VALL D'HEBRON
Institute
of Oncology

SCIENTIFIC REPORT

2018

Myriad highlights and new horizons

Centres de recerca de Catalunya

Vall d'Hebron Institute of Oncology (VHIO)

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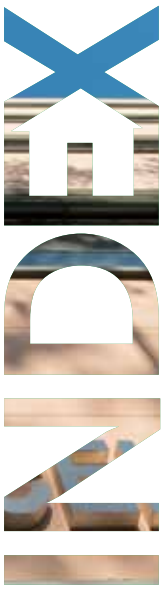

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VHIO in 2018: myriad highlights and new horizons

This year's Vall d'Hebron Institute of Oncology's (VHIO) Scientific Report branding features the infinity symbol. Indeed, flipped on its head it is of course a number 8 in celebration of VHIO embarking on its second decade ahead.

For me, this symbol represents much more than a concept or a figure. Rather, it depicts a virtuous cycle of knowledge; the seamless and unrestricted flow of discovery in oncology from the bench to the bedside and back. It is also illustrative of the multidisciplinary and translational research model for which VHIO is famed.

As I reflect on the past year and consider the current state of oncology within the broader context of precision medicine, the progress we are collectively making to solve cancer sooner is undeniably great.

At the research level, thanks to the past decade's increased focus on prevention and early diagnosis, as well as the expanding portfolio of potent anti-cancer medicines matched to molecular signatures of individual tumors, we continue to translate progress into proven benefits for our patients.

These successes have been driven, in parallel, through the rapid development of omics platforms and prescreening tests, the better harnessing, sharing and interpretation of big data, and novel treatment approaches.

The recent addition of promising immunotherapeutics to the arsenal of anti-cancer weaponry, coupled with circulating tumor (ct)DNA analysis for more predictive tracking of disease, are helping us to deliver on the true promise of personalized medicine in oncology.

As Director of VHIO, it is both a privilege and pleasure for me to mention just some of the many important contributions driven by our research teams in 2018, often in partnership with colleagues across the globe as well as pioneering international consortia.

These exceptional advances and developments in cancer science and medicine will help us to collectively up the tempo in more effectively reversing cancer resistance and halting metastatic cell spread, in 'real time', on time.

Let's dig into a few of the myriad VHIO highlights over this past year:

Cancer modelling, predictive biomarkers and the unmasking of novel drug-targets: three jewels in VHIO's crown

Empowering predictive and reproducible cancer science

At VHIO, we are dedicated to accelerating robust preclinical data required to reliably guide the clinical development of innovative agents and approaches, as well as evidence its reproducibility before moving into the clinic.

An area of strength is in cancer modelling, with particular emphasis on tuning patient-derived xenograft (PDX), avatar and organoid models to identify factors governing tumor progression and response to therapy. VHIO is both a founding member and sits on the Board of Coordinators to steer strategic directions of the *EurOPDX Consortium–Translating Knowledge in Oncology* (launched in 2013).

Announced in 2018, the EurOPDX partners secured funding from the EU's Horizon 2020 research and innovation programme to construct a repository for the open access sharing of more than 1500 established PDX models, complete with their clinical, molecular and pharmacological annotations: *EDIReX–EurOPDX Distributed Infrastructure for Research on patient-derived cancer Xenografts* (page 17-18).

Coordinated by Enzo Medico, Candiolo Cancer Center IRCCS (Turin, Italy), this platform counts on the research excellence of 19 entities spanning 13 European countries, including VHIO.

With one of the biggest PDX collections in Europe, particularly in breast, glioblastoma and colorectal cancers, we will assume a leading role in strengthening this essential open access resource. In addition, as we strive to more accurately model immunotherapy strategies through our generation and development of humanized PDX to validate the performance of T-cell bispecific antibodies, our research promises to reveal precious insights that we will be sharing via this exciting new platform (see sub-section, *Immunotherapy: hope v's the over-hyped*, in this Foreword).

A second pan-European undertaking fueled by EU's Horizon 2020, MESI-STRAT (page 18) will establish the interplay of breast cancer metabolism and oncogenic signaling by systems medicine approaches. Co-coordinated by Kathrin Thedieck, University Medical Center Groningen (The Netherlands), and Tobias Anzeneder, PATH Biobank (Munich, Germany), this consortium combines the expertise of 14 partners including VHIO. It centers on breast cancer metabolism as a novel approach for the stratification of patients, tracing resistance, and better informing clinical decision-making throughout the course of endocrine therapy.

VHIO's library of in vitro and in vivo models will provide data required to individualize and validate MESI-STRAT's computational models. Violeta Serra, PI of our Experimental Therapeutics Group (page 44), will help to develop metabolite marker panels to guide established targeted therapies for the treatment ER-positive tumors that are resistant to endocrine therapy.

Coordinated by Cristina Saura, PI of VHIO's Breast Cancer & Melanoma Group (page 62), we will also interrogate the predictive value of specific biomarkers in liquid biopsies from patients enrolled in our clinical studies with novel therapies.

Busted: exposing new drug-targets

A study [1] published in *The Journal of Clinical Investigation*, led by PI of our Stem Cells & Cancer Group (page 52), Héctor G. Palmer, in collaboration with several other VHIO groups, revealed a novel drug-target to 'strangle' sleeper cancer cells.

Their findings have evidenced an epigenetic enzyme, TET2, as a biomarker to identify dormant tumor cells (DTC), also known as slow-cycling cancer cells (SCCC), which go undetected by current treatments that have mostly been designed to target rapidly dividing tumor cells.

Having secretly travelled and settled in other parts of the body, when DTC awake they behave like cancer stem cells, regenerate the original tumor and drive metastasis in patients thought to be cured.

Palmer and colleagues identified TET2 as the Achilles heel of dormant tumor cells and also sought to develop novel inhibitors aimed at preventing their seeding of metastasis. By establishing that TET activity correlates with elevated levels of 5hmC as well as a greater risk of resistance to therapies and disease relapse, these insights into the molecular intricacies of DTC provide a promising translational opportunity toward potentiating treatments, preventing cancer recurrence, and extending the survival of patients.

Teaching an old protein new tricks, research headed by Josep Villanueva, PI of our Tumor Biomarkers Group (page 54), in collaboration with the CIBERONC Center for the Biomedical Research Network in Oncology (scientifically led by VHIO's Joaquín Arribas, Co-Director of our Preclinical and Translational Research Program), has unmasked extracellular HMGA1 as a novel drug target for the treatment of metastatic triple-negative breast cancer (TBNC) and a predictive biomarker of cancer cell spread.

By elegantly reporting the correlation between HMGA1 secretion and its nucleus-to-cytoplasm migration in *Clinical Cancer Research* [2], these important insights change the view on this protein's role in tumorgenesis, and support the relevance of unconventional protein secretion in cancer diagnostics and therapeutics.

Led by our Mouse Models of Cancer Therapies Group (page 50), directed by PI Laura Soucek, a study published in *Oncotarget* [3] offers preclinical evidence for the role of a novel BET inhibitor in more effectively treating *KRAS*-driven cancers.

Their results in mouse models of *KRAS*-mutated pancreatic ductal andenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC) support the further evaluation of BET inhibition in solid tumors in the clinic. Future directions will need to focus on how to

potentiate the blocking of BET either as monotherapy or in combination with other drugs, as well as reduce the toxicity reported in some early clinical studies.

Another VHIO contribution to the science of cancer progression this year was reported in *Nature Communications* [4] by Sandra Peiró and her Chromatin Dynamics in Cancer Group (page 42). They showed that the inner nuclear protein, lamin B1, is necessary for the 3D genome rewiring required to transform an epithelial cell and enable it to migrate and invade other tissues.

By reducing levels of this protein, her team showed that by effectively eliminating part of it, the cells lose their ability to become mesenchymal stem cells, thus reducing their capacity to travel and relocate. These findings represent another forward step towards better understanding the drivers of disease spread.

Powerful blows against *BRCA1/2* mutated disease

Speaking of drug-targeting, in our determined pursuit to establish more effective treatment strategies that target vulnerabilities in *BRCA1/2*-associated cancer, my first selection are the results from the phase III SOLO-1 multi-center trial led by Kathleen Moore, Stephenson Cancer Center (Oklahoma, USA), and co-authored by Ana Oaknin who leads our Gynecological Malignancies Group (page 72).

Selected to first outing at the 2018 ESMO Congress (19-23 October, Munich, Germany), during the Presidential Symposium that I co-chaired and timed in parallel to publish in *The New England Journal of Medicine* [5], data showed that treatment with olaparib maintenance therapy led to a spectacular extension of progression-free survival by 3 years in over 50% of patients with newly diagnosed advanced ovarian cancer. This pivotal study also revealed that this novel treatment approach reduced the risk of disease progression by an impressive 70%.

Judith Balmaña's Hereditary Cancer Genetics Group (page 74), in collaboration with our Breast Cancer & Melanoma (PI Cristina Saura, page 62), and Experimental Therapeutics (PI Violeta Serra, page 44) Groups co-authored a paper in *The Journal of Clinical Oncology* [6] from a USA-Spanish multicenter phase II trial that signposts new direction in the treatment of *BRCA1/2* mutated advanced breast cancer.

Blocking transcription and induces DNA double-strand breaks leading to apoptosis, they have proposed the novel agent lurbinectedin as a potentially more powerful therapy against this tumor type. Importantly, this research also included a translational sub-study assessing potential mechanisms of resistance to this promising inhibitor. These important findings were covered in a news review published by *The Lancet Oncology* [7].

At the preclinical and translational level, research led by Violeta Serra, in collaboration with the other VHIO groups mentioned in my previous highlight, among others, culminated in two publications [8] [9], this year that provided important new insights into resistance and response to PARPi both in BRCA-mutated breast cancer and beyond.

This year the group developed their RAD51 foci assay, PARPiPRED, which accurately identifies germline BRCA tumors that have restored functionality, as well as other tumor types that are sensitive to these inhibitors. Importantly, they have also shown that this test is both feasible in routine tumor samples and a simple technique to apply.

While we hope for ease and speed in its translation to the clinic, further studies are now underway to more precisely define the sensitivity and specificity of PARPiPRED in predicting PARPi benefit and thus more informed patient selection.

Immunotherapy: hope vs the over-hyped

The promise and performance of novel immunotherapies (not to mention the price tags of those approved to-date) have once again been under intense scrutiny this year, with several editorials and opinion pieces, including one by *The Lancet Oncology* [10], calling for an adjusted alignment of expectations with current realities.

I also touched on this in an editorial that I was invited to pen for *ESMO Open* [11] to mark the mid-term of my Presidency of the European Society for Medical Oncology.

The emergence of these novel drug contenders should be celebrated, but much work still needs to be done to better predict those patients who would most likely benefit from them, extend their early promise to more patients as well as tumor types–either as monotherapy or, most likely, in combination, and tackle important concerns regarding safety and toxicity.

While immunotherapies are largely not yet benefiting as many patients as they promise, I believe that we are on the cusp of change. I am not alone: at the close of the year, several reports in the specialized and general media including F*orbes* [12] magazine as well as the official blog of the American Association for Cancer Research (AACR), *CANCER RESEARCH Catalyst* [13], predicted great things to come in 2019.

This will only happen by extending our efforts aimed at potentiating and personalizing this armory to successfully unleash the power of the immune system in a greater number of individu als to attack disease. We must deliver the robust immune data required to better guide treatment decisions that benefit all patients and not just the so-called 'super-responders'.

VHIO continues to lead cancer discovery in this direction. Our preclinical research culminated in a publication in *Science Translational Medicine* [14], showing that a decade-old protein, p95HER2, previously described by VHIO, offers a target for novel therapy that steers the immune system to hone in on and eliminate tumor cells.

Findings reported by our Growth Factors Group (page 48), led by Co-Director of Preclinical & Translational

Research at VHIO and ICREA Professor, Joaquín Arribas, revealed that p95HER2-T cell bispecific antibody (TCB), enables a targeted response by attacking cancer cells directly without affecting normal ones.

Thanks to the distinct specificity of TCB and this particular protein's exclusive location in malignant cells, the authors have described a 'home-delivery' of immune-based therapy. Approximately 10% of patients with HER2-positive breast cancers expressing p95HER2 could ultimately stand to benefit from this novel strategy.

Having now completed the preclinical phase of development, Joaquín's team is now focusing on advancing this therapy so that it can be administered in patients enrolled in clinical trials. Next steps will also include developing additional therapies against p95HER2 such as antibody-drug conjugates or chimeric antigen receptors (CARs).

I am excited to report our Experimental Hematology Group, directed by Francesc Bosch (page 66) is participating in the first international, multi-center phase II clinical trial, TRANSCEND World, to assess the efficacy of chimeric antigen receptor (CAR) T cell therapy for patients with aggressive B-cell non-Hodgkin lymphoma. We are the first Spanish site to conduct a CAR T cell clinical study in this population and also the first to have been granted authorization for patient enrolment.

In collaboration with an additional 15 selected sites across Europe as well as two in Japan, this study has been designed to determine the efficacy and safety of JCAR017 to treat clinically selected adult patients with relapsed or refractory disease. The investigators will seek to validate the promising response rates and superior profile of this immunotherapy observed in early phase trials.

A paper [15] in *The New England Journal of Medicine*, co-first authored by Enriqueta Felip who leads our Thoracic Tumors & Head and Neck Cancer Group (page 84), showed promise for the more effective treatment of patients with metastatic non-small-cell lung cancer (NSCLC). Results from a phase II study reported that treatment with pembrolizumab paired with chemotherapy led to higher rates of response as well as longer progression-free survival than with chemotherapy alone.

This study exemplifies the progress that we are making by empowering immunotherapeutics in combination with the cornerstones of cancer therapy–chemotherapy, surgery and radiation. We are also better understanding the cellular and molecular mechanisms modulating immune response and learning from the outcomes of immune-based clinical trials.

Flanking our other research programs and priorities, the Obra Social "la Caixa" International Program for Cancer Research and Education, as well as the BBVA Foundation's Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI), represent pioneering research endeavors aimed at delivering on the true promise of this array of novel 'immunoarmory' in oncology (page 16).

Guiding treatment decision making through novel approaches, platforms and scales

Liquid biopsies: ready for prime time?

At the preclinical and translational level, VHIO was the first academic test center to incorporate in-house BEAMING liquid biopsy RAS biomarker technology (2015). We have since made significant progress in validating and developing liquid biopsy technologies for the more effective, less invasive monitoring of cancer in real time.

These efforts, focused on both ctDNA and tumor educated platelets (TEP), continue to advance thanks to our multidisciplinary teams in collaboration with our two of VHIO's core facilities, our Cancer Genomics and Molecular Oncology Groups (pages 90-93) headed by Ana Vivancos and Paolo Nuciforo, respectively.

This year, Joan Seoane, Co-Director of our Preclinical and Translational Program, also an ICREA Professor, was the corresponding author of a paper published in *Clinical Cancer Research* [16], showing proof-of-concept that cerebrospinal fluid (CSF) can be exploited for liquid biopsies as it contains ctDNA.

Carried out in collaboration with other researchers and clinical investigators at VHIO, as well as oncologists, pathologists and neurosurgeons across the Vall d'Hebron Barcelona Hospital Campus, this study has not only unmasked the molecular characteristics of diffuse gliomas but also promises a more precise and rapid diagnosis that could help steer treatment decision making matched to the classification of these tumors, as well as more closely monitor the course of disease and response to therapy.

Ready for prime time? Not quite. My caution is echoed in a superb commentary in *Annals of Oncology* [17], authored by Ana Vivancos, with co-contributors, Elena Élez, Clinical Investigator and Molecular Oncologist of our Gastrointestinal & Endocrine Tumors Group (page 68) led by Teresa Macarulla, and Ramón Salazar, Catalan Institute of Oncology – ICO.

Reviewing a study [18] in *Annals of Oncology* led by Jakob Vasehus Schou, Department of Oncology, Herlev & Gentofte Hospital, Copenhagen (Denmark), the authors concluded that several issues including timing, simplicity, time to results and cost-effectiveness should all be tackled when considering ctDNA liquid biopsy in the routine testing in cancer patients. They call for clinical trials to bring this exciting technique even closer to the clinic.

Based on the collective body of evidence, coupled with the tremendous progress thus far, I believe this goal is well within reach.

Facilitating the in-depth, accelerated interpretation of cancer genomes

At the core of VHIO's research activities lies our suite of cutting-edge core technology platforms, which provide our teams with the necessary expertise to apply next-

generation whole-genome sequencing for precision oncology as well as develop and improve existing applications to drive faster results.

Our prescreening program (page 14), powered by VHIO's Cancer Genomics and Molecular Oncology Groups, led by Ana Vivancos and Paolo Nuciforo respectively, performs molecular profiling in more than 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 (page 100).

Two of VHIO's guiding principles are team science and the open exchange and sharing of data to accelerate precious insights in oncology. This has resulted in numerous cross-border alliances and partnerships; several in the form of international consortia (pages 123-127), others in novel platforms, programs as well as value framework tools.

Our Oncology Data Science (ODysSey) Group (page 76) directed by Rodrigo Dienstmann, is dedicated to interpreting and exchanging meaningful mass data in oncology.

As a reference in driving 'big' data-derived insights and exploring molecular profiles to more precisely guide treatment decisions, VHIO was invited to participate the American Association for Cancer Research's (AACR) Project GENIE: *Genomics Evidence Neoplasia Information Exchange*.

I am proud to report that VHIO is the only GENIE member from Spain, selected for our expertise in better identifying and describing the clinical relevance of driver genomic alterations that trigger cancer.

Rodrigo has pioneered the design of several open access online tools to help physicians and investigators interpret genomic data and apply this knowledge in practice. Published this year in *Genome Medicine* [19], Rodrigo and VHIO's Ana Vivancos co-authored a paper describing the Cancer Genome Interpreter (CGI) platform.

Led by ICREA Professor Nuria Lopez-Bigas, Institute for Research in Biomedicine (IRB, Barcelona), CGI represents an important step in providing the scientific community with access to this data in a more structured, consolidated and user-friendly way.

Speaking of cancer classification, 2018 celebrated the launch of the European Commission Horizon 2020-supported project led by Annette Byrne, Royal College of Surgeons in Ireland (Dublin), powered by 14 partners, including VHIO: COLOSSUS–*Advancing a Precision Medicine Paradigm in metastatic Colorectal Cancer: Systems based patient stratification solutions* (see page 18).

Set to simplify and standardize choices for the selection of targeted cancer therapies, the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT) published in *Annals of Oncology* [20].

Led by Joaquin Mateo, Principal Investigator of our Prostate Cancer Translational Research Group (page 78), also co-authored by Rodrigo Dienstmann, this new tumor DNA scale classes alterations according to their relevance as markers for the selection of patients matched to targeted treatments, based on the strength of clinical evidence.

Importantly, this new grading system will help guide physicians to distinguish between the genetic alterations that are important for treatment decisions or access to clinical trials, and those which are not.

The Last Word

While the important advances described so far (and more to follow) are gratifying, there is much more work to be done.

Due to late-stage diagnosis, metastatic cell spread, drug resistance and disease relapse, treatment options for an unacceptable number of patients are anything but limitless. They are finite, as seen in the daunting global cancer data.

Recently published statistics in the GLOBOCAN 2018 database [21] report that the cancer burden rose to 18.1 million new cases and 9.6 million cancer deaths in 2018. Additionally, cancer cases are forecast to rise by 75% over the next two decades.

While we can be optimistic that personalized medicine in oncology is starting to happen in practice, we still have far to travel if we are to extend our successes in cancer research to an increasing number of our patients.

VHIO's talents can only continue to do so thanks to the precious funding received from our treasured institutional supporters–the *Generalitat de Catalunya, Fundació Privada CELLEX, FERO Fundación de Investigación Oncológica, Fundació Bancària "la Caixa", Fundación BBVA,* (pages 11-13), as well as our many other supporters, funding entities and agencies (pages 120-122).

Year in, year out, VHIO's preclinical, translational and clinical teams work tirelessly to broaden the array of more effective treatments and enabling technologies tailored to the specificities of individual patients. Importantly, we also do so in collaboration.

I believe in forging essential collaborations with other specialties and partners. We can only continue to tackle the current challenges that are impacting on our ability to more rapidly advance precision medicine against cancer together (see pages 17-19, and 123-127).

I am confident that we can collectively turn obstacles into opportunity and optimal outcomes for all stakeholders in oncology. Above all, we must continue to listen and respond to the needs of those who matter most–our patients.

As VHIO embarks on its second decade ahead, I am confident that we can, and will, do even better.

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

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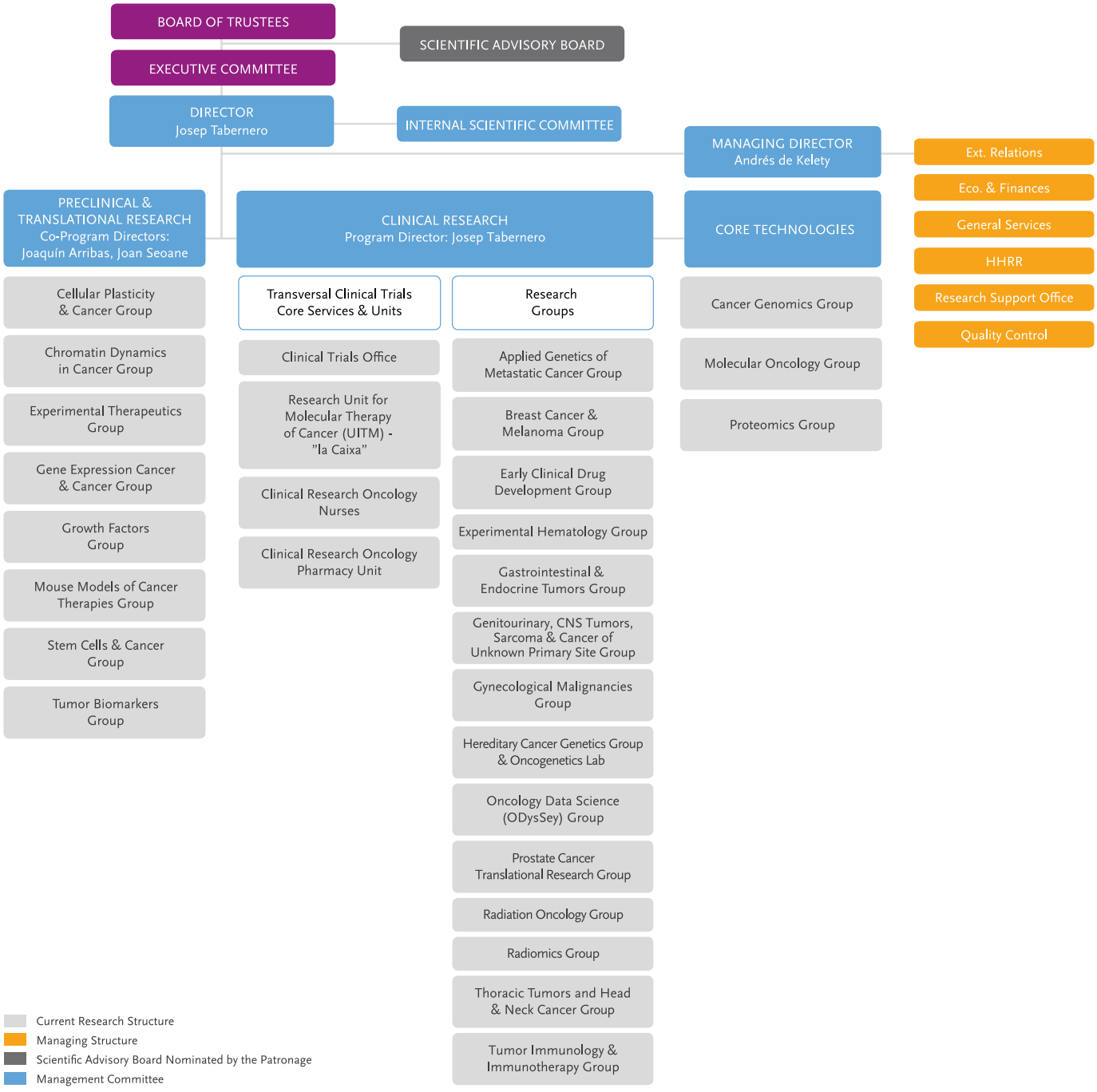
Who we are and what we do

VHIO's Organigram 2018

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 2018

Under the leadership of Josep Tabernero, the Vall d'Hebron Institute of Oncology (VHIO), created in 2006, has established itself as a comprehensive cancer centre of proven excellence internationally. It is thanks to the devotion of our Principal Investigators and their teams, coupled with 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.

That said, our Institute would cease to exist without the generous support it receives from its Institutional Supporters, public funding, private institutions, companies, and individuals, as well as International and National Competitive Grants (see pages 120-122).

Special mention here highlights the tremendous belief and backing that we continue to receive from our dedicated patrons: the *Generalitat de Catalunya, Fundació Privada CELLEX, FERO Fundación de Investigación Oncológica, Fundació Bancària "la Caixa",* and *Fundación BBVA*.

Just some of their respective, major contributions include the following:

Generalitat de Catalunya

Our public patron, the *Generalitat de Catalunya* (the Government of Catalonia) – together with the Vall d'Hebron University Hospital (HUVH) – represented by its Departments of Health (*Departament de Salut*), and Industry and Knowledge (*Departament de Empresa I Coneixement*), has from the very outset been a dedicated supporter of VHIO's cancer science and medicine.

As a devoted ambassador of VHIO and our various research programs and projects, it has been institutionally and financially supporting us throughout our first decade and now, beyond, with the Catalan Minister of Health as the President of our Board of Trustees.

At 'home' VHIO's translational and multidisciplinary approach to cancer research is greatly facilitated through the connectivity and tremendous collaboration we have with the entire spectrum of oncology professionals at HUVH (see page 15), and the rest of the Catalan Public Health System.

The Catalan Department of Health has played an essential role in integrating VHIO's research activity into the Catalan Health System, representing a successful example of how the public and private sectors can work closely together 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*), this collaboration affords us access to the Catalan Research System and the fiscal and legal benefits that this represents.

The financial support it has provided has consequently contributed majorly to VHIO's structural overheads, allowing us to center our efforts on our core research activities.

Fundació Privada CELLEX

It is thanks to one of our private patrons, the *Fundació Privada* CELLEX (CELLEX Foundation), that we have been able to build new facilities that have subsequently spurred our efforts aimed at advancing precision oncology and providing optimal patient treatment and care.

As a first example, it is thanks to this Foundation that 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. 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, now promotes the purely translational and multidisciplinary model for which VHIO is famed.

CELLEX also financed the construction and infrastructures of our state-of-the-art building - the CELLEX Center - that was completed in 2015. Marking a new VHIO chapter, our premises provided the necessary space and amenities to expand our research activities and further foster our multidisciplinary connectivity and exchange by bringing all VHIO research teams together under the same roof.

Providing the valuable space through which to grow, the CELLEX Center has not only further enhanced collaborations and accelerated our dedicated efforts to combat cancer, it has also allowed us to expand our groups in order to pursue new emerging research areas including immunology & immunotherapies, as well as fortify our research structure.

As importantly, thanks to CELLEX, our cutting-edge Animal Facility has spurred the more precise development of our predictive cancer models. Incoporating the latest platforms and technologies for analyzing small animals of human disease, this facility that we share with other colleagues across the Vall d´Hebron Barcelona Hospital Campus, has enabled us to further establish VHIO as a European reference in cancer modelling.

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fero
Fundación
de Investigación
Oncológica

Support received from the *Fundación FERO* (FERO Foundation), has, from the very beginning, enabled science of excellence at VHIO as well as promoted the careers of up-and-coming talents in oncology through its annual Fellowships. Concerning the former, the labs of Josep Villanueva, PI of our Tumor Biomarkers Group (page 54), Laura Soucek, PI of VHIO's Mouse Models of Cancer Therapies Group (page 50) and ICREA Professor, Violeta Serra, PI of VHIO's Experimental Therapeutics Group (page 44), Joaquín Arribas, Co-Director of our Preclinical and Translational Program and ICREA Professor, who also heads our Growth Factors Group (page 48), and Sandra Peiró, who leads our Chromatin Dynamics Group (page 42), have been able to grow their groups and advance their pioneering research lines thanks to FERO.

Regarding its Annual Award for Translational Research, a total of seven of our research scientists have been honored with this prize: Laura Soucek (2011), Héctor G. Palmer (2012), Ibrahim Yasir – formerly an investigator of VHIO's Experimental Therapeutics Group directed by Violeta Serra (2013), César Serrano (2015), Beatriz Morancho (2016), María Abad (2017), and Alena Gros (2018).

FERO has also contributed to the expansion of our facilities. As an example, the Foundation was a sponsor of our Breast Cancer Center "*Endavant i de Cara*", along with a personal donation received from Maria Angels Sanahuja. Funding received from FERO also enables us to develop our Droplet Digital PCR (ddpCR) Bio-Rad Technology platform and advancing research into the more effective and less invasive tracking of cancer by liquid biopsy.

Obra Social "la Caixa"

Thanks to the support received from our private patron, the *Fundació Bancària "la Caixa"* ("la Caixa" Foundation), VHIO's Research Unit for Molecular Therapies of Cancer (UITM) – "la Caixa" opened its doors in 2010 to pioneer early drug discovery and clinical studies tailored to the specificities of patients (page 100).

This Unit, under the co-direction of Josep Tabernero and Elena Garralda, has subsequently established itself as a leading reference in developing novel therapies based on the molecular profile of each tumor and optimize treatment strategies using combinations of new agents with already existing ones.

Furthermore, in addition to various grants supporting several VHIO groups, this Foundation also fuels one of our two major institutional programs: Obra Social "la Caixa" International Program for Cancer Research and Education –page 16.

Fundación BBVA

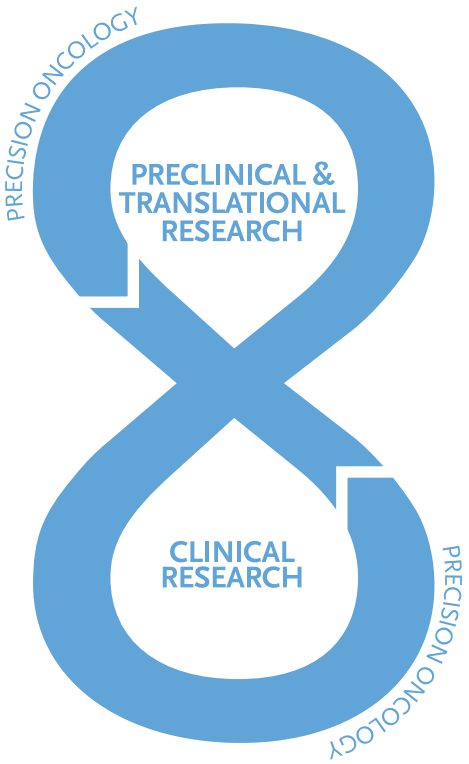
Also driving programs to spur VHIO's avant-garde translational research in precision oncology, another of our private patrons, *Fundación* BBVA (BBVA Foundation), financed our Tumor Biomarkers Research Program back in 2011. This five-year major framework agreement fueled collaborative science centering on the development of personalized therapies for cancer patients through biomarker research.

Building on the successes of this first program, our second BBVA-VHIO Institutional Program: the BBVA 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 16). It also supports various research lines across other VHIO groups. Leading these research efforts are Alena Gros and Elena Garralda, PIs of our Tumor Immunology & Immunotherapy and Early Clinical Drug Development Groups, respectively (pages 86 and 64).

For a full listing of all VHIO's supporters, funding entities and agencies see pages 120-122.

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.



VHIO's multidisciplinary and translational model: the seamless, unrestricted flow of discovery in oncology.

Principal areas of cancer research at VHIO: at a glance

- 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.

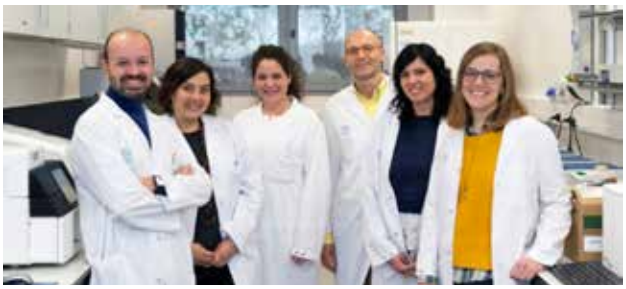
Driving and applying powerful technology platforms

At the core of VHIO's research activities are 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 (page 90), headed by Ana Vivancos, serves as a Core Technology laboratory and provides 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). Her 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.

