely active given that chemotherapy is released specifically inside the tumor with increased potency and less toxicity. We are pleased to report that we have already treated patients with SYD-985, CDX011, SAR566658, and very soon, with IMMU-132.

**cfDNA:** In collaboration with VHIO's Cancer Genomics Group, led by Ana Vivancos, we are analyzing tumor tissue and cfDNA that will, in the near future, provide crucial insights into the evolution of genetic alterations of tumors both in the advanced setting as well as the challenging scenario of early disease.

Our **Melanoma Group** is led by Eva Muñoz, also Medical Oncologist and Clinical Fellow of our group, and has made significant progress throughout 2017 by actively participating in several phase I, II and III clinical trials focused on melanoma and other skin tumors to study several emerging therapies in metastatic and adjuvant cancer treatment. The group has consolidated its own research program incorporating clinical investigators and cancer researchers at VHIO. Collectively, we conduct purely translational research centered on melanoma acquisition and progression towards developing new treatment options for our patients.

## PI paper pick:

Saura C, Roda D, Roselló S, Oliveira M, Macarulla T, Pérez-Fidalgo JA, Morales-Barrera R, Sanchis-García JM, Musib L, Budha N, Zhu J, Nannini M, Chan WY, Sanabria Bohórquez SM, Meng RD, Lin K, Yan Y, Patel P, Baselga J, Tabernero J, Cervantes A. A First-in-Human Phase I Study of the ATP-Competitive AKT Inhibitor Ipatasertib Demonstrates Robust and Safe Targeting of AKT in Patients with Solid Tumors. *Cancer Discov.* 2017 Jan;7(1):102-113.

Llombart-Cussac A, Cortés J, Paré L, Galván P, Bermejo B, Martínez N, Vidal M, Pernas S, López R, Muñoz M, Nuciforo P, Morales S, Oliveira M, de la Peña L, Peláez A, Prat A. HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. *Lancet Oncol.* 2017 Apr;18(4):545-554,

Dickler MN, Tolaney SM, Rugo HS, Cortés J, Diéras V, Patt D, Wildiers H, Hudis CA, O'Shaughnessy J, Zamora E, Yardley DA, Frenzel M, Koustenis A, Baselga J. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR+/HER2- Metastatic Breast Cancer. *Clin Cancer Res.* 2017 Sep 1;23(17):5218-5224.

Pérez-Alea M, McGrail K, Sánchez-Redondo S, Ferrer B, Fournet G, Cortés J, Muñoz E, Hernandez-Losa J, Tenbaum S, Martin G, Costello R, Ceylan I, Garcia-Patos V, Recio JA. ALDH1A3 is epigenetically regulated during melanocyte transformation and is a target for melanoma treatment. *Oncogene.* 2017 Oct 12;36(41):5695-5708.

# Early Clinical Drug Development Group

## Strategic goals:

- Clinical early development of the best-in-class targeted therapies, determining the optimal schedule and patient population that would most likely benefit most from these drugs by participating in novel clinical trials.
- Analyze patients' tumors for molecular aberrations that may predict the efficacy of targeted agents and enable a more precise selection of the most appropriate treatment matched to the specificities of individual patients with advanced cancer.
- Link clinical research at the UITM with the various preclinical and translational research groups at VHIO, and foster powerful collaborations with different partners involved in drug development and translational research (phase I units, academic centers, consortia, pharmaceutical companies).

## Highlights:

- As a leading institute in drug development at global level (PI3K/akt/mTOR inhibitors, MAPK, FGFR and MET inhibitors, or drugs targeting developmental pathways such as TGF-beta, SHH, WNT, and NOTCH), we clinically test the best in-class drugs. We have expanded our expertise to other cell-signaling pathway inhibitors such as immunotherapeutics including agents targeting PD1/PDL1, OX40, CD40, and engineered antibodies.
- We have carried out many clinical trials with novel-novel combinations including the pairing of targeted therapies (novel/novel) and, in immuno-oncology, coupling checkpoint inhibitors with either chemotherapy, radiation (abscopal effect), targeted therapies, or other immunomodulatory agents (TGFbeta, LAG3, anti VEGFR2, CD40).
- Performed several clinical trials with patients selected on molecular alterations: mutations in AKT1, EGFR, PIK3CA, PIK3CB, PTEN, IDH1, ALK, ROS1, BRAF, NRAS, KRAS, FGFR1 and 2, MET, HER2, HER3; amplifications in HER2, AKT 1, 2, and 3, FGFR1, MET, NOTCH1-4, rearrangements of NTRK1-3 ROS1, ALK, BRAF, RSPO2/3 and FGFR1-3, and alteration in protein expression of PTEN, or overexpression of PDL1, CEA and FAP.
- Funding for a program to explore primary and acquired resistance to targeted therapies. This project integrates patient-derived xenografts and the analysis of next-generation sequencing of multiple tissue samples and circulating-free tumor DNA. In collaboration with VHIO's Ana Vivancos, Violeta Serra, Héctor G. Palmer and Joaquín Arribas, we are focusing on the fibroblast growth factor and the WNT pathway.
- Co-development of molecular tests for patient screening (disease-oriented mutation panels for NGS platforms and Nanostring nCounter).
- Funding for the first module of the Basket of Baskets (BoB) study, fully endorsed by the Cancer Core Europe Consortium, to assess the value of checkpoint inhibition in molecularly selected populations.
- We also received funding to perform the 360° Resistance in ImmunoOncology Project (360RIO) for the evaluation of mechanisms of resistance to immune therapy. We perform NGS, RNA seq, TIL expansion and TC line establishment from tumor biopsies in patients receiving immune therapy.
- 2017 launch of the VHIO-BBVA Foundation Comprehensive Program of Cancer Immunotherapy & Immunology in collaboration with Memorial Sloan Kettering Cancer Center.
- VHIO received a Health Innovation Five 'HI-5' Award from the European Alliance for Personalised Medicine (EAPM) under the category of *Best EU-based hospital for integrating personalised cancer medicine.*

Director of Clinical Research at VHIO
Josep Tabernero

Principal Investigator,
Early Clinical Drug Development Group
Executive Director, UITM
Elena Garralda

Associate Investigators
Senior Consultants
Judith Balmaña
Joan Carles
Enriqueta Felip
Teresa Macarulla
Ana Oaknin
Cristina Saura

Phase I Investigators
Maria Alsina
Guillermo Argilés
Analía B. Azaro
Irene Braña
Marta Capelan
Cristina Cruz
Maria Elena Élez
Santiago Ignacio Escrivá
Lorena Fariñas
Patricia Gómez
Jorge Hernando
Cinta Hierro
Juan Jesús Martín Liberal
Ignacio Matos
Alex Martínez
Rafael Morales
Eva Muñoz
Alejandro Navarro
Alba Noguerido
Maria Ochoa de Olza
Mafalda Oliveira
Nuria Pardo
Maria Coral Perez
Jordi Remon
Víctor Rodríguez
Enrique Sanz
Tamara Saurí
César Serrano
Cristina Suarez
Helena Verdaguer
Maria Vieito
Esther Zamora

## Summary:

We focus on proof-of-concept and proof-of-mechanism trials with targeted therapies with special emphasis on cell signaling, cancer stem cells, and immuno-oncology. These include first-in-human studies of targeted therapies, rational combinations of targeted therapies, biomarker-driven trials, and studies in molecularly selected populations.

We link clinical research at the UITM with different areas of investigation carried out at VHIO, following a truly translational model. For selected projects, we match molecular biology and optimal tumor models with pharmacology and innovative clinical research by involving VHIO scientists in our trials (biomarker development, profound understanding of mechanisms of action and resistance).

We have collaborated with VHIO's Molecular Oncology and Cancer Genomics Groups, led by Paolo Nuciforo and Ana Vivancos respectively, to perform molecular analysis of patients' tumors. This enables us to select the optimal treatment for our patients with the experimental therapies available in our portfolio of clinical trials.

Importantly, in relation to precision oncology, VHIO is a founding member of both the WIN (Worldwide Innovative Networking in personalized cancer medicine), and the Cancer Core Europe Consortia. Both are non-governmental organizations that connect international (WIN) and/or European (CCE) cancer centers including VHIO to advance cancer diagnostics and therapeutics.

This year, our group and VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", have led the design the Basket of Baskets (BoB) trial. This academic study and endorsed by Cancer Core Europe will integrate molecular prescreening, the development of new diagnostic tests such as circulating DNA, with the assessment of targeted therapies in populations of patients who, matched to specific molecular alterations, will be most likely to benefit from these treatments. The protocol of its first module, to be supported by a pharmaceutical company, was approved this year. It will be sent to the relevant authorities next year and first patient enrolment is envisaged towards the end of 2018.

We are expanding our expertise in immuno-oncology with a large portfolio of trials covering some of the most promising targets in immune checkpoints and cytokines. We are also converging immuno-oncology and genomics to further enhance and expand precision medicine against cancer, and initiating a working group focused on epigenetics.

Our Early Drug Development Group and the Phase I Unit (UITM) continue to establish VHIO as a leading reference in driving drug development and targeted therapies in oncology. Testament to this is the number of patients who entrust us with their care (445 patients enrolled in phase I and basket studies in 2017), the portfolio of different trials available (120 phase I trials and 17 basket studies in 2017), and the novelty of our programs in precision medicine and immunotherapy drug development. This is also evidenced by our leading role in Cancer Core Europe's Clinical Trials Task Force.

We have also fostered important alliances with the pharmaceutical industry (5 active and many more currently under evaluation), other clinical research organizations and academic centers of excellence, as well as several companies dedicated to advancing personalized cancer medicine and care.

## PI paper pick:

Shaw AT, Felip E, Bauer TM, Besse B, Navarro A, Postel-Vinay S, Gainor JF, Johnson M, Dietrich J, James LP, Clancy JS, Chen J, Martini JF, Abbattista A, Solomon BJ. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol.* 2017 Dec;18(12):1590-1599.

Ott PA, Elez E, Hiret S, Kim DW, Morosky A, Saraf S, Piperdi B, Mehnert JM. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study. *J Clin Oncol.* 2017 Dec 1;35(34):3823-3829.

Hierro C, Alsina M, Sánchez M, Serra V, Rodon J, Tabernero J. Targeting the fibroblast growth factor receptor 2 in gastric cancer: promise or pitfall? *Ann Oncol.* 2017 Jun 1;28(6):1207-1216.

Martin- Liberal J, Ochoa de Olza M, Hierro C, Gros A, Rodon J, Tabernero J. The expanding role of immunotherapy. *Cancer Treat Rev.* 2017 Mar;54:74-86.

Clinical Research

# Gastrointestinal & Endocrine Tumors Group

## Strategic goals:

- Discovery and validation of novel biomarkers in gastrointestinal tumors.
- Development of relevant preclinical models *in vitro* and *in vivo* with emphasis on the identification of predictive markers.
- Molecular characterization of GI diseases: i.e. colorectal, gastric, pancreatic, biliary tract cancers. Study of targetable subtypes.
- Early clinical research with innovative targets.
- Clinical research in late stage with more translational endpoints, focusing on the identification of prognostic/ predictive biomarkers.
- Design and leadership of investigator initiated trials (IIT), including Basket studies.
- Participation in multidisciplinary/multinational consortia and collaborative research programs of excellence.
- Validation of repurposed drugs or candidate drugs, in partnership with pharma companies or academic groups.
- Expansion of our collaboration with other VHIO teams (Tumor Biomarkers, Cancer Genomics, and Stem Cells & Cancer Groups) and research institutions including the Catalan Institute of Oncology (ICO).
- Expansion of research lines in GI cancers including the study of microbiota & immunology/ immunotherapy.

## Highlights:

- Early drug development and Phase I clinical trials in solid tumors with particular emphasis on developing molecular targeted therapies.
- Molecular markers in gastrointestinal malignancies: we have significantly contributed to advancing insights into prognostic and predictive factors for response and efficacy with targeted agents across various gastrointestinal malignancies.
- The design of investigator initiated trials as well as participation in several studies developed in collaboration with national and international cooperative groups (Symo04), as well as academic collaborative studies including research focused on *Fusobacterium* and colorectal cancer.
- Participation in ongoing EU Horizon 2020-funded projects, MoTriColor and IntraColor, as Principal Investigators.
- Our group is partner of many national and international consortia and networks including Cancer Core Europe, WIN and CIBERONC.

Director
Josep Tabernero

Principal Investigator
Teresa Macarulla

Medical Oncologists and Clinical Fellows
Maria Alsina
Guillermo Argilés
Jaume Capdevila
Maria Elena Élez
Jorge Hernando
Ignacio Matos
Nuria Mulet
Alba Noguerido
Fabricio Eugenio Racca
Enrique Sanz
Tamara Saurí
Helena Verdaguer

Translational Investigator
Rodrigo A. Toledo

Clinical Nurse Specialist
Ariadna Garcia

Masters Student
Giulia Martini

Bioinformatician
Pol Cusco

## Summary:

In 2017, we have led and participated in several cooperative and singular research projects in gastrointestinal malignancies in addition to our key participation in existing international consortia of excellence including Cancer Core Europe, the WIN Consortium and EU FP7/H2020 supported studies (see pages 140-143).

Concerning the EU Horizon 2020 supported MoTricolor Consortium, coordinated by VHIO, I am pleased to report that the prescreening of patients commenced in 2017 and enrolment in the three clinical trials with different treatment strategies against the molecularly defined subtypes of colorectal cancer begins in 2018.

For the first time, patients will be stratified based on their gene expression profiles according to recently established predictive signatures, and we will seek to identify sensitivity of individual patients to the proposed experimental therapies. Additionally, comprehensive translational research will be performed using MoTriColor patients' samples through the INTRACOLOR project (supported by EU H2020's TRANSCAN-2 ERA NET), which is also coordinated by VHIO.

Reflected by publications in the most prestigious scientific titles in 2017, our group has also directed and collaborated in studies with important clinical implications, just some of which include:

**Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer. Bullman S et al.** *Science*. 2017 Dec 15;358(6369):1443-1448.

This seminal study showed that the colonization of human colorectal cancer (CRC) with *Fusobacterium* and its associated microbiome is found in primary tumors and persists in liver metastases. Findings also revealed that it survives through the multiple generation of PDX and that treating mice bearing bacterium-positive models with metronidazole significantly decreases tumor growth.

These observations suggest that this bacterium is more than a mere bystander of tumorigenesis. It could in fact be a driver of metastases and selective antimicrobial therapy could therefore represent important weaponry for the treatment of patients with *Fusobacterium*-associated CRC.

**HELOISE: Phase IIIb Randomized Multicenter Study Comparing Standard-of-Care and Higher-Dose Trastuzumab Regimens Combined With Chemotherapy as First-Line Therapy in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma.** Shah MA et al. *J Clin Oncol*. 2017 Aug 1;35(22):2558-2567.

This multicenter and international study was designed to compare standard-of-care trastuzumab combined with chemotherapy with higher-dose trastuzumab plus chemotherapy. Co-authors assessed whether higher-dose trastuzumab increases trastuzumab serum trough concentration levels and increases overall survival (OS) in first-line human epidermal growth factor receptor 2-positive metastatic gastric or gastroesophageal junction adenocarcinoma.

Findings showed that increased trastuzumab maintenance dosing was associated with higher trastuzumab concentrations, no increased efficacy, and no new safety signals. HELOISE confirms standard-dose trastuzumab with chemotherapy as the standard of care for the first-line treatment of human epidermal growth factor receptor 2-positive metastatic gastric or gastroesophageal junction adenocarcinoma.

**Prognostic and Predictive Relevance of Primary Tumor Location in Patients With RAS Wild-Type Metastatic Colorectal Cancer: Retrospective Analyses of the CRYSTAL and FIRE-3 Trials.** Tejpar S et al. *JAMA Oncol*. 2017 3:194-201.

My third pick of our group's papers for 2017 is a study that was designed to evidence the prognostic and predictive value of primary tumor location in patients with RAS wild-type (RAS wt) metastatic colorectal cancer (mCRC) treated with first-line combination fluorouracil, leucovorin, and irinotecan (FOLFIRI) chemotherapy plus cetuximab in the *Cetuximab Combined With Irinotecan in First-line Therapy for Metastatic Colorectal Cancer* (CRYSTAL), and *FOLFIRI Plus Cetuximab Versus FOLFIRI Plus Bevacizumab as First-Line Treatment For Patients With Metastatic Colorectal Cancer* (FIRE-3) trials.

In the RAS wt populations of CRYSTAL and FIRE-3, patients with left-sided tumors had a markedly better prognosis than those with right-sided tumors. The pairing of First-line FOLFIRI with cetuximab showed clinical benefit in patients with left-sided tumors (vs FOLFIRI or FOLFIRI plus bevacizumab, respectively), while those patients with right-sided tumors derived limited benefit from standard therapies.

In our efforts to advance insights into the heterogeneity of metastatic colorectal cancer and better tackle the distinct molecular makeup of primary tumors arising from different regions of the colon, this study represents an important forward step by describing how primary tumor location impacts prognosis and response to therapy in patients with metastatic disease.

**Effect of Fluorouracil, Leucovorin, and Oxaliplatin With or Without Onartuzumab in HER2-Negative, MET-Positive Gastroesophageal Adenocarcinoma: The METGastric Randomized Clinical Trial.** Shah MA et al. *JAMA Oncol*. 2017 May 1;3(5):620-627.

In the current era of precision medicine we must continue to assess and compare outcomes of novel combinations paired with standard treatments in our collective quest to improve response to therapy and halt metastatic spread. This collaborative phase III METGastric study assessed the combination of the MET inhibitor onartuzumab with standard first-line chemotherapy for human epidermal growth factor receptor 2 (HER2)-negative, MET-positive, advanced gastroesophageal adenocarcinoma (GEC), a tumor type with a typically poor prognosis.

Results revealed that the addition of onartuzumab to the mFOLFOX6 combination chemotherapy regimen, compared with mFOLFOX6 plus placebo, did not improve clinical benefit in the selected population. Subgroup analysis suggests non-Asian patients and patients without prior gastrectomy may stand to benefit. Additional studies may therefore establish the role of the MET pathway in GEC and thus ultimately represent an important forward step in improving outcomes for these patients.

**A phase Ib dose-escalation study of encorafenib and cetuximab with or without alpelisib in metastatic BRAF-mutant colorectal cancer.** Van Geel RM et al. 2017. *Cancer Discov.* 7: 610-619.

Speaking of combinations, results from this study, timed to coincide with the 2017 Annual Meeting of the American Association for Cancer Research (AACR), showed the promise of combining encorafenib with cetuximab, with or without alpelisib as a strategy against metastatic BRAF-mutant metastatic colorectal cancer (mCRC).

Both pairings demonstrated efficacy and acceptable safety profiles, with similar overall response rates: 19% in the dual and 18%in the triple combination group. In our efforts to suppress MAPK signalling and halt tumor growth in this difficult-to-treat population, these findings promise a new therapeutic avenue towards improving outcomes for patients.

As documented throughout this year's Report, 2017 has celebrated important updates concerning VHIO's various partnerships at national and international levels as well as the launch of new initiatives. To name but two:

Based on the successes marked to-date our CIBOT Program (Translational Biomedical and Oncological Research Consortium) supported by the pharmaceutical company Novartis has for the fourth time been renewed. Under the acronym SCITRON, this edition will focus on two subprojects:

Immunotherapy and early stage development: Translational study in patients accessing novel immunotherapy regimens at our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa".

Colorectal cancer: Comprehensive genomic study in blood by liquid biopsy in samples from patients with this tumor type.

This agreement will certainly contribute to fortifying our determined efforts aimed at developing liquid biopsy as a clinically tried and tested approach for the more effective, less invasive 'policing' of cancer over time, in real time.

Additionally, as a direct reflection of our expertise in developing liquid biopsy at clinical level, driven in collaboration with our Cancer Genomics Group, VHIO counted two out of the five projects selected under the TRANSCAN Joint Translational Call on *Minimally and non-invasive methods for early detection and/or progression of cancer*.

Awarded by the Spanish Association against Cancer (AECC) and the Institute of Health Carlos III (ISCIII) through the ERA-NET TRANSCAN-2 program funded by EU's Horizon 2020, one of VHIO's two TRANSCANs focuses on the early detection of relapse in advanced colon cancer patients by longitudinally following a personalized molecular signature by liquid biopsy. This proof-of-concept, prospective and multi-center study seeks to evaluate the clinical feasibility of tracking tumor progression by dynamically detecting a molecular signature from a blood test. As an innovative approach for the early detection of disease relapse, this project represents an important next step in more accurately monitoring cancer's next moves.

## PI paper pick:

Bullman S, Pedamallu CS, Sicinska E, Clancy TE, Zhang X, Cai D, Neuberg D, Huang K, Guevara F, Nelson T, Chipashvili O, Hagan T, Walker M, Ramachandran A, Diosdado B, Serna G, Mulet N, Landolfi S, Ramon Y Cajal S, Fasani R, Aguirre AJ, Ng K, Élez E, Ogino S, Tabernero J, Fuchs CS, Hahn WC, Nuciforo P, Meyerson M. Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. *Science*. 2017 Dec 15;358(6369):1443-1448.

Shah MA, Xu RH, Bang YJ, Hoff PM, Liu T, Herráez-Baranda LA, Xia F, Garg A, Shing M, Tabernero J. HELOISE: Phase IIIb Randomized Multicenter Study Comparing Standard-of-Care and Higher-Dose Trastuzumab Regimens Combined With Chemotherapy as First-Line Therapy in PatientsWith Human Epidermal Growth Factor Receptor 2-Positive Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma. *J Clin Oncol*. 2017 Aug 1;35(22):2558-2567.

Shah MA, Bang YJ, Lordick F, Alsina M, Chen M, Hack SP, Bruey JM, Smith D, McCaffery I, Shames DS, Phan S, Cunningham D. Effect of Fluorouracil, Leucovorin, and Oxaliplatin With or Without Onartuzumab in HER2-Negative, MET-Positive Gastroesophageal Adenocarcinoma: The METGastric Randomized Clinical Trial. *JAMA Oncol*. 2017 May 1;3(5):620-627.

Tejpar S, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F, Esser R, Lenz HJ, Heinemann V. Prognostic and Predictive Relevance of Primary Tumor Location in Patients With RAS Wild-TypeMetastatic Colorectal Cancer: Retrospective Analyses of the CRYSTAL and FIRE-3 Trials. *JAMA Oncol*. 2017 3:194-201.

# Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site Group

## Strategic goals:

- Design and develop clinical trials covering all malignancies studied by our group. We strive to provide our patients with the most novel and optimal treatments including immune-based therapeutics, targeted therapies and new chemotherapies.
- Conduct clinical trials at different stages of disease with emphasis on a histology-tailored design and multidisciplinary approach.
- Develop new approaches including liquid biopsies for our patients in order to more precisely tailor treatments against CRPC, GIST and kidney cancer.
- Consolidate our biopsy program (mainly in bone), for patients with CRPC to target main genomic alterations including PI3K pathways, DNA repair genes, and androgen receptor alterations.
- Further consolidate our Prostate Cancer Task Force at VHIO and the Vall d'Hebron Research Institute (VHIR).
- Expand our translational research platform for glioblastoma in collaboration with VHIO's Gene Expression & Cancer Group.
- Create a translational platform for kidney cancer and sarcomas and basic research in partnership with the Biomedical Research Institute of Bellvitge (IDIBELL).
- Set up a translational platform for GIST and expand research in collaboration with the Spanish Sarcoma Group (GEIS), and other European referral centers.

## Highlights:

- New cancer medicines against GU malignancies: we have participated in important trials with different drugs (ODM 201; combination of abiraterone acetate with or without radium 223, PARP inhibitors), that have shown promise in improving outcomes for patients with prostate cancer. We are also participating in pioneering clinical studies with BET inhibitors and immune checkpoint inhibitors.
- Other GU malignancies (renal and bladder): we are involved in clinical trials to evidence the utility of novel agents in modulating the host immune response against cancer (PD-1 and PDL-1) in first and second line treatment. These agents may be administered alone or in combination with other targeted therapies or chemotherapeutics.
- Central Nervous System (CNS) tumors: research has expanded with the development of additional clinical trials and the creation of a tumor board comprised of experts in neurosurgery, radiology, radiotherapy, translational research, and medical oncology.
- Sarcoma: we are developing new therapies for liposarcomas (MDM2 inhibitors), and GIST.

Principal Investigator
Joan Carles

Medical Oncologists
and Clinical Fellows
Rafael Morales
Fabricio Eugenio Racca
Jordi Rodón
César Serrano
Cristina Suarez
Claudia Valverde

## Summary:

Our group is dedicated to both clinical and translational research, and has broad experience and grounded expertise in the treatment of various neoplasms. We design and develop clinical trials for genitourinary malignancies at different stages of disease in collaboration with urologists and radiation therapists. During 2017 we set up our Prostate Task Force. By closely connecting clinical and translational researchers at VHIO and the Vall d'Hebron Research Institute (VHIR), we are now initiating translational projects focused on these tumors. We will aim to extend our efforts to other malignancies studied by our group.

Over recent years, many developments have been reported in GU malignancies; in prostate, bladder, and kidney cancer in particular. Immunotherapy is proving increasingly important in the treatment of bladder and kidney cancer, and in 2017 we observed that it could also be important in the treatment of certain subgroups of patients with castration-resistant prostate cancer. Our group has participated in various clinical trials using checkpoint inhibitors that have changed the standard treatment for second line metastatic bladder cancer and first line metastatic kidney cancer. Close connectivity with all specialists involved in the treatment of these tumors is consequently paramount.

We also continue to develop our translational research platform for urologic cancer, as well as conduct clinical trials in early, adjuvant as well as metastatic disease. Our group collaborates with other research centers of excellence including the Cleveland Clinic (Ohio, USA), University of California, San Francisco (California, USA). We also work on clinical studies carried out in partnership with the Gustave Roussy Institute (Paris, France), Barts Hospital (London, UK), Kantonsspital St. Gallen (Switzerland), as well as the Biomedical Research Institute of Bellvitge - IDIBELL (Barcelona, Spain).

Throughout 2017, we have consolidated our translational research program with the establishment of a new research group at VHIO. Our Prostate Cancer Translational Research Group (see pages 120-121 of this Scientific Report), led by Principal Investigator Joaquin Mateo (MD trained at the in the Institute of Cancer Research – Royal Marsden NHS Foundation Trust, London, UK), will focus on metastatic castration-resistant prostate cancer.

His group will aim to refine a predictive biomarker suite for DNA repair targeting agents in metastatic prostate cancer. Research will center on how AR and TP53 status modulate the functional impact of DNA repair gene mutations, and how these factors determine tumor drug sensitivity. Joaquin will also establish a platform for systematic metastatic tissue acquisition from prostate cancer patients at VHIO.

We have also expanded our avatar program for kidney cancer tumors in collaboration with IDIBELL and have now implanted more than 25 samples. Additionally, we are partner of REVOLUTION: *pREdiction of niVOLUmab acTION metastatic renal cancer patients: Treg function, tumoral access and NK interactions as predictive biomarkers of immunotherapy,* funded by TRANSCAN-2 ERA-NET, under the EU framework programme Horizon 2020.

In addition, our group develops several multidisciplinary clinical studies and phase I trials in CNS tumors, in close connectivity with other professionals in neurosurgery and radiation therapy.

In collaboration with VHIO's Gene Expression & Cancer Group led by Joan Seoane, Director of Translational Research at our Institute, we are expanding our translational research platform for glioblastoma. We are working with different centers across Europe to develop a vaccine for patients with glioblastoma, and are now initiating the Phase I program. This project is supported by the European Commission's 7th Framework Programme of Research and Development. We also received a national grant to analyze cfDNA in blood and cephaloraquidic liquid for the analysis of primary CNS tumors and metastases.

We also work closely with the Spanish Sarcoma Group (GEIS) to conduct clinical trials at different stages of disease with emphasis on a histology-tailored design and are currently setting up a translational platform for sarcomas and basic research in partnership with IDIBELL and the Cancer Research Center of Salamanca - CIC (Spain). For GIST tumors we are working with J. Fletcher's lab at the Brigham and Women's Hospital (Boston, USA). One of our group members, César Serrano, who carried out a three-year fellowship at the Dana Farber Cancer Institute (Boston), has established an independent line of experimental research focused on sarcomas. Importantly, his translational studies have led to new treatment strategies in sarcoma, including the design of a phase Ib clinical trial to assess, for the first time in oncology, a rapid-alternation drug schedule of targeted therapies (NCT02164240). We are also currently developing novel strategies in GIST therapy in partnership with other referral centers across Europe and pharmaceutical companies.

Our Serum Bank now includes the majority of our tumor types (CNS tumors, GIST; renal cell carcinoma and CRPC), and we will continue to recruit samples from our patients. Dedicated to promoting education and exchange, in 2017 we welcomed five fellows from in and outside of Spain for three-month short stay visits.

## PI paper pick:

Eisenberger M, Hardy-Bessard AC, Kim CS, Géczi L, Ford D, Mourey L, Carles J, Parente P, Font A, Kacso G, Chadjaa M, Zhang W, Bernard J, de Bono J. Phase III Study Comparing a Reduced Dose of Cabazitaxel (20 mg/m2) and the Currently Approved Dose (25 mg/m2) in Postdocetaxel Patients With Metastatic Castration-Resistant Prostate Cancer-PROSELICA. *J Clin Oncol.* 2017 Oct 1;35(28):3198-3206.

García-Donas J, Font A, Pérez-Valderrama B, Virizuela JA, Climent MÁ, Hernando-Polo S, Arranz JÁ, Del Mar Llorente M, Lainez N, Villa-Guzmán JC, Mellado B, Del Alba AG, Castellano D, Gallardo E, Anido U, Del Muro XG, Domènech M, Puente J, Morales-Barrera R, Pérez-Gracia JL, Bellmunt J. Maintenance therapy with vinflunine plus best supportive care versus best supportive care alone in patients with advanced urothelial carcinoma with a response after first-line chemotherapy (MAJA; SOGUG 2011/02): a multicentre, randomised, controlled, open-label, phase 2 trial. *Lancet Oncol.* 2017 May;18(5):672-681.

Necchi A, Sonpavde G, Lo Vullo S, Giardiello D, Bamias A, Crabb SJ, Harshman LC, Bellmunt J, De Giorgi U, Sternberg CN, Cerbone L, Ladoire S, Wong YN, Yu EY, Chowdhury S, Niegisch G, Srinivas S, Vaishampayan UN, Pal SK, Agarwal N, Alva A, Baniel J, Golshayan AR, Morales-Barrera R, Bowles DW, Milowsky MI, Theodore C, Berthold DR, Daugaard G, Sridhar SS, Powles T, Rosenberg JE, Galsky MD, Mariani L; RISC Investigators. Nomogram-based Prediction of Overall Survival in Patients with Metastatic Urothelial Carcinoma Receiving First-line Platinum-based Chemotherapy: Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC). *Eur Urol.* 2017 Feb;71(2):281-289.

Saura C, Roda D, Roselló S, Oliveira M, Macarulla T, Pérez-Fidalgo JA, Morales-Barrera R, Sanchis-García JM, Musib L, Budha N, Zhu J, Nannini M, Chan WY, Sanabria Bohórquez SM, Meng RD, Lin K, Yan Y, Patel P, Baselga J, Tabernero J, Cervantes A. A First-in-Human Phase I Study of the ATP-Competitive AKT Inhibitor Ipatasertib Demonstrates Robust and Safe Targeting of AKT in Patients with Solid Tumors. *Cancer Discov.* 2017 Jan;7(1):102-113.

Clinical Research

# Gynecological Malignancies Group


## Strategic goals:

- Determine the best treatment approaches in advanced gynecologic malignancies through well designed international clinical trials.
- Contribute to early drug development in gynecologic malignancies.
- Build a translational research program to advance precision medicine.

## Highlights:

- As a result of our clinical research of excellence, we continue to lead pivotal studies in gynecological malignancies which could potentially change the standard of care.
- As lead investigator for GOG in Spain, our group is heading a Phase III clinical trial in advanced cervical cancer with a novel vaccine to prevent and/or delay disease recurrence.
- Our involvement in several international cooperative groups of excellence further enables us to participate in outstanding clinical research programs.
- Ana Oaknin's Vice Presidency of the GEICO group. This role has allowed our group to help lead clinical research in gynecological malignancies throughout Spain.
- The involvement of our principal investigator, Ana Oaknin, in ESMO's Educational Program of its next two annual Congresses further reinforces our position within Europe as a reference site.

Principal Investigator
Ana Oaknin

Medical Oncologists and Clinical Fellows
Lorena Fariñas
Jose Loureiro
Maria Roca
Víctor Rodríguez

Clinical Nurse Specialist
Cristina Casal

## Summary:

Our group focuses on clinical research in gynecological malignancies and the development of novel therapies against these tumors. Notably, over the past few years, our clinical studies have led to the approval of a new standard of care in both resistant relapsed ovarian cancer (e.g. the AURELIA Trial), and metastatic cervical cancer (e.g. GOG240 trial). Our research has led to important advancements throughout 2017. Of particular reference has been our involvement in the development of Rucaparib.

Rucaparib belongs to the family of novel agents known as PARP inhibitors and has recently been approved by the FDA for patients with ovarian cancer with BRCA mutations, and we are now focused on obtaining this same approval in Europe. Importantly, most of our clinical research is carried out in close collaboration and connectivity with other international research groups of excellence.

To further develop PARP inhibitors, we aim to identify resistance mechanisms to these agents. This important research is being performed using patient-derived xenograft models (PDX). We obtain biopsies from patients for whom the agents are no longer active and through ex vivo implantation in mice, we will analyze their molecular characteristics and test new drugs that may overcome primary resistance.

We are also actively working on the development of immunotherapeutic agents for patients with gynecologic tumors, and are involved in Phase I studies to test the efficacy and toxicity profile in a particular subgroup of gynecological tumors, namely, endometrial cancer. Therapeutic options for patients diagnosed with relapsed endometrial cancer are currently limited. The emerging suite of novel immunotherapeutics is opening up new treatment opportunities.

As part of an international collaboration, we will also be pioneering cellular therapy for patients with metastatic and/or recurrent cervical cancer. Adoptive cell transfer of tumor infiltrating lymphocytes (TILs) represents a potentially effective treatment for patients with cervical cancer. This method involves the recovery and ex vivo expansion of autologous antitumor lymphocytes that have infiltrated a patient's tumor. TILs isolated from human cervical tumors and expanded ex vivo have shown anti-tumor activity. Preliminary data from this therapeutic approach show great promise and VHIO will play an active role in developing this adoptive therapy for our young patients with cervical cancer.

We are active members of some of the most relevant societies in gynecological oncology including the Gynecologic Cancer Inter Group (GCIG), for which we are appointed as the Spanish Representative on the Cervical Cancer Committee, the Gynecologic Oncology Group (GOG), as Spanish Clinical Lead, as well as the European Network of Gynecological Oncology Trial Groups (ENGOT). Our group's Principal Investigator, Ana Oaknin, serves on the Executive Board as Vice President for the *Grupo Español de Investigación en Cáncer de Ovario* - GEICO (Spanish Gynecological Group). These roles enable us to initiate the development of new drugs and novel treatment approaches from the very outset, providing our patients with greater opportunity to potentially benefit from these advances in cancer therapeutics.

In addition, Víctor Rodriguez-Freixinos as a senior staff Medical Oncologist of the Gynecologic Cancer and Drug Development Program at the Vall d'Hebron University Hospital, (Vall d'Hebron Barcelona Hospital Campus), has been appointed as member of GEICO's Scientific Committee and its representative in the ENGOT Rare Tumor Group initiative.

It is thanks to our expanding clinical research of excellence that we are potentiating more effective therapies for the treatment and management of gynecological tumors. As a renowned leader within the field, we are also the Reference Site for the majority of regional hospitals and sites at national level. This has consequently led to a steady increase in the number of patients treated with new therapies enrolled in our clinical trials and, most importantly, provided new hope for these patients.

In parallel, we are key members of multidisciplinary committees and teams in gynecological tumors at the Vall d'Hebron University Hospital (HUVH). Our involvement, in partnership with other professionals and specialties (including surgeons, radiotherapists, radiologists, and pathologists), leads to new treatment protocols and clinical guidelines to further improve clinical practice at our hospital.

Moreover, over the past year, we have established a regional collaborative group – our Gynecologic Task Force. This team is composed of a variety of disciplines involved in gynecological tumors. We currently count on the expertise of a pathologist, gynecologist, genetic counselors and a medical oncologist from the Hospitals of the Catalan Institute of Oncology (ICO), and VHIO. The aim of this group is to exchange experiences, share expertise and collectively develop clinical research projects.

We are continuously invited to participate at international conferences of excellence through the delivery of presentations, invited lectures, and the sharing of our latest findings with colleagues and peers at the most prestigious oncology meetings across the globe.

Our group's Principal Investigator, Ana Oaknin, is currently Faculty Member of the Education Program for the Gynecologic Tumors Track for the forthcoming 2018 Congress of the European Society for Medical Oncology (ESMO), 19 – 23 October, Munich, Germany, and has been appointed as Chair, Gynecological Cancers, for ESMO's 2019 Congress, 27 September – 01 October, Barcelona, Spain.

## PI paper pick:

Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, Colombo N, Weberpals JI, Clamp A, Scambia G, Leary A, Holloway RW, Gancedo MA, Fong PC, Goh JC, O'Malley DM, Armstrong DK, Garcia-Donas J, Swisher EM, Floquet A, Konecny GE, McNeish IA, Scott CL, Cameron T, Maloney L, Isaacson J, Goble S, Grace C, Harding TC, Raponi M, Sun J, Lin KK, Giordano H, Ledermann JA; ARIEL3 investigators. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2017 Oct 28;390(10106):1949-1961

Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM, Landrum LM, Oaknin A, Reid TJ, Leitao MM, Michael HE, DiSaia PJ, Copeland LJ, Creasman WT, Stehman FB, Brady MF, Burger RA, Thigpen JT, Birrer MJ, Waggoner SE, Moore DH, Look KY, Koh WJ, Monk BJ. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet.* 2017 Oct 7;390(10103):1654-1663.

Swisher EM, Lin KK, Oza AM, Scott CL, Giordano H, Sun J, Konecny GE, Coleman RL, Tinker AV, O'Malley DM, Kristeleit RS, Ma L, Bell-McGuinn KM, Brenton JD, Cragun JM, Oaknin A, Ray-Coquard I, Harrell MI, Mann E, Kaufmann SH, Floquet A, Leary A, Harding TC, Goble S, Maloney L, Isaacson J, Allen AR, Rolfe L, Yelensky R, Raponi M, McNeish IA. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2017 Jan;18(1):75-87.

Oaknin A, Guarch R, Barretina P, Hardisson D, González-Martín A, Matías-Guiu X, Pérez-Fidalgo A, Vieites B, Romero I, Palacios J. Recommendations for biomarker testing in epithelial ovarian cancer: a National Consensus Statement by the Spanish Society of Pathology and the Spanish Society of Medical Oncology. *Clin Transl Oncol.* 2017 Aug 16.

Clinical Research

# High Risk & Cancer Prevention Group

## Strategic goals:

- Clinical development of specific therapeutic strategies for tumors associated with hereditary genetic alterations.
- Testing new combinations of therapies for BRCA-associated PDXs that have progressed to PARP inhibitors.
- Identification of new genes involved in hereditary breast cancer through the application of next generation sequencing (NGS).
- The yield of multigene panel testing in hereditary cancer syndromes and its impact on patient care.
- Psychological impact of hereditary cancer multiplex gene testing in the Spanish population.

## Highlights:

- Active participation in international phase II and phase III clinical trials with targeted therapies for BRCA-associated tumors.
- Identification of a functional biomarker of homologous recombination deficiency and PARPi sensitivity in preclinical models.
- Analysis of the rate of pathogenic variants in phenotype-driven panels versus core panels in patients with hereditary cancer, the yield of opportunistic testing, and actionability of novel breast and ovarian cancer susceptibility genes.

Principal Investigator
Judith Balmaña

Staff Scientists
Estela Carrasco
Marta Codina
Cristina Cruz
Adriá López
Neda Stjepanovic

Administrative Support
Carmen Aguilar

Clinical Nurse Specialist
Neus Gadea

Data Curator
Sara Torres

## Summary:

We develop novel targeted therapies for patients with breast cancer and a genetic susceptibility. During 2017, patients with local and advanced breast cancer and a BRCA germline mutation participated in several phase II/III trials with a specific DNA binding agent or PARP inhibitor.

The consolidation of our collaboration with VHIO's Experimental Therapeutics Group, led by Violeta Serra, has resulted in a large collection of BRCA-associated patient-derived xenografts (PDX) implanted in athymic mice. We are using these murine models to identify mechanisms of resistance to targeted therapies, identify novel biomarkers and assess new combinatorial treatments at progression. We have focused on identifying a biomarker for PARP inhibitor sensitivity. A functional biomarker of homologous recombination has been tested both preclinically and in human samples, with validation ongoing. Two mechanisms of resistance to PARP inhibitors have been evidenced in our cohort of PDX samples.

In the field of genetic epidemiology, we mainly focus on identifying new genetic susceptibilities to hereditary breast cancer. Analysis of a panel of 98 cancer susceptibility genes in 193 breast and/or ovarian cancer families with no mutation in BRCA1/BRCA2 has been finalized and we have now submitted our findings as a scientific article. We are also committed to performing co-segregation analysis in these families and investigating the cancer spectrum and phenotype of these lesser-known non-BRCA genes.

We have finalized our psychological study of the impact of multigene cancer panel testing in more than 200 centres across Spain (see Figure).

In hereditary colorectal cancer, we are participating in a clinical study led by the EPICOLON group to gauge cancer risk estimates in Lynch Syndrome mutation carriers.

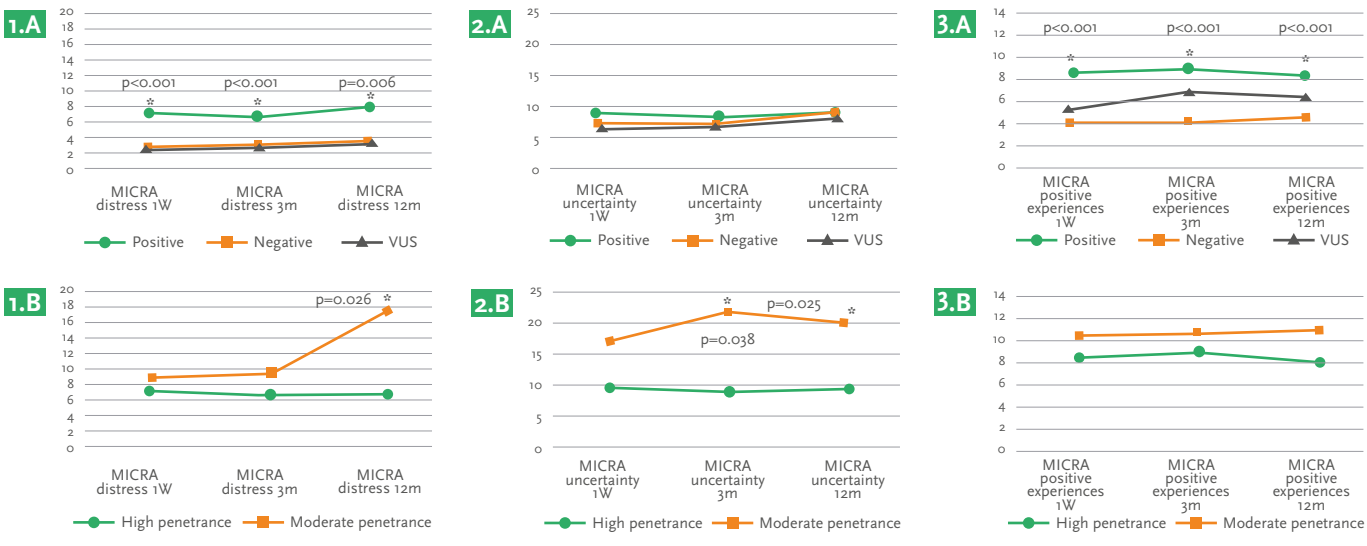



Figure: Psychological impact (MICRA scale) of multi-gene cancer panel testing in patients with a clinical suspicion of hereditary cancer across Spain.

