2012 SCIENTIFIC REPORT

VALL D'HEBRON INSTITUTE OF ONCOLOGY

Centres de recerca de Catalunya

VHIO

INDEX 2012 SCIENTIFIC REPORT

more info at **www.vhio.net**

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INTRODUCING VHIO

PRECLINICAL RESEARCH

TRANSLATIONAL RESEARCH

CLINICAL RESEARCH

CORE TECHNOLOGIES

VHIO TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

Josep Tabernero, Director

José Baselga, President, Scientific Committee

FOREWORD

For more than a decade, personalized medicine has grown hand-in-hand with a multidisciplinary approach to the treatment and management of disease, and in so doing has marked some important milestones in how we diagnose, treat and care for patients, leading to a transformative new model of health care.

In oncology, the successes have been wide and far reaching, yet we are still far from a point in time when we can walk into a doctor's office with a memory stick storing our medical data and personal genetic information that will enable physicians to more rationally devise a treatment plan. Nevertheless, we should celebrate advances over the past ten years and reflect on the successes on the long road to personalized medicine, whereby tailoring treatments based on characteristics of patients' individual tumors is becoming part of daily clinical practice.

Personalized goes precise

The term 'precision medicine' is rapidly replacing personalized in the oncology lexicon, promising a new paradigm in cancer research, treatment and care. (Many physicians have pointed out that medicine has always been personalized to some extent!) Although originally coined back in 2008, this term did not start to gain momentum until a committee set up by the US National Research Council drafted a proposal in 2011 for modernizing the taxonomy of disease based on molecular data as opposed to symptom-based classification. They named the recommendation *Toward Precision Medicine*.

Terminology aside, we are on the brink of embracing an exciting new era. By rendering a more precise form of medicine, we aim to offer an expanded and more effective menu of targeted treatments for our cancer patients.

Our understanding of the range of cellular mechanism that drive cancer has grown dramatically over the past decade, thanks to profound advances in molecular biology, cell biology and genomics, fueled by the reduced costs of next-generation sequencing. Cancer treatment is increasingly focused on the genomic profile of patient – driver mutations, copy number changes and aberrant gene expression -- in order to match diagnosis and treatment strategy to each patient's unique molecular makeup.

VHIO – at the forefront of 'Precision Oncology'

At VHIO, we are beginning to deliver on the promise of precision medicine thanks to two key elements that underscore VHIO's success in advancing cancer discovery and medicine.

First, our location within the heart of the Vall d'Hebron University Hospital affords direct access to our patients as well as the entire spectrum of oncology professionals who care for them. Our privileged environment has not only been the driving force behind VHIO's translational model but has also facilitated the tight connectivity and cross-talk necessary to carry out multidisciplinary research and medical practice.

Second, we have also benefited tremendously from the stunning advances in genome sequencing to better steer clinical decisions. One important development this year has been the introduction of Illumina's MiSeq technology at VHIO, implemented by our Cancer Genomics Group led by Ana Vivancos. We can now obtain faster results at increasingly affordable costs in patient screening. This will set us in good stead to further improve upon cancer patient planning and management by ultimately selecting the best possible treatment for individual patients.

It's not just about quantity. In order to consolidate our internationally recognized work in developing new drugs based on the molecular profile of each tumor and optimizing treatment regimes with existing ones, we are currently applying for ISO accreditation for our Cancer Genomics Group and Molecular Oncology Group, headed by Paolo Nuciforo, as well as the Research Unit for Molecular Therapy of Cancer "la Caixa" (UITM). This research is carried out by our Early Clinical Drug Development Group led by Jordi Rodón, in collaboration with other VHIO groups in order to integrate molecular biology and optimal tumor models with pharmacology and cutting-edge clinical research.

Obtaining such accreditation will not only recognize the quality, competence and excellence synonymous with our activities, but will also ensure that we continue to meet all the statutory and regulatory requirements to further develop our research, programs and projects.

As we promised in last year's report, we have successfully incorporated the nCounter Nanostring platform, thanks to the expertise of the recently created Translational Genomics Group, led by Aleix Prat. Flanking our 'omics' efforts, his group participates in retrospective studies using tumor samples from our clinical trials, validates predictive and/or prognostic genomic-based biomarkers in prospective clinical trials, and evaluates gene expression data as a tool to identify drug sensitivity/resistance mechanisms.

While our preclinical, translational and clinical research efforts are benefiting more and more patients 'at-home', we must continue to share our expertise -- and benefit from the experiences of many others -- through international collaboration. Such cross-border exchange of data and ideas is critical not only in accelerating advances but also to avoid duplication of efforts -- now more important than ever given the bleak economic climate. In this respect, we are pleased to announce our participation in a unique clinical trial, as part of the Worldwide Innovative Networking in personalized cancer medicine (WIN).

The WINTHER trial, an original academic and international clinical trial, aims to develop a comprehensive analysis of the genetic background of tumors in order to predict drug sensitivity using powerful bioinformatics tools and optimize individualized therapeutic decisions with improved clinical outcome for patients.

Despite undeniable progress, we are all acutely aware that there is no silver bullet. While precision medicine will not benefit all patients today – we still have so much to learn about the 'cytological anarchy' that is cancer -- we have a responsibility to ensure that it lives up to its promise -- getting the right treatment at the right dose, at the right time.

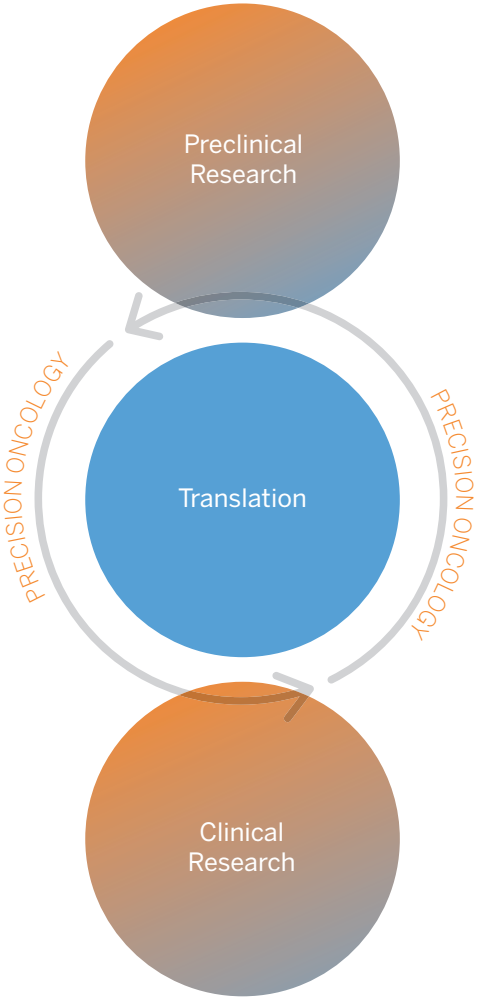
Rising to the challenge, VHIO seeks to significantly expand its research activities. The construction of a new home, the CELLEX building, will spur much needed growth by providing valuable space and by bringing all our multidisciplinary teams together under the same roof for even faster exchange of ideas and results. With cancer patients' lives in the balance, the current physical separation (200 meters) between our clinical and preclinical teams is 200 meters too many. We will not only *go* the distance, but also *close* the distance, in our tireless efforts to combat cancer.

At VHIO, as we demonstrate year in, year out, we can and will do better.

Josep Tabernero
Director

José Baselga
President, Scientific Committee

VHIO in 2012: translation toward precision



VHIO'S TRANSLATIONAL RESEARCH MODEL

Two key factors enable VHIO to do one of the things that it does best, namely, translate research findings for the benefit of patients in record time.

First, its purely translational, multidisciplinary research model facilitates the detailed study of each patient and each tumor which in turn, enables us to apply discovery from the laboratory to patients and from the clinical side, tumor samples are analyzed in the laboratory.

Organised into four main programs -- Preclinical, Translational, Clinical, and Core Technologies, research at VHIO focuses on understanding the fundamental biology of human cancer from cellular and molecular biology and genetics through to therapeutics, in order to address the many unresolved questions in ultimately combating this multifaceted, heterogeneous and highly complex disease (see VHIO's Organigram on facing page).

It's not only about the research. While VHIO continues to significantly contribute to important advances in cancer science and medicine (see pages 81 - 87 for VHIO's full list of publications in 2012, and an overview of Scientific Productivity as well as selected articles on pages 13 - 15), it does so largely thanks to its setting. Located within the heart of the Vall d'Hebron University Hospital, VHIO benefits immensely from direct access to patients as well as the entire spectrum of oncology professionals who care for them. VHO is organized into multidisciplinary, integrated teams whereby our researchers can closely collaborate and interact with Vall d'Hebron physician-scientists. Translational science and clinical research are therefore tightly connected, accelerating the bench-bedside-bed virtuous cycle of knowledge.

Vall d'Hebron Hospital

The Vall d'Hebron University Hospital: an ideal base and environment for VHIO's multidisciplinary cancer teams.

As discussed in the Foreword to this Scientific Report, we are now facing an exciting new 'post-personalized' era. As we begin to see the tremendous milestones marked over the last decade reap reward, whereby tailoring treatments based on characteristics of patient's individual tumors is becoming part of daily clinical practice, we still have a long way to travel.

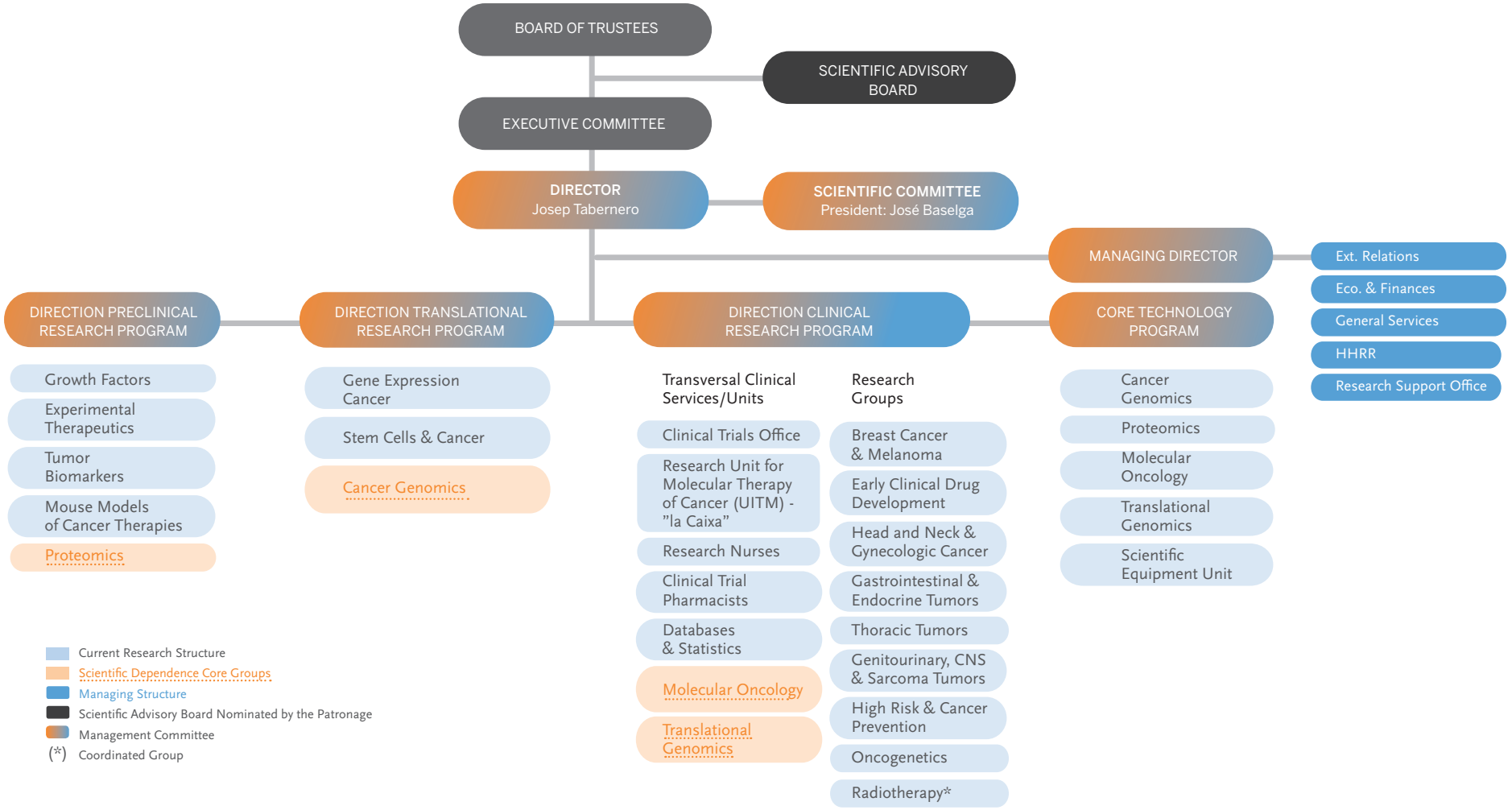
Simply put, we must cover the remaining distance by making personalized medicine more precise. Only then will we succeed in expanding more targeted treatment options for an increasing number of cancer patients, providing the right treatment at the right dose, at the right time. VHIO can only deliver this next step through the continued public funding it receives as well as the generous support from our patrons, private institutions, companies, individuals, funding entities and agencies (please see pages 88 - 90 for further details).

POISED FOR PRECISION ONCOLOGY

VHIO's Organigram 2012

VHIO provides the optimal organizational structure allowing researchers contact with cancer patients using the most advanced technologies and interaction between specialties.

In 2012 VHIO incorporated a new Translational Genomics Group. Joining VHIO's Cancer Genomics, Molecular Oncology, and Proteomics Groups, as part of our Core Technology Program, the group is responsible for the implementation and development of the nCounter Nanostring platform and also functions as a scientific dependence group, leading and developing independent research lines.