Our Prescreening Program, pioneered by Ana's Group in collaboration with VHIO's Molecular Oncology Group led by Paolo Nuciforo (page 92), Early Clinical Drug Development Group headed by Elena Garralda (page 64), and Oncology Data Science (ODysSey) Group directed by Rodrigo Dienstmann (page 76), performs 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", also championed by Elena Garralda (page 100).



VHIO's Prescreening Team (left to right): Paolo Nuciforo, Ana Vivancos, Elena Garralda, Rodrigo Dienstmann, Susana Aguilar and Jenifer Gonzalez.

Patients' suitability for inclusion in any given clinical trial is assessed based on their respective genomic or pathologic profile. Ana's group has developed and routinely implemented several tests for this program. Two are based on NGS: an Amplicon-seq approach to sequence 67 genes as well as a 450-gene capture panel (Illumina). This panel is currently being validated.

Another two are based on nCounter (Nanostring). The gene fusion panel, with the capacity of detecting over 100 recurrent gene fusions, is also enabling us to assess gene expression patterns in tumors. Copy Number Alterations are evaluated with a 59 gene panel for genes with frequent gains or losses in cancer. Reflective of excellence and

quality, they have attained ISO 15189 flexible accreditation for the Amplicon-seq testing method.

Importantly, our prescreening efforts have established VHIO as one of the few centers in Europe to run such a comprehensive program. We will continue to extend our efforts to an increasing number of patients thanks to expanded collaborations with other centers.

At the preclinical and translational level, VHIO was the first academic test center to incorporate in-house BEAMING liquid biopsy RAS biomarker technology (2015). We have since made significant progress in validating and developing liquid biopsy technologies for the more effective, less invasive monitoring of cancer in real time.

These efforts, focused on both ctDNA and tumor educated platelets (TEP), continue to advance thanks to our multidisciplinary teams in collaboration with VHIO's Cancer Genomics and Molecular Oncology Groups. As an example, as updated by our Director in his Foreword (page 7), Joan Seoane, Co-Director of our Preclinical and Translational Program and ICREA Professor, and colleagues showed proof-of-concept that cerebrospinal fluid (CSF) can be exploited for liquid biopsies as it contains ctDNA.

The hub and heart of VHIO's early clinical drug development: our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa"

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 (page 100), under the direction of Elena Garralda as Executive Director, alongside Josep Tabernero, 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 (see page 64), 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 2018, our Unit participated in 161 ongoing phase I clinical trials, 22 of which were Basket trials. Our facilities, coupled with our multidisciplinary clinical teams, enable us to continue to expand our portfolio of phase I studies. This year we opened 51 new trials; 4 as Baskets. 508 patients were recruited, 64 of whom were enrolled in Baskets. Our Clinical Trials Office (page 98), directed by Gemma Sala and also located in the patient environment of the Vall d'Hebron University Hospital (HUVH), coordinates a large portfolio of Phase I, Baskets, Phase II & III clinical trials. In 2018 the number of patients included in these trials totaled at 1198 across 399 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.

Speaking of novel immunotherapeutics, our Unit's Taskforce spearheads the early drug development of these agents and cell signalling. Specifically, we focus on second generation immunotherapies, including new cytokines, bispecifics, immunomodulatory agents and immune checkpoint inhibitors and combinations, as well as translational research in immuno-oncology in collaboration with several VHIO groups.

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.

Championing research aimed at solving cancer sooner

2018 celebrated a record breaking year in terms of the impact of our cancer science. 282 scientific articles were published by VHIO researchers as corresponding/ senior or co-authors with a cumulative Impact Factor (IF) totalling at 3501.

This figure reflects an increase in the importance of VHIO's contribution to the oncology field. For the complete list of articles published by VHIO researchers and clinical investigators in 2018 see page 106. To view this year's selection of just some of the most relevant articles by VHIO faculty published please refer to page 27.

Delivering on the promise of novel immunotherapies

As cautioned by our Director in his Foreword, while the emergence of these novel drug contenders are showing promise in the treatment of an increasing number of tumour types, much work still needs to be done if we are to collectively extend their early promise to more patients and seek out ways to potentiate and better personalize these agents and, in parallel, tackle important concerns regarding safety and toxicity.

In addition to the aforementioned research pioneered by our clinical programs, VHIO is also advancing this field at preclinical and translational level.

A bispecific antibody against p95HER2 guides cells of the immune system to malignant cells. Pink cells represent healthy breast epithelial cells, brown cells represent malignant cells. Only malignant cells express p95HER2 (in blue), which is recognized by the p95HER2 bispecific antibody which, in turn, guide lymphocytes form the immune system of the patients (blue cells), against the tumor cells.

As an example in 2018, research led by Joaquín Arribas, Co-Director of Preclinical and Translational Research at VHIO, and ICREA Professor (page 38), revealed a target for novel therapy that steers the immune system to hone in on and kill tumor cells (see Foreword page 6).

Among the many other immune-based VHIO studies and approaches that feature throughout the pages to follow, Josep Tabernero selected two other illustrative examples as part of his Foreword's sub-section *Immunotherapy: hope vs the over-hyped.*

Led by Francesc Bosch, PI of our Experimental Hematology Group (page 66),VHIO is the first Spanish site to conduct a CAR T cell study to assess the efficacy of this therapy in patients with aggressive B-cell non-Hodgkin lymphoma, as part of The TRANSCEND World multi-center phase II clinical trial.

An additional pick for this year's highlighted research was spearhead by Enriqueta Felip, who leads our Thoracic Tumors and Head & Neck Cancer Group, which showed promise for patients suffering from metastatic non-small-cell lung cancer. Specifically, results from a phase II clinical trial showed that combining pembrolizumab with chemotherapy led to higher response rates and longer progression-free survival than with chemotherapy alone.

Set to significantly impact on our ongoing research efforts focused on advancing immunotherapies against cancer, are our two institutional programs supported by our private patrons, *Obra Social "la Caixa"* and the *Fundación BBVA*:

Obra Social "la Caixa"

Obra Social "la Caixa": advancing research toward rendering anti-cancer medicines more precise

Aimed at pioneering collaborative projects co-led by VHIO and the Memorial Sloan Kettering Cancer Center – MSKCC (New York, USA), the ***Obra Social "la Caixa"* International Program for Cancer Research and Education** renewed as a second initiative in 2017 to consolidate and further pursue the established synergies between the two leading institutions.

This second edition, co-directed by Josep Tabernero and Maurizio Scaltriti (MSKCC), will include several initiatives focused on the pan-omic exploration (genomics and radiomics) of solid tumors, with particular emphasis on Big Data analysis, coupled with clinical insights from real-life patients.

Driven in collaboration with several VHIO groups, one of the three projects currently underway is dedicated to radiomics and immunotherapy. The other two focus on the impact of gene mutations in DNA damage on the impact of gene mutations in DNA damage repair and metastatic prostate cancer, and Big data mining to uncover molecular and genetic determinants of sensitivity to targeted therapy in solid cancers.

Fundación BBVA

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

Considering the successes of the very first VHIO-BBVA Foundation Program on Tumor Biomarkers Research that launched back in 2011, VHIO and the BBVA Foundation renewed their agreement in in 2017.

Building on the achievements of the first program, the **BBVA 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 leadership of Josep Tabernero, this ambitious undertaking counts on the expertise of several clinical and translational VHIO groups, and has launched six translational sub-projects linked to the early clinical development phases of immunotherapy. These pioneering research endeavors are currently underway.

Potentiating our programs in partnership: at 'home' and away

Accelerating precision medicine through 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 ten groups covering colorectal, breast, lung, gynecologic, prostate, melanoma, pancreatic, gastric tumor types as well as immunotherapy and onco-imaging, 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.

VHIO's task-forcing teams in action

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 include the following:

Cancer Core Europe (CEE) is a unique partnership aimed at addressing the cancer care and research continuum. Launched in 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 6 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), VHIO, as well as the National Cancer Institute of Milan (Italy).

CEE promotes the pooling and exchange of expertise, research findings, common 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 designed and leads the CCE-endorsed Basket of Baskets (BoB) trial.

BoB promises a more flexible and adaptive model in order to significantly accelerate patients' access to an array of novel therapeutics. Its multi-modularity within the same trial, using common diagnostic and screening tools, will facilitate the assessment of alterations at the same time, as well as the efficacy of different agents, either as monotherapy or in combination. Several baskets/modules and different drugs will therefore co-exist with a single molecular screening, which will optimize patient stratification and enrolment.
www.cancercoreeurope.eu

As an important aside, independent of our CCE-endorsed BoB model, VHIO's lead and participation in 'designer' trials including Basket, Octopus and first-in-human studies, is also exemplified by a selection featuring under *From the Program Director*, by Josep Tabernero (page 58).

Carried out in collaboration with VHIO's Breast Cancer & Melanoma Group (page 62), directed by Cristina Saura, the SUMMIT basket trial showed how a single study can advance discovery into the biological dependencies in human cancers, and revealed that response to neratinib is driven by the characteristics of both tumor type and genomic variant.

The EurOPDX Consortium – *Translating Knowledge in Oncology*, launched in 2013 to create a network of clinically relevant models of human cancer, patient-derived xenografts (PDXs) in particular. Connecting 18 cancer centers across 13 countries that are developing PDX cancer models, this initiative promotes the sharing and exchange of findings on promising therapeutics as well as leads multi-center 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.

In 2018 Consortium members, along with additional European academia and SME partners secured funding from the European Union's Horizon 2020 research and innovation programme to construct a repository for the open access sharing of over 1500 established PDX models complete with their clinical, molecular and pharmacological annotations.

This new platform, coordinated by colleagues at the University of Turin (Italy), with Principal Investigator

Enzo Medico at the helm, is entitled EDIReX–EuroPDX Distributed Infrastructure for Research on patient-derived cancer Xenografts. Led by the EurOPDX Consortium and counting on the research excellence of 19 entities spanning 13 European countries, the resource will increase the predictability of preclinical data through the use of more reliable cancer models, extend the reach of EurOPDX, and further build on its outstanding achievements marked to-date.

The main aim of EDIReX is twofold. First, to facilitate data exchange among preclinical and translational cancer professionals working in academia as well as industry, and second, to promote, spur and consolidate scientific collaboration in PDX research across Europe.
www.europdx.eu

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 39 leading organizations, including VHIO, spanning 21 countries and 4 continents, united by their vision to deliver on the promise of effective, personalized cancer medicine to patients worldwide.

Under the tagline *WINning together*, WIN was formed on the premise that members can accomplish more together than each organization can achieve working alone. Aimed at improving cancer patients' survival and quality of life, WIN members also collaboratively design and carry out global studies designed to achieve breakthroughs for cancer patients across the globe.

In 2018, results from the WINTHER trial; the first study promoted within the scope of WIN that was designed to navigate patients with advanced disease to therapy based on either next generation sequencing or transcriptomic analysis that compared tumor to normal tissue through its pioneering dual biopsy approach, were presented as an oral presentation during a Clinical Science Symposium at the American Society of Clinical Oncology's (ASCO) Annual Meeting (01-05 June, Chicago, USA).

This talk, delivered by first author Jordi Rodón, Investigator at the MD Anderson Cancer Center (Texas, USA), also Associate Investigator of VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", directed by Elena Garralda (page 100), showed that both genomic and transcriptomic analyses helped to more precisely guide therapy selection. Patients who received personalized treatments based on their genetic alterations independently associated with longer progression-free survival and overall survival.

In Memorandum

April 2018 marked the terrible loss of Thomas Tursz, a dedicated champion of WIN, eminent oncologist and recognized thought leader within our field.

As this Report entered into print, we were informed about the sad passing in January 2019 of John Mendelsohn, Chairman Emeritus of the WIN Consortium, also an internationally renowned leader in oncology.

Both were undisputed trailblazers who also spearhead many other ground breaking research programs, initiatives and cross-border collaborations. They will be sorely and deeply missed by us all.
www.winconsortium.org

Launched in 2018

Led by Annette Byrne, Associate Professor, Royal College of Surgeons in Ireland (RSCI) Department of Physiology and Medical Physics, in partnership with leading clinical investigators and researchers spanning eight European countries, the Horizon 2020-supported **COLOSSUS–*Advancing a Precision Medicine Paradigm in metastatic Colorectal Cancer: Systems based patient stratification solutions***, launched in early 2018 to more precisely define molecular subclasses of colorectal cancer (CRC).

By studying patient samples and applying cutting-edge, multi-omic modelling approaches, this Consortium is set to drive important progress towards developing, matching and measuring novel therapies according to the specificities of each identified molecular subtype.

Powered by 14 partners with expertise in cancer immunology, systems biology, computational modelling, bioinformatics, omics analysis, clinical oncology/ pathology, preclinical research, medical imaging, clinical trials, health economics and patient management, this five-year research program focuses on microsatellite stable RAS mutant (MSS RAS mt) disease – a genetically identified type of CRC with very few therapeutic options available once patients develop resistance to existing chemotherapies.

The COLOSSUS team will strive to both expand and refine the classification of this particular subset of colorectal cancer.

Reflective of its promise to deliver multidisciplinary team science of excellence, the COLOSSUS proposal ranked first among the other 200 European projects that were submitted to the Horizon 2020 Personalized Medicine Call for *New Concepts in Patient Stratification*.
www.colossusproject.eu

Led by Kathrin Thedieck, University Medical Center Groningen–UMCG (The Netherlands), and co-coordinated by Tobias Anzeneder from the German patient organization PATH Biobank, the **MESI-STRAT Consortium** combines the expertise of 14 partners, including VHIO, to establish the interplay of breast cancer metabolism and oncogenic signaling (Metabolic Signaling) by systems medicine approaches. Aimed at developing new models for knowledge-based stratification of patients into subgroups with different endocrine

therapy resistance mechanisms, this pan-European undertaking, supported by the European Union's Horizon 2020 research and innovation programme, represents an important forward step towards improving outcomes for these patients.

Spanning 6 countries, MESI-STRAT's team is comprised of leading oncologists, modelers, bioinformaticians and experimentalists who will collectively pioneer breast cancer metabolism as a novel approach for the stratification of patients, tracking of resistance and better guiding clinical decision-making throughout the course of endocrine therapy.

Through the development of new computational models in combination with network analyses, pharmacogenomics and integrated multi-omics data, MESI-STRAT will play a decisive role in better deciphering the metabolic and signaling networks that drive resistance to endocrine-based therapies.
www.mesi-strat.eu

Announced in November, one of the **U.S. Department of Defense's (DoD) Innovative Minds in Prostate Cancer (IMPaCT) Awards** will fund a three-year collaborative partnership to advance precision medicine against metastatic prostate cancer (mPC). This coalition will count on the multidisciplinary expertise of investigators at VHIO, the Spanish National Cancer Research Centre–CNIO (Madrid, Spain), and the University of Washington (USA). Aimed at more precisely gauging response in patients to standard therapies, the team will also seek to develop new, more effective and tailored treatment strategies, as well as design a clinical trial to assess the performance of a DNA damaging platinum chemotherapy, carboplatin, that is already used to treat other tumor types including ovarian and breast cancer.

Research at VHIO led by Joaquin Mateo, Principal Investigator of our Prostate Cancer Translational Research Group (page 78), will search for DNA damage and repair biomarkers in these patients, since these deficiencies do not always originate from an inherited mutation.

His team will focus on biological parameters with clinical value by studying these tumors using a range of tools and techniques in the laboratory. The objective is to count on these new signals as indicators of damage – more so than genetic mutations – that will guide and accelerate more precise treatment decisions.
https://cdmrp.army.mil/pcrp

To browse the complete list of consortia and other collaborations that VHIO either leads or participates in as selected partner see pages 123-127.

Accolades and achievements:a snapshot

We are delighted to report that 2018 has brought many important accolades and recognitions 'at home' and away. Here are just some of the many that made the headlines:

International recognitions

VHIO's Director, Josep Tabernero, and Enriqueta Felip, PI of our Thoracic Cancers & Head and Neck Cancer Group (page 84), were both named in the **Global Highly Cited Researchers list 2018**.

The Web of Science serves as the basis for the regular listings of researchers whose citation records rank them in the top 1% for their field and year. Their consistent production of highly cited papers reflects their essential contributions and utility of their work as repeatedly judged by their peers.

Featuring among the 4000+ top drawer leading researchers across 21 fields of the sciences and social sciences covered by the Essential Science Indicator (ESI), Josep was selected, for a consecutive year, for his exceptional advancements in cancer research under the category of Clinical Medicine that listed a total of 497 named leaders across the globe in 2018.

Devised to 'house' frontier areas of research that are frequently interdisciplinary, the newly launched cross-field category recognized some additional 2000 researchers who have been identified as having an exceptional performance based on high impact papers in several fields during the last decade. Among these multi-field contributors who have been selected in one or more of the 21 broad fields, was VHIO's Enriqueta Felip.

Now in their 6th Annual edition, the ***OncLive Giants of Cancer Care* Awards** recognize trailblazers in oncology for their remarkable achievements in advancing cancer research, clinical practice and patient care. The 2018 class of 21 Giants were nominated by the oncology community and finalists were selected by an especially appointed seven-member Advisory Board chaired by Patrick I. Borgen. Nominees were then voted on by a 100-plus member selection committee.

One of the 2018 Award recipients was our Director, Josep Tabernero. Specifically, under the category of gastrointestinal cancer, this recognition salutes Josep's determined efforts aimed at advancing cancer research and precision treatment and care in oncology. Fittingly, the special ceremony took place on 31 May 2018 upon the eve of the Annual Meeting of the American Society of Clinical Oncology (ASCO) Annual Meeting, 01-05 June, in Chicago (IL, USA).

Upon the eve of ASCO: Josep Tabernero, Director of VHIO and one of the 21 recipients of the OncLive Giants of Cancer Awards 2018. Left to right: Robert Goldsmith, OncLive, Josep Tabernero, Patrick Borgen, Chair of Giants of Cancer Care.

2018 proved a particularly great year for VHIO's Laura Soucek, PI of our Mouse Models of Cancer Therapies Group (page 50), ICREA Professor, and Co-Founder & CEO of VHIO spin-off, Peptomyc S.L. (www.peptomyc.com). This VHIO-born spin-off was established in 2014 and was co-created by Marie-Eve Beaulieu, CSO of the company and formerly a Postdoc in Laura's group.

The European Research Council (ERC), among other 'believers' including its partners, venture capital firms Alta Life Sciences and HealthEquity, and ICREA, has consistently supported Laura and her group's efforts in advancing discovery into Myc's biology and function, and progressing novel targeting strategies towards finally delivering a clinically viable inhibitor.

In 2018 Laura was named as one among fifty other current ERC grant holders (totaling five from Spain, all located across Catalonia) to receive top-up funding via her Proof of Concept Grant (PoC), to explore the commercial and societal potential of the results of her ERC-funded frontier research, under EU's research and innovation programme, Horizon 2020.

Laura Soucek, PI of our Mouse Models of Cancer Therapies Group.

Laura was the only woman in Catalonia to receive a **"la Caixa" EntrepreneurXXI Award** in 2018. These annual recognitions, established by CaixaBank through Caixa Capital Risc in 2007, are co-granted by the Spanish Ministry of Economy, Industry and Competitiveness through ENISA – *Empresa Nacional de Innovación*, and support the development of innovative start-up companies throughout Spain and Portugal.

At the end of last year, on the occasion of the BioFIT meeting – Europe's premier event for early-stage innovations in Life Sciences, Peptomyc was jointly awarded as the ***Most Innovative Life Sciences Start-up of 2018.***

The Prostate Cancer Foundation (PCF), granted Raquel Perez-Lopez, who leads our Radiomics Group (page 82), with one of its 29 **Young Investigator Awards 2018** for early career scientists with unique approaches and ground-breaking ideas to drive the critical research needed to more effectively combat prostate cancer.

More specifically, Raquel received the **2018 Gina Rinehart–PCF Young Investigator Award**, to support her winning research proposal entitled: *A Two-Stage study to Clinically Qualify Whole-Body Diffusion-Weighted MRI in Patients with Metastatic Castration Resistant Prostate Carcinoma with Bone Metastases*.

Raquel Perez-Lopez, PI of our Radiomics Group

Celebrated during a special ceremony hosted and organized by the **Swiss Bridge Foundation** in Zurich, Switzerland, Rodrigo A. Toledo, Translational Investigator of VHIO's Gastrointestinal and Endocrine Tumors Group (page 68), headed by Teresa Macarulla and directed by Josep Tabernero, was officially announced as joint recipient of the Foundation's Annual Award in 2018.

Empowering exceptional cancer research across Europe, this year's Call, inviting proposals from internationally-driven young research talents on the topic of immune-oncology biomarkers, received a total of 111 applications.

Recognized alongside his fellow winner, Ping-Chih Ho, Department of Fundamental Oncology at the University of Lausanne/Ludwig Lausanne Branch (Switzerland), Rodrigo A. Toledo's project entitled, *IMMUNOMICS: Co-evolutionary dynamics landscape of neoplastic cells and T-cells interactions during cancer immunotherapy*, will be fueled by a half share of the 2018 Swiss Bridge Award funding.

Swiss Bridge Award Ceremony. Left to right: co-Award Recipient Ping-Chih Ho and his family, Jakob Passweg, President of Swiss Bridge, VHIO's Rodrigo A. Toledo, co-Award Recipient, Gordon McVie, President of the Award's Scientific Jury, and Philipp Lücke, the Foundation's CEO

At the regional and national levels

Celebrated during the 10th Research Workshop of the Catalan Institute of Health (ICS), Elena Élez, Clinical Investigator of VHIO's Gastrointestinal & Endocrine

At the ICS Award Ceremony from left to right: Josep Tabernero (VHIO's Director), Elena Élez (ICS Awardee, VHIO), Miquel Casas (ICS Awardee, VHIR), Joan X. Comella (Director of VHIR), and Josep Antoni Ramos-Quiroga (Head of Psychiatry, Vall d'Hebron University Hospital).

Tumors Group (page 68), directed by Josep Tabernero and co-led by Principal Investigator Teresa Macarulla, was awarded the **Young Investigator of the Year** by ICS in recognition for her dedication to advancing precision research, treatment and care in colorectal cancer.

Created to both prize and promote biomedical, translational research of excellence led by researchers at entities belonging or affiliated to the ICS, this year's recognition acknowledges the tremendous work of two up and coming young investigators. Both Elena and Beatriz Mothe, Investigator of the HIV Unit – Department of Infectious Diseases, the *Germans Trias i Pujol* University Hospital, were equally awarded.

In Elena's case, this accolade not only recognizes her important contributions in biomarker development and rendering targeted therapies more precise, it applauds her essential collaboration in some 200 clinical studies spanning the early phases of clinical drug development, and congratulates her already renowned excellence as a tremendously devoted medical oncologist at the Vall d'Hebron University Hospital's Medical Oncology Department (Vall d'Hebron Barcelona Hospital Campus), also spearhead by Josep Tabernero.

Celebrated at a gala event hosted by the National Royal Academy of Medicine in Madrid, the ***Fundación para la Excelencia y la Calidad en la Oncología*** **(ECO)** presented this year's recipients with its annual awards. Now in its seventh edition, this accolade recognizes the outstanding contributions of individuals, bodies, societies and institutions to advancing the oncology field.

VHIO's Director and Head of the Medical Oncology Department at the Vall d'Hebron University Hospital (HVUH–Vall d'Hebron Barcelona Hospital Campus), Josep Tabernero, was among the twenty awardees for 2018. To inaugurate the award ceremony, Josep was also invited to deliver the opening lecture on *The Future of Oncology in Europe*.

VHIO's Director, Josep Tabernero (to the right), with ECO's President, Vicente Guillem.

Importantly, ECO also recognized the tremendous successes marked to-date of the recently created Center for the Biomedical Research Network in Oncology (CIBERONC), which is expertly directed by Joaquín Arribas, Co-Director of VHIO's Preclinical and Translational Research Program (page 38), and ICREA Professor. This virtual hub, incorporating and connecting fifty of the most renowned national research groups in cancer, promotes excellence in oncology throughout Spain and seeks to more swiftly and collectively translate new findings to clinical practice.

Timed to coincide with World Cancer Research Day (WCRD), celebrated each year on 24 September 2018, the **Spanish Association against Cancer (AECC)** announced its 2018 awardees during a special ceremony.

The 2018 AECC Awards Ceremony.

This essential support will fuel some 160 projects, two of which will be led by Ana Vivancos, Principal Investigator of Cancer Genomics at VHIO (page 90), and Marta Crespo, Translational Research Coordinator of our Experimental Hematology Group (page 66), who were awarded under the categories AECC Lab and AECC Project, respectively.

Ana will lead research on *Moving liquid biopsy beyond current applications: the study of prognostic and predictive values of circulating tumor DNA in metastatic colorectal cancer*, which she will carry out in collaboration with other VHIO teams and talents, including members of our Colorectal Taskforce (see page 17).

Marta's team will focus on *Macrophage-mediated immunotherapy optimization in lymphomas affecting the central nervous system*, to test their hypothesis that macrophages play a central role in the development of central nervous system lymphoma (CNSL) and its potential response to immunotherapies.

VHIO's Director, Josep Tabernero, was also recognized as Co-Principal Investigator of one of the six international projects to have received an Accelerator Award from the newly established Cancer Research UK (CRUK), *Associazione Italiana per la Ricerca sul Cancro* (AIRC), and AECC charity partnership.

These highly competitive Accelerator Awards support international collaborations that promise to accelerate translational research against cancer. *ACRCelerate: Colorectal Cancer Stratified Medicine Network*, led by Owen Sansom, Director of the Cancer Research UK Beatson Institute in Glasgow, will count on VHIO's expertise as one of its project partners. Incorporating a total of 20 international trailblazers in colorectal cancer, including Josep, this *tour de force* collaboration will seek to identify new therapeutic avenues for the treatment of this disease by discovering and validating novel targets so that patients can be more precisely matched to therapies under study.

The 6th annual edition of **Gilead's Fellowships in Biomedical Research 2018** awarded VHIO's Experimental Hematology Group for research on: *Understanding the tumor immune microenvironment in diffuse large B-cell lymphoma for the development of immunotherapeutic strategies that target each individual's immune biology*, under the leadership of Principal Investigator of the project, Francesc Bosch (also PI of the same VHIO group – page 66).

Photo:GILEAD.

Gilead Sciences Inc. actively supports and promotes Spanish research of excellence that focuses on advancing biomedicine and improving the quality of life of patients. Gilead's funding spurs collaborations between public and private entities across the fields of HIV, Hepatitis and Hemato-oncology.

Evaluated and selected by the Institute of Health Carlos III (ISCIII), and organized in collaboration with the GeSIDA aids research group, the Spanish Association for the Study of the Liver (AEEH), and Spanish Association of Hematology & Hemotherapy (SEHH), 21 projects were awarded – eight of which were presented to researchers in Catalonia.

Specifically, Gilead will fuel their research focused on better understanding the role of the individual immune system in the treatment of diffuse large B-cell lymphoma (DLBCL), the most common type of adult and aggressive non-Hodgkin's lymphoma, towards developing more effective therapies.

Recognition through accreditation

The **European Commission's Human Resources for Research (HRS4R)** strategy enables research institutions of excellence to actively implement and uphold the requisites of The European Charter for Researchers and Code of Conduct for the Recruitment of Researchers for their HR policies and practices.

VHIO's comprehensive analysis and action plan was officially approved by HRS4R assessors in 2018 and our Institute was consequently granted permission to use the HR Excellence in Research Award logo as demonstration of its stimulating and favorable work environment.

Importantly, it's not just a matter of the working environment. VHIO is dedicated to providing a bias-free environment that stimulates our faculty to follow their research ambitions, develop their careers and seize on the same, equal opportunities.

Throughout 2018, several editorials and opinion pieces published in leading specialized media rightly called for targeted action against gender gaps and the need to advance equity in science, medicine and global health.

To name but two, our Director was invited to pen an editorial in *ESMO Open* exploring the current status of women in oncology, particularly in terms of fair access to more senior roles [1]. As this Scientific Report entered into print, a piece in *The Lancet* [2] argued that achieving gender balance is a shared responsibility of everyone and is not just about equal rights; it is imperative in producing the very best research and providing optimal patient care.

We are proud to report that 74% of VHIO's workforce are women, and over half of our Principal Investigators are female.

1. Tabernero J. All change: closing the gender gap in oncology. *ESMO Open.* 2018 Nov 15;3(7):e000448.

2. Feminism is for everybody. *Lancet.* 2019 Feb 9;393(10171):493.

For details of other accreditations, please see page 127.

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.

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.

Exchanging latest discovery in cancer science and medicine, VHIO organized and hosted a total of 50 Courses, Workshops, Observerships and Perceptorships in 2018.

1. Towards New Horizons in Metastatic Colorectal Cancer, 19 April 2018, Course Directors: Elena Élez and Jaume Capdevila. 2. Medical Education Program on Immunotherapy, 17-18 May 2018, Program Director: Elena Garralda. 3. Highlights in Chronic Lymphocytic Leukemia Dates: 05-06 July 2018, Course Director: Francesc Bosch.

Co-organized and hosted by VHIO: EACR's *LIF As We Know IT*

Scientifically co-organized by Joan Seoane, Co-Director of Preclinical and Translational Research at VHIO, ICREA

An EACR Masterclass celebrated at VHIO's CELLEX CENTER: LIF as We Know It – from Basic Science to Clinical Trials, 28-29 May, 2018.

Professor, Secretary General of the European Association for Cancer Research (EACR) and Chairman of its Conference Series Committee, VHIO opened the doors of its Auditorium to welcome speakers and participants of EACR's two-day meeting on *LIF As WE Know It*: *from Basic Science to Clinical Trials*.

This inspired meeting was superbly engineered to offer a broad, stimulating and comprehensive overview of the most recent advances in the LIF field from the preclinical, translational and clinical perspectives. Testament to the caliber of this event, a post-conference survey achieved a 100% recommendation rate and ranking of scientific quality as 'excellent' or 'very good'.

BENCH ST RMING SEMINARS

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.

Benchstorming co-Chairs, Elena Senís and Toni Jauset.

As the Benchstormings turned two years old, Verónica and Jordi handed over to new Co-Chairs in March 2018, Elena Senís, Post-Doctoral Fellow of VHIO's Cellular Plasticity & Cancer Group, and Toni Jauset, formerly a graduate student of VHIO's Mouse Models of Cancer Therapies Group and now researcher at VHIO-born spin-off Peptomyc S.L.

In 2018, a total of 20 researchers discussed and 'benchstormed' their research areas. Elena and Toni also introduced an additional element to this popularly attended program: the 'spin-off' *Techstorming* sessions to present on novel technologies and latest lab approaches in cancer research.

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 2018, VHIO led and/or participated in over 30 public outreach events, programs and initiatives spurred through the dedication of the following entities, events as well as fundraising efforts (listed in alphabetical order):

- II Jornadas Baby Beatles
- 48H Open House BCN
- Al cáncer, donem-li recerca!
- Asociación Cáncer de Mama Metastásico's visit to VHIO
- BCNspiracy
- Concierto "Jarabe y amigos contra el cáncer", Pau Donés
- El Corte Inglés se viste de rosa
- Festival de la Ciencia

- Healthio 2018
- Marató de TV3 i Cataluna Ràdio
- Pink Run Mir
- Projecte Mexcla't
- The Youth Mobile Festival: YoMo
- VHIO's Escuela y Ciencia program (see opposite)
- VHIO-HUVH's annual series of workshops for patients suffering from breast cancer
- VHIO-IDIBELL-ICO workshops on prostate cancer (see page 24)
- VHIO's Running for Research (R4R) (see below)
- Zumba solidario

VHIO Vall d'Hebron Institute of Oncology
RUNNING FOR RESEARCH
www.vhio.net

Inspired by Daniel Massó Vallés, formerly a Postdoc of our Mouse Models of Cancer Therapies Group, and now researcher of VHIO spin-off Peptomyc S.L., and Irene Rius, Graduate Student of our Growth Factors Groups, VHIO's *Running for Research (R4R)* currently comprises a team of some 20 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.

Our dedicated runners, who officially enter sports events in the name of VHIO, are kitted out with R4R-branded baseball caps and t-shirts to increase visibility and trigger conversation with fellow runners and other members of the public present.

Just two of the many runathons in which R4R participated in 2018 included the Barcelona half marathon for a FERO Foundation crowdfunding in support of research at VHIO, and the Spanish Association against Cancer's (AECC), *Run against Cancer*.

VHIO's R4R rallying for research against cancer: 1. At the Barcelona half marathon for FERO Foundation's inspired crowdfunding. 2. Participating at the Spanish Association against Cancer's (AECC) *Run against Cancer*.

Concerning the former, they teamed up with FERO Foundation participants for their crowdfunding initiative to help fuel the continued development of liquid biopsy technology at VHIO. At AECC's second annual Barcelona-based fundraising run, R4R joined other runners to help rally for research in the 10K race, 5K run, and the gentler paced 2.5K.