## PI paper pick:

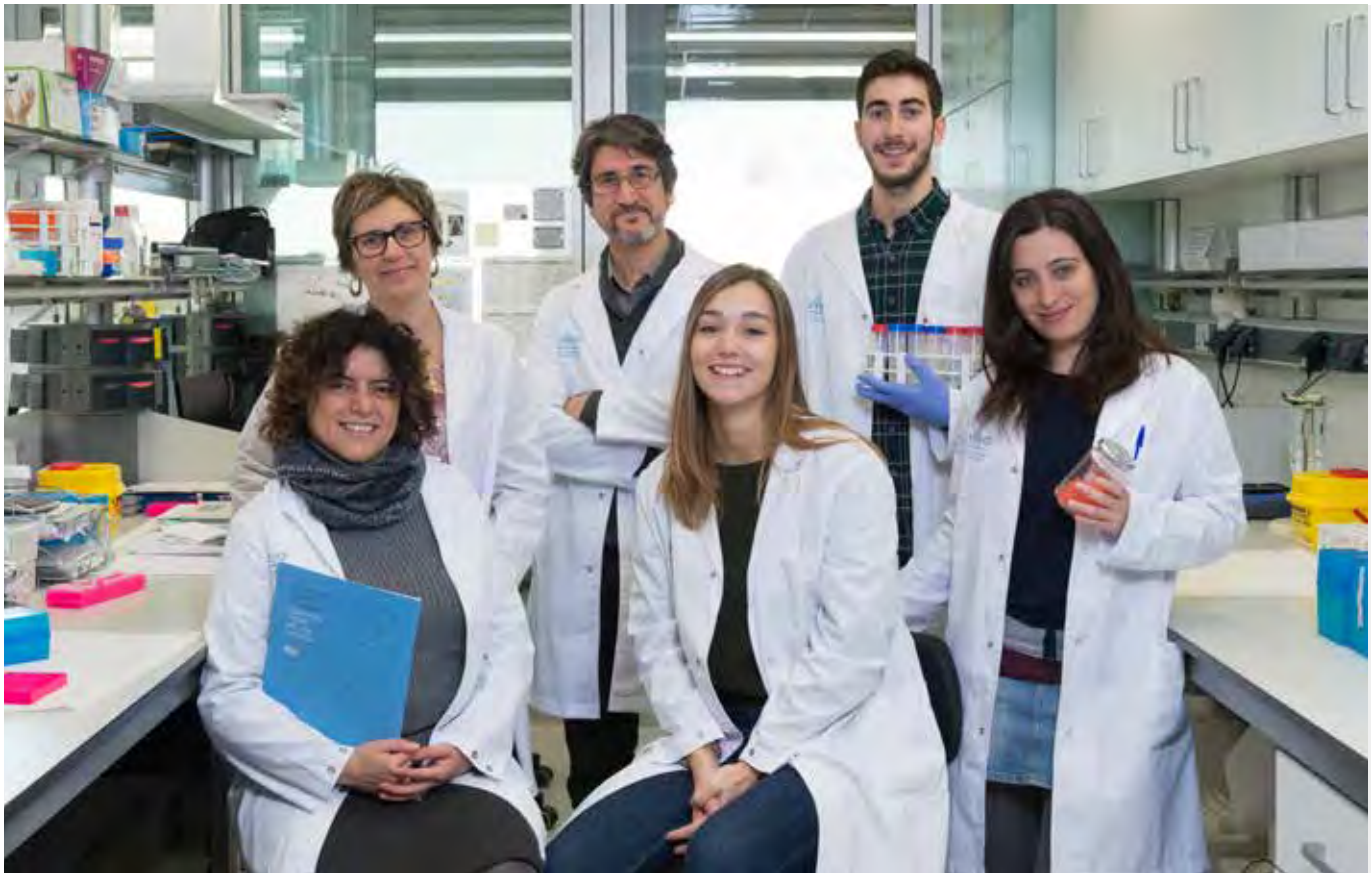
Kristeleit R, Shapiro GI, Burris HA, Oza AM, LoRusso P, Patel MR, Domchek SM, Balmaña J, Drew Y, Chen LM, Safra T, Montes A, Giordano H, Maloney L, Goble S, Isaacson J, Xiao J, Borrow J, Rolfe L, Shapira-Frommer R. A Phase I-II Study of the Oral PARP Inhibitor Rucaparib in Patients with Germline BRCA1/2-Mutated Ovarian Carcinoma or Other Solid Tumors. *Clin Cancer Res.* 2017 Aug 1;23(15):4095-4106.

Esteban-Jurado C, Giménez-Zaragoza D, Muñoz J, Franch-Expósito S, Álvarez-Barona M, Ocaña T, Cuatrecasas M, Carballal S, López-Cerón M, Marti-Solano M, Díaz-Gay M, van Wezel T, Castells A, Bujanda L, Balmaña J, Gonzalo V, Llort G, Ruiz-Ponte C, Cubiella J, Balaguer F, Aligué R, Castellví-Bel S. POLE and POLD1 screening in 155 patients with multiple polyps and eardly-onset colorectal cancer. *Oncotarget.* 2017 April 18:8(16): 26732-26743.

Egoavil C, Juárez M, Guarinos C, Rodríguez-Soler M, Hernández-Illán E, Alenda C, Payá A, Castillejo A, Serradesanferm A, Bujanda L, Fernández-Bañares F, Cubiella J, de-Castro L, Guerra A, Aguirre E, Herreros-de-Tejada A, Bessa X, Herráiz M, Marín-Gabriel JC, Balmaña J, Piñol V, Rodríguez Moranta F, Nicolás-Pérez D, Cuatrecasas M, Balaguer F, Castells A, Soto JL, Zapater P, Jover R. Increased risk of colorectal cancer in patients with multiples serrated polyps and their first-degree relatives. *Gastroenterology.* 2017 Jul; 153(1):106-112

Clinical Research

# Oncogenetics Group



## Strategic goals:

- As member of the Catalan Cancer Network's Hereditary Cancer Program, decipher the spectrum, frequency and clinical actionability of pathogenic variants in cancer predisposing genes in our population.
- Identify new alleles for the genetic predisposition to hereditary cancer.
- Perform expression and functional analysis of genetic variants with unknown clinical significance in familiar cancer predisposition.
- Study genetic variants in regulatory regions of breast/ovarian cancer susceptibility genes that may confer an increased risk.
- Discover common low-penetrance alleles for breast/ovarian cancer risk.
- Analyze *BRCA1/2* tumoral expression in response to therapy.
- Identify cellular and molecular biomarkers for the prediction of late toxicity after radiotherapy.
- Assess the role of microRNAs and long non coding RNAs in the susceptibility to radiotherapy-induced clinical toxicity.

## Highlights:

- Our group has classified genetic variants of unknown clinical significance by expression and functional analyses in the field of hereditary cancer predisposition.
- The massive sequencing of large gene panels and exomes to identify new susceptibility alleles to familial breast/ovarian cancer, and confirmation of candidate genes in collaboration with the COMPLEXO Consortium.
- We have tested the most suitable bioinformatics prediction algorithms to identify splicing variants in familial cancer genes.
- In partnership with the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), we have described new alleles of breast/ovarian cancer susceptibility and modifiers of risk conferred by *BRCA1/2* pathogenic variants.
- We have enrolled breast and lung cancer patients in the European Commission FP7-funded project REQUITE to validate predictive models of toxicity from radiotherapy.
- Our group co-organized and hosted the REQUITE European Project's 5th annual meeting and the 9th Radiogenomics Consortium Meeting, 20-22 June, CELLEX Building, VHIO, Barcelona, with Sara Gutiérrez-Enríquez, Senior Scientist, as Co-Chair.

Principal Investigator
Orland Díez

Senior Scientist
Sara Gutiérrez

Post-Doctoral Fellow
Sandra Bonache

Clinical Nurse Specialist
Bibiana Piqué

Graduate Students
Laura Durán
Alejandro Moles
Gemma Montalban

## Summary:

We focus on two main lines of research: 1) the genetic predisposition to hereditary cancer, and 2) genetic predisposition to radiotherapy-induced toxicity.

Inherited predisposition to breast and ovarian cancer is caused by an expanding list of genes such as *BRCA1, BRCA2, PALB2, RAD51C, RAD51D and TP53*. We search for other alleles and new genes that may predispose to these types of cancer using massive sequencing to analyze panel genes and whole exomes.

Due to high allelic heterogeneity many results from genetic testing are variants with unknown clinical significance (VUS). The analysis of these variants and other alterations in untranslated regions in genes of clinical significance constitutes another major focus of our research.

We carry out splicing studies, *in silico* analyses, and collaborate with other partners in international consortia including the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA), to develop multifactorial studies aimed at ascertaining the effect of VUS. We are also working to establish a biological model derived from the carriers themselves through which to evaluate the *in vitro* functional effect of VUS and determine their potential pathogenicity. In addition, we are testing the most suitable bioinformatics prediction algorithms to select the variants that cause aberrant gene splicing in familial cancer genes.

Similarly, in collaboration with the Vall d'Hebron Research Institute's (VHIR) Translational Bioinformatics Group headed by X. de la Cruz, we participate in the development of a novel *in silico* tool to evaluate the effect of *BRCA1/2* genetic variants identified in patients with cancer predisposition.

As a partner of the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), we collaborate in wide case-control studies to identify low-penetrance alleles and genes that modify penetrance of *BRCA1/2* pathogenic variants.

We also collaborate with VHIO's High Risk & Cancer Prevention and Experimental Therapeutics Groups to analyze the role of expression changes in new or natural *BRCA1* mRNA isoforms as a mechanism of resistance to PARP inhibitors using patient-derived tumor xenografts (PDXs).

Around half of all cancer patients receive radiotherapy and among 3-5% of them suffer from severe long-term side-effects. Current evidence suggests the heritability of radiosensitivity. We are participating in the European Commission FP7-funded REQUITE international study, *Validating Predictive Models and Biomarkers of Radiotherapy Toxicity to Reduce Side-Effects and Improve Quality of Life in Cancer Survivors,* to identify potential genetic and cellular markers for radiotherapy toxicity. As member of the International Consortium of Radiogenomics we perform meta-analysis to confirm the association between different SNPs and toxicity post-radiotherapy.

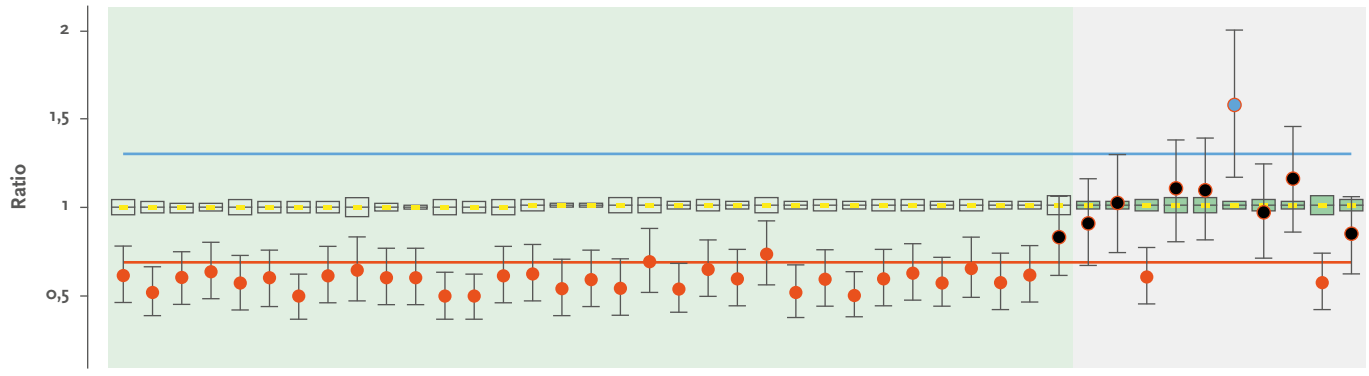



Figure: Identification of allelic loss in *BRCA2* gene in tumoral tissue.

## PI paper pick:

Phelan CM, Kuchenbaecker KB, Tyrer JP, et al. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. *Nat Genet.* 2017 May;49(5):680-691.

Lecarpentier J, Silvestri V, Kuchenbaecker KB, et al. Prediction of Breast and Prostate Cancer Risks in Male BRCA1 and BRCA2 Mutation Carriers Using Polygenic Risk Scores. *J Clin Oncol.* 2017 Jul 10;35(20):2240-2250.

Milne RL, Kuchenbaecker KB, Michailidou K et al. Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer. *Nat Genet.* 2017 Dec;49(12):1767-1778.

Hamdi Y, Soucy P, Kuchenbaeker KB, et al. Association of breast cancer risk in BRCA1 and BRCA2 mutation carriers with genetic variants showing differential allelic expression: identification of a modifier of breast cancer risk at locus 11q22.3. *Breast Cancer Res Treat.* 2017 Jan;161(1):117-134.

Clinical Research

# Oncology Data Science (ODysSey) Group

## Strategic goals:

Facilitate clinical-molecular correlative studies at VHIO:

- Provide guidance to medical oncologists and cancer biologists during the development, validation and interpretation of omics-based tests that have direct clinical application.
- Development and maintenance of clinical-molecular databases as a resource for medical oncologists, molecular pathologists and translational investigators at VHIO.

Promote evidence-based medicine:

- Maintenance of the publicly available cancer bioMarkers database (part of the Cancer Genome Interpreter webtool - https://www.cancergenomeinterpreter.org/home), a structured database that integrates existing knowledge on tumor types, genes, variants, response/resistance patterns to approved and experimental agents, PubMed identifiers and levels-of-evidence for targetability.
- Continued medical education with standardized reports of genomic alterations and weekly molecular tumor boards. We facilitate data exchange among a wide range of experts for the review of patient medical histories and cancer molecular profiles in order to more precisely guide treatment decisions.

## Highlights:

- We have provided support to VHIO's preclinical and clinical investigators working on biomarker research and its implications for patient management. This has resulted in several impactful publications in the field, as well as presentations at leading oncology congresses.
- Throughout 2017 we have explored and developed tools that help translate the strong signals of biological dependencies of colorectal cancer subtypes into druggability in clinical practice. We have also studied the impact of driver gene clonality/subclonality patterns and microenvironment features on prognosis and response to matched targeted and immunotherapies in colorectal cancer.
- Participation in the MedBioinformatics European Consortium: our group has been extensively involved in the development of integrative bioinformatics tools to analyze the huge amount of data and knowledge generated in healthcare and biomedical research in order to advance translational research and precision medicine. Our Cancer Biomarkers database is publicly available and has become a reference for clinical investigators across the globe.

Principal Investigator
Rodrigo Dienstmann

Biostatistician
Guillermo Villacampa

Data Curators
Raquel Comas
Fiorella Ruiz
Sara Torres
Cristina Viaplana

Molecular Prescreening Program
Susana Aguilar

## Summary:

VHIO's ODysSey Group facilitates translational research in precision oncology by integrating latest advances in cancer molecular profiling from patients treated at the Vall d'Hebron University Hospital (HUVH) with their clinical outcome under standard and experimental therapies.

To do so, we design and maintain comprehensive clinical-molecular databases and provide statistical support to investigators interested in correlative analyses for hypothesis-generation and biomarker validation. We also provide standardized reports of next-generation sequencing tests and educate clinicians on the interpretation of these data, thereby offering patients the most appropriate targeted agent and immunotherapy in clinical trials.

Furthermore, we participate in international genomics data sharing projects and foster collaborative research in computational oncology. Our group is dedicated to connecting cancer researchers working on predictive/prognostic modelling, the identification of cancer drivers, intra-tumor heterogeneity, microenvironment signatures and druggability in solid tumors.

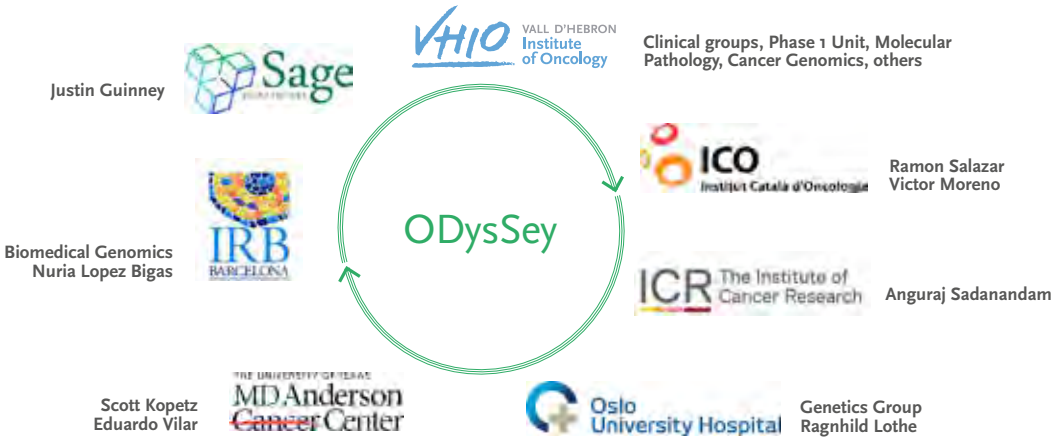



Figure: VHIO's Oncology Data Science (ODysSey) Group's strategic alliances and key collaborations.

## PI paper pick:

Dienstmann R, Vermeulen L, Guinney J, Kopetz S, Tejpar S, Tabernero J. Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. *Nat Rev Cancer.* 2017;7(2):79-92.

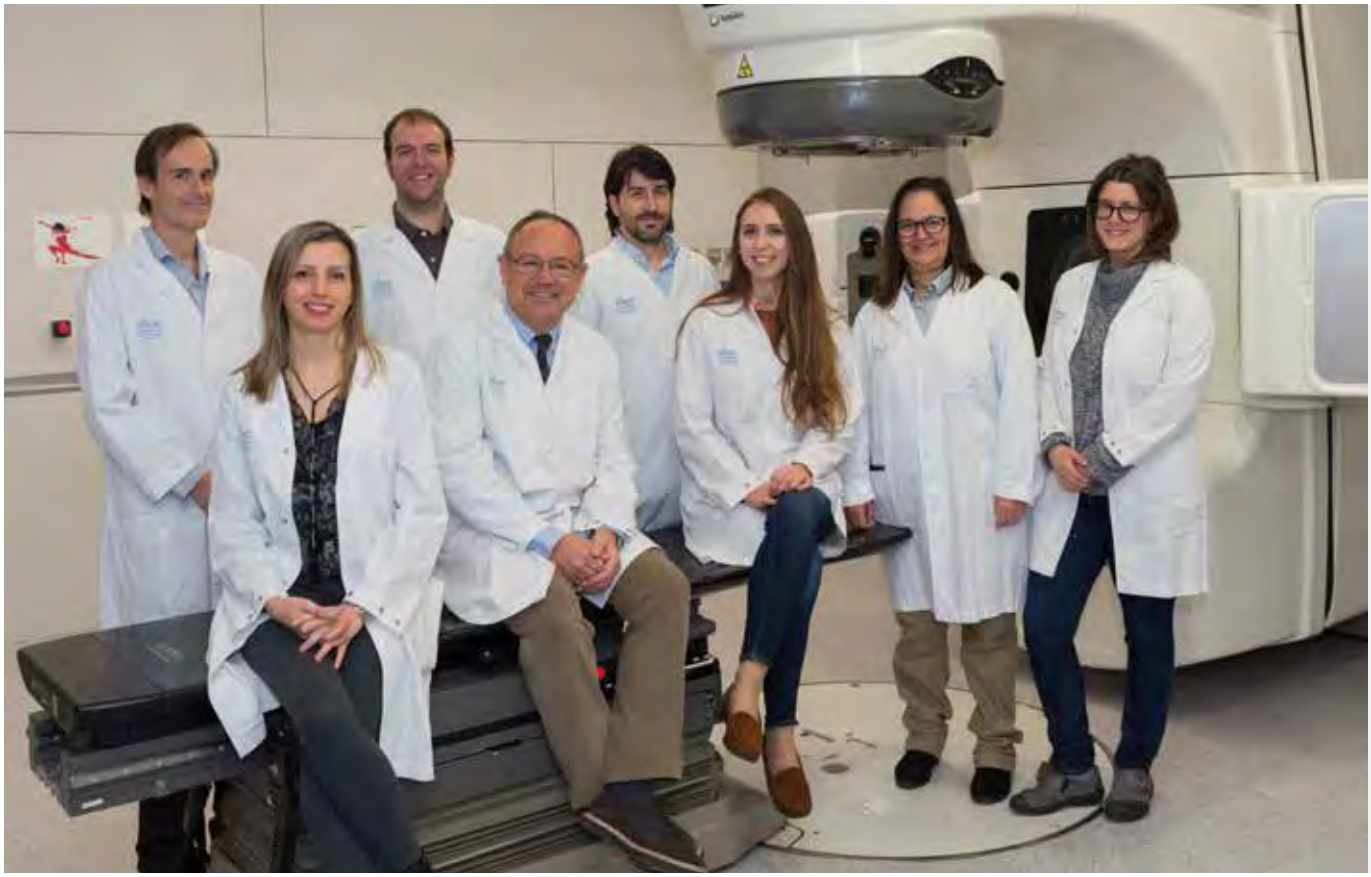
Dienstmann R, Mason MJ, Sinicrope FA, Phipps AI, Tejpar S, Nesbakken A, Danielsen SA, Sveen A, Buchanan DD, Clendenning M, Rosty C, Bot B, Alberts SR, Milburn Jessup J, Lothe RA, Delorenzi M, Newcomb PA, Sargent D, Guinney J. Prediction of overall survival in stage II and III colon cancer beyond the American Joint Commission on Cancer TNM system: a retrospective, pooled biomarker study. *Ann Oncol.* 2017;28(5):1023-1031.

Dienstmann R, Elez E, Argiles G, Matos I, Sanz-Garcia E, Ortiz C, Macarulla T, Capdevila J, Alsina M, Sauri T, Verdaguer H, Vilaro M, Ruiz-Pace F, Viaplana C, Garcia A, Landolfi S, Palmer HG, Nuciforo P, Rodon J, Vivancos A, Tabernero J. Analysis of mutant allele fractions in driver genes in colorectal cancer - biological and clinical insights. *Mol Oncol.* 2017;11(9):1263-1272.

Dienstmann R, Tabernero J. Cancer: A precision approach to tumor treatment. *Nature.* 2017 Aug 3;548(7665):40-41.

Clinical Research

# Radiation Oncology Group



## Strategic goals:

- Technology development: acquisition of new equipment to implement cutting edge clinical treatment techniques such as rotational radiotherapy - with intensity modulated arc therapy (VMAT), adaptive radiotherapy, and image-guided radiotherapy (IGRT).
- Translational research: application of insights into cancer biology as well as healthy tissue in order to personalize therapy matched to the characteristics and specificities of each patient, each individual tumor.

## Highlights:

- An increase in the number of patients treated with IMRT and RC/SBRT. In 2017 we treated 815 patients with IMRT and 93 patients with RC/SBRT; representing an increase of 34% and 24%, respectively.
- The Adaptive and innovative Radiation Treatment FOR improving Cancer treatment outcomE (ARTFORCE) project began in the year 2013. At present we have included 57 patients and are consequently the top recruiters in this collaboration.
- We initiated a dose escalation program using Image Guided RadioTherapy (IGRT) with fiducials, and have since treated 21 patients.
- New clinical studies in the treatment of prostate cancer with enzalutamide, and in lung/liver metastases with atezolizumab immunotherapy.

Principal Investigator
Jordi Giralt

Radiation Oncologists
Manuel Altabas
Sergi Benavente
Alexandra Giraldo
Beatriz Gutierrez
Xavier Maldonado
Andrés Muñiz
Begoña Navaltropo
Mónica Ramos
Victoria Reyes
Ramona Vergés

## Summary:

Our group is integrated within the Radiation Oncology Department of the Vall d'Hebron University Hospital (HUVH), and is actively involved in the multidisciplinary treatment of patients with malignant tumors. We also participate either as principal investigators or research collaborators across a number of pioneering clinical trials, translational research projects, as well as technology development programs.

Current and future research priorities include the following key areas:

- Development of an estereotactic extracranial radiotherapy program in pancreas and prostate.
- The setting up of a 4D program for lung cancer.
- In breast cancer, the validation of partial breast irradiation in prone position technique.
- Establishing benefit of dose painting and adaptive radiotherapy in head and neck cancer in a clinical trial.
- Analyzing the combination of PD-1 immunotherapy monoclonal antibodies with hypofractionated radiotherapy in metastasis and in locally advanced squamous cell carcinoma of the head and neck.
- Dose escalation trials in prostate cancer using hypofractionation and IGRT.

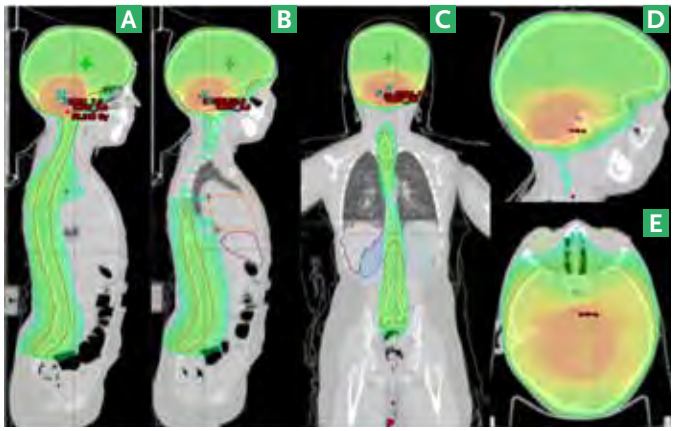



Figure: Dose distribution in a 4 years old child treated with cranio-spinal irradiation for a standard-risk medulloblastoma, using VMAT IMRT. A) Sagittal view at mid-line B) Sagittal view at eye's level C) Coronal view D) Cranial-sagittal view (in yellow the hippocampus, in blue the cochlea) E) Axial view (in yellow the hippocampus, in blue the hypophysis).

## PI paper pick:

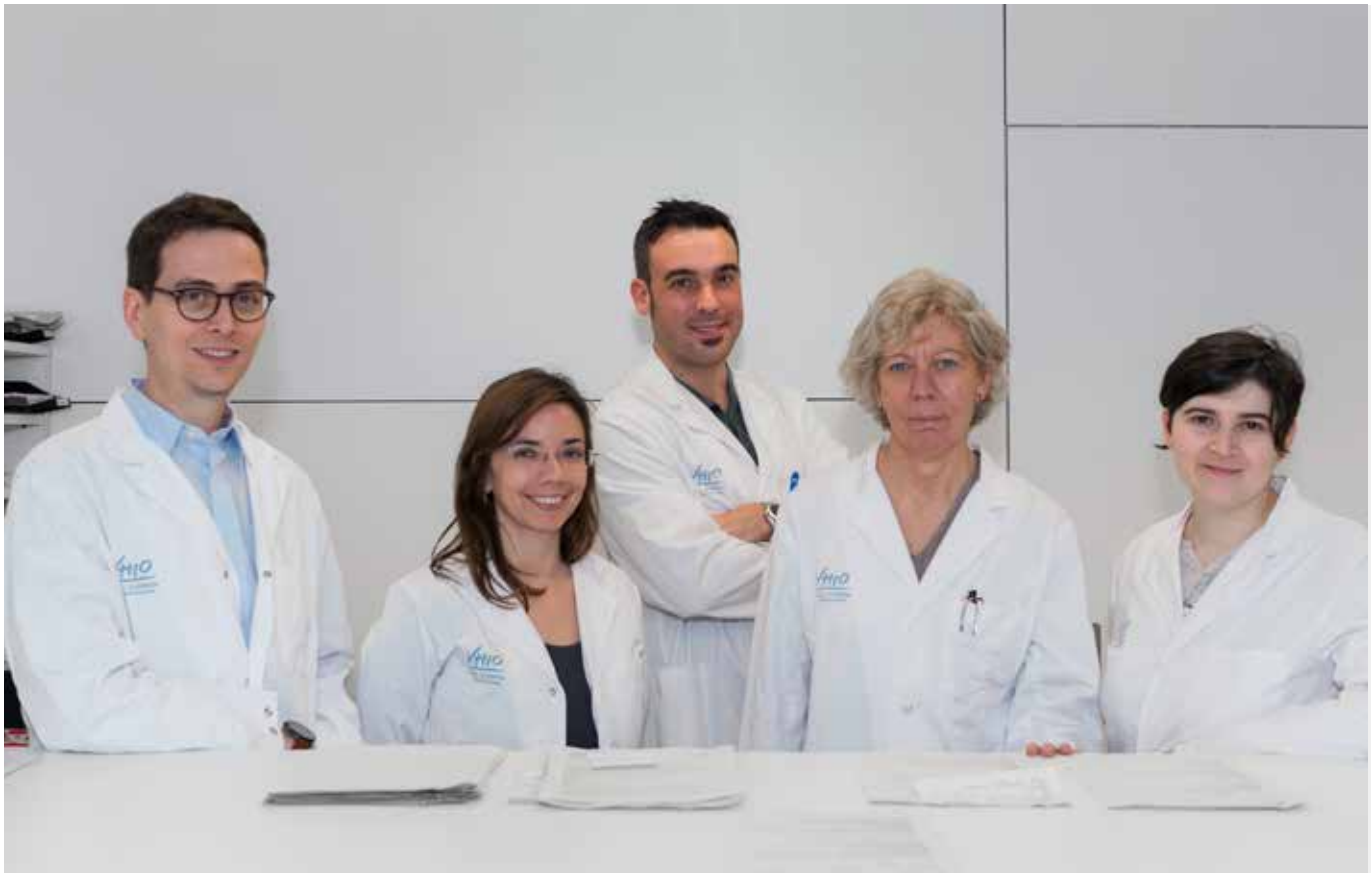
Mañós M, Giralt J, Rueda A, Cabrera J, Martinez-Trufero J, Marruecos J, et al. Multidisciplinary management of head and neck cancer: First expert consensus using Delphi methodology from the Spanish Society for Head and Neck Cancer (part 1). *Oral Oncol.* 2017 Jul;70:58-64.

Christiaens M, Collette S, Overgaard J, Gregoire V, Kazmierska J, Castadot P, Giralt J, Grant W, Tomsej M, Bar-Deroma R, Monti AF, Hurkmans CW, Weber DC. Quality assurance of radiotherapy in the ongoing EORTC 1219-DAHANCA-29 trial for HPV/p16 negative squamous cell carcinoma of the head and neck: Results of the benchmark case procedure. *Radiother Oncol.* 2017 Jun;123(3):424-430.

Bonner JA, Mesia R, Giralt J, Psyrri A, Keilholz U, Rosenthal DI, Beier F, Schulten J, Vermorken JB. p16, HPV, and Cetuximab: What Is the Evidence? *Oncologist.* 2017 Jul;22(7):811-822.

Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. Grégoire V, Evans M, Le QT, Bourhis J, Budach V, Chen A, Eisbruch A, Feng M, Giralt J, Gupta T, Hamoir M, Helito JK, Hu C, Hunter K, Johansen J, Kaanders J, Laskar SG, Lee A, Maingon P, Mäkitie A, Micciche' F, Nicolai P, O'Sullivan B, Poitevin A, Porceddu S, Składowski K, Tribius S, Waldron J, Wee J, Yao M, Yom SS, Zimmermann F, Grau C. *Radiother Oncol.* 2018 Jan;126(1):3-24. Epub 2017 Nov 24.

# Thoracic Tumors & Head and Neck Cancer Group



## Strategic goals:

- Contribute to early drug development and targeted therapies for thoracic and head and neck tumors.
- Advance personalized medicine for lung cancer patients through translational research and the application of cutting-edge technologies and novel approaches.
- Potentiate new therapies including immunotherapeutics and targeted agents for the management of patients with thoracic and head and neck malignancies.
- Further strengthen multidisciplinarity to provide optimal care for our patients.

## Highlights:

- 500 new lung cancer patients including 20 cases of mesothelioma and 5 thymoma.
- 250 new head and neck cancer patients.
- We continue to foster multidisciplinarity through our Thoracic Tumors Committee that convenes twice a week.
- Our head and neck cancer patients are discussed by a multidisciplinary team, twice a week.
- Implementation of pharmacogenomic approaches in advanced lung cancer in collaboration with VHIO's Cancer Genomics Group led by Ana Vivancos, and the Vall d'Hebron University Hospital Pathology Service, working with Javier Hernández and Irene Sansano.
- Implementation of liquid biopsy for certain patients with advanced NSCLC.
- Our group has collaborated in the development of a number of drugs in lung cancer matched to specific molecular alterations. As a result of these studies some of these agents have already been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).
- We have successfully led two translational projects resulting in the publication of scientific articles: one reporting on the tumor heterogeneity and treatment response of a EGFR-mutated lung cancer patient (Martinez-Martí A et al. *Ann Oncol.* 2017), and the second, establishing immune-related expression profiles in NSCLC and head and neck tumors (Navarro A et al. *Cancer Res.* 2017)
- Development of immune-based strategies in thoracic and head and neck malignancies.

Principal Investigator
Enriqueta Felip

Medical Oncologists
Neus Basté
Irene Braña
Susana Cedrés
Alex Martínez
Ana Maria Martínez
Alejandro Navarro
Nuria Pardo
Jordi Remon

Clinical Nurse Specialists
Carlos Justicia
Gisela Rodriguez

## Summary:

VHIO's Thoracic Tumors & Head and Neck Cancer Group tackles the challenges posed by thoracic malignancies, including lung cancer, mesothelioma and thymic malignancies, and head and neck cancers. We concentrate on disease prevention, early detection and more precise techniques in diagnosis and staging towards advancing personalized medicine in oncology. Our group also focuses on targeted therapies in patients with specific molecular alterations, and is dedicated to both unmasking molecular mechanisms of acquired resistance and optimizing novel immunotherapy strategies.

For our patients with early-stage thoracic malignancies, we liaise closely with a multidisciplinary team incorporating thoracic surgeons, radiation therapists, radiologists, pulmonologists and pathologists, in order to optimize various treatment approaches and modalities. Given that these individuals can suffer from severe symptoms we strive to ameliorate patient outcomes by working in tight connectivity with professionals from other disciplines.

Personalized therapy for patients with advanced lung cancer is now the standard approach. We therefore aim to widely establish molecular determinants to better match therapies to the specificities of individual patients, not only in tumors but also in circulating-free DNA (liquid biopsy).

Novel immunotherapy strategies have a role in the treatment algorithm for the management of lung cancer; a number of protocols are now ongoing in our unit. We actively contribute to VHIO's early clinical drug development efforts, led by Elena Garralda (see pages 72-73 of this report), and also manage other less common thoracic malignancies including small-cell lung cancer, mesothelioma, thymoma and neuroendocrine tumors.

For patients with head and neck tumors we work in close collaboration with expert surgeons, radiotherapists, radiologists, pathologists, and nutritionists, and also lead a clinical trial program analyzing immunotherapeutic approaches and targeted agents in this particular setting.

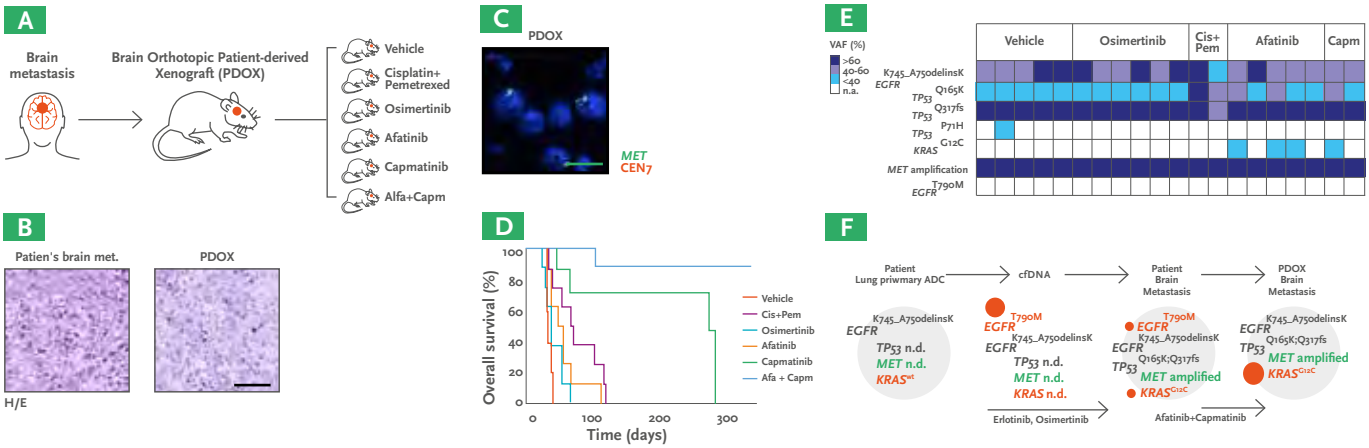



Figure: Martinez-Martí A, et al. *Ann Oncol.* 2017. The figure shows experiments performed in a PDX model from a metastatic brain biopsy at the time of progression to osimertinib. The results showed differential treatment response to a drug combination (d) and clonal evolution of tumor (e and f).

## PI paper pick:

Shaw AT, Felip E, Bauer TM, Besse B, Navarro A, Postel-Vinay S, Gainor JF, Johnson M, Dietrich J, James LP, Clancy JS, Chen J, Martini JF, Abbattista A, Solomon BJ. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol.* 2017 Dec;18(12):1590-1599.

Martinez-Marti A, Felip E, Matito J, Mereu E, Navarro A, Cedrés S, Pardo N, Martinez de Castro A, Remon J, Miquel JM, Guillaumet-Adkins A, Nadal E, Rodriguez-Esteban G, Arqués O, Fasani R, Nuciforo P, Heyn H, Villanueva A, Palmer HG, Vivancos A. Dual MET and ERBB inhibition overcomes intratumor plasticity in osimertinib-resistant-advanced non-small-cell lung cancer (NSCLC). *Ann Oncol.* 2017 Oct 1;28(10):2451-2457.

Peters S, Gettinger S, Johnson ML, Jänne PA, Garassino MC, Christoph D, Toh CK, Rizvi NA, Chaft JE, Carcereny Costa E, Patel JD, Chow LQM, Koczywas M, Ho C, Früh M, van den Heuvel M, Rothenstein J, Reck M, Paz-Ares L, Shepherd FA, Kurata T, Li Z, Qiu J, Kowanetz M, Mocci S, Shankar G, Sandler A, Felip E. Phase II Trial of Atezolizumab As First-Line or Subsequent Therapy for Patients With Programmed Death-Ligand 1-Selected Advanced Non-Small-Cell Lung Cancer (BIRCH). *J Clin Oncol.* 2017 Aug 20;35(24):2781-2789

Shaw AT, Kim TM, Crinò L, Gridelli C, Kiura K, Liu G, Novello S, Bearz A, Gautschi O, Mok T, Nishio M, Scagliotti G, Spigel DR, Deudon S, Zheng C, Pantano S, Urban P, Massacesi C, Viraswami-Appanna K, Felip E. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised , controlled, open-label, phase 3 trial. *Lancet Oncol.* 2017 Jul;18(7):874-886.

# Core Technologies

# Core Technologies

Cancer Genomics Group ..... 92

Molecular Oncology Group ..... 94

Proteomics Group ..... 96

VHIO's Cancer Genomics, Molecular Oncology, and Proteomics, led by Ana Vivancos, Paolo Nuciforo, and Francesc Canals respectively, are responsible for the development of VHIO's cutting-edge core technologies and platforms. These groups also pursue, implement and develop their own independent research lines and projects.

Core Technologies

# Cancer Genomics Group

## Strategic goals:

- Develop and implement improved strategies for routine patient prescreening in a setting of excellence (ISO 15189 accreditation).
- Provide cutting-edge applications in cancer genomics through the use of novel technologies and protocol development.
- Prioritize translational projects and partnerships that reinforce VHIO's renowned excellence in oncology, such as those we are currently pursuing with our Thoracic Tumors Group, led by Enriqueta Felip, and Gastrointestinal & Endocrine Tumors Group, directed by Josep Tabernero.

## Highlights:

- VHIO is one of the six founding partners of the Cancer Core Europe Consortium alongside the Gustave Roussy Cancer Campus Grand Paris (Villejuif, France), Cambridge Cancer Centre (Cambridge, UK), Karolinska Institute (Stockholm, Sweden), Netherlands Cancer Institute – NKI (Amsterdam, The Netherlands), and the National Center for Tumor Diseases – DKFZ-NCT (Heidelberg, Germany), and, most recently incorporating the National Cancer Institute of Milan (INT). Our group is appointed co-leader of the Consortium's Genomics Taskforce and is responsible for the alignment of genomic testing across all 7 member institutions.

  We are currently developing a 400 gene capture panel to be used by all Cancer Core Europe Consortium partners.
- Since VHIO incorporated in-house BEAMing liquid biopsy RAS biomarker technology early in 2015, the first academic test center to do so, significant progress has been made in validating and developing liquid biopsy and Droplet Digital PCR Bio-Rad technologies for the more effective, less invasive 'policing' of cancer over time, in real time.
- VHIO is one of the few centers in Europe to run such a comprehensive prescreening program. Molecular profiling in around 1500 patients per year as candidates for enrollment in UITM's early clinical trials enables our teams to more precisely match an increasing number of individual patients with a particular study.

Principal Investigator
Ana Vivancos

Specialized Technicians
Ginevra Caratù
Chiara Chianese
Judit Matito
Zighereda Ogbah

Bioinformatician
Francesco M. Mancuso

Bioinformatics Technical Auxiliary
Laura Muiños

Post-Doctoral Fellows
Deborah G. Lo Giacco
Miriam Navarro
Miriam Sansó

## Summary:

VHIO's Cancer Genomics Group serves as a Core Technology laboratory. In addition, we are dedicated to translational research as well as novel genomic test development.

We provide cutting-edge applications in cancer genomics through state-of-the-art technologies and the development of novel, fully validated tests that are used in the clinical research setting (Prescreening Program). Our lab is equipped with an n-Counter (Nanostring) platform, two digital PCR platforms (BEAMing Sysmex and ddPCR, BIO-RAD) and two NextGen Sequencers; MiSeq and HiSeq2500, Illumina.

VHIO's Prescreening Program is nucleated around the activity of two VHIO groups - our Cancer Genomics Group and Molecular Oncology led by Paulo Nuciforo, and centers on performing molecular profiling in over 1500 patients each year as potential candidates for enrollment in our Phase I clinical trials led by VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", directed by Elena Garralda (see pages 102-103 of this report).

Patients' suitability for inclusion in any given clinical trial is assessed based on their respective genomic or pathologic profile. Our Group has developed and routinely implemented several tests for our Prescreening Program. Two are based on NGS: an Amplicon-seq approach to sequence 67 genes (Illumina), as well as a 400-gene capture panel. Another two are based on nCounter (Nanostring): a gene fusion panel (with the capacity of detecting over 100 recurrent gene fusions) and a Copy Number Alteration panel (detecting 59 genes). As a reflection of our dedication to excellence and quality in the services we provide, we have achieved ISO 15189 accreditation for our Amplicon-seq testing method.

Our research activities focus on developing novel multiplexed tests that are optimized to FFPE-derived nucleic acids. Once developed, they are validated and used in clinical and translational research.

We are involved in a number of translational research projects including the identification of mechanisms of resistance to targeted therapies, with particular emphasis on liquid biopsy, specifically ctDNA as well as tumor educated platelets (TEPs).

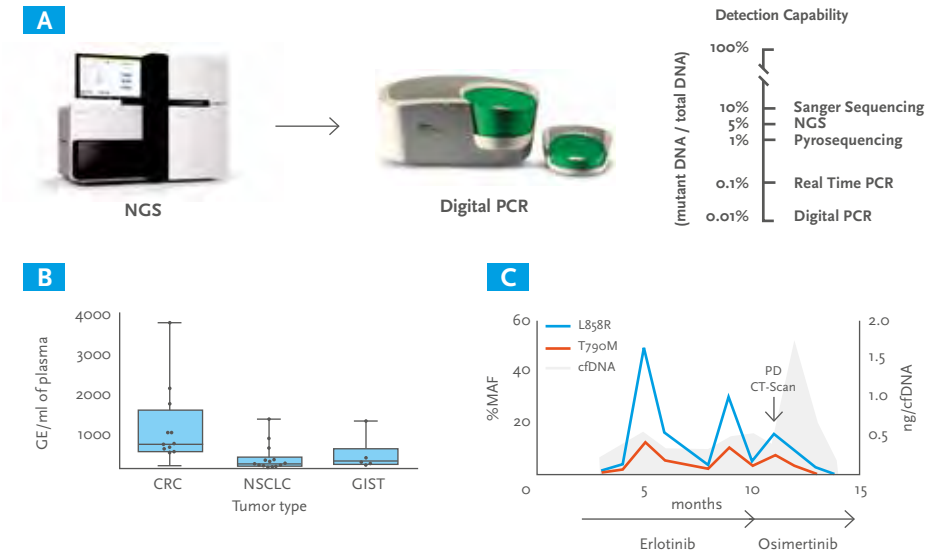



Figure: A.- Digital PCR arises 500 times superior sensitivity compared to Next Generation Sequencing (NGS). This improvement in technology allows detection of mutations in circulating tumor DNA from plasma samples, a revolutionary technic known as liquid biopsy. B.-The amount of cell free DNA (cfDNA) in plasma is minimum but varies greatly depending on the tumor type (CRC, colorectal cancer; NSCLC, non-small cell lung cancer; GIST, gastrointestinal stroma tumors). C.- NSCLC patient follow up of tumor evolution along treatments. Measurement of EGFR sensitizing L858R and resistance T790M mutant allele frequencies (MAFs) in plasma, both increase during second generation anti-EGFR treatment (erlotinib) and are detectable 6 months prior to standard CT-Scan progression disease (PD) diagnosis; upon initiation of anti-EGFR third generation treatment (osimertinib), MAFs substantially diminish revealing a good response to treatment. Finally, total cfDNA increases upon PD, and decreases upon effectiveness of osimertinib treatment.

## PI paper pick:

Martinez-Marti A, Felip E, Matito J, Mereu E, Navarro A, Cedrés S, Pardo N, Martinez de Castro A, Remon J, Miquel J M, Guillaumet-Adkins A, Nadal E, Rodriguez-Esteban G, Arqués O, Fasani R, Nuciforo P, Heyn H, Villanueva A, Palmer H G, Vivancos A. Dual MET and ERBB inhibition overcomes intratumor plasticity in osimertinib-resistant-advanced non-small-cell lung cancer (NSCLC). *Ann Oncol.* 2017 Oct 1;28(10):2451-2457.