VHIO: the 'Omic' Era and Beyond

At VHIO, thanks to our suite of cutting-edge technology platforms as well as the talents who not only implement and provide these services, but also develop them, we are not only applying next-generation genome sequencing to identify novel cancer mutations but also starting to see it applied to individual patients to guide treatment decisions.

2012 has chaptered essential developments which will undoubtedly help VHIO deliver on making the personalized approach to cancer medicine more precise:

First, joining VHIO's genotyping platform (MassARRAY, Sequenom) and next- generation sequencer HiSeq2000, the MiSeq sequencing system (Illumina) was implemented by our Cancer Genomics Group (please see 60 page for more information), which will significantly accelerate results at increasingly lower costs in patient screening. VHIO's 'omics' will be progressively brought to the clinical setting whereby tumor genomic analysis will be used to steer cancer treatment and management decisions for an increasing number of patients.

MiSeq sequencing system (Illumina).

Another key development in 2012 has been the incorporation of the Translational Genomics Group and with it, the implementation of the nCounter Nanostring platform. The integration of such technology promises faster, more efficient generation of gene expression data to better characterize different cancer types. Flanking the efforts of VHIO's Cancer Genomics Group, we will be able to increasingly use genomic data to better guide clinical trial design and biomarker development and indentify optimal treatment regimens for cancer patients.

The nCounter Nanostring Platform of VHIO's recently incorporated Translational Genomics Group.

Clinical Trials at VHIO

VHIO has increasingly established itself as a leading reference in drug discovery from concept to clinic by driving drug development and targeted therapies against cancer:

Research Unit for Molecular Therapies of Cancer (UITM) - "la Caixa": fighting cancer's biology, one patient at a time

Obra Social "la Caixa"

Directed by Josep Tabernero, under the clinical coordination of Jordi Rodón, the Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa" was inaugurated in June 2010 thanks to the support received from the Welfare Projects Division of "la Caixa" Foundation in order to develop new drugs based on the molecular profile of each tumor and optimize treatment regimes using combinations of new drugs with existing ones.

This Unit, a pioneering project at national level, also benefits from the same privileged environment enjoyed by VHIO; located in the patient care environment of the Vall d'Hebron University Hospital and set within the research context. This excellent bridging and tight connectivity between health care and research 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.

In just two years since it was inaugurated, among many other successes, through the research carried out by VHIO's Early Clinical Drug Development Group (see pages 42 - 43) the Unit has firmly established itself as a leading reference with the most expertise in various areas of drug development including P13K/akt/mTOR inhibitors, FGFR inhibitors or drugs targeting developmental pathways such as TGF beta, SHH, Wnt and Notch.

Thanks to the Unit's outstanding facilities coupled with the excellent multidisciplinary clinical teams of professionals, 2012 witnessed a further increase in Phase I trials numbering at 66 and enrolling a total of almost 300 patients. While we continue to expand our portfolio of Phase I trials, adding new targeted therapies against novel, promising targeted therapies and best-in-class therapies, the new technology platforms that have been recently implemented by VHIO's Cancer Genomics (pages 60 - 61) and Translational Cancer Genomics groups (pages 66 - 67) - the MiSeq sequencing system and nCounter Nanostring platform respectively, will drive faster and more precise mutational analysis of tumor-suppressor genes as well as translocations and gene amplifications.

To discover more please see pages 74 - 75, or consult our Scientific Report online at: **http://memorias.vhio.net/2012/.**

Clinical Trials Office

Established in 1997, the Clinical Trials Office at the Vall d'Hebron University Hospital coordinates studies from Phase I to Phase III and is organized in three separate teams: Phase I, Breast Cancer, and Phase II - III. Thanks to the dedication and drive of more than 30 professionals including study coordinators, data managers and administrative staff, this Office reports exciting growth in both the number of patients enrolled in trials as well as trials conducted each year. 2012 continues the trend - totaling 219 Phase I - II - III trials with 719 patients recruited.

To consult the full list of highlights and a summary of activity in 2012 see pages 70 - 73. For a detailed listing of all clinical trials conducted in 2012 visit our Scientific Report 2012 online at: **http://memorias.vhio.net/2012/.**

The CELLEX Building: Set to Spur Even Faster Exchange of Ideas and Results

Fundació Privada
CELLEX

As envisaged, 2012 has quite literally laid the foundations for VHIO's new home: the CELLEX building. In the space of just one year since we compiled our 2011 Scientific Report, we can now publish a real image of the building under construction, as opposed to a virtual depiction.

Marking an exciting new era towards precision oncology, the final completion of the CELLEX building (scheduled for the end of 2013), will not only provide VHIO with the space it desperately requires to be able to expand its programs and activities, but will also bring all our multidisciplinary teams together under the same roof to yet further promote multidisciplinary cross-talk and connectivity between our researchers and physician-scientists.

The CELLEX building: bringing VHIO's multidisciplinary teams together under the same roof to further accelerate our translational research for tomorrow's targeted therapy.

DISCOVERY, DEBATE AND EXCHANGE OF THE HIGHEST DEGREE

VHIO Publications 2012

As a relatively young Institute established in 2006, the rapid expansion of our facilities coupled with attracting the very best talents from 'home' and abroad to work with us at VHIO, have resulted in our increased scientific productivity and Median Impact Factor each and every year (see pages 12, and 81 - 87 for the full list of publications in 2012).

Thanks to the efforts and drive of our preclinical, translational and clinical researchers as corresponding/ senior or co-authors, we can report 135 published papers with a Median Factor of 10.07 for 2012.

Statistics aside, as a community, we do what we do with one common aim in mind: improve outcomes for our cancer patients, now and in the future. VHIO will determinately continue to play a significant role in advancing scientific discovery to progress against cancer.

Consortia

As highlighted in the Foreword to this Scientific Report, we can only hope to accelerate discovery and thus improved cancer treatment and care in collaboration. Cross-border exchange of data and ideas will not only avoid duplication of efforts but spur advancements during these increasingly difficult and challenging economic times.

In 2012, VHIO has participated in the following international consortia of excellence:

SEVENTH FRAMEWORK PROGRAMME

RATHER
Rational Therapy for Breast Cancer

Rational Therapy for Breast Cancer (RATHER) - supported by the European Commission's 7th Framework Programme of Research and Development.

Initiated in January 2011, RATHER is a 5-year consortium project focusing on several key aspects of breast cancer research, and involves the combined efforts of six research institutions including VHIO and two biomedical companies.

The project aims to deliver on proof-of-concept for novel therapeutic interventions, together with matched molecular diagnostic approaches for improved patient stratification.

For more information please visit: www.ratherproject.com

EurocanPlatform

A European Platform for Translational Cancer Research (Eurocan Platform) - supported by the European Commission's 7th Framework Programme of Research and Development.

EurocanPlatform comprises 28 European leading cancer Institutions and organizations including VHIO, working together as a unique collaboration. The participating centers share infrastructures and collaborate on projects to help advance cancer research and treatment.

More specifically, the project focuses on three key areas of research: prevention, early detection, and improved treatments. It will ultimately facilitate the necessary resources and know-how to advance cancer care from bench-bedside-bed, covering all levels from preclinical, early-to-late translational, clinical, epidemiological, implementation in care, and population-based outcome research.

Find out more here: http://eurocanplatform.eu/

COLTHERES
colon therapy research consortium

Colon Therapy Research Consortium (COLTHERES) - funded by the European Commission's 7th Framework Programme of Research and Development.

COLTHERES is a unique consortium of European clinical research centers of excellence including VHIO, 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.

This is a 4-year program that uses comprehensively molecularly-annotated colon cancers as a 'test-bed' to define specific biomarkers of response or resistance to signaling pathway agents. Efforts focus on identifying validated risk and patient response stratification criteria which can then be used to rationally develop companion diagnostic assays and more stream-lined clinical trials.

To discover more about this project visit: www.coltheres.eu

WIN
Worldwide Innovative Networking in personalized cancer medicine

Worldwide Innovative Networking in personalized cancer medicine (WIN) - initiated by the Institut Gustave Roussy [France] and The University of Texas, MD Anderson Cancer Center [USA].

WIN, Worldwide Innovative Networking in personalized cancer medicine, is a non profit, non-governmental organization that brings together 22 cancer centers including VHIO and industry partners from five continents to address the challenge of increasing the efficacy of cancer diagnostics and therapeutics.

Its mission is to rapidly translate ground-breaking, early diagnostic and personalized cancer medicine discovery into a clinical reality for cancer patients. More specifically, dedicated efforts will aim at generating the first, relevant clinical study data within the ambitious time frame of between 3-5 years, identifying new biomarkers and develop standardized kits useful for improved cancer care.

A major development in 2012 has been WIN's launch of a unique academic and international clinical trial - WINTHER. Representing a major step forward in the evaluation of precision treatments, this trial will demonstrate the validity of the biological approach in oncology. VHIO will join the other trial partners to collectively develop a comprehensive analysis of the genetic background of tumors in order to predict drug sensitivity adopting powerful bioinformatics tools, and optimize individualized therapeutic decisions with improved clinical outcome for patients.

Detailed information can be found at: www.winconsortium.org

VHIO events

VHIO *Meet the Editors*

Launched with *Nature* journal's Senior Editor, cancer research, Barbara Marte on *Inside Nature* in **October 2011**, our 2012 annual series of VHIO *Meet the Editors* prestigious talks provided oncology professionals of research institutes of excellence in Barcelona with unique opportunity to learn more about scientific publishing and cancer research and put questions and comments to the editors directly during the Q & A with the audience. They also provided a rare opportunity to get to know the editors of the highest impact factor journals personally.

VHIO's *Meet the Editors* in 2012

Speaker: Paula Kiberstis, Senior Editor, cancer research
Talk: Demystifying Science
Date: 23 January 2012

Synopsis: Marking the second in the prestigious series of talks: VHIO *Meet the Editors, Science's* Paula Kiberstis, Senior Editor, cancer research, delivered a highly insightful presentation on *Demystifying Science*. More specifically her presentation focused on the following topics:

- How *Science* editors select manuscripts (and what makes them lose sleep!)
- Optimizing your paper's chance of acceptance at *Science*
- The ever-evolving landscape of "general interest" topics in cancer research
- What do *Science and Science Translational Medicine* look for in cancer research papers?
- The future of science publishing

Speaker: Bette Phimister, Deputy Editor
Talk: Publishing Advances in Cancer Research
Date: 14 May 2012

Synopsis: *The New England Journal of Medicine's* Bette Phimister, Deputy Editor, presented on: *Publishing Advances in Cancer Research.*

Bette Phimister reviewed progress and pitfalls in cancer research and issues concerning its publication, with a focus on targeted therapies and an eye to future developments. True to the unique format of these special meetings, the second half of the session was dedicated to a Q & A round with the audience whereby participants addressed Bette directly with questions and comments they had about the journal and future directions in cancer research.

Speaker: Victoria Aranda, Senior Editor
Talk: *Nature Medicine*: an in-depth look at scientific publishing, criteria for cancer research publications and future trends in oncology
Date: 17 September 2012

Synopsis: Victoria Aranda's presentation offered all participants a stepwise look at the inner workings of the peer review process at *Nature Medicine*, including initial submission, internal editorial review, peer review, rebuttals and appeals. She also covered how editorial decisions are made to help increase publication success rate, and decrease stress levels. She concluded her talk by surveying in detail *Nature Medicine's* criteria for cancer research publications, and provided an overview of future trends in Oncology.

Workshops, Courses, and Observerships

At VHIO we share our expertise, learn from eminent guest speakers, discuss and debate latest findings through the organization of VHIO ad-hoc courses and workshops. For further information about these events in 2012 and much more, please visit our extended Scientific Report 2012 online at: **http://memorias.vhio.net/2012/**.

Coming to VHIO in 2013

In addition to a 2013 series of VHIO Meet the Editors (welcoming Editors-in-Chief including *Cancer Cell's* Li-Kuo Su and *The Lancet Oncology's* David Collingridge) and Workshops, Courses, and Observerships, we are delighted to advance that, in collaboration with the Fritz Bender Foundation, we will be co-organizing the forthcoming international symposium on ***Progress Towards Individualized Cancer Treatments*** , 07 - 09 November 2013, Barcelona, Spain.

Incorporating an outstanding panel of internationally renowned speakers, the symposium will run for two and a half days organized into five main sessions: 1) Genetic Profiling of Patients, 2) Tumor Characterization, 3) Tumor-Host Relationships, 4) Therapeutic Targets I, and 5) Therapeutic Targets II. While we are currently engineering what we hope to be a scientific program par excellence, we trust that this meeting will match and celebrate the successes of past Fritz Bender Foundation International Symposia.

For forthcoming announcements, abstract submission and registration, please bookmark and visit VHIO's website: **www.vhio.net**.

Last Word

To find out more about our teams, activities and all our latest news, we invite you to visit and bookmark our recently re-launched institutional website at: **www.vhio.net**.

Scientific Productivity: research articles

ARTICLES PUBLISHED IN 2012

In 2012, 135 scientific articles were published by VHIO researchers as corresponding/ senior authors of co-authors with a Median Impact Factor (MIF) of 10.07. Both of these figures reflect the increasing quality of scientific productivity at VHIO as well as the importance of its research and contribution to the oncology field:

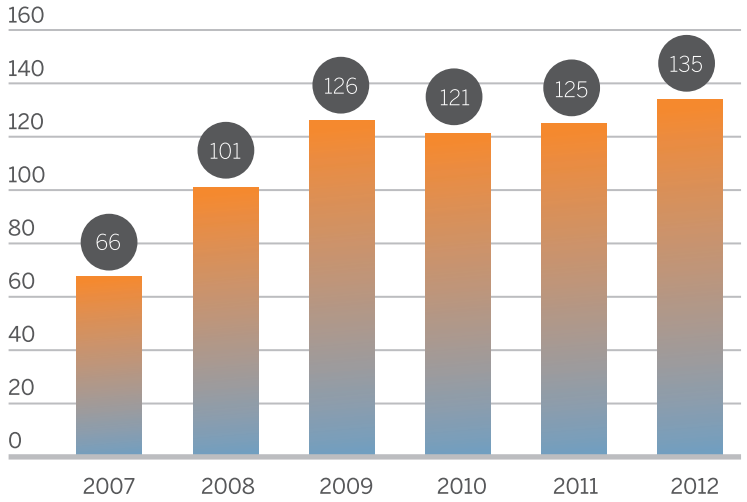


Figure 1: Number of articles published by VHIO researchers from 2007 - 2012.