To discover more about FERO's as well as AECC's essential and continued backing of VHIO's programs and groups see pages 12 and 21, respectively.

escolaciència

In 2018 VHIO's education program, *Schools and Science*, welcomed a total of over 250 under-twelves from 6 local primary schools to meet our faculty, tour our laboratories and learn more about cancer biology and research.

Junior masterclasses and hands-on workshops to explain 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 visits 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 program, with dates already in the diary for next 2019.

In 2018 we celebrated the launch of a new institutional public engagement program: **VHIO-IDIBELL-ICO's workshop series focused on prostate cancer**.

Pioneered by the patient advocacy group, *The Prostate Net*, these informal meetings aimed at patients, their families, and the public at large, are co-organized by Joaquin Mateo (PI of our Prostate Cancer Translational Group), and Álavaro Aytes (PI of the Resistance and Progression Mechanisms in Prostate Cancer Group, Bellvitge Biomedical Research Institute, Barcelona), and aim at increasing awareness on and around the importance of cancer science and clinical discovery in advancing treatments against this tumor type, as well as update on the latest developments within the field.

Co-organizers Joaquin Mateo and Álvaro Aytes at the inaugural morning workshop, pioneered by Virgil H. Simons, Founder and President of *The Prostate Net*, that took place at the Harley Davidson 99%, Barcelona.

These workshops are conducted in Castilian and Catalan and the inaugural, entitled, *Fighting Prostate Cancer: From the Laboratory to the Patient*, 23 November, explored the bench-to-bedside (and back) steps and stages that drive the advancement and delivery of more effective anti-prostate cancer therapies.

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 translational research lines, programs and projects.

Its sub-portals in Castilian and Catalan, generally aimed at less specialized, lay audiences, publish our media releases in these two languages, as well as update on our local public outreach activities.

VHIO's International Communications, directed by Amanda Wren, continues to upgrade and constantly update our website's content, adding exciting programs as they launch, and implementing new features aimed at further generating traffic, maintaining and attracting new visitors.

Just some of the many additions in 2018 included the incorporation of VHIO's Twitter account @VHIO which we launched just as this Scientific Report entered into print (end January 2019), as well as our new corporate video:

Kicking-off with the question, *How can you translate basic discovery into more precise and potent anticancer therapies?*, our newly launched video responds by telling VHIO's story.

It does so by dipping into our Institute's history, presenting a snapshot of our main programs and activities, and signposting a promising future ahead.

The film's title? Simply, VHIO's tagline: *Translation toward precision oncology*.

To discover more about our purely translational and multidisciplinary research model and just how we bridge preclinical and clinical research, we invite you to access our video here: **www.vhio.net/en/corporate-video.**

Celebrating its first birthday in December 2018, *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. Reflective of its popularity and keen VHIO following, *Wren's Lens* has since become more of an internal blog spot than a 'news desk' update.

SCIENTIFIC PRODUCTIVITY: RESEARCH ARTICLES

Articles published in 2018

In 2018, 282 scientific articles (77% Q1) were published by VHIO researchers as corresponding/ senior or co-authors with a cumulative Impact Factor (IF) totaling at 3501 and a Median Impact Factor (MIF) of 12,41.

These figures reflect an increase in scientific impact 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 - 2018

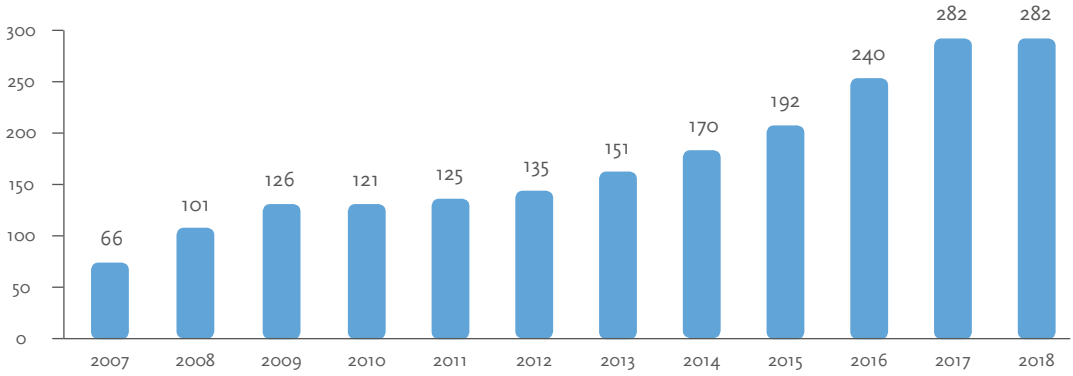
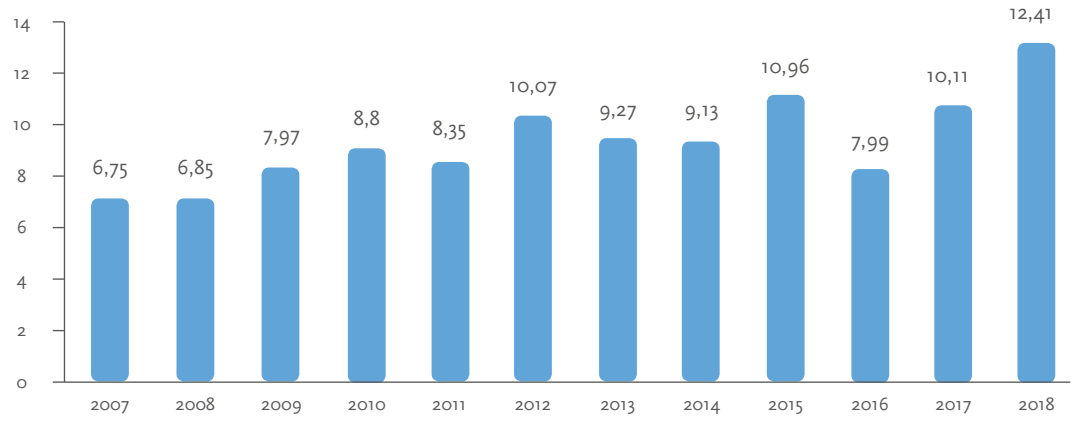


Figure II

Median Impact Factor of papers published by VHIO faculty from 2007 - 2018



For the complete list of VHIO scientific articles published in 2018 in journals with allocated Impact Factor please see pages 106-119. To view a selection of most relevant articles by VHIO researchers published in 2018 please refer to pages 27-33 of this Scientific Report.

To view our Principal Investigators' cherry-picked 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 2018, as compiled by our Principal Investigators, visit the extended version of our Scientific Report online at: **http://memorias.vhio.net/2018**

SELECTION OF SOME OF THE MOST RELEVANT ARTICLES BY VHIO RESEARCHERS PUBLISHED IN 2018

Below is a selected list of articles published by VHIO researchers in 2018 with respective Impact Factors indicated. For the complete list of VHIO scientific articles published in 2018 in journals with allocated Impact Factor please see pages 106–119.

Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. Smith MR; Saad F; Chowdhury S; Oudard S; Hadaschik BA; Graff JN; Olmos D; Mainwaring PN; Lee JY; Uemura H; Lopez-Gitlitz A; Trudel GC; Espina BM; Shu Y; Park YC; Rackoff WR; Yu MK; Small EJ; SPARTAN Investigators. *N Engl J Med.* 378: 1408-1418. IF: 79,258

Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. Camidge DR; Kim HR; Ahn MJ; Yang JC; Han JY; Lee JS; Hochmair MJ; Li JY; Chang GC; Lee KH; Gridelli C; Delmonte A; Garcia Campelo R; Kim DW; Bearz A; Griesinger F; Morabito A; Felip E; Califano R; Ghosh S; Spira A; Gettinger SN; Tiseo M; Gupta N; Haney J; Kerstein D; Popat S. *N Engl J Med.* 379: 2027-2039. IF: 79,258

Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. Mateos MV; Dimopoulos MA; Cavo M; Suzuki K; Jakubowiak A; Knop S; Doyen C; Lucio P; Nagy Z; Kaplan P; Pour L; Cook M; Grosicki S; Crepaldi A; Liberati AM; Campbell P; Shelekhova T; Yoon SS; Iosava G; Fujisaki T; Garg M; Chiu C; Wang J; Carson R; Crist W; Deraedt W; Nguyen H; Qi M; San-Miguel J; ALCYONE Trial Investigators. *N Engl J Med.* 378: 518-528. IF: 79,258

EPAS1 Mutations and Paragangliomas in Cyanotic Congenital Heart Disease. Vaidya, Anand; Flores, Shahida K.; Cheng, Zi-Ming; Nicolas, Marlo; Deng, Yilun; Opotowsky, Alexander R.; Lourenco, Jr., Delmar M.; Barletta, Justine A.; Rana, Huma Q.; Adelaide Pereira, M.; Toledo, Rodrigo A.; Dahia, Patricia L. M. *N Engl J Med.* 378: 1259-1261. IF: 79,258

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. Moore, K.; Colombo, N.; Scambia, G.; Kim, B. -G.; Oaknin, A.; Friedlander, M.; Lisyanskaya, A.; Floquet, A.; Leary, A.; Sonke, G. S.; Gourley, C.; Banerjee, S.; Oza, A.; Gonzalez-Martin, A.; Aghajanian, C.; Bradley, W.; Mathews, C.; Liu, J.; Lowe, E. S.; Bloomfield, R.; DiSilvestro, P. *N Engl J Med.* 379: 2495-2505. IF: 79,258

PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. Migden MR; Rischin D; Schmults CD; Guminski A; Hauschild A; Lewis KD; Chung CH; Hernandez-Aya L; Lim AM; Chang ALS; Rabinowits G; Thai AA; Dunn LA; Hughes BGM; Khushalani NI; Modi B; Schadendorf D; Gao B; Seebach F; Li S; Li J; Mathias M; Booth J; Mohan K; Stankevich E; Babiker HM; Brana I; Gil-Martin M; Homsi J; Johnson ML; Moreno V; Niu J; Owonikoko TK; Papadopoulos KP; Yancopoulos GD; Lowy I; Fury MG. *N Engl J Med.* 379: 341-351. IF: 79,258

Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. Gandhi L; Rodríguez-Abreu D; Gadgeel S; Esteban E; Felip E; De Angelis F; Domine M; Clingan P; Hochmair MJ; Powell SF; Cheng SY; Bischoff HG; Peled N; Grossi F; Jennens RR; Reck M; Hui R; Garon EB; Boyer M; Rubio-Viqueira B; Novello S; Kurata T; Gray JE; Vida J; Wei Z; Yang J; Raftopoulos H; Pietanza MC; Garassino MC; KEYNOTE-189 Investigators. *N Engl J Med.* 378: 2078-2092. IF: 79,258

Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma. Morschhauser F; Fowler NH; Feugier P; Bouabdallah R; Tilly H; Palomba ML; Fruchart C; Libby EN; Casasnovas RO; Flinn IW; Haioun C; Maisonneuve H; Ysebaert L; Bartlett NL; Bouabdallah K; Brice P; Ribrag V; Daguindau N; Le Gouill S; Pica GM; Martin Garcia-Sancho A; López-Guillermo A; Larouche JF; Ando K; Gomes da Silva M; André M; Zachée P; Sehn LH; Tobinai K; Cartron G; Liu D; Wang J; Xerri L; Salles GA; RELEVANCE Trial Investigators. *N Engl J Med.* 379: 934-947. IF: 79,258

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Obinutuzumab plus bendamustine in previously untreated patients with CLL: a subgroup analysis of the GREEN study. Stilgenbauer S; Leblond V; Foà R; Böttcher S; Ilhan O; Knauf W; Mikuskova E; Renner C; Tausch E; Woszczyk D; Gresko E; Lundberg L; Moore T; Morris T; Robson S; Bosch F. *Leukemia.* 32: 1778-1786. IF: 10,023

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JOAQUÍN ARRIBAS

From the Co-Program Directors

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. We 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 our ambitions, we 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.

Considering the many research highlights reported by our program this year, 2018 has been a particularly fruitful one. These advances, aimed at collectively solving cancer sooner, have undoubtedly been driven by our purely collaborative approach to cancer science and superb teamwork with other VHIO groups and leading institutes in oncology.

As Co-Program Director it is both a pleasure and privilege to update on just a few of our many highlights in 2018:

VHIO's Tumor Biomarkers Group (page 54), headed by Josep Villanueva has shown that HMGA1, as a suspected intracellular protein, is in fact secreted. They have also evidenced that secreted HMGA1 promotes the invasive growth of triple negative breast cancer. To do so, they employed a variety of patient-derived experimental models and counted on additional expertise from other groups belonging to this program as well as other VHIO teams.

Further underpinning the relevance of Josep's group's pioneering discovery, this paper was also selected for the front cover of the December issue of *Clinical Cancer Research* (Méndez et al. *Clin Cancer Res.* 2018).

Our Experimental Therapeutics Group (page 44), directed by Violeta Serra, has marked several major milestones over the past year. Of the utmost importance, they implemented their companion diagnostic test, PARPiPRED (predictor of PARP inhibitor - PARPi - response), as an immune-based assay performed on FFPE tumor sections. Developed by her group, thanks to the support received from the *CaixaImpulse* (*Fundació Bancària la Caixa* and Caixa Capital Risk) program in 2017, this test facilitates a more precise selection of patients who would be most likely to clinically benefit from these therapies.

Additionally, her group has unveiled novel mechanisms of resistance to targeted therapies in hereditary BRCA1/2 breast cancer, and identified new biomarkers of sensitivity and resistance. These findings have been elegantly reported as publications in renowned titles including *Annals of Oncology* (Cruz et al. *Ann Oncol.* 2018), *EMBO Molecular Medicine* (Castroviejo-Bermejo et al. *EMBO Mol Med.* 2018), and the *Journal of Clinical Oncology* (Cruz et al. *J Clin Oncol.* 2018). Again, the close collaboration and connectivity with researchers belonging to our program, as well as those from other VHIO groups, are key to these important achievements.

VHIO's Mouse Models of Cancer Therapies Group (page 50), led by Laura Soucek, has continued to pursue a novel therapeutic strategy centered on Myc inhibition based on peptides that enter the cell and block this particular oncogene that is found activated in the majority of cancers.

In a paper published in *Oncotarget* (Jauset et al. *Oncotarget.* 2018), her group has shown that this potentially ground-breaking approach is effective against pancreatic cancer. Research led by Laura has been recognized through several grants, including those awarded this year by the Canadian Institutes of Health Research (CIHR), and the European Institute of Innovation & Technology (EIT).

Finally, my own Growth Factors Group (page 48), has continued to develop a novel immune therapy against a subtype of breast cancer. It is based on the recruitment of cytotoxic lymphocytes by a bispecific antibody. This antibody binds to a tumor specific antigen, p95HER2, and 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. These results were published in *Science Translational Medicine* (Rius Ruiz et al. *Sci Transl Med.* 2018). Once more, I cannot emphasize enough that these findings were only possible through collaborations with many other leading researchers at VHIO.

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).

Last but not least, I am also proud to report that I continue to lead the largest network of cancer research groups in Spain as Scientific Director of CIBERONC.

Translational research at VHIO promotes the integration of preclinical and clinical research. By attacking cancer from all angles and establishing synergies between molecular and clinical cancer research, we seek to translate scientific advances into benefits at the bedside.

To get smarter and move faster in our efforts to more effectively treat this disease, we need to more successfully tackle tumor diversity. Cancer is an extremely complex, heterogeneous, fluctuating and 'smart' disease given that tumors are molecularly diverse and evolve over time.

Each individual patient consequently has a unique tumor with a particular combination of genomic aberrations that can alter during disease progression. Patients should therefore be treated with the optimal compound/combination of therapies that are matched to specificities of their respective cancer.

To potentiate 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 to recapitulate the characteristics of patients' tumors as faithfully as possible. Both VHIO's Stem Cells & Cancer Group (page 52), led by Héctor G. Palmer, and my own Gene Expression & Cancer Group (page 46), have helped to develop these models for brain and colon cancer respectively.

In 2018, Héctor's Group has continued to explore 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 our Hospital.

More specifically, his team has discovered that a core circuit of epigenetic and transcription factors govern cancer cell dormancy. TET2 is one of the master epigenetic enzymes controlling the survival of dormant tumor cells (DTCs), and its produce is found in tumors of patients with higher risk of relapse after initially effective treatment with chemotherapy.

This pioneering research, demonstrating the promise of TET2 as a new drug target for the future treatment of these patients, resulted in an important publication this year in *The Journal of Clinical Investigation* (Puig et al. *J Clin Invest.* 2018).

His group also continues to accumulate evidence on the efficacy and mechanisms of action of a novel generation of Wnt/beta-catenin inhibitors against colorectal cancer (CRC), and have identified biomarkers to predict response.

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.

This work led to the publication of our findings on the molecular diagnosis of diffuse gliomas through sequencing of cell-free circulating tumour DNA from cerebrospinal fluid this year in *Clinical Cancer Research* (Martínez-Ricarte et al. *Clin Cancer Res.* 2018).

We have also generated insights into the genomic evolution of thyroid cancer. We have described the molecular history of anaplastic thryroid cancer and papillary thyroid cancer observing that both tumor types are largely divergent and should therefore be clinically managed differently. These findings were published in *Annals of Oncology* (Capdevila et al. *Ann Oncol.* 2018).

Additionally, we have developed an anti-cancer drug, MSC1, in close collaboration with VHIO-born spin-off company, Mosaic Biomedicals S.L. MSC1, a humanized LIF neutralizing antibody, is now being tested in clinical trials initiated in 2018.

We are immensely grateful to all the patients who kindly participated in our projects, as well as the funding agencies and entities for their tremendous support of our research endeavors. Finally, it is thanks to VHIO's strong ethos of teamwork and our purely multidisciplinary approach to our science, that translational and clinical research at VHIO are tightly connected.

More rapidly transforming cancer research into real benefits for our patients can and will only continue to happen through our pooling of expertise from bench to bedside and back.

JOAN SEOANE

CELLULAR PLASTICITY & CANCER GROUP

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Student
Noé Crespo

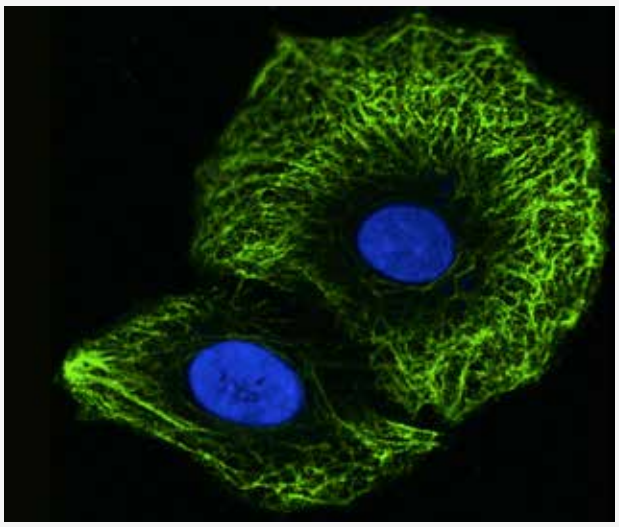
Strategic goals

- Discover and characterize novel micropeptides involved in cancer cell plasticity.
- Generate new patient-stratification tools based on cancer micropeptides.
- Identify new therapeutic-agents based on novel micropeptides.
- Decipher the molecular mechanisms governing the acquisition of stem cell properties during tumorigenesis.
- Develop new anti-cancer therapies based on the inhibition of cancer cell plasticity.

Highlights

- We have pioneered proof-of-concept for the potential of micropeptides in oncology.
- Our cancer micropeptides have been protected by a patent this year.
- We have reported a new strategy to induce reprogramming in vivo based on adeno-associated viruses (AAVs).

Figure



Detection of DMNTR, a novel micropeptide identified by our group in lung cancer cells.

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 enables them to transit between different cellular states, including reversible transitions between mesenchymal and epithelial phenotypes, or stem cell-like and differentiated states.

In tumors, the acquisition of stem cell properties correlates with increased malignancy and poor prognosis, and Cancer Stem Cells (CSCs) sustain the tumor bulk and contribute to treatment resistance and disease relapse post-therapy.

In this respect, we have reported that inducing dedifferentiation with the so-called Yamanaka factors can lead to the development of a variety of tumors. We have also demonstrated that tissue damage, the main driver of cancer, triggers cell dedifferentiation and the acquisition of stem cell properties *in vivo*.

These observations have important therapeutic implications given that chemotherapy and radiotherapy - cornerstones 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 novel therapies based on the inhibition of cancer cell plasticity.

Recent 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 that have been identified to-date play key functions in elemental cellular processes, leading to a new level of complexity with major implications - from basic research to the clinical setting.

Over the past two years we have focused on identifying and characterizing novel micropeptides implicated in cancer stemness that could represent novel actors in carcinogenesis.

We have already discovered six new micropeptides. During 2018 we have obtained compelling evidence *in vitro* and *in vivo* that four of them act as novel tumor suppressors, inducing apoptosis, differentiation, cell cycle arrest, or inhibition of mesenchymal traits in cancer cells.

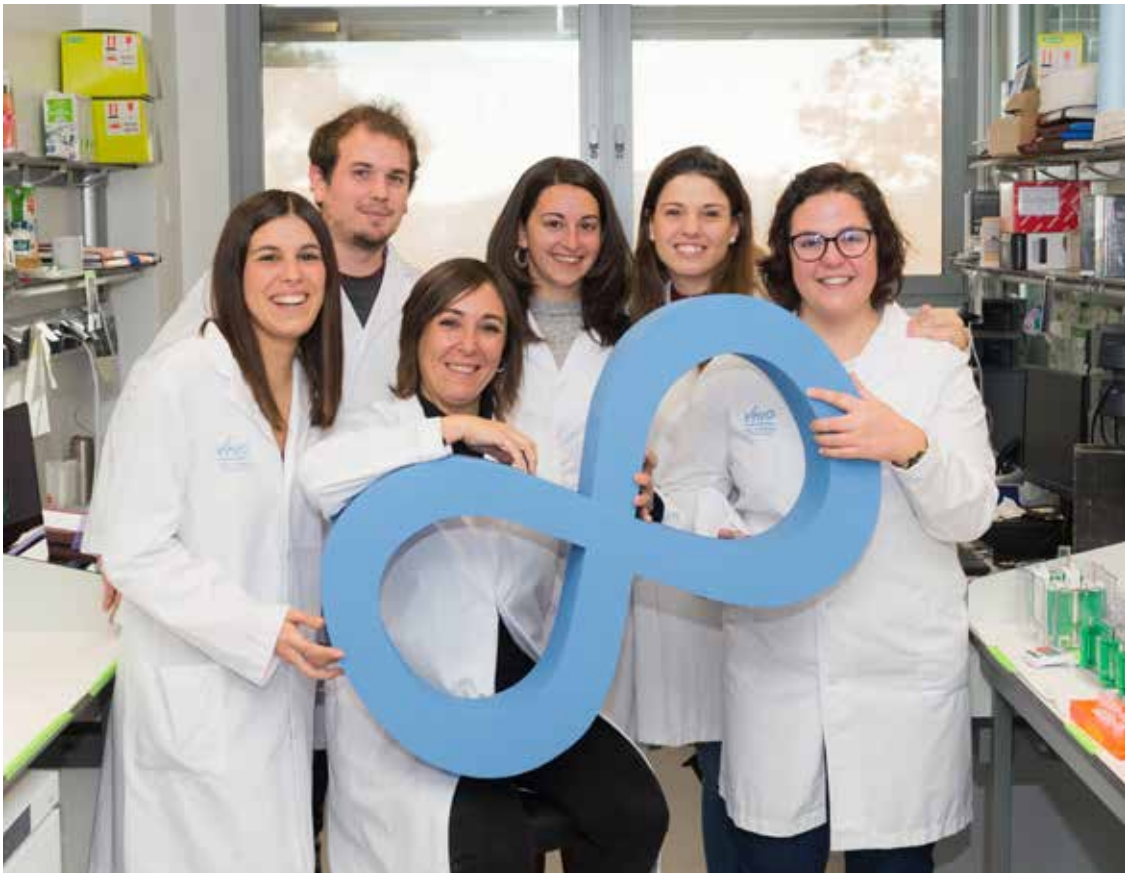
The identification of tumor-micropeptides could be crucial in advancing insights into cancer physiopathology. Moreover, they could serve as new cancer biomarkers for the early detection of disease and patient stratification for tailored therapies, as well as therapeutic targets.

This year we have also reported a new strategy to induce reprogramming in vivo based on adeno-associated viruses (AAVs) - an efficient and versatile approach to induce cellular plasticity in a tissue-specific manner - without genetic modifications (Senís et al. *Nat Commun*. 2018).

PI paper pick

Senis E, Mosteiro Ll, Wilkening S, Wiedtke E, Nowrouzi A, Afzal S, Fronza R, Landerer H, Abad M, Niopek D, Schmidt M, Serrano M, Grimm D. AAV vector-mediated in vivo reprogramming into pluripotency. *Nat Commun*. 2018 Jul 9;9(1):2651.

CHROMATIN DYNAMICS IN CANCER GROUP



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Technician
Jessica Querol

Student
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Strategic goals

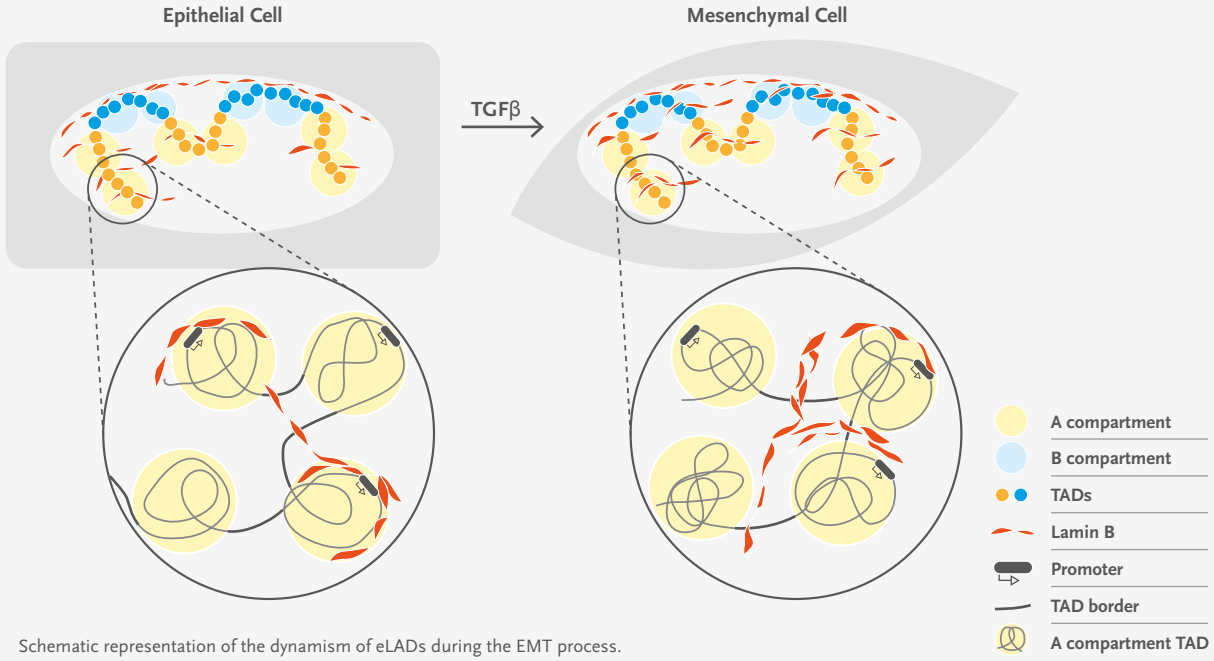
We aim to describe the epigenetic mechanisms controlling the expression of eukaryotic genes during tumor progression. Our group is particularly interested in the role of the primary structure of chromatin fiber, as determined by histone tail modifications, and the 3D chromatin structure implicated in the regulation of transcription.

- Identify the molecular mechanisms involved in chromatin conformation changes in breast cancer cells and in cholangiocarcinomas; identify potential druggable proteins.
- Discover the key enhancer-promoter interactions and the role of BRD proteins during the 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

- For the first time, Sandra Peiró's group demonstrated the existence of lamin-associated domains in contact with euchromatin with a key role in genome reorganization during the acquisition of malignant traits.
- We have established an ex vivo culture model for cholangiocarcinomas that enable us to evaluate different therapies and study molecular mechanisms of resistance.
- In collaboration with VHIO's Experimental Therapeutics Group (page 44), led by Violeta Serra, our group has been working with patient-derived xenograft (PDX) models from ER+ breast cancer resistant to cdk4/6 inhibitors. We hope this work will lead to the discovery of promising new therapies.

Figure



Schematic representation of the dynamism of eLADs during the EMT process.

Summary

Our group mainly focuses on the characterization of chromatin dynamics and epigenetics in cancer and epithelial-to-mesenchymal transition (EMT).

Based on our parevious work (Millanes-Romero et al. *Mol Cell*. 2013), 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 and ultimately advance our understanding of how they are transformed into malignant cells.

We have partially answered this question in a recent publication in *Nature Communications* (Pascual-Reguant et al. *Nat Commun*. 2018), in which we not only evidenced the 3D re-organization of the genome during EMT, but also revealed the key role of lamin B1 in this phenomena.

Dedicated to fully applying these insights to the epigenetic landscape and 3D structure during this malignant transformation, we have adopted chromosome conformation–based techniques together with ChIP-seq, ATAC-seq and RNA-seq. By combining these data with excellent computational and statistical tools in standard cancer models, such as cancer cell lines, and in a large and unique collection of patient-derived xenograft (PDX) models, we will continue to better navigate this largely uncharted area which shows great promise in the early diagnosis of disease.

We are equally committed to describing the association of chromatin conformation changes with the acquisition of malignant traits and evaluating the functional consequences of these developments in genes and pathways. Next steps will involve deciphering how these alterations occur at the molecular level and more precisely identifying these putative culprits for future targeted therapy.

PI paper pick

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EXPERIMENTAL THERAPEUTICS GROUP

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Strategic goals

- Developing predictive biomarkers of PI3K-pathway, AR, CDK4/6, FGFR and PARP inhibitors in ER+ and TN breast cancers.
- Exploring novel treatment combinations for ER+ and TN breast cancers.
- Revealing novel mechanisms of resistance against targeted therapies in germline *BRCA1/2* mutated breast cancer.
- Contributing to personalized medicine by developing the RAD51 assay to better guide treatment strategies.
- Establishing patient tumor-derived breast cancer preclinical models to explore hypothesis-based combinatorial therapies.

Highlights

- We have established an organoid culture model to assess the activity of CDK4/6 inhibitors, AKT inhibitors, PARP inhibitors and chemotherapeutic agents, and recapitulates the *in vivo* response.
- CDK4/6 inhibitor sensitive PDXs exhibit pRb expression and loss of p16.
- Lack of RAD51 nuclear foci formation, a functional biomarker of homologous recombination repair (HRR) deficiency, correlates with PARP inhibitor response in a panel of over one hundred PDXs and a dozen of clinical samples. We have also validated the feasibility of the RAD51 assay in different tumor types, including breast, ovarian and prostate cancers. A patent to protect the use of this assay has been filed.
- We have established a panel of almost one hundred ER+ and TN breast cancer PDXs. Of these, 17 PDXs harbor FGF/FGFR amplification and 33 PDXs are derived from *BRCA1/2* mutation carriers.

Figures

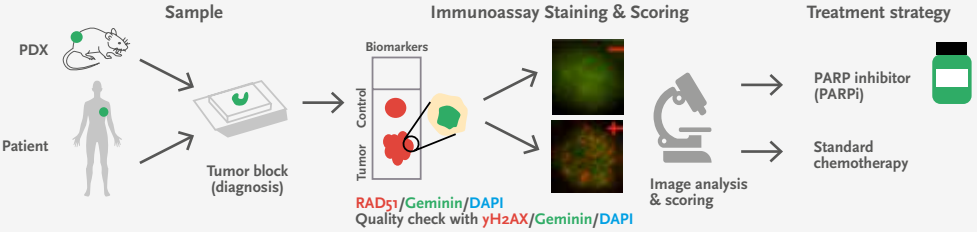

Figure 1: PARPiPRED (predictor of PARPi response) is an immune-based assay, performed on FFPE tumor sections, that identifies nuclear biomarkers and determines the functionality of the HRR DNA-damage pathway and the response to PARPi therapy. It has been validated in PDX models and we are currently extending the clinical validation to several tumor types.