García-Foncillas J, Alba E, Aranda E, Díaz-Rubio E, López-López R, Tabernero J, Vivancos A. Incorporating BEAMing technology as a liquid biopsy into clinical practice for the management of colorectal cancer patients: an expert taskforce review. *Ann Oncol.* 2017 Dec 1;28(12):2943-2949.

Dienstmann R, Elez E, Argiles G, Matos I, Sanz-Garcia E, Ortiz C, Macarulla T, Capdevila J, Alsina M, Sauri T, Verdaguer H, Vilaro M, Ruiz-Pace F, Viaplana C, Garcia A, Landolfi S, Palmer HG, Nuciforo P, Rodon J, Vivancos A, Tabernero J. Analysis of mutant allele fractions in driver genes in colorectal cancer - biological and clinical insights. *Mol Oncol.* 2017 Sep;11(9):1263-1272.

Grasselli J, Elez E, Caratù G, Matito J, Santos C, Macarulla T, Vidal J, Garcia M, Viéitez JM, Paéz D, Falcó E, Lopez Lopez C, Aranda E, Jones F, Sikri V, Nuciforo P, Fasani R, Tabernero J, Montagut C, Azuara D, Dienstmann R, Salazar R, Vivancos A. Concordance of blood- and tumor-based detection of RAS mutations to guide anti-EGFR therapy in metastatic colorectal cancer. *Ann Oncol.* 2017 Jun 1;28(6):1294-1301.

Core Technologies

# Molecular Oncology Group

## Strategic goals:

- Discovery and validation of novel biomarkers using tissue-based technologies.
- Identification of targetable alterations as part of VHIO's Prescreening Program.
- Application of molecular pathology strategies to support early clinical drug development programs.
- Better define molecular target epidemiology to render treatment strategies more precise.
- Act as a central and local laboratory in clinical trials.
- Serve as a Core Facility for VHIO research programs.

## Highlights:

- Development of biomarker strategies for patients treated with passive (anti-HER2 antibodies) or active (anti-PD1/PD-L1) immunotherapy, FGFR, and MET clinical development programs.
- Identification of Fusobacterium and associated microbiota in liver metastases from colorectal cancer patients and sensitivity to antibiotic therapy.
- Maintenance and expansion of tests under ISO15189 accreditation.
- Supported over 250 clinical trials for sample management and analyses.
- Selected as the central laboratory for different international studies.
- Over 4000 molecular determinations on samples for patient inclusion in clinical trials and over 24,000 tests performed for basic and translation research programs.

Principal Investigator
Paolo Nuciforo

Attending Physicians
Laura Comerma
Roberta Fasani

Laboratory Supervisor
Jose Jiménez

Laboratory Assistant
Mª Ángeles Díaz

Technicians
Mª del Carmen Díaz
Francisca Gallego
Xavier Guardia
Tania López
Paola Martínez
Gertrudis Sánchez
Lidia Sánchez
Garazi Serna
César Sevillano

## Summary:

The mission of VHIO's Molecular Oncology Group is to apply state-of-the-art tissue-based technologies to basic, translational, and clinical research with a clear focus on the development and validation of novel tumor biomarkers for precision medicine against cancer. Our group also serves as one of VHIO's Core Technology Platforms and is therefore central to research performed at our Institute.

We actively participate in all research projects involving the use of human tissue collected from patients, including biomarker analyses for patient stratification and inclusion in clinical trials, tissue banking and the development of primary xenograft models.

Activities as a Core Facility in 2017: We provided support for approximately 250 clinical trials conducted at Vall d'Hebron, representing approx. 70% of all trials open at our institution. Our involvement in clinical trials ranges from the coordination of sample collection, storage and shipment, developing and running multiple assays for real-time patient inclusion, as well as pharmacodynamic monitoring and dose finding.

In 2017, we have performed more than 4000 molecular determinations on samples for patient inclusion in clinical trials and over 24,000 tests to support basic and translation research programs. We have also been the central laboratory of choice for 10 international studies, and successfully maintained the prestigious ISO15189 quality accreditation. Additionally, we have achieved the flexible scope and expansion of the catalogue of molecular tests run under accreditation.

Group research activities in 2017: We developed a predictive model based on tumor cellularity and tumor-infiltrating lymphocytes (CelTIL) in HER2-posiive breast cancer treated with chemo-free dual HER2 blockade (Nuciforo et al. *Ann Oncol.* 2017). We have also collaborated in developing recommendations on assessing TILs in different types of solid tumors (Hendry et al. *Adv Anat Pathol.* 2017) and in identifying an adaptive immune response gene signature predictive of clinical outcome after PD-1 blockade (Prat et al. *Cancer Res.* 2017).

We have explored the importance of microbiota in colorectal cancer development. By developing an in situ hybridization mRNA assay, we evidenced *Fusobacterium* nucleatum persistence in liver metastases of colorectal cancer patients and antibiotic response in patient-derived tumor models (Bullman et al. *Science.* 2017) – see Figure.

Results of the first-in-human phase I study of oral S49076, a MET/AXL/FGFR inhibitor, in advanced solid tumors were also published together with the associated pharmacodynamics readouts generated in our laboratory (Rodon et al. *Eur J Cancer.* 2017).

Lastly, our group is currently working on developing a multiplex in situ technology to enable a complete set of diagnostic and research immunohistochemistry and in situ hybridization markers on a single tissue slide.

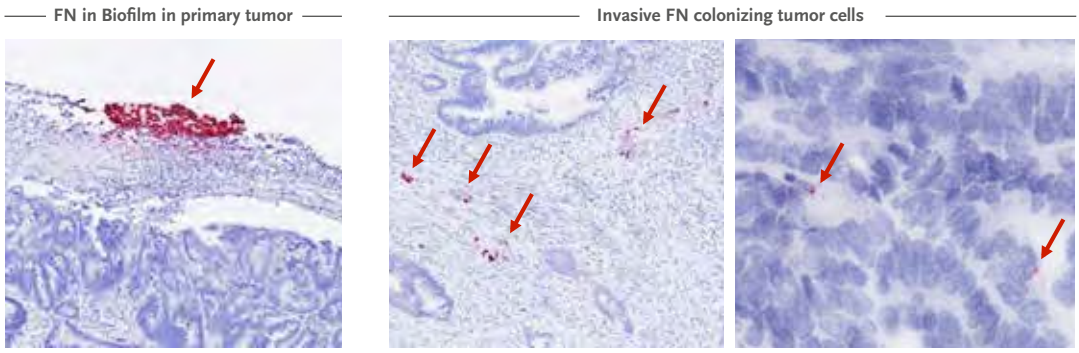



Figure: Fusobacterium nucleatum (FN) in colorectal cancer - 1 red dot = 1 bacteria RNA molecule

## PI paper pick:

Bullman S, Pedamallu CS, Sicinska E, Clancy TE, Zhang X, Cai D, Neuberg D, Huang K, Guevara F, Nelson T, Chipashvili O, Hagan T, Walker M, Ramachandran A, Diosdado B, Serna G, Mulet N, Landolfi S, Ramon Y Cajal S, Fasani R, Aguirre AJ, Ng K, Élez E, Ogino S, Tabernero J, Fuchs CS, Hahn WC, Nuciforo P, Meyerson M. Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. *Science* 2017 Dec 15;358(6369):1443-1448. doi: 10.1126/science.aal5240. Epub 2017 Nov 23.

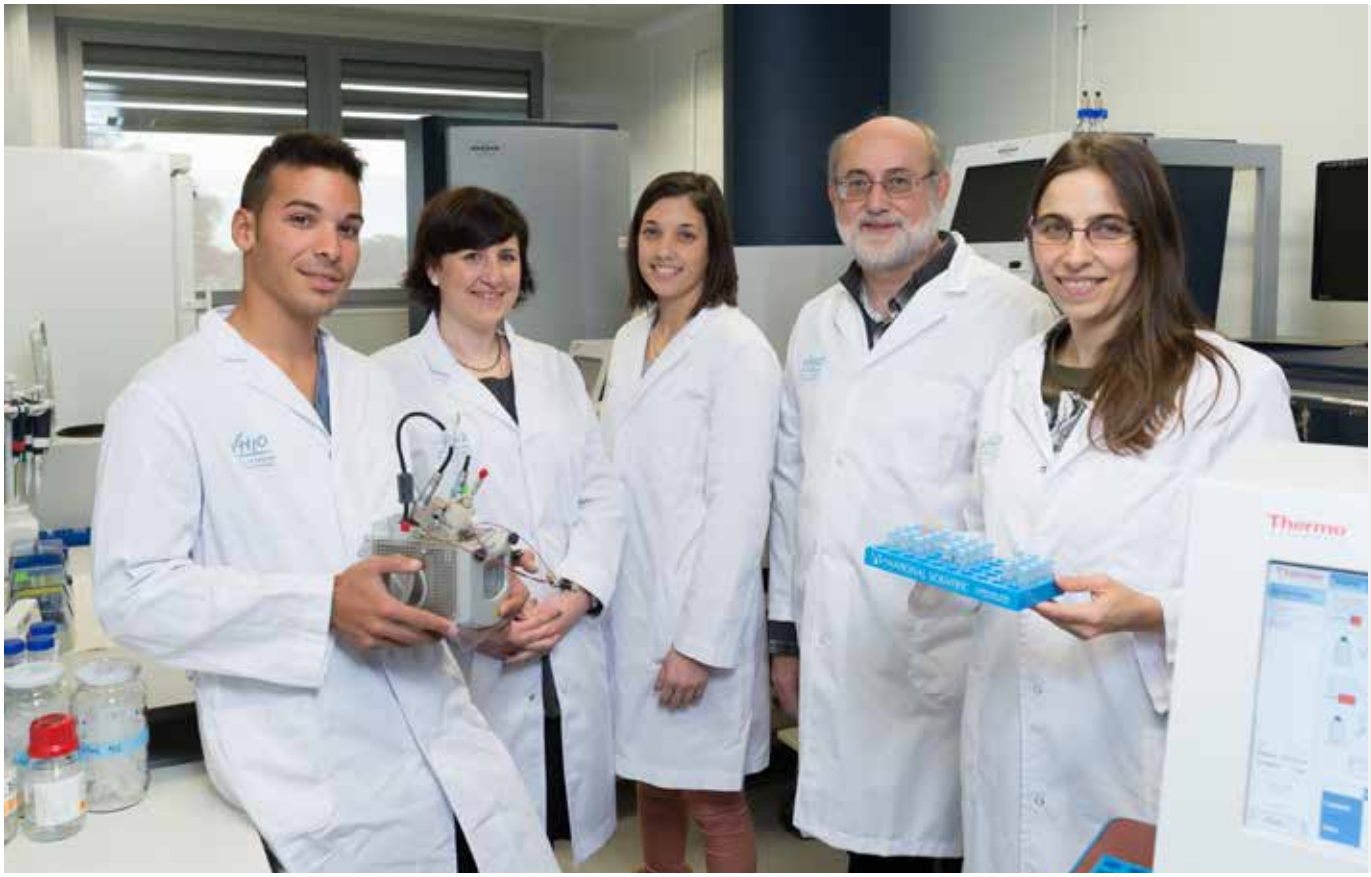
Nuciforo P, Pascual T, Cortés J, Llombart-Cussac A, Fasani R, Paré L, Oliveira M, Galvan P, Martínez N, Bermejo B, Vidal M, Pernas S, López R, Muñoz M, Garau I, Manso L, Alarcón J, Martínez E, Rodrik-Outmezguine V, Brase JC, Villagrasa P, Prat A, Holgado E. A predictive model of pathological response based on tumor cellularity and tumor-infiltrating lymphocytes (CelTIL) in HER2-positive breast cancer treated with chemo-free dual HER2 blockade. *Ann Oncol.* 2017 Oct 12. doi: 10.1093/annonc/mdx647. [Epub ahead of print].

Zabala-Letona A, Arruabarrena-Aristorena A, Martín-Martín N, Fernandez-Ruiz S, Sutherland JD, Clasquin M, Tomas-Cortazar J, Jimenez J, Torres I, Quang P, Ximenez-Embun P, Bago R, Ugalde-Olano A, Loizaga-Iriarte A, Lacasa-Viscasillas I, Unda M, Torrano V, Cabrera D, van Liempd SM, Cendon Y, Castro E, Murray S, Revandkar A, Alimonti A, Zhang Y, Barnett A, Lein G, Pirman D, Cortazar A, Arreal L, Prudkin L, Astobiza I, Valcarcel-Jimenez L, Zuñiga-García P, Fernandez-Dominguez I, Piva M, Caro-Maldonado A, Sánchez-Mosquera P, Castillo-Martín M, Serra V, Beraza N, Gentilella A, Thomas G, Azkargorta M, Elortza F, Farràs R, Olmos D, Efeyan A, Anguita J, Muñoz J, Falcón-Pérez JM, Barrio R, Macarulla T, Mato JM, Martinez-Chantar ML, Cordon-Cardo C, Aransay AM, Marks K, Baselga J, Tabernero J, Nuciforo P, Manning BD, Marjon K, Carracedo A. MTORC1-dependent AMD1 regulation sustains polyamine metabolism in prostate cancer. *Nature.* 2017 Jul 6;547(7661):109-113.

Llombart-Cussac A, Cortes J, Paré L, Galvan P, Bermejo B, Martínez N, Vidal M, Pernas S, López R, Muñoz M, Nuciforo P, Morales S, Oliveira M, de la Peña L, Peláez A, Prat A. HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. *Lancet Oncol.* 2017 Apr;18(4):545-554. doi: 10.1016/S1470-2045(17)30021-9. Epub 2017 Feb 24.

Core Technologies

# Proteomics Group




## Strategic goals:

- Provide services in proteomic techniques to other research groups as a Core Facility.
- Proteomic screening for new biomarkers to help develop cancer therapeutics.
- Development of mass spectrometry-based assays for the analysis of biomarkers in clinical samples.
- Contribute to mapping the Chromosome 16 proteome as part of the Human Proteome Project.

## Highlights:

- The provision of proteomic services to VHIO groups, oncology professionals at the Vall d'Hebron University Hospital (HUVH), and members of the *ProteoRed-Instituto Salud Carlos III* network.
- Setting up workflows for the proteomic and phosphoproteomic screening of CRC PDX models.
- Participation in the Spanish Consortium Chromosome 16 HPP, the HUPO Human Proteome Project.

Principal Investigator
Francesc Canals

Post-Doctoral Fellow
Núria Colomé

Technicians
Luna Martin
Anna Sabé

Graduate Student
Marc Fernández

## Summary:

Proteomics involves the characterization of the entire set of proteins - proteome - expressed by a particular cell or tissue under specific physiological or pathological conditions. The application of proteomic technologies to cancer research is a rapidly expanding field - not only for basic research but also for the discovery of diagnostic or disease-progression biomarkers. We mainly focus on applying proteomic techniques to the identification and characterization of substrates of metalloproteases involved in tumor progression.

Metalloproteases of the ADAM and ADAMTS families play a crucial role in the regulation of the tumor microenvironment by mediating the remodeling of the extracellular matrix and the cleavage of specific extracellular and membrane proteins. Insights into the substrates of these proteases in the context of tumor cells are required in order to elucidate their role in tumor growth and metastasis as well as evaluate their potential as therapeutic targets.

Our group employs mass spectrometry-based proteomic strategies to search for new substrates of these proteases and analyze their involvement in tumor progression.

We also adopt proteomic techniques for the screening and validation of biomarkers for cancer diagnostics, precision therapy against cancer, and the tracking of disease. Our focus centers on the development of mass spectrometry-based assays for the analysis of biomarkers in clinical samples. VHIO's Proteomics Group is a member of the Spanish Consortium Chromosome 16 HPP which forms part of the HUPO Human Proteome Project. Following a chromosome-centric strategy, this multicenter and international project aims at developing an entire map of the proteins encoded by the human genome to advance our understanding of human biology in health and disease.

As a Core Facility, we provide state-of-the-art proteomic methodologies to VHIO researchers as well as implement new developments within the field to offer the very latest proteomic strategies and technologies.

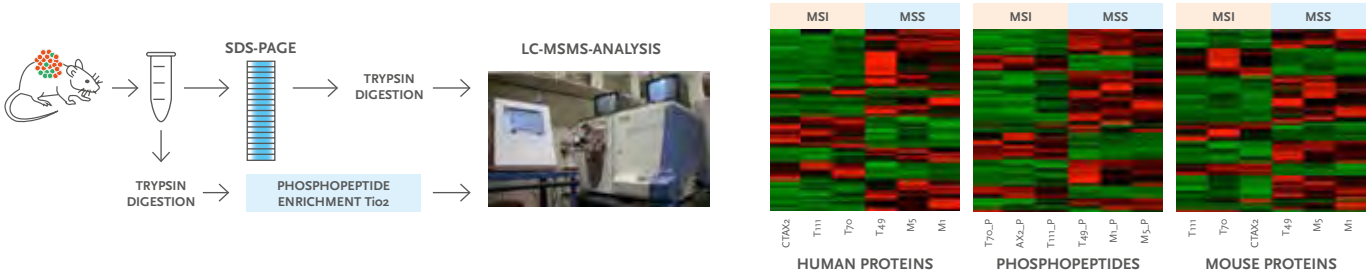



Figure: Proteomic characterization of colorectal patient-derived xenograph (PDX) models. Proteomic and phosphoproteomic analysis of patient-derived mouse model tumors allows the molecular characterization of tumor subtypes. Colorectal tumors of MSS and MSI subtypes can be correctly classified on the basis of tumor derived proteins, phosphorylated proteins involved in signaling, or microenvironment proteins, of mouse origin in the PDX model.

## PI paper pick:

García-Berrocoso T, Llombart V, Colàs-Campàs L, Hainard A, Licker V, Penalba A, Ramiro L, Simats A, Bustamante A, Martínez-Saez E, Canals F, Sanchez JC, Montaner J. Single Cell Immuno-laser Microdissection Coupled to Label-free Proteomics to Reveal the Proteotypes of Human Brain Cells After Ischemia. *Mol Cell Proteomics.* 2017 Nov 13. [Epub ahead of print]

Mateo F, Arenas EJ, Aguilar H, Serra-Musach J, de Garibay GR, Boni J, Maicas M, Du S, Iorio F, Herranz-Ors C, Islam A, Prado X, Llorente A, Petit A, Vidal A, Català I, Soler T, Venturas G, Rojo-Sebastian A, Serra H, Cuadras D, Blanco I, Lozano J, Canals F, Sieuwerts AM, de Weerd V, Look MP, Puertas S, García N, Perkins AS, Bonifaci N, Skowron M, Gómez-Baldó L, Hernández V, Martínez-Aranda A, Martínez-Iniesta M, Serrat X, Cerón J, Brunet J, Barretina MP, Gil M, Falo C, Fernández A, Morilla I, Pernas S, Plà MJ, Andreu X, Seguí MA, Ballester R, Castellà E, Nellist M, Morales S, Valls J, Velasco A, Matias-Guiu X, Figueras A, Sánchez-Mut JV, Sánchez-Céspedes M, Cordero A, Gómez-Miragaya J, Palomero L, Gómez A, Gajewski TF, Cohen EE, Jesiotr M, Bodnar L, Quintela-Fandino M, López-Bigas N, Valdés-Mas R, Puente XS, Viñals F, Casanovas O, Graupera M, Hernández-Losa J, Ramón Y Cajal S, García-Alonso L, Saez-Rodriguez J, Esteller M, Sierra A, Martín-Martín N, Matheu A, Carracedo A, González-Suárez E, Nanjundan M, Cortés J, Lázaro C, Odero MD, Martens JW, Moreno-Bueno G, Barcellos-Hoff MH, Villanueva A, Gomis RR, Pujana MA. Stem cell-like transcriptional reprogramming mediates metastatic resistance to mTOR inhibition. *Oncogene.* 2017. May 11;36(19):2737-2749

Vialas V, Colomé-Calls N, Abian J, Aloria K, Alvarez-Llamas G, Antúnez O, Arizmendi JM, Azkargorta M, Barceló-Batllori S, Barderas MG, Blanco F, Casal JI, Casas V, de la Torre C, Chicano-Gálvez E, Elortza F, Espadas G, Estanyol JM, Fernandez-Irigoyen J, Fernandez-Puente P, Fidalgo MJ, Fuentes M, Gay M, Gil C, Hainard A, Hernaez ML, Ibarrola N, Kopylov AT, Lario A, Lopez JA, López-Lucendo M, Marcilla M, Marina-Ramírez A, Marko-Varga G, Martín L, Mora MI, Morato-López E, Muñoz J, Odena MA, de Oliveira E, Orera I, Ortea I, Pasquarello C, Ray KB, Rezeli M, Ruppen I, Sabidó E, Del Pino MM, Sancho J, Santamaría E, Vazquez J, Vilaseca M, Vivanco F, Walters JJ, Zgoda VG, Corrales FJ, Canals F, Paradela A. A multicentric study to evaluate the use of relative retention times in targeted proteomics. *J Proteomics.* 2017 Jan 30;152:138-149.

Llombart V, Trejo SA, Bronsoms S, Morancho A, Feifei M, Faura J, García-Berrocoso T, Simats A, Rosell A, Canals F, Hernández-Guillamón M, Montaner J. Profiling and identification of new proteins involved in brain ischemia using MALDI-imaging-mass-spectrometry. *J Proteomics.* 2017Jan 30;152:243-253.


# VHIO's Transversal Clinical Trials Core Services & Units

# VHIO's Transversal Clinical Trials Core Services & Units

Clinical Trials Office..... 100

Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa".....102

Clinical Research Oncology Nurses.....104

Clinical Research Oncology Pharmacy Unit..... 106

VHIO's Transversal Clinical Trials Core Services & Units

# Clinical Trials Office

Director
Gemma Sala

**HEAD OF PHASE I CLINICAL TRIALS OFFICE**
Elisabet Sicart
Silvia Pérez

Study Coordinators
Sonia Abad
Eulalia Aliende
Ainhoa Balague
Raquel Blanco
Lluïsa Carbonell
Raquel de La Torre
Maria Garcia
Maria Herranz
Iris Martinez
Sonia Martinez
Laura Maynés
Montserrat Moreno
Gemma Mur
Laura Oliva
Adelaida Piera
Mireia Sole

Data Managers
Ariadna Arasanz
Ignacio Carcela
Marina Coll
Giovanni De Marino
Gloria Garcia
Jordina Llavall
Anna Martinez
Lidia Martinez De Arenzana
Marta Monserrat
Sergi Pérez
Isabel Rico
Montserrat Pujadas
Rosa Maria Romero

**HEAD, GI, LUNG, HEAD & NECK PHASE II-III CLINICAL TRIALS**
Marta Beltran

Study Coordinators
Izar Achaerandio
Carlota Aguilera
Alejandra Caballero
Iris De La Fuente
Elena Fernandez
Laura Garcia
Patricia Garcia
Irene Garrido
Cristina Pérez
Iratxe Puebla
Sergi Recasens
Andrea Retter
Eulalia Scheenaard
Sandra Tijeras
Lorena Trejo
Román Vidal

Data Managers
Laia Gregori
Raquel Gutierrez
Eva Mª Lázaro
Eva Marín
Silvia Marín
Sergio Pérez
Asal Rinaldi
Julia Serra
Eduard Solà

**HEAD, BREAST, GU, CNS, SARCOMA, GYNECOLOGICAL CLINICAL TRIALS**
Meritxell Soler

Study Coordinators
Judith Alonso
Enric Álvarez
Beatriz Bruno
Nuria Collantes
Carlos Fernandez
Sergio Fernandez
Berta Garrido
Alba Meire
Thaïs Miquel
Olga Padrós
Mariona Pocarull
Angela Maria Quintana
Ester Serra
Anna Serrano

Data Managers
Cristina Aguilar
David Alvarez
Marta Batista
Maria Isabel Martinez
Carina Monclús
Nuria Ortega

**HEAD, CLINICAL RESEARCH SUPPORT UNIT**
Susana Muñoz

Sample Managers
Gemma Pruna
Cristina Resina

Clinical Trials Office Administrative Support
Núria Carballo
Cristina Garcia
Marc Palomar
Alexandre Valle

Quality Manager
Silvia García Matas

## Strategic goals:

- Contribute to the development of novel therapies against cancer.
- Consolidation as an international reference for clinical trials in oncology.
- Guide patients enrolled in trials to comply with the protocol requirements and help them with daily life throughout the duration of their participation.
- Ensure that the protocol is appropriately conducted from initiation to the close of the respective clinical study.
- Standardize clinical trial processes to ensure optimal quality and the compliance of Good Clinical Practice (GCP).

## Highlights:

- Our Clinical Research Support Unit, which was set up in 2016, continues to guide investigators with the start-up and management of independent research lines.
- We continue to report important numbers of clinical trials performed and respective patient recruitment.
- Optimal management of the complexity of protocols which are increasingly demanding.
- We have provided tailored training for our staff in order to further improve the quality of work and expand related skill sets.
- Implemented new tools and procedures aimed at increasing the quality and efficacy of research.
- 20 sponsor audits and 1 inspection by the European Medicines Agency (EMA) have been conducted with satisfactory results.
- Continue with the high standard of quality and procedures achieved through the Inspection for Accreditation of the phase I Unit, the Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", by the *Generalitat de Catalunya*, carried out in 2016.
- Improved sample management through the incorporation of 2 sample managers who are responsible for correct log registration of study samples and also help study coordinators with shipments.
- Expansion of office space available for the coordination and monitoring of our activities.

## Summary:

Established in 1997, our Clinical Trials Office incorporates experts conducting clinical trials at the Vall d'Hebron University Hospital's (HUVH) Oncology Department. More specifically, our professionals including study coordinators, data managers, administrative staff and quality control, coordinate studies from Phase I to Phase III as well as various research projects. Divided into three groups, covering all tumor types and studies, our teams are managed by the Clinical Trials Office Director, Gemma Sala.

In 2017 we had 355 Phase I, Basket studies, Phases II & III trials with active recruitment during the same year (see Figure II), with patient enrolment totaling at 1096. 100 new trials were initiated, including 20 post-authorisation trials and rollover studies. In addition, we continue to follow up patients who were recruited prior to 2017 and are still enrolled and receiving study treatment (more than 1800 patients in total).

As we continue to render personalized medicine more precise by better targeting therapies to respond to the specificities of each individual patient, each individual tumor, the requirements and selection criteria for inclusion in certain studies are also becoming more complex. While we are dedicated to expanding our portfolio of trials in order to ultimately establish new treatment models with highly selective drugs, we must also continue to fine-tune patient selection criteria in order to best identify those patients who are most likely to benefit from novel therapies, including emerging immunotherapeutics, matched to each individual's molecular 'measurements'.

The Vall d'Hebron University Hospital's Oncology Department has gained much prestige which has been acknowledged by pharmaceutical companies. It has consequently become a reference center selected by the industry to carry out complex clinical trials for which the number of participating centers is highly restricted. Selected sites are chosen based on their high standards of quality and capacity for carrying out state-of-the-art research. We have taken part in early phase trials of different drugs, ultimately enabling the pharmaceutical industry to market novel anti-cancer medicines. We participate in both clinical trials promoted by the pharmaceutical industry as well as those developed by our department in collaboration with other hospitals.

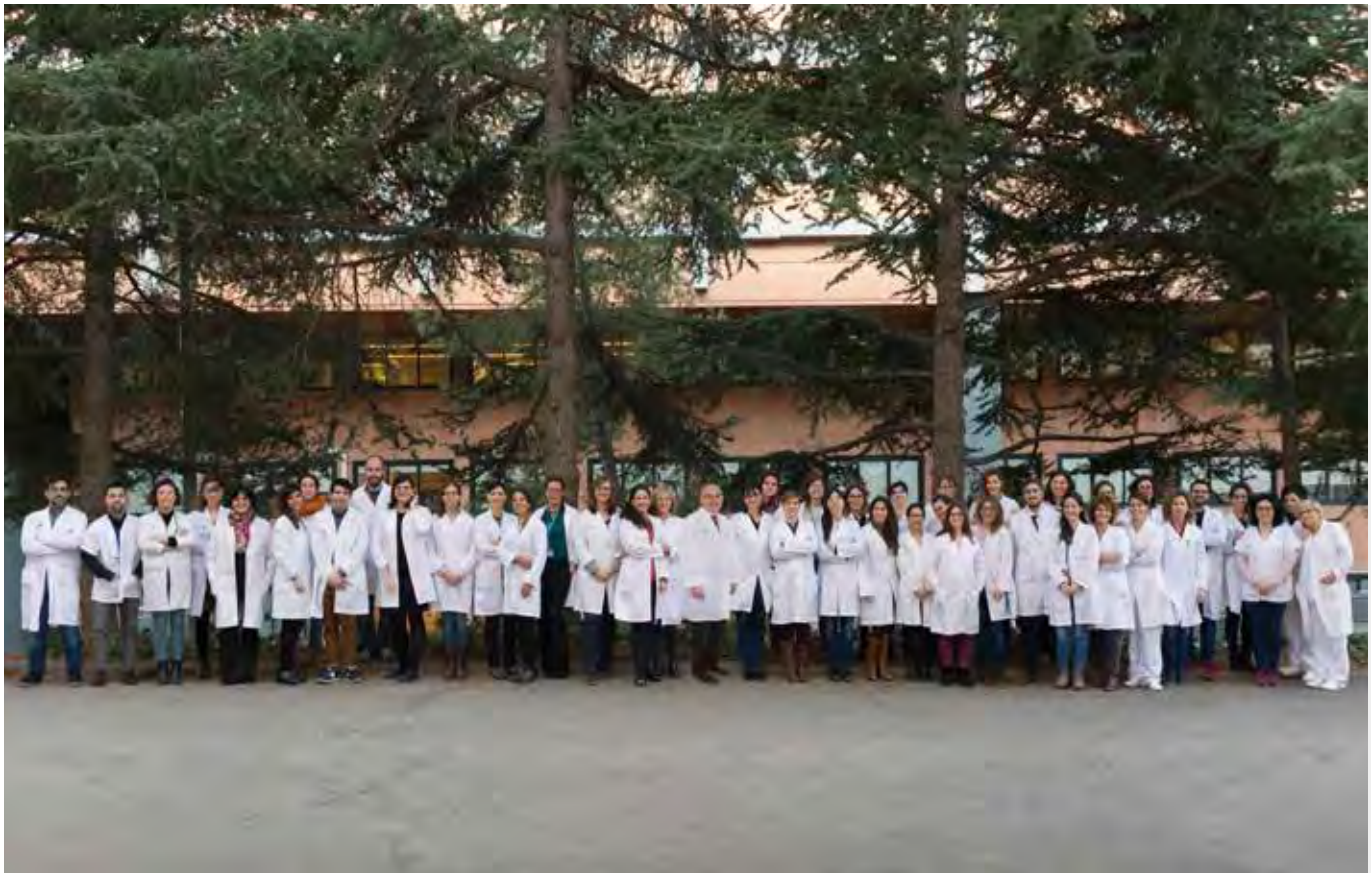
Figure I: **Annual recruitment of patients enrolled in Clinical Trials (Phases I + Baskets - II – III)**

| | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Included in phase I | 35 | 59 | 57 | 110 | 130 | 120 | 108 | 132 | 139 | 171 | 222 | 245 | 277 | 290 | 345 | 303 | 370 | 453 | 445 |
| Included in phase II | 59 | 72 | 66 | 94 | 91 | 130 | 73 | 165 | 170 | 133 | 161 | 207 | 180 | 253 | 257 | 302 | 327 | 333 | 323 |
| Included in phase III | 95 | 128 | 175 | 109 | 84 | 129 | 111 | 85 | 143 | 180 | 189 | 221 | 218 | 236 | 241 | 166 | 282 | 343 | 328 |
| N° of patients included | 189 | 259 | 298 | 313 | 305 | 379 | 292 | 382 | 452 | 484 | 572 | 673 | 675 | 779 | 843 | 771 | 979 | 1.129 | 1.096 |

Figure II: **Annual Distribution of Phase I + Basket, II and III Trials**

| | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Phase I trials | 6 | 10 | 12 | 14 | 17 | 15 | 16 | 19 | 20 | 26 | 31 | 37 | 48 | 66 | 75 | 83 | 106 | 129 | 137 |
| Phase II trials | 19 | 22 | 23 | 23 | 22 | 19 | 30 | 32 | 42 | 40 | 55 | 54 | 57 | 85 | 96 | 99 | 94 | 117 | 107 |
| Phase III trials | 14 | 17 | 22 | 25 | 18 | 20 | 21 | 21 | 31 | 37 | 45 | 49 | 56 | 68 | 61 | 64 | 89 | 108 | 111 |
| N° of clinical trials | 39 | 49 | 57 | 62 | 57 | 54 | 67 | 72 | 93 | 103 | 131 | 140 | 161 | 219 | 232 | 246 | 289 | 354 | 355 |
| Post-authorisation & Rollover Trials | | | | | | | | | | | | | | | | 5 | 14 | 16 | 20 |

# Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa"



Director
Josep Tabernero

Executive Director
Elena Garralda

Executive Team
Gemma Sala
Angeles Peñuelas

Associate Investigators - Senior Consultants
Judith Balmaña
Joan Carles
Enriqueta Felip
Teresa Macarulla
Ana Oaknin
Jordi Rodón
Cristina Saura
Josep Tabernero

Associate Investigators - Phase I
Maria Alsina
Guillermo Argilés
Analía B. Azaro
Irene Braña
Marta Capelan
Cristina Cruz
María Elena Élez
Santiago Ignacio Escrivà
Lorena Fariñas
Patricia Gómez
Jorge Hernando
Cinta Hierro
Juan Jesús Martín
Alex Martínez
Ignacio Matos
Rafael Morales
Eva Muñoz
Alejandro Navarro
María Ochoa de Olza
Mafalda Oliveira
Nuria Pardo
Maria Coral Perez
Jordi Remon
Víctor Rodríguez
César Serrano
Cristina Suárez
Claudia Valverde
Helena Verdaguer
Maria Vieito
Esther Zamora

Director, Clinical Trials Office
Gemma Sala

Heads, Phase I Clinical Trials Office
Silvia Perez Pujol

Study Coordinators
Sonia Abad
Eulalia Aliende
Ainhoa Balague
Raquel Blanco
Lluïsa Carbonell
Raquel de La Torre
Maria Garcia
Maria Herranz
Iris Martinez
Sonia Martinez
Lidia Martinez De Arenzana
Laura Maynés
Montserrat Moreno
Gemma Mur
Laura Oliva
Adelaida Piera
Mireia Sole

Data Managers
Ariadna Arasanz
Ignacio Carcela
Marina Coll
Giovanni De Marino
Gloria Garcia
Jordina Llavall
Anna Martinez
Marta Monserrat
Sergi Pérez
Montserrat Pujadas
Isabel Rico
Rosa Maria Romero

Pharmacy FOUITM
Maria Josep Carreras Soler

Pharmacy USIFO
Laura Maños

Nurse Supervisor
Ángeles Peñuelas

Nurse Coordinators
Sonia Valverde
Lydia Vélez

Nurses
Meritxell Cucurell
Elisabet Hernández
Margarida Marcos
Isabel Muñoz
Tania Sánchez

Nursing Assistants
Alicia López
María Martín
Ana Belen Ortiz

Nurse Supervisor's Assistant
Juan Manuel García

Secretary
Teresa Mendoza

Obra Social "la Caixa"

## Strategic goals:

- Early drug development and translational research led by UITM physician-researchers and VHIO scientists: expansion of our broad portfolio of promising novel anticancer therapies, across a balanced spectrum of studies, with special focus on first-in-human studies, novel-novel combinations, best-in class compounds, and a new class of drugs.
- Perform complex trials such as organ dysfunction trials, Octopus as well as Basket studies, and link clinical research at UITM with VHIO's preclinical and translational research groups.
  Our Unit also collaborates with the different partners involved in drug development and translational research.
- Genomic medicine trials in early drug development: perform molecular analysis of patients' tumors in order to select the best possible treatment with the experimental treatments available, co-develop medical informatics applied to genomic medicine, and integrate preclinical and clinical research by incorporating novel drugs, new insights, and study designs together with customized molecular diagnostics.
- Immunotherapy: our Unit's taskforce in early drug development of immunotherapeutics and cell signaling focuses on second generation immunotherapies, including new cytokines, immunomodulatory agents and immune checkpoint inhibitors and combinations, as well as translational research in immuno-oncology.

## Highlights:

- We have performed some of the most complex phase I trials, including those focused on molecularly-selected patient populations (trials in complex molecularly-selected patient populations Basket/Octopus trials) as well as trials in immuno-oncology.
- We have expanded our expertise in drugs targeting developmental pathways, cell signaling (PI3K, BRAF, MET, FGFR), and immunotherapy (PD1/PDL1, OX40, CD40, engineered antibodies).
- In collaboration with VHIO's Cancer Genomics and Translational Genomics Groups, we benefit from cutting-edge technology platforms including the MiSeq, Hiseq 2500 NextGen sequencers, and nCounter Nanostring to analyze circulating-free tumor DNA.

  We also co-develop customized molecular tests for VHIO's Prescreening Program (disease-oriented mutation panels for our NGS platforms).
- We have developed alliances with many pharma companies as the preferred site for testing their novel and most relevant therapies, including GlaxoSmithKline OCTC, Roche ImCORE, and AstraZeneca/MedImmune. We also participate in a project supported by Horizon 2020's European Union funding for Research and Innovation to co-develop integrative bioinformatics tools for genomic analysis: MedBioinformatics (www.medbioinformatics.eu). Lastly, we have also partnered with Thomson Reuters/ Clarivate Analytics to develop tools for determining the relevance of mutations detected in tumors.

## Summary:

Inaugurated in June 2010, thanks to the support received from the *Fundació Bancària "la Caixa"*, the Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", is dedicated to complex clinical trials with drugs in early development (Phase I and early Phase II trials), focusing on novel targets. Occupying a total surface area of 1000 m2 our Unit is located within the General Area of the Vall d'Hebron University Hospital, the Vall d'Hebron Barcelona Hospital Campus. This privileged environment with direct access to patients, coupled with VHIO's translational approach to research and superb scientific framework, has enabled our Unit to rapidly establish itself as one of the few comprehensive facilities in Europe to rapidly transform latest discovery into benefits for patients.

By promoting tight connectivity between oncology care and research we establish novel treatment models for patients with highly selective drugs and advance insights into tumor diseases and how to treat them in an individualized way - getting the right therapy to the right patient at the right time. As the figures show, we are gradually doing so for an increasing number of patients. In 2017, 120 phase I clinical trials and 17 basket studies were performed at the Unit with a total of 445 patients enrolled. The Unit's facilities coupled with our multidisciplinary clinical teams, enable us continue to expand our portfolio of phase I studies.

Research carried out at our Unit by VHIO's Early Clinical Drug Development Group, centers on the development of new drugs based on the molecular profile of each tumor as well as the optimization of treatment regimens using combinations of new agents with those that already exist. In accordance with VHIO's purely translational model, our studies are also linked with several research lines led by other VHIO groups, thus connecting molecular biology and optimal tumor models with pharmacology and innovative clinical research. VHIO scientists also collaborate closely in our trials to facilitate biomarker development, a profound understanding of the mechanism of action, as well as research into mechanisms of resistance.

In partnership with VHIO's Molecular Oncology and Cancer Genomics Groups, we perform molecular analyses of patients' tumors to select the best possible treatment with the experimental therapeutics available. Thanks to our Cancer Genomics Group's development of existing applications for faster results including n-counter Nanostring, BEAMing (Sysmex), Droplet Digital PCR (ddpCR) Bio-Rad Technology, MiSeq and HiSeq (Illumina), we continue to drive faster and more precise mutational analyses of tumor suppressor genes as well as translocations and gene amplifications. UITM incorporates a multidisciplinary team comprised of medical oncologists, clinical trial coordinators and data managers, nurses and nurse technicians, pharmacists, as well as administrative personnel.

Excellent patient treatment and care as well as pioneering research is also made possible thanks to the collaboration of many other oncology professionals including our team of Clinical Research Oncology Nurses (pages 104-105), pathologists from the Vall d'Hebron University Hospital's Molecular Pathology Department, radiologists and interventional radiologists, as well as our Clinical Trials Office (pages 100-101), Database Management, Clinical Research Oncology Pharmacy Unit (pages 106-107), and other healthcare specialists including dermatologists, cardiologists, and ophthalmologists.

VHIO's Transversal Clinical Trials Core Services & Units

# Clinical Research Oncology Nurses


Nurse Supervisor
Ángeles Peñuelas

Nurse Coordinators
Sonia Valverde
Lydia Velez

Nurses
Irene Calzado
Cristina Casal
Meritxell Cucurell
Elena de Cabo
Carla Junyent
Margarida Marcos
Marta Mate
Núria Membrives
Mireia Milán
Isabel Muñoz
Silvia Puyalto
Sandra Rojas
Tania Sánchez
Alex Sierra

Nursing Assistants
Dominika Dudek
Alicia López
María Martín
Ana Belén Ortiz

Nurse Supervisor's Assistant
Juan Manuel García

Secretary
Teresa Mendoza

## Summary:

Clinical trials in oncology are essential for the identification of novel, more effective targeted therapies against cancer as well as improving survival, side effect profiles and the quality of life of patients. Advances in oncology care and the development of more powerful anti-cancer medicines are driven by optimal processes in clinical trials.

Our expert clinical research oncology nurses assume a central role in these processes by undertaking a variety of roles including identifying trends in side effects, closely collaborating with multidisciplinary teams to develop and evaluate patient management, contributing to clinical studies by collating samples and quality data, as well as providing excellence in nursing care and symptom management of all our patients enrolled in clinical trials.

VHIO's Clinical Research Oncology Nurses, specialized in molecular therapies, are headed by Angeles Peñuelas and represent a critical element of the multidisciplinary oncology teams involved in the clinical trials performed and coordinated at VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" and Clinical Trials Office, directed by Elena Garralda and Gemma Sala, respectively.

Supporting these teams comprised of medical oncologists, molecular pathologists, oncology pharmacists, clinical researchers, and study coordinators, VHIO's oncology nurses are key to ensuring the delivery of excellent care whereby patients receive the full range of expertise, guidance, and the necessary follow-up throughout the course of their participation in a particular clinical study.

In 2017, across the 355 actively recruiting trials patient enrollment totalled at 1096. Additionally our clinical teams follow up all patients that were recruited prior to 2017 who are still enrolled and receiving treatment.

As VHIO continues to expand its portfolio of clinical trials to ultimately establish novel treatments with highly selective drugs and fine-tune patient selection criteria in order to identify those patients who are most likely to benefit from them, we can expect a steady increase in patient recruitment across our clinical studies - now and in the future.

VHIO's Transversal Clinical Trials Core Services & Units

# Clinical Research Oncology Pharmacy Unit

## Strategic goals:

- Excellence in the services we provide to clinical oncology research programs through optimal efficacy, efficiency and safety.
- Traceability of management and preparation of drugs for clinical trials.
- Preparation and administration of clinical study drugs according to protocol specifications.
- Maximize control of storage temperature of samples and preparations.
- Incorporation and validation of a new computerized program named IPharma/ FUNDANET for the management of clinical trial supplies.
- Incorporation of oral administration therapeutic schedules in our prescription software. Provide a pharmaceutical care program for patients in Phase I trials with oral medication (to improve safety, compliance and efficacy of treatments), as well as instructions and indications to patients for orally administered therapies in Phase II and III studies.
- Successful sponsor audits as well as inspections carried out by regulatory authorities.

## Highlights:

- Substitution of the current computerized program for the management of clinical trial drugs with the new IPharma/FUNDANET.
- Initiation of the implementation of an electronic program for oral drug prescriptions.
- Clinical and technical support for the prescription /preparation /administration of cytostatics in clinical trials, providing e-records of usage and timings.
- Qualitative and quantitative quality control of all parenteral anticancer preparations to guarantee patient safety and protocol compliance.
- ISO9001:2015 certification renewed.
- 28 successful sponsor audits.

Coordinator Of The Clinical Research Oncology Pharmacy Unit
Maria Josep Carreras Soler

Coordinator Of Pharmacological Research In Oncology Support Unit
Laura Mañós Pujol

Pharmacists
María Alcalde
Faten Ahmad
Isabel de la Paz
Anna Farriols Danés
Cristina Fernández
Celia Gonzalez
Pablo La Torre
Gloria Molas
Eugenia Palacio
Núria Sabaté
Carol Valdivia Vadell
Jana Vidal Otero

Technicians
Romina Bellini
Laura Blanch
Esther Carabantes
Rafa Diaz
Susana Mulet
Isabel Pérez
Marta Pozo
Gemma Tomás
Sílvia Torralba
Noemí Visús

Clinical Trials Re-Supplies Managers
Maria Hidalgo
Sara Pizarro López
Esther Vilaró

## Summary:

Our Unit is ISO 9001:2015 certified and associated to the Medical Oncology Service of the Vall d'Hebron University Hospital (HUVH). We focus on two main clinical research programs:

1) Oncology Pharmaceutical Care Program: incorporating a team of pharmacists specializing in hospital pharmacy and oncology pharmacy as well as laboratory technicians, we prepare cytostatics and other parenteral anti-cancer drugs used in clinical trials. We also monitor and follow-up patients.
2) Pharmacological Research in Oncology Support Program: led by a team of pharmacists and laboratory technicians specialized in clinical trials, we manage, store, issue and control samples for clinical trials.