IMPACT FACTOR ARTICLES PUBLISHED IN 2012

For the complete list of VHIO scientific articles published in 2012 in journals with allocated Impact Factor please see pages 81 - 87. To view a selection of most relevant articles by VHIO researchers published in 2012 please see pages 13 - 15 of this Scientific Report.

Alternatively visit our Scientific Report online at: http://memorias.vhio.net/2012/ (select tab 'Publications, Projects & Awards' to view publications per group as selected by each of our Principal Investigators).

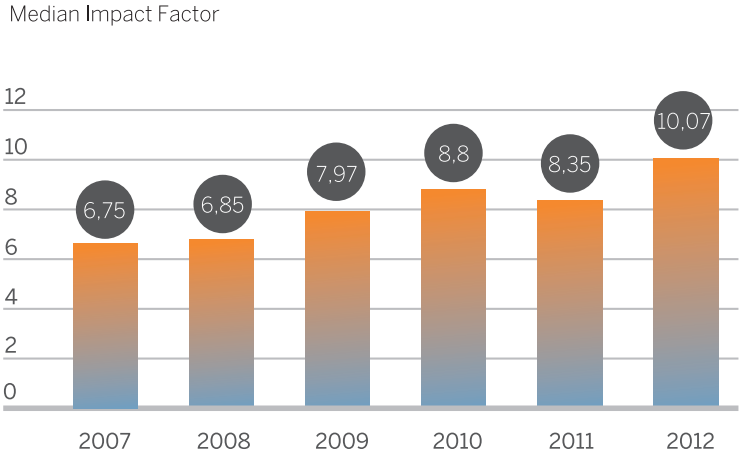


Figure 2: Median Impact Factor (MIF) of papers published by VHIO faculty from 2007 - 2012.

Selection of some of the most relevant articles by VHIO researchers published in 2012

Below is a **selected list** of articles published by VHIO researchers in 2012 with respective Impact Factors. For the complete list of VHIO scientific articles published in 2012 in journals with allocated Impact Factor please see pages 81 - 87 of this Scientific Report.

Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer. *Baselga, Jose*; Campone, Mario; Piccart, Martine; Burris, III, Howard A.; Rugo, Hope S.; Sahmoud, Tarek; Noguchi, Shinzaburo; Gnant, Michael; Pritchard, Kathleen I.; Lebrun, Fabienne; Beck, J. Thaddeus; Ito, Yoshinori; Yardley, Denise; Deleu, Ines; Perez, Alejandra; Bachelot, Thomas; Vittori, Luc; Xu, Zhiying; Mukhopadhyay, Pabak; Lebwohl, David; Hortobagyi, Gabriel N.. 2012. ***N Engl J Med*** 366: 520-529. **IF: 53,298**

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. *Baselga, Jose*; *Cortes, Javier*; Kim, Sung-Bae; Im, Seock-Ah; Hegg, Roberto; Im, Young-Hyuck; Roman, Laslo; Pedrini, Jose Luiz; Pienkowski, Tadeusz; Knott, Adam; Clark, Emma; Benyunes, Mark C.; Ross, Graham; Swain, Sandra M.; CLEOPATRA Study Grp. 2012. ***N Engl J Med***.366: 109-119. **IF: 53,298**

TrastuzumabEmtansine for HER2-Positive Advanced Breast Cancer. Verma S; Miles D; Gianni L; Krop IE; Welslau M; *Baselga J*; Pegram M; Oh DY; Diéras V; Guardino E; Fang L; Lu MW; Olsen S; Blackwell K. 2012. ***N Engl J Med*** 367: 1783-1791. **IF: 53,298**

Lapatinib with trastuzumab for HER2-positive early breastcancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Baselga J*, Bradbury I, Eidtmann H, Di Cosimo S, de Azambuja E, Aura C, GómezH, Dinh P, Fauria K, Van Dooren V, Aktan G, Goldhirsch A, Chang TW, HorváthZ,Coccia-Portugal M, Domont J, Tseng LM, Kunz G, Sohn JH, Semiglazov V, LerzoG,Palacova M, Probachai V, Pusztai L, Untch M, Gelber RD, Piccart-GebhartM;NeoALTTO Study Team. ***Lancet*** 2012. 379(9816):633-640. **IF: 38,278**

Sequence analysis of mutations and translocations across breast cancer subtypes. Banerji, Shantanu; Cibulskis, Kristian; Rangel-Escareno, Claudia; Brown, Kristin K.; Carter, Scott L.; Frederick, Abbie M.; Lawrence, Michael S.; Sivachenko, Andrey Y.; Sougnez, Carrie; Zou, Lihua; Cortes, Maria L.; Fernandez-Lopez, Juan C.; Peng, Shouyong; Ardlie, Kristin G.; Auclair, Daniel; Bautista-Pina, Veronica; Duke, Fujiko; Francis, Joshua; Jung, Joonil; Maffuz-Aziz, Antonio; Onofrio, Robert C.; Parkin, Melissa; Pho, Nam H.; Quintanar-Jurado, Valeria; Ramos, Alex H.; Rebollar-Vega, Rosa; Rodriguez-Cuevas, Sergio; Romero-Cordoba, Sandra L.; Schumacher, Steven E.; Stransky, Nicolas; Thompson, Kristin M.; Uribe-Figueroa, Laura; *Baselga, Jose*; Beroukhim, Rameen; Polyak, Kornelia; Sgroi, Dennis C.; Richardson, Andrea L.; Jimenez-Sanchez, Gerardo; Lander, Eric S.; Gabriel, Stacey B.; Garraway, Levi A.; Golub, Todd R.; Melendez-Zajgla, Jorge; Toker, Alex; Getz, Gad; Hidalgo-Miranda, Alfredo; Meyerson, Matthew. 2012. ***Nature*** 486: 405-409. **IF: 36,280**

Systematic identification of genomic markers of drug sensitivity in cancer cells. Garnett MJ, Edelman EJ, Heidorn SJ, Greenman CD, Dastur A, Lau KW, Greninger P, Thompson IR, Luo X, Soares J, Liu Q, Iorio F, Surdez D, Chen L, Milano RJ, Bignell GR, Tam AT, Davies H, Stevenson JA, Barthorpe S, Lutz SR, Kogera F, Lawrence K, McLaren-Douglas A, Mitropoulos X, Mironenko T, Thi H, Richardson L, Zhou W, Jewitt F, Zhang T, O'Brien P, Boisvert JL, Price S, Hur W, Yang W, Deng X, Butler A, Choi HG, Chang JW, *Baselga J*, Stamenkovic I, Engelman JA, Sharma SV, Delattre O, Saez-Rodriguez J, Gray NS, Settleman J, Futreal PA, Haber DA, Stratton MR, Ramaswamy S, McDermott U, Benes CH. ***Nature*** 2012. 28;483(7391):570-575. **IF: 36,280**

Cancer: Pinprickdiagnostics. Vilar E, *Tabernero J*. ***Nature*** 2012. 486(7404):482-483. **IF: 36,280**

Lunatic Fringe Deficiency Cooperates with the Met/Caveolin Gene Amplicon to Induce Basal-like Breast Cancer. Xu, Keli; Usary, Jerry; Kousis, Philaretos C.; *Prat, Aleix*; Wang, Dong-Yu; Adams, Jessica R.; Wang, Wei; Loch, Amanda J.; Deng, Tao; Zhao, Wei; Cardiff, Robert

Darrell; Yoon, Keejung; Gaiano, Nicholas; Ling, Vicki; Beyene, Joseph; Zacksenhaus, Eldad; Gridley, Tom; Leong, Wey L.; Guidos, Cynthia J.; Perou, Charles M.; Egan, Sean E.. 2012. ***Cancer Cell*** 21: 626-641. **IF: 26,566**

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VHIO MULTIDISCIPLINARY RESEARCH PROGRAMS

PRECLINICAL RESEARCH

Joaquín Arribas DIRECTOR, PRECLINICAL RESEARCH PROGRAM

During 2012 we have continued developing our lines of research in a highly interactive way. Focusing mainly on breast, colon and lung cancer, our program has identified novel mechanisms of resistance to targeted therapies and searched for novel biomarkers of response.

The Experimental Therapeutics Group, led by José Baselga, has focused on understanding the mechanism of action of, as well as the resistance to, targeted therapies in breast cancer, with particular focus on the blockade of the HER2/PI3K/mTOR pathway. Research aimed at identifying novel candidates of PI3K resistance through overexpression of an kinase library in several *in vitro* models, showed the importance of sustained ERK/RSK-pathway activation in limiting the activity of PI3K inhibitors. They have further established novel patient tumor-derived breast cancer models *in vivo*. These preclinical models faithfully resemble the clinical setting and have been extremely useful in the study PI3K-therapy resistance. In particular, they demonstrated that PI3K blockade results in DNA homologous recombination impairment and sensitization to PARP inhibition in triple negative breast cancer without BRCA mutations, providing a rationale to combine PI3K and PARP inhibitors in this indication.

My own group, the Growth Factors Group, has continued its research on HER2-positive, breast cancers. We have identified a novel fragment of HER2 frequently expressed. This fragment, that we have named HER2-NTF, encompass the extracellular and transmembrane domains of HER2 but lacks most of its cytoplasmic domain and it is, therefore inactive. HER2-NTFs associates with other HER receptors to form inactive complexes. However, the expression of this fragment does not affect treatment with Herceptin, a therapeutic monoclonal antibody currently used to treat HER2-positive breast cancers. We have continued to analyze the role of HER2-induced premature senescence in breast cancer progression and shown the prometastatic effect of the secretome of HER2-induced senescent cells.

The most unbiased approach to search for novel biomarkers is the analysis of the tumour proteome, i. e. the entire protein content of a given tumor. Two of our groups have developed state-of the art proteomic techniques to accomplish this goal. These groups constitute one of the major technological strengths of our program.

Francesc Canals leads VHIO's Proteomics Facility and research group. In collaboration with VHIO's Gene Expression & Cancer Group led by Joan Seoane, Canals' group is actively looking for novel markers of response to the transforming growth factor-beta, which plays a pivotal role in the development of different tumors. In collaboration with the Growth Factors Group, they are identifying novel substrates of proteases that determine malignant progression.

In addition, the Proteomics Facility, continues to provide services in proteomic techniques to other research groups as well as collaborate in both national and international projects and networks including the Instituto *Salud Carlos III* Cancer Research and *ProteoRed* networks as well as the Consortium on Chromosome 16 HPP, as part of the HUPO Human Proteome Project.

Led by Josep Villanueva, our Tumor Biomarker Group's research into the characterization of the effect of the EGFR signalling pathway on the secretome of colorectal cancer cells has progressed. The final aim is to identify novel biomarkers of response to anti-EGFR therapies.

From the technical point of view, this group has also developed a novel mathematical algorithm that facilitates improved reproducibility of proteomic data obtained. They are also developing an exciting project to characterize novel mechanisms by which cells secrete factors and, thus, communicate with and modify the tumour microenvironment.

Finally, despite having being with us for only one year, our Mouse Models of Cancer Therapies Group has already expanded to five members. The main focus of this group headed by Laura Soucek, is the pleiotropic and ubiquitous Myc oncoprotein whose deregulation is implicated in almost all human cancer types. Soucek's laboratory previously demonstrated that Myc inhibition has a dramatic therapeutic impact on different types of cancer, including lung tumors, with very mild and reversible side effects in normal tissues. They are now interested in Myc's role in the coordination of the response to different ocogenic signals and how this compares between different tissues, especially in relation to the cross-talk between tumor and microenvironment.

In summary, we are continuing to mark significant progress in accomplishing one essential, common goal: to develop better treatments against different tumors including, breast, colon and lung cancers.

