2015 SCIENTIFIC REPORT

VALL D'HEBRON INSTITUTE OF ONCOLOGY

The CELLEX building: marking a new VHIO chapter

Centres de recerca de Catalunya

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FOREWORD

As this Scientific Report goes to print, President Barack Obama's Cancer *Moonshot*, announced during his final State of the Union address in January 2016, has positively inspired the broad cancer community.

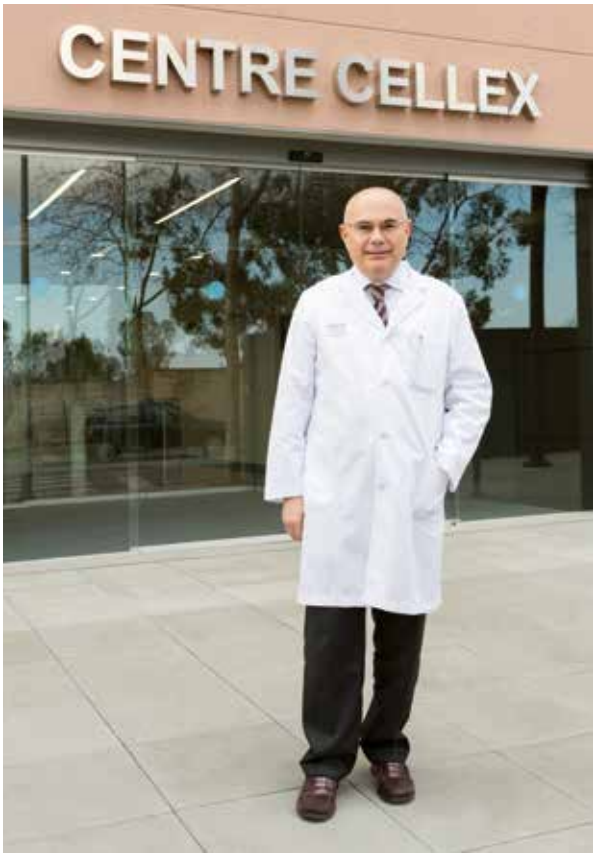
Obama and his wingman Vice President Biden "in charge of Mission Control" make for a powerful duo, but it's not only about the crowd-pleasing appeal of injecting new life into a 45-year-old global War on Cancer. They are backing their Moonshot by injecting increased funding into the National Institutes of Health (NIH) and the National Cancer Institute (NCI) -- promising more resources after a decade of decline (in real terms). Housing some of the world's leading cancer scientists and physician-researchers, NIH-spurred progress has been hampered through years of stagnant NIH funding appropriations during the global economic downturn. Thus, for cancer NIH-NCI researchers right now, President Obama represents the rocket man behind the US-based science.

While we certainly all applaud the Moonshot initiative, it is important to remember that this is not the first, and I suspect, will not be the last major anti-cancer pledge and punch. The first 'hit' came through the signing of the National Cancer Act of 1971 by then US President Nixon -- generally considered as the beginning of our collective war on cancer. Almost three decades later, the global community renewed its commitment to cancer research, prevention and advocacy during the World Summit Against Cancer in the New Millennium, February 2000. This momentous gathering celebrated the historic signing of the Charter of Paris against cancer by an international group of government officials, leading researchers and patient advocates.

As we continue to advance our understanding of the molecular basis of cancer, the battlefield boundaries change, the war continues. As a global force, we can celebrate our successes but we must also recognize that there is still so much ground to cover.

To shoot for the moon we've got to build the Apollo program for cancer first.

With today's rapid application and translation of 'omics' data into prediction science against cancer, breakthroughs in molecular medicine and gene sequencing, we are continuously unmasking important molecular drivers of cancer, with many more to come. These cancer 'conspirators' greatly affect the outcome and trajectory of a cancer, as well as the therapeutic options available that can attack the genetic origins of disease in the most effective means possible. It is thanks to such continued discovery that we are



"Marking a new era in VHIO's translational trajectory, 2015 brought all our multidisciplinary teams under the same roof to enhance collaboration and spur our dedicated efforts aimed at conquering cancer."

Josep Tabernero,

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

collectively stripping back the complexity, biological 'intelligence', and vastly diverse nature of cancer as a multi-form disease.

VHIO: tackling a constellation of challenges to conquer cancer

As I reflect on the past year, I am pleased to report that VHIO's multidisciplinary teams continue to make vital contributions to cancer science and medicine at the preclinical, translational and clinical research level. We have consequently marked significant progress in more precisely tackling the specificities of each individual cancer across large array of tumor types.

Throughout 2015, we also succeeded in reinforcing our infrastructure, increased our portfolio of technologies and clinical trials, and strengthened and expanded our cross-border partnerships through major research projects as well as powerful pan-European consortia of excellence (see '*Translation toward precision oncology: a little more on how we did it in 2015*' pages 10-15 of this report).

Through the many insights driven by our multidisciplinary and translational research approach, powerful genomic sequencing and pre-screening progamme, coupled with our expanding suite of enabling technologies and novel approaches, we at VHIO have significantly upped our tempo in rendering cancer treatments more precise.

Two representative examples in 2015 of how we continue to drive translation towards more effective therapies firstly include a study published in *Cancer Research*[1] by VHIO's Mouse Models of Cancer Therapies Group. Findings showed ibrutinib, a targeted therapy already used to treat some leukemias and lymphomas, to be effective in the treatment of pancreatic cancer. Not only does this research predict a potential therapeutic avenue against this notoriously aggressive tumor type, it also promises a fast-track set up of a clinical study aimed at validating these results.

Second, as an important next step towards advancing precision therapy against brain cancer, VHIO's Gene Expression Group, in close collaboration with many other VHIO scientists and oncoprofessionals from the Vall d'Hebron University Hospital, evidenced the use of cerebrospinal fluid (CSF) as liquid biopsy for the prognosis, treatment, identification, and tracking of brain tumor genomic alterations.

This novel approach, reported in *Nature Communications*[2], not only represents a potential tool for stratifying patients, assessing their prognoses, and closely monitoring the course of disease and their response to therapy in 'real time', in a minimally invasive manner, but also mirrors successes to-date of applying liquid biopsy across other tumor types.

The potential of liquid biopsy 'policing' of cancer

In my Foreword to last year's report I announced our collaboration with Merck Serono and Sysmex Inostics, whereby VHIO was the first academic test center to use in-house BEAMing liquid biopsy RAS biomarker technology. Already promising a more precise treatment for metastatic colorectal cancer patients by improved determination of which patients stand to benefit from anti-epidermal growth factor receptor (EGFR) therapies such as cetuximab, I am delighted to report that this RAS biomarker test has just received European Conformity approval (CE Mark), which makes it available and accessible for patients in Europe, Asia, and Australia.

Based on our own experiences at VHIO, we continue to witness first-hand how this technology is more accurately and rapidly guiding treatment decisions for an increasing number of our patients. As an example, we co-led the first large clinical trial, the CORRECT phase III study, to compare liquid versus conventional tissue biopsy data. The data, published in July 2015 in *The Lancet Oncology*[3], showed that BEAMing technology produced more data on tumor mutation throughout the course of the disease, enabling us to better target therapy to individual patients.

The importance of the CORRECT trial is that, unlike the majority of clinical studies published on the use of DNA in blood to determine tumor genotype which have only enrolled relatively small numbers of patients, it involved a large number of patients, providing correlative analyses on the activity of regorafenib, an inhibitor of diverse proteins implicated in tumor evolution, in all the subgroups in which mutations had been identified.

Although there remain critical questions concerning the clinical validity and accuracy of the liquid biopsy, such as the possibility that not all tumors release enough DNA into the blood for it to be detected, as well as the challenge of assigning a particular genotype for each particular tumor in patients with multiple metastases, this study is representative of a stream of compelling research that points to liquid biopsies as the future of cancer detection and an essential tool in clinical practice.

VHIO: dedicated to reversing cancer drug resistance

One of the major challenges in our collective efforts to combat cancer is resistance to anti-cancer therapies and strategies. At VHIO, as reported throughout this Scientific Report, we are dedicated to identifying and advancing more precise and effective novel therapeutic avenues matched to molecular subtypes of disease to reverse drug resistance and counteract tumor cell spread factors.

Work from a tremendous collaboration between investigators from VHIO and colleagues at the Dana-

Farber Cancer Institute in Boston revealed a new phenomenon of resistance to novel therapy for advanced lung cancer, as described in *Nature Medicine* in May 2015[4]. The study, in which VHIO's Thoracic Tumors Group and Cancer Genomics Group both participated, analysed circulating DNA in plasma and tumor biopsies from patients with advanced non-microcytic lung cancer, and consequently described resistance mutations to a novel therapy inhibiting the EGFR protein. This discovery will enable a more precise understanding as to acquired mechanisms of resistance in using this therapy and ultimately allow us to develop new molecules against this type of cancer.

Driving faster, more effective treatments 'in mono' or as drug-drug combinations

Utilizing targeted cancer therapeutic agents in combinations to tackle notoriously difficult to treat tumor types is often as complex as the cancer itself. At the preclinical level, thanks to the tremendously sophisticated, wide variety of modelling systems including novel contenders such as organoids and PDX models, we are advancing in our abilities to predict response to treatment, whether as monotherapy or in combination. Concerning PDX, not only does VHIO have one of the most expansive collections of these models in Europe, it is also a partner in the EuroPDX collaboration aimed at sharing key findings on promising therapeutics as well as carrying out multi-center preclinical studies. We are consequently better armed than ever before to incorporate and integrate critical preclinical insights into clinical trial design and improved patient outcomes.

Representing an excellent example of translation from preclinical findings to drug development were the results of a phase I study published in *Cancer Discovery* in May 2015[5], in which both VHIO's Gastrointestinal & Endocrine Tumors and Oncology Data Science (ODysSey) Groups participated, which was also selected by the American Association for Cancer Research (AACR) for its media program. Sym004, a mixture of two anti-EGFR antibodies, was shown to be clinically active in patients with advanced colorectal cancer that had become resistant to earlier therapies. This is a promising development for patients with advanced colorectal cancer.

As we finely-tune drug-drug combinations in clinical studies, we are also beginning to see increasingly important outcomes across tumor types. Just one example in 2015 was the phase III Cleopatra trial published in *The New England Journal of Medicine*[6]. As part of an international, multicenter effort, led by VHIO's Breast Cancer and Melanoma Group, the practice-changing data showed improved survival in patients with advanced-stage HER2-positive breast cancer by 16 months, which led to the recommendation of administering the trio of agents under study -- Pertuzumab, Trastuzumab, and Docetaxel -- in the treatment of patients with this tumor type.

VHIO counted an additional seven *New England Journal of Medicine* publications throughout 2015 (please see page 87 of this report), two of which both promise new hope for lung cancer patients as well as position immunological strategies as game changers in the way we will be treating cancer in the future:

A phase III international trial[7] showed novel immunotherapeutic nivolumab to be more effective over chemotherapy in the treatment of patients with advanced non-small-cell lung cancer (NSCLC), with overall longer survival. Similarly, a phase I study exploring the potential efficacy of the anti-PD1 inhibitor Pembrolizumb in patients with metastatic NSCLC, showed promise in its capacity to boost the immune system to mount an effective antitumor response.

These two papers, co-authored by VHIO's Thoracic Tumor Group, certainly provide compelling evidence on the use of novel immune agents as mono therapy or in combination, now and in the future.

My final pick of the NEJM papers published by VHIO in 2015 is a phase II basket trial[8], both co-designed and co-led by VHIO's Gastrointestinal & Endocrine Tumors Group and colleagues from Memorial Sloan Kettering Cancer Center (MSKCC, New York). Enrolling patients who had different types of cancer with the BRAFV600 mutation, recruited from some 23 hospitals across the globe, we showed the efficacy of vemurafenib, an inhibitor of the BRAF protein, as therapy against multiple tumor types that share the BRAFV600 mutation. Importantly, this is the first broad trial of its kind that has been conducted to establish the presence of one of the most common mutations occurring in melanoma across other tumors. These results will enable us to extend the same therapy, already effective in melanoma, to other different cancers, as well as more precisely match therapy to the specificities of each patient, and ultimately slam the brakes on disease progression.

These collaborative efforts are just some of the many examples of how we are advancing our endeavours at potentiating anti-cancer therapies and finely tuning strategies to the peculiarities of each individual tumor.

VHIO among the H2020 'chart-toppers'

At VHIO, we continue to secure the necessary and precious funding so desperately required in our efforts to combat cancer. Fortunately as it turns out, I was right to be optimistic regarding the outcome of our proposals submitted to the biggest EU Research and Innovation program to-date totalling at almost €80 billion of funding available over 7 years (2014-2020): *Horizon 2020*.

At the close of 2015, the Centre for the Development of Industrial Technology (CDTI), under the auspices of the Spanish Ministry of Economy and Competitiveness, issued a report documenting results at national level from the very first Horizon 2020 Call. Under the topic *Health, Demographic Change and Wellbeing*, VHIO ranked among the top sixteen H2020-funded research entities across Spain. By example, we are currently participating in two pan-European H2020 projects, MoTricolor, led by VHIO, and MedBioinformatics (see page 102 of this report).

VHIO faired similarly well in the ERA-NET on Translational Cancer Research (TRANSCAN) funded proposals. Out of a total of six projects awarded from within the region of Catalonia, VHIO counted four. Tackling a range of tumor types, these projects each explore tumor heterogeneity within the context of resistance to treatment.

These gratifying successes give us no reason to become complacent. Within the extremely competitive European research arena of excellence, EU programs only support projects that promise delivery on the objectives outlined in each particular call. Based on both the existing funded projects as well as those in the pipeline (to be announced in our 2016 report) I am confident that VHIO will remain a strong contender in Calls to come.

The CELLEX building: affording VHIO with the critical space to expand its activities and programmes

I am delighted to report that 2015 celebrated the move into our new premises, the CELLEX building. Marking a new chapter in VHIO's evolution and providing us with the valuable space through which to grow, our new home brings all our teams under the same roof which will be instrumental in further enhancing collaboration and the connection between our various programs. Crucially too, as I have previously advanced, we will be welcoming new groups over the coming months that will complement and expand our current lines of research.

VHIO Validation: rapidly translating cancer discovery into clinical benefit

Thanks to the wonderful sustained support received from our devoted institutional supporters -- the Generalitat de Catalunya, the FERO Foundation, the Fundació Bancària "la Caixa", the Fundación BBVA, with the invaluable support from the Fundació Privada Cellex, as well as VHIO's many other supporters, funding entities and agencies (see pages 99-103 of this report) -- VHIO continues to accelerate the pace in advancing personalized and targeted therapies against cancer.

We will only continue to raise the bar in our ambitions through the public funding we receive, as well as the generous support from private institutions, companies and individuals, all of whom share the same intense desire as we do: to alleviate and reduce the devastating impact that this disease has on society.

The Last Word

Recent statistics[9] show that cancer claimed the lives of over 8 million people worldwide in 2013 and has moved from the third leading cause of death in 1990 to now rank in second place behind cardiovascular disease. Furthermore, cancer burden is on the rise at an alarming rate, owing to a growing and aging global population as well as risk factors including smoking, obesity and dietary patterns.

In tune with the undeniable progress that we are collectively making, we all need to take a hard look at current policies and priority setting on a region-per-region basis. Without this essential overhaul, today's advances in predictive cancer science, treatment and care, as well as prevention strategies, cannot possibly hope to benefit an increasing number of our patients, across borders, now and in the future.

We will need to work together to transform healthcare models accordingly, based on careful regional planning, the implementation of solid frameworks, and 'local' forecasting to ensure that resources allocated in each country throughout Europe deliver optimal outcomes.

Some difficult choices will have to be made in terms of selecting which therapy, for whom, based on clearly demonstrated benefits across patient populations. A multi-stakeholder review of cost settings and the suitably adjusted pricing of cancer therapies to enable equitable access to the most effective therapies, is also as important as investing in the cancer research itself.

Only in unison, by engaging the entire oncology ecosystem and considering the views and the perspectives of all stakeholders in oncology, including patients and families, researchers, payers, regulators, the policymakers, and industry, will we be able to pursue our dedicated efforts aimed at conquering cancer.

Only through collaboration will we continue to get smarter and move faster – we can and will do better.

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

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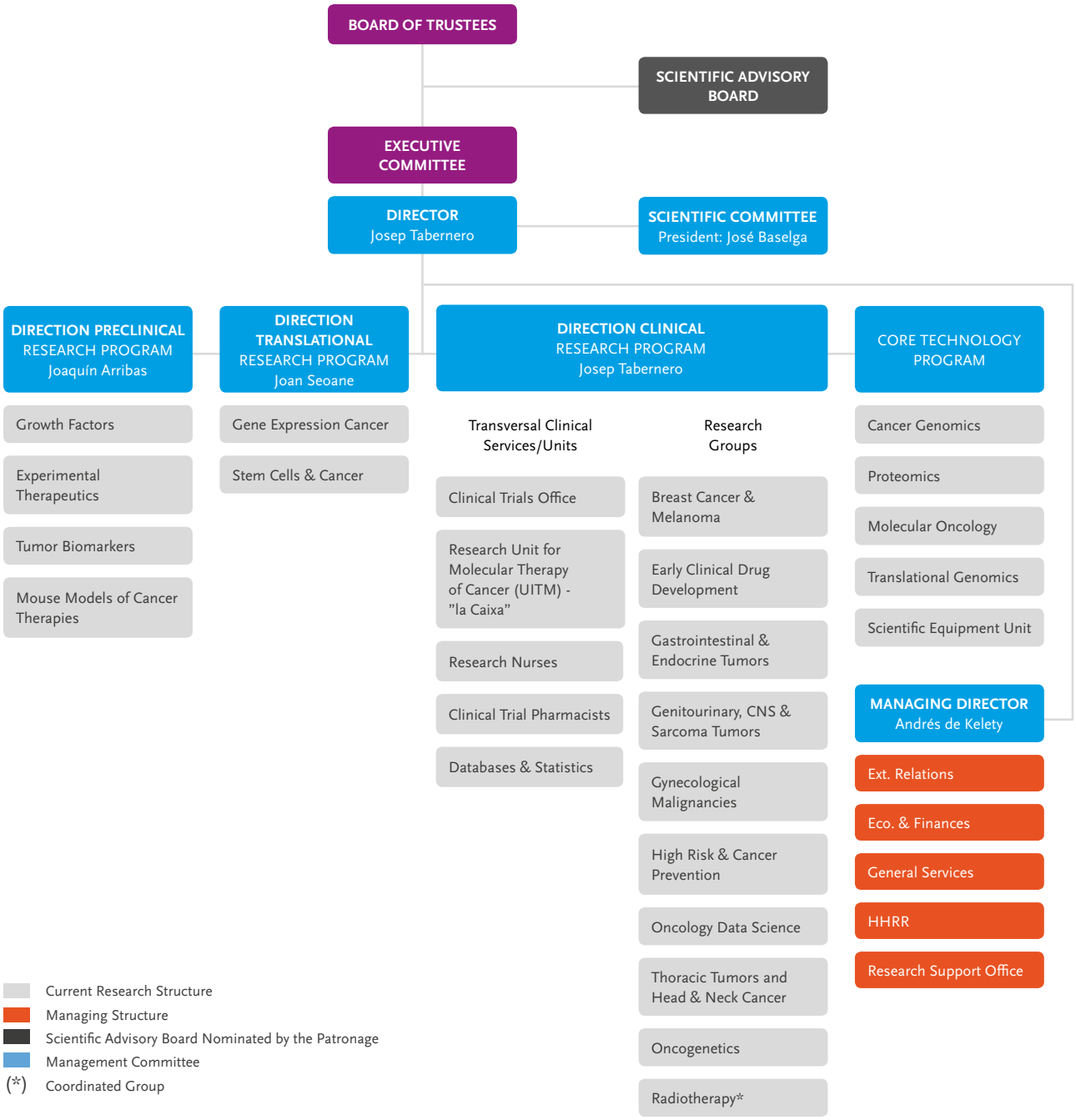
VHIO IN 2015: TACKLING A CONSTELLATION OF CHALLENGES TO CONQUER CANCER

Who we are and what we do

VHIO's Organigram 2015

In order to translate cancer discovery into real benefit for an increasing number patients, VHIO has, from the very outset, 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:

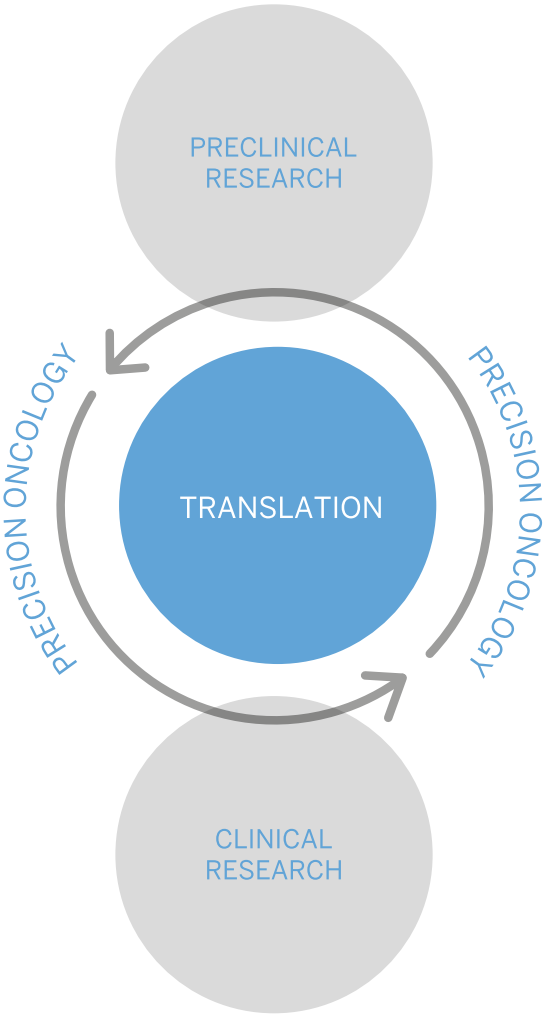


VHIO's translation toward precision oncology: a little more on how we did it in 2015

Aside from the many highlights described by each of our groups in this report, we would like to underline a few other important factors and developments in 2015 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:

Established in 2006, 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 personalized and 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 effective treatments and better practice for the care of our patients.



Oncogenomics and pre-screening

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 gauge the potential efficacy of specific agents for individual patients. In parallel, these technologies (Hiseq2500, MiSeq, nCounter Nanostring), 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 pre-screening program of mutations in patients who are candidates for our portfolio of Phase I clinical trials carried out at our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", is nucleated around the activity of two VHIO groups: Cancer Genomics and Molecular Oncology (see pages 68-71). Performing molecular profiling in over 1500 patients per year, we assess the molecular make-up of each patient which provides us with vital insights regarding the suitability for enrollment in clinical studies aimed at testing the efficacy of novel anti-cancer therapeutics. Our molecular tests for patient screening (disease-orientated mutation panels for NGS panels and nCounter Nanostring), are co-developed in partnership with our Early Clinical Drug Development Group.

As a reflection of our dedication to excellence and quality services we provide, we have under gone ISO 15189 accreditation for our main testing methods and our pre-screening 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 this year's Foreword, in collaboration with Merck Serono and Sysmex Inostics, we continue to develop our in-house BEAMing liquid biopsy RAS biomarker technology and 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. Based on results thus far, we are confident that we will increasingly evidence the power of liquid biopsy in the 'policing' of cancer. Having just received its European Conformity approval, this technology will be extended to conventional routine care and to additional tumor types.

BEAMing digital PCR/flow cytometry technology: empowering VHIO's existing suite of cutting-edge technologies.

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

Pioneering early drug discovery and clinical studies tailored to the specificities of patients

Jordi Rodón, Director & Medical Coordinator of the UITM, and PI of VHIO's Early Clinical Drug Development Group, Gemma Sala, Director of the Clinical Trials Office, with VHIO's Director, Josep Tabernero.