In 2017 we managed clinical trial drugs for 564 active studies in oncology, and supply deliveries totaled at 5957. We also continue to benefit from our cutting-edge system for controlling storage temperature which, performing electronic temperature recordings every 5 minutes, displays readings on computers equipped with audiovisual alarms as well as an around the clock SMS alert system for temperature deviations.

Regarding the design and validation of our drug preparation process traceability system we ensure the qualitative and quantitative quality control of our computerized system incorporating barcode technology, electronic scales and voice technology (Verbio Speech Technologies-Directed Work system).

This year, dispensing staff have participated in 87 pre-study visits, 156 initial visits, 1784 monitoring visits, 99 close-out visits, and have successfully passed 23 audits, 2 mock inspections and 1 EMA inspection. In addition, 31,635 clinical trial drugs have been dispensed and validated by a pharmacist; 11,052 of which are for oral administration and 1067 for IM/ Subcutaneous Administration. A total of 156 Standardized Dispensing Procedures for clinical trials have been drawn up and we have performed 675 updates of these procedures. 108 storage temperature data reports have been prepared by dispensing staff.

Preparation staff have participated in 11 pre-study visits, 127 initial visits, 563 monitoring visits, and 17 audits. Preparations of cytostatics, monoclonal antibodies and other parenteral antitumor drugs for clinical trials totaled at 14,375. 127 Standardized Preparation Procedures were compiled, and we also incorporated 404 antineoplastic therapeutic schedules in our prescription software.

Our Pharmaceutical Care Program for patients enrolled in Phase I clinical trials: we carried out 701 visits, 278 screenings, 225 C1D1s, and 198 follow-ups, also compiling patient diaries and/ or instructions for patients in the instance that this documentation was not provided by the respective sponsor. This year we compiled 15 different diaries and 21 instruction manuals, and our dispensing staff also provided these for patients included in all Phase II and Phase III trials involving orally administered drugs. 47 diaries and patient manuals for Phase II and Phase III clinical trials were elaborated in 2017.

# Recently Incorporated VHIO Groups

# Recently Incorporated VHIO Groups

## Recently incorporated

Cellular Plasticity & Cancer Group ..... 110

Experimental Hematology Group ..... 112

Tumor Immunology & Immunotherapy Group ..... 114

## New to VHIO in 2017

Applied Genetics of Metastatic Cancer Group ..... 116

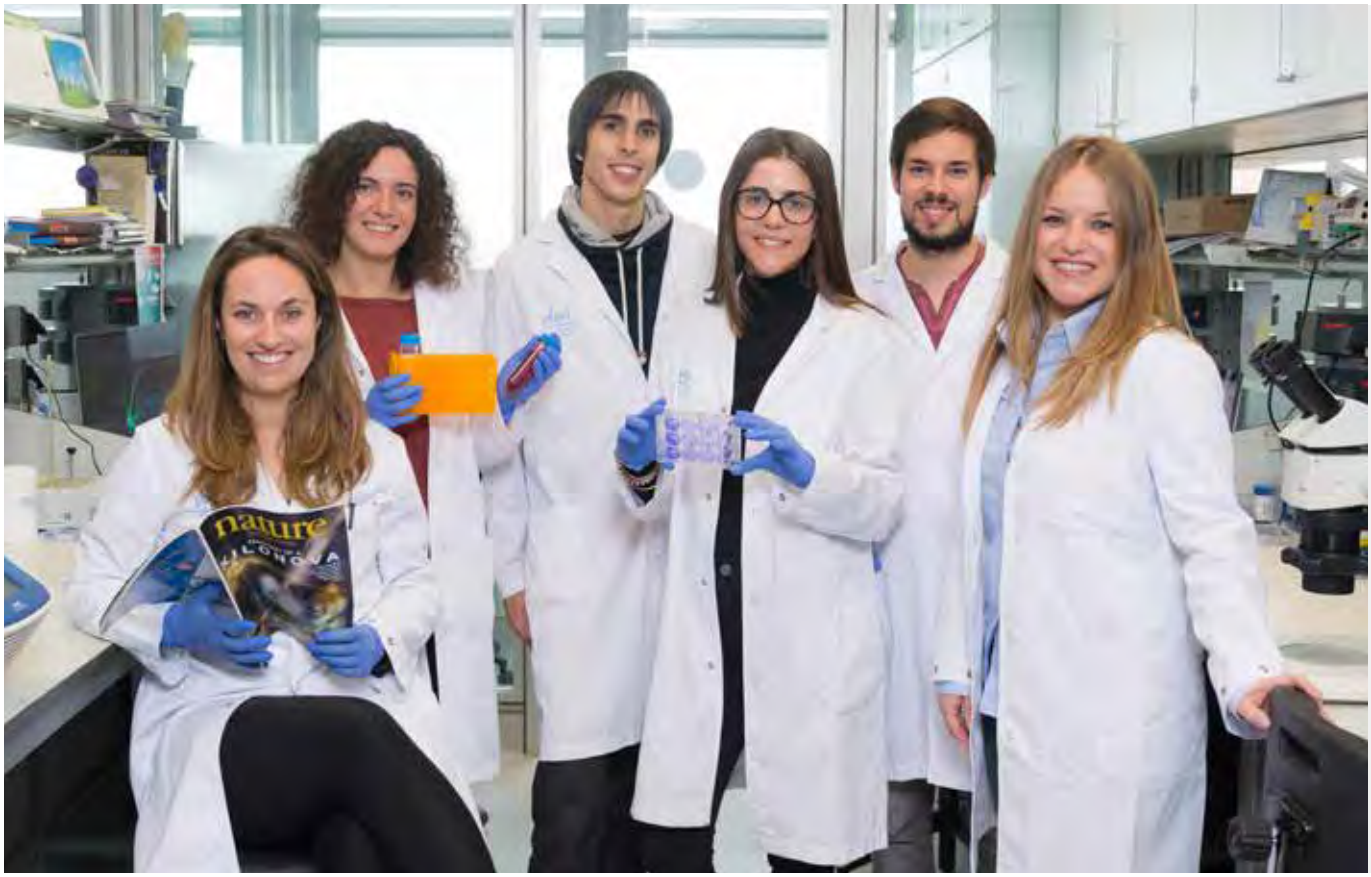
Chromatin Dynamics in Cancer Group ..... 118

Prostate Cancer Translational Research Group ..... 120

Radiomics Group ..... 122

Recently Incorporated VHIO Groups

# Cellular Plasticity & Cancer Group




## Strategic goals:

- Decipher the molecular mechanisms governing the acquisition of stem cell properties during tumorigenesis.
- Identify and characterize novel micropeptides involved in cancer cell plasticity.
- Determine the impact of inducing cellular dedifferentiation in various stages of tumorigenesis (tumor initiation, maintenance, and metastasis), and in the resistance of cancer cells to chemotherapeutic agents.
- Develop new anti-cancer therapies based on the inhibition of cancer cell plasticity.

## Highlights:

- Our group received a grant from the Spanish Association for Cancer Research (AECC) to identify novel cancer-related micropeptides.
- Maria Abad was awarded with the XII FERO Fellowship.
- We have identified three new micropeptides with tumor suppressor activities, and 5 lncRNA-coded micropeptides that are potentially involved in cancer stemness.

Principal Investigator
María Abad

Post-Doctoral Fellow
Elena Senís

Graduate Students
Olga Boix
Emanuela Greco
Iñaki Merino

Student
Noé Crespo

## Summary:

Our group focuses on the interplay between cellular plasticity, stem cells and cancer. Cellular plasticity is recognized today as a critical feature of cancer cells that allows them to transit between different cellular states, including reversible transitions between mesenchymal and epithelial phenotypes, or between stem cell-like and differentiated states.

In 2013, we demonstrated that cellular plasticity can be induced *in vivo*, and somatic cells can dedifferentiate in the adult organism, even reaching pluripotency. Furthermore, we have demonstrated that tissue damage, the main driver of cancer, triggers cell dedifferentiation and the acquisition of stem cell properties.

Importantly, pluripotent stem cells and cancer cells manifest many parallels, and cellular reprogramming and neoplastic transformation are currently viewed as related processes governed by common molecular mechanisms. These observations strongly indicate that cellular plasticity and the acquisition of stem cell properties are important players in carcinogenesis. Moreover, they also bear important therapeutic implications given that chemotherapy and radiotherapy - the cornerstone for the treatment of most cancers - could have the side effect of inducing stemness in non-stem cancer cells and, in turn, possibly contribute to tumor recurrence and metastasis.

Our main objective is to better understand the mechanisms and players implicated in this process, with the ultimate goal of developing new therapies based on the inhibition of cancer cell plasticity.

Recent and surprising findings have demonstrated that some genomic regions, previously considered as non-coding (including lncRNAs), contain small open reading frames encoding for evolutionary conserved, unannotated, micropeptides.

The few identified to-date have been shown to play key functions in processes such as muscle performance, embryonic development and regeneration, opening a new level of complexity with tremendous implications, from basic research to the clinical setting. One of our objectives is to identify micropeptides involved in cancer stemness that could represent novel actors in carcinogenesis.

During 2017, we have made great progress: we have already identified 6 lncRNA-coded micropeptides, analyzed them *in silico*, and cloned them. We are currently performing an exhaustive functional characterization *in vitro* and *in vivo*. So far, we have compelling evidence that three of them act as novel tumor suppressors. The identification and characterization of novel micropeptides could be crucial in advancing insights into cancer physiopathology and better understanding the lack of success with current therapies. Moreover, they could serve as new cancer biomarkers for early detection and patient stratification for tailored therapies as well as therapeutic targets.

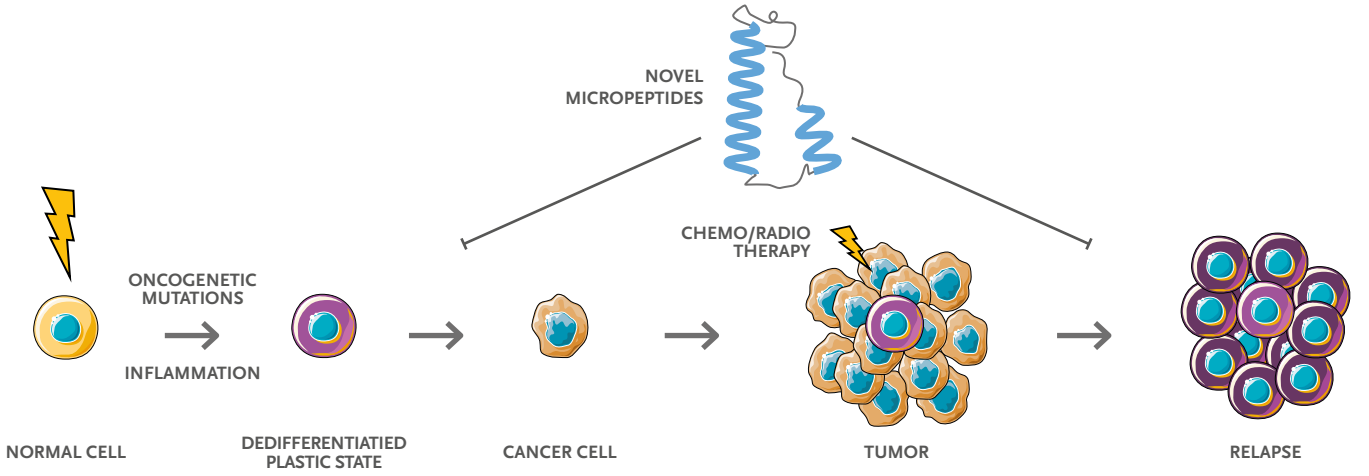



Figure: Working hypothesis by which cellular plasticity and the acquisition of stem cell properties are important players during tumor initiation, maintenance, as well as in tumor relapse after therapy. One of our objectives is to identify novel micropeptides involved in cancer cell plasticity which could offer new therapeutic opportunities.

## PI paper pick:

Abad M, Hashimoto H, Zhou H, Morales MG, Chen B, Bassel-Duby R, Olson EN. Notch inhibition enhances cardiac reprogramming by increasing MEF2c transcriptional activity. *Stem Cell Reports.* 2017 Mar 14;8(3):548-560.

Marión RM, Lopez-de Silanes I, Mosteiro L, Gamache B, Abad M, Guerra C, Megías D, Serrano M, Blasco MA. Common telomere changes during in vivo reprogramming and early stages of tumorigenesis. *Stem Cell Reports.* 2017 Feb 14;8(2):460-475.

Gómez-Cabello D, Checa-Rodriguez C, Abad M, Serrano M, Huertas P. CtIP specific roles during cell reprogramming have long term consequences in iPSC survival and fitness. *Stem Cell Reports.* 2017 Feb 14;8(2):432-445.

Recently Incorporated VHIO Groups

# Experimental Hematology Group

## Strategic goals:

Our main purpose is to translate preclinical findings into clinical benefit through the development of early phase clinical trials and defining new prognostic and predictive factors.

Main research lines currently center on:

- Deciphering the mechanisms involved in pathogenesis and progression of hematological neoplasias.
- The preclinical study of new therapeutic regimens in experimental models that mimic the tumoral microenvironment using primary cells and PDXs.
- Defining new biomarkers for a more rational and precise treatment of patients.

## Highlights:

- We have studied a novel SYK protein inhibitor using our preclinical model of CLL, which has fueled the transition of the drug into the clinic (Purroy et al, *Oncotarget*. 2016).
- In an ortothopic mouse model we have shown that XPO-1 inhibition is effective in CNS lymphomas. We are currently designing a clinical trial for these patients.
- We have defined how an immunosuppressive scenario is related to clinical progression in CLL.
- Leading the work package dedicated to CLL, our group is a member of the European Innovative Medicines Initiative 2 (MI2) Programme's HARMONY Consortium which focuses on all hematological diseases.

Principal Investigator
Francesc Bosch

Translational Research Coordinator
Marta Crespo

Clinical Research Coordinator
Pau Abrisqueta

Phd Students
Sabela Bobillo
Júlia Carabia
Cecilia Carpio
Isabel Jiménez
Júlia Montoro
Guillermo Orti

Post-Doctoral Scientists
Juan Camilo Nieto
Bárbara Tazón

Technician
Lluis Puigdefàbregas

Hematologists/Lab specialists
Pere Barba
Adoración Blanco
Laura Gallur
Merche Gironella
Andrés López
Ana Marín
Bryan Merchan
Pavel Olivera
Margartia Ortega
Carlos Palacio
Verónica Pons
Gaël Roué
Olga Salamero
Amparo Santamaría
David Valcárcel

## Summary:

Biomedical research at VHIO's Experimental Hematology Group focuses on the translational study of hematological neoplasms of both lymphoid and myeloid origin.

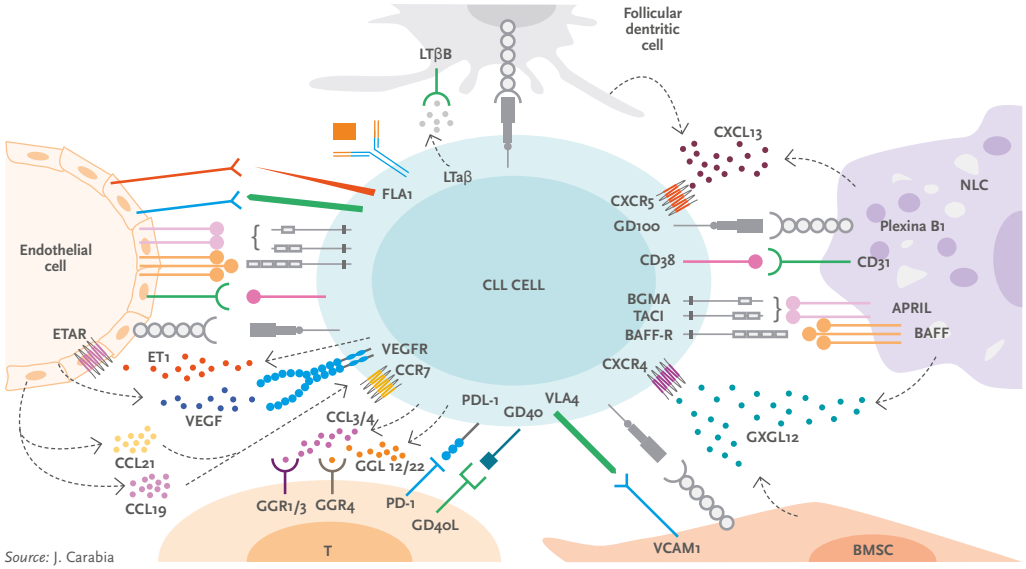
We aim to decipher factors and mechanisms involved in the pathogenesis and progression of hematological malignancies by studying the molecular and microenvironmental mechanisms related to disease progression, response, and resistance to novel therapies, with particular emphasis on the cross-talk between malignant and healthy immune cells. Current projects include the study of chronic lymphocytic leukemia (CLL), diffuse large B cell lymphoma (DLBCL), and acute myeloid leukemia (AML).

Our group also explores new therapeutic avenues for patients diagnosed with hematological malignancies through the ex-vivo assessment of response to novel treatments, taking into account the microenvironmental protection that neoplastic cells found in lymphoid tissues and bone marrow. Over the last few years we have reported important insights into the role of the microenvironment in CLL natural history. This has enabled us to develop a highly reproducible and reliable pre-clinical model of CLL that recapitulates the favorable microenvironment using primary tumoral cells from patients.

We have also developed a PDX model for central nervous system lymphomas in collaboration with Joan Seoane, Director of Translational Research at VHIO and Principal Investigator of our Institute's Gene Expression and Cancer Group. Using this approach we study novel therapeutic options for patients in close collaboration with different pharmaceutical and biotech companies in order to drive new drugs to market, as well design a clinical trial for CNS lymphoma patients. In addition we are studying the role of novel targeted therapies in primary samples from patients with AML.

We are also committed to defining new biomarkers in hematology that will allow for a more rational and precise treatment of patients. These projects include the development of a genetic biomarker platform for lymphoproliferative malignancies through a combination of a customized Next Generation Sequencing panel of genes and detection of gene expression using Nanostring technology. Our group is also studying the role of circulating tumoral DNA detection in cerebrospinal liquid in CNS lymphomas in order to facilitate diagnosis and prediction of CNS relapse in a less invasive manner.

Lastly, we are initiating an ambitious project aimed at unmasking biomarkers of immune activation related to the clinical results of an allogeneic stem cell transplant.




*Source:* J. Carabia

Figure: Interaction between chronic lymphocytic leukemia cells and the tumoral immune microenvironment.

## PI paper pick:

Abrisqueta P, Scott DW, Slack GW, Steidl C, Mottok A, Gascoyne RD, Connors JM, Sehn LH, Savage KJ, Gerrie AS, Villa D. Observation as the initial management strategy in patients with mantle cell lymphoma. *Ann Oncol.* 2017 Oct 1;28(10):2489-2495.

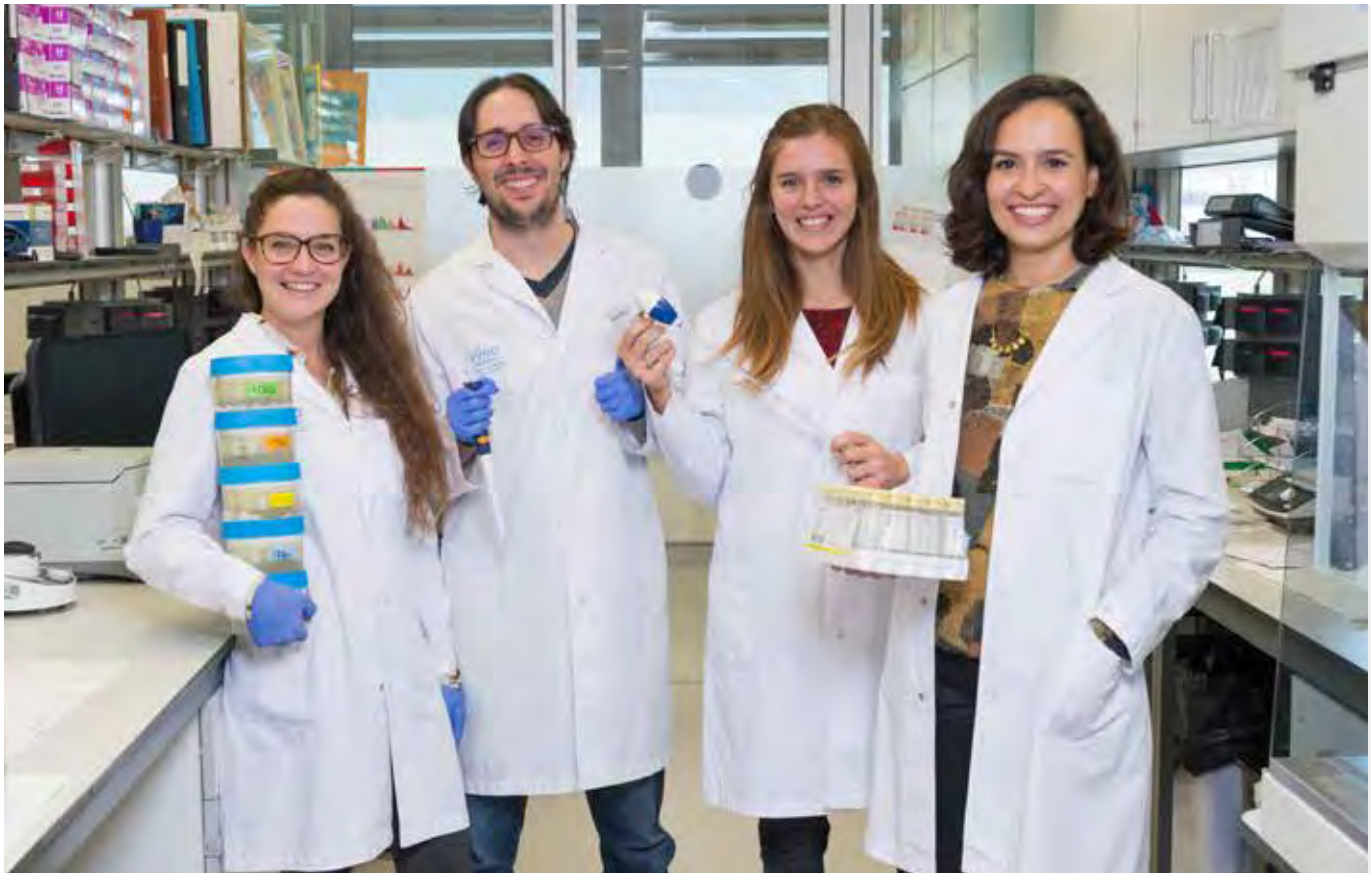
Purroy N, Carabia J, Abrisqueta P, Egia L, Aguiló M, Carpio C, Palacio C, Crespo M, Bosch F. Inhibition of BCR signaling using the Syk inhibitor TAK-659 prevents stroma-mediated signalingin chronic lymphocytic leukemia cells. *Oncotarget.* 2017 Jan 3;8(1):742-756.

Scott DW, Abrisqueta P, Wright GW, Slack GW, Mottok A, Villa D, Jares P, Rauert-Wunderlich H, Royo C, Clot G, Pinyol M, Boyle M, Chan FC, Braziel RM, Chan WC, Weisenburger DD, Cook JR, Greiner TC, Fu K, Ott G, Delabie J, Smeland EB, Holte H, Jaffe ES, Steidl C, Connors JM, Gascoyne RD, Rosenwald A, Staudt LM, Campo E, Rimsza LM; Lymphoma/Leukemia Molecular Profiling Project. New Molecular Assay for the Proliferation Signature in Mantle Cell Lymphoma Applicable to Formalin-Fixed Paraffin-Embedded Biopsies. *J Clin Oncol.* 2017 May 20;35(15):1668-1677.

Vitolo U, Trněný M, Belada D, Burke JM, Carella AM, Chua N, Abrisqueta P, Demeter J, Flinn I, Hong X, Kim WS, Pinto A, Shi YK, Tatsumi Y, Oestergaard MZ, Wenger M, Fingerle-Rowson G, Catalani O, Nielsen T, Martelli M, Sehn LH. Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. *J Clin Oncol.* 2017 Nov 1;35(31):3529-3537.

Recently Incorporated VHIO Groups

# Tumor Immunology & Immunotherapy Group



## Strategic goals:

- Characterize personalized anti-tumor T-cell response in patients with cancer.
- Mine the personalized repertoire of tumor-reactive lymphocytes for potential biomarkers of response to cancer immunotherapy.
- Investigate novel strategies to rapidly identify tumor-reactive lymphocytes as well as the target antigens driving this response.
- Develop personalized T-cell-based cancer immunotherapies for patients with solid cancers.

## Highlights:

- Alena Gros secured funding for 4 new projects.
- Our group has collected over 100 samples from patients treated at the Vall d'Hebron University Hospital (HUVH) to study mechanisms of response and resistance to immunotherapy.
- Alena's group is setting up a collaboration with the Blood and Tissue Bank in Barcelona, to make adoptive cell transfer a clinical reality throughout the region.

Principal Investigator
Alena Gros

Post-Doctoral Fellow
Carlos Alberto Fajardo

Graduate Students
Andrea Garcia
Maria Lozano

Technicians
Daniela Grases
Alejandro Negro

## Summary:

The immune system can recognize and eliminate cancer. However, tumors evade the immune response through multiple mechanisms. Cancer immunotherapy exploits the immune system to attack disease. Clinical studies have established that immune checkpoint inhibitors and T cell-based therapies can mediate tumor regression in patients with metastatic cancer. Thus, in addition to surgery, radiation therapy and chemotherapy, immunotherapy has become the fourth pillar of anti-cancer therapy.

Despite encouraging antitumor responses, only a fraction of patients treated with immunotherapy respond and some develop autoimmune adverse events. There is thus a critical need to personalize these therapies. We are currently investigating mechanisms of response, toxicity and resistance to cancer immunotherapeutics in patients at the Vall d'Hebron University Hospital (HUVH). Our goal is to identify biomarkers of response to these therapies in liquid biopsies.

One of the correlative biomarkers of response to immunotherapy described to-date is mutation burden.

Tumor-specific somatic mutations are optimal targets for cancer immunotherapy and render tumors immunogenic; some of these can bind to the patient's HLA molecules and elicit T-cell responses. Our group uses a highly personalized approach to screen for T-cell mediated recognition of mutated antigens as well as shared antigens using autologous antigen presenting cells that can process and present in all the potential HLA restriction elements (see Figure). Following this strategy, we will explore whether the presence of lymphocytes recognizing these antigens is associated with response. In parallel, we plan to advance personalized T-cell therapies to treat metastatic colorectal cancer, which is largely resistant to current therapeutic strategies.

In summary, our group focuses on better understanding the naturally occurring T-cell response to cancer and establishing ways to exploit these antitumor responses to develop more effective, powerful, and precise immunotherapies against cancer.

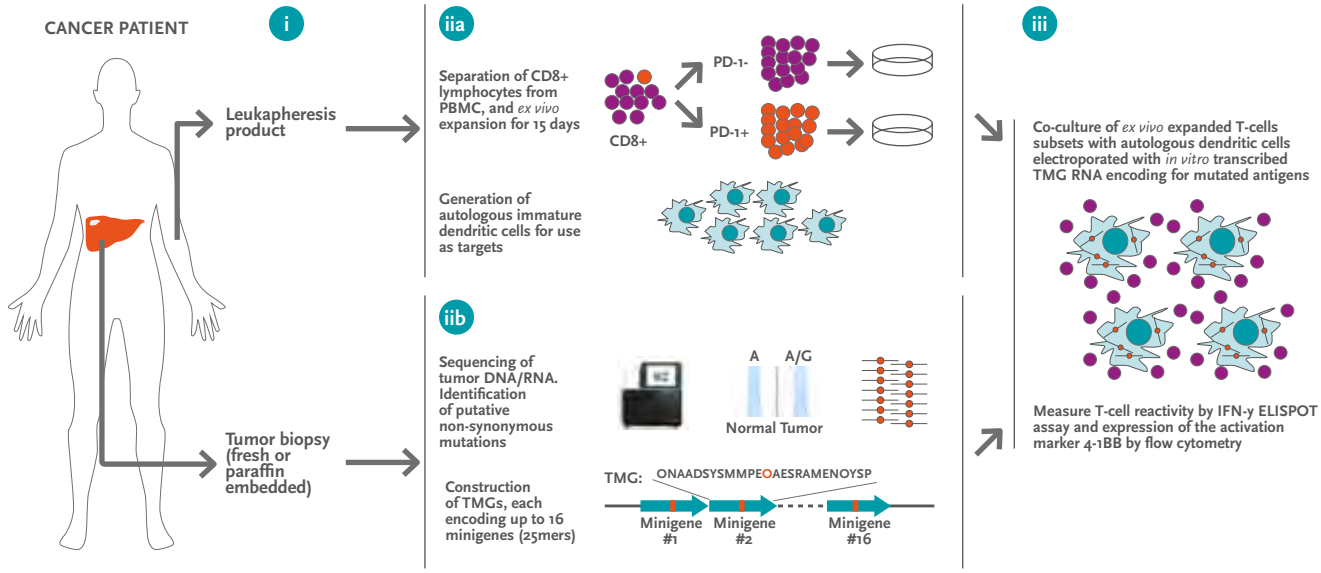



Figure: Personalized strategy to identify neoantigen specific lymphocytes in peripheral blood of cancer patients. (i) Peripheral blood mononuclear cells (PBMC) and a tumor biopsy (fresh or archived) are obtained. (iia) PD-1+ lymphocytes are sorted from the peripheral blood and expanded *ex vivo*. (iib) We extract DNA and RNA from the tumor biopsy and perform exome and RNA sequencing to identify non-synonymous somatic mutations. Tandem minigene (TMG) constructs encoding all the putative mutated 25mers are used as templates to generate *in vitro* transcribed (IVT) RNA. (iii) IVT TMG RNA is used to transfect autologous antigen presenting cells (APCs) used as targets in a co-culture with the *ex vivo* expanded lymphocyte subsets. At 20h, T-cell reactivity is analyzed. (Gros, A. *et al. Nat Med*, 2016).

New to VHIO in 2017

# Applied Genetics of Metastatic Cancer Group

Junior Principal Investigator
Leticia De Mattos-Arruda

## Strategic goals:

- Integrate multi-omics data to better understand genetic heterogeneity and the role of the immune system within and between tumors - longitudinally and in warm autopsy specimens - from patients with metastatic breast cancers.
- Identify biomarkers to more precisely guide the selection of anti-cancer therapies based on the specificities of individual patients.
- Optimize the post-mortem studies of metastatic breast cancer patients in collaboration with VHIO's Breast Cancer Group.
- Use multi-omics to understand differential clinical responses in metastatic breast cancer patients.

## Highlights:

- In collaboration with the Cancer Research UK Cambridge Institute (Carlos Caldas' laboratory), we continue to pursue potentially ground-breaking research aimed at characterising tissue location-dependent and independent genome sequence and microenvironmental changes in metastatic breast cancers.
- Leticia was appointed as ESMO faculty member for breast cancer and also joined the Editorial Board of *ESMO Open: Cancer Horizons*, the Society's online oncology journal, in the breast cancer field (2018 / 2019).
- She has frequently been invited as speaker at national international conferences (13th Meet the Professor, Advanced International Breast Cancer Course(AIBCC) – lecture: *Liquid biopsy: Circulating tumor DNA (ctDNA), Circulating tumor cells (CTCs): Are they ready for clinical use?*, Padua, Italy; 2017 ECCO Congress – lecture: *Circulating tumor DNA: Today,* Amsterdam, Netherlands, January 2017).
- Leticia has participated as an ad hoc breast cancer expert member on the Advisory Board of the European Medicines Agency (EMA).

## Summary:

Established this year, VHIO's Applied Genetics of Metastatic Cancer Group, led by Junior Principal Investigator, Leticia De Mattos-Arruda, leads research using integrated multi-omics data to better understand genetic heterogeneity and the role of the immune system within and between tumors for the identification of new biomarkers to guide patient therapy.

With grounded expertise in applying high-throughput molecular approaches to breast cancer, including cutting-edge massively parallel sequencing methods, her group uses liquid biopsies to more effectively track disease and render targeted therapies more precise.

Currently setting up a multidisciplinary and collaborative effort between VHIO researchers, breast cancer clinicians, pathologists, and bioinformaticians to apply genomics, transcriptomics, *in silico* bioinformatics and histopathologic assessment of tumors, her team will provide further insights into tumor genomic heterogeneity and the role of the microenvironment within and between tumors. The group also aims to discover biomarkers that can be subsequently deployed for monitoring response to therapy and the early detection of disease progression.

Her group has extensive collaborations with leading international investigators in cancer genomics, immuno-oncology and molecular pathology.

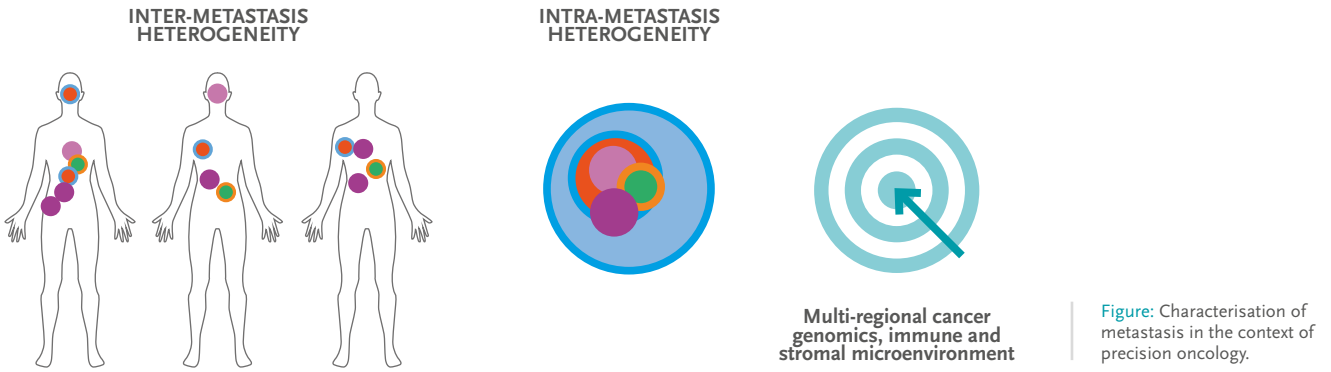



Figure: Characterisation of metastasis in the context of precision oncology.

## PI paper pick:

De Mattos-Arruda L. Liquid biopsy for HER2-positive breast cancer brain metastasis: the role of the cerebro-spinal fluid. *ESMO Open*. 2017 Oct 9;2(4):e000270.

Callari M, Sammut SJ, De Mattos-Arruda L, Bruna A, Rueda OM, Chin SF, Caldas C. Intersect-then-combine approach: improving the performance of somatic variant calling in whole exome sequencing data using multiple aligners and callers. *Genome Med*. 2017 Apr 18;9(1):35.

Ramon YCS, Capdevila C, Hernandez-Losa J, De Mattos-Arruda L, Ghosh A, Lorent J, Larsson O, Aasen T, Postovit L M, Topisirovic I. Cancer as an ecomolecular disease and a neoplastic consortium. *Biochim Biophys Acta*. 2017 Dec;1868(2):484-499.

Banerjee S, Califano R, Corral J, de Azambuja E, De Mattos-Arruda L, Guarneri V, Hutka M, Jordan K, Martinelli E, Mountzios G, Ozturk MA, Petrova M, Postel-Vinay S, Preusser M, Qvortrup C, Volkov MNM, Tabernero J, Olmos D, Strijbos MH. Professional Burnout in European Young Oncologists: Results of The European Society For Medical Oncology (ESMO) Young Oncologists Committee Burnout Survey. *Ann Oncol*. 2017 Jul 1;28(7):1590-1596.

New to VHIO in 2017

# Chromatin Dynamics in Cancer Group

## Strategic goals:

We aim to describe the epigenetic mechanisms controlling the expression of eukaryotic genes during tumor progression. Our group is particularly interested in the role of the primary structure of chromatin fiber, as determined by histone tail modification, and the 3D chromatin structure implicated in the regulation of transcription.

- Identify the molecular mechanisms of chromatin conformation changes in tumor cells; identify potential druggable proteins.
- Discover the key enhancer-promoter interactions during acquisition of malignant traits as well as associated transcription factors.
- The molecular characterization of the LOXL2_BRD4 axis in triple-negative breast cancer (TNBC) cells.

## Highlights:

- Sandra Peiró's group joined VHIO in December 2016.
- We have revealed the role of oxidized histone H3 in chromatin compaction and cell death resistance in triple-negative breast cancer (TNBC).
- Our group has also evidenced the role of Lamin B1 in chromatin reorganization during epithelial-to-mesenchymal transition (EMT).

Principal Investigator
Sandra Peiró

Post-Doctoral Fellow
Gaetano Verde

PhD Students
Marc Cosin
Laura Pascual Reguant
Gemma Serra Bardenys

Technician
Jessica Querol Paños

## Summary:

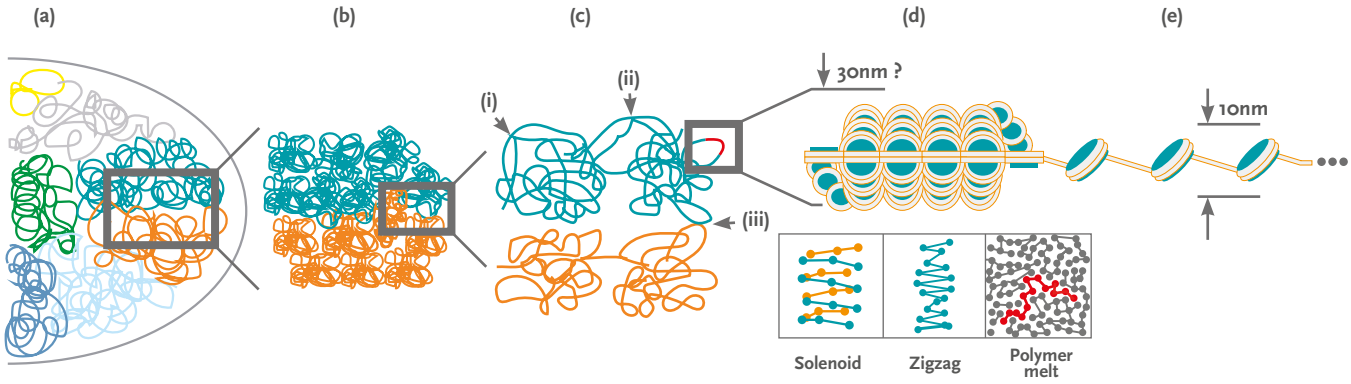
Our group mainly focuses on the characterization of chromatin dynamics and epigenetics in cancer and epithelial-to-mesenchymal transition (EMT). We hypothesize that during tumor progression and acquisition of malignant traits, global epigenetic changes and high-order chromatin reorganization conspire to convert non-invasive cells with the same DNA sequence into more malignant and aggressive ones. Since these cells behave completely differently within the same biological environment, large-scale mapping of genome-related parameters and their subsequent comparison are necessary to better explore genomes towards advancing our understanding as to how they are transformed into malignant cells.

We aim to use highly-established EMT cellular *in vitro* models and patient–derived xenografts (PDXs) in different tumor stages (low to high metastatic states) to fully characterize the necessary epigenetic alterations and high-order chromatin reorganization implicated in this process.

Dedicated to fully exploiting these insights into the epigenetic landscape and 3D structure during this malignant transformation, we will adopt chromosome conformation–based techniques together with ChIP-seq, ATAC-seq and RNA-seq. By combining these data with excellent computational and statistical tools during EMT, we will better navigate this largely uncharted area which promises tremendous potential in early diagnosis.

We also aim to describe the association of chromatin conformation changes with the acquisition of malignant traits and evaluate the functional consequences of these developments in genes and pathways. The next step will involve deciphering how these alterations occur at molecular level to more precisely identify these putative culprits for future targeted therapy.

Finally, we will design a multi-genome PCR set of primes and FISH detection paired with a complete bioinformatics analysis platform, with the ultimate aim of translating our research into benefits for patients at clinical level.




Hübner et al, Current Opinion in Genetics and Development, 2012.

Figure: Chromatin organization in the mammalian nucleus. (a) Chromosomes are organized in chromosome territories. (b) Chromosome territories are comprised of fractal globules, and fractal globules from adjacent chromosome territories can interdigitate. (c) Chromatin fibers interact (i) within a fractal globule (frequent), (ii) between fractal globules of the same chromosome territory (rare), or (iii) between adjacent chromosome territories (very rare). (d) Chromatin may form a 30 nm fiber with a solenoid zigzag, or polymer melt organization (see text). (e) Chromatin is resolved as a 10 nm 'beads on a string' fiber consisting of nucleosomes.

## PI paper pick:

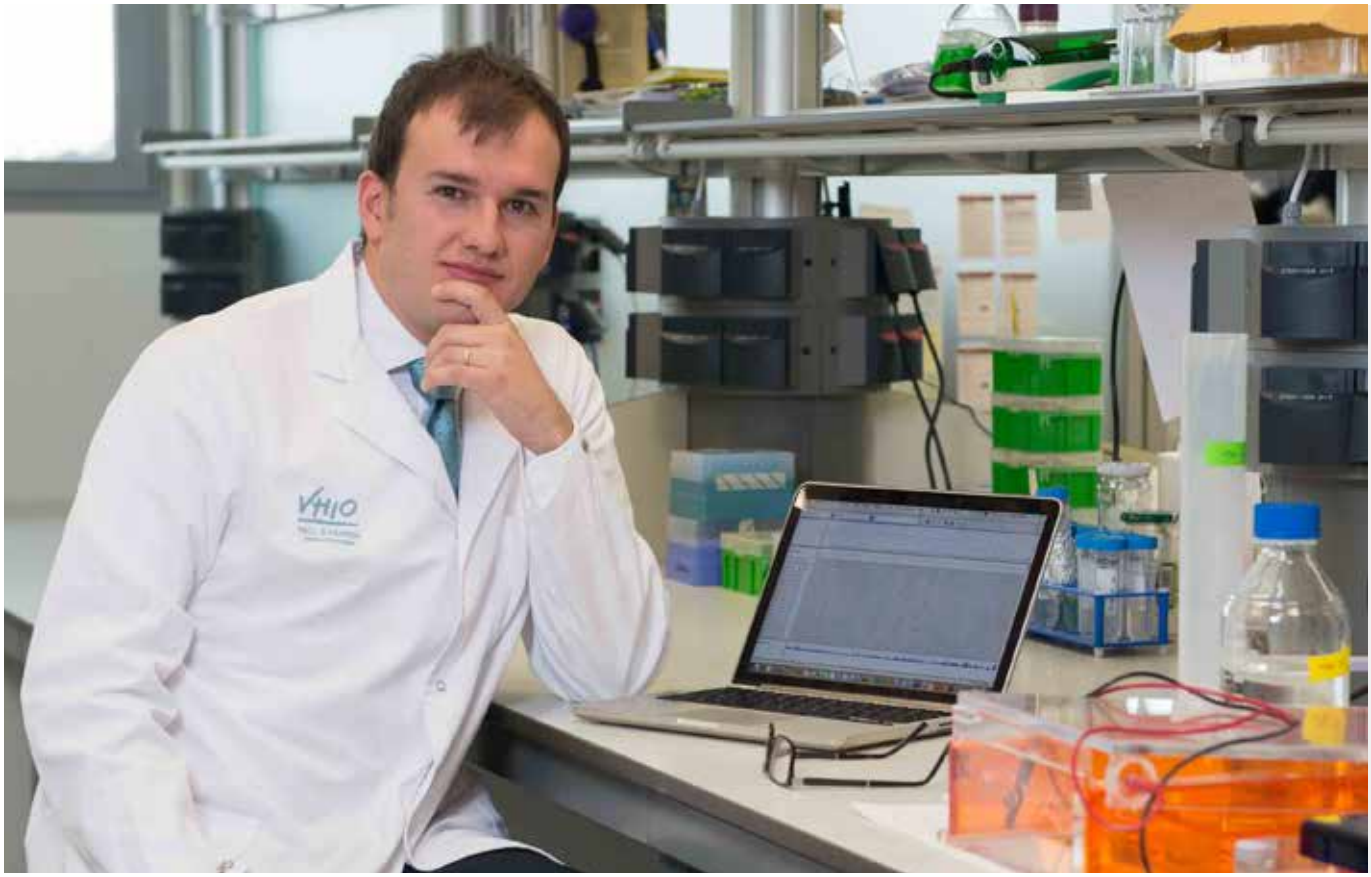
Mazzolini R, Gonzalez N, Garcia-Garijo A, Millanes-Romero A, Peiró S, Smith S, Garcia de Herreros A and Canudas S. Snail1 transcription factor controls telomere transcription and integrity. *Nucleic Acids Res.* 2017 Oct 20.

Izquierdo-Bouldstridge A, Bustillos A, Bonet-Costa C, Aribau-Miralbés P, l García-Gomis D, Dabad M, Esteve-Codina A, Pascual-Reguant L, Peiró S, Esteller M, Murtha M, Millán-Ariño L, Jordan A. Histone H1 depletion triggers an interferon response in cancer cells via activation of heterochromatic repeats. *Nucleic Acids Res.* 2017 Nov 16;45(20):11622-11642.