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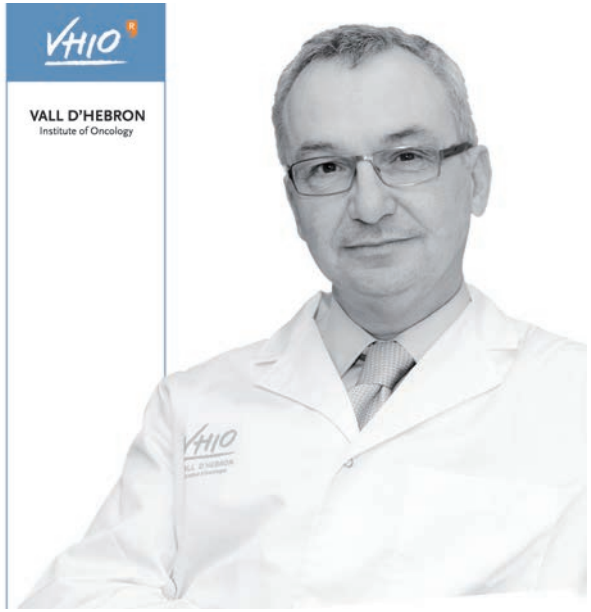

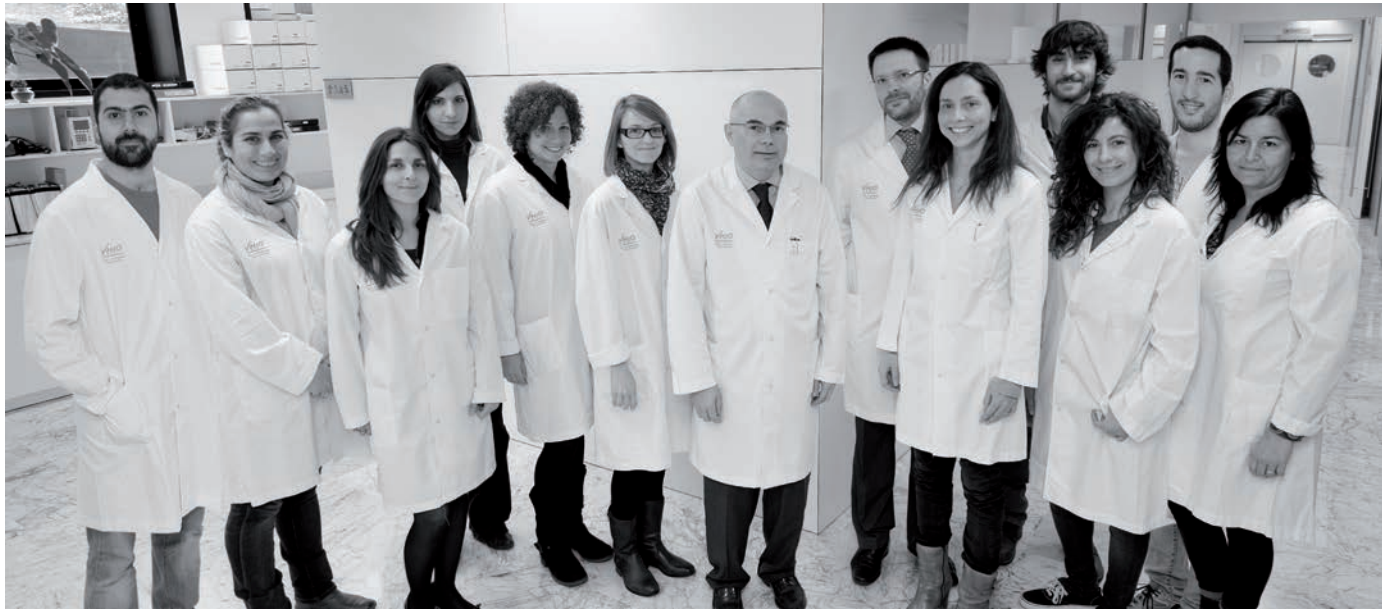

Strategic Goals

1. Unveiling novel mechanisms of resistance against HER2- and PI3K-targeted therapies.
2. Studying early molecular responses following PI3K inhibition to rationally design novel combination therapy in breast cancer.
3. Developing predictive and pharmacodynamic biomarkers of PI3K-pathway inhibitors.
4. Establishing a novel patient tumor-derived breast cancer preclinical model to explore hypothesis-based combinatorial therapies.

Highlights in 2012

- Combined therapy against the mTORC1/2 and HER2 blocked HER2/HER3-activation following PI3K/mTOR-pathway inhibition.
- PI3K blockade induced DNA homologous recombination impairment and sensitization to PARP inhibition in triple negative breast cancer without BRCA mutations, providing a rationale to combine PI3K and PARP inhibitors in this indication.
- In collaboration with VHIO's Growth Factors Group led by Joaquín Arribas and the Molecular Oncology Group led by Paolo Nuciforo, we have developed and validated an antibody-based assay for the detection of P95HER2 in clinical specimens. The assay is implemented to query the predictive value of P95HER2 in the Neo-ALTTO clinical trial.
- Patient-derived tumor models enable testing PI3K-inhibitors in a co-clinical manner to further establish predictive biomarkers.
- In a cooperative effort with VHIO's Hight Risk and Cancer Prevention Group, we initiated studies to elucidate mechanims of resistance to PARP inhibition.

SUMMARY

During 2012 our research has focused on understanding the mechanisms of resistance to targeted therapy in breast cancer, with special emphasis on the blockade of the HER2/PI3K/Akt/mTOR pathway. Our major aim has been to provide hypothesis-based strategies to combine targeted therapy and, in so doing, improve outcomes for patients.

Insight 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. Several strategies were tested to overcome this phenomenon including combined therapy against the mTORC1/2 and HER2.

Further efforts were initiated to identify novel candidates of PI3K resistance through overexpression of a kinase library in several in vitro models. This research is now showing the importance of sustained ERK-pathway activation in limiting the activity of PI3K inhibitors. A collaboration involving VHIO's Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa" and Molecular Oncology Group, led us to identify pharmacodynamic markers of Akt inhibition that can be exploited in the clinical development of these inhibitors.

Finally, through a cooperative effort with VHIO's Breast Cancer & Melanoma Group, and High Risk and Cancer Prevention Group led by Judith Balmaña, we established novel patient tumor-derived breast cancer models in vivo. These preclinical models have shown to faithfully resemble the clinical setting and have been extremely useful in the study of PI3K-therapy resistance. In detail, we show that PI3K blockade results in DNA homologous recombination impairment and sensitization to PARP inhibition in triple negative breast cancer without BRCA mutations, providing a rationale to combine PI3K and PARP inhibitors in this indication (see figure).

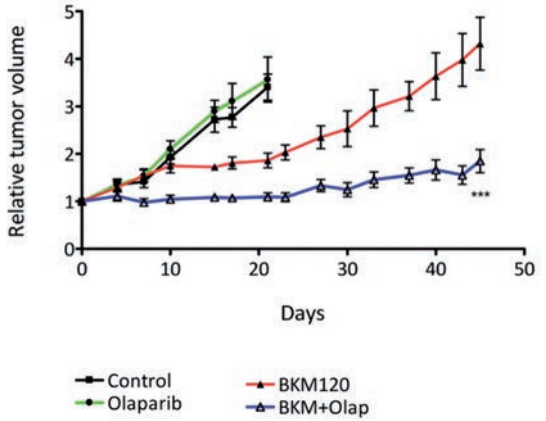

Figure: Combined PI3K and PARP suppression in vivo. Tumor growth of TNBC1, TNBC2, and TNBC3 xenografts treated with vehicle control, BKM120 (27.5 mg/kg), olaparib (Olap; 50 mg/kg), or the combination of both agents. Relative tumor volumes are displayed as mean Â} SE of a minimum of 6 tumors per arm. *, P < 0.001 combination versus BKM120 arm.

To find out more about us, our research, publications and even our group's horizons for 2013, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2012

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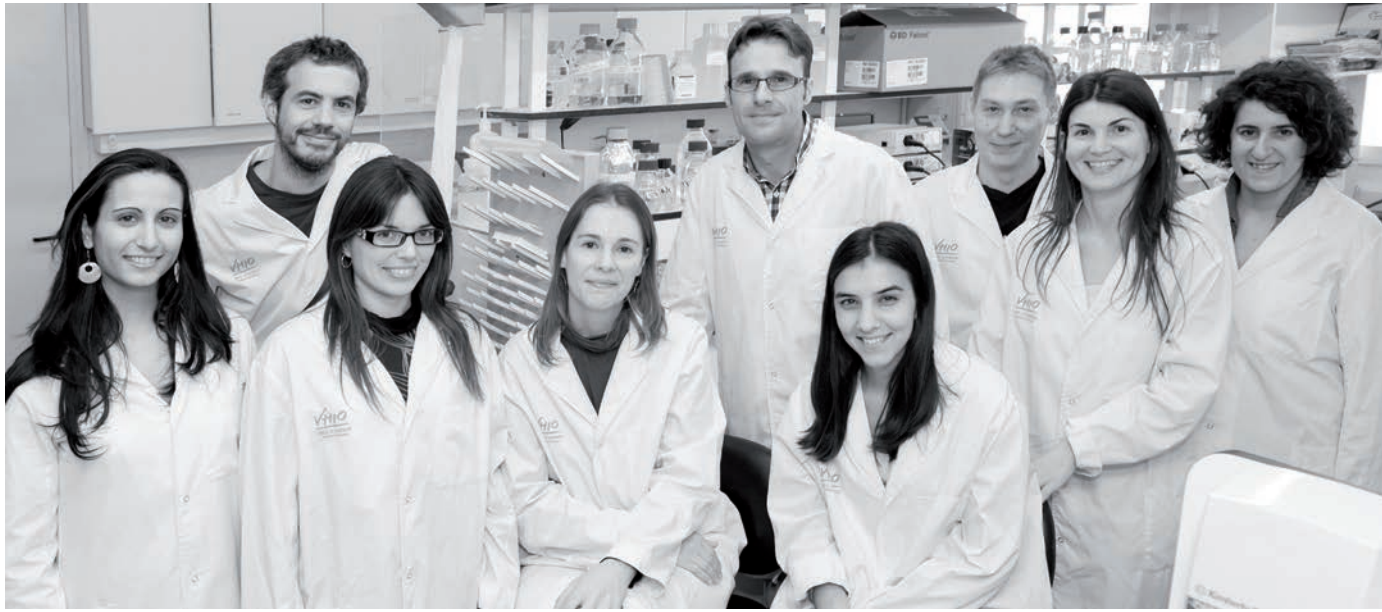

Strategic Goals

1. Functional characterization of HER2 fragments and their impact on breast cancer progression and treatment.
2. Characterization of the proteolytic remodeling of the cell surface during breast cancer progression.
3. Analysis of the role of HER2-induced senescence on breast cancer metastasis.

Highlights in 2012

- We have identified and characterized a dominant-negative N-terminal Fragment of HER2 frequently expressed in HER2-positive breast cancers.
- We have collaborated in the characterization of the degradome of the metalloprotease MT1-MMP.
- We have shown the pro-metastatic effect of the secretome of HER2-induced senescent breast cancer cells.

SUMMARY

Continuing our research on a subtype of breast cancers known as HER2-positive, in 2012 we have identified a novel fragment of HER2 frequently expressed in this type of cancer. This fragment, that we have named HER2-NTF, encompasses the extracellular and transmembrane domains of HER2 but lacks most of its cytoplasmic domain and it is, therefore, inactive. HER2-NTFs associates with other HER receptors to form inactive complexes. However, the expression of this fragment does not affect treatment with Herceptin, a therapeutic monoclonal antibody currently used to treat HER2-positive breast cancers. We have continued our analysis on the role of HER2-induced premature senescence on breast cancer progression. As a result, we have shown the prometastatic effect of the secretome of HER2-induced senescent cells; these results will be published at the beginning of next year.

In addition, we have collaborated with the group of A. Arroyo at the *Centro Nacional de Investigaciones Cardiovasculares* (CNIC, Madrid) to identify the array of substrates (i.e. the degradome) of the metalloprotease MT1-MMP. This metalloprotease is involved in the degradation of the extracellular matrix and promotes cell invasion and metastasis. The comprehensive identification of the secretome of MT1-MMP has unveiled novel components likely to be involved in the metastatic process and, in the future, will facilitate the development of novel anti-cancer therapies.

This year the Spanish Association Against Cancer (AECC) approved a project, coordinated by our group and to be carried out in collaboration with the group of A. Pandiella at the *Centro de Investigación del Cáncer* (CIC, Salmanca). Further, the AVON Cosmetics Foundation also confirmed its support for another project. Both projects are aimed at identifying mechanisms of resistance to current anti-HER2 therapies and development of novel therapies to counteract such resistance.

Finally, our group was selected to coordinate the Breast Cancer Program within the *Red Territorial de Investigación Cooperativa en Cáncer*, supported by the *Insituto de Salud Carlos III* (ISCIII). The program includes thirteen groups, six clinics and seven basic research entities, that will collaborate in several translational research projects in breast cancer.

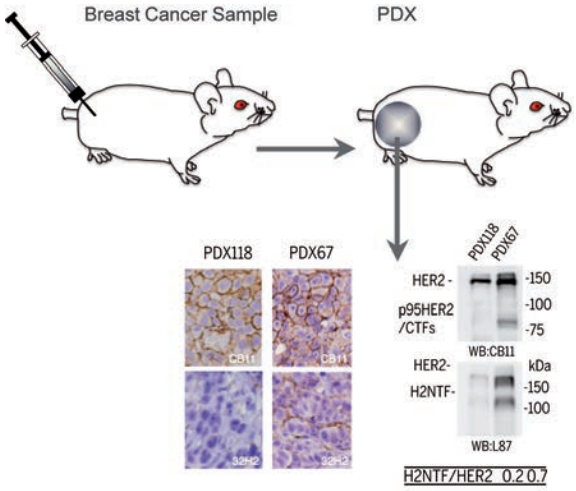

Figure: Surgical samples from breast cancers operated at Vall d'Hebron are routinely implanted into nude mice to obtain a PDX, i.e. a model of the breast cancer. These models have been instrumental to characterize the HER2-NTFs. Left, immunohistochemical analysis of samples from breast cancer PDXs with the indicated antibodies. Right, samples from the same PDXs were analyzed as by western blot with the indicated antibodies.

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Preclinical Research

MOUSE MODELS OF CANCER THERAPIES GROUP

Strategic Goals

1. Validation of Myc inhibition as a therapeutic strategy in various mouse models of cancer.
2. Development of pre-clinical models of pancreatic, brain, and lung cancer therapy.
3. Defining the role of Myc inflammatory effectors in tumorigenesis and tumor maintenance.

Highlights in 2012

- Endogenous Myc is shown to be responsible for the maintenance of tumor microenvironment and for macrophage polarization.
- Toni Jauset González, a post-graduate student in the lab, was awarded a PFIS Fellowship from the *Instituto Salud Carlos III* (ISCIII), (*Ayudas Predoctorales de Formación en Investigación en Salud* (PFIS)).
  Title: *Identificación de los subtipos de cáncer de pulmón potencialmente susceptibles a tratamientos con inhibidores de myc.*
- A new postdoc, Marie-Eve Beaulieu, an expert in structural biology and peptide design, was contracted from Quebec, Canada.