Obra Social "la Caixa"

VHIO has increasingly established itself as a leading reference in driving 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 scientists and physician researchers but also through its Research Unit for Molecular Therapies of Cancer (UITM) "la Caixa" (see pages 80-81) located in the patient care environment of the Vall d'Hebron University Hospital (see below), and set within the research context, as well as the Clinical Trials Office of the same hospital (see pages 78-79).

Research at the UITM is led by VHIO's Early Clinical Drug Development Group (pages 48-49), focusing on both 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 drugs with existing ones. In 2015, 106 Phase I clinical trials, including over a dozen trials in molecularly-selected patient populations (Basket/ Ocotpus Trials) as well as in immuno-oncology, were performed at the Unit totaling at 370 patients enrolled. The Clinical Trials Office coordinates a large portfolio of Phase I – II – III studies and consistently reports an increase in the number of trials conducted each year. In 2015 the number of patients included in our studies totaled at 979 across 289 trials.

VHIO's direct access to cancer patients: a critical asset in VHIO's purely translational research model

Vall d'Hebron Hospital

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

As evidenced throughout this report, across our preclinical, translational and clinical research programs, VHIO's talents continue to advance cancer discovery and medicine (see pages 87-98 for our full list of publications in 2015, and an overview of scientific productivity as well as selected articles on

pages 16-19). Our research endeavors largely benefit from VHIO's privileged location within the heart of the Vall d'Hebron University Hospital, affording direct access to patients as well as the entire spectrum of oncology patients 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.

VHIO discovery aimed at stripping back cancer's armory

Commandeering research aimed at combating cancer, our preclinical, translational and clinical researchers as corresponding/senior authors or co-authors, published 192 scientific articles in 2015 (74% Q1), with a cumulative Impact Factor totaling at 2104, and a Median Impact Factor (MIF) of 10.96. These figures reflect an increase in scientific productivity and MIF score, as well as the importance of VHIO's research and contribution to the oncology field.

New for this year's Scientific Report, we have invited each our Principal Investigators to select a maximum of four of their top publications among their respective lists of publications: see 'PI PAPER PICK' corresponding to each individual group.

For the complete list of articles published by VHIO researchers and physician-scientists in 2015 see pages 87-98. To view this year's selection of just some of the most relevant articles by VHIO Faculty published in 2015, refer to pages 16-19.

VHIO's participation in consortia and networks of excellence

To accelerate advancements in oncology we are committed to combining strengths and overcoming current challenges in collaboration. Our cross-border alliances and partnerships will undoubtedly help to spur insights aimed at rendering cancer treatment and care more precise for an increasing number of cancer patients.

In addition to VHIO's continued participation in some of the most forward-thinking and inspired consortia at international level (see pages 101-103 of this report), 2015 celebrated the launch of two major collaborations funded through EU's Research and Innovation program, Horizon 2020:

MoTriColor

Spurred by Horizon 2020 funding, MoTriColor, 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 (CRCm), patients will be stratified based on their gene expression profiles according to recently established predictive signatures.

According to gene expression profiles, patients will then be matched to a particular clinical trial. 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.

For more information and project updates visit: **www.motricolor.eu.**

MedBioinformatics

Launched in 2015, MedBioinformatics is also 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.

To discover more visit: **www.medbioinformatics.eu.**

Other partnering opportunities in 2015

AstraZeneca

The AstraZeneca/MedImmune and VHIO's Alliance agreement, 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.**

UHN Princess Margaret Cancer Centre

In February 2015 VHIO and the Princess Margaret Cancer Centre, University Health Network (Toronto, Canada), signed a Memorandum of Understanding to establish the principles and framework for their collaboration.

The two cancer centers will consequently seek to exchange data and share information surrounding best practice in clinical research, encourage academic collaboration by promoting faculty visits, as well as facilitate exchange among students and trainees -- representing important career development opportunities for junior faculty at both institutions of scientific excellence.

Throughout 2015, based on common synergies and a shared forward-thinking with several other leading research entities at global level, we have been paving the way for future collaborations and key alliances - to be announced in next year's Scientific Report, 2016.

The CELLEX building: marking a new VHIO chapter

The CELLEX building: affording VHIO with the critical space to expand its programmes and groups

Providing the valuable space through which to grow, VHIO's new home, the CELLEX building, connects our multidisciplinary teams together under the same roof. This eagerly anticipated development will enable us to further accelerate our dedicated efforts aimed at conquering cancer.

Located at the top of the Vall d'Hebron University Hospital (HUVH) campus, nestling at the foot of the Collserola Mountains, we occupied our new 7-floor premises at the end of August 2015. With a surface area of 6500m2 we can now seek to expand our existing programs as well as incorporate new groups that both complement and develop our current lines of research.

As this Scientific Report goes to print we are about to open our new Animal Facility which occupies the basement of the CELLEX building. With a dedicated surface area of 1347 m2 and a capacity of 5471 cages, this Facility incorporates the very latest platforms and technologies including a high-sensitivity in-vivo imaging technology platform, computed tomography (CT) for high resolution 3D anatomical imaging, and a MicroPET R4 scanner specifically engineered for analyzing small animal models of human disease.

Thanks to our new building and facilities, we are already seeing the benefits of even closer connectivity among and across our programs and groups. 2015 consequently marked the beginning of VHIO's next chapter in translation toward precision oncology.

With the invaluable support from:

Fundació Privada CELLEX

VHIO-organized events: stimulating thought-provoking, two-way exchange

In 2015 VHIO opened its doors to participants at the following events:

- **VHIO's *Meet the Editors***

nature REVIEWS CANCER

Continuing with our VHIO *Meet the Editors* series of specially programmed talks, in 2015 we invited M. Teresa Villanueva, Senior Editor of *Nature Reviews Cancer,* to deliver the next in these insightful presentations. True to the established fame and format of these educational opportunities that were devised by VHIO back in 2011, the session provided oncology professionals of research institutes of excellence in Barcelona with unique opportunity to learn more about scientific publishing and cancer research and put questions and comments directly to M. Teresa Villanueva during the Q & A with the

audience. More specifically, her talk included a stepwise look at the life of a Review, including commissioning, developmental editing, the assessment of unsolicited Reviews, and a glance into a 'day in the life' of a Reviews editor.

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

- **The Weizmann Institute of Science and VHIO exploration of latest insights into Cellular Communication in Translational Research**

מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE

Superbly hosted by WIS, this jointly organized meeting incorporated an outstanding panel of speakers cherry-picked by scientific Co-Chairs Irit Sagi, Principal Investigator, Department of Biological Regulation, and Dean of the Fienberg Graduate School at WIS, and Joaquín Arribas, Director of Preclinical Research at VHIO:

Cell Communication in Translational Research - bringing basic research into the clinic, 22 – 23 January 2015, Rehovot, Israel.

This two-day conference not only provided a platform through which to share and debate the latest research in the realm of cell communication in cancer, but also endorsed the research strengths and synergies between WIS and VHIO. As we consider the successes of this first joint initiative, we are more than confident that the meeting also represented the 'kick-off' for future partnering including research projects, an exchange program, and perhaps even a conference sequel to come.

- **VHIO's ad-hoc Courses, Workshops & Observerships**

Based on specific research lines and areas that have successfully established 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 attendance at International Cancer Conferences.

For more information about all our events in 2015 and much more, we invite you to browse our extended Scientific Report 2015 online at: http://memorias.vhio.net/2015/.

- **Coming soon to VHIO: Towards Predictive Cancer Models, 26 – 27 May 2016**

As this Scientific Report goes to print, we are making the necessary preparations for our forthcoming Special VHIO Symposium, *Towards Predictive Cancer Models*, 26 -27 May, 2016.

Co-chaired by VHIO's Joaquín Arribas, Director of Preclinical Research, and Laura Soucek, Principal Investigator of our Mouse Models of Cancer Therapies Group, this international meeting has been expertly engineered to bring together an expert panel of internationally acclaimed speakers who will present and debate on and around the five especially selected sessions:

Cancer Immunology and Tumor Microenvironment, New Prospectives, Circumventing Therapy Resistance, Redefining the Targets, and New Opportunities from Human Tumor Samples: Explants, Organoids, and PDX.

Just some of the must-have conversations during our Symposium will focus on future study design and how best to report, validate and share results so that we can ultimately build on the undeniable progress marked to-date by each and every model explored throughout our two-day symposium. We will be updated on the very latest research evidencing the 'tried, tested and validated' of a variety of modeling systems and combined approaches across various tumor types as well as cutting-edge data coming from within the 'stable' of novel contenders -- organoids and PDX models. We will also discuss how data from preclinical models can be complementary to tumor genetic testing and thus push the boundaries of sequence-based approaches.

Our focus will center firmly on empowering current predictive cancer models by pooling knowledge, sharing perspectives, and moving together to more swiftly and more cost-effectively advance cancer precision medicine.

On behalf of VHIO, the Symposium Co-Chairs gratefully thank the generous support received from the "la Caixa" Foundation:

"la Caixa" Foundation

To view the Scientific Program and discover more please visit VHIO's website:

www.vhio.net (select 'Events' > 'Symposia')

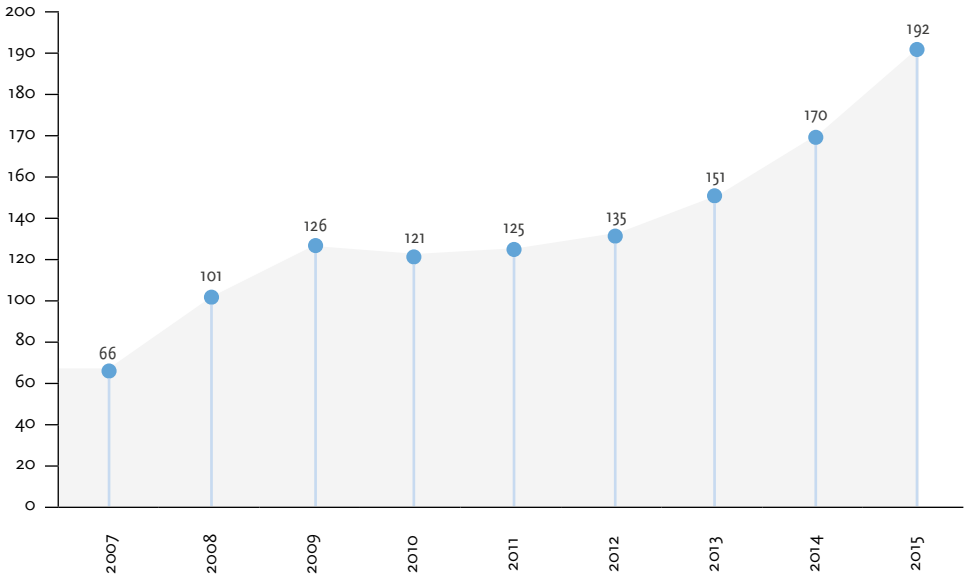
SCIENTIFIC PRODUCTIVITY: RESEARCH ARTICLES

Articles published in 2015

In 2015, 192 scientific articles (74% Q1) were published by VHIO researchers as corresponding/senior or co-authors with a cumulative Impact Factor totaling at 2104, and a Median Impact Factor (MIF) of 10.96.

These figures reflect an increase in both scientific productivity and MIF, 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 - 2015

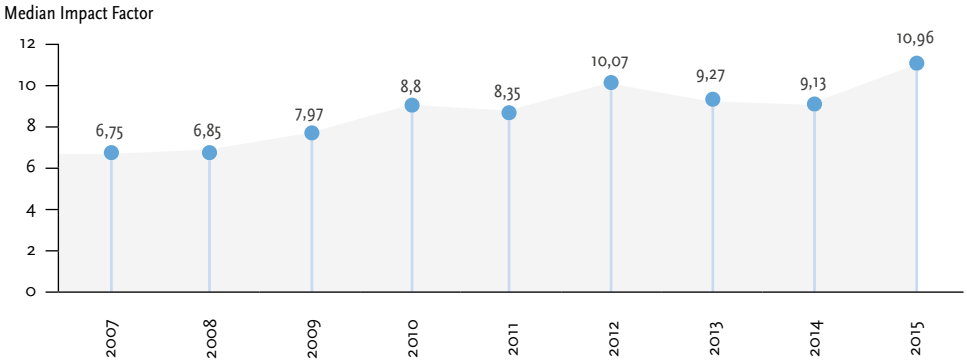


Impact factor articles published in 2015

For the complete list of VHIO scientific articles published in 2015 in journals with allocated Impact Factor please see pages 87-98. To view a selection of most relevant articles by VHIO researchers published in 2015 please refer to pages 16-19 of the Scientific Report.

To consult publications per group as selected by our Principal Investigators, visit the extend version of this Scientific Report online at: http://memorias.vhio.net/2015/ (select tab 'Publications & Awards').

Figure II / Median Impact Factor (MIF) of papers published by VHIO faculty from 2007 – 2015



SELECTION OF SOME OF THE MOST RELEVANT ARTICLES BY VHIO RESEARCHERS PUBLISHED IN 2015

Below is a selected list of articles published by VHIO researchers in 2015 with respective Impact Factors indicated. For the complete list of VHIO scientific articles published in 2015 in journals with allocated Impact Factor please see pages 87-98 of this Scientific Report.

Adjuvant Ovarian Suppression in Premenopausal Breast Cancer. Francis PA; Regan MM; Fleming GF; Láng I; Ciruelos E; *Bellet M*; Bonnefoi HR; Climent MA; Da Prada GA; Burstein HJ; Martino S; Davidson NE; Geyer CE; Walley BA; Coleman R; Kerbrat P; Buchholz S; Ingle JN; Winer EP; Rabaglio-Poretti M; Maibach R; Ruepp B; Giobbie-Hurder A; Price KN; Colleoni M; Viale G; Coates AS; Goldhirsch A; Gelber RD. *2015. N Engl J Med.* 372: 436-446. IF:55,873

AZD9291 in EGFR Inhibitor-Resistant Non-Small-Cell Lung Cancer. Jänne PA; Yang JC; Kim DW; Planchard D; Ohe Y; Ramalingam SS; Ahn MJ; Kim SW; Su WC; Horn L; Haggstrom D; *Felip E*; Kim JH; Frewer P; Cantarini M; Brown KH; Dickinson PA; Ghiorghiu S; Ranson M. *2015. N Engl J Med.* 372: 1689-1699. IF:55,873

Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. Borghaei H; Paz-Ares L; Horn L; Spigel DR; Steins M; Ready NE; Chow LQ; Vokes EE; *Felip E*; Holgado E; Barlesi F; Kohlhäufl M; Arrieta O; Burgio MA; Fayette J; Lena H; Poddubskaya E; Gerber DE; Gettinger SN; Rudin CM; Rizvi N; Crinò L; Blumenschein GR; Antonia SJ; Dorange C; Harbison CT; Graf Finckenstein F; Brahmer JR. *2015. N Engl J Med.* 373: 1627-1639. IF:55,873

Pembrolizumab for the Treatment of Non-Small-Cell Lung Cancer. G aron EB; Rizvi NA; Hui R; Leighl N; Balmanoukian AS; Eder JP; Patnaik A; Aggarwal C; Gubens M; Horn L; Carcereny E; Ahn MJ; *Felip E*; Lee JS; Hellmann MD; Hamid O; Goldman JW; Soria JC; Dolled-Filhart M; Rutledge RZ; Zhang J; Lunceford JK; Rangwala R; Lubiniecki GM; Roach C; Emancipator K; Gandhi L. *2015. N Engl J Med.* 372: 2018-2028. IF:55,873

Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer. Swain SM; *Baselga J*; Kim SB; Ro J; Semiglazov V; Campone M; Ciruelos E; Ferrero JM; Schneeweiss A; Heeson S; Clark E; Ross G; Benyunes MC; *Cortés J. 2015. N Engl J Med.* 372: 724-734. IF:55,873

Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. Mayer RJ; Van Cutsem E; Falcone A; Yoshino T; Garcia-Carbonero R; Mizunuma N; Yamazaki K; Shimada Y; *Tabernero J*; Komatsu Y; Sobrero A; Boucher E; Peeters M; Tran B; Lenz HJ; Zaniboni A; Hochster H; Cleary JM; Prenen H; Benedetti F; Mizuguchi H; Makris L; Ito M; Ohtsu A. *2015. N Engl J Med.* 372: 1909-1919. IF:55,873

Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. Hyman DM; Puzanov I; Subbiah V; Faris JE; Chau I; Blay JY; Wolf J; Raje NS; Diamond EL; Hollebecque A; Gervais R; *Elez E*; Italiano A; Hofheinz RD; Hidalgo M; Chan E; Schuler M; Lasserre SF; Makrutzki M; Sirzen F; Veronese ML; *Tabernero J*; *Baselga J. 2015. N Engl J Med.* 373: 726-736. IF:55,873

Convergent loss of PTEN leads to clinical resistance to a PI(3)K alpha inhibitor. Juric D; Castel P; Griffith M; Griffith OL; Won HH; Ellis H; Ebbesen SH; Ainscough BJ; Ramu A; Iyer G; Shah RH; Huynh T; Mino-Kenudson M; Sgroi D; Isakoff S; Thabet A; Elamine L; Solit DB; Lowe SW; Quadt C; Peters M; Derti A; Schegel R; Huang A; Mardis ER; Berger MF; *Baselga J*; Scaltriti M. *2015. Nature.* 518: 240-230. IF:41,456

Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. Rebbeck TR; Mitra N; Wan F; Sinilnikova OM; Healey S; McGuffog L; Mazoyer S; Chenevix-Trench G; Easton DF; Antoniou AC; Nathanson KL; Laitman Y; Kushnir A; Paluch-Shimon S; Berger R; Zidan J; Friedman E; Ehrencrona H; Stenmark-Askmalm M; Einbeigi Z; Loman N; Harbst K; Rantala J; Melin B; Huo D; Olopade OI; Seldon J; Ganz PA; Nussbaum RL; Chan SB; Odunsi K; Gayther SA; Domchek SM; Arun BK; Lu KH; Mitchell G; Karlan BY; Walsh C; Lester J; Godwin AK; Pathak H; Ross E; Daly MB; Whittemore AS; John EM; Miron A; Terry MB; Chung WK; Goldgar DE; Buys SS; Janavicius R; Tihomirova L; Tung N; Dorfling CM; van Rensburg EJ; Steele L; Neuhausen SL; Ding YC; Ejlertsen B; Gerdes AM; Hansen Tv; Ramón y Cajal T; Osorio A; Benitez J; Godino J; Tejada MI; Duran M; Weitzel JN; Bobolis KA; Sand SR; Fontaine A; Savarese A; Pasini B; Peissel B; Bonanni B; Zaffaroni D; Vignolo-Lutati F; Scuvera G; Giannini G; Bernard L; Genuardi M; Radice P; Dolcetti R; Manoukian S; Pensotti V; Gismondi V; Yannoukakos D; Fostira F; Garber J; Torres D; Rashid MU; Hamann U; Peock S; Frost D; Platte R; Evans

DG; Eeles R; Davidson R; Eccles D; Cole T; Cook J; Brewer C; Hodgson S; Morrison PJ; Walker L; Porteous ME; Kennedy MJ; Izatt L; Adlard J; Donaldson A; Ellis S; Sharma P; Schmutzler RK; Wappenschmidt B; Becker A; Rhiem K; Hahnen E; Engel C; Meindl A; Engert S; Ditsch N; Arnold N; Plendl HJ; Mundhenke C; Niederacher D; Fleisch M; Sutter C; Bartram CR; Dikow N; Wang-Gohrke S; Gadzicki D; Steinemann D; Kast K; Beer M; Varon-Mateeva R; Gehrig A; Weber BH; Stoppa-Lyonnet D; Sinilnikova OM; Mazoyer S; Houdayer C; Belotti M; Gauthier-Villars M; Damiola F; Boutry-Kryza N; Lasset C; Sobol H; Peyrat JP; Muller D; Fricker JP; Collonge-Rame MA; Mortemousque I; Nogues C; Rouleau E; Isaacs C; De Paepe A; Poppe B; Claes K; De Leeneer K; Piedmonte M; Rodriguez G; Wakely K; Boggess J; Blank SV; Basil J; Azodi M; Phillips KA; Caldes T; de la Hoya M; Romero A; Nevanlinna H; Aittomäki K; van der Hout AH; Hogervorst FB; Verhoef S; Collée JM; Seynaeve C; Oosterwijk JC; Gille JJ; Wijnen JT; Garcia EB; Kets CM; Ausems MG; Aalfs CM; Devilee P; Mensenkamp AR; Kwong A; Olah E; Papp J; *Diez O*; Lazaro C; Darder E; Blanco I; Salinas M; Jakubowska A; Lubinski J; Gronwald J; Jaworska-Bieniek K; Durda K; Sukiennicki G; Huzarski T; Byrski T; Cybulski C; Toloczko-Grabarek A; Zlowocka-Perlowska E; Menkiszak J; Arason A; Barkardottir RB; Simard J; Laframboise R; Montagna M; Agata S; Alducci E; Peixoto A; Teixeira MR; Spurdle AB; Lee MH; Park SK; Kim SW; Friebel TM; Couch FJ; Lindor NM; Pankratz VS; Guidugli L; Wang X; Tischkowitz M; Foretova L; Vijai J; Offit K; Robson M; Rau-Murthy R; Kauff N; Fink-Retter A; Singer CF; Rappaport C; Gschwantler-Kaulich D; Pfeiler G; Tea MK; Berger A; Greene MH; Mai PL; Imyanitov EN; Toland AE; Senter L; Bojesen A; Pedersen IS; Skytte AB; Sunde L; Thomassen M; Moeller ST; Kruse TA; Jensen UB; Caligo MA; Aretini P; Teo SH; Selkirk CG; Hulick PJ; Andrulis I. *2015. JAMA.* 313: 1347-1361. IF:35,289

