VHIO

VALL D'HEBRON
Institute of Oncology

# 2016 SCIENTIFIC REPORT

## Turning ten and defining 'next gen' directions

Centres de recerca de Catalunya

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# INDEX SCIENTIFIC REPORT

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

## VHIO in 2016:

# Turning 10 and defining 'next gen' directions

The Vall d'Hebron Institute of Oncology (VHIO) was officially established in 2006 by former Director José Baselga, Physician-in-Chief at the Memorial Sloan Kettering Cancer Center in New York, President and creator of the FERO Foundation, and current President of our Internal Scientific Committee. From the outset, José had one pioneering and guiding principle for VHIO: To seamlessly bridge preclinical and clinical research in order to foster a continuous virtuous cycle of knowledge from bench to bedside and back again.

As evidenced throughout this Scientific Report, this bold approach continues to be at the very core of VHIO's philosophy, passionately pursued by our strong multidisciplinary teams. Prior to the establishment of the comprehensive cancer centers of today -- indeed before 'translational' entered into the oncology lexicon – José's vision establishes him as one of the godfathers of this connective, multidisciplinary approach. This strategy has been widely adopted as the model of excellence in the current era of precision oncology against this brutal disease that continues to outsmart and evade our most powerful arsenal of anti-cancer weaponry.

Over the past decade, I have been privileged to observe the many milestones marked by VHIO and other leading research institutes, often through combining strengths across borders, that spur our drive towards treating the most undruggable and resistant tumor types.

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

As Director of VHIO, I can say that the secret behind our translational successes so far is not only down to the incredible talent who have joined our community, but also about carefully planned strategies, infrastructure, and 'smart' expansion – especially in view of the current uncertain economic and political times (more about that later in this foreword).

Last year I advanced the opening of our new home, the CELLEX Center, and announced the near completion of our Animal Facility, which occupies the basement of our building and serves as a shared facility across the Vall d'Hebron Barcelona Hospital Campus (see page 10). With a surface area of 1347 $m^2$ and nearly 5500 cages, this facility (the entrance to which features on the cover to welcome readers into this year's Report) incorporates the latest platforms and technologies, including a high-sensitivity in vivo imaging technology platform, computed tomography (CT) for high-resolution 3D imaging, and a MicroPET R4 scanner engineered for analyzing small animal models of human disease. VHIO's expertise in developing and rendering cancer models more predictive including patient-derived xenografts (PDX) will continue thanks to our ability to deploy and harness the latest technologies within our cutting-edge facility – an additional jewel in VHIO's current crown.

## Welcome, welcome, welcome!

In pursuit of new emerging research areas, VHIO welcomed three new talents in 2016 (see pages 85-91): Francesc Bosch, Professor of Hematology and Head of the Department of

Hematology of the Vall d'Hebron University Hospital (HUVH), joined us as Principal Investigator of Experimental Hematology to lead the development of early phase clinical trials and defining new prognostic and predictive factors. The Bosch group focuses on deciphering the mechanisms involved in pathogenesis of hematological neoplasias, the preclinical study of new therapeutic regimens in experimental models that mimic the tumoral microenvironment using primary cells and PDXs, and defining new biomarkers for a more rational and precise treatment of patients.

María Abad was formerly a member of Eric Olson's group at the University of Texas Southwestern Medical Center (Dallas, USA), and prior to that, served as a Postdoc Fellow in Manuel Serrano's lab at the Spanish Cancer Research Centre (CNIO) in Madrid. She returned to Spain last summer to head up VHIO's Cellular Plasticity and Cancer Group which aims to advance insights into the interplay between reprogramming, cellular plasticity and cancer. María plans to identify the molecular mechanisms that govern the acquisition of stem cell properties during tumorigenesis, and determine the impact of inducing cellular dedifferentiation in various stages of tumorigenesis (tumor initiation, maintenance, and metastasis), and in the resistance of cancer cells to chemotherapeutic agents, and establish chemical compounds that specifically target cancer stem cells.

Leading VHIO's newly established Tumor Immunology and Immunotherapy Group, Alena Gros joins us from Steve Rosenberg's group at the National Cancer Institute (NCI), National Institutes of Health (NIH – Bethesda, USA) to achieve a better understanding of the naturally occurring T-cell response to cancer, and establish ways in which to exploit these responses towards developing more effective and precise immunotherapies against cancer. Her team will explore whether the presence of lymphocytes recognizing mutated antigens is associated with response, and advance personalized T-cell therapies to treat metastatic colorectal cancer.

As this Report goes to print, I am pleased to say we have also recruited Sandra Peiró as Principal Investigator of VHIO's Chromatin Dynamics in Cancer Group. Sandra joins us from the Hospital del Mar Medical Research Institute (IMIM, Barcelona). Her group will study the epigenetic mechanisms controlling gene expression during tumor progression, and the role of the primary 3D structure of chromatin (determined by histone modification) in the regulation of transcription.

Additionally, Leticia De Mattos, formerly a Medical Oncologist and Physician-Scientist at Vall d'Hebron, has recently returned from Carlos Caldas' lab at the Cancer Research UK, Cambridge, as Junior Group Leader to lead research using integrated multi-omics data to better understand tumor genetic heterogeneity and the role of the immune system within and between tumors to identify new biomarkers to guide patient therapy.

## A Golden Decade

I congratulate VHIO on its 10th anniversary and salute our amazing leaders, teams, supporters (see pages 106-107) and partners for their continued dedication, which enables us to do what we do best – translate discovery into more precise, individualized treatment and care of cancer patients; this is exactly what has established our young institute as a leading center of excellence at the global level. We will continue to expand and accelerate our efforts towards thwarting cancer.

2016 also marked the landmark 15-year birthday of ICREA – the Catalan Institution for Research and Advanced Studies. I congratulate ICREA for doing a phenomenal job in both attracting major talents to Catalonia and promoting the careers of its appointed Professors at international level. Awarded to experts across continents, these highly sought after contracts are considered a seal of global academic merit – as are the reputations of the institutes at which recipients are appointed. VHIO currently counts three ICREA Professors: Joaquín Arribas, Joan Seoane, and Laura Soucek (awarded in 2007, 2004, and 2014 respectively).

## Transforming the personalized care of cancer patients

In 2016 *Nature* published an Outlook collection of viewpoints surrounding the progress and promise of precision oncology. The *Perspective* piece that particularly caught my attention was on *"The precision-oncology illusion"*[1] authored by Vinay Prasad, assessing the success of genome sequencing programs and trials that pair individual patients with a targeted therapy matched to mutations and disease specificities. Whether one agrees or not with the arguments provided, one thing is true: we still have long road to travel if we are to deliver on the true promise of precision medicine. That said, I believe that we have every reason to be optimistic.

## Empowering predictive cancer science towards the next generation of precise anti-cancer therapies

It is thanks to the expertise of VHIO's preclinical and translational groups that 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.

Debate surrounding which predictive cancer models outperform others has been widely documented. The reliability of data generated by current models is frequently called into question upon review of false-positive results coupled with compounds that, while showing efficacy in preclinical studies, ultimately fail in early phase trials.

By focusing our efforts on advancing today's array of modeling systems, we will increasingly deliver the predictive data required to reliably inform the clinical development of innovative agents and evidence reproducibility before moving to the clinic. This year, VHIO's Growth Factors Group, led by Joaquín Arribas, has been striving to more accurately model anti-tumor immunotherapy strategies. The generation of humanized PDX models (Hu PDXs), in which the human immune system is established in PDX-bearing immunodeficient mice, has proven successful. His team is using these models to validate the efficacy of T-cell bispecific antibodies (TCBs).

Our Mouse Models of Cancer Therapies Group, led by Laura Soucek, has demonstrated in several models that Myc inhibition has a dramatic impact across several tumor types, with both mild and reversible side effects in normal tissue. Their spin-off company, Peptomyc S.L., created at VHIO (see section 'Spin-off success: VHIO-born entrepreneurship' of this Foreword), is developing Myc-inhibiting peptides for cancer therapy and validating this new therapeutic strategy across a number of notoriously untreatable tumor types.

Thanks to our prowess in advancing preclinical cancer models, our groups are called upon to participate in important studies involving modelling. One example this year was the participation of VHIO's Experimental Therapeutics Group, led by Violeta Serra, in important research published in *Nature Medicine* [2]. The study, directed by Andrew Tutt, King's College London (and in collaboration with colleagues from the Memorial Sloan Kettering Cancer Center) evidenced the molecular machinery that renders triple-negative breast cancer resistant to conventional chemotherapy. Using cell models and PDX, the study reveals PIM1 proto-oncogene inhibitors as novel contenders aimed at reversing resistance of triple-negative breast cancer to standard chemotherapies. This could ultimately open up a promising new therapeutic avenue for these patients.

As I previously mentioned, VHIO 'lives and breathes' multidisciplinarity and a purely translational approach to research against cancer. One study that exemplifies VHIO's translational 'tour de force' and the connectivity between our teams was published in *Clinical Cancer Research* [3], led by VHIO's Stem Cells and Cancer Group, headed by Héctor G. Palmer. Using colorectal cancer PDX, they demonstrated that Wnt inhibitors can overcome β-catenin-induced resistance to PI3K and AKT inhibitors and experimentally showed a rational stratification of patients to be treated with this trio of inhibitors using β-catenin and FOXO3A as predictive biomarkers of response. This marks an important milestone in ultimately advancing therapy against colorectal cancer.

To build on this progress in advancing a variety of modeling systems across various tumor types, we hope to empower predictive cancer models by continuing to pool knowledge, share perspectives, and move together more swiftly and cost-effectively to render cancer medicines more precise. Important collaborations such as the EurOPDX Consortium, of which VHIO is partner (see page 108), will most certainly help us to collectively progress prediction science against cancer. By promoting the exchange of findings on promising next-generation therapeutics as well as leading multi-center studies, we will also crucially reduce the duplication of efforts in drug development and preclinical cancer research.

In this respect too, VHIO's 2016 International Symposium: *Towards Predictive Cancer Models,* supported by the Fundació Bancària "la Caixa" (see page 14), proved a stunning success. It also underpinned the importance of identifying synergies between different experimental models and the need to connect experts across an array of various models in order to obtain the most reliable data about a particular drug or disease.

By providing equal attention across every model throughout the symposium, this two-day timely gathering, organized and co-chaired by VHIO's Joaquín Arribas and Laura Soucek, also represented an important step in advancing prediction science against cancer.

In collaboration with the Catalan Institute of Oncology (ICO) and the Program Against Therapeutic Resistance (proCURE), we co-organized the Biocat and Obra Social "la Caixa" B-Debate conference *Cancer Therapeutic Resistance: Progress and Perspectives* (see page 13), hosted by the CosmoCaixa Science Museum of the Fundació Bancària "la Caixa",Barcelona.

This superb meeting, under the co-chairmanship of ICO's Miguel Angel Pujana and VHIO's Joaquín Arribas, highlighted the opportunities and current challenges surrounding novel strategies and approaches aimed at overcoming drug resistance and counteracting tumor cell spread factors.

## The sharing, reporting and interpreting of clinically meaningful mass data

Novel technologies aimed at determining the function of genetic variants, coupled with new ways to harness, store and share data, means that basic and clinical scientists can work closer together to translate data more rapidly into clinical benefits. Our ambition is to accelerate discovery into the genetic causes of disease and the development of new, more effective and tailored treatments. Genome sequencing technologies are generating massive quantities of patient data, unmasking many new genetic variants. The challenge is in mining all these data for genes and variants of high clinical relevance. To do so, we must continue to improve our data management practices from bench to bedside.

The genomic profiling of each patient's tumor represents powerful weaponry in our current arsenal of novel approaches and techniques aimed at rendering anti-cancer therapies more precise. Importantly, better establishing the role and relevance of these genomic drivers -- particularly those inducing oncogenic addiction -- represents the Achilles' heel in matching targeted therapies to these alterations. In view of the vast amount of data, tools and platforms must be designed and developed in a unified format so that investigators and oncologists can access these insights in a user-friendly and coherent manner.

Throughout 2016, VHIO significantly contributed to such determined efforts. Leading important advances in data mining, literature curation and knowledge interpretation of somatic gene alterations that have a therapeutic impact in cancer, Rodrigo Dienstmann, Principal Investigator of our Oncology Data Science (ODysSey) Group, and colleagues created the Cancer Genome Interpreter (CGI) Cancer bioMarkers database. This resource is curated and maintained by several clinical and scientific experts in precision oncology supported by the European Union's Horizon 2020 funding. Publically available, this database has become a reference for clinical investigators across the globe, and the terminology that they have developed has been adopted by the ClinGen Somatic Cancer Working Group, which will harmonize biomarker curation through consensus minimum variant level data.

Similarly, his group has also participated in the Horizon 2020 supported consortium, MedBioinformatics, to develop integrative bioinformatics tools and autonomously usable software applications for scientists and clinicians to analyse the vast amount of data and knowledge generated in order to advance precision cancer medicine.

It's not only a matter of the effective sharing and reporting of clinically meaningful data; it's also a question of interpretation. Published this year in the *Journal of Clinical Oncology* [4], VHIO's Judith Balmaña, Principal Investigator of our High Risk and Cancer Prevention Group, authored a study revealing the lack of consistency in genetic variant interpretation in the context of shared data. In collaboration with several US-based cancer research centers of excellence, the article explored the conflicting classification of genetic variants and associated cancer risk reported by commercial laboratories in the online Prospective Registry of Multiplex Testing (PROMPT).

Importantly, one quarter of the clinical genetic results from commercial multiplex cancer panels reported in the PROMPT

registry had conflicting interpretations. Prior to publication, preliminary data were selected by the American Society of Clinical Oncology (ASCO) to showcase as an oral presentation presented by Judith at its Annual Meeting (Chicago, 03 – 07 June 2016).

Based on this study, initiatives aimed at further harmonizing variant interpretation in the context of shared data should be widely embraced and supported. The time is now to collectively speak the same 'language'.

## The power and potential of cancer subtyping

To deliver transformative therapies we must continue to validate molecular subclasses of disease as well as better develop, match, and measure novel therapies according to the specificities of each molecular subtype. Only then will we put the brakes on the molecular culprits that drive tumor initiation, development and growth.

With particular thanks to the dedication of our Cancer Genomics, Molecular Oncology, and Oncology Data Science (ODysSey) Groups led by Ana Vivancos, Paolo Nuciforo and Rodrigo Dienstmann, we are promoting the multi-molecular approach to developing novel anti-cancer therapies based on established subtypes, and continue to make important contributions to colorectal and breast cancer in particular.

Concerning the latter, one paper published this year in *JAMA Oncology* [5], evidenced the intrinsic subtyping of breast cancer by means of a genomic test as the most important prognostic factor in advanced or metastatic hormone-sensitive breast cancer. Led by Aleix Prat, Principal Investigator of VHIO's Translational Genomics Group, in collaboration with physician-researchers at VHIO and the August Pi I Sunyer Biomedical Research Institute (IDIBAPS, Barcelona), along with colleagues at The Royal Marsden Foundation Trust, London (UK), the team reported that genomic classification of tumors can predict the evolution of cancer from the onset of metastasis, and that this intrinsic classification can better guide treatment decisions in the first-line metastatic setting.

High-throughput genomic technologies, novel approaches, and cutting-edge platforms, coupled with big data generated through international networks and collaborations of excellence, including the Horizon 2020-supported MoTriColor (for a full listing of VHIO's participation in leading Consortia see pages 108-110), and the open sharing of results have advanced our understanding of the molecular drivers and subtyping of cancer.

To better tackle tumoral diversity and heterogeneity we must render the classification of cancers more precisely to be able to guide the prognosis of each individual patient as well as use intrinsic biological intelligence to better inform treatment decisions. Only by working together will we succeed in accelerating the translation of molecular subclasses and biomarkers into benefits at patient level.

## Spin-off success: VHIO-born entrepreneurship

At the close of 2016, Mosaic Biomedicals S.L., a spin-off co-founded by VHIO's Joan Seoane in 2014, announced the momentous merger of Mosaic with Northern Biologics Inc. (Toronto, Canada), and the consequent promise of the accelerated clinical development of humanized antibody, MSC-1.

Pioneering research headed by Joan Seoane previously led to both establishing the role of leukemia inhibitor factor (LIF) as a promoter of cancer progression by regulating the tumor microenvironment and inducing self-renewal in tumor-initiating cells, and his seminal discovery of MSC-1's capacity to effectively target LIF. MSC-1's transition to the clinic would represent a tremendous addition to our current arsenal of anti-cancer weaponry. MSC-1 is entering clinical trials this year, with sites planned throughout Europe and North America.

Peptomyc S.L. – a biopharmaceutical spin-off company co-founded in 2014 by VHIO's Laura Soucek, who is also CEO of the company – has already marked important milestones. Built on the research led by Laura over the last 20 years, this company centers on developing anti-Myc peptides for the treatment of non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC) and glioblastoma (GBM) – all of which have a dismal prognosis and are in desperate need of new therapies.

Laura and her team are focused on successfully translating Omomyc-based therapy into clinical application and ultimately, direct benefit for numerous cancer patients. In so doing, the Omomyc cell-penetrating peptide (CPP) would become the first ever clinically viable and direct inhibitor of Myc – a protein implicated in the formation of most tumor types. This anti-Myc peptide would also offer a less invasive form of therapy since Laura's group has already proven preclinically that it can be successfully administered intranasally to deliver its powerful anti-cancer blows.

Peptomyc represents the driving force behind de-risking Omomyc-CPP from a Proof of Concept Development Stage into a successful Phase I/II product and then licensing it to a pharmaceutical company.

## VHIO's commitment to cross-border collaborations of excellence

2016 has marked great progress led by VHIO's participation in several consortia. Here I should mention Cancer Core Europe – a unique partnership connecting renowned European comprehensive cancer centers. VHIO is one of the six founding research entities (see pages 11,108).

This year, VHIO's Early Clinical Drug Development Group led by Jordi Rodón, and VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", which he also directs, in collaboration with VHIO's prescreening program directed by Ana Vivancos – have led the design of the Cancer Core Europe's endorsed Basket of Baskets (BoB) trial.

Set to launch next year, this novel study in personalized medicine integrates molecular prescreening, the development of new diagnostic tests such as circulating DNA, with the testing of targeted therapies in populations of patients who, matched to the molecular alterations detected in their respective tumors, will be most likely to benefit from them.

Thanks to VHIO's prescreening program and its personalized medicine and immunotherapy early drug development programs, our expanding expertise in immuno-oncology with trials spanning many promising targets in immune checkpoints and cytokines, we are converging immuno-oncology and genomics to further enhance and advance precision science against cancer. As a reflection of our expertise, VHIO, in collaboration with an appointed expert from each of the six founding centers, co-leads Cancer Core Europe's Clinical Trials, Data Sharing, Molecular Diagnostics, Immuno-Oncology, Training and Education Task Forces.

Regarding our participation in WIN – Worldwide Innovative Networking in personalized cancer medicine – I am delighted to report that enrolment for the WINTHER trial (a pilot study in personalized medicine) was completed and results are currently being analysed. I will have important updates concerning these insights in next year's report. In the meantime, this unique academic and international clinical trial has led to the design of WIN trial number two: Survival Prolongation by Rationale Innovative Genomics (SPRING). Bringing key stakeholders from industry and academia, this study will firmly center on advancing precision medicine against lung cancer.

2016 has also marked the launch of new and essential partnerships including a 21-strong academic powerhouse set to progress discovery in cancer immunotherapy: the immunotherapy Centres of Research Excellence (imCORE) Network powered by Roche and Genentech, as well as the Horizon 2020-supported NoCanTher Consortium (see pages 13,109).

## Pioneering novel programs and anti-cancer armoury

In order to more precisely detect cancer mutations, track the evolution of disease and circulating tumor cells that drive metastasis, as well as predict response to therapy, we continue to mark important progress using our in-house BEAMing liquid biopsy RAS biomarker technology (a collaboration with Merck Serono and Sysmex Inostics), as well as Droplet Digital PCR (ddpCR) Bio-Rad technology. While we are increasingly witnessing just how potentially game changing the blood-based 'policing' of cancer is proving at clinical level, more must be done to develop and empower this approach.

Similarly, we are starting to see the efficacy of immunotherapeutics across several clinical studies. VHIO groups and colleagues from other leading cancer research centers across Europe and beyond, continue to report and advance the use of novel immune agents either as mono therapy or in combination, across an increasing number of cancer types. Despite such progress, we must strive to achieve a better understanding of the cellular and molecular mechanisms modulating immune response to cancer and learn from the outcomes of current and future trials.

### VHIO to pair liquid biopsy with immunotherapy

Fuelled by Merck's 2016 Grant for Oncology Innovation (GOI), VHIO's Enriqueta Felip, Principal Investigator of our Thoracic Tumors and Head and Neck Cancer Group and Ana Vivancos, in collaboration with colleagues at the Catalan Institute of Oncology (ICO), will lead the project entitled: *New technologies for new treatments – liquid biopsy meets immunotherapy*.

Aimed at characterizing blood-based tumor-educate platelets (TEPs) for the evaluation of patients treated with immune checkpoint inhibitors using novel sequencing technologies, Enriqueta's team will explore Platelet RNA as an easily accessibly liquid biopsy technology that may more accurately and effectively guide immunotherapeutic strategies for the treatment of patients with non-small lung cancer (NSCLC).

## The Last Word

*"As far as the laws of mathematics refer to reality, they are not certain; and as far as they are certain, they do not refer to reality."*

- Albert Einstein

Arguably, the same can be said for politics. 2016 has triggered an uncertain climate following Britain's vote to exit the EU. Just how the 'Brexit' will impact on oncology and cancer research across Europe remains to be seen, but serious concerns have been widely expressed by leading experts. Prior to the 'divorce' a duo of commentaries and accompanying editorial published in *The Lancet Oncology* [6], outlined the potential consequences from both the UK and European perspectives.

Now more than ever, all stakeholders in oncology must stand together, actively engage with the policy makers and politicians, and collectively identify the necessary next steps to protect our cross-border partnerships, strengthen our research through continued funding, and promote the mobility and exchange of talent throughout our laboratories and hospitals.

'Brexit' is a reality but must not translate into broken.

Over the past decade, we at VHIO have been dedicated to breaking down barriers, not only between basic and clinical research communities but also between nations across Europe and beyond. Cancer knows no boundaries and we shall not let something like Brexit sidetrack us from our passion and our mission to break this disease.

According to a study published in *JAMA Oncology* [7], in 2015 there were an estimated 17.5 million cancer cases globally and 8.7 million deaths. Each and every one of us on this planet have, either directly or indirectly, been affected by this hideous disease. Only with the continued and most appreciated support received from our dedicated and dear institutional supporters -- Generalitat de Catalunya, Fundació Privada CELLEX, Fundació Bancaria "la Caixa", Fundación BBVA, as well as our many other supporters including funding entities, agencies, associations, fundraisers, and individual donors, can we at VHIO determinedly continue to more speedily advance personalized and targeted therapies against cancer.

As this year's Report goes to print, we recently received the sad news of the passing of one of the greatest supporters of biomedical research and healthcare across Catalonia, Dr. Pere Mir, Founder and President of the Fundació Privada CELLEX which he created in 2002. I take this opportunity to recognize his immeasurable generosity, backing and belief in our Institute (as well as many others). Without his support, VHIO would not have been able to mark the many milestones to date in its development, expansion, and contribution to advancing cancer research and improving outcomes for patients.

I have been extremely fortunate and honoured to have known such a remarkably kind human being, a true gentleman and scholar. Needless to say, he will be sorely missed by all.

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

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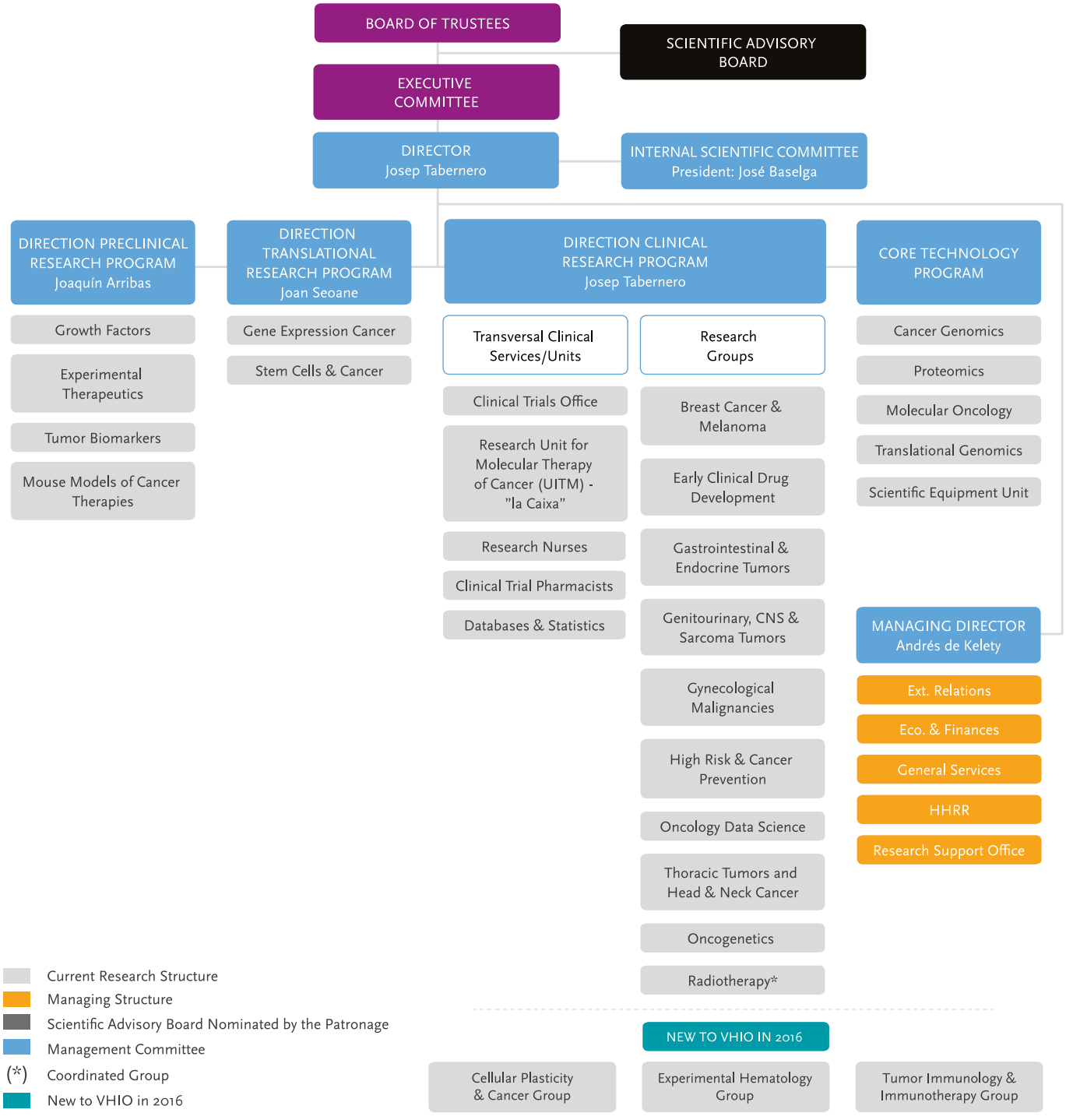
# VHIO IN 2016: TURNING 10 AND DEFINING 'NEXT GEN' DIRECTIONS

## Who we are and what we do

### VHIO's Organigram 2016

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:

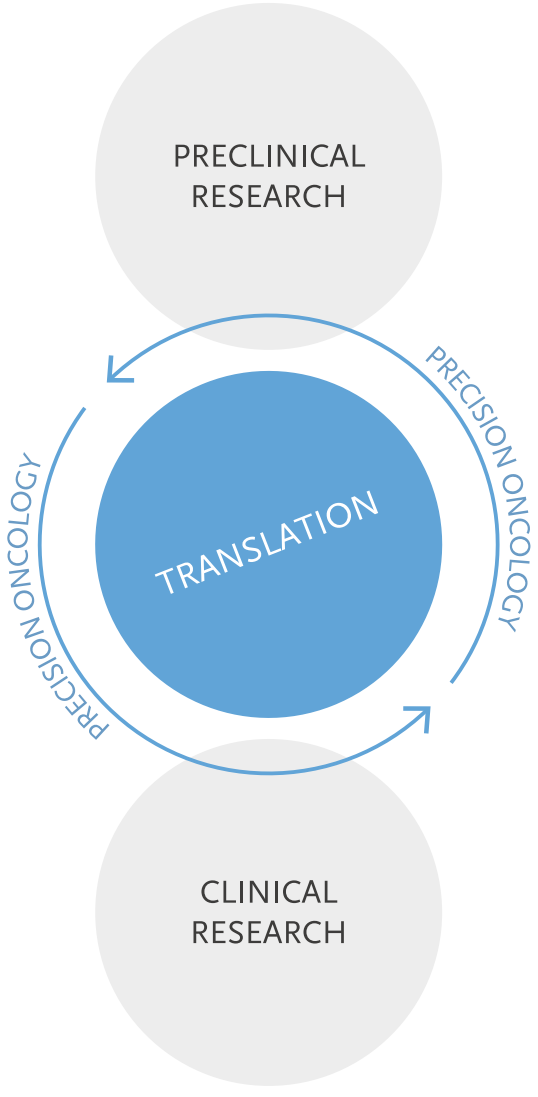


# VHIO's translation toward precision oncology: a little more on how we did it in 2016

Aside from the many highlights described by each of our programs and groups in this report, we would like to underline a few other important factors and developments in 2016 that enabled us to further advance cancer discovery through the integration and translational science and clinical research within a multidisciplinary setting - the winning formula behind what we do and how we do it at VHIO year in, year out.

Celebrating its 10th birthday, VHIO is a leading comprehensive cancer center of excellence where its scientists and research physicians adopt a purely translational research model, working together as multidisciplinary teams to both accelerate and advance more precise and effective targeted therapies against cancer.

Undertaking one of Spain's most dynamic cancer research programs, VHIO is dedicated to delivering on the promise of precision medicine in oncology – turning cancer discovery into more powerfully tailored treatments and better practice for the care of our patients.




## Oncogenomics and prescreening

At the core of VHIO's research activities lies our suite of cutting-edge core technology platforms which allow our expert teams to apply next-generation whole-genome sequencing for precision oncology as well as develop and improve existing applications to drive faster results. By sequencing panels of genes or entire genomes in cancer patients, we are now better equipped than ever before to identify specific molecular risk factors and better predict the potential efficacy of specific agents matched to the specificities individual patients.

VHIO's Cancer Genomics Group headed by Ana Vivancos, serves as a Core Technology laboratory to bridge the preclinical and clinical levels of cancer discovery. Her lab is equipped with a genotyping platform (MassARRAY, Sequenom), an n-counter (Nanostring) platform, two digital PCR platforms (BEAMing, Sysmex, and Droplet Digital PCR (ddpCR) Bio-Rad technology), and a duo of NextGen Sequencers; MiSeq and HiSeq2500, Illumina. These technologies accelerate our research efforts of our preclinical, translational and clinical scientists, enabling the identification of mechanisms of resistance to targeted therapies, the study of clonal populations, as well as defining novel therapeutic opportunities based on mutation profiles.

VHIO's BEAMing digital PCR/flow cytometry technology

VHIO's Prescreening Program, pioneered by VHIO's Cancer Genomics Group and Molecular Oncology Group led by Paulo Nuciforo, performs molecular profiling in over 1500 patients per year as candidates for enrollment in Phase I clinical trials carried out at our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", directed by Jordi Rodón. Suitability for enrollment in a given trial is evaluated based on the genomic or pathologic profile of individual patients. Our capacity to more precisely match individual patients with a particular clinical study represents a significant forward step in the collective and collaborative ambition to deliver on the true promise of personalized treatment and care in oncology.