SUMMARY

Current targeted cancer therapies are directed against few targets within the cancer cell, and are frequently restricted only to particular tumor types. Unfortunately, many of these targets reside in the most degenerate, redundant, plastic and adaptive parts of the aberrant signaling networks that drive cancer. Hence, tumors often adapt to such inhibitors, either directly or evolutionarily, evolving into more aggressive cancers as a consequence of the imposed selective pressure. We have adopted a very different, heterodox approach in which we seek to establish the therapeutic utility of targeting essential common signaling conduits that are shared by some - if not all - cancers.

The main focus of our group is the pleiotropic and ubiquitous Myc oncoprotein, whose deregulation is implicated in almost all human cancer types. Despite this, the technical challenges of targeting nuclear transcriptional 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 on different types of cancer, with very mild and reversible side effects in normal tissues.

We are now interested in Myc's role in the coordination of the response to different oncogenic signals and how this compares between different tissues, especially in relation to the cross-talk between tumor and microenvironment, which could present some non-redundant and tractable targets for cancer therapy. We will also determine the therapeutic impact of Myc inhibition in metastasis, where Myc's role is still debated.

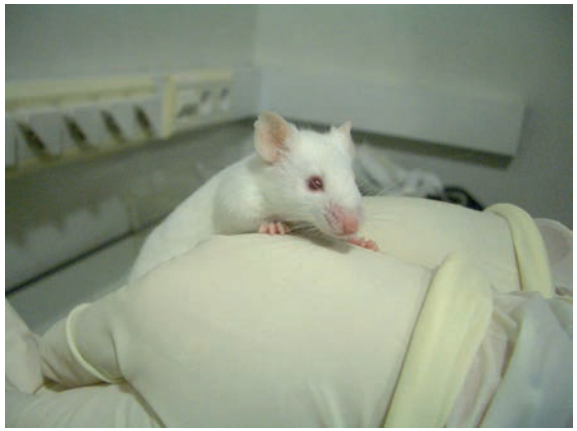

Figure: Mouse models have significantly contributed to our understanding of normal tissue and cancer biology, facilitating a timely control of initiation, progression and evolution of physiological and pathological events.

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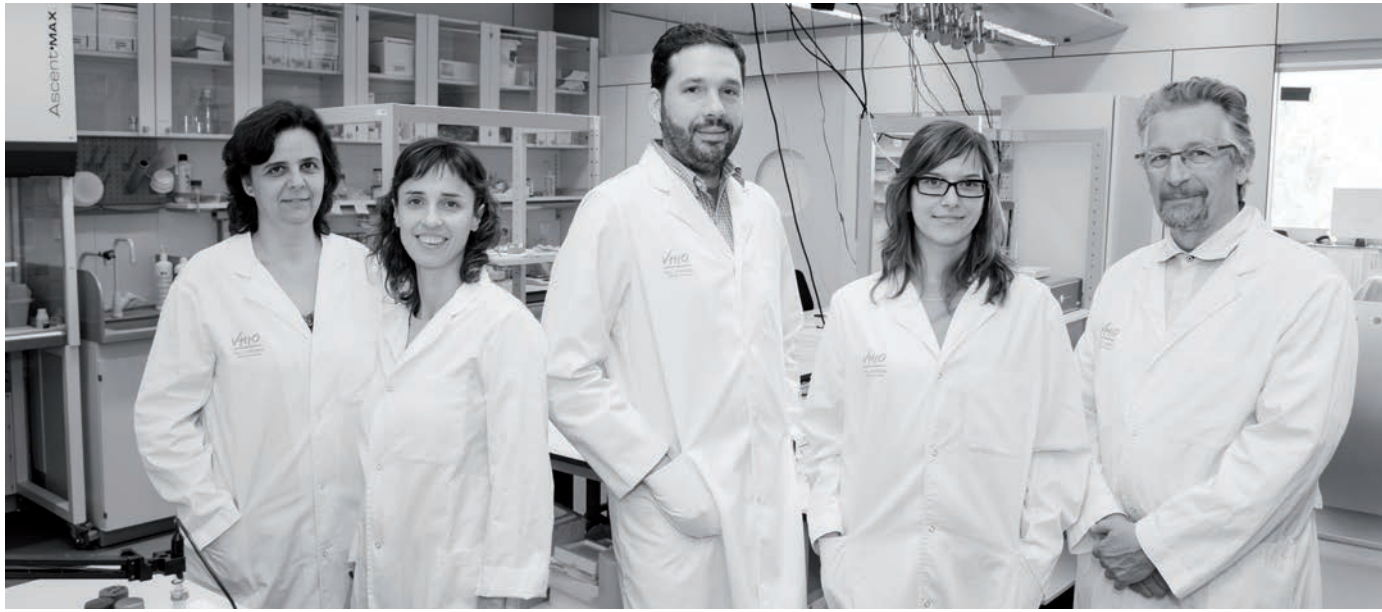

Strategic Goals

1. Characterize the mechanisms used by tumor cells to communicate with their microenvironment during tumorigenesis, and use this data for biomarker discovery.
2. Discover secreted signaling pathway-based tumor biomarkers and therapeutic targets using quantitative proteomics.
3. Establish secreted response/resistance biomarkers to targeted drug therapy measurable through non-invasive methods.

Highlights in 2012

- We have characterized the secretomes of colorectal cancer cells when the EGFR pathway is stimulated and blocked by anti-EGFR targeted drugs showing promising results for developing new response biomarkers for these drugs (see figure).
- Improved mass spectrometry-based proteomics quantification by implementing a batch effect correction algorithm. This tool will improve proteomics-based tumor biomarker discovery.
- Unmasked the important influence of non-classical secretion in tumor cells. This discovery reveals an untapped source of new potential tumor secreted biomarkers.

SUMMARY

Tumor cell communication with its microenvironment plays a key role in tumor initiation and progression. Tumor cells hijack the tumor microenvironment ecosystem via paracrine signaling to promote a pro-oncogenic microenvironment that is critical for the establishment of primary and metastatic tumors.

Our main goal is to characterize the mechanisms used by tumor cells to communicate amongst themselves as well as with their microenvironment during tumorigenesis, and exploit this for biomarker discovery. Our working hypothesis is that cellular signaling pathways are altered during the tumorigenesis process and that these alterations are translated into differential protein secretion, which potentially can also be exploited to discover secreted markers. Furthermore, some of the differentially regulated proteins could be direct extracellular messengers of intracellular signaling pathways contributing to key steps in cancer initiation and progression, therefore becoming potential therapeutic targets.

Proteomic technologies facilitate a genome-scale search for tumor-specific biomarkers and drug targets and could therefore revolutionize early detection and molecular characterization of cancer through non-invasive methods. The methodological focus of our group is based 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 have a high probability of being 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 cancer detection and monitoring.

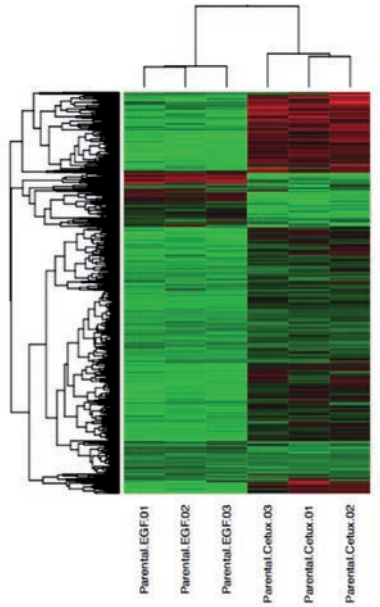

Figure: We have undertaken a project to study how paracine and autocrine signalling is involved in the activation and the inhibition of the EGFR pathway in colorectal cancer. Our long term goal is to exploit these results for monitoring anti-EGFR therapeutic treatments using non-invasive techniques. The figure shows the effect of the activation with EGF and the inhibition with cetuximab of the EGFR pathway in SW48 colon cells at the secretion level by secretome profiling. The secretome of SW48 cells changes dramatically when we compare the activation and the blockage of the EGFR pathway.

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VHIO MULTIDISCIPLINARY RESEARCH PROGRAMS

TRANSLATIONAL RESEARCH


SmartSampler

Joan Seoane DIRECTOR, TRANSLATIONAL RESEARCH PROGRAM

VHIO's Translational Research Program is dedicated to improving and accelerating the integration of basic and clinical research. We aim to translate advances in molecular research to patient care as rapidly as possible tackling the disease from all angles, and generating synergies between molecular and clinical research in oncology.

One of the main challenges in combating cancer is tumor diversity. Cancer is an extremely heterogenous disease since tumors from different patients are molecularly diverse. Moreover, tumors are formed by cells with diverse states of proliferation, differentiation, motility, and, importantly, differential sensitivity to treatment. This implies that each patient has a unique tumor with a particular combination of genomic aberrations. Our patients should therefore be treated with the optimal compound or combination of compounds according to the specificities of their disease. Since the selection of the most appropriate treatment depends on the specific molecular make up of the tumor, the challenge is to identify which treatment should be linked to which patient and develop precision medicine.

In order to improve cancer treatment through the combination of compounds targeting all cell types within a tumor, it is also critical to 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 Stem Cells (CSCs), these cells are characterized by their self-renewing capacity, their multi-lineage differentiation properties and their high oncogenic potential -- reproducing the heterogeneity of original human tumors in mouse models. CSCs are considered responsible for the initiation, recurrence and chemo- and radio-resistance of tumors indicating that more effective therapies will result from approaches aimed at targeting the stem-cell-like component of tumors. Few pharmacological compounds however have yet been shown to target cancer stem cells.

To explore the two levels of cancer heterogeneity, we must research cancer as closely as possible to that of a real tumor from an actual patient. We therefore generate patient-derived models both *in vitro* and *in vivo*. Tumor specimens are obtained shortly upon surgical resection and we then study the tumor cells including cancer stem cells. We then 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 brain and colon cancer respectively, work with which has led to both groups describing key findings in *Nature Medicine* this year.

Tumor diversity and heterogeneity are due to variations in the genome or the epigenome of cancer. Hence, the study of cancer genomics that includes epigenomics is required to understand tumor heterogeneity. VHIO's Cancer Genomics Group led by Ana Vivancos is devoted to this line of essential research. Serving as a VHIO Core Technology, her lab is equipped with a genotyping platform (MassARRAY, Sequenom) and two NextGen sequencers (MiSeq and HiSeq2000, Illumina), providing cutting-edge applications in cancer genomics through the use of new technologies and protocol development (see 'Core Technologies', pages 59 - 67).

Effective cancer treatment can only be achieved through team work, studying cancer as closely as possible to the real patient and dealing with cancer heterogeneity. VHIO's Translational Research Program is devoted to advancing cancer treatment and catalyzing the transfer of new insight generated by scientific research into the true benefit for patients.

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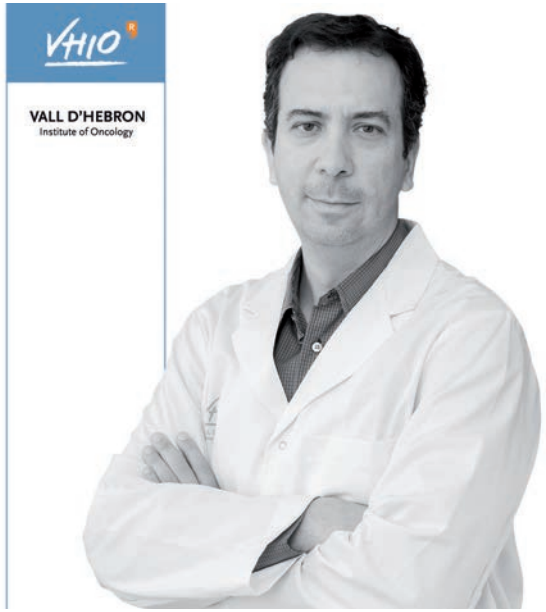
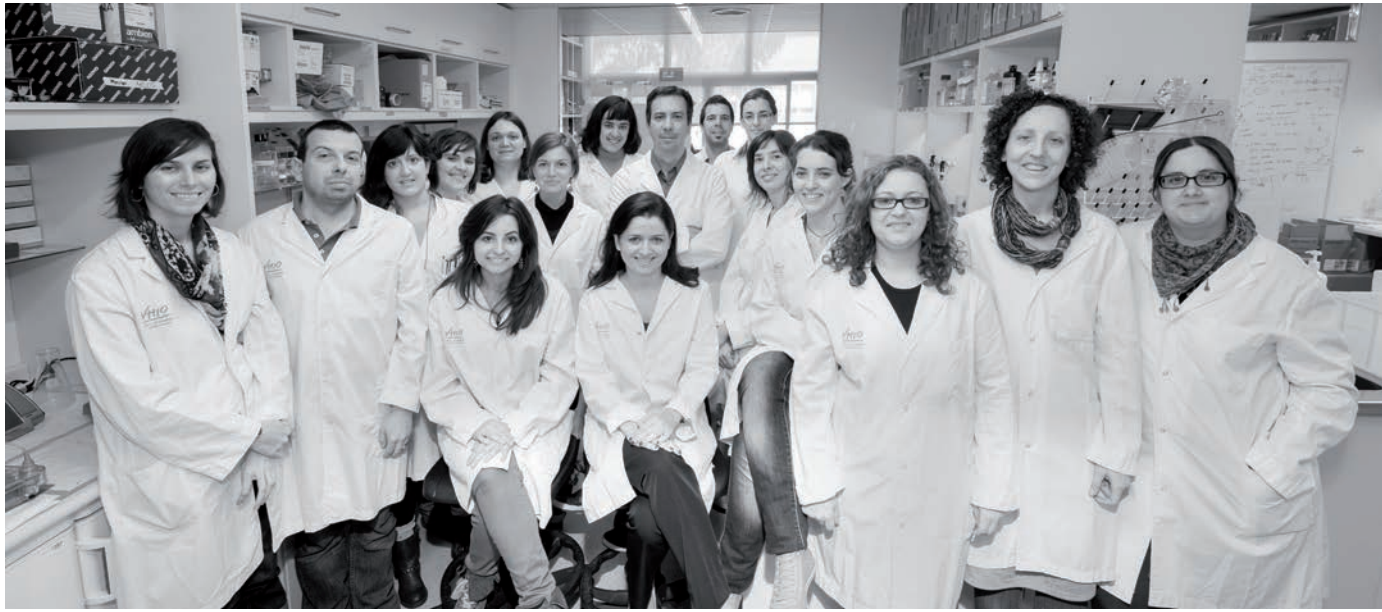
Translational Research
GENE EXPRESSION & CANCER GROUP





Strategic Goals

1. Identify novel biomarkers to develop personalized medicine based on the characteristics of each tumor.
2. Understand the molecular mechanisms involved in brain cancer.
3. Understand the molecular mechanisms involved in cancer stem cells.
4. Develop specific treatments to each of the different cellular entities present within a tumor.