Identification of six new susceptibility loci for invasive epithelial ovarian cancer. Kuchenbaecker KB; Ramus SJ; Tyrer J; Lee A; Shen HC; Beesley J; Lawrenson K; McGuffog L; Healey S; Lee JM; Spindler TJ; Lin YG; Pejovic T; Bean Y; Li Q; Coetzee S; Hazelett D; Miron A; Southey M; Terry MB; Goldgar DE; Buys SS; Janavicius R; Dorfling CM; van Rensburg EJ; Neuhausen SL; Ding YC; Hansen TV; Jønson L; Gerdes AM; Ejlertsen B; Barrowdale D; Dennis J; Benitez J; Osorio A; Garcia MJ; Komenaka I; Weitzel JN; Ganschow P; Peterlongo P; Bernard L; Viel A; Bonanni B; Peissel B; Manoukian S; Radice P; Papi L; Ottini L; Fostira F; Konstantopoulou I; Garber J; Frost D; Perkins J; Platte R; Ellis S; Godwin AK; Schmutzler RK; Meindl A; Engel C; Sutter C; Sinilnikova OM; Damiola F; Mazoyer S; Stoppa-Lyonnet D; Claes K; De Leeneer K; Kirk J; Rodriguez GC; Piedmonte M; O'Malley DM; de la Hoya M; Caldes T; Aittomäki K; Nevanlinna H; Collée JM; Rookus MA; Oosterwijk JC; Tihomirova L; Tung N; Hamann U; Isaccs C; Tischkowitz M; Imyanitov EN; Caligo MA; Campbell IG; Hogervorst FB; Olah E; *Diez O*; Blanco I; Brunet J; Lazaro C; Pujana MA; Jakubowska A; Gronwald J; Lubinski J; Sukiennicki G; Barkardottir RB; Plante M; Simard J; Soucy P; Montagna M; Tognazzo S; Teixeira MR; Pankratz VS; Wang X; Lindor N; Szabo CI; Kauff N; Vijai J; Aghajanian CA; Pfeiler G; Berger A; Singer CF; Tea MK; Phelan CM; Greene MH; Mai PL; Rennert G; Mulligan AM; Tchatchou S; Andrulis IL; Glendon G; Toland AE; Jensen UB; Kruse TA; Thomassen M; Bojesen A; Zidan J; Friedman E; Laitman Y; Soller M; Liljegren A; Arver B; Einbeigi Z; Stenmark-Askmalm M; Olopade OI; Nussbaum RL; Rebbeck TR; Nathanson KL; Domchek SM; Lu KH; Karlan BY; Walsh C; Lester J; Hein A; Ekici AB; Beckmann MW; Fasching PA; Lambrechts D; Van Nieuwenhuysen E; Vergote I; Lambrechts S; Dicks E; Doherty JA; Wicklund KG; Rossing MA; Rudolph A; Chang-Claude J; Wang-Gohrke S; Eilber U; Moysich KB; Odunsi K; Sucheston L; Lele S; Wilkens LR; Goodman MT; Thompson PJ; Shvetsov YB; Runnebaum IB; Dürst M; Hillemanns P; Dörk T; Antonenkova N; Bogdanova N; Leminen A; Pelttari LM; Butzow R; Modugno F; Kelley JL; Edwards RP; Ness RB; du Bois A; Heitz F; Schwaab I; Harter P; Matsuo K; Hosono S; Orsulic S; Jensen A; Kjaer SK; Hogdall E; Hasmad HN; Azmi MA; Teo SH; Woo YL; Fridley BL; Goode EL; Cunningham JM; Vierkant RA; Bruinsma F; Giles GG; Liang D; Hildebrandt MA; Wu X; Levine DA; Bisogna M; Berchuck A; Iversen ES; Schildkraut JM; Concannon P; Weber RP; Cramer DW; Terry KL; Poole EM; Tworoger SS; Bandera EV; Orlow I; Olson SH; Krakstad C; Salvesen HB; Tangen IL; Bjorge L; van Altena AM; Aben KK; Kiemeney LA; Massuger LF; Kellar M; Brooks-Wilson A; Kelemen LE; Cook LS; Le ND; Cybulski C; Yang H; Lissowska J; Brinton LA; Wentzensen N; Hogdall C; Lundvall L; Nedergaard L; Baker H; Song H; Eccles D; McNeish I; Paul J; Carty K; Siddiqui N; Glasspool R; Whittemore AS; Rothstein JH; McGuire V; Sieh W; Ji BT; Zheng W; Shu XO; Gao YT; Rosen B; Risch HA; McLaughlin JR; Narod SA; Monteiro AN; Chen A; Lin HY; Permuth-Wey J; Sellers TA; Tsai YY; Chen Z; Ziogas A; Anton-Culver H; Gentry-Maharaj A; Menon U; Harrington P; Lee AW; Wu AH; Pearce CL; Coetzee G; Pike MC; Dansonka-Mieszkowska A; Timorek A; Rzepecka IK; Kupryjanczyk J; Freedman M; Noushmehr H; Easton DF; Offit K; Couch FJ; Gayther S; Pharoah PP; Antoniou AC; Chenevix-Trench G. *2015. Nature Genet.* 47: 164-171. IF:29,352

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Epigenetic activation of a cryptic TBC1D16 transcript enhances melanoma progression by targeting EGFR. Vizoso M; Ferreira HJ; Lopez-Serra P; Carmona FJ; Martínez-Cardús A; Girotti MR; Villanueva A; Guil S; Moutinho C; Liz J; Portela A; Heyn H; Moran S; Vidal A; Martinez-Iniesta M; Manzano JL; Fernandez-Figueras MT; *Elez E*; *Muñoz E*; Botella-Estrada R; Berrocal A; Pontén F; Oord JV; Gallagher WM; Frederick DT; Flaherty KT; McDermott U; Lorigan P; Marais R; Esteller M. *2015. Nat. Med.* 21: 741-0. IF:27,363

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Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Ryan CJ; Smith MR; Fizazi K; Saad F; Mulders PF; Sternberg CN; Miller K; Logothetis CJ; Shore ND; Small EJ; *Carles J*; Flaig TW; Taplin ME; Higano CS; de Souza P; de Bono JS; Griffin TW; De Porre P; Yu MK; Park YC; Li J; Kheoh T; Naini V; Molina A; Rathkopf DE. *2015. Lancet Oncol.* 16: 152-160. IF:24,690

Afatinib alone or afatinib plus vinorelbine versus investigator's choice of treatment for HER2-positive breast cancer with progressive brain metastases after trastuzumab, lapatinib, or both (LUX-Breast 3): a randomised, open-label, multicentre, phase 2 trial. *Cortés J*; Dieras V; Ro J; Barriere J; Bachelot T; Hurvitz S; Le Rhun E; Espié M; Kim SB; Schneeweiss A; Sohn JH; Nabholtz JM; Kellokumpu-Lehtinen PL; Taguchi J; Piacentini F; Ciruelos E; Bono P; Ould-Kaci M; Roux F; Joensuu H. *2015. Lancet Oncol.* 16: 1700-1710. IF:24,690

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Bevacizumab for advanced cervical cancer: patient-reported outcomes of a randomised, phase 3 trial (NRG Oncology-Gynecologic Oncology Group protocol 240). Penson RT; Huang HQ; Wenzel LB; Monk BJ; Stockman S; Long HJ; Ramondetta LM; Landrum LM; *Oaknin A*; Reid TJ; Leitao MM; Method M; Michael H; Tewari KS. *2015. Lancet Oncol.* 16: 301-311. IF:24,690

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Correction to *Lancet Oncol.* 2015; 16: 499-508. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised,

double-blind, multicentre, phase 3 study. *Tabernero J*; Takayuki Y; Cohn AL. *2015. Lancet Oncol.* IF:24,690

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- Puntes low
- X-Terminator
- AM i SM Qiagen
- H2O nuclease-free
- Pots autoclavables
- Finnipipette

PROGRAMS

VHIO'S MULTIDISCIPLINARY RESEARCH PROGRAMS

PRECLINICAL RESEARCH


PATHWAYS IN
HUMAN CANCER
Cell Signaling
VHIO

DIRECTOR PRECLINICAL RESEARCH PROGRAM

JOAQUÍN ARRIBAS

"Our Program is dedicated to advancing prediction science against cancer. At molecular level we develop xenograft models with explant tumors from patients in mice to study tumor development in optimized research models. By accelerating the detection of mutations and mechanisms of resistance to current therapies we are ultimately contributing to better outcomes for cancer patients."

VHIO's Preclinical Program is dedicated to developing novel strategies to treat highly aggressive tumors affecting the breast, pancreas, colon, lung or brain. These tumors are either resistant to therapy that worked for a limited period of time or lack an effective therapy, resulting in a bad prognosis. We aim to contribute to the discovery of new therapeutic opportunities for these patients and improve their outcomes. Furthermore, our Program also focuses on the discovery of novel tumor biomarkers that will help in the early diagnosis and follow-up of tumors.

We have developed several models to accomplish these objectives, including genetically modified mice and patient-derived xenografts. The latter, generated by implanting tumor pieces resected from patients at the Vall d'Hebron University Hospital (HUVH) into immunodeficient mice, closely resemble the original tumors. Mouse models are also adequate for the study of tumor progression and the interactions between the microenvironment and tumor cells. These combined strategies allow us to both discover and tackle mechanisms of resistance to current anti-cancer agents and as well as test novel therapies.

Our Mouse Models of Cancer Therapies Group, headed by Laura Soucek, has continued to carry out research on the Myc oncogene and inflammatory components in cancer. They recently showed that inhibition of the tyrosine kinase BTK is an effective strategy to reduce fibrosis in pancreatic cancer. Pursuing the inactivation of Myc, they are developing several strategies based on cell-penetrating peptides and nanoparticles with particular emphasis on metastatic breast cancer and glioblastoma.

Josep Villanueva leads our Tumor Biomarkers Group which centers research on the characterization of mechanisms used by tumor cells to communicate with their microenvironment during tumorigenesis, mainly through secretion. Their expertise has been presented in a recent review providing an excellent overview of the main technical and biological issues related to cell line secretome analysis, discussing both the challenges and opportunities in its use for tumor biomarker discovery.

VHIO's Experimental Therapeutic's Group led by Violeta Serra has focused on the blockade of the PI3K/mTOR pathway, CDK4/6 as well as therapies targeting homologous recombination deficiency.

Finally, my own Growth Factors Group has continued to characterize a subtype of breast cancer known as HER2, and we have identified senescent cells as principal contributors to the growth of these tumors. We have also expanded insights into the mechanisms of resistance to anti-HER2 treatments and their relationship with different patterns of gene amplification. We have also characterized the role of proteolytic remodeling of the cell surface during breast cancer progression.

Our groups' results have been published in several journals of excellence including *The Journal of the National Cancer Institute (JNCI)*, *Cancer Research*, and *Clinical Cancer Research* among others. Our teams are also supported through international and national competitive grants from the Breast Cancer Research Foundation (BCRF), *Instituto de Salud Carlos III* (Institute of Health Carlos III, ISCIII), the BBVA Foundation and the *Asociación Española Contra el Cáncer* (Spanish Association Against Cancer, AECC).

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PI PAPER PICK

García-García C, Rivas MA, Ibrahim YH, Calvo MT, Gris-Oliver A, Rodriguez O, Grueso J, Anton P, Guzman M, Aura C, Nuciforo P, Jessen K, Argiles G, Dienstmann R, Bertotti A, Trusolino L, Matito J, Vivancos A, Chicote I, Palmer HG, Tabernero J, Scaltriti M, Baselga J, Serra V. MEK plus PI3K/mTORC1/2 therapeutic efficacy is impacted by TP53 mutation in preclinical models of colorectal cancer. *Clin Cancer Res*. 2015;21(24):5499-5510.

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Muellner MK, Mair B, Ibrahim Y, Kerzendorfer C, Lechtermann H, Trefzer C, Klepsch F, Müller AC, Leitner E, Macho-Maschler S, Superti-Furga G, Bennett KL, Baselga J, Rix U, Kubicek S, Colinge J, Serra V, Nijman SM. Targeting a cell state common to triple-negative breast cancers. *Mol Syst Biol*. 2015;11(1):789.

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SUMMARY

VHIO's Experimental Therapeutics Group was set up to conduct bench-to-bedside preclinical research in breast cancer to advance insights into HER2- and PI3K-therapeutic resistance. We have contributed to the field of PI3K-inhibitor resistance by firstly evidencing that an adaptive response activating the MEK/ERK pathway through receptor tyrosine kinase upregulation bypasses the PI3K-survival pathway and mediates resistance to PI3Ki 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, i.e. 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 PI3K-alpha inhibitor results in improved and prolonged disease control in all experimental models tested.

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. Nonetheless, PM01183 is 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, discovered new response biomarkers, and demonstrated the efficacy of hypothesis-based drug combinations.

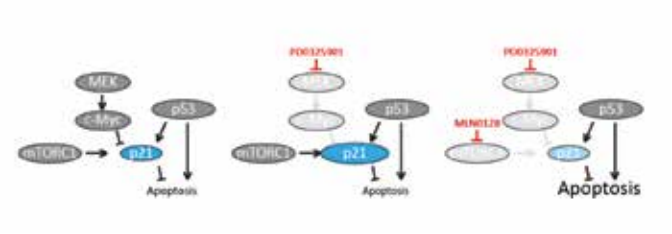

Figure: Mode of action of combined MEK and mTORC inhibitors in dual pathway activated CRC. Model depicting the proposed mechanism of action for the combination of anti-MEK and mTOR therapy in KRAS/BRAF- and PI3K/PTEN-mutated colorectal cancer in p53 wild-type cells. In wild-type p53 backgrounds, p21 is under transcriptional and translational control of p53, c-Myc, and mTORC1. PD0325901 blocks the negative transcriptional control of p21 by MEK/c-Myc and enhances the p21 levels, which inhibit apoptosis induction. Concomitant blockade of mTORC1 prevents translation of p21, thereby enabling apoptosis.

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 in 2015

- We have uncovered a potential mechanism or resistance to combined MEK and PI3K/mTORC blockade in dual pathway Ras/PI3K- activated CRC.
- We have screened the antitumor activity of PI3K and CDK4/6 in six estrogen receptor-positive PDX, and establish that the combination of these two inhibitors results in superior response rate compared to single agents.
- 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 twenty-eight PDX.

GROWTH FACTORS GROUP

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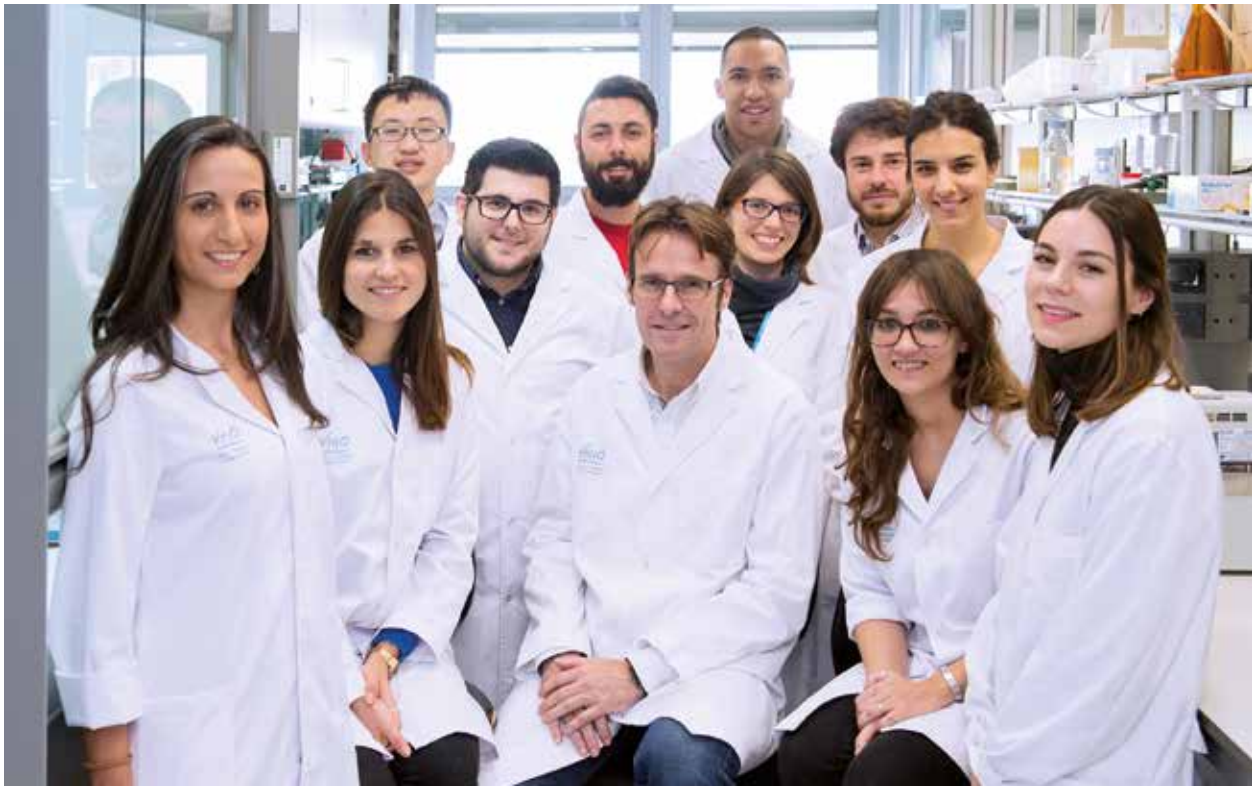

PI PAPER PICK

Morancho B, Martínez-Barriocanal Á, Villanueva J, Arribas J. Role of ADAM17 in the non-cell autonomous effects of oncogene-induced senescence. *Breast Cancer Res.* 2015;17:106.

Vicario R, Peg V, Morancho B, Zacarias-Fluck M, Zhang J, Martínez-Barriocanal Á, Navarro Jiménez A, Aura C, Burgues O, Lluch A, Cortés J, Nuciforo P, Rubio IT, Marangoni E, Deeds J, Boehm M, Schlegel R, Tabernero J, Mosher R, Arribas J. Patterns of HER2 Gene Amplification and Response to Anti-HER2 Therapies. *PLoS One.* 2015;10(6):e0129876.

Zacarias-Fluck MF, Morancho B, Vicario R, Luque Garcia A, Escorihuela M, Villanueva J, Rubio IT, Arribas J. Effect of cellular senescence on the growth of HER2-positive breast cancers. *J Natl Cancer Inst.* 2015;107(5).

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SUMMARY

Our group has continued to investigate tumor progression and mechanisms of resistance to therapy focusing on HER2-positive breast cancer. We have previously shown that constitutively activated HER2 leads to premature senescence. These senescent cells remain metabolically active and display a remarkable secretory phenotype with a pro-metastatic effect. We have now deeply analyzed this secretome and evidenced that is enriched in the extracellular domain of membrane-bound proteins, concluding that cell-surface proteolytic remodeling tightly regulates secretion. Critically, this contributes to the prometastatic effect of HER2-induced senescent cells.

Throughout 2015 we have also 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 have identified IL-6 as one of the main contributors of this senescent secretome. Furthermore, we have investigated whether the patterns of HER2 gene amplification are related to resistance to current treatments against HER2-positive breast cancer. In contrast to other tumor types, we have shown in both clinical and preclinical samples that loss of one pattern of gene amplification is not necessary for acquired resistance.

Our group continues to collaborate with other VHIO teams, particularly with our Tumor Biomarkers Group led by Josep Villanueva, to characterize how senescent cells remodel the extracellular environment.

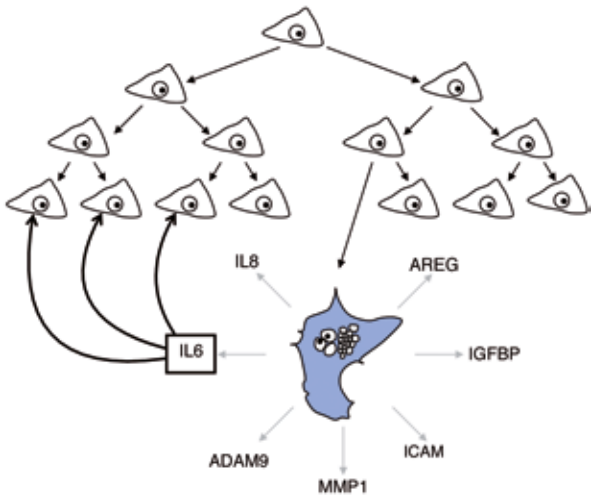

Figure: Senescent cells may contribute to tumor progression. Schematic illustration showing that among the factors secreted by senescent cells, IL-6 contributes to tumor progression by inducing proliferation of non-senescent cells.

We are extremely grateful to the Spanish Association against Cancer (AECC) and the Breast Cancer Research Foundation (BCRF) for their continued support of our research. Lastly, but by no means least, we continue to coordinate the Breast Cancer Program within the *Red Territorial de Investigación Cooperativa en Cáncer* (RTICC), supported by the *Instituto de Salud Carlos III* (ISCIII). This network is comprised of several of the most active groups working in breast cancer across Spain. We work in close connection to deliver on complex projects that require the input and expertise of multiple groups.

Strategic Goals

- Develop novel therapeutic strategies to treat HER2-positive tumors and identify mechanisms of resistance to current therapies.
- Characterize the role of premature senescence in breast cancer progression and treatment.
- Study the involvement of the immune system in cancer progression.
- Evaluate the activity of novel therapeutic strategies in our panels of breast and pancreatic patient-derived xenografts.
- Continue to develop a pancreatic cancer research program in close collaboration with VHIO's Clinical Research Program, directed by Josep Tabernero.

Highlights in 2015

- Our group has shown that senescent cells contribute to tumor growth by providing cytokines to proliferating cells.
- We have further explored the pro-metastatic effect of the secretome of HER2-induced senescent breast cancer cells, establishing the critical contribution of cell-surface proteolytic remodeling.
- In contrast to other tumors models, we have reported that the different patterns of amplification of the gene encoding HER2 are not related to acquired resistance to anti-HER2 treatments in breast cancer.
- Our paper *Effect of p95HER2/611CTF on the response to trastuzumab and chemotherapy, J Natl Cancer Inst.* 2014 Sep 24;106(11), was awarded the 2015 annual prized for collaborative research in oncology by the *Red Temática de Investigación Cooperativa en Cáncer* (RTICC).
- This same manuscript was also selected by the prestigious journal *Cancer Discovery* for a News in Brief review: *Chemotherapy Helps Overcome Trastuzumab Resistance*.

MOUSE MODELS OF CANCER THERAPIES GROUP

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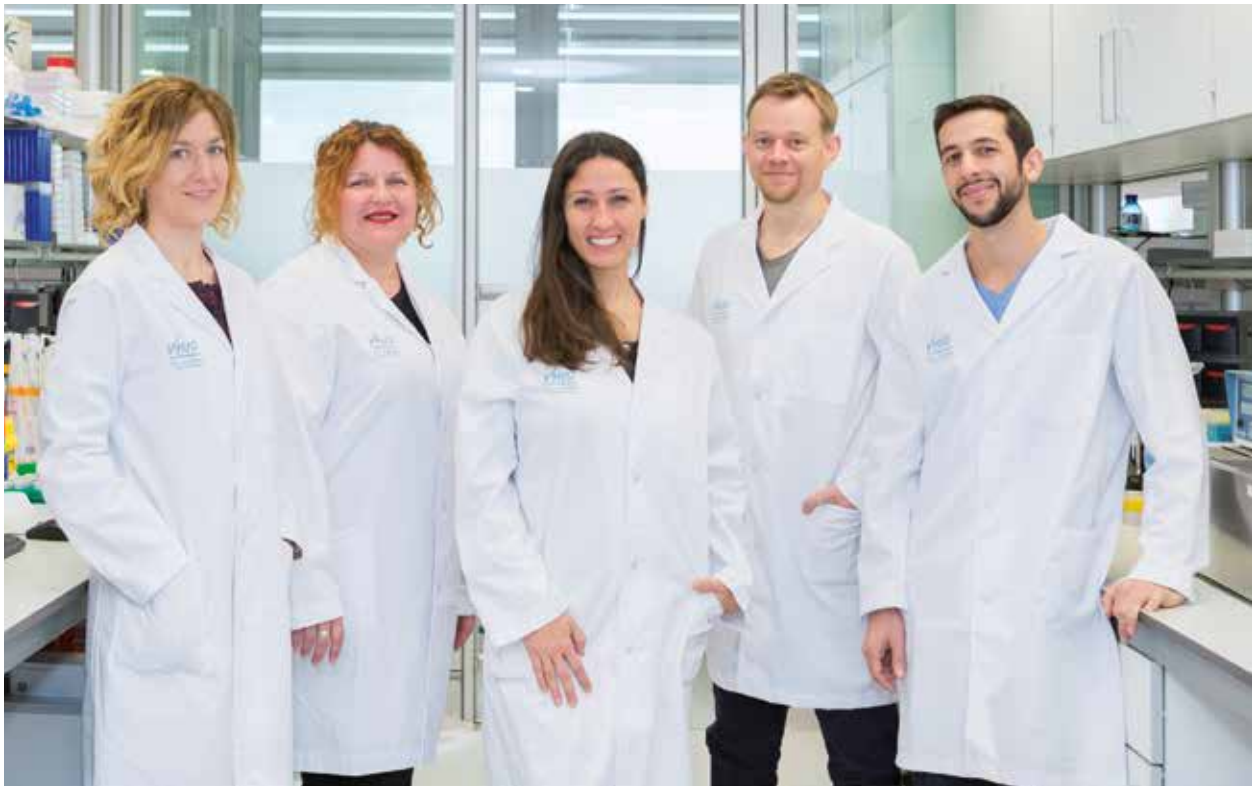
Technician
Érika Serrano del Pozo



PI PAPER PICK

Massó-Vallés D, Jauset T, Serrano E, Sodir NM, Pedersen K, Affara NI, Whitfield JR, Beaulieu ME, Evan GI, Elias L, Arribas J, Soucek L. Ibrutinib exerts potentantifibrotic and antitumor activities in mouse models of pancreatic adenocarcinoma. *Cancer Res.* 2015;75(8):1675-1681.