As a reflection of our dedication to excellence and quality services we provide, we continue to undergo ISO 15189 accreditation for our main testing methods and our prescreening efforts have already established VHIO as one of the few centers in Europe to run such a comprehensive program. We will continue to expand our efforts to an increasing number of patients thanks to the VHIO - Catalan Institute of Oncology (ICO) Research Alliance, representing the biggest clinical care provider in Catalonia.

As updated by our Director in his Foreword, in collaboration with Merck Serono and Sysmex Inostics, we continue to employ our in-house Digital-PCR Platform, BEAMING liquid biopsy RAS biomarker technology, for the detection of RAS mutations in first-line metastatic colorectal cancer.

While we are already seeing how this avant-garde approach is promising a more precise treatment for metastatic colorectal cancer patients by improved stratification of which patients stand to benefit from anti-EGFR therapies, we will aim to further develop and empower this technology towards its application to conventional care across an increasing number of tumor types.

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

## Driving early drug discovery and novel clinical studies matched to the molecular make-up of individual patients

Obra Social "la Caixa"

VHIO continues to establish itself as a leading reference in progressing drug development and targeted therapies against cancer. It has been able to do so not only through the bridging and tight connectivity between health care professionals, VHIO researchers and physician-scientists, but also through its Research Unit for Molecular Therapies of Cancer (UITM) "la Caixa" (see pages 78-79) and Clinical Trials Office located in the patient care environment of the Vall d'Hebron University Hospital.

At the close of 2016, VHIO further expanded its management team by recruiting another leading talent, Elena Garralda, as Executive Director of the UITM.

Research at the UITM is led by Jordi Rodón's Early Clinical Drug Development Group (pages 46 - 47), and focuses on the development of novel agents based on the molecular profile of each tumor as well as the optimization of treatment regimens using combinations of new drugs with existing ones. In 2016, 115 Phase I clinical trials and 14 basket studies were performed at our Unit with a total of 453 patients enrolled. Our Clinical Trials Office, directed by Gemma Sala, coordinates a large portfolio of Phase I – II – III studies and consistently reports an increase in the number of trials conducted each year. In 2016 the number of patients included in our studies totaled at 1129 across 354 actively recruiting trials.

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

Vall d´Hebron Hospital


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 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. Research at VHIO therefore benefits immensely from its privileged location; just a few meters away from the Campus, and the superb interaction and teamwork with clinical colleagues at HUVH.

## VHIO discovery aimed at dismantling cancer's armory

Commandeering research aimed at combating cancer, our preclinical, translational and clinical researchers as corresponding/senior authors or co-authors, published 240 scientific articles in 2016 (73% Q1), with a cumulative Impact Factor (IF) totalling at 1918,57 and a Median Impact Factor (MIF) of 7,99. These figures reflect an increase in scientific productivity as well as the importance of VHIO's research contribution to the oncology field.

For the complete list of articles published by VHIO researchers and physician-scientists in 2016 see pages 92-105. To view this year's selection of just some of the most relevant articles by VHIO Faculty published in 2016, refer to pages 16-17.

## VHIO's Animal Facility: key to advancing predictive cancer models

Occupying the basement of our building and serving as a shared facility across the Vall d'Hebron Barcelona Hospital Campus, our Animal Facility has a surface area of 1347 $m^2$ and is equipped with nearly 5500 cages. This facility incorporates the latest platforms and technologies, including

a high-sensitivity in vivo imaging technology platform, computed tomography (CT) for high-resolution 3D imaging, and a MicroPET R4 scanner engineered for analyzing small animal models of human disease. VHIO's expertise in developing and rendering cancer models including patient-derived xenografts (PDX) more precise and predictive, will further expand thanks to these cutting-edge technologies.


2016 marked the opening of VHIO's cutting-edge Animal Facility.

## In pursuit of new emerging research areas at VHIO

As introduced by VHIO's Director, Josep Tabernero, in his Foreword to this Report, we were fortunate to attract the following trio of new talents to our Institute in 2016:

Francesc Bosch, Principal Investigator of VHIO's Experimental Hematology Group, Professor of Hematology and Head of the Department of Hematology, the Vall d'Hebron University Hospital (HUVH).

María Abad, Principal Investigator, VHIO's Cellular Plasticity & Cancer Group.

Alena Gros, Principal Investigator, VHIO's Tumor Immunology & Immunotherapy Group

As Principal Investigator of VHIO's Experimental Hematology Group, Francesc Bosch will lead the development of early phase clinical studies and define new prognostic and predictive factors. More specifically, his group will unmask the mechanisms involved in pathogenesis of hematological neoplasias, lead preclinical research into new therapeutic regimens in experimental models that mimic the tumoral microenvironment using primary cells and PDXs, and define novel biomarkers for a more rational and precise treatment of patients.

Heading up VHIO's Cellular Plasticity and Cancer Group, María Abad's team will focus on advancing insights into the interplay between reprogramming, cellular plasticity and cancer. Her group plans to identify the molecular mechanisms that rule the acquisition of stem cell properties during tumorigenesis, and determine the impact of inducing cellular dedifferentiation in various stages of tumorigenesis and in the resistance of cancer cells to chemotherapeutics, and establish chemical compounds that specifically target cancer stem cells.

Leading VHIO's Tumor Immunology and Immunotherapy Group, Alena Gros will head research to achieve a better understanding of the naturally occurring T-cell response to cancer, and identify ways in which to exploit these responses towards developing more powerful and precise anti-cancer immunotherapies. Her group will also establish whether the presence of lymphocytes recognizing mutated antigens is associated with response, and advanced personalized T-cell therapies to treat metastatic colorectal cancer.

For more information about our three new groups see pages 85-91.

## Cross-border collaborations of excellence

In 2016 VHIO has continued to significantly contribute to several European and International Consortia of excellence (pages 108 – 109).

Important updates concerning our participation in existing collaborations are as follows:

Cancer Core Europe

Launched back in 2014, Cancer Core Europe – a European cancer association conducting pioneering research aimed at propelling cancer medicine into a new era, is championed by its six founding partners and comprehensive cancer Institutes of renowned excellence: Gustave Roussy (Villejuif, France), Cambridge Cancer Centre (Cambridge, UK), Karolinska Institutet (Stockholm, Sweden), Netherlands Cancer Institute – NKI (Amsterdam, The Netherlands), German Cancer Research Center & National Center for Tumor Diseases – DKFZ-NCT (Heidelberg, Germany), and VHIO.

Its pooling of exchange of expertise, research findings, common platforms and processes, empowers researchers

and clinicians to rapidly exploit this trove of biological insights and clinical data for the benefit of patients. Driving this pioneering undertaking are the task forces comprised of researchers, clinicians, biostatisticians, and imaging and IT specialists from across the six member centers who are responsible for identifying challenges, sharing best practices, harmonizing procedures, establishing recommendations, and launching new common research projects.

In collaboration with an appointed expert from each of the six founding centers, VHIO co-directs its Clinical Trials, Data Sharing, Molecular Diagnostics, Immuno-Oncology, Training and Education Task Forces.

This year, VHIO's Early Clinical Drug Development Group and our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", both directed by Jordi Rodón, have led the design of the Cancer Core Europe's endorsed Basket of Baskets (BoB) trial. This academic study, set to launch next year, integrates molecular prescreening, the development of new diagnostic tests such as circulating DNA, with the testing of targeted therapies in populations of patients who, matched to the molecular alterations detected in their respective tumors, will be most likely to benefit from them.
**www.cancercoreeurope.eu.**

MoTriColor

Fueled by the European Union's Horizon 2020 research and innovation programme, MoTriColor (Molecularly guided Trials with specific treatment strategies in patients with advanced newly molecular defined subtypes of Colorectal cancer), is a four year project led by VHIO and powered by a total of eight clinical centers of excellence across Europe.

Dedicated to conducting three clinical trials, colorectal cancer patients with advanced disease will for the first time be stratified based on their gene expression profiles according to recently established predictive signatures. Response and resistance to selected therapies will be tracked by liquid biopsy.

Using these pioneering approaches, MoTriColor aims at identifying sensitivity of individual patients to the proposed experimental therapies and develop more precise anti-cancer treatments for these patients.

2016 marked the initiation of the prescreening of patients from the different clinical sites and enrollment in the MoTriColor studies will commence next year. In addition, comprehensive translational research will be performed using the patients' samples through the INTRACOLOR project (supported by EU H2020's TRANSCAN-2 ERA NET) – also coordinated by VHIO.
**www.motricolor.eu**

WIN
Worldwide Innovative Networking in personalized cancer medicine

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

With enrollment for the WINTHER (WINTherapeutics) clinical trial completed, results are currently being analyzed. This unique academic and international study which launched in 2012, has led to the design of a second innovative WIN trial: Survival Prolongation by Rationale Innovative Genomics (SPRING). Bringing key stakeholders from industry and academia, this collaborative undertaking will firmly center on advancing precision medicine against lung cancer.
**www.winconsortium.org**

## New partnerships in 2016

Roche

Powered by Roche and Genentech, a global partnership connecting 21 academic centers and leading experts in cancer immunotherapy: immunotherapy Centres of Research Excellence (imCORE) Network, launched in 2016.

Working in collaboration with scientists from Roche and Genentech, renowned researchers and physician-scientists in cancer immunotherapy from across the globe have joined together to drive the application and extension of novel immune-based therapeutics to more tumor types as well as advance research into the cellular and molecular mechanisms modulating immune response to cancer.

The goal is to rapidly initiate pre-clinical and clinical research based on the latest scientific discoveries and to aggregate and share data to accelerate the search for cures for cancer patients. This unique network will significantly contribute to advancing anti-cancer immunological strategies and advance discovery aimed at ultimately benefiting patients who may stand to gain from novel immune agents as mono therapy or in combination.

Among the 21 different academic partners, VHIO and the Clinical University of Navarra are the only two to have been selected from within Spain.
**www.roche.com**

# NoCanTher

Funded through a grant received from the European Union's Horizon 2020 research and innovation programme, NoCanTher – Nanomedicine upscaling for early clinical phases of multimodal cancer therapy – comprises five Spanish institutions: VHIO, Spanish National Cancer Research Centre (CNIO), Vall d'Hebron Research Institute (VHIR), Biopraxis, and IMDEA Nanoscience, in partnership with Trinity College Dublin (Ireland), Jena University Hospital (Germany), Paris Diderot University (France), Resonant Circuits Ltd. (UK), Immupharma Plc (UK), and Chemicell GmbH (Germany).

Led by IMDEA Nanoscience, this collaboration represents an important forward step in utilizing nanoparticles than can better target and more precisely combat cancer cells. It aims to build 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.

More specifically, NoCanTher will assess this nano-based approach and provide preliminary data on its efficacy in humans and seeks to translate these preclinical findings into early clinical development for the treatment of pancreatic cancer.

**www.nocanther-project.eu**

Phd PI3K biology in health & disease

The PhD PI3K biology in health & disease Network incorporates ten academic, clinical and industrial partners with renowned expertise in research focused on PI3K signaling. This unique training network 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 inspired program not only represents unparalleled educational opportunity for these young scientists, but will also ultimately increase the international competitiveness of European research in PI3K discovery and drug development.
**www.pi3k-phdproject.eu**

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

Obra Social "la Caixa"

**Cancer Therapeutic Resistance - Progress and Perspectives. The Biocat and Obra Social "la Caixa" B-Debate, 07 – 08 April 2016**

Co-Organized by the Catalan Institute of Oncology (ICO), the Program Against Therapeutic Resistance (ProCURE), and VHIO, *Cancer Therapeutic Resistance: Progress and Perspectives*, 07 – 08 April 2016, celebrated at the CosmoCaixa Science Museum of the Fundació Bancària "la Caixa" in Barcelona, provided unparalleled opportunity to discuss and debate the very latest insights aimed at tackling the major obstacle in combating cancer: resistance to anti-cancer therapies.


Left to right: Joaquín Arribas, Co-Chair (VHIO), Albert Barberà, Director of Biocat, Jordi Portabella, Director of the Research and Knowledge Area of the Fundació Bancària "la Caixa", Miguel Angel Pujana, Co-Chair (ProCURE, ICO).

Thanks to the co-chairmanship of Miguel Angel Pujana (ProCURE, ICO) and Joaquín Arribas (VHIO), coupled with an outstanding panel of world-class speakers, participants and speakers alike exchanged expertise and explored experiences from a variety of different perspectives at preclinical, translational, and clinical research levels.

This two-day meeting highlighted both the opportunities and current challenges surrounding novel strategies and approaches that promise to overcome drug resistance and counteract tumor cell spread factors through the development of more effective and precise targeted therapies.

Just some of the many must-have conversations centered on and around the application and extension of immunotherapies to different tumor types, the cancer genome and epigenome and how latest data is being applied to advance cancer detection, monitoring and therapy, as well as current therapeutic strategies matched to molecular subtypes of disease and new avenues for molecularly targeted therapy against metastatic disease.

The meeting also updated on the latest translation of cancer 'omic' intelligence into accelerated development and application of personalized cancer medicine, explored current preclinical models and programs that track cancer progression and predict response to anti-cancer drugs, and delivered insights into the development of therapies and approaches targeted at CSCs in order to better forecast outcomes and checkmate therapeutic resistance.

In short, this first-class B-Debate meeting tiggered the many must-have conversations in our collective and determined efforts to reverse cancer drug resistance.

To view the meeting report online visit:
**www.biocat.cat/en/reportages/synopsis-bdebate-treating-cancer-fight-against-resistance.**

**Towards Predictive Cancer Models, 26 – 27 May 2016: empowering predictive cancer models by pooling knowledge and sharing perspectives**


Symposium Organizers and Co-Chairs: VHIO's Laura Soucek and Joaquín Arribas

Supported by an educational grant from the Fundació Bancària "la Caixa", VHIO organized a two-day International Symposium aimed at empowering predictive cancer models by exploring the most relevant and recent advances in predictive cancer science: *Towards Predictive Cancer Models,* 26 – 27 May 2016, Barcelona.

Co-chaired by Joaquín Arribas, Director of Preclinical Research at VHIO, and Laura Soucek, Principal Investigator of VHIO's Mouse Models of Cancer Therapy Group this meeting par excellence convened internationally acclaimed experts within the field to share, debate and exchange the very latest data, discuss how best to report, validate and share results, and roadmap next directions in building on the undeniable progress marked to-date by each model under the lens throughout the course of the Symposium.

During the meeting, some of the most important talks also focused on future study design, explored the 'tried, tested and validated' of a variety of modelling systems and combined approaches across various tumor types, and delivered cutting-edge data coming from within the 'stable' of novel contenders - organoids and PDX models. Additional conversation centered on how data from preclinical models can be complementary to tumor genetic testing and thus push the boundaries of sequence-based approaches.

By illustrating how current efforts aimed at advancing today's array of modeling systems are providing increasingly more predictive data as well as better evidencing reproducibility in science before moving to the clinic, this Symposium represented an important forward step in progressing prediction science against cancer.

As a reflection of the scientific program of excellence, *Nature Reviews Cancer* sponsored two poster prizes that were awarded to the top two posters – selected among some 50 accepted abstracts. The prize winners were Daniel Massó Vallés, VHIO's Mouse Models of Cancer Therapies Group, and Irene Gutierrez Perez, the Instituto de Neurociencias de Alicante (Alicante, Spain).

To consult the Meeting Report published in *Drugs Today*, please see: Cancer Therapeutic Resistance: Progress and Perspectives (April 7 – 8, 2016 – Barcelona). Hutchinson E; Pujana MA; Arribas J. 2016. *Drugs Today (Barc)*. 52: 347-354.

## VHIO's 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 as well as VHIO Faculty presenting at International cancer conferences of excellence.

Exchanging latest discovery in cancer science and medicine, VHIO organized and hosted a total of 29 Courses, Workshops, Observerships and Perceptorships in 2016.

**1- Breast Cancer Educational Programme: HER2+ Breast Cancer – Challenges and Unanswered Questions**, 04 - 05 April 2016, Coordinator: Javier Cortés **2-Medical Education Program Cervical Cancer**, 14 - 15 April 2016, Coordinator: Ana Oaknin **3. Towards New Horizons in Metastasic Colorectal Cancer**, 25 October 2016, Director: Josep Tabernero

Launched in February 2016 by Co-Chairs and Founders Verónica Rodilla and Jordi Martínez Quintanilla, Post-Doctoral Fellows of VHIO's Growth Factors and Stem Cells & Cancer Groups respectively, our monthly 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 currently underway, they can also express their ideas surrounding a given topic presented at each seminar; the specially crafted informal format favors free thought, flow, and interaction between the speakers and participants.

**For more information about all our events in 2016 and much more, we invite you to browse our extended Scientific Report 2016 online at: memorias.vhio.net/2016**

# SCIENTIFIC PRODUCTIVITY: RESEARCH ARTICLES

## Articles published in 2016

In 2016, 240 scientific articles (73% Q1) were published by VHIO researchers as corresponding/senior or co-authors with a cumulative Impact Factor (IF) totaling at 1918,57 and a Median Impact Factor (MIF) of 7,99.

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

Figure I: Number of articles published by VHIO researchers from 2007 - 2016

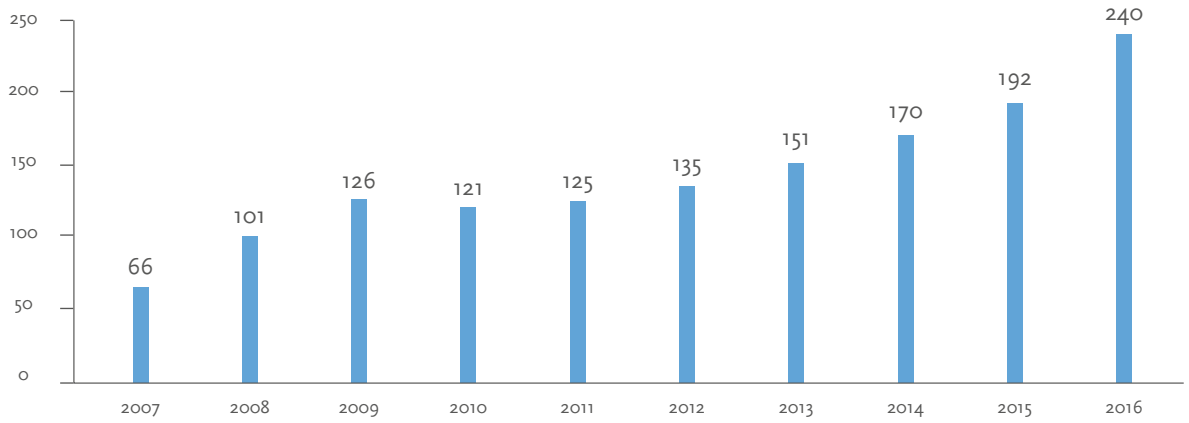
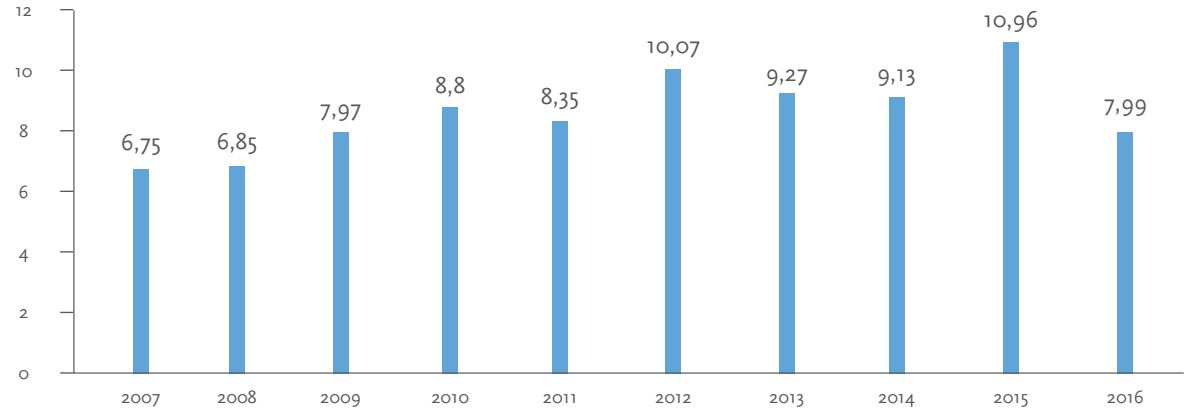



Figure II: Median Impact Factor of papers published by VHIO faculty from 2007 – 2016




For the complete list of VHIO scientific articles published in 2016 in journals with allocated Impact Factor please see pages 92-105. To view a selection of most relevant articles by VHIO researchers published in 2016 please refer to pages 16-17 of this Scientific Report.

To consult publications per group as selected by our Principal Investigators, visit the extended version of this Scientific Report online at: **http://memorias.vhio.net/2016**

# SELECTION OF SOME OF THE MOST RELEVANT ARTICLES BY VHIO RESEARCHERS PUBLISHED IN 2016

Below is a selected list of articles published by VHIO researchers in 2016 with respective Impact Factors indicated. For the complete list of VHIO scientific articles published in 2016 in journals with allocated Impact Factor please see pages 92-105 of this Scientific Report.

Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. Reck M; Rodríguez-Abreu D; Robinson AG; Hui R; Csoszi T; Fülöp A; Gottfried M; Peled N; Tafreshi A; Cuffe S; O'Brien M; Rao S; Hotta K; Leiby MA; Lubiniecki GM; Shentu Y; Rangwala R; Brahmer JR; KEYNOTE-024 Investigators. 2016. *N Engl J Med.* 375: 1823-1833. IF: 59,558

Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Wang-Gillam A; Li CP; Bodoky G; Dean A; Shan YS; Jameson G; Macarulla T; Lee KH; Cunningham D; Blanc JF; Hubner RA; Chiu CF; Schwartsmann G; Siveke JT; Braiteh F; Moyo V; Belanger B; Dhindsa N; Bayever E; Von Hoff DD; Chen LT; NAPOLI-1 Study Group. 2016. *Lancet.* 387: 545-557. IF: 44,002

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. Herbst RS; Baas P; Kim DW; Felip E; Pérez-Gracia JL; Han JY; Molina J; Kim JH; Arvis CD; Ahn MJ; Majem M; Fidler MJ; de Castro G; Garrido M; Lubiniecki GM; Shentu Y; Im E; Dolled-Filhart M; Garon EB. 2016. *Lancet.* 387: 1540-1550. IF: 44,002

Ionic immune suppression within the tumour microenvironment limits T cell effector function. Eil R; Vodnala SK; Clever D; Klebanoff CA; Sukumar M; Pan JH; Palmer DC; Gros A; Yamamoto TN; Patel SJ; Guittard GC; Yu Z; Carbonaro V; Okkenhaug K; Schrump DS; Linehan WM; Roychoudhuri R; Restifo NP. 2016. *Nature.* 537: 539-0. IF: 38,138

Tissue damage and senescence provide critical signals for cellular reprogramming in vivo. Mosteiro L; Pantoja C; Alcazar N; Marión RM; Chondronasiou D; Rovira M; Fernandez-Marcos PJ; Muñoz-Martin M; Blanco-Aparicio C; Pastor J; Gómez-López G; De Martino A; Blasco MA; Abad M; Serrano M. 2016. *Science.* IF: 34,661

Breast cancer risk variants at 6q25 display different phenotype associations and regulate ESR1, RMND1 and CCDC170. Dunning AM; Michailidou K; Kuchenbaecker KB; Thompson D; French JD; Beesley J; Healey CS; Kar S; Pooley KA; Lopez-Knowles E; Dicks E; Barrowdale D; Sinnott-Armstrong NA; Sallari RC; Hillman KM; Kaufmann S; Sivakumaran H; Marjaneh MM; Lee JS; Hills M; Jarosz M; Drury S; Canisius S; Bolla MK; Dennis J; Wang Q; Hopper JL; Southey MC; Broeks A; Schmidt MK; Lophatananon A; Muir K; Beckmann MW; Fasching PA; Dos-Santos-Silva I; Peto J; Sawyer EJ; Tomlinson I; Burwinkel B; Marme F; Guénel P; Truong T; Bojesen SE; Flyger H; González-Neira A; Perez JI; Anton-Culver H; Eunjung L; Arndt V; Brenner H; Meindl A; Schmutzler RK; Brauch H; Hamann U; Aittomäki K; Blomqvist C; Ito H; Matsuo K; Bogdanova N; Dörk T; Lindblom A; Margolin S; Kosma VM; Mannermaa A; Tseng CC; Wu AH; Lambrechts D; Wildiers H; Chang-Claude J; Rudolph A; Peterlongo P; Radice P; Olson JE; Giles GG; Milne RL; Haiman CA; Henderson BE; Goldberg MS; Teo SH; Yip CH; Nord S; Borresen-Dale AL; Kristensen V; Long J; Zheng W; Pylkäs K; Winqvist R; Andrulis IL; Knight JA; Devilee P; Seynaeve C; Figueroa J; Sherman ME; Czene K; Darabi H; Hollestelle A; van den Ouweland AM; Humphreys K; Gao YT; Shu XO; Cox A; Cross SS; Blot W; Cai Q; Ghoussaini M; Perkins BJ; Shah M; Choi JY; Kang D; Lee SC; Hartman M; Kabisch M; Torres D; Jakubowska A; Lubinski J; Brennan P; Sangrajrang S; Ambrosone CB; Toland AE; Shen CY; Wu PE; Orr N; Swerdlow A; McGuffog L; Healey S; Lee A; Kapuscinski M; John EM; Terry MB; Daly MB; Goldgar DE; Buys SS; Janavicius R; Tihomirova L; Tung N; Dorfling CM; van Rensburg EJ; Neuhausen SL; Ejlertsen B; Hansen TV; Osorio A; Benitez J; Rando R; Weitzel JN; Bonanni B; Peissel B; Manoukian S; Papi L; Ottini L; Konstantopoulou I; Apostolou P; Garber J; Rashid MU; Frost D; EMBRACE; Izatt L; Ellis S; Godwin AK; Arnold N; Niederacher D; Rhiem K; Bogdanova-Markov N; Sagne C; Stoppa-Lyonnet D; Damiola F; GEMO Study Collaborators; Sinilnikova OM; Mazoyer S; Isaacs C; Claes KB; De Leeneer K; de la Hoya M; Caldes T; Nevanlinna H; Khan S; Mensenkamp AR; HEBON; Hooning MJ; Rookus MA; Kwong A; Olah E; Diez O; Brunet J; Pujana MA; Gronwald J; Huzarski T; Barkardottir RB; Laframboise R; Soucy P; Montagna M; Agata S; Teixeira MR; kConFab Investigators; Park SK; Lindor N; Couch FJ; Tischkowitz M; Foretova L; Vijai J; Offit K; Singer CF; Rappaport C; Phelan CM; Greene MH; Mai PL; Rennert G; Imyanitov EN; Hulick PJ; Phillips KA; Piedmonte M; Mulligan AM; Glendon G; Bojesen A; Thomassen M; Caligo MA; Yoon SY; Friedman E; Laitman Y; Borg A; von Wachenfeldt A; Ehrencrona H; Rantala J; Olopade OI; Ganz PA; Nussbaum RL; Gayther SA; Nathanson KL; Domchek SM; Arun BK; Mitchell G; Karlan BY; Lester J; Maskarinec G; Woolcott C; Scott C; Stone J; Apicella C; Tamimi R; Luben R; Khaw KT; Helland Å; Haakensen V; Dowsett M; Pharoah PD; Simard J; Hall P; García-Closas M; Vachon C; Chenevix-Trench G; Antoniou AC; Easton DF; Edwards SL. 2016. *Nat Genet.* 48: 374-386. IF: 31,616

PIM1 kinase regulates cell death, tumor growth and chemotherapy response in triple-negative breast cancer. Brasó-Maristany F; Filosto S; Catchpole S; Marlow R; Quist J; Francesch-Domenech E; Plumb DA; Zakka L; Gazinska P; Liccardi G; Meier P; Gris-Oliver A; Cheang MC; Perdrix-Rosell A; Shafat M; Noël E; Patel N; McEachern K; Scaltriti M; Castel P; Noor F; Buus R; Mathew S; Watkins J; Serra V; Marra P; Grigoriadis A; Tutt AN. 2016. *Nat Med.* 22: 1303-1313. IF: 30,357

Prospective identification of neoantigen-specific lymphocytes in the peripheral blood of melanoma patients. Gros A; Parkhurst MR; Tran E; Pasetto A; Robbins PF; Ilyas S; Prickett TD; Gartner JJ; Crystal JS; Roberts IM; Trebska-McGowan K; Wunderlich JR; Yang JC; Rosenberg SA. 2016. *Nat Med.* 22: 433-0. IF: 30,357

A Biobank of Breast Cancer Explants with Preserved Intra-tumor Heterogeneity to Screen Anticancer Compounds. Bruna A; Rueda OM; Greenwood W; Batra AS; Callari M; Batra RN; Pogrebniak K; Sandoval J; Cassidy JW; Tufegdzic-Vidakovic A; Sammut SJ; Jones L; Provenzano E; Baird R; Eirew P; Hadfield J; Eldridge M; McLaren-Douglas A; Barthorpe A; Lightfoot H; O'Connor MJ; Gray J; Cortes J; Baselga J; Marangoni E; Welm AL; Aparicio S; Serra V; Garnett MJ; Caldas C. 2016. *Cell.* 167: 260-27422. IF: 28,710

Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Kim DW; Mehra R; Tan DS; Felip E; Chow LQ; Camidge DR; Vansteenkiste J; Sharma S; De Pas T; Riely GJ; Solomon BJ; Wolf J; Thomas M; Schuler M; Liu G; Santoro A; Sutradhar S; Li S; Szczudlo T; Yovine A; Shaw AT. 2016. *Lancet Oncol.* 17: 452-463. IF: 26,509

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# PROGRAMS

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# PRECLINICAL RESEARCH

# PRECLINICAL RESEARCH

› EXPERIMENTAL THERAPEUTICS GROUP

› GROWTH FACTORS GROUP

› MOUSE MODELS OF CANCER THERAPIES GROUP

› TUMOR BIOMARKERS GROUP

DIRECTOR, PRECLINICAL RESEARCH PROGRAM

# JOAQUÍN ARRIBAS

"We strive to advance prediction science against cancer by developing xenograft models to study tumorigenesis, elucidate the cross-talk between tumor cells and the microenvironment, and evaluate the efficacy of novel therapies. By upping the tempo in unmasking mutations and mechanisms of resistance to current anti-cancer medicines we are ultimately contributing to improved outcomes for patients."

VHIO's Preclinical Program is dedicated to establishing how highly aggressive tumors affecting the breast, pancreas, colon, lung, or brain can be treated more precisely. 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 therapy, resulting in poor prognosis. The overarching goal of our Program is to investigate novel anti-cancer treatment approaches for these patients and to unveil mechanisms of resistance to currently available cancer medicines.

To deliver on this ambition, VHIO's Mouse Models of Cancer Therapies led by Laura Soucek has developed a novel therapeutic strategy consisting of the inhibition of Myc, an oncogene activated in many of the aforementioned tumors, based on peptides that enter the cell and block Myc. This novel approach has been recognized through several grants, including those awarded by the European Commission's Horizon 2020 program, the European Commission's European Research Council's Proof-of-Concept, the Institute of Health Carlos III (ISCIII), the Spanish Ministry of Economy, Industry and Competitiveness, FERO Foundation, and BBVA Foundation. In addition, Laura has attracted funding from the EIT Health Summit as well as the Catalan Agency for Trade and Investment (ACCIÓ), to develop this therapy with Peptomyc S.L. - a start-up company based at VHIO.

