VHIO

2014 SCIENTIFIC REPORT VALL D'HEBRON INSTITUTE OF ONCOLOGY

Centres de recerca de Catalunya

INDEX

SCIENTIFIC REPORT

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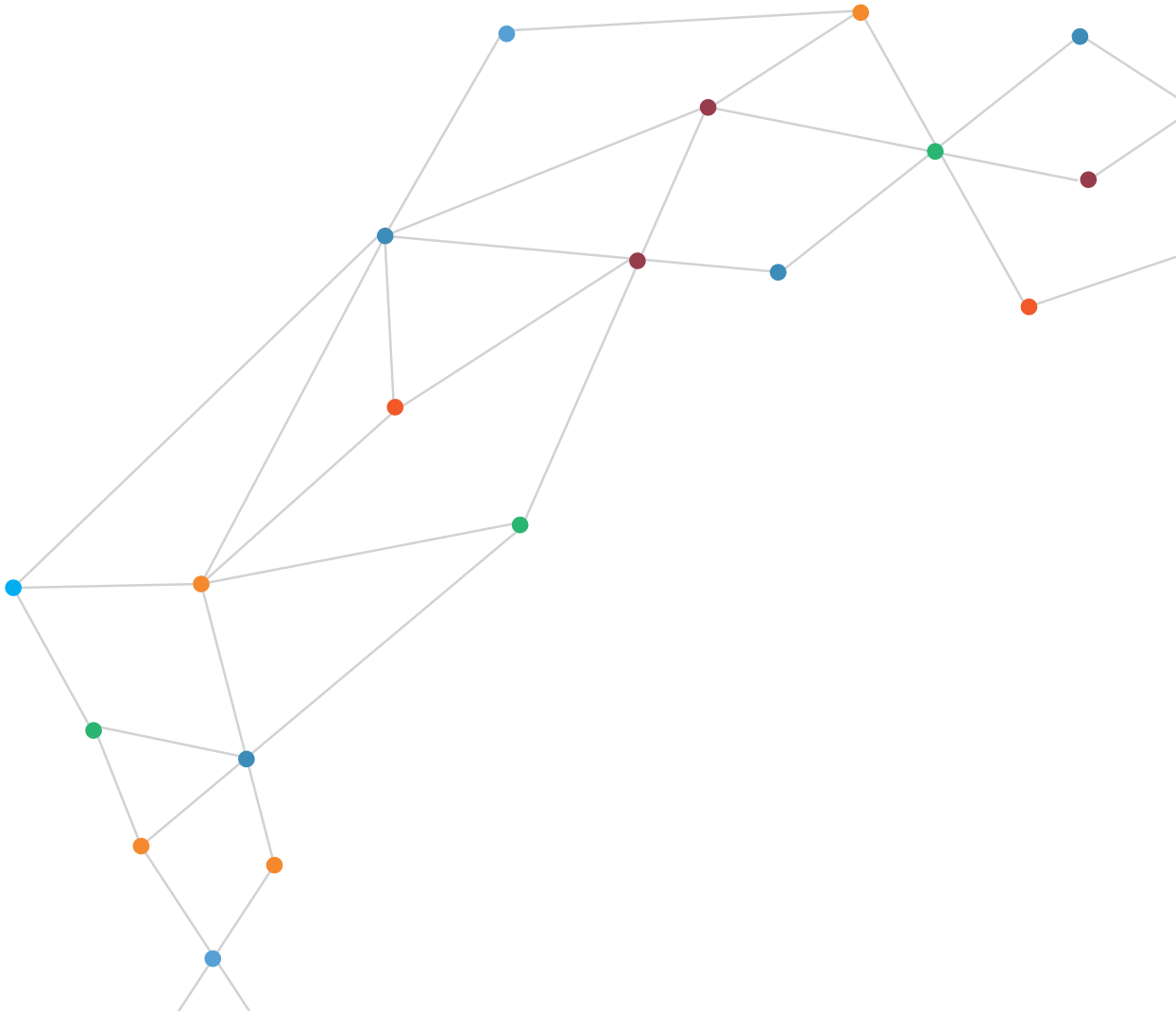

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INTRODUCING VHIO

PRECLINICAL RESEARCH

TRANSLATIONAL RESEARCH

CLINICAL RESEARCH

CORE TECHNOLOGIES

VHIO TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

Foreword

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

As I reflect on the past year, not only considering the many positive advances reported by VHIO's outstanding and committed multidisciplinary teams but also major achievements of our colleagues from comprehensive cancer centers of excellence around the globe, I am pleased to report that yes, we are collectively progressing in rendering precision medicine in oncology a reality for an increasing number of patients.

There are many factors that have led us to this turning point in the delivery of more precise and powerful anti-cancer therapies. Important advancements in defining the molecular basis of cancer, for example, have enabled us to leverage those insights in the selection of rational, targeted therapies.

We can most certainly afford to be optimistic, but, with caution. I was recently asked to respond to the question: *Will all cancer patients be treated by targeted therapies in the next ten years?* On the one hand, while translational research efforts are driving cancer discovery at a rapid pace, cutting-edge technologies are becoming yet more powerful and indeed precise, and the lower costs associated with genomic sequencing and pre-screening platforms are making precision medicine more accessible to more of our patients. But we still have a long road to travel. Regretfully, in view of the present scenario, my answer to that question had to be no.

Although mortality from cancer is on the decrease in Europe, thanks to our increased understanding of the hallmarks of cancer, earlier diagnosis, and more powerful anti-cancer therapeutics, incidence is on the rise. In a recent paper published in the *British Journal of Cancer*, colleagues from Cancer Research UK (CRUK) forecast that one in two people will develop cancer at some point in their lives. The one in three has now alarmingly increased to two. This, coupled with an ever-increasing ageing population, translates into a daunting prospect over the next decades. We must therefore combine forces, working more closely with all oncology professions and stakeholders to ensure faster, streamlined results, a quicker development and implementation of targeted, more affordable treatment plans for an increasing number of our patients.

At the close of 2014, hot debate was sparked by a paper published in *Science* authored by Bert Vogelstein and colleagues at Johns Hopkins University School of Medicine. The study made headlines around the world as the Hopkins team concluded that a large proportion of cancer cases was attributed to "bad luck." Whatever conclusion you may draw, the major risk drivers of cancer are known. Adding to the mix is the so-called *exposome* -- environmental exposures that may contribute to increased probability of disease. This aspect of cancer research warrants much more attention even as we celebrate successes in the genomic profiling of patients' tumors.

Throughout 2014, VHIO has continued to up the tempo in its basic, translational and clinical research efforts by reinforcing current infrastructures, increasing its portfolio of technologies and clinical trials, as well as building upon cross-border partnerships. We have one collective goal in mind: to get the right treatment, to the right patient, at the right dose, at the right time. We are better equipping our teams to more precisely tackle the specificities of each individual cancer, across all tumor types, and thus respond to the many challenges and yet unanswered questions that still remain in our battle against cancer.

VHIO's cutting-edge technologies, tests, and platforms: powerful armory against cancer

Thanks to the dedicated work of our Cancer Genomics Group headed by Ana Vivancos, our pre-screening efforts for mutations in patients who are candidates for enrollment in our broad portfolio of Phase I clinical trials carried out at the Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa", led by Jordi Rodón's Early Clinical Drug Development Group -- have established VHIO as one of the few groups in Europe to run such a comprehensive program. Using a custom amplicon panel, VHIO-Card, we study mutations in 61 oncogenes and tumor supressors at the same time, across all tumor types. Ana's team screens for both known mutations as well as those for which there are novel targeted therapies in the drug development pipeline. By broadening the scope of mutations under study we unmask more mutated samples, thus opening up more possibilities for patient stratification.

Deciphering the molecular profile of each patient indicates his/her suitability for inclusion in a given clinical trial aimed at testing the usefulness of novel targeted therapies, such as PI3K, AKT, BRAF or MEK inhibitors. These endeavors are not only revolutionizing tumor classification but also increasingly impacting on how cancer treatment decisions are made.

Importantly, VHIO's pre-screening program currently analyses the tumors of some 1000 patients per year -- those individuals who have exhausted all other standard therapies and are in critical need of alternative treatment regimens. If we are to extend these efforts to an increasing number of patients, we will need to do so in collaboration. In this respect, I am proud to announce the VHIO-Catalan Institute of Oncology (ICO) Research Alliance. Representing the biggest clinical cancer care provider in Catalonia, this powerful collaboration incorporates four comprehensive cancer centers throughout the region, providing clinical care to some 16,000 patients on a yearly basis. Direct access to extended patient populations will undoubtedly provide essential insights to more rapidly translate research into more effective, targeted treatments and better practice for the future care of our deserving patients.

VHIO's suite of cutting-edge technologies and assays including the nCounter Nanostring and RNAseq platforms, coupled with the expertise of our Core Technology teams who both develop and implement these techniques, enable us to bring more detailed prognostics directly to the clinical setting, and further develop and validate the next generation of tests. 2014 marked the successful implementation of a clinically applicable gene expression based test, known as PAM 50, for the management of breast cancer patients. Significantly, our Translational Genomics Group led by Aleix Prat was the first to do so in Europe. Such pioneering efforts will continue to empower VHIO in significantly contributing to better-guided treatment decisions as well as improved outcomes for patients.

Liquid biopsy 'policing' of cancer: ready for prime time?

One of the main challenges of cancer is its complex genetic landscape coupled with its ability to outsmart and dodge potent anti-cancer therapeutics. The need to better monitor and predict its every move is critical if we are to improve outcomes for our patients and deliver on the promise of precision medicine.

In this emerging era of personalized medicine in cancer, research breakthroughs have now rendered biopsies more precise in detecting cancer mutations, tracking the evolution of disease and circulating tumor cells that drive metastasis, as well as predicting response to therapy. There is enormous excitement about liquid biopsies -- blood tests that can non-invasively reveal circulating tumor DNA that is released by tumor cells into the bloodstream. This circulating DNA contains vital signals, components and genetic information about what is actually occurring in the tumor, providing us with a much bigger picture regarding the specificities and status of the patient's cancer.

Of tremendous importance in improving detection and following cancer's every move, is that these blood-based biopsies also allow for serial samples in order to identify tumor genomic alterations not only in real time, but *over* time.

As this Scientific Report goes to print, as part of a collaboration with Merck Serono and Sysmex Inostics, we have just announced that VHIO will be the first academic test center of its kind to use in-house BEAMing liquid biopsy RAS biomarker technology. Initially we will use blood-based technology to evaluate patients with metastatic colorectal cancer at research level. Expected to receive its European Conformity approval (CE mark) in 2015, this RAS biomarker test promises a more precise treatment for metastatic colorectal cancer patients.

I see enormous potential for liquid biopsies, so much so that I think they could, in the near future, replace tumor-section analysis and expand the scope of personalized medicine for our patients. In short, the liquid biopsy

undoubtedly represents a potent new contender in our current weaponry against cancer.

Synergies and the same score sheet: empowerment through collaboration

While our preclinical, translational and clinical research efforts are certainly translating into benefits for patients, we must continue to share our expertise -- and benefit from the knowledge of others -- through cross-border collaboration (see pages 94 - 95 for VHIO's participation in various Consortia of international excellence). Such global exchange of data and ideas is crucial not only in accelerating advances but also to avoid wasteful duplication of efforts.

Launched at a special press conference during the 2014 Congress of the European Society for Medical Oncology (ESMO) last Autumn, Cancer Core Europe is a unique partnership aimed at addressing the cancer care-cancer research continuum. This working consortium represents a critical mass of activity for the successful integration of all cancer care information, clinical research and outcome research, spearhead by the six founding partners and leading European comprehensive cancer centers: 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.

This consortium marks a significant forward step in harnessing, storing and sharing an overwhelming wealth of data generated through the 'onco'omics, clinical trials, cancer science and medicine. 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.

I also want to highlight the successes to date of the SPECTAcolor - Screening Platform for Efficient Clinical Trials Access in Colorectal Cancer. Set up in September 2013 and funded by a corporate social responsibility program of Alliance Boots, SPECTAcolor is an initiative set within the framework of the research program of the EORTC and is a unique undertaking as the first ever prospective, fully annotated tumor biobank and biomarker analysis platform for the genetic profiling of patients suffering from advanced colorectal cancer.

Implemented across 19 clinical centers located in nine countries throughout Europe, including VHIO, it has succeeded in recruiting over 500 patients. This promising start has demonstrated its viability to facilitate next-generation cancer clinical trials and that a logistically complex infrastructure in a multinational setting is achievable -- proving that where there is willing, there is certainly a way.

As dedicated partner, VHIO will continue to accrue patients at local level through the Vall d'Hebron University Hospital's Medical Oncology Department, as well as advance biomarker discovery aimed at the rapid development of novel therapies targeted to the needs of each individual colorectal cancer patient.

"We are told that talent creates its own opportunities. But it sometimes seems that intense desire creates not only its own opportunities, but its own talents"

- Eric Hoffer, American social writer and philosopher (1902-1983).

As Director of VHIO, I am extremely proud of our talented teams of excellence who work together across programs in order to ensure the tight connectivity and cross-talk necessary to carry out multidisciplinary and translational research and medical practice -- as is evidenced by the updates described by each group in this Scientific Report.

VHIO's leading scientists and physician-researchers are tirelessly advancing their research, and, as a reflection of excellence, continue to secure precious funding that fuels their efforts in combating cancer. As I noted in last year's Foreword, *Horizon 2020* replaced the European Union Framework Programmes with the emphasis on frontier and interdisciplinary research with one of the topics favoring novel studies and clinical approaches supporting the optimization of available therapies, specifically drug repurposing. Since talent fosters opportunity, we are optimistic that our proposals will be suitably considered and ultimately rewarded through this European funding.

I would also like to personally thank our devoted institutional supporters, the *Generalitat de Catalunya*, FERO, 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 92 - 93 of this report).

VHIO will only deliver on its goal of accelerating the pace in advancing personalized and targeted therapies against cancer thanks to the public funding it receives, as well as through such generous support from private institutions, companies and individuals, all of whom share the intense desire and drive to ensure the clock continue to tick in our favor - against cancer. This collective ambition not only allows us to do what we at VHIO do best -- rapidly translate cancer discovery into real benefit at clinical level -- but it also fosters essential growth and expansion of our programs.

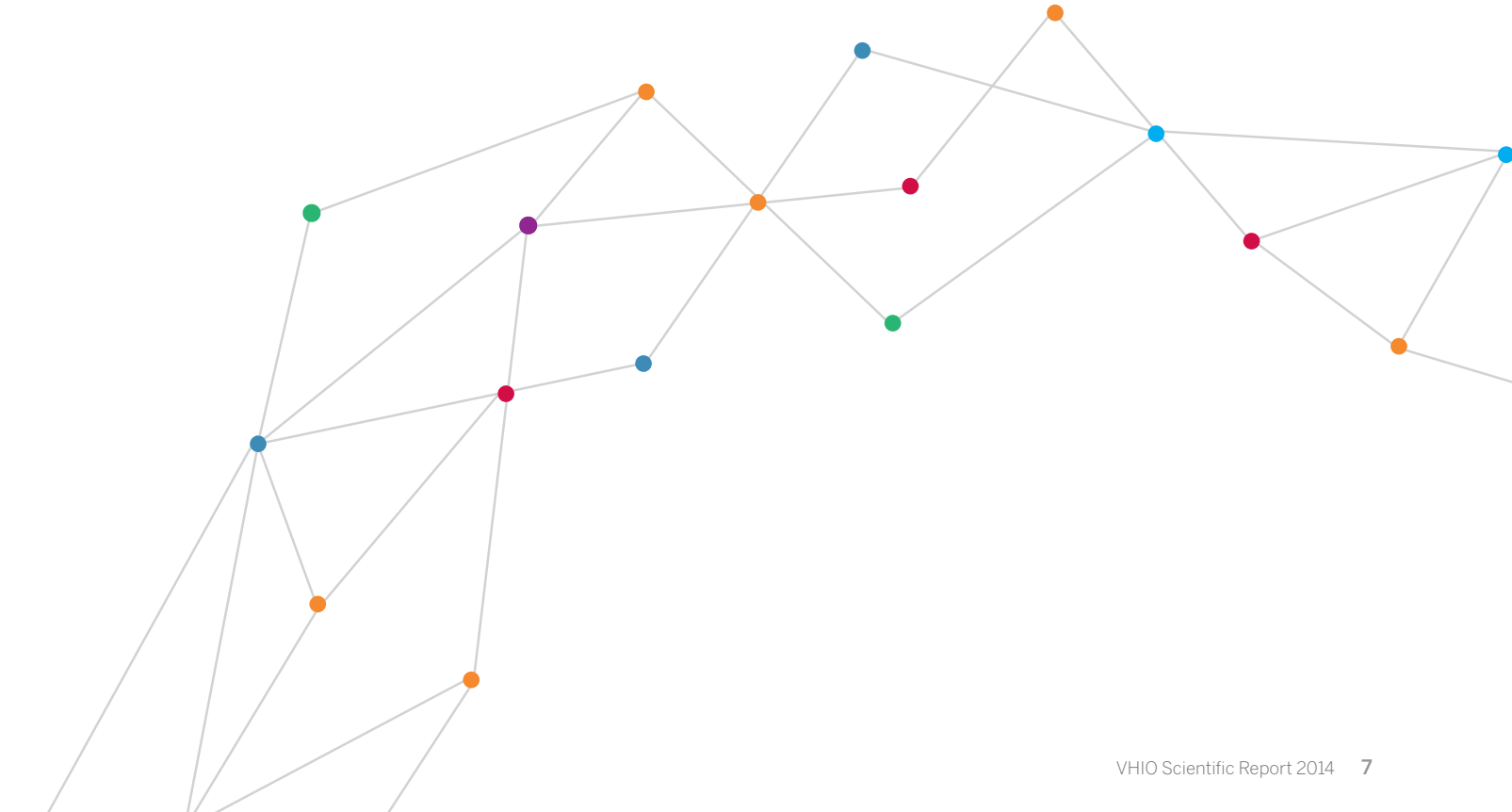
In this respect, I am delighted to confirm that we have now successfully recruited new talent and groups in areas

including cancer immunology and immunotherapy that will join us in 2015 to lead novel research focused on areas such as the tumor microenvironment, immuno-oncology, and the development of immune-based personalized therapeutics. To flank our efforts aimed at integrating clinical translational research with genomics for precision cancer therapy, I am delighted that Rodrigo Dienstmann will be returning to VHIO from Sage Bionetworks, Fred Hutchinson Cancer Research Center, USA, to set up and lead VHIO's Oncology Data Science Group.

Mention of expansion cannot be made without updating on the status of our new home -- the CELLEX building. We are now ready to move in -- marking a new era in VHIO's translational trajectory. Providing the valuable space through which to grow, the new building will bring all our multidisciplinary teams together under the same roof to enhance collaboration and spur our dedicated efforts to combat cancer.

At VHIO, as we demonstrate year after year, we have the desire, the talent and the opportunity to raise the bar and set our ambitions even higher.

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



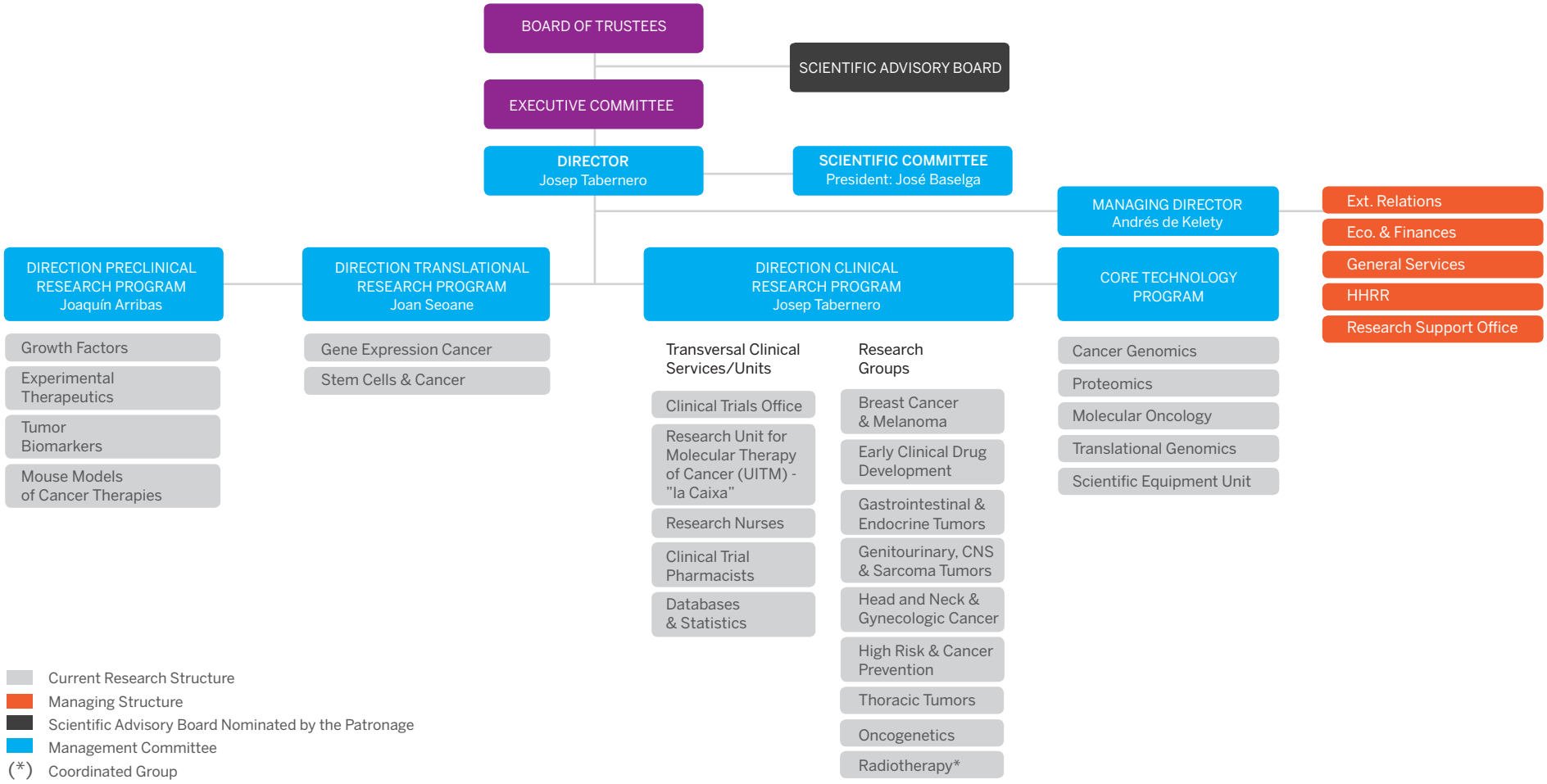
VHIO in 2014: the transformative power of forward-thinking talent

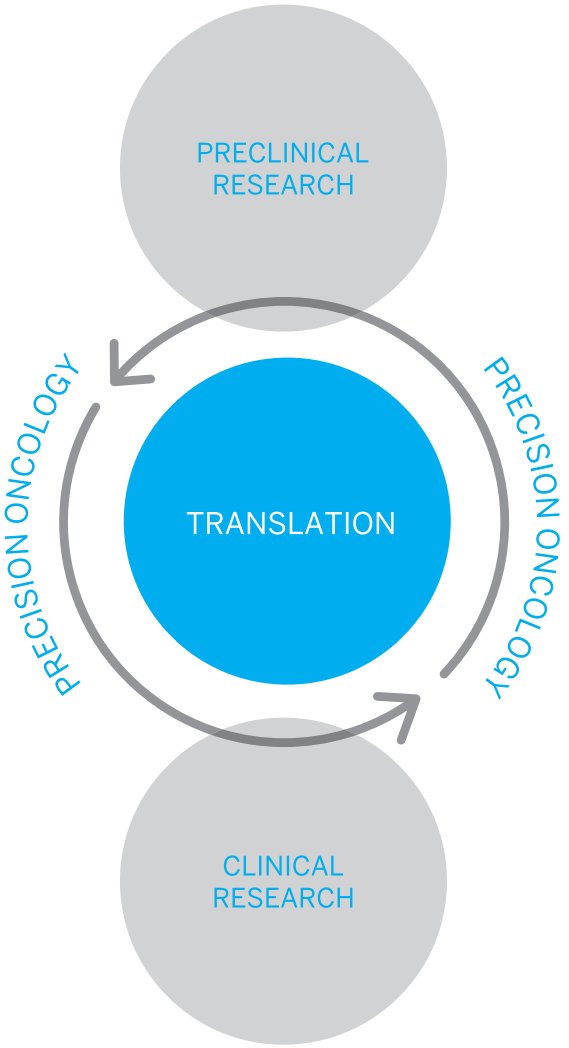
WHO WE ARE AND WHAT WE DO

VHIO's Organigram 2014

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:





A LITTLE EXTRA ON HOW WE DID IT IN 2014

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 2014 that enabled us to further advance cancer discovery through the integration of translational science and clinical research within a multidisciplinary setting - - the winning formula behind what we do and how we do it at VHIO:

VHIO's translation towards precision oncology

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.

Our Cancer Genomics Group (see pages 62 - 63) leads VHIO's pre-screening program of mutations in patients who are candidates for our portfolio of Phase I clinical trials. Assessing the molecular make-up of each patient provide us with vital insights regarding the suitability for enrollment in clinical studies aimed at testing the efficacy of novel anti-cancer therapeutics. Our pre-screening efforts have already established VHIO as one of the few centers in Europe to run such a comprehensive program. We will be looking 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 – see page 5 of the Foreword to this report for more details.

As also detailed in our Director's Foreword, VHIO, in collaboration with Merck Serono and Sysmex Inostics, will be the first academic test center of its kind to use in-house BEAMing liquid biopsy RAS biomarker technology. This technology will initially be employed to evaluate metastatic colorectal cancer patients at research level. Once it receives its European Conformity approval, envisaged in 2015, this technology will be extended to conventional routine care and to addtional tumor types.

BEAMing digital PCR/flow cytometry technology: set to empower 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.

Clinical trials at VHIO: driving drug development and targeted therapies against cancer

Obra Social "la Caixa"

VHIO has increasingly established itself as a leading reference in drug discovery from concept to the clinic. 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 76 - 77) located in the patient care environment of the Vall d'Hebron University Hospital (see next page), and set within the research context, as well as the Clinical Trials Office of the same hospital (see pages 72 - 75).

Research at the UITM is led by VHIO's Early Clinical Drug Development Group (pages 44 - 45), 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 2014, 83 Phase I clinical trials were performed at the Unit, with a total of 303 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 2014 the number of patients included in our studies totaled at 771 across 246 trials.

In December 2014, in recognition of the support we receive from the *Fundació Bancària "la Caixa"* and the tremendous successes marked since the UITM was inaugurated in 2010, we hosted and celebrated a joint press conference. Attended by some 20 leading journalists throughout Spain, the conference also counted on the participation of two of our wonderful patients who related their respective patient journeys as well as addressed the many questions put directly to them by the media.

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 83 - 91 for our full list of publications in 2014, and an overview of scientific productivity as well as selected articles on pages 14 - 17). 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.