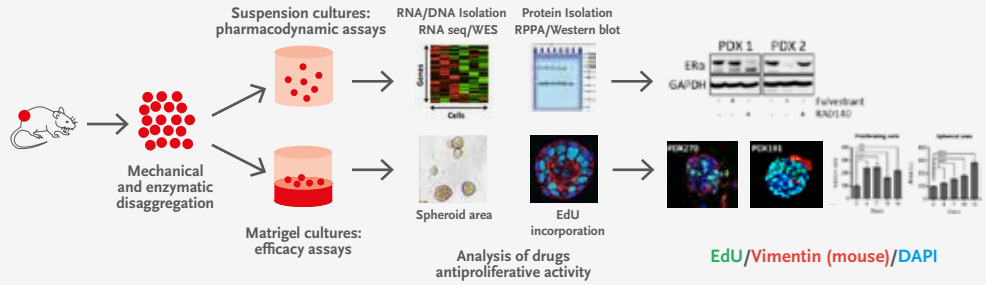

Figure 2: Generation of patient-derived culture cells (PDCs) coming from breast cancer PDXs: after mechanical and enzymatic disaggregation, cells are seeded in suspension cultures for pharmacodynamic analysis (RNA, DNA and protein levels) or on Matrigel cultures for drug efficacy assay (spheroid area and EdU incorporation). Representative images and data of each approach are shown.

Summary

VHIO's Experimental Therapeutics Group conducts bench-to-bedside preclinical research in breast cancer to advance insights into biomarkers of response to targeted therapies. To do so, we generate preclinical models such as patient-derived xenografts (PDXs) and patient-derived cultures (PDCs) from breast cancer patient samples.

Among others, our group has significantly contributed to the field of PI3K inhibitor resistance and we are currently exploring the mode of action and mechanisms of resistance to CDK4/6 inhibitors (as a single agent or combined with PI3K inhibitors and hormone therapy), FGFR inhibitors, AKT inhibitors and AR modulators (SARMs) in breast tumors.

Using clinically relevant PDXs 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 oestrogen receptor positive breast cancer. We have also generated a collection of PDXs containing either FGF ligand or receptor amplifications to study biomarkers of sensitivity to FGFR inhibitors; both pan-FGFR1-4 and Multi-targeted Tyrosine Kinase Inhibitors (MTKIs).

Encouraged by the early success of DNA damage repair inhibitors in germline *BRCA1/2* mutated tumors, we initiated a project aimed at identifying response biomarkers of PARP inhibitors (PARPi) and DNA binding agents including PM01183, a novel derivative of trabectedin, in homologous recombination repair (HRR) deficient tumors.

Our studies underpin the capacity of germline *BRCA* mutant tumors to recover HRR functionality and develop resistance to PARPi. We have developed an assay, the RAD51 test, which accurately identifies germline *BRCA* tumors that have restored HRR functionality, as well as tumors that are sensitive to PARPi through HRR alterations beyond the germline *BRCA* condition. We filed a patent (EU application in 2017 and PCT in 2018) and we are currently validating the use of this test in tumor samples from breast, ovarian and prostate cancer patients.

Finally, we are also studying the effects of PARPi on the tumor immune environment. HRR-deficient tumors have been shown to accumulate cytosolic DNA, which can elicit an innate immune signal (the STING pathway) and upregulate interferon-related genes, leading to lymphocytic infiltration and PD-L1 expression. We are testing the hypothesis that treatment of HRR-deficient tumors with PARPi elicits a DNA damage response that results in upregulation of PD-L1 and may limit the antitumor immune-mediated cytotoxicity by lymphocytes, but sensitizes to anti-PD-L1 treatments.

In short, our group has significantly advanced the understanding of the mode of action of novel targeted therapies, identified new response biomarkers, developed a biomarker-based assay with potential clinical application, and demonstrated the efficacy of hypothesis-based drug combinations.

PI paper pick

Cruz C, Castroviejo-Bermejo M, Gutiérrez-Enríquez S, Llop-Guevara A, Ibrahim YH, Gris-Oliver A, Bonache S, Morancho B, Bruna A, Rueda OM, Lai Z, Polanska UM, Jones GN, Kristel P, de Bustos L, Guzman M, Rodríguez O, Grueso J, Montalban G, Caratú G, Mancuso F, Fasani R, Jiménez J, Howat WJ, Dougherty B, Vivancos A, Nuciforo P, Serres-Créixams X, Rubio IT, Oaknin A, Cadogan E, Barrett JC, Caldas C, Baselga J, Saura C, Cortés J, Arribas J, Jonkers J, Díez O, O'Connor MJ, Balmaña J, and Serra V. RAD51 foci as a functional biomarker of homologous recombination repair and PARP inhibitor resistance in germline BRCA-mutated breast cancer. *Ann Oncol.* 2018 May 1;29(5):1203-1210.

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GENE EXPRESSION & CANCER GROUP

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Ester Planas
Carlota Rubio

Graduate Student
Ester Arroba

Technicians
Alexandra Arias
Mª Isabel Cuartas

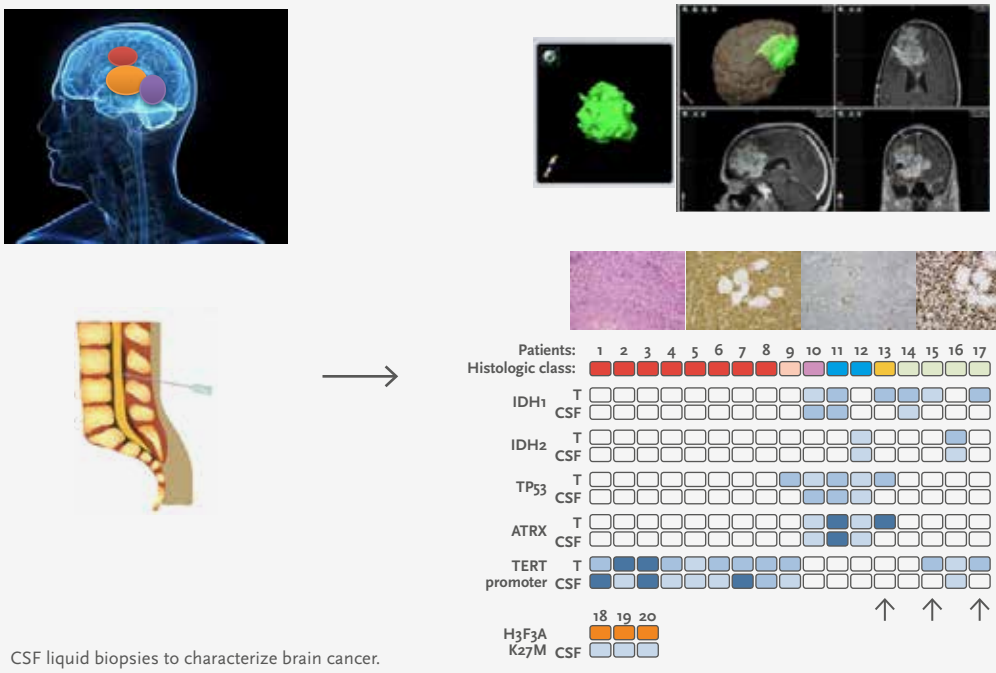
Strategic goals

- 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 cancers.

Highlights

- We have translated our discoveries into a clinical trial. During 2018, we opened a first-in-human and first-in-class clinical trial with a novel compound for the treatment of cancer patients. This compound, MSC01, was designed by our group based on our research, and developed by a VHIO born spin-off that Joan Seoane founded in 2012, Mosaic Biomedicals.
- We have designed a methodology for the use of liquid biopsies based on the analysis of cell free circulating tumour DNA in the cerebrospinal fluid for the diagnosis, prognosis and monitoring of patients with brain tumors.

Figure



CSF liquid biopsies to characterize brain cancer.

Summary

We study primary brain tumors and brain metastasis; some of the most aggressive of all cancers. Advancing progress in this field towards ultimately improving outcomes for our patients is therefore critical.

As is the case for many other tumor types, evolving heterogeneity is among one of the major challenges that are currently hampering our efforts aimed at more effectively treating brain cancers. We focus on genomic heterogeneity at the level of genomic alterations.

Tumors are composed of a mosaic of cell subclones that differ in their genomic alterations. Our group explores the genomic diversity present in glioblastoma and analyzes intratumor genomic heterogeneity as it evolves over time in response to therapy.

We are designing tools to monitor evolving genomic heterogeneity and studying the use of liquid biopsies for brain cancer through the study of circulating cell free tumor DNA in the cerebrospinal fluid from patients.

We are dedicated to tackling the genomic evolution of cancer head-on, and in so doing have recently succeeded in revealing the molecular history of anaplastic thryroid and papillary thyroid cancers, showing that both these tumor types are largely divergent. They should therefore be managed differently at the clinical level.

We are as equally committed to furthering insights into the role of the tumor microenvironment which, in the case of brain cancers, assumes a crucial role in cancer progression. Advancing discovery into the tumor microenvironment might be a way of combating cancer independently of its heterogeneity. By eliminating the niche where tumors reside and thrive should help us to develop more effective anti-cancer compounds. In this context, we have reported that the cytokine LIF assumes an essential role in the tumor microenvironment and is consequently a promising therapeutic target.

PI paper pick

Martínez-Ricarte F, Mayor R, Martínez-Sáez E, Rubio-Pérez C, Pineda E, Cordero E, Cicuéndez M, Poca MA, López-Bigas N, Ramon y Cajal S, Vieito M, Carles J, Tabernero J, Vivancos A, Gallego S, Graus F, Sahuquillo J, Seoane J. Molecular diagnosis of diffuse gliomas through sequencing of cell-free circulating tumour DNA from cerebrospinal fluid. *Clin Cancer Res.* 2018 Jun 15;24(12):2812-2819.

Capdevila J, Mayor R, Mancuso FF, Iglesias C, Caratù G, Matos I, Zafón C, Hernando J, Petit A, Nuciforo P, Cameselle-Teijeiro JM, Álvarez 4, Recio JA, Tabernero J, Matias-Guiu X, Vivancos A, Seoane J. Early evolutionary divergence between papillary and anaplastic thyroid cancers. *Ann Oncol.* 2018 June 1; 29(6): 1454–1460.

Seoane J, Capdevila J. The right compound for the right target: tackling RET. *Ann Oncol.* 2018 Aug 1; 29(8):1623 -1625.

Yates LR, Seoane J, Le Tourneau C, Siu LL, Marais R, Michiels S, Soria JC, Campbell P, Normanno N, Scarpa A, Reis-Filho J, Rodon J, Swanton C, Andre F. The European Society of Medical Oncology (ESMO) Precision Medicine Glossary. *Ann Oncol.* 2018; 29(1):30-35.

GROWTH FACTORS GROUP

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Daniel Fernandeo Pilco
Marina Polo

Strategic goals

- Develop novel therapeutic strategies against HER2-positive tumors and identify mechanisms of resistance to current therapies.
- Preclinical characterization of T cell-based therapies to treat HER2 positive tumors.
- Characterization of the role of premature senescence in breast cancer progression and treatment.
- Evaluate the activity of novel anti-cancer therapies in our panels of breast and pancreatic cancer patient-derived xenograft (PDX) models.

Highlights

- We have generated and validated a novel bispecific antibody for the treatment of breast cancer.
- Our group has characterized novel biomarkers and mechanisms of resistance against anti-HER2 therapies in breast cancer
- We have further developed our platform of patient-derived models for immuno-oncology.

Figure

A bispecific antibody against p95HER2 guides cells of the immune system to malignant cells. Pink cells represent healthy breast epithelial cells, brown cells represent malignant cells. Only malignant cells express p95HER2 (in blue), which is recognized by the p95HER2 bispecific antibody which, in turn, guide lymphocytes form the immune system of the patients (blue cells), against the tumor cells.

Summary

During 2018, our research line on novel immune therapies against breast cancer crystalized in the generation of a novel anti-tumor drug. It is currently clear that the immune system can recognize tumors as foreign entities that should be eliminated. One of the most promising strategies to boost the anti-tumor immune response is establishing physical contact between immune and malignant cells that facilitate the killing of the latter by the former.

In order to promote this contact, an anchoring factor in the malignant cell is required. Unfortunately, there are very few anchoring factors in malignant cells that are not present in normal cells. Due to this scarcity, novel therapies have been developed using anchors present at relatively low levels in normal cells.

These efforts have largely failed because these low levels triggered an immune response against normal tissues. This year, our group showed that a protein, p95HER2, is an anchor that is only present in certain breast and gastric tumors and is completely absent in normal tissues. We went on to generate an antibody that binds to p95HER2 and to a component of lymphocytes, directing them against cancer cells (Rius Ruiz I. *Sci Transl Med.* 2018). This antibody, known as p95HER2-TCB, showed a remarkable anti-tumor effect with no apparent side effects in normal cells.

Our expanding platform of breast and pancreatic cancer patient-derived experimental models, allowed us to establish and develop several important collaborations and partnerships with various national and international groups.

Working with colleagues at the Imperial College in London (UK), our models facilitated the characterization of novel factors controlling the secretory machinery of senescent cells (Georgilis et al. *Cancer Cell.* 2018). Our models were also instrumental to unveiling novel factors regulating the dormancy of breast cancers (Gawrzak et al. *Nat Cell Biol.* 2018), and the response of HER2-positive tumors to targeted therapies (Floros et al. *Proc Natl Acad Sci.* 2018).

We have also collaborated with VHIO's Experimental Therapeutics Group (page 44), headed by Violeta Serra, alongside Cesar Serrano, Medical *Oncologist* and Clinical Investigator of my own group, to reveal the progression of gastrointestinal tumors (Serrano-Candelas et al.; Serrano et al.; *Molec Oncol.* 2018, *Oncologist.* 2018, respectively.) In addition, we have worked with VHIO's Tumor Biomarkers Group (page 54), headed by Josep Villanueva to characterize the role of an intracellular factor secreted by triple negative breast cancers (Méndez et al. *Clin Cancer Res.* 2018).

In 2018, our highly collaborative approach to research has led to our participation in several large-scale projects funded by the EU Horizon 2020 Research and Innovation Programme.

The first is entitled *EurOPDX Distributed Infrastructure for Research on patient-derived cancer Xenografts* (EDIReX) - see page 18. Launched at the 2018 AACR annual meeting in Chicago, it will seek to provide a cutting-edge distributed research infrastructure comprised of 6 nodes, for free transnational access to PDX resources for academic and industrial cancer researchers.

The second; *Advancing a Precision Medicine Paradigm in metastatic Colorectal Cancer: Systems based patient stratification solutions* (COLOSSUS) see page 18, is powered by 14 partners who combine their respective expertise to more precisely define molecular subclasses of colorectal cancer (CRC), match and measure novel therapies according to the specificities of each identified subtype. Our group will focus on developing humanized mouse models for this particular project.

Other recognitions include received from the Spanish Association Against Cancer (AECC), as well as the Breast Cancer Research Foundation (BCRF). We are extremely grateful to these two major supporters for their continued backing and belief in our research programs against cancer.

This year two members of our group, Veronica Rodilla and Enrique J. Arenas, were awarded the highly sought after *Stop Fuga de Cerebros* and *Juan de la Cierva* fellowships. Congratulations as well to Junjie Zhang, who defended his PhD on *Mechanisms of resistance to T-DM1 in HER2 positive breast cancers.*

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 network, for which I am proud to serve as Scientific Director, is comprised of several of the most important cancer research groups across Spain, including three from VHIO.

PI paper pick

Rius Ruiz I, Vicario R, Morancho B, Bernadó Morales C, Arenas EJ, Herter S, Freimoser-Grundschober A, Somandin J, Sam J, Ast O, Barriocanal ÁM, Luque A, Escorihuela M, Varela I, Cuartas I, Nuciforo P, Fasani R, Peg V2, Rubio I, Cortés J, Serra V, Escriva-de-Romani S, Sperinde J, Chenna A, Huang W, Winslow J, Albanell J, Seoane J, Scaltriti M, Baselga J, Tabernero J, Umana P, Bacac M3, Saura C, Klein C, Arribas J. p95HER2-T Cell Bispecific Antibody for Breast Cancer Treatment. *Sci Transl Med.* 2018 Oct 3;10(461).

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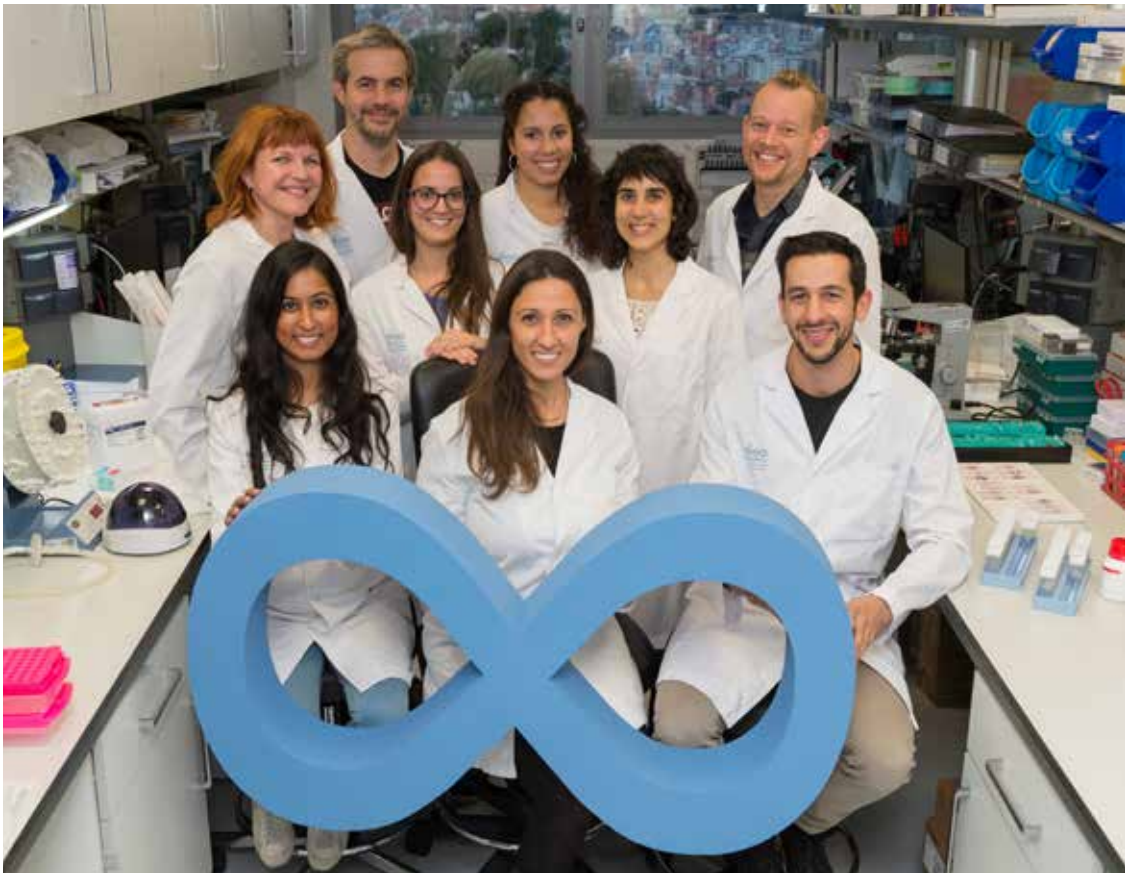
Georgilis A, Klotz S, Hanley CJ, Herranz N, Weirich B, Morancho B, Leote AC, D'Artista L, Gallage S, Seehawer M, Carroll T, Dharmalingam G, Wee KB, Mellone M, Pombo J, Heide D, Guccione E, Arribas J, Barbosa-Morais NL, Heikenwalder M, Thomas GJ, Zender L, Gil J. PTBP1-Mediated Alternative Splicing Regulates the Inflammatory Secretome and the Pro-tumorigenic Effects of Senescent Cells. *Cancer Cell.* 2018 Jul 9;34(1):85-102.

Gawrzak S, Rinaldi L, Gregorio S, Arenas EJ, Salvador F, Urosevic J, Figueras-Puig C, Rojo F, Del Barco Barrantes I, Cejalvo JM, Palafox M, Guiu M, Berenguer-Llergo A, Symeonidi A, Bellmunt A, Kalafatovic D, Arnal-Estapé A, Fernández E, Müllauer B, Groeneveld R, Slobodnyuk K, Stephan-Otto Attolini C, Saura C, Arribas J, Cortes J, Rovira A, Muñoz M, Lluch A, Serra V, Albanell J, Prat A, Nebreda AR, Benitah SA, Gomis RR. MSK1 regulates luminal cell differentiation and metastatic dormancy in ER+ breast cancer. *Nat Cell Biol.* 2018 Aug;20(8):990.

MOUSE MODELS OF CANCER THERAPIES



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Erika Serrano del Pozo

Fulbright Scholar
Jessica Lee Chambers

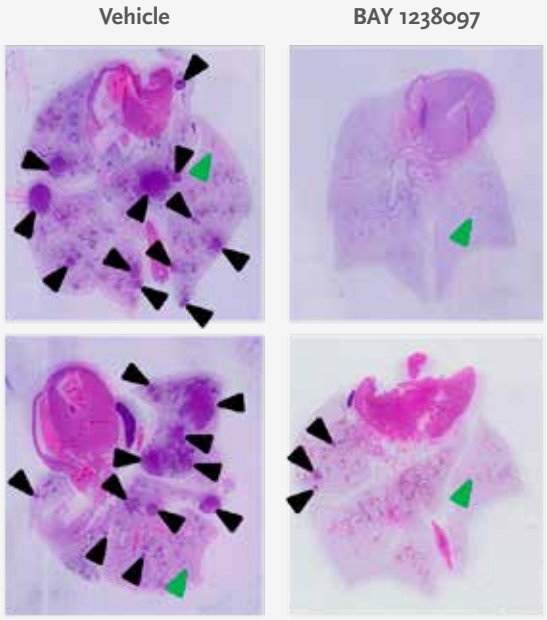
Strategic goals

- Validation of new Omomyc-based cell penetrating peptides for cancer therapy.
- Preclinical validation of novel anti-Myc therapies in breast, brain, lung, neuroblastoma, melanoma, colorectal cancer and multiple myeloma.
- Define the role of Myc in cancer-associated immune tolerance.
- Elucidate the role of the Myc network in Max-defective Gastrointestinal stromal tumors (GISTs), Small-Cell Lung Cancer (SCLC) and Pheochromocytomas (PCC).

Highlights

- Toni Jauset González, formerly a Graduate Student in this group and now a Research Scientist at Peptomyc S.L., was awarded his PhD for a project entitled: *Inhibiting Myc in cancer using Omomyc*. Congratulations Toni!
- As part of the U.S. Department of Education's international exchange program, the Soucek lab has been hosting a Fulbright Scholar, Jessica Chambers.
- Thanks to a collaboration with Pierre Lavigne, Nicolas Gévry and Martin Lepage at the University of Sherbrooke, Québec (Canada), Laura Soucek was the co-recipient of a Canadian Institutes of Health Research Grant. Title: *Development of cancer therapies targeting Myc with cell penetrating b-HLH-LZ domains.*
- Laura received the EIT (European Institute of Innovation and Technology) Public Award 2018 (selected among 38 nominees across Europe.
- Peptomyc received a *Catapult* Award from EIT (European Institute of Innovation and Technology) Health and the *Start Up Slam* Award for the most innovative start-up at Biofit 2018.

Figure



Treatment with BAY 1238097 reduces tumor burden in genetic mouse models of NSCLC. Therapeutic impact of BAY 1238097 after 4 weeks of treatment compared to vehicle treated mice. Representative images of H&E-stained sections of lungs from vehicle (left panels) and BAY 1238097 treated samples (right panels) are shown. Black arrows indicate tumors and green arrows indicate normal tissue. Adapted from (1).

(1) Jauset T, Masso-Valles D, Martinez-Martin S, Beaulieu ME, Foradada L, Fiorentino FP, et al. BET inhibition is an effective approach against KRAS-driven PDAC and NSCLC. *Oncotarget.* 2018;9(27):18734-46.

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 by publishing in journals of prestige (Jauset et al. *Oncotarget.* 2018., and Casacuberta-Serra & Soucek, *Transl Cancer Res.* 2018).

This year the lab has also had the privilege of hosting a Fulbright Scholar (as part of the U.S. Department of Education's International Exchange Program), Jessica Chambers, who graduated from Princeton University.

PI paper pick

Jauset T, Massó-Vallés D, Martínez-Martín S, Beaulieu ME, Foradada L, Fiorentino FP, Yokota J, Haendler B, Siegel S, Whitfield JR, Soucek L. BET inhibition is an effective approach against KRAS-driven PDAC and NSCLC. *Oncotarget.* 2018 Apr 10;9(27):18734-18746.

STEM CELLS & CANCER GROUP

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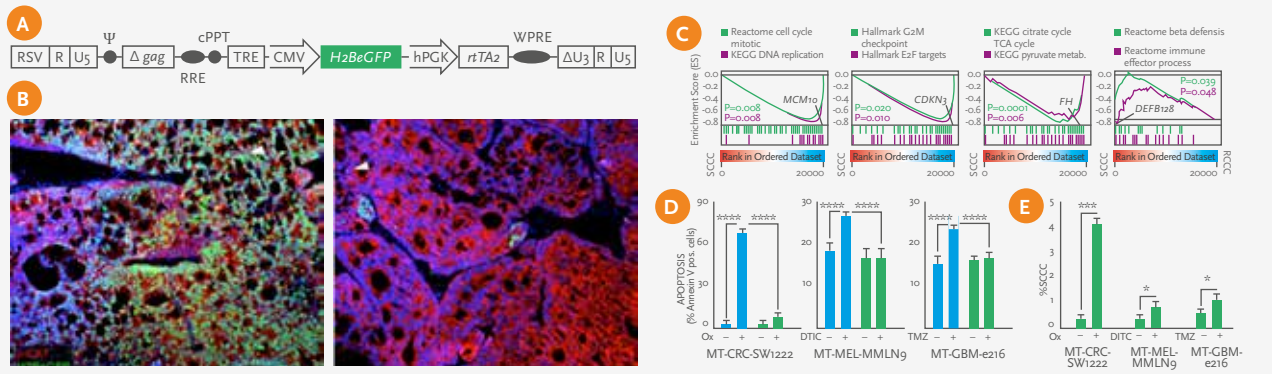
Strategic goals

- Describe the molecular circuitry ruling cancer cell dormancy that is responsible for drug-resistance, tumor recurrence and disease relapse.
- Develop new small drug modulators of cancer cell dormancy as a novel therapy against advanced refractory cancer.
- Validate biomarkers to detect dormant tumor cells to predict drug resistance and the risk of relapse in different types of solid tumors.
- Understand the molecular determinants of response to new targeted-drugs blocking EGFR, Wnt/ beta-catenin or Notch pathways and immune checkpoint inhibitors.
- Expand our collection of PDX models and start working on those derived from other tumor types.

Highlights

- We have identified the molecular mechanisms governing the delicate link between stemness and quiescence in chemoresistant cancer cells. Many genes and proteins playing a central role in this process are epigenetic chromatin remodelers or transcription factors. Their activity could potentially be inhibited as a new therapeutic approach to eliminating slow-cycling cancer-initiating cells. These molecular mechanisms are found in several solid tumors (CRC, breast, lung, melanoma, glioblastoma).
- The identification of a biomarker and a drug target to pinpoint and eliminate slow-cycling cancer-initiating cells. Both could become essential tools in improving patient survival and reducing disease relapse.
- We have developed the first small drug lead compounds to pharmacologically modulate cancer cell dormancy.
- Our group has accumulated evidence on the efficacy and mechanisms of action of a novel generation of Wnt/ beta-catenin inhibitors against CRC and identified biomarkers to predict response.

Figure



Characterization of slow-cycling cancer cells (SCCCs). **(A)** Diagram of the lentivirus structure for the DOX inducible expression of H2BeGFP. **(B)** Tumor xenografts labelled for SCCC upon a pulse-chase treatment of mice with DOX. Arrowhead indicates SCCC. Scale bar: 100μm. **(C)** Gene set enrichment analysis (GSEA) plots showing enrichment of the indicated gene sets from all integrated cancer models. P values by 1-way ANOVA. **(D)** Plots representing the level of apoptosis in slow-cycling (SCCC, green bars) versus rapid-cycling (RCCC, blue bars) cells derived from colorectal, glioblastoma or melanoma tumors upon treatment with indicated chemotherapy. OX, oxaliplatin; DTIC, light-activated dacarbazine; TMZ, temozolomide. 1-way ANOVA. (E) Enrichment of SCCC upon treatment with chemotherapy in the same tumor types. 2-tail Student's t-test. **(D, E)** Data are represented as mean ± SEM. *P≤0.05; ***P≤0.001; ****P≤0.0001.

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.

We have discovered that a core circuit of epigenetic and transcription factors govern cancer cell dormancy. Cells in this latent state seed chemoresistance responsible of future metastases and disease recurrence in patients suffering from various types of solid tumors. TET2 is one of these master epigenetic enzymes controlling the survival of dormant tumor cells (DTC).

Its product, 5hmC, is found accumulated in tumors of patients with higher risk of relapse after initially effective treatment with chemotherapy. Our most recent results demonstrate the relevance of TET2 as a new drug target for the future treatment of advanced refractory cancer patients.

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 inhibitors conferred by beta-catenin in colorectal cancer. This is of great relevance since many patients in clinical studies do not respond to these anti-cancer therapies, and no molecular explanation behind this resistance had previously been described.

Our findings will facilitate the more precise selection of treatment sensitive patients based on the expression of particular biomarkers predicting response to therapy. 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 novel agents in pre-clinical models of colorectal cancer with patient-derived xenograft (PDX) models.

This marks an important milestone within our 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 cancer medicines that could consequently become robust biomarkers for the selection of 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.

Our collaboration with the Vall d'Hebron University Hospital's Medical Oncology Department, led by VHIO's Director, Josep Tabernero, as well as partnerships with pharmaceutical companies will accelerate the application of our findings in the clinic and hopefully revert the long-stalled scenario of therapies against CRC.

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 now generating PDX models, evaluating mechanisms of drug action, treatment resistance and sensitivity to novel therapeutic strategies tested in clinical trials.

PI paper pick

Puig I, Tenbaum SP, Chicote I, Arqués O, Martínez-Quintanilla J, Cuesta-Borrás E, Ramírez L, Gonzalo P, Soto A, Aguilar S, Eguizabal C, Caratù G, Prat A, Argilés G, Landolfi S, Casanovas O, Serra V, Villanueva A, Arroyo AG, Terracciano L, Nuciforo P, Seoane J, Recio JA, Vivancos A, Dienstmann R, Tabernero J, Palmer HG. TET2 controls chemoresistant slow-cycling cancer cell survival and tumor recurrence. *J Clin Invest.* 2018 Aug 31;128(9):3887-3905.

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TUMOR BIOMARKERS GROUP

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Gabriel Tamayo

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 published the first paper uncovering a new role for HMGA1 in the tumor invasion of breast cancer cells. Our findings suggest that HMGA1 could be a new drug target for Triple-Negative Breast Cancer.
- The functional validation of non-classical secreted proteins in breast cancer experimental models is bringing us closer to propose new candidate drug targets and tumor biomarkers for breast cancer.

Figure

The cover of the December 15 issue of *Clinical Cancer Research* shows an invasive front of a breast tumor derived from an orthotropic xenograft of the MDA231i cells. The image shows how HMGA1 expression (green) is enriched in the invasive front of the tumor. Cytokeratin (red) is used to stain human epithelial cells, and Hoechst to counterstain the nuclei.

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 aim 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 belief, our recent efforts within the context of therapeutics and tumor invasion have led us to hypothesize that the characterization of non-classical protein secretion could lead to the development of novel anti-cancer therapies.

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.