Our Experimental Therapies Group headed by Violeta Serra focuses on understanding the mechanism of action and resistance to targeted therapy in breast cancer, with special emphasis on the blockade of the PI3K and CDK4/6 to overcome endocrine resistance, as well as treatments targeting homologous recombination deficiency. They have further established novel patient tumor-derived breast cancer models *in vivo*. These preclinical models have shown to faithfully recapitulate the clinical setting and have been extremely useful in the study of resistance to anti-cancer therapies. Of particular note, Violeta's group has established that RAD51 nuclear foci formation, a marker of DNA repair by homologous recombination, is associated with resistance to PARP inhibitors. Her group's research of excellence has been recognized through support received from funding entities including the European Commission's Horizon 2020 ERA (European Research Area) NET and Marie Skłodowska-Curie Innovative Training Networks (ITN-ETN) programs, the Susan G. Komen Foundation, the Institute of Health Carlos III (ISCIII), and the Agency for Management of University and Research Grants (AGAUR).

VHIO's Tumor Biomarkers Group directed by Josep Villanueva re-routed its principal focus of research three years ago which has this year crystallized in the form of additional funding received from the Susan G. Komen Foundation, the Institute of Health Carlos III (ISCIII), and most recently, important support from the pharmaceutical company Servier. This has led to the recruitment of additional lab members to enable the expansion of his group. More specifically, Josep's team has transitioned from studying the cancer secretome following a methodology-driven approach to a more biologically-focused one, where non-classical secretion pathways play an important role. They will consequently continue to extend their studies to characterizing the non-classical secretome linked to tumor invasion and metastasis.

Finally, my own Growth Factors Group has continued to characterize a subtype of breast cancer known as HER2, and we have expanded our observations to the importance of the cytokine IL-6 in the progression of this tumor type. We have developed, characterized, and identified several new patient-derived xenografts and we are currently adapting them to analyze novel immune therapeutics against breast cancer. In recognition of our efforts, we continue to receive essential support through international and national competitive grants from the European Commission, the Breast Cancer Research Foundation (BCRF), Institute of Health Carlos III (ISCIII), the FERO Foundation, and the Spanish Association Against Cancer (AECC).

In 2016, our groups' findings have been published in several journals of excellence including *Cancer Research, Clinical Cancer Research, Nature Medicine, Oncotarget, Oncoscience,* among others.

PRECLINICAL RESEARCH

# ›EXPERIMENTAL THERAPEUTICS GROUP

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› Marta Guzmán
› Olga Rodríguez

## STRATEGIC GOALS:

› Developing predictive and pharmacodynamic biomarkers of PI3K-pathway as well as CDK4/6 inhibitors.
› Unveiling novel mechanisms of resistance against targeted therapies in germline BRCA1/2 breast cancer.
› Establishing a patient tumor-derived breast cancer preclinical model to explore hypothesis-based combinatorial therapies.

## HIGHLIGHTS:

› Small molecule inhibitors of the CDK4/6 cell cycle kinases have shown clinical efficacy in estrogen receptor (ER)-positive metastatic breast cancer. We have reported that ER-positive breast cancer cells can adapt quickly to CDK4/6 inhibition and evade cytostasis, in part via non-canonical cyclin D1-CDK2 mediated S-phase entry.
› Combined targeting of both CDK4/6 and PI3K triggered cancer cell apoptosis *in vitro* and in patient-derived tumor xenograft (PDX) models, resulting in tumor regression and improved disease control.
› CDK4/6-inhibitor resistance in estrogen receptor positive breast cancer is mediated by early adaptation and bypass of cyclin D1–CDK4/6 dependency through selection of CCNE1 amplification or RB1 loss.
› In breast tumors from *BRCA1*-mutation carriers, resistance to PARP inhibitors is frequently associated with reactivation of functional DNA repair by homologous recombination.
› We have established that lack of RAD51 nuclear foci formation, a functional biomarker of homologous recombination deficiency, correlates with PARP inhibitor response in a panel of over 50 PDX.

## SUMMARY:

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

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

Encouraged by the early success of DNA damage repair inhibitors in germline BRCA1/2 tumors we have initiated a project aimed at identifying response biomarkers of PARP inhibitors (PARPi) and DNA binding agents including PM01183, a novel derivative of trabectedine, in homologous recombination (HR) DNA repair deficient tumors. Our studies underpin the capacity of germline BRCA mutant tumors to recover HR functionality and develop resistance to PARPi. PM01183 is however active in most PARPi resistant tumors, as well as PARPi combinations that bypass cell cycle checkpoints such as WEE1 inhibitors.

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

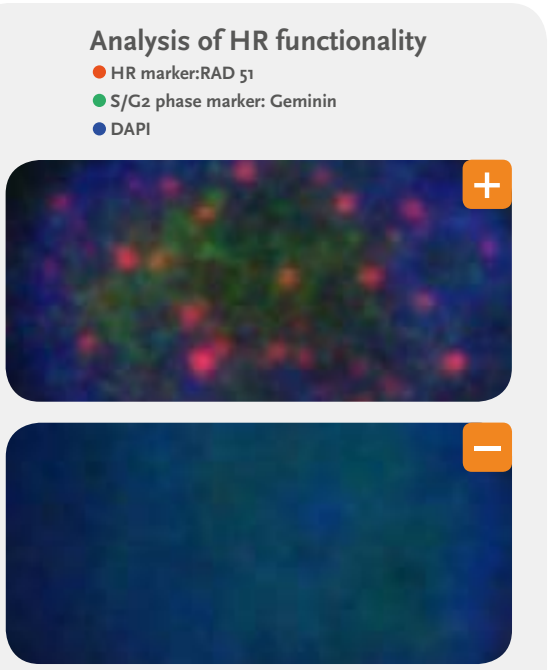


Figure: **RAD51 and DNA repair by homologous recombination functionality.** The homologous recombination (HR) protein RAD51 is recruited to finalize the repair of double strand breaks in HR-competent cells. This biomarker enables the identification of breast tumors that lack HR-functionality and therefore sensitive to PARP inhibitors, both in the BRCA1/2-germline and in the somatic context.

## PI PAPER PICK:

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PRECLINICAL RESEARCH

# ›GROWTH FACTORS GROUP

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**Technicians**
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› Antoni Luque
› David Olivares
› Ismael Varela

## STRATEGIC GOALS:

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

## HIGHLIGHTS:

› Our group has shown that tumors in which the activation of the downstream factor STAT3 depends on IL-6, respond to therapies based on IL-6 blocking antibodies.
› In collaboration with Roche Innovation Center Zurich (RICZ), we have co-developed T cell bispecific antibodies against p95HER2 (p95HER2-TCB). Promising preliminary results have shown p95HER2-TCB as favorable properties for therapeutic application, leading to the filing of a patent in September 2016.
› The project entitled *New Immunotherapies to Treat Colorectal and Breast Cancer*, presented by Beatriz Morancho from our group, was awarded with the 10th FERO Foundation Annual Grant.

## SUMMARY:

Our group is dedicated to studying tumor progression and mechanisms of resistance to therapy in HER2-positive breast cancer as well as the development of novel immunotherapy strategies against this tumor subtype.

We have previously shown that constitutively activated HER2 leads to premature senescence. These senescent cells remain metabolically active and display a remarkable secretory phenotype. We deeply analyzed this secretome and evidenced that it contributes to the prometastatic effect of HER2-induced senescent cells. We extended our studies to naturally-occurring senescent cells in HER2-positive tumors. In this scenario, senescent cells contribute to tumor growth by secreting cytokines that are required for non-senescent cells to proliferate. We identified IL-6 as one of the main contributors and established that the autocrine production of this element by naturally occurring senescent cells promotes growth of HER2-positive tumors.

Throughout 2016 our group has also evaluated the efficacy of anti-IL-6 therapies using breast cancer patient derived xenografts (PDXs). Results indicate that only tumors in which activation of STAT3 depends on IL-6, respond to the blocking antibodies, suggesting the necessary development of functional assays to determine the dependence of STAT3 activation on IL-6, and identify responsive tumors.

Most recently, we have focused on developing tools to better model anti-tumor immunotherapy strategies. The development of humanized PDX models (Hu PDXs), in which the human immune system is established in PDX-bearing immunodeficient mice, has proven a successful approach. We are currently using these models to preclinically validate the efficacy of T cell bispecific antibodies (TCBs).

In addition, our group has been setting up a new line of research focused on pancreatic cancer. In close collaboration with VHIO's Gastrointestinal & Endocrine Tumors Group, led by Josep Tabernero, we are expanding our research to explore resistance mechanisms implicated in the response to targeted therapies against this tumor type.

We are extremely grateful to both the Spanish Association Against Cancer (AECC), and the Breast Cancer Research Foundation (BCRF), for their continued funding of our research. Lastly, after several years' coordination of the Breast Cancer Program of the *Red Territorial de Investigación Cooperativa en Cáncer* (RTICC), supported by the *Instituto de Salud Carlos III* (ISCIII), I am honored to have recently been appointed as Scientific Director of the virtual *Centro de Investigación Biomédica en Red* (CIBER-ONC: Center for the Biomedical Research Network in Oncology). This new network is comprised of several of the most active cancer research groups across Spain. We work in close connectivity to collectively deliver on complex projects requiring the collaboration and expertise of multiple groups.

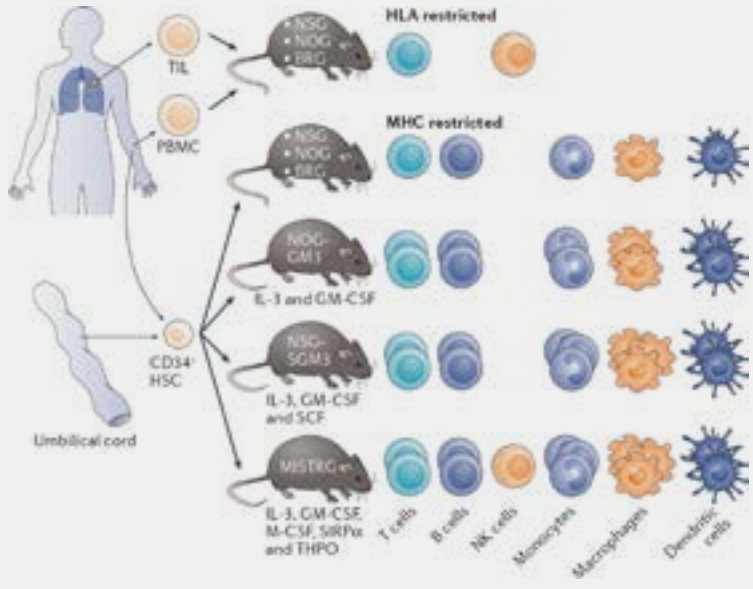


Figure: Strategies to generate humanized PDXs. *Nature Reviews Cancer* (2017) doi:10.1038/nrc.2016.140.

## PI PAPER PICK:

Morancho B, Zacarías-Fluck M, Esgueva A, Bernadó-Morales C, Di Cosimo S, Prat A, Cortés J, Arribas J, Rubio IT. Modeling anti-IL-6 therapy using breast cancer patient-derived xenografts. *Oncotarget.* 2016 Oct 18;7(42):67956-67965.

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Hergueta-Redondo M, Sarrio D, Molina-Crespo Á, Vicario R, Bernadó-Morales C, Martínez L, Rojo-Sebastián A, Serra-Musach J, Mota A, Martínez-Ramírez Á, Castilla MÁ, González-Martin A, Pernas S, Cano A, Cortes J, Nuciforo PG, Peg V, Palacios J, Pujana MÁ, Arribas J, Moreno-Bueno G. Gasdermin B expression predicts poor clinical outcome in HER2-positive breast cancer. *Oncotarget.* 2016 Aug 30;7(35):56295-56308.

Nuciforo, P., Thyparambil, S., Aura, C., Garrido-Castro, A., Marta Vilaro, M., Peg, V., Jimenez, J., Hoos, W., Burrows, J., Todd Hembrough, T., Ferreres, J. C., Perez-Garcia, J., Arribas, J., Cortes, J., and Scaltriti, M. High HER2 protein levels correlate with increased overall survival in breast cancer patients treated with anti-HER2 therapy. *Mol. Oncol.* 2016 Jan;10(1):138-47.

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PRECLINICAL RESEARCH

# ›MOUSE MODELS OF CANCER THERAPIES GROUP

**Principal Investigator**
› Laura Soucek

**Staff Scientist**
› Jonathan Whitfield

**Post-Doctoral Fellows**
› Marie-Eve Beaulieu
› Silvia Casacuberta
› Mariano F. Zacarias

**Graduate Students**
› Toni Jauset González
› Sandra Martínez
› Daniel Massó Vallés

**Technicians**
› Virginia Castillo
› Laia Foradada
› Érika Serrano del Pozo

**Visiting Postdoctoral Scholar**
› Roberta Laranga

## STRATEGIC GOALS:

› Validation of new cell penetrating peptides for cancer therapy.
› Pre-clinical validation of novel anti-Myc therapies in breast, brain, lung, prostate, colorectal cancer, melanoma, and multiple myeloma.
› Define the role of Myc in cancer-associated immune tolerance.
› To evaluate the activity of novel anti-cancer therapies in our panels of breast and pancreatic patient derived xenografts.

## HIGHLIGHTS:

› Laura's laboratory was awarded a European Research Council (ERC) Proof-of-Concept grant within the framework of the EU's Horizon 2020 Program. Title: *Developing an anti-Myc cell-penetrating peptide for cancer treatment.*
› Her group also received a grant from the *Instituto de Salud Carlos III* (Institute of Health Carlos III, ISCIII) for a FIS - *Fondo de Investigación en Salud* (Health Research Fund) to support the project entitled *In vivo validation of innovative anti-Myc therapies in glioblastoma.*
› She also received a *Retos de Colaboración* grant from the Spanish Ministry of Economy, Industry and Competitiveness for the *Preclinical development of Omomyc-CPP as a therapy for cancer treatment*, as well as funding from the FERO Foundation for the project: *Use of liposomal nanotechnology to optimize systemic administration of Omomyc in metastatic breast cancer.*
› In collaboration with Jun Yokota's group, the Institute of Predictive and Personalized Medicine (IMPPC), Badalona - Barcelona, Spain, we demonstrated a dramatic therapeutic impact of Myc inhibition in the treatment of Small Cell Lung Cancer (SCLC) (Fiorentino et al. *Oncotarget* 2016)
› Thanks to another successful year of awards and grants, VHIO's Mouse Models of Cancer Therapies Group has now expanded to incorporate a total of 12 people.
› Peptomyc S.L. was awarded an SME Instrument Phase I by the European Commission within the Horizon 2020 Program. Title: *Feasibility study of a novel treatment for cancer based on a recombinant peptide therapy — PEPTO1.* Of note, this grant was the only one awarded in biotechnology for this specific call.
› Peptomyc S.L. also received a Business Plan Aggregator Prize at the EIT Health Summit, as well as a grant from Catalonia Trade & Investment (a unit of ACCIÓ, the Agency for Business Competitiveness), for the *Pre-clinical development of Omomyc-CPP: characterization of the immune response.*

## 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 approach. However, over the past few years, we have 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, nontoxic 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, and we are validating our new therapeutic strategy in notoriously difficult to treat cancers that are currently resistant to standard therapies and are in dire need of new therapeutic options (i.e. KRas-driven Non-Small Cell Lung Cancer, glioblastoma, and metastatic triple negative breast cancer).

In recognition of research of excellence, Laura's laboratory has been awarded numerous grants since its inception. This year she has received a prestigious European Research Council (ERC) Proof-of-Concept grant within the framework of the EU's Horizon 2020 Program, a grant from the *Instituto de Salud Carlos III* (Institute of Health Carlos III, ISCIII) for a FIS - *Fondo de Investigación en Salud* (Health Research Fund) project, and a grant from the Spanish Ministry of Economy, Industry and Competitiveness within the *Retos de Colaboración* program.

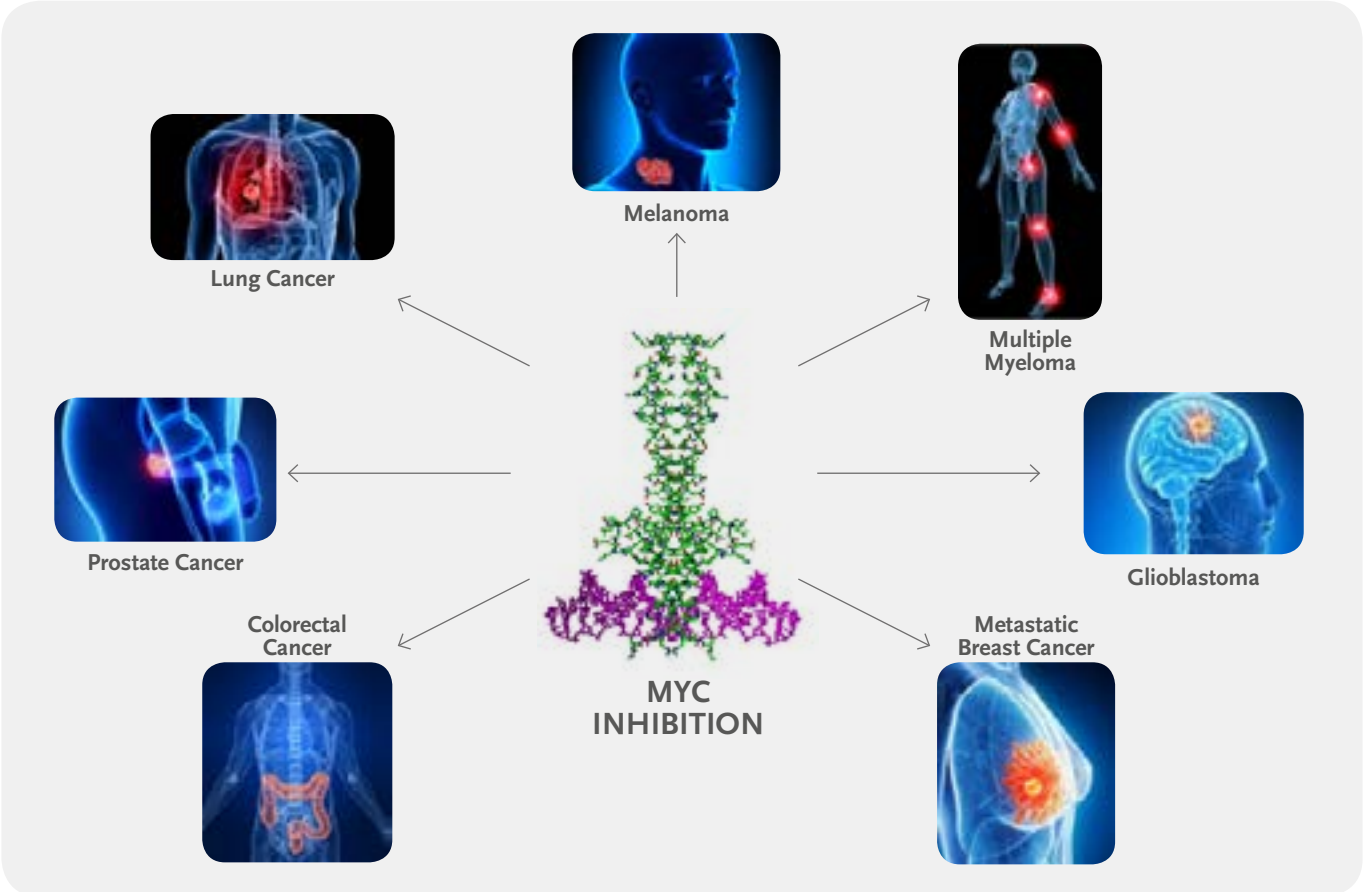


Figure: Laura Soucek's laboratory is pre-clinically validating Myc inhibition as a therapeutic strategy in different types of cancer. To do so, among other strategies, they are using Omomyc, the best Myc inhibitor known to date, and Omomyc-derived peptides.

## PI PAPER PICK:

Massó-Vallés D, Jauset T, Soucek L. Ibrutinib repurposing: from B cell malignancies to solid tumors. *Oncoscience.* 2016 Jun 10;3(5-6):147-8.

Fiorentino FP, Tokgün E, Solé-Sánchez S, Giampaolo S, Tokgün O, Jauset T, Kohno T, Perucho M, Soucek L, Yokota J. Growth Suppression by MYC Inhibition in Small Cell Lung Cancer Cells with TP53 and RB1 Inactivation. *Oncotarget.* 2016 May 24;7(21):31014-28.

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PRECLINICAL RESEARCH

# ›TUMOR BIOMARKERS GROUP

**Principal Investigator**
› Josep Villanueva

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

**Graduate Student**
› Mireia Pujals

**Technicians**
› Ana Matres
› Candida Salvans

## 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:

› Initiated three years ago, our subsequent switch in research direction has attracted additional funding and led to the recruitment of additional lab members in 2016. We transitioned from studying the cancer secretome following a methodology-driven approach to a biology-orientated approach, whereby non-classical secretion pathways will constitute an important area of our research over the coming years.

› We have also established an important collaboration with the pharmaceutical company Servier.

## SUMMARY:


Tumor cell communication with its microenvironment plays 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 both amongst themselves as well as with their microenvironment during tumorigenesis. We then exploit these findings to contribute to the advancement of biomarker and drug target discovery. Our group's working hypothesis is that cellular signaling pathways undergo alteration during tumorigenesis and that these changes translate in differential protein secretion, which can also potentially be explored 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, however, is that they contain hundreds of theoretical intracellular proteins. Recent reports evidence intracellular proteins with alternative extracellular functions, suggesting that new protein functions associated with alternative subcellular localizations might be implicated in tumorigenesis. Considering this novel concept, in the context of therapeutics and tumor invasion, we hypothesize that the characterization of non-classical protein secretion could lead to novel therapies against cancer.

The cancer secretome contains classical and non-classical secreted proteins that tumor cells use as molecular messaging to communicate with each other and their microenvironment during tumorigenesis. Our principal goal is to characterize the mechanisms adopted by cancer cells which enable this cross-talk, and exploit our findings in order to accelerate biomarker and drug target discovery.


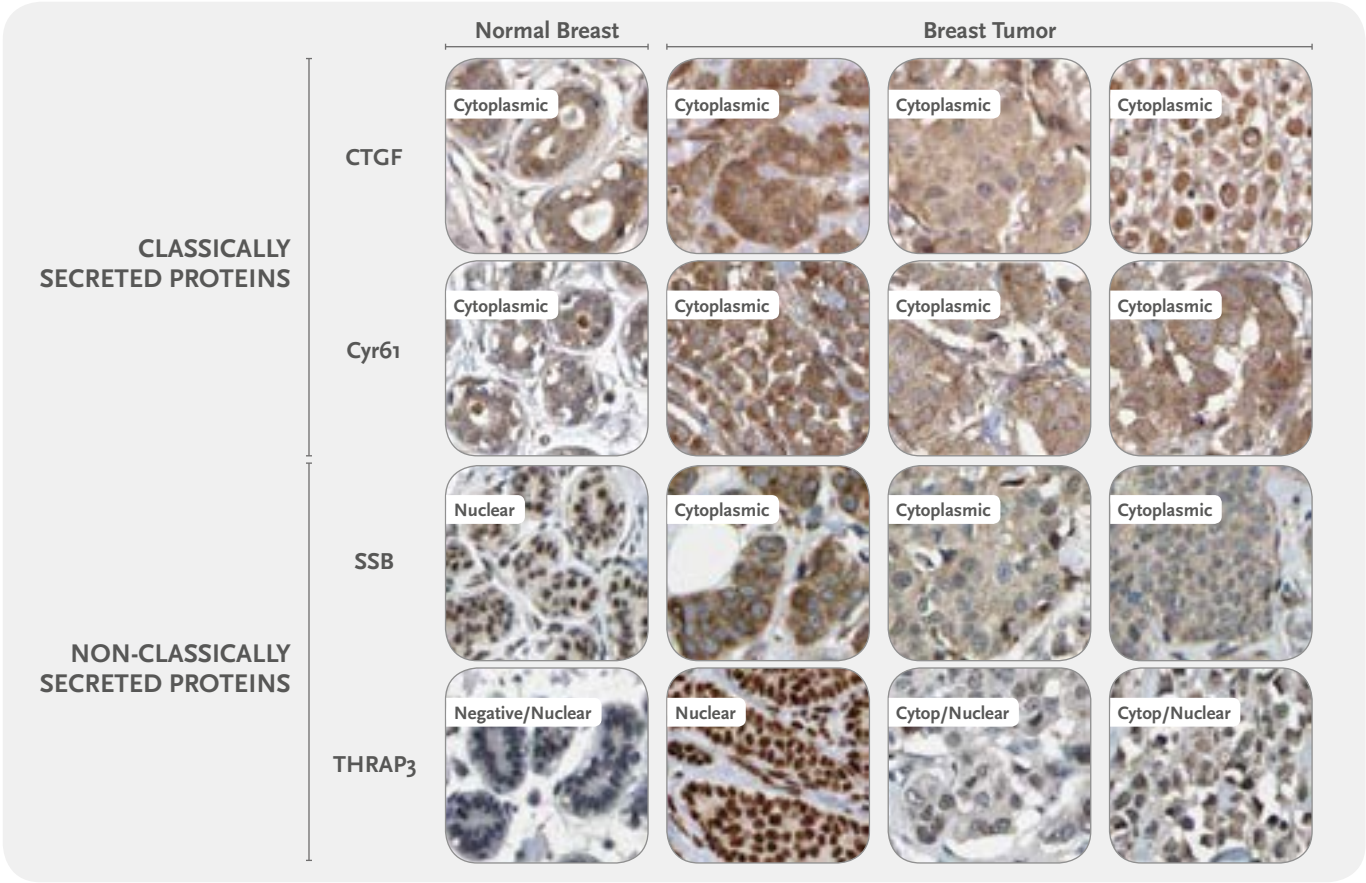


Figure: Proteins change their sub-cellular localization in breast cancer. IHC analysis of secretome proteins in both normal and cancer breast tissue obtained from Protein Atlas database. In each case, one normal breast tissue and three different breast tumors are shown. (Top panel) IHC analysis of known extracellular proteins (CTGF and Cyr61) showing a clear cytoplasmic/membranous staining in both normal and breast cancer. (Bottom panel) IHC analysis of the two secretome proteins: Ssb and Thrap3, both classified as nuclear by Gene Ontology. In this case, these theoretically nuclear proteins show a clear cytoplasmic staining in some tumors but not in normal tissue, which is compatible with a change in subcellular localization in breast cancer.


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DIRECTOR, TRANSLATIONAL RESEARCH PROGRAM
JOAN SEOANE

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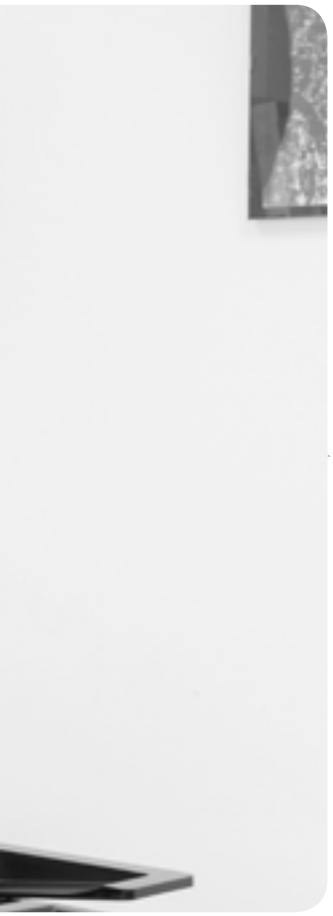
# TRANSLATIONAL RESEARCH



# TRANSLATIONAL RESEARCH

› GENE EXPRESSION & CANCER GROUP

› STEM CELLS & CANCER GROUP

DIRECTOR, TRANSLATIONAL RESEARCH PROGRAM

# JOAN SEOANE

"To better understand and ultimately outsmart intratumor heterogeneity as well as address the dynamics that drive resistance to the current arsenal of anti-cancer treatments, translational research at VHIO aims at tackling current challenges head-on as well as seizing opportunities arising from the very latest research towards preclinically and clinically dissecting intra-tumor heterogeneity."

VHIO's Translational Research Program strives to promote and accelerate the integration of preclinical and clinical research. By translating these advances in molecular research into benefits at patient level as rapidly as possible, we tackle cancer from all angles and generate synergies between molecular and clinical cancer research.

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

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

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

To explore the two levels of cancer heterogeneity, we investigate cancer as closely as possible to the real tumor and generate patient-derived models both in vitro and in vivo. Tumor specimens are obtained shortly upon surgical resection and we study tumor cells as well as cancer stem cells. The next step is the development of mouse models that reproduce the characteristics of the tumor from the patient.

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

TRANSLATIONAL RESEARCH

# ›GENE EXPRESSION & CANCER GROUP

**Principal Investigator**
› Joan Seoane

**Post-Doctoral Fellows**
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› Isabel Huber
› Raffaella Iurlaro
› Regina Mayor
› Josep Lluis Parra-Palau
› Monica Pascual
› Atenea Soto

**Graduate Students**
› Ester Arroba
› Ada Sala

**Technicians**
› Alexandra Arias
› Isabel Cuartas
› Carolina Raventós
› Cristina Sánchez

## STRATEGIC GOALS:

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

## HIGHLIGHTS:

› Translating our discoveries into a clinical trial. Our efforts during 2016 will next year result in a novel compound for cancer patients designed and developed in our lab in partnership with the spin off company derived from our group; Mosaic Biomedicals.

## SUMMARY:


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

In brain tumors, as in many other malignancies, evolving heterogeneity represents one of the most important challenges in the treatment of cancer. We are studying genomic heterogeneity at the level of genomic alterations.

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

We have identified some of the candidate genes responsible for relapse and are designing therapeutic approaches to prevent the recurrence of brain tumors.

Moreover, in order to monitor and better understand the evolving genomic heterogeneity of tumors, we are studying cell-free circulating tumor DNA in fluids from patients with brain tumors. Tumors shed DNA into the blood stream and the subsequent sequencing of the circulating DNA enables the accurate, noninvasive molecular characterization of tumors, and these circulating markers facilitate the diagnosis, monitoring and identification of actionable gene mutations.

Finally, we are also studying the role of the tumor microenvironment which, in the case of brain tumors, plays a crucial role in facilitating cancer progression. Tackling the tumor microenvironment might be a way of attacking cancer independently of its heterogeneity. By eliminating the niche where cancer thrives should help us to develop more effective anti-cancer compounds.


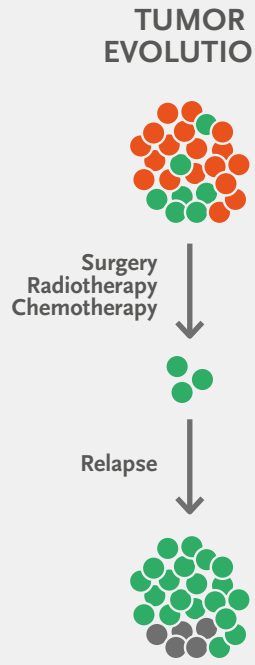


Figure I: The Darwinian selection of the fittest subclone dictates the tumor evolution. Anti-cancer treatments act as selective pressure to promote the enrichment of the resistant subclone.