Cancer research at VHIO: dismantling cancer's armory

Commandeering research aimed at combating cancer, our preclinical, translational and clinical researchers as corresponding/senior authors or co-authors, published 170 scientific articles in 2014 (83% Q1), with a cumulative Impact Factor totaling at 1551.677, and a Median Impact Factor (MIF) of 9.13. These figures reflect an increase in scientific productivity, maintained MIF score, as well as the importance of VHIO's research and contribution to the oncology field.

For the complete list of articles published by VHIO researchers and physician-scientists in 2014 see pages 83 - 91. To view this year's selection of just some of the most relevant articles by VHIO Faculty published in 2014, refer to pages 15 - 17.

VHIO's participation in consortia and networks of excellence

To accelerate discovery and thus improved cancer treatment and care, we are committed to combining strengths and overcoming current obstacles in collaboration. Such strategic cross-border alliances and partnerships will undoubtedly help to spur advancements rendering personalized medicine more precise and accessible for an increasing number of cancer patients.

In addition to VHIO's continued participation in some of the most forward-thinking, inspired and pioneering consortia at international level (see pages 94 - 95 of this report), 2014 witnessed its partnering with the Cancer Core Europe working consortium:

Cancer Core Europe

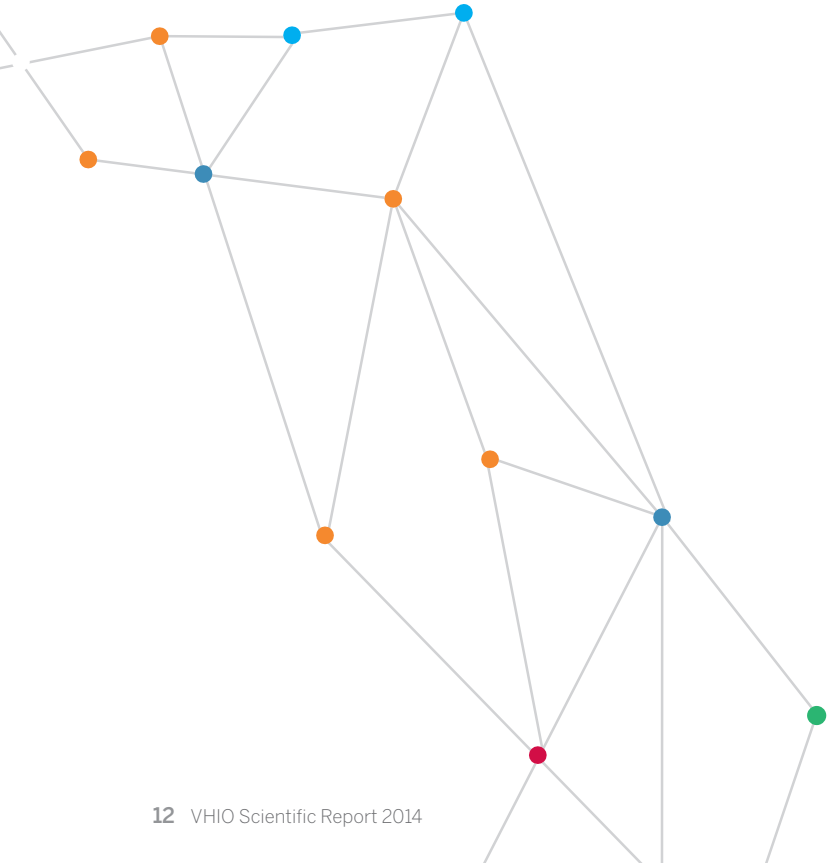
Powered by the six founding partners, the Gustave Roussy Cancer Campus Grand Paris (Villejuif, France), Cambridge Cancer Centre (Cambridge, UK), Karolinska Institute (Stockholm, Sweden), Netherlands Cancer Institute - NKI (Amsterdam, The Netherlands), National Center for Tumor Diseases - DKFZ-NCT (Heidelberg, Germany), and VHIO, this unique undertaking represents a transformative initiative whereby leading cancer comprehensive cancer centers will work collectively to address the cancer care – cancer research continuum.

Since the optimal treatment of cancer remains one of the major medical challenges globally due to the high diversity in the spectrum of mutations in individual cancer patients, among many other implicated factors, Cancer Core Europe will drive towards better integrated cancer programs performed at large scale.

Yearly within the Cancer Core Europe Consortium around 60.000 newly diagnosed cancer patients are seen, 300.000 cancer treatments are delivered, around 1.000.000 outpatient visits are performed, and more than 1.500 clinical trials are being conducted across the six cancer centers. Together with the strengths in basic and translational cancer research, this represents a unique critical mass of activity than once successfully harmonized as one operational research structure, will constitute a major force in European cancer science and clinical care.

For all forthcoming Cancer Core Europe updates and news please bookmark and visit VHIO's website:

www.vhio.net



Other collaborative opportunity in 2014

BIOINFORMATICS BARCELONA

2014 also marked the exciting launch of a regionally-based multi-center bioinformatics platform as part of a joint initiative of the Government of Catalonia and the *Fundació Bancària "la Caixa"*. VHIO joined 43 other partners incorporating research centers and clinical institutes, universities, pharmaceutical and IT companies, among others to support and participate in the Bioinformatics Barcelona (BIB) platform.

BIB will establish itself as a central point and facilitator of new initiatives to respond to the needs of the bioinformatics community. By capitalizing on the critical mass of like-minded, internationally renowned researchers, currently available IT infrastructures, and an entire network of biotech companies, the platform will strive to become an international reference within the bioinformatics field.

For more information visit:
www.bioinformaticsbarcelona.eu

Throughout 2014, 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, 2015.

The CELLEX building: marking a new era in VHIO's translational trajectory

Providing the valuable space through which to grow, the new building will bring all our multidisciplinary teams together under the same roof to enhance collaboration and spur our dedicated efforts to combat cancer. As this Scientific Report goes to print, we are now ready to move into our new premises.

With the invaluable support from:

Fundació Privada CELLEX

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

In 2014 VHIO opened its doors to participants at the following events:

- VHIO's annual series of *Meet the Editors*

Our VHIO *Meet the Editors* prestigious talks continued to provide 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 to the editors directly during the Q & A with the audience. They also continued to provide valuable opportunity to get to know the editors of the highest impact factor journals personally:

VHIO *Meet the Editors* in 2014:

CANCER DISCOVERY

Speaker: Judy Quong, Executive Editor of *Cancer Discovery*
Talk: *Cancer Discovery: Looking Back, Moving Forward*
Date: 24 February 2014

OXFORD JOURNALS
Annals of Oncology

Speaker: Jean-Charles Soria, Editor-in-Chief, *Annals of Oncology*
Talk: *Annals of Oncology: an Editorial Perspective*
Date: 08 September 2014

- The Weizmann Institute of Science and VHIO: a powerful duo in advancing insights into Cellular Communication in Translational Research

מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE

Jointly organized by the Weizmann Institute of Science (WIS) and VHIO, a two-day must-have conversation on *Cell Communication in Translational Research: bringing basic research into the clinic*, 22 – 23 January 2015, Rehovot, Israel, will not only provide a platform through which to share and debate the latest research aimed at combating cancer, but also endorse the strengths and synergies between WIS and VHIO.

To be hosted by WIS, the meeting incorporates 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.

Internationally renowned experts from among WIS and VHIO Faculty, as well as other leading research institutes from Spain, have been specially selected not only for their respective areas of expertise in the realm of cell communication in cancer, but also for their shared dedication and drive towards translating and accelerating cancer discovery at preclinical level into real benefit for cancer patients. Engineered to report on pioneering research into cancer molecular mechanisms and efforts towards precision cancer science and medicine, the conference has been purposely devised to encourage the active participation of our up-coming talents in the oncology -- our young scientists and physician-researchers.

It is thanks to the generosity of the following WIS-VHIO meeting sponsors that we will be able to share latest insights with colleagues and peers, as well as explore possible new avenues for collaboration: Mr. David Gebler, Madrid, Spain, Casa Cresques Barcelona Israeli-Catalan Hub, The Weizmann Institute of Science, The Weizmann Institute of Science Feinberg Graduate School, The Nancy & Stephen Grand Israel National Center for Personalized Medicine, Conferences and Schools Program, WIS-CSP, and VHIO.

To discover more about this WIS-VHIO exploration into the breakdown of cell communication, the consequential cancer growth and spread, and promising therapeutic avenues against it, visit: wws.weizmann.ac.il/conferences/CCTR2015/.

- VHIO 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 2014 and much more, we invite you to browse our extended Scientific Report 2014 online at: http://memorias.vhio.net/2014/.

Scientific Productivity: research articles

ARTICLES PUBLISHED IN 2014

In 2014, 170 scientific articles (83% Q1) were published by VHIO researchers as corresponding/ senior or co-authors with a cumulative Impact Factor totaling at 1551.677, and a Median Impact Factor (MIF) of 9.13.

These figures reflect an increase in scientific productivity, maintained MIF score, 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 - 2014

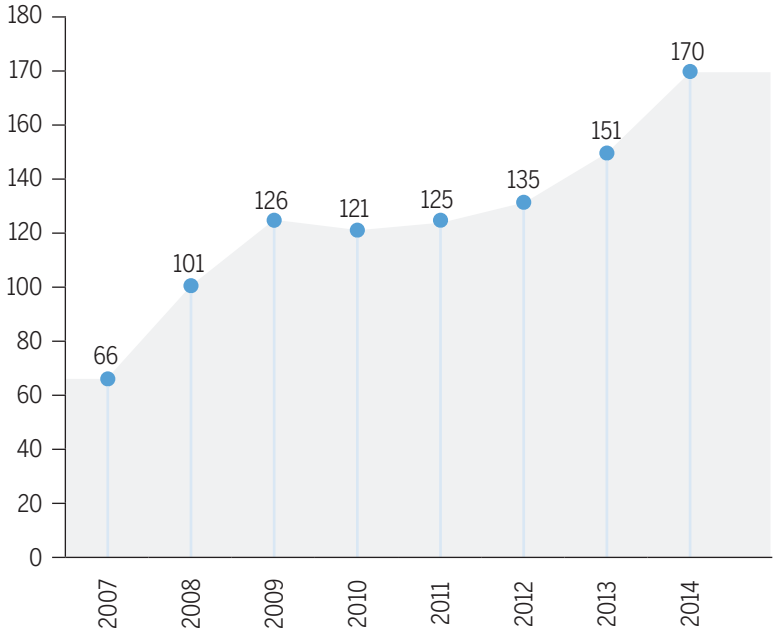


Figure I

IMPACT FACTOR ARTICLES PUBLISHED IN 2014

For the complete list of VHIO scientific articles published in 2014 in journals with allocated Impact Factor please see pages 83 - 91. To view a selection of most relevant articles by VHIO researchers published in 2014 please refer to pages 15 - 17 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/2014/ (select tab 'Publications & Awards').

Figure II: MEDIAN IMPACT FACTOR (MIF) OF PAPERS PUBLISHED BY VHIO FACULTY FROM 2007 – 2014

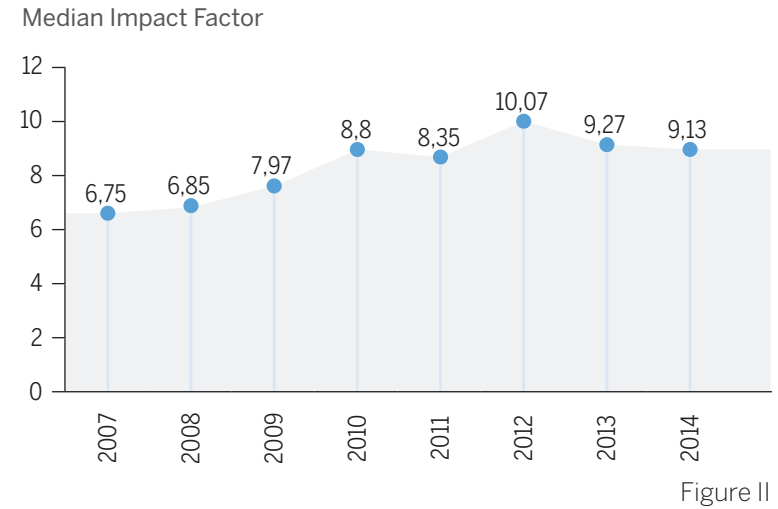


Figure II

Selection of some of the most relevant articles by VHIO researchers published in 2014

Below is a selected list of articles published by VHIO researchers in 2014 with respective Impact Factors indicated. For the complete list of VHIO scientific articles published in 2014 in journals with allocated Impact Factor please see pages 83 - 91 of this Scientific Report.

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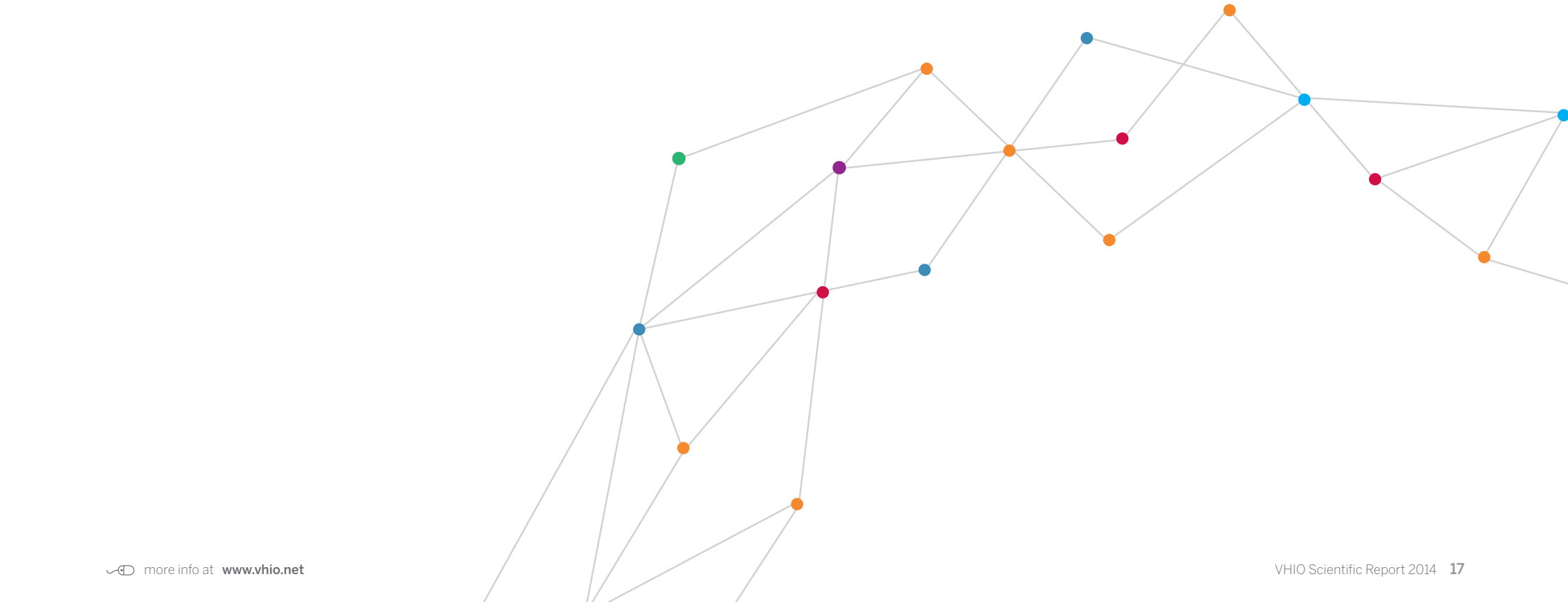

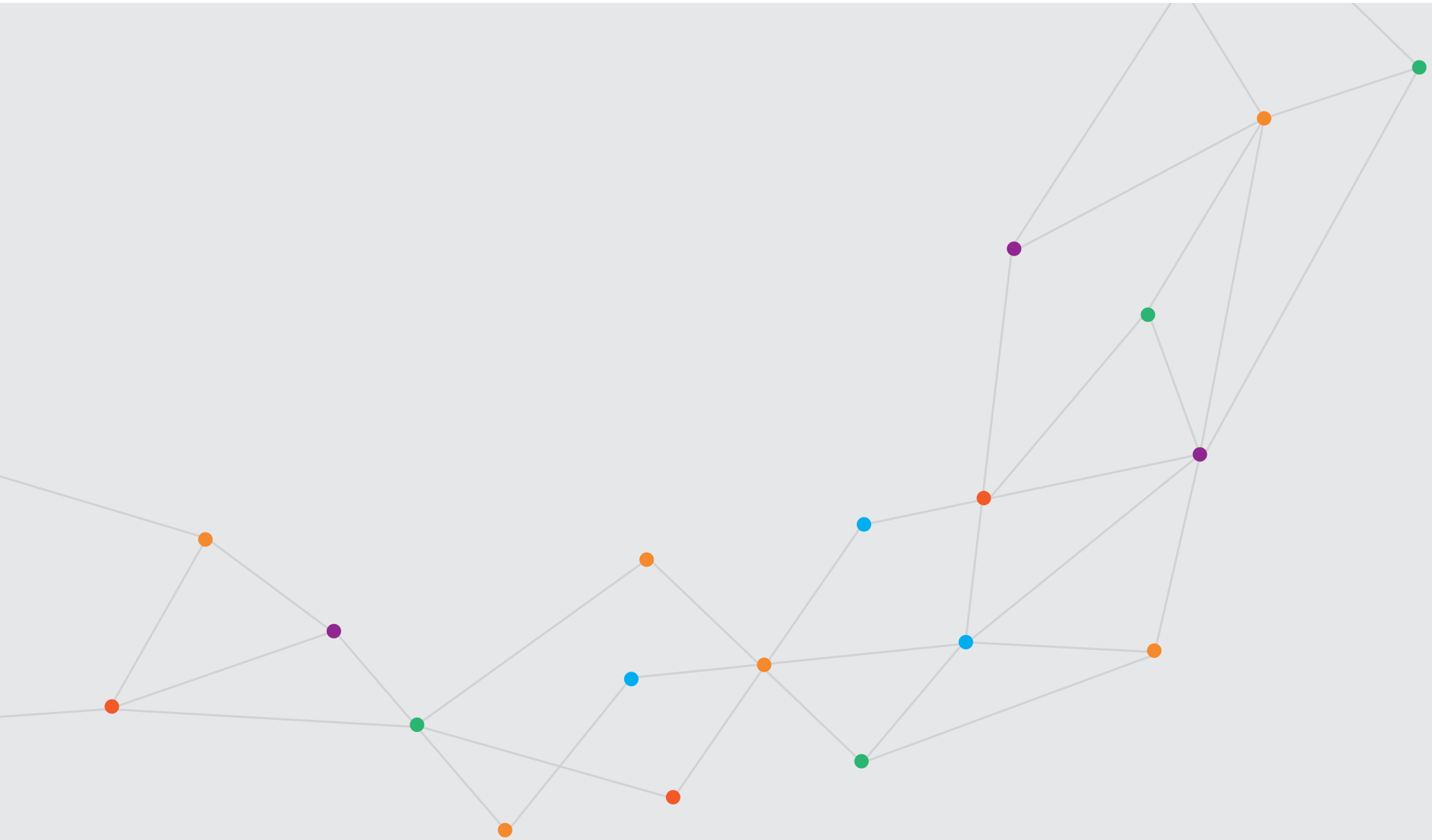

VHIO'S MULTIDISCIPLINARY RESEARCH PROGRAMS

PRECLINICAL RESEARCH

DIRECTOR, PRECLINICAL RESEARCH PROGRAM

Joaquín Arribas

VHIO's Preclinical Program focuses on developing new strategies to treat highly aggressive tumors including those that affect the breast, pancreas, colon, or brain. These cancers have a very poor prognosis either because we do not have suitably effective therapies against them or the tumors have become resistant to treatments that worked, but only for a limited period of time.

To model these tumors and test novel therapies in the laboratory we have developed a series of genetically modified mice. In addition, we implant tumor pieces resected from patients at the Vall d'Hebron University Hospital into immunodeficient mice. Once established in mice, these tumors, known as patient-derived xenografts, constitute a model that closely resembles the original tumors allowing our groups to test their novel therapies and discover mechanisms of resistance to current anti-cancer agents.

Using these models we analyze how some critical signaling pathways affect the progression of primary or secondary resistant tumors. These pathways, including the MEK-ERK and the PI3K-mTOR, both activated by the tyrosine kinases receptor, converge on Myc, a central regulator of gene expression. We are also interested in how malignant cells modify extracellular media and normal neighbor cells to generate the environment that promotes tumor growth. We are constantly searching for components and mechanisms against which to develop drugs to block malignant progression.

Our Mouse Models of Cancer Therapies Group, headed by Laura Soucek, has continued to carry out outstanding research on the Myc oncogene and has recently evidenced that its inhibition is a valuable and effective therapeutic target to treat glioblastoma, a brain tumor of dismal prognosis. 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. In addition, the group has identified that c-KIT activation impairs the antitumor activity of PI3K inhibitors in a subset of triple negative breast cancer, providing a rationale to combine PI3K and c-KIT inhibitors in this indication.

Using cutting-edge proteomic techniques, our Tumor Biomarkers Group, under the leadership of Josep Villanueva, has identified a novel biomarker, phosphorylated-EGFR, in patients with colorectal cancer that may provide insights into the response of these tumors to a drug directed against EGFR.

Finally, my own Growth Factors Group has continued to characterize the response to treatment of a subtype of breast cancer known as HER2-positive. We have described novel components of the signaling pathway activated by the receptor tyrosine kinase HER2 that are relevant to the progression of breast cancers. We have also identified a biomarker that predicts the response of HER2-positive tumors to targeted therapies.

Our groups' results have been published in several top-tier scientific journals of scientific excellence including *The Journal of the National Cancer Institute* (JNCI), *Nature Communications, Clinical Cancer Research*, and *Oncogene*, among others. Furthermore, as a direct reflection of the high caliber of cancer science that we conduct, our groups are supported through International and National Competitive Grants from Worldwide Cancer Research (formerly known as AICR), the Breast Cancer Research Foundation (BCRF), *Instituto de Salud Carlos* (Institute of Health Carlos III, ISCIII), and the Spanish Association Against Cancer (AECC). Finally I would like to highlight that our colleague, Laura Soucek, has been awarded a Professorship from ICREA (Catalan Institute of Research and Advanced Studies), which is arguably the most prestigious academic Catalan institution.

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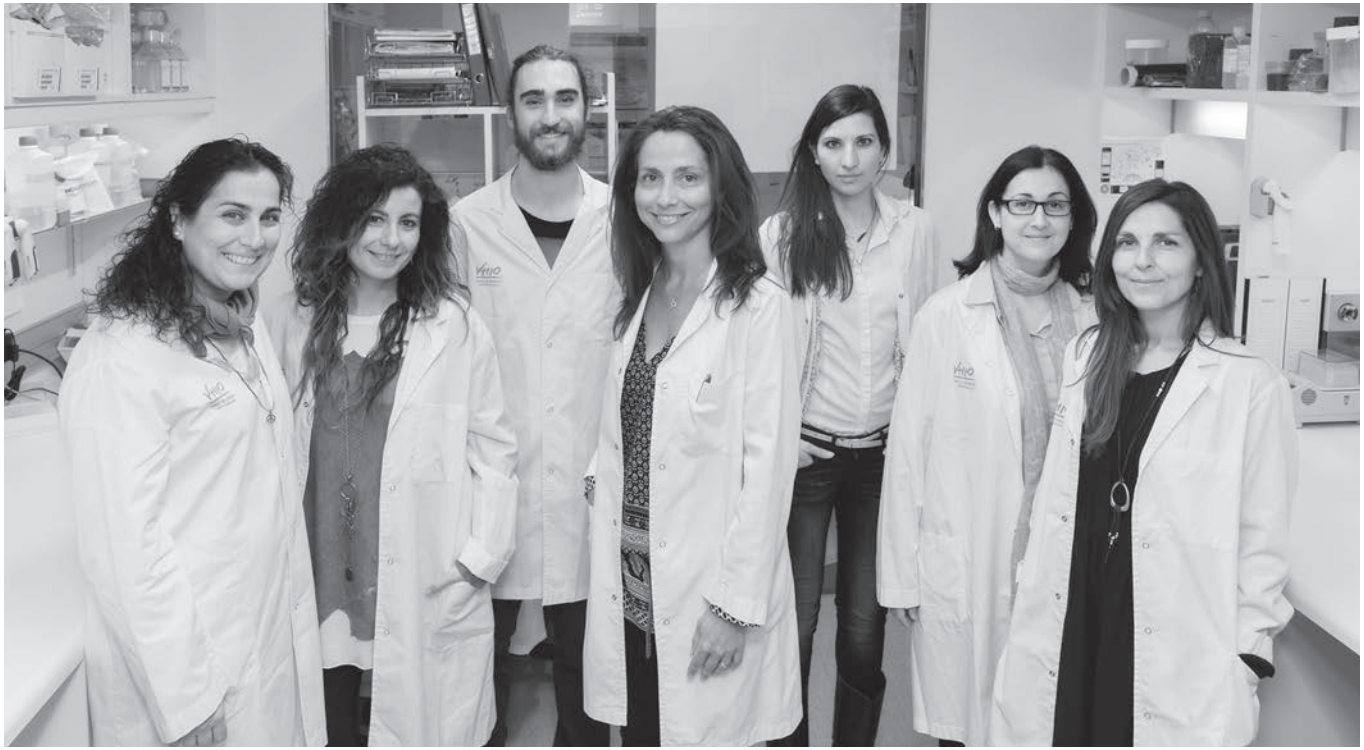

Strategic Goals

1. Study early molecular responses following PI3K inhibition to rationally design novel combination therapies in breast cancer.
2. Develop predictive and pharmacodynamic biomarkers of PI3K-pathway inhibitors.
3. Unveil novel mechanisms of resistance against targeted therapies in germline BRCA1/2 breast cancer.
4. Establish a patient tumor-derived breast cancer preclinical model to explore hypothesis-based combinatorial therapies.

Highlights in 2014

- We have identified two mechanisms that lead to activation of mTORC1 signaling and impair sensitivity to PI3K inhibitors. This preclinical observation has been linked with limited activity of these agents in the clinic and supports combination therapeutic strategies to improve the activity of this class of agents.
- We have developed a panel of twenty patient-derived triple negative breast cancer xenografts (PDX) and evaluated the activity of novel therapeutic strategies exploiting their deficiency in DNA damage repair and cell cycle checkpoints.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

SUMMARY

During 2014 our research has advanced the understanding of mechanisms of sensitivity and resistance to targeted therapy in breast cancer, with two main areas of focus: the blockade of the PI3K-pathway as well as therapies targeting homologous recombination deficiency. Our ultimate aim is to provide hypothesis-based strategies to combine targeted therapy and, in so doing, improve outcomes for patients. To address these questions, we have established novel patient tumor-derived breast cancer models *in vivo*, in collaboration with VHIO's Breast Cancer and Melanoma Group led by Javier Cortés. These preclinical models faithfully recapitulate the disease and have been extremely useful in the study of targeted therapy sensitivity and resistance (see figure).