Cecconi F, Soucek L, Taub DD, Ziparo E. Live or Die: Choice Mechanisms in Stressed Cells. *Mediators Inflamm.* 2015;2015:454863.

William H. Goodson III, Leroy Lowe, David O. Carpenter, Michael Gilbertson, Abdul Manaf Ali, Adela Lopez de Cerain Salsamendi, [...], Laura Soucek, [...], Zhiwei Hu. Assessing the Carcinogenic Potential of Low Dose Exposures to Chemical Mixtures in the Environment: The Challenge Ahead. *Carcinogenesis.* 2015;36 Suppl 1:S254-S296.

Stephanie C. Casey, Monica Vaccari, Fahd Al-Mulla, Rabeah Al-Temaimi, Amedeo Amedei, Mary Helen Barcellos- Hoff, Dustin Brown, Marion Chapellier, [...], Sandra Ryeom, Hosni K. Salem, Ivana Scovassi, Neetu Singh, Laura Soucek, Louis Vermeulen, Jonathan R. Whitfield, Jordan Woodrick, Annamaria Colacci, William H. Bisson, and Dean W. Felsher. Assessing the Carcinogenic Potential of Environmental Chemicals: The Tumor Microenvironment. *Carcinogenesis.* 2015;36 Suppl 1:S160-S183.

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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, non-toxic pharmacological options for Myc targeting in the clinic. To do so, we have created a spin-off company, Peptomyc S.L., for the development of Myc-inhibiting peptides for cancer therapy. Of note, our project was awarded a national prize for Innovation and Peptomyc obtained a 'seal of excellence' for an SME Instrument Phase I by the European Commission, under the scope of *H2020*.

We are currently validating our new therapeutic strategy in the 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, metastatic breast cancer). Glioblastoma in particular is the focus of our recently obtained grant for biomedical studies awarded by the BBVA Foundation.

In parallel, we have been pre-clinically validating new therapeutic strategies against components of the tumor microenvironment. One of these has been particularly successful, resulting in a paper published in *Cancer Research*: Ibrutinib exerts potent antifibrotic and antitumor activities in mouse models of pancreatic adenocarcinoma, Massó-Vallés D, Jauset T, Serrano E, Sodir NM, Pedersen K, Affara NI, Whitfield JR, Beaulieu ME, Evan GI, Elias L, Arribas J, Soucek L. *Cancer Res*. 2015 Apr 15;75(8):1675-81), which led to new clinical trials for pancreatic cancer patients.

In recognition of research of excellence, Laura Soucek, ICREA Professor since 2014, was this year appointed as Associate Professor of the *Universidad Autónoma de Barcelona*.

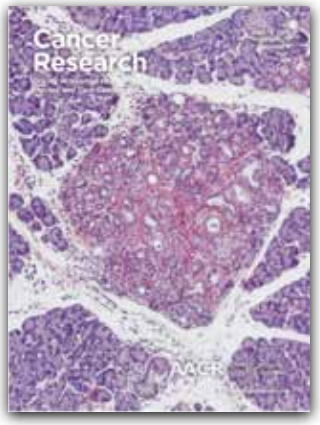

Figure I: *Cancer Research* front cover, April 15, 2015; 75 (8) issue. Bruton's tyrosine kinase inhibitor ibrutinib blocks mast cell degranulation, which triggers reduction of collagen content (red staining) in tumors from a transgenic mouse model of pancreatic ductal adenocarcinoma. This dramatic reduction in fibrosis is accompanied by a decrease in Ki-67+ proliferating cells, CD11b+ leukocytes and F4/80+ macrophages. Overall, ibrutinib extends survival of PDAC-bearing mice as monotherapy or in combination with the standard of care chemotherapy gemcitabine.

Strategic Goals

- Design and characterization of new cell penetrating peptides for cancer therapy.
- Pre-clinical validation of a new generation of Omomyc-based peptides as a therapeutic strategy in breast, brain, and lung cancer.
- Define the role of Myc inflammatory effectors in pancreatic tumorigenesis and tumor maintenance.
- Preclinical validation of Myc inhibition in breast cancer metastasis.

Highlights in 2015

- Peptomyc was awarded a "Seal of Excellence" for a SME Instrument Phase I by the European Commission within the *Horizon 2020* Program.
- We showed BTK inhibition as an effective strategy to reduce fibrosis in pancreatic cancer (Massó-Vallés et al., *Cancer Research* 2015).
- Laura Soucek was awarded a FERO fellowship for a nanotechnology project aiming at treating metastatic breast cancer with Omomyc-based nanoparticles.
- The Soucek laboratory was awarded a BBVA Foundation Grant in Biomedicine. Title: *Validation of an innovative anti-Myc therapy in glioblastoma*.

TUMOR BIOMARKERS GROUP

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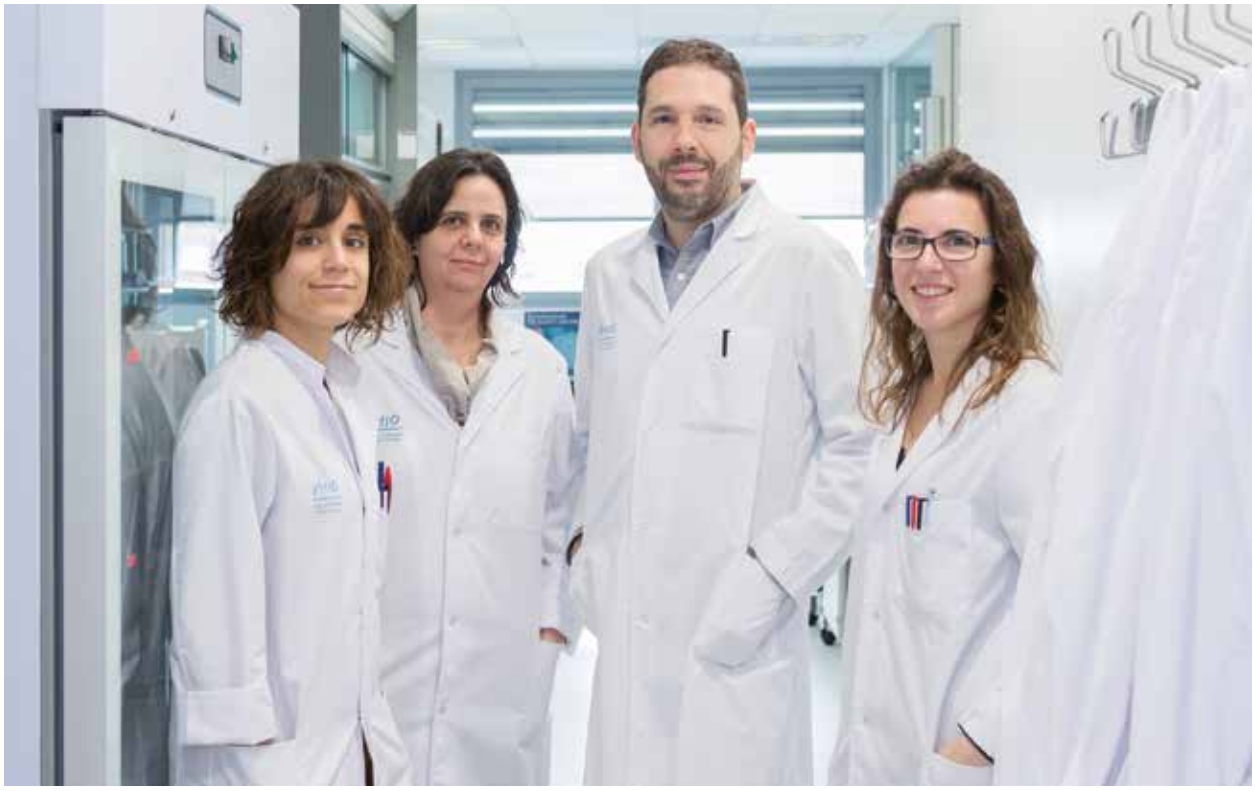

PI PAPER PICK

Méndez O, Villanueva J. Challenges and opportunities for cell line secretomes in cancer proteomics. *Proteomics Clin Appl*. 2015;9(3-4):348-357.

Zacarias Fluck M, Morancho B, Vicario R, Luque-García A, Ferrer-Ramón C, Escorihuela M, Villanueva J, Rubio I, Arribas J. Effect of cellular senescence on the growth of HER2-positive breast cancers. *J Natl Cancer Inst*. 2015;107(5).

Morancho B, Martínez-Barriocanal Á, Villanueva J, Arribas J. Role of ADAM17 in the non-cell autonomous effects of oncogene-induced senescence. *Breast Cancer Res*. 2015;17:106.

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SUMMARY

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

Our main aim is to characterize the mechanisms adopted by cancer cells to communicate amongst themselves as well as with their microenvironment during tumorigenesis, and exploit these findings to advance biomarker and drug target discovery. Our group's working hypothesis is that cellular signaling pathways undergo alteration during the tumorigenesis process and that such changes are translated into differential protein secretion, which can also potentially be exploited 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.

Proteomic technologies facilitate a genome-scale hunt for tumor-specific biomarkers and drug targets and could therefore revolutionize early detection and molecular characterization of cancer through non-invasive methods. The methodological focus of our group centers on quantitatively profiling the secreted sub-proteome ('secretome') of cells. One of the most striking observations when secretome profiles are carefully produced and analyzed is that they contain hundreds of theoretical intracellular proteins. Recent reports showing intracellular proteins with alternative extracellular functions, suggest that new protein functions associated with alternative subcellular localizations could be relevant in tumorigenesis. Our recent efforts in the context of therapeutics and tumor invasion have led us to hypothesize that the characterization of non-classical protein secretion could lead to novel therapies against cancer.

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

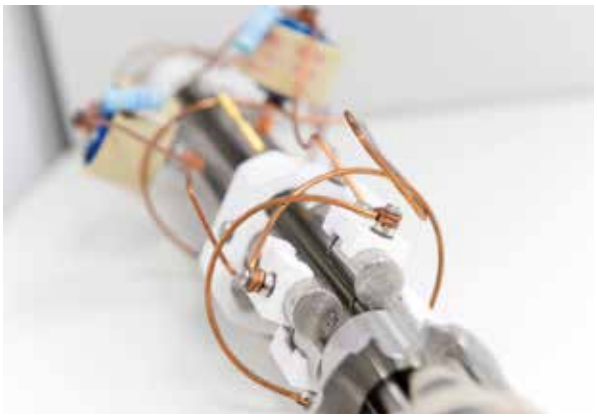

Figure: A collision cell of a QTOF mass spectrometer. The collision cell in the picture is the part of the mass spectrometer where secretome peptides are fragmented. The fragmentation spectra provides the key information to identify and quantify secreted proteins in the cancer secretome.

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.
- Discovery of secreted signaling pathway-based tumor biomarkers and therapeutic targets using quantitative proteomics.
- Characterize the influence of non-classical secretion during tumorigenesis, particularly in tumor invasion and metastasis.

Highlights in 2015

- In a recent review, Méndez O, Villanueva J. Challenges and opportunities for cell line secretomes in cancer proteomics. *Proteomics Clin Appl*. 2015, our group has presented an overview of the main technical and biological issues related to cell line secretome analysis, where we discussed both the challenges and opportunities for its use in tumor biomarker discovery.

VHIO'S MULTIDISCIPLINARY RESEARCH PROGRAMS

TRANSLATIONAL RESEARCH


Intratumor heterogeneity
Resistance

DIRECTOR TRANSLATIONAL RESEARCH PROGRAM

JOAN SEOANE

"At VHIO we aim to deliver on the promise of precision oncology by translating discovery into more effective treatments for patients as quickly as possible."

VHIO's Translational Research Program is dedicated to improving and accelerating the integration of preclinical and clinical research. We consequently strive to translate advances in molecular research into benefits at patient level as swiftly as possible by both tackling the disease from all angles and generating synergies between molecular and clinical cancer research.

One of the main challenges we face in our collective battle to conquer cancer is tumor diversity. Cancer is an extremely complex, heterogeneous, and fluctuating disease given that tumors are molecularly diverse and evolve over time. Moreover, tumors are formed by cells with multifarious states of proliferation, differentiation, motility, and, importantly, varying sensitivity to treatment. In short, each patient has a unique tumor with a particular combination of genomic aberrations that can change during tumor progression. Patients should therefore be treated with the optimal compound/combination of therapies to respond to the specificities of their respective disease. Since the selection of the most appropriate treatment depends on the specific molecular taxonomy of the tumor in a given time, the challenge is to identify which treatment should be linked to which patient and in so doing, further advance precision medicine in oncology.

In order to improve anti-cancer therapies through the combination of compounds targeting all cell types within a tumor, we must better understand 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), these cells 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 considered responsible for the initiation, recurrence and chemo- and radio-resistance of tumors indicating that more effective therapies will be identified via strategies aimed at targeting the stem-cell-like component of tumors. Few pharmacological compounds have yet been shown to successfully do so.

In order to explore the two levels of cancer heterogeneity, we investigate cancer as faithfully as possible to that of a 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 to generate mouse models reproducing 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 findings published in top-tier journals.

Providing optimal treatment tailored to individual patients relies on team work, studying cancer as closely as possible to the real patient, and tackling cancer heterogeneity head-on. VHIO's Translational Research Program is committed to delivering on this promise by catalyzing the transfer of new insight generated by scientific research into the true benefit for patients.

GENE EXPRESSION & CANCER GROUP

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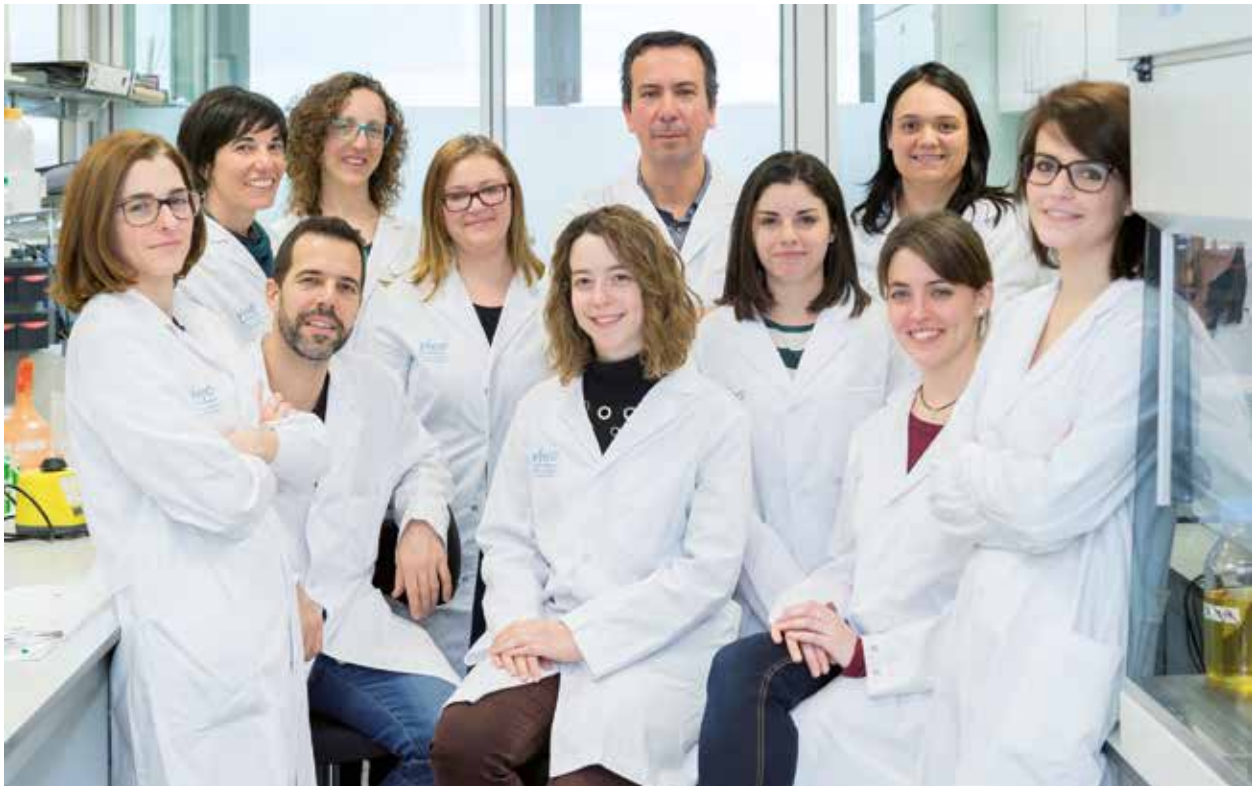

PI PAPER PICK

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For VHIO's full listing of articles published by VHIO Investigators in 2015 see pages 87-98.

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.

One of the most important challenges in cancer is the heterogeneity of tumors, which we are studying at both the level of genomic alterations and that of cell differentiation state.

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

Besides the genomic intratumor diversity, cells within tumors although having the same genomic alterations might present differences in the epigenomic state. In particular, we are analyzing a subpopulation of undifferentiated cells responsible for tumor initiation and relapse. These cells have stem cell-like characteristics and are known as cancer-initiating cells (CICs) or cancer stem cells. CICs are considered to be responsible for the initiation, recurrence and chemo- and radio-resistance of tumors and therefore represent crucial therapeutic targets. Advancing our understanding of the molecular mechanisms involved in these cells is consequently paramount. We aim to identify novel markers for CICs, obtain new insights into the signaling pathways and molecular mechanisms involved in CICs, and design novel therapeutic approaches to target them.

Finally, due to genomic intratumor heterogeneity, we are interested in developing non-invasive methods to assess the genomic alterations present in 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, non-invasive molecular characterization of tumors. These circulating markers facilitate the diagnosis, monitoring and identification of actionable gene mutations of tumors.

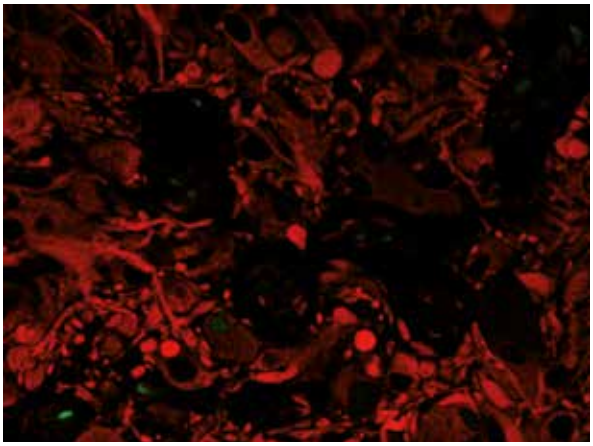

Figure: Intratumor heterogeneity in glioblastoma.

Strategic Goals

- Identify both new therapeutic targets against brain tumors as well as novel biomarkers to predict response to therapy.
- Study intratumor heterogeneity.
- Achieve a better understanding of the molecular mechanisms implicated in cancer initiating cells/ cancer stem cells.
- Develop methods for non-invasive molecular diagnosis through the study of circulating biomarkers.
- Generate patient-derived mouse models of brain tumors.

Highlights in 2015

- Our efforts have led to several publications in 2015 (for all our group's publications please visit the 2015 VHIO Scientific Report online at: http://memorias.vhio.net/2015/).
  Specifically, we would like to highlight the publication De Mattos Arruda *et al. Nature Communications* 2015. Liquid biopsy in plasma has already proven useful across several tumor types but not, until now, in brain tumors. Our group has discovered cerebrospinal fluid to be highly enriched in circulating tumor DNA -- enabling the characterization of brain tumors. Cerebrospinal fluid flows through the brain parenchyma and the spinal cord and can be sampled via lumbar puncture. Cerebrospinal fluid liquid biopsy is a less invasive approach promising a novel, pioneering line of research into biomarkers that will both enable the crucial tracking of disease as well as ultimately help to evaluate and monitor drug efficacy as the cancer progresses (see Figure).
- Joan Seoane received the prestigious *Doctores Diz-Pintado* National Prize.

STEM CELLS & CANCER GROUP

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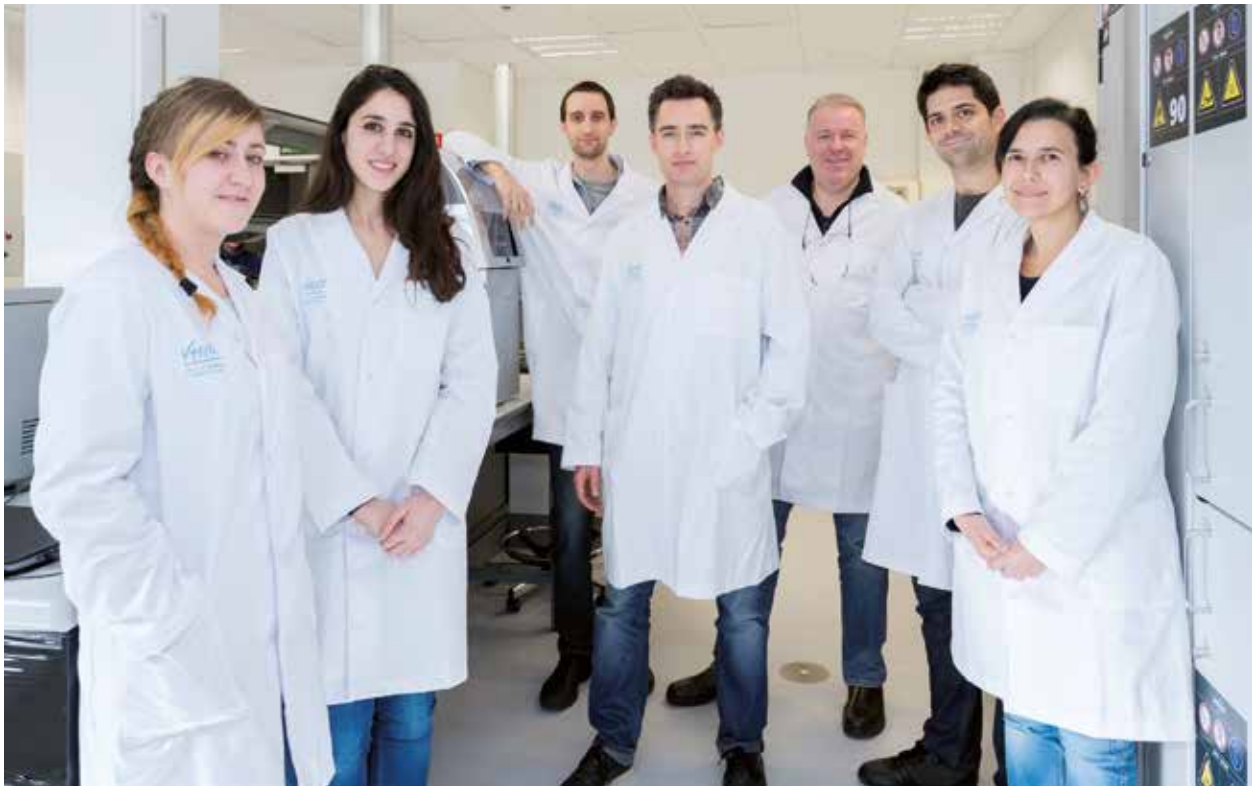

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SUMMARY

Our main interest is to better understand the molecular mechanisms that confer tumors the ability to self-renew, resist therapy, relapse and metastasize – all definitive factors in the survival of patients.

We are dedicated to studying the consequences of intra-tumoral cell heterogeneity for tumor evolution and patient survival. Among the different cell populations that build an heterogeneous tumor, 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 are responsible for relapse after chemotherapy-induced remission, or give rise to distant metastasis. It is therefore becoming evident that therapies failing to eliminate cancer stem cells may allow re-growth of the tumor.

Colorectal cancer is our prime focus of study. At molecular level, we are analyzing the role of those oncogenic pathways that control 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 trials are not responding to these drugs and no molecular explanation behind resistance had previously been evidenced. These 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 inhibitory drugs in close collaboration with several major pharmaceutical companies and have already produced experimental evidence on 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 in the field – for decades colorectal cancer was described as a paradigmatic tumor addicted to the oncogenic Wnt/beta-catenin pathway. We also work on identifying the molecular determinants of response to these drugs that could become robust biomarkers to select 'sensitive' patients and 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 Medical Oncology Service at the Vall d'Hebron University Hospital and pharmaceutical companies will accelerate the translation of our findings into clinical practice and hopefully revert the long-stalled scenario of CRC therapies.