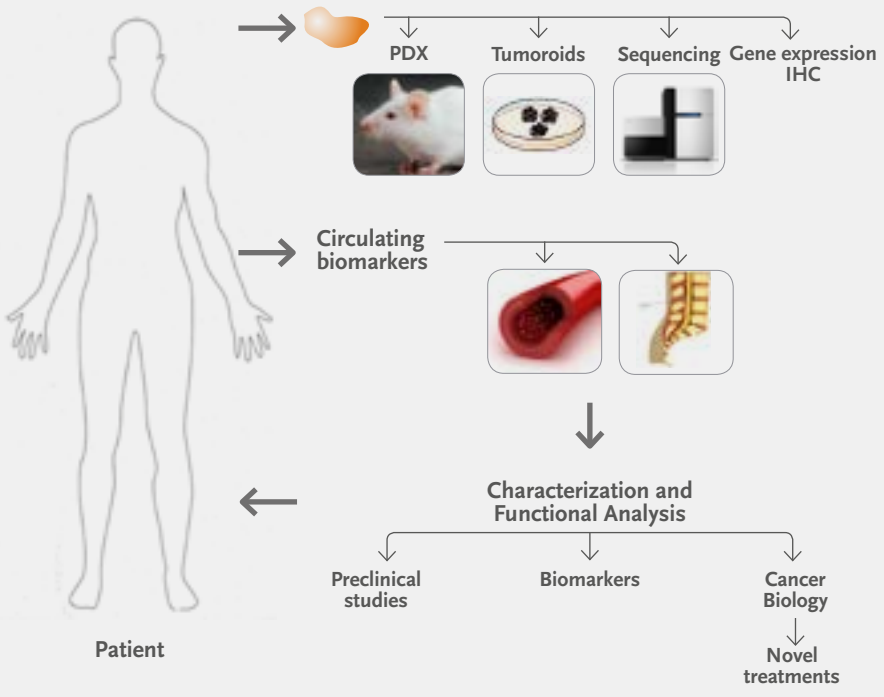


Figure II: Translational platform to study cancer and translate discoveries into the benefit of patients.

## PI PAPER PICK:

Gueorguieva I, Cleverly A, Desaiah D, Azaro A, Seoane J, Braña I, Sicart E, Miles C, Lahn MM, Mitchell MI, Rodon J. Relative bioavailability of three formulations of galunisertib administered as monotherapy in patients with advanced or metastatic cancer. *Drugs Context.* 2016 Dec 2;5:212303. eCollection 2016.

Seoane J. The Taming of the TAMs. *Trends Cell Biol.* 2016 Aug;26(8):562-3.

TRANSLATIONAL RESEARCH

# ›STEM CELLS & CANCER GROUP

**Principal Investigator**
› Hector G. Palmer

**Post-Doctoral Fellows**
› Oriol Arqués
› Jordi Martínez-Quintanilla
› Isabel Puig
› Stephan Tenbaum

**Graduate Student**
› Estefania Cuesta

**Technicians**
› Irene Chicote
› Génesis Martín
› Lorena Ramírez

## STRATEGIC GOALS:

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

## HIGHLIGHTS:

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

## SUMMARY:


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

Our studies mainly center on colorectal cancer where, at molecular level, we are analyzing the role of oncogenic pathways controlling the fate of Colon Cancer Stem Cells (CoCSC). RAS/PI3K/AKT and Wnt/beta-catenin pathways are two drivers of cancer stem cell fate and lead to progression across many tumor types. Over recent years we have described a novel mechanism of resistance to PI3K and AKT inhibitory drugs conferred by beta-catenin in colorectal cancer. This is of great clinical relevance since many patients in clinical studies do not respond to these therapies, and no molecular explanation behind such resistance had previously been described. Our findings will facilitate the selection of 'sensitive' patients based on their expression of particular biomarkers predicting drug-response. We are currently focusing on a new generation of Wnt/beta-catenin inhibitors in close collaboration with several major pharmaceutical companies, and have already experimentally evidenced the efficacy and mechanisms of action of these drugs in pre-clinical models of colorectal cancer with patient-derived xenografts. This marks an important milestone within the field; for decades colorectal cancer had been described as a paradigmatic tumor addicted to the oncogenic Wnt/beta-catenin pathway.

We also seek to identify the molecular determinants of response to these anti-cancer therapies that could consequently become robust biomarkers for the selection 'sensitive' patients as well as better guide the design of future clinical trials. Some of these predictive biomarkers are mutations affecting components of the Wnt/beta-catenin pathway, whose identification can be perfectly standardized in clinical practice for patient selection. Our collaboration with the Vall d'Hebron University Hospital's Medical Oncology Department, led by Josep Tabernero, in addition to pharmaceutical companies, will accelerate the translation of our findings into clinical practice, and hopefully revert the long-stalled scenario of CRC medicines.

Our group has developed a collection of PDX models derived from primary tumors or liver metastasis of more than 100 CRC patients. Most recently, we have also generated around 30 clinical trial associated xenografts (CTAX) from patients enrolled in these studies.


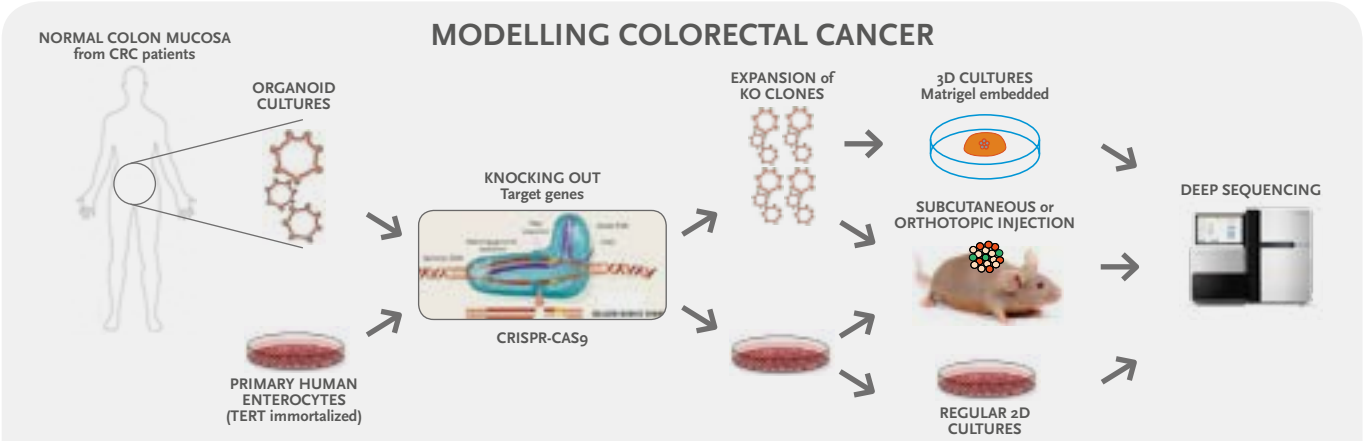


Figure: Cells derived from human normal mucosa are genetically modified to reproduce mutations in oncogenes or tumor suppressors using CRISPR-Cas9 technology. Functional and genetic evolution of single derived clones with specific genetic modifications is then characterized. This experimental design permits to reproduce cancer initiaton as well as clonal heterogeneity and tumor evolution. Acquisition of metastatic potential, genetic epistasis, clone cooperation and competition and drug resistance can be studied using this experimental models.

## PI PAPER PICK:


Arqués O, Chicote I, Puig I, Tenbaum SP, Argilés G, Dienstmann R, Fernández N, Caratù G, Matito J, Silberschmidt D, Rodon J, Landolfi S, Prat A, Espín E, Charco R, Nuciforo P, Vivancos A, Shao W, Tabernero J, Palmer HG. Tankyrase Inhibition Blocks Wnt/β-Catenin Pathway and Reverts Resistance to PI3K and AKT Inhibitors in the Treatment of Colorectal Cancer. *Clin Cancer Res.* 2016 Feb 1;22(3):644-56.

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DIRECTOR, CLINICAL RESEARCH PROGRAM
JOSEP TABERNERO

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# CLINICAL RESEARCH

# CLINICAL RESEARCH

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› EARLY CLINICAL DRUG DEVELOPMENT GROUP

› GASTROINTESTINAL & ENDOCRINE TUMORS GROUP

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

› GYNECOLOGICAL MALIGNANCIES GROUP

› HIGH RISK & CANCER PREVENTION GROUP

› ONCOGENETICS GROUP

› ONCOLOGY DATA SCIENCE (ODYSSEY) GROUP

› RADIATION ONCOLOGY GROUP

› THORACIC TUMORS & HEAD AND NECK CANCER GROUP

DIRECTOR, CLINICAL RESEARCH PROGRAM

# JOSEP TABERNERO

"VHIO's Clinical Research Program incorporates multidisciplinary cancer teams of excellence to spur the development of novel agents and approaches aimed at diagnosing cancer earlier and better predicting response to therapy. The studies we lead involve both preclinical and early-drug development discovery and are specially designed to render anti-cancer therapies more precise."

Our multidisciplinary and translational approach to clinical research closely connects VHIO scientists with our physician-researchers and in so doing, enables VHIO's Clinical Research Program to spearhead cooperative preclinical, Phase I & II studies aimed at developing novel therapeutics, as well as new or redefined prognostic/diagnostic tools to better detect disease and predict response to anti-cancer therapies.

Throughout 2016 we have continued to develop next generation blood-based diagnostics to monitor disease, its respective molecular specificities, and response to novel targeted therapies. More specifically, through our collaboration with Merck Serono and Sysmex Inostics, we continue to employ our in-house BEAMing digital PCR/flow cytometry technology to evaluate patients with metastatic colorectal cancer.

One particular study led by VHIO (ESMO World Congress on Gastrointestinal Cancer 2016, 29 June - 02 July, Barcelona, Spain 2016): **Concordance of blood- and tumor-based detection of RAS mutations to guide anti-EGFR therapy in metastatic colorectal cancer** (Grasselli J et al. 2017. *Ann Oncol*) has demonstrated the practicability and feasibility of using ctDNA analysis as an alternative and less invasive strategy to establishing eligibility of patients for anti-EGFR therapy.

In addition to this potentially game changing approach, cancer immunotherapy also represents a firm contender in dismantling cancer's armory and is as exciting for our preclinical scientists as it is for our clinical researchers. As we start to see the benefit of immunotherapeutics across several clinical studies, immuno-oncology could well be poised to impact the way we will treat cancer in the future.

Our Program is collaborating closely with other VHIO groups including our newly established Tumor Immunology and Immunotherapy Group (page 90), and colleagues from other leading cancer research centers throughout Europe and beyond, to evidence and advance the use of novel immune agents either as mono therapy or in combination, across an increasing number of cancer types.

Importantly, 2016 marked the creation of a global partnership powered by 21 academic centers and leading experts in cancer immunotherapy: immunotherapy Centres of Research Excellence (imCORE), launched by Roche in collaboration with Genentech. This unique undertaking will drive the application and extension of novel immune-based therapeutics to more tumor types as well as further research into the cellular and molecular mechanisms modulating immune response to cancer.

We are also collaborating in the development of molecular tests for patient screening (disease-oriented mutation panels for NGS platforms and Nanostring nCounter), led by Ana Vivancos' Cancer Genomics Group. Driving our efforts aimed at integrating clinical translational research with genomics for precision cancer therapy, VHIO's Oncology Data Science (ODysSey) headed by Rodrigo Dienstmann, has made important progress in the datamining, molecular profiling and sub-typing of different cancers.

Mirroring the purely translational and multidisciplinary research model for which VHIO is famed, data driven in close collaboration with my own group, our Cancer Genomics Group, and Molecular Oncology Group directed by Paolo Nuciforo, was selected to showcase as an oral presentation during the 2016 Annual Meeting of the American Society of Clinical Oncology. Presented by Rodrigo, this research focused on establishing whether multiple mutations in a tumor can determine a patient's prognosis as well as response to treatment targeted at cells with BRAF gene mutations. Evidencing the existence of tumors presenting a gene mutation in all cells (so-called clonal) and others that do not; heterogeneous tumors or those with subclonal alterations, we exposed the clinical relevance of clonal mutations in colorectal cancer for the very first time.

It is thanks to the expertise of our clinical groups, in collaboration with other VHIO programs, that results from our early phase trials and translational investigations have also resulted in publications in top-tier journals in 2016, just some of which include:

**Twelve-Month Estrogen Levels in Premenopausal Women With Hormone Receptor-Positive Breast Cancer Receiving Adjuvant Triptorelin Plus Exemestane or Tamoxifen in the Suppression of Ovarian Function Trial (SOFT): The SOFT-EST Substudy.** Bellet M et al. *J Clin Oncol*. 2016 May 10;34(14):1584-93.

**A First-in-Human Phase I Study of the ATP-Competitive AKT Inhibitor Ipatasertib Demonstrates Robust and Safe Targeting of AKT in Patients with Solid Tumors.** Saura C et al. *Cancer Discov.* 2017 Jan; 7(1):102-113.

**Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial.** Kim DW et al. *Lancet Oncol.* 2016 Apr; 17(4):452-63.

**Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial.** Wang-Gillam A et al. *Lancet.* 2016 Feb 6;387(10018):545-57.

VHIO continues to significantly advance cancer discovery and therapeutics in partnership, across borders. In colorectal cancer, we coordinate the EU H2020 funded MoTriColor Consortium which focuses on validating three novel therapeutic approaches linked to three gene expression signatures.

In 2016, we initiated the prescreening of patients from the different clinical sites and next year we will start enrolling patients in the three MoTriColor clinical trials. Additionally, comprehensive translational research will be performed using MoTriColor patients' samples through the INTRACOLOR project (supported by EU H2020's TRANSCAN-2 ERA NET) which is also coordinated by VHIO.

Lastly but by no means least, I believe in forging closer collaborations with other specialties and key partners in oncology. Only by engaging and listening to all stakeholders in oncology including patients and families, researchers, payers, regulators, the policymakers, and industry, will we accelerate our dedicated efforts aimed at conquering cancer. We can and will do better.

CLINICAL RESEARCH

# ›BREAST CANCER & MELANOMA GROUP


**Principal Investigator**
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**Associate Translational Investigators**
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› Isabel Rubio

**Medical Oncologists and Clinical Fellows**
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› Analía Azaro
› Judith Balmaña
› Meritxell Bellet
› Cristina Cruz
› Santiago Ignacio Escrivà
› Laia Garrigós
› Patricia Gómez
› Eva Muñoz
› Mafalda Oliveira
› Vanesa Ortega
› José Manuel Pérez
› Beatriz Rojas
› Jesús Soberino
› Mª Jesús Vidal
› Esther Zamora

## STRATEGIC GOALS:

› Optimization of the treatment of metastatic breast cancer with the introduction of new drugs and incorporation of rational combinations to overcome mechanisms of resistance.
› Incorporation of proteomics, genomics, and circulating tumor cell platforms in translational research to better understand tumor biology.
› Use the results of preclinical research to design innovative clinical trials.
› Improve clinical care of patients suffering with cutaneous or ocular melanoma and advance insights into melanoma acquisition and progression.
› Identify biomarkers of tumour progression and validate novel therapeutic targets in melanoma.

## HIGHLIGHTS:

› We have published practice-changing data in the field of adjuvant and metastatic breast cancer.
› Thanks to collaboration with clinical departments at the Vall d'Hebron University Hospital (HUVH), we have established our group as one of the most active in neoadjuvant and metastatic studies worldwide within the context of translational research.
› Expansion of our collection of patient-derived xenografts, distinguishing us as one of the most important institutes at European level, coupled with our ambitious cfDNA program for genotyping breast cancer.
› Our melanoma group is one of the largest melanoma networks in Spain and across Europe, and is now one of the most active groups in metastatic and adjuvant studies in melanoma. Each trial is tightly connected with the corresponding translational research project at VHIO.

## SUMMARY:

Our Breast Cancer & Melanoma Group is one of the most active and renowned Europe-wide. In 2016, 25 publications totaled at an Impact Factor (IF) of 194, 64. Our group is not only committed to participating in clinical trials, but also leads several of them; reflected by our representation on many Steering Committees. We drive the translational data that helps to both guide and advance the clinical development of several compounds.

Our key areas of interest include:

**HER-positive disease:** we are particularly proud to report our continued involvement in the major trials testing new drugs. We recruit patients in clinical studies with the most promising agents including neratinib, margetuximab, MM302 or MCLA128. We also treat patients in trials with combinations that are designed to overcome mechanisms of resistance such as T-DM1+atezolizumab or trastuzumab+palbociclib. In collaboration with VHIO's Growth Factors Group, led by Joaquín Arribas, we continue to explore other mechanisms of resistance to these therapies.

**Discovery of new mechanisms of resistance:** In close collaboration with VHIO's Experimental Therapeutics Group, headed by Violeta Serra, we have demonstrated that resistance to eribulin may be overcome through the addition of PI3K inhibitors and to confirm this hypothesis in patients, a clinical trial is already open. Our leadership in triple negative breast cancer and BRCA tumors is possible through a broad program focused on the evaluation of immunotherapies and different PARP inhibitors in the clinic coupled with translational research of excellence in both areas. In hormone receptor-positive disease we are leading different trials using the most novel compounds (PI3K-AKT-mTOR and CDK4/6 inhibitors), and have observed encouraging activity of neratinib for tumors harboring HER2 mutations.

**New compounds:** an emerging group of drugs known as immunoconjugates are surely here to stay. Their innovative design makes them extremely active given that chemotherapy is released specifically inside the tumor with a consequently increased potency with less toxicity. We are delighted to have treated patients with SYD-985 and CDX011, and IMMU-132 and SAR566658 will soon be available for our patients.

**Optimizing benefit of standard approved treatments:** the extraordinary work carried out by Meritxell Bellet, Medical Oncologist and Clinical Fellow of our group, to accurately analyze hormone levels of patients receiving anti-hormonal treatments has proven highly relevant to the medical community in guiding clinical decisions (see Figure).

**cfDNA:** In collaboration with VHIO's Cancer Genomics Group, led by Ana Vivancos, we are analyzing tumour tissue and cfDNA that will, in the near future, provide crucial information about the evolution of genetic alterations of tumors.

Our **Melanoma Group** led by Eva Muñoz, also Medical Oncologist and Clinical Fellow of our group, has marked significant progress throughout 2016 by actively participating in phase I, II and III clinical trials with several emerging treatments in metastatic and adjuvant melanoma. It has consolidated its own research program incorporating physician-scientists and cancer researchers at VHIO who conduct purely translational research centered on melanoma acquisition and progression.

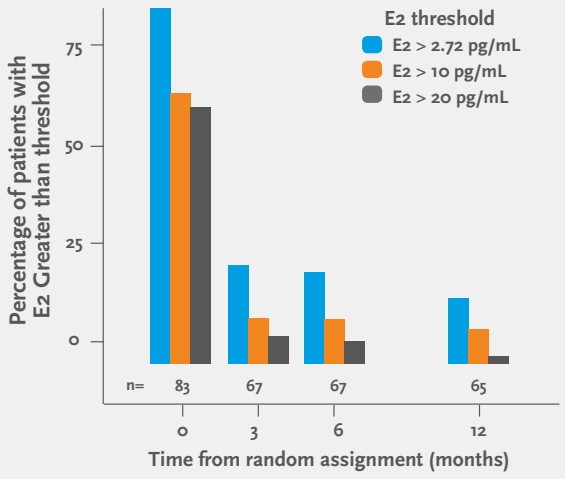


Figure: Percentages of patients in the exemestane plus triptorelin group with estradiol (E2) values greater than the predefined threshold (. 2.72 pg/mL, which defines a strict threshold to indicate E2 inconsistent with postmenopausal levels on an aromatase inhibitor), and greater than two additional exploratory thresholds (.10 and . 20 pg/mL, representing a less strict threshold above which E2 was clearly inconsistent with postmenopausal levels on an aromatase inhibitor and a threshold above which E2 was inconsistent with gonadotropin-releasing hormone agonist–related postmenopausal status, respectively), at each time point.

## PI PAPER PICK:


Bellet M, Gray KP, Francis PA, Láng I, Ciruelos E, Lluch A, Climent MA, Catalán G, Avella A, Bohn U, González-Martin A, Ferrer R, Catalán R, Azaro A, Rajasekaran A, Morales J, Vázquez J, Fleming GF, Price KN, Regan MM. Twelve-Month Estrogen Levels in Premenopausal Women With Hormone Receptor-Positive Breast Cancer Receiving Adjuvant Triptorelin Plus Exemestane or Tamoxifen in the Suppression of Ovarian Function Trial (SOFT): The SOFT-EST Substudy. *J Clin Oncol.* 2016 May 10;34(14):1584-93.

Bruna A, Rueda OM, Greenwood W, Batra AS, Callari M, Batra RN, Pogrebniak K, Sandoval J, Cassidy JW, Tufegdzic-Vidakovic A, Sammut SJ, Jones L, Provenzano E, Baird R, Eirew P, Hadfield J, Eldridge M, McLaren-Douglas A, Barthorpe A, Lightfoot H, O'Connor MJ, Gray J, Cortes J, Baselga J, Marangoni E, Welm AL, Aparicio S, Serra V, Garnett MJ, Caldas C. A Biobank of Breast Cancer Explants with Preserved Intra-tumor Heterogeneity to Screen Anticancer Compounds. *Cell.* 2016 Sep 22;167(1):260-274.e22.

Herrera-Abreu MT, Palafox M, Asghar U, Rivas MA, Cutts RJ, Garcia-Murillas I, Pearson A, Guzman M, Rodriguez O, Grueso J, Bellet M, Cortés J, Elliott R, Pancholi S, Baselga J, Dowsett M, Martin LA, Turner NC, Serra V. Early Adaptation and Acquired Resistance to CDK4/6 Inhibition in Estrogen Receptor-Positive Breast Cancer. *Cancer Res.* 2016 Apr 15;76(8):2301-13.

Pérez-Alea M, Vivancos A, Caratú G, Matito J, Ferrer B, Hernandez-Losa J, Cortés J, Muñoz E, Garcia-Patos V, Recio JA. Genetic profile of GNAQ-mutated blue melanocytic neoplasms reveals mutations in genes linked to genomic instability and the PI3K pathway. *Oncotarget.* 2016 May 10;7(19):28086-95.


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CLINICAL RESEARCH

# ›EARLY CLINICAL DRUG DEVELOPMENT GROUP

**Director of Clinical Research at VHIO**
› Josep Tabernero

**Principal Investigator, Early Clinical Drug Development Group, Director & Medical Coordinator, UITM**
› Jordi Rodón

**Associate Investigators**
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› Maria Alsina
› Guillermo Argilés
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› Irene Braña
› Cristina Cruz
› Maria Elena Élez
› Santiago Ignacio Escrivá
› Lorena Fariñas
› Patricia Gómez
› Julieta Grasselli
› Cinta Hierro
› Teresa Macarulla
› Juan Jesús Martín
› Alex Martínez
› Rafael Morales
› Eva Muñoz
› Alejandro Navarro
› Maria Ochoa de Olza
› Mafalda Oliveira
› Nuria Pardo
› José Manuel Pérez
› Jordi Remon
› Víctor Rodríguez
› Enrique Sanz
› Tamara Saurí
› César Serrano
› Cristina Suarez
› Claudia Valverde
› Helena Verdaguer
› Maria Vieito
› Esther Zamora

## STRATEGIC GOALS:

› Clinical early development of the best-in-class targeted therapies, determining the optimal schedule and patient population that would most likely benefit most from these drugs by participating in novel clinical trials.

› Analyze patients' tumors for molecular aberrations that may predict the efficacy of targeted agents and enable a more precise selection of the most appropriate treatment matched to the specificities of individual patients with advanced cancer.

› Link clinical research at the UITM with the various preclinical and translational research groups at VHIO, and foster powerful collaborations with different partners involved in drug development and translational research (phase I units, academic centers, consortia, pharmaceutical companies).

## HIGHLIGHTS:

› As a leading institute in drug development at global level (PI3K/akt/mTOR inhibitors, MAPK, FGFR and MET inhibitors, or drugs targeting developmental pathways such as TGF-beta, SHH, WNT, and NOTCH), we clinically test the best in-class drugs. We have expanded our expertise to other cell-signaling pathway inhibitors such as immunotherapeutics including agents targeting PD1/PDL1, OX40, CD40, and engineered antibodies.

› We have carried out many clinical trials with novel-novel combinations including the pairing of targeted therapies (novel/novel) and, in immuno-oncology, coupling checkpoint inhibitors with either chemotherapy, radiation (abscopal effect), targeted therapies, or other immunomodulatory agents (TGFbeta, LAG3, anti VEGFR2, CD40).

› Performed several clinical trials with patients selected on molecular alterations: mutations in AKT1, EGFR, PIK3CA, PIK3CB, PTEN, IDH1, ALK, ROS1, BRAF, NRAS, KRAS, FGFR1 and 2, MET, HER2, HER3; amplifications in HER2, AKT 1, 2, and 3, FGFR1, MET, NOTCH1-4, rearrangements of NTRK1-3 ROS1, ALK, BRAF, RSPO2/3 and FGFR1-3, and alteration in protein expression of PTEN, or overexpression of PDL1, CEA and FAP.

› We secured funding for the implementation of an ambitious program aimed at exploring primary and acquired resistance to targeted therapies. This project integrates patient-derived xenografts and the analysis of next-generation sequencing of multiple tissue samples and circulating-free tumor DNA. In collaboration with VHIO's Ana Vivancos, Violeta Serra, Héctor G. Palmer, and Joaquin Arribas, we are focusing on the fibroblast growth factor and the WNT pathway.

› Co-development of molecular tests for patient screening (disease-oriented mutation panels for NGS platforms and Nanostring nCounter).

› Completed enrollment for the WINTHER trial, a pilot study in personalized medicine. Results are being analyzed. This experience has facilitated the design of SPRING, a study focused on precision medicine in lung cancer, and the second WIN study, headed at VHIO by Enriqueta Felip.

› We designed the Basket of Baskets (BoB) study, fully endorsed by Cancer Core Europe, and have already secured part-funding for the trial.

## SUMMARY:

We focus on proof-of-concept and proof-of-mechanism trials with targeted therapies with special emphasis on those in 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 trials in molecularly selected populations.

We strive to link clinical research at the UITM with the different areas of investigation carried out at VHIO, following a truly translational model. 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), for selected projects.

We have collaborated with VHIO's Molecular Oncology Group, headed by Paolo Nuciforo, as well as the Cancer Genomics Group led by Ana Vivancos, to perform molecular analysis of patients' tumors in order to select the optimal treatment for our patients with the experimental therapies available in our portfolio of clinical trials - one step closer to realizing the true promise of precision medicine.

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

This year, our group and VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (see pages 78-79), have designed the Basket of Baskets (BoB) trial; a novel study in personalized medicine that integrates cutting edge molecular prescreening, the development of new diagnostic tests such as circulating DNA or Nanostring with marketable pathways, with the testing of targeted therapies in populations of patients who, matched to the molecular alterations detected in their respective tumors, will be most likely to benefit from them. This academic study, designed at Vall d'Hebron and endorsed by Cancer Core Europe, will be funded by pharmaceutical companies. Roche has already committed to finance a part of the trial and open conversations are ongoing with an additional three more companies.

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

Over time, our Early Drug Development Group and the Phase I Unit (UITM) has become one of the largest and most prestigious in Europe. Testament to this, is not only the number of patients who entrust us with their care (453 patients enrolled in phase I and basket studies in 2016), the number of different trials available (115 phase I trials and 14 basket studies in 2016), but mainly the novelty of both our Precision Medicine and Immunotherapy Early Drug Development Programs; evidenced by our leading role in the Clinical Trials Task Force of the Cancer Core Europe Consortium.

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

Lastly, VHIO has recently expanded its management team by recruiting Elena Garralda as Executive Director of the UITM, and the *Departament de Salut de la Generalitat* has visited our Unit in order to define criteria for certifying other similar Units.

## PI PAPER PICK:

Almhanna K, Kalebic T, Cruz C, Faris JE, Ryan DP, Jung J, Wyant T, Fasanmade AA, Messersmith W, Rodon J. Phase I Study of the Investigational Anti-Guanylyl Cyclase Antibody-Drug Conjugate TAK-264 (MLN0264) in Adult Patients with Advanced Gastrointestinal Malignancies. *Clin Cancer Res.* 2016 Oct 15;22(20):5049-5057.

CLINICAL RESEARCH

# ›GASTROINTESTINAL & ENDOCRINE TUMORS GROUP

**Principal Investigator**
› Josep Tabernero

**Medical Oncologists and Clinical Fellows**
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› Guillermo Argilés
› Jaume Capdevila
› Maria Elena Élez
› Julieta Grasselli
› Teresa Macarulla
› Ignacio Matos
› Nuria Mulet
› Enrique Sanz
› Tamara Saurí
› Helena Verdaguer

**Clinical Nurse Specialist**
› Ariadna García

## 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 major diseases, with particular focus on colorectal cancer, in different 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 of/increased participation in novel Basket trials.
› Participation in multidisciplinary/multinational consortia and collaborative research programs of excellence.
› Validation of repurposed drugs or candidate drugs, in partnership with pharma companies or academic groups.
› Expansion of our collaboration with other VHIO teams (Tumor Biomarkers, Cancer Genomics, Translational Genomics, and Stem Cells & Cancer Groups).

## 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.
› Design of investigator-initiated clinical trials as well as participation in numerous trials developed in the context of national and international cooperative groups.
› Led by VHIO, the Horizon 2020-funded MoTricolor Consortium designs and conducts multi-center early phase trials to identify anti-tumor activity of novel therapies against mCRC.
› Participation in CIBERONC. Our Group was selected to be part of the new CIBER in Oncology (CIBERONC) and coordinate the GI cancers groups (*Temporo-spatial molecular profiling of GI tumors: characterization, functional models, and clinical utility*).

## SUMMARY:

In 2016, we have led and participated in numerous cooperative and singular research projects related to Gastrointestinal Malignancies. In addition to our key participation in existing international consortia of excellence including Cancer Core Europe and the EU FP-7 supported EurocanPlatform, and MerCuRIC Consortia.

Concerning the EU Horizon 2020 supported MoTricolor Consortium, coordinated by VHIO, I am pleased to report that in 2016 we initiated the pre-screening of patients from the different clinical sites and next year we will start enrolling patients in the three MoTriColor clinical trials with specific treatment strategies against the molecularly defined subtypes of colorectal cancer.

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

Reflected by publications in the most prestigious scientific titles in 2016, our group has also directed and collaborated in studies with important clinical implications, just some of which include:

**Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial.** Wang-Gillam A et al. *Lancet.* 2016 Feb 6;387(10018):545-57.

This phase III trial evidenced that nanoliposomal irinotecan combined with fluorouracil and folinic acid extends survival of patients with metastatic pancreatic cancer, providing a new and promising therapeutic avenue to treat gemcitabine-resistant pancreatic cancer. Reflecting the importance of these findings, journals including *Nature Reviews Clinical Oncology* and *The Lancet* covered this study.

**Epigenetic Homogeneity Within Colorectal Tumors Predicts Shorter Relapse-Free and Overall Survival Times for Patients With Locoregional Cancer.** Martínez-Cardús A et al. *Gastroenterology.* 2016 Nov; 151(5):961-972.

With few validated biomarkers that can be used to predict outcomes for colorectal cancer patients, this study explored epigenetic intratumor heterogeneity in colorectal tumors. Results showed significant heterogeneity in patterns of DNA methylation within each individual tumor; the level of heterogeneity correlating with times of relapse-free and overall survival.

Advancing insights into the epigenetic intra-tumor heterogeneity of CRC promises a more accurate prediction of clinical outcomes for individual patients with the goal of developing more effective and personalized treatment strategies.

**Tankyrase Inhibition Blocks Wnt/β-Catenin Pathway and Reverts Resistance to PI3K and AKT Inhibitors in the Treatment of Colorectal Cancer.** Arqués O et al. *Clin Cancer Res.* 2016 Feb 1;22(3):644-56.