Verde G, Querol-Paños J, Cebrià-Costa JP, Pascual-Regu ant L, Serra-Bardenys G, Iturbide A and Peiró S. Lysine-Specific Histone Demethylases Contribute to Cellular Differentiation and Carcinogenesis. *Epigenomes.* 2017, 1(1), 4.

New to VHIO in 2017

# Prostate Cancer Translational Research Group




Principal Investigator
Joaquin Mateo

## Strategic goals:

- Advance towards a clinically relevant re-classification of metastatic prostate cancer integrating genotypic and phenotypic data with functional assays.
- Develop prostate cancer molecular stratification assays based on circulating biomarkers.
- Build a precision medicine core for prostate cancer patients treated at the Vall d'Hebron University Hospital (HUVH).

## Highlights:

- Joaquin Mateo joined VHIO in November 2017.
- By the close of 2017, 3 scientists were recruited and will join the group throughout Q1 2018: Alejandro Athie, for genomics and bioinformatics analysis, Gonzalo Hernández, to work on functional molecular biology assays, and Teresa Casals as lab manager.
- Our group, together with VHIO's Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site Group, led by Joan Carles (see pages 76-77 of this Scientific Report), has launched a program to prospectively acquire samples from metastatic lesions and circulating biomarkers from patients with metastatic prostate cancer treated at Vall d'Hebron.

## Summary:

Over the last decade, we have witnessed a true revolution in the treatment of metastatic castration-resistant prostate cancer (mCRPC; the advanced and lethal form of prostate cancer). An improved understanding of its underlying biology has led to the successful development of compounds targeting the androgen signaling pathway, immune system as well as taxanes and radiopharmaceuticals.

Despite the progress in the management of mCRPC, it remains a fatal condition, causing significant morbidity and mortality worldwide. Arguably, the most critical need now in drug development for CRPC is molecular treatment stratification, with the development of drugs in parallel with predictive biomarkers of response. Moreover, the introduction of these novel therapies has driven tumor evolution towards a change in the genomic landscape observed in patients with advanced disease.

Our group aims to serve patients with mCRPC by developing tools towards delivering more individualized patient care based on predictive biomarkers of response and prioritizing the most beneficial anti-cancer medicines and avoiding inefficient treatments for each patient. We will pursue this goal by integrating drug development and clinical trials with correlative biomarker studies from tumor tissue and circulating biomarkers in our laboratory.

Defects in DNA repair genes, particularly in double-strand breaks, are present in 20-25% of mCRPC cases, and will serve as the model to study how we can deliver more precise patient care. We will research how one same gene defect has a functional impact on tumor evolution which can be modulated by the presence of secondary events. Our group will also study the impact of this functional modulation in drug sensitivity assays, focusing on DNA damaging drugs and DNA repair inhibitors to generate hypotheses on optimal patient stratification strategies for clinical trials. We will also study how the use of these drugs can be best combined with therapies targeting androgen signalling.

In order to translate our research into clinical practice, we are setting up the necessary pathways for the systematic collection of tumor metastatic samples - primarily from lesions infiltrating bones - from patients with metastatic prostate cancer treated at Vall d'Hebron, in parallel with blood samples for the study of circulating tumor material.

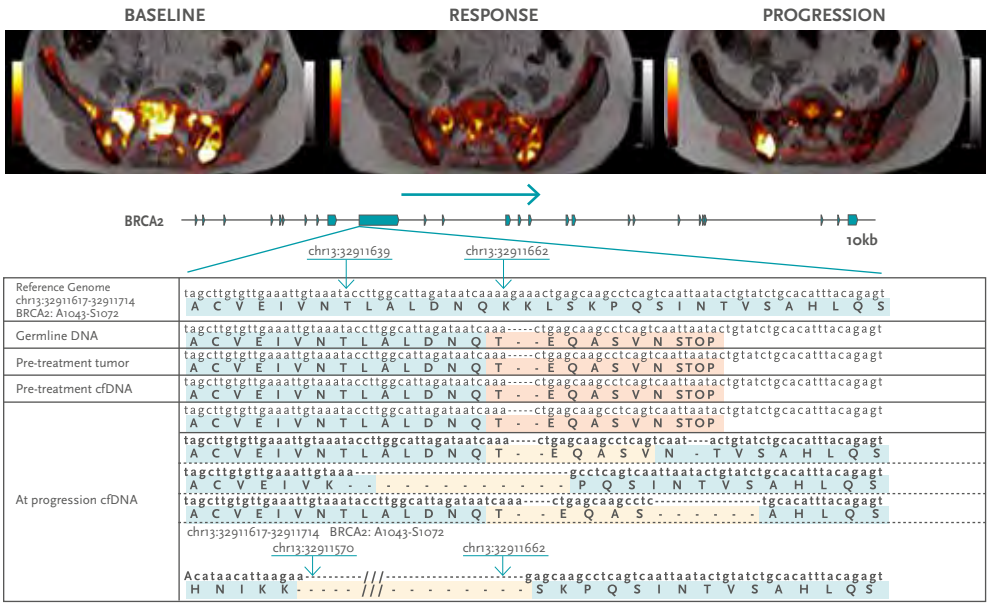



Figure: Studying prostate cancer genomic evolution in response to treatment-induced pressure. Whole-exome sequencing of circulating cfDNA from a prostate cancer patient receiving a PARP inhibitor treatment identifies polyclonal evolution, in parallel to the disease relapse in some of the original locations in the pelvis (adapted from Goodall, Mateo, Yuan et al; *Cancer Discov.* 2017).

## PI paper pick:

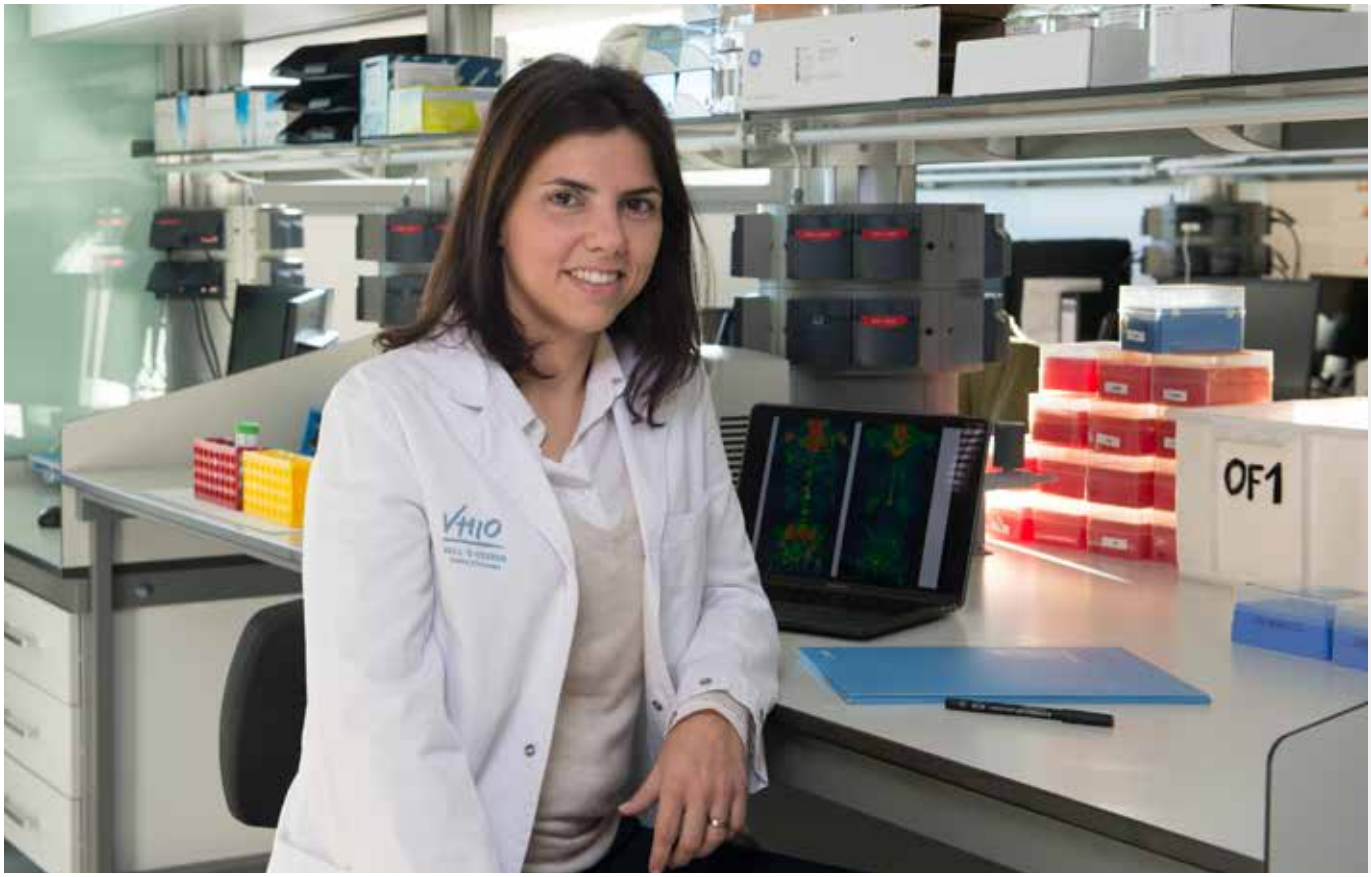
Mateo J, Ganji G, Lemech C, Burris H A, Han S W, Swales K, et al. A First-Time-in-Human Study of GSK2636771, a Phosphoinositide 3 Kinase Beta-Selective Inhibitor, in Patients with Advanced Solid Tumors. *Clin Cancer Res.* 2017 Oct 1;23(19):5981-5992

Goodall J, Mateo J, Yuan W, Mossop H, Porta N, Miranda S, et al. (2017). Circulating Cell-Free DNA to Guide Prostate Cancer Treatment with PARP Inhibition. *Cancer Discov.* 2017 Sep;7(9):1006-1017.

Seed G, Yuan W, Mateo J, Carreira S, Bertan C, Lambros M, Boysen G, Ferraldeschi R, Miranda S, Figueiredo I, Riisnaes R, Crespo M, Rodrigues DN, Talevich E, Robinson DR, Kunju LP, Wu YM, Lonigro R, Sandhu S, Chinnayan A, de Bono JS. Gene Copy Number Estimation From Targeted Next Generation Sequencing Of Prostate Cancer Biopsies: Analytic Validation and Clinical Qualification. *Clin Cancer Res.* 2017 Oct 15;23(20):6070-6077.

New to VHIO in 2017

# Radiomics Group




Principal Investigator
Raquel Perez-Lopez

## Strategic goals:

- Provide expertise in engineering and bioinformatics for the development and clinical qualification of quantitative imaging biomarkers for precision medicine to improve outcomes for cancer patients.
- Use functional imaging for optimizing drug development through clinical trials.
- Integrate radiomics and genomics in translational studies towards a deeper understanding of tumor evolution and mechanisms of resistance to anti-cancer therapies.
- Optimize and standardize imaging acquisition protocols.
- Develop and implement computational models for advanced image processing.

## Highlights:

- Our Radiomics Group launched at VHIO in October 2017.
- Research focuses on the development and validation of novel imaging biomarkers in oncology.
- Multiple collaborations with VHIO groups and other institutions have already been established.
- We continue to expand existing partnerships with other groups and establish new ones in order to increase the incorporation of imaging studies within translational research projects.
- We apply imaging biomarkers and radiomics to research in oncology.

## Summary:

The Radiomics Group was set up at VHIO in October 2017. Since then we have acquired the necessary devices to review medical images and perform post-processing imaging analysis. Two workstations with 4MP display systems, DICOM viewers and imaging analysis software with segmenting tools are available for our group's exclusive use.

We have established collaborations with leading imaging research groups such as the Computing Vision Centre (CVC, Barcelona) and the biomedical research company for imaging biomarkers development, QUIBIM S.L (Valencia). In partnership, we have designed different projects for which we have applied for funding through international grants. We will first initiate an imaging study with functional and anatomical MRI sequences for patients treated with immunotherapy to further establish VHIO as a leading cancer research center in the development of immunotherapeutics. Our goal is to develop and validate novel predictive and response biomarkers for immunotherapy.

We have also established interdisciplinary collaborations with various VHIO groups to work together on several translational research projects. This team science approach is key to optimizing imaging and accelerating translational cancer discovery.

Our group will soon incorporate a postdoc MR researcher to provide support towards advancing novel imaging biomarker development in oncology. We are also pleased to soon welcome our first MSc student and clinical research fellow, and are currently recruiting other new talents to join us.

Aimed at applying imaging biomarkers and radiomics to cancer science, our efforts center on advancing precision imaging in personalized medicine towards ultimately improving outcomes for cancer patients.

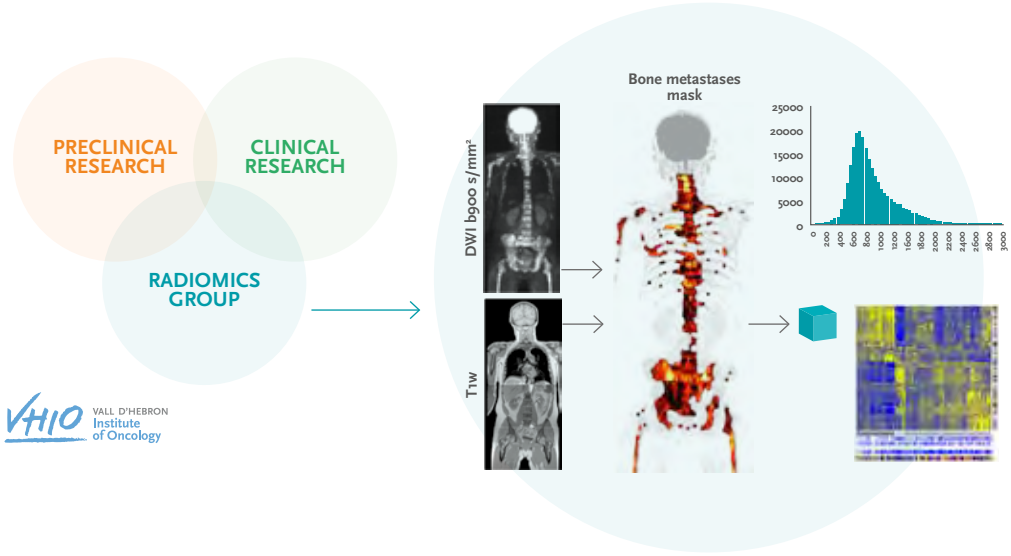



Figure: Integrating radiomics in translational research to advance precision medicine in oncology.

## PI paper pick:

Perez-Lopez R, Roda D, Jimenez B, Brown J, Mateo J, Carreira S, Lopez J, Banerji U, Molife R, Koh DM, Kaye S, de Bono J, Tunariu N and Yap T. High Frequency of Radiological Differential Responses with Poly (ADP-ribose) Polymerase Inhibitor Therapy. *Oncotarget.* 2017 Nov 6;8(61):104430-104443.

Perez-Lopez R, Nava Rodrigues D, Figueiredo I, Mateo J, Collins D, Koh DM, de Bono J, Tunariu N. Multi-Parametric Magnetic Resonance Imaging of Prostate Cancer Bone Disease: Correlation with Bone Biopsy Histological and Molecular Features. *Invest Radiol.* 2017 Sep 12.

Perez-Lopez R, Mateo J, Mossop H, Blackledge MD, Collins DJ, Rata M, Morgan VA, Macdonald A, Sandhu S, Lorente D, Rescigno P, Zafeiriou Z, Bianchini D, Porta N, Hall E, Leach MO, de Bono JS, Koh DM, Tunariu N. Diffusion-weighted Imaging as a Treatment Response Biomarker Evaluating Bone Metastases in Prostate Cancer: A Pilot Study. *Radiology.* 2017 Apr; 283(1):168-177.

# Full listing of articles published by VHIO investigators in 2017

## Articles published by VHIO Investigators in 2017 with allocated Impact Factor (IF):

First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. Carbone DP; Reck M; Paz-Ares L; Creelan B; Horn L; Steins M; Felip E; van den Heuvel MM; Ciuleanu TE; Badin F; Ready N; Hiltermann TJN; Nair S; Juergens R; Peters S; Minenza E; Wrangle JM; Rodriguez-Abreu D; Borghaei H; Blumenschein GR; Villaruz LC; Havel L; Krejci J; Corral Jaime J; Chang H; Geese WJ; Bhagavatheeswaran P; Chen AC; Socinski MA; CheckMate 026 Investigators. 2017. *N Engl J Med.* 376: 2415-2426. IF: 72,406

Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. Peters S; Camidge DR; Shaw AT; Gadgeel S; Ahn JS; Kim DW; Ou SI; Pérol M; Dziadziuszko R; Rosell R; Zeaiter A; Mitry E; Golding S; Balas B; Noe J; Morcos PN; Mok T; ALEX Trial Investigators. 2017. *N Engl J Med.* 377: 829-838. IF: 72,406

Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Tewari KS; Sill MW; Penson RT; Huang H; Ramondetta LM; Landrum LM; Oaknin A; Reid TJ; Leitao MM; Michael HE; DiSaia PJ; Copeland LJ; Creasman WT; Stehman FB; Brady MF; Burger RA; Thigpen JT; Birrer MJ; Waggoner SE; Moore DH; Look KY; Koh WJ; Monk BJ. 2017. *Lancet.* 390: 1654-1663. IF: 47,831

Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Coleman RL; Oza AM; Lorusso D; Aghajanian C; Oaknin A; Dean A; Colombo N; Weberpals JI; Clamp A; Scambia G; Leary A; Holloway RW; Gancedo MA; Fong PC; Goh JC; O'Malley DM; Armstrong DK; Garcia-Donas J; Swisher EM; Floquet A; Konecny GE; McNeish IA; Scott CL; Cameron T; Maloney L; Isaacson J; Goble S; Grace C; Harding TC; Raponi M; Sun J; Lin KK; Giordano H; Ledermann JA; ARIEL3 investigators. 2017. *Lancet.* 390: 1949-1961. IF: 47,831

mTORC1-dependent AMD1 regulation sustains polyamine metabolism in prostate cancer. Zabala-Letona A; Arruabarrena-Aristorena A; Martín-Martín N; Fernandez-Ruiz S; Sutherland JD; Clasquin M; Tomas-Cortazar J; Jimenez J; Torres I; Quang P; Ximenez-Embun P; Bago R; Ugalde-Olano A; Loizaga-Iriarte A; Lacasa-Viscasillas I; Unda M; Torrano V; Cabrera D; van Liempd SM; Cendon Y; Castro E; Murray S; Revandkar A; Alimonti A; Zhang Y; Barnett A; Lein G; Pirman D; Cortazar AR; Arreal L; Prudkin L; Astobiza I; Valcarcel-Jimenez L; Zuñiga-García P; Fernandez-Dominguez I; Piva M; Caro-Maldonado A; Sánchez-Mosquera P; Castillo-Martín M; Serra V; Beraza N; Gentilella A; Thomas G; Azkargorta M; Elortza F; Farràs R; Olmos D; Efeyan A; Anguita J; Muñoz J; Falcón-Pérez JM; Barrio R; Macarulla T; Mato JM; Martinez-Chantar ML; Cordon-Cardo C; Aransay AM; Marks K; Baselga J; Tabernero J; Nuciforo P; Manning BD; Marjon K; Carracedo A. 2017. *Nature.* 547: 109-0. IF: 40,137

CANCER: A precision approach to tumour treatment. Dienstmann R; Tabernero J. 2017. *Nature.* 548: 40-41. IF: 40,137

CANCER: Division hierarchy leads to cell heterogeneity. Seoane J. 2017. *Nature.* 549: 164-166. IF: 40,137

Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. Bullman S; Pedamallu CS; Sicinska E; Clancy TE; Zhang X; Cai D; Neuberg D; Huang K; Guevara F; Nelson T; Chipashvili O; Hagan T; Walker M; Ramachandran A; Diosdado B; Serna G; Mulet N; Landolfi S; Ramon Y Cajal S; Fasani R; Aguirre AJ; Ng K; Élez E; Ogino S; Tabernero J; Fuchs CS; Hahn WC; Nuciforo P; Meyerson M. 2017. *Science.* 358: 1443-0. IF: 37,205

Consensus molecular subtypes and the evolution of precision medicine in colorectal cancer. Dienstmann R; Vermeulen L; Guinney J; Kopetz S; Tejpar S; Tabernero J. 2017. *Nat Rev Cancer.* 17: 79-92. IF: 37,147

Interrogating open issues in cancer precision medicine with patient-derived xenografts. Byrne AT; Alférez DG; Amant F; Annibali D; Arribas J; Biankin AV; Bruna A; Budinská E; Caldas C; Chang DK; Clarke RB; Clevers H; Coukos G; Dangles-Marie V; Eckhardt SG; Gonzalez-Suarez E; Hermans E; Hidalgo M; Jarzabek MA; de Jong S; Jonkers J; Kemper K; Lanfrancone L; Mælandsmo GM; Marangoni E; Marine JC; Medico E; Norum JH; Palmer HG; Peeper DS; Pelicci PG; Piris-Gimenez A; Roman-Roman S; Rueda OM; Seoane J; Serra V; Soucek L; Vanhecke D; Villanueva A; Vinolo E; Bertotti A; Trusolino L. 2017. *Nat Rev Cancer.* 17: 254-268. IF: 37,147

Drugging the 'undruggable' cancer targets. Dang CV; Reddy EP; Shokat KM; Soucek L. 2017. *Nat Rev Cancer.* 17: 502-508. IF: 37,147

Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Swisher EM; Lin KK; Oza AM; Scott CL; Giordano H; Sun J; Konecny GE; Coleman RL; Tinker AV; O'Malley DM; Kristeleit RS; Ma L; Bell-McGuinn KM; Brenton JD; Cragun JM; Oaknin A; Ray-Coquard I; Harrell MI; Mann E; Kaufmann SH; Floquet A; Leary A; Harding TC; Goble S; Maloney L; Isaacson J; Allen AR; Rolfe L; Yelensky R; Raponi M; McNeish IA. 2017. *Lancet Oncol.* 18: 75-87. IF: 33,900

HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. Llombart-Cussac A; Cortés J; Paré L; Galván P; Bermejo B; Martínez N; Vidal M; Pernas S; López R; Muñoz M; Nuciforo P; Morales S; Oliveira M; de la Peña L; Peláez A; Prat A. 2017. *Lancet Oncol.* 18: 545-554. IF: 33,900

Maintenance therapy with vinflunine plus best supportive care versus best supportive care alone in patients with advanced urothelial carcinoma with a response after first-line chemotherapy (MAJA; SOGUG 2011/02): a multicentre, randomised, controlled, open-label, phase 2 trial. García-Donas J; Font A; Pérez-Valderrama B; Virizuela JA; Climent MÁ; Hernando-Polo S; Arranz JÁ; Del Mar Llorente M; Lainez N; Villa-Guzmán JC; Mellado B; Del Alba AG; Castellano D; Gallardo E; Anido U; Del Muro XG; Domènech M; Puente J; Morales-Barrera R; Pérez-Gracia JL; Bellmunt J. 2017. *Lancet Oncol.* 18: 672-681. IF: 33,900

Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Baselga J; Im SA; Iwata H; Cortés J; De Laurentiis M; Jiang Z; Arteaga CL; Jonat W; Clemons M; Ito Y; Awada A; Chia S; Jagiello-Gruszfeld A; Pistilli B; Tseng LM; Hurvitz S; Masuda N; Takahashi M; Vuylsteke P; Hachemi S; Dharan B; Di Tomaso E; Urban P; Massacesi C; Campone M. 2017. *Lancet Oncol.* 18: 904-916. IF: 33,900

Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Shaw AT; Kim TM; Crinò L; Gridelli C; Kiura K; Liu G; Novello S; Bearz A; Gautschi O; Mok T; Nishio M; Scagliotti G; Spigel DR; Deudon S; Zheng C; Pantano S; Urban P; Massacesi C; Viraswami-Appanna K; Felip E. 2017. *Lancet Oncol.* 18: 874-886. IF: 33,900

Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Kim SB; Dent R; Im SA; Espié M; Blau S; Tan AR; Isakoff SJ; Oliveira M; Saura C; Wongchenko MJ; Kapp AV; Chan WY; Singel SM; Maslyar DJ; Baselga J; LOTUS investigators. 2017. *Lancet Oncol.* 18: 1360-1372. IF: 33,900

The Cancer Moonshot from a European perspective. Ciardiello F; Tabernero J. 2017. *Lancet Oncol.* 18: 626-0. IF: 33,900

Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Shaw AT; Felip E; Bauer TM; Besse B; Navarro A; Postel-Vinay S; Gainor JF; Johnson M; Dietrich J; James LP; Clancy JS; Chen J; Martini JF; Abbattista A; Solomon BJ. 2017. *Lancet Oncol.* 18: 1590-1599. IF: 33,900

CIViC is a community knowledgebase for expert crowdsourcing the clinical interpretation of variants in cancer. Griffith M; Spies NC; Krysiak K; McMichael JF; Coffman AC; Danos AM; Ainscough BJ; Ramirez CA; Rieke DT; Kujan L; Barnell EK; Wagner AH; Skidmore ZL;

Wollam A; Liu CJ; Jones MR; Bilski RL; Lesurf R; Feng YY; Shah NM; Bonakdar M; Trani L; Matlock M; Ramu A; Campbell KM; Spies GC; Graubert AP; Gangavarapu K; Eldred JM; Larson DE; Walker JR; Good BM; Wu C; Su AI; Dienstmann R; Margolin AA; Tamborero D; Lopez-Bigas N; Jones SJ; Bose R; Spencer DH; Wartman LD; Wilson RK; Mardis ER; Griffith OL. 2017. *Nat Genet.* 49: 170-174. IF: 27,959

Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Phelan CM; Kuchenbaecker KB; Tyrer JP; Kar SP; Lawrenson K; Winham SJ; Dennis J; Pirie A; Riggan MJ; Chornokur G; Earp MA; Lyra PC; Lee JM; Coetzee S; Beesley J; McGuffog L; Soucy P; Dicks E; Lee A; Barrowdale D; Lecarpentier J; Leslie G; Aalfs CM; Aben KKH; Adams M; Adlard J; Andrulis IL; Anton-Culver H; Antonenkova N; AOCS study group; Aravantinos G; Arnold N; Arun BK; Arver B; Azzollini J; Balmaña J; Banerjee SN; Barjhoux L; Barkardottir RB; Bean Y; Beckmann MW; Beeghly-Fadiel A; Benitez J; Bermisheva M; Bernardini MQ; Birrer MJ; Bjorge L; Black A; Blankstein K; Blok MJ; Bodelon C; Bogdanova N; Bojesen A; Bonanni B; Borg Å; Bradbury AR; Brenton JD; Brewer C; Brinton L; Broberg P; Brooks-Wilson A; Bruinsma F; Brunet J; Buecher B; Butzow R; Buys SS; Caldes T; Caligo MA; Campbell I; Cannioto R; Carney ME; Cescon T; Chan SB; Chang-Claude J; Chanock S; Chen XQ; Chiew YE; Chiquette J; Chung WK; Claes KBM; Conner T; Cook LS; Cook J; Cramer DW; Cunningham JM; D'Aloisio AA; Daly MB; Damiola F; Damirovna SD; Dansonka-Mieszkowska A; Dao F; Davidson R; DeFazio A; Delnatte C; Doheny KF; Diez O; Ding YC; Doherty JA; Domchek SM; Dorfling CM; Dörk T; Dossus L; Duran M; Dürst M; Dworniczak B; Eccles D; Edwards T; Eeles R; Eilber U; Ejlertsen B; Ekici AB; Ellis S; Elvira M; EMBRACE Study; et al. 2017. *Nat Genet.* 49: 680-691. IF: 27,959

Identification of ten variants associated with risk of estrogen-receptor-negative breast cancer. Milne RL; Kuchenbaecker KB; Michailidou K; Beesley J; Kar S; Lindström S; Hui S; Lemaçon A; Soucy P; Dennis J; Jiang X; Rostamianfar A; Finucane H; Bolla MK; McGuffog L; Wang Q; Aalfs CM; ABCTB Investigators; Adams M; Adlard J; Agata S; Ahmed S; Ahsan H; Aittomäki K; Al-Ejeh F; Allen J; Ambrosone CB; Amos CI; Andrulis IL; Anton-Culver H; Antonenkova NN; Arndt V; Arnold N; Aronson KJ; Auber B; Auer PL; Ausems MGEM; Azzollini J; Bacot F; Balmaña J; Barile M; Barjhoux L; Barkardottir RB; Barrdahl M; Barnes D; Barrowdale D; Baynes C; Beckmann MW; Benitez J; Bermisheva M; Bernstein L; Bignon YJ; Blazer KR; Blok MJ; Blomqvist C; Blot W; Bobolis K; Boeckx B; Bogdanova NV; Bojesen A; Bojesen SE; Bonanni B; Børresen-Dale AL; Bozsik A; Bradbury AR; Brand JS; Brauch H; Brenner H; Bressac-de Paillerets B; Brewer C; Brinton L; Broberg P; Brooks-Wilson A; Brunet J; Brüning T; Burwinkel B; Buys SS; Byun J; Cai Q; Caldés T; Caligo MA; Campbell I; Canzian F; Caron O; Carracedo A; Carter BD; Castelao JE; Castera L; Caux-Moncoutier V; Chan SB; Chang-Claude J; Chanock SJ; Chen X; Cheng TD; Chiquette J; Christiansen H; Claes KBM; Clarke CL; Conner T; Conroy DM; Cook J; Cordina-Duverger E; Cornelissen S; Coupier I; Cox A; Cox DG; Cross SS; Cuk K; Cunningham JM; Czene K; Daly MB; Damiola F; Darabi H; Davidson R; De Leeneer K; Devilee P; Dicks E; Diez O; Ding YC; Ditsch N; Doheny KF; Domchek SM; Dorfling CM; Dörk T; Dos-Santos-Silva I; Dubois S; Dugué PA; Dumont M; Dunning AM; Durcan L; Dwek M; Dworniczak B; Eccles D; Eeles R; Ehrencrona H; Eilber U; Ejlertsen B; Ekici AB; Eliassen AH; EMBRACE; et al. 2017. *Nat Genet.* 49: 1767-1778. IF: 27,959

Pembrolizumab in patients with extensive-stage small-cell lung cancer: Results from the phase Ib KEYNOTE-028 study. Ott PA; Elez E; Hiret S; Kim DW; Morosky A; Saraf S; Piperdi B; Mehnert JM. 2017. *J Clin Oncol.* 35: 3823-3829. IF: 24,008

Targeting RET in patients with RET-rearranged lung cancers: Results from the global, multicenter RET registry. Gautschi O; Milia J; Filleron T; Wolf J; Carbone DP; Owen D; Camidge R; Narayanan V; Doebele RC; Besse B; Remon-Masip J; Janne PA; Awad MM; Peled N; Byoung CC; Karp DD; Van Den Heuvel M; Wakelee HA; Neal JW; Mok TSK; Yang JCH; Ou SI; Pall G; Froesch P; Zalcman G; Gandara DR; Riess JW; Velcheti V; Zeidler K; Diebold J; Früh M; Michels S; Monnet I; Popat S; Rosell R; Karachaliou, N; Rothschild SI; Shih JY; Warth A; Muley T; Cabillic F; Mazières J; Drilon A. 2017. *J Clin Oncol.* 35: 1403-1410. IF: 24,008

Pertuzumab Use in the Adjuvant Setting: Why Not? Prat A. 2017. *J Clin Oncol.* 35: 1138-0. IF: 24,008

Reply to R.L. Nussbaum et al and J.S. Dolinsky et al. Balmaña J; Nathanson K; Offit K; Robson M; Domchek S. 2017. *J Clin Oncol.* 35: 1262-1263. IF: 24,008

Osimertinib in Pretreated T790M-Positive Advanced Non-Small-Cell Lung Cancer: AURA Study Phase II Extension Component. Yang JC; Ahn MJ; Kim DW; Ramalingam SS; Sequist LV; Su WC; Kim SW; Kim JH; Planchard D; Felip E; Blackhall F; Haggstrom D; Yoh K; Novello S; Gold K; Hirashima T; Lin CC; Mann H; Cantarini M; Ghiorghiu S; Jänne PA. 2017. *J Clin Oncol.* 35: 1288-0. IF: 24,008

New Molecular Assay for the Proliferation Signature in Mantle Cell Lymphoma Applicable to Formalin-Fixed Paraffin-Embedded Biopsies. Scott DW; Abrisqueta P; Wright GW; Slack GW; Mottok A; Villa D; Jares P; Rauert-Wunderlich H; Royo C; Clot G; Pinyol M; Boyle M; Chan FC; Braziel RM; Chan WC; Weisenburger DD; Cook JR; Greiner TC; Fu K; Ott G; Delabie J; Smeland EB; Holte H; Jaffe ES; Steidl C; Connors JM; Gascoyne RD; Rosenwald A; Staudt LM; Campo E; Rimsza LM; Lymphoma/Leukemia Molecular Profiling Project. 2017. *J Clin Oncol.* 35: 1668-1677. IF: 24,008

Prediction of breast and prostate cancer risks in male BRCA1 and BRCA2 mutation carriers using polygenic risk scores. Lecarpentier J; Silvestri V; Kuchenbaecker KB; Barrowdale D; Dennis J; McGuffog L; Soucy P; Leslie G; Rizzolo P; Navazio AS; Valentini V; Zelli V; Lee A; Amin Al Olama A; Tyrer JP; Southey M; John EM; Conner TA; Goldgar DE; Buys SS; Janavicius R; Steele L; Ding YC; Neuhausen SL; Hansen TVO; Osorio A; Weitzel JN; Toss A; Medici V; Cortesi L; Zanna I; Palli D; Radice P; Manoukian S; Peissel B; Azzollini J; Viel A; Cini G; Damante G; Tommasi S; Peterlongo P; Fostira F; Hamann U; Evans DG; Henderson A; Brewer C; Eccles D; Cook J; Ong KR; Walker L; Side LE; Porteous ME; Davidson R; Hodgson S; Frost D; Adlard J; Izatt L; Eeles R; Ellis S; Tischkowitz M; EMBRACE; Godwin AK; Meindl A; Gehrig A; Dworniczak B; Sutter C; Engel C; Niederacher D; Steinemann D; Hahnen E; Hauke J; Rhiem K; Kast K; Arnold N; Ditsch N; Wang-Gohrke S; Wappenschmidt B; Wand D; Lasset C; Stoppa-Lyonnet D; Belotti M; Damiola F; Barjhoux L; Mazoyer S; GEMO Study Collaborators; Van Heetvelde M; Poppe B; De Leeneer K; Claes KBM; de la Hoya M; Garcia-Barberan V; Caldes T; Perez Segura P; Kiiski JI; Aittomäki K; Khan S; Nevanlinna H; van Asperen CJ; HEBON; Vaszko T; Kasler M; Olah E; Balmaña J; Gutiérrez-Enríquez S; Diez O; Teulé A; Izquierdo A; Darder E; Brunet J; et al. 2017. *J Clin Oncol.* 35: 2240-2250. IF: 24,008

Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1–positive endometrial cancer: Results from the KEYNOTE-028 study. Ott PA; Bang YJ; Berton-Rigaud D; Elez E; Pishvaian MJ; Rugo HS; Puzanov I; Mehnert JM; Aung KL; Lopez J; Carrigan M; Saraf S; Chen M; Soria JC. 2017. *J Clin Oncol.* 35: 2535-2541. IF: 24,008

HELOISE: Phase IIIb randomized multicenter study comparing standard-of-care and higher-dose trastuzumab regimens combined with chemotherapy as first-line therapy in patients with human epidermal growth factor receptor 2–positive metastatic gastric or gastroesophageal junction adenocarcinoma. Shah MA; Xu RH; Bang YJ; Hoff PM; Liu T; Herráez-Baranda LA; Xia F; Garg A; Shing M; Tabernero J. 2017. *J Clin Oncol.* 35: 2558-2567. IF: 24,008

Phase II Trial of Atezolizumab As First-Line or Subsequent Therapy for Patients With Programmed Death-Ligand 1-Selected Advanced Non-Small-Cell Lung Cancer (BIRCH). Peters S; Gettinger S; Johnson ML; Jänne PA; Garassino MC; Christoph D; Toh CK; Rizvi NA; Chaft JE; Carcereny Costa E; Patel JD; Chow LQM; Koczywas M; Ho C; Früh M; van den Heuvel M; Rothenstein J; Reck M; Paz-Ares L; Shepherd FA; Kurata T; Li Z; Qiu J; Kowanetz M; Mocci S; Shankar G; Sandler A; Felip E. 2017. *J Clin Oncol.* 35: 2781-0. IF: 24,008

Treatment Efficacy, Adherence, and Quality of Life Among Women Younger Than 35 Years in the International Breast Cancer Study Group TEXT and SOFT Adjuvant Endocrine Therapy Trials. Saha P; Regan MM; Pagani O; Francis PA; Walley BA; Ribi K; Bernhard J; Luo W; Gómez HL; Burstein HJ; Parmar V; Torres R; Stewart J; Bellet M; Perelló A; Dane F; Moreira A; Vorobiof D; Nottage M; Price KN; Coates AS; Goldhirsch A; Gelber RD; Colleoni M; Fleming GF; SOFT; TEXT Investigators; International Breast Cancer Study Group. 2017. *J Clin Oncol.* 35: 3113-0. IF: 24,008

Phase III study comparing a reduced dose of cabazitaxel (20 mg/m2) and the currently approved dose (25 mg/m2) in postdocetaxel patients with metastatic castration-resistant prostate cancer - PROSELICA. Eisenberger M; Hardy-Bessard AC; Kim CS; Géczi L; Ford D; Mourey L; Carles J; Parente P; Font A; Kacso G; Chadjaa M; Zhang W; Bernard J; de Bono J. 2017. *J Clin Oncol.* 35: 3198-3206. IF: 24,008

Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. Vitolo U; Trnený M; Belada D; Burke JM; Carella AM; Chua N; Abrisqueta P; Demeter J; Flinn I; Hong X; Kim WS; Pinto A; Shi YK; Tatsumi Y;

Oestergaard MZ; Wenger M; Fingerle-Rowson G; Catalani O; Nielsen T; Martelli M; Sehn LH. 2017. *J Clin Oncol.* 35: 3529-3537. IF: 24,008

Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). Horn L; Spigel DR; Vokes EE; Holgado E; Ready N; Steins M; Poddubskaya E; Borghaei H; Felip E; Paz-Ares L; Pluzanski A; Reckamp KL; Burgio MA; Kohlhäeufl M; Waterhouse D; Barlesi F; Antonia S; Arrieta O; Fayette J; Crinò L; Rizvi N; Reck M; Hellmann MD; Geese WJ; Li A; Blackwood-Chirchir A; Healey D; Brahmer J; Eberhardt WEE. 2017. *J Clin Oncol.* 35: 3924-0. IF: 24,008

Targeting c-MET in gastrointestinal tumours: Rationale, opportunities and challenges. Bradley CA; Salto-Tellez M; Laurent-Puig P; Bardelli A; Rolfo C; Tabernero J; Khawaja HA; Lawler M; Johnston PG; Van Schaeybroeck S; MErCuRIC consortium. 2017. *Nat Rev Clin Oncol.* 14: 562-576. IF: 20,693

A first-in-human phase I study of the ATP-competitive AKT inhibitor Ipatasertib demonstrates Robust and safe targeting of AKT in patients with solid tumors. Saura C; Roda D; Roselló S; Oliveira M; Macarulla T; Pérez-Fidalgo JA; Morales-Barrera R; Sanchis-García JM; Musib L; Budha N; Zhu J; Nannini M; Chan WY; Sanabria Bohórquez SM; Meng RD; Lin K; Yan Y; Patel P; Baselga J; Tabernero J; Cervantes A. 2017. *Cancer Discov.* 7: 102-113. IF: 20,011

A phase Ib dose-escalation study of encorafenib and cetuximab with or without alpelisib in metastatic BRAF-mutant colorectal cancer. van Geel RM; Tabernero J; Elez E; Bendell JC; Spreafico A; Schuler M; Yoshino T; Delord JP; Yamada Y; Lolkema M; Faris JE; Eskens FA; Sharma S; Yaeger R; Lenz HJ; Wainberg ZA; Avsar E; Chatterjee A; Jaeger S; Tan E; Maharry K; Demuth T; Schellens JH. 2017. *Cancer Discov.* 7: 610-619. IF: 20,011

Improving the armamentarium of PI3K inhibitors with isoform-selective agents: A new light in the darkness. Rodon J; Tabernero J. 2017. *Cancer Discov.* 7: 666-669. IF: 20,011

Erlotinib and bevacizumab in patients with advanced non-small-cell lung cancer and activating EGFR mutations (BELIEF): an international, multicentre, single-arm, phase 2 trial. Rosell R; Dafni U; Felip E; Curioni-Fontecedro A; Gautschi O; Peters S; Massutí B; Palmero R; Aix SP; Carcereny E; Früh M; Pless M; Popat S; Kotsakis A; Cuffe S; Bidoli P; Favaretto A; Froesch P; Reguart N; Puente J; Coate L; Barlesi F; Rauch D; Thomas M; Camps C; Gómez-Codina J; Majem M; Porta R; Shah R; Hanrahan E; Kammler R; Ruepp B; Rabaglio M; Kassapian M; Karachaliou N; Tam R; Shames DS; Molina-Vila MA; Stahel RA; BELIEF collaborative group. 2017. *Lancet Respir Med.* 5: 435-444. IF: 19,287

Increased Risk of Colorectal Cancer in Patients With Multiple Serrated Polyps and Their First-Degree Relatives. Egoavil C; Juarez M; Guarinos C; Rodríguez-Soler M; Hernández-Illán E; Alenda C; Payá A; Castillejo A; Serradesanferm A; Bujanda L; Fernández-Bañares F; Cubiella J; de-Castro L; Guerra A; Aguirre E; Herreros-de-Tejada A; Bessa X; Herráiz M; Marín-Gabriel JC; Balmaña J; Piñol V; Cuatrecasas M; Balaguer F; Castells A; Soto JL; Zapater P; Jover R. 2017. *Gastroenterology.* 153: 106-1122. IF: 18,392

Association of survival benefit with docetaxel in prostate cancer and total number of cycles administered: A post hoc analysis of the Mainsail study. de Morrée ES; Vogelzang NJ; Petrylak DP; Budnik N; Wiechno PJ; Sternberg CN; Doner K; Bellmunt J; Burke JM; Ochoa de Olza M; Choudhury A; Gschwend JE; Kopyltsov E; Flechon A; van As N; Houede N; Barton D; Fandi A; Jungnelius U; Li S; Li JS; de Wit R. 2017. *JAMA Oncol.* 3: 68-75. IF: 16,559

RNA Sequencing to Predict Response to Neoadjuvant Anti-HER2 Therapy A Secondary Analysis of the NeoALTTO Randomized Clinical Trial. Fumagalli, Debora; Venet, David; Ignatiadis, Michail; Azim, Jr., Hatem A.; Maetens, Marion; Rothe, Francoise; Salgado, Roberto; Bradbury, Ian; Pusztai, Lajos; Harbeck, Nadia; Gomez, Henry; Chang, Tsai-Wang; Coccia-Portugal, Maria Antonia; Di Cosimo, Serena; de Azambuja, Evandro; de la Pena, Lorena; Nuciforo, Paolo; Brase, Jan C.; Huober, Jens; Baselga, Jose; Piccart, Martine; Loi, Sherene; Sotiriou, Christos. 2017. *JAMA Oncol.* 3: 227-234. IF: 16,559

Prognostic and Predictive Relevance of Primary Tumor Location in Patients With RAS Wild-Type Metastatic Colorectal Cancer Retrospective Analyses of the CRYSTAL and FIRE-3 Trials. Tejpar, Sabine; Stintzing, Sebastian; Ciardiello, Fortunato; Tabernero, Josep; Van Cutsem, Eric; Beier, Frank; Esser, Regina; Lenz, Heinz-Josef; Heinemann, Volker. 2017. *JAMA Oncol.* 3: 194-201. IF:16,559

Effect of fluorouracil, leucovorin, and oxaliplatin with or without onartuzumab in HER2-negative, MET-positive gastroesophageal adenocarcinoma: The METGastric randomized clinical trial. Shah MA; Bang YJ; Lordick F; Alsina M; Chen M; Hack SP; Bruey JM; Smith D; McCaffery I; Shames DS; Phan S; Cunningham D. 2017. *JAMA Oncol.* 3: 620-627. IF: 16,559

Nomogram-based Prediction of Overall Survival in Patients with Metastatic Urothelial Carcinoma Receiving First-line Platinum-based Chemotherapy: Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC). Necchi A; Sonpavde G; Lo Vullo S; Giardiello D; Bamias A; Crabb SJ; Harshman LC; Bellmunt J; De Giorgi U; Sternberg CN; Cerbone L; Ladoire S; Wong YN; Yu EY; Chowdhury S; Niegisch G; Srinivas S; Vaishampayan UN; Pal SK; Agarwal N; Alva A; Baniel J; Golshayan AR; Morales-Barrera R; Bowles DW; Milowsky MI; Theodore C; Berthold DR; Daugaard G; Sridhar SS; Powles T; Rosenberg JE; Galsky MD; Mariani L; RISC Investigators. 2017. *Eur Urol.* 71: 281-289. IF: 16,265