Our group has developed a collection of patient-derived xenograft (PDX) models from more than 100 CRC patients. They are derived from primary tumors or liver metastasis. More recently we have also generated around 30 clinical trial associated xenografts (CTAX) from patients enrolled in clinical studies. All these models faithfully recapitulate original patient tumors and, most importantly, their response to treatments, becoming the gold standard for studying mechanisms of drug-resistance or sensitivity.

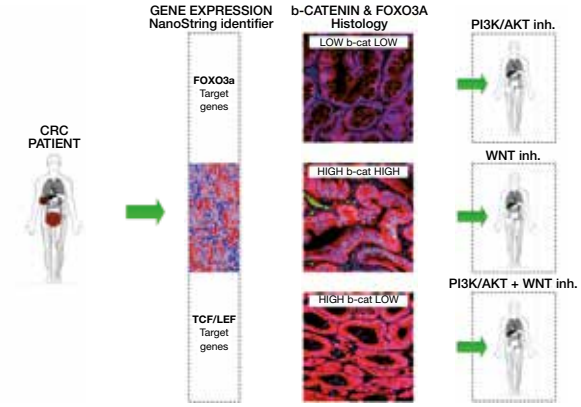

Figure: Molecular pre-screening and selection of colorectal cancer patients to be included in clinical trials with target-directed drugs.

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 PDX models derived from other tumor types such as lung cancer.

Highlights in 2015

- We have revealed the molecular mechanisms governing the delicate link between stemness and quiescence in chemoresistant 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 eliminate 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 on the efficacy and mechanisms of action of a new generation of Wnt/beta-catenin inhibitory drugs on CRC and identified biomarkers to predict response to these inhibitors.

VHIO'S MULTIDISCIPLINARY RESEARCH PROGRAMS

CLINICAL RESEARCH


VHIO

DIRECTOR CLINICAL RESEARCH PROGRAM

JOSEP TABERNERO

"Our Program, incorporating multidisciplinary cancer teams, develops novel agents and approaches to diagnose cancer earlier and better predict response to therapy. Pioneering studies involving both preclinical and early-drug development discovery, we also lead several clinical trials 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 more precisely predict response to anti-cancer therapies.

Throughout 2015 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 have been using our in-house BEAMing digital PCR/flow cytometry technology to evaluate patients with metastatic colorectal cancer. We have already reported promising findings from a large, multi-center phase III trial – the CORRECT study. These results, published in *The Lancet Oncology*, are illustrative of a body of compelling research positioning liquid biopsy as the future of cancer detection and an essential tool in clinical practice. Importantly, as this Scientific Report goes to print, this RAS biomarker test has just received European Conformity approval (CE Mark), which makes it available and accessible for patients in Europe, Asia, and Australia.

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. This year, out of VHIO Thoracic Tumors Group's impressive trio of 2015 *New England Journal of Medicine* papers, in collaboration with our Early Clinical Drug Development Group, two indicated new hope for lung cancer patients based on novel immunological strategies. As we are starting 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. I can predict that our Program, in collaboration with other VHIO groups and colleagues from other leading cancer research centers across Europe and beyond, will continue to both evidence and advance the use of novel immune agents either as mono therapy or in combination, across an increasing number of cancer types.

Joining our important portfolio of clinical trials, we are now leading and implementing a number of new Basket trials. One such study, actually the very first of them, was a broad phase II trial that evidenced the potential of a BRAF inhibitor, already effective in the treatment of melanoma, as anti-cancer therapy for other malignancies. This discovery, co-led by Memorial Sloan Kettering Cancer Center (MSKCC) and VHIO, was published in *NEJM* in 2015.

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 VHIO's Cancer Genomics Group. Driving our efforts aimed at integrating clinical translational research with genomics for precision cancer therapy, VHIO's recently incorporated Oncology Data Science (ODysSey), has made important progress in the datamining, molecular profiling and sub-typing of different cancers. Research in 2015 contributed to both establishing and achieving consensus on newly defined molecular subtypes of colorectal cancer, as published in *Nature Medicine*.

It is thanks to the excellence and expertise of all 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 many other top-tier journals including: *Nature*, *The Lancet Oncology*, *Cancer Cell*, *Cancer Discovery*, and the *Journal of Clinical Oncology* (pages 87-98 for the full listing of articles published by VHIO investigators in 2015).

Just as VHIO continues to significantly advance cancer discovery and therapeutics to ultimately benefit an increasing number of patients, it must continue to progress in partnership, across borders. In addition to our continued participation in existing consortia of excellence, I am pleased to announce the launch of the MoTriColor consortium, led by VHIO, as well the MedBioinformatics project -- both of which are backed by Horizon 2020 funding (see page 101).

Lastly but by no means least, I believe in forging closer collaborations with other specialties and key partners in oncology including pharmaceutical companies and policymakers. Only then will we collectively better serve the most deserved stakeholders of all -- our patients.

BREAST CANCER & MELANOMA GROUP

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PI PAPER PICK

Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, Ciruelos E, Ferrero JM, Schneeweiss A, Heeson S, Clark E, Ross G, Benyunes MC, Cortés J; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724-734.

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SUMMARY

Our Breast Cancer (BC) Program is one of the most active and renowned across Europe. In 2015, 32 publications totaled at an impact factor of 383,45. Our group is not only committed to participating in clinical and preclinical studies, but also leads several reflected by our representation on many Steering Committees.

In clinical research, our key areas of interest include:

HER-positive disease: we are particularly proud to have led the most important trials with pertuzumab, reporting the best results ever seen in survival in the history of BC. (See figure).

We are leading the only two studies that combine TDM-1 with different chemotherapies (CT), the phase III NALA trial, and attracted promising molecules including MM-302 and margetuximab. In collaboration with VHIO's Growth Factors Group, led by Joaquín Arribas, we are exploring different mechanisms of resistance to these therapies.

Optimize CT-based strategies: we strongly believe that overcoming mechanisms of resistance to CT will enhance their efficacy. In 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. Our leadership in TNBC overcomes treatment with chemotherapy through a broad program focused on the evaluation of immunotherapy and PARP inhibitors in patients with *BRCA1/2* mutations.

Reversing mechanisms of resistance to endocrine therapy: 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.

In collaboration with VHIO's Cancer Genomics Group, led by Ana Vivancos, we are analysing tumour tissue and cfDNA. We explore genes that mediate BC metastasis to leptomeninges to better characterise alterations that have emerged over time in the development of metastatic BC. Working with VHIO's Early Drug Development Group headed by Jordi Rodón, we are witnessing promising preliminary results using certain compounds, which we will be looking to develop against breast cancer.

Our emerging Melanoma Group led by Eva Muñoz has made significant progress throughout 2015: the number of patients treated in our clinical trials has doubled and a translational research group has been set up to further promote multidisciplinarity and collaboration by closely connecting basic, translational, and clinical investigators. This collaboration has already resulted in publications in prestigious journals including *Nature Genetics* and *Nature Medicine*.

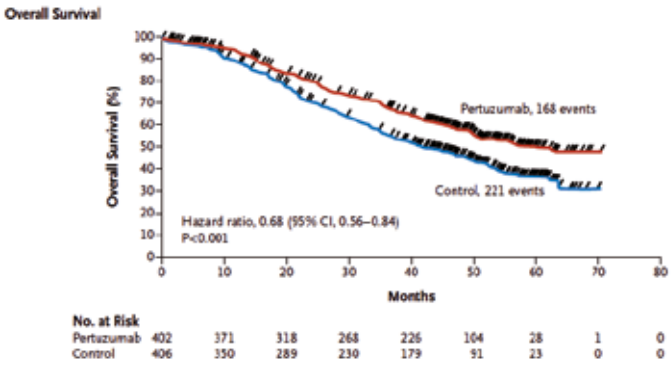

Figure: Kaplan–Meier estimates of overall survival in the intention-to-treat population: the median overall survival among patients receiving pertuzumab, trastuzumab, and docetaxel(pertuzumab group) was 56.5 months, 15.7 months longer than survival among patients receiving placebo, trastuzumab, and docetaxel (control group).

Strategic Goals

- Optimize treatment options focusing on new targeted agents which overcome resistance to therapy.
- Application of precision medicine through the detection of alterations found in tumor samples and cfDNA.
- Continue to lead early clinical trials and collaborate closely with VHIO's preclinical groups -- thus transitioning to smarter studies based on sound knowledge obtained from preclinical research.
- Maintain our leadership in melanoma as a reference for treatment, providing more appealing combinations of currently available therapies. We will also expand our activities as an emerging research group.

Highlights in 2015

- We published practice-changing data in the field of adjuvant and metastatic breast cancer.
- We have been involved in Steering Committees of the most relevant trials and thanks to collaboration with clinical departments at the Vall d'Hebron University Hospital, we have established ourselves as one of the most active groups in neoadjuvant studies worldwide.
- Expansion of our collection of patient-derived xenografts that distinguishes us as one of the most important institutes at European level, coupled with our ambitious cfDNA program for genotyping breast cancer.

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PI PAPER PICK

Rodon J, Carducci MA, Sepulveda-Sánchez JM, Azaro A, Calvo E, Seoane J, Braña I, Sicart E, Gueorguieva I, Cleverly AL, Pillay NS, Desaiah D, Estrem ST, Paz-Ares L, Holdhoff M, Blakeley J, Lahn MM, Baselga J. First-in-human dose study of the novel transforming growth factor-β receptor I kinase inhibitor LY2157299 monohydrate in patients with advanced cancer and glioma. *Clin Cancer Res*. 2015;21(3):553-560.

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SUMMARY

Our main interest surrounds proof-of-concept and proof-of-mechanism trials with targeted therapies, especially those aimed at 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 try to link clinical research at the UITM with the different areas of research carried out at VHIO, following a truly translational model: linking molecular biology and the best tumor models with pharmacology and innovative clinical research. We are therefore dedicated to 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 best possible 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 the WIN (Worldwide Innovative Networking in personalized cancer medicine) and the Cancer Core Europe Consortia. Both are non-governmental organizations that bring together international (WIN) and/or European (CCE) cancer centers including VHIO to advance cancer diagnostics and therapeutics, especially in the area of precision medicine.

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.

Strategic Goals

- Early development of the best-in-class targeted therapies by experienced multidisciplinary teams incorporating physician-researchers from the Research Unit for Molecular Therapy of Cancer (UITM) "la Caixa" and VHIO scientists.
- Accelerate early drug development and translational research through the management and treatment of patients in Phase I trials.
- Genomic trials in early drug development; analyzing patients' tumors for molecular aberrations that may predict the efficacy of targeted agents. Connect preclinical science and clinical research by incorporating novel drugs, new insights and study designs together with molecular diagnostics.
- UITM Task Force in early drug development of immunotherapeutics and cell signaling (with special focus on cytokines, immunomodulatory agents and immune checkpoint inhibitors) and translational research in immuno-oncology.
- Collaborate with different partners in drug development and translational research (phase I units, academic centers, consortia, pharmaceutical companies).

Highlights in 2015

- As a leading institute worldwide in drug development (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 performed many clinical trials with novel-novel combinations such as combination of targeted therapies (novel/novel), or, in the area of immunoncology, combining checkpoint inhibitors with either chemo, radiation (abscopal effect), targeted therapies or other immunomodulatory agents (TGFbeta, LAG3, anti VEGFR2, CD40).
- We have performed many 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 have performed 22 Basket studies. These 'Baskets' are a novel type of clinical trial design enabling analysis of the antitumor effect of a given therapy in many small patient populations. We have now designed our *Basket of Baskets* project to launch in 2017.
- Co-development of molecular tests for patient screening (disease-oriented mutation panels for NGS platforms and Nanostring nCounter).

GASTROINTESTINAL & ENDOCRINE TUMORS GROUP

Principal Investigator
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Medical Oncologists and Clinical Fellows
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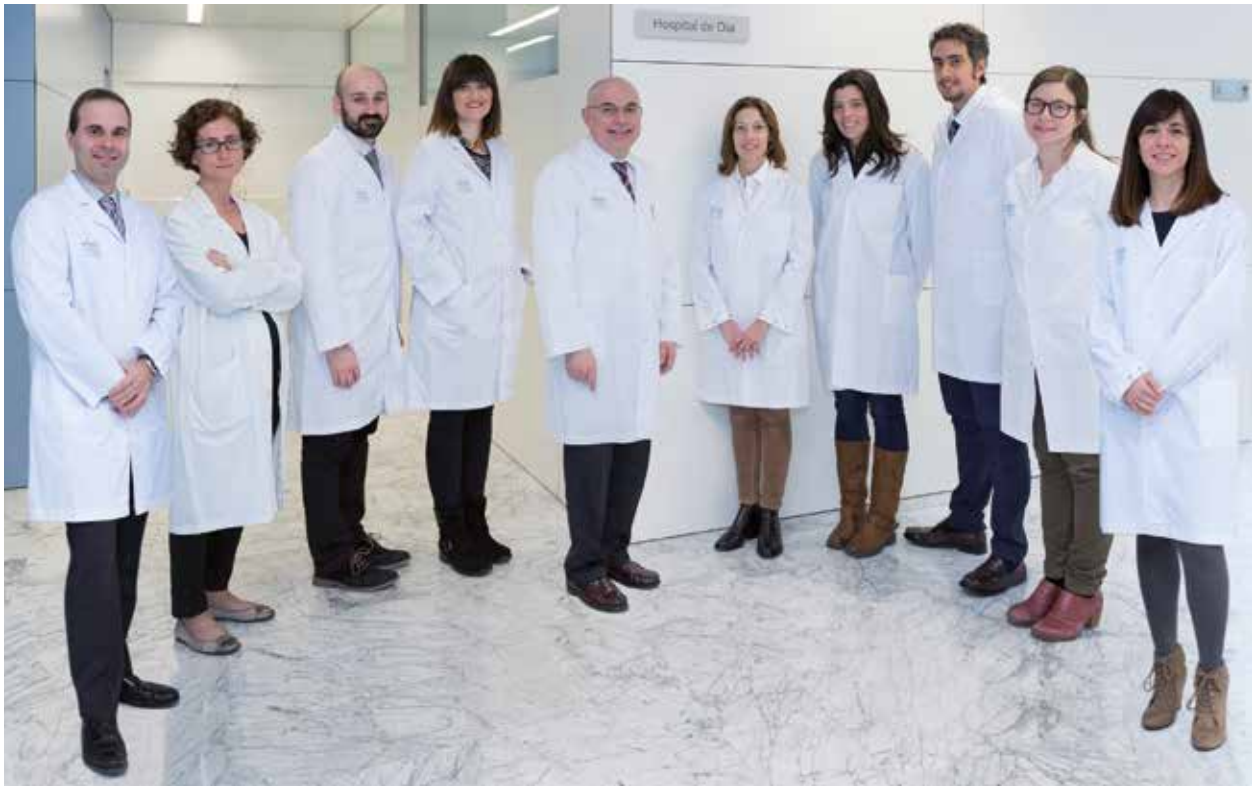
Guillem Argilés
Jaume Capdevila
María Elena Élez
Julieta Grasselli
Teresa Macarulla
Ignacio Matos
Tamara Saurí
Helena Verdaguer

Clinical Nurse Specialist
Ariadna García



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Tabernero J; Yoshino T; Cohn AL; Obermannova R; Bodoky G; Garcia-Carbonero R; Ciuleanu TE; Portnoy DC; Van Cutsem E; Grothey A; Prausová J; Garcia-Alfonso P; Yamazaki K; Clingan PR; Lonardi S; Kim TW; Simms L; Chang SC; Nasroulah F. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol*. 2015;16(5):499-508.

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SUMMARY

In 2015, 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 FP-7 supported COLTHERES, EurocanPlatform, and MerCuRIC Consortia (please see page 101 of this report), I am delighted to announce that 2015 celebrated the launch of the MoTricolor Consortium. Spurred by EU's Horizon 2020 program, and led by VHIO, this pan-European project will design and lead Molecularly guided Trials with specific treatment strategies in patients with advanced newly molecular defined subtypes of Colorectal cancer, and for the first time, stratify patients based on their gene expression profiles according to recently established predictive signatures. We will collectively aim to identify sensitivity of individual patients to the proposed experimental therapies towards ultimately developing more precise anti-cancer therapies.

Reflected by publications in the most prestigious scientific titles in 2015, our group has also led and collaborated in studies with important clinical implications, just some of which include:

- *Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer*. Mayer RJ et al. 2015. *N Engl J Med*. 372: 1909-1919. This international Phase III study evidenced that TAS-102, an oral antitumor agent combining a duo of drugs (trifluridine & tipiracil hydrochloride), improved overall survival by two months for patients with treatment-resistant metastatic CRC.
- *Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations*. Hyman DM. et al. 2015. *N Engl J Med*. 373: 726-736. This phase II basket trial co-designed and led by our group, enrolled patients who had different types of cancer with the BRAFV600 mutation, and showed the efficacy of vemurafenib as therapy against multiple tumor types that share this mutation.
- *Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study*.Tabernero J et al. 2015. *Lancet Oncol*.16: 499-508. The large RAISE multi-center international trial reported significant improvement in the global survival of patients with metastatic CRC who were treated with a combination of ramucirumab and chemotherapy as second-line treatment.
- *Abituzumab combined with cetuximab plus irinotecan versus cetuximab plus irinotecan alone for patients with KRAS wildtype metastatic colorectal cancer: the randomised phase I/II POSEIDON trial*. Elez E et al. 2015. *Ann Oncol*. 26:132-40. This early phase trial assessed the tolerability and efficacy of abituzumab in combination with cetuximab and irinotecan in patients with metastatic CRC. Predefined exploratory biomarker analyses identified subgroups of patients for whom abituzumab may have benefit.

We continue to develop next generation blood-based diagnostics to monitor disease, its respective molecular specificities, and response to novel targeted therapies. Findings from the first large clinical trial to compare liquid versus conventional tissue biopsy data, the CORRECT phase III study, showed that BEAMing technology produced more data on tumor mutation throughout the course of the disease (Tabernero J. et al. 2015. *Lancet Oncol*. 16: 937-948).

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.

Strategic Goals

- Discovery of novel biomarkers in gastrointestinal tumorigenesis.
- Validation of new prognostic biomarkers.
- 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 (Proteomics, Tumor Biomarkers, Cancer Genomics, Translational Genomics, and Stem Cells & Cancer Groups).

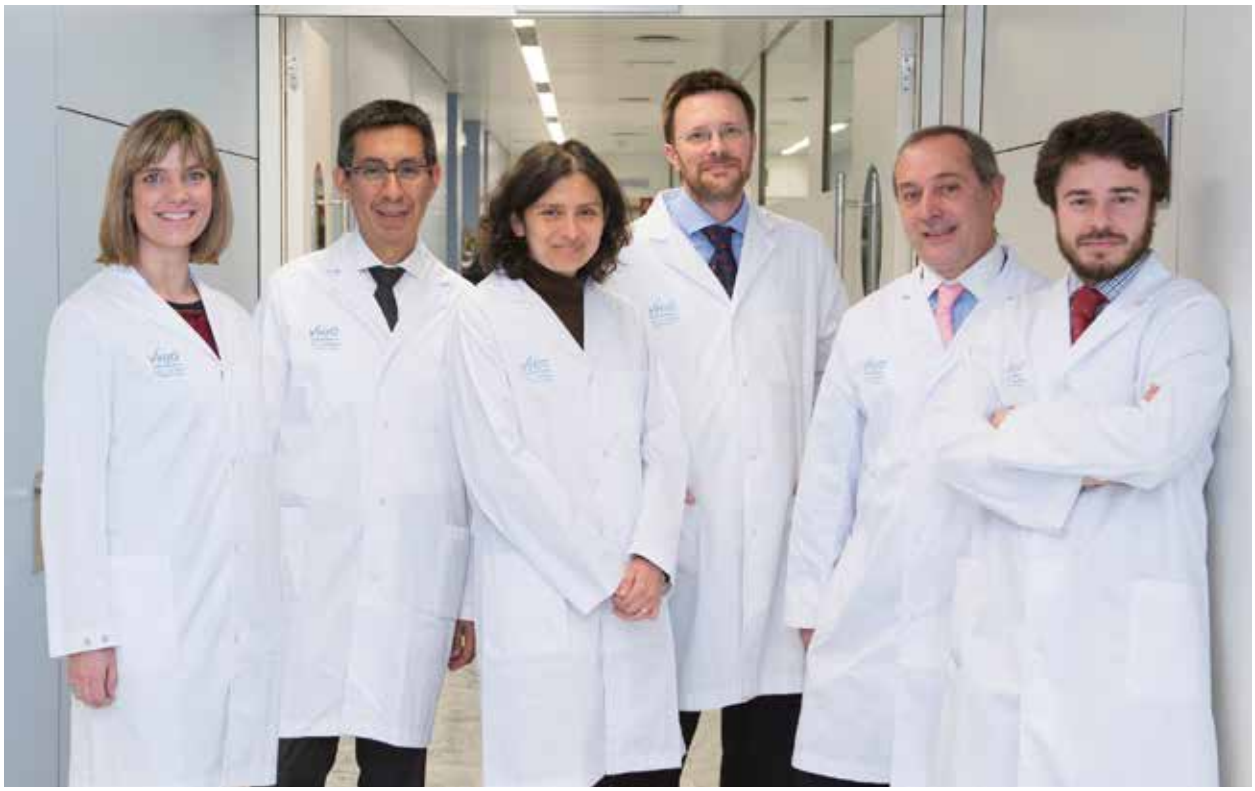
Highlights in 2015

- 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.
- Co-designed and led by our group and colleagues at the Memorial Sloan Kettering Cancer Center (MSKCC, New York), a phase II novel basket trial evidenced the efficacy of vemurafenib as therapy against multiple tumor types that share the BRAFV600 mutation, Hyman DM et al. 2015. *N Engl J Med*. 373:726-736.
- Studies evidencing improved treatment efficacy against metastatic colorectal cancer led to important publications incl. Mayer RJ et al. 2015 *N Engl J Med*. 372: 1909-1919 and, Tabernero J et al. 2015. *Lancet Oncol*. 16: 937-948.
- Led by VHIO, the Horizon 2020-funded MoTricolor Consortium will design and conduct multi-center early phase trials to identify anti-tumor activity of novel therapies against CRCm.

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 Suárez
Claudia Valverde



PI PAPER PICK

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SUMMARY

Our group is interested in both clinical and translational research with 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; particularly in prostate, bladder and kidney cancer. Immunotherapy is proving increasingly important in the treatment of bladder and kidney cancer. We have been able to participate in different clinical trials using checkpoint inhibitors. Close collaboration with all specialists involved in the treatment of these tumors is consequently essential. We are also focused on the continued development of our translational research platform for urologic cancer, as well as conducting clinical trials in early, adjuvant as well as metastatic disease.

Our group collaborates with other research centers of excellence including the Cleveland Clinic (USA), University of California San Francisco (USA), Gustave Roussy Hospital (France), and the Biomedical Research Institute of Bellvitge (IDIBELL), here in 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 collaboration with professionals in neurosurgery and radiation therapy. We are also dedicated 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 we are now initiating the phase I program. This project is supported by the European Commission's 7th Framework Programme of Research and Development.

Our group works 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 work in partnership with J. Fletcher's lab at Brigham and Women's Hospital (USA).

Cesar Serrano joined our group as VHIO researcher in 2014 having spent the previous three years at 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. We are currently developing novel strategies in GIST therapy in close collaboration 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 2015 we welcomed five fellows from in and out Spain to visit our group for short stays of three months.

Strategic Goals

- Design and develop clinical trials for the malignancies covered by our group. We provide patients with the most novel and optimal treatments for their respective diesease, including immunotherapeutics, targeted therapies, and new chemotherapeutics.
- Conduct clinical trials at different stages of disease with emphasis on a histology-tailored design and a multidisciplinary approach.
- Develop new 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.