PI paper pick

Méndez O, Peg V, Salvans C, Pujals M, Fernández Y, Abasolo I, Pérez J, Matres A, Valeri M, Gregori J, Villarreal L, Schwartz S Jr, Ramon Y Cajal S, Tabernero J, Cortés J, Arribas J, Villanueva J. Extracellular HMGA1 Promotes Tumor Invasion and Metastasis in Triple-Negative Breast Cancer. *Clin Cancer Res.* 2018 Dec 15;24(24):6367-6382


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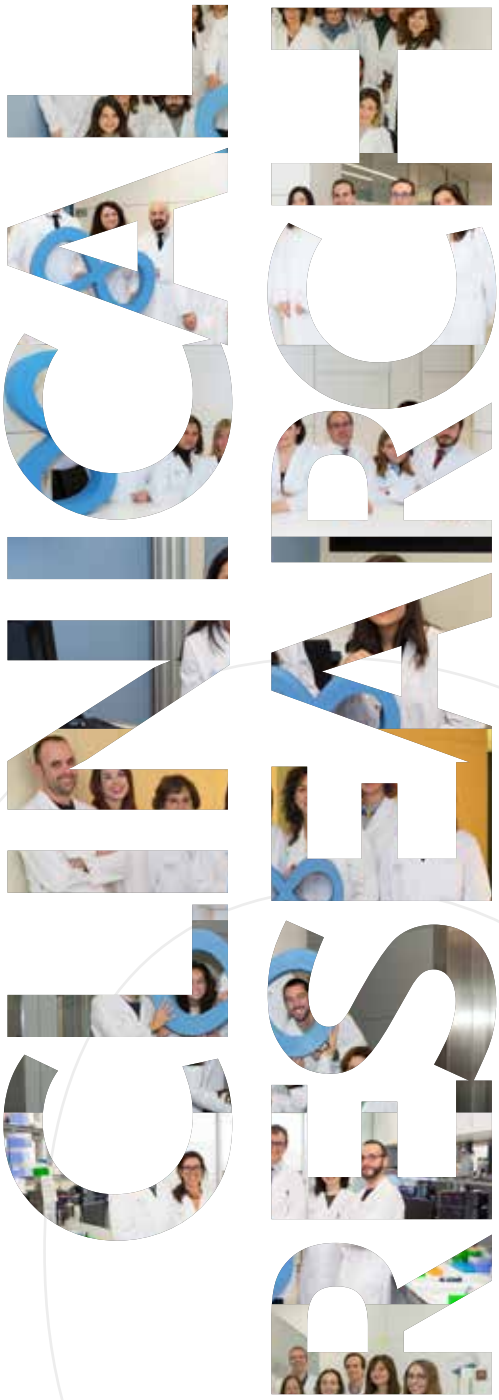

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JOSEP TABERNERO

From the Program Director

VHIO's multidisciplinary and translational approach to team science tightly connects its cancer scientists with our clinical investigators. From the very outset, this model has enabled our program to spearhead cooperative preclinical, early phase studies aimed at developing novel anti-cancer therapies, as well as new or redefined prognostic/diagnostic tools and techniques to better detect disease, track progression and more accurately predict response to treatments.

We pioneer novel study design including Baskets and first-in-human trials. Concerning the former, our Basket of Baskets (BoB) two-stage clinical study, endorsed by the Cancer Core Europe (CCE) Consortium and designed by our researchers at VHIO's Research Unit for Molecular Therapy of Cancer (UITM) "la Caixa" (page 100), directed by Elena Garralda, also PI of our Early Clinical Drug Development Group (page 64), is now underway.

Ringing in a pioneering approach in the design of these studies, BoB promises a more flexible and adaptive model in order to significantly accelerate patients' access to an array of novel therapeutics. Its multi-modularity within the same trial, using common diagnostic and screening tools, will facilitate the assessment of alterations at the same time, as well as the efficacy of different agents, either as monotherapy or in combination. Several baskets/modules and different drugs will therefore co-exist with a single molecular screening, which will optimize patient stratification and enrolment.

Also reflecting our expertise in basket design, a first-in-human study (Subbiah et al. *Cancer Discov.* 2018), assessed the efficacy of novel *RET* inhibitor, BLU-667, against RET-driven cancers medullary thyroid cancer (MTC), and non-small cell lung cancer (NSCLC).

Spearhead by Vivec Subbiah, University of Texas MD Anderson Cancer Center (Houston, USA), co-authors including VHIO's Elena Garralda, reported a durable clinical responses in patients with *RET*-altered tumors and clinically validated BLU-667 as a more precise and potent therapeutic avenue. Importantly, this paper was also selected for *Cancer Discovery*'s *In This Issue* feature.

Also making the headlines this year, results from the SUMMIT basket trial (Hyman et al. *Nature.* 2018), evaluating neratinib in HER2/3 cancers, were reported by David M. Hyman and colleagues at the Memorial Sloan Kettering Cancer Center–MSKCC (New York, USA), in collaboration with other groups including VHIO's Breast Cancer & Melanoma Group (page 62), directed by Cristina Saura.

Raising the bar in genome-driven oncology by demonstrating how a single clinical study can advance insights into the biological dependencies in human cancers, it also revealed that response to neratinib is driven by the characteristics of both tumor type and genomic variant.

First authored by Adriana Sanchez-Danés, *Université Libre de Bruxelles* (Brussels, Belgium), in partnership with investigators including Eva Muñoz-Couselo, Medical Oncologist and Clinical Investigator of our Breast Cancer & Melanoma Group, a study (Sánchez-Danés et al. *Nature.* 2018), showed that a slow-cycling tumor population expressing LGR5 renders cells resistant to therapy leading to disease relapse in basal cell carcinoma (BCC); the most frequent form of skin cancer.

Not only does this research represent an important advance in unmasking the drivers of recurrence in patients with BCC, it also proposes a promising new treatment combination of vismodegib with Wnt inhibitors.

Findings from a multi-center and ctDNA-guided phase II trial (Montagut et al. *JAMA Oncol.* 2018), assessed the efficacy of a novel antibody combination, Sym004, in patients suffering from refractory metastatic colorectal cancer with acquired resistance to anti-EGFR therapy.

Co-led by myself and Clara Montagut, Hospital del Mar (Barcelona), in collaboration with clinical investigators of my own Gastrointestinal & Endocrine Tumors Group (PI, Teresa Macarulla, page 68), including Guillem Argilés, results evidenced that while Sym004 effectively targeted EGFR ECD-mutated cells leading to their decrease observed in ctDNA, this treatment approach did not show improved overall survival.

While these results prove negative, this study nonetheless prompts a prospective clinical validation of this approach in a molecularly defined subgroup of patients as we seek to more precisely match this targeted therapy to those patients who would most likely benefit.

My next two Clinical Program paper picks were published in *The New England Journal of Medicine*. Firstly, promising results from a phase II trial (Gandhi et al. *N Engl J Med.* 2018), led by Leena Gandhi, NYU Perlmutter Cancer Center (New York, USA), and co-first authored by Enriqueta Felip, PI of our Thoracic Tumors & Head and Neck Cancer Group (page 84), reported that treatment with pembrolizumab in combination with chemotherapy led to higher response rates and longer progression-free survival in patients with metastatic non-small-cell lung cancer (NSCLC), than with chemotherapy alone.

Results from the phase III SOLO-I multi-center study (Morre et al. *N Engl J Med.* 2018) directed by Kathleen Moore, Stephenson Cancer Center (Oklahoma, USA), co-authored by VHIO's Ana Oaknin, PI of our Gynecological Malignancies Group (page 72), were presented during a Presidential Symposium at the 2018 ESMO Congress (19-23 October, Munich, Germany), and published in parallel.

Heralded as potentially practice changing, data showed that treatment with olaparib maintenance therapy resulted in an extension of progression-free survival by 3 years in over half of the patients with newly diagnosed advanced ovarian cancer. Findings also showed that this new strategy reduced the risk of disease progression by 70%.

As a reference in driving 'big' data-derived insights as well as cancer subtyping to better steer treatment decisions, VHIO joined forces as participant in the American Association for Cancer Research's (AACR) Project GENIE: *Genomics Evidence Neoplasia Information Exchange.* Led by Rodrigo Dienstmann, PI of our Oncology Data Science (ODysSey) Group (page 76), VHIO is the only GENIE member to-date from Spain.

We also continue to pioneer open access online tools for the in-depth, accelerated interpretation of cancer genomes. As an example, a recent study (Tamborero et al. *Genome Med.* 2018), led by ICREA Professor Nuria Lopez-Bigas Institute for Research in Biomedicine (IRB, Barcelona), co-authored by Rodrigo Dienstmann and Ana Vivancos (PI, VHIO's Cancer Genomics Group, page 90), described the Cancer Genome Interpreter (CGI). This novel resource represents an important step in providing the scientific community with access to this data in a consolidated and user-friendly way.

Speaking of platforms, designed to simplify and standardize choices for the selection of targeted cancer therapies, the European Society for Medical Oncology's (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT), launched this year (Mateo J et al. *Ann Oncol.* 2018).

Led by Joaquin Mateo, PI of our Prostate Cancer Translational Research Group (page 78), this new tumor DNA scale classes alterations according to their relevance as markers for the selection of patients matched to targeted treatments, based on robust clinical evidence.

From the very outset, VHIO is also dedicated to advancing personalized medicine in oncology through various international consortia and networks of excellence (pages 123-127).

2018 celebrated the launch of the European Commission Horizon 2020-supported project directed by Annette Byrne, Royal College of Surgeons in Ireland (RSCI, Dublin), powered by 14 partners, including VHIO: COLOSSUS– *Advancing a Precision Medicine Paradigm in metastatic Colorectal Cancer: Systems based patient stratification solutions* (see page 18). Scientifically co-led by Rodrigo Dienstmann, alongside Annette Byrne and Jochen Prehn, the COLOSSUS proposal ranked first among the other 200 European projects that were submitted under the H2020 Personalized Medicine Call for *New Concepts in Patient Stratification.*

Last but not least, I am proud to highlight just some of the many recognitions of our research in 2018. At home, Elena Élez, Medical Oncologist and Clinical Investigator of our Gastrointestinal & Endocrine Tumors Group, was awarded by the Catalan Institute of Health (ICS) for her important contributions in biomarker development and advancing targeted therapies against colorectal cancer.

One of this year's Gilead Sciences' Fellowships in Biomedical Research was presented to VHIO's Experimental Hematology Group, directed by Francesc Bosch (page 66). This fellowship will fuel their research into the tumor immune microenvironment in diffuse large B-cell lymphoma for the development of immunotherapeutic strategies that target the immune biology of individual patients.

At international level, Raquel Perez-Lopez, PI of our Radiomics Group (page 82), received a Prostate Cancer Foundation (PCF) Young Investigator Award. These grants support early career scientists with unique approaches and pioneering research ideas against prostate cancer.

Under the category of Clinical Medicine, I am truly honoured to be included in Clarivate Analytics' annual Global Highly Cited Researchers List for 2018. Among the total of 497 named professionals in this specific grouping, a total of ten are from Spain, with five of these listees working in Catalonia.

Joining me in the listings from VHIO, under the newly launched cross-field category recognizing researchers who have been identified as having an exceptional performance based on high impact papers in several fields over the last decade, is Enriqueta Felip, PI of our Thoracic Tumors & Head and Neck Cancer Group (page 84).

For more details and updates on some of the other accolades granted to VHIO faculty across our other programs and groups this year please see pages 19-22.

Importantly, my selection of the clinical science that has shaped our year offers a mere snapshot of the many contributions driven by VHIO talents. These accomplishments have only been possible in collaboration with other VHIO groups, and thanks to strong cross-border partnerships.

Together, we can and will do better.

APPLIED GENETICS OF METASTATIC CANCER GROUP

Junior Principal Investigator
Leticia De Mattos-Arruda

Post-Doctoral Fellow
Samuel Gonçalves

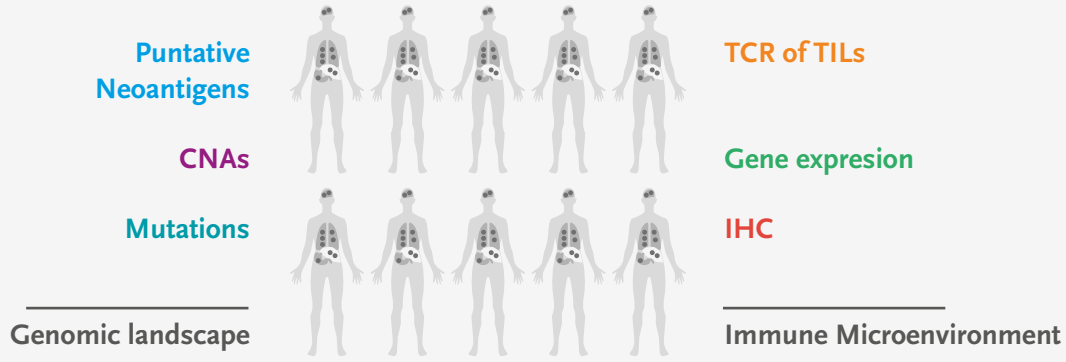
Strategic goals

- Integrate multi-omics data to better understand genomic heterogeneity and the role of the immune system within and between tumors - longitudinally and in warm autopsy specimens - from patients with metastatic breast cancers, particularly from the integrated genomic and immune landscapes of lethal metastatic breast cancer (MET-breast-Landscapes) VHIO-Cancer Research Cambridge Institute collaborative database, and a prospective cohort of patients' samples.
- Identify biomarkers to more precisely guide the selection of anti-cancer therapies based on the specificities of individual patients.

Highlights

- 2018 ASCO Meeting, 01-05 July, Chicago (USA). Clinical Science Symposium, oral presentation: *The integrated landscape of genome and immune landscape of lethal metastatic breast cancer.*
- 2018 EACR Meeting, 29 June-03 July, Amsterdam (The Netherlands). Oral presentation: *The heterogeneous landscape of genome and immune landscape of lethal metastatic breast cancer.*
- Leticia was appointed as ESMO faculty member for the ESMO Translational Research and Precision Medicine Working Group, 2019-2020.
- She also became member (2018-2019), of the Editorial Board of *ESMO Open: Cancer Horizons,* ESMO's open access online oncology journal for her expertise in breast cancer field.
- Leticia has participated as an ad hoc breast cancer Expert Member on the Advisory Board of the European Medicines Agency (EMA).

Figure



Multi-dimensional molecular profiling of warm autopsied metastatic breast cancer patients.

Summary

VHIO's Applied Genetics of Metastatic Cancer Group, headed 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 multiregional biopsies from autopsy proven patients and liquid biopsies to more effectively track disease and render targeted therapies more precise.

By applying genomics, transcriptomics, *in silico* bioinformatics and the 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 translate insights provided by in silico approaches in tumor tissues into the identification of non-invasive biomarkers that can be subsequently deployed for monitoring response to therapy and the early detection of disease progression.

VHIO's Applied Genetics of Metastatic Cancer Group has extensive collaborations with leading international investigators in cancer genomics, immuno-oncology and molecular pathology.

PI paper pick

Balic M, Dedic N, De Mattos-Arruda L, *et al.* News from ASCO 2018. *Breast Care (Basel)* 2018; 13: 298-302.

Preusser M, De Mattos-Arruda L, Thill M, Criscitiello C, Bartsch R, Ruhstaller T, de Azambuja E, Zielinski CC. CDK4/6 inhibitors in the treatment of patients with breast cancer: summary of a multidisciplinary round-table discussion. *ESMO Open.* 2018 Aug 20;3(5):e000368.

De Mattos-Arruda L, Ng CKY, Piscuoglio S, Gonzalez-Cao M, Lim RS, De Filippo MR, Fusco N, Schultheis AM, Ortiz C, Viteri S, Arias A, Macedo GS, Oliveira M, Gomez P, Teixidó C, Nuciforo P, Peg V, Saura C, Ramon Y Cajal S, Casas FT, Weigelt B, Cortes J, Seoane J, Reis-Filho JS. Genetic heterogeneity and actionable mutations in HER2-positive primary breast cancers and their brain metastases. *Oncotarget.* 2018 Apr 17;9(29):20617-20630.

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BREAST CANCER & MELANOMA GROUP

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Associate Translational Investigator
Javier Cortés

Medical Oncologists and Clinical Fellows
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Miriam Arumi
Analía Azaro
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Meritxell Bellet
Marta Capelan
Cristina Cruz
Santiago Escrivà
Laia Garrigós
Patricia Gómez
Eva Muñoz
Mafalda Oliveira
Carolina Ortiz
Raul Sánchez
Esther Zamora

Clinical Nurse Specialist
Anna Suñol

Nutritionist
Nuria Durán

Strategic goals

- Optimize therapies by introducting novel anti-cancer therapies and adding rational combinations to combat mechanisms of resistance.
- Incorporate proteomics, genomics, and circulating tumor cell platforms in translational research to advance insights into tumor biology.
- Apply preclinical and 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 treatment outcomes.

Highlights

- We have published practice-changing data in 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 most active in metastatic and adjuvant studies. Each clinical trial is tightly connected with VHIO's translational research lines.

Summary

Our Breast Cancer & Melanoma Group is one of the most active and renowned in Europe. In 2018 we published a total of 41 papers with a cumulative Impact Factor (IF) of 535,055.

In the **Breast Cancer Unit** we are not only committed to participating in clinical trials, but also lead several of them. We apply translational data to help both guide and accelerate the clinical development of anti-cancer medicines. Our main 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 designed to overcome mechanisms of resistance with agents such as the targeted therapy, palbociclib, or immune-based treatments. In collaboration with VHIO's Growth Factors Group (page 48), directed 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 (page 44), headed by Violeta Serra, we have developed several patient-derived xenograft (PDX) models to advance insights into the mechanisms of resistance that may be overcome through treatment with PI3K, CDK4/6 inhibitors, immunotherapies and different PARP inhibitors. In hormone receptor-positive disease we are leading different studies using some of the most novel compounds including CDK4/6 inhibitors, SERDs and BET inhibitors.

New compounds: an emerging family of anti-cancer therapies 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, DS-8201, IMMU-132, and very soon with PF-C0541001.

cfDNA: In collaboration with VHIO's Cancer Genomics Group (page 90), led by Ana Vivancos, we have analyzed concordance of genomic alterations in synchronous tumor biopsies and ctDNA from metastatic breast cancer patients. In the challenging scenario of early disease, we are now leading various projects aimed at improving outcomes for these patients.

Our **Melanoma Group** is led by Eva Muñoz. She has participated actively in several phase I, II and III trials focused on melanoma and other skin tumors to study various emerging therapies for the treatment of metastatic and adjuvant disease.

The group has consolidated its own research program incorporating clinical investigators and cancer researchers at VHIO. They focus on resistance to standard therapies by conducing purely translational research centered on melanoma and basocelular carcinoma resistance acquisition and progression. Their efforts also centre on opening new therapeutic avenues and identifying biomarkers for a more precise treatment selection matched to the specificities of our patients.

PI paper pick

Hyman DM, Piha-Paul SA, Won H, Rodon J, Saura C, Shapiro GI, Juric D, Quinn DI, Moreno V, Doger B, Mayer IA, Boni V, Calvo E, Loi S, Lockhart AC, Erinjeri JP, Scaltriti M, Ulaner GA, Patel J, Tang J, Beer H, Selcuklu SD, Hanrahan AJ, Bouvier N, Melcer M, Murali R, Schram AM, Smyth LM, Jhaveri K, Li BT, Drilon A, Harding JJ, Iyer G, Taylor BS, Berger MF, Cutler RE Jr, Xu F, Butturini A, Eli LD, Mann G, Farrell C, Lalani AS, Bryce RP, Arteaga CL, Meric-Bernstam F, Baselga J, Solit DB. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. *Nature.* 2018 Feb 8;554(7691):189-194.

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EARLY CLINICAL DRUG DEVELOPMENT GROUP

Director of Clinical Research at VHIO
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Principal Investigator, Early Clinical Drug Development Group, Director, UITM
Elena Garralda

Associate Investigators
Senior Consultants
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Joan Carles
Enriqueta Felip
Elena Garralda
Teresa Macarulla
Ana Mazaltob Oaknin
Cristina Saura
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Guillermo Argiles
Analia Beatriz Azaro
Meritxell Bellet
Irene Braña
Ana Callejo
Jaume Capdevila
Marta Capelan
Susana Maria Cedres
Cristina Cruz
Maria Elena Elez
Santiago Ignacio Escriva De Romani
Lorena Fariñas
Itziar Gardeazabal
Patricia Gomez
Macarena Gonzalez
Jorge Hernando
Cinta Hierro
Juan Jesus Martin
Alexandre Martinez
Joaquin Mateo
Ignacio Matos
Rafael Morales
Nuria Mulet
Eva Muñoz
Alejandro Navarro
Alba Noguerido
Nuria Pardo
Maria Coral Perez
Jordi Remon
Victor Rodriguez
Omar Saavedra
Cesar Serrano
Cristina Suarez
Claudia Valverde
Helena Verdaguer
Maria Vieito
Esther Zamora

Clinical Nurse Specialist
Patricia Prieto

Strategic goals

- Early clinical 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 (RET, NTRKK) such as immunotherapeutics including agents targeting LAG3, TIGIT, OX40,CD40, IDO, arginase inhibitors and bispecifics (such as CEA-TCB, FAP-4IBB, FAP- IL2v).
- We have carried out several 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, IDO, Arginase inhibitors, 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, RET; amplifications in HER2, AKT 1, 2, and 3, FGFR1, MET, NOTCH1-4, rearrangements of NTRK1-3 ROS1, ALK, BRAF, RSPO2/3, RET 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 xenograft (PDX) models and the analysis of next-generation sequencing of multiple tissue samples and circulating-free tumor DNA. In collaboration with VHIO's Ana Vivancos (page 90), Violeta Serra (page 44), Héctor G. Palmer (page 52), and Joaquín Arribas (page 48), 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).
- We also received funding to perform the 360° Resistance in ImmunoOncology Project (360RIO) for the evaluation of mechanisms of resistance to immune therapy in collaboration with Novartis. We perform NGS, RNA seq, TIL expansion and TC line establishment from tumor biopsies in patients receiving immune therapy.
- We are seeking to characterize hyperprogressive disease with immunotherapy and are involved in a collaboration with the EORTC to advance insights into this phenomenon.
- We have are working with Rodrigo Toledo, Translational Investigator of VHIO's Gastrointestinal & Endocrine Tumors Group (PI Teresa Macarulla, page 68), to monitor the cfDNA of patients receiving immunotherapy and characterize the clonal evolution of these patients (this project received a Swiss Bridge Award during 2018 - see page 20).
- We are working with Raquel Perez-Lopez, PI of our Radiomics Group (page 82) to identify a radiomic signature for the prediction of response to immunotherapy.

Summary

We focus on proof-of-concept and proof-of-mechanism trials with targeted therapies, with particular 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 Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 100), 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 (page 92) and Cancer Genomics Groups (page 90), 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 (CCE) 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 UITM, have led the initiation of our Basket of Baskets (BoB) trial. This academic study, endorsed by Cancer Core Europe, integrates 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.

Our Early Drug Development Group and 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 (508 patients enrolled in phase I and basket studies in 2018), the portfolio of different trials available (161 phase I trials including 22 basket studies in 2018), 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, including this year's Partner of Choice Initiative with MedInmune, and collaborate closely with other clinical research organizations and academic centers of excellence, as well as companies dedicated to advancing personalized cancer medicine and care.

PI paper pick

Ochoa de Olza M, Oliva M, Hierro C, Matos I, Martin-Liberal J, Garralda E. Early-drug development in the era of immuno-oncology: are we ready to face the challenges? *Ann Oncol.* 2018 Aug 1;29(8):1727-1740.

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EXPERIMENTAL HEMATOLOGY GROUP

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Pau Abrisqueta

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Diana Reyes
Marcelo Ribeiro

Technicians
Magdalena Munuera
Lluis Puigdefàbregas

Hematologists/Lab Specialists
Pere Barba
David Benéitez
Adoración Blanco
Laura Gallur
Merche Gironella
Gloria Iacoboni
Andrés López
Ana Marín
Margarita Ortega
Carlos Palacio
Gaël Roué
Olga Salamero
Amparo Santamaría
Silvia Saumell
Bárbara Tazón
David Valcárcel

Strategic goals

We translate preclinical findings into clinical benefit by developing early phase clinical trials and defining new prognostic and predictive factors.

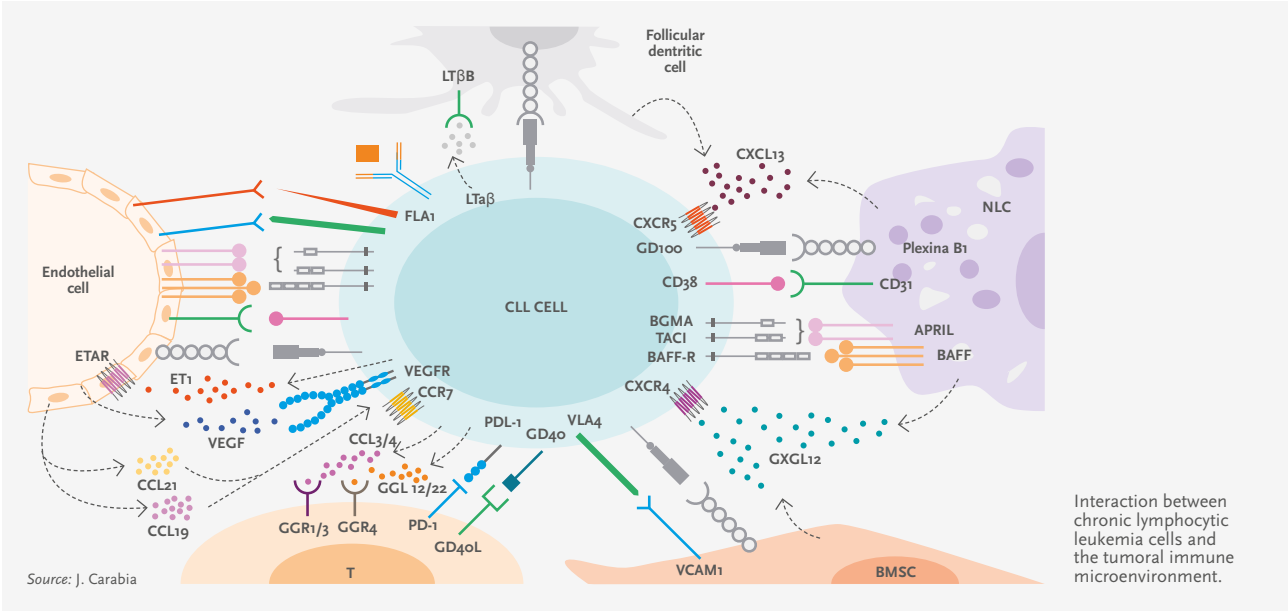
Main research lines currently focus on:

- 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 patient-derived xenograft (PDX) models.
- Defining new biomarkers for a more rational and precise treatment of patients.

Highlights

- Our new Advanced Therapy Unit is currently under construction for patients receiving CAR-T and other advanced cellular therapies. We expect that this new facility will open in June 2019.
- We have joined imCORE–immunotherapy Centres of Research Excellence Network, launched by Roche back in 2016. We will lead a project entitled: *Optimization of immunotherapy design in CD20+ lymphomas and in AML by developing humanized mice models and characterizing malignant cells-immune system crosstalk.*
- We have led, and participated in, several clinical projects aimed at improving the non-chemotherapy-based treatment of patients diagnosed with CLL.

Figure



Source: J. Carabia

Interaction between chronic lymphocytic leukemia cells and the tumoral immune microenvironment.

Summary

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 factors related to disease progression, response, and resistance to novel therapies. Our group is particularly interested in the cross-talk between malignant and healthy immune cells.

Current projects include the study of chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL), myelodysplastic syndromes (MDS), and acute myeloid leukemia (AML).

We also explore new therapeutic avenues for patients diagnosed with hematological malignancies through the ex-vivo and in-vivo assessment of response to novel treatments, considering the microenvironmental protection that neoplastic cells find 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 preclinical model of CLL that recapitulates the favorable microenvironment using primary tumoral cells from patients. In addition we are studying the role of novel targeted therapies in primary samples from patients with AML.

We have also developed a PDX model for central nervous system lymphomas. 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 clinical trials for CNS lymphoma patients. We are currently expanding our PDX models to systemic NHL.

Our group is 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. We are 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, this year we have started treating patients diagnosed with NHL with CAR-T cells and are currently initiating an ambitious project aimed at unraveling determinants of response and mechanisms of resistance.

PI paper pick

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GASTROINTESTINAL & ENDOCRINE TUMORS GROUP

Director
Josep Tabernero

Principal Investigator
Teresa Macarulla

Medical Oncologists and Clinical Fellows
Maria Alsina
Guillermo Argilés
Alvaro Javier Arroyo
Elvira Buxo
Jaume Capdevila
José Luis Cuadra
Maria Elena Élez
Jorge Hernando
Nuria Mulet
Alba Noguerido
Helena Verdaguer

Clinical Nurse Specialist
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Translational Investigator
Rodrigo A. Toledo

Translational Graduate Student
Carlota Arenillas

Translational Technician
Ana Belen Moreno

Masters Student
Giulia Martini

Bioinformatician
Pol Cusco

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, leadership and development 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 including our Tumor Biomarkers (page 54), Cancer Genomics (page 90), and Stem Cells & Cancer (page 52) 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 (IIT) as well as participation in several studies developed in collaboration with national and international cooperative groups, as well as academic collaborative studies including research focused on *Fusobacterium* and colorectal cancer; Cancer Research UK's Grand Challenge: *Bugs, Guts, Cells. Understanding the colorectal cancer microbiome: implications for diagnosis and therapy*.
- Participation in ongoing EU Horizon 2020-funded projects and consortia including MoTriColor and IntraColor, as Principal Investigators. 2018 celebrated the launch of a new Horizon 2020-supported consortium: COLOSSUS–*Advancing a Precision Medicine Paradigm in metastatic Colorectal Cancer: Systems based patient stratification solutions* (page 18).
- Our group is partner of many national and international consortia and networks including Cancer Core Europe (CCE), WIN, and the CIBERONC.
- Elena Élez was awarded by the Catalan Institute of Health (ICS) in recognition for her contributions to the colorectal cancer field (page 20).

Summary

In 2018, 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 (CCE), the WIN Consortium, and EU FP7/H2020 supported studies.

Concerning CCE, our Basket of Baskets (BoB) two-stage clinical study, designed by our researchers at VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 100) directed by Elena Garralda, also PI of our Early Clinical Drug Development Group (page 64), is now underway. Its multi-modularity within the same trial, using common diagnostic and screening tools, allows the assessment of alterations at the same time, as well as the efficacy of different agents, either as monotherapy or in combination. Several baskets/modules and different drugs will therefore co-exist with a single molecular screening, which will optimize patient stratification and enrolment.

Launched this year, we are also participating in the Horizon 2020-supported consortium directed by Annette Byrne, Royal College of Surgeons in Ireland (RSCI, Dublin): COLOSSUS–*Advancing a Precision Medicine Paradigm in metastatic Colorectal Cancer: Systems based patient stratification solutions* (page 18). This collaboration is scientifically co-led by Rodrigo Dienstmann, PI of our Oncology Data Science (ODysSey) Group (page 76). Importantly, the COLOSSUS proposal ranked first among the other 200 European projects that were submitted under the H2020 Personalized Medicine Call for *New Concepts in Patient Stratification*.

Another promising collaboration involves Cancer Research UK's (CRUK) Grand Challenge. Specifically, a multi-center undertaking including our group, was selected in the second round of this Call to improve treatment responses in colorectal cancer by manipulating the composition and status of the microbiota.

Led by Matthew Meyerson, Dana-Farber Cancer Institute and Harvard Medical School (Boston, USA), we seek to collectively advance insights into the CRC microbiome and how it influences disease initiation, progression and response to therapy in order to apply this knowledge to targeting the CRC-associated microbiota towards improved outcomes for patients. Watch this space!

Reflected by publications in some of the most prestigious scientific titles in 2018, our group has both directed and collaborated in important studies, just some of which include:

Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Tabernero et al. *Lancet Oncol.* 2018 Oct;19(10):1372-1384.

First authored by VHIO's Director and our group's Josep Tabernero, in partnership with Yoon-Koo Kang, University of Ulsan College of Medicine (Seoul, South Korea), this multi-center phase III clinical trial assessed the efficacy and safety of combining targeted therapies pertuzumab and trastuzumab with chemotherapy to treat patients suffering from either HER2-positive metastatic gastric or gastro-oesophagael junction cancer.

Importantly, while this approach did not significantly improve overall survival in either patient populations compared with placebo, these findings call for further research to identify improved first-line treatments for these tumor types as well as more precisely match patients with HER2-driven cancers to dual HER2-targeted therapy.

3 versus 6 months of adjuvant oxaliplatin-fluoropyrimidine combination therapy for colorectal cancer (SCOT): an international, randomised, phase 3, non-inferiority trial. Iveson et al. *Lancet Oncol.* 2018 Apr;19(4):562-578.

Directed by Tim J. Iveson, Southampton University Hospital NHS Foundation Trust (UK), and co-authored by Josep Tabernero, this international phase III non-inferiority trial sought to establish how 3 months' treatment with oxaliplatin-containing chemotherapy, would compare with the usual 6 months' adjuvant treatment for patients suffering from high-risk stage II and III colorectal cancer.

Not only did the results show this approach to be non-inferior to 6 months of the same therapy in these patients, but it was also associated with reduced toxicity and improved quality of life, pointing at a potential new standard of care.

Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Shitara et al. *Lancet Oncol.* 2018 Nov;19(11):1437-1448.