Insights into the biochemical adaptation following PI3K-pathway blockade had revealed the presence of a FOXO/HER3-mediated ERK activation that limits the activity of the PI3K inhibitors in HER2 positive breast cancer. Further studies have identified c-KIT and IGF-1R as important players mediating the PI3K-compensatory response in some subsets of triple negative and in luminal B breast cancer, respectively. Given that targeting these membrane receptors *in vivo* results in therapeutic benefit when combined with PI3K-pathway inhibitors in certain models, predictive biomarkers are required.

We are further exploring potential predictive biomarkers in PI3K-targeting therapies by dissecting single agent PI3K-inhibitor responders and patients' genotypes. Specifically, we have analyzed genomic differences between tumors that have become resistant to single-agent PI3K-pathway inhibitors, following a significant clinical response. Interested in the impact of PI3K activation in other cancers, we have dissected the potential role of *TP53* as a biomarker for dual PI3K/MEK-targeting in colorectal cancer. We have also demonstrated sensitization of chemotherapy-resistant breast cancer tumors to combined PI3K-therapeutic regimens --a study that has resulted in the activation of a Phase Ib clinical trial internationally led by our institution.

Encouraged by the clinical activity of PARP inhibitors (PARPi) in early clinical trials with germline BRCA1/2 mutation carriers (gBRCA1/2) and their profound response in PDX, we initiated a project in collaboration with VHIO's High Risk & Cancer Prevention Group headed by Judith Balmaña to anticipate novel genetic and epigenetic mechanisms of resistance to novel therapies in gBRCA1/2. We have tested the activity of PARPi in twenty triple negative breast cancers, of which ten harbor gBRCA1 mutations. These models exhibit differential sensitivity to PARP blockade, ranging from sensitive to upfront resistant. Acquired resistance to PARPi has been generated in sensitive models by continuous exposure to the drug. Exome sequencing of these models has been performed in collaboration with VHIO's Cancer Genomics Group led by Ana Vivancos, and we have identified a number of resistance candidate genes, currently under functional validation.

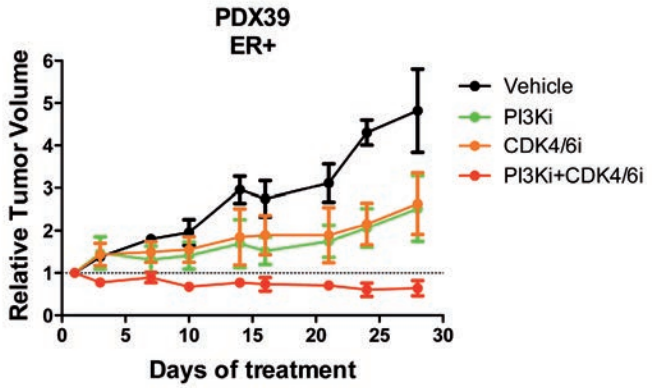

Figure: Upfront combination activity of PI3K- plus CDK4/6- blockade in an estrogen receptor (ER) positive patient-derived tumor model.

Growth Factors Group

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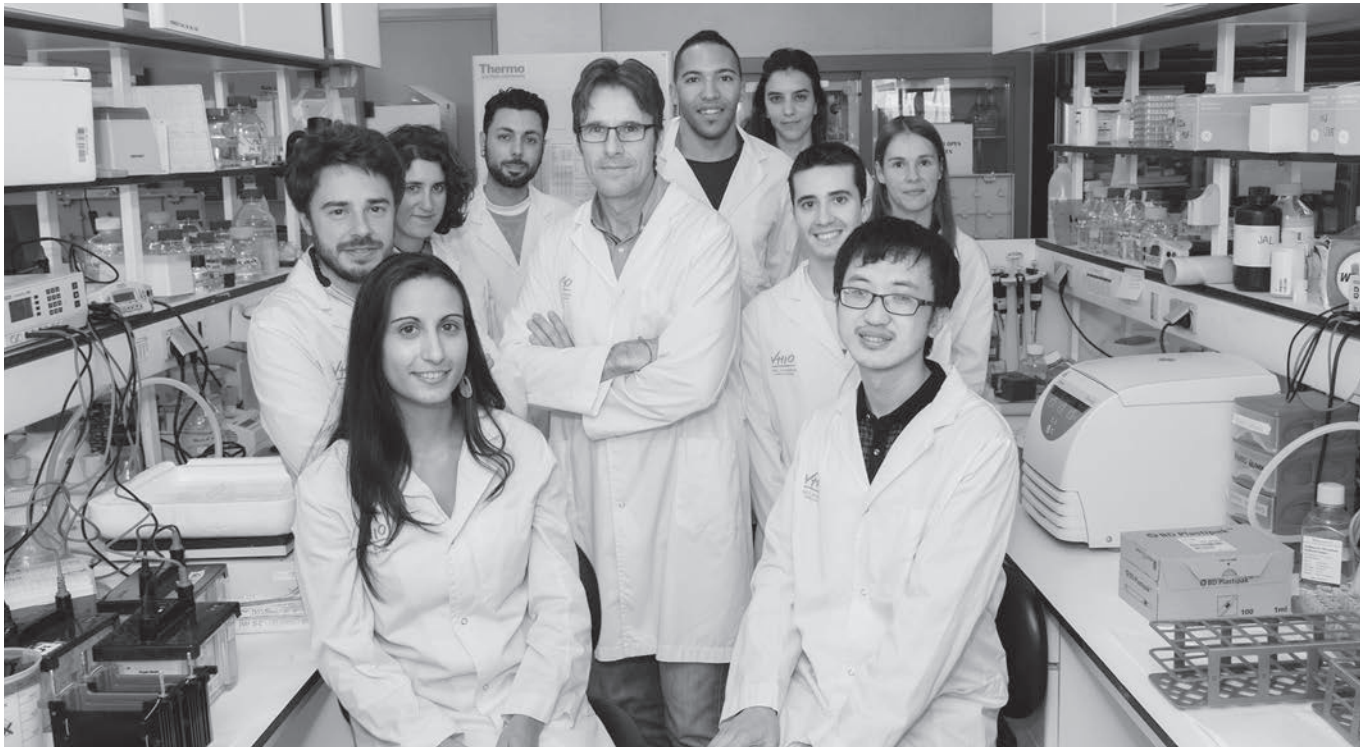

Strategic Goals

1. Characterize the role of premature senescence in breast cancer progression.
2. Develop novel therapeutic strategies to treat HER2-positive tumors and identify mechanisms of resistance to current therapies.
3. Continue to develop a pancreatic cancer research program in close collaboration with VHIO's Clinical Research Program, directed by Josep Tabernero.

Highlights in 2014

- We have established that PELO is a novel regulator of the signals transduced by HER2.
- Our group has also shown that chemotherapy sensitizes breast tumors expressing p95HER2 to treatment with trastuzumab, a monoclonal antibody against HER2.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

SUMMARY

Continuing our focus on breast cancer and receptor tyrosine kinases, during 2014 we completed the characterization of the role of the receptor tyrosine kinase HER2 in breast cancer progression and identified PELO as a negative regulator of the signaling pathways initiated by HER2. Importantly, the knock down of PELO increases the metastatic ability of breast cancer cells. In addition, we showed that breast cancer cells that express a fragment of HER2, known as p95HER2, are particularly sensitive to chemotherapy combined with targeted therapies.

We have also been collaborating with other VHIO groups, particularly with the Tumor Biomarkers group led by Josep Villanueva, to characterize how cancer cells remodel the extracellular environment.

We are extremely grateful to the Spanish Association Against Cancer (AECC) and the Breast Cancer Research Foundation (BCRF) for their continued, critical 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*, supported by the *Insituto de Salud Carlos III* (ISCIII). This network incorporates many of the most active groups working on breast cancer in Spain. We work in close connection to deliver on complex projects that require the input and expertise of multiple groups.

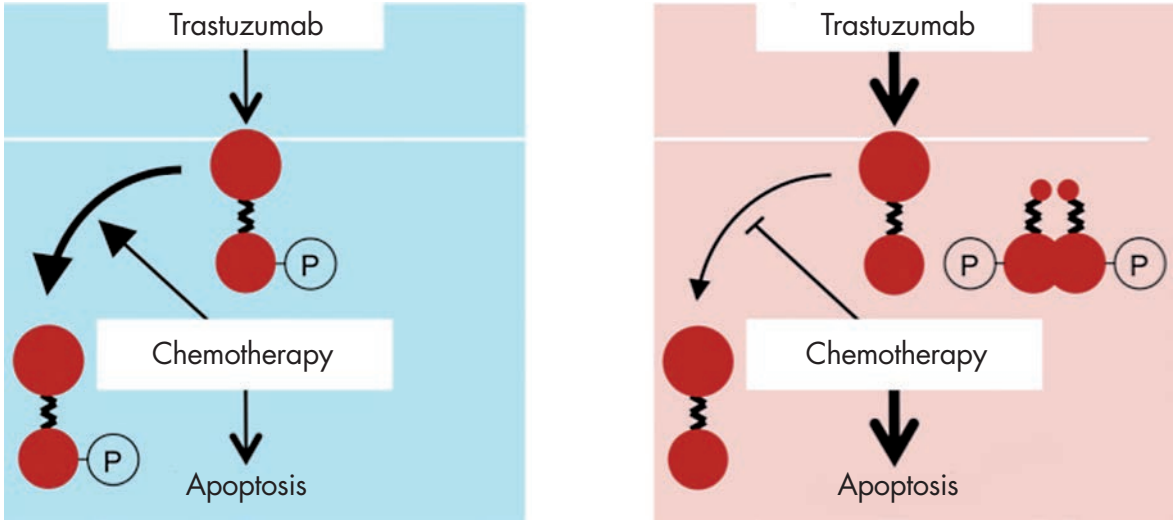

Figure: Chemotherapy sensitized breast cancer cells expressing p95HER2 to treatment with trastuzumab. Schematic drawing showing the effect of the combination of trastuzumab and doxorubicin on p95HER2/611CTF- negative cells (blue background) or p95HER2/611CTF-positive cells (red background). HER2 is represented by two large filled red circles linked by a broken line, the p95HER2/611CTF constitutively active fragment is represented by a small filled red circle linked with a broken line to a big one.Treatment with doxorubicin induces apoptosis more efficiently in p95HER2/611CTF-positive cells and, additionally, destabilizes phospho-HER2 and stabilizes HER2 in p95HER2/611CTF-negative and -positive cells, respectively.

Mouse Models of Cancer Therapies Group

Principal Investigator
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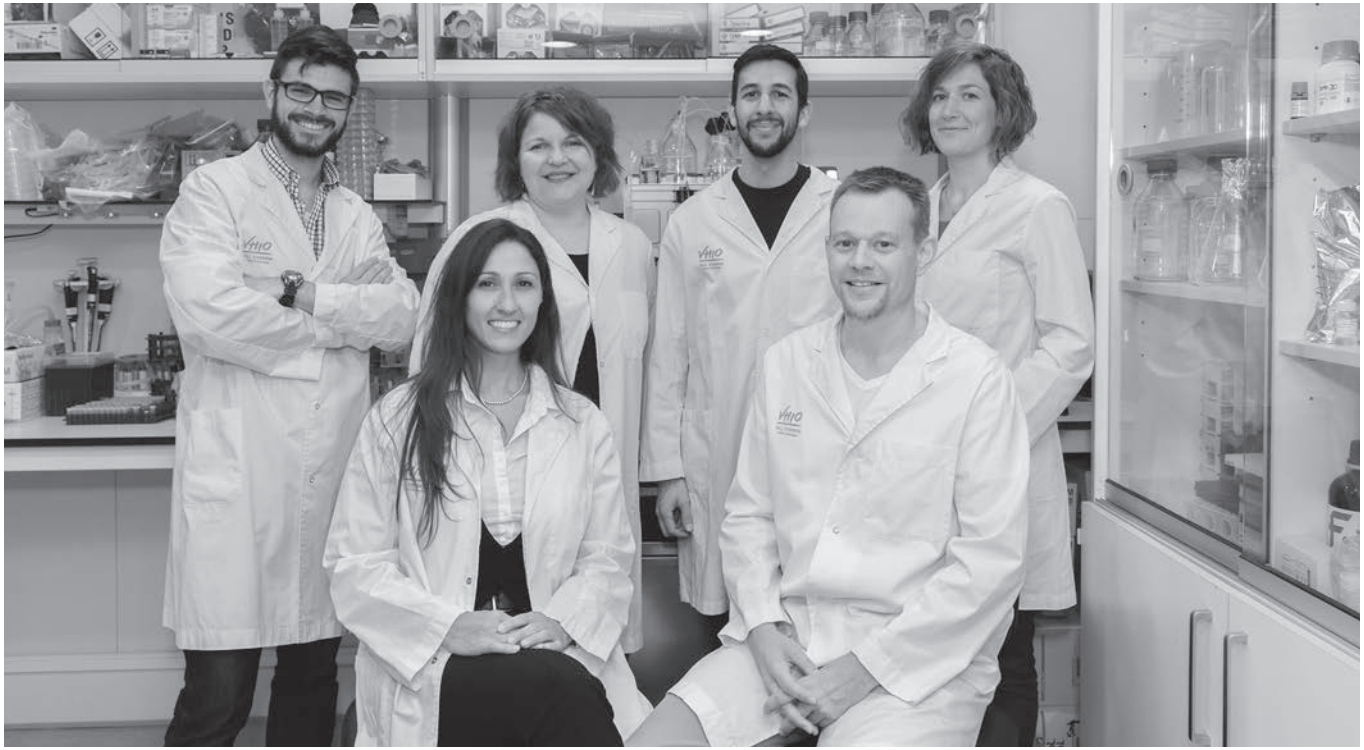
Jonathan Whitfield

Post-Doctoral Fellow
Marie-Eve Beaulieu

Graduate Students
Toni Jauset González
Daniel Massó Vallés

Technician
Erika Serrano del Pozo



Strategic Goals

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

Highlights in 2014

- Laura Soucek was awarded the prestigious European Research Council (ERC) Consolidator Grant to develop a new generation of Omomyc-based peptides for the treatment of lung cancer.
- The Soucek laboratory was recognized as an Emerging Research Group of Catalunya from the Agency for Management of University and Research Grants (AGAUR).
- The group was also awarded a grant from *Instituto de Salud Carlos III: Proyectos FIS de Investigación en Salud*, for the project *Advancing Myc inhibition towards the clinic for the treatment of lung cancer*.
- Laura Soucek was appointed as an ICREA (Catalan Institute of Research and Advanced Studies) Research Professor.
- Myc inhibition was shown to be an effective strategy against glioma and to cause mitotic catastrophe in cancer cells.
- Laura Soucek and lab members Toni Jauset González and Daniel Massó-Vallés were the inventors in a Patent application for the US patent *Methods for the Treatment of Fibrosis*, presented by Pharmacyclics. Inc.
- Marie-Eve Beaulieu, Post-doctoral Fellow in the lab, was granted a postdoctoral training award from the *Fonds de Recherche en Santé du Québec* (FRQS).

SUMMARY

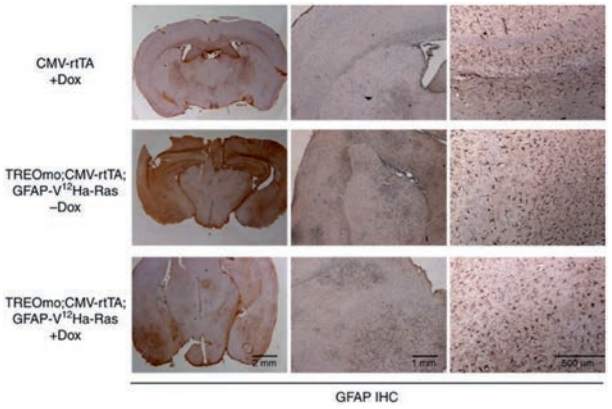
The ideal cancer drug should target a signaling conduit common to multiple cancer types, be both non-redundant and also necessary for tumor maintenance, as well as dispensable for normal tissue function. In the search for this ideal target our group focuses on the pleiotropic and ubiquitous Myc oncoprotein, 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.

We are currently extending our studies to the notoriously difficult to treat cancers that are currently resistant to standard therapy 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 has been the focus of our recently published study in *Nature Communications* (Annibali et al., *Nat Commun*. 2014), in which we demonstrated that Myc inhibition would be a valuable therapeutic approach by causing mitotic catastrophe, arrest and death of cancer cells.

Encouraged by our results in mouse models, we are now interested in developing viable, non-toxic pharmacological options for Myc targeting in the clinic. In this context, this year we obtained a prestigious European Research Council (ERC) Consolidator Grant, to develop, produce and purify Omomyc-based cell penetrating peptides for direct delivery to cancer cells and tumors. Studies assessing their therapeutic impact are currently underway.

In recognition of research of excellence, Laura Soucek was appointed as one of ICREA's (Catalan Institute of Research and Advanced Studies) newly contracted Professors in 2014. ICREA is a prestigious and internationally renowned virtual research institute which today incorporates a total of 244 scientists selected from a global pool of researchers.

Lastly, but by no means least, we are pleased to report the set-up of our own spin-off company, Peptomyc S.L., for the development of Myc-inhibiting peptides for cancer therapy.



Adapted from Annibali *et al*., 2014

Figure: Histological analysis of symptomatic mice. Representative GFAP immunostaining of normal CMVrtTA and triple transgenic TRE-Omomyc;CMVrtTA;GFAP-V12Ha-Ras brains. Left panels show that astrocytic density is reduced in Omomyc-expressing mice. Center panels focus on residual GFAP-positive regions. Right panels show higher magnification of astrocytes and active microglia. Mice treated with Omomyc display reduced astrocytic hyperplasia and density compared to untreated mice.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

Tumor Biomarkers Group

Principal Investigator
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Post-Doctoral Fellows
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Theodora Katsila
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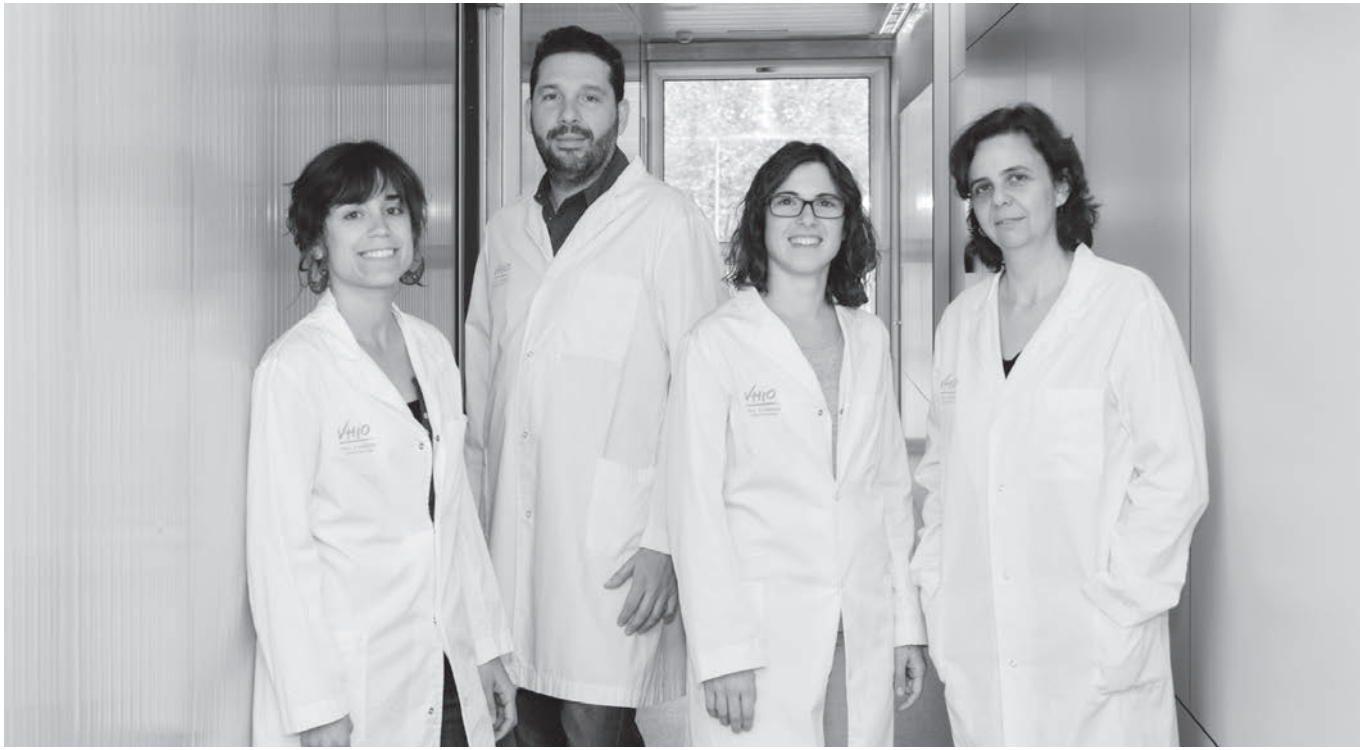
PhD Student
Josep Gregori



Strategic Goals

1. The characterization of mechanisms adopted by tumor cells to communicate with their microenvironment during tumorigenesis. This data is then used for biomarker discovery.
2. Discovery of secreted signaling pathway-based tumor biomarkers and therapeutic targets using quantitative proteomics.
3. To establish secreted response/resistance biomarkers to targeted drug therapy, measurable through non-invasive methods.

Highlights in 2014

- Our group has described an EGFR-centric secretome induced by cetuximab in 3D spheroids of colorectal cancer cells. Furthermore, in plasma of colorectal cancer patients we have identified and preliminarily validated that phosphorylated-EGFR is a candidate-secreted biomarker of response to cetuximab. We have also shown that intracellular and extracellular signaling are connected in tumor cells, and how this connection can lead to the non-invasive monitoring of anti-EGFR treatment in patients with colorectal cancer.
- We have developed and implemented a normalization algorithm that corrects the statistical results of secretome-based comparative proteomic studies by the global protein secretion rate of cells. The application of this normalization to two different biological scenarios altered the statistical significance of several secreted proteins. In an epithelial-to-mesenchymal transition (EMT), known EMT effectors were only statistically significant when the normalization was applied. Therefore, the cell-centric normalization of secretomes increases the sensitivity of statistical tests by increasing the number of true-positives among the list of candidate biomarkers.

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 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, therefore representing potential therapeutic targets.

Proteomic technologies facilitate a genome-scale hunt for tumor-specific biomarkers and drug targets and could consequently revolutionize early detection and molecular characterization of cancer through non-invasive methods. The methodological focus of our group centers on a new proteomic approach capable of quantitatively profiling the secreted sub-proteome ('secretome') of cells. Secretome signatures in different breast cancer model systems - as well as from clinical samples, will be generated and analyzed using differential expression statistics, and then set within the context of intracellular signaling transduction using bioinformatic tools.

The cancer secretome contains secreted proteins that tumor cells use as molecular SMS to communicate to each other and with their microenvironment. Since they are secreted they are most probably present in biological fluids such as blood. Our final goal is to identify tumor-specific secreted proteins that can be used to develop blood-based diagnostic tests for the detection and monitoring of cancer.

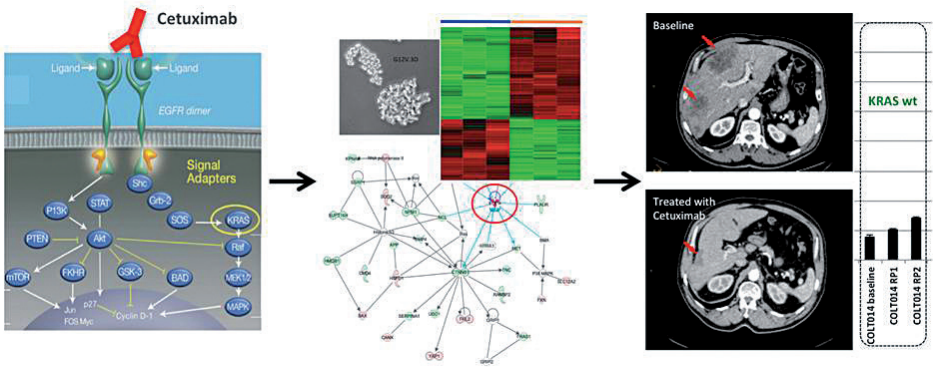
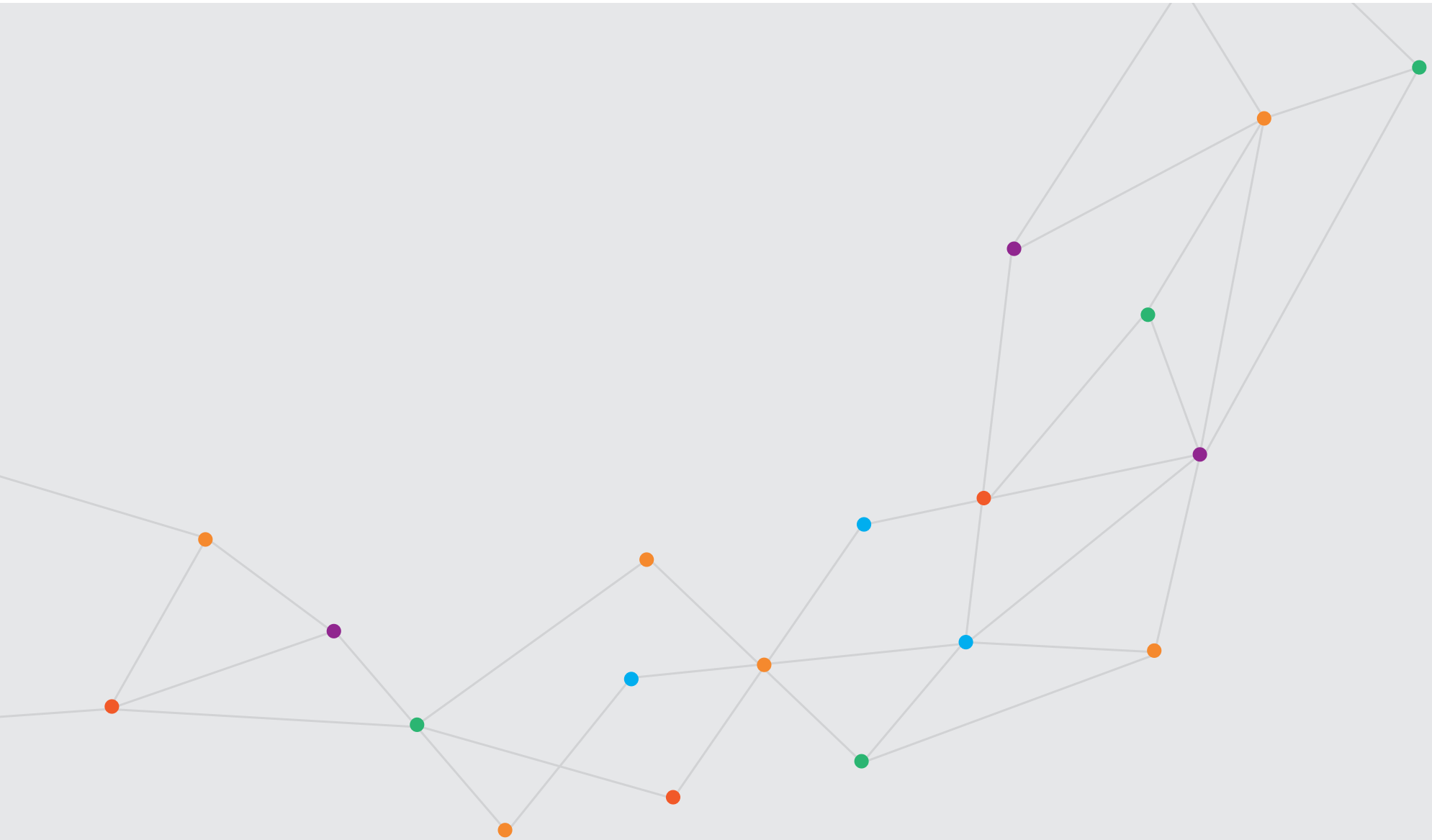


Figure: Workflow of a project aimed at the identification of response biomarkers of action of cetuximab in colorectal cancer. The left hand side of the figure shows a schematic representation of the EGFR pathway in the context of cetuximab treatment. The middle part of the figure depicts the experimental approach adopted, consisting of a combination of 3D culture, quantitative secretome-based proteomics and pathway analysis-based statistics and bioinformatics. The right side of the figure illustrates the translation of the proteomic results to a non-invasive blood test that correlates well with standard radiologic imaging of the therapy in patients.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/



VHIO'S MULTIDISCIPLINARY RESEARCH PROGRAMS

TRANSLATIONAL RESEARCH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DIRECTOR, TRANSLATIONAL RESEARCH PROGRAM

Joan Seoane

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 to patient care as rapidly as possible by 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 combat cancer is tumor diversity. Cancer is an extremely complex and heterogeneous disease given that tumors are molecularly diverse. 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. Patients should therefore be treated with the optimal compound/combination of compounds 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, 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 cancer treatment through the combination of compounds targeting all cell types within a tumor, it is also imperative to 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, their multi-lineage differentiation properties, their 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 result from 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 effectively 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 the tumor cells including cancer stem cells are studied. 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 types of models of colon and brain cancer respectively, work which has led to important findings published in top-tier journals.