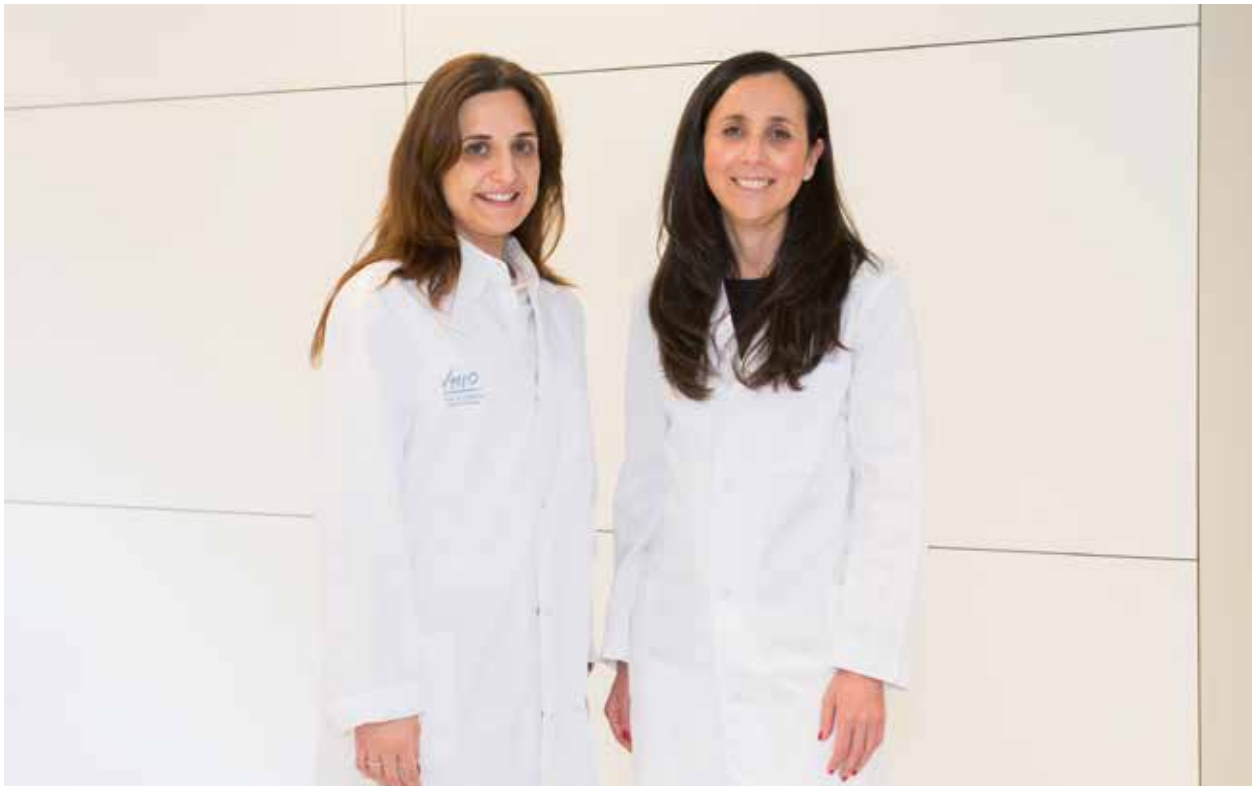
Highlights in 2015

- 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.
- 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). 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.

GYNECOLOGICAL MALIGNANCIES GROUP

Principal Investigator
Ana Oaknin

Medical Oncologist and Clinical Fellow
Lorena Fariñas



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Amit M Oza, David Cibula, Ana Oaknin, Christopher Poole, Ron H J Mathijssen, Gabe S Sonke, Nicoletta Colombo, Jiří Špaček, Peter Vuylsteke, Holger Hirte, Sven Mahner, Marie Plante, Barbara Schmalfeldt, Helen Mackay, Jacqui Rowbottom, Elizabeth S Lowe, Brian Dougherty, J Carl Barrett, Michael Friedlander. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. *Lancet Oncol*. 2015;16(1):87-97.

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SUMMARY

Our group mainly focuses on clinical research in gynecological malignancies. We are majorly involved in the development of new therapies in the treatment of gynecologic tumors. Notably, our clinical research work has led to approval of new standard of care in both resistant relapsed ovarian cancer (e.g. AURELIA Trial) and in metastatic cervical cancer (e.g. GOG240 trial).

Our clinical research is largely developed through our close collaboration 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) serving 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 PI, Ana Oaknin serves on the Executive Board as Vice President for the *Grupo Español de Investigación en Cáncer de Ovario* (Spanish Gynecological Group - GEICO). Such involvement allows 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 research efforts.

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

We are currently leading clinical studies with novel PARP inhibitors for both patients with ovarian cancer associated to the BRCA mutation as well as a well-defined group of patients with high grade ovarian carcinoma. These new drugs have the potential to change the course of history in the treatment of ovarian cancer since they act at specific molecular points in DNA repair pathways. Our group also has a keen interest in immunotherapy and angiogenesis.

In parallel with our clinical research, we play a central and key role as members of multidisciplinary committees and teams in Gynecological Cancer Tumors at the Vall d'Hebron University Hospital (HUVH). Our involvement, in close connectivity and collaboration with other professionals and specialties (including surgeons, radiotherapists, radiologists and pathologists), contributes to establishing new treatment protocols and clinical guidelines to further advance clinical practice within our Hospital.

We are continuously invited to participate at international conferences of excellence through the delivery of presentations, invited lectures, and the sharing and debating of key findings with colleagues and peers across the globe.

Strategic Goals

- We are focused on clinical research in gynecological cancer in order to improve outcomes for our patients. Our goal is to play an active part in the development of new drugs from the early beginning, from Phase I clinical trials, and later, through to Phase II and III trials. We are determined that as many of our patients as possible may stand to benefit from the best available treatments, at the earliest stages.
- In order to advance research at clinical level, we are dedicated to fostering and developing close collaboration with VHIO colleagues at preclinical level in order to translate insights into the molecular basis of gynecological cancers into benefits for patients, as swiftly as possible.

Highlights in 2015

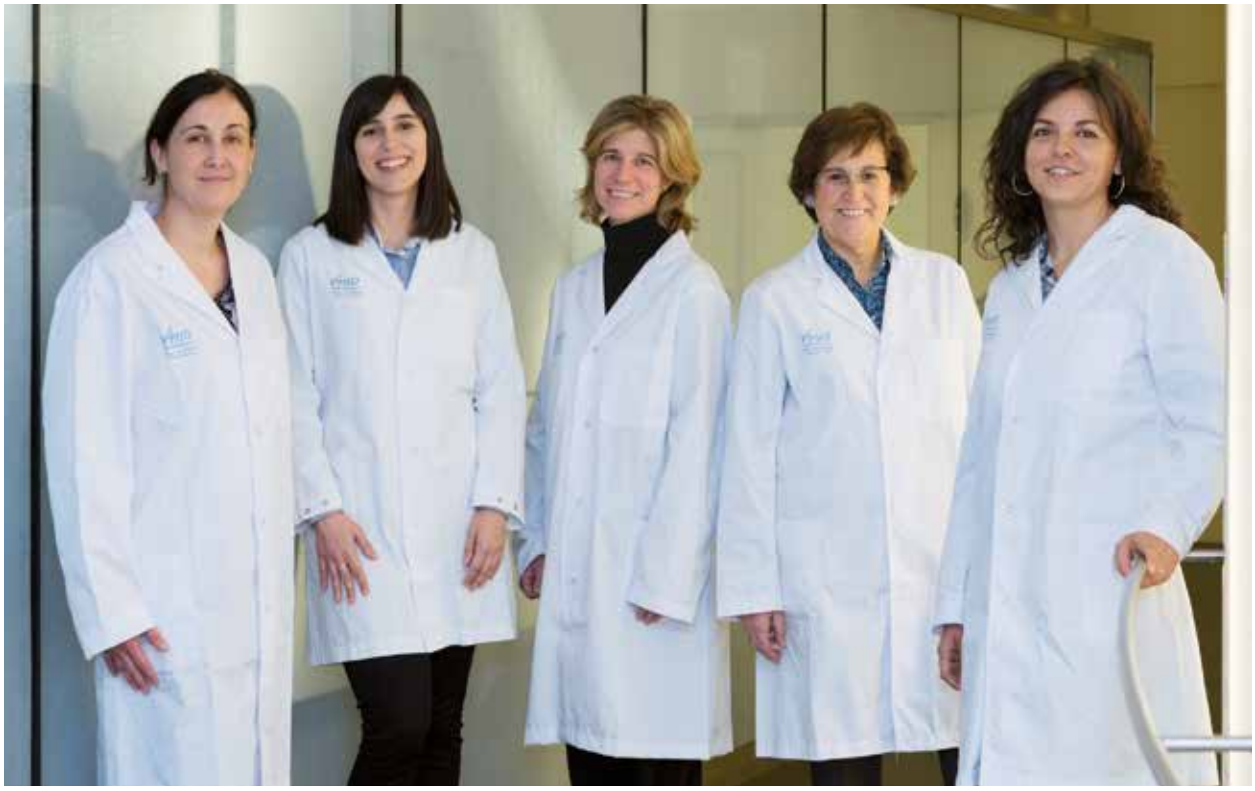
- As a result of our outstanding clinical research, our group has (co) authored pivotal studies in both cervical and ovarian cancer which have subsequently changed the standard of care of these malignancies.
- As lead investigator for GOG in Spain, we have been able to participate in some of the most interesting and practice changing studies in gynecological tumors.
- Our participation in the GCIG Cervical Cancer Committee to develop novel anti-cancer therapies.
- Ana Oaknin's Vice Presidency of the GEICO group. This role has allowed our group to help lead clinical research into gynecological malignancies throughout Spain.

HIGH RISK & CANCER PREVENTION GROUP

Principal Investigator
Judith Balmaña

Staff Scientists
Estela Carrasco
Cristina Cruz
Irene Esteban

Clinical Nurse Specialist
Neus Gadea



PI PAPER PICK

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SUMMARY

We are committed to developing new targeted therapies for patients with hereditary breast cancer. During 2015, 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 other VHIO groups led by Violeta Serra, Ana Vivancos, and Orland Díez, 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 test new combinatorial treatments at progression.

In the field of genetic epidemiology we are mainly focused on identifying new genetic susceptibilities to hereditary breast cancer. We are collaborating with VHIO's Oncogenetics Group headed by Orland Díez on next generation sequencing studies with a panel of 98 cancer susceptibility genes in breast cancer families with no mutation in *BRCA1/BRCA2*. Analysis of the first 120 families has provided 9 genetic results with clinical utility. We are committed to performing cosegregation 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 study to identify mutations in *POLD1* and *POLE* in families with polyposis, or young-onset colorectal cancer with microsatellite stability; and we are participating in a national registry led by the EPICOLON group to describe the characteristics of extracolonic tumors in Lynch syndrome mutation carriers.

Our group continues to actively participate in the international multi-center IMPACT study to analyze the efficacy of early detection of prostate cancer in patients with a mutation in the *BRCA1/2* genes, as well as an additional study aimed at the characterization of prostate cancer in BRCA and MMR-deficient mutation carriers.

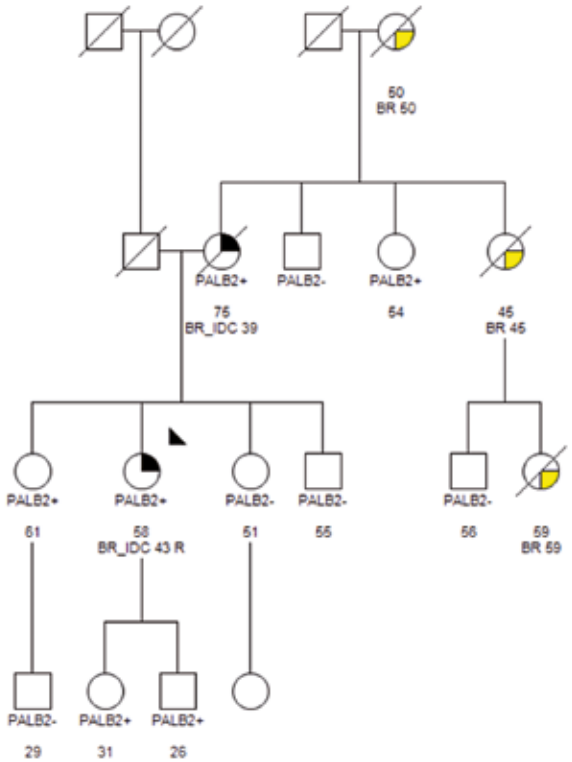

Figure: Segregation analysis of a new mutation identified in the PALB2 gene.

Strategic Goals

- Clinical development of specific therapeutic strategies for tumors associated with hereditary genetic alterations.
- Identification of mechanisms of resistance to targeted therapies in BRCA-associated breast cancer.
- Testing new combination of therapies for BRCA-associated PDX's 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 in 2015

- Active participation in international Phase II and Phase III clinical trials with targeted therapies for *BRCA*-associated tumors.
- Establishing a large collection of BRCA-associated patient-derived xenografts implanted in athymic mice.
- Preliminary analysis -- prevalence and clinical utility, of multiplex panel testing in hereditary breast cancer patients without mutations in *BRCA1* or *BRCA2*.

ONCOGENETICS GROUP

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Manuel Altabas

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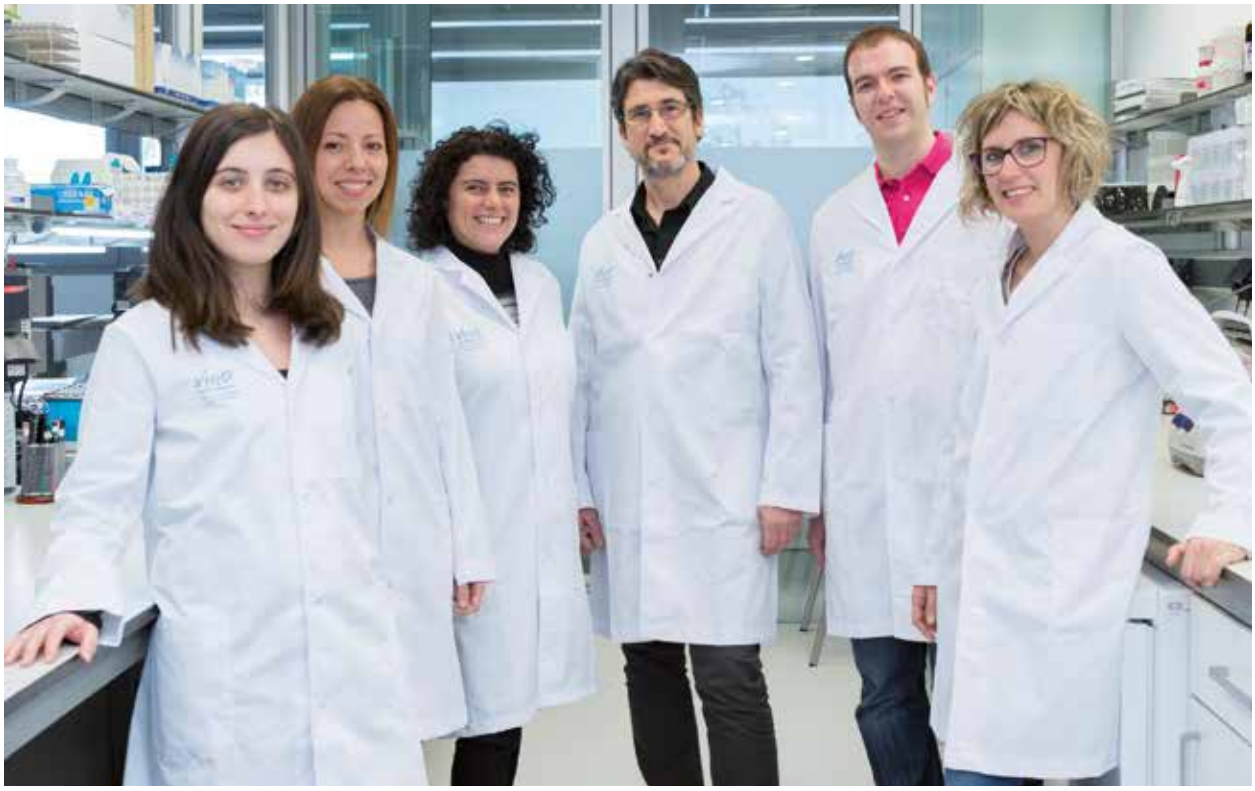

PI PAPER PICK

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SUMMARY

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

Inherited predisposition to breast and ovarian cancer is caused mainly by *BRCA1, BRCA2, PALB2, RAD51C, TP53,* as well as some other genes. We search for other alleles that may predispose to these types of cancer using massive sequencing technologies to study panels of potentially predisposing genes. Moreover, we analyze whole exomes to discover new genes that could explain the presence of multiple cancers in families and individual patients.

BRCA1/2 genes have an extraordinary high allelic heterogeneity and many results of genetic testing are variants with unknown clinical significance (VUS). The analysis of these variants and other alterations in untranslated regions in both genes constitutes another area of intensive study. We carry out splicing studies, *in silico* analyses, and collaborate with other partners in international consortia (ENIGMA) to develop multifactorial studies aimed at ascertaining the effect of VUS. We are also working to establish a biological model 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 are actively participating in the development of a novel *in silico* tool to evaluate the effect of *BRCA1/2* genetic variants identified in patients with cancer predisposition.

During 2015, we initiated a project (PI: Cristina Cruz) in collaboration with VHIO's High Risk & Cancer Prevention and Experimental Therapeutics Groups, headed 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 at some point during the course of their treatment and between 3-5% of these patients suffer from severe long-term side-effects. Current evidence suggests the heritability of radiosensitivity, triggering growing interest in identifying the genetic variants associated with increased sensitivity to radiation. To identify those patients who will develop toxicity, we are investigating potential genetic and cellular markers for radiotherapy toxicity (allelic variants, cell apoptosis, and transcriptional profiles). In collaboration with the International Consortium of Radiogenomics we have participated in a meta-analysis showing an association between the *ATM* rs1801516 SNP and toxicity post-radiotherapy.

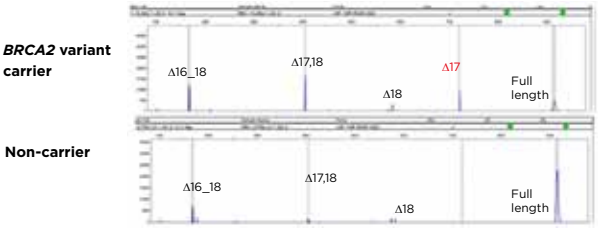

Figure: Semi-quantitative assays of *BRCA1* and *BRCA2* transcripts amplified with fluorescence labelled primers.

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 that modify breast/ovarian cancer risk for *BRCA1* and *BRCA2* mutation carriers.
- Study of apoptosis assay and genetic markers as predictive tests for late toxicity after radiotherapy.
- Assess the role of microRNAs and long non coding RNAs in the susceptibility to radiotherapy-induced clinical toxicity.

Highlights in 2015

- Exome sequence analysis of breast cancer families negative for *BRCA1/2* to unmask new potential predisposing genes, and involvement in the COMPLEXO Consortium to identify the missing heritability of breast cancer via exorne studies.
- Our group has analyzed an extensive panel of cancer genes by massive sequencing, and revealed new predisposing alleles in affected families.
- Participation in a multicenter study to determine the association of variants in the *FANCM* gene to breast cancer predisposition.
- In partnership with the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA), we have described new susceptibility genes of ovarian cancer and modifier alleles for *BRCA1/BRCA2* mutation carriers.
- Our confirmation that severe, late side effects induced by breast cancer radiotherapy are associated with low levels of irradiation-induced apoptosis.
- The enrolment of breast cancer patients in the European Commission FP7-funded project REQUITE to validate predictive models of toxicity from radiotherapy.

ONCOLOGY DATA SCIENCE (ODysSey) GROUP

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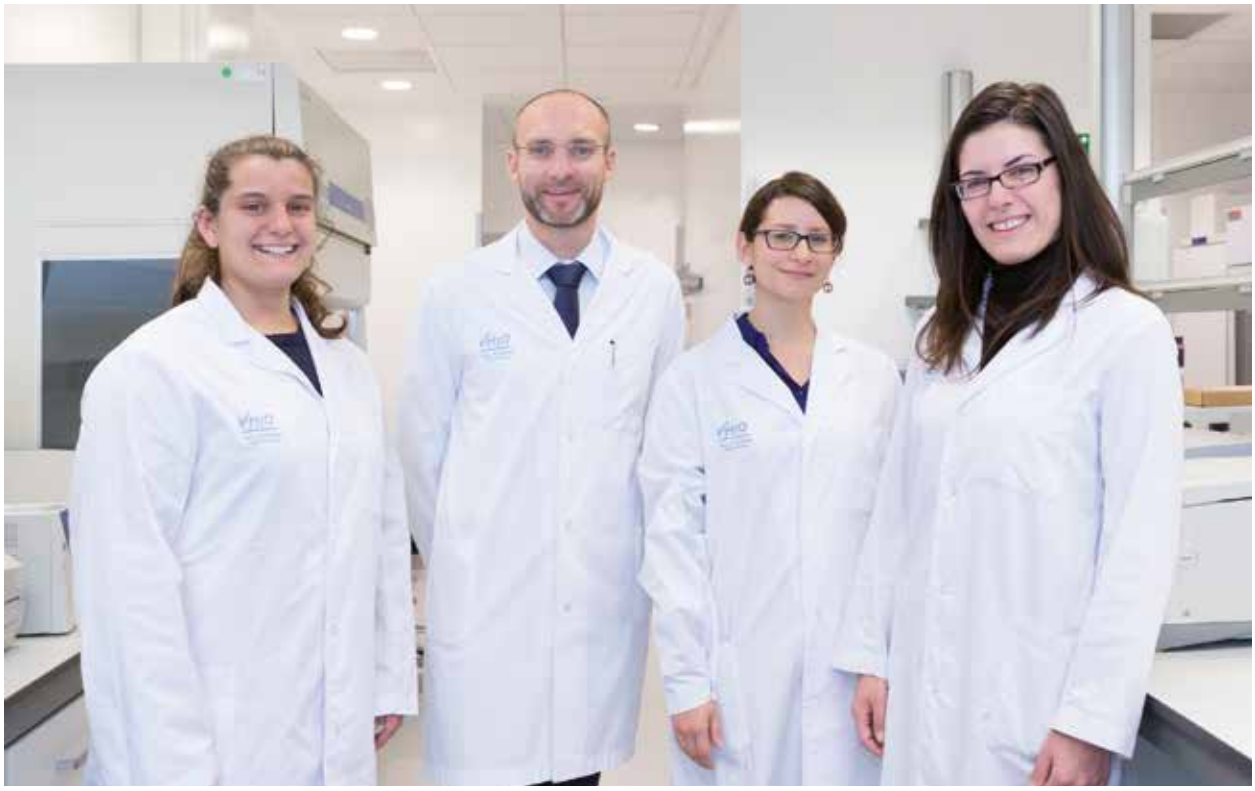

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SUMMARY

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-omics" tumor profiling tests performed at VHIO with information available in electronic medical records, including treatment benefit and patient survival across multiple tumor types. This represents a critical resource for medical oncologists, molecular pathologists and translational investigators at VHIO studying predictive and prognostic biomarkers. We also manage the Gene Drug Knowledge Database (GDKD) (doi:10.7303/syn2370773), a structured database that uses standardized terminology to describe associations linking different layers of annotations: tumor types, genes, variants, response/resistance patterns to approved and experimental agents under clinical investigation, and PubMed identifiers.

We also 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.

Strategic Goals

- Integration of clinical translational research with "omics" for precision cancer therapy.
- Clinical-molecular databases of matched targeted agents and immunotherapies.
- Standardized reports of next-generation sequencing tests.
- Collaborative research in cancer genomics/computational oncology and its clinical implications.