Carried out across 110 academic hospitals spanning 1 countries, this phase III, co-led by Kohei Shitara, National Cancer Center Hospital East (Chiba, Japan), and our Director, and Josep Tabernero, sought to confirm results from a phase II trial reporting efficacy and safety in the treatment of patients with advanced gastric cancer in Japan, in a global population.

This novel combination significantly improved overall survival and was well tolerated in this pretreated population of patients. These promising results could propose a new therapeutic avenue and thus provide fresh hope for these patients.

Efficacy of Symo04 in Patients With Metastatic Colorectal Cancer With Acquired Resistance to Anti-EGFR Therapy and Molecularly Selected by Circulating Tumor DNA Analyses A Phase 2 Randomized Clinical Trial. Montagut et al. *JAMA Oncol.* 2018 Apr 12;4(4): e175245.

This phase II study, that was directed by Clara Montagut, Hospital del Mar (Barcelona), and alongside Josep, evidenced that while Symo04 effectively targeted EGFR ECD-mutated cells leading to their decrease observed in ctDNA, this treatment approach did not show improved overall survival.

While these results are negative, they do however prompt a prospective clinical validation of this approach in a molecularly defined subgroup of patients as we seek to more precisely match this targeted therapy to those patients who would most likely benefit.

Phase II Study of BGJ398 in Patients With FGFR-Altered Advanced Cholangiocarcinoma. Javle et al. *J Clin Oncol.* 2018 Jan 20;36(3):276-282.

Co-first authored by Teresa Macarulla, PI of our group, with study lead Milind Javle, University of Texas MD Anderson Cancer Center (Texas, USA), this phase II trial was developed based on preliminary clinical activity of first-in-class pan-FGFR kinase inhibitor, BGJ398, against FGFR-altered advanced cholangiocarcinoma in patients whose disease had progressed on prior treatment with chemotherapy.

Results confirmed the earlier phase II findings. Also showing promising antitumor activity, this study supports the further development of this inhibitor which could provide this highly selected patient population, for whom no current standard therapy exists, with new hope.

Nintedanib for the treatment of patients with refractory metastatic colorectal cancer (LUME-Colon1): a phase III, international, randomized, placebo-controlled study. Van Cutsem et al. *Ann Oncol.* 2018 Sep 1;29(9):1955-1963.

Led by Eric Van Cutsem, University Hospitals Gasthuisberg Leuven (Belgium), and Guillem Argilés, Medical Oncologist and Clinical Investigator of our group, this global phase III trial investigated the efficacy and safety of the targeted drug nintedanib for the treatment of patients with refractory metastatic colorectal cancer.

The results did not confirm the efficacy previously reported in early phase studies in patients with metastatic CRC. While this therapy was found to be well tolerated, it did not improve overall survival. A significant but modest increase in progression-free survival was observed.

Last but not least, and reflective of our group's excellence, Elena Élez, Medical Oncologist and Clinical Investigator, was awarded this year by the Catalan Institute of Health (ICS) for her important contributions in biomarker development and advancing targeted therapies against colorectal cancer (page 20).

PI paper pick

Tabernero J, Hoff PM, Shen L, Ohtsu A, Shah MA, Cheng K, Song C, Wu H, Eng-Wong J, Kim K, Kang YK. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. *Lancet Oncol.* 2018 Oct;19(10):1372-1384.

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GENITOURINARY, CNS TUMORS, SARCOMA & CANCER OF UNKNOWN PRIMARY SITE GROUP

Principal Investigator
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Medical Oncologists and Clinical Fellows
Macarena Gonzalez
Joaquin Mateo
Rafael Morales
Cesar Serrano
Cristina Suarez
Claudia Valverde
Maria Vieito

Clinical Nurse Specialist
Alexandre Sierra

Strategic goals

- Design and develop clinical trials covering all malignancies studied by our group. We seek 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 tools and techniques 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 in collaboration with researchers at the Vall d'Hebron Research Institute (VHIR).
- Expand our translational research platform for glioblastoma in collaboration with VHIO's Gene Expression & Cancer Group (page 46).
- Create a translational platform for kidney cancer and sarcomas and basic research in partnership with the Biomedical Research Institute of Bellvitge (IDIBELL).
- Develop our 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 (Immunotherapies in combination with PARP inhibitors or new hormonal therapies; different PARP inhibitors in second and third line treatment; chromatin modulators such as BET inhibitors), that have shown promise in improving outcomes for patients with prostate cancer.
- Other GU malignancies (renal and bladder): we are involved in clinical studies to validate 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 (antiangiogenics in kidney cancer) or chemotherapeutics (bladder cancer).
- Central Nervous System (CNS) tumors: we have developed additional clinical trials and set up 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.

Summary

Our group is dedicated to clinical and translational research and has extensive 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 2018 we consolidated our expert 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 that mainly focus on prostate cancer. We aim to extend these efforts to other tumor types including bladder and kidney cancer.

Over recent years, several developments have been reported in GU malignancies; in prostate, bladder, and kidney cancer. Immunotherapy (IO) is proving increasingly important in the treatment of bladder and kidney cancer in particular. As an example, IO is considered the standard treatment for second line therapy to treat the former, and has been shown as superior to antiangiogenic therapy for the therapeutic management of the latter. Our group has now observed that IO could be also be important for subgroups of patients with castration-resistant prostate cancer. We are currently participating in phase I studies to assess IO for the treatment of this patient population.

Importantly, we have participated in various clinical trials using checkpoint inhibitors in the adjuvant treatment bladder and kidney cancers with high risk of recurrence. Working closely with our Vall d'Hebron University Hospital's Urology Department and other experts in high risk tumors, we are currently running studies aimed at ultimately improving outcomes for patients with non-muscle- invasive bladder cancer.

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

This year we have expanded our translational research program in prostate cancer working alongside VHIO's Prostate Cancer Translational Research Group (see page 78), led by Principal Investigator Joaquin Mateo. We have performed more than 40 bone biopsies in our patients and aim to correlate blood samples with these tests. Our main focus centers on metastatic castration-resistant prostate cancer and we are working with Joaquin on one of his projects granted this year entitled: *Clinical Qualification of DNA Repair Defects as Biomarkers in Metastatic Prostate Cancer Using Integrated Genomics and Tissue-Based Functional Assays.* This research is supported by the US Department of Defense (DoD) Congressionally-Directed Medical Research Program

We have also initiated a collaboration with VHIO's Radiomics Group (PI: Raquel Perez-Lopez, see page 82), to analyze MRI changes in patients who start new hormonal treatments and correlate these with bone biopsies performed in parallel

This particular project, *iPROMET: a study for clinical validation of whole-body diffusion-weighed MRI as a response biomarker of bone metastases in patients with prostate cancer,* counts on the combined expertise of a urologist, radio-oncologist, radiologist and medical oncologist in order to establish a circuit for the systematic metastatic tissue acquisition from prostate cancer patients at our Hospital.

We have also expanded our avatar program for kidney cancer tumors in collaboration with IDIBELL and have now implanted more than 30 samples. Additionally, we continue to partner in REVOLUTION: *pREdiction of niVOLUmab acTION metastatic renal cancer patients: Treg function, tumoral access and NK interactions as predictive biomarkers of immunotherapy,* supported by TRANSCAN-2 ERA-NET, under the EU framework programme Horizon 2020.

In connectivity with other professionals in neurosurgery and radiation therapy, we lead and develop several multidisciplinary clinical studies and phase I trials in CNS tumors. Furthermore, it is thanks to a collaboration with our Gene Expression & Cancer Group (PI: Joan Seoane - page 46), that we are successfully developing VHIO's translational research platform for glioblastoma. We also work with other reference centers across Europe to develop a vaccine for patients with glioblastoma, and are now initiating our Phase I program. This research is supported by the European Commission's 7th Framework Programme of Research and Development. We have also received national funding to analyze cfDNA in blood and cephaloraquidic liquid for the analysis of primary CNS tumors and metastases.

We continue to work closely with the Spanish Sarcoma Group (GEIS) on 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).

Group member, César Serrano, who carried out a three-year fellowship at the Dana Farber Cancer Institute (Boston, USA), has established an independent line of experimental research on sarcomas. Notably, his translational studies have led to new treatment strategies against 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 pursue novel therapeutic strategies in GIST by leading and participating in phase I-II-III studies, as well as developing new therapies in partnership with other European referral centers.

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 2018 we welcomed two fellows from in and outside of Spain for three-month short stay visits.

PI paper pick

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GYNECOLOGICAL MALIGNANCIES GROUP

Principal Investigator
Ana Oaknin

Medical Oncologists and
Clinical Fellows
Lorena Fariñas
Victor Rodriguez

Strategic goals

- Determine the best treatment approaches against advanced gynecologic malignancies through optimally designed international clinical trials.
- Contribute to early drug development in gynecologic cancers.
- Expand our translational research program to advance precision medicine.

Highlights

- As a result of our group's clinical research of excellence, we continue to lead pivotal studies in gynecological malignancies which could change the standard of care.
  1. Our group has designed and is heading a new international phase III clinical trial in metastatic or recurrent cervical cancer with a novel regimen including immunotherapy towards improving the overall survival of this population of patients.
  2. Involvement in early clinical drug development contributing to the development of a novel check-point inhibitor in recurrent or metastatic endometrial cancer that may offer a new therapeutic avenue for our patients.
- Our collaboration with several international and cooperative groups of excellence further enables us to participate in leading clinical research projects.
- Ana Oaknin's Vice Presidency of the GEICO group. This appointment has led to our leadership of clinical research lines in gynecological tumors throughout Spain.
- The involvement of Ana Oaknin in ESMO's Educational Program for its next two annual Congresses further reinforces our position within Europe as a reference site.

Summary

We focus on clinical research in gynecological malignancies and the development of novel therapies against these tumors. Importantly, over recent 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 group has continued to drive important advances throughout 2018. Particularly noteworthy has been our involvement in the development of olaparib in newly diagnosed BRCA mutated ovarian cancer patients, dostarlimab in MSI-H to treat endometrial cancer, and atezolizumab against metastatic and recurrent cervical cancer.

Olaparib belongs to the family of novel cancer medicines known as PARP inhibitors (PARPi). This agent was previously approved by the FDA and EMA for patients with sensitive recurrent ovarian cancer harboring BRCA mutations. In 2013 we began to develop this agent for the treatment of newly diagnosed Stage III and IV BRCA carriers with ovarian cancer. We hypothesized that it might be effective as maintenance therapy following first line treatment, reduce the risk of recurrence for these high-risk patients, and lead to improved survival and cure rates.

Heralded as potentially practice-changing data, results from this study were presented during a Presidential Symposium at the 2018 Congress of the European Society for Medical Oncology (ESMO), 19-23 October (Munich, Germany). Showing that olaparib therapy dramatically extends progression-free survival in patients with advanced ovarian cancer and a BRCA1/2 mutation, the study was selected by ESMO for its media program, and was also timed to publish simulatenously as an open access Original Article in *The New England Journal of Medicine* (Moore et al. *N Engl J Med*. 2018).

The results of this research subsequently led to the FDA approval of olaparib in first line treatment, and we are currently awaiting approval from EMA. Importantly, as with the majority of our clinical research lines, this investigation - the SOLO-1 phase III multi center clinical trial - was carried out in close collaboration and connectivity with other reference research sites.

We are also dedicated to developing immunotherapeutics for patients with gynecologic tumors, and are involved in phase I-III studies to assess the efficacy and toxicity profile in a subgroup of gynecological tumors; endometrial cancer and cervical cancer. Therapeutic options for patients diagnosed with relapsed endometrial cancer are currently limited and we focus on a novel checkpoint inhibitor, dostarlimab (formely TSR-042). We have already shown exciting preliminary results which we also presented at ESMO Congress 2018, and envisage reporting our final results in early 2019. They may lead to the approval of a new therapeutic option for these patients.

As part of an international collaboration, we are also pioneering immunotherapy for patients with metastatic and/or recurrent cervical cancer. We are leading a new phase III trial - BEATcc trial (ClinicalTrials.gov Identifier: NCT03556839) - comparing the current standard of care with a novel regimen incorporating a checkpoint inhibitor. This study will recruit 404 patients across sites in the USA, Japan, and Europe, and could ultimately be practice-changing.

In addition, we are working on adoptive cell transfer of tumor infiltrating lymphocytes (TILs) that could offer a more effective treatment option for patients with cervical cancer. This method involves the recovery and ex vivo expansion of autologous antitumor lymphocytes that have infiltrated a tumor. TILs isolated from human cervical tumors and expanded ex vivo have shown antitumor activity. Preliminary data show great promise and VHIO will play an active role in developing this adoptive approach for the treatment of 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 as well as phase II trial Committees, 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 memberships and appointments enable us to develop new drugs and novel treatment approaches from the very outset, providing our patients with greater opportunity to hopefully benefit from these advances in cancer therapeutics.

As a renowned and leading group within the field, we are the reference site for the majority of regional hospitals and sites at the 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 therapeutic options for these patients.

Addtionally, we are members of multidisciplinary 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 improved treatment protocols and clinical guidelines to further advance clinical practice at our hospital.

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 Vall d'Hebron. The aim of this group is to exchange experiences, share expertise and collectively advance clinical research.

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 PI, Ana Oakinin, also serves as Chair of the Gynecological Cancers Track for the 2019 ESMO Congress, 27 September-01 October, Barcelona, Spain.

PI paper pick

Van Nieuwenhuysen E, Busschaert P, Neven P, Han SN, Moerman P, Liontos M, Papaspirou M, Kupryjanczyk J, Hogdall C, Hogdall E, Oaknin A, Garcia A, Mahner S, Trillsch F, Cibula D, Heitz F, Concin N, Speiser P, Salvesen H, Sehouli J, Lambrechts D, Vergote I. The genetic landscape of 87 ovarian germ cell tumors. *Gynecol Oncol*. 2018 Oct;151(1):61-68.

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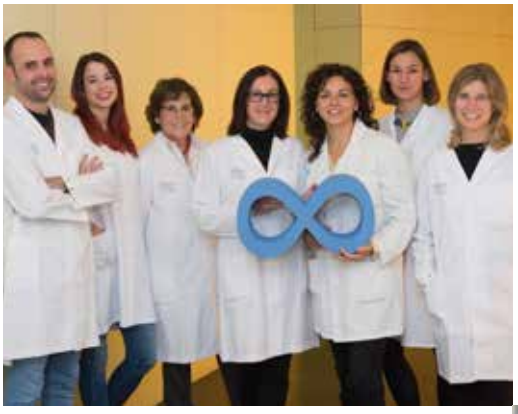
HEREDITARY CANCER GENETICS GROUP & ONCOGENETICS LAB



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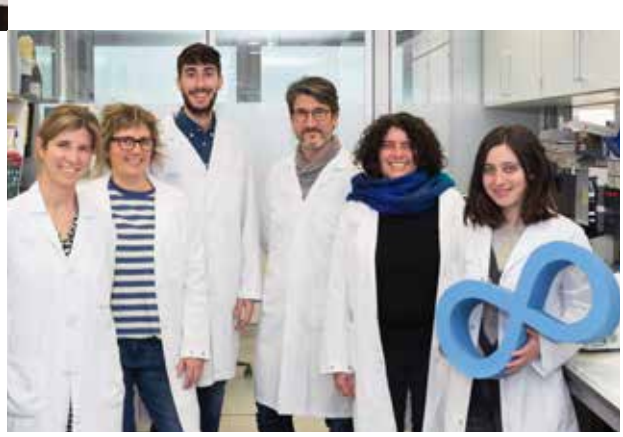


Strategic goals

- Clinical development of specific therapeutic strategies for tumors associated with *BRCA1/2* and homologous recombination repair deficient tumors.
- Testing new combinations of therapies for *BRCA1/2*-associated PDXs that have progressed to PARP inhibitors.
- Describe the yield of multigene panel testing in hereditary cancer syndromes and its impact on patient care.
- Investigate the psychological impact of hereditary cancer multiplex gene testing in our Spanish population.
- Reveal new breast/ovarian cancer susceptibility genes.
- Discover genetic variants in non-coding DNA regions of breast/ovarian cancer susceptibility genes that may confer an increased risk.
- Unveil the pathogenicity of variants of unknown significance in hereditary breast/ovarian cancer genes.
- Identify cellular and genomic biomarkers as predictors of late toxicity after radiotherapy.

Highlights

- Active participation in international phase II and phase III clinical trials with targeted therapies for *BRCA1/2*-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.
- Our group has provided data indicating that the accuracy, for splicing defect prediction of the most used *in silico* tools in molecular diagnosis of familial cancer, depends on whether the natural splicing sites are donors or acceptors.
- Our comprehensive characterization of *in vitro* splicing effect has enabled the clinical re-classification as pathogenic, of *BRCA2* c.7976+5G > T variant, that was previously classified as likely benign.
- Psychological study of the impact of undergoing cancer genetic testing.
- We collected radiotherapy toxicity clinical data of breast and lung cancer patients in the EC FP7-funded project REQUITE to validate predictive models of toxicity from radiotherapy.

Figures

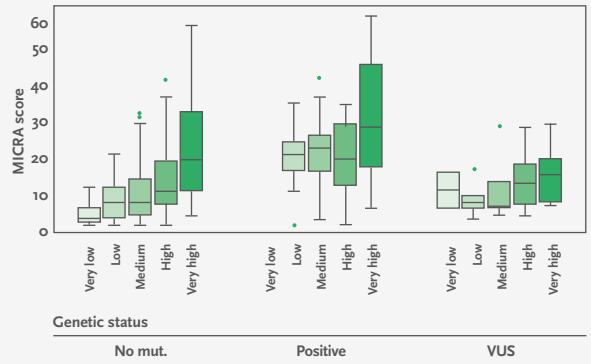
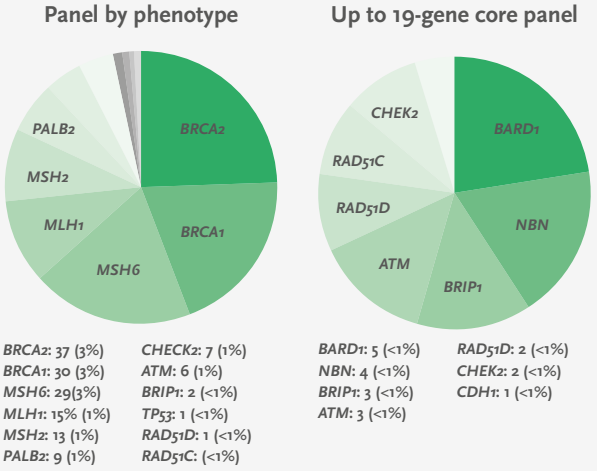


Figure 1: Impact of neuroticism score on psychological impact of germline genetic testing measured by MICRA scale.



BRCA2: 37 (3%)
BRCA1: 30 (3%)
MSH6: 29(3%)
MLH1: 15% (1%)
MSH2: 13 (1%)
PALB2: 9 (1%)
CHECK2: 7 (1%)
ATM: 6 (1%)
BRIP1: 2 (<1%)
TP53: 1 (<1%)
RAD51D: 1 (<1%)
RAD51C: (<1%)

BARD1: 5 (<1%)
NBN: 4 (<1%)
BRIP1: 3 (<1%)
ATM: 3 (<1%)
RAD51D: 2 (<1%)
CHEK2: 2 (<1%)
CDH1: 1 (<1%)

Figure 2: Prevalence of pathogenic variants in panel testing for hereditary cancer.

Summary

We are participating in the clinical development of PARPi in early *gBRCA1/2* breast cancer and new combinations in the advanced setting. The consolidation of our collaboration with VHIO's Experimental Therapeutics Group (page 44), led by Violeta Serra, has resulted in a large collection of *BRCA1/2*-associated patient-derived xenograft (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 functional biomarker for PARP inhibitor sensitivity that has been tested preclinically and in human samples, and we are now collecting samples for a larger clinical validation.

Our group has contributed to the field of genetic epidemiology of hereditary breast and ovarian cancer by identifying the prevalence and clinical actionability of new breast and ovarian cancer genes in our population. We have co-led a collaboration with the hereditary cancer program at the Catalan Institute of Oncology (ICO) to define the role of opportunistic testing of the *BRCA1/2* and mismatch repair genes in addition to phenotype-based panels for diagnosis of hereditary cancer.

We have tested a set of commonly used bioinformatics algorithms to predict aberrant gene splicing in familial cancer genes, and have shown that the performance of each specific predictor varies depending on whether the natural splicing sites are donors or acceptors. In addition, our research has led to the comprehensive splicing characterization of genetic variants, clinically unclassified, generating complex splicing profiles when located in regions linked to high levels of alternative splicing.

Our psychological study on the impact of multigene cancer panel testing spanning more than 200 centers across Spain, has been published and we have now finished recruiting more than 600 patients to analyze the predictive role of personality traits on the psychological impact of genetic test results.

Finally, we are also dedicated to investigating the heritability of radiotherapy-induced toxicity. Around half of all cancer patients receive radiotherapy and among 3-5% of them suffer from severe long-term side-effects. Current evidence suggests that radiosensitivity is a heritable trait. We have participated in the REQUITE European project aimed at identifying potential genetic and cellular markers for radiotherapy toxicity.

PI paper pick

Cruz C, Castroviejo-Bermejo M, Gutiérrez-Enríquez S, Llop-Guevara A, Ibrahim YH, Gris-Oliver A, Bonache S, Morancho B, Bruna A, Rueda OM, Lai Z, Polanska UM, Jones GN, Kristel P, de Bustos L, Guzman M, Rodríguez O, Grueso J, Montalban G, Caratú G, Mancuso F, Fasani R, Jiménez J, Howat WJ, Dougherty B, Vivancos A, Nuciforo P, Serres-Créixams X, Rubio IT, Oaknin A, Cadogan E, Barrett JC, Caldas C, Baselga J, Saura C, Cortés J, Arribas J, Jonkers J, Díez O, O'Connor MJ, Balmaña J, Serra V. RAD51 foci as a functional biomarker of homologous recombination repair and PARP inhibitor resistance in germline BRCA-mutated breast cancer. *Ann Oncol.* 2018 May 1;29(5):1203-1210.

Castroviejo-Bermejo M, Cruz C, Llop-Guevara A, Gutiérrez-Enríquez S, Ducy M, Ibrahim YH, Gris-Oliver A, Pellegrino B, Bruna A, Guzmán M, Rodríguez O, Grueso J, Bonache S, Moles-Fernández A, Villacampa G, Viaplana C, Gómez P, Vidal M, Peg V, Serres-Créixams X, Dellaire G, Simard J, Nuciforo P, Rubio IT, Dientsmann R, Barrett JC, Caldas C, Baselga J, Saura C, Cortés J, Déas O, Jonkers J, Masson JY, Cairo S, Judde JG, O'Connor MJ, Díez O, Balmaña J, Serra V.A RAD51 assay feasible in routine tumor samples calls PARP inhibitor response beyond BRCAmutation. *EMBO Mol Med.* 2018 Dec;10(12).

Bonache S, Esteban I, Moles-Fernández A, Tenés A, Duran-Lozano L, Montalban G, Bach V, Carrasco E, Gadea N, López-Fernández A, Torres-Esquius S, Mancuso F, Caratú G, Vivancos A, Tuset N, Balmaña J, Gutiérrez-Enríquez S, Diez O. Multigene panel testing beyond BRCA1/2 in breast/ovarian cancer Spanish families and clinical actionability of findings. *J Cancer Res Clin Oncol.* 2018 Dec;144(12):2495-2513.

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ONCOLOGY DATA SCIENCE (ODYSSEY) GROUP

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Guillermo Villacampa

Biomedical Engineer
Anna Pedrola

Data Curators
Raquel Comas
Fiorella Ruiz
Sara Torres
Cristina Viaplana

Molecular Prescreening Program
Susana Aguilar
Jenifer Gonzalez

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.

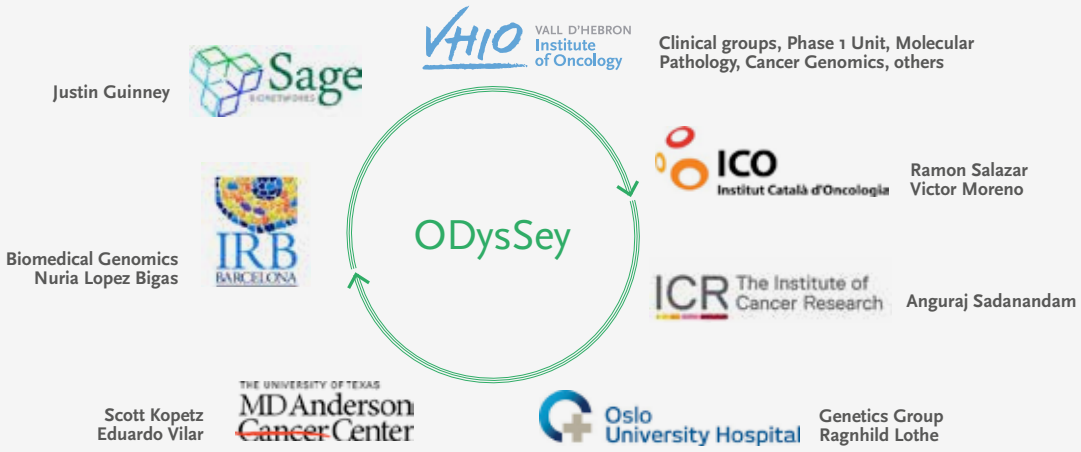
Promote evidence-based medicine:

- 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.
- Development of web tools to help clinicians match cancer biomarkers to approved and experimental therapies in clinical trials. Assist investigators in the design of molecularly-guided studies.

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 2018 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 genes, transcriptomic subtypes and microenvironment features on prognosis of colorectal cancer patients.
- Comprehensive bioinformatics analysis of the immune infiltrates of solid tumors that may help interpret the response to immunotherapies and guide the development of novel drug combination strategies.
- Definition of actionability frameworks to rank molecular alterations as targets for precision medicine in an effort to help all relevant stakeholders to prioritize patients for matched therapies.

Figure



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

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.

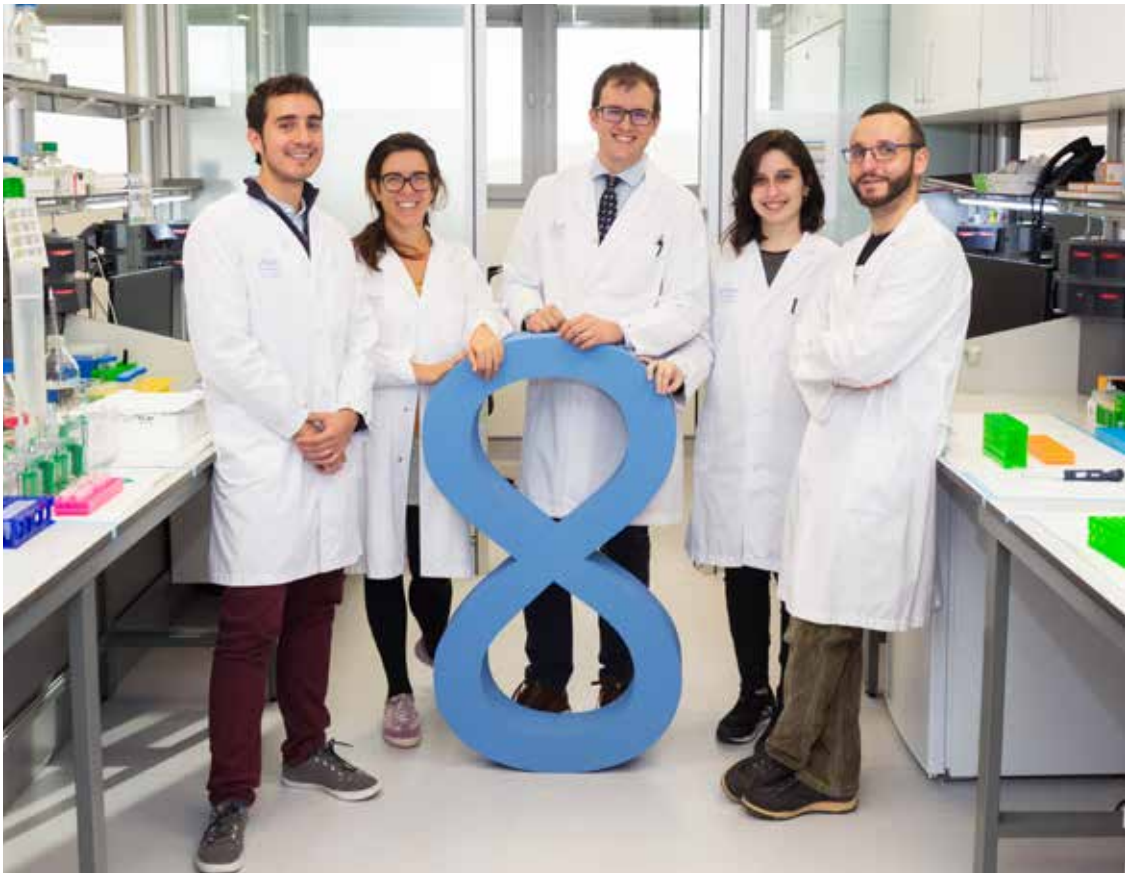
To explore real world evidence and big data, we design and maintain comprehensive clinical-molecular databases and provide statistical support to investigators interested in correlative analyses for hypothesis-generation and biomarker validation. We also provide standardized reports of next-generation 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.

PI paper pick

Remon J, Dienstmann R. Precision oncology: separating the wheat from the chaff. *ESMO Open*. 2018 Oct 30;3(6):e000446.

PROSTATE CANCER TRANSLATIONAL RESEARCH GROUP



Principal Investigator
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Gonzalo Hernandez

Technicians
Sara Arce
Teresa Casals

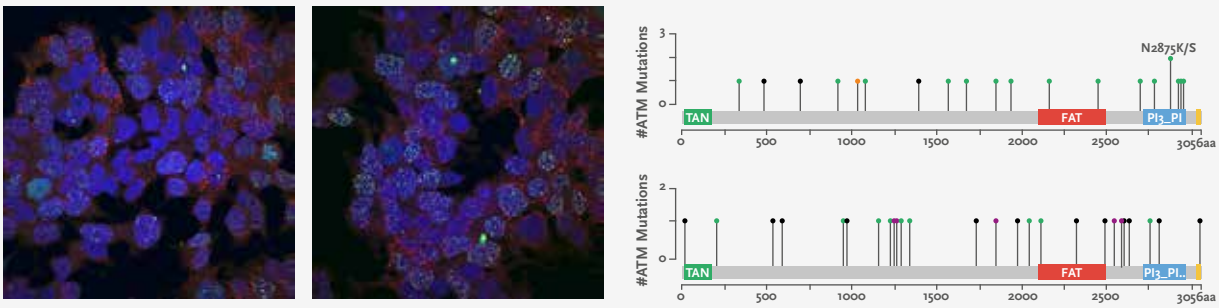
Strategic goals

- To establish 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.
- Optimize the combination of DNA repair-targeting drugs with androgen receptor inhibitors.
- Build a precision medicine core for prostate cancer patients treated at the Vall d'Hebron University Hospital (HUVH).

Highlights

- Our group, in collaboration with VHIO's Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site Group (page 70), led by Joan Carles, has initiated a study prospectively acquiring metastatic biopsies and longitudinal liquid biopsies from patients with prostate cancer treated at the Vall d'Hebron University Hospital (HUVH).
- We have completed a retrospective study of the impact on clinical outcomes of certain DNA repair mutations in prostate cancer.
- We have been awarded by both the US Department of Defense and the Spanish Ministry of Science and Innovation (FIS Program) to study genomic and transcriptomic signatures of metastatic prostate cancer.

Figure



We are interested in understanding the impact of different DNA damage repair defects in AR signalling and prostate cancer progression, with a particular focus in ATM gene alterations. In the left panels, multicolour immunofluorescence images show induction of DNA damage (gH2AX foci in green; induction of RAD51 foci in red indicating focus of HR repair) in DAPI-stained castration-resistant prostate cancer cell lines, after exposure to PARP inhibition (right) compared to basal conditions (left). On the right, location of mutations within the ATM gene identified in patients with loco-regional prostate cancer (top) and metastatic prostate cancer (bottom)

Summary

Over the last decade, we have witnessed a true revolution in the treatment of metastatic castration-resistant prostate cancer (mCRPC) which is an advanced and lethal form of prostate cancer. An improved understanding of its underlying biology has led to the development of compounds targeting the androgen signaling pathway and the immune system, as well as taxanes and radiopharmaceuticals.

Despite these advances in more effectively managing mCRPC, it remains a fatal condition resulting in significant morbidity and mortality worldwide. Arguably, the most critical need in drug development for CRPC is molecular treatment stratification, with the development of anti-cancer therapies in parallel with the identification of robust predictive biomarkers of response. Moreover, the introduction of these novel treatments has driven tumor evolution towards a change in the genomic landscape observed in patients with advanced disease.