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

**Nanofluidic Digital PCR and Extended Genotyping of RAS and BRAF for Improved Selection of Metastatic Colorectal Cancer Patients for Anti-EGFR Therapies.** Azuara D et al. *Mol Cancer Ther.* 2016 May; 15(5):1106-12.

To better predict and thus more precisely stratify patients with metastatic colorectal cancer who are most likely to benefit from anti-EGFR therapy this study, led by colleagues from the Catalan Institute of Oncology (ICO), Bellvitge Biomedical Research Institute (IDIBELL), in collaboration with our group, successfully established the superior predictive power of genotyping an extended RAS panel using nanofluidic digital PCR (dPCR). This research represents an important forward step towards better matching anti-cancer therapies to the specificities of individual patients.

We continue to develop next generation blood-based diagnostics to monitor disease, its respective molecular specificities, and response to novel targeted therapies. One particular study led by VHIO (preliminary data first presented during the ESMO World Congress on Gastrointestinal Cancer 2016, 29 June - 02 July, Barcelona, Spain 2016): Concordance of blood- and tumor-based detection of RAS mutations to guide anti-EGFR therapy in metastatic colorectal cancer. Grasselli J et al. *Ann Oncol.* 2017 Mar 20., has demonstrated the practicability and feasibility of using ctDNA analysis as an alternative and less invasive approach to establishing eligibility of patients for anti-EGFR therapy.

2016 has also celebrated the launch of two more important partnerships:

The EU Horizon 2020 funded NoCanTher (Nanomedicine upscaling for early clinical phases of multimodal cancer therapy) Consortium (pages 13, 109). Building on preclinical successes of the former FP7-supported MultiFun Consortium that evidenced the efficacy of a novel multi-modal therapeutic approach based on fuctionalized magnetic nanoparticles and magnetic hyperthermia for the intra-tumoral treatment of both breast and pancreatic tumors, NoCAnTher will assess the safety of this strategy and generate preliminary data on its efficacy in humans. It will then aim to translate these findings into early clinical development for the treatment of pancreatic cancer by rolling out to a Phase I trial designed and coordinated by VHIO in collaboration with the Spanish National Cancer Research Center (CNIO), and Biopraxis.

The CRC Match colorectal cancer collaboration was driven by an alliance comprised of the Catalan Institute of Oncology (ICO), Bellvitge Biomedical Research Institute (IDIBELL), and VHIO – a trio of Catalonia-based research institutes of excellence whose respective clinical cancer experts, across the three sites, attend more than 60% of all CRC patients from within our region. Thanks to the expertise of a multidisciplinary team of outstanding basic and translational scientists, medical oncologists, data mining experts and platform managers, the CRC Match project will combine strengths and establish a circuit through which to better guide clinicians in matching the optimal treatment to the specificities of each individual patient.

Lastly, our group has participated in several pre-clinical and clinical studies on predicted responsive patient subsets using genetically annotated tumor surgical specimens ('Xenopatients') in mice; further expanding our collaboration with VHIO's Stem Cells & Cancer Group, led by Héctor G.Palmer.

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CLINICAL RESEARCH

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


**Principal Investigator**
› Joan Carles

**Medical Oncologists and Clinical Fellows**
› Rafael Morales
› Jordi Rodón
› César Serrano
› Cristina Suarez
› Claudia Valverde

## STRATEGIC GOALS:

› Design and develop clinical trials for the malignancies covered by our group.
› Provide patients with the most novel and optimal treatments for their respective diseases, including immunotherapies, targeted treatments, and new chemotherapeutics.
› Conduct clinical trials at different stages of disease with emphasis on a histology-tailored design and a multidisciplinary approach.
› 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.
› Implement a task force for prostate cancer at VHIO and Vall d'Hebron Research Institute (VHIR).
• Develop novel approaches such as liquid biopsy to better tailor treatments against CRPC, GIST, and kidney cancer.
• Expand our translational research platform for glioblastoma in collaboration with VHIO's Gene Expression & Cancer Group.
• Create a translational platform for kidney cancer and sarcomas and basic research in partnership with the Biomedical Research Institute of Bellvitge (IDIBELL).
• Set up a translational platform for GIST and expand research in collaboration with the Spanish Sarcoma Group (GEIS), and other European referral centers.

## HIGHLIGHTS:

› New drugs GU malignancies: we have participated in important trials with different drugs (ARN 509; ODM 201; combination of abiraterone acetate with or without radium 223), that have shown promise in improving outcomes for patients with prostate cancer. We are also participating in very new clinical trials with BET inhibitors and immune checkpoint inhibitors
› Other GU malignancies (renal and bladder): we are participating in clinical trials to evidence the utility of novel agents that can modulate the host immune response against cancer (PD-1 and PDL-1) in first and second line treatment. These drugs may be administered alone or in combination with other targeted therapies or chemotherapeutics.
› Central Nervous System (CNS) tumours: research has been further consolidated with the development of additional clinical trials and the creation of a 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 both clinical and translational research, and has broad experience and grounded expertise in the treatment of different neoplasms. We design and develop clinical trials for genitourinary malignancies at different stages of disease in collaboration with urologists and radiation therapists.

Over recent years, many developments have been reported in GU tumors; in prostate, bladder, and kidney cancer in particular. Immunotherapy is proving increasingly important in the treatment of bladder and kidney cancer, and in 2016 we have observed that it could also be important in the treatment of castration-resistant prostate cancer. Our group has participated in various clinical trials using checkpoint inhibitors that have changed the standard treatment for second line metastatic bladder cancer. Close collaboration with all specialists involved in the treatment of these tumors is consequently paramount. It is evident that radiologists are assuming an increasingly important role in the development of novel therapies against the majority of our tumor types.

We also continue to further develop our translational research platform for urologic cancer, as well as conduct clinical trials in early, adjuvant as well as metastatic disease. Our group collaborates with other research centers of excellence including the Cleveland Clinic (Ohio,USA), University of California, San Francisco (USA), Gustave Roussy Institute (Paris, France), and the Biomedical Research Institute of Bellvitge - IDIBELL (Barcelona, Spain).

We have developed the avatar program for kidney cancer tumors in collaboration with IDIBELL and have now implanted more than 20 samples. Another key area is the development of several multidisciplinary clinical studies and phase I trials in CNS tumors, in close connectivity with professionals in neurosurgery and radiation therapy.

Our group is also committed to expanding our translational research platform for glioblastoma in collaboration with VHIO's Gene Expression & Cancer Group led by Joan Seoane. We have consolidated a collaborative study with different centers across Europe to develop a vaccine for patients with glioblastoma, and are now initiating the phase I program. This project is supported by the European Commission's 7th Framework Programme of Research and Development.

We work closely with the Spanish Sarcoma Group (GEIS), to conduct clinical trials at different stages of disease with emphasis on a histology-tailored design. We 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). César Serrano joined our group as VHIO researcher in 2014 having spent the previous three years at the Brigham and Women's Hospital. He was awarded a Grant from the SARC (Sarcoma Alliance for Research through Collaboration), to develop new therapies against GIST tumors and is leading the young investigators subgroup at GEIS. We are now collaborating with different pharmaceutical companies to initiate phase I studies in GIST and also developing translational research for these studies at VHIO.

Our group is currently developing novel strategies in GIST therapy in close connectivity with other referral centers throughout Europe and pharmaceutical companies. The serum bank has expanded to include the majority of our tumor types (CNS tumors, GIST; renal cell carcinoma and CRPC), and will continue to recruit samples from our patients. Importantly, in terms of education and exchange, in 2016 we welcomed five fellows from in and outside of Spain to visit our group for three month short stay visits.

## PI PAPER PICK:


Saad F, Carles J, Gillessen S, Heidenreich A, Heinrich D, Gratt J, Lévy J, Miller K, Nilsson S, Petrenciuc O, Tucci M, Wirth M, Federhofer J, O'Sullivan JM; Radium-223 International Early Access Program Investigators. Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: an international, early access, open-label, single-arm phase 3b trial. *Lancet Oncol.* 2016 Sep;17(9):1306-16.

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CLINICAL RESEARCH

# ›GYNECOLOGICAL MALIGNANCIES GROUP

**Principal Investigator**
› Ana Oaknin

**Medical Oncologists and Clinical Fellows**
› Lorena Fariñas-Madrid
› Víctor Rodriguez-Freixinos

## STRATEGIC GOALS:

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

## HIGHLIGHTS:

› As a result of our clinical research of excellence, we continue to lead pivotal studies in gynecological malignancies which could potentially change the standard of care.
› As lead investigator for GOG in Spain, our group is heading a Phase III clinical trial in advanced cervical cancer with a novel vaccine to prevent and/or delay disease recurrence.
› Our involvement in several International cooperative groups of excellence enables us to participate in outstanding clinical research programs.
› Ana Oaknin's Vice Presidency of the GEICO group. This role has allowed our group to help lead clinical research in gynecological malignancies throughout Spain.

## SUMMARY:

Our group mainly focuses on clinical research in gynecological malignancies and the development of novel anti-cancer therapies against gynecologic tumors. Notably, over the past few years, our clinical studies have led to the approval of a new standard of care in both resistant relapsed ovarian cancer (e.g. the AURELIA Trial), and metastatic cervical cancer (e.g. GOG240 trial). Our research has driven outstanding results this year – of particular reference has been our involvement in the development of the new treatment, Rucaparib.

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

We are active members of some of the most relevant societies in gynecological oncology including the Gynecologic Cancer Inter Group (GCIG), for which we are appointed as the Spanish Representative on the Cervical Cancer Committee, the Gynecologic Oncology Group (GOG), as Spanish Clinical lead, as well as the European Network of Gynecological Oncology Trial Groups (ENGOT). In addition, 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). Such participation enables us to initiate the development of new drugs and novel treatment approaches from the very outset, which in turn provides our patients with greater opportunity to potentially benefit from these advances.

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

We are currently leading studies with innovative cancer medicines targeting the immune system in orphan pathologies such as metastatic cervical and endometrial cancer, and continue to clinically develop PARP inhibitors. We are introducing these in the early stages of treatment of patients with ovarian cancer associated to the BRCA mutation as well as a well-defined group of patients with high-grade ovarian carcinoma. Acting at specific molecular points in DNA repair pathways, these new therapies could potentially change the course of history in the treatment of ovarian cancer. Our group is also dedicated to exploring novel therapeutic combinations; we are now leading new trials pairing immunotherapy with angiogenesis inhibitors.

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

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.

## PI PAPER PICK:

Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, Oaknin A, Ray-Coquard I, Provencher; DM, Karlan BY, Lhommé C, Richardson G, Rincón DG, Coleman RL, Marth C, Brize A, Fabbro M, Redondo A, Bamias: A, Ma H, Vogl FD, Bach BA, Oza AM. Final results of a phase 3 study of trebananib plus weekly paclitaxel in recurrent ovarian cancer (TRINOVA-1): Long-term survival, impact of ascites, and progression-free survival-2. *Gynecol Oncol.* 2016 Oct;143(1):27-34.

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CLINICAL RESEARCH

# ›HIGH RISK & CANCER PREVENTION GROUP

**Principal Investigator**
› Judith Balmaña

**Staff Scientists**
› Estela Carrasco
› Marta Codina
› Cristina Cruz
› Irene Esteban
› Adrià López
› Neda Stjepanovic

**Auxiliary Clinician**
› Carmen Aguilar

**Clinical Nurse Specialist**
› Neus Gadea

**Data Curator**
› Sara Torres

## STRATEGIC GOALS:

› Clinical development of specific therapeutic strategies for tumors associated with hereditary genetic alterations.
› In vivo validation of mechanisms of resistance to targeted therapies in BRCA-associated breast cancer.
› Testing new combinations of therapies for BRCA-associated PDXs that have progressed to PARP inhibitors.
› Identification of new genes involved in hereditary breast cancer through the application of next generation sequencing (NGS).
› Psychological impact of hereditary cancer multiplex gene testing in the Spanish population.

## HIGHLIGHTS:

› Active participation in international phase II and phase III clinical trials with targeted therapies for BRCA-associated tumors.
› Validation of mechanisms of resistance to targeted therapies in a large collection of BRCA-associated patient-derived xenografts implanted in athymic mice.
› Analysis of the prevalence of pathogenic variants in new genes in hereditary breast cancer patients without mutations in BRCA1 or BRCA2.

## SUMMARY:

We are dedicated to developing novel targeted therapies for patients with hereditary breast cancer. During 2016, patients with local and advanced breast cancer and a BRCA germline mutation participated in several phase II/III trials with a specific DNA binding agent or PARP inhibitor.

Consolidation of our collaboration with VHIO's Experimental Therapeutics, Cancer Genomics, and Oncogenetics Groups led by Violeta Serra, Ana Vivancos, and Orland Díez, respectively, has resulted in a large collection of BRCA-associated patient-derived xenografts implanted in athymic mice. These murine models are being used to identify mechanisms of resistance to targeted therapies, identify novel biomarkers, and assess new combinatorial treatments at progression.

In the field of genetic epidemiology, we mainly focus on identifying new genetic susceptibilities to hereditary breast cancer.

We are collaborating with VHIO's Experimental Therapeutics Group on biomarker selection for PARP inhibitor sensitivity. A functional biomarker of homologous recombination has been tested preclinically and in human samples. Validation is ongoing. Two mechanisms of resistance to PARP inhibitors have been validated in our cohort of PDX samples.

Analysis of a panel of 98 cancer susceptibility genes in 193 breast and/or ovarian cancer families with no mutation in BRCA1/BRCA2 has been finalized Preparation of the manuscript is underway. We are committed to performing co-segregation analysis in these families and investigating the cancer spectrum and phenotype of these lesser-known non-BRCA genes.

In hereditary colorectal cancer, we are participating in a national registry led by the EPICOLON group to describe the characteristics of extracolonic tumors in Lynch Syndrome mutation carriers.

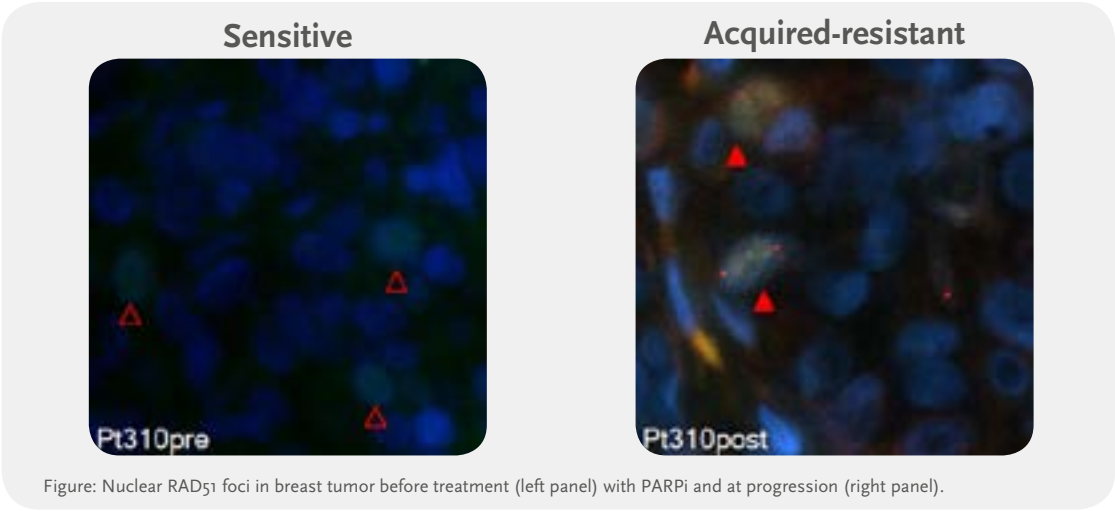


Figure: Nuclear RAD51 foci in breast tumor before treatment (left panel) with PARPi and at progression (right panel).

## PI PAPER PICK:

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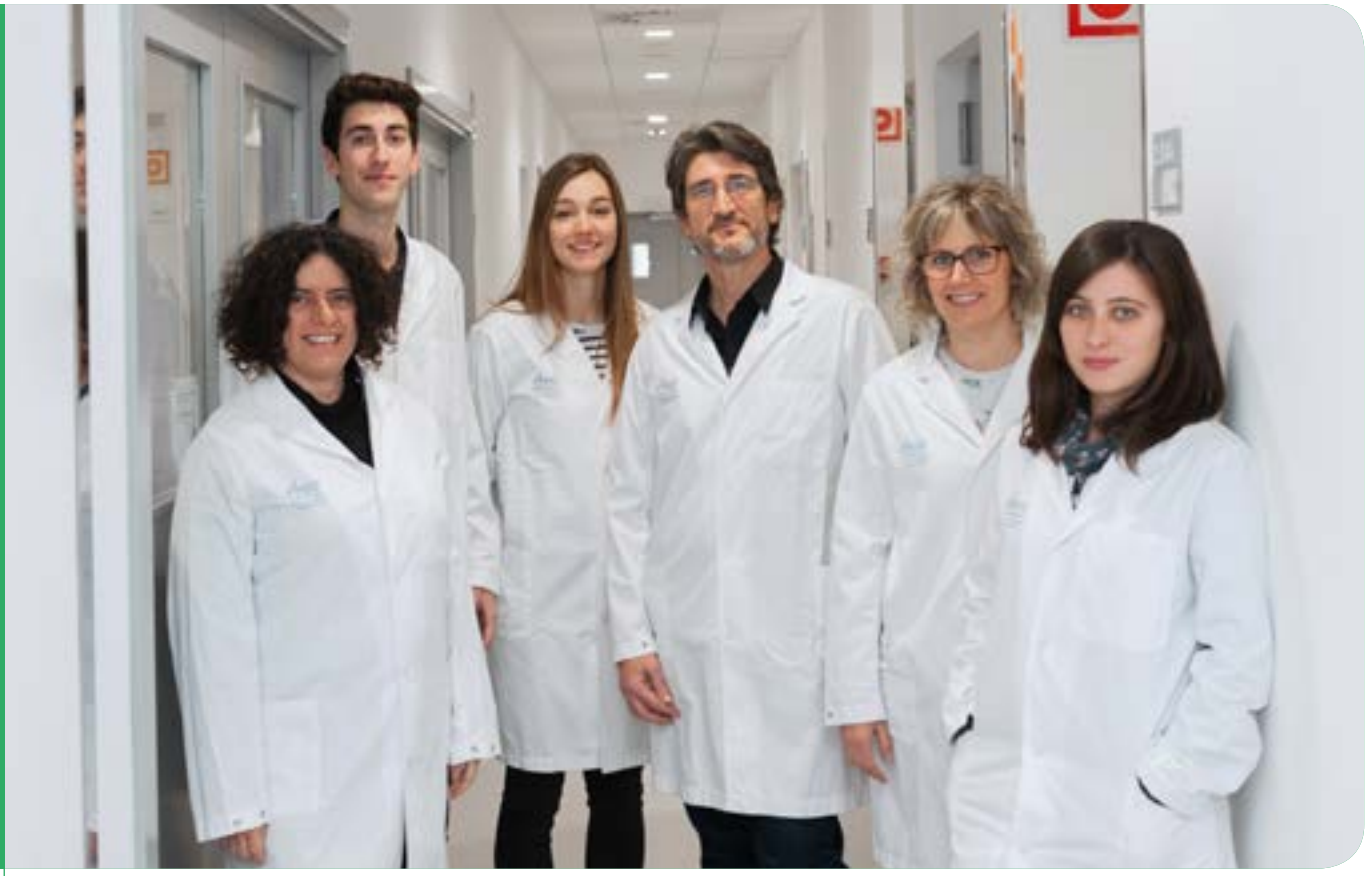
CLINICAL RESEARCH

# ›ONCOGENETICS GROUP



**Principal Investigator**
› Orland Díez

**Senior Scientist**
› Sara Gutiérrez-Enríquez

**Post-Doctoral Fellow**
› Sandra Bonache

**Radiation Oncologist**
› Manuel Altabas

**Clinical Nurse Specialist**
› Bibiana Piqué

**Graduate Students**
› Laura Durán
› Alejandro Moles
› Gemma Montalban

**Technicians**
› Vanesa Bach
› David García

## STRATEGIC GOALS:

› Application of massive sequencing to the diagnosis of hereditary cancer.
› Identification of new alleles for genetic predisposition to breast/ovarian cancer.
› Expression and functional analysis of genetic variants with unknown clinical significance in familiar cancer predisposition.
› Identification of common low-penetrance alleles for breast/ovarian cancer risk.
› Study of apoptosis assay as predictive test for late toxicity after radiotherapy.
› Assess the role of microRNAs and long non coding RNAs in the susceptibility to radiotherapy-induced clinical toxicity.

## HIGHLIGHTS:

› After exome and gene panel analysis, a list of candidate breast/ovarian cancer predisposing genes were prioritized. For confirmation in collaboration with the COMPLEXO (a name selected to reflect the complexity of the exome) Consortium.
› We characterized the blood spectrum of *BRCA2* mRNA alternate-splicing events.
› In partnership with CIMBA, we described new alleles of breast/ovarian cancer susceptibility and modifiers of risk conferred by *BRCA1/2* pathogenic variants.
› We enrolled breast and lung cancer patients in the European Commission FP7-funded project REQUITE to validate predictive models of toxicity from radiotherapy.

## SUMMARY:

VHIO's Oncogenetics Group focuses on two main lines of research: 1) the genetic predisposition to hereditary cancer, and 2) genetic predisposition to radiotherapy-induced toxicity.

Inherited predisposition to breast and ovarian cancer is mainly caused by *BRCA1, BRCA2, PALB2, RAD51C, TP53,* among other genes. We search for different alleles and new genes that may predispose to these types of cancer using massive sequencing to analyze gene panels and whole exomes.

Due to high allelic heterogeneity many results from genetic testing are variants with unknown clinical significance (VUS). The analysis of these variants and other alterations in untranslated regions in clinically significant genes constitutes an additional area of our group's intensive study.

We carry out splicing studies, *in silico* analyses, and collaborate with other partners in international consortia including the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA), to develop multifactorial studies aimed at ascertaining the effect of VUS. We are also working to establish a biological model derived from the carriers themselves through which to evaluate the *in vitro* functional effect of VUS and determine their potential pathogenicity.

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

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

We are working with VHIO's High Risk & Cancer Prevention and Experimental Therapeutics Groups, led by Judith Balmaña and Violeta Serra respectively, to analyze the role of expression changes in new or natural *BRCA1* mRNA isoforms as a mechanism of resistance to PARP inhibitors, using patient-derived tumor xenografts (PDXs).

Around half of all cancer patients receive radiotherapy and 3-5% of these patients suffer from severe long-term side-effects. Current evidence suggests the heritability of radiosensitivity. We are participating in the REQUITE project: Validating predictive models of radiotherapy toxicity to improve quality-of-life and reduce side-effects in cancer survivors. This research is supported by the European Union's Seventh Framework Programme for research and aims at identifying potential genetic and cellular markers (cell apoptosis) for radiotherapy toxicity.

As member of the International Radiogenomics Consortium (RGC), we also participate in meta-analysis to confirm association between different SNPs and toxicity post-radiotherapy.

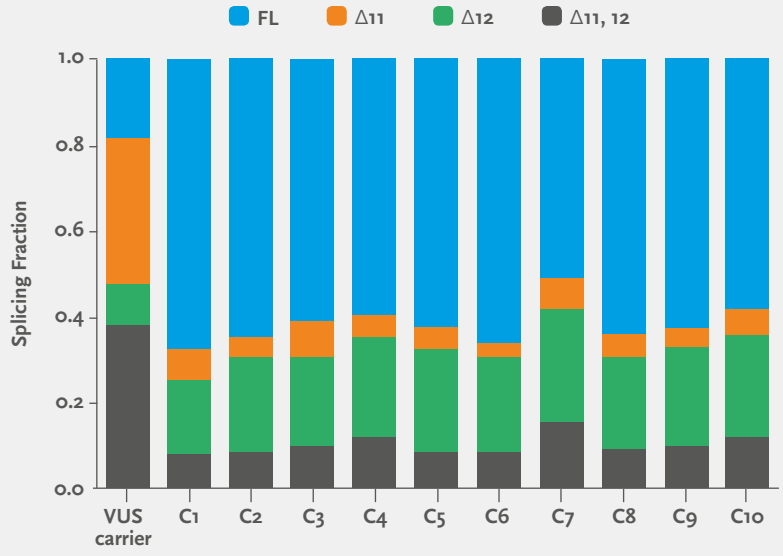



Figure: Fraction of four alternative transcripts detected by capillary electrophoresis of RT-PCR products, to estimate the spliceogenic effect of germline *PALB2* variant of unknown clinical significance in a breast cancer patient

## PI PAPER PICK: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CLINICAL RESEARCH

# ›ONCOLOGY DATA SCIENCE (ODysSey) GROUP

**Principal Investigator**
› Rodrigo Dienstmann

**Biostatistician**
› Guillermo Villacampa

**Data Curators**
› Fiorella Ruiz
› Sara Torres
› Cristina Viaplana

## STRATEGIC GOALS:

› Integration of clinical translational research with genomics for precision cancer therapy.
› Clinical-molecular databases with matched targeted agents and immunotherapies.
› Continued medical education in the interpretation of next-generation sequencing tests.
› Collaborative research in cancer genomics/computational oncology and its clinical implications.

## HIGHLIGHTS:

› Throughout 2016 we have led important advances in data mining, expert curation of the literature and knowledge interpretation of somatic gene alterations that have a therapeutic impact in cancer. Our Cancer bioMarkers database is publicly available and has become a reference for clinical investigators across the globe. The terminology that we have developed has been adopted by the ClinGen Somatic Cancer Working Group, which will harmonize biomarker curation through consensus minimum variant level data.
› Participation in the MedBioinformatics European Consortium: our group was extensively involved in the development of integrative bioinformatics tools and autonomously usable software applications for scientists and clinical practitioners to analyze the huge amount of data and knowledge generated in healthcare and biomedical research in order to advance translational research and precision medicine.
› Participation in the MoTriColor European Consortium: we assumed a critical role in the design and implementation of molecularly-guided clinical trials with specific targeted and immunotherapies for the newly defined colorectal cancer subtypes based on gene expression.
› Throughout 2016 we have provided support to preclinical and clinical investigators from VHIO working on biomarkers research and its implications for patient management, which resulted in impactful publications in the field, as well as presentations at leading oncology congresses.

## SUMMARY:

VHIO's Oncology Data Science (ODysSey) Group provides guidance to medical oncologists and cancer biologists during the development, validation and interpretation of "omics"- based tests that have direct clinical application. Our main objective is to provide researchers with reliable tools to investigate biomarkers developed to optimize patient stratification, based on differences in response patterns to cancer therapies or outcome.

To do so, we design and maintain clinical-molecular databases, integrating the results of "multi-molecular" tumor profiling tests performed at VHIO with information available in electronic medical records, including treatment benefit with targeted drugs and immunotherapies as well as patient survival across multiple tumor types. This represents a critical resource for medical oncologists, molecular pathologists, and translational investigators at VHIO who are studying predictive and prognostic biomarkers.

We also contribute to the Cancer bioMarkers database (https://www.cancergenomeinterpreter.org/biomarkers); a structured platform that uses standardized terminology to describe associations between tumor types, genes, variants, response/resistance patterns to approved and experimental agents under clinical investigation, and PubMed identifiers.

We encourage and promote collaborative research among computational oncology scientists on predictive and prognostic modeling, identification of cancer drivers, intra-tumor heterogeneity, and druggability in solid tumors. Leadership in the Variant Interpretation for Cancer Consortium, an international initiative of the Global Alliance for Genomics and Health, reflects our dedication to the sharing and open exchange of data.

### KEY ALLIANCES

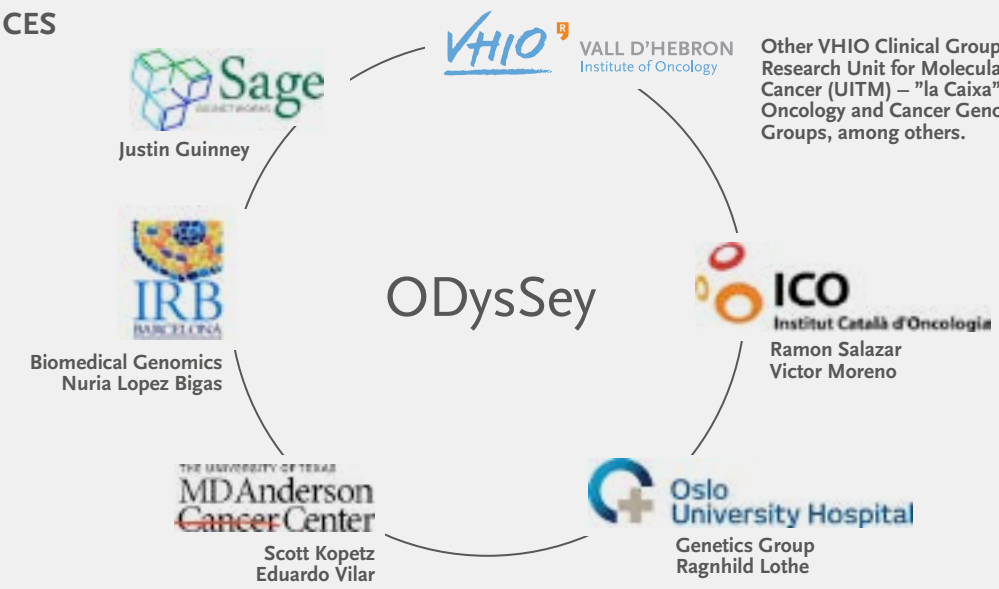


Figure: VHIO's Oncology Data Science (ODysSey) Group's strategic alliances and key collaborations.

## PI PAPER PICK:

Arques O, Chicote I, Puig I, Tenbaum SP, Argiles G, Dienstmann R, Fernandez N, Caratu G, Matito J, Silberschmidt D, Rodon J, Landolfi S, Prat A, Espin E, Charco R, Nuciforo P, Vivancos A, Shao W, Tabernero J, Palmer HG. Tankyrase inhibition blocks Wnt/β-catenin pathway and reverts resistance to PI3K and AKT inhibitors in the treatment of colorectal cancer. *Clin Cancer Res.* 2016 Feb 1;22(3):644-56.