Highlights in 2015

- Participation in the European Consortium MedBioinformatics: our group was deeply 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 facilitate translational research and precision medicine.
- Our collaboration in the international Colorectal Cancer Subtyping Consortium: we were responsible for detailed characterization of the transcriptomic subtypes of colorectal cancer achievng consensus on newly defined molecular subgroups as published in *Nature Medicine* (Guinney J. et al. 2015. *Nat Med*. 21:1350-1356).
- Throughout 2015 we have led important advances in datamining, expert curation of the literature and knowledge interpretation of somatic gene alterations that have therapeutic impact in cancer, as published in *Cancer Discovery* (Dienstmann R. et al. *Cancer Discov.* 2015;5(2):118-23). Our Gene Drug Knowledge Database is publicly available and has become a reference for clinical investigators across the globe.
- Participation in the European Consortium MoTriColor: we had a critical role in the design of molecularly-guided clinical trials with specific targeted and immunotherapies for the newly defined colorectal cancer subgroups.

RADIATION ONCOLOGY GROUP

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Mónica Ramos
Victoria Reyes
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PI PAPER PICK

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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 as principal investigators or research collaborators in a number of important clinical trials, translational research projects, as well as technology development programs.

Current and future research priorities include the following key areas:

- The continued implementation of IMRT in sarcoma, pediatric and gastrointestinal tumors.
- Development of an estereotactic extracranial radiotherapy program in pancreas and bone metastases.
- Develop a 4D program for lung cancer.
- For breast cancer: the validation of partial breast irradiation in prone position technique.
- The identification of factors associated with clinical response in advanced head and neck tumors treated with radiotherapy and chemotherapy or target therapies.
- To seek 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.

Strategic Goals

- Technology development: acquisition of new equipment to implement cutting edge clinical treatment techniques such as rotational radiotherapy - with intensity modulated arc therapy (IMAT), adaptive radiotherapy and image-guided radiotherapy.
- Translational research: application of biological knowledge of both cancer and healthy tissue in order to individualize treatment to the characteristics of each patient, each individual tumor.

Highlights in 2015

- We achieved an increase in the number of patients treated with IMRT. In 2015 we treated 418 patients with IMRT, representing a 28% increase.
- The Adaptive and innovative Radiation Treatment FOR improving Cancer treatment outcomE (ARTFORCE) project was initiated in 2013. At present we have included 26 patients (see Figure II).
- 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 cancer program and we have treated 4 patients.

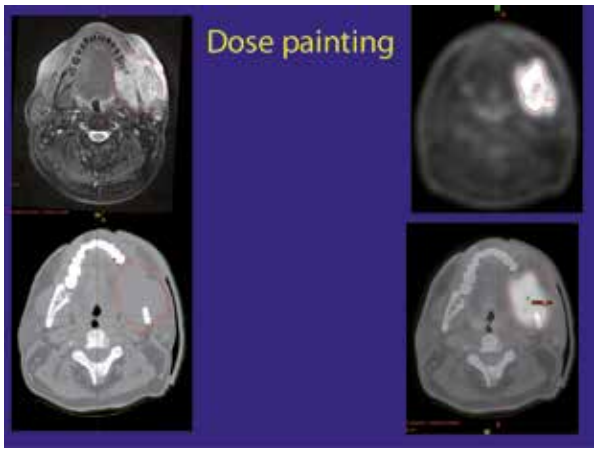

Figure I: Dose painting in head and neck cancer.

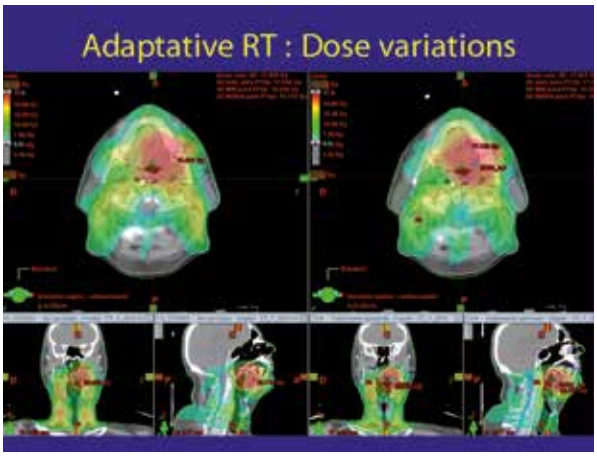

Figure II: Adaptive RT in locally advanced squamous cell carcinoma.

THORACIC TUMORS & HEAD AND NECK CANCER GROUP

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PI PAPER PICK

Jänne PA; Yang JC; Kim DW; Planchard D;Ohe Y; Ramalingam SS; Ahn MJ; Kim SW; Su WC; Horn L; Haggstrom D; Felip E; Kim JH; Frewer P; Cantarini M; Brown KH; Dickinson PA; Ghiorghiu S; Ranson M. AZD9291 in EGFR Inhibitor-Resistant Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;372(18):1689-1699.

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SUMMARY

The main focus of the Thoracic Tumors & Head and Neck Cancer Group is to tackle various aspects of lung cancer, the most frequently diagnosed tumor to date. Our group concentrates on a number of areas ranging from disease prevention, early detection, more accurate techniques in diagnosis and staging to advancing precision medicine and treatment of lung cancer. We are also highly dedicated to our program which focuses on targeted therapies in patients with specific molecular alterations and immunotherapy strategies.

In lung cancer patients with early-stage disease, we collaborate closely with thoracic surgeons and radiation therapists to better optimize the different treatment approaches and modalities set within a truly multidisciplinary setting. Since lung cancer patients sometimes suffer from severe symptoms associated with the disease, we strive to ameliorate them by working closely with a number of professionals from other disciplines. In patients with advanced-stage disease, personalized therapy is now the standard approach and our key objective is the early implementation of molecular determinants to better select treatment options tailored to individual patients. Immunotherapy strategies have a role in the lung cancer management treatment algorithm; a number of protocols using this strategy are now ongoing in our unit.

We actively contribute to VHIO's efforts aimed at early clinical drug development, and also deal with other less common thoracic malignancies such as small-cell lung cancer, mesothelioma, thymoma, and neuroendocrine tumors.

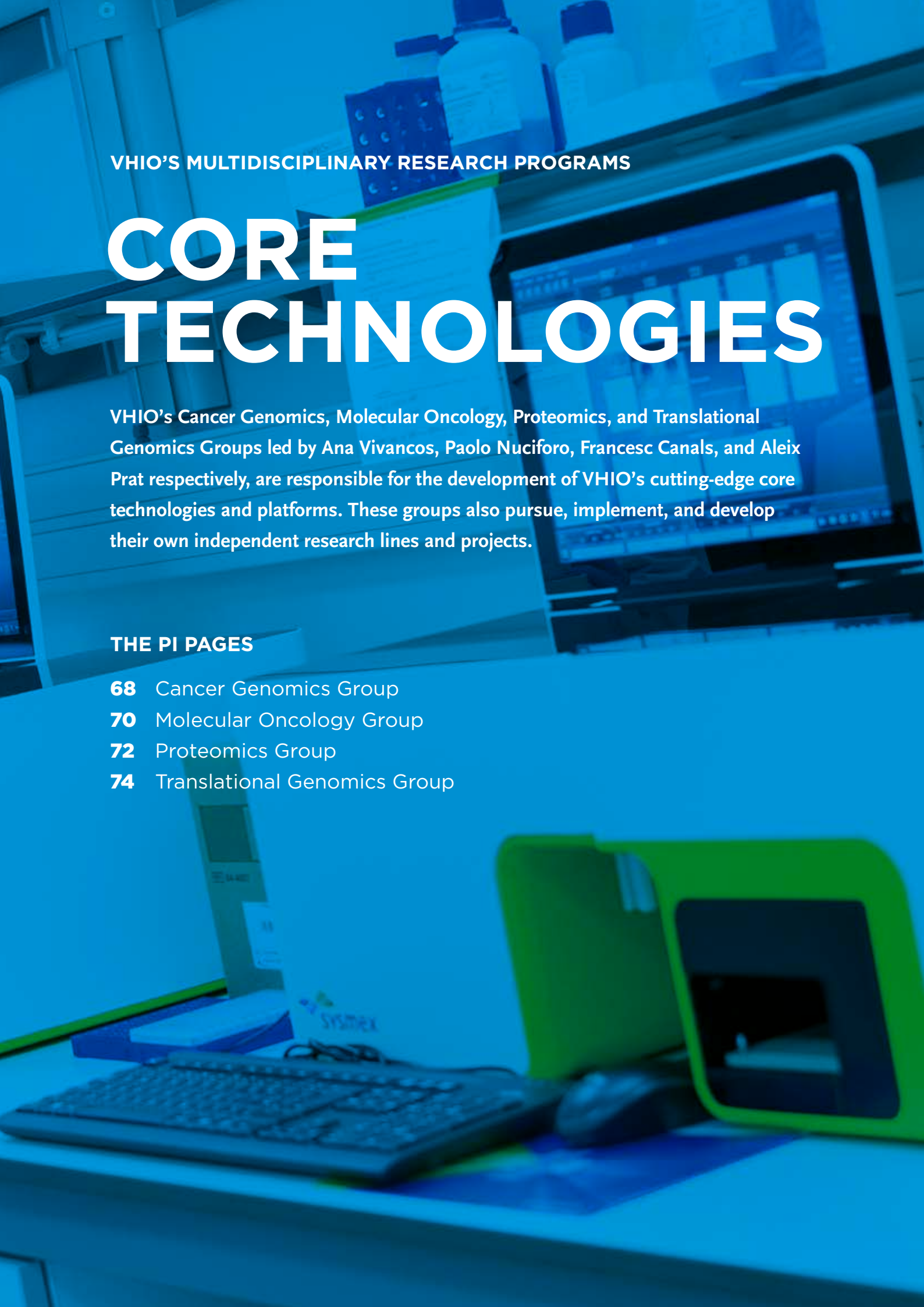
Strategic Goals

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

Highlights in 2015

- 500 new lung cancer patients including 20 cases of mesothelioma and 5 of thymoma.
- We continue to foster close multidisciplinary collaboration through our established lung cancer tumors committee which convenes twice a week.
- Implementation of pharmacogenomic approaches in advanced NSCLC 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.
- 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.
- Active development of immunotherapy strategies in lung cancer patients.


VHIO



VHIO'S MULTIDISCIPLINARY RESEARCH PROGRAMS

CORE TECHNOLOGIES

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.

THE PI PAGES

CANCER GENOMICS GROUP

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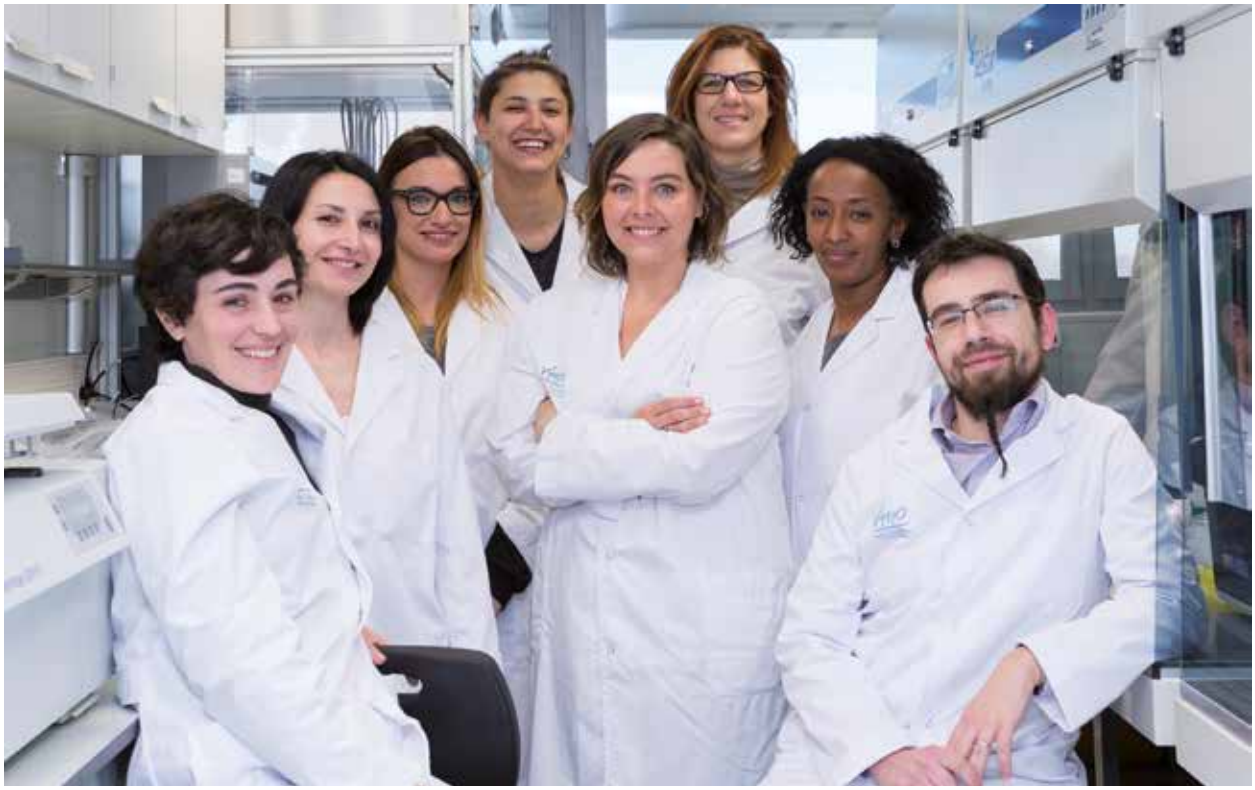
Bioinformatician
Francesco M. Mancuso

Bioinformatics Technical Auxiliary
Laura Muiños



PI PAPER PICK

Thress KS, Paweletz CP, Felip E, Cho BC, Stetson D, Dougherty B, Lai Z, Markovets A, Vivancos A, Kuang Y, Ercan D, Matthews SE, Cantarini M, Barrett JC, Jänne PA, Oxnard GR. Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M. *Nat Med*. 2015;21(6):560-562.

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SUMMARY

VHIO's Cancer Genomics Group serves as a Core Technology laboratory. Our activities bridge the preclinical and clinical fields of cancer research. We provide cutting-edge applications in cancer genomics through the use of state-of-the-art technologies and also develop novel fully validated tests that are used in the clinical research setting (Prescreening Program).

Our lab is equipped with a genotyping platform (MassARRAY, Sequenom), an n-Counter (Nanostring) platform and two NextGen Sequencers; MiSeq and HiSeq2500, Illumina (see figure).

Our research activities focus on developing 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. We have developed and routinely implemented an Amplicon-seq approach to sequence >60 genes (Illumina), as well as a gene fusion panel (with the capacity of detecting over 100 recurrent gene fusions) based on nCounter technology.

VHIO's Prescreening Program is nucleated around the activity of two VHIO groups - our Cancer Genomics group and Molecular Oncology led by Paulo Nuciforo, and is dedicated to performing molecular profiling in over 1500 patients per year that are candidates for enrollment in Phase I clinical trials carried out at our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa". Patients' suitability for inclusion in a given clinical trial is decided upon based on their respective genomic or pathologic profile. As a reflection of our dedication to excellence and quality in the services we provide, we have undergone ISO 15189 accreditation for our main testing methods.

We are also involved in a number of translational research projects including the identification of mechanisms of resistance to targeted therapies, study of clonal populations, as well as defining novel therapeutic opportunities based on mutation profiles, in collaboration with both preclinical and clinical researchers at VHIO, working on solid tumors.

Figure: Technologies in Cancer Genomics: an ongoing revolution.

Strategic Goals

- Develop and implement improved strategies for routine patient pre-screening in a high quality setting (ISO 15189 accreditation).
- Provide cutting-edge applications in cancer genomics through the use of novel technologies and protocol development.

Highlights in 2015

- Validation and implementation of an Amplicon-seq VHIO-Card panel (NGS) to allow mutation detection in over 60 genes. Validation and implementation of a Gene Fusion panel based on nCounter technology.
- 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 have incorporated a Digital-PCR platform, BEAMing, for the detection of RAS mutations in first-line metastatic colorectal cancer.

MOLECULAR ONCOLOGY GROUP

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Mª Alejandra Iglesias

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;10(1):138-147. Epub 2015 Sep 15.

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To discover more about us, our group's full list of publications, and our horizons for 2016, visit VHIO's Scientific Report online at: http://memorias.vhio.net/2015/
For VHIO's full listing of articles published by VHIO Investigators in 2015 see pages 87-98.

SUMMARY

The Molecular Oncology Group's mission is to apply state-of-the-art tissue-based technologies to basic, translational, and clinical research with a clear focus on developing and validating novel tumor biomarkers for precision cancer medicine. The group is one of VHIO's Core Technology Platforms and is therefore central to VHIO's research activities. 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 circulating tumor cells (CTC) analyses.

Core Facility activities in 2015:

We provided support to more than 180 clinical trials conducted at Vall d'Hebron, representing more than 60% of all trials open at our institution. Our clinical trials activities 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.

During this year, we have performed over 3000 molecular determinations on samples for patient inclusion in clinical trials and over 14,000 tests to support basic and translation research programs. We have also been the central laboratory for 2 national and 6 international studies.

In 2015, our laboratory successfully maintained and expanded the catalogue of molecular tests run under the prestigious ISO15189 quality accreditation.

Research activities in 2015:

We published two papers addressing the role of PI3K pathway activation as a mechanism of resistance in HER2-positive breast cancer (Nuciforo et al, *Annals of Oncology* 2015; Majewski et al, *Journal of Clinical Oncology* 2015).

In addition, we established and strengthened several key collaborations with pharmaceutical companies to carry out translational studies focused on the identification of predictive biomarkers of response to FGFR inhibitors, the definition of target populations for two antibody-drug conjugates projects and HER family proteins quantification in breast cancer using Selected Reaction Monitoring Mass Spectrometry (SRM-MS).

The latter study, conducted in collaboration with MGH and OncoplexDx/Nantomics, aimed to demonstrate the feasibility of using SRM-MS in clinical samples and highlighted the relevance of quantitative target measurement in predicting response to targeted therapies (Nuciforo et al, *Breast Cancer Research* 2015; Scaltriti et al, *Clinical Cancer Research* 2015).

Additional projects included a study exploring the prevalence of MET copy number variation, MET expression and MET related genomic alterations in solid tumors.

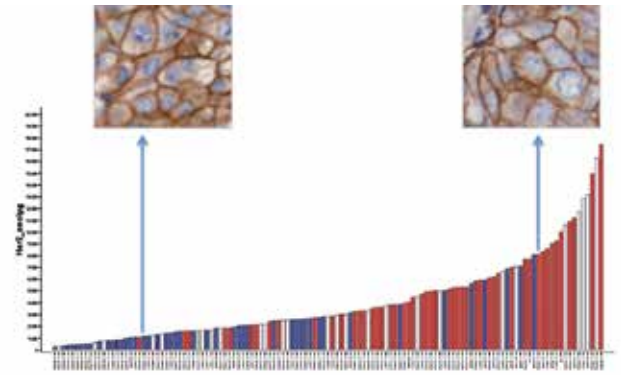

Figure: Variability of HER2 protein expression (amol/ug) by quantitative SRM-MS in HER2-positive (IHC 3+ or FISH amplified) breast cancer. Red bars: FISH-positive; Blue bars: FISH-negative; White bars: undetermined.

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 targets epidemiology to improve personalized treatment strategies.

Highlights in 2015

- Supported over 180 clinical trials for sample management and analyses. Central laboratory in different national and international studies.
- Over 3000 molecular determinations on samples for patient inclusion into clinical trials and over 14,000 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 the ISO15189 accreditation.

PROTEOMICS GROUP

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Laura Villarreal

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Luna Martin
Anna Sabé

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Aguilera Ó, González-Sancho JM, Zazo S, Rincón R, Fernández AF, Tapia O, Canals F, Morte B, Calvanese V, Orgaz JL, Niell N, Aguilar S, Freije JM, Graña O, Pisano DG, Borrero A, Martínez-Useros J, Jiménez B, Fraga MF, García-Foncillas J, López-Otín C, Lafarga M, Rojo F, Muñoz A. Nuclear DICKKOPF-1 as a biomarker of chemoresistance and poor clinical outcome in colorectal cancer. *Oncotarget*. 2015;6(8):5903-5917.

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Andrew J. Percy, Jessica Tamura-Wells, Juan Pablo Albar, Jesus M. Arizmendi, Francisco J. Blanco, Francesc Canals, Fernando Corrales, Gilberto Domont, Guadalupe Espadas, Concha Gill, Mark Molloy, Young-Ki Paik, Mark Raftery, Lekha Sleno, Justina C. Wolters, Jong Shin Yoo, Victor Zgoda, Carol E. Parker, and Christoph H. Borchers. Inter-laboratory Evaluation of Instrument Platforms and Workflows for Quantitative Accuracy and Reproducibility. *EuPA Open Proteomics*. 2015;8:6-15.

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SUMMARY

Proteomics is directed to 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 are known to 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. Knowledge surrounding the substrates of these proteases in the context of tumor cells is 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.

Our research also uses proteomic techniques for the screening and validation of biomarkers for cancer diagnostics, personalized therapy and the tracking of disease. Our group's focus has mainly centered on the establishment of a TGF beta activity-related protein signature, to be used for patient stratification and monitoring of glioma.

Our laboratory is a member of the Spanish Consortium Chromosome 16 HPP which forms part of the HUPO Human Proteome Project. This multicenter, international project aims to develop an entire map of the proteins encoded by the human genome following a chromosome-centric strategy to advance our understanding of human biology in health and disease. Focusing on important aspects of biology, this project is set to impact on ongoing disease-oriented research.

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

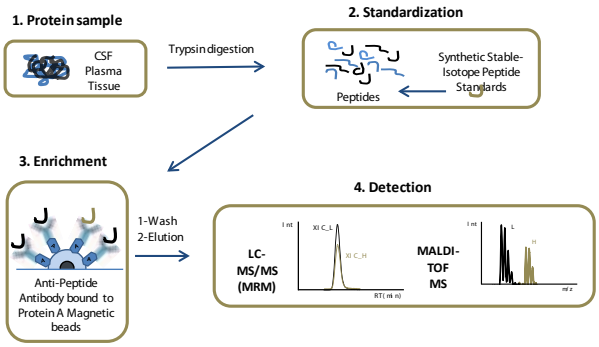

Figure: Immuno MS assay. Combining the specificitiy of affinity capture and mass spectrometry detection enables the development of highly sensitive protein assays, that allow the measurement of protein biomarkers in clinical samples.

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 in 2015

- The provision of proteomic services to VHIO groups, oncoprofessionals at the Vall d'Hebron University Hospital (HUVH), and members of the *ProteoRed-Instituto Salud Carlos III* network.
- Work in progress towards the validation of a biomarker signature to facilitate patient selection and the monitoring of TGFbeta inhibitor-based treatment of glioma.
- Participation in the Spanish Consortium Chromosome 16 HPP (part of the HUPO Human Proteome Project).