Providing optimal treatment tailored to individual patients relies on teamwork, 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 insights generated by scientific research into the true benefit for patients.

Gene Expression & Cancer Group

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Isabel Cuartas
Rosa Gil
Carolina Raventós
Cristina Sánchez
Sara Sánchez-Redondo Campos

Strategic Goals

1. Generate patient-derived mouse models of brain tumors.
2. Study intratumoral heterogeneity.
3. Identify both novel therapeutic targets against brain tumors as well as novel biomarkers to predict response to treatment.
4. Better understand the molecular mechanisms implicated in cancer initiating cells/ cancer stem cells.
5. Develop methods for non-invasive molecular diagnosis through the study of circulating biomarkers.

Highlights in 2014

- Our efforts have led to several publications in 2014 (for all our group's publications please visit the 2014 VHIO Scientific Report online at: http://memorias.vhio.net/2014/). Specifically we would like to highlight the publication Rodon L. *et al*. *Cancer Discovery* 2014, reporting on molecular mechanisms involved in the aberrantly high levels of TGFb2 present in some glioblastoma. We found that a malignant autocrine loop occurs in glioblastoma where TGFb2 induces TGFb2 which in turn induces more TGFb2. The work identified CREB as a therapeutic target against glioblastoma and a biomarker to predict the response to anti-TGFb agents since CREB is the transcription factor involved in the generation of the autocrine loop.
- Joan Seoane received the prestigious *Doctores Diz-Pintado* National Prize (5th edition).

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

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 the field is consequently critical. Our studies are largely based on research into patient-derived tumors. Since 2005, we have been generating animal models that recapitulate the tumor of the patient at genomic and gene expression levels. We inoculate the patient-derived tumor cells into the brain of immunocompromised mice and they generate tumors with the same characteristics as the original human tumor, which we can then monitor by MRI. This mouse model for human glioma is of major interest in the study of the molecular mechanisms involved in cancer as well as the evaluation of the efficacy of pharmacological compounds.

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 the genomic diversity present in glioblastoma and how the intratumor genomic heterogeneity evolves with time in response to treatment. Following Darwinian selection rules, the cellular subclones enriched in response to treatment are the ones that will confer resistance to treatment and will facilitate the identification of novel therapeutic targets to avoid 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. CICs are, therefore, crucial therapeutic targets and advancing our understanding of the molecular mechanisms involved in these cells is paramount. We aim to identify novel markers for CICs, gain 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 sequencing of the circulating DNA allows for the accurate, non-invasive molecular characterization of tumors. These circulating markers facilitate the diagnosis, monitoring and identification of actionable gene mutations of tumors.

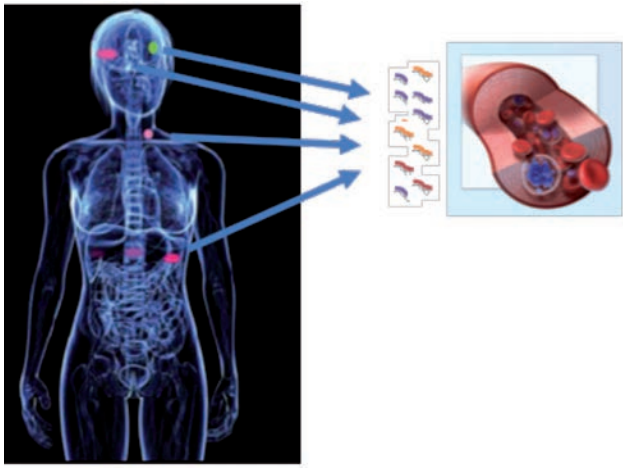

Figure: Cell-free circulating tumor DNA allows the genomic characterization of tumors.

TRANSLATIONAL RESEARCH

Stem Cells & Cancer Group

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Post-Doctoral Fellows
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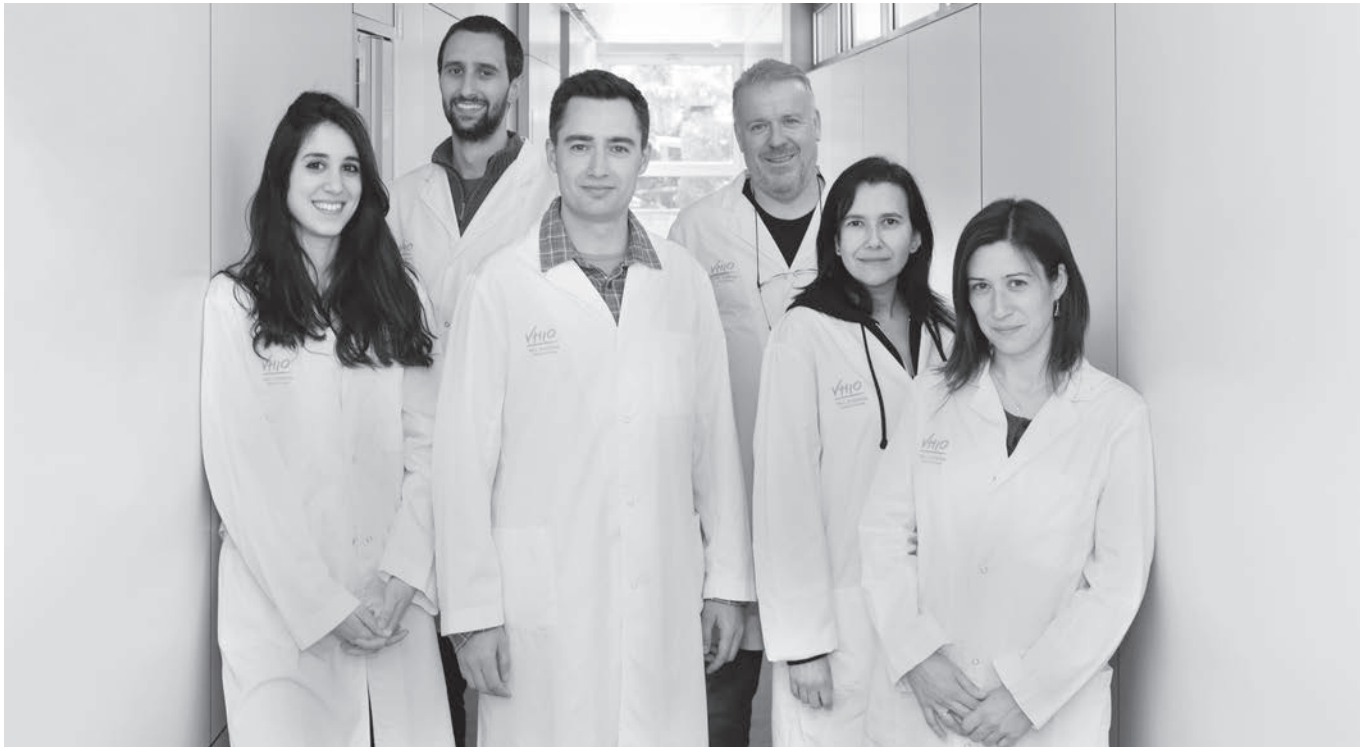
Stephan Tenbaum

Graduate Student
Oriol Arqués

Technician
Irene Chicote

PhD Student
Estefania Cuesta



Strategic Goals

1. Describe the key molecular mechanisms that confer Colon Cancer Stem Cells (CoCSC) their capacity to self-renew and resist conventional or target directed therapies.
2. Unmask the molecular drivers of Cancer Stem Cells (CSC) quiescence, clinical relevance in cancer progression and evaluate their potential inhibition to eradicate CoCSC.
3. Study the efficacy and mechanism of action of new Wnt/beta-catenin inhibitory drugs for the treatment of Colorectal Cancer (CRC) patients.
4. Identify the genetic determinants of sensitivity or resistance to the novel generation of Wnt/beta-catenin inhibitors.
5. Implement predictive biomarkers of response to therapeutic Wnt/beta-catenin inhibitors and other targeted therapies.

Highlights in 2014

- We have discovered the molecular mechanisms governing the delicate link between stemness and quiescence in chemo-resistant colon cancer cells. Many of the genes and proteins that play a central role in this process are epigenetic chromatin remodelers. The activity of these factors can potentially be inhibited as a new therapeutic approach to eliminate CoCSC.
- Our group has accumulated evidence regarding the efficacy and mechanisms of action of a new generation of Wnt/beta-catenin inhibitory drugs on CRC. We have also indentified biomarkers to predict response to these inhibitors.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

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.

In particular, 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. Furthermore, CSC can 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 a cancer treatment that fails to eliminate cancer stem cells may allow re-growth of the tumor.

As a hideous disease with such a devastating impact on society, 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 such driving forces that direct cancer stem cell fate and lead the progression of many tumor types.

Over recent years we have succeeded in describing a new mechanism of resistance to PI3K and AKT inhibitory drugs conferred by beta-catenin in colorectal cancer. Such discovery 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 described. These new findings will facilitate the selection of sensitive patients based on their expression of particular biomarkers that predict drug-response.

We are currently leading research focusing on a new generation of Wnt/beta-catenin inhibitory drugs in close collaboration with several major pharmaceutical companies. We have already provided experimental evidence regarding the efficacy and mechanisms of action of such drugs in pre-clinical models of colorectal cancer with patient-derived xenografts. This marks an important milestone in the field, since colorectal cancer was described as a paradigmatic tumor addicted to the oncogenic Wnt/beta-catenin pathway many decades ago. We are also identifying the molecular determinants of response to these drugs that could become robust biomarkers to select sensitive patients and guide the design of new clinical trials in the future. 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 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.

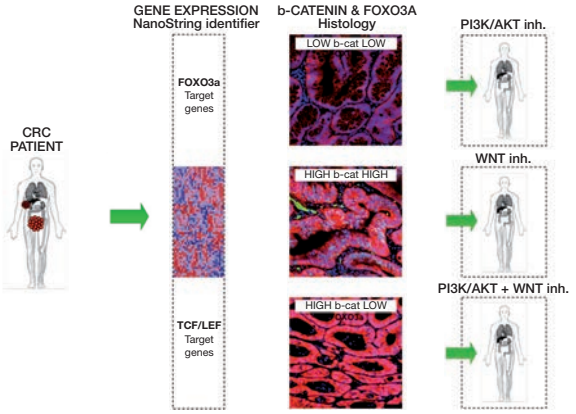
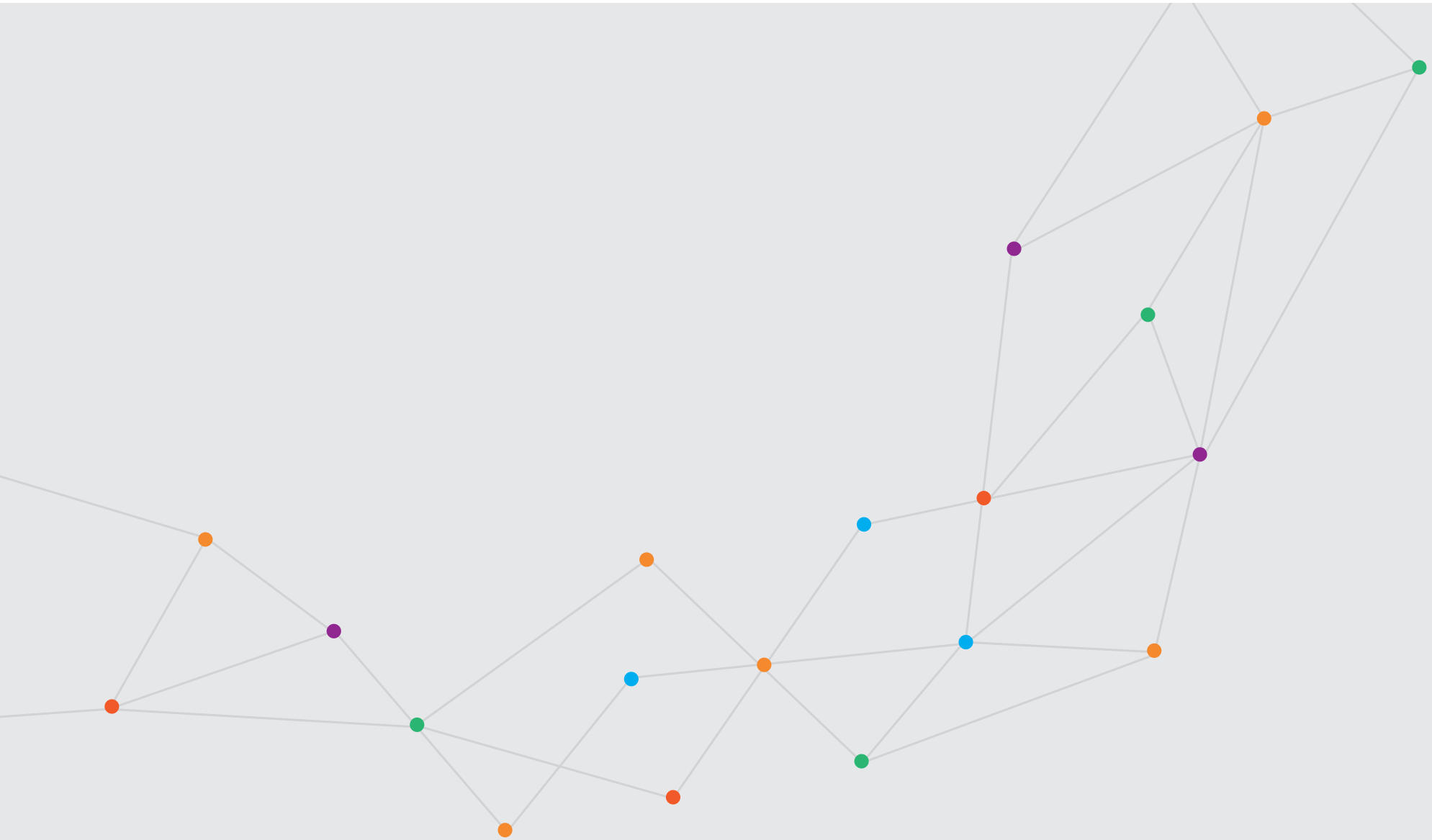


Figure: Molecular pre-screening and selection of colorectal cancer patients to be included in precise clinical trials with target-directed drugs.



VHIO'S MULTIDISCIPLINARY RESEARCH PROGRAMS

CLINICAL RESEARCH


VHIO

DIRECTOR, CLINICAL RESEARCH PROGRAM

Josep Tabernero

Our patients and our multidisciplinary approach are at the center of everything we do at VHIO. Our scientists and physician-researchers enable VHIO's Clinical Research Program to spearhead cooperative preclinical, Phase I & II studies aimed at developing novel therapeutics directed to specific signaling pathways across different tumor types, as well as new or redefined prognostic/diagnostic tools to better detect disease and more precisely predict response to anti-cancer therapies.

As this Scientific Report goes to print, we have just announced our collaboration with Merck Serono and Sysmex Inostics whereby VHIO will be the first academic center of its kind to use in-house BEAMing liquid biopsy RAS biomarker technology, initially to evaluate patients with metastatic colorectal cancer at research level -- to be extended to conventional routine care upon receiving European Conformity approval (CE Mark), and to other tumor types. Having successfully implemented BEAMing digital PCR/ flow cytometry technology, this tool will empower our existing suite of cutting-edge technologies.

The non-invasive and more accurate blood-based monitoring of patients may reveal disease recurrence as well as resistance driven by specific mutations such as that of the KRAS oncogene prior to the point at which treatment actually ceases to be effective. The tumor-derived somatic mutation profiling in plasma not only represents an alternative to tumor-tissue, it promises real-time insights into tumor dynamics and the pathways that drive cancer metastasis, and could enable us to explore additional treatment options and strategies aimed at either delaying or perhaps even preventing disease progression.

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, we collaborated in a multicenter study reporting promising results of a phase I clinical trial using immunotherapy to treat patients with metastatic bladder cancer. The findings, published in *Nature* at the end of 2014, supported the idea that immune response could be manipulated to achieve an objective reduction in tumor size in these patients. As we are starting to see the benefit of novel immunotherapeutic strategies across several clinical studies, immuno-oncology could well be poised to impact the way we will treat cancer in the future.

We have also developed a combined oncogenic pathway signature that allows the identification of colorectal cancer patients with an active epidermal growth factor receptor (EGFR)-signaling pathway that may benefit from downstream pathway inhibition.

Important studies involving both preclinical and early-drug development have resulted in the design of clinical trials aimed at identifying more effective cancer therapies tailored to the molecular makeup of individual patients. Our dedicated efforts in early phase trials including the exploration of novel agents as well as new drug combinations with the current cornerstones of cancer - - chemotherapy and radiation, have led to key findings published in journals such as the *New England Journal of Medicine*, *Lancet Oncology,* and *Journal of Clinical Oncology* to name a but a few (see pages 83 - 91 for the full listing of articles published by VHIO investigators in 2014).

While VHIO continues to significantly advance cancer discovery and therapeutics to ultimately benefit an increasing number of patients, we must continue to progress in partnership, across borders. In this respect, we continue to improve trial design through our participation in ongoing, multi-center studies including the WINTHER (WINTherapeutics) study and the POSEIDON trial. Another pioneering initiative is the MErCuRIC Phase Ib/II collaborative study to assess a novel therapeutic strategy to combat metastasis, improve survival and clinical practice for colorectal cancer patients. As a reflection of our expertise in early clinical drug development, we are currently participating in the Phase I trial, and we will be leading the Phase II study to come.

In addition to our participation in consortia of excellence, including Cancer Core Europe which launched this year in 2014 (see page 94), I also 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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Meritxell Bellet
Patricia Gómez
Esther Zamora
Leticia de Mattos
Eva Muñoz
Mafalda Oliveira
Vanesa Ortega
José Manuel Pérez
Aleix Prat
Cristina Saura
Jesús Soberino
Mª Jesús Vidal

Strategic Goals

1. Optimize treatment options for patients with resistant HER2- positive tumors and triple negative breast cancer, with particular focus on new targeted agents which overcome resistance to standard anti-HER2 agents.
2. To continue to lead Phase I-based- Phase II trials and closely collaborate with VHIO's Experimental Therapeutics Group, transitioning to more advanced studies with data obtained from early drug development.
3. Implement 'omic' tools to better design clinical trials.
4. To continue working with VHIO's preclinical groups to ultimately provide "smarter" therapy for our patients as rapidly as possible.
5. Advance onco-immunology towards improved management of patients with breast cancer, specifically HER2 and triple negative.
6. Establish our group as a leader in the field of melanoma in Spain.

Highlights in 2014

- We have observed that combining eribulin with PI3K inhibitors might enhance the activity of both drugs, which has in turn opened up new possibilities for our patients. A phase Ib/II trial commenced in 2014, led by VHIO investigators.
- We continue to develop patient-derived xenografts in collaboration with VHIO's Preclinical Research Program.
- We have been involved in the steering committees of the most relevant randomized Phase II and III clinical trials, and participated in some of the most important clinical trials, which has previously led to the approval of drugs such as pertuzumab and eribulin. In 2014-2015, we aim to lead two global phase III trials.
- Thanks to collaboration with surgeons, pathologists and other oncology professionals at the Vall d'Hebron University Hospital, our group has established itself as the most active in neoadjuvant studies in Spain.
- A circulating free DNA Program for genotyping and characterization was set up in 2012. We now have our first results which will be published next year.
- We have provided more than 10 different new molecules in close collaboration with VHIO's Experimental Therapeutics Group. More than 50% of our patients with metastatic melanoma have entered clinical trials.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

SUMMARY

Our Breast Cancer Program continues to be one of the most active in Spain and one of the most renowned across Europe. In 2014, our 28 publications, totaled an impact factor of 366.76, with a mean IF of 13.1. Notabily, we published a newly proposed concept surrounding cancer research in January 2014 (published ahead of print, Nov 2013), in the highest impact factor journal, *CA: A Cancer Journal for Clinicians* (IF:164). In addition, we have initiated more than 20 new clinical trials and studies. Our group is not only committed to participating in clinical and preclinical studies, but also leads several - reflected by our representation of Steering Committees for some, and appointed international leaders for others.

Our main areas of interest continue to center on the development of novel therapies and the search for mechanisms of resistance to current ones. Multidisciplinary collaboration and management with surgeons, pathologists, radiologists and radiotherapists, among others, facilitates the incorporation of the most innovative treatments in clinical practice and optimizes therapeutic alternatives. In clinical research, our key areas of activity include:

1. Over recent years, new targeted therapies against HER2 have become available. We are particularly proud to lead one of them, pertuzumab, which has improved outcomes of our patients. In close collaboration with VHIO's Growth Factors and Experimental Therapeutics Groups, different mechanisms of resistance to this therapy and other strategies are currently under study, with particular interest in the design of new approaches to overlap such mechanisms.

   There are two interesting new compounds which are currently being tested in Phase III trials; Neratinib and TDM-1. We are leading the NALA Trial – a pivotal phase III trial which compares neratinib plus capecitabine vs the standard lapatinib plus capecitabine. Importantly, we have observed that TDM-1 activity, although impressive, is not very significant during the first weeks of administration. For this reason, we are conducting a Phase Ib/II trial of TDM-1 in combination with chemotherapy.
2. The majority, if not all, of our patients with metastatic breast cancer will at some point require treatment with chemotherapy, and, unfortunately, they will eventually develop resistance. For this reason, we strongly believe that overcoming mechanisms of resistance to chemotherapy will enhance the activity of these drugs. In collaboration with VHIO's Experimental Therapeutics Group, we aim to improve the efficacy of eribulin, a new chemotherapeutic agent, with targeted agents based on a new mechanism of resistance. We demonstrated that the efficacy of eribulin depends on PI3K status. This resistance might be overcome by the addition of different PI3K inhibitors. In 2015, we will led the first Phase Ib/II trial.
3. Application of new biological agents to reverse mechanisms of resistance to classical drugs, not only to anti-HER2 therapy and chemotherapy, but also endocrine therapy.
4. Collaborating closely with VHIO's Early Clinical Drug Development Group, we are evaluating drugs that have been tested in early studies and have shown sufficient activity to expand research in patients.
5. Triple Negative Breast Cancer. We have started an ambitious clinical research program with a few specific clinical trials already underway. We are dedicated to leading this field of research over the next 4-5 years.
6. In collaboration with VHIO's Cancer Genomics Group, we are involved in exploring genes that mediate breast cancer metastasis to leptomeninges, in order to establish a model of gene-mediated leptomeningeal metastases in breast cancer. The ultimate goal is to identify the patients who are at increased risk of leptomeningeal metastasis from breast cancer. In so doing, therapeutic strategies based on the molecular characteristics of tumors can then be developed to prevent and treat leptomeningeal carcinomatosis from breast cancer:

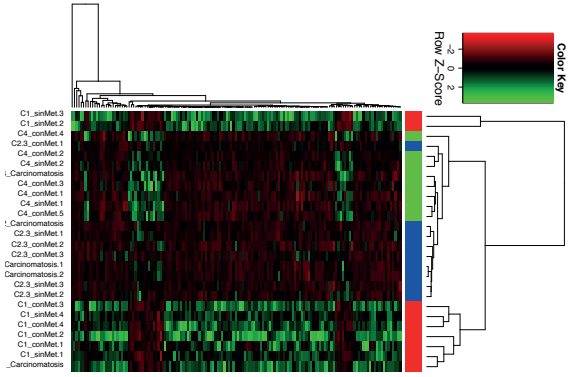

Figure: Heat-map of breast cancer tumours showing significant differences among 3 groups of patients: Luminal (red samples), young TNBC (blue) and old TNBC (green). Columns represent the 26 patients and rows the log2-fold change of 145 genes differentially expressed among the groups (adjusted p-value < 0.05).

Early Clinical Drug Development Group

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Esther Zamora

Strategic Goals

1. Early development of the best-in-class targeted therapies let by highly experienced and multidiciscplinary teams incorporating physician-researchers from the Research Unit for Molecular Therapy of Cancer (UITM) "la Caixa" and VHIO scientists. We collectively strive to accelerate early drug development and translational research through the management and treatment of patients in Phase I trials set within the optimal environment of the UITM (see pages 76 - 77).
2. Develop a program in genomic trials in early drug development; analyzing patients' tumors for molecular aberrations that may predict the efficacy of targeted agents, as well as better connect preclinical science and clinical research by incorporating novel drugs, new insights and study designs together with customized molecular diagnostics.
3. Set up a task force within the UITM with expertise 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.
4. Link clinical research at the UITM with the various preclinical and translational research groups at VHIO, and collaborate with the different partners involved in drug development and translational research (phase I units, academic centers, consortia, pharmaceutical companies).

Highlights in 2014

- As one of the leading institutes worldwide with expertise in areas of drug development including PI3K/akt/mTOR inhibitors, MAPK inhibitors or drugs targeting developmental pathways such as TGFbeta, SHH, WNT, and NOTCH, we have been clinically testing the best-in-class drugs. We have also expanded our expertise to other cell-signaling pathway inhibitors such as MET and FGFR, immunotherapeutics including agents targeting PD1/PDL1, OX40, CD40, and engineered antibodies.
- We have performed several clinical trials with novel-novel combinations - linking the following inhibitors: PI3K with MEK, IGF-1R with PI3K or MEK, Smo with a PI3K, and NOTCH with mTOR. In immunotherapeutics, we have explored combinations such as a CXCR4 antagonist with chemotherapy or a CD40 agonist with an anti-PDL1 agent.
- We have performed many clinical trials with patients selected on molecular alterations (mutations in AKT, EGFR, PIK3CA, PTEN, ALK, BRAF, NRAS, KRAS, FGFR1 and 2, MET, HER2, HER3; amplifications in HER2, AKT 1, 2, and 3, FGFR1, MET, NOTCH1-4, traslocation of RSPO2/3 and FGFR1-3, and alteration in protein expression of PTEN, or overexpression of PDL1, GCC or of prolactin receptor).
- Co-development of several molecular tests for patient screening such as disease-oriented mutation panels for Sequenom.