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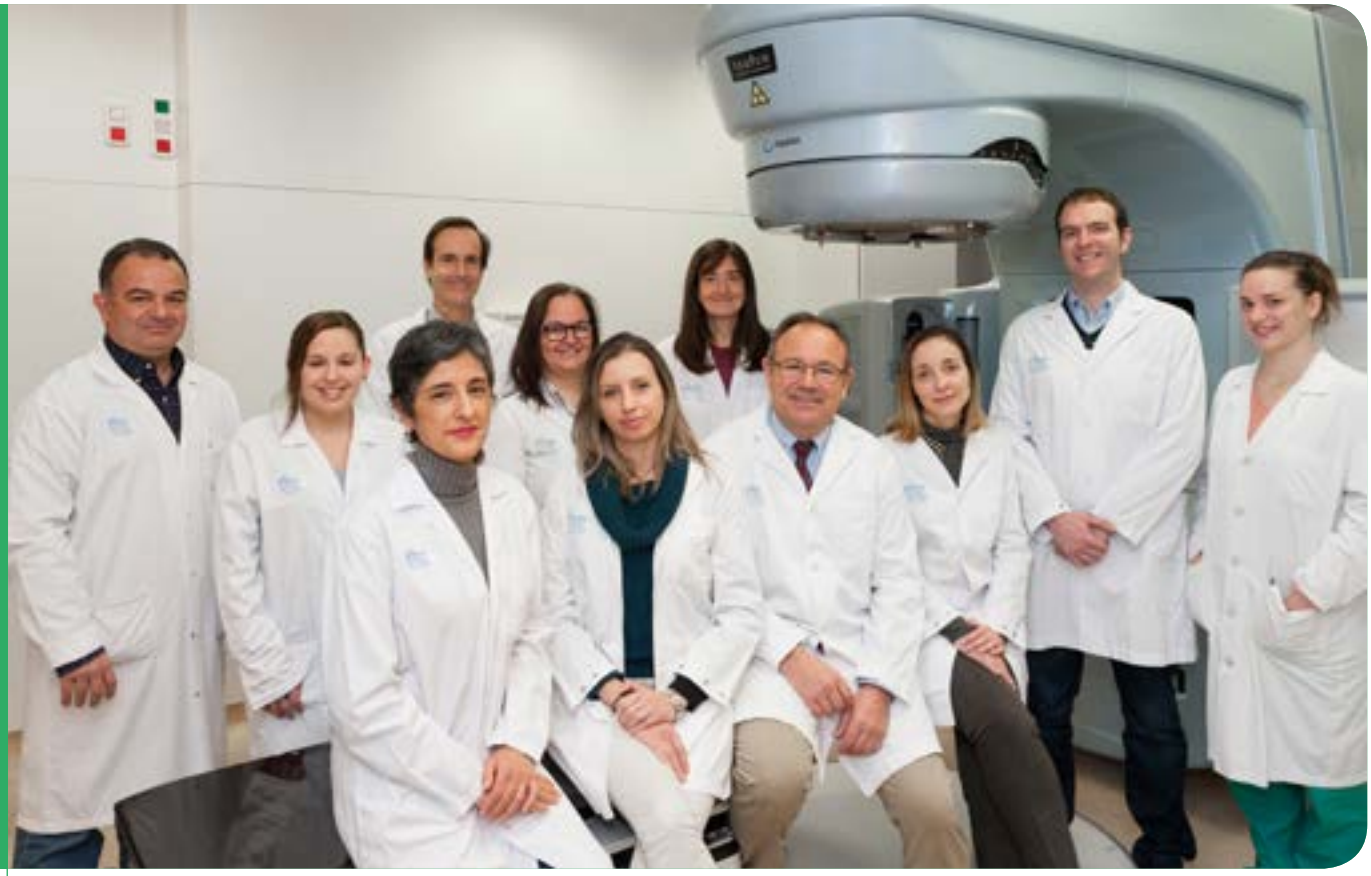
CLINICAL RESEARCH

# ›RADIATION ONCOLOGY GROUP



**Principal Investigator**
› Jordi Giralt

**Radiation Oncologists**
› Manuel Altabas
› Sergi Benavente
› Alexandra Giraldo
› Xavier Maldonado
› Andrés Muñiz
› Begoña Navaltropo
› Mónica Ramos
› Victoria Reyes
› Ramona Verges

## STRATEGIC GOALS:

› Technology development: acquisition of new equipment to implement cutting edge clinical treatment techniques such as rotational radiotherapy - with intensity modulated arc therapy (VMAT), adaptive radiotherapy, and image-guided radiotherapy (IGRT).

› Translational research: application of insights into cancer biology as well as healthy tissue in order to personalize therapy matched to the characteristics and specificities of each patient, each individual tumor.

## HIGHLIGHTS:

› An increase in the number of patients treated with IMRT and RC/SBRT. In 2016 we treated 605 patients with IMRT and 93 patients with RC/SBRT; representing an increase of 34% and 82%, respectively.

› The Adaptive and innovative Radiation Treatment FOR improving Cancer treatment outcomE (ARTFORCE) project began in the year 2013. At present we have included 48 patients and are consequently the top recruiters in this collaboration.

› We initiated a dose escalation program using Image Guided RadioTherapy (IGRT) with fiducials, and have since treated 21 patients.

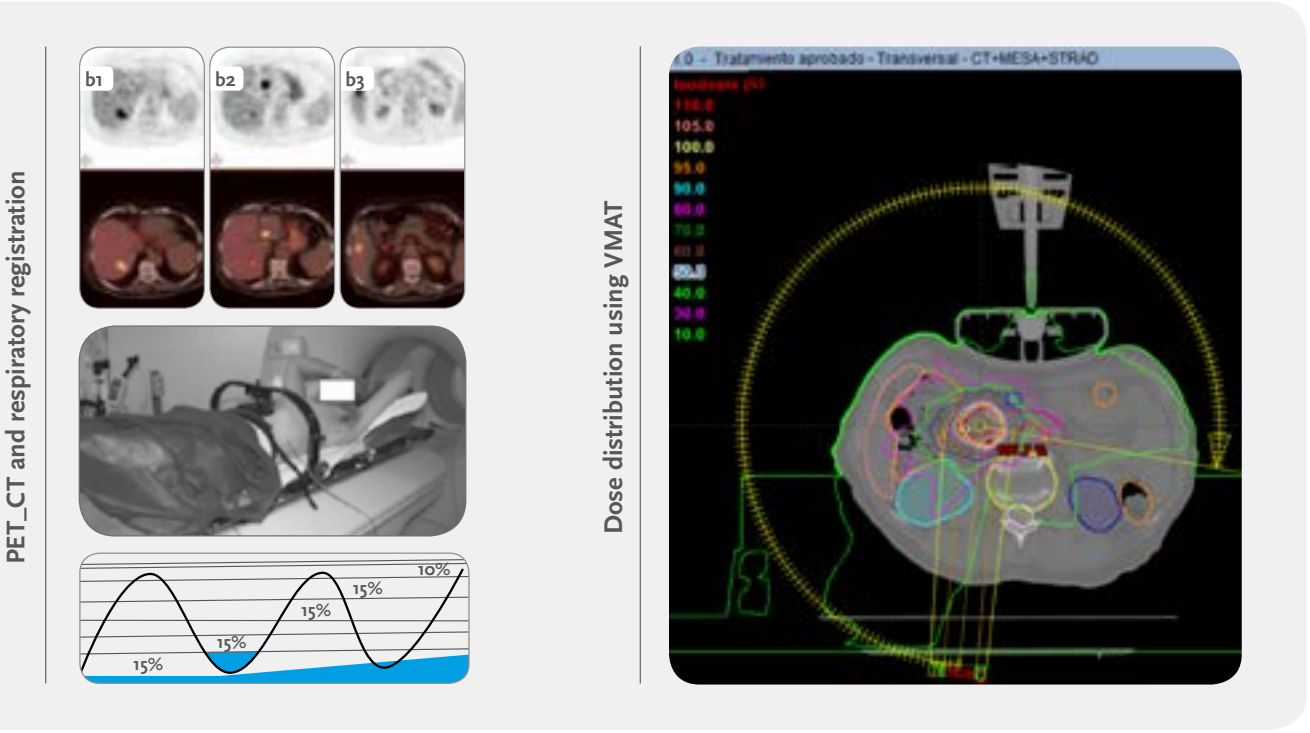
› Our group has set up a stereotaxic extracranial RT in lung, liver, and pancreas, and we have treated 64 patients.

## SUMMARY:

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

Current and future research priorities include the following key areas:

- Development of an estereotactic extracranial radiotherapy program in pancreas and bone metastases.
- Develop a 4D program for lung cancer.
- In breast cancer, the validation of partial breast irradiation in prone position technique.
- To establish the benefit of dose painting and adaptive radiotherapy in head and neck cancer in a clinical trial.
- The use of nanoparticles as radiotherapy enhancement for soft tissue sarcomas.
- Analyze the combination of PD-1 immunotherapy monoclonal antibodies with hypofractionated radiotherapy in metastasis.
- Dose escalation trials in prostate cancer using hypofractionation and IGRT.
- Obtain ISO 9001 (2015) accreditation.

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CLINICAL RESEARCH

# ›THORACIC TUMORS & HEAD AND NECK CANCER GROUP

**Principal Investigator**
› Enriqueta Felip

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

## STRATEGIC GOALS:

› Contribute to early drug development and matched therapies for thoracic and head & neck tumors.
› Advance personalized medicine for lung cancer patients through translational research.
› Optimize novel treatment approaches (immunotherapy and targeted agents), for the management of patients with thoracic and head & neck malignancies.
› Further strengthen multidisciplinarity to provide optimal care for our patients.

## HIGHLIGHTS:

› 500 new lung cancer patients including 20 cases of mesothelioma and 5 of thymoma.
› 250 new head & neck cancer patients.
› We continue to foster multidisciplinarity through our thoracic tumors committee that convenes twice a week.
› Head & neck cancer patients are discussed by a multidisciplinary team, twice a week.
› Implementation of pharmacogenomic approaches in advanced lung cancer in collaboration with VHIO's Cancer Genomics Group led by Ana Vivancos, and the Vall d'Hebron University Hospital Pathology Service, working with Javier Hernández and Irene Sansano.
› Implementation of liquid biopsy for certain advanced NSCLC patients.
› Our group has collaborated in the development of a number of drugs in lung cancer patients selected according to specific molecular alterations; some of which have already been approved by FDA and EMA as result of these studies.
› Identification of mechanisms of resistance to innovative targeted therapies; we have collaborated in the identification of C797S as a mechanism of acquired resistance to osimertinib.
› Development of immunotherapy strategies in thoracic and head & neck malignancies.

## SUMMARY:

The main focus of VHIO's Thoracic Tumors & Head and Neck Cancer Group is to tackle the challenges posed by thoracic malignancies, including lung cancer, mesothelioma and thymic malignancies, and tumors of the head and neck. Our group concentrates on areas ranging from disease prevention, early detection, more accurate techniques in diagnosis and staging to advancing precision medicine and anti-cancer thearpies. We focus on targeted therapies in patients with specific molecular alterations, unmasking molecular mechanisms of acquired resistance, and optimizing novel immunotherapy strategies.

In patients with early-stage thoracic malignancies, we liaise closely with a multidisciplinary team incorporating thoracic surgeons, radiation therapists, radiologists, pulmonologists and pathologists to better optimize the different treatment approaches and modalities. Given that patients with thoracic malignancies can suffer from severe symptoms associated with their disease, we strive to ameliorate these by working in tight connectivity with professionals from other disciplines.

In patients with advanced-stage lung cancer personalized therapy is now the standard approach and our key objective is therefore to achieve wide implementation of molecular determinants to better select therapy tailored to individual patients, not only in tumors but also in circulating-free DNA (liquid biopsy). Immunotherapy strategies have a role in the lung cancer management and treatment algorithm; a number of protocols are now ongoing in our unit. We actively contribute to VHIO's early clinical drug development efforts, and also deal with other less common thoracic malignancies such as small-cell lung cancer, mesothelioma, thymoma, and neuroendocrine tumors.

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

## PI PAPER PICK:

Solomon BJ, Cappuzzo F, Felip E, Blackhall FH, Costa DB, Kim DW, Nakagawa K, Wu YL, Mekhail T, Paolini J, Tursi J, Usari T, Wilner KD, Selaru P, Mok TS. Intracranial Efficacy of Crizotinib Versus Chemotherapy in Patients With Advanced ALK-Positive Non-Small-Cell Lung Cancer: Results From PROFILE 1014. *J Clin Oncol.* 2016 Aug 20;34(24):2858-65.

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# CORE TECHNOLOGIES

## THE PI PAGES



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

CORE TECHNOLOGIES

# ›CANCER GENOMICS GROUP

**Principal Investigator**
› Ana Vivancos

**Specialized Technicians**
› Ginevra Caratù
› Chiara Chianese
› Judit Matito
› Leire Mendizabal
› Zighereda Ogbah

**Bioinformatician**
› Francesco M. Mancuso

**Bioinformatics Technical Auxiliary**
› Laura Muiños

**Post-Doctoral Fellows**
› Deborah G. Lo Giacco
› Miriam Sansó

## STRATEGIC GOALS:

› Develop and implement improved strategies for routine patient prescreening in a setting of excellence (ISO 15189 accreditation).

› Provide cutting-edge applications in cancer genomics through the use of novel technologies and protocol development.

## HIGHLIGHTS:

› International Standarization Organization ISO15189 accreditation for our VHIO-Card Amplicon-seq panel (NGS).

› 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). Our group is appointed co-leader of the Consortium's Genomics Taskforce and is responsible for the alignment of genomic testing across all 6 institutions.

› Implementation of liquid biopsy in routine clinical practice. We incorporated a Digital-PCR platform, BEAMing, for the detection of RAS mutations in first-line metastatic colorectal cancer, as well as a ddPCR (BIO-RAD) to profile lung cancer.

› Validation and introduction of a routine CNA detection in patient FFPE samples. Copy number alterations (CNA) are a well-known mechanisms driving tumorigenesis and resistance to therapy. There are a number of molecules in the clinical setting that target proteins coded by genes suffering copy number gains or losses in the genome including EGFR, ERBB2, MET, and RB1. We plan to develop and implement an approach that will enable us to routinely profile these events in FFPE samples. In combination with our Mutation and Gene Fusion Cards, we will be able to provide a comprehensive profile of patient samples.

## SUMMARY:


VHIO's Cancer Genomics Group serves as a Core Technology laboratory to bridge the preclinical and clinical levels of cancer discovery. Providing cutting-edge applications in cancer genomics through state-of-the-art technologies, we also develop novel and fully validate tests that are applied to the clinical research setting.

Our lab is equipped with a genotyping platform (MassARRAY, Sequenom), an n-Counter (Nanostring) platform, two digital PCR platforms (BEAMing, Sysmex and ddPCR, BIO-RAD), and two NextGen Sequencers; MiSeq and HiSeq2500, Illumina (see figure), and our research drives the development of novel multiplexed tests that are optimized to FFPE-derived nucleic acids. Once developed, our tests are validated and used in clinical research; VHIO's Prescreening Program.

In addition, we have developed and routinely implemented an Amplicon-seq approach to sequence 67 genes (Illumina), a gene fusion panel with the capacity of detecting over 100 recurrent gene fusions, as well as a Copy Number Alteration panel detecting 59 genes based on nCounter technology.

VHIO's Prescreening Program is nucleated around the activity of two groups - our Cancer Genomics Group and VHIO's Molecular Oncology led by Paulo Nuciforo, and is dedicated to performing molecular profiling in over 1500 patients per year as candidates for enrollment in Phase I clinical trials carried out at our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", directed by Jordi Rodón. Suitability for enrollment in a given clinical trial is assessed based on the respective genomic or pathologic profile of individual patients.

As a reflection of the excellence and quality in the services we provide, we have undergone ISO 15189 accreditation for our main testing methods. Focused on solid tumors and in collaboration with VHIO's preclinical researchers and physician-scientists, we are also involved in a number of translational projects including the identification of mechanisms of resistance to targeted therapies, study of clonal populations, liquid biopsy, and defining novel therapeutic opportunities based on mutation profiles.


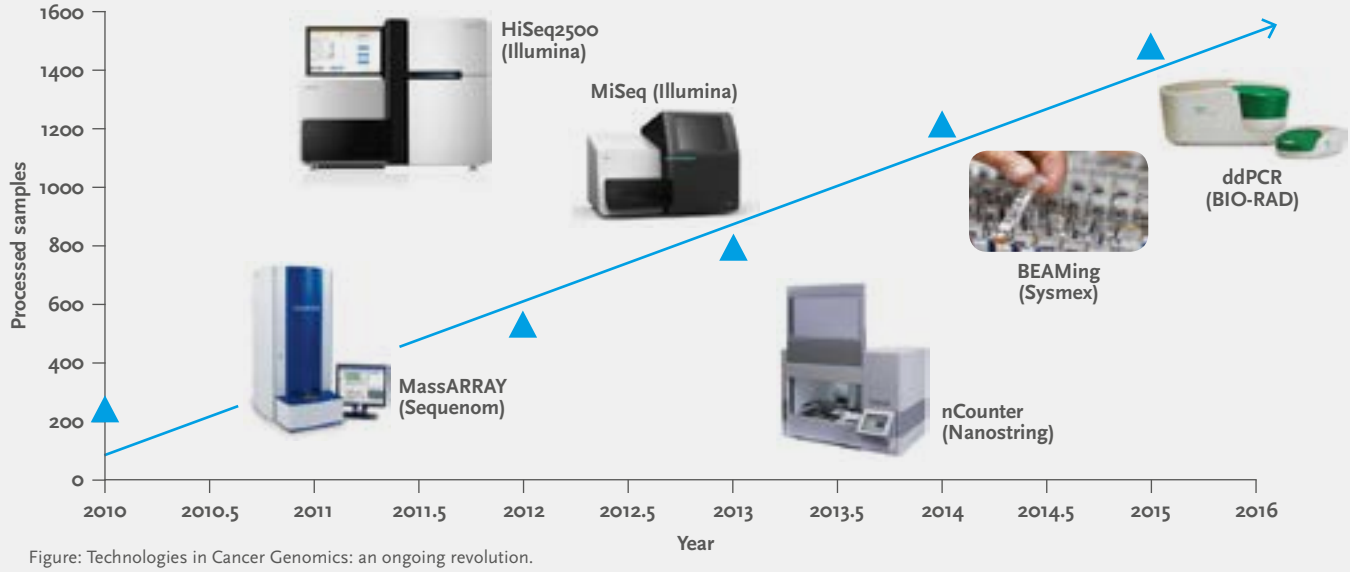


Figure: Technologies in Cancer Genomics: an ongoing revolution.

## PI PAPER PICK:


Arqués O, Chicote I, Puig I, Tenbaum SP, Argilés G, Dienstmann R, Fernández N, Caratù G, Matito J, Silberschmidt D, Rodon J, Landolfi S, Prat A, Espín E, Charco R, Nuciforo P, Vivancos A, Shao W, Tabernero J, Palmer HG. Tankyrase Inhibition Blocks Wnt/β-Catenin Pathway and Reverts Resistance to PI3K and AKT Inhibitors in the Treatment of Colorectal Cancer. *Clin Cancer Res.* 2016 Feb 1;22(3):644-56.

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CORE TECHNOLOGIES

# ›MOLECULAR ONCOLOGY GROUP

**Principal Investigator**
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**Attending Physicians**
› Laura Comerma
› Roberta Fasani

**Laboratory Supervisor**
› Jose Jiménez

**Laboratory Assistant**
› Mª Ángeles Díaz

**Technicians**
› Mª del Carmen Díaz
› Francisca Gallego
› Xavier Guardia
› Paola Martínez
› Gertrudis Sánchez
› Garazi Serna
› César Sevillano

## STRATEGIC GOALS:

› Discovery and validation of novel biomarkers using tissue-based technologies.
› Serve as a Core Facility for VHIO research programs.
› Act as a central and local laboratory in clinical trials.
› Apply molecular pathology strategies to support early clinical drug development programs.
› Define molecular target epidemiology to improve personalized treatment strategies.

## HIGHLIGHTS:

› Supported over 200 clinical trials for sample management and analyses. Central laboratory in different national and international studies.
› Over 4000 molecular determinations on samples for patient inclusion into clinical trials and over 12,000 tests performed for basic and translation research programs.
› Development of biomarker strategies for FGFR, MET, and Antibody-drug conjugates early clinical development programs.
› Validation of the predictive value of protein quantification using SRM-MS.
› Maintenance and expansion of tests under ISO15189 accreditation.

## SUMMARY:


The mission of VHIO's Molecular Oncology Group is to apply state-of-the-art tissue-based technologies to basic, translational, and clinical research with a clear focus on the development and validation of novel tumor biomarkers for precision medicine against cancer. Our group also serves as one of VHIO's Core Technology Platforms and is therefore central to research performed at our Institute. We actively participate in all research projects involving the use of human tissue collected from patients, including biomarker analyses for patient stratification, tissue banking, the development of primary xenograft models, and analyses of liquid biopsies.

Core Facility activities in 2016: We provided support for approximately 200 clinical trials conducted at Vall d'Hebron, representing more than 60% of all trials open at our institution. Our activities in clinical trials range 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 2016, we have performed more than 4000 molecular determinations on samples for patient inclusion in clinical trials and over 12,000 tests to support basic and translation research programs. We have also been the central laboratory for 10 international studies. Our laboratory also successfully maintained the prestigious ISO15189 quality accreditation as well as achieved the flexible scope and expansion of the catalogue of molecular tests run under accreditation.

Research activities in 2016: We focused on identifying better predictive biomarkers in breast cancer (Prat et al, *JAMA Oncol.* 2016; Prat el al, *Clin Cancer Res.* 2016; Hergueta-Redondo, *Oncotarget.* 2016). Of particular note, we demonstrated that HER2 protein quantification by Selected Reaction Monitoring Mass Spectrometry (SRM-MS) is a better predictive marker of response to anti-HER2 in breast cancer as compared to standard IHC/FISH (Nuciforo et al, *Mol Oncol.* 2016). Based on these results, we are now expanding this observation to HER2+ gastric cancers.

By targeted multiplex proteomics, we identified Mesothelin as a prognostic marker in advanced colorectal cancer (CRC). This has led to an independent project currently ongoing in our lab aimed at refining the role of MSLN as a putative target in CRC (ESMO's MAP 2016 Conference – Molecular Analysis for Personalised Therapy, 23 - 24 September, London, UK).

Our third line of research explores the value of MET and FGFR proteins quantification in improving the identification of patients sensitive to selective MET and FGFR inhibitor therapies (Annual Meeting of the United States and Canadian Academy of Pathology (USCAP), 12 - 18 March 2016, Washington, USA, and the San Antonio Breast Cancer Symposium (SABCS), 06 - 10 December 2016, Texas, USA).


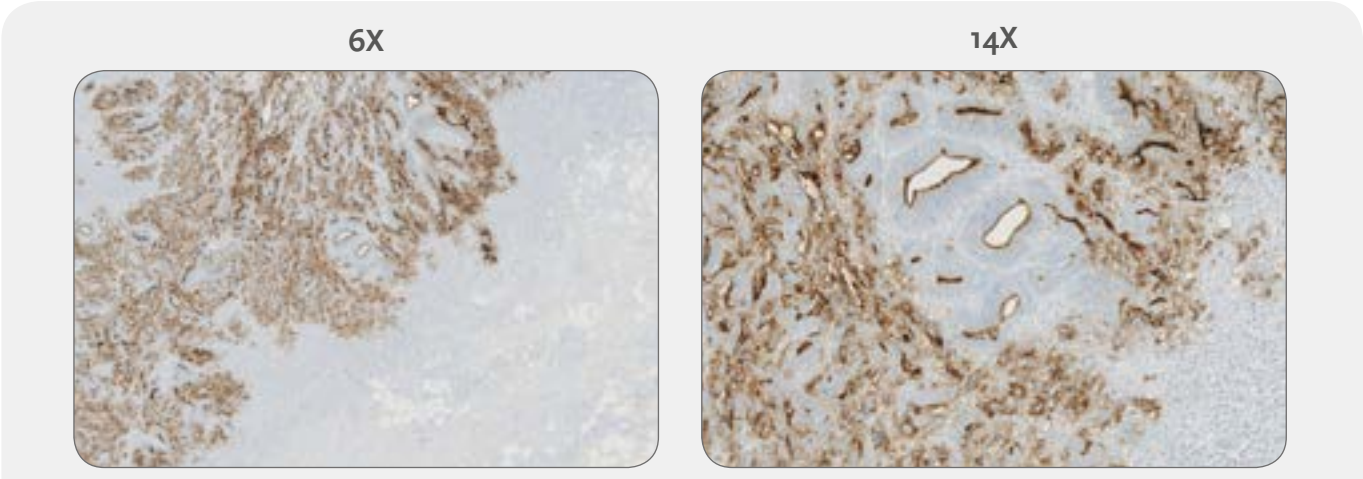


Figure: Tissue expression of CEACAM5 in colorectal cancer with microsatellite instability.

## PI PAPER PICK:

Nuciforo P, Thyparambil S, Aura C, Garrido-Castro A, Vilaro M, Peg V, Jimenez J, Vicario R, Cecchi F, Hoos W, Burrows J, Hembrough T, Ferreres JC, Perez-Garcia J, Arribas J, Cortes J, Scaltriti M. High HER2 protein levels correlate with increased survival in breast cancer patients treated with anti-HER2 therapy. *Mol Oncol.* 2016 Jan;10(1):138-147.


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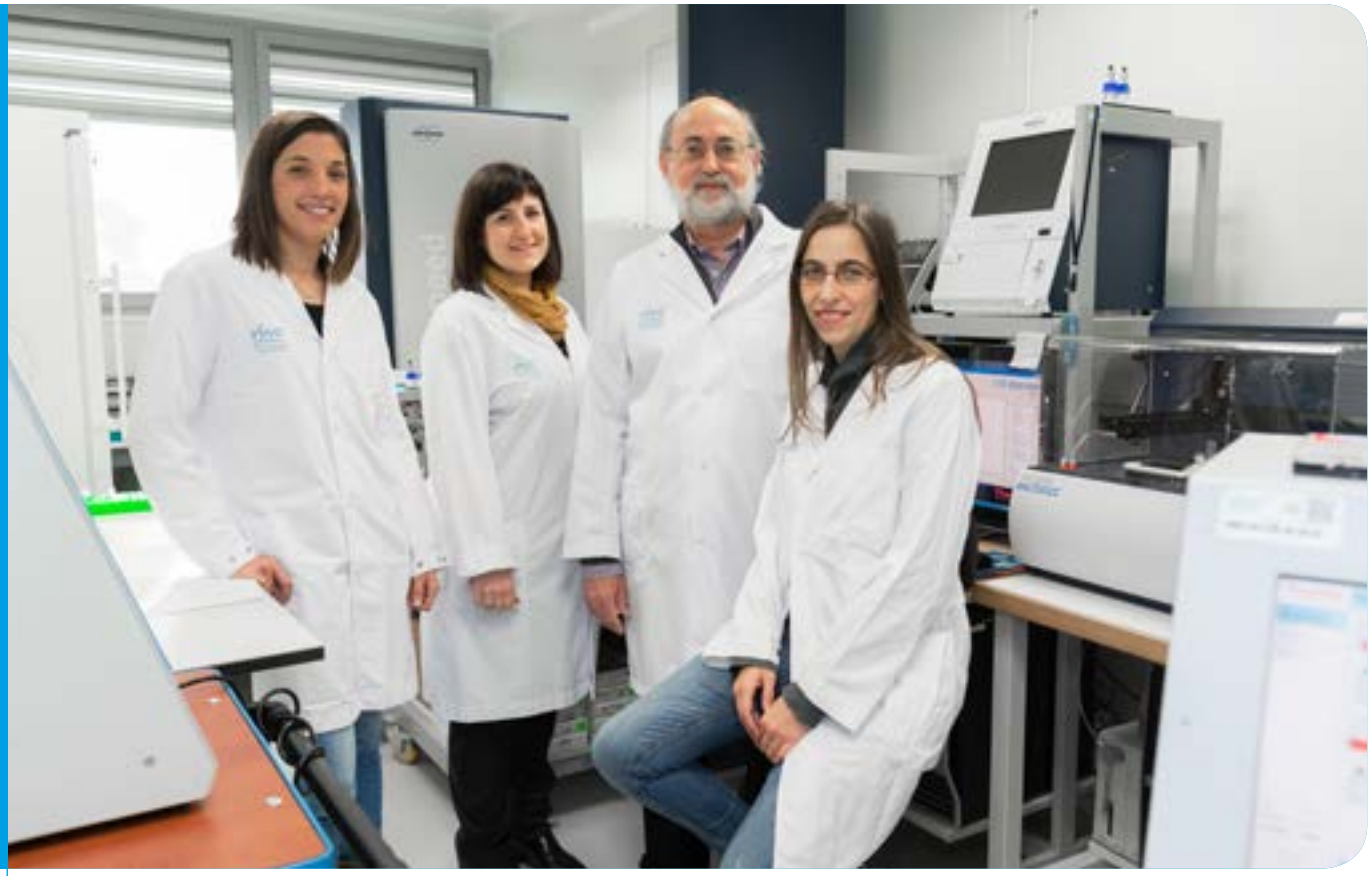
CORE TECHNOLOGIES

# ›PROTEOMICS GROUP



**Principal Investigator**
› Francesc Canals

**Post-Doctoral Fellow**
› Núria Colomé

**Technicians**
› Luna Martin
› Anna Sabé

## STRATEGIC GOALS:

› Provide services in proteomic techniques to other research groups as a Core Facility.
› Explore the role of ADAM and ADAMTS metalloproteases in cancer through proteomic analysis.
› Proteomic screening for new biomarkers to help develop cancer therapeutics.
› 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.
› Development of an immuno-MS assay to monitor LIF protein for patient selection and monitoring of LIF-targeted treatment of cancer.
› Participation in the Spanish Consortium Chromosome 16 HPP - part of the HUPO Human Proteome Project.

## SUMMARY:


Proteomics involves the characterization of the entire set of proteins - proteome - expressed by a particular cell or tissue under specific physiological or pathological conditions. The application of proteomic technologies to cancer research is a rapidly expanding field - not only for basic research but also for the discovery of diagnostic or disease-progression biomarkers. We mainly focus on the application of proteomic techniques to the identification and characterization of substrates of metalloproteases involved in tumor progression.

Metalloproteases of the ADAM and ADAMTS families play a crucial role in the regulation of the tumor microenvironment by mediating the remodeling of the extracellular matrix and the cleavage of specific extracellular and membrane proteins. Insights into the substrates of these proteases in the context of tumor cells are required in order to elucidate their role in tumor growth and metastasis as well as evaluate their potential use as therapeutic targets.

Our group employs mass spectrometry-based proteomic strategies to search for new substrates of these proteases and analyze their involvement in tumor progression.

We also adopt proteomic techniques for the screening and validation of biomarkers for cancer diagnostics, precision therapy against cancer, and the tracking of disease. Our focus centers on the development of mass spectrometry-based assays for the analysis of biomarkers in clinical samples. VHIO's Proteomics Group is a member of the Spanish Consortium Chromosome 16 HPP which forms part of the HUPO Human Proteome Project. Following a chromosome-centric strategy, this multicenter and international project aims at developing an entire map of the proteins encoded by the human genome in order to advance our understanding of human biology in health and disease, and is consequently set to impact on ongoing disease-oriented research.

As a Core Facility, we provide state-of-the-art proteomic methodologies to VHIO researchers as well as implement new developments within the field to offer the very latest proteomic strategies and technologies.