Highlights in 2012

- We have identified USP15 - a crucial gene in tumor progression. USP15 is a de-ubiquitinating enzyme (DUB) that regulates the stability of the TGF-beta receptor to ensure the physiological levels of the TGF-beta activity. We found that USP15 is aberrantly expressed in a proportion of glioblastoma, breast cancer and ovarian cancer promoting oncogenesis. Being an enzyme, pharmacological inhibitors of USP15 are available and act as anti-tumoral agents in tumors with an aberrant regulation of USP15.
- In 2012 Joan Seoane served as the Local Chair of the 22nd Biennial Congress of the European Association for Cancer Research, EACR22, Barcelona, *From Basic Research to Personalised Cancer Treatment*, attracting a record number of 2000 participants.

SUMMARY

Our group's research focuses on the study of glioblastoma, the most common and aggressive of all brain tumors. Treatment for these malignancies remains elusive and progress in this area of research is critical. Our studies are mostly based on the study of cells obtained from patient-derived tumors. We obtain tumor samples 30 minutes after surgery, set up primary cultures and isolate cell populations from the tumor such as the cancer stem-cell-like pool. The study of patient-derived cells provides us with more reliable information about the original tumor than the study of established cell lines. Moreover, we inoculate the patient-derived glioma stem cells into the brain of immunocompromised mice and are able to 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 great interest in the study of the molecular mechanisms involved in cancer as well as the evaluation of the efficiency of pharmacological compounds.

We are also studying a subpopulation of undifferentiated cells with stem cell-like characteristics called 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 achieving a better understanding of the molecular mechanisms involved in this type of cells, is paramount. Our group aims to identify novel markers for CICs, understand the signaling pathways and molecular mechanisms involved in CICs, and design novel therapeutic approaches to target CICs (see figure).

Cancer-initiating cell /Cancer stem cell

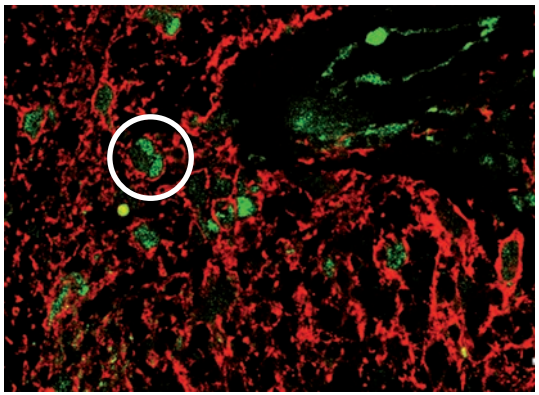


Figure: Identification of CD44high/Id1+ CICs in glioblastoma. Immunofluorescence of CD44 (red) and Id1 (green) in a section of a patient's glioblastoma.

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Graduate Students
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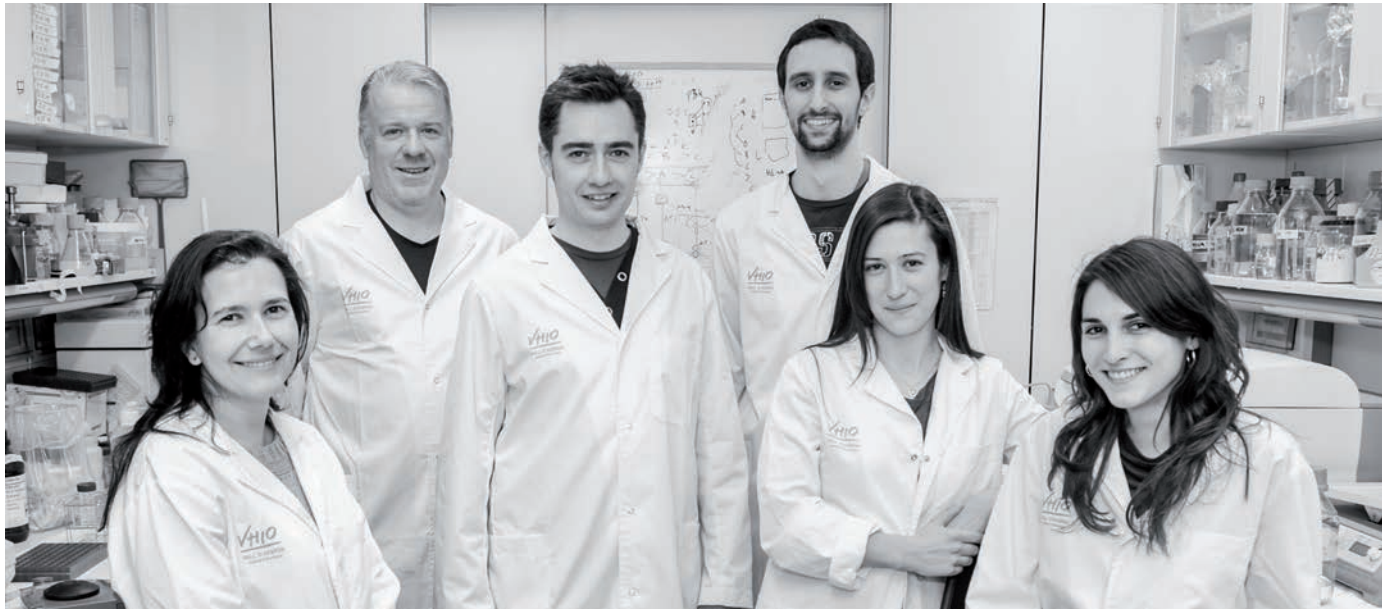
Technician
Irene Chicote

Translational Research
STEM CELLS & CANCER GROUP



Strategic Goals

1. Describe the key molecular mechanisms that confer CoCSC their capacity to self-renew and resist conventional or target directed therapies.
2. Unmask the molecular drivers of CSC quiescence, clinical relevance in cancer progression, and evaluate their potential inhibition to eradicate CoCSC.
3. Identify the central molecules responsible for the development of metastasis in colon cancer.
4. Study the efficacy and mechanism of action of new Wnt/beta-catenin inhibitory drugs for the treatment of CRC patients.

Highlights in 2012

- We discovered an unexpected cooperation between Wnt/beta-catenin pathway and PI3K/Akt/FOXO signaling in promoting colon cancer metastasis. Interaction between their mutual nuclear effectors drives cancer cells towards motility and invasion. This phenomenon appears to occur in colon cancer patients as well, leading us to propose new biomarkers to predict tumor metastasis and clinical response to PI3K and AKT inhibitors.
- We have revealed the molecular mechanisms that govern the delicate link between stemness and quiescence in chemoresistant 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.
- We have accumulated evidence on the efficacy and mechanisms of action of a new generation of Wnt/beta-catenin inhibitory drugs on CRC and are indentifying potential biomarkers to predict response to these inhibitors.

SUMMARY

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

We are dedicated to studying the consequences of intra-tumoral cell heterogeneity for tumor evolution and patient survival. Among the different cell populations that build a heterogeneous tumor, Cancer Stem Cells (CSC) are at the apex of a differentiation process within the cancerous tissue, somewhat reminiscent of the hierarchy present in the normal tissue from which they originate. CSC can 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 failing to eliminate cancer stem cells may allow re-growth of the tumor.

Colorectal cancer is a disease of high social impact and thus, our prime focus. 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 of these driving forces that direct cancer stem cell fate and lead the progression of many types of cancer.

We have succeeded in describing a new mechanism of resistance to PI3K and AKT inhibitory drugs conferred by beta-catenin in colorectal cancer. This is of great clinical relevance since many patients in clinical trials are not responding to these drugs and no molecular explanation behind resistance had previously been described. These findings will facilitate the selection of sensitive patients based on their expression of particular biomarkers that predict drug-response. In addition, we have described a new molecular mechanism that drives metastasis in colorectal cancer, a process responsible for the majority of patient deaths.

We are currently leading research focusing on a new generation of Wnt/beta-catenin inhibitory drugs. In collaboration with major pharmaceutical companies, we have already produced experimental evidence on the efficacy and mechanisms of action of such drugs in pre-clinical models of colorectal cancer with patient-derived xenografts. This is a historical breakthrough since colorectal cancer was described as a paradigmatic tumor addicted to the oncogenic Wnt/beta-catenin pathway many decades ago. We are 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. 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: In this issue of *Nature Medicine*, Tenbaum *et al.* uncover a malignant crosstalk between activated β-catenin and FOXO signaling that promotes metastasis of colon tumors, a potential negative outcome of targeted therapy. The cover shows a confocal microscopy image of a double immunofluorescence staining for β-catenin (red), FOXO3a (green) and Hoechst (blue) in a paraffin section of a human colon adenoma. Image courtesy of Irene Chicote and Héctor G. Palmer, Stem Cells and Cancer Laboratory, Vall d'Hebron Institute of Oncology, Barcelona, Spain.

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VHIO MULTIDISCIPLINARY RESEARCH PROGRAMS

CLINICAL RESEARCH

For our Molecular Oncology and Translational Genomics clinical research groups, please see “Core Technologies”:

Josep Tabernero DIRECTOR, CLINICAL RESEARCH PROGRAM

Incorporating multidisciplinary cancer teams, VHIO's Clinical Research Program is dedicated to carrying out preclinical, Phase I & II research studies aimed at developing novel agents directed to specific signaling pathways in different cancer types, as well as new or redefined prognostic/diagnostic tools to better detect disease and more precisely predict response to treatment.

As a direct reflection of VHIO's purely translational and multidisciplinary research model, our Clinical Research groups work hand-in-hand with researchers from our Preclinical, Translational, Core Technology Programs. In 2012, VHIO's stunning suite of 'omic' technologies welcomed two important additions: the MiSeq sequencing system and nCounter Nanostring Platform. These will both undoubtedly enable us to increasingly use genomic data to better guide clinical trial design and biomarker development, and identify optimal treatment regimens for our patients.

We are also committed to developing molecular therapies targeting specific oncoproteins. In breast cancer, for example, we are identifying genes that mediate leptomeningeal metastasis. In so doing, we will be able to develop more precise, personalized therapies for those patients displaying genetic lesions or pathway disregulation.

Another of our ongoing research lines concentrates on gene expression profiles that characterize KRAS-, BRAF- or PIK3CA-activated- colorectal tumors. We are exploring whether these profiles might be useful in predicting the response to the epidermal growth factor receptor (EGFR) pathway inhibitors rather than mutation status alone.

We are also pioneering important studies involving both preclinical and early-drug development, leading to clinical trials designed to identify more effective cancer therapies tailored to individual patients.

Although target discovery has resulted in numerous novel drugs in clinical development, signal transduction inhibition does not always guarantee tumor response (target presence and dependence, redundancy, cross-talk, etc.). There is consequently an urgent call for exhaustive molecular profiling in order to select the best drug combinations while searching for mechanistic interactions of the drugs under study.

In order to sequentially evaluate tumor cells (tumor tissue, CTCs, cfDNA, etc.) we are establishing the role of plasma cfDNA as a predictor of response for anti-EGFR drugs and demonstrating that the measurement of plasma cfDNA quantitative and qualitative alterations may have a prognostic value in metastatic patients (e.g. colorectal cancer patients). The results of these (genotype) determinations have been correlated with those of tumor biopsies to determine whether the data obtained may substitute the information obtained from tumor biopsies.

At the preclinical level, we are developing xenograft models with explant tumors from patients (so-called patient-derived xenografts or 'xenopatients') in mice in order to mimic the patient's disease and study tumor development in the controlled, optimized setting of an animal model. In 2012, our efforts have focused on creating a xenograft murine model to validate rationally designed combination therapies after progression to targeted therapies for BRCA-mutated breast cancer patients.

Another leading project this year surrounds the in depth study of a panel of genes associated with hereditary breast/ovarian cancer by selective capture and massive sequencing methodologies in a series of Spanish families, in order to reveal the susceptibility alleles of each gene in our population. The outcomes of this study may have important clinical, therapeutic and preventive implications for future, providing a molecular diagnosis and potential therapeutic targets to a greater number of families and individuals, cases which currently remain without a clear genetic explanation.

Through the molecular characterization of tumors, we are making tremendous progress in patient stratification for the rational exploration of targeted cancer therapies. The study of cancer genomes will lead to the discovery of novel mutations in genes that can be considered as therapeutic targets and markers to determine sensitivity or resistance to pharmacological compounds.

In this new era of 'precision oncology', we are turning research into more effective, personalized treatments and improved practice. Thanks to the direct access to our amazing and devoted patients, coupled with the expertise of our talented, multidisciplinary teams dedicated to the translational nature of our research, we are collectively striving to improve the survival and quality of life for our patients.