TRANSLATIONAL GENOMICS GROUP

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Technician
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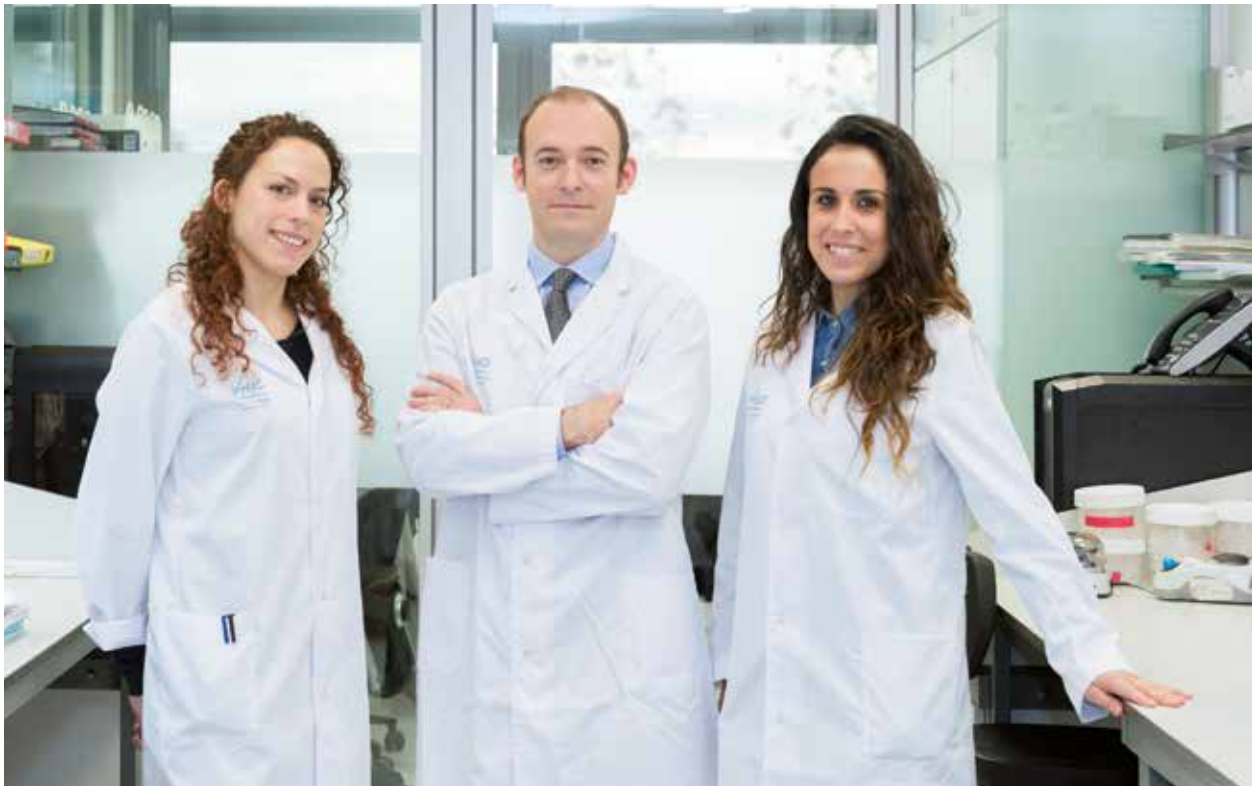

PI PAPER PICK

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Vidal M, Peg V, Galván P, Tres A, Cortés J, Ramón y Cajal S, Rubio IT, Prat A. Gene expression-based classifications of fibroadenomas and phyllodes tumours of the breast. *Mol Oncol*. 2015;9(6):1081-1090.

Prat A, Pineda E, Adamo B, Galván P, Fernández A, Gaba L, Díez M, Viladot M, Arance A, Muñoz M. Clinical implications of the intrinsic molecular subtypes of breast cancer. *Breast*. 2015;24 Suppl 2:S26-S35.

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SUMMARY

2015 has been another highly productive year for VHIO's Translational Genomics Group. On the one hand, we have been the first in Europe to successfully implement a clinically applicable gene expression-based test, known as PAM50, in two prospective clinical trials in patients with metastatic breast cancer. In addition, we have analyzed >1.000 samples and have continued to provide scientific guidance and advice to several collaborators both at VHIO and overseas, leading to multiple publications in high-impact factor journals. Moreover, my lab has expanded its participation in the retrospective genomic analyses of tumor samples from several national and international clinical trials (e.g. PAMELA, GEICAM2012-09, NeoEribulin, EGF30008, EGF104900, LPT109096, CIBOMA/2004-01/GEICAM 2003-11 and CHER-LOB).

Our group has also led important advances regarding the clinical implications of breast cancer heterogeneity. In a first article, published in *Clinical Cancer Research*, we were the first to validate the PAM50 assay in core biopsies from primary and metastatic tumors and evidence that this approach can help predict response to chemotherapy. In a second paper, published in *BMC Medicine*, in one of the largest datasets reported to date with more than 900 patients with breast cancer, we showed that PAM50 intrinsic subtyping predicts response and survival following multi-agent chemotherapy. These findings have led to the clinical implementation at our hospital of the PAM50 assay at diagnosis before any therapeutic strategy is established for breast cancer patients.

Finally, we have collaborated with several renowned investigators. In one study, published in *Science Translational Medicine*, we showed that during PI3K inhibition in patients with luminal breast cancer, the tumor becomes more estrogen-dependent (i.e. more Luminal A). These findings have led, in part, to the development of these agents in combination with endocrine therapy. In a second study, we identified a gene, called MAF, as being potentially responsible for the development of breast cancer bone metastasis.

Our group has participated in 15 articles providing scientific advice and/or performing gene expression analyses including 13 original research articles and 1 review article: 3 as first author, 1 as second and 2 as last author. For 2015 our group's Impact Factor totaled at 110.5 (average of 8 per publication).

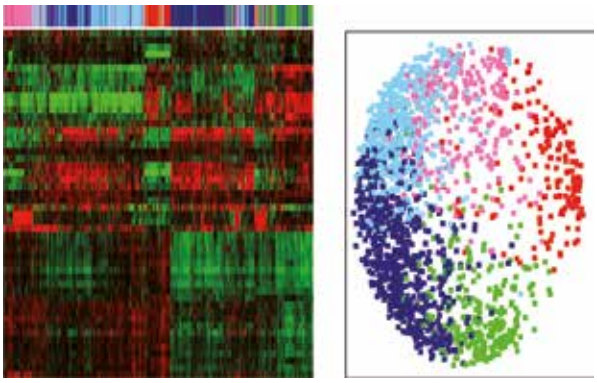

Figure: Intrinsic subtype identification using the PAM50 subtype predictor across 1,834 tumors.

Strategic Goals

- Use genomic data to guide clinical trial design and biomarker development in order to identify more optimal treatment regimens for cancer patients.
- Use gene expression data to better characterize different tumor types and better understand cancer biology.
- Help implement gene expression-based tests in the clinical setting.

Highlights in 2015

- 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.
- Fund for National Healthcare Research (FIS) grant to study triple-negative breast cancer.
- Participation in correlative science studies across ~10 clinical trials.

VHIO'S TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

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Maria Herranz
Sonia Martínez
Lidia Martínez de Arenzana
Laura Maynés
Adelaida Piera
Josep Roman
Elisabet Sicart

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Montserrat Solà
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Sergio Pérez
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Quality Assurance Manager
Silvia García

To find out more about our Office, our clinical trials, as well as our horizons for 2016, visit VHIO's Scientific Report online at: http://memorias.vhio.net/2015/

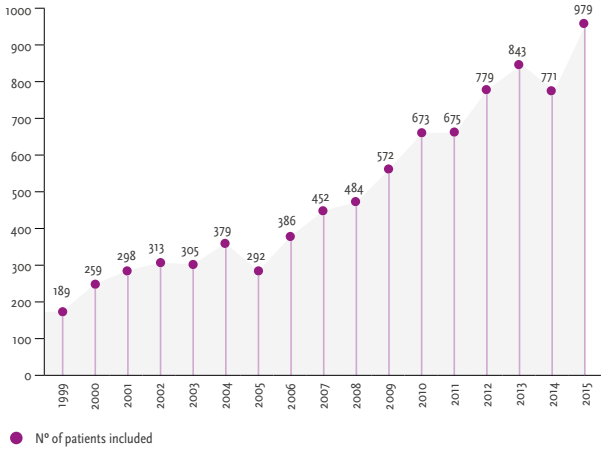
Strategic Goals

- Contribute to the development of novel therapies against cancer.
- Consolidation as an international reference hospital for clinical trials in oncology.
- Guide patients taking part in a trial to comply with the requirements of the protocol and help them with daily life throughout this period.
- Ensure that the protocol is appropriately conducted from initiation to the close of the respective trial.
- Standardize clinical trial processes to ensure optimal quality and the compliance of Good Clinical Practice (GCP).

Highlights in 2015

- Increase in both the number of clinical trials performed and the number of patients included.
- Increase in the complexity of the protocols which are increasingly demanding.
- We have provided tailored training to our staff in order to improve the quality of their work and expand upon skills.
- Implemented new tools and procedures aimed at increasing the quality and efficacy of research.
- 7 sponsor audits and 2 FDA inspections have been conducted with satisfactory results.

Figure I / Annual Recruitment Evolution (Phase I-II-III Trials)



SUMMARY

Set up in 1997, the Clinical Trials Office comprises an operational team conducting clinical trials at the Vall d'Hebron University Hospital's Oncology Department with more than 35 professionals including study coordinators, data managers, administrative staff and quality control. Our office coordinates studies from Phase I to Phase IV as well as research projects, and is divided into three teams to cover all tumor types and trials. In 2015 we conducted 289 actively recruiting trials (see Figure II) with patient enrolment totaling at 979 (Figure I). In addition, we continue to follow up all patients that were recruited prior to 2015 who are still enrolled and receiving study treatment.

As we strive 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 and treatment approaches, based on each individual's molecular 'measurements' -- thus delivering on the promise of precision medicine in oncology.

The Vall d'Hebron University Hospital's Oncology Department has gained much prestige which has been acknowledged by the pharmaceutical industry. 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 - chosen for their high standards of quality and capacity to carry out state-of-the-art research. Our hospital has taken part in phase I trials of different drugs and allowed the pharmaceutical industry to market novel therapies aimed against cancer. We consequently participate in clinical trials promoted by the pharmaceutical industry as well as those developed in our department in collaboration with other hospitals.

Figure II / Annual Distribution of Phase I, II and III Trials

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Phase I trials	6	10	12	14	17	15	16	19	20	26	31	37	48	66	75	83	106
Phase II trials	19	22	23	23	22	19	30	32	42	40	55	54	57	85	96	99	94
Phase III trials	14	17	22	25	18	20	21	21	31	37	45	49	56	68	61	64	89
Nº of clinical trials	39	49	57	62	57	54	67	72	93	103	131	140	161	219	232	246	289

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

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Maria Herranz
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Lidia Martínez de Arenzana
Laura Maynés
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Lydia Vélez

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Elisabet Hernández
Margarida Marcos
Isabel Muñoz
Tania Sánchez

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María Martín

Nurse Supervisor's Assistant
Juan Manuel García

Secretary
Teresa Mendoza

To find out more about our Unit as well as VHIO's Transversal Clinical Trials Core Services and Units, visit VHIO's Scientific Report online at: http://memorias.vhio.net/2015/

Strategic Goals

- Early drug development and translational research led by UITM physician-researchers and VHIO scientists: Expansion of our broad portfolio of promising novel anti-cancer 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, link clinical research at UITM with VHIO's preclinical and translational research groups, and 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: UITM Task Force in early drug development of immunotherapeutics and cell signaling (with sepcia focus on cytokines, immunomodulatory agents and immune checkpoint inhibitors) and translational research in immune-oncology.

Highlights in 2015

- We have performed some of the most complex phase I trials, including those focused on molecularly-selected patient populations (more than a dozen trials in molecularly-selected patient populations Basket/Octopus trials as well as trials in immuno-oncology. One such phase II novel basket trial carried out at UITM showed the efficacy of vemurafenib as therapy against multiple tumor types that share the BRAFV600 mutation – results which were published in the prestigious journal *The New England Journal of Medicine* (Hyman DM et al. 2015. *N Engl J Med*. 373:726-736).
- 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 Cancer Genomics Groups, we benefit from cutting-edge technology platforms including the MiSeq, Hiseq 2500 NextGen sequencers, and the nCounter Nanostring. We also co-develop molecular tests for VHIO's Pre-screening Program (disease-oriented mutation panels for our NGS platforms).

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. Due to such a privileged environment with direct access to patients, coupled with VHIO's translational approach to research and superb scientific framework, our Unit has rapidly established itself as one of the few comprehensive facilities in Europe to rapidly transform latest discovery into benefits for patients.

UITM promotes tight connectivity between health care and research which enables us to establish new treatment models for patients with highly selective drugs, expanding the knowledge of tumor diseases and how to treat them in an individualized way - getting the right drug to the right patient at the right time. As the figures show, we are gradually doing so for an increasing number of patients. In 2015, 106 phase I clinical trials were performed at the Unit with a total of 370 patients enrolled. It is thanks to the Unit's facilities coupled with our multidisciplinary clinical teams that we 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 48-49), focuses on the development of new drugs based on the molecular profile of each tumor as well as the optimization of treatment regimes using combinations of new drugs with those already existing. In line with VHIO's translational model, research is also linked with other research areas carried out by VHIO groups, connecting molecular biology and optimal tumor models with pharmacology and innovative clinical research. VHIO scientists also collaborate closely in the 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 analysis 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, more precise mutational analysis 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 with many other oncology professionals including clinical research oncolgy nurses, pathologists from Vall d'Hebron's Molecular Pathology Department, radiologists and interventional radiologists, as well as the Clinical Trials Office, Database Management, and healthcare specialists (dermatologists, cardiologists, ophthalmologists).

To find out more about the full spectrum of clinical trials (Phases I - III) at Vall d'Hebron, as well as our Transversal Clinical Trials Services and Units, please visit VHIO's Scientific Report online at: http://memorias.vhio.net/2015/.

CLINICAL RESEARCH ONCOLOGY NURSES

Nurse Supervisor
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Lydia Vélez

Nurses
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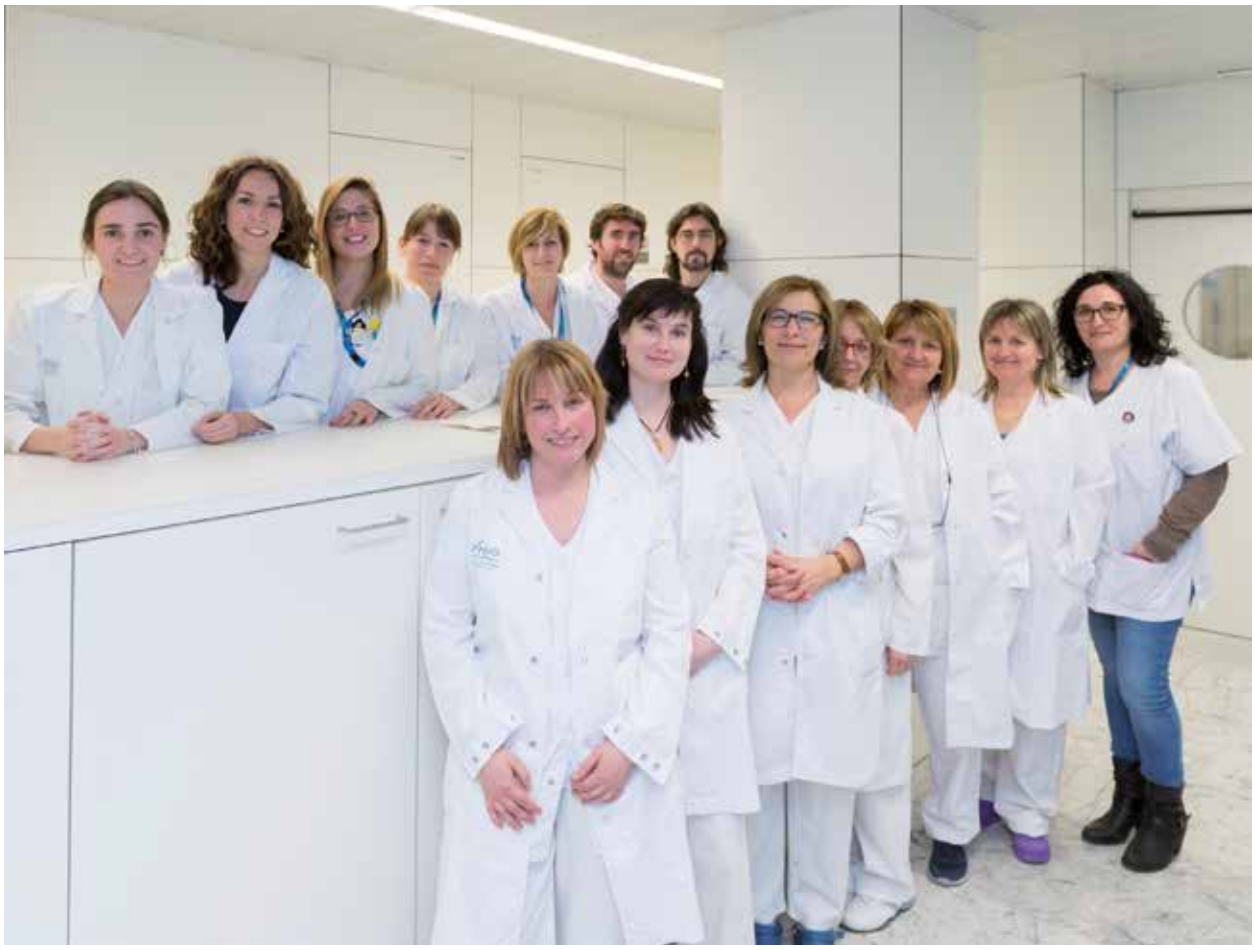
Margarida Marcos
Marta Mate
Núria Membrives
Mireia Milán
Isabel Muñoz
Raquel Muriel
Tania Sánchez
Álex Sierra

Nursing Assistants
Alicia López
María Martín

Nurse Supervisor's Assistant
Juan Manuel García

Secretary
Mª Teresa Mendoza



To find out more about VHIO's Transversal Clinical Trials Core Services and Units, visit VHIO's Scientific Report online at: http://memorias.vhio.net/2015/

SUMMARY

Clinical trials in oncology are essential for both the identification of new, more effective therapies for cancer as well as improving outcomes such as survival, side effect profiles, combination therapies and quality of life.

Such advances in cancer care and the development of more effective cancer therapeutics depend on an optimal clinical trial process.

Clinical Research Oncology Nurses play a key role in that process by assuming a variety of roles including identifying trends in side effects, collaborating with the multidisciplinary team to develop and evaluate patient management, contributing to the scientific process by collating samples and quality data as well as providing excellence in nursing care and symptom management of trial participants.

VHIO's Clinical Research Oncology Nurses, specialized in molecular therapies, are headed by Angeles Peñuelas and represent a critical and expert element of the multidisciplinary oncology team involved in clinical trials peformed and coordinated at VHIO's Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa" (see pages 80-81 for more information) and Clinical Trials Office (see pages 78-79), directed by Jordi Rodón, also Principal Investigator of VHIO's Early Clinical Drug Development Group (see pages 48-49), and Gemma Sala, respectively.

Supporting these expert multidisciplinary teams comprised of medical oncologists, molecular pathologists, oncology pharmacists, clinical researchers and study coordinators, VHIO's clinical research oncology nurses play a central role in ensuring the delivery of optimal care whereby patients receive the full range of expertise, guidance, and necessary follow-up throughout the course of their enrolment in a particular clinical study.

In 2015, across the 289 actively recruiting trials, patient enrolment totaled at 979, and, in addition, we continue to follow up all patients that were recruited prior to 2015 who are still enrolled and receiving treatment.

As VHIO continues to expand its portfolio of clinical trials in order to ultimately establish novel treatments with highly selective drugs, and its research teams collaborate in close connectivity to fine-tune patient selection criteria in order to identify those patients who are most likely to benefit from them, we can expect a steady increase in patient recruitment across our clinical studies -- now and in the future.

CLINICAL RESEARCH ONCOLOGY PHARMACY UNIT

Coordinator of the Clinical Research Oncology Pharmacy Unit
Maria Josep Carreras Soler

Coordinator of Pharmacological Research in Oncology Support Unit
Laura Mañós Pujol

Pharmacists
Isabel de la Paz
Anna Farriols Danés
Inés Jiménez Lozano
Marta Munné García
Berta Renedo Miró
Núria Sabaté
Carol Valdivia Vadell
Jana Vidal Otero

Technicians
Romina Bellini Martínez
Esther Carabantes González
María Hidalgo Casas
Susana Mulet Lozano
Isabel Pérez Fernández
Gemma Tomás Alonso
Sílvia Torralba Bernal

Clinical Trials Re-Supplies Manager
Sara Pizarro López

To find out more about our Unit and VHIO's Transversal Clinical Trials Core Services, visit VHIO's Scientific Report online at: http://memorias.vhio.net/2015/

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.
- 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: ISISH-TRI program.

Highlights in 2015

- Preparation for the opening of our Unit's new facilities – incorporating new computerized systems for the management of clinical trial drugs and improved facilities for clinical trial development.
- Validation of the traceability system: ISISH-TRI program.
- Improved 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.
- 12 successful sponsor audits.

SUMMARY

Our Unit is ISO 9001:2008 certified and associated with the Medical Oncology Programs of the Vall d'Hebron University Hospital. 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 as well as 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 2015 we managed clinical trial drugs for 309 active trials in oncology and deliveries of supplies totaled at 3787. 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. We also continue to finely-tune our drug accountability procedure for drugs returned by patients using a Cabin Vertical Laminar FLOW (CVLF), for verifying treatment compliance safely. Study drugs returned by patients are accounted for by pharmacy personnel in CVLF and pills are stored in a transparent, sealed bag. This year our Unit has carried out drug accountability for returned medication from 121 clinical trials.Traceability of the management of storage, custody and dispensing of clinical trial drugs: we have a computerized storage area for controlling 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 are dedicated to 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 personnel have participated in 69 pre-study visits, 166 initial visits, 1609 monitoring visits, 73 close-out visits, and have successfully passed 12 audits. Preparation staff participated in 25 pre-study visits, 132 initial visits, 248 monitoring visits, and 4 audits. In addition, 17,865 clinical trial drugs have been dispensed, validated by a pharmacist -- 7975 of these are for orally administered drugs. A total of 366 Standardized Dispensing Procedures have also been drawn up/ updated as well as 169 storage temperature data reports. Preparations of cytostatics, monoclonal antibodies and other parenteral antitumor drugs for clinical trials totaled at 9836 and 131 Standardized Preparation Procedures were compiled. We also incorporated 287 antineoplastic therapeutic schedules in our prescription software.

Pharmaceutical care program for patients enrolled in Phase I clinical trials: we carried out 793 visits, 317 screenings, 253 C1D1s, and 223 follow-ups, also compiling patient diaries and/ or instructions for patients if the respective sponsor does not supply this documentation. This year we compiled 6 different diaries and 21 instruction manuals. Our Unit also provides diaries and instruction manuals for patients included in all Phase II and Phase III trials involving orally administered drugs. 57 diaries and patient manuals for Phase II and Phase III clinical trials were compiled this year.

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FULL LISTING OF ARTICLES PUBLISHED BY VHIO INVESTIGATORS IN 2015

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Correction to *Lancet Oncol*. 2015; 16: 499-508. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study.*Tabernero J*; Takayuki Y; Cohn AL. *2015. Lancet Oncol*. IF:24,690

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FUNDING & CONSORTIA

Funding

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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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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

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The Dr. Josef Steiner
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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 2014:

Cancer Core Europe is a unique partnership aimed at addressing the cancer care-cancer research continuum. Launched in the Autumn of 2014, this working consortium represents a critical mass of activity for the successful integration of all cancer care information, clinical research and outcome research, 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.
Bookmark and visit VHIO's website forthcoming project updates:
www.vhio.net.

COLTHERES - Colon Therapy Research Consortium partners European clinical research centers as well as translational researchers who have 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 4-year programme uses comprehensively molecularly-annotated colon cancers as a 'test-bed' to define specific biomarkers of response or resistance to signalling pathway agents.
www.coltheres.eu.

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 14 cancer centers across 9 European countries that are developing PDX cancer models, this initiative promotes the sharing and exchange of findings on promising therapeutics as well as leads multi-center preclinical studies. EuroPDX strives to reduce the duplication of efforts in oncology drug development and ultimately improve the quality of life and overall survival of cancer patients.
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 academic-industry 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 (CRCm), patients will be stratified based on their gene expression profiles according to recently established predictive signatures.
According to gene expression profiles, patients will then be matched to a particular clinical trial. 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.

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 collaboration:

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 or more efficient 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.

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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