Prognostic Significance of Venous Thromboembolic Events in Disseminated Germ Cell Cancer Patients. Gonzalez-Billalabeitia E; Castellano D; Sobrevilla N; Guma J; Hervas D; Luengo MI; Aparicio J; Sanchez-Muñoz A; Mellado B; Saenz A; Valverde C; Fernandez A; Margeli M; Duran I; Fernandez S; Sastre J; Ros S; Maroto P; Manneh R; Cerezuela P; Carmona-Bayonas A; Spanish Germ Cell Cancer Group/Grupo Germinal (SGCCG). 2017. *J Natl Cancer Inst.* IF: 12,589

Prognostic Value of BRAF and KRAS Mutations in MSI and MSS Stage III Colon Cancer. Taieb J; Le Malicot K; Shi Q; Penault Lorca F; Bouché O; Tabernero J; Mini E; Goldberg RM; Folprecht G; Luc Van Laethem J; Sargent DJ; Alberts SR; Francois Emile J; Laurent Puig P; Sinicrope FA. 2017. *J Natl Cancer Inst.* IF: 12,589

Evaluation of Polygenic Risk Scores for Breast and Ovarian Cancer Risk Prediction in BRCA1 and BRCA2 Mutation Carriers. Kuchenbaecker KB; McGuffog L; Barrowdale D; Lee A; Soucy P; Dennis J; Domchek SM; Robson M; Spurdle AB; Ramus SJ; Mavaddat N; Terry MB; Neuhausen SL; Schmutzler RK; Simard J; Pharoah PDP; Offit K; Couch FJ; Chenevix-Trench G; Easton DF; Antoniou AC; Lush M; Hamann U; Southey M; John EM; Chung WK; Daly MB; Buys SS; Goldgar DE; Dorfling CM; van Rensburg EJ; Chun Ding Y; Ejlertsen B; Gerdes AM; Hansen TV; Slager S; Hallberg E; Benitez J; Osorio A; Cohen N; Lawler W; Weitzel JN; Peterlongo P; Pensotti V; Dolcetti R; Barile M; Bonanni B; Azzollini J; Manoukian S; Peissel B; Radice P; Savarese A; Papi L; Giannini G; Fostira F; Konstantopoulou I; Adlard J; Brewer C; Cook J; Davidson R; Eccles D; Eeles R; Ellis S; Frost D; Hodgson S; Izatt L; Lalloo F; Ong KR; Godwin AK; Arnold N; Dworniczak B; Engel C; Gehrig A; Hahnen E; Hauke J; Kast K; Meindl A; Niederacher D; Schmutzler RK; Varon-Mateeva R; Wang-Gohrke S; Wappenschmidt B; Barjhoux L; Collonge-Rame MA; Elan C; Golmard L; GEMO Study Collaborators; EMBRACE; Barouk-Simonet E; Lesueur F; Mazoyer S; Sokolowska J; Stoppa-Lyonnet D; Isaacs C; Claes KBM; Poppe B; de la Hoya M; Garcia-Barberan V; Aittomaki K; Nevanlinna H; Ausems MGEM; de Lange JL; Gomez Garcia EB; Hogervorst FB; HEBON; Kets CM; Meijers-Heijboer HE; Oosterwijk JC; Rookus MA; van Asperen CJ; van den Ouweland AMW; van Doorn HC; van Os TAM; Kwong A; Olah E; Diez O; Brunet J; et al. 2017. *J Natl Cancer Inst.* IF: 12,589

Convergent Akt activation drives acquired EGFR inhibitor resistance in lung cancer. Jacobsen K; Bertran-Alamillo J; Molina MA; Teixidó C; Karachaliou N; Pedersen MH; Castellví J; Garzón M; Codony-Servat C; Codony-Servat J; Giménez-Capitán A; Drozdowskyj A; Viteri S; Larsen MR; Lassen U; Felip E; Bivona TG; Ditzel HJ; Rosell R. 2017. *Nat Commun.* 8: 410-0. IF: 12,124

Modulation of telomere protection by the PI3K/AKT pathway. Méndez-Pertuz M; Martínez P; Blanco-Aparicio C; Gómez-Casero E; Belen García A; Martínez-Torrecuadrada J; Palafox M; Cortés J; Serra V; Pastor J; Blasco MA. 2017. *Nat Commun.* 8: 1278-0. IF: 12,124

Single-cell transcriptome conservation in cryopreserved cells and tissues. Guillaumet-Adkins A; Rodríguez-Esteban G; Mereu E; Mendez-Lago M; Jaitin DA; Villanueva A; Vidal A; Martinez-Marti A; Felip E; Vivancos A; Keren-Shaul H; Heath S; Gut M; Amit I; Gut I; Heyn H. 2017. *Genome Biol.* 18: 45-0. IF: 11,908

An update on the management of sporadic desmoid-type fibromatosis: A European Consensus Initiative between Sarcoma PAtients EuroNet (SPAEN) and European Organization for Research and Treatment of Cancer (EORTC)/Soft Tissue and Bone Sarcoma Group (STBSG). Kasper, B.;

Baumgarten, C.; Garcia, J.; Bonvalot, S.; Haas, R.; Haller, F.; Hohenberger, P.; Penel, N.; Messiou, C.; van der Graaf, W.T.; Gronchi, A.; Bauer, S.; Blay, J.Y.; van Coevorden, F.; Dileo, P.; Dürr, H.R.; Fiore, M.; Grünwald, V.; Jones, R.; Judson, I.; Kettelhack, C.; Kopeckova, K.; Lazar, A.; Lindner, L.H.; Martin-Broto, J.; Rutkowski, P.; Stacchiotti, S.; Stoeckle, E.; Valverde, C.; Verhoef, K.; Wardelmann, E.; Wartenberg, M. 2017. *Ann Oncol.* 28: 2399-2408. IF: 11,855

Improving brain penetration of kinase inhibitors in lung cancer patients with oncogene dependency. Remon, J.; Soria, J.C. 2017. *Ann Oncol.* 28: 196-198. IF: 11,855

Research needs in breast cancer. Cardoso F; Harbeck N; Barrios CH; Bergh J; Cortés J; El Saghir N; Francis PA; Hudis CA; Ohno S; Partridge AH; Sledge GW; Smith IE; Gelmon KA. 2017. *Ann Oncol.* 28: 208-217. IF: 11,855

Adherence to capecitabine in preoperative treatment of stage II and III rectal cancer: Do we need to worry? Font R; Espinas JA; Layos L; Martinez Villacampa M; Capdevila J; Tobeña M; Pisa A; Pericay C; Lezcano C; Fort E; Cardona I; Berga N; Solà J; Borras JM. 2017. *Ann Oncol.* 28: 831-835. IF: 11,855

Osimertinib benefit in EGFR-mutant NSCLC patients with T790M-mutation detected by circulating tumour DNA. Remon, J.; Caramella, C.; Jovelet, C.; Lacroix, L.; Lawson, A.; Smalley, S.; Howarth, K.; Gale, D.; Green, E.; Plagnol, V.; Rosenfeld, N.; Planchard, D.; Bluthgen, M.V.; Gazzah, A.; Pannet, C.; Nicotra, C.; Auclin, E.; Soria, J.C.; Besse, B. 2017. *Ann Oncol.* 28: 784-790. IF: 11,855

Pathway level alterations rather than mutations in single genes predict response to HER2-targeted therapies in the neo-ALTTO trial. Shi W; Jiang T; Nuciforo P; Hatzis C; Holmes E; Harbeck N; Sotiriou C; Peña L; Loi S; Rosa DD; Chia S; Wardley A; Ueno T; Rossari J; Eidtmann H; Armour A; Piccart-Gebhart M; Rimm DL; Baselga J; Pusztai L. 2017. *Ann Oncol.* 28: 128-135. IF: 11,855

Incidence and management of diarrhea in patients with HER2-positive breast cancer treated with pertuzumab. Swain SM; Schneeweiss A; Gianni L; Gao JJ; Stein A; Waldron-Lynch M; Heeson S; Beattie MS; Yoo B; Cortes J; Baselga J. 2017. *Ann Oncol.* 28: 761-768. IF: 11,855

Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer: A phase 1 trial. Hui R; Garon EB; Goldman JW; Leighl NB; Hellmann MD; Patnaik A; Gandhi L; Eder JP; Ahn MJ; Horn L; Felip E; Carcereny E; Rangwala R; Lubiniecki GM; Zhang J; Emancipator K; Roach C; Rizvi NA. 2017. *Ann Oncol.* 28: 874-881. IF: 11,855

Adjuvant FOLFOX +/- cetuximab in full RAS and BRAF wildtype stage III colon cancer patients. Taieb J; Balogoun R; Le Malicot K; Tabernero J; Mini E; Folprecht G; Van Laethem JL; Emile JF; Mulot C; Fratté S; Levaché CB; Saban-Roche L; Thaler J; Petersen LN; Bridgewater J; Perkins G; Lepage C; Van Cutsem E; Zaanan A; Laurent-Puig P; for PETACC8 investigators. 2017. *Ann Oncol.* 28: 824-830. IF: 11,855

Prediction of overall survival in stage II and III colon cancer beyond TNM system: a retrospective, pooled biomarker study. Dienstmann, R.; Mason, M. J.; Sinicrope, F. A.; Phipps, A. I.; Tejpar, S.; Nesbakken, A.; Danielsen, S. A.; Sveen, A.; Buchanan, D. D.; Clendenning, M.; Rosty, C.; Bot, B.; Alberts, S. R.; Jessup, J. Milburn; Lothe, R. A.; Delorenzi, M.; Newcomb, P. A.; Sargent, D.; Guinney, J. 2017. *Ann Oncol.* 28: 1023-1031. IF: 11,855

A step towards the harmonization of clinical trials inform consent forms. Remon J; Ferté C. 2017. *Ann Oncol.* 28: 910-912. IF: 11,855

Intratumoral heterogeneity in gastric cancer: a new challenge to face. Alsina M; Gullo I; Carneiro F. 2017. *Ann Oncol.* 28: 912-913. IF: 11,855

A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial. Kulke MH; Ruszniewski P; Van Cutsem E; Lombard-Bohas C; Valle JW; De Herder WW; Pavel M; Degtyarev E; Brase JC; Bubuteishvili-Pacaud L; Voi M; Salazar R; Borbath I; Fazio N; Smith D; Capdevila J; Riechelmann RP; Yao JC. 2017. *Ann Oncol.* 28: 1309-1315. IF: 11,855

Concordance of blood- and tumor-based detection of RAS mutations to guide anti-EGFR therapy in metastatic colorectal cancer. Grasselli J; Elez E; Caratù G; Matito J; Santos C; Macarulla T; Vidal J; Garcia M; Viéitez JM; Paéz D; Falcó E; Lopez Lopez C; Aranda E; Jones F; Sikri V; Nuciforo P; Fasani R; Tabernero J; Montagut C; Azuara D; Dienstmann R; Salazar R; Vivancos A. 2017. *Ann Oncol.* 28: 1294-1301. IF: 11,855

Targeting the fibroblast growth factor receptor 2 in gastric cancer: Promise or pitfall? Hierro C; Alsina M; Sánchez M; Serra V; Rodon J; Tabernero J. 2017. *Ann Oncol.* 28: 1207-1216. IF: 11,855

The search for simplicity: Is this compatible with precision medicine? Nuciforo PG. 2017. *Ann Oncol.* 28: 10-12. IF: 11,855

Phase II randomized study of PM01183 versus topotecan in patients with platinum-resistant/refractory advanced ovarian cancer. Poveda A; Del Campo JM; Ray-Coquard I; Alexandre J; Provansal M; Guerra Alía EM; Casado A; Gonzalez-Martin A; Fernández C; Rodriguez I; Soto A; Kahatt C; Fernández Teruel C; Galmarini CM; Pérez de la Haza A; Bohan P; Berton-Rigaud D. 2017. *Ann Oncol.* 28: 1280-1287. IF: 11,855

A prospective examination of circulating tumor cell profiles in non-small-cell lung cancer molecular subgroups. Lindsay CR; Faugeroux V; Michiels S; Pailler E; Facchinetti F; Ou D; Bluthgen MV; Pannet C; Ngo-Camus M; Bescher G; Caramella C; Billiot F; Remon J; Planchard D; Soria JC; Besse B; Farace F. 2017. *Ann Oncol.* 28: 1523-1531. IF: 11,855

A randomized phase II/III study of cabazitaxel versus vinflunine in metastatic or locally advanced transitional cell carcinoma of the urothelium (SECAVIN). Bellmunt J; Kerst JM; Vázquez F; Morales-Barrera R; Grande E; Medina A; González Graguera MB; Rubio G; Anido U; Fernández Calvo O; González-Billalabeitia E; Van den Eertwegh AJM; Pujol E; Perez-Gracia JL; González Larriba JL; Collado R; Los M; Maciá S; De Wit R; SOGUG and DUOS. 2017. *Ann Oncol.* 28: 1517-1522. IF: 11,855

Professional burnout in European young oncologists: results of the European Society for Medical Oncology (ESMO) Young Oncologists Committee Burnout Survey. Banerjee S; Califano R; Corral J; de Azambuja E; De Mattos-Arruda L; Guarneri V; Hutka M; Jordan K; Martinelli E; Mountzios G; Ozturk MA; Petrova M; Postel-Vinay S; Preusser M; Qvortrup C; Volkov MNM; Tabernero J; Olmos D; Strijbos MH. 2017. *Ann Oncol.* 28: 1590-1596. IF: 11,855

Reply to the letter to the editor 'Addressing the quality of the ESMO-MCBS' by Del Paggio. Cherny NI; Dafni U; Bogaerts J; Pentheroudakis G; Tabernero J; Zielinski C; de Vries EGE. 2017. *Ann Oncol.* 28: 2031-2032. IF: 11,855

Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Arnold D; Lueza B; Douillard JY; Peeters M; Lenz HJ; Venook A; Heinemann V; Van Cutsem E; Pignon JP; Tabernero J; Cervantes A; Ciardiello F. 2017. *Ann Oncol.* 28: 1713-1729. IF: 11,855

Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: Results from two randomized first-line panitumumab studies. Boeckx N; Koukakis R; Op de Beeck K; Rolfo C; Van Camp G; Siena S; Tabernero J; Douillard JY; André T; Peeters M. 2017. *Ann Oncol.* 28: 1862-1868. IF: 11,855

An antisense oligonucleotide targeting TGF-ß2 inhibits lung metastasis and induces CD86 expression in tumor-associated macrophages. Huber-Ruano I; Raventós C; Cuartas I; Sánchez-Jaro C; Arias A; Parra JL; Wosikowski K; Janicot M; Seoane J. 2017. *Ann Oncol.* 28: 2278-2285. IF: 11,855

A randomized, open-label, multicenter, phase 3 study to compare the efficacy and safety of eribulin to treatment of physician's choice in patients with advanced non-small cell lung cancer. Katakami N; Felip E; Spigel DR; Kim JH; Olivo M; Guo M; Nokihara H; Yang JC; Iannotti N; Satouchi M; Barlesi F. 2017. *Ann Oncol.* 28: 2241-2247. IF: 11,855

Reply to the letter to the editor 'Can we trust burnout research?' by Bianchi et al. Banerjee S; Preusser M; Tabernero J; Strijbos M. 2017. *Ann Oncol.* 28: 2625-2626. IF: 11,855

ESMO-Magnitude of Clinical Benefit Scale version 1.1. Cherny NI; Dafni U; Bogaerts J; Latino NJ; Pentheroudakis G; Douillard JY; Tabernero J; Zielinski C; Piccart MJ; de Vries EGE. 2017. *Ann Oncol.* 28: 2340-2366. IF: 11,855

Dual MET and ERBB inhibition overcomes intratumor plasticity in osimertinib-resistant-advanced non-small-cell lung cancer (NSCLC). Martinez-Marti A; Felip E; Matito J; Mereu E; Navarro A; Cedrés S; Pardo N; Martinez de Castro A; Remon J; Miquel JM; Guillaumet-Adkins A; Nadal E; Rodriguez-Esteban G; Arqués O; Fasani R; Nuciforo P; Heyn H; Villanueva A; Palmer HG; Vivancos A. 2017. *Ann Oncol.* 28: 2451-2457. IF: 11,855

Observation as the initial management strategy in patients with mantle cell lymphoma. Abrisqueta P; Scott DW; Slack GW;

Steidl C; Mottok A; Gascoyne RD; Connors JM; Sehn LH; Savage KJ; Gerrie AS; Villa D. 2017. *Ann Oncol.* 28: 2489-2495. IF: 11,855

Reply to the letter to the editor `Including lynch syndrome in personalized prognostication and follow-up of stage II and III colon cancer' by Sciallero et al. Dienstmann R; Guinney J. 2017. *Ann Oncol.* 28: 2889-2890. IF: 11,855

BRAF mutant colorectal cancer: prognosis, treatment, and new perspectives. Sanz-Garcia E; Argiles G; Elez E; Tabernero J. 2017. *Ann Oncol.* 28: 2648-2657. IF: 11,855

Gemcitabine plus sirolimus for relapsed and progressing osteosarcoma patients after standard chemotherapy: a multicenter, single-arm phase II trial of Spanish Group for Research on Sarcoma (GEIS). Martin-Broto J; Redondo A; Valverde C; Vaz MA; Mora J; Garcia Del Muro X; Gutierrez A; Tous C; Carnero A; Marcilla D; Carranza A; Sancho P; Martinez-Trufero J; Diaz-Beveridge R; Cruz J; Encinas V; Taron M; Moura DS; Luna P; Hindi N; Lopez-Pousa A. 2017. *Ann Oncol.* 28: 2994-2999. IF: 11,855

Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab. Arnold D; Fuchs C; Tabernero J; Ohtsu A; Zhu AX; Garon EB; Mackey JR; Paz-Ares L; Baron AD; Okusaka T; Yoshino T; Yoon HH; Das M; Ferry D; Zhang Y; Lin Y; Binder P; Sashegyi A; Chau I. 2017. *Ann Oncol.* 28: 2932-2942. IF: 11,855

Incorporating BEAMing technology as a liquid biopsy into clinical practice for the management of colorectal cancer patients: an expert taskforce review. García-Foncillas J; Alba E; Aranda E; Díaz-Rubio E; López-López R; Tabernero J; Vivancos A. 2017. *Ann Oncol.* 28: 2943-2949. IF: 11,855

DPYD genotype-guided fluoropyrimidines dose: is it ready for prime time? Páez D; Salazar R; Tabernero J. 2017. *Ann Oncol.* 28: 2913-2914. IF: 11,855

A phase 1b/2b multicenter study of oral panobinostat plus azacitidine in adults with MDS, CMML or AML with ≤ 30% blasts. Garcia-Manero G; Sekeres MA; Egyed M; Breccia M; Graux C; Cavenagh JD; Salman H; Illes A; Fenaux P; DeAngelo DJ; Stauder R; Yee K; Zhu N; Lee JH; Valcarcel D; MacWhannell A; Borbenyi Z; Gazi L; Acharyya S; Ide S; Marker M; Ottmann OG. 2017. *Leukemia.* 31: 2799-2806. IF: 11,702

TALEN/CRISPR-mediated engineering of a promoterless anti-viral RNAi hairpin into an endogenous miRNA locus. Senís E; Mockenhaupt S; Rupp D; Bauer T; Paramasivam N; Knapp B; Gronych J; Grosse S; Windisch MP; Schmidt F; Theis FJ; Eils R; Lichter P; Schlesner M; Bartenschlager R; Grimm D. 2017. *Nucleic Acids Res.* IF: 10,162

Histone H1 depletion triggers an interferon response in cancer cells via activation of heterochromatic repeats. Izquierdo-Bouldstridge A; Bustillos A; Bonet-Costa C; Aribau-Miralbés P; García-Gomis D; Dabad M; Esteve-Codina A; Pascual-Reguant L; Peiró S; Esteller M; Murtha M; Millán-Ariño L; Jordan A. 2017. *Nucleic Acids Res.* 45: 11622-11642. IF: 10,162.

miR-206 Inhibits Stemness and Metastasis of Breast Cancer by Targeting MKL1/IL11 Pathway. Samaeekia R; Adorno-Cruz V; Bockhorn J; Chang YF; Huang S; Prat A; Ha N; Kibria G; Huo D; Zheng H; Dalton R; Wang Y; Moskalenko G; Liu H. 2017. *Clin Cancer Res.* 23: 1091-1103. IF: 9,619

F-18-fluoromisonidazole PET and Activity of Neoadjuvant Nintedanib in Early HER2-Negative Breast Cancer: A Window-of-Opportunity Randomized Trial. Quintela-Fandino M; Lluch A; Manso LM; Calvo I; Cortes J; García-Saenz JA; Gil JM; Martinez-Jañez N; González-Martín A; Adrover E; De Andres R; Viñas G; Llombart Cussac A; Alba E; Guerra J; Bermejo B; Zamora E; Moreno-Anton F; Pernas-Simon S; Carrato A; Lopez A; Escudero MJ; Campo R; Carrasco EM; Palacios J; Mulero F; Colomer R. 2017. *Clin Cancer Res.* 23: 1432-1441. IF: 9,619

Isolation of T-cell receptors specifically reactive with mutated tumor-associated antigens from tumor-infiltrating lymphocytes based on CD137 expression. Parkhurst MR; Gros A; Pasetto A; Prickett TD; Crystal JS; Robbins PF; Rosenberg SA. 2017. *Clin Cancer Res.* 23: 2491-2505. IF: 9,619

A PAM50-Based Chemoendocrine Score for Hormone Receptor-Positive Breast Cancer with an Intermediate Risk of Relapse. Prat A; Lluch A; Turnbull AK; Dunbier AK; Calvo L; Albanell J; de la Haba-Rodríguez J; Arcusa A; Chacón I; Sánchez-Rovira P; Plazaola A; Muñoz M; Paré L; Parker JS; Ribelles N; Jimenez B; Bin Aiderus AA; Caballero R; Adamo B; Dowsett M; Carrasco EM; Martín M; Dixon JM; Perou CM; Alba E. 2017. *Clin Cancer Res.* 23: 3035-3044. IF: 9,619

Genomic Profiling of Patient-Derived Xenografts for Lung Cancer Identifies B2M Inactivation Impairing Immunorecognition. Pereira C; Gimenez-Xavier P; Pros E; Pajares MJ; Moro M; Gomez A; Navarro A; Condom E; Moran S; Gomez-Lopez G; Graña O; Rubio-Camarillo M; Martinez-Martí A; Yokota J; Carretero J; Galbis JM; Nadal E; Pisano D; Sozzi G; Felip E; Montuenga LM; Roz L; Villanueva A; Sanchez-Cespedes M. 2017. *Clin Cancer Res.* 23: 3203-3213. IF: 9,619

A phase I–II study of the oral PARP inhibitor rucaparib in patients with germline BRCA1/2-mutated ovarian carcinoma or other solid tumors. Kristeleit R; Shapiro GI; Burris HA; Oza AM; LoRusso PM; Patel M; Domchek SM; Balmaña J; Drew Y; Chen LM; Safra T; Montes A; Giordano H; Maloney L; Goble S; Isaacson J; Xiao J; Borrow J; Rolfe L; Shapira-Frommer R. 2017. *Clin Cancer Res.* 23: 4095-4106. IF: 9,619

A first-in-human, Phase I, dose-escalation study of TAK-117, A selective PI3Ka isoform inhibitor, in patients with advanced solid malignancies. Juric D; de Bono JS; LoRusso PM; Nemunaitis J; Heath EI; Kwak EL; Macarulla Mercadé T; Geuna E; Jose de Miguel-Luken M; Patel C; Kuida K; Sankoh S; Westin EH; Zohren F; Shou Y; Tabernero J. 2017. *Clin Cancer Res.* 23: 5015-5023. IF: 9,619

MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR+/HER2- Metastatic Breast Cancer. Dickler MN; Tolaney S; Rugo HS; Cortés J; Dieras V; Patt DA; Wildiers H; Hudis CA; O'Shaughnessy JA; Zamora E; Yardley D; Frenzel M; Koustenis AG; Baselga J. 2017. *Clin Cancer Res.* 23: 5218-5224. IF: 9,619

Phase Ib Study of Lumretuzumab Plus Cetuximab or Erlotinib in Solid Tumor Patients and Evaluation of HER3 and Heregulin as Potential Biomarkers of Clinical Activity. Meulendijks D; Jacob W; Voest EE; Mau-Sørensen M; Martinez-Garcia M; Taus A; Fleitas T; Cervantes A; Lolkema M; Langenberg MH; de Jonge MJA; Sleijfer S; Han JY; Calles A; Felip E; Kim SW; Schellens JHM; Wilson S; Thomas M; Ceppi M; Meneses-Lorente G; James I; Harring SV; Dua R; Nguyen M; Steiner L; Adessi C; Michielin F; Bossenmaier B; Weisser M; Lassen U. 2017. *Clin Cancer Res.* 23: 5406-5415. IF: 9,619

Defective Cyclin B1 Induction in Trastuzumab-emtansine (T-DM1) Acquired Resistance in HER2-positive Breast Cancer. Sabbaghi M; Gil-Gómez G; Guardia C; Servitja S; Arpi O; García-Alonso S; Menéndez S; Arumi-Uria M; Serrano L; Salido M; Muntasell A; Martinez-Garcia M; Zazo S; Chamizo C; González-Alonso P; Madoz-Gúrpide J; Eroles P; Arribas J; Tusquets I; Lluch A; Pandiella A; Rojo F; Rovira A; Albanell J. 2017. *Clin Cancer Res.* 23: 7006-7019. IF: 9,619

Efficacy of Neoadjuvant Carboplatin plus Docetaxel in Triple-Negative Breast Cancer: Combined Analysis of Two Cohorts. Sharma P; López-Tarruella S; García-Saenz JA; Ward C; Connor C; Gómez HL; Prat A; Moreno F; Jerez-Gilarranz Y; Barnadas A; Picornell A; Del Monte-Millán M; Gonzalez-Rivera M; Massarrah T; Pelaez-Lorenzo B; Palomero MI; González Del Val R; Cortes J; Fuentes Rivera H; Bretel Morales D; Márquez-Rodas I; Perou CM; Wagner J; Mammen JM; McGinness M; Klemp JR; Amin A; Fabian CJ; Heldstab J; Godwin AK; Jensen RA; Kimler BF; Khan QJ; Martin M. 2017. *Clin Cancer Res.* 23: 649-657. IF: 9,619

Tumor-infiltrating lymphocytes in Breast Cancer and implications for clinical practice. de Melo Gagliato, Debora; Cortes, Javier; Curigliano, Giuseppe; Loi, Sherene; Denkert, Carsten; Perez-Garcia, Jose; Holgado, Esther. 2017. *Biochim Biophys Acta.* 1868: 527-537. IF: 9,452

Intrinsic subtypes and gene expression profiles in primary and metastatic breast cancer. Cejalvo JM; Martínez de Dueñas E; Galvan P; García-Recio S; Burgués Gasión O; Paré L; Antolin S; Martinello R; Blancas I; Adamo B; Guerrero-Zotano A; Muñoz M; Nuciforo P; Vidal M; Pérez RM; Chacón López-Muñiz JI; Caballero R; Peg V; Carrasco E; Rojo F; Perou CM; Cortes J; Adamo V; Albanell J; Gomis RR; Lluch A; Prat A. 2017. *Cancer Res.* 77: 2213-2221. IF: 9,122

Circulating tumor cells with aberrant ALK copy number predict progression-free survival during crizotinib treatment in ALK-rearranged non-small cell lung cancer patients. Pailler, E.; Oulhen, M.; Borget, I.; Remon, J.; Ross, K.; Auger, N.; Billiot, F.; Ngo Camus, M.; Commo, F.; Lindsay, C.R.; Planchard, D.; Soria, J.-C.; Besse, B.; Farace, F.. 2017. *Cancer Res.* 77: 2222-2230. IF: 9,122

Immune-Related Gene Expression Profiling After PD-1 Blockade in Non-Small Cell Lung Carcinoma, Head and Neck Squamous Cell Carcinoma, and Melanoma. Prat A; Navarro

A; Paré L; Reguart N; Galvan P; Pascual T; Martínez A; Nuciforo P; Comerma L; Alos L; Pardo N; Cedrés S; Fan C; Parker JS; Gaba L; Victoria I; Viñolas N; Vivancos A; Arance A; Felip E. 2017. *Cancer Res.* 77: 3540-3550. IF: 9,122

Resistance to the Antibody-Drug Conjugate T-DM1 Is Based in a Reduction in Lysosomal Proteolytic Activity. Ríos-Luci C; García-Alonso S; Díaz-Rodríguez E; Nadal-Serrano M; Arribas J; Ocaña A; Pandiella A. 2017. *Cancer Res.* 77: 4639-4651. IF: 9,122

TGF-beta Family Signaling in Tumor Suppression and Cancer Progression. Seoane J; Gomis RR. 2017. *Cold Spring Harb Perspect Biol.* IF: 8,769

Strategies to design clinical studies to identify predictive biomarkers in cancer research. Perez-Gracia JL; Sanmamed MF; Bosch A; Patiño-Garcia A; Schalper KA; Segura V; Bellmunt J; Tabernero J; Sweeney CJ; Choueiri TK; Martín M; Fusco JP; Rodriguez-Ruiz ME; Calvo A; Prior C; Paz-Ares L; Pio R; Gonzalez-Billalabeitia E; Gonzalez Hernandez A; Páez D; Piulats JM; Gurpide A; Andueza M; de Velasco G; Pazo R; Grande E; Nicolas P; Abad-Santos F; Garcia-Donas J; Castellano D; Pajares MJ; Suarez C; Colomer R; Montuenga LM; Melero I. 2017. *Cancer Treat Rev.* 53: 79-97. IF: 8,589

Leptomeningeal carcinomatosis in non-small cell lung cancer patients: A continuing challenge in the personalized treatment era. Remon, J.; Le Rhun, E.; Besse, B. 2017. *Cancer Treat Rev.* 53: 128-137. IF: 8,589

The expanding role of immunotherapy. Martin-Liberal J; Ochoa de Olza M; Hierro C; Gros A; Rodon J; Tabernero J. 2017. *Cancer Treat Rev.* 54: 74-86. IF: 8,589

GEIS guidelines for gastrointestinal sarcomas (GIST). Poveda A; García Del Muro X; López-Guerrero JA; Cubedo R; Martínez V; Romero I; Serrano C; Valverde C; Martín-Broto J; GEIS (Grupo Español de Investigación en Sarcomas/Spanish Group for Sarcoma Resea. 2017. *Cancer Treat Rev.* 55: 107-119. IF: 8,589

The accelerated path of ceritinib: Translating pre-clinical development into clinical efficacy. Mok TSK; Crino L; Felip E; Salgia R; De Pas T; Tan DSW; Chow LQM. 2017. *Cancer Treat Rev.* 55: 181-189. IF: 8,589

The next era of treatment for hormone receptor-positive, HER2-negative advanced breast cancer: Triplet combination-based endocrine therapies. Cortés J; Im SA; Holgado E; Perez-Garcia JM; Schmid P; Chavez-MacGregor M. 2017. *Cancer Treat Rev.* 61: 53-60. IF: 8,589

Genomic Determinants of Protein Abundance Variation in Colorectal Cancer Cells. Roumeliotis TI; Williams SP; Gonçalves E; Alsinet C; Del Castillo Velasco-Herrera M; Aben N; Ghavidel FZ; Michaut M; Schubert M; Price S; Wright JC; Yu L; Yang M; Dienstmann R; Guinney J; Beltrao P; Brazma A; Pardo M; Stegle O; Adams DJ; Wessels L; Saez-Rodriguez J; McDermott U; Choudhary JS. 2017. *Cell Rep.* 20: 2201-2214. IF: 8,282

Identification of ALK, ROS1, and RET fusions by a multiplexed mRNA-based assay in formalin-fixed, paraffin-embedded samples from advanced non-small-cell lung cancer patients. Reguart N; Teixidó C; Giménez-Capitán A; Paré L; Galván P; Viteri S; Rodríguez S; Peg V; Aldeguer E; Viñolas N; Remon J; Karachaliou N; Conde E; Lopez-Rios F; Nadal E; Merkelbach-Bruse S; Büttner R; Rosell R; Molina-Vila MA; Prat A. 2017. *Clin Chem.* 63: 751-760. IF: 8,008

Successes and failures: What did we learn from recent first-line treatment immunotherapy trials in non-small cell lung cancer? Remon J; Besse B; Soria JC. 2017. *BMC Med.* 15: 55-0. IF: 7,901

Risk of thrombosis according to need of phlebotomies in patients with polycythemia vera treated with hydroxyurea. Alvarez-Larrán A; Pérez-Encinas M; Ferrer-Marín F; Hernández-Boluda JC; Ramírez MJ; Martínez-López J; Magro E; Cruz Y; Mata MI; Aragües P; Fox ML; Cuevas B; Montesdeoca S; Hernández-Rivas JA; García-Gutiérrez V; Gómez-Casares MT; Steegmann JL; Durán MA; Gómez M; Kerguelen A; Bárez A; García MC; Boqué C; Raya JM; Martínez C; Albors M; García F; Burgaleta C; Besses C; Grupo Español de Neoplasias Mieloproliferativas Filadelfia Negativas. 2017. *Haematologica.* 102: 103-109. IF: 7,702

The BET bromodomain inhibitor CPI203 improves lenalidomide and dexamethasone activity in in vitro and in vivo models of multiple myeloma by blockade of Ikaros and MYC signaling. Díaz T; Rodríguez V; Lozano E; Mena MP; Calderón M; Rosiñol L; Martínez A; Tovar N; Pérez-Galán P; Bladé J; Roué G; de Larrea CF. 2017. *Haematologica.* 102: 1776-1784. IF: 7,702

The Bruton tyrosine kinase inhibitor CC-292 shows activity in mantle cell lymphoma and synergizes with lenalidomide and NIK inhibitors depending on nuclear factor-?B mutational status. Vidal-Crespo A; Rodriguez V; Matas-Cespedes A; Lee E; Rivas-Delgado A; Giné E; Navarro A; Beà S; Campo E; López-Guillermo A; Lopez-Guerra M; Roué G; Colomer D; Pérez-Galán P. 2017. *Haematologica.* IF: 7,702

Translational research in neuroendocrine tumors: Pitfalls and opportunities. Capdevila J; Casanovas O; Salazar R; Castellano D; Segura A; Fuster P; Aller J; García-Carbonero R; Jimenez-Fonseca P; Grande E; Castaño JP. 2017. *Oncogene.* 36: 1899-1907. IF: 7,519

Stem cell-like transcriptional reprogramming mediates metastatic resistance to mTOR inhibition. Mateo F; Arenas EJ; Aguilar H; Serra-Musach J; de Garibay GR; Boni J; Maicas M; Du S; Iorio F; Herranz-Ors C; Islam A; Prado X; Llorente A; Petit A; Vidal A; Català I; Soler T; Venturas G; Rojo-Sebastian A; Serra H; Cuadras D; Blanco I; Lozano J; Canals F; Sieuwerts AM; de Weerd V; Look MP; Puertas S; García N; Perkins AS; Bonifaci N; Skowron M; Gómez-Baldó L; Hernández V; Martínez-Aranda A; Martínez-Iniesta M; Serrat X; Cerón J; Brunet J; Barretina MP; Gil M; Falo C; Fernández A; Morilla I; Pernas S; Plà MJ; Andreu X; Seguí MA; Ballester R; Castellà E; Nellist M; Morales S; Valls J; Velasco A; Matias-Guiu X; Figueras A; Sánchez-Mut JV; Sánchez-Céspedes M; Cordero A; Gómez-Miragaya J; Palomero L; Gómez A; Gajewski TF; Cohen EE; Jesiotr M; Bodnar L; Quintela-Fandino M; López-Bigas N; Valdés-Mas R; Puente XS; Viñals F; Casanovas O; Graupera M; Hernández-Losa J; Ramón Y Cajal S; García-Alonso L; Saez-Rodriguez J; Esteller M; Sierra A; Martín-Martín N; Matheu A; Carracedo A; González-Suárez E; Nanjundan M; Cortés J; Lázaro C; Odero MD; Martens JW; Moreno-Bueno G; Barcellos-Hoff MH; Villanueva A; Gomis RR; Pujana MA. 2017. *Oncogene.* 36: 2737-2749. IF: 7,519

Pancreatic cancer heterogeneity and response to Mek inhibition. Pedersen K; Bilal F; Bernadó Morales C; Salcedo MT; Macarulla T; Massó-Vallés D; Mohan V; Vivancos A; Carreras MJ; Serres X; Abu-Suboh M; Balsells J; Allende E; Sagi I; Soucek L; Tabernero J; Arribas J. 2017. *Oncogene.* 36: 5639-5647. IF: 7,519

ALDH1A3 is epigenetically regulated during melanocyte transformation and is a target for melanoma treatment. Pérez-Alea M; McGrail K; Sánchez-Redondo S; Ferrer B; Fournet G; Cortés J; Muñoz E; Hernandez-Losa J; Tenbaum S; Martin G; Costello R; Ceylan I; Garcia-Patos V; Recio JA. 2017. *Oncogene.* 36: 5695-5708. IF: 7,519

CtIP-Specific Roles during Cell Reprogramming Have Long-Term Consequences in the Survival and Fitness of Induced Pluripotent Stem Cells. Gómez-Cabello D; Checa-Rodríguez C; Abad M; Serrano M; Huertas P. 2017. *Stem Cell Reports.* 8: 432-445. IF: 7,338

Common Telomere Changes during In Vivo Reprogramming and Early Stages of Tumorigenesis. Marión RM; López de Silanes I; Mosteiro L; Gamache B; Abad M; Guerra C; Megías D; Serrano M; Blasco MA. 2017. *Stem Cell Reports.* 8: 460-475. IF: 7,338

Notch Inhibition Enhances Cardiac Reprogramming by Increasing MEF2C Transcriptional Activity. Abad M; Hashimoto H; Zhou H; Morales MG; Chen B; Bassel-Duby R; Olson EN. 2017. *Stem Cell Reports.* 8: 548-560. IF: 7,338

Resistance to Taxanes in Triple-Negative Breast Cancer Associates with the Dynamics of a CD49f+Tumor-Initiating Population. Gómez-Miragaya J; Palafox M; Paré L; Yoldi G; Ferrer I; Vila S; Galván P; Pellegrini P; Pérez-Montoyo H; Igea A; Muñoz P; Esteller M; Nebreda AR; Urruticoechea A; Morilla I; Pernas S; Climent F; Soler-Monso MT; Petit A; Serra V; Prat A; González-Suárez E. 2017. *Stem Cell Reports.* 8: 1392-1407. IF: 7,338

Lenalidomide maintenance after first-line therapy for high-risk chronic lymphocytic leukaemia (CLLM1): final results from a randomised, double-blind, phase 3 study. Fink AM; Bahlo J; Robrecht S; Al-Sawaf O; Aldaoud A; Hebart H; Jentsch-Ullrich K; Dörfel S; Fischer K; Wendtner CM; Nösslinger T; Ghia P; Bosch F; Kater AP; Döhner H; Kneba M; Kreuzer KA; Tausch E; Stilgenbauer S; Ritgen M; Böttcher S; Eichhorst B; Hallek M. 2017. *Lancet Haematol.* 4: 475-486. IF: 7,123

Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. Aguilar-Guisado M; Espigado I; Martín-Peña A; Gudiol C; Royo-Cebrecos C; Falantes J; Vázquez-López L; Montero MI; Rosso-Fernández C; de la Luz Martino M; Parody R; González-Campos J; Garzón-López S; Calderón-Cabrera C; Barba P; Rodríguez N; Rovira M; Montero-Mateos E;

Carratalá J; Pérez-Simón JA; Cisneros JM. 2017. *Lancet Haematol.* IF: 7,123

Intersect-then-combine approach: Improving the performance of somatic variant calling in whole exome sequencing data using multiple aligners and callers. Callari M; Sammut SJ; De Mattos-Arruda L; Bruna A; Rueda OM; Chin SF; Caldas C. 2017. *Genome Med.* 9: 35-0. IF: 7,071

Brain Radionecrosis Treated with Bevacizumab in a Patient with Resected Squamous Cell Carcinoma of the Lung. Remon, J.; Le Péchoux, C.; Caramella, C.; Dhermain, F.; Louvel, G.; Soria, J.-C.; Besse, B. 2017. *J Thorac Oncol.* 12: 1-3. IF: 6,595

The Potential of Combined Immunotherapy and Antiangiogenesis for the Synergistic Treatment of Advanced NSCLC. Manegold C; Dingemans AC; Gray JE; Nakagawa K; Nicolson M; Peters S; Reck M; Wu YL; Brustugun OT; Crino L; Felip E; Fennell D; Garrido P; Huber RM; Marabelle A; Moniuszko M; Mornex F; Novello S; Papotti M; Pérol M; Smit EF; Syrigos K; van Meerbeeck JP; van Zandwijk N; Chih-Hsin Yang J; Zhou C; Vokes E. 2017. *J Thorac Oncol.* 12: 194-207. IF: 6,595

Dalotuzumab in chemorefractory KRAS exon 2 mutant colorectal cancer: Results from a randomised phase II/III trial. Sclafani F; Kim TY; Cunningham D; Kim TW; Tabernero J; Schmoll HJ; Roh JK; Kim SY; Park YS; Guren TK; Hawkes E; Clarke SJ; Ferry D; Frodin JE; Ayers M; Nebozhyn M; Peckitt C; Loboda A; Watkins DJ. 2017. *Int J Cancer.* 140: 431-439. IF: 6,513

Type I and type III interferons display different dependency on mitogen-activated protein kinases to mount an antiviral state in the human gut. Pervolaraki K; Stanifer ML; Münchau S; Renn LA; Albrecht D; Kurzhals S; Senís E; Grimm D; Schröder-Braunstein J; Rabin RL; Boulant S. 2017. *Front Immunol.* 8: 459-0. IF: 6,429

Phase II, randomized, placebo-controlled study of dovitinib in combination with fulvestrant in postmenopausal patients with HR(+), HER2(-) breast cancer that had progressed during or after prior endocrine therapy. Musolino A; Campone M; Neven P; Denduluri N; Barrios CH; Cortes J; Blackwell K; Soliman H; Kahan Z; Bonnefoi H; Squires M; Zhang Y; Deudon S; Shi MM; André F. 2017. *Breast Cancer Res.* 19: 18-0. IF: 6,345

GEIS-21: A multicentric phase II study of intensive chemotherapy including gemcitabine and docetaxel for the treatment of Ewing sarcoma of children and adults: A report from the Spanish sarcoma group (GEIS). Mora J; Castañeda A; Perez-Jaume S; Lopez-Pousa A; Maradiegue E; Valverde C; Martin-Broto J; Garcia Del Muro X; Cruz O; Cruz J; Martinez-Trufero J; Maurel J; Vaz MA; de Alava E; de Torres C. 2017. *Br J Cancer.* 117: 767-774. IF: 6,176

Dovitinib in patients with gastrointestinal stromal tumour refractory and/or intolerant to imatinib. Joensuu H; Blay JY; Comandone A; Martin-Broto J; Fumagalli E; Grignani G; Del Muro XG; Adenis A; Valverde C; Pousa AL; Bouché O; Italiano A; Bauer S; Barone C; Weiss C; Crippa S; Camozzi M; Castellana R; Le Cesne A. 2017. *Br J Cancer.* 117: 1278-1285. IF: 6,176

Comparison between MRI and pathology in the assessment of tumour regression grade in rectal cancer. Sclafani F; Brown G; Cunningham D; Wotherspoon A; Mendes LST; Balyasnikova S; Evans J; Peckitt C; Begum R; Tait D; Tabernero J; Glimelius B; Roselló S; Thomas J; Oates J; Chau I. 2017. *Br J Cancer.* 117: 1478-1485. IF: 6,176

Health-related quality of life in patients with locally recurrent or metastatic breast cancer treated with etirinotecan pegol versus treatment of physician's choice: Results from the randomised phase III BEACON trial. Twelves, C.; Cortés, J.; O'Shaughnessy, J.; Awada, A.; Perez, E.A.; Im, S.–A.; Gómez-Pardo, P.; Schwartzberg, L.S.; Diéras, V.; Yardley, D.A.; Potter, D.A.; Mailliez, A.; Moreno-Aspitia, A.; Ahn, J.-S.; Zhao, C.; Hoch, U.; Tagliaferri, M.; Hannah, A.L.; Rugo, H.S. 2017. *Eur J Cancer.* 76: 205-215. IF: 6,029

Baseline carcinoembryonic antigen as a predictive factor of ramucirumab efficacy in RAISE, a second-line metastatic colorectal carcinoma phase III trial. Yoshino T; Obermannová R; Bodoky G; Garcia-Carbonero R; Ciuleanu T; Portnoy DC; Kim TW; Hsu Y; Ferry D; Nasroulah F; Tabernero J. 2017. *Eur J Cancer.* 78: 61-69. IF: 6,029

Clinical research in small genomically stratified patient populations. Martin-Liberal J; Rodon J. 2017. *Eur J Cancer.* 80: 73-82. IF: 6,029

A European randomised controlled trial of the addition of etoposide to standard vincristine and carboplatin induction as part of an 18-month treatment programme for childhood (=16 years) low grade glioma - A final report. Gnekow AK; Walker DA; Kandels D; Picton S; Giorgio Perilongo; Grill J; Stokland T; Sandstrom PE; Warmuth-Metz M; Pietsch T; Giangaspero F; Schmidt R; Faldum A; Kilmartin D; De Paoli A; De Salvo GL; of the Low Grade Glioma Consortium and the participating centers. 2017. *Eur J Cancer.* 81: 206-225. IF: 6,029