We can and will do better.

Principal Investigator

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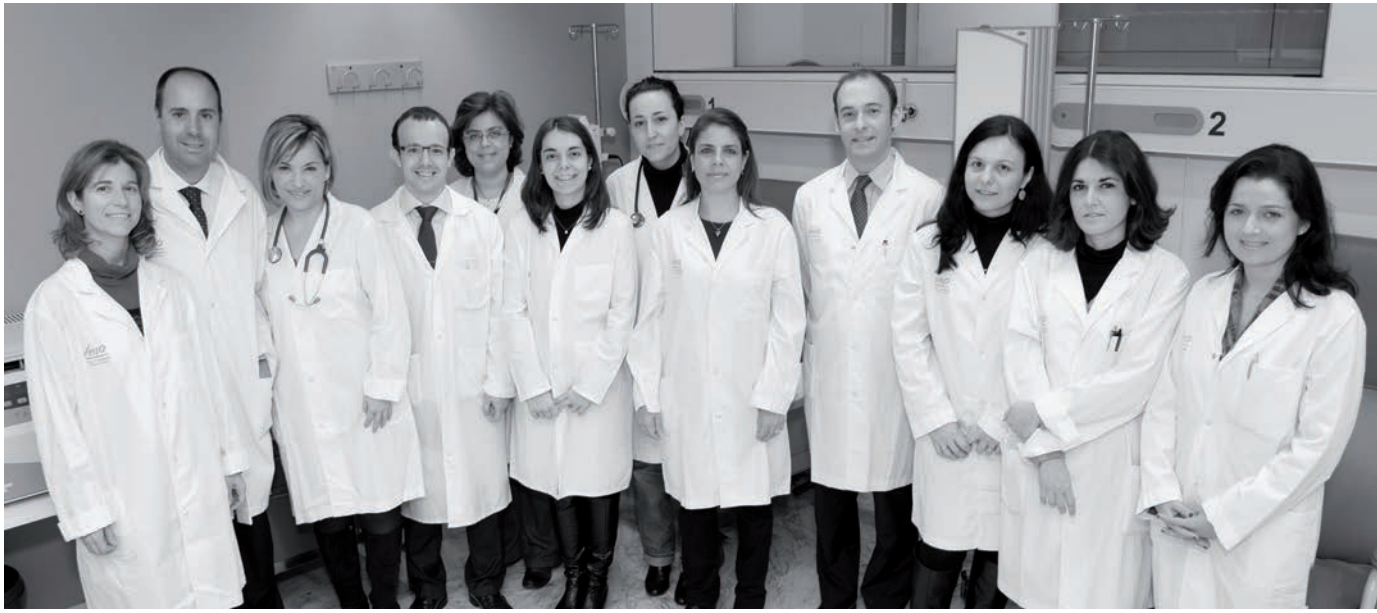
Clinical Research

BREAST CANCER & MELANOMA GROUP



Strategic Goals

1. Optimizing treatment options in patients with resistant HER2- positive tumors, with special focus on new targeted agents which overcome resistance to standard anti-HER2 agents, such as trastuzumab, or better therapeutic strategies to be explored in preclinical models prior to using them in patients.
2. Expand the above to other scenarios, such as chemo or endocrine resistant tumors.
3. To lead Phase I/II trials. Working closely with VHIO's Experimental Therapeutics Group, moving into more advance studies with the data obtained from early drug development.
4. The implementation of genomic tools to better design clinical trials.
5. To continue working with VHIO's preclinical groups to provide "smarter" treatments to our patients as rapidly as possible.

Highlights in 2012

- We have observed that combining eribulin with PI3K inhibitors might enhance the activity of both drugs, which has opened new opportunities for our patients. A Phase I trial will commence in 2013.
- In close collaboration with the VHIO's Preclinical Research Program, we have developed some patient-derived xenografts.
- We have actively participated in some of the most important clinical trials, which have led to the approval of drugs such as pertuzumab and everolimus. These important studies were published in 2012.
- Thanks to the tremendous collaboration with surgeons, pathologists and other oncology professionals and departments at Vall d'Hebron, our group has established itself as the most active in neoadjuvant studies in Spain.
- A circulating free DNA Program for genotyping and characterization has been developed.

SUMMARY

Our Breast Cancer Program is one of the most active in Spain and one of the most renowned across Europe. We are not only committed to participating in clinical and preclinical studies, but we also lead several -- reflected by our representation on Steering Committees for some, and appointed international leaders for others.

In 2012, we have initiated more than 20 new clinical trials and studies.

Our main areas of interest continue to focus on the development of new treatments 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. HER-positive breast tumors. 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 for our patients. In close collaboration with VHIO's Growth Factors and Experimental Therapeutics Group led by Joaquín Arribas and José Baselga respectively, different mechanisms of resistance to this therapy and other strategies are under study. We are especially interested in the design of new strategies to overlap these mechanisms.

2. To optimize chemotherapy-based strategies. The majority, if not all, of our patients with metastatic breast cancer will at some point require treatment with chemotherapy, and, unfortunately, they will become resistant to it. 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.

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. The possibility of using drugs that have been tested in very early studies and have shown sufficient activity

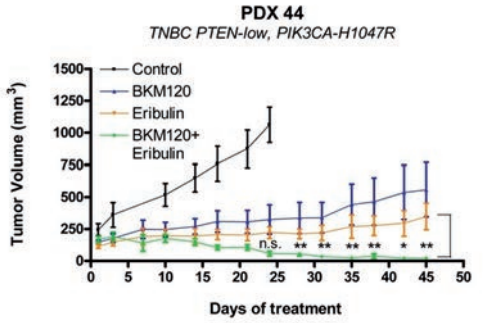


Figure: The combination of eribulin and BKM120, a PI3K inhibitor, in a patient-derived xenograft shows greater activity than either agent alone.

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Cristina Suarez
Claudia Valverde

Clinical Research
EARLY CLINICAL DRUG DEVELOPMENT GROUP

Strategic Goals

1. Clinical early development of the best-in-class targeted therapies, determining the optimal schedule and patient population to benefit most from these drugs by participating in novel clinical trials.
2. Analyze patients' tumors for molecular aberrations that may predict the efficacy of targeted agents, in order to select the most appropriate treatment for each individual with advanced cancer.
3. Link clinical research at the Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa" 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 2012

- As one of the leading institutes worldwide with expertise in areas of drug development such as 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. Also, we have rapidly expanded our expertise to other cell-signaling pathway inhibitors such as MET and FGFR.
- We have performed several clinical trials with novel-novel combinations - combining several PI3K inhibitors with MEK inhibitors, IGF1R inhibitor with PI3K or MEK inhibitors, Smo inhibitor with a PI3K inhibitor, and a NOTCH inhibitor with mTOR inhibitor.
- We have performed 19 clinical trials with patients selected on molecular alterations (mutations in AKT, PIK3CA, PTEN, ALK, BRAF, NRAS, KRAS, FGFR1 and 2, MET; amplifications in HER2, AKT 1,2, and 3, FGFR1, MET, and alteration in protein expression of PTEN, or overexpression of PDL1, GCC or of prolactin receptor).
- We have co-developed 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 targeted therapies aimed at cell signaling and cancer stem cells. 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 by VHIO's research groups, 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 the trials (biomarker development, profound understanding of the mechanism of action, research into mechanisms of resistance) for selected projects. In addition, 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 treatments 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 and industry partners from five continents to address the challenge of increasing the efficacy of cancer diagnostics and therapeutics.

Our group is now involved in the design and implementation of the first WIN clinical trial, launched in 2012. WINTHER, a unique academic and international clinical trial, represents a major step forward in the evaluation of precision treatments. VHIO will join the other trial partners to collectively develop a comprehensive analysis of the genetic background of tumors in order to predict drug sensitivity adopting powerful bioinformatics tools, and optimize individualized therapeutic decisions with improved clinical outcome for patients.

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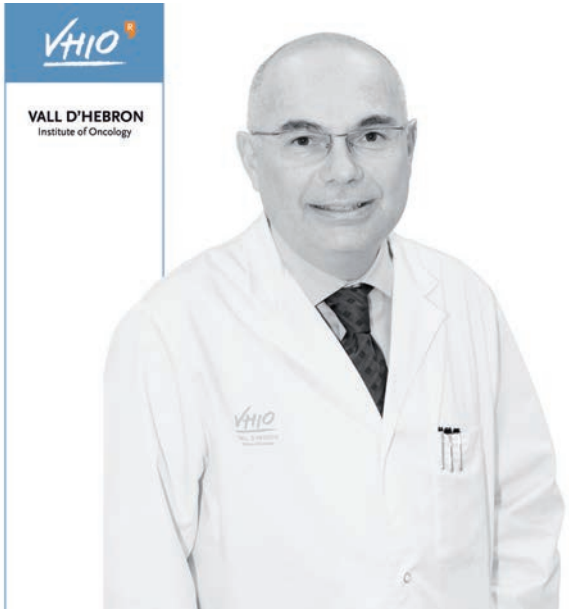
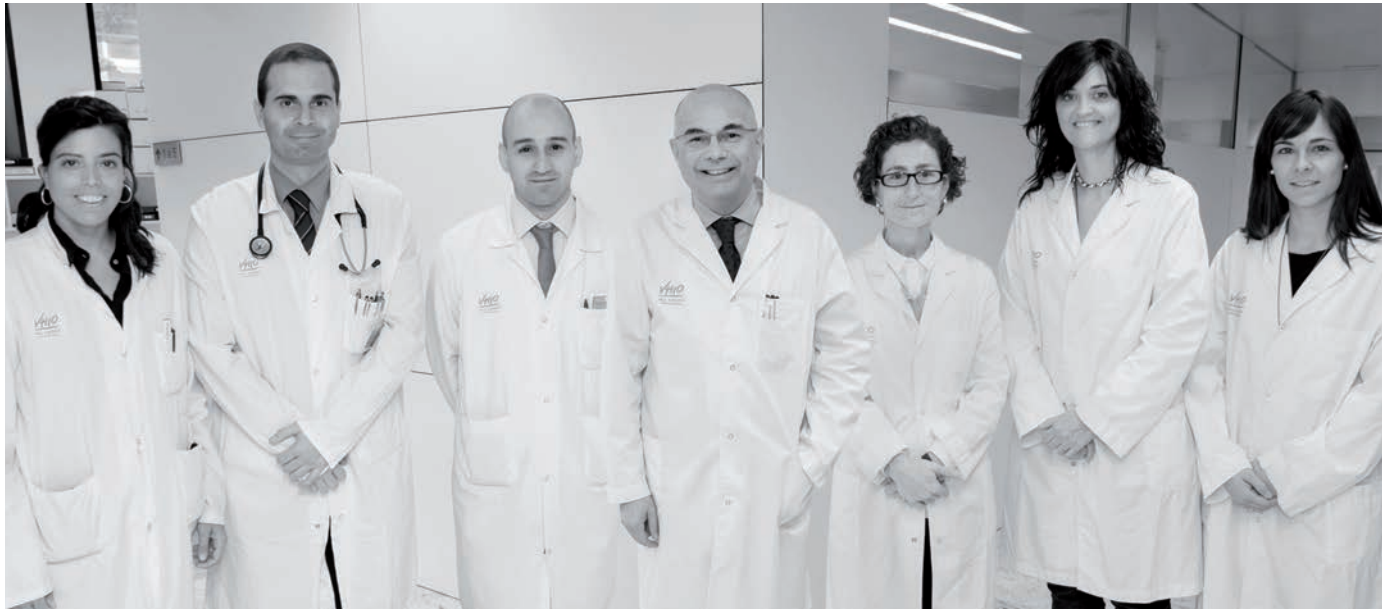
Clinical Research

GASTROINTESTINAL & ENDOCRINE TUMORS GROUP





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, Cancer Genomics, Translational Genomics and Stem Cells & Cancer Groups).

Highlights in 2012

- 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: furthered insight 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. Pioneered the consecution of clinical trials that have led to the approval of targeted drugs by the European Medicines Agency (EMA).

SUMMARY

In 2012, we have led or actively participated in numerous cooperative and singular research projects related to Gastrointestinal Malignancies. Besides our increasing participation in international collaborations and alliances including the WIN (Worldwide Innovative Networking in personalized cancer medicine) Consortium and other initiatives funded by the European Commission's 7th Framework Program (EurocanPlatform, COLTHERES, etc.), for which we have performed multiple preclinical and clinical tasks, we have also reinforced the multidisciplinary aspects of our research.

During the course of the year, we have worked on developing techniques aimed at detecting cancer mutations at extremely low levels of circulating tumor DNA. Through serial monitoring of circulating free DNA extracted from plasma samples from patients with metastatic disease, we are analyzing their genetic profile and comparing it with the primary tumor and/ or metastasis. We will then assess the correlation with therapeutic responses or the development of tumor drug resistance, and identify new molecular targets in order to seek more precise, personalized treatments.

Another of our research projects focuses on the use of validated biomarkers (and their respective reference isogenic cell lines), to develop next generation, non-invasive, diagnostics that can monitor the burden of disease, its molecular features as well as response to novel targeted therapies.

Among many other projects in 2012, our group has participated in:

- Various cutting-edge pre-clinical and clinical studies on predicted responsive patient subsets using genetically annotated tumor surgical specimens ('Xenopatients') in mice (strengthening our collaboration with the Stem Cells & Cancer Group, led by Héctor Palmer).

- The validation of re-profiled drugs or candidate drugs in partnership with pharmaceutical companies or other academic groups.

- The development of gene expression profiles that characterize KRAS-, NRAS-, BRAF- or PIK3CA-activated-tumours, exploring whether these profiles might be helpful in predicting the response to the epidermal growth factor receptor (EGFR) pathway inhibitors, rather than mutation status alone.