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) Consortium, initiated by the Institut Gustave Roussy (IGR), Paris, (France) and University of Texas MD Anderson Cancer Center, Texas (USA). WIN is a non profit, non-governmental organization that brings together 22 cancer centers including VHIO, along with various industry partners, to advance cancer diagnostics and therapeutics.

Our group is conducting the first WIN clinical trial, launched in 2012. WINTHER, a unique academic and international trial, represents a major step forward in the evaluation of precision therapy. We are collectively developing a comprehensive analysis of the genetic background of tumors in order to predict drug sensitivity and optimize individualized therapeutic decisions with improved clinical outcomes for patients.

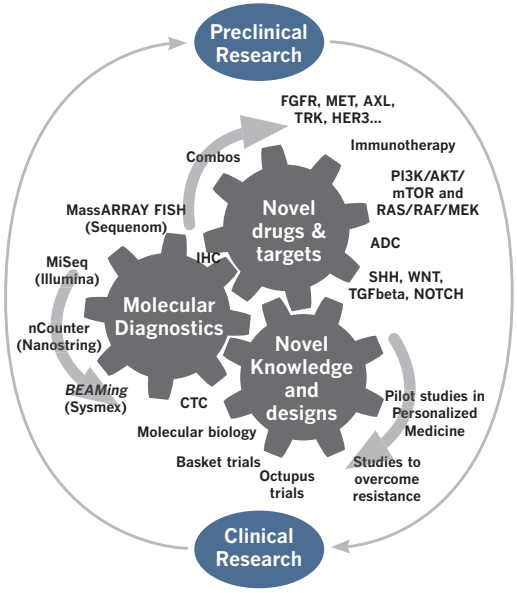

Figure: A model for translational research in Early Drug Development.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

Gastrointestinal & Endocrine Tumors Group

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Tamara Saurí

Strategic Goals

1. Discovery of new biomarkers in gastrointestinal tumorigenesis.
2. Validation of new prognostic biomarkers.
3. Development of relevant preclinical models *in vitro* and *in vivo* with a special emphasis on the identification of predictive markers.
4. Early clinical research with innovative targets.
5. Clinical research in late stage with more translational endpoints, focusing on the identification of prognostic/predictive biomarkers.
6. Participation in multidisciplinary/multinational consortia and research programs.
7. Expansion of our intra-institutional collaborations including VHIO's Proteomics, Tumor Biomarkers, Cancer Genomics, Translational Genomics, and Stem Cells & Cancer Groups.

Highlights in 2014

- Early Clinical Research: drug development & 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 in different gastrointestinal malignancies.
- Clinical Research: design of investigator-initiated clinical trials as well as participation in numerous trials developed in the context of national and international cooperative groups.
- Continued collaboration in research consortia of excellence including WIN (Worldwide Innovative Networking in personalized cancer medicine). More specifically, we are participating in the WINTHER (WIN Therapeutics) academic and international trial aimed at better predicting drug sensitivity and optimizing individualized therapeutic decisions with improved clinical outcomes for patients.
- We are also dedicated partner of the COLTHERES – Colon Therapy Research Consortium, EurocanPlatform, and MerCuRIC – all of which are supported by funding from the European Commission's 7th Framework Programme of Research and Development:
  - –COLTHERES is a four-year multi-center program aimed at defining and performing biomarker driven clinical trials to improve cancer therapy outcomes for colorectal cancer patients.
  - –EurocanPlatform comprises 28 leading cancer entities of excellence, working together in a unique collaboration aimed at advancing cancer research, treatment and care across Europe through improved prevention, detection and therapeutic strategies.
  - –The MerCuRIC Consortium is pioneering a multi-center Phase Ib/II clinical trial to assess a novel therapeutic strategy to combat metastasis, improve survival and clinical practice for colorectal cancer patients.

SUMMARY

In 2014, we have led and participated in numerous cooperative and singular research projects related to Gastrointestinal Malignancies. In addition to our key participation in international consortia of excellence including the WIN (Worldwide Innovative Networking in personalized cancer medicine) Consortium and other initiatives funded by the European Commission's 7th Framework Program (e.g. EurocanPlatform, COLTHERES, MErCuRIC – see our group Highlights 2014, and pages 94 - 95 of this report), at both preclinical and clinical levels, we have continued to further strengthen our purely multidisciplinary and translational approach to research.

Reflected by publications in the most prestigious scientific titles in 2014, our group has led and collaborated in studies with important clinical implications including:

1. **Cyclin E amplification/overexpression is associated with poor prognosis in gastric cancer.** Alsina M et al. *Ann Oncol. 2015 Feb;26(2):438-9.* Importantly this study showed that cyclin E amplification/overexpression, present in up to a third of gastric cancer patients, may correlate with poor clinical outcome.
2. **Abituzumab combined with cetuximab plus irinotecan versus cetuximab plus irinotecan alone for patients with KRAS wild-type metastatic colorectal cancer: the randomised phase I/II POSEIDON trial.** Elez E et al. *Ann Oncol. 2015 Jan;26(1):132-40.* The early phase trial was designed to assess the tolerability and explore the efficacy of abituzumab (antibody targeting integrin αv heterodimers) in combination with cetuximab and irinotecan in patients with metastatic CRC. Predefined exploratory biomarker analyses identified subgroups of patients in whom abituzumab may have benefit.
3. **Randomized phase Ib/II trial of rilotumumab or ganitumab with panitumumab versus panitumumab alone in patients with wild-type KRAS metastatic colorectal cancer.** Van Cutsem E et al. *Clin Cancer Res. 2014* Aug *15;20(16):4240-50.* This is the first clinical study to suggest a benefit for combining an HGF inhibitor (rilotumumab) with panitumumab in previously treated patients with wild-type KRAS mCRC.
4. **Phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of lucitanib in advanced solid tumors.** Soria JC et al. *Ann Oncol. 2014 Nov;25(11):2244-51.* Demonstrating promising efficacy and a manageable side-effect profile by Lucitanib (a potent, oral inhibitor of FGFR, VEGFR and PGFRα/β) this study showed clinical benefit in both FGF-aberrant and angiogenesis-sensitive populations (advanced solid tumors).
5. **A pharmacodynamic/pharmacokinetic study of ficlatuzumab in patients with advanced solid tumors and liver metastases.** Tabernero J et al. *Clin Cancer Res. 2014 May 15;20(10):2793-804.* Our findings revealed good safety/tolerability of ficlatuzumab (a humanized hepatocyte growth factor -HGF- inhibitory monoclonal antibody) as monotherapy in patients with advanced solid tumors and liver metastases, and demonstrated its ability to modulate the HGF/c-Met pathway and downstream signaling in patients with advanced solid tumors.
6. **First-in-human phase I study of Lurbinectedin (PM01183) in patients with advanced solid tumors.** Elez ME et al. *Clin Cancer Res. 2014 Apr 15;20(8):2205-14.* This first-in-human phase I study allowed to established the recommended dose for Lurbinectedin (synthetic marine-derived compound that covalently binds to the minor groove of the DNA), and assessed its dose-limiting toxicities (DLT) in patients with advanced solid tumors.

For the full list of our publications including key studies in collaboration with other VHIO groups, as well as groups at other institutions, visit the extended version of this report online: **http://memorias.vhio.net/2014** (select tab 'Publications, Projects, & Awards).

Other research lines have included the use of validated biomarkers and their respective reference isogenic cell lines to develop next generation, non-invasive, blood-based diagnostics that can monitor the burden of disease, its respective molecular specificities, and response to novel targeted therapies.

We have also participated in several pre-clinical and clinical studies on predicted responsive patient subsets using genetically annotated tumor surgical specimens ('Xenopatients') in mice, further expanding our collaboration with VHIO's Stem Cells & Cancer Group, led by Héctor G. Palmer. In partnership with pharmaceutical companies or academic groups, our dedicated efforts have continued to focus on the validation of repurposed drugs or candidate drugs.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

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

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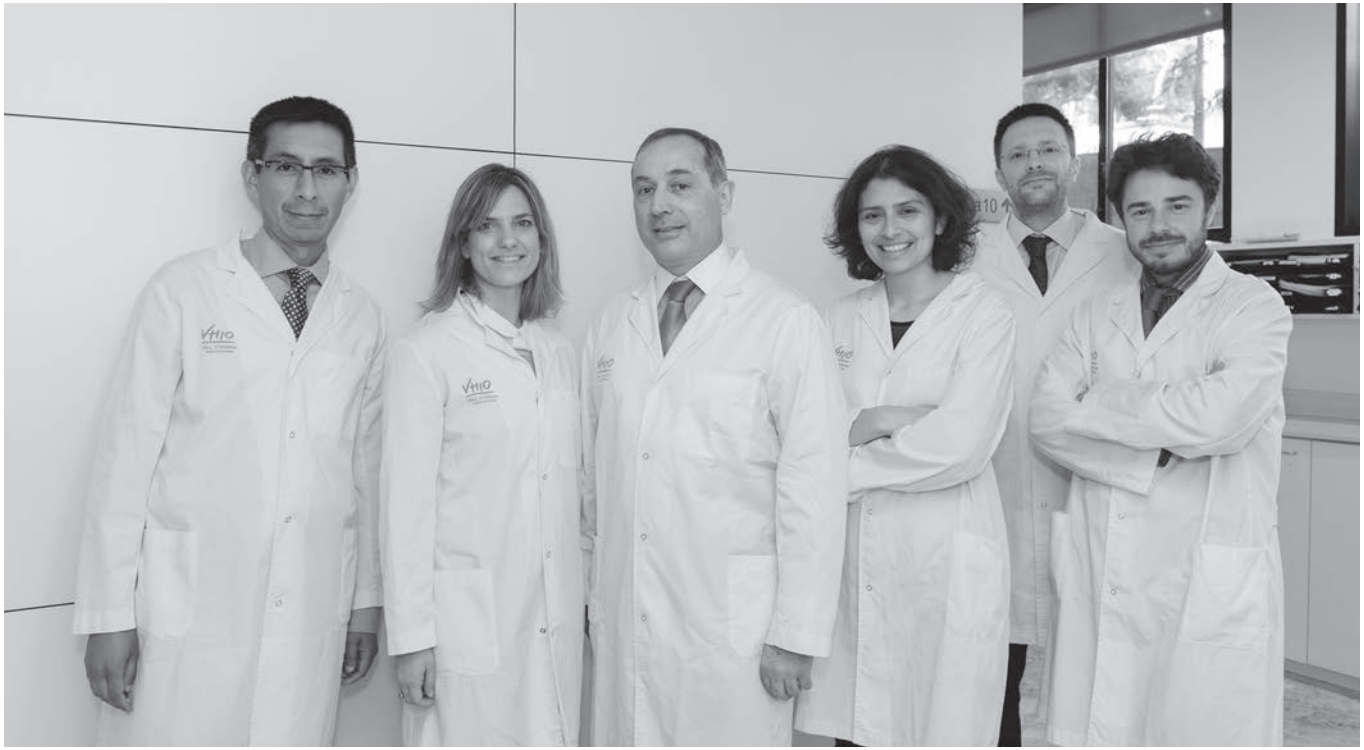
César Serrano
Cristina Suárez
Claudia Valverde



Strategic Goals

1. Design and develop clinical trials for all the malignancies covered by our group. We strive to provide our patients with the most novel and optimal treatments for their respective diesease, including immunotherapeutics, targeted therapies or new chemotherapeutics.
2. Conduct clinical trials at different stages of disease with emphasis on a histology-tailored design.
3. Develop new tools such as liquid biopsy for our patients in order to better tailor treatments against CRPC and kidney cancer.
4. Expand our translational research platform for glioblastoma in collaboration with VHIO's Gene Expression & Cancer Group.
5. Create a translational platform for sarcomas and basic research in partnership with the Biomedical Research Institute of Bellvitge (IDIBELL) and the Cancer Research Centre of Salamanca (CIC).
6. Set up a translational platform for GIST and expand our research in collaboration with the Spanish Sarcoma Group (GEIS).

Highlights in 2014

- New drugs in GU malignancies: we have participated in the most important trials with different drugs that, throughout 2013-2014, have demonstrated that they will change the prognosis of patients with prostate cancer. These new drugs include vaccines (Prostvac), Enzalutamide, and Radium-223 – all of which to-date show that they may improve the survival of our patients.
- In other GU malignancies we are participating in clinical trials to show the utility of adjuvant treatment in renal cancer, or new drugs in second and third line treatment. In bladder cancer we are conducting new clinical studies that combine classical chemotherapy with novel targeted agents and second line treatments. We have collaborated in the development of new agents that are able to modulate the host immune response and combat cancer (PD-1 and PDL-1). In 2014 we have also participated in Phase I/II clinical trials to test new therapies and immunotherapeutics for bladder and prostate cancer.
- Our research in Central Nervous System (CNS) tumours 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.

SUMMARY

Our group is interested in both clinical and translational research with broad experience and grounded expertise in treating tumors since we are involved in tackling different neoplasms.

We focus on the design and development of clinical trials for genitourinary malignancies at different stages of the disease with the active participation of urologists, radiation therapists and medical oncologists. Over recent years, many developments have been reported in GU tumors; particularly in prostate, bladder and kidney cancer. Close collaboration between all specialists involved in the treatment of these tumors is therefore mandatory. It is also important to continue with our translational research platform for urologic cancer as well as conduct clinical trials in early, adjuvant as well as metastatic disease.

We also collaborate 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). Results from this collaboration have been presented at the Second Cleveland-Vall d'Hebron meeting that took place on October 10, 2014. We have developed the avatar program for kidney cancer tumors in collaboration with the IDIBELL. To-date we have been able to develop 11 avatars from patients with high risk disease and to correlate the response between the avatar and the patient.

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 focused on consolidating the 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 in 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 is also working 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 involved in setting up a translational platform for sarcomas and basic research in partnership with the Biomedical Research Institute of Bellvitge (IDIBELL) and the Cancer Research Center of Salamanca (CIC – Spain). For GIST tumors we have developed a close relationship with J. Fletcher's lab at Brigham and Women's Hospital, Boston (USA). In this context, further research updates and discovery were reported at the *New Insights in GIST* meeting that took place on April 04, 2014.

Cesar Serrano joined our group as VHIO researcher having spent the past 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 in our group. We are currently applying for additional resources in order to consolidate his position at VHIO.

The serum bank dedicated to various tumor types such as CNS tumors, renal cell carcinoma and CRPC, will continue to recruit samples from our patients.

Lastly, we promote education and exchange by offering our group members the opportunity to spend a minimum of 3 months in research centers of prestige within a specific field. In the near future we envisage that this program will promote shorter stays for joint project development. Importantly, in terms of education and exchange, in 2014 we welcomed three fellows to visit our group; two for short stays of six months, and the other for the duration of a year.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

Head and Neck & Gynecological Tumors Group

Principal Investigator
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Medical Oncologists and Clinical Fellows
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Irene Braña
Ana Oaknin
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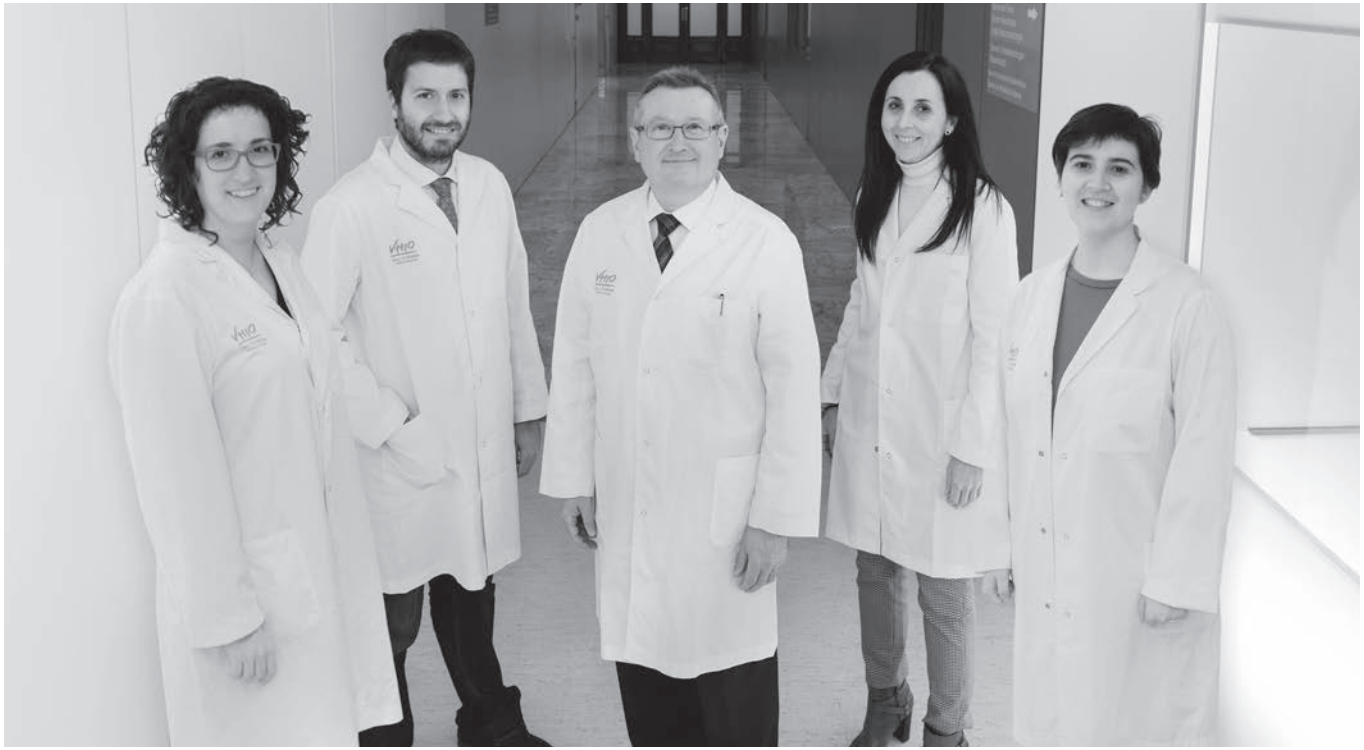

Strategic Goals

1. We are focused on clinical and traslational research and are members of the most relevant international cooperative groups in head, neck and gynecological tumors. Such collaboration allows us to participate in the initial development of new drugs, from Phase I to Phase III trials.
2. Further expand our recognized expertise in clinical research within our field and continue to lead an increasing number of international projects.

Highlights in 2014

- As a result of our collaboration with the Gynecologic Oncology Group (GOG), established in 2011, and the ENGOT Group, we are authors of pivotal or relevant studies in cervical cancer, ovarian cancer as well as head and neck cancer, presented at the 2014 Annual Meeting of the American Society of Clinical Oncology (ASCO), May 30 - 03 June, Chicago, USA, as well as at the 2014 Meeting of the European Society For Medical Oncology (ESMO), September 26 – 30, Madrid, Spain.

SUMMARY

Our group focuses on standard patient care as well as clinical research. The continous development and research into new anticancer drugs represents a major area of our activity. Notably, based on our expertise, we have also actively participated in the revision of all Spanish guidelines in gynaecological cancer.

We are either members or affiliate members of some of the most relevant groups and alliances in gynecology including the Gynecologic Cancer Inter Group (GCIG), European Network of Gynaecological Oncology Trial Groups (ENGOT), *Grupo Español de Investigación en Cáncer de Ovario* (Spanish Gynecologial Group - GEICO), and the Gynecologic Oncology Group (GOG). In addition our group is involved in developing new strategies, approaches, and optimal trial design for research.

With regards to clinical activities at the Vall d'Hebron University Hospital, we play a central, key role as members of multidisciplinary committees and teams in head, neck and gynecological cancer tumors. Our contribution, in close connectivity and collaboration with other professionals and specialties (including surgeons, radiotherapists, radiologists and pathologists), leads to the establishment of new treatment protocols and clinical guidelines to further advance clinical practice.

As a reference group for other specialties as well as several research centers of excellence, we have steadily increased the number of patients treated in clinical trials with new drugs. Currently we are involved in more than twenty trials as either Principal Investigators and/or Coordinators of National and International investigational studies.

We are continuously contributing to 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 (for more information please select the 'Publications, Projects & Awards' tab of our Scientific Report 2014 online at: http://memorias.vhio.net/2014/).

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High Risk & Cancer Prevention Group

Principal Investigator
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Staff Scientists
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Cristina Cruz
Irene Esteban

Clinical Nurse Specialist
Neus Gadea

Strategic Goals

1. Clinical development of specific therapeutic strategies for tumors associated with hereditary genetic alterations.
2. Identification of mechanisms of resistance to targeted therapies in BRCA-associated breast cancer.
3. Testing new combination therapies for BRCA-associated PDX's that have progressed to PARP inhibitors.
4. Identification of new genes involved in hereditary breast cancer through the application of next generation sequencing.
5. Psychological impact of hereditary cancer multiplex gene testing in the Spanish population.

Highlights in 2014

- 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 with no mutations in *BRCA1* or *BRCA2*.

SUMMARY

We are committed to developing new targeted therapies for patients with hereditary breast cancer. In this context, during 2014, patients with advanced breast cancer and a *BRCA* mutation participated in several phase II or phase III trials with a specific DNA binding agent or a PARP inhibitor. In addition, three years after initiating our collaboration with VHIO's Experimental Therapeutics Group and the Cancer Genomics Group led by Violeta Serra and Ana Vivancos respectively, such teamwork has resulted in a large collection of BRCA-associated patient-derived xenografts implanted in athymic mice. These murine models recapitulate the clinical behaviour of the tumors and have been used to identify mechanisms of resistance to targeted therapies 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* or *BRCA2*. Analysis of the first 40 families has provided 4 genetic results with clinical utility. In hereditary colorectal cancer we are participating in a study of mutations in POLD1 and POLE in families with polyposis, or young onset colorectal cancer with microsatellite stability.

We continue to actively participate in the international multi-center IMPACT study (Identification of Men with a genetic predisposition to ProstAte Cancer: Targeted Screening in BRCA1/2 mutation carriers and controls, MREC 05/MRE07/25, Chief Investigator: R. Eeles MA; PhD;FRCR.FRCP), to analyze the efficacy of early detection of prostate cancer in patients with a mutation in the *BRCA1/2* genes.

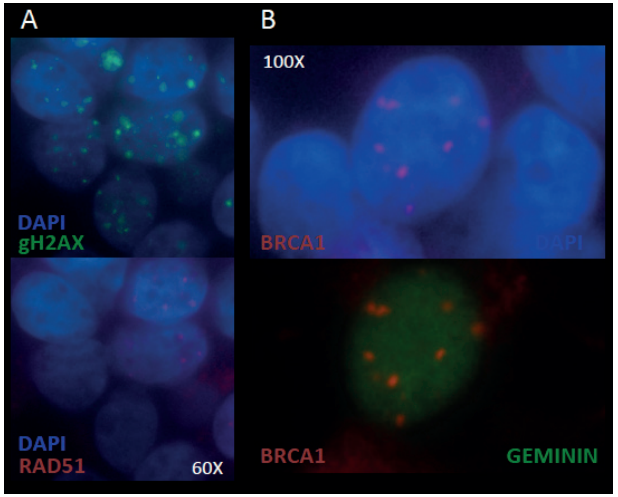

Figure: DNA repair markers assessed with inmunofluorescence techniques in tumor cells from PDX (patient-derived xenografts). A, top panel: DNA double-strand breaks can be detected with an anti-gH2AX antibody. Bottom panel: RAD51 nuclear foci are a marker of homologous recombination repair. B, top panel: nuclear BRCA1 foci. Bottom panel: geminin stains cells in S- and G2-phase. Nuclei are stained with DAPI.

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Oncogenetics Group

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Radiation Oncologist
Manuel Altabas

Graduate Student
Gemma Montalban

Technicians
Miriam Masas
Anna Tenés

Strategic Goals

1. Application of massive sequencing to the diagnosis of hereditary cancer.
2. Molecular analysis of new candidate breast/ovarian cancer genes.
3. Transcriptional and functional characterization of variants with unknown biological significance in breast/ovarian cancer predisposition genes.
4. Identification of common low-penetrance alleles that modify breast cancer risk for *BRCA1* and *BRCA2* mutation carriers.
5. Study apoptosis assay and genetic markers as predictive tests for late toxicity after radiotherapy.

Highlights in 2014

- We performed exome sequence analysis of affected relatives from breast cancer families negative for *BRCA1/2* pathogenic variants in order to unmask new potential predisposing genes.
- Our group has developed a panel of around one hundred predisposition cancer genes by massive sequencing.
- We have led a multicenter study to determine the prevalence of *RAD51D* disease-causing variants in Spanish breast/ovarian cancer families.
- We described the evaluation of methodologies for DNA/RNA analysis, and alternative transcripts in *BRCA1* and *BRCA2* genes, collaborating with the working groups of the Evidence Based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) International Consortium.
- We have also participated in the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA), which has established new susceptibility genes of ovarian cancer and modifier alleles for *BRCA1/BRCA2* mutation carriers.
- Our research has confirmed that severe, late side effects induced by radiotherapy of breast cancer are associated with low levels of irradiation-induced apoptosis.
- We have enrolled breast cancer patients to collaborate in the European Commission FP7-funded project REQUITE which is aimed at validating predictive models of radiotherapy toxicity to improve quality-of-life and reduce side-effects in cancer survivors.

SUMMARY

Our work focuses on two main lines of research: 1) genetic predisposition to hereditary breast/ovarian cancer, and 2) genetic predisposition to radiotherapy-induced toxicity.

Inherited predisposition to breast and ovarian cancer is caused by the *BRCA1* and *BRCA2* genes, but only about one fourth of families carry mutations in these genes. We search for other alleles which might predispose to these types of cancer and use massive sequencing technologies to study panels of potentially predisposing genes in families tested negative for *BRCA1* and *BRCA2*. Moreover, we are sequencing whole coding regions (exome) to discover new genes that might explain the presence of multiple cases of cancer in families and individual patients.

BRCA1/2 genes have an extraordinary high allelic heterogeneity and many results of genetic testing are variants with unknown biological significance. 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 laboratories to develop multifactorial studies aimed at ascertaining the effect of variants with unknown clinical significance.

Radiotherapy represents the most effective non-surgical modality in the curative treatment of cancer. Around half of all cancer patients receive radiotherapy at some point during their treatment. While around 3-5% of individuals suffer from severe long-term side-effects, more experience moderate toxicity. There is now good evidence for the heritability of radiosensitivity as a trait as well as a 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).