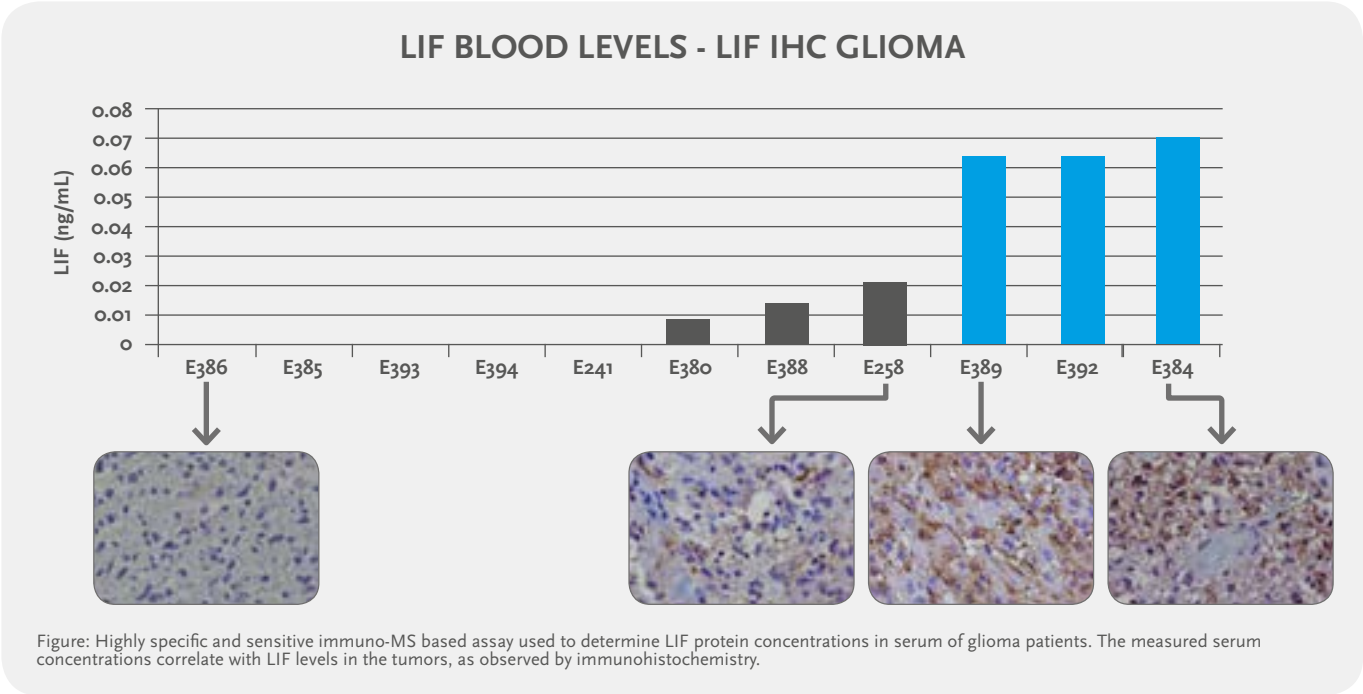




Figure: Highly specific and sensitive immuno-MS based assay used to determine LIF protein concentrations in serum of glioma patients. The measured serum concentrations correlate with LIF levels in the tumors, as observed by immunohistochemistry.

## PI PAPER PICK:


Llombart V, García-Berrocoso T, Bech-Serra JJ, Simats A, Bustamante A, Giralt D, Reverter-Branchat G, Canals F, Hernández-Guillamon M, Montaner J. Characterization of secretomes from a human blood brain barrier endothelial cells in-vitro model after ischemia by stable isotope labeling with aminoacids in cell culture (SILAC). *J Proteomics.* 2016 Feb 5; 133:100-12.

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# ›TRANSLATIONAL GENOMICS GROUP

**Principal Investigator**
› Aleix Prat

**Clinical Research Technician**
› Patricia Galván

**Specialist Physician in Breast Cancer (collaboration)**
› María Jesús Vidal Losada

**Technician**
› Débora Martínez

## STRATEGIC GOALS:

› Use genomic data to guide clinical trial design and biomarker development aimed at identifying more effective treatment regimens for cancer patients.
› Use gene expression data to better characterize different tumor types and further understand cancer biology.
› Help implement gene expression-based tests in the clinical setting.

## HIGHLIGHTS:

› Implementation of the PAM50/PROSIGNA® nCounter-based assay in the clinical setting.
› Identification and molecular characterization of the intrinsic molecular subtypes of breast cancer within HER2+ breast cancer.
› Susan G. Komen Career Catalyst Grant to identify patients with HER2+ breast cancer that do not need chemotherapy.
› We received a FIS – *Fondo de Investigación en Salud* (National Health Research Fund) grant to study triple-negative breast cancer.
› Participation in correlative science studies across ~10 clinical trials.

## SUMMARY:


2016 has proven highly productive for VHIO's Translational Genomics Group:

We have performed more than 300 assays of the clinically applicable and standardized gene expression-based test, known as PAM50. In addition, we have analyzed >1.000 samples and continued to provide scientific guidance and advice to several collaborators both at VHIO and overseas, leading to various publications in high-impact factor journals. Moreover, our group has continued to participate in the retrospective genomic analyses of tumor samples from several national and international clinical trials including PAMELA, GEICAM2012-09, NeoEribulin, EGF30008, EGF104900, LPT109096, CIBOMA/2004-01/ GEICAM 2003-11, OPTI-HER and CHER-LOB; many of which have been published this year.

We have also continued to demonstrate the clinical validity of breast cancer heterogeneity as determined by gene expression analysis. In a first article, published in *JAMA Oncology*, we analyzed 821 breast tumor samples from a phase III clinical trial (EGF30008). Our results showed, for the very first time, that the intrinsic molecular subtypes are the most important prognostic variable in the metastatic setting.

In a second paper, published in *Clinical Cancer Research*, we developed and validated, across 675 patients and 4 independent studies, a new PAM50-based chemo-endocrine predictor for patients with luminal early breast cancer. These findings should help oncologists and patients decide on the best treatment strategy should the respective tumors have an intermediate risk of relapse. In 2016 we also presented the final results of the PAMELA clinical trial during a Plenary Session at the San Antonio Breast Cancer Symposium - SABCS, December 06 - 10, Texas, USA. In this study, we showed that PAM50 can help to identify a group of patients with HER2+ disease that could be cured with dual HER2 blockade without chemotherapy.

Finally, we have continued to collaborate with several renowned investigators. In one paper, published in *Clinical Cancer Research*, we identified a particular miRNA, miR-206, that inhibits stemness and metastasis in breast cancer. In a second article, published in the same journal, we reported the results of a clinical trial that enrolled 190 patients with triple-negative disease who were treated with a non-anthracycline regimen. In this study, we showed this treatment strategy to be highly effective for this group of patients.

In a third article, published in *Annals of Oncology*, we collaborated in a study that, using samples from the CHER-LOB clinical trial in HER2+ breast cancer, evidenced immune gene expression and intrinsic subtype as predictors of pathological response following chemotherapy and anti-HER2 therapy.

Our group has participated in 8 original research articles providing scientific advice and/or performing gene expression analyses: 2 as first author, and 2 as second author. For 2016 our group's Impact Factor (IF) totaled at 47.1 (an average of 6.7 per publication).


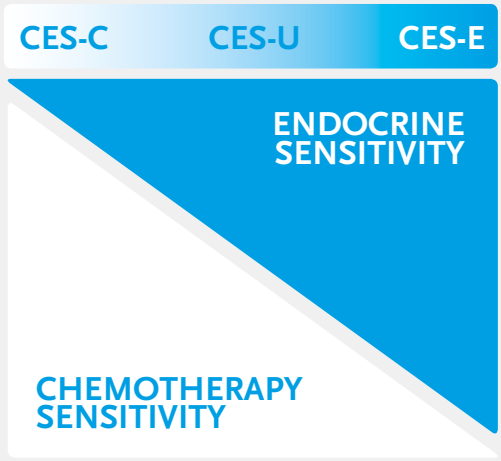


Figure: The newly developed PAM50-based chemo-endocrine score.

## PI PAPER PICK:


Prat A, Cheang MC, Galván P, Nuciforo P, Paré L, Adamo B, Muñoz M, Viladot M, Press MF, Gagnon R, Ellis C, Johnston S. Prognostic Value of Intrinsic Subtypes in Hormone Receptor-Positive Metastatic Breast Cancer Treated With Letrozole With or Without Lapatinib. *JAMA Oncol.* 2016 Oct 1;2(10):1287-1294.

Prat A, Lluch A, Turnbull AK, Dunbier AK, Calvo L, Albanell J, de la Haba-Rodríguez J, Arcusa A, Chacón I, Sánchez-Rovira P, Plazaola A, Muñoz M, Paré L, Parker JS, Ribelles N, Jimenez B, Bin Aiderus AA, Caballero R, Adamo B, Dowsett M, Carrasco EM, Martín M, Dixon JM, Perou CM, Alba E. A PAM50-based Chemo-Endocrine Score for Hormone Receptor-Positive Breast Cancer with an Intermediate Risk of Relapse. *Clin Cancer Res.* 2016 Nov 30.

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› Elisabet Sicart

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› Ainhoa Balague
› Marta Beltran
› Raquel Blanco
› Lluïsa Carbonell
› Raquel de La Torre
› María García
› María Herranz
› Sonia Martínez
› Lidia Martínez De Arenzana
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› Laia Cano
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› Anna González
› Paola Ley
› Anna Martínez
› Montserrat Pujadas
› Silvia Puyalto
› Isabel Rico
› Rosa María Romero

**Head, GI, Lung, Head & Neck Phase II-III Clinical Trials**
› Marta Beltran
› Isabel Grau

**Study Coordinators**
› Alejandra Caballero
› Iris de la Fuente
› Maria Mercè García
› Patricia García
› Irene Garrido
› Cristina González
› Débora Moreno
› Iratxe Puebla
› Sergi Recasens
› Andrea Retter
› Eulalia Scheenard
› Sandra Tijeras
› Ingrid Vilimelis

**Data Managers**
› Anna Aguilar
› Laia Gregori
› Eva Mª Lázaro
› Eva Marín
› Silvia Marín
› Cristina Pérez
› Sergio Pérez
› Julia Serra

**Head, Breast, GU, CNS, Sarcoma, Gynecological Clinical Trials**
› Susana Muñoz
› Meritxell Soler

**Study Coordinators**
› Judith Alonso
› Enric Álvarez
› Marta Batista
› Beatriz Bruno
› María Alba Calamardo
› Violeta Esteban
› Carlos Fernández
› Sergio Fernández
› Berta Garrido
› Jordi Humbert
› Gina Mares
› Alba Meire
› Thaïs Miquel
› Olga Padros
› Mariona Pocarull
› Ángela María Quintana
› Ester Serra
› Anna Serrano

**Data Managers**
› David Álvarez
› Marta Batista
› Maria Isabel Martínez
› Carina Monclus
› Nuria Ortega

**Head, Clinical Research Support Unit**
› Susana Muñoz

**Sample Managers**
› Gemma Pruna
› Cristina Resina

**Clinical Trials Office Administrative Support**
› Núria Carballo
› Cristina García
› Alexandre Gonzalo
› Marc Palomar
› Pau Ruiz-Olalla

**Quality Assurance Manager**
› Silvia García

## 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:

› Internal restructuring with the newly created position and appointment of the Director of the Clinical Trials Office, Gemma Sala.
› In 2016 we set up our Clinical Research Support Unit to help our investigators with the start-up and management of independent research lines.
› We continue to report an increase in both the number of clinical trials performed and the number of patients included.
› Optimal management of the complexity of protocols which are increasingly demanding.
› We have provided tailored training for our staff in order to further improve the quality of work and expand related skill sets.
› Implemented new tools and procedures aimed at increasing the quality and efficacy of research.
› 20 sponsor audits have been conducted with satisfactory results.
› Inspection for Accreditation of the phase I Unit, the Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", by the *Generalitat de Catalunya*.

## SUMMARY:

Established in 1997, our Clinical Trials Office incorporates an expert team that conducts clinical trials at the Vall d'Hebron University Hospital's (HUVH) Oncology Department. More specifically, our 45 professionals including study coordinators, data managers, administrative staff and quality control, coordinate studies from Phase I to Phase IV as well as various research projects. Divided into three to cover all tumor types and trials, our teams are managed by the Clinical Trials Office Director, Gemma Sala.

In 2016 we conducted 354 actively recruiting trials - Phase I, Basket studies, Phases II & III (see Figure II) with patient enrolment totaling at 1129 (Figure I). 136 new trials were initiated (Figure III). In addition, we continue to follow up patients who were recruited prior to 2016 and are still enrolled and receiving study treatment (more than 1600 patients in total).

As we continue to render personalized medicine more precise by better targeting therapies to respond to the specificities of each individual patient, each individual tumor, the requirements and selection criteria for inclusion in certain studies are also becoming more complex. While we are dedicated to expanding our portfolio of trials in order to ultimately establish new treatment models with highly selective drugs, we must also continue to fine-tune patient selection criteria in order to best identify those patients who are most likely to benefit from novel therapies, including emerging immunotherapeutics, matched to each individual's molecular 'measurements'.

The Vall d'Hebron University Hospital's Oncology Department has gained much prestige which has been acknowledged by the pharmaceutical companies. It has consequently become a reference center selected by the industry to carry out complex clinical trials for which the number of participating centers is highly restricted. Selected site are chosen based on their high standards of quality and capacity for carrying out state-of-the-art research. Our hospital has taken part in phase I trials of different drugs, ultimately enabling the pharmaceutical industry to market novel anti-cancer medicines. We consequently participate in clinical trials promoted by the pharmaceutical industry as well as those developed by our department in collaboration with other hospitals.

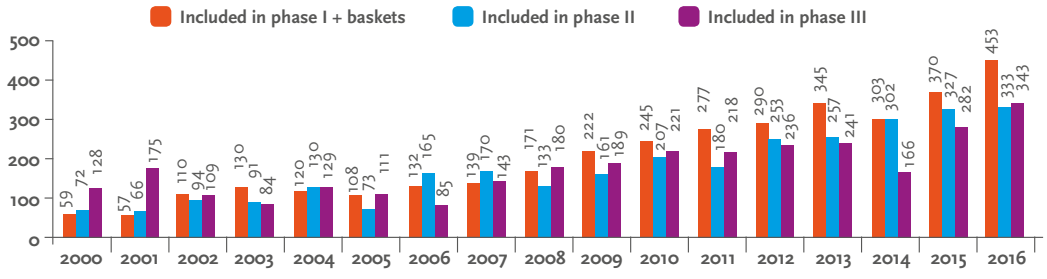


Figure I: Annual Recruitment Evolution (Phase I + Basket Trials, Phase II and III)

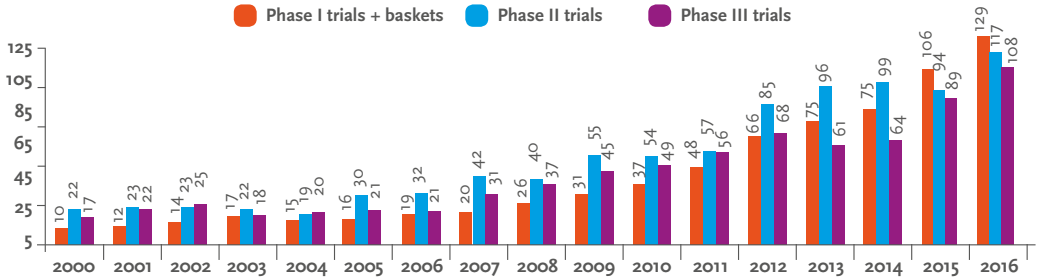


Figure II: Annual Distribution of Phase I, Phase II, Phase III, Basket, and Post Authorization Trials

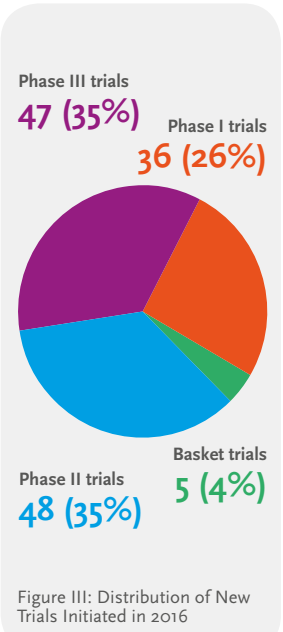


Figure III: Distribution of New Trials Initiated in 2016

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# RESEARCH UNIT FOR MOLECULAR THERAPY OF CANCER (UITM) - "la Caixa"

**Director**
- Jordi Rodón

**Co-Director**
- Josep Tabernero

**Executive Team**
- Ángeles Peñuelas
- Jordi Rodón
- Gemma Sala

**Medical Coordinator**
- Jordi Rodón

**Associate Investigators**
**Senior Consultants**
- Judith Balmaña
- Joan Carles
- Enriqueta Felip
- Ana Oaknin
- Cristina Saura
- Josep Tabernero

**Phase I Investigators**
- Maria Alsina
- Guillermo Argilés
- Analía B. Azaro
- Irene Braña
- Cristina Cruz
- Maria Elena Élez
- Santiago Ignacio Escrivá
- Lorena Fariñas
- Patricia Gómez
- Julieta Grasselli
- Cinta Hierro
- Teresa Macarulla
- Juan Jesús Martín
- Alex Martínez
- Rafael Morales
- Eva Muñoz
- Alejandro Navarro
- Maria Ochoa de Olza
- Mafalda Oliveira
- Nuria Pardo
- Jose Manuel Pérez
- Jordi Remon
- Víctor Rodríguez
- Enrique Sanz
- Tamara Saurí
- César Serrano
- Cristina Suarez
- Claudia Valverde
- Helena Verdaguer
- Maria Vieito
- Esther Zamora

**Director, Clinical Trials Office**
- Gemma Sala

**Heads, Phase I Clinical Trials**
- Gemma Sala
- Elisabet Sicart

**Study Coordinators**
- Eulalia Aliende
- Ainhoa Balague
- Marta Beltrán
- Raquel Blanco
- Lluïsa Carbonell
- Raquel de la Torre
- Maria García
- Maria Herranz
- Elisabet Sicart
- Sonia Martínez
- Lidia Martínez De Arenzana
- Sandra Matas
- Laura Maynes
- Montserrat Moreno
- Gemma Mur
- Silvia Pérez
- Adelaida Piera
- Veronica Ripoll
- Josep Bernat Román
- Sofia Rubio
- Mireia Sole

**Data Entries**
- Miguel Ángel Caelles
- Laia Cano
- Gloria García
- Anna González
- Paola Ley
- Anna Martínez
- Montserrat Pujadas
- Silvia Puyalto
- Isabel Rico
- Rosa Maria Romero

**Pharmacy**
**FOUITM**
- Maria Josep Carreras Soler

**USIFO**
- Laura Maños

**Nurse Supervisor**
- Ángeles Peñuelas

**Nurse Coordinators**
- Sonia Valverde
- Lydia Vélez

**Nurses**
- Meritxell Cucurell
- Elena de Cabo
- Margarida Marcos
- Isabel Muñoz
- Tania Sánchez

**Nursing Assistants**
- Jetzabel Gil
- Alicia López
- Maria Martín

**Nurse Supervisor's Assistant**
- Juan Manuel García

**Secretary**
- Teresa Mendoza

## 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 trials, Basket trials, and link clinical research at UITM with VHIO's preclinical and translational research groups, as well as collaborate with the different partners involved in drug development and translational research.
- Genomic medicine trials in early drug development: perform molecular analysis of patient tumors in order to select the best possible treatment with the experimental treatments available, co-develop medical informatics applied to genomic medicine, and integrate preclinical and clinical research by incorporating novel drugs, new insights, and study designs together with customized molecular diagnostics.
- Immunotherapy: the UITM Task Force in early drug development of immunotherapeutics and cell signaling is specially focused on second generation immunotherapies, including new cytokines, immunomodulatory agents and immune checkpoint inhibitors and combinations, as well as translational research in immuno-oncology.

## HIGHLIGHTS:

- We have performed some of the most complex phase I trials, including those focused on molecularly-selected patient populations (trials in complex molecularly-selected patient populations Basket/Octopus trials) as well as trials in immuno-oncology.
- We have expanded our expertise in drugs targeting developmental pathways, cell signaling (PI3K, BRAF, MET, FGFR), and immunotherapy (PD1/PDL1, OX40, CD40, engineered antibodies).
- In collaboration with VHIO's Cancer Genomics and Translational Genomics Groups, we benefit from cutting-edge technology platforms including the MiSeq, Hiseq 2500 NextGen sequencers, and nCounter Nanostring to analyze circulating-free tumor DNA. We also co-develop customized molecular tests for VHIO's Prescreening Program (disease-oriented mutation panels for our NGS platforms).
- We have developed alliances with many pharma companies as the preferred site for testing their novel and most relevant therapies, including GlaxoSmithKline OCTC, Roche ImCORE, and AstraZeneca/MedImmune. We also participate in a project supported by Horizon 2020's European Union funding for Research and Innovation to co-develop integrative bioinformatics tools for genomic analysis: MedBioinformatics (www.medbioinformatics.eu). Lastly, we have also partnered with Thomson Reuters/ Clarivate Analytics to develop tools for determining the relevance of mutations detected in tumors.

## SUMMARY:

Inaugurated in June 2010, thanks to the support received from the *Fundació Bancària "la Caixa"*, the Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa", is dedicated to complex clinical trials with drugs in early development (Phase I and early Phase II trials), focusing on novel targets. Occupying a total surface area of 1000 m2 our Unit is located within the General Area of the Vall d'Hebron University Hospital, the Vall d'Hebron Barcelona Hospital Campus. This privileged environment with direct access to patients, coupled with VHIO's translational approach to research and superb scientific framework, has enabled our Unit to rapidly establish itself as one of the few comprehensive facilities in Europe to rapidly transform latest discovery into benefits for patients.

By promoting tight connectivity between health care and research we establish novel treatment models for patients with highly selective drugs and advance insights into tumor diseases and how to treat them in an individualized way - getting the right therapy to the right patient at the right time. As the figures show, we are gradually doing so for an increasing number of patients. In 2016, 115 phase I clinical trials and 14 basket studies were performed at the Unit with a total of 453 patients enrolled. The Unit's facilities coupled with our multidisciplinary clinical teams, enable us continue to expand our portfolio of phase I trials.

Research carried out at our Unit by VHIO's Early Clinical Drug Development Group (see pages 46-47), centers on the development of new drugs based on the molecular profile of each tumor as well as the optimization of treatment regimens using combinations of new agents with those that already exist. In accordance with VHIO's purely translational model, our studies are also linked with several research lines led by other VHIO groups, thus connecting molecular biology and optimal tumor models with pharmacology and innovative clinical research. VHIO scientists also collaborate closely in our trials to facilitate biomarker development, a profound understanding of the mechanism of action, as well as research into mechanisms of resistance.

In partnership with VHIO's Molecular Oncology and Translational Cancer Genomics groups, we perform molecular analyses of the patients' tumors to select the best possible treatment with the experimental therapeutics available. Thanks to additional technology platforms implemented by VHIO's Cancer Genomics and Translational Cancer Genomics groups – including MiSeq, HiSeq2500, and nCounter Nanostring, 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 (see pages 80-81), pathologists from the Vall d'Hebron University Hospital's Molecular Pathology Department, radiologists and interventional radiologists, as well as our Clinical Trials Office (pages 76-77), Database Management, Clinical Research Oncology Pharmacy Unit (pages 82-83), and other healthcare specialists including dermatologists, cardiologists, and ophthalmologists.

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# ›CLINICAL RESEARCH ONCOLOGY NURSES

**Nurse Supervisor**
› Ángeles Peñuelas

**Nurse Coordinators**
› Sonia Valverde
› Lydia Vélez

**Nurses**
› Elena de Cabo
› Meritxell Cucurell
› Carla Junyent
› Margarida Marcos
› Marta Mate
› Núria Membrives
› Mireia Milán
› Isabel Muñoz
› Tania Sánchez
› Alex Sierra

**Nursing Assistants**
› Alicia López
› María Martín

**Nurse Supervisor's Assistant**
› Juan Manuel García

**Secretary**
› Teresa Mendoza

## SUMMARY:

Clinical trials in oncology are essential for the identification of novel, more effective targeted therapies against cancer as well as improving survival, side effect profiles and the quality of life of patients. Advances in oncology care and the development of more powerful anti-cancer medicines are driven by optimal processes in clinical trials.

Our expert clinical research oncology nurses assume a central role in these processes by undertaking a variety of roles including identifying trends in side effects, closely collaborating with multidisciplinary teams to develop and evaluate patient management, contributing to clinical studies by collating samples and quality data, as well as providing excellence in nursing care and symptom management of all our patients enrolled in clinical trials.

VHIO's Clinical Research Oncology Nurses, specialized in molecular therapies, are headed by Angeles Peñuelas and represent a critical element of the multidisciplinary oncology teams involved in the clinical trials performed and coordinated at VHIO's Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa" and Clinical Trials Office, directed by Jordi Rodón and Gemma Sala, respectively.

Supporting these teams comprised of medical oncologists, molecular pathologists, oncology pharmacists, clinical researchers, and study coordinators, VHIO's oncology nurses are key to ensuring the delivery of excellent care whereby patients receive the full range of expertise, guidance, and the necessary follow-up throughout the course of their participation in a particular clinical study.

In 2016, across the 354 actively recruiting trials patient enrollment totalled at 1129. Additionally our clinical teams follow up all patients that were recruited prior to 2016 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.

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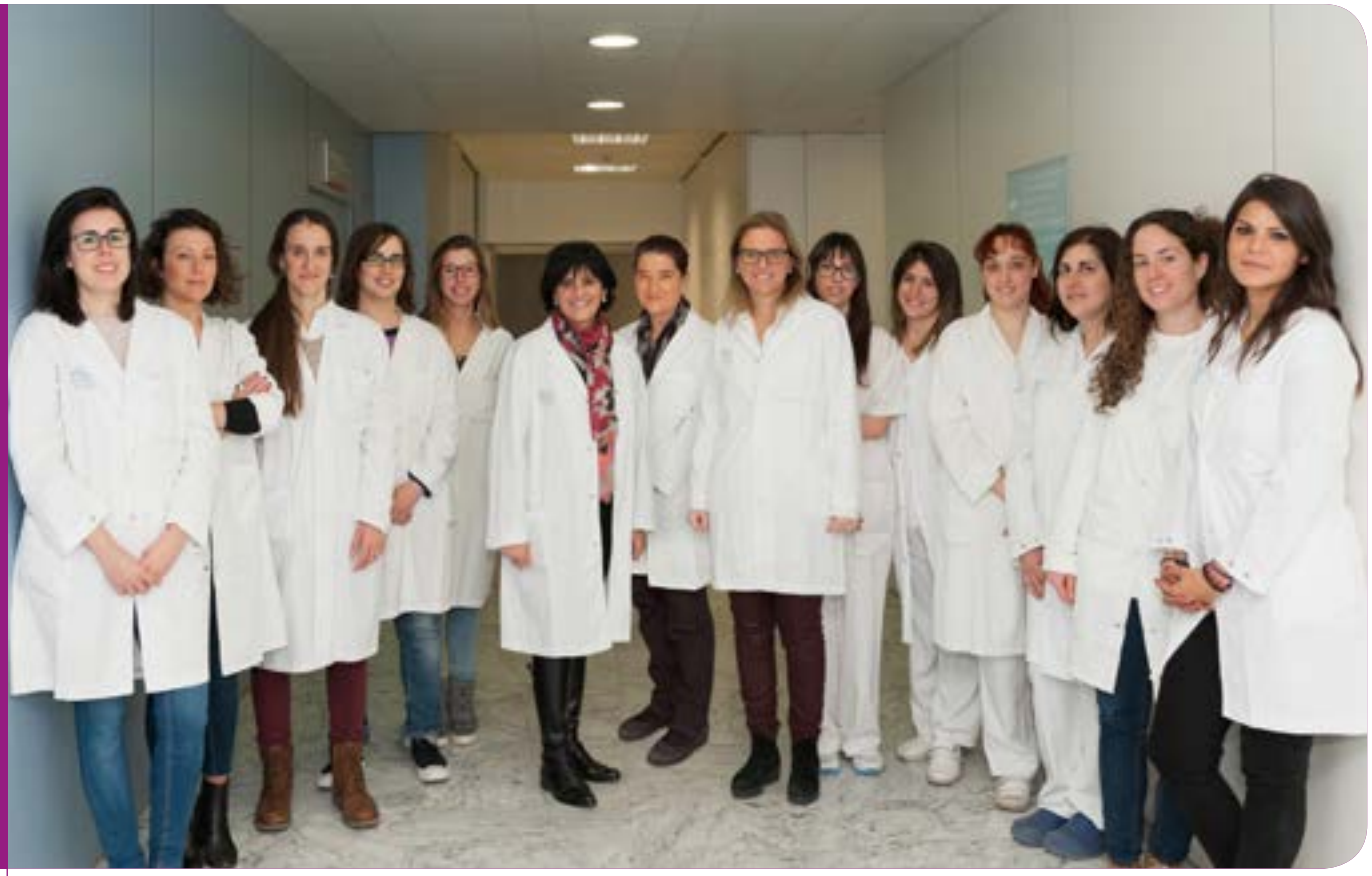
# ›CLINICAL RESEARCH ONCOLOGY PHARMACY UNIT



**Coordinator, Clinical Research Oncology Pharmacy Unit**
› Maria Josep Carreras Soler

**Coordinator, Pharmacological Research in Oncology Support Unit**
› Laura Mañós Pujol

**Pharmacists**
› María Alcalde
› Isabel de la Paz
› Anna Farriols Danés
› Celia Gonzalez
› Inés Jiménez Lozano
› Gloria Molas
› Maria Oliveras
› Eugenia Palacio
› Berta Renedo
› Núria Sabaté
› Carol Valdivia Vadell
› Jana Vidal Otero

**Technicians**
› Romina Bellini
› Elisabet Bordas
› Esther Carabantes
› Maria Hidalgo
› Susana Mulet
› Isabel Pérez
› Marta Pozo
› Gemma Tomás
› Sílvia Torralba
› Esther Vilaró
› Noemí Visús

**Clinical Trials Re-Supplies Manager**
› Sara Pizarro López

## STRATEGIC GOALS:

› Excellence in services we provide to clinical oncology research programs through optimal efficacy, efficiency and safety.
› Traceability of management and preparation of drugs for clinical trials.
› Preparation and administration of clinical trial drugs according to protocol specifications.
› Maximize control of storage temperature of samples and preparations.
› Enhanced documented control of drugs returned by patients.
› Incorporation and validation of a new computerized program named IPharma / FUNDANET for the management of clinical trial supplies.
› Incorporation of oral administration therapeutic schedules in our prescription software.
› Provide a pharmaceutical care program for patients in Phase I trials with oral medication (to improve safety, compliance and efficacy of the treatment), as well as instructions and indications to patients for orally administered treatments in Phase II and III trials.
› Final validation of a traceability program in clinical trial supplies management (storage, dispensation and accountability), to be enhanced through an interphase with the traceability program used in the Cytostatics and Monoclonal Antibodies Preparation Unit: ISISHTRI program.
› Successful sponsor audits as well as inspections carried out by regulatory authorities.

## HIGHLIGHTS:

› Substitution of the current computerized program for the management of clinical trial drugs with the new IPharma /FUNDANET.
› Validation of traceability system ISISH-TRI program.
› Further improved the documented control of drugs returned by patients.
› Clinical and technical support for the prescription /preparation /administration of cytostatics in clinical trials, providing e-records of usage and timings.
› Qualitative and quantitative quality control of all parenteral anticancer preparations to guarantee patient safety and protocol compliance.
› ISO9001:2008 certification renewed.
› 28 successful sponsor audits.

## SUMMARY:


Our Unit is ISO 9001:2008 certified and associated with the Medical Oncology Service of the Vall d'Hebron University Hospital (HUVH). We focus on two main clinical research programs:

1) Oncology Pharmaceutical Care Program: incorporating a team of pharmacists specializing in hospital pharmacy and oncology pharmacy, as well as laboratory technicians, we prepare cytostatics and other parenteral anti-cancer drugs used in clinical trials and monitor patients.
2) Pharmacological Research in Oncology Support Program: led by a team of pharmacists and laboratory technicians specialized in clinical trials, we are dedicated to managing, storing, issuing and controlling samples for clinical trials.

In 2016 we managed clinical trial drugs for 411 active trials in oncology, and deliveries of supplies totaled at 5154. We also continue to benefit from our cutting-edge system for controlling storage temperature which, performing electronic temperature recordings every 5 minutes, displays readings on computers equipped with audiovisual alarms as well as an around the clock SMS alert system for temperature deviations.

For the traceability of storage, custody and dispensing of clinical trial drugs, we have a computerized storage area to manage and control samples, expiry dates and traceability using a barcode reader- ISISH-TRI program. Regarding the design and validation of the drug preparation process traceability system we ensure the qualitative and quantitative quality control of our computerized system incorporating barcode technology, electronic scales and voice technology (Verbio Speech Technologies-Directed Work system).