Our group aims to improve outcomes for patients with mCRPC by delivering more personalized patient care based on predictive biomarkers of response, prioritizing the most beneficial anti-cancer medicines, and avoiding less effective treatments based on the specificities of each individual patient. We 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 allow us to study how we can deliver more precise cancer treatment and care. Some of these mutations have prognostic and predictive implications which are crucial in delivering on the promise of personalized medicine in oncology.

We use a range of tools (CRISPR gene editing, shRNA, siRNA and pharmacological inhibitors) to induce loss-of-function of key DNA repair genes in prostate cancer in-vitro models to establish how tumors adapt their DNA repair machinery, and how this is affected by modulation of oncogenic AR signaling.

Aiming at translating our findings into benefits for patients as rapidly as possible, we study the same genomic and transcriptomic signatures in biopsies from patients with metastatic prostate cancer. In parallel, we collect longitudinal liquid biopsies to study of how a tumor evolves during response and progression to targeted agents.

Our research focuses on optimal patient stratification strategies for clinical care, with particular emphasis on combining DNA repair targeting drugs with those inhibiting androgen signaling.

PI paper pick

Mateo J, Cheng HH, Beltran H, Dolling D, Xu W, Pritchard CC, Mossop H, Rescigno P, Perez-Lopez R, Sailer V, Kolinsky M, Balasopoulou A, Bertan C, Nanus DM, Tagawa ST, Thorne H, Montgomery B, Carreira S, Shahneen Sandhu S, Rubin MA, Nelson PS, de Bono JS.Clinical outcome of prostate cancer patients with germline DNA repair mutations: follow-up from an international study. *Eur Urol.* 2018 doi:10.1016/j.euro.2018.01.010

Mateo J, Chakravarty D, Dienstmann R, Jezdic S, Gonzalez-Perez A, Lopez-Bigas N, Ng CKY, Bedard PL, Tortora G, Douillard JY, Van Allen EM, Schultz N, Swanton C, André F, Pusztai L. A framework to rank genomic alterations as targets for cancer precision medicine: The ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol.* 2018 Sep 1;29(9):1895-1902.

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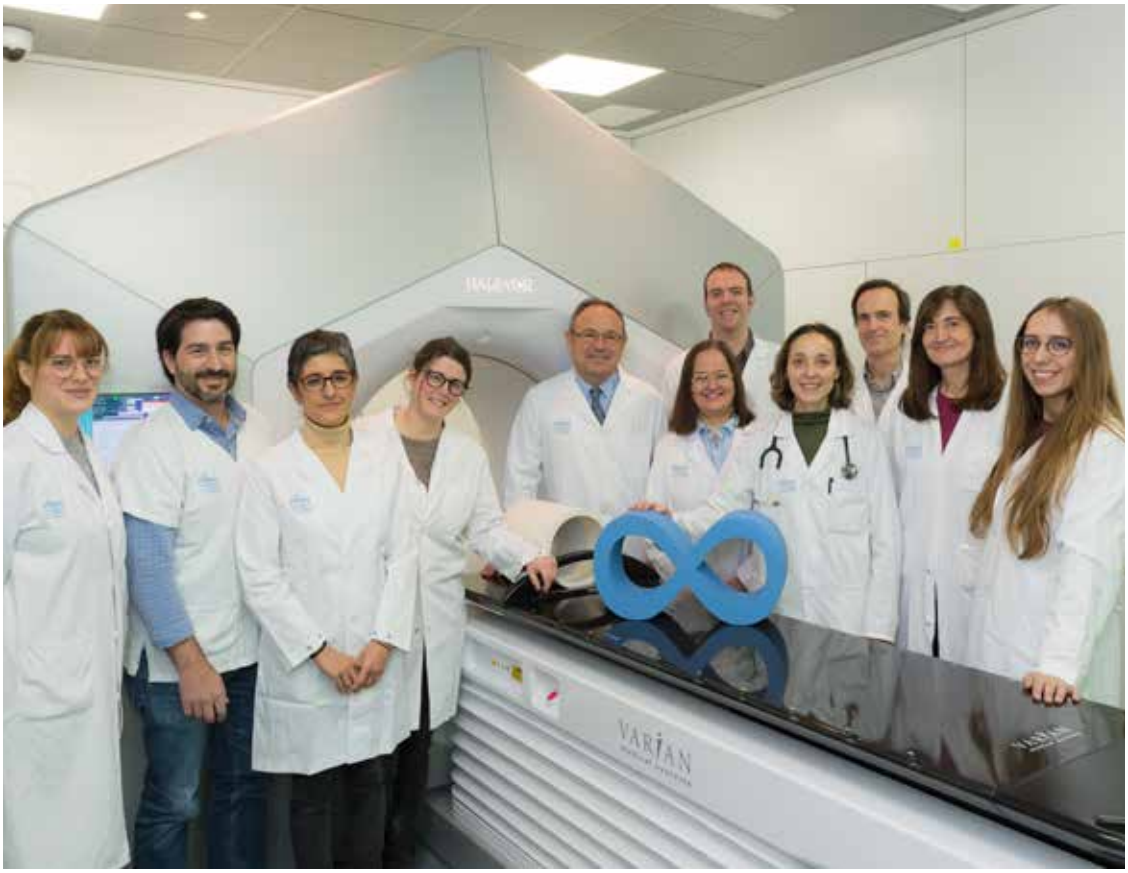
Boysen G, Rodrigues DN, Rescigno P, Seed G, Dolling D, Riisnaes R, Crespo M, Zafeiriou Z, Sumanasuriya S, Bianchini D, Hunt J, Moloney D, Perez-Lopez R, Tunariu N, Miranda S, Figueiredo I, Ferreira A, Christova R, Gil V, Aziz S, Bertan C, de Oliveira FM, Atkin M, Clarke M, Goodall J, Sharp A, MacDonald T, Rubin MA, Yuan W, Barbieri CE, Carreira S, Mateo J, de Bono JS. SPOP-Mutated/CHD1-Deleted Lethal Prostate Cancer and Abiraterone Sensitivity. *Clin Cancer Res.* 2018 Nov 15;24(22):5585-5593.

RADIATION ONCOLOGY GROUP



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Beatriz Gutierrez
Xavier Maldonado
Soraya Mico
Begoña Navalpotro
Monica Ramos
Victoria Reyes
Ramona Vergés

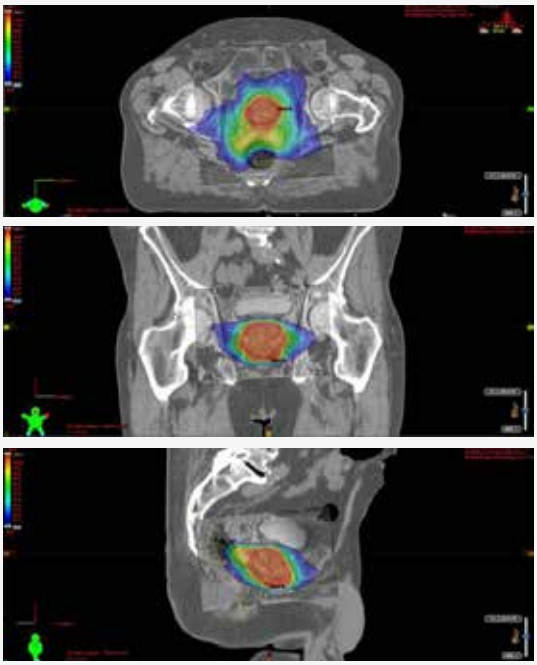
Strategic goals

- 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.
- The Adaptive and innovative Radiation Treatment FOR improving Cancer treatment outcomE (ARTFORCE) project began in the year 2013. Our group is the top patient recruiter in this collaboration.
- We have consolidated a dose escalation program using Image Guided RadioTherapy (IGRT) with fiducials.
- Clinical studies in the treatment of prostate cancer with enzalutamide, and in lung/liver metastases with atezolizumab immunotherapy.

Figure



Dose distribution in axial, sagittal and coronal images with MRI fusion of a patient with prostate cancer treated with the new Halcyon accelerator.

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 a stereotactic extracranial radiotherapy program in pancreatic and prostate cancers.
- The setting up of a 4D program for lung cancer.
- 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.

PI paper pick

Verges R, Giraldo A, Seoane A, Toral E, Ruiz MC, Pons A, Giralt J. Does ITV vaginal procedure ensure dosimetric coverage during IMRT of post-operative gynaecological tumours without instructions concerning rectal filling? *Rep Pract Oncol Radiother.* 2018 Mar-Apr;23(2):136-142.

Morote J, Comas I, Planas J, Maldonado X, Celma A, Placer J, Ferrer R, Carles J, Regis L. Serum Testosterone Levels in Prostate Cancer Patients Undergoing Luteinizing Hormone-Releasing Hormone Agonist Therapy. *Clin Genitourin Cancer.* 2018 Apr;16(2):e491-e496.

Ajithkumar T, Horan G, Padovani L, Thorp N, Timmermann B, Alapetite C, Gandola L, Ramos M, Van Beek K, Christiaens M, Lassen-Ramshad Y, Magelssen H, Nilsson K, Saran F, Rombi B, Kortmann R, Janssens GO; SIOPE BTG Radiotherapy Group. SIOPE – Brain tumor group consensus guideline on craniospinal target volume delineation for high-precision radiotherapy. *Radiother Oncol.* 2018 Aug;128(2):192-197.

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. 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. *Radiother Oncol.* 2018 Jan;126(1):3-24.

RADIOMICS GROUP

Principal Investigator
Raquel Perez-Lopez

Technicians
Alonso Garcia
Marta Ligero

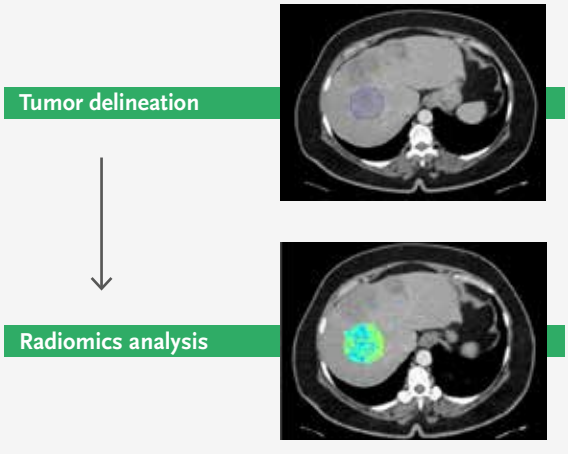
Strategic goals

- 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 group was awarded with an Institute of Health Carlos III (ISCIII) Program grant and our PI, Raquel Perez-Lopez, received a Young Investigator Award from the Prostate Cancer Foundation (PCF) - see page 20.
- We are part of the ImmuneImage European Consortium supported by the EU's Innovative Medicines Initiative (IMI). This collaboration seeks novel molecular imaging response biomarkers to immunotherapies.
- We have developed and validated a CT-radiomics signature with predictive value of response to immunotherapy. The preliminary results of this study were presented at the 2018 European Congress of Radiology, 28 February-04 March, Vienna, Austria.
- We continue to expand existing partnerships including other groups and establish new ones in order to increase the incorporation of imaging studies within translational research projects.
- Our group applies imaging biomarkers and radiomics to research in oncology.

Figure



A radiomics signature from the CT-scan before starting treatment predicts response of solid tumors to immune checkpoint inhibitors.

Summary

Our group has expanded during 2018. We have now incorporated a laboratory technician, PhD student and a research fellow, and will soon welcome a Post-Doctoral MR researcher who will provide support in advancing novel imaging biomarker development in oncology. We are also pleased to announce that a second PhD student will soon be joining our group, and that we are currently recruiting for additional new talents.

We are fostering new collaborations with additional leading imaging research groups including the Computing Vision Centre (CVC–*Universitat Autónoma de Barcelona*), and cutting-edge centers such as Bellvitge Institute for Biomedical Research (IDIBELL), in Barcelona, the Institute of Cancer Research (ICR), London, UK, the Netherlands Cancer Institute (NKI), Amsterdam, and the Cancer Research UK (CRUK) Cambridge Institute. In partnership, we have designed various projects for which we have applied for funding through national and international grants.

Thanks to the support received through a grant received from the Institute of Health Carlos III (ISCIII), and a Young Investigator Award from the Prostate Cancer Foundation (PCF), we have initiated the first prospective study of whole-body diffusion-weighted MRI as a response biomarker of bone metastases in prostate cancer patients.

We have also established close collaborations with the VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 100), towards developing and validating novel predictive and early response biomarkers for immunotherapies.

By applying advanced computational image analysis tools and machine learning methods, in an external cohort we have developed and validated a CT-radiomics signature for predicting response to immunotherapy. This could improve patient stratification and thus optimize patient selection for immunotherapy both as standard of care and in clinical trials.

We have also established interdisciplinary partnerships with various VHIO groups to work together on several translational research projects. Our ethos of team science is key to optimizing imaging and accelerating translational cancer research.

Aimed at applying imaging biomarkers and radiomics to cancer discovery, our efforts center on advancing precision imaging in personalized medicine towards ultimately improving outcomes for cancer patients.

PI paper pick

Rescigno P, Lorente D, Dolling D, Ferraldeschi R, Rodrigues DN, Riisnaes R, Miranda S, Bianchini D, Zafeiriou Z, Sideris S, Ferreira A, Figueiredo I, Sumanasuriya S, Mateo J, Perez-Lopez R, Sharp A, Tunariu N, de Bono JS. Docetaxel Treatment in PTEN- and ERG-aberrant Metastatic Prostate Cancers. *Eur Urol Oncol.* 2018 May;1(1):71-77.

Mateo J, Fizazi K, Gillessen S, Heidenreich A, Perez-Lopez R, Oyen WJG, Shore N, Smith M, Sweeney C, Tombal B, Tomlins SA, de Bono JS. Managing Nonmetastatic Castration-resistant Prostate Cancer. *Eur Urol.* 2019 Feb;75(2):285-293. doi: 10.1016/j.eururo.2018.07.035. Epub 2018 Aug 14.

Mateo J, Cheng HH, Beltran H, Dolling D, Xu W, Pritchard CC, Mossop H, Rescigno P, Perez-Lopez R, Sailer V, Kolinsky M, Balasopoulou A, Bertan C, Nanus DM, Tagawa ST, Thorne H, Montgomery B, Carreira S, Sandhu S, Rubin MA, Nelson PS, de Bono JS. Clinical Outcome of Prostate Cancer Patients with Germline DNA Repair Mutations: Retrospective Analysis from an International Study. *Eur Urol.* 2018 May;73(5):687-693. doi: 10.1016/j.eururo.2018.01.010. Epub 2018 Feb 8.

G Boysen, D Nava Rodrigues, P Rescigno, G Seed, DI Dolling, R Riisnaes, M Crespo, Z Zafeiriou, S Sumanasuriya, D Bianchini, J Hunt, D Moloney, R Perez-Lopez, N Tunariu, S Miranda, I Figueiredo, A Ferreira, Ro Christova, V Gil, S Aziz, C Bertan, FM de Oliveira, M Atkin, M Clarke, J Goodall, A Sharp, TY MacDonald, MA Rubin, W Yuan , CE Barbieri, S Carreira, J Mateo, JS deBono. SPOP mutated/CHD1 deleted lethal prostate cancer and abiraterone sensitivity. *Clin Cancer Res.* 2018 Nov 15;24(22):5585-5593.

THORACIC TUMORS & HEAD AND NECK CANCER GROUP

Principal Investigator
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Medical Oncologists and Clinical Fellows
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Ana Callejo
Susana Cedrés
Alexandre Martinez
Alejandro Navarro
Nuria Pardo
Jordi Remon

Clinical Nurse Specialists
Victor Monton
Gisela Rodríguez

Strategic goals

- Contribute to early drug development and targeted therapies for the treatment of thoracic and head and neck tumors.
- Advance precision 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 for optimal patient care.
- The creation and setting up of a new translational thoracic cancer genomics group.

Highlights

- Strengthening of multidisciplinarity through our Thoracic Tumors Committee that convenes twice a week.
- Our head and neck cancer patients are discussed by a multidisciplinary team, also twice a week.
- Implementation of pharmacogenomic approaches in advanced lung cancer in collaboration with VHIO's Cancer Genomics Group led by Ana Vivancos (page 90), and the Vall d'Hebron University Hospital's Pathology Service, working with Javier Hernández and Irene Sansano.
- The use of liquid biopsy for the evaluation of 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 been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA): osimertinib (Jänne et al. *N Eng J Med.* 2015), ceritinib (Shaw et al. *N Eng J Med.* 2014; Shaw et al. *Lancet Oncol.* 2017), brigatinib (Camidge et al. *N Eng J Med.* 2018) and lorlatinib (Shaw et al. *Lancet Oncol.* 2017; Solomon et al. *Lancet Oncol.* 2018).
- We have successfully led a translational project resulting in the publication of scientific article: a case of a woman presenting different primary tumors in the lung and the breast, but with extensive mutational overlap. Moreover, we showed that this patient had an exceptional response to cisplatin/gemcitabine in combination with HSP90i, who nowadays continues with HSP90i maintenance after three years (Cedres et al. *J Natl Cancer Inst.* 2018).
- Development of immune-based strategies against thoracic and head and neck malignancies.
- Creation of a new translational thoracic cancer genomics group to be led by Ramon Amat, who is a molecular biologist with extensive experience in genomics and transcriptional regulation, and has worked at national and international research institutions such as Weill Cornell University, Mount Sinai, University of Cambridge, *Universitat Pompeu Fabra,* University of Toronto and Institute of Biomedical Research of Barcelona (IIBB–CSIC).

Summary

VHIO's Thoracic Tumors & Head and Neck Cancer Group is dedicated to advancing cancer treatment and care for patients suffering from thoracic malignancies, including lung cancer, mesothelioma and thymic malignancies, and head and neck cancers. We focus on disease prevention, early detection and the more precise diagnosis and staging of disease towards improved clinical outcomes.

Our group strives to match currently available targeted therapies with specific molecular alterations identified in patients, seek out molecular mechanisms of acquired resistance, and optimize novel immunotherapy strategies.

For our patients with early-stage thoracic malignancies, we collaborate closely with a multidisciplinary team incorporating thoracic surgeons, radiation therapists, radiologists, pulmonologists, pathologists and biologists. In so doing, we are accelerating the optimization of several treatment approaches and modalities. Since these patients can suffer from severe symptoms we are also deeply committed to ameliorating clinical outcomes by working in tight connectivity with professionals from other disciplines.

Precision medicine for the treatment advanced lung cancer is no longer an ambition. It represents a guiding principle. We establish molecular determinants of disease in individual tumors and circulating-free DNA (cfDNA) by liquid biopsy, to better tailor treatments to the specificities of each patient.

For patients with head and neck tumors we work alongside expert surgeons, radiotherapists, radiologists, pathologists, and nutritionists, and also lead a clinical trial program to assess novel immunotherapeutics and targeted agents in this particular setting.

Immunotherapy-based strategies have a role in the treatment algorithm for the management of non-small cell lung cancer; a number of protocols are now ongoing at our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 100). We contribute to VHIO's early clinical drug development efforts, led by Elena Garralda (page 64), and also manage other less common thoracic malignancies including head and neck cancer, small-cell lung cancer, mesothelioma, thymoma and neuroendocrine tumors.

PI paper pick

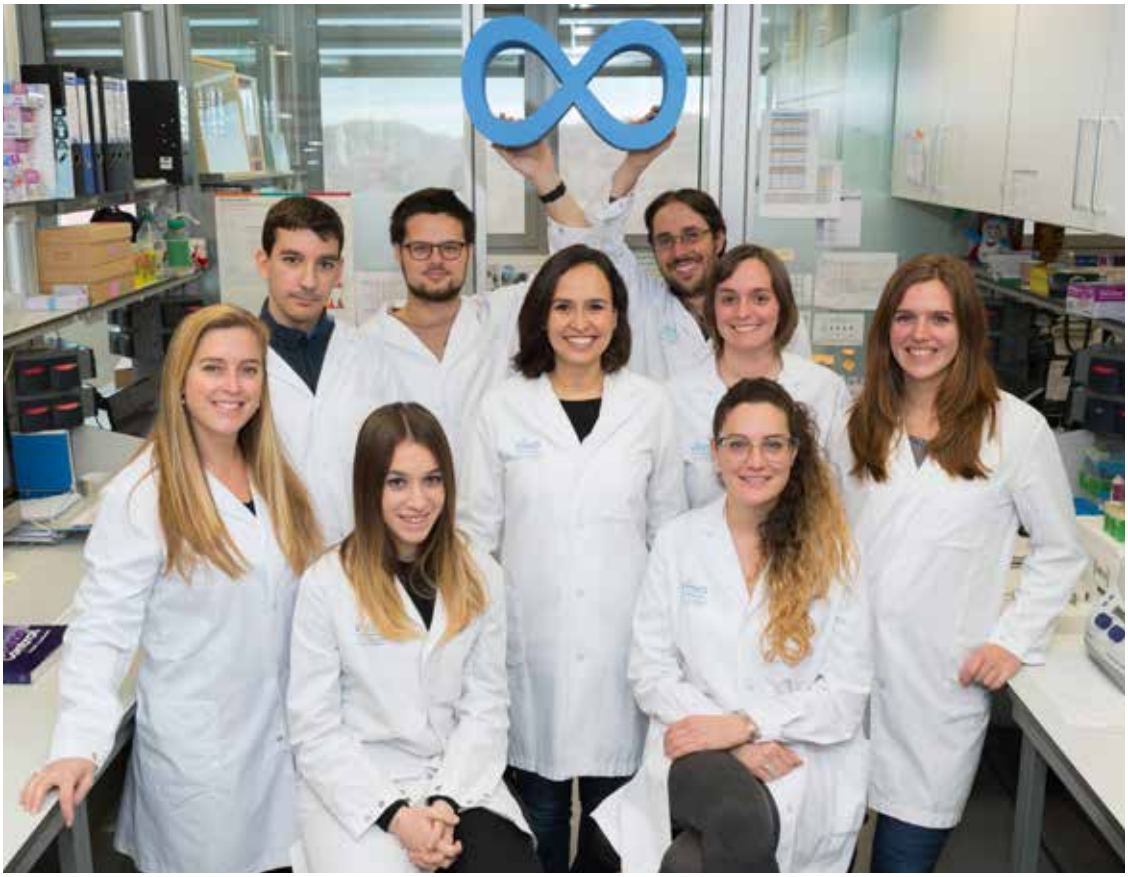
Solomon BJ, Besse B, Bauer TM, Felip E, Soo RA, Camidge DR, Chiari R, Bearz A, Lin CC, Gadgeel SM, Riely GJ, Tan EH, Seto T, James LP, Clancy JS, Abbattista A, Martini JF, Chen J, Peltz G, Thurm H, Ou SI, Shaw AT. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol.* 2018 Dec;19(12):1654-1667.

Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS, Hochmair MJ, Li JY, Chang GC, Lee KH, Gridelli C, Delmonte A, Garcia Campelo R, Kim DW, Bearz A, Griesinger F, Morabito A, Felip E, Califano R, Ghosh S, Spira A, Gettinger SN, Tiseo M, Gupta N, Haney J, Kerstein D, Popat S. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med.* 2018 Nov 22;379(21):2027-2039.

Goss GD, Felip E, Cobo M, Lu S, Syrigos K, Lee KH, Göker E, Georgoulias V, Li W, Guclu S, Isla D, Min YJ, Morabito A, Ardizzoni A, Gadgeel SM, Fülöp A, Bühnemann C, Gibson N, Krämer N, Solca F, Cseh A, Ehrnrooth E, Soria JC. Association of ERBB Mutations With Clinical Outcomes of Afatinib- or Erlotinib-Treated Patients With Lung Squamous Cell Carcinoma: Secondary Analysis of the LUX-Lung 8 Randomized Clinical Trial. *JAMA Oncol.* 2018 Sep 1;4(9):1189-1197.

Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC; KEYNOTE-189 Investigators. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med.* 2018 May 31;378(22):2078-2092.

TUMOR IMMUNOLOGY & IMMUNOTHERAPY GROUP



Principal Investigator
Alena Gros

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Graduate Students
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Maria Lozano
Anna Yuste

Technicians
Daniela Grases
Albert Marin

Students
Albert Montoliu
Helena Pasamar

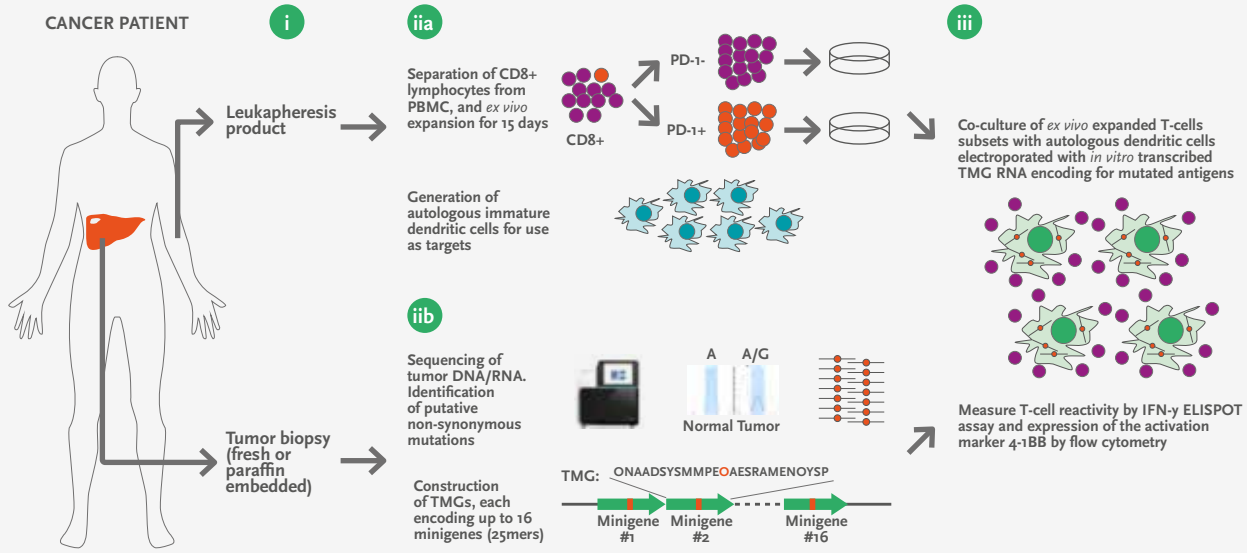
Strategic goals

- Characterize the personalized anti-tumor T-cell response in cancer patients.
- 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

- Our PI, Alena Gros, secured funding through a FERO Foundation Award (page 12), for a new research project.
- In collaboration with Elena Garralda's Group (page 64), we lead research for our BBVA Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI) – page 16.
- We have collected over 100 samples from patients treated at the Vall d'Hebron University Hospital (HUVH) to study mechanisms of response and resistance to immunotherapy.
- Aimed at making adoptive cell transfer a clinical reality throughout the region of Catalonia, our group has initiated clinical validation runs in collaboration with Barcelona's Blood and Tissue Bank.

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).

Summary

The immune system can recognize, hone in on and eliminate cancer. Through multiple mechanisms however, tumors can evade and dodge the immune response. Immunotherapies against cancer exploit the immune system to more effectively attack disease. Clinical studies have shown 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 is increasingly representing the fourth pillar of anti-cancer therapy across a variety of different tumor types.

Despite encouraging antitumor responses, currently only a fraction of patients treated with immunotherapeutics respond and some unfortunately report autoimmune-related adverse events. There is therefore a critical need to develop and personalize these promising treatments.

To do so, we study 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 in liquid biopsies.

One correlative biomarker 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 patients' human leukocyte antigen (HLA) molecules and elicit T-cell responses.

We adopt 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. Following this strategy, we aim to establish 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.

PI paper pick

Yossef R, Tran E, Deniger DC, Gros A, Pasetto A, Parkhurst MR, Gartner JJ, Prickett TD, Cafri G, Robbins PF, Rosenberg SA. Enhanced detection of neoantigen-reactive T cells targeting unique and shared oncogenes for personalized cancer immunotherapy. *JCI Insight*. 2018 Oct 4;3(19). pii: 122467.

VHIO's Cancer Genomics, Molecular Oncology and Proteomics Groups 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.

CANCER GENOMICS GROUP

Principal Investigator
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Post-Doctoral Fellows
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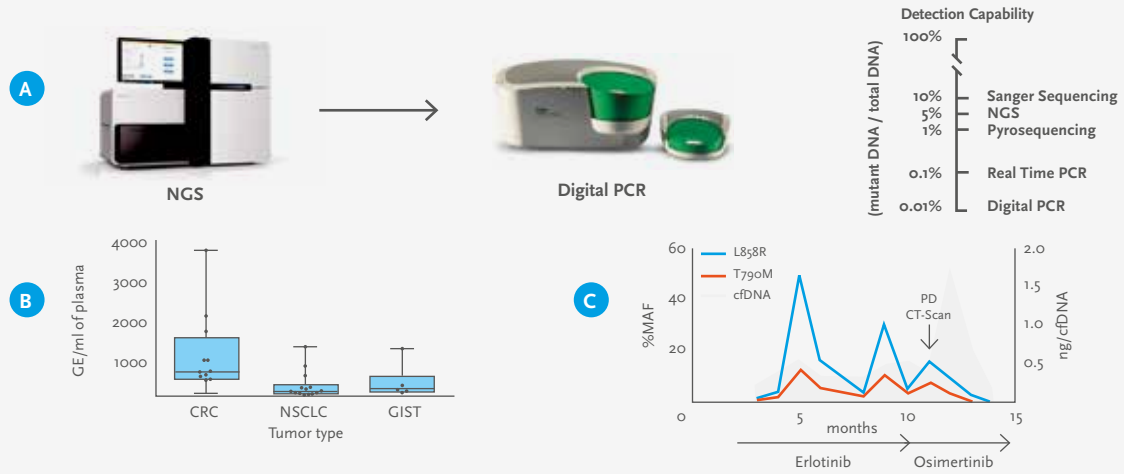
Strategic goals

- Develop and implement improved strategies for routine patient prescreening in a setting of excellence (ISO 15189 flexible 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 (page 84), led by Enriqueta Felip, and Gastrointestinal & Endocrine Tumors Group (page 68), 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 member institutions.
- We are now validating our 450 gene capture panel to be used in our Prescreening Program and by all Cancer Core Europe Consortium partners.
- In liquid biopsy we are developing our custom NGS test with Unique Molecular Identifiers (UMI) chemistry and envision that this will be our first disease tracking test in the clinical setting.
- 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 our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", (page 100), early clinical trials enables our teams to more precisely match an increasing number of individual patients with a particular study.

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.

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 (page 14), is nucleated around the activity of two VHIO groups - Cancer Genomics and Molecular Oncology, led by Paolo Nuciforo, in collaboration with VHIO's Elena Garralda (PI of our Early Clinical Drug Development Group, page 64), and Rodrigo Dienstmann (PI, Oncology Data Science - ODysSey - Group, page 76), 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 (page 100).

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 as well as a 450-gene capture panel (Illumina). This panel is currently being validated.

Another two are based on nCounter (Nanostring). The gene fusion panel, with the capacity of detecting over 100 recurrent gene fusions, is also enabling us to assess gene expression patterns in tumors. Copy Number Alterations are evaluated with a 59 gene panel for genes with frequent gains or losses in cancer.

As a reflection of our dedication to excellence and quality in the services we provide, we have attained ISO 15189 flexible 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, as well as predictive biomarkers for immunotherapeutics. Our group is particularly interested in liquid biopsy; ctDNA as well as tumor educated platelets (TEPs).

PI paper pick

Vivancos A, Élez E, Salazar R. Circulating cell-free DNA as predictor of treatment failure after neoadjuvant chemoradiotherapy before surgery in patients with locally advanced rectal cancer: is it ready for primetime? *Ann Oncol.* 2018 Mar 1;29(3):532-534.

Capdevila J, Mayor R; Mancuso FF, Iglesias C; Caratù G, Matos I, Zafón C, Hernando J, Petit A, Nuciforo P, Cameselle-Teijeiro JM, Álvarez C, Recio JA, Tabernero J, Matias-Guiu X, Vivancos A, Seoane J. Early evolutionary divergence between papillary and anaplastic thyroid cancers. *Ann Oncol.* 2018 Jun 1;29(6):1454-1460.