First-in-human phase I study of oral S49076, a unique MET/AXL/FGFR inhibitor, in advanced solid tumours. Rodon J; Postel-Vinay S; Hollebecque A; Nuciforo P; Azaro A; Cattan V; Marfai L; Sudey I; Brendel K; Delmas A; Malasse S; Soria JC. 2017. *Eur J Cancer.* 81: 142-150. IF: 6,029

Prospective validation of a lymphocyte infiltration prognostic test in stage III colon cancer patients treated with adjuvant FOLFOX. Emile JF; Julié C; Le Malicot K; Lepage C; Tabernero J; Mini E; Folprecht G; Van Laethem JL; Dimet S; Boulagnon-Rombi C; Allard MA; Penault-Llorca F; Bennouna J; Laurent-Puig P; Taieb J; PETACC8 Study Investigators; Austrian Breast and Colorectal cancer Study Group (ABCSG); Belgian Group of Digestive Oncology (BGDO); Lone Nørgård Petersen; Fédération Francophone de Cancérologie Digestive (FFCD); Fédération Nationale des Centres de Lutte Contre le Cancer (UNICANCER); Fédération Nationale des Centres de Lutte Contre le Cancer Association Européenn; Arbeitsgemeinschaft Internistische Onkologie (AIO); Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD); Gruppo Oncologico dell'Italia Meridionale (GOIM); Istituto Oncologico Romagnolo (IOR); Gruppo Cooperativo Chirurgico Italiano (GOCCI); Gruppo Oncologico Nord Ovest (GONO); Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC); Gruppo Cooperativo do Cancro Digestivo da Associação Portuguesa de Investigação; Grupo Español para el Tratamiento de los Tumores Digestivos (TTD); John Allen Bridgewater. 2017. *Eur J Cancer.* 82: 16-24. IF: 6,029

Identifying critical steps towards improved access to innovation in cancer care: a European CanCer Organisation position paper. Aapro M; Astier A; Audisio R; Banks I; Bedossa P; Brain E; Cameron D; Casali P; Chiti A; De Mattos-Arruda L; Kelly D; Lacombe D; Nilsson PJ; Piccart M; Poortmans P; Riklund K; Saeter G; Schrappe M; Soffietti R; Travado L; van Poppel H; Wait S; Naredi P. 2017. *Eur J Cancer.* 82: 193-202. IF: 6,029

A first-in-human phase I study of SAR125844, a selective MET tyrosine kinase inhibitor, in patients with advanced solid tumours with MET amplification. Angevin E; Spitaleri G; Rodon J; Dotti K; Isambert N; Salvagni S; Moreno V; Assadourian S; Gomez C; Harnois M; Hollebecque A; Azaro A; Hervieu A; Rihawi K; De Marinis F. 2017. *Eur J Cancer.* 87: 131-139. IF: 6,029

Weekly cabazitaxel plus prednisone is effective and less toxic for 'unfit' metastatic castration-resistant prostate cancer: Phase II Spanish Oncology Genitourinary Group (SOGUG) trial. Climent MÁ; Pérez-Valderrama B; Mellado B; Fernández Parra EM; Fernández Calvo O; Ochoa de Olza M; Muinelo Romay L; Anido U; Domenech M; Hernando Polo S; Arranz Arija JÁ; Caballero C; Juan Fita MJ; Castellano D. 2017. *Eur J Cancer.* 87: 30-37. IF: 6,029

Optimization of RAS/BRAF mutational analysis confirms improvement in patient selection for clinical benefit to anti-EGFR treatment in metastatic colorectal cancer. Santos C; Azuara D; Garcia-Carbonero R; García Alfonso P; Carrato A; Elez E; Gómez A; Losa F; Montagut C; Massuti B; Navarro V; Varela M; López-Doriga A; Moreno V; Valladares M; Manzano JL; Viéitez JM; Aranda E; Sanjuan X; Tabernero J; Capella G; Salazar R. 2017. *Mol Cancer Ther.* 16: 1999-2007. IF: 5,764

Exposure-response analyses of ramucirumab from two randomized, phase III trials of second-line treatment for advanced gastric or gastroesophageal junction cancer. Tabernero J; Ohtsu A; Muro K; Van Cutsem E; Oh SC; Bodoky G; Shimada Y; Hironaka S; Ajani JA; Tomasek J; Safran H; Chandrawansa K; Hsu Y; Heathman M; Khan A; Ni L; Melemed AS; Gao L; Ferry D; Fuchs CS. 2017. *Mol Cancer Ther.* 16: 2215-2222. IF: 5,764

Prognostic significance of performing universal HER2 testing in cases of advanced gastric cancer. Jiménez-Fonseca P; Carmona-Bayonas A; Sánchez Lorenzo ML; Plazas JG; Custodio A; Hernández R; Garrido M; García T; Echavarría I; Cano JM; Rodríguez Palomo A; Mangas M; Macías Declara I; Ramchandani A; Visa L; Viudez A; Buxó E; Díaz-Serrano A; López C; Azkarate A; Longo F; Castañón E; Sánchez Bayona R; Pimentel P; Limón ML; Cerdá P; Álvarez Llosa R; Serrano R; Lobera MP; Alsina M; Hurtado Nuño A; Gómez-

Martin C. 2017. *Gastric Cancer.* 20: 465-474. IF: 5,454

Analysis of mutant allele fractions in driver genes in colorectal cancer - biological and clinical insights. Dienstmann R; Elez E; Argiles G; Matos I; Sanz-Garcia E; Ortiz C; Macarulla T; Capdevila J; Alsina M; Sauri T; Verdaguer H; Vilaro M; Ruiz-Pace F; Viaplana C; Garcia A; Landolfi S; Palmer HG; Nuciforo P; Rodon J; Vivancos A; Tabernero J. 2017. *Mol Oncol.* 11: 1263-1272. IF: 5,314

Advanced cell-based modeling of the royal disease: characterization of the mutated F9 mRNA. Martorell, L.; Luce, E.; Vazquez, J. L.; Richaud-Patin, Y.; Jimenez-Delgado, S.; Corrales, I.; Borras, N.; Casacuberta-Serra, S.; Weber, A.; Parra, R.; Altisent, C.; Follenzi, A.; Dubart-Kupperschmitt, A.; Raya, A.; Vidal, F.; Barquinero, J. 2017. *J Thromb Haemost.* 15: 2188-2197. IF: 5,287

Excess mortality in the myelodysplastic syndromes. Nomdedeu M; Pereira A; Ramos F; Valcárcel D; Costa D; Arnan M; Calvo X; Pomares H; Luño E; Díaz-Campelo M; Collado R; de Paz R; Falantes JF; Pedro C; Marco J; Oirtzabal I; Sánchez-García J; Tormo M; Cedena MT; Nomdedeu B; Sanz G; Spanish MDS Group. 2017. *Am J Hematol.* 92: 149-154. IF: 5,275

Enumerating bone marrow blasts from nonerythroid cellularity improves outcome prediction in myelodysplastic syndromes and permits a better definition of the intermediate risk category of the Revised International Prognostic Scoring System (IPSS-R). Calvo X; Arenillas L; Luño E; Senent L; Arnan M; Ramos F; Pedro C; Tormo M; Montoro J; Díez-Campelo M; Blanco ML; Arrizabalaga B; Xicoy B; Bonanad S; Jerez A; Nomdedeu M; Ferrer A; Sanz GF; Florensa L. 2017. *Am J Hematol.* 92: 614-621. IF: 5,275

Inhibition of BCR signaling using the Syk inhibitor TAK-659 prevents stroma-mediated signaling in chronic lymphocytic leukemia cells. Purroy N; Carabia J; Abrisqueta P; Egia L; Aguiló M; Carpio C; Palacio C; Crespo M; Bosch F. 2017. *Oncotarget.* 8: 742-756. IF: 5,168

Unveiling changes in the landscape of patient populations in cancer early drug development. Hierro C; Azaro A; Argilés G; Elez E; Gómez P; Carles J; Rodon J. 2017. *Oncotarget.* 8: 14158-14172. IF: 5,168

Critically short telomeres and toxicity of chemotherapy in early breast cancer. Quintela-Fandino, M.; Soberon, N.; Lluch, A.; Manso, L.; Calvo, I.; Cortes, J.; Moreno-Antón, F.; Gil-Gil, M.; Martinez-Jánez, N.; Gonzalez-Martin, A.; Adrover, E.; de Andres, R.; Viñas, G.; Llombart-Cussac, A.; Alba, E.; Mouron, S.; Guerra, J.; Bermejo, B.; Zamora, E.; García-Saenz, J.A.; Simon, S.P.; Carrasco, E.; Escudero, M.J.; Campo, R.; Colomer, R.; Blasco, M.A. 2017. *Oncotarget.* 8: 21472-21482. IF: 5,168

Limitations in predicting PAM50 intrinsic subtype and risk of relapse score with Ki67 in estrogen receptor-positive HER2- negative breast cancer. Fernandez-Martinez, A.; Pascual, T.; Perrone, G.; Morales, S.; de la Haba, J.; González-Rivera, M.; Galván, P.; Zalfa, F.; Amato, M.; Gonzalez, L.; Prats, M.; Rojo, F.; Manso, L.; Paré, L.; Alonso, I.; Albanell, J.; Vivancos, A.; González, A.; Matito, J.; González, S.; Fernandez, P.; Adamo, B.; Muñoz, M.; Viladot, M.; Font, C.; Aya, F.; Vidal, M.; Caballero, R.; Carrasco, E.; Altomare, V.; Tonini, G.; Prat, A.; Martin, M.. 2017. *Oncotarget.* 8: 21930-21937. IF: 5,168

POLE and POLD1 screening in 155 patients with multiple polyps and early-onset colorectal cancer. Esteban-Jurado C; Giménez-Zaragoza D; Muñoz J; Franch-Expósito S; Álvarez-Barona M; Ocaña T; Cuatrecasas M; Carballal S; López-Cerón M; Marti-Solano M; Díaz-Gay M; van Wezel T; Castells A; Bujanda L; Balmaña J; Gonzalo V; Llort G; Ruiz-Ponte C; Cubiella J; Balaguer F; Aligué R; Castellví-Bel S. 2017. *Oncotarget.* 8: 26732-26743. IF: 5,168

Novel potential predictive markers of sunitinib outcomes in long-term responders versus primary refractory patients with metastatic clear-cell renal cell carcinoma. Puente, J.; Laínez, N.; Dueñas, M.; Méndez-Vidal, M.J.; Esteban, E.; Castellano, D.; Martinez-Fernández, M.; Basterretxea, L.; Juan-Fita, M.J.; Antón, L.; León, L.; Lambea, J.; Pérez-Valderrama, B.; Vázquez, S.; Suarez, C.; del Muro, X.G.; Gallardo, E.; Maroto, J.P.; Luz Samaniego, M.; Suárez-Paniagua, B.; Sanz, J.; Paramio, J.M.. 2017. *Oncotarget.* 8: 30410-30421. IF: 5,168

Clinical validation of prospective liquid biopsy monitoring in patients with wild-type RAS metastatic colorectal cancer treated with FOLFIRI-cetuximab. Toledo RA; Cubillo A; Vega E; Garralda E; Alvarez R; de la Varga LU; Pascual JR; Sánchez G; Sarno F; Prieto SH; Perea S; Lopéz-Casas PP; López-Ríos F; Hidalgo M. 2017. *Oncotarget.* 8: 35289-35300. IF: 5,168

Patients with chronic lymphocytic leukemia and complex karyotype show an adverse outcome even in absence of TP53/ATM FISH deletions. Puiggros, Anna; Collado, Rosa; Jose Calasanz, Maria; Ortega, Margarita; Ruiz-Xiville, Neus; Rivas-Delgado, Alfredo; Luno, Elisa; Gonzalez, Teresa; Navarro, Blanca; Garcia-Malo, MaDolores; Valiente, Alberto; Angel Hernandez, Jose; Teresa Ardanaz, Maria; Angeles Pinan, Maria; Laura Blanco, Maria; Hernandez-Sanchez, Maria; Batlle-Lopez, Ana; Salgado, Rocio; Salido, Marta; Ferrer, Ana; Abrisqueta, Pau; Gimeno, Eva; Abella, Eugenia; Ferra, Christelle; Jose Terol, Maria; Ortuno, Francisco; Costa, Dolors; Moreno, Carol; Carbonell, Felix; Bosch, Francesc; Delgado, Julio; Espinet, Blanca. 2017. *Oncotarget.* 8: 54297-54303. IF: 5,168

Improving circulating tumor cells enumeration and characterization to predict outcome in first line chemotherapy mCRPC patients. León-Mateos L; Casas H; Abalo A; Vieito M; Abreu M; Anido U; Gómez-Tato A; López R; Abal M; Muinelo-Romay L. 2017. *Oncotarget.* 8: 54708-54721. IF: 5,168

Novel combinations of PI3K-mTOR inhibitors with dacomitinib or chemotherapy in PTEN-deficient patient-derived tumor xenografts. Brana, Irene; Nhu-An Pham; Kim, Lucia; Sakashita, Shingo; Li, Ming; Ng, Christine; Wang, Yuhui; Loparco, Peter; Sierra, Rafael; Wang, Lisa; Clarke, Blaise A.; Neel, Benjamin G.; Siu, Lillian L.; Tsao, Ming-Sound. 2017. *Oncotarget.* 8: 84659-84670. IF: 5,168

Oncogenic p95HER2/611CTF primes human breast epithelial cells for metabolic stress-induced down-regulation of FLIP and activation of TRAIL-R/Caspase-8-dependent apoptosis. Martin-Perez, Rosa; Yerbes, Rosario; Mora-Molina, Rocio; Cano-Gonzalez, Ana; Arribas, Joaquin; Mazzone, Massimiliano; Lopez-Rivas, Abelardo; Palacios, Carmen. 2017. *Oncotarget.* 8: 93688-93703. IF: 5,168

Recent advances in genitourinary tumors: A review focused on biology and systemic treatment. González Del Alba A; Arranz JÁ; Puente J; Méndez-Vidal MJ; Gallardo E; Grande E; Pérez-Valderrama B; González-Billalabeitia E; Lázaro-Quintela M; Pinto Á; Lainez N; Piulats JM; Esteban E; Maroto Rey JP; García JA; Suárez C. 2017. *Crit Rev Oncol Hematol.* 113: 171-190. IF: 4,971

Advances in the management of HER2-positive early breast cancer. Baselga J; Coleman RE; Cortés J; Janni W. 2017. *Crit Rev Oncol Hematol.* 119: 113-122. IF: 4,971

Randomized phase II trial of parsatuzumab (Anti-EGFL7) or placebo in combination with FOLFOX and bevacizumab for first-line metastatic colorectal cancer. García-Carbonero R; van Cutsem E; Rivera F; Jassem J; Gore I; Tebbutt N; Braiteh F; Argiles G; Wainberg ZA; Funke R; Anderson M; McCall B; Stroh M; Wakshull E; Hegde P; Ye W; Chen D; Chang I; Rhee I; Hurwitz H. 2017. *Oncologist.* 22: 375-30. IF: 4,962

p16, HPV, and cetuximab: What is the evidence? Bonner JA; Mesia R; Giralt J; Psyrri A; Keilholz U; Rosenthal DI; Beier F; Schulten J; Vermorken JB. 2017. *Oncologist.* 22: 811-822. IF: 4,962

Cell-Free DNA in metastatic colorectal cancer: A systematic review and Meta-Analysis. Spindler KG; Boysen AK; Pallisgård N; Johansen JS; Tabernero J; Sørensen MM; Jensen BV; Hansen TF; Sefrioui D; Andersen RF; Brandslund I; Jakobsen A. 2017. *Oncologist.* 22: 1049-1055. IF: 4,962

A phase ib dose-escalation study of the safety, tolerability, and pharmacokinetics of cobimetinib and duligotuzumab in patients with previously treated locally advanced ormetastatic cancers with mutant KRAS. Lieu CH; Hidalgo M; Berlin JD; Ko AH; Cervantes A; LoRusso P; Gerber DE; Eder JP; Eckhardt SG; Kapp AV; Tsuhako A; McCall B; Pirzkall A; Uyei A; Tabernero J. 2017. *Oncologist.* 22: 1024-89. IF: 4,962

Development of Molecularly Driven Targeted Combination Strategies. Yap, Timothy A.; Rodon, Jordi. 2017. *Oncologist.* 22: 1421-1423. IF: 4,962

Antitumor activity and safety of the PARP inhibitor rucaparib in patients with high-grade ovarian carcinoma and a germline or somatic BRCA1 or BRCA2 mutation: Integrated analysis of data from Study 10 and ARIEL2. Oza AM; Tinker AV; Oaknin A; Shapira-Frommer R; McNeish IA; Swisher EM; Ray-Coquard I; Bell-McGuinn K; Coleman RL; O'Malley DM; Leary A; Chen LM; Provencher D; Ma L; Brenton JD; Konecny GE; Castro CM; Giordano H; Maloney L; Goble S; Lin KK; Sun J; Raponi M; Rolfe L; Kristeleit RS. 2017. *Gynecol Oncol.* 147: 267-275. IF: 4,959

Multidisciplinary management of head and neck cancer: First expert consensus using Delphi methodology from the Spanish Society for Head and Neck Cancer (part 1). Mañós M; Giralt J; Rueda A; Cabrera J; Martinez-Trufero J; Marruecos J; Lopez-Pousa A; Rodrigo JP; Castelo B; Martínez-Galán J; Arias F; Chaves

M; Herranz JJ; Arrazubi V; Baste N; Castro A; Mesía R. 2017. *Oral Oncol.* 70: 58-64. IF: 4,794

Multidisciplinary management of head and neck cancer: First expert consensus using Delphi methodology from the Spanish Society for Head and Neck Cancer (part 2). Rueda A; Giralt J; Mañós M; Lozano A; Sistiaga A; García-Miragall E; Cacicedo J; Esteban F; Scola B; Contreras J; Ruiz A; Carral A; Sanchez-Aniceto G; Pastor M; Herranz JJ; Bernal M; Mesía R. 2017. *Oral Oncol.* 70: 65-72. IF: 4,794

Hematopoietic Cell Transplantation Comorbidity Index Predicts Outcomes in Patients with Acute Myeloid Leukemia and Myelodysplastic Syndromes Receiving CD34(+) Selected Grafts for Allogeneic Hematopoietic Cell Transplantation. Barba P; Ratan R; Cho C; Ceberio I; Hilden P; Devlin SM; Maloy MA; Barker JN; Castro-Malaspina H; Jakubowski AA; Koehne G; Papadopoulos EB; Ponce DM; Sauter C; Tamari R; van den Brink MR; Young JW; O'Reilly RJ; Giralt SA; Perales MA. 2017. *Biol Blood Marrow Transplant.* 23: 67-74. IF: 4,704

Ex Vivo CD34(+)-Selected T Cell-Depleted Peripheral Blood Stem Cell Grafts for Allogeneic Hematopoietic Stem Cell Transplantation in Acute Leukemia and Myelodysplastic. Syndrome Is Associated with Low Incidence of Acute and Chronic Graft-versus-Host Disease and High Treatment Response. Barba P; Hilden P; Devlin SM; Maloy M; Dierov D; Nieves J; Garrett MD; Sogani J; Cho C; Barker JN; Kernan NA; Castro-Malaspina H; Jakubowski AA; Koehne G; Papadopoulos EB; Prockop S; Sauter C; Tamari R; van den Brink MR; Avecilla ST; Meagher R; O'Reilly RJ; Goldberg JD; Young JW; Giralt S; Perales MA; Ponce DM. 2017. *Biol Blood Marrow Transplant.* 23: 452-458. IF: 4,704

Early and Long-Term Impaired T Lymphocyte Immune Reconstitution after Cord Blood Transplantation with Antithymocyte Globulin. Castillo N; García-Cadenas I; Barba P; Canals C; Díaz-Heredia C; Martino R; Ferrà C; Badell I; Elorza I; Sierra J; Valcárcel D; Querol S. 2017. *Biol Blood Marrow Transplant.* 23: 491-497. IF: 4,704

Do Patients and Physicians Agree When They Assess Quality of Life? Barata A; Martino R; Gich I; García-Cadenas I; Abella E; Barba P; Briones J; Brunet S; Esquirol A; García-Pallarols F; Garrido A; Granell M; Martinez J; Mensa I; Novelli S; Sanchez-Blanco B; Valcárcel D; Sierra J. 2017. *Biol Blood Marrow Transplant.* 23: 1005-1010. IF: 4,704

Outcomes after Umbilical Cord Blood Transplantation for Myelodysplastic Syndromes. Gerds AT; Woo Ahn K; Hu ZH; Abdel-Azim H; Akpek G; Aljurf M; Ballen KK; Beitinjaneh A; Bacher U; Cahn JY; Chhabra S; Cutler C; Daly A; DeFilipp Z; Gale RP; Gergis U; Grunwald MR; Hale GA; Hamilton BK; Jagasia M; Kamble RT; Kindwall-Keller T; Nishihori T; Olsson RF; Ramanathan M; Saad AA; Solh M; Ustun C; Valcárcel D; Warlick E; Wirk BM; Kalaycio M; Alyea E; Popat U; Sobecks R; Saber W. 2017. *Biol Blood Marrow Transplant.* 23: 971-979. IF: 4,704

A Time-to-Event Model for Acute Kidney Injury after Reduced-Intensity Conditioning Stem Cell Transplantation Using a Tacrolimus- and Sirolimus-based Graft-versus-Host Disease Prophylaxis. Piñana JL; Perez-Pitarch A; Garcia-Cadenas I; Barba P; Hernandez-Boluda JC; Esquirol A; Fox ML; Terol MJ; Queraltó JM; Vima J; Valcarcel D; Ferriols-Lisart R; Sierra J; Solano C; Martino R. 2017. *Biol Blood Marrow Transplant.* 23: 1177-1185. IF: 4,704

Autologous Stem Cell Transplantation for Follicular Lymphoma: Favorable Long-Term Survival Irrespective of Pretransplantation Rituximab Exposure. Jiménez-Ubieto A; Grande C; Caballero D; Yáñez L; Novelli S; Hernández-Garcia MT; Manzanares M; Arranz R; Ferreiro JJ; Bobillo S; Mercadal S; Galeo A; López Jiménez J; Moraleda JM; Vallejo C; Albo C; Pérez E; Marrero C; Magnano L; Palomera L; Jarque I; Martínez-Sánchez P; Martín A; Coria E; López-Guillermo A; Salar A; Lahuerta JJ. 2017. *Biol Blood Marrow Transplant.* 23: 1631-1640. IF: 4,704

Molecular and hydrodynamic properties of human epidermal growth factor receptor HER2 extracellular domain and its homodimer: Experiments and multi-scale simulations. Vega, J. F.; Ramos, J.; Cruz, V. L.; Vicente-Alique, E.; Sanchez-Sanchez, E.; Sanchez-Fernandez, A.; Wang, Y.; Hu, P.; Cortes, J.; Martinez-Salazar, J. 2017. *BBA-GEN SUBJECTS.* 1861: 2406-2416. IF: 4,702

Myeloid-derived suppressor cells can be efficiently generated from human hematopoietic progenitors and peripheral blood monocytes. Casacuberta-Serra S; Parés M; Golbano A; Coves E; Espejo C; Barquinero J. 2017. *Immunol Cell Biol.* 95: 538-548. IF: 4,557

Glucose Deprivation Induces ATF4-Mediated Apoptosis through TRAIL Death Receptors. Iurlaro R; Püschel F; León-Annicchiarico CL; O'Connor H; Martin SJ; Palou-Gramón D; Lucendo E; Muñoz-Pinedo C. 2017. *Mol Cell Biol.* IF: 4,398

Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. Grégoire, V.; Evans, M.; Le, Q.-T.; Bourhis, J.; Budach, V.; Chen, A.; Eisbruch, A.; Feng, M.; Giralt, J.; Gupta, T.; Hamoir, M.; Helito, J.K.; Hu, C.; Hunter, K.; Johansen, J.; Kaanders, J.; Laskar, S.G.; Lee, A.; Maingon, P.; Mäkitie, A.; Micciche', F.; Nicolai, P.; O'Sullivan, B.; Poitevin, A.; Porceddu, S.; Skladowski, K.; Tribius, S.; Waldron, J.; Wee, J.; Yao, M.; Yom, S.S.; Zimmermann, F.; Grau, C.. 2017. *Radiother Oncol.* IF: 4,328

Quality assurance of radiotherapy in the ongoing EORTC 1219-DAHANCA-29 trial for HPV/p16 negative squamous cell carcinoma of the head and neck: Results of the benchmark case procedure. Christiaens M; Collette S; Overgaard J; Gregoire V; Kazmierska J; Castadot P; Giralt J; Grant W; Tomsej M; Bar-Deroma R; Monti AF; Hurkmans CW; Weber DC. 2017. *Radiother Oncol.* 123: 424-430. IF: 4,328

Efficacy of ß-Lactam/ß-Lactamase Inhibitor Combinations for the Treatment of Bloodstream Infection Due to Extended-Spectrum-ß-Lactamase-Producing Enterobacteriaceae in Hematological Patients with Neutropenia. Gudiol C; Royo-Cebrecos C; Abdala E; Akova M; Álvarez R; Maestro-de la Calle G; Cano A; Cervera C; Clemente WT; Martín-Dávila P; Freifeld A; Gómez L; Gottlieb T; Gurguí M; Herrera F; Manzur A; Maschmeyer G; Meije Y; Montejo M; Peghin M; Rodríguez-Baño J; Ruiz-Camps I; Sukiennik TC; Tebe C; Carratalà J; BICAR Study Group. 2017. *Antimicrob Agents Chemother.* IF: 4,302

Immune-checkpoint inhibition in first-line treatment of advanced non-small cell lung cancer patients: Current status and future approaches. Remon, J.; Pardo, N.; Martinez-Martí, A.; Cedrés, S.; Navarro, A.; Martinez de Castro, A.M.; Felip, E. 2017. *Lung Cancer.* 106: 70-75. IF: 4,294

Symptomatic leptomeningeal metastasis improvement with nivolumab in advanced non-small cell lung cancer patient. Gion M; Remon J; Caramella C; Soria JC; Besse B. 2017. *Lung Cancer.* 108: 72-74. IF: 4,294

CD52, CD22, CD26, EG5 and IGF-1R expression in thymic malignancies. Remon, J.; Abedallaa, N.; Taranchon-Clermont, E.; Bluthgen, V.; Lindsay, C.R.; Besse, B.; Thomas de Montpréville, V. 2017. *Lung Cancer.* 108: 168-172. IF: 4,294

Evaluation of the VeriStrat (R) serum protein test in patients with advanced squamous cell carcinoma of the lung treated with second-line afatinib or erlotinib in the phase III LUX-Lung 8 study. Gadgeel S; Goss G; Soria JC; Felip E; Georgoulias V; Lu S; Cobo M; Syrigos K; Lee KH; Göker E; Guclu SZ; Isla D; Morabito A; Dupuis N; Bühnemann C; Krämer N; Solca F; Ehrnrooth E; Ardizzoni A. 2017. *Lung Cancer.* 109: 101-108. IF: 4,294

Peritoneal recurrence of thymoma treated by surgery and hyperthermic intraperitoneal chemotherapy. Mazza, Camille; Remon, Jordi; Honore, Charles; Besse, Benjamin. 2017. *Lung Cancer.* 111: 59-60. IF: 4,294

LKB1/STK11 mutations in non-small cell lung cancer patients: Descriptive analysis and prognostic value. Facchinetti F; Bluthgen MV; Tergemina-Clain G; Faivre L; Pignon JP; Planchard D; Remon J; Soria JC; Lacroix L; Besse B. 2017. *Lung Cancer.* 112: 62-68. IF: 4,294

Prognostic value of HLA-A2 status in advanced non-small cell lung cancer patients. Mezquita L; Charrier M; Faivre L; Dupraz L; Lueza B; Remon J; Planchard D; Bluthgen MV; Facchinetti F; Rahal A; Polo V; Gazzah A; Caramella C; Adam J; Pignon JP; Soria JC; Chaput N; Besse B. 2017. *Lung Cancer.* 112: 10-15. IF: 4,294

Functional PTGS2 polymorphism-based models as novel predictive markers in metastatic renal cell carcinoma patients receiving first-line sunitinib. Cebrián A; Gómez Del Pulgar T; Méndez-Vidal MJ; Gonzálvez ML; Lainez N; Castellano D; García-Carbonero I; Esteban E; Sáez MI; Villatoro R; Suárez C; Carrato A; Munárriz-Ferrándiz J; Basterrechea L; García-Alonso M; González-Larriba JL; Perez-Valderrama B; Cruz-Jurado J; González Del Alba A; Moreno F; Reynés G; Rodríguez-Remírez M; Boni V; Mahillo-Fernández I; Martin Y; Viqueira A; García-Foncillas J. 2017. *Sci Rep.* 7: 41371-0. IF: 4,259

Prognostic impact of CD133 expression in Endometrial Cancer Patients. Mancebo, G.; Sole-Sedeno, J. M.; Pino, O.; Miralpeix, E.; Mojal, S.; Garrigos, L.; Lloveras, B.; Navarro,

P.; Gibert, J.; Lorenzo, M.; Aran, I.; Carreras, R.; Alameda, F. 2017. *Sci Rep.* IF: 4,259

Microenvironment regulates the expression of miR-21 and tumor suppressor genes PTEN, PIAS3 and PDCD4 through ZAP-70 in chronic lymphocytic leukemia. Carabia J; Carpio C; Abrisqueta P; Jiménez I; Purroy N; Calpe E; Palacio C; Bosch F; Crespo M. 2017. *Sci Rep.* 7: 12262-0. IF: 4,259

Cytoplasmic cyclin D1 controls the migration and invasiveness of mantle lymphoma cells. Body S; Esteve-Arenys A; Miloudi H; Recasens-Zorzo C; Tchakarska G; Moros A; Bustany S; Vidal-Crespo A; Rodriguez V; Lavigne R; Com E; Casanova I; Mangues R; Weigert O; Sanjuan-Pla A; Menéndez P; Marcq B; Picquenot JM; Pérez-Galán P; Jardin F; Roué G; Sola B. 2017. *Sci Rep.* 7: 13946-0. IF: 4,259

Proteotoxicity in cardiac amyloidosis: Amyloidogenic light chains affect the levels of intracellular proteins in human heart cells. Imperlini E; Gnecchi M; Rognoni P; Sabidò E; Ciuffreda MC; Palladini G; Espadas G; Mancuso FM; Bozzola M; Malpasso G; Valentini V; Palladini G; Orrù S; Ferraro G; Milani P; Perlini S; Salvatore F; Merlini G; Lavatelli F. 2017. *Sci Rep.* 7: 15661-0. IF: 4,259

Disulfide driven folding for a conditionally disordered protein. Fraga H; Pujols J; Gil-Garcia M; Roque A; Bernardo-Seisdedos G; Santambrogio C; Bech-Serra JJ; Canals F; Bernadó P; Grandori R; Millet O; Ventura S. 2017. *Sci Rep.* 7: 16994-0. IF: 4,259

Electronic tongues to assess wine sensory descriptors. Cetó X; González-Calabuig A; Crespo N; Pérez S; Capdevila J; Puig-Pujol A; Valle MD. 2017. *Talanta.* 162: 218-224. IF: 4,162

Axitinib treatment in advanced RAI-resistant differentiated thyroid cancer (DTC) and refractory medullary thyroid cancer (MTC). Capdevila J; Trigo JM; Aller J; Manzano JL; Garcia-Adrian S; Zafon C; Reig O; Bohn U; Ramon Y Cajal T; Duran M; Gonzalez-Astorga B; Lopez-Alfonso A; Medina J; Porras I; Reina JJ; Palacios N; Grande E; Cillan E; Matos I; Grau JJ. 2017. *Eur J Endocrinol.* 177: 309-317. IF: 4,101

Profiling and identification of new proteins involved in brain ischemia using MALDI-imaging-mass-spectrometry. Llombart V; Trejo SA; Bronsoms S; Morancho A; Feifei M; Faura J; García-Berrocoso T; Simats A; Rosell A; Canals F; Hernández-Guillamón M; Montaner J. 2017. *J Proteomics.* 152: 243-253. IF: 3,914

A multicentric study to evaluate the use of relative retention times in targeted proteomics. Vialas V; Colomé-Calls N; Abian J; Aloria K; Alvarez-Llamas G; Antúnez O; Arizmendi JM; Azkargorta M; Barceló-Batllori S; Barderas MG; Blanco F; Casal JI; Casas V; de la Torre C; Chicano-Gálvez E; Elortza F; Espadas G; Estanyol JM; Fernandez-Irigoyen J; Fernandez-Puente P; Fidalgo MJ; Fuentes M; Gay M; Gil C; Hainard A; Hernaez ML; Ibarrola N; Kopylov AT; Lario A; Lopez JA; López-Lucendo M; Marcilla M; Marina-Ramírez A; Marko-Varga G; Martín L; Mora MI; Morato-López E; Muñoz J; Odena MA; de Oliveira E; Orera I; Ortea I; Pasquarello C; Ray KB; Rezeli M; Ruppen I; Sabidó E; Del Pino MM; Sancho J; Santamaría E; Vazquez J; Vilaseca M; Vivanco F; Walters JJ; Zgoda VG; Corrales FJ; Canals F; Paradela A. 2017. *J Proteomics.* 152: 138-149. IF: 3,914

Patterns of infection and infection-related mortality in patients with steroid-refractory acute graft versus host disease. García-Cadenas I; Rivera I; Martino R; Esquirol A; Barba P; Novelli S; Orti G; Briones J; Brunet S; Valcarcel D; Sierra J. 2017. *Bone Marrow Transplant.* 52: 107-113. IF: 3,874

Tacrolimus plus sirolimus with or without ATG as GVHD prophylaxis in HLA-mismatched unrelated donor allogeneic stem cell transplantation. Kharfan-Dabaja MA; Parody R; Perkins J; Lopez-Godino O; Lopez-Corral L; Vazquez L; Caballero D; Falantes J; Shapiro J; Ortí G; Barba P; Valcárcel D; Esquirol A; Martino R; Piñana JL; Solano C; Tsalatsanis A; Pidala J; Anasetti C; Perez-Simón JA. 2017. *Bone Marrow Transplant.* 52: 438-444. IF: 3,874

Long-term prognosis for 1-year relapse-free survivors of CD34+ cell-selected allogeneic hematopoietic stem cell transplantation: a landmark analysis. Cho C; Hsu M; Barba P; Maloy MA; Avecilla ST; Barker JN; Castro-Malaspina H; Giralt SA; Jakubowski AA; Koehne G; Meagher RC; O'Reilly RJ; Papadopoulos EB; Ponce DM; Tamari R; van den Brink MRM; Young JW; Devlin SM; Perales MA. 2017. *Bone Marrow Transplant.* 52: 1629-1636. IF: 3,874

Free Testosterone During Androgen Deprivation Therapy Predicts Castration-Resistant Progression Better Than Total Testosterone. Regis L; Planas J; Carles J; Maldonado X; Comas I; Ferrer R; Morote J. 2017. *Prostate.* 77: 114-120. IF: 3,820

Association of breast cancer risk in BRCA1 and BRCA2 mutation carriers with genetic variants showing differential allelic expression: identification of a modifier of breast cancer risk at locus 11q22.3. Hamdi, Y.; Soucy, P.; Kuchenbaeker, K.B.; Pastinen, T.; Droit, A.; Lemaçon, A.; Adlard, J.; Aittomäki, K.; Andrulis, I.L.; Arason, A.; Arnold, N.; Arun, B.K.; Azzollini, J.; Bane, A.; Barjhoux, L.; Barrowdale, D.; Benitez, J.; Berthet, P.; Blok, M.J.; Bobolis, K.; Bonadona, V.; Bonanni, B.; Bradbury, A.R.; Brewer, C.; Buecher, B.; Buys, S.S.; Caligo, M.A.; Chiquette, J.; Chung, W.K.; Claes, K.B.M.; Daly, M.B.; Damiola, F.; Davidson, R.; de la Hoya, M.; de Leeneer, K.; Diez, O.; Ding, Y.C.; Dolcetti, R.; Domchek, S.M.; Dorfling, C.M.; Eccles, D.; Eeles, R.; Einbeigi, Z.; Ejlertsen, B.; EMBRACEb; et al. 2017. *Breast Cancer Res Treat.* 161: 117-134. IF: 3,626

A phase II study of combined ridaforolimus and dalotuzumab compared with exemestane in patients with estrogen receptor-positive breast cancer. Baselga J; Morales SM; Awada A; Blum JL; Tan AR; Ewertz M; Cortes J; Moy B; Ruddy KJ; Haddad T; Ciruelos EM; Vuylsteke P; Ebbinghaus S; Im E; Eaton L; Pathiraja K; Gause C; Mauro D; Jones MB; Rugo HS. 2017. *Breast Cancer Res Treat.* 163: 535-544. IF: 3,626

Prolonged survival in patients with breast cancer and a history of brain metastases: results of a preplanned subgroup analysis from the randomized phase III BEACON trial. Cortés J; Rugo HS; Awada A; Twelves C; Perez EA; Im SA; Gómez-Pardo P; Schwartzberg LS; Diéras V; Yardley DA; Potter DA; Mailliez A; Moreno-Aspitia A; Ahn JS; Zhao C; Hoch U; Tagliaferri M; Hannah AL; O'Shaughnessy J. 2017. *Breast Cancer Res Treat.* 165: 329-341. IF: 3,626

A randomized phase II trial of ridaforolimus, dalotuzumab, and exemestane compared with ridaforolimus and exemestane in patients with advanced breast cancer. Rugo HS; Trédan O; Ro J; Morales SM; Campone M; Musolino A; Afonso N; Ferreira M; Park KH; Cortes J; Tan AR; Blum JL; Eaton L; Gause CK; Wang Z; Im E; Mauro DJ; Jones MB; Denker A; Baselga J. 2017. *Breast Cancer Res Treat.* 165: 601-609. IF: 3,626

ENETS Consensus Recommendations for the Standards of Care in Neuroendocrine Neoplasms: Follow-Up and Documentation. Knigge U; Capdevila J; Bartsch DK; Baudin E; Falkerby J; Kianmanesh R; Kos-Kudla B; Niederle B; Nieveen van Dijkum E; O'Toole D; Pascher A; Reed N; Sundin A; Vullierme MP; all other Antibes Consensus Conference Participants. 2017. *Neuroendocrinology.* 105: 310-319. IF: 3,608

ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumours: Surgery for Small Intestinal and Pancreatic Neuroendocrine Tumours. Partelli S; Bartsch DK; Capdevila J; Chen J; Knigge U; Niederle B; Nieveen van Dijkum EJ; Pape UF; Pascher A; Ramage J; Reed N; Ruszniewski P; Scoazec JY; Toumpanakis C; Kianmanesh R; Falconi M; all other Antibes Consensus Conference participants. 2017. *Neuroendocrinology.* 105: 255-265. IF: 3,608

An analysis of the kinetics of molecular response during the first trimester of treatment with nilotinib in newly diagnosed chronic myeloid leukemia patients in chronic phase. Steegmann JL; Colomer D; Gómez-Casares MT; García-Gutiérrez V; Ortí G; Ramírez-Payer A; Olavarria E; Vall-Llovera F; Giraldo P; Conde E; Vallansot R; López-Lorenzo JL; Palomera L; Álvarez-Larrán A; Conesa V; Bautista G; Casas L; Giles F; Hochhaus A; Casado-Montero LF. 2017. *J Cancer Res Clin Oncol.* 143: 2059-2066. IF: 3,503

Phase II study of the antibody-drug conjugate TAK-264 (MLN0264) in patients with metastatic or recurrent adenocarcinoma of the stomach or gastroesophageal junction expressing guanylyl cyclase C. Almhanna K; Miron ML; Wright D; Gracian AC; Hubner RA; Van Laethem JL; López CM; Alsina M; Muñoz FL; Bendell J; Firdaus I; Messersmith W; Ye Z; Fasanmade AA; Danaee H; Kalebic T. 2017. *Invest New Drugs.* 35: 235-241. IF: 3,484

Immuno-Oncology: The Third Paradigm in Early Drug Development. Martin-Liberal J; Hierro C; Ochoa de Olza M; Rodon J. 2017. *Target Oncol.* 12: 125-138. IF: 3,438

Novel Insights into the Treatment of Imatinib-Resistant Gastrointestinal Stromal Tumors. Serrano C; George S; Valverde C; Olivares D; García-Valverde A; Suárez C; Morales-Barrera R; Carles J. 2017. *Target Oncol.* 12: 277-288. IF: 3,438

Resistance to Targeted Therapies in Renal Cancer: The Importance of Changing the Mechanism of Action. Duran I; Lambea J; Maroto P; González-Larriba JL; Flores L; Granados-Principal S; Graupera M; Sáez B;

Vivancos A; Casanovas O. 2017. *Target Oncol.* 12: 19-35. IF: 3,438

A Multi-Arm Phase I Study of the PI3K/mTOR Inhibitors PF-04691502 and Gedatolisib (PF-05212384) plus Irinotecan or the MEK Inhibitor PD-0325901 in Advanced Cancer. Wainberg ZA; Alsina M; Soares HP; Braña I; Britten CD; Del Conte G; Ezeh P; Houk B; Kern KA; Leong S; Pathan N; Pierce KJ; Siu LL; Vermette J; Tabernero J. 2017. *Target Oncol.* 12: 775-785. IF: 3,438

The Treatment Landscape and New Opportunities of Molecular Targeted Therapies in Gastroenteropancreatic Neuroendocrine Tumors. Amair-Pinedo F; Matos I; Saurí T; Hernando J; Capdevila J. 2017. *Target Oncol.* 12: 757-774. IF: 3,438

The APPLE Trial: Feasibility and Activity of AZD9291 (Osimertinib) Treatment on Positive PLasma T790M in EGFR-mutant NSCLC Patients. EORTC 1613. Remon J; Menis J; Hasan B; Peric A; De Maio E; Novello S; Reck M; Berghmans T; Wasag B; Besse B; Dziadziuszko R. 2017. *Clin Lung Cancer.* 18: 583-588. IF: 3,434

Immune checkpoint inhibitors in first-line therapy of advanced non-small cell lung cancer. Remon J; Besse B. 2017. *Curr Opin Oncol.* 29: 97-104. IF: 3,414

Progression-free survival at 2 years post-autologous transplant: a surrogate end point for overall survival in follicular lymphoma. Jiménez-Ubieto A; Grande C; Caballero D; Yáñez L; Novelli S; Hernández MT; Manzanares M; Arranz R; Ferreiro JJ; Bobillo S; Mercadal S; Galego A; Jiménez JL; Moraleda JM; Vallejo C; Albo C; Pérez E; Marrero C; Magnano L; Palomera L; Jarque I; Coria E; Rodriguez A; Martín A; López-Guillermo A; Salar A; Lahuerta JJ; GELTAMO (Grupo Español de Linfomas y Trasplantes de Médula Ósea) cooperative stu. 2017. *Cancer Med.* 6: 2766-2774. IF: 3,362

A phase I open-label dose-escalation study of the anti-HER3 monoclonal antibody LJM716 in patients with advanced squamous cell carcinoma of the esophagus or head and neck and HER2-overexpressing breast or gastric cancer. Reynolds KL; Bedard PL; Lee SH; Lin CC; Tabernero J; Alsina M; Cohen E; Baselga J; Blumenschein G; Graham DM; Garrido-Laguna I; Juric D; Sharma S; Salgia R; Seroutou A; Tian X; Fernandez R; Morozov A; Sheng Q; Ramkumar T; Zubel A; Bang YJ. 2017. *BMC Cancer.* 17: 646-0. IF: 3,288

Biomarker and Histopathology Evaluation of Patients with Recurrent Glioblastoma Treated with Galunisertib, Lomustine, or the Combination of Galunisertib and Lomustine. Capper D; von Deimling A; Brandes AA; Carpentier AF; Kesari S; Sepulveda-Sanchez JM; Wheeler HR; Chinot O; Cher L; Steinbach JP; Specenier P; Rodon J; Cleverly A; Smith C; Gueorguieva I; Miles C; Guba SC; Desaiah D; Estrem ST; Lahn MM; Wick W. 2017. *Int J Mol Sci.* IF: 3,226

Genetics of Pheochromocytomas and Paragangliomas: An Overview on the Recently Implicated Genes MERTK, MET, Fibroblast Growth Factor Receptor 1, and H3F3A. Toledo RA. 2017. *Endocrinol Metab Clin North Am.* 46: 459-489. IF: 3,204

Calreticulin mutations are exceedingly rare in patients with myelodysplastic syndromes with myelofibrosis. Montoro J; Robledo C; Zamora L; Valcárcel D; Ramos F. 2017. *Ann Hematol.* 96: 317-318. IF: 3,083

Cytomorphology review of 100 newly diagnosed lower-risk MDS patients in the European LeukemiaNet MDS (EUMDS) registry reveals a high inter-observer concordance. de Swart L; Smith A; MacKenzie M; Symeonidis A; Neukirchen J; Mikulenková D; Vallespí T; Zini G; Paszkowska-Kowalewska M; Kruger A; Saft L; Fenaux P; Bowen D; Hellström-Lindberg E; Cermák J; Stauder R; Tatic A; Holm MS; Malcovati L; Madry K; Droste J; Blijlevens N; de Witte T; Germing U. 2017. *Ann Hematol.* 96: 1105-1112. IF: 3,083