This year, dispensing staff have participated in 57 pre-study visits, 149 initial visits, 1583 monitoring visits, 98 close-out visits, and have successfully passed 28 audits. In addition, 18.569 clinical trial drugs have been dispensed and validated by a pharmacist; 8444 of which are for oral administration. A total of 149 Standardized Dispensing Procedures for clinical trials in oncology have been drawn up and we have performed 308 updates of these procedures. 84 storage temperature data reports have been prepared by dispensing staff.

Preparation staff participated in 12 pre-study visits, 138 initial visits, 396 monitoring visits, and 18 audits. Preparations of cytostatics, monoclonal antibodies and other parenteral antitumor drugs for clinical trials totaled at 11392 and 138 Standardized Preparation Procedures were compiled. We also incorporated 416 antineoplastic therapeutic schedules in our prescription software.

Pharmaceutical care program for patients enrolled in Phase I clinical trials: we carried out 871 visits, 347 screenings, 272 C1D1s, and 252 follow-ups, also compiling patient diaries and/ or instructions for patients in the instance that this documentation is not provided by the respective sponsor. This year we compiled 62 different diaries and 28 instruction manuals, and our dispensing staff also provided diaries and instruction manuals for patients included in all Phase II and Phase III trials involving orally administered drugs. 25 diaries and patient manuals for Phase II and Phase III clinical trials were compiled in 2016.

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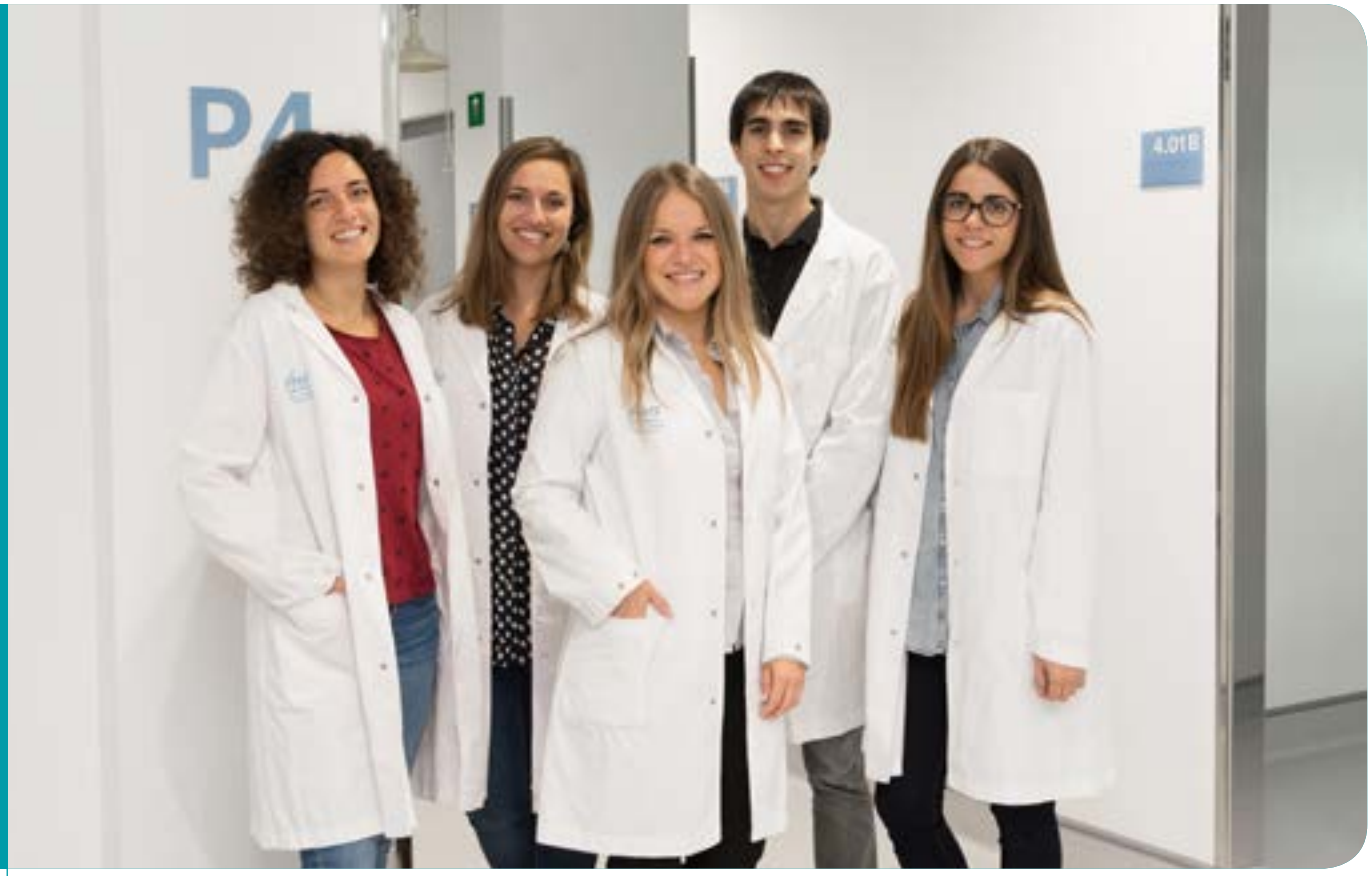
# NEW TO VHIO IN 2016



NEW TO VHIO IN 2016

# ›CELLULAR PLASTICITY & CANCER GROUP




**Principal Investigator**
› María Abad

**Post-Doctoral Fellow**
› Elena Senís

**Graduate Students**
› Emanuela Greco
› Iñaki Merino
› Olga Boix

## STRATEGIC GOALS:

› Advance understanding of the interplay between reprogramming, cellular plasticity and cancer.
› Decipher the molecular mechanisms governing the acquisition of stem cell properties during tumorigenesis.
› Determine the impact of inducing cellular dedifferentiation in various stages of tumorigenesis (tumor initiation, maintenance, and metastasis), and in the resistance of cancer cells to chemotherapeutic agents.
› Identify chemical compounds that specifically target cancer stem cells.

## HIGHLIGHTS:

› VHIO's Cellular Plasticity and Cancer Group moved into the CELLEX building (4th floor) in October 2016.
› Our group received a grant from the Spanish Ministry of Economy and Competitiveness (MINECO), under the Governmental Program of R&D focused on addressing Societal Challenges.
› We recruited one Post-Doctoral Fellow and three PhD Students.
› Our research has demonstrated that tissue damage, through cellular senescence and IL6, induces cellular dedifferentiation and reprogramming *in vivo* (Mosteiro et al., *Science* 2016).
› We have identified 5 lncRNA-coded micropeptides that are potentially involved in cancer stemness.

## SUMMARY:


Our recently established group is dedicated to better deciphering the interplay between cellular plasticity, stemness and cancer. This is an emerging topic of intense investigation since cellular plasticity is believed to have an important role during different stages of tumorigenesis and in resistance to chemotherapeutics. Pluripotent stem cells are extremely plastic, are only present during early embryo development, and possess the ability to differentiate into any somatic cell type. In 2006, S. Yamanaka discovered that adult somatic cells can recover pluripotency *in vitro* through a process termed cellular reprogramming leading to the generation of induced pluripotent stem cells (iPS cells).

In 2013, we showed that this process is also feasible *in vivo*; somatic cells can be dedifferentiated in the adult organism, even reaching pluripotency. Importantly, pluripotent stem cells and cancer cells manifest many parallels, and cellular reprogramming and neoplastic transformation are currently viewed as related processes governed by common molecular mechanisms. Furthermore, recent findings described by our group - as well as those of others - demonstrate that tissue damage, the main driver of cancer, triggers cell dedifferentiation and the acquisition of stem cell properties.

These observations strongly indicate that cellular plasticity and the acquisition of stem cell properties are important players at the origin of cancer. Moreover, they also bear important therapeutic implications given that chemotherapy and radiotherapy remain the cornerstone for the treatment of most cancers, which 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 demonstrate that cellular plasticity, through dedifferentiation, is essential for carcinogenesis and tumor relapse after therapy, and its specific targeting could lead to the development of novel anti-cancer therapies. Our approach consists of genetic mouse models, patient-derived samples, and cancer drug screening, with "reprogrammable mice" that enable us to express Yamanaka reprogramming factors in an experimental manner, and induce *in vivo* dedifferentiation and stemness at will in the adult organism.

We joined VHIO in October 2016. During our first three months we have recruited one Post-Doctoral Fellow and three PhD Students, focused on setting up the laboratory, began to network with other VHIO colleagues and groups to explore possible collaboration and research synergies, and also initiated our main projects. To-date we have generated our first VHIO iPS cell lines, as well as spheres from a panel of cancer cell lines. We have also identified novel micropeptides potentially involved in cancer stemness.

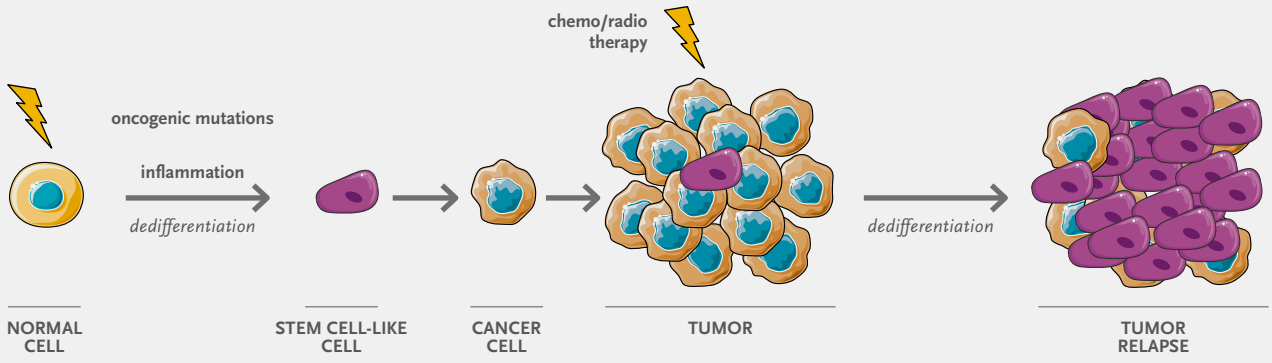




Figure: Working hypothesis by which cellular dedifferentiation and the acquisition of stem cell properties are important players during cancer initiation as well as in tumor relapse upon treatment with chemotherapy and radiotherapy.

## PI PAPER PICK:

Mosteiro L, Pantoja C, Alcazar N, Marión RM, Chondronasiou D, Rovira M, Fernandez-Marcos PJ, Muñoz-Martin M, Blanco-Aparicio C, Pastor J, Gómez-López G, De Martino A, Blasco MA, Abad M and Serrano M. Tissue damage and senescence provide critical signals for cellular reprogramming *in vivo*. *Science*. 2016 Nov 25;354(6315).

# EXPERIMENTAL HEMATOLOGY GROUP

**Principal Investigator**
› Francesc Bosch

**Translational Research Coordinator**
› Marta Crespo

**Hematologists**
› Júlia Montoro
› Carlos Palacio
› Laura Gallur
› Margarita Ortega
› Pau Abrisqueta
› Pere Barba
› David Valcárcel
› Olga Salamero
› Ana Marín
› Amparo Santamaría
› Andrés López
› Merche Gironella

**Post-Doctoral Fellows**
› Noelia Purroy
› Bárbara Tazón

**PhD Students**
› Isabel Jiménez
› Júlia Carabia
› Júlia Montoro
› Sabela Bobillo
› Cecilia Carpio
› Guillermo Orti

**Technician**
› Lluis Puigdefàbregas

## STRATEGIC GOALS:

Our main purpose is to translate preclinical findings into clinical benefit through the development of early phase clinical trials and defining new prognostic and predictive factors.

Main research lines currently center on:

› Deciphering the mechanisms involved in pathogenesis and progression of hematological neoplasias.
› The preclinical study of new therapeutic regimens in experimental models that mimic the tumoral microenvironment using primary cells and PDXs.
› Defining new biomarkers for a more rational and precise treatment of patients.

## HIGHLIGHTS:

› We have studied of a novel SYK protein inhibitor using our preclinical model of CLL, which has fueled the transition of the drug into the clinics (Purroy et al, *Oncotarget.* 2016).
› In an ortothopic mouse model we have shown that XPO-1 inhibition is effective in CNS lymphomas. We are currently designing a clinical trial for these patients.
› We have defined how an immunosuppressive scenario is related to clinical progression in CLL.
› Leading the work package dedicated to CLL, our group is a member of the European Innovative Medicines Initiative 2 (MI2) Programme's HARMONY Consortium which focuses on all hematological diseases.

## SUMMARY:


Biomedical research at VHIO's Experimental Hematology Group focuses on the translational study of hematological neoplasms of both lymphoid and myeloid origin.

We aim to decipher factors and mechanisms involved in the pathogenesis and progression of hematological malignancies by studying the molecular and microenvironmental mechanisms related to disease progression, response, and resistance to novel therapies, with particular emphasis on the cross-talk between malignant and healthy immune cells. Current projects include the study of chronic lymphocytic leukemia (CLL), diffuse large B cell lymphoma (DLBCL), and acute myeloid leukemia (AML).

Our group also explores new therapeutic avenues for patients diagnosed with hematological malignancies through the ex-vivo assessment of response to novel treatments, taking into account the microenvironmental protection that neoplastic cells 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 allowed us to develop a highly reproducible and reliable pre-clinical model of CLL that mimics the favorable microenvironment using primary tumoral cells from patients.

We have also developed a PDX model for central nervous system lymphomas in collaboration with Joan Seoane, Director of Translational Research at VHIO and Principal Investigator of our Institute's Gene Expression and Cancer Group. Using this approach we study novel therapeutic options for patients in close collaboration with different pharmaceutical and biotech companies in order to drive new drugs to market, as well designing a clinical trial for CNS lymphoma patients. Finally, we are also studying the role of novel targeted therapies in primary samples from patients with AML.

We are also fostering the definition of 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. In addition, we are studying the role of circulating tumoral DNA detection in cerebrospinal liquid in CNS lymphomas in order to facilitate diagnosis and prediction of CNS relapse in a less invasive manner.

Lastly, we are initiating an ambitious project aimed at unmasking biomarkers of immune activation related to the clinical results of an allogeneic stem cell transplant.

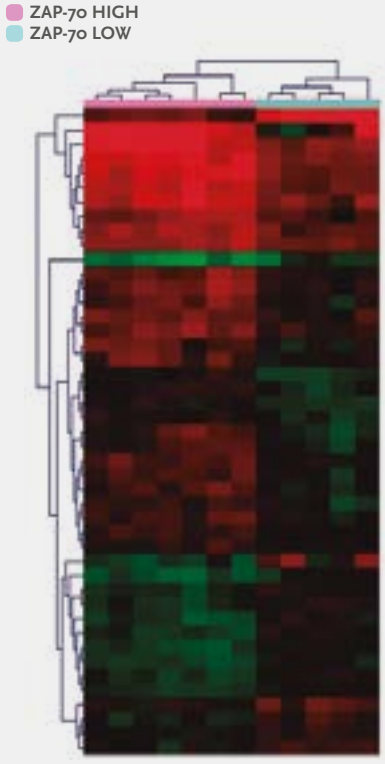




Figure: Differential response to treatment according to prognosis factors in CLL.

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NEW TO VHIO IN 2016

# ›TUMOR IMMUNOLOGY & IMMUNOTHERAPY GROUP


**Principal Investigator**
› Alena Gros

**Technician**
› Maria Lozano

## STRATEGIC GOALS:

› Characterize personalized anti-tumor T-cell response in patients with cancer.
› Mine the personalized repertoire of tumor-reactive lymphocytes for potential biomarkers of response to cancer immunotherapy.
› Investigate novel strategies to rapidly identify tumor-reactive lymphocytes as well as the target antigens driving this response.
› Develop personalized T-cell-based cancer immunotherapies for patients with solid cancers.

## HIGHLIGHTS:

› Alena Gros was recruited to join VHIO and arrived in October 2016.
› First authored by Alena, she and colleagues published findings in *Nature Medicine* describing a novel strategy to identify and enrich for neoantigen-specific lymphocytes from liquid biopsies.
› Our group has initiated the collection and cryopreservation of samples from patients treated at Vall d'Hebron in order to study mechanisms of response and resistance to immunotherapy.

## SUMMARY:


The immune system can recognize and eliminate cancer. However, tumors evade the immune response through multiple mechanisms. Cancer immunotherapy exploits the immune system to attack disease. Clinical studies have established that immune checkpoint inhibitors and T cell-based therapies can mediate tumor regression in patients with metastatic cancer. Thus, in addition to surgery, radiation therapy, and chemotherapy, immunotherapy has become the fourth pillar of anti-cancer therapy.

Despite the encouraging antitumor responses, only a fraction of patients treated respond to immunotherapy, and some develop autoimmune adverse events. There is thus a critical need to personalize these therapies. We are currently investigating mechanisms of response, toxicity and resistance to cancer immunotherapeutics in patients at the Vall d'Hebron University Hospital (HUVH). Our goal is to identify biomarkers of response to these therapies in liquid biopsies.

One of the correlative biomarkers of response to immunotherapy described to-date is mutation burden.

Tumor-specific somatic mutations are optimal targets for cancer immunotherapy and render tumors immunogenic; some of these can bind to the patient's HLA molecules and elicit T-cell responses. Our group uses a highly personalized approach to screen for T-cell mediated recognition of mutated antigens as well as shared antigens using autologous antigen presenting cells that can process and present in all the potential HLA restriction elements (see Figure). Using this strategy, we will explore whether the presence of lymphocytes recognizing these antigens is associated with response. In parallel, we plan to advance personalized T-cell therapies to treat metastatic colorectal cancer, which is largely resistant to current therapeutic strategies.

In summary, our Tumor Immunology & Immunotherapy Group focuses on understanding the naturally occurring T-cell response to cancer, and establishing ways to exploit these antitumor responses to develop more effective, powerful, and precise immunotherapies against cancer.


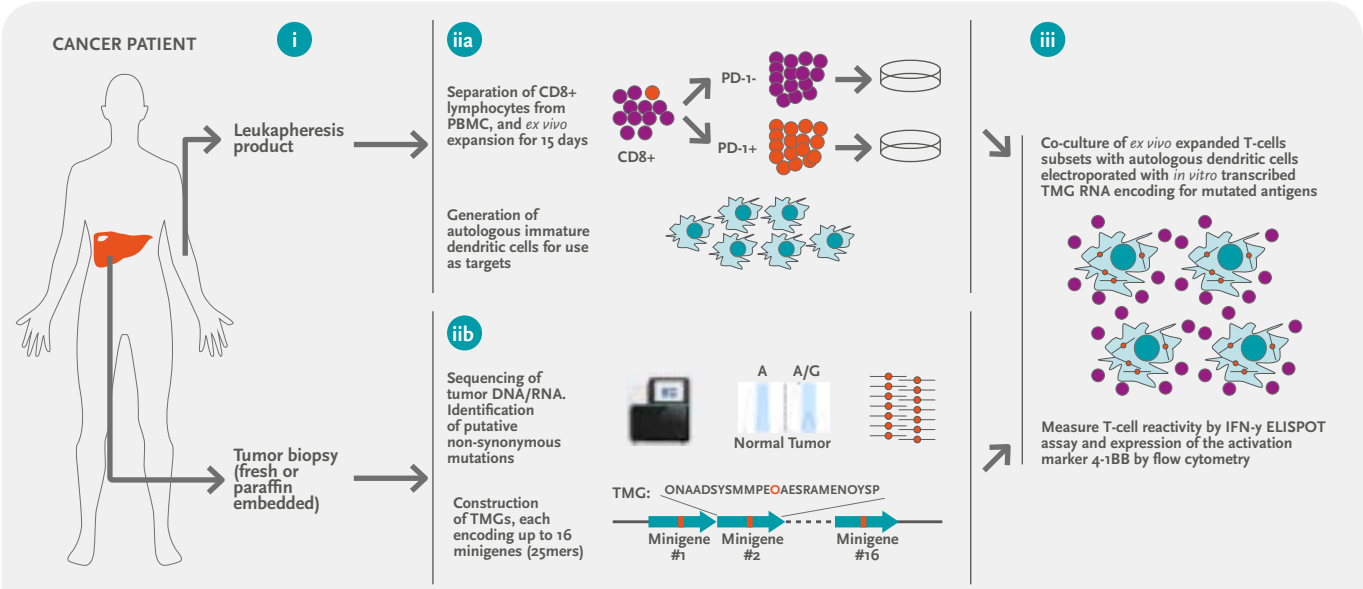


Figure: Personalized strategy to identify neoantigen specific lymphocytes in peripheral blood of cancer patients. (i) Peripheral blood mononuclear cells (PBMC) and a tumor biopsy (fresh or archived) are obtained. (iia) PD-1+ lymphocytes are sorted from the peripheral blood and expanded *ex vivo*. (iib) We extract DNA and RNA from the tumor biopsy and perform exome and RNA sequencing to identify non-synonymous somatic mutations. Tandem minigene (TMG) constructs encoding all the putative mutated 25mers are used as templates to generate *in vitro* transcribed (IVT) RNA. (iii) IVT TMG RNA is used to transfect autologous antigen presenting cells (APCs) used as targets in a co-culture with the *ex vivo* expanded lymphocyte subsets. At 20h, T-cell reactivity is analyzed. (Gros, A. *et al. Nat Med*, 2016).

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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.

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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Fundación BBVA

## PUBLIC FUNDING

### International

erc European Research Council Established by the European Commission

SEVENTH FRAMEWORK PROGRAMME

European Commission | Horizon 2020 European Union funding for Research & Innovation

FEDER Fondo Europeo de Desarrollo Regional

### National

AGAUR Agència de Gestió d'Ajuts Universitaris i de Recerca

*iCrea INSTITUCIÓ CATALANA DE RECERCA I ESTUDIS AVANÇATS

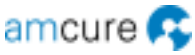
Institució CERCA Centres de Recerca de Catalunya

ISC Instituto de Salud Carlos III

## PRIVATE FUNDING





























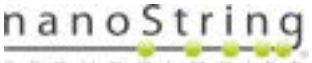





















































The Dr. Josef Steiner Cancer Research Foundation

## CONSORTIA

As a reflection of VHIO's expertise in preclinical, translational and clinical research in oncology, it participated in the following Consortia of excellence in 2016:

**Cancer Core Europe** is a unique partnership aimed at addressing the cancer carecancer research continuum. Launched in the Autumn of 2014, this working consortium represents a critical mass of activity for the successful integration of all cancer care information, clinical research and outcome research, led by the six founding partners and European comprehensive cancer centers of excellence: the Gustave Roussy Cancer Campus Grand Paris (Villejuif, France), Cambridge Cancer Centre (Cambridge, UK), Karolinska Institute (Stockholm, Sweden), Netherlands Cancer Institute - NKI (Amsterdam, The Netherlands), National Center for Tumor Diseases - DKFZ-NCT (Heidelberg, Germany), and VHIO. The Cancer Core Europe's pooling and exchange of expertise, research findings, common platforms and processes, will empower researchers and clinicians to rapidly exploit this trove of biological insights and clinical data for the benefit of patients.
**www.cancercoreeurope.eu**

**COLTHERES - Colon Therapy Research Consortium** partners European clinical research centers as well as translational researchers received core funding from the European Commission's 7th Framework Programme of Research and Development to define and perform biomarker driven clinical trials to improve cancer therapy outcomes. Launched in 2011, this 5-year programme used comprehensively molecularly-annotated colon cancers as a 'test-bed' to define specific biomarkers of response or resistance to signalling pathway agents.

Aimed at improved outcomes for cancer patients and reduced mortality across Europe through prevention, early detection and improved treatments, **EurocanPlatform**, founded in 2011, is funded by the European Commission's 7th Framework Programme and comprises 28 European leading cancer Institutions and organisations working together in a unique collaboration. The centers share infrastructures and collaborate on projects to help advance cancer research and treatment.
**www.eurocanplatform.eu**

The **EuroPDX Consortium** – *Translating Knowledge in Oncology,* launched in 2013 with the common goal of creating a network of clinically relevant models of human cancer, and in particular patient-derived xenograft (PDX) models. Connecting 17 cancer centers across 12 countries that are developing PDX cancer models, this initiative promotes the sharing and exchange of findings on promising therapeutics as well as leads multicenter preclinical studies. EuroPDX strives to reduce the duplication of efforts in oncology drug development and ultimately improve the quality of life and overall survival of cancer patients.
**www.europdx.eu**

Announced in 2013, The **MErCuRIC** Consortium, funded by the European Commission's 7th Framework Programme of Research and Development, incorporates 13 partners in eight different European countries to lead and pioneer a multicentre phase Ib/II clinical trial. This study evaluates a novel therapeutic strategy aimed at combating metastasis, improving survival and developing new approaches to treat patients with colorectal cancer.
**www.mercuric.eu**

Launched in 2011 (VHIO joined in 2013), supported by the IMI Innovative Medicines Initiative – a Joint Undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA), **OncoTrack,** *Methods for systematic next generation oncology biomarker development,* is an international consortium of over 80 scientists and constitutes one of Europe's largest collaborative academicindustry efforts aimed at developing and assessing novel approaches for the identification of new markers for colon cancer.
**www.oncotrack.eu**

Launched in 2015, **MedBioinformatics** is a project supported by Horizon 2020's European Union funding for Research and Innovation. Through the development of integrative bioinformatics tools and software applications useful and autonomously usable by translational scientists and clinical practitioners for analysing the huge amount of data and knowledge generated in healthcare and biomedical research, the project will ultimately facilitate translational research and precision medicine. Incorporating 13 groups from nine renowned research entities of excellence, including VHIO, this Consortium will strive to address the deficit of integrative approaches that effectively combine different types of data from different sources as well as actively involve end-users that are not experts in bioinformatics in the design of the applications.
**www.medbioinformatics.eu**

Spurred by Horizon 2020's European Union funding for Research and Innovation funding, **MoTriColor** (Molecularly guided Trials with specific treatment strategies in patients with advanced newly molecular defined subtypes of Colorectal cancer), led by VHIO, is powered by a total of eight clinical research centers of excellence, spanning Spain, Italy, The Netherlands and Belgium, as well as a European organization in cancer research and a diagnostic/prognostic SME. Dedicated to conducting multi-center early phase clinical trials to establish the anti-tumor activity of novel experimental therapies for patients with metastatic or advanced colorectal cancer, patients will be stratified based on their gene expression profiles according to recently established predictive signatures.
This pioneering approach aims at identifying sensitivity of individual patients to the proposed experimental therapies towards ultimately developing more precise anti-cancer therapies for these patients.
**www.motricolor.eu**

Funded through a grant received from the European Union's Horizon 2020 research and innovation programme, the **NoCanTher – Nanomedicine upscaling for early clinical phases of multimodal cancer therapy is a multi-center – Consortium** is led by IMDEA Nanoscience and represents an important forward step in utilizing nanoparticles than can better target and more precisely combat cancer cells.
It builds on the preclinical successes reported by the former FP7-funded MultiFun Consortium that evidenced the efficacy of a multi-modal therapeutic approach based on functionalized magnetic nanoparticles and magnetic hyperthermia for the intra-tumoral treatment of breast and pancreatic tumors
NoCanTher will assess this nano-based approach and provide preliminary data on its efficacy in humans and aim to translate these preclinical findings into early clinical development for the treatment of pancreatic cancer.
**www.nocanther-project.eu**

The **PhD PI3K biology in health & disease Network** incorporates ten academic, clinical and industrial partners with renowned expertise in research focused on PI3K signaling. Leading a unique training network, this collaboration connects complementary expertise and brings additional value, novel tools and leadership of excellence in order to train talented early stage researchers and suitably equip them for leading roles in cancer science and drug discovery in European industry and academia.
This research training programe not only represents unparalleled educational opportunity for these young scientists, but also aims to increase the international competitiveness of European research in PI3K discovery and drug development.
**www.pi3k-phdproject.eu**

**RATHER - Rational Therapy for Breast Cancer**, is funded by the European Commission's 7th Framework Programme of Research and Development. Representing an important step in delivering on precision oncology by developing tailored therapies using a rational approach, this project will focus on two specific difficult-to-treat subtypes of breast cancer. Involving the combined efforts of six research institutions and two biomedical companies this is a five-year project that commenced in January 2011.
**www.ratherproject.com**

Incorporating a network of 27 research entities spanning 10 countries, **SPECTAcolor -Screening Platform for Efficient Clinical Trials Access in Colorectal cancer**, is an initiative within the framework of the research program of the EORTC, supported by Alliance Boots. Launched in 2013, this is the first prospective fully annotated tumor samples Biobank and Biomarker analysis platform for genetic profiling of patients suffering from advanced colorectal cancer.
**http://spectacolor.eortc.org**

**WIN - Worldwide Innovative Networking in personalized cancer medicine,** initiated by the Institut Gustave Roussy (France) and The University of Texas, MD Anderson Cancer Center (USA) is a non profit, non-governmental organization incorporating 22 cancer centers and industry partners from five continents to address the challenge of increasing the efficacy of cancer diagnostics and therapeutics.
Promoted within the scope of this Consortium, WINTHER (WINTherapeutics) is a unique academic and international clinical trial (launched in 2012), aimed at better predicting drug sensitivity and optimizing individualized therapeutic decisions with improved clinical outcome for patients.
**www.winconsortium.org**

## OTHER COLLABORATIONS:

The **AstraZeneca/MedImmune and VHIO Alliance**, announced in 2015, will stimulate advancements at preclinical, clinical and translational research levels across the AstraZeneca's oncology portfolio. Combining VHIO's strengths in promoting cancer discovery through the integration of translational science and clinical research with AstraZeneca's promising early stage oncology pipeline, the alliance will initially focus on areas including DNA damage repair, drug resistance, new drug combinations and molecular profiles for patient selection.
Bookmark and visit VHIO's website for forthcoming updates: **www.vhio.net**

The **CIBOT** *Consorcio de Investigación Biomédica y Oncología Traslacional* (Consortium for Biomedical and Translational Research in Oncology), is a scientific program established in collaboration with Novartis in 2013. This initiative defines and develops research aimed at: determining the etiopathogenic mechanisms of cancer as well as developing novel diagnostic and therapeutic tools; investigating the therapeutic potential of new antineoplastic agents; and applying cutting-edge technologies and latest data to advance cancer research.
Specific areas of interest include the effects of HER-2 amplification pattern and prior Herceptin/TDM-1 therapy on HER-2 expression, the therapeutic inhibition of the oncogenic Wnt/beta-catenin pathway, and targeting wild type c-KIT combination with PI3K pathway inhibition in basal-like PDXs.
**www.novartis.com**

Launched by Roche in 2016, the **imCORE - immunotherapy Centres of Research Excellence Network** - a 21-strong academic powerhouse set to progress discovery in cancer immunotherapy, brings together internationally renowned scientific and clinical experts in cancer immunotherapy to collaborate in investigating the most promising novel treatment approaches. Working in collaboration with scientists from Roche and Genentech, expert researchers and physician-scientists in cancer immunotherapy from across the globe have joined together to drive the application and extension of immune-based strategies to more tumor types as well as advance research into the cellular and molecular mechanisms modulating immune response to cancer.
This Network aims to significantly advance anti-cancer immunotherapeutics and accelerate discovery towards benefiting patients who may stand to gain from novel immune agents as mono therapy or in combination.
**www.roche.com**

**The OCTC - Oncology Clinical and Translational Consortium,** a collaborative scientific research network comprised of six renowned comprehensive cancer centers, was launched by GSK in 2013. While GSK gains OCTC's expertise in preclinical, translational and clinical development of novel anticancer therapeutics, the participating centers have access to studies with GSK's early stage oncology pipeline and opportunities to accelerate and advance the next generation of novel oncology therapeutics.
**www.gsk.com**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