Cedrés S, Felip E, Cruz C, Martinez de Castro A, Pardo N, Navarro A, Martinez-Marti A, Remon J, Zeron-Medina J, Balmaña J, Llop-Guevara A, Miquel JM, Sansano I, Nuciforo P, Mancuso F, Serra V, Vivancos A. Activity of HSP90 Inhibition in a Metastatic Lung Cancer Patient With a Germline BRCA1 Mutation. *J Natl Cancer Inst.* 2018 Aug 1;110(8):914-917.

Puig I, Tenbaum SP, Chicote I, Arqués O, Martínez-Quintanilla J, Cuesta-Borrás E, Ramírez L, Gonzalo P, Soto A, Aguilar S, Eguizabal C, Caratù G, Prat A, Argilés G, Landolfi S, Casanovas O, Serra V, Villanueva A, Arroyo AG, Terracciano L, Nuciforo P, Seoane J, Recio JA, Vivancos A, Dienstmann R, Tabernero J, Palmer HG. TET2 controls chemoresistant slow-cycling cancer cell survival and tumor recurrence. *J Clin Invest.* 2018 Aug 31;128(9):3887-3905.

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MOLECULAR ONCOLOGY GROUP

Principal Investigator
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Attending Physicians
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PhD Student
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Xavier Guardia
Tania Lopez
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Lidia Sánchez
César Sevillano

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Gemma Sauch

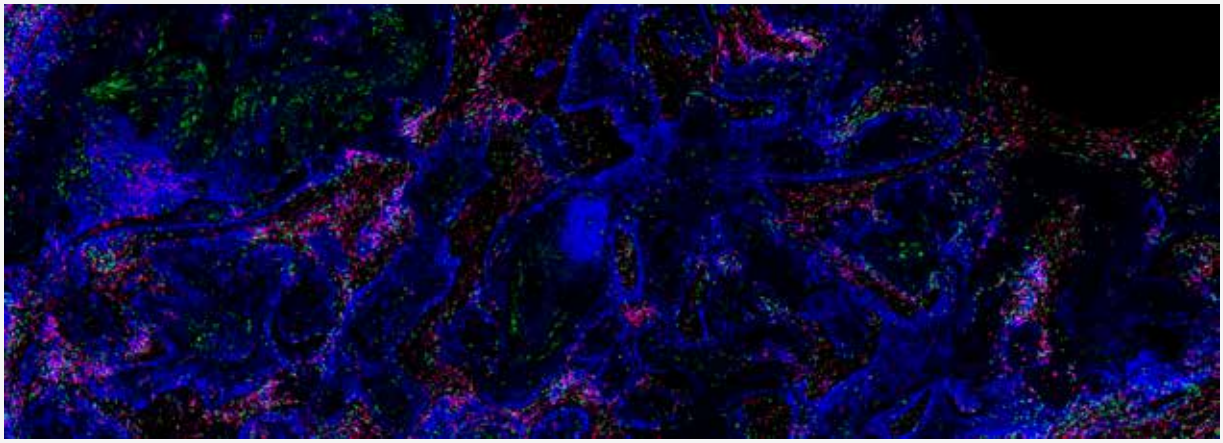
Strategic goals

- Discovery and validation of novel biomarkers using tissue-based technologies.
- Identification of targetable alterations as part of VHIO's Prescreening Program (page 14).
- Application of molecular pathology strategies to support early clinical drug development programs.
- Clarify the impact of *Fusobacterium nucleatum* in colorectal cancer development and progression.
- 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

- Performing over 4400 molecular determinations for patient inclusion in early clinical trials as part of VHIO's Prescreening Program.
- Supported over 280 clinical trials for sample management and analyses.
- Over 24,600 tests performed for basic and translation research programs.
- Being central laboratory for several international clinical studies.
- Development of novel diagnostic approaches to study the microbiome within the tumor tissue context.
- Maintenance and expansion of tests under ISO15189 accreditation.

Figure



Multiplex immunohistochemistry (IHC) assay showing PD-L1 expression in cancer cells (blue) and in CD163+ (pink) and CD8+ (cyan) immune cells. Red, CD163+PD-L1-; Green, CD8+PD-L1-. (Virtual image generated using ImageJ after alignment of 3 sequential IHC staining on the same tissue section).

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.

Together with our Cancer Genomics Group (PI Ana Vivancos, page 90), our group is central our Institute's Molecular Prescreening Program by performing molecular profiling in over 1500 patients per year as candidates for enrolment in early phase clinical trials. We also serve as one of VHIO's Core Technology Platforms and is therefore key to our translational research lines and programs.

We actively participate in all 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 patient-derived xenograft (PDX) models. Our contribution is reflected by several high-impact factor collaborative papers published throughout 2018.

Our group also continues to work independently and in partnership to establish the impact of microbiome in colorectal cancer development and progression.

In particular, we are developing a Fusobacterium nucleatum diagnostic assay that permits simultaneous visualization and quantification of the bacteria within tumors.

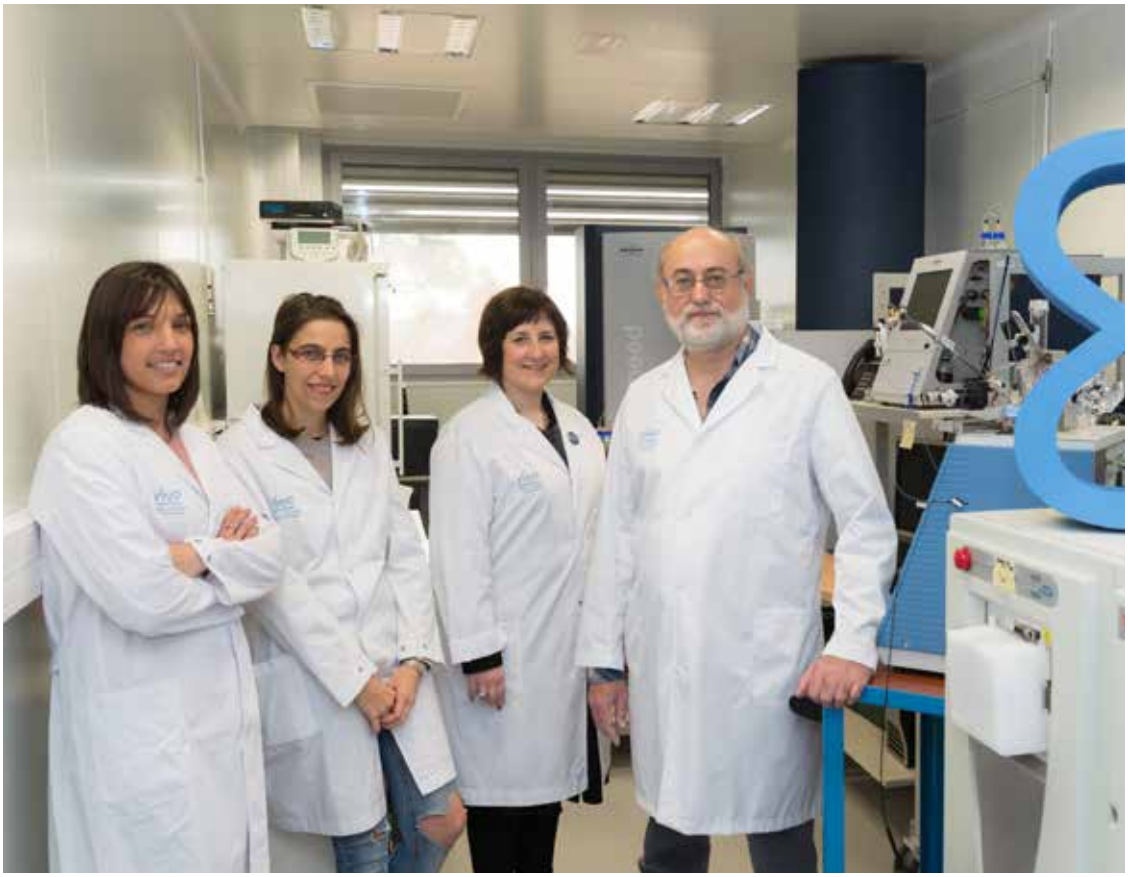
As a VHIO Core Facility, we provided support for approximately 280 clinical trials conducted at Vall d'Hebron, representing around 70% of all currently open trials at our institution. Our involvement in clinical studies ranges from the coordination of sample collection, storage and shipment, developing and running multiple assays for real-time patient inclusion, as well as pharmacodynamic monitoring and dose finding.

In 2018 we performed more than 4400 molecular determinations on samples for patient inclusion in clinical trials, and over 24,600 tests to support basic and translation research. 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 that are run under accreditation.

PI paper pick

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 pathologic response based on tumor cellularity and tumor-infiltratinglymphocytes (CelTIL) in HER2- positive breast cancer treated with chemo-free dual HER2blockade. *Ann Oncol.* 2018 Jan 1;29(1):170-177.

PROTEOMICS GROUP



Principal Investigator
Francesc Canals

Post-Doctoral Fellow
Nuria Colomé

Technicians
Luna Martin
Anna Sabé

Students
Marc Fernández
Maria Judit Tello

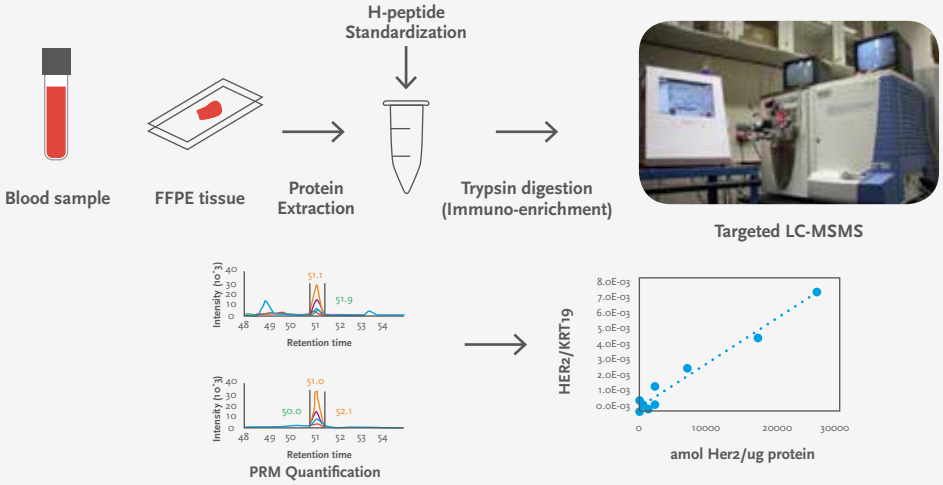
Strategic goals

- 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.
- Application of proteomic and phosphoproteomic screening to the characterization of CRC PDX models.
- Development of analytical tools to facilitate research into epigenetic enzymes as potential drug targets.
- Participation in the Spanish Consortium Chromosome 16 HPP, the HUPO Human Proteome Project.

Figure



Mass spectrometry based assays for biomarker proteins in clinical samples. We have set up procedures for the analysis of different types of routine clinical specimens. Proteins extracted from plasma, CSF, tissue biopsies or FFPE tissue slices are digested with trypsin and isotopically labeled peptides of the target proteins are added as internal standards.
For very low abundance biomarkers, the targeted peptides are then affinity-enriched using specific antibodies. The peptide mixtures are then analyzed by liquid chromatography- mass spectrometry using the targeted Parallel Reaction Monitoring (PRM) methodology. In the example shown, we measured Her2 protein contents in breast cancer FFPE tissue samples.
The plot shows how normalization by the measured Krt19 amount in the samples corrects for tumor cellularity. The corrected Her2 contents measured correlate with independent measurements from microdissected tumor samples, and shows how HER2 protein concentration displays a very broad range in a set of IHC positive samples.

Summary

VHIO's Proteomics Group serves as a Core Technology Platform and provides state-of-the-art proteomic methodologies to VHIO researchers as well as incorporates new developments within the field to offer the very latest strategies and technologies in proteomics.

We employ mass spectrometry-based proteomic strategies for the screening and validation of biomarkers for cancer diagnostics, precision therapy and a closer monitoring of disease.

One of our research lines focuses on the development of mass spectrometry-based assays for the analysis of biomarkers in clinical samples. We have been developing immune-MS based assays with improved selectivity and accuracy in the analysis of low abundance biomarker proteins in plasma or CSF samples.

Our group also develops MS based assays for marker proteins in FFPE tissue samples, aimed at providing accurate quantitative measurements that can translate in superior stratification compared with routine IHC scoring methods.

We have set up workflows for the proteomic and phosphoproteomic characterization of patient-derived xenograft (PDX) models of colorectal cancer. PDX constitute an ideal platform for the molecular characterization at the proteomic level of this tumor type. Complementary to genomic classification, we are exploring the suitability of this characterization as a tool for tumor subtype classification.

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 seeks to develop an entire map of the proteins encoded by the human genome to advance our understanding of human biology in health and disease.

PI paper pick

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VHIO'S TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

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Cristina Resina
David Vendrell

Clinical Trials Office Administrative Support
Nuria Carballo
Marc Palomar

Clinical Trials Office Assistant
Alexandre Valle

Clinical Trials Quality Assurance Management
Francisco Javier Fonts
Silvia Garcia
Isabel Gonzalez

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 our work and expand related skill sets.
- Implemented new tools and procedures aimed at increasing the quality and efficacy of research.
- 16 sponsor audits and 1 inspection by the US Food and Drug Administration (FDA) have been conducted with satisfactory results.
- Continued optimal quality and procedures achieved through the Inspection for Accreditation of our phase I Unit, the Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", by the *Generalitat de Catalunya*, carried out in 2016.
- New patient monitoring system employing electronic medical records.
- Increased office space for the management and coordination 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) Medical Oncology Department, headed by VHIO's Director, Josep Tabernero. Our team incorporates study coordinators, data managers, sample managers, administrative as well as quality control staff, who coordinate phase I–IV clinical studies and collaborate in various translational research projects at VHIO.

Organized into three groups, covering all tumor types and studies, our personnel is managed by the Clinical Trials Office Director, Gemma Sala.

In 2018 we managed 139 Phase I, 22 Basket studies, 131 phase II, and 107 phase III clinical trials with active recruitment throughout the year (see Figure), with patient enrolment totaling at 1198. 146 new trials were initiated, including 17 post-authorization trials and rollover studies. In addition, we continue to follow up patients who were recruited prior to 2018 and are still enrolled and receiving study treatment (more than 900 patients in total, and 1200 in follow up).

As we continue to render personalized medicine more precise by matching 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, fwe 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, tailored to each individual patients' molecular 'measurements'.

The prestige of our Hospital's Medical Oncology Department is increasingly recognized by pharmaceutical as well as biotechnology companies. It has consequently become a reference center and selected by the industry to carry out complex clinical trials for which the number of participating centers is highly restricted.

Clinical sites are selected based on the highest standards of quality and capacity for carrying out state-of-the-art research. We have participated in early phase trials of different drugs, ultimately enabling the pharmaceutical industry to market novel anti-cancer medicines. We are involved in studies promoted by the pharmaceutical industry as well as those developed by us in collaboration with other hospitals. We have also conducted more than 10 Investigator-Initiated Trials (IITs).

Figure

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	2018
Included in phase I	35	59	57	110	130	120	108	132	139	171	222	245	277	290	345	303	370	453	445	508
Included in phase II	59	72	66	94	91	130	73	165	170	133	161	207	180	253	257	302	327	333	323	361
Included in phase III	95	128	175	109	84	129	111	85	143	180	189	221	218	236	241	166	282	343	328	329
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**	**1.198**
Post Authorization & Rollovers trials																20	56	50	80	184

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	2018
Phase I trials	6	10	12	14	17	15	16	19	20	26	31	37	48	66	75	83	106	129	137	161
Phase II trials	19	22	23	23	22	19	30	32	42	40	55	54	57	85	96	99	94	117	107	131
Phase III trials	14	17	22	25	18	20	21	21	31	37	45	49	56	68	61	64	89	108	111	107
N° of clinical trials	**39**	**49**	**57**	**62**	**57**	**54**	**67**	**72**	**93**	**103**	**131**	**140**	**161**	**219**	**232**	**246**	**289**	**354**	**355**	**399**
Post-authorisation & Rollover Trials																5	14	16	19	33

RESEARCH UNIT FOR MOLECULAR THERAPY OF CANCER (UITM) - "LA CAIXA"

Director
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Executive Director
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Medical Coordinator
Elena Garralda

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Raquel De La Torre
Nuria Farras
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Marc Gimenez
Maria Herranz
Guillermo Joaquin Mainar
Andreu Martinez
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Clinical Trials Office Assistant
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Sample Managers
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Mª Elena De Cabo
Margarida Marcos
Isabel Muñoz
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Mª Ascension Martin
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Inventory Manager
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Ismael Delgado
Rafael Diaz
Susana Mulet
Isabel Perez
Marta Pozo
Alan Paul Thompson
Silvia Torralba
Noemi Visus

Pharmacy Logistics Managers
Maria Hidalgo
Sara Pizarro

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 to VHIO's preclinical and translational projects. Our Unit also collaborates with the various 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 design 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, bispecifics, immunomodulatory agents and immune checkpoint inhibitors and combinations, as well as translational research in immuno-oncology.

Obra Social "la Caixa"

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 (ERK, MET, FGFR, RET, NOTCH, NTRK), and immunotherapy (LAG3, TIGIT, OX40, CD40, IDO, arginase inhibitors and engineered antibodies).
- Developed by VHIO's Cancer Genomics Group, we benefit from applications for faster results including an n-Counter (Nanostring) platform, two digital PCR platforms (BEAMing Sysmex and ddPCR, BIO-RAD), and two NextGen Sequencers; MiSeq and HiSeq2500 (Illumina). We also co-develop customized molecular tests for VHIO's Prescreening Program - page 14, (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, Partners of Choice.
- We have initiated the Basket of Baskets (BoB) trial which is a novel study in personalized medicine integrating cutting-edge molecular prescreening, the development of new diagnostic tests such as circulating DNA or Nanostring, with the testing of targeted therapies in populations of patients with identified molecular alterations in their tumors and a high probability of benefiting from the selected treatments. This is an academic study, endorsed by the Cancer Core Europe (CCE) consortium (page 17), and co-funded by pharmaceutical companies. The first module evaluating atezolizumab in a molecularly-selected population opened this year and we are engaged in ongoing and advanced negotiations with other pharmaceutical companies.
- We have introduced Molecular Tumor Board meetings to discuss the most relevant genomic features of complicated cases to evaluate possible treatment options.
- In collaboration with several other VHIO groups, we head the Obra Social "la Caixa" International Program for Cancer Research and Education (page 16).

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 (page 98), we are gradually doing so for an increasing number of patients.

In 2018, our Unit participated in 161 ongoing phase I clinical trials, 22 of which were Basket trials. Our facilities, coupled with our multidisciplinary clinical teams, enable us to continue to expand our portfolio of phase I studies. This year we opened 51 new trials; 4 as Baskets. 508 patients were recruited, 64 of whom were enrolled in Baskets.

Research carried out at our Unit by VHIO's Early Clinical Drug Development Group (PI Elena Garralda, page 64) 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.

Reflective of VHIO's purely translational model, our studies are also linked to 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 deep understanding of the mechanism of action, as well as research into mechanisms of cancer drug resistance.

In partnership with VHIO's Cancer Genomics (PI Ana Vivancos, page 90) and Molecular Oncology (PI Paolo Nuciforo, page 92) 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 an n-Counter (Nanostring) platform, two digital PCR platforms (BEAMing Sysmex and ddPCR, BIO-RAD), and two NextGen Sequencers; MiSeq and HiSeq2500 (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 (page 102), pathologists from the Vall d'Hebron University Hospital's Molecular Pathology Department, radiologists and interventional radiologists, as well as our Clinical Trials Office (page 98), Database Management, Clinical Research Oncology Pharmacy Unit (page 104), and other healthcare specialists including dermatologists, cardiologists, and ophthalmologists.

CLINICAL RESEARCH ONCOLOGY NURSES

Nurse Supervisor
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Irene Calzado
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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 for all our patients enrolled in clinical trials.

VHIO's Clinical Research Oncology Nurses, specialized in molecular therapies, are headed by Angeles Peñuelas and represent an important element of the multidisciplinary 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 (see pages 98-100).

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 optimal 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.

As importantly is the psychological support they provide, alongside the other superbly trained oncology care givers and specialists including psychologists. Our nurses also assume a key role in providing patients and their families with the information they need to make fully informed decisions concerning their treatment options.

In 2018, across the 399 actively recruiting trials patient enrollment totaled at 1198. Our clinical teams also continue to follow up patients that were recruited prior to 2018 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.

CLINICAL RESEARCH ONCOLOGY PHARMACY UNIT

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Isabel De La Paz
Carla Esteban
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Ismael Delgado
Rafael Diaz
Roser Klimt
Susana Mulet
Isabel Perez
Marta Pozo
Alan Paul Thompson
Silvia Torralba
Noemi Visus

Clinical Trial Assistants (Technicians)
Maria Hidalgo
Sara Pizarro

Secretary
Isabel M. Alerany

Strategic goals

- Excellence in the services we provide to clinical oncology research programs through optimal efficacy, efficiency and safety.
- Management, dispensing, preparation and administration of clinical study drugs according to protocol specifications. Ensure traceability of the entire circuit with the development and implementation of new software.
- Maximized control of storage temperature of samples and preparations.
- Optimal use of a new computerized program, IPharma-FUNDANET®, for the management of clinical trials' supplies.
- Provision of a pharmaceutical care program for patients in phase I studies treated with orally administered medicines to improve safety, compliance and efficacy of these therapies.
- Provide 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

- Replacing paper medical orders, we have implemented electronic prescription ordering for IV administration medication in our site prescription software.
- We have developed new traceability software that includes global pharmacotherapeutic processes; the prescription, validation, dispensing, preparation and administration of drugs in the oncology and hematology clinical trial setting.
- Our Unit has provided clinical and technical support for the prescription, preparation, and 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. Successful sponsor audits, regulatory inspections, and participation in renewal of Phase I Unit reaccreditation.

Summary

Our Unit is ISO 9001:2015 certified and affiliated with the Medical Oncology Service of the Vall d'Hebron University Hospital (HUVH). We focus on two main areas of clinical research in oncology:

1. Our 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 therapies used in clinical trials. We also monitor and follow-up patients.

2. Our Pharmacological Research in Oncology Support Program: led by a team of pharmacists and laboratory technicians specialized in clinical trials, who are responsible for clinical trials supplies management, storage, dispensation and control to guarantee traceability.

In 2018 we performed clinical trial drugs management of 565 active studies in oncology & hematology, and 7,158 resupply deliveries/clinical trials supplies receptions. We continue to benefit from our cutting-edge system for controlling storage temperature which, performing electronic temperature recordings every 5 minutes daily, displays readings on computers equipped with audiovisual alarms as well as an around-the-clock SMS alert system to monitor and report temperature deviations.

Regarding the design and validation of our drug preparation process traceability system we ensure qualitative and quantitative quality control of our computerized system that incorporates barcode technology, electronic scales, and voice technology.

In 2018 our dispensing staff participated actively in 86 pre-study visits, 172 initial visits, 1,861 monitoring visits, 112 close-out visits, and have also successfully passed 19 audits, 3 mock inspections, 1 FDA inspection, 1 ISO inspection, and 1 inspection by local regulatory authorities for Oncology Phase I Unit reaccreditation.

Additionally, 39,002 clinical trial drugs have been dispensed and validated by our pharmacists, 11,733 of which were for oral administration, 1,100 for IM/ subcutaneous administration, and 26,175 for IV administration. A total of 172 Standardized Dispensing Procedures for clinical trials have been drawn up and we have performed 752 updates of these procedures due to subsequent amendments to protocols or pharmacy manuals. 121 storage temperature data reports have also been prepared by our dispensing team.

This year, our preparation staff have participated in 15 pre-study visits, 136 initial visits, 723 monitoring visits, and 15 audits, 3 mock inspections, 1 FDA inspection, and 1 assessment by local regulatory authorities. Preparations of cytostatics, monoclonal antibodies and other parenteral antitumor drugs for clinical trials totaled at 20,353. 135 Standardized Preparation Procedures were compiled with 384 updates because of changes to protocols or pharmacy manuals. We also included 394 antineoplastic therapeutic schedules in our prescription software.

Our Pharmaceutical Care Program for patients enrolled in phase I clinical trials: we performed 1,005 visits, 247 screenings, 215 C1D1s, and 211 follow-ups, also compiling patient diaries and/ or instructions for patients (in the absence of documentation provided by the respective sponsor).

In addition, we have compiled 6 different diaries and 16 instruction manuals for patients enrolled in the phase I studies involving orally administered drugs by our preparation staff. 21 diaries and patient manuals for phase II and phase III clinical trials were also elaborated in 2018 for patients enrolled in all phase II and III studies involving orally administered drugs by our dispensing staff.

FULL LISTING OF ARTICLES PUBLISHED BY VHIO INVESTIGATORS IN 2018

Articles published by VHIO Investigators in 2018 with allocated Impact Factor (IF):

Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. Smith MR; Saad F; Chowdhury S; Oudard S; Hadaschik BA; Graff JN; Olmos D; Mainwaring PN; Lee JY; Uemura H; Lopez-Gitlitz A; Trudel GC; Espina BM; Shu Y; Park YC; Rackoff WR; Yu MK; Small EJ; SPARTAN Investigators. *N Engl J Med.* 378: 1408-1418. IF: 79,258

Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. Camidge DR; Kim HR; Ahn MJ; Yang JC; Han JY; Lee JS; Hochmair MJ; Li JY; Chang GC; Lee KH; Gridelli C; Delmonte A; Garcia Campelo R; Kim DW; Bearz A; Griesinger F; Morabito A; Felip E; Califano R; Ghosh S; Spira A; Gettinger SN; Tiseo M; Gupta N; Haney J; Kerstein D; Popat S. *N Engl J Med.* 379: 2027-2039. IF: 79,258

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FUNDING & CONSORTIA

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. Regarding the latter, we would like to also recognize the *Asociación Española Contra el Cáncer* (AECC) for its longstanding support of several VHIO groups and researchers (page 21).

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:

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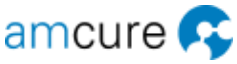


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CONSORTIA

As a reflection of VHIO's expertise in preclinical, translational and clinical research in oncology, we participated in the following Consortia of excellence in 2018:

Cancer Core Europe is a unique partnership aimed at addressing the cancer carecancer research continuum. Launched in 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 6 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), VHIO, as well as The National Cancer Institute of Milan (Italy). CEE promotes the pooling and exchange of expertise, research findings, common platforms and processes, and 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 to create a network of clinically relevant models of human cancer, and in particular patient-derived xenograft (PDX) models. Connecting 18 cancer centers across 13 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, it incorporates 6 of MoTriColor's members 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 that are autonomously usable by translational scientists and clinical practitioners for analysing big data, the project will ultimately facilitate translational research and advance medicine. Incorporating 13 groups from 9 renowned research entities of excellence, including VHIO, this consortium will address the deficit of integrative approaches that effectively combine different types of data from different sources as well as actively involve non-experts in bioinformatics in the design of the applications.
www.medbioinformatics.eu

Inaugurated in 2013, The **MErCuRIC** Consortium, funded by the European Commission's 7th Framework Programme of Research and Development, incorporates 13 partners in 8 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.
The project focuses on MEK/MET inhibition applying a combinatorial approach, and prioritizes colorectal cancer patients with *KRAS*-mutated disease and wildtype patients with aberrant c-MET tumours. By targeting these groups, researchers aim to identify which patient groups will benefit from a particular treatment regime, as well as better understand and characterise the heterogenous nature of cancer, while simultaneously targeting tumors and routes to metastasis.
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 8 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 are 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
Connecting 11 leading European research centers, including industry partners, NoCanTher assesses 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 10 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; Invasive Lobular Carcinoma (ILC), and Triple Negative Breast Cancer (TNBC).
Involving the combined efforts of 6 research institutions and two biomedical companies this is a 7.5 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

The Spanish Association against Cancer (AECC), and the *Institute of Health Carlos III* (ISCIII) through the *ERA-NET: Aligning national/regional translational cancer research activities* awarded VHIO with two **TRANSCAN-2** projects funded by the EU's Horizon 2020 framework program in 2017.
Supported through 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 (NSCLC) by assessing the role of circulating and exosomal miRNAs and free circulating DNA (fcDNA); as well as characterize blood-based tumor-educate platelets (TEPs) for the evaluation of patients treated with immune checkpoint inhibitors using novel sequencing technologies.
The second project will focus 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, multi-center study will primarily seek to evaluate the clinical feasibility of tracking tumor progression by dynamically detecting a molecular and personalized signature from a blood test.
www.transcanfp7.eu

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 39 leading organizations representing all stakeholders in personalized cancer medicine covering 21 countries and 4 continents, united by their vision to deliver on the promise of effective, personalized cancer medicine to patients worldwide.
Under the tagline *WINning together*, WIN was formed on the premise that members can accomplish more together than each organization can achieve working alone. Aimed at improving cancer patients' survival and quality of life, WIN members also collaboratively design and carry out global studies designed to achieve breakthroughs for cancer patients across the globe.
www.winconsortium.org

NEW CONSORTIA (launched in 2018)

COLOSSUS–***Advancing a Precision Medicine Paradigm in metastatic Colorectal Cancer: Systems based patient stratification solutions,*** is a multi-center European Commission Horizon 2020-supported project powered by 14 leading clinical investigators and researchers spanning 8 European countries, with expertise in cancer immunology, systems biology, computational modelling, bioinformatics, omics analysis, clinical oncology/pathology, preclinical research, medical imaging, clinical trials, health economics and patient management.
This 5-year undertaking aims at better classifying and treating metastatic colorectal cancer (mCRC).
Focused on microsatellite stable RAS mutant (MSS RAS mt) disease–a genetically identified type of CRC with very few therapeutic options available once patients develop resistance to existing chemotherapies, the COLOSSUS team will strive to both expand and refine the classification of this particular subset of colorectal cancer.
www.colossusproject.eu

MESI-STRAT combines the expertise of 14 partners from 6 European countries to establish the interplay of breast cancer metabolism and oncogenic signaling (Metabolic Signaling) by systems medicine approaches. Aimed at developing new models for knowledge-based STRATification of patients into subgroups with different endocrine therapy resistance mechanisms, this pan-European 57-month project , supported by the European Union's Horizon 2020 research and innovation programme, represents an important forward step towards improving outcomes for these patients.
The team will pioneer breast cancer metabolism as a novel approach for the stratification of patients, tracking of resistance and better guiding clinical decision-making throughout the course of endocrine therapy. Through the development of new computational models in combination with network analyses, pharmacogenomics and integrated multi-omics data, MESI-STRAT will play a decisive role in better deciphering the metabolic and signaling networks that drive resistance to endocrine-based therapies.
www.mesi-strat.eu

Announced in November, one of the **U.S. Department of Defense's (DoD) Innovative Minds in Prostate Cancer (IMPaCT)** Awards will fund a three- year collaborative partnership to advance precision medicine against metastatic prostate cancer (mPC). This coalition will count on the multidisciplinary expertise of investigators at VHIO, the Spanish National Cancer Research Centre–CNIO (Madrid, Spain), and the University of Washington (USA).
Aimed at more precisely gauging response in patients to standard therapies, the team will also seek to develop new, more effective and tailored treatment strategies, as well as design aclinical trial to assess the performance of a DNA damaging platinum chemotherapy, carboplatin, that is already used to treat other tumor types including ovarian and breast cancer.
https://cdmrp.army.mil/pcrp

Other collaborations:

The **AstraZeneca VHIO Alliance** announced in 2015, and the **MedImmune VHIO Alliance** launched in 2018, drive 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 focuses 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 **SCITRON** *Consorcio público-privado de Investigación Científica y Translacional en Oncología* (Consortium for Scientific Translational Research in Oncology) is a scientific program established in collaboration with Novartis in 2017 as a new model of R&D collaboration. This initiative connects expertise from Novartis and VHIO in applied and translational research to increase the impact of basic research in clinical practice.
The specific areas of interest include the development of a technology platform that analyses tumor clonal evolution and resistance mechanisms to targeted immunotherapy.
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, researchers and physician-scientists in cancer immunotherapy from across the globe aim 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 was designed 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.
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 6 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 the maximum qualification of an A grading.

The European Commission's Human Resources for Research (HRS4R) strategy enables research institutions of excellence to actively implement and uphold the requisites of The European Charter for Researchers and Code of Conduct for the Recruitment of Researchers for their HR policies and practices.
VHIO's comprehensive analysis and action plan was officially approved by HRS4R assessors in 2018 and our Institute was consequently granted permission to use the HR Excellence in Research Award logo as demonstration of its stimulating and favorable work environment.
www.vhio.net/en/hr-excellence-research

Also reflecting our dedication to excellence and the quality of our services and procedures, our Cancer Genomics and Molecular Groups are both ISO 15189 accredited 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.

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