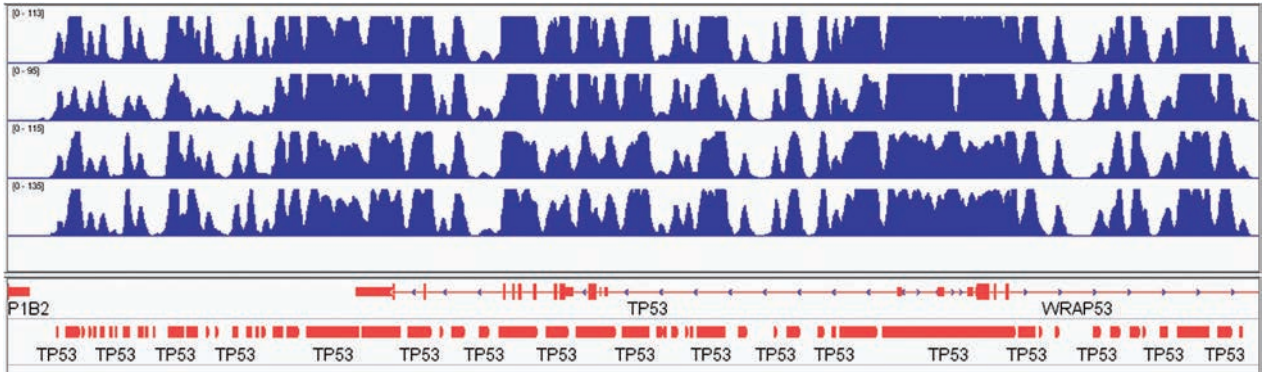


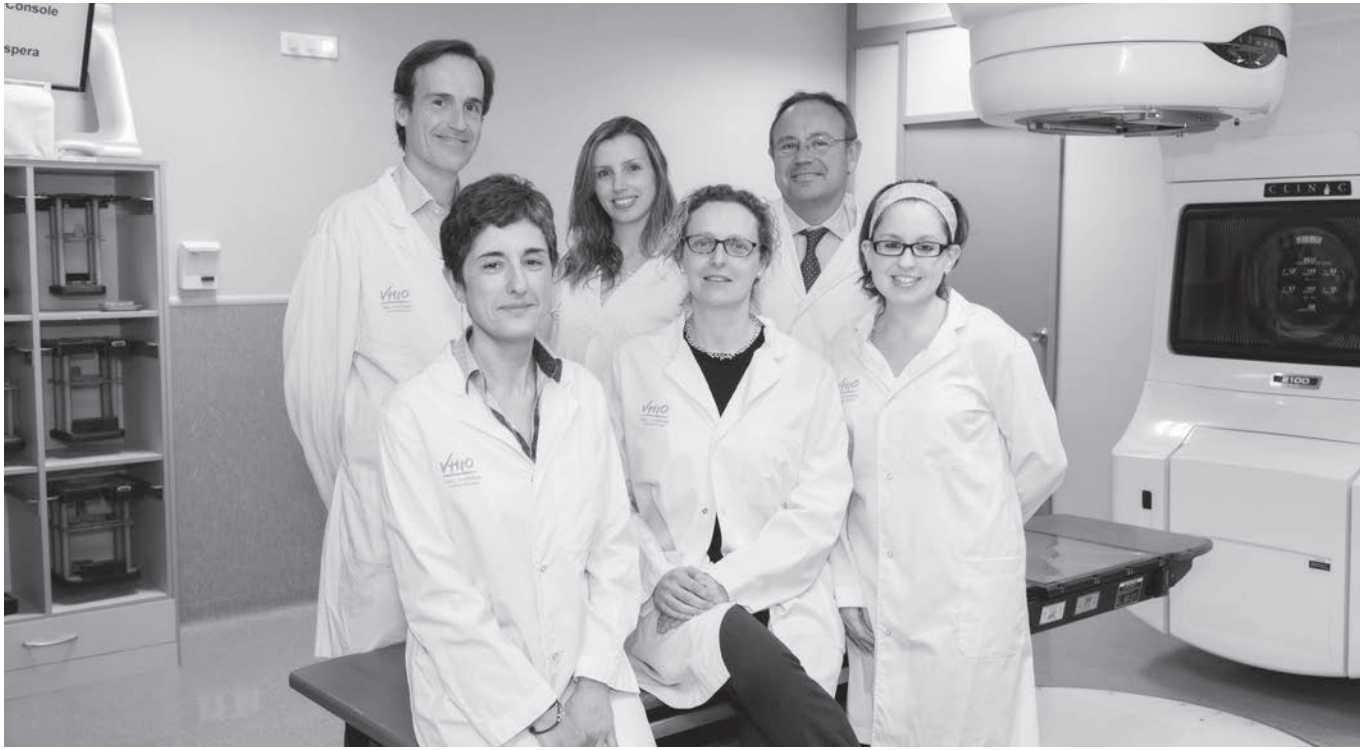
Figure: Coverage of the TP53 gene in a massive sequencing analysis.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

Radiation Oncology Group

Principal Investigator
Jordi Giralt

Radiation Oncologists
Sergi Benavente
Xavier Maldonado
Meritxell Molla
Begoña Navaltropo
Mónica Ramos
Victoria Reyes
Ramona Verges



Strategic Goals

1. **Technology development.** Acquisition of new equipment to implement clinically the most modern treatment techniques such as rotational radiotherapy - with intensity modulated arc therapy (IMAT), adaptive radiotherapy and image-guided radiotherapy.
2. **Translational research.** Application of biological knowledge of both cancer and healthy tissue in order to individualize treatment to the characteristics of each patient and each tumor.

Highlights in 2014

- We achieved an increase in the number of patients treated with IMRT. In 2014 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 started a stereotaxic extracranial RT in lung cancer program and we have treated 4 patients.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

SUMMARY

Our group is integrated within the Radiation Oncology Department of the Vall d'Hebron University Hospital 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 main areas:
- The continued implementation of IMRT in sarcoma, pediatric and gastrointestinal tumors.
- Development of an estereotactic extracranial radiotherapy program in lung and liver metastases.
- Develop a 4D program for lung cancer.
- For breast cancer, to validate the partial breast irradiation in prone position technique.
- Image guided radiotherapy (IGRT) with seeds in prostate cancer.
- The identification of factors associated with clinical response in advanced head and neck tumors treated with radiotherapy and cetuximab .
- To seek the benefit of dose painting and adaptive radiotherapy in head and neck cancer in a clinical trial.

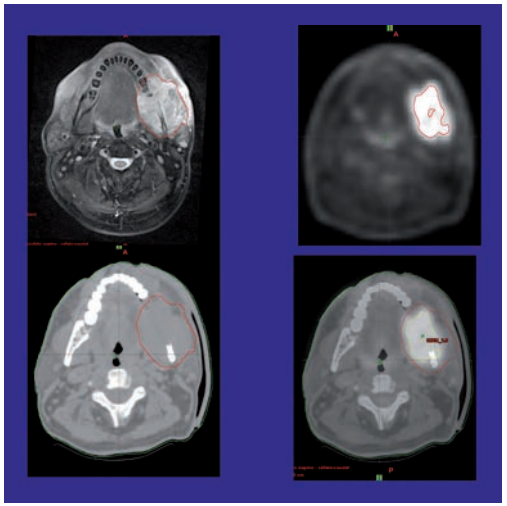


Figure I: Dose painting in head and neck cancer.

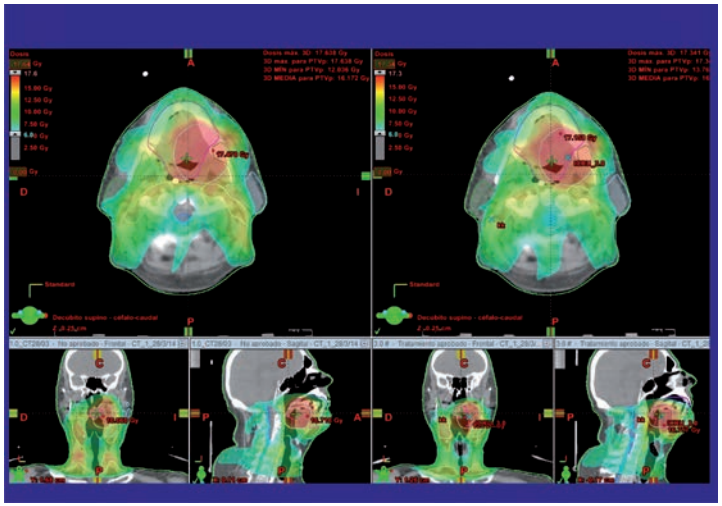


Figure II: Adaptive RT in locally advanced squamous cell carcinoma.

Thoracic Tumors Group

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Medical Oncologists
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Álex Martínez
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Study Coordinators
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Adelaida Piera

Data Manager
Soraya Fernández Ruiz

Strategic Goals

1. Close multidisciplinary collaboration with the different professionals involved in thoracic malignancies diagnosis, management, and research.
2. Optimization of different treatment approaches to the management of early-stage lung cancer patients.
3. Implementation of personalized medicine using pharmacogenomic tools.
4. Clinical trial development using immunotherapy approaches, and in uncommon subsets of lung cancer patients defined by molecular alterations.
5. Consolidation of a translational research program.
6. Contribution to early-drug development in lung cancer.
7. Collaboration with other research groups dealing with thoracic malignancies.

Highlights in 2014

- 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.
- Involvement in exome sequencing in NSCLC patients.
- Analysis of PDL1 expression in mesothelioma patients.
- Active participation in two *New England Journal of Medicine* papers published in 2014 including ALK positive patients (Shaw A.T. et al., *N Engl J Med* 2014, and, Solomon B.J. et al, *N Engl J Med* 2014).
- The organization of the 2014 European Lung Cancer Conference (ELCC), 26 – 29 March, Geneva, Switzerland.

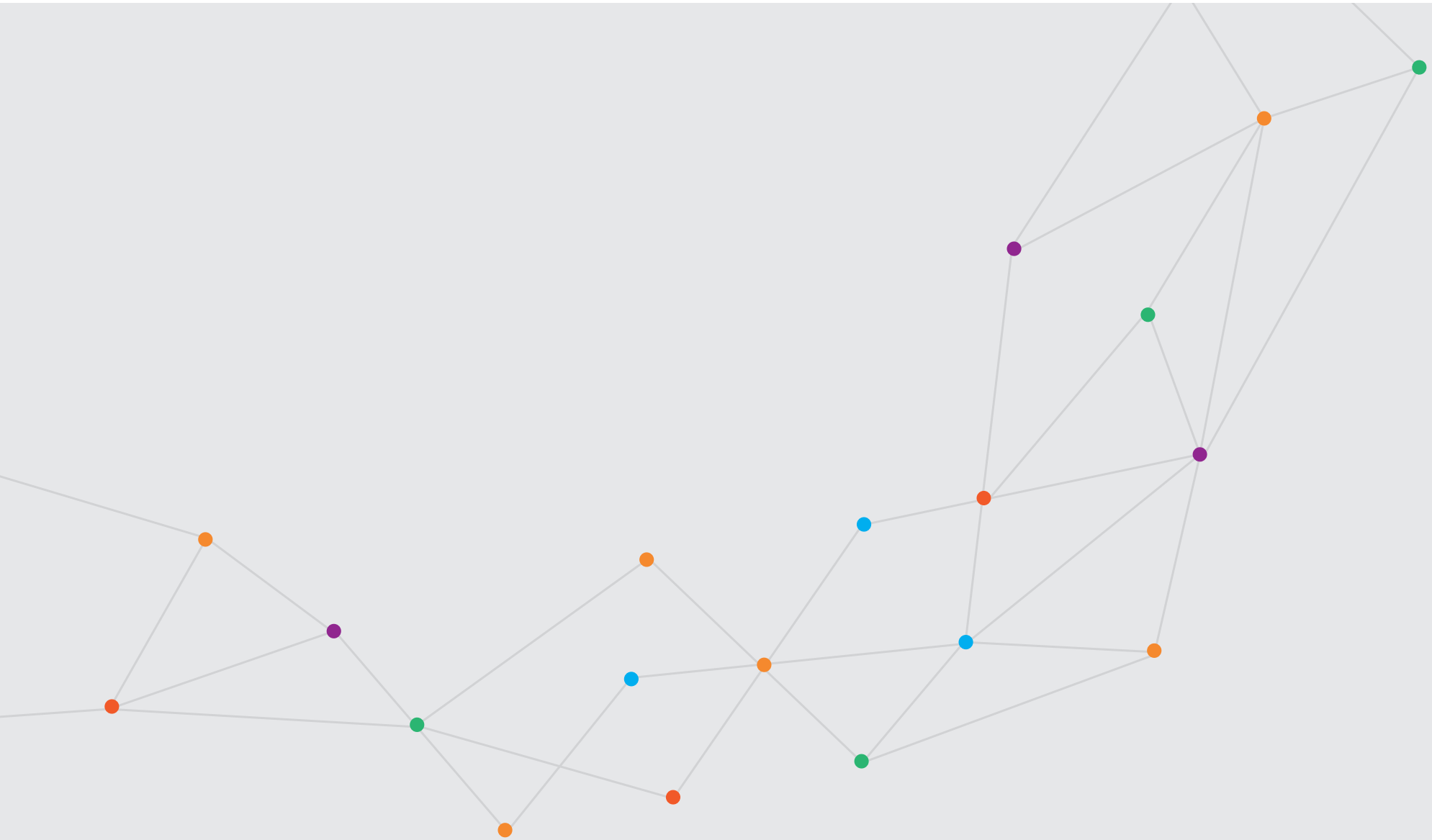
SUMMARY

The main focus of the Thoracic Tumors 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 these symptoms 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 will 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.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/



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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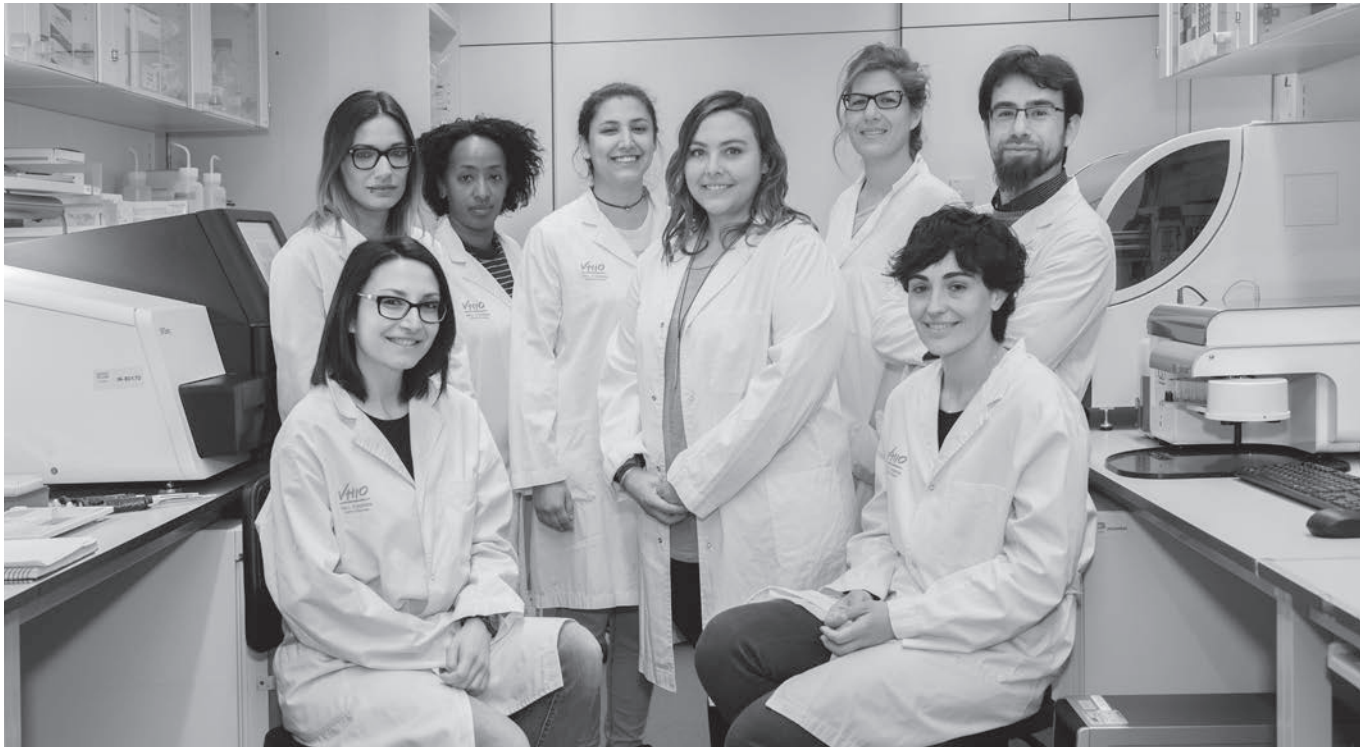

Strategic Goals

1. Develop and implement improved strategies for routine patient pre-screening in a high quality setting (ISO15189 accreditation).
2. Provide cutting-edge applications in Cancer Genomics through the use of new technologies and protocol development.

Highlights in 2014

- Validation and implementation of an Amplicon-seq VHIO-Card panel (NGS) to facilitate mutation detection in 61 genes and, therefore, improve our routine patient pre-screening. Analysis of frequent point mutations (hotspots) in oncogenes is achievable through the use of various techniques including sequencing, qPCR, BEAMing or single-base extension chemistries. The analysis and relevance of mutations in tumor suppressor genes (e.g. TP53, PTEN, VHL, NF1 etc.), is however hampered by the fact that they occur broadly along the coding sequence. The wide mutation distribution in tumor suppressor genes is due to the fact that tumor cells need only inactivate their products.
- Assessment of the mutational status of tumor suppressor genes, therefore, must be accomplished by Next Generation Sequencing-based approaches such as NextGen sequencing. We have developed and validated a panel of over 800 amplicons in 61 genes that allows for the interrogation of mutations in oncogenes as well as tumor suppressor genes , and a five-fold increase in mutation detection (compared to our genotyping platform), in a cost effective manner.
- Validation and implementation of a Gene Fusion panel based on nCounter technology in order to prescreen patient samples. Gene fusions are well-known examples of oncogene-driver events (e.g. ALK, ROS1, RET, etc). The ability to robustly detect frequent relevant gene fusions in a multiplexed manner is now possible by digital detection through the nCounter Nanostring platform, implemented in our lab in 2013.

SUMMARY

VHIO's Cancer Genomics Group serves as a Core Technology Lab. Our activities bridge the preclinical and clinical fields of cancer research. We work on providing cutting-edge applications in cancer genomics through the use of new technologies and protocol development.

We provide services to preclinical and clinical researchers as well as develop our own research projects in technology development and translational research. The lab is equipped with a genotyping platform (MassARRAY, Sequenom) and two NextGen Sequencers; MiSeq and HiSeq2500, Illumina (see figure).

The lab takes part in VHIO's pre-screening program, performing somatic mutation profiling with our genotyping platform in patients that are candidates to be enrolled in Phase I clinical trials. The molecular profile of each patient indicates his/her suitability for inclusion in a given clinical trial aimed at testing the usefulness of novel targeted therapies, such as PIK3CA, AKT1, BRAF or MEK inhibitors. As a reflection of our dedication to excellence and quality services we provide, we have undergone ISO 15189 accreditation.

Protocol development and improving Next Generation Sequencing applications are the main focus of our research activities as well as developing efficient strategies for our pre-screening program, involving FFPE-derived DNA and state-of-the-art techniques and technologies.

We are involved in a number of translational projects, such as identifying mechanisms of resistance to targeted therapies, studying clonal populations, defining novel therapeutical opportunities based on mutation profiles, in collaboration with both preclinical and clinical researchers working on solid tumors.

Figure: Our Cancer Genomics Group's Technologies: MassARRAY (Sequenom), HiSeq 2500 (Illumina), MiSeq (Illumina).

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/.

Molecular Oncology Group

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Laboratory Supervisor
Jose Jiménez

Laboratory Assistant
Mª Ángeles Díaz

Technicians
Mª del Carmen Díaz
Paola Martínez
Nerea Peiró
Gertrudis Sánchez
César Sevillano

Administration
Mª Alejandra Iglesias

Strategic Goals

1. Discovery and validation of novel biomarkers using tissue-based technologies.
2. Translate basic research findings into clinical application.
3. Apply molecular pathology strategies to clinical oncology.
4. Serve as a core facility for VHIO research programs.
5. Act as a central and local laboratory in clinical trials.

Highlights in 2014

Core Facility:

- Maintenance of ISO15189 quality accreditation to conduct tissue-based analyses on clinical samples.
- Central laboratory for biorepository, biomarkers and CTC analyses in different national and international studies (including NeaALTTO, SOLTI-1007, SOLTI-1114, CL1-49076, EGF117165).
- Over 2700 molecular determinations on samples for patient inclusion into clinical trials.
- Supported over 160 clinical trials for sample management and analyses.
- Supported basic and translation research programs with over 14,000 tests performed.

Translational Research Projects:

- Identification and validation of pharmacodynamic biomarkers related to the development of a new multityrosine kinase inhibitor and analysis of clinical samples obtained from the PhI clinical trial. (SERVIER).
- Validation of MET analysis and prescreening related to the clinical trial TED11449. (SANOFI).
- WINTHER. A Phase II study to select rational therapeutics based on the analysis of matched tumor and normal biopsies in Subjects with Advanced Solid Tumors. (WIN Consortium).
- Collaborative research project to study the prevalence of EPIREGULIN (EREG) in cancer for the promotion of ANTI-EPIREGULIN (EREG) therapies. (CHUGAI).
- Determination of CEACAM5 expression in primary and metastatic colorectal cancer. (SANOFI).
- Analysis of FGFR1, FGFR2 and FGFR3 Gene Copy Number and Protein Expression Level in Tumor Tissue Samples coming from Patient Derived Xenografts. (DEBIOPHARM).
- Quantitative measurement of HER2 levels by multiplexed mass spectrometry from FFPE tissue in patients treated with anti-HER2 based therapy (ONCOPLEX DX).

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. Our 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.

We currently provide support to more than 160 clinical trials conducted at the Vall d'Hebron University Hospital, representing ~70% of all trials open in our institution. Our activities relating to clinical trials range from the coordination of sample collection, storage and shipment, developing and running multiple assays for real-time patient inclusion, as well as pharmacodynamic monitoring and dose finding.

In 2014, our laboratory successfully maintained the prestigious ISO15189 quality accreditation for running tissue-based analyses on clinical samples. During this year, we have performed over 2700 molecular determinations on samples for patient inclusion into clinical trials and over 14,000 tests to support basic and translation research programs, with a ~40% overall increase in testing activity as compared to 2013. We have also been the central laboratory for 8 national and international studies.

In addition to core services, VHIO's Molecular Oncology Group runs its own independent research projects. In 2014, 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 and HER family proteins quantification in breast cancer using Selected reaction monitoring mass spectrometry.

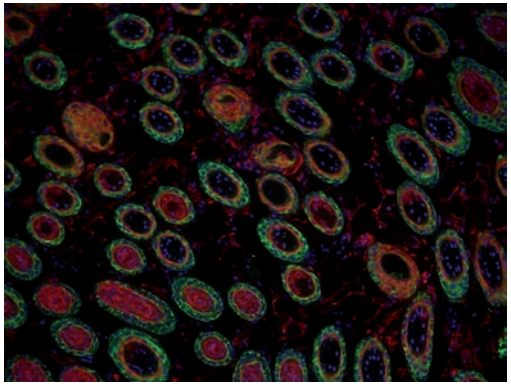

Figure I: Mouse skin. Double immunofluorescence stain for pan-cytokeratin & EGFR. AQUA platform.

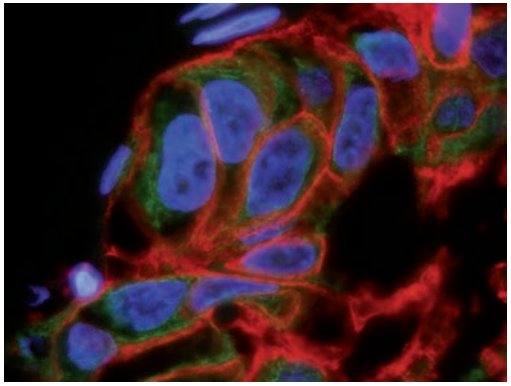

Figure II: Breast Human tissue. Double immunofluorescence stain for AE1-AE3 cytokeratin & HER2.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

Proteomics Group

Principal Investigator
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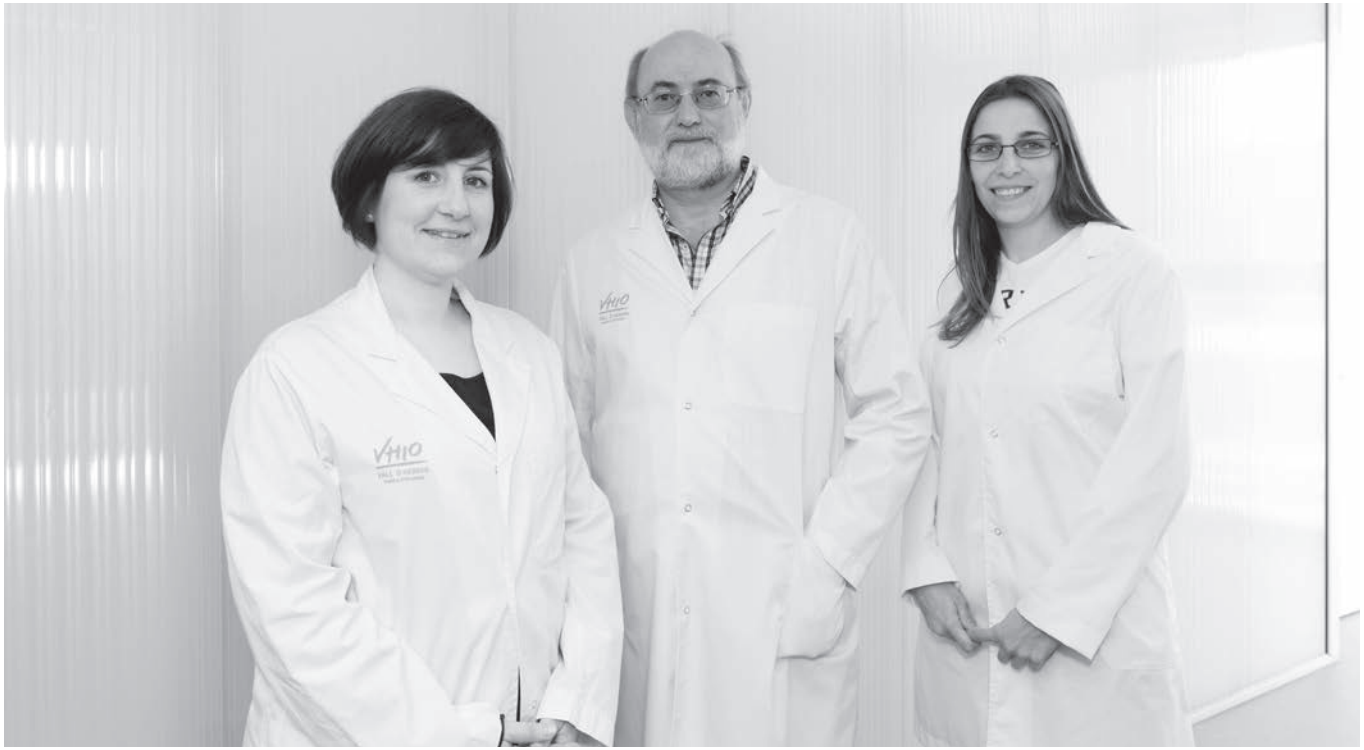
Marta Monge
Laura Villarreal

Technician
Luna Martin



Strategic Goals

1. Provide services in proteomic techniques to other research groups as a core facility.
2. Explore the role of ADAM and ADAMTS metalloproteases in cancer through proteomic analysis.
3. Proteomic screening for new biomarkers to help develop cancer therapeutics.
4. Contribute to mapping the Chromosome 16 proteome as part of the Human Proteome Project.