Clinical characteristics of patients with central nervous system relapse in BCR-ABL1-positive acute lymphoblastic leukemia: the importance of characterizing ABL1 mutations in cerebrospinal fluid. Sanchez R; Ayala R; Alonso RA; Martínez MP; Ribera J; García O; Sanchez-Pina J; Mercadal S; Montesinos P; Martino R; Barba P; González-Campos J; Barrios M; Lavilla E; Gil C; Bernal T; Escoda L; Abella E; Amigo ML; Moreno MJ; Bravo P; Guàrdia R; Hernández-Rivas JM; García-Guiñón A; Piernas S; Ribera JM; Martínez-López J. 2017. *Ann Hematol.* 96: 1069-1075. IF: 3,083

Prophylaxis with enoxaparin for prevention of venous thromboembolism after lung transplantation: a retrospective study. Sáez-Giménez B; Berastegui C; Sintes H; Perez-Miranda J; Figueredo A; López Meseguer M; Monforte V; Bravo C; Santamaría A; Ramon MA; Gómez-Ollés S; Roman A. 2017. *Transpl Int.* 30: 1266-1274. IF: 3,079

Overexpression of Yes Associated Protein 1, an Independent Prognostic Marker in Patients with Pancreatic Ductal Adenocarcinoma, Correlated with Liver Metastasis and Poor Prognosis. Salcedo Allende MT; Zeron-Medina J; Hernandez J; Macarulla T; Balsells J; Merino X; Allende H; Tabernero J; Ramon Y Cajal Agüeras S. 2017. *Pancreas.* 46: 913-920. IF: 2,967

Further psychometric validation of the GAH scale: Responsiveness and effect size. Cruz-Jentoft AJ; González B; de la Rubia J; Hernández Rivas JÁ; Soler JA; Fernández Lago C; Arnao M; Gironella M; Pérez Persona E; Zudaire MT; Olivier C; Altés A; García Guiñón A; Nomdedeu B; Arnan M; Ramírez Payer Á; Sánchez-Godoy P; Pajuelo N; Vilanova D; Monjil DF; Bonanad S; GAH Group. 2017. *J Geriatr Oncol.* 8: 211-215. IF: 2,852

Donor lymphocyte infusions in AML and MDS: Enhancing the graft-versus-leukemia effect. Orti G; Barba P; Fox L; Salamero O; Bosch F; Valcarcel D. 2017. *Exp Hematol.* 48: 1-11. IF: 2,820

Desmoid-Type Fibromatosis: Who, When, and How to Treat. Martínez Trufero J; Pajares Bernad I; Torres Ramón I; Hernando Cubero J; Pazo Cid R. 2017. *Curr Treat Options Oncol.* 18: 29-0. IF: 2,820

RESILIENCE: Phase III Randomized, Double-Blind Trial Comparing Sorafenib With Capecitabine Versus Placebo With Capecitabine in Locally Advanced or Metastatic HER2-Negative Breast Cancer. Baselga J; Zamagni C; Gómez P; Bermejo B; Nagai SE; Melichar B; Chan A; Mángel L; Bergh J; Costa F; Gómez HL; Gradishar WJ; Hudis CA; Rapoport BL; Roché H; Patricia M; Huang L; Meinhardt G; Zhang J; Schwartzberg LS. 2017. *Clin Breast Cancer.* IF: 2,816

Safety and antitumor activity of the anti–PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma. O'Neil, B.H.; Wallmark, J.M.; Lorente, D.; Elez, E.; Raimbourg, J.; Gomez-Roca, C.; Ejadi, S.; Piha-Paul, S.A.; Stein, M.N.; Abdul Razak, A.R.; Dotti, K.; Santoro, A.; Cohen, R.B.; Gould, M.; Saraf, S.; Stein, K.; Han, S.-W.. 2017. *PLoS One.* IF: 2,806

Biophysical characterization of the b-HLH-LZ of d Max, an alternatively spliced isoform of Max found in tumor cells: Towards the validation of a tumor suppressor role for the Max homodimers. Maltais, L.; Montagne, M.; Bédard, M.; Tremblay, C.; Soucek, L.; Lavigne, P. 2017. *PLoS One.* IF: 2,806

Crystal digital droplet PCR for detection and quantification of circulating EGFR sensitizing and resistance mutations in advanced non-small cell lung cancer. Jovelet C; Madic J; Remon J; Honoré A; Girard R; Rouleau E; André B; Besse B; Droniou M; Lacroix L. 2017. *PLoS One.* IF: 2,806

Role of total tumour load of sentinel lymph node on survival in early breast cancer patients. Peg V; Sansano I; Vieites B; Bernet L; Cano R; Córdoba A; Sancho M; Martín MD; Vilardell F; Cazorla A; Espinosa-Bravo M; Pérez-García JM; Cortés J; Rubio IT; Ramón Y Cajal S. 2017. *Breast.* 33: 8-13. IF: 2,801

De-escalation of treatment in HER2-positive breast cancer: Determinants of response and mechanisms of resistance. Veeraraghavan J; De Angelis C; Reis-Filho JS; Pascual T; Prat A; Rimawi MF; Osborne CK; Schiff R. 2017. *Breast.* IF: 2,801

Frequency and prognostic significance of t(v;11q23)/KMT2A rearrangements in adult patients with acute lymphoblastic leukemia treated with risk-adapted protocols. Motlló C; Ribera JM; Morgades M; Granada I; Montesinos P; Brunet S; Bergua J; Tormo M; García-Boyero R; Sarrà J; Del Potro E; Grande C; Barba P; Bernal T; Amigo ML; Grau J; Cervera J; Feliu E; PETHEMA Group, Spanish Society of Hematology. 2017. *Leuk Lymphoma.* 58: 145-152. IF: 2,755

Exposure–response relationship of ramucirumab in patients with advanced second-line colorectal cancer: exploratory analysis of the RAISE trial. Cohn AL; Yoshino T; Heinemann V; Obermannova R; Bodoky G; Prausová J; Garcia-Carbonero R; Ciuleanu T; Garcia-Alfonso P; Portnoy DC; Van Cutsem E; Yamazaki K; Clingan PR; Polikoff J; Lonardi S; O'Brien LM; Gao L; Yang L; Ferry D; Nasroulah F; Tabernero J. 2017. *Cancer Chemother Pharmacol.* 80: 599-608. IF: 2,737

Malignant bone tumors (other than Ewing's): clinical practice guidelines for diagnosis, treatment and follow-up by Spanish Group for Research on Sarcomas (GEIS). Redondo A; Bagué S; Bernabeu D; Ortiz-Cruz E; Valverde C; Alvarez R; Martinez-Trufero J; Lopez-Martin JA; Correa R; Cruz J; Lopez-Pousa A; Santos A; García Del Muro X; Martin-Broto J. 2017.

*Cancer Chemother Pharmacol.* 80: 1113-1131. IF: 2,737

Association of Performance Status and Pain in Metastatic Bone Pain Management in the Spanish Clinical Setting. Dómine Gómez, M.; Díaz Fernández, N.; Cantos Sánchez de Ibargüen, B.; Zugazabeitia Olabarría, L.; Martínez Lozano, J.; Poza de Celis, R.; Trujillo Vílchez, R.; Peláez Fernández, I.; Capdevila Castillón, J.; Traseira Lugilde, S.; Esteban González, E. 2017. *Adv Ther.* 34: 136-147. IF: 2,709

Predictive factors for anemia response to erythropoiesis-stimulating agents in myelofibrosis. Hernández-Boluda JC; Correa JG; García-Delgado R; Martínez-López J; Alvarez-Larrán A; Fox ML; García-Gutiérrez V; Pérez-Encinas M; Ferrer-Marín F; Mata-Vázquez MI; Raya JM; Estrada N; García S; Kerguelen A; Durán MA; Albors M; Cervantes F. 2017. *Eur J Haematol.* 98: 407-414. IF: 2,653

Optimizing Somatostatin Analog Use in Well or Moderately Differentiated Gastroenteropancreatic Neuroendocrine Tumors. Carmona-Bayonas A; Jiménez-Fonseca P; Custodio A; Grande E; Capdevila J; López C; Teule A; Garcia-Carbonero R; Spanish Neuroendocrine Tumor Group (GETNE). 2017. *Curr Oncol Rep.* 19: 72-0. IF: 2,608

Assessing Tumor-infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method from the International Immunooncology Biomarkers Working Group: Part 1: Assessing the Host Immune Response, TILs in Invasive Breast Carcinoma and Ductal Carcinoma in Situ, Metastatic Tumor Deposits and Areas for Further Research. Hendry, Shona; Salgado, Roberto; Gevaert, Thomas; Russell, Prudence A.; John, Tom; Thapa, Bibhusal; Christie, Michael; van de Vijver, Koen; Estrada, M. V; Gonzalez-Ericsson, Paula I; Sanders, Melinda; Solomon, Benjamin sss; Solinas, Cinzia; Van den Eynden, Gert G. G. M.; Allory, Yves; Preusser, Matthias; Hainfellner, Johannes; Pruneri, Giancarlo; Vingiani, Andrea; Demaria, Sandra; Symmans, Fraser; Nuciforo, Paolo; Comerma, Laura; Thompson, E. A.; Lakhani, Sunil; Kim, Seong-Rim; Schnitt, Stuart; Colpaert, Cecile; Sotiriou, Christos; Scherer, Stefan J.; Ignatiadis, Michail; Badve, Sunil; Pierce, Robert H.; Viale, Giuseppe; Sirtaine, Nicolas; Penault-Llorca, Frederique; Sugie, et al. 2017. *Adv Anat Pathol.* 24: 235-251. IF: 2,570

Assessing Tumor-Infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method from the International Immuno-Oncology Biomarkers Working Group: Part 2: TILs in Melanoma, Gastrointestinal Tract Carcinomas, Non-Small Cell Lung Carcinoma and Mesothelioma, Endometrial and Ovarian Carcinomas, Squamous Cell Carcinoma of the Head and Neck, Genitourinary Carcinomas, and Primary Brain Tumors. Hendry, S.; Salgado, R.; Gevaert, T.; Russell, P.A.; John, T.; Thapa, B.; Christie, M.; Van De Vijver, K.; Estrada, M.V.; Gonzalez-Ericsson, P.I.; Sanders, M.; Solomon, B.; Solinas, C.; Van Den Eynden, G.G.G.M.; Allory, Y.; Preusser, M.; Hainfellner, J.; Pruneri, G.; Vingiani, A.; Demaria, S.; Symmans, F.; Nuciforo, P.; Comerma, L.; Thompson, E.A.; Lakhani, S.; Kim, S.-R.; Schnitt, S.; Colpaert, C.; Sotiriou, C.; Scherer, S.J.; Ignatiadis, M.; Badve, S.; Pierce, R.H.; Viale, G.; Sirtaine, N.; Penault-Llorca, F.; Sugie, T.; Fineberg, S.; Paik, S.; Srinivasan, A.; Richardson, A.; Wang, Y.; Chmielik, E.; Brock, J.; Johnson, D.B.; Balko, J.; Wienert, S.; Bossuyt, V.; Michiels, S.; Ternes, N.; Burchardi, N.; et al. 2017. *Adv Anat Pathol.* 24: 311-335. IF: 2,570

Second-line Chemotherapy in Older Patients With Metastatic Urothelial Carcinoma: Pooled Analysis of 10 Second-line Studies. Salah S; Lee JL; Rozzi A; Kitamura H; Matsumoto K; Vis DJ; Srinivas S; Morales-Barrera R; Carles J; Al-Rimawi D; Lee S; Kim KH; Izumi K; Lewin J. 2017. *Clin Genitourin Cancer.* 15: 563-571. IF: 2,535

Effect of Visceral Disease Site on Outcomes in Patients With Metastatic Castration-resistant Prostate Cancer Treated With Enzalutamide in the PREVAIL Trial. Alumkal JJ; Chowdhury S; Loriot Y; Sternberg CN; de Bono JS; Tombal B; Carles J; Flaig TW; Dorff TB; Phung; Forer D; Noonberg SB; Mansbach H; Beer TM; Higano CS. 2017. *Clin Genitourin Cancer.* 15: 610-6173. IF: 2,535

Spuriously low pulse oximetry saturation associated with hemoglobin Sydney in a child and relatives: Identification of this unstable hemoglobin may avoid unnecessary testing and hospital admissions. de Sevilla MF; Català A; Rives S; Berrueco R; Vidiella N; Camós M; Torrebadell M; Alonso-Saladrigues A; Mesegué M; Ruiz-Llobet A; Blanco-Álvarez A; Benéitez D. 2017. *Pediatr Blood Cancer.* IF: 2,513

Clinical and biological significance of isolated Y chromosome loss in myelodysplastic syndromes and chronic myelomonocytic leukemia. A report from the Spanish MDS Group. Nomdedeu M; Pereira A; Calvo X; Colomer J; Sole F; Arias A; Gomez C; Luño E; Cervera J; Arnan M; Pomares H; Ramos F; Oiartzabal I; Espinet B; Pedro C; Arrizabalaga B; Blanco ML; Tormo M; Hernandez-Rivas JM; Díez-Campelo M; Ortega M; Valcárcel D; Cedena MT; Collado R; Grau J; Granada I; Sanz G; Campo E; Esteve J; Costa D; Spanish MDS Group. 2017. *Leuk Res.* 63: 85-89. IF: 2,501

Clinical efficacy of ß-lactam/ß-lactamase inhibitor combinations for the treatment of bloodstream infection due to extended-spectrum ß-lactamase-producing Enterobacteriaceae in haematological patients with neutropaenia: a study protocol for a retrospective observational study (BICAR). Gudiol C; Royo-Cebrecos C; Tebe C; Abdala E; Akova M; Álvarez R; Maestro-de la Calle G; Cano A; Cervera C; Clemente WT; Martín-Dávila P; Freifeld A; Gómez L; Gottlieb T; Gurguí M; Herrera F; Manzur A; Maschmeyer G; Meije Y; Montejo M; Peghin M; Rodríguez-Baño J; Ruiz-Camps I; Sukiennik TC; Carratalà J; BICAR study group. 2017. *BMJ Open.* IF: 2,369

A Phase 2, Randomized, Open-Label Study of Irosustat Versus Megestrol Acetate in Advanced Endometrial Cancer. Pautier P; Vergote I; Joly F; Melichar B; Kutarska E; Hall G; Lisyanskaya A; Reed N; Oaknin A; Ostapenko V; Zvirbule Z; Chetaille E; Geniaux A; Shoaib M; Green JA. 2017. *Int J Gynecol Cancer.* 27: 258-266. IF: 2,369

Epileptic features and survival in glioblastomas presenting with seizures. Toledo M; Sarria-Estrada S; Quintana M; Maldonado X; Martinez-Ricarte F; Rodon J; Auger C; Aizpurua M; Salas-Puig J; Santamarina E; Martinez-Saez E. 2017. *Epilepsy Res.* 130: 1-6. IF: 2,367

Spanish consensus for the management of patients with anaplastic cell thyroid carcinoma. Jiménez-Fonseca P; Gómez Saez JM; Santamaria Sandi J; Capdevila J; Navarro Gonzalez E; Zafon Llopis C; Ramón Y Cajal Asensio T; Riesco-Eizaguirre G; Grande E; Galofré JC. 2017. *Clin Transl Oncol.* 19: 12-20. IF: 2,353

Effectiveness of a Double-Carbapenem Regimen in a KPC-Producing Klebsiella pneumoniae Infection in an Immunocompromised Patient. Piedra-Carrasco N; Miguel L; Fàbrega A; Viñado B; Campany D; Mir A; Fox ML; Almirante B; Larrosa N; Ruiz-Camps I; González-López JJ. *Microb Drug Resist.* IF: 2,306

Sequential treatment with immunotherapy and BRAF inhibitors in BRAF-mutant advanced melanoma. Aya F; Fernandez-Martinez A; Gaba L; Victoria I; Tosca M; Pineda E; Gascon P; Prat A; Arance A. 2017. *Clin Transl Oncol.* 19: 119-124. IF: 2,353

Efficacy of trifluridine and tipiracil (TAS-102) versus placebo, with supportive care, in a randomized, controlled trial of patients with metastatic colorectal cancer from Spain: results of a subgroup analysis of the phase 3 RECOURSE trial. Longo-Muñoz F; Argiles G; Tabernero J; Cervantes A; Gravalos C; Pericay C; Gil-Calle S; Mizuguchi H; Carrato-Mena A; Limón ML; Garcia-Carbonero R. 2017. *Clin Transl Oncol.* 19: 227-235. IF: 2,353

Consensus on the management of advanced radioactive iodine-refractory differentiated thyroid cancer on behalf of the Spanish Society of Endocrinology Thyroid Cancer Working Group (GTSEEN) and Spanish Rare Cancer Working Group (GETHI). Capdevila J; Galofré JC; Grande E; Zafón Llopis C; Ramón Y Cajal Asensio T; Navarro González E; Jiménez-Fonseca P; Santamaría Sandi J; Gómez Sáez JM; Riesco Eizaguirre G. 2017. *Clin Transl Oncol.* 19: 279-287. IF: 2,353

Medical oncology future plan of the Spanish Society of Medical Oncology: challenges and future needs of the Spanish oncologists. Rivera F; Andres R; Felip E; Garcia-Campelo R; Lianes P; Llombart A; Piera JM; Puente J; Rodriguez CA; Vera R; Virizuela JA; Martin M; Garrido P. 2017. *Clin Transl Oncol.* 19: 508-518. IF: 2,353

A consensus statement on the gender perspective in lung cancer. Isla D; Majem M; Viñolas N; Artal A; Blasco A; Felip E; Garrido P; Remón J; Baquedano M; Borrás JM; Die Trill M; García-Campelo R; Juan O; León C; Lianes P; López-Ríos F; Molins L; Planchuelo MÁ; Cobo M; Paz-Ares L; Trigo JM; de Castro J. 2017. *Clin Transl Oncol.* 19: 527-535. IF: 2,353

A definition for aggressive disease in patients with HER-2 negative metastatic breast cancer: an expert consensus of the Spanish Society of Medical Oncology (SEOM). González A; Lluch A; Aba E; Albanell J; Antón A; Álvarez I; Ayala F; Barnadas A; Calvo L; Ciruelos E; Cortés J; de la Haba J; López-Vega JM; Martínez E; Muñoz M; Peláez I; Redondo A; Rodríguez Á; Rodríguez CA; Ruíz A; Llombart A. 2017. *Clin Transl Oncol.* 19: 616-624. IF: 2,353

Gastrointestinal stromal tumors (GISTs): SEAP-SEOM consensus on pathologic and molecular diagnosis. Martin-Broto J; Martinez-

Marín V; Serrano C; Hindi N; López-Guerrero JA; Ramos-Asensio R; Vallejo-Benítez A; Marcilla-Plaza D; González-Cámpora R. 2017. *Clin Transl Oncol.* 19: 536-545. IF: 2,353

Pembrolizumab for advanced melanoma: experience from the Spanish Expanded Access Program. Gonzalez-Cao, M.; Arance, A.; Piulats, J. M.; Marquez-Rodas, I.; Manzano, J. L.; Berrocal, A.; Crespo, G.; Rodriguez, D.; Perez-Ruiz, E.; Berciano, M.; Soria, A.; Castano, A. G.; Espinosa, E.; Montagut, C.; Alonso, L.; Puertolas, T.; Aguado, C.; Royo, M. A.; Blanco, R.; Rodriguez, J. F.; Munoz, E.; Mut, P.; Barron, F.; Martin-Algarra, S.; Spanish Melanoma Grp. 2017. *Clin Transl Oncol.* 19: 761-768. IF: 2,353

Consensus guidelines for diagnosis, treatment and follow-up of patients with pancreatic cancer in Spain. Hidalgo M; Álvarez R; Gallego J; Guillén-Ponce C; Laquente B; Macarulla T; Muñoz A; Salgado M; Vera R; Adeva J; Alés I; Arévalo S; Blázquez J; Calsina A; Carmona A; de Madaria E; Díaz R; Díez L; Fernández T; de Paredes BG; Gallardo ME; González I; Hernando O; Jiménez P; López A; López C; López-Ríos F; Martín E; Martínez J; Martínez A; Montans J; Pazo R; Plaza JC; Peiró I; Reina JJ; Sanjuanbenito A; Yaya R; Carrato A. 2017. *Clin Transl Oncol.* 19: 667-681. IF: 2,353

Adjuvant treatment for pancreatic ductal carcinoma. Macarulla T; Fernández T; Gallardo ME; Hernando O; López AM; Hidalgo M. 2017. *Clin Transl Oncol.* 19: 1199-1204. IF: 2,353

Efficacy of tyrosine kinase inhibitors in EGFR-mutant lung cancer women in a real-world setting: the WORLD07 database. Remon J; Isla D; Garrido P; de Castro J; Majem M; Viñolas N; Artal A; Carcereny E; García-Campelo MR; Lianes P; Provencio M; Juan O; Diz P; Blanco R; Lopez-Castro R; Maestu I; Vadell C; Felip E. 2017. *Clin Transl Oncol.* 19: 1537-1542. IF: 2,353

The role of mTOR inhibition as second-line therapy in metastatic renal carcinoma: clinical evidence and current challenges. González-Larriba, J.L.; Maroto, P.; Durán, I.; Lambea, J.; Flores, L.; Castellano, D.; Anido, U.; Basterrechea, L.; Casanovas, O.; Chirivella, I.; Climent, M.Á.; Dur, I.; Gallardo, E.; Garc, R.; Guix, M.; Laínez, N.; Marino, A.M.; Montesa, Á.; Pinto, A.; Puente, J.; Romero, G.R.; Suárez, C.; Virizuela, J.A.. 2017. *Expert Rev Anticancer Ther.* 17: 217-226. IF: 2,212

Capecitabine and temozolomide in grade 1/2 neuroendocrine tumors: A Spanish multicenter experience. Crespo G; Jiménez-Fonseca P; Custodio A; López C; Carmona-Bayonas A; Alonso V; Navarro M; Aller J; Sevilla I; Grande E; Gajate P; Alonso-Gordoa T; Matos I; Capdevila J; Nieto B; Barriuso J. 2017. *Future Oncol.* 13: 615-624. IF: 2,131

Lung Cancer in Never-Smoking Women: A Sub-Analysis of the Spanish Female-Specific Database WORLD07. Viñolas N; Garrido P; Isla D; Provencio M; Majem M; Artal A; Carcereny E; Garcia Campelo R; Lianes P; De La Peñas R; Felip E. 2017. *Cancer Invest.* 35: 358-365. IF: 2,007

nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: a subgroup analysis of the Western European cohort of the MPACT trial. Tabernero J; Kunzmann V; Scheithauer W; Reni M; Shiansong Li J; Ferrara S; Djazouli K. 2017. *Onco Targets Ther.* 10: 591-596. IF: 1,653

NRAS-mutant melanoma: Current challenges and future prospect. Muñoz-Couselo E; Adelantado EZ; Ortiz C; García JS; Perez-Garcia J. 2017. *Onco Targets Ther.* 10: 3941-3947. IF: 1,653

New and safe experimental model of radiation-induced neurovascular histological changes for microsurgical research. Barrera-Ochoa S; Gallardo-Calero I; Sallent A; López-Fernández A; Vergés R; Giralt J; Aguirre-Canyadell M; Velez R. 2017. *Lab Anim.* 51: 124-137. IF: 1,532

Is dose-dependent response to bacillus Calmette-Guérin treatment in urothelial carcinoma? Racca, Fabricio; Morales-Barrera, Rafael; Carles, Joan. 2017. *Transl Cancer Res.* 6: 179-181. IF: 1,167

Unraveling the hurdles in the development of HER2-targeted agents for metastatic gastro-esophageal cancer patients. Hierro, Cinta; Alsina, Maria; Tabernero, Josep. 2017. *Transl Cancer Res.* 6: 1035-1039. IF: 1,167

Asparaginase use for the treatment of acute lymphoblastic leukemia. Barba P; Dapena JL; Montesinos P; Rives S. 2017. *Med Clin (Barc).* 148: 225-231. IF: 1,125

Update of the Grupo Español de Leucemia Linfocítica Crónica clinical guidelines of the management of chronic lymphocytic leukemia. García-Marco JA; Delgado J; Hernández-Rivas JA; Ramírez Payer Á; Loscertales Pueyo J; Jarque I; Abrisqueta P; Giraldo P; Martínez R; Yáñez L; Terol MJ; González M; Bosch F; en nombre del Grupo Español de Leucemia Linfocítica Crónica (GELLC). 2017. *Med Clin (Barc).* 148: 3811-3819. IF: 1,125

Bridge therapy in patients under anticoagulation: Is it still the question? Santamaría A. 2017. *Med Clin (Barc).* 149: 303-304. IF: 1,125

## Articles published by VHIO Investigators in journals with no Impact Factor (IF) allocted at the time of publication of this Scientific Report:

The European Cancer Patient's Bill of Rights, update and implementation 2016. Højgaard L; Löwenberg B; Selby P; Lawler M; Banks I; Law K; Albreht T; Armand JP; Barbacid M; Barzach M; Bergh J; Cameron D; Conte P; de Braud F; de Gramont A; De Lorenzo F; Diehl V; Diler S; Erdem S; Geissler J; Gore-Booth J; Henning G; Horgan D; Jassem J; Johnson P; Kaasa S; Kapitein P; Karjalainen S; Kelly J; Kienesberger A; La Vecchia C; Lacombe D; Lindahl T; Luzzatto L; Malby R; Mastris K; Meunier F; Murphy M; Naredi P; Nurse P; Oliver K; Pearce J; Pelouchov J; Piccart M; Pinedo B; Spurrier-Bernard G; Sullivan R; Tabernero J; Van de Velde C; van Herk B; Vedsted P; Waldmann A; Weller D; Wilking N; Wilson R; Yared W; Zielinski C; Zur Hausen H; Le Chevalier T; Johnston P. 2017. *ESMO Open.*

Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. Tabernero J; Vyas M; Giuliani R; Arnold D; Cardoso F; Casali PG; Cervantes A; Eggermont AM; Eniu A; Jassem J; Pentheroudakis G; Peters S; Rauh S; Zielinski CC; Stahel RA; Voest E; Douillard JY; McGregor K; Ciardiello F. 2017. *ESMO Open.*

Radiological imaging markers predicting clinical outcome in patients with metastatic colorectal carcinoma treated with regorafenib: post hoc analysis of the CORRECT phase III trial (RadioCORRECT study). Ricotta R; Verrioli A; Ghezzi S; Porcu L; Grothey A; Falcone A; Van Cutsem E; Argilés G; Adenis A; Ychou M; Barone C; Bouché O; Peeters M; Humblet Y; Mineur L; Sobrero AF; Hubbard JM; Cremolini C; Prenen H; Tabernero J; Jarraya H; Mazard T; Deguelte-Lardiere S; Papadimitriou K; Van den Eynde M; Pastorino A; Redaelli D; Bencardino K; Funaioli C; Amatu A; Carlo-Stella G; Torri V; Sartore-Bianchi A; Vanzulli A; Siena S. 2017. *ESMO Open.*

Towards shedding some light on regorafenib treatment in refractory metastatic colorectal cancer. Prager, Gerald; Argiles, Guillem. 2017. *ESMO Open.*

Detailed statistical assessment of the characteristics of the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) threshold rules. Dafni U; Karlis D; Pedeli X; Bogaerts J; Pentheroudakis G; Tabernero J; Zielinski CC; Piccart MJ; de Vries EGE; Latino NJ; Douillard JY; Cherny NI. 2017. *ESMO Open.*

Liquid biopsy for HER2-positive breast cancer brain metastasis: the role of the cerebrospinal fluid. De Mattos-Arruda L. 2017. *ESMO Open.*

Proxies of quality of life in metastatic colorectal cancer: analyses in the RECOURSE trial. Van Cutsem E; Falcone A; Garcia-Carbonero R; Komatsu Y; Pastorino A; Peeters M; Shimada Y; Yamazaki K; Yoshino T; Zaniboni A; Amellal N; Kanehisa A; Winkler R; Makris L; Mayer RJ; Ohtsu A; Tabernero J. 2017. *ESMO Open.*

QTWiST analysis of the RECOURSE trial of trifluridine/tipiracil in metastatic colorectal cancer. Tabernero J; Van Cutsem E; Ohtsu A; Amellal N; Cadour S; Fougeray R; Haffemayer B; Mayer RJ. 2017. *ESMO Open.*

A brief up-date and consensus about the pathological and molecular diagnosis of gastrointestinal stromal tumours from the SEAP-SEOM. González-Cámpora, R.; Ramos Asensio, R.; Vallejo-Benítez, A.; Marcilla-Plaza, D.; Biscuola, M.; Martínez-Marín, V.; Serrano, C.; Hindi, N.; López-Guerrero, J.-A.; Martin-Broto, J. 2017. *Revista Espanola De Patologia.* 50: 89-99.

Personalizing Adjuvant Therapy for Stage II/III Colorectal Cancer. McCleary NJ; Benson AB; Dienstmann R. 2017. *Am Soc Clin Oncol Educ Book.* 37: 232-245.

Pharmacokinetic/Pharmacodynamic Modeling for Drug Development in Oncology. Garralda E; Dienstmann R; Tabernero J. 2017. *Am Soc Clin Oncol Educ Book.* 37: 210-215.

Future Genetic/Genomic Biomarker Testing in Non-Small Cell Lung Cancer. Planchard D; Remon J; Nowak F; Soria JC. 2017. *Am Soc Clin Oncol Educ Book.* 37: 12-17.

Effectiveness of radiotherapy for metastatic spinal cord compression in patients with short life expectancy. Giraldo, Alexandra; Benavente, Sergi; Ramos, Monica; Verges, Ramona; Coronil, Odimar; Arbelaez, Lina; Maldonado, Xavier; Altabas, Manuel; Molla, Meritxell; Reyes, Victoria; Navalpotro, Begona;

Giralt, Jordi. 2017. *Rep Pract Oncol Radiother.* 22: 58-63.

Analytical parameters and vital signs in patients subjected to dental extraction. Jané-Pallí E; Arranz-Obispo C; González-Navarro B; Murat J; Ayuso-Montero R; Rojas S; Santamaría A; Jané-Salas E; López-López J. 2017. *J Clin Exp Dent.*

Strategies to inhibit Myc and their clinical applicability. Whitfield JR; Beaulieu ME; Soucek L. 2017. *Front Cell Dev Biol.* 5: 10-0.

Sensitizing HR-proficient cancers to PARP inhibitors. Lim E; Johnson SF; Geyer M; Serra V; Shapiro GI. 2017. *Mol Cell Oncol.*

Predictive and prognostic biomarkers in personalized gastrointestinal cancer treatment. Verdaguer H; Saurí T; Macarulla T. 2017. *J Gastrointest Oncol.* 8: 405-417.

The Role of Fluoropirimidines in Gastrointestinal Tumours: from the Bench to the Bed. Hernando-Cubero J; Matos-García I; Alonso-Orduña V; Capdevila J. 2017. *J Gastrointest Cancer.* 48: 135-147.

Single umbilical cord blood with or without CD34+ cells from a third-party donor in adults with leukemia. Sanz J; Kwon M; Bautista G; Sanz MA; Balsalobre P; Piñana JL; Solano C; Duarte R; Ferrá C; Lorenzo I; Martín C; Barba P; Pascual MJ; Martino R; Gayoso J; Buño I; Regidor C; de la Iglesia A; Montoro J; Díez-Martín JL; Sanz GF; Cabrera R. 2017. *Blood Adv.* 1: 1047-1055.

The AURORA pilot study for molecular screening of patients with advanced breast cancer-a study of the breast international group. Maetens M; Brown D; Irrthum A; Aftimos P; Viale G; Loibl S; Laes JF; Campbell PJ; Thompson A; Cortes J; Seiler S; Vinnicombe S; Oliveira M; Rothé F; Bareche Y; Fumagalli D; Zardavas D; Desmedt C; Piccart M; Loi S; Sotiriou C. 2017. *NPJ Breast Cancer.* 3: 23-0.

Report from the II Melanoma Translational Meeting of the Spanish Melanoma Group (GEM). Gonzalez-Cao, Maria; Berrocal, Alfonso; Puig, Susana; Karachaliou, Niki; De Matos-Arruda, Leticia; Seoane, Joan; Escors, David; Alvarez, Carmen; Pedro Vaque, Jose; Prat, Aleix; Wellbrock, Claudia; Arozarena, Imanol; Marquez-Rodas, Ivan; Espinosa, Enrique; Angel Molina, Migue; Puertolas, Teresa; Juan-Otero, Manuel; Malagrida, Rosina; Jantus-Lewintre, Eloisa; Soriano, Virtudes; Arance, Ana; Luis Manzano, Jose; Lorigan, Paul; Gajewski, Thomas F.; Rosell, Rafael; Martin-Algarra, Salvador; Spanish Melanoma Grp GEM. 2017. *Ann Transl Med.*

Pembrolizumab in advanced pretreated small cell lung cancer patients with PD-L1 expression: data from the KEYNOTE-028 trial: a reason for hope? Navarro A; Felip E. 2017. *Transl Lung Cancer Res.* 6: 78-83.

# Funding, Consortia & Accreditation

## FUNDING

VHIO can and will only deliver on its goal of accelerating the pace in advancing personalized and targeted therapies against cancer thanks to the public funding it receives, as well as through the generous support from private institutions, companies and individuals. Furthermore, and as a direct reflection of VHIO's research of excellence, VHIO continues to secure essential funding through several International and National Competitive Grants.

Only with such continued support will the clock continue to tick in our favor - against cancer. VHIO would therefore like to express its immense gratitude to its following supporters, funding entities and agencies:

## INSTITUTIONAL SUPPORTERS

Generalitat de Catalunya

Fundació Privada CELLEX

fero Fundación de Investigación Oncológica

Obra Social "la Caixa"

Fundación BBVA

## PUBLIC FUNDING

### International

erc European Research Council
Established by the European Commission

SEVENTH FRAMEWORK PROGRAMME

European Commission
Horizon 2020
European Union funding
for Research & Innovation

Unión Europea
FONDO EUROPEO DE DESARROLLO REGIONAL
*Una manera de hacer Europa*
FONDO SOCIAL EUROPEO
*El FSE invierte en tu futuro*

### National

AGAUR Agència de Gestió d'Ajuts Universitaris i de Recerca

*iCrea INSTITUCIÓ CATALANA DE RECERCA I ESTUDIS AVANÇATS

Institució CERCA Centres de Recerca de Catalunya

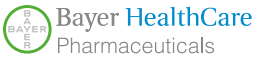
ISC Instituto de Salud Carlos III

## PRIVATE FUNDING





















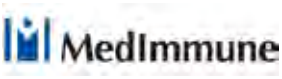

































































The Dr. Josef Steiner
Cancer Research Foundation

## CONSORTIA

As a reflection of VHIO's expertise in preclinical, translational and clinical research in oncology, it participated in the following Consortia of excellence in 2017:

**Cancer Core Europe** is a unique partnership aimed at addressing the cancer carecancer research continuum. Launched in the Autumn of 2014, this working consortium represents a critical mass of activity for the successful integration of all cancer care information, clinical research and outcome research, led by the six founding partners and European comprehensive cancer centers of excellence: the Gustave Roussy Cancer Campus Grand Paris (Villejuif, France), Cambridge Cancer Centre (Cambridge, UK), Karolinska Institute (Stockholm, Sweden), Netherlands Cancer Institute - NKI (Amsterdam, The Netherlands), National Center for Tumor Diseases - DKFZ-NCT (Heidelberg, Germany), and VHIO. Recently incorporating The National Cancer Institute of Milan (Italy), CEE promotes the pooling and exchange of expertise, research findings, common platforms and processes. CEE empowers researchers and clinicians to rapidly exploit this trove of biological insights and clinical data for the benefit of patients.
**www.cancercoreeurope.eu**

The **EuroPDX Consortium** – *Translating Knowledge in Oncology,* launched in 2013 with the common goal of creating a network of clinically relevant models of human cancer, and in particular patient-derived xenograft (PDX) models. Connecting 17 cancer centers across 12 countries that are developing PDX cancer models, this initiative promotes the sharing and exchange of findings on promising therapeutics as well as leads multicenter preclinical studies. EuroPDX strives to reduce the duplication of efforts in oncology drug development and ultimately improve the quality of life and overall survival of cancer patients.
**www.europdx.eu**

Intracolor

Initiated in 2016, INTRACOLOR (Evolution of resistant clones to novel target-directed drugs in colorectal tumors: a genetic and epigenetic study of intratumoural heterogeneity dynamics), is supported by EU Horizon 2020 funding and led by VHIO. Running in parallel with the Phase I/II MoTriColor trials (see page 141), it incorporates six of MoTriColor's to assesses three novel targeted therapies for mCRC, each matched to distinctive gene expression signatures.
Representing a comprehensive framework for translational research, emerging molecular data is prospectively integrated in preclinical models and proof-of-concept clinical trials in mCRC. This project is carried out in collaboration with SPECTAcolor – Screening Platform for Efficient Clinical Trials Access in Colorectal Cancer, which is an initiative of the EORTC, supported by Alliance Boots.
**www.motricolor.eu**

Launched in 2015, **MedBioinformatics** is a project supported by Horizon 2020's European Union funding for Research and Innovation. Through the development of integrative bioinformatics tools and software applications useful and autonomously usable by translational scientists and clinical practitioners for analysing the huge amount of data and knowledge generated in healthcare and biomedical research, the project will ultimately facilitate translational research and precision medicine. Incorporating 13 groups from nine renowned research entities of excellence, including VHIO, this Consortium will strive to address the deficit of integrative approaches that effectively combine different types of data from different sources as well as actively involve end-users that are not experts in bioinformatics in the design of the applications.
**www.medbioinformatics.eu**

Announced in 2013, The **MErCuRIC** Consortium, funded by the European Commission's 7th Framework Programme of Research and Development, incorporates 13 partners in eight different European countries to lead and pioneer a multicentre phase Ib/II clinical trial. This study evaluates a novel therapeutic strategy aimed at combating metastasis, improving survival and developing new approaches to treat patients with colorectal cancer.
**www.mercuric.eu**

Spurred by Horizon 2020's European Union funding for Research and Innovation funding, **MoTriColor** (Molecularly guided Trials with specific treatment strategies in patients with advanced newly molecular defined subtypes of Colorectal cancer), led by VHIO, is powered by a total of eight clinical research centers of excellence, spanning Spain, Italy, The Netherlands and Belgium, as well as a European organization in cancer research and a diagnostic/prognostic SME. Dedicated to conducting multi-center early phase clinical trials to establish the anti-tumor activity of novel experimental therapies for patients with metastatic or advanced colorectal cancer, patients will be stratified based on their gene expression profiles according to recently established predictive signatures.
This pioneering approach aims at identifying sensitivity of individual patients to the proposed experimental therapies towards ultimately developing more precise anti-cancer therapies for these patients.
**www.motricolor.eu**

Funded through a grant received from the European Union's Horizon 2020 research and innovation programme, the **NoCanTher – Nanomedicine upscaling for early clinical phases of multimodal cancer therapy is a multi-center – Consortium** is led by IMDEA Nanoscience and represents an important forward step in utilizing nanoparticles than can better target and more precisely combat cancer cells.
It builds on the preclinical successes reported by the former FP7-funded MultiFun Consortium that evidenced the efficacy of a multi-modal therapeutic approach based on functionalized magnetic nanoparticles and magnetic hyperthermia for the intra-tumoral treatment of breast and pancreatic tumors
NoCanTher will assess this nano-based approach and provide preliminary data on its efficacy in humans and aim to translate these preclinical findings into early clinical development for the treatment of pancreatic cancer.
**www.nocanther-project.eu**

The **PhD PI3K biology in health & disease Network** incorporates ten academic, clinical and industrial partners with renowned expertise in research focused on PI3K signaling. Leading a unique training network, this collaboration connects complementary expertise and brings additional value, novel tools and leadership of excellence in order to train talented early stage researchers and suitably equip them for leading roles in cancer science and drug discovery in European industry and academia.
This research training programe not only represents unparalleled educational opportunity for these young scientists, but also aims to increase the international competitiveness of European research in PI3K discovery and drug development.
**www.pi3k-phdproject.eu**

**RATHER - Rational Therapy for Breast Cancer**, is funded by the European Commission's 7th Framework Programme of Research and Development. Representing an important step in delivering on precision oncology by developing tailored therapies using a rational approach, this project will focus on two specific difficult-to-treat subtypes of breast cancer. Involving the combined efforts of six research institutions and two biomedical companies this is a five-year project that commenced in January 2011.
**www.ratherproject.com**

Incorporating a network of 27 research entities spanning 10 countries, **SPECTAcolor -Screening Platform for Efficient Clinical Trials Access in Colorectal cancer**, is an initiative within the framework of the research program of the EORTC, supported by Alliance Boots. Launched in 2013, this is the first prospective fully annotated tumor samples Biobank and Biomarker analysis platform for genetic profiling of patients suffering from advanced colorectal cancer.
**http://spectacolor.eortc.org**

**WIN - Worldwide Innovative Networking in personalized cancer medicine,** initiated by the Institut Gustave Roussy (France) and The University of Texas, MD Anderson Cancer Center (USA) is a non profit, non-governmental organization incorporating 22 cancer centers and industry partners from five continents to address the challenge of increasing the efficacy of cancer diagnostics and therapeutics. Promoted within the scope of this Consortium, WINTHER (WINTherapeutics) is a unique academic and international clinical trial (launched in 2012), aimed at better predicting drug sensitivity and optimizing individualized therapeutic decisions with improved clinical outcome for patients.
**www.winconsortium.org**

## Other collaborations:

The **AstraZeneca/MedImmune and VHIO Alliance**, announced in 2015, will stimulate advancements at preclinical, clinical and translational research levels across the AstraZeneca's oncology portfolio. Combining VHIO's strengths in promoting cancer discovery through the integration of translational science and clinical research with AstraZeneca's promising early stage oncology pipeline, the alliance will initially focus on areas including DNA damage repair, drug resistance, new drug combinations and molecular profiles for patient selection.
Bookmark and visit VHIO's website for forthcoming updates: **www.vhio.net**

The **CIBOT** *Consorcio de Investigación Biomédica y Oncología Traslacional* (Consortium for Biomedical and Translational Research in Oncology), is a scientific program established in collaboration with Novartis in 2013. This initiative defines and develops research aimed at: determining the etiopathogenic mechanisms of cancer as well as developing novel diagnostic and therapeutic tools; investigating the therapeutic potential of new antineoplastic agents; and applying cutting-edge technologies and latest data to advance cancer research.
Specific areas of interest include the effects of HER-2 amplification pattern and prior Herceptin/TDM-1 therapy on HER-2 expression, the therapeutic inhibition of the oncogenic Wnt/beta-catenin pathway, and targeting wild type c-KIT combination with PI3K pathway inhibition in basal-like PDXs.
**www.novartis.com**

Launched by Roche in 2016, the **imCORE - immunotherapy Centres of Research Excellence Network** - a 21-strong academic powerhouse set to progress discovery in cancer immunotherapy, brings together internationally renowned scientific and clinical experts in cancer immunotherapy to collaborate in investigating the most promising novel treatment approaches. Working in collaboration with scientists from Roche and Genentech, expert researchers and physician-scientists in cancer immunotherapy from across the globe have joined together to drive the application and extension of immune-based strategies to more tumor types as well as advance research into the cellular and molecular mechanisms modulating immune response to cancer.
This Network aims to significantly advance anti-cancer immunotherapeutics and accelerate discovery towards benefiting patients who may stand to gain from novel immune agents as mono therapy or in combination.
**https://www.roche.com/research_and_development/what_we_are_working_on/oncology/cancer-immunotherapy/collaboration-in-cancer-immunotherapy.htm**

**The OCTC - Oncology Clinical and Translational Consortium,** a collaborative scientific research network comprised of six renowned comprehensive cancer centers, was launched by GSK in 2013. While GSK gains OCTC's expertise in preclinical, translational and clinical development of novel anticancer therapeutics, the participating centers have access to studies with GSK's early stage oncology pipeline and opportunities to accelerate and advance the next generation of novel oncology therapeutics.
**www.gsk.com**

## ACCREDITATION

In 2017 VHIO underwent evaluation for accreditation of the CERCA Institute of Research Centres of Catalunya (*Institució CERCA – Centres de Recerca de Catalunya*) for the period 2013 – 2016. In recognition of VHIO's progress, performance in knowledge transfer activities and management of excellence, VHIO was awarded with the maximum qualification of an A grading.

Also reflecting our dedication to excellence and the quality of our services and procedures, our Cancer Genomics and Molecular Groups have both received ISO 15189 accreditation for their testing methods and technologies. Similarly, we continue to meet the high standards in quality and procedures in the audit of our clinical trials Units, carried out by the *Generalitat de Catalunya*. Our Research Management is also endorsed by ISO 9001 Certification.

Patrons:

Generalitat de Catalunya

Fundació Privada CELLEX

fero Fundación de Investigación Oncológica

Obra Social "la Caixa"

Fundación BBVA

www.vhio.net

Extended version online: memorias.vhio.net/2017/
PDF version: memorias.vhio.net/2017/SR-VHIO-2017.pdf

Scan to visit mobile version >