Highlights in 2014

- The provision of proteomic services to VHIO and Vall d'Hebron University Hospital groups as well as to 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.
- Identification of proteins shed by metalloproteases in breast cancer cells, using a new, highly efficient, proteomic methodology developed in our laboratory.
- Characterization of the role of proteolysis by the metalloprotease ADAMTS1 of the insulin-like growth factor binding protein IGFBP2 in glioma.
- We have collaborated in the unmasking of a new role of the kinase LKB1 as a UV damage sensor in melanoma.
- Participation in the Spanish Consortium Chromosome 16 HPP (part of the HUPO Human Proteome Project).

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

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 (see figure). We also use proteomic techniques for screening and the validation of biomarkers for cancer diagnostics, personalized treatment and monitoring.

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.

In parallel, as a core facility, we also provide state-of-the-art proteomic methodologies to VHIO research groups as well as implement new developments within the field to offer the very latest in proteomic strategies and technologies.

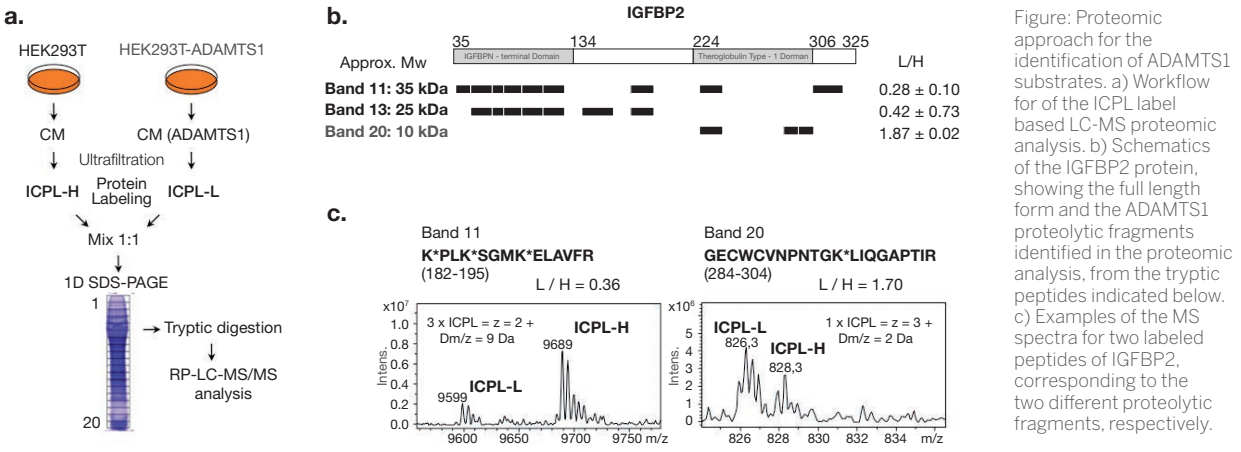


Figure: Proteomic approach for the identification of ADAMTS1 substrates. a) Workflow for of the ICPL label based LC-MS proteomic analysis. b) Schematics of the IGFBP2 protein, showing the full length form and the ADAMTS1 proteolytic fragments identified in the proteomic analysis, from the tryptic peptides indicated below. c) Examples of the MS spectra for two labeled peptides of IGFBP2, corresponding to the two different proteolytic fragments, respectively.

Translational Genomics Group

Principal Investigator
Aleix Prat

Clinical Research Technician
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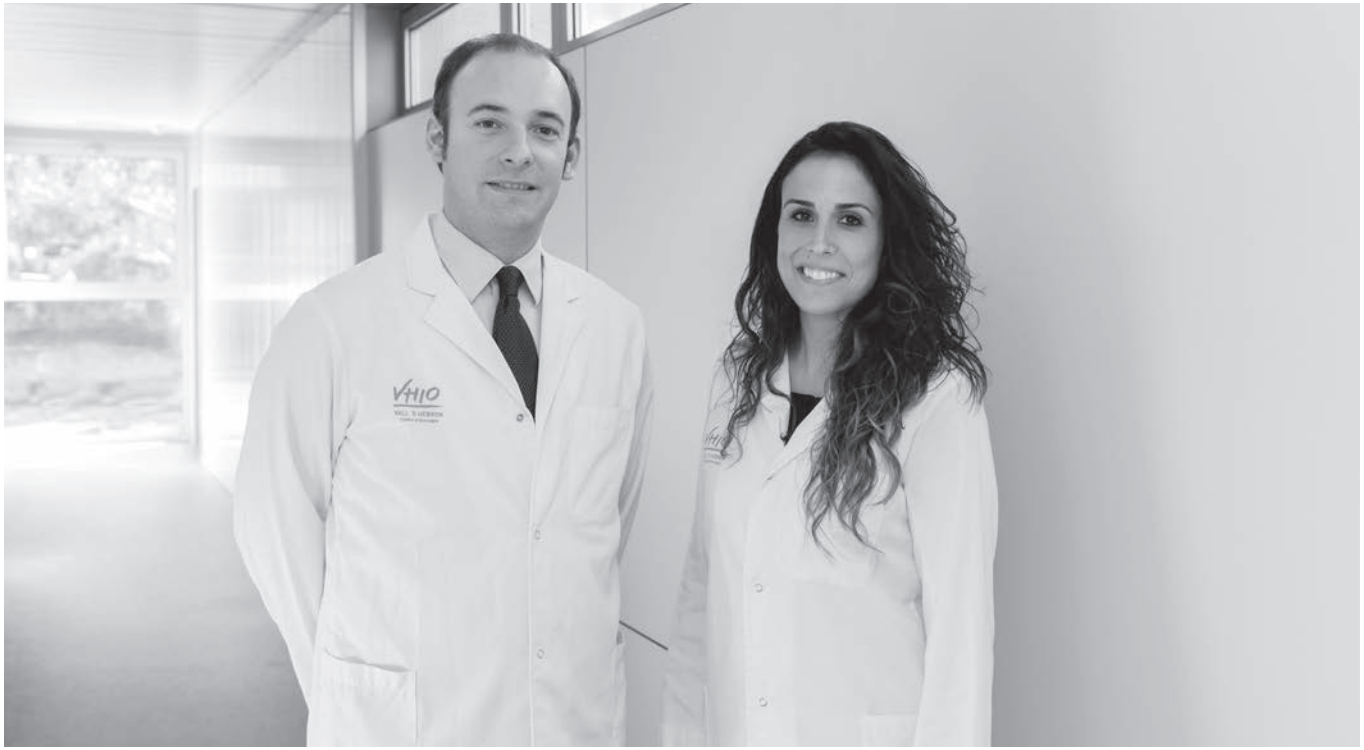
Specialist Physician in Breast Cancer (Collaboration)
María Jesús Vidal Losada



Strategic Goals

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

Highlights in 2014

- 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 Health of Spain (FIS) research grant to study triple-negative breast cancer.
- Participation in correlative science studies across ~10 clinical trials.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

SUMMARY

2014 has been a highly productive year for VHIO's Translational Genomics Group. We have been the first in Europe to successfully implement a clinically applicable gene expression-based test, known as PAM50, for the management of breast cancer patients. In addition, we have analyzed >500 samples and provided 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 started participating in the genomic analyses of tumor samples from several national and international clinical trials (e.g. PAMELA, NOAH, NeoEribulin, EGF30008, TBCRC018, EGF104900, LPT109096, CIBOMA/2004-01/GEICAM 2003-11 and CHER-LOB).

Our group has led important advances regarding HER2-positive breast cancer, in part, thanks to a Susan G. Komen Career Catalyst Research Grant. In a first article, published in the *Journal of the National Cancer Institute* (JNCI), we showed that HER2-positive disease can be classified as four different subtypes according to respective molecular characteristics, and these different groups might predict a different response to therapies and survival outcome. In a second article, published in *Clinical Cancer Research*, we reported that among the different subtypes of HER2+ disease, the HER2-enriched is the one to benefit the most from anti-HER2 therapies. These findings have led to the initiation of a prospective clinical trial in HER2+ breast cancer that will test a particular hypothesis using genomic data.

Finally, we led a study in collaboration with clinical trial groups in Spain and in the US, published in the *British Journal of Cancer* (BJC), where we showed that triple-negative breast cancer is biologically heterogeneous and distinguishing Basal-like disease versus not, is critical for predicting response and survival following poly-chemotherapy. These findings suggest that future clinical trials in patients with triple-negative should consider this biological heterogeneity.

Our group has also participated in 12 additional articles providing scientific advice and/or performing gene expression analyses. These include 1 research perspective, 1 brief communication, 10 original research articles: 5 as first author (and 3 of them as correspondent) and 2 as third author. The total Impact Factor of our group in 2014 totaled at 103.05 (average of 8.59 per publication).

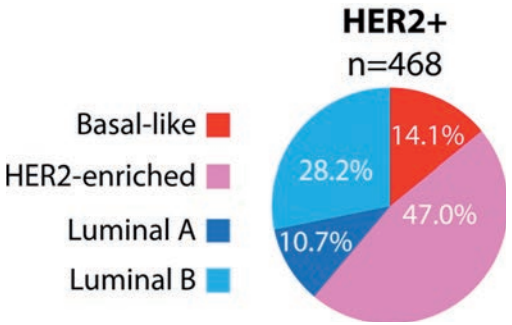


Figure I: Identification of the intrinsic molecular subtypes within HER2-positive breast cancer.

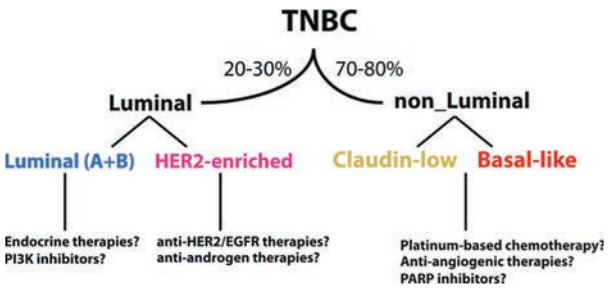
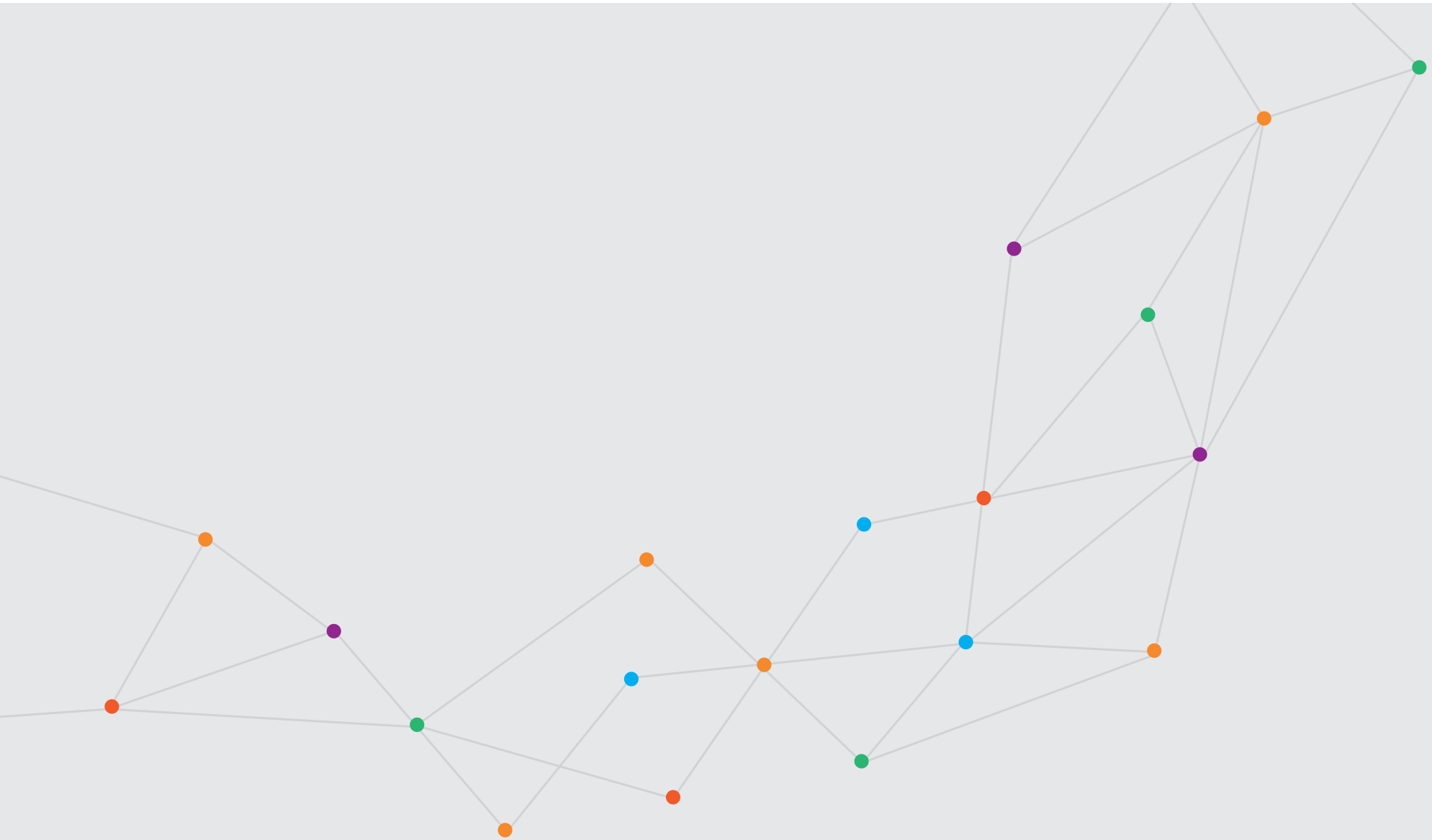


Figure II: Dividing and conquering triple-negative breast cancer.



VHIO'S MULTIDISCIPLINARY RESEARCH PROGRAMS

VHIO TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

Clinical Trials Office

Office Manager
Gemma Sala

Head, Clinical Trials Office for Phase I Trials
Gemma Sala

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Marta Beltrán
María Herranz
Lidia Martínez de Arenzana
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Adelaida Piera
Josep Roman
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Data Managers
Beatriz Blanco
Laia Cano
Gloria García
Isabel Rico
Gina Marés
Sheila Nieves
Cristina Viaplana

Head, Clinical Trials Office for Phase II-III (Gi, Lung, Head & Neck, and Gyne)
Isabel Grau

Study Coordinators
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Anna Casas
Soraya Fernández
Cristina González
Marta Malo
Olga Padrós
Iratxe Puebla
Mireia Sanchís
Montserrat Solà
Natalia Verde

Data Managers
Anna Aguilar
Berta Garrido
Sergio Pérez
Andrea Retter
Eulàlia Scheenaard

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Susana Muñoz

Study Coordinators
Judith Alonso
Mª Alba Calamardo
Raquel Espallargas
Violeta Esteban
Julia Esteban
Jordi Humbert
Gina Marés
Thaïs Miquel
Oriol Nualart
Mariona Pocarull
Anna Serrano

Data Managers
David Álvarez
Rosa María Romero

Clinical Trials Assistants
Núria Carballo
Angel Marín

Quality Assurance Manager
Silvia García

Database Managers Office
Alba Meire Barrio
Débora Moreno
Núria Murtra

Strategic Goals

1. Contribute to the development of novel therapies against cancer.
2. Consolidation as an international reference hospital for clinical trials in oncology.
3. Guide patients taking part in a trial to comply with the requirements of the protocol and to help them with daily life throughout the duration of the study.
4. Provide high quality data adhering to deadlines.
5. Facilitate workflow and communication between the different staff involved in each trial (oncologists, nurses, pharmacists, pathologists, etc.).
6. Ensure that the protocol is appropriately conducted from initiation to the close of the respective trial.
7. Standardize clinical trial processes to ensure optimal quality and the compliance of Good Clinical Practice (GCP).
8. To prepare for, and successfully pass, audits carried out by sponsors and regulatory agencies.
9. Organize an annual post-graduate course of clinical trials in oncology to train study coordinators, data managers, nurses, and CRA's.
10. Maintenance of patient data in the software for clinical trial management and data exploitation (annual statistics, patient activity, etc.).

Highlights in 2014

- Increase in the number of clinical trials performed.
- 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.
- 15 sponsor audits have been conducted with satisfactory results.
- Improvement and maintenance of new software implemented for clinical trial management.
- Organization of a new GCP training course for all oncology staff.
- The incorporation of a Quality Manager to improve both the quality and data of our clinical trials.

SUMMARY

Clinical trials are one of the best treatment options since they compare current state-of-the-art treatment with a potentially superior treatment and may even offer new drugs to patients for whom there are no alternative treatments. All patients in our oncology department are therefore considered as potential candidates for inclusion in our clinical trials. Although all patients may not be eligible or do not agree to take part in a clinical trial, we offer this option to all who meet the necessary criteria as per the different research protocols.

As a highly established center in cancer treatment we continue to report a steady, annual increase in the number of trials we run across Phase I, II, and III, totaling at 246 for 2014 (see figure III overleaf). This year we have witnessed an overall decrease in the number of patients recruited in clinical trials in our department compared to previous years (see figures I & II). 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 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'.

- 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. Hence, our hospital has taken part in phase I trials of different drugs and allowed the pharmaceutical industry to market novel therapies aimed at cancerous cells.
  We take part in clinical trials promoted by the pharmaceutical industry as well as those developed in our department in collaboration with other hospitals.
- Finally, the Clinical Trials Office has been involved in training future study coordinators, data managers, nurses, and junior CRAs. Since 2005, we have continued to organize a 36-hour postgraduate course -- 2014 marked the 9th edition.

Figure I: TOTAL ANNUAL RECRUITMENT IN CLINICAL TRIALS (PHASE I-II-III)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Included in phase I	35	59	57	110	130	120	108	132	139	171	222	245	277	290	345	303
Included in phase II	59	72	66	94	91	130	73	165	170	133	161	207	180	253	257	302
Included in phase III	95	128	175	109	84	129	111	85	143	180	189	221	218	236	241	166
Nº of patients included	**189**	**259**	**298**	**313**	**305**	**379**	**292**	**382**	**452**	**484**	**572**	**673**	**675**	**779**	**843**	**771**

Figure II: ANNUAL RECRUITMENT EVOLUTION (PHASE I-II-III TRIALS)

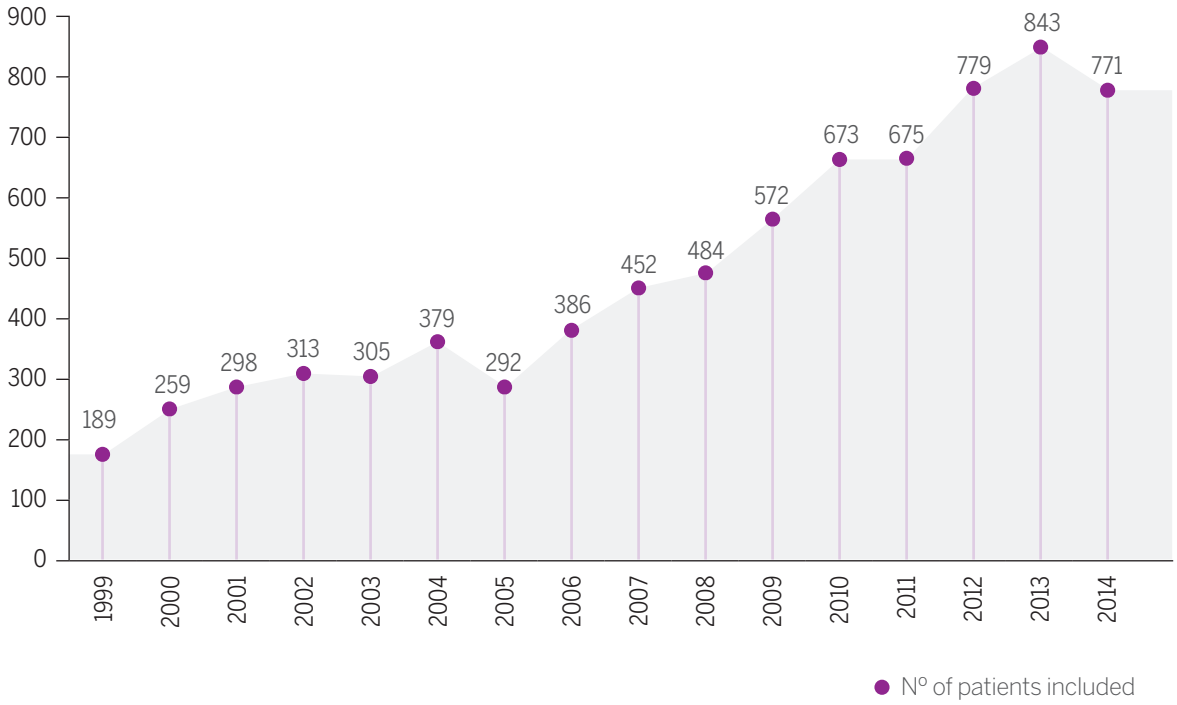


Figure III: ANNUAL DISTRIBUTION OF PHASE I,II AND III TRIALS

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

SUMMARY

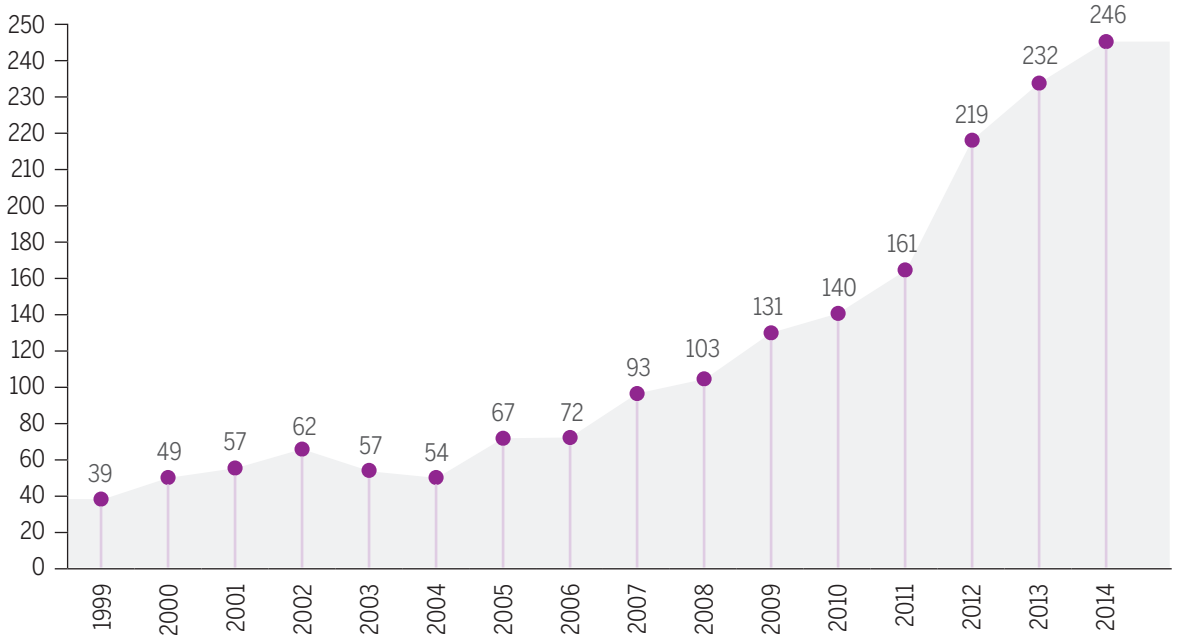
Set up in 1997, the Clinical Trials Office comprises an operational team conducting clinical trials at the Vall d'Hebron University Hospital's Oncology Department with more than 30 professionals including study coordinators, data managers and administrative staff working on some 246 trials. They are responsible for the logistics, coordination, data management and also the start-up process for new studies.

Each trial has an appointed coordinator and a data manager. Responsible for managing the procedures and assessments required in accordance with the protocol, the coordinator acts as the link between the study sponsor and the research team. The data manager provides the sponsor with all the necessary clinical data and monitors the quality of these data.

The Clinical Trials Office coordinates studies from Phase I to Phase III and is divided into three teams to cover all tumor groups and all trial. Our Office has conducted 246 actively recruiting trials and succeeded in recruiting and coordinating a total of 771 patients included in clinical trials. In addition, we are following up all patients that were recruited prior to 2014 who are still enrolled and receiving study treatment.

This year we have also continued to organize a Good Clinical Practice (GCP) course with the aim of ensuring that all our staff involved in clinical trials is suitably trained in GCP. Considering that they participate in several clinical trials from different sponsors, we wanted to offer a unique GCP training course independent of any sponsor in particular. Our course is certified by the *Consell Català de Formació Continuada de Professions Sanitàries* (CCFCPS), and *La Comisión de Formación Continuada del Sistema Nacional de Salud*, official Spanish Authorities, and has also been accepted by all the sponsors as well as the TransCelerate platform.

Figure IV: NUMBER OF CLINICAL TRIALS PER YEAR (PHASE I-II-III TRIALS)



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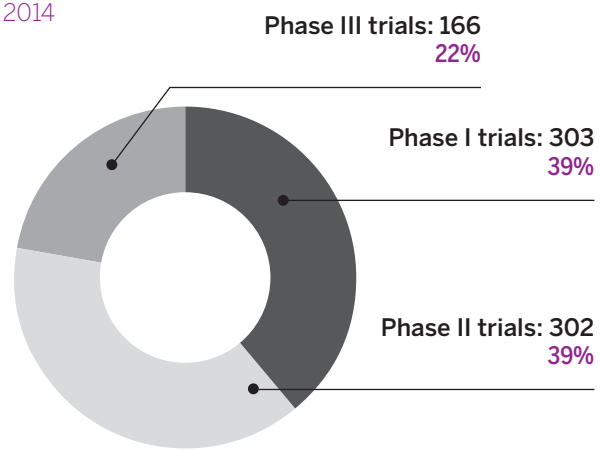
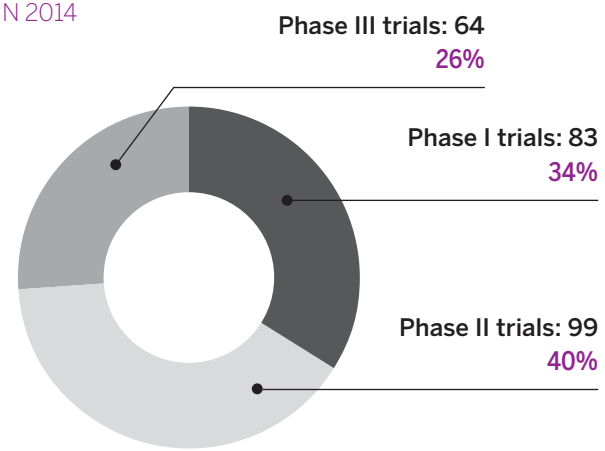
PATIENTS RECRUITED IN 2014



Percentage distribution across trials

DISTRIBUTION OF TRIALS IN 2014



Percentage distribution across trials

Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa"

Director of Clinical Research at VHIO
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Director and Medical Coordinator UITM, Principal Investigator, Early Clinical Drug Development Group
Jordi Rodón

Head, Clinical Trials Office
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Pablo Martínez
Leticia de Mattos
Eva Muñoz
Ana Oaknin
Mafalda Oliveira
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Víctor Rodríguez
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Laia Cano
Gloria García
Sheila Nieves
Isabel Rico
Cristina Viaplana

Pharmacy
FOUITM
Maria Josep Carreras Soler
USIFO
Laura Maños

Nurse Supervisor
Ángeles Peñuelas

Nurse Coordinator
Sonia Valverde

Nurses
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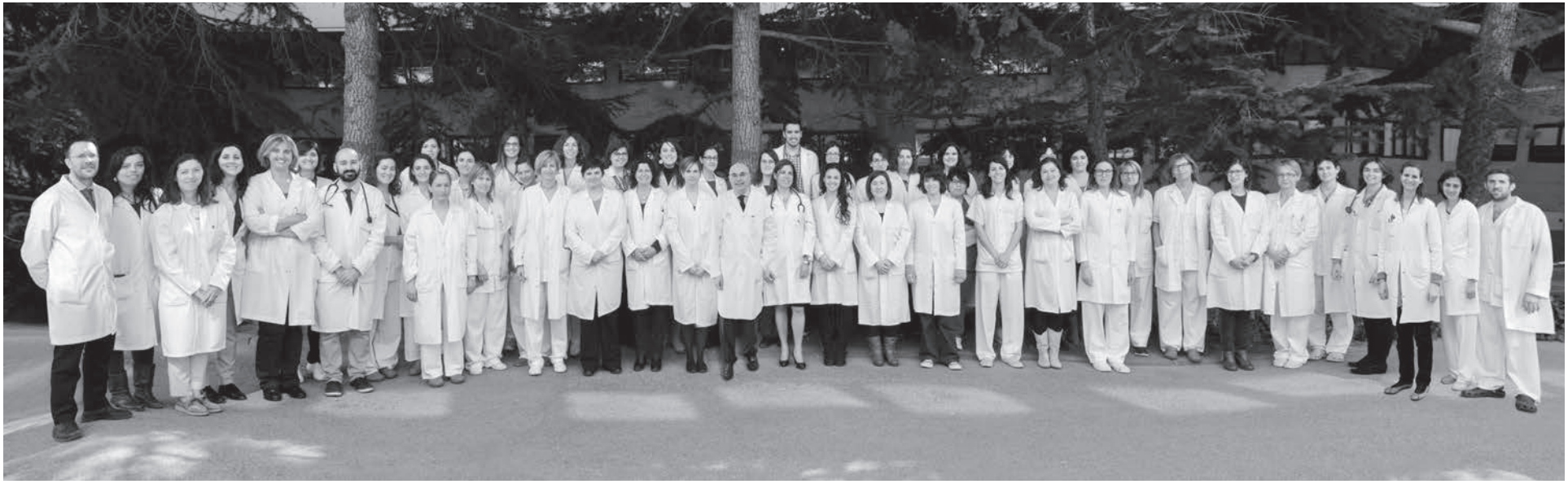
Meritxell Cucurell
Margarida Marcos
María Martín (Auxiliar)
Marta Mate
Núria Membrives
Mireia Milán
Isabel Muñoz
Raquel Muriel
Tania Sánchez
Alex Sierra
Lydia Vélez

Nurses' Assistant
Alicia López

Secretary
Teresa Mendoza



Strategic Goals

1. Early drug development and translational research led by UITM physician-researchers (please see pages 44 - 45: Early Clinical Drug Development Group) and VHIO scientists:
   – To further expand 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.
   – Enable VHIO to perform complex trials such as organ dysfunction trials, Octopus trials, Basket trials, among others.
   – Link clinical research at UITM with the various preclinical and translational research groups at VHIO and collaborate with the different partners involved in drug development and translational research.
2. 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.
   – To develop the area of medical informatics applied to genomic medicine.
   Integrate preclinical research and clinical research by incorporating novel drugs, new insights and study designs together with customized molecular diagnostics.
3. Immunotherapy:
   – To develop a task force among the UITM with expertise in early drug development of immunotherapeutics and cell signaling and translational research in Immuno-oncology.

Highlights in 2014

- 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. 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.

SUMMARY

Obra Social "la Caixa"

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 m^2 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 transform latest discovery into benefits for patients in record time.

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 2014, 83 phase I clinical trials were performed at the Unit with a total of 303 patients enrolled. It is thanks to the Unit's facilities coupled with the excellent 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 44 - 45), 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 (see Core Technologies, pages 61 - 69) we perform molecular analysis of the patients' tumors in order to select the best possible treatment with the experimental therapeutics available. Furthermore, 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 up the pace in driving faster, more precise mutational analysis of tumor-suppressor genes as well as translocations and gene amplifications.

The 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 pathologists from the Vall d'Hebron University Hospital'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 see pages 71 - 82.

For more specific information about our clinical trials please visit our extended Scientific Report online at: http://memorias. vhio.net/2014.

To find out more about us, our research, publications and even our group's horizons for 2015, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2014/

Clinical Research Oncology Nurses

Supervisor
Ángeles Peñuelas

Nurse Coordinators
Sonia Valverde
Lydia Vélez

Nurses
Mª Elena de Cabo
Meritxell Cucurell
Elisabet Hernández
Margarida Marcos
Marta Mate
Núria Membrives
Mireia Milán
Isabel Muñoz
Raquel Muriel
Tania Sánchez
Alex Sierra
Lidia Vegas

Nursing Assistants
Alicia López
Mª Ascensión Martín

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.

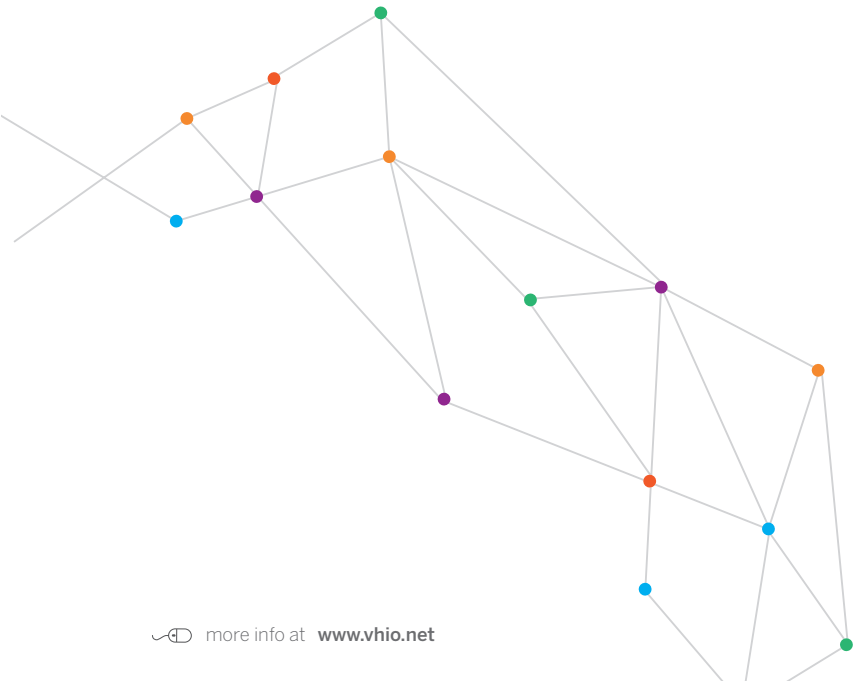
Such advances in cancer care and the development of more effective cancer therapeutics depend on an optimal clinical trial process.

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 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 treatments, are headed by Angeles Peñuelas and represent a critical and expert element of the multidisciplinary oncology team involved in clinical trials managed by VHIO's Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa" (see page 76 for more information) and the Clinical Trials Office (see page 72).

Incorporating medical oncologists, specialists in molecular pathology, pharmacists exclusively dedicated to this field (see VHIO's Clinical Research Oncology Pharmacy Unit on page 80), clinical research oncology nurses and study coordinators,

VHIO's multidisciplinary approach means that the patient receives the full range of expertise for his/her illness as well as detailed advice on the characteristics of his/her particular treatment.



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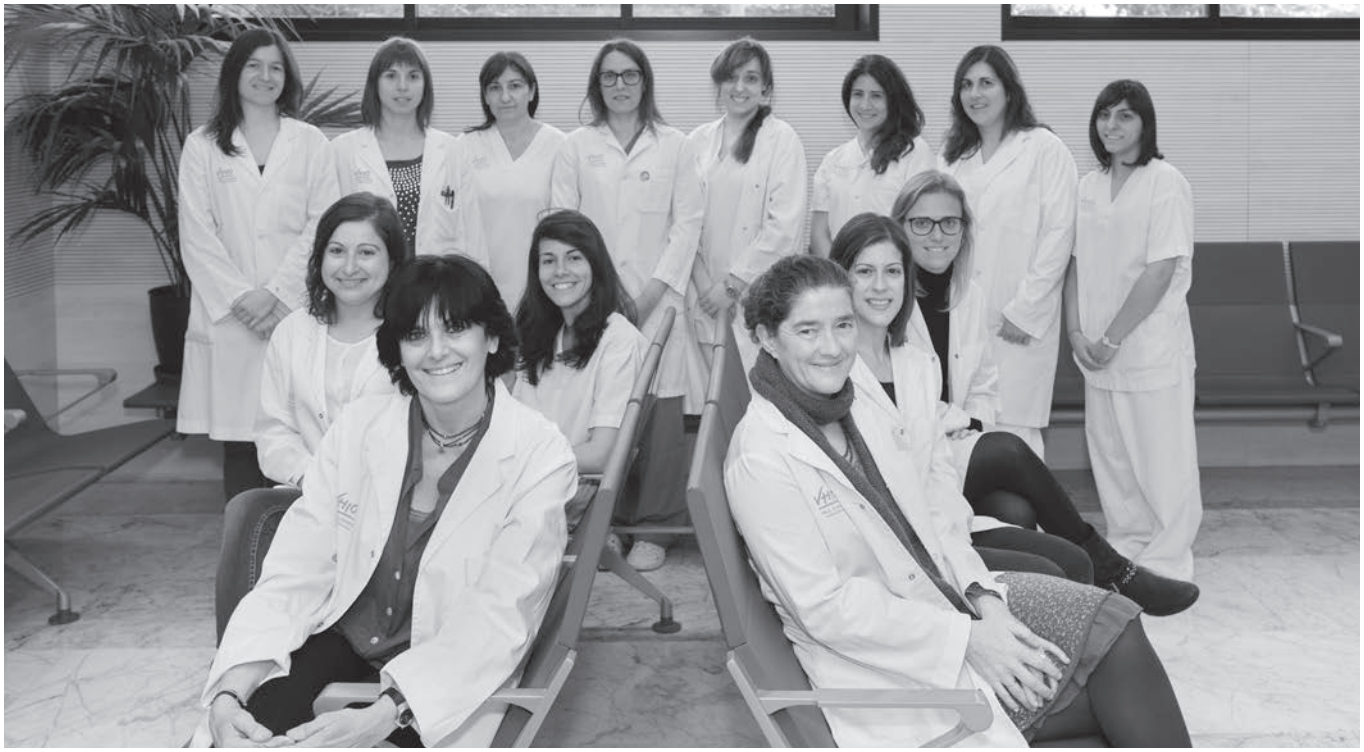
Clinical Research Pharmacy Unit

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

Coordinator of Pharmacological Research in Oncology Support Unit
Laura Mañós Pujol

Pharmacists
Anna Farriols Danés
Inés Jiménez Lozano
Marta Munné García
Berta Renedo Miró
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

Strategic Goals

1. Achieve excellence in the quality of service we provide to the different clinical oncology research programs through optimal efficacy, efficiency and safety.
2. Ensure traceability of management and preparation of drugs for clinical trials.
3. To guarantee that all the drugs involved in clinical trials are prepared and administered following protocol and pharmacy manual specifications.
4. Provide and ensure maximum control of the storage temperature of samples and preparations.
5. Increase documented control of drugs returned by patients.
6. Pharmaceutical care program for patients included in Phase I clinical trials with oral medication to improve safety, compliance and efficacy of the treatment.
7. Provide instructions and indications to patients for orally administered treatments in Phase II and III clinical trials.
8. Final implementation and validation of a traceability program in intravenous 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. Design and validation of traceability program in oral clinical trial supplies management (including storage, dispensation, and accountability).

Highlights in 2014

- Preparation for the opening of new facilities for our Unit with the incorporation of new computerized and technological systems for the management, control and storage of clinical trial as well as providing improved facilities for clinical trial development.
- Centralization of all preparations in clinical trials carried out by the UITM Pharmacy Unit.
- Validation of the traceability system: ISISH-TRI program. CFMTrials computerized system: traceability system for the management, control and storage of clinical trial supplies to both ensure and record the traceability of the relevant documentation of both the trials in digital format and the supplies upon reception until they are dispensed (oral medication or drugs for intravenous infusion). Documentation is transferred electronically to the traceability system of the Preparation Unit, thereby minimizing the possibility of medication errors.
- Improved documented control of drugs returned by patients as well as the coordination between the Oncology and Pharmacy departments.
- Clinical and technical support for the prescription / preparation /administration of cytostatics in clinical trials, providing an e-record of all actions, users, dates and times.
- Qualitative and quantitative quality control of all cytostatic and monoclonal antibodies preparations to guarantee the correct preparation of all trial drugs, without medication errors.
- To provide pharmaceutical care to patients included in Phase I clinical trials involving oral medication.
- ISO9001:2008 certification renewed.
- Conducted 15 sponsor audits with satisfactory results.

SUMMARY

Our Unit is ISO 9001:2008 certified and associated with the Medical Oncology Programs of the Vall d'Hebron University Hospital.

Our clinical research activities are carried out through two different programs:

The Oncology Pharmaceutical Care Program is responsible for preparing cytostatics, monoclonal antibodies, biological products and other parenteral anti-cancer drugs used in clinical trials, and for monitoring the clinical activity in our patients. This program incorporates a team of pharmacists specializing in hospital and oncology pharmacy, as well as laboratory technicians.

The Pharmacological Research in Oncology Support Program comprises a team of pharmacists and laboratory technicians specialized in clinical trials. The program is dedicated to managing, storing, issuing and controlling samples for clinical trials in oncology.

In 2014 our activity centered on the following main areas:

- *Management of clinical trial drugs:* we have managed clinical trial drugs for 246 active oncology studies. The number of deliveries of clinical trial supplies totaled at 3071 in 2014.

- *Maintenance of a novel system for controlling storage temperature:* performing electronic temperature recordings every 5 minutes. These readings are displayed on computers equipped with an audio and visual alarm as well as a system for sending an alert via SMS to the pharmacist on duty, continuously for 24 hours in case of temperature deviations.

- *Maintenance and improved efficiency of a new safety drug accountability procedure for drugs returned by patients:* this allows either our Unit's personnel or that of the sponsor to perform drug accountability and verify treatment compliance using a vertical laminar flow cabinet. The study drug returned by the patient is

accounted for by pharmacy personnel in the vertical laminar flow cabinet and the pills are stored in a transparent and sealed bag. This year, we carried out drug accountability for medication returned by patients from 110 clinical trials.

- *Ensuring and implementing traceability of the management of storage, custody and dispensing of clinical trial drugs:* the design of a computerized storage area for controlling samples, their location, expiry dates and traceability using a barcode reader. ISISH-TRI program system.

- *Design and validation of the drug preparation process traceability system:* qualitative and quantitative quality control of the computerized system that incorporates barcode technology, electronic scales and voice technology (Verbio Speech Technologies-Directed Work system).

- *Support for, and liaison with, the trial sponsors:* dispensing personnel have participated in 37 pre-study visits, 108 initial visits, 1243 monitoring visits, 91 close-out visits, as well as successfully passing 15 audits in the oncology setting. In addition, preparation staff has participated in 20 pre-study visits, 75 initial visits, 160 monitoring visits, and 11 audits.

- *Dispensing:* a total of 16,135 oncology clinical trial drugs have been dispensed with the validation of a pharmacist, 7372 of these are for orally administered clinical trial drugs. We have also conditioned and re-labeled the primary containers for clinical trial drugs. We have drawn up and updated a total of 307 Standardized Dispensing Procedures and performed 218 storage temperature data reports.

- *Validation and preparation:* all electronic prescriptions are reviewed by the pharmacist before preparation. In 2014 a total of 9632 preparations of cytostatics, monoclonal antibodies and other parenteral antitumor drugs for clinical trials were completed. A total of 92 Standardized Preparation Procedures have been compiled.

- *Prescription software maintenance:* after SIV, the pharmacist sets up the prescription software to introduce the requirements as specified in the protocol (dose, preparation instructions, premedication, administration instructions, and stability). In 2014, 184 different antineoplastic therapeutic schedules were incorporated in the software.

- *Pharmaceutical care program for patients enrolled in Phase I clinical trials with oral medication.* Three visits are scheduled: screening, C1D1 and follow-up. The screening visit involves checking the potential drug-drug interactions between the patients' usual treatment (medicines, complementary and alternative therapies) and the study medication under investigation. Should a potential interaction be detected, recommendations are proposed according to the protocol. During the C1D1s patients are advised about how to take the study medication, briefed regarding the management of possible side effects as well as informed about dietary recommendations. The follow-up is to verify whether patients are taking the medication correctly as well as evaluate compliance. During 2014 a total of 736 visits were carried out: 317 screenings, 246 C1D1s, and 173 follow-ups.

  If the study sponsor does not supply patient diaries and/or instructions for patients, we compile the necessary documentation. During 2014 a total of 12 different diaries and 15 instructive documents were elaborated.

  Support by telephone is available for patients throughout the entirety of a Phase I clinical trial in order to address all questions concerning concomitant medications and the study drug.

- *Improved pharmaceutical care of patients enrolled in Phase II /III trials* through diaries and instructions for patients included in all Phase II and Phase III clinical trials involving orally administered drugs. A total of 23 diaries and instructions for Phase II and Phase III clinical trials were compiled during 2014.

- *ISO9001:2008 certification renewed.*

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Full listing of articles published by VHIO Investigators in 2014

Articles published by VHIO Investigators in 2014 with allocated Impact Factor

Ceritinib in ALK-Rearranged Non-Small-Cell Lung Cancer. Shaw AT; Kim DW; Mehra R; Tan DS; *Felip E*; Chow LQ; Camidge DR; Vansteenkiste J; Sharma S; De Pas T; Riely GJ; Solomon BJ; Wolf J; Thomas M; Schuler M; Liu G; Santoro A; Lau YY; Goldwasser M; Boral AL; Engelman JA. 2014. *N Engl J Med*. 370: 1189-1197. IF: 54,420

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Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Cortazar P; Zhang L; Untch M; Mehta K; Costantino JP; Wolmark N; Bonnefoi H; Cameron D; Gianni L; Valagussa P; Swain SM; Prowell T; Loibl S; Wickerham DL; Bogaerts J; *Baselga J*; Perou C; Blumenthal G; Blohmer J; Mamounas EP; Bergh J; Semiglazov V; Justice R; Eidtmann H; Paik S; Piccart M; Sridhara R; Fasching PA; Slaets L; Tang S; Gerber B; Geyer CE; Pazdur R; Ditsch N; Rastogi P; Eiermann W; von Minckwitz G. 2014. *Lancet*. 384: 164-172. IF: 39,207

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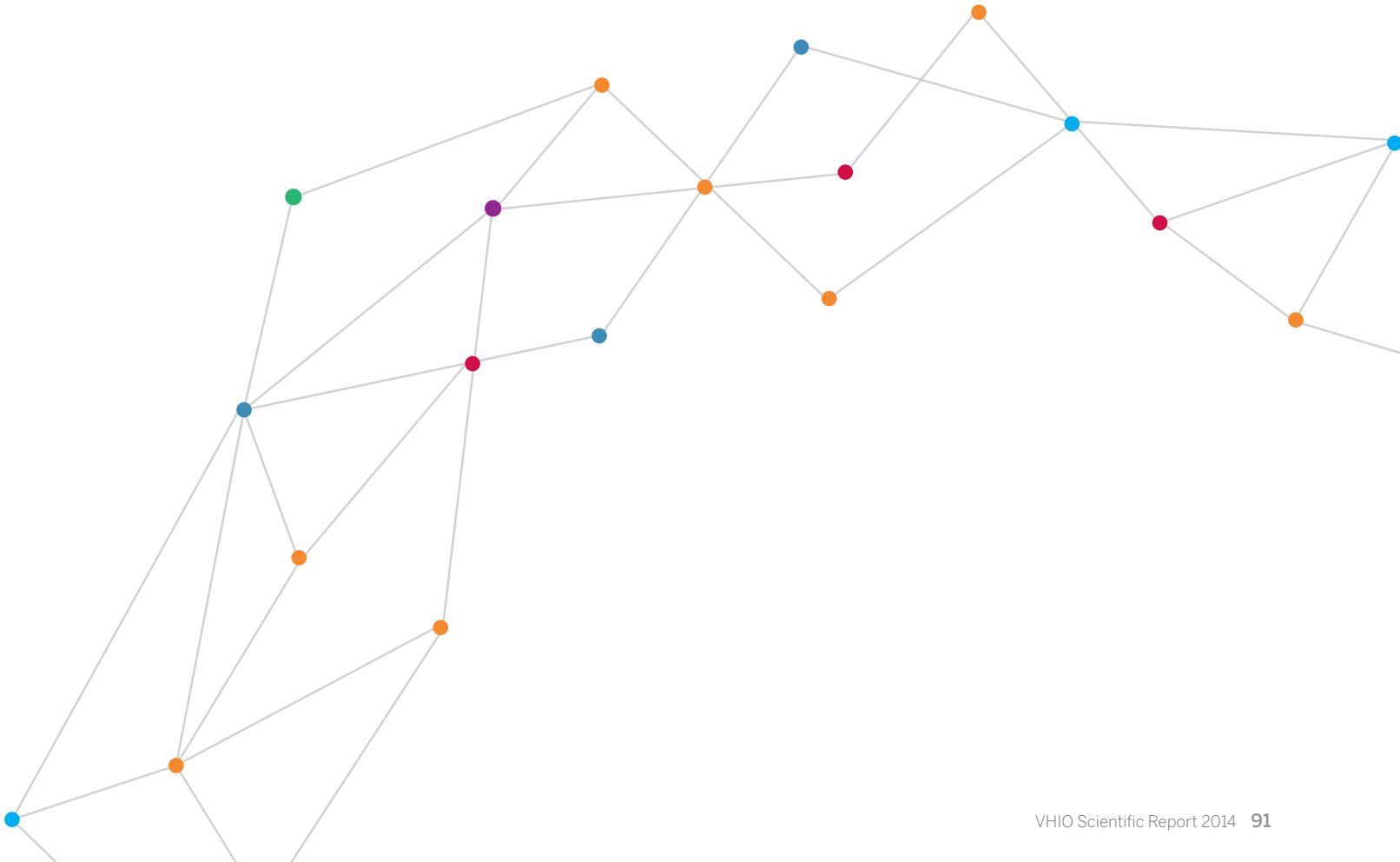

Funding & Consortia

FUNDING

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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.

For forthcoming information please bookmark VHIO's website:

www.vhio.net.

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.

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.

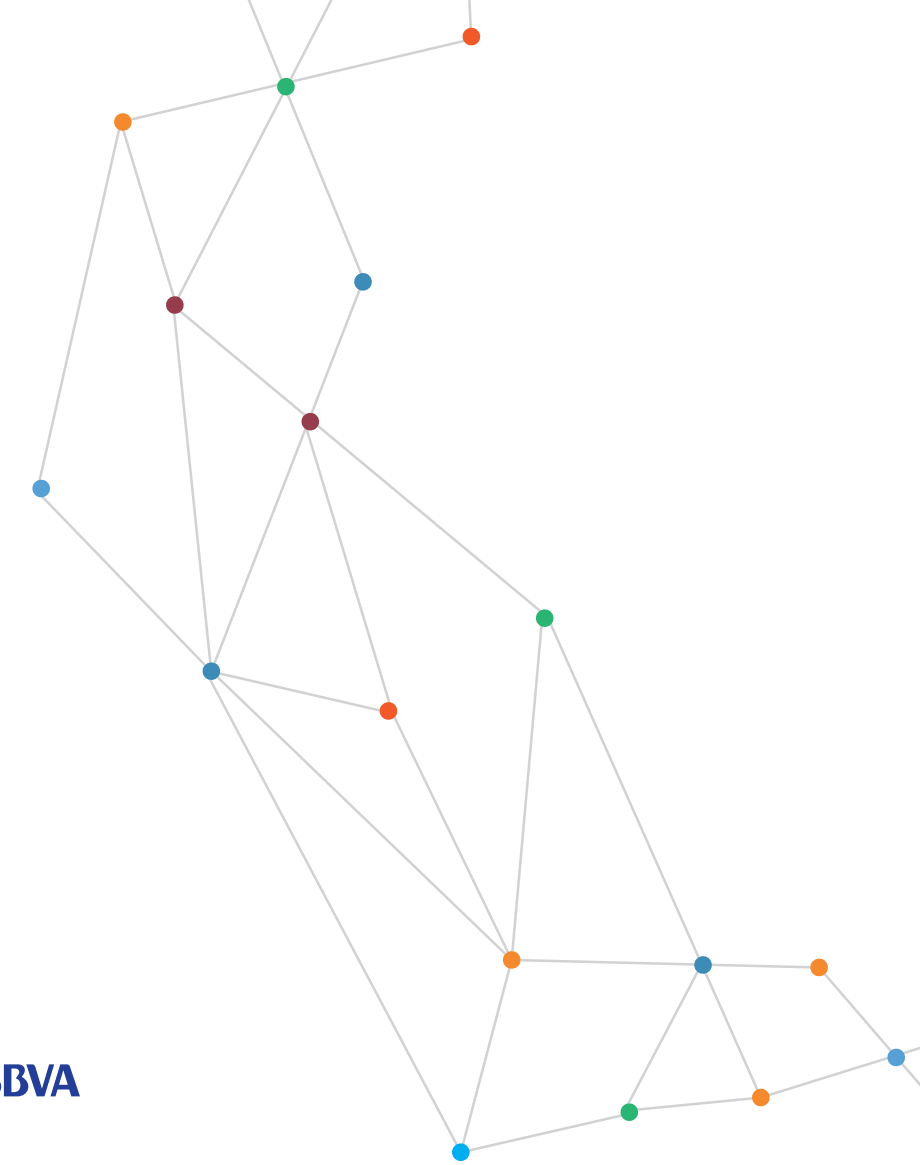
Other collaboration:

The 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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