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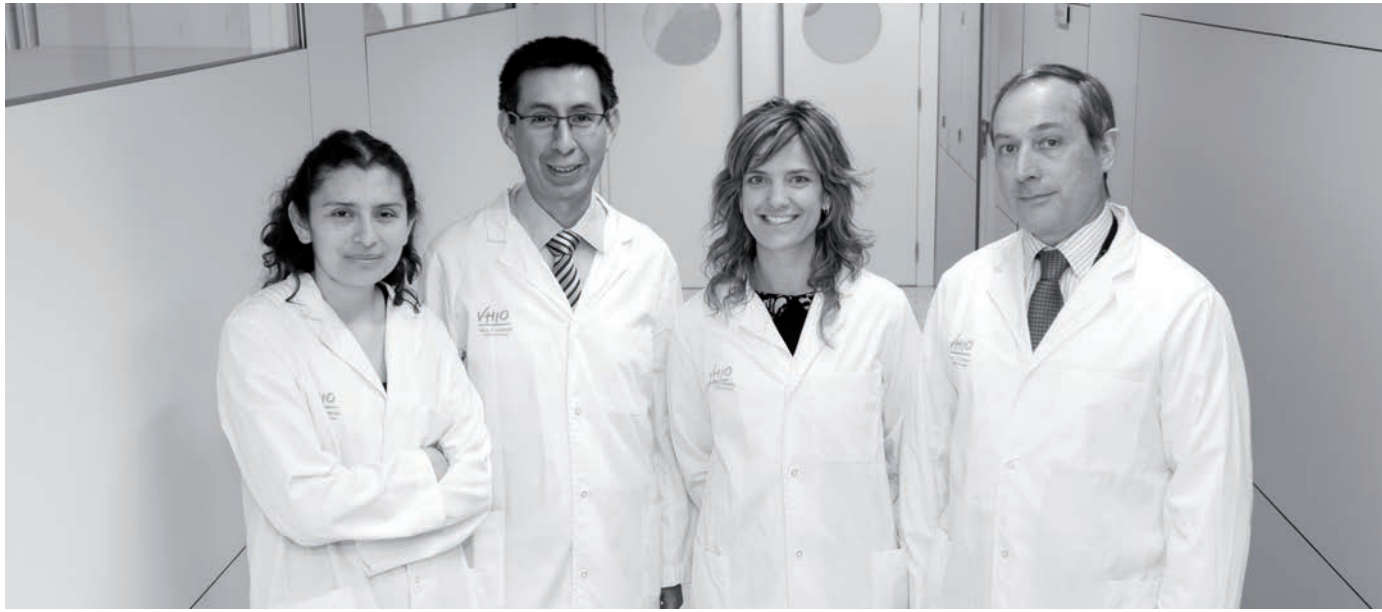
Núria Mulet
Isaac Núñez
Jordi Rodón
Cristina Suárez
Claudia Valverde

Clinical Research

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



Strategic Goals

1. Design and development of clinical trials for all the malignancies covered by our group. We strive to provide our patients the newest/best treatment for their respective malignancies.
2. Conduct clinical trials at different stages of the disease with emphasis on a histology-tailored design.
3. Develop new tools such as liquid biopsy for our patients for tailored treatment in CRPC.
4. Expand our translational research platform for glioblastoma in collaboration with VHIO's Gene Expression & Cancer Group led by Joan Seoane.
5. Creation of 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).

Highlights in 2012

- New drugs in GU malignancies: we have participated in the most important trials with different drugs that, throughout 2011/2012, have demonstrated that they will change the prognosis of patients with prostate cancer including: Vaccines, Enzalutamide, Cabazitaxel or Radium 223, and other new immunotherapy drugs (Ipilimumab) that may improve the prognosis of our patients. Furthermore, 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 participating in new clinical trials that combine classical chemotherapy with new targeted agents and second line treatments.
- Our research in Central Nervous System (CNS) tumours has been further consolidated with the development of new 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 the treatment of different neoplasms.

We are interested in 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. We have also created a translational research platform for urologic cancer and are running clinical trials in early, adjuvant, as well as metastatic disease.

Our group is also collaborating with other research centers of excellence including the Cleveland Clinic, Cleveland (USA), University of California San Francisco (USA), Gustave Roussy Hospital, Paris (France), and the Biomedical Research Institute of Bellvitge (IDIBELL), Barcelona (Spain). Results from these collaborations have been presented at the First Cleveland Vall d'Hebron Meeting in Renal Cell Carcinoma that took place on July 12th 2012. Further research updates and new discovery will also be presented at the forthcoming meeting on Castrate-Resistant Prostate Cancer that will take place at VHIO on May 24th, next year, 2013.

Another key area is the development of several multidisciplinary clinical trials 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 also initiated a collaborative study with different centers in Europe to develop a vaccine for patients with glioblastoma. 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) in order 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 close collaboration with the Biomedical Research Institute of Bellvitge (IDIBELL) and the Cancer Research Center of Salamanca (CIC).

We are also setting up a serum bank in different tumors such as CNS tumors and CRPC.

Lastly, but by no means least, we promote education and exchange by offering our group members the exciting 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.

To find out more about us, our research, publications and even our group's horizons for 2013, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2012

Principal Investigator
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Medical Oncologists
Ana Oaknin
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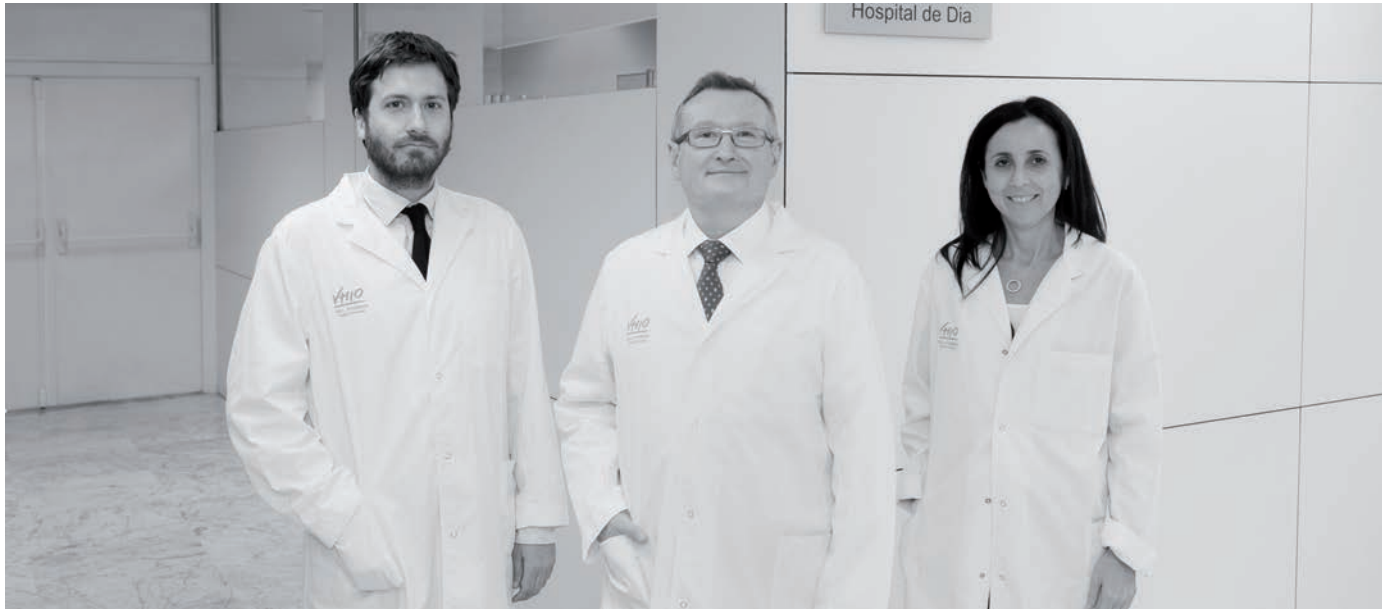
Clinical Research
HEAD AND NECK & GYNECOLOGICAL TUMORS GROUP



Strategic Goals

1. Our main focus is clinical research. We are members of the most relevant international cooperative groups in Gynecological and Head & Neck 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 2012

- As a result of our collaboration with the Gynecologic Oncology Group(GOG) - established in 2011, we have this year finished the pivotal trial in cervical cancer. We now have important data surrounding this trial which will be presented at the forthcoming annual meeting of the American Society of Clinical Oncology (ASCO), May 31 - 04 June, 2013.
- This year we have been nominated as International Coordinator of a Phase III trial in ovarian cancer. This trial will be conducted in almost all European Countries as well as in the US.

SUMMARY

Our group focuses on standard patient care as well as clinical research. Development and research into new anticancer drugs represent major areas of our activity. We have also actively participated in the development of new Spanish guidelines in ovarian, endometrial and cervical cancer.

As members of some of the most important societies in oncology 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), Gynecologic Oncology Group (GOG), and the National Cancer Institute (NCI), we are involved in developing new strategies and approaches as well as designing optimal trials for research.

With regards to our clinical activity at the Vall d'Hebron University Hospital, we play a key role as members of various multidisciplinary committees in collaboration with other professionals and specialties (surgeons, radiotherapists, radiologists and pathologists). Such connectivity and cross-talk leads to establishing new, improved treatment protocols and clinical guidelines within our Hospital.

Our collaboration with other specialties as well as other research centers of excellence has resulted in a steady, annual increase in the number of patients treated either in clinical trials or with standard treatment. Currently we are involved in more than fifteen trials as Principal Investigators or Coordinating National and International Investigators.

Our group has also collaborated with other departments from the Vall d'Hebron University Hospital as well as other Spanish and International groups in several projects including the Cancer Genome Atlas Project (TCGA) in Early High-Grade Serous Ovarian Cancer.

We have also actively participated in international conferences, given several presentations, Invited Lectures and published key findings (for more information please select the 'Publications, Projects & Awards' tab of our Scientific Report 2012 online at: http://memorias.vhio.net/2012/).

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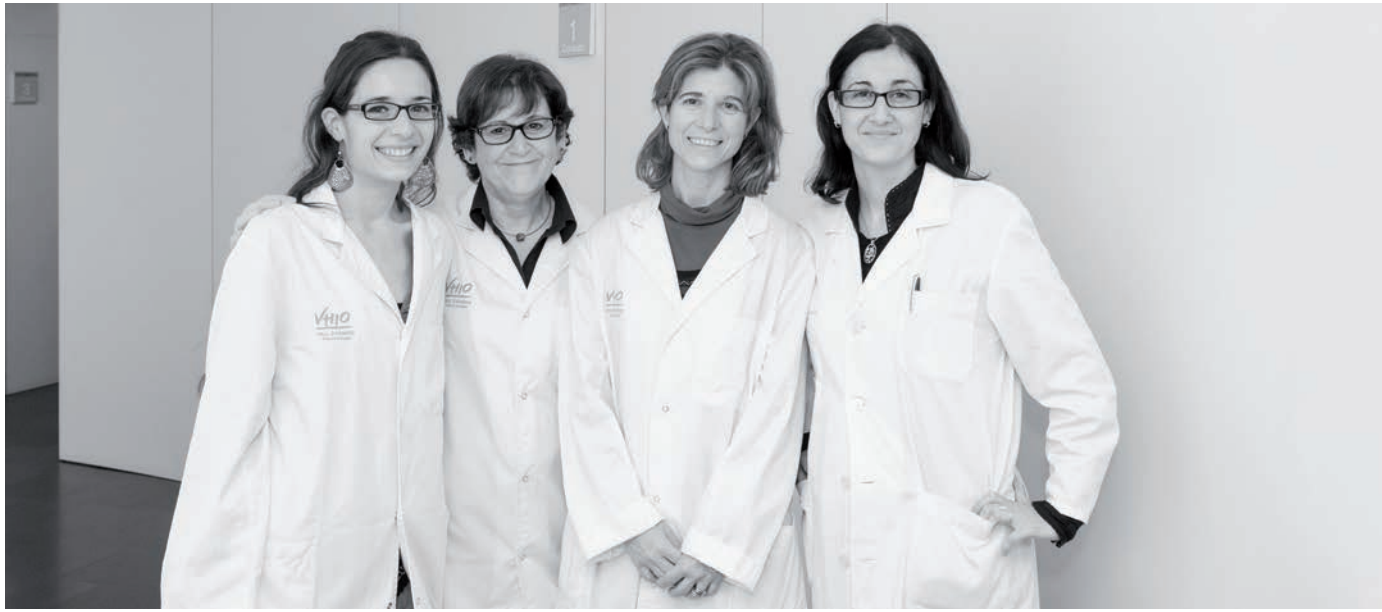
Principal Investigator
Judith Balmaña

Staff Scientists
Nina Bosch
Estela Carrasco

Clinical Nurse Specialist
Neus Gadea

Clinical Research

HIGH RISK & CANCER PREVENTION GROUP



Strategic Goals

1. Clinical development of specific therapeutic strategies for tumors associated with hereditary genetic alterations.
2. Identification of genetic mechanisms of resistance to targeted therapies in *BRCA*-associated breast cancer.
3. Early detection of prostate cancer in *BRCA* mutation carriers.
4. Development of a clinical and molecular database for adult survivors of Fanconi Anemia and evaluation of their cancer risk.
5. Identification of new genes involved in hereditary cancer through application of next generation sequencing.
6. Validation of prediction models in Lynch Syndrome.

Highlights in 2012

- Participation in international clinical trials with targeted therapies for *BRCA*-associated tumors.
- Collaboration in an international study for early detection of prostate cancer in *BRCA* mutation carriers (IMPACT).
- Participation in a national study to assess the role of breast density as a risk factor for breast cancer in *BRCA* mutation carriers.
- Participation in the international validation of PREMM1,2,6 model for Lynch Syndrome.

To find out more about us, our research, publications and even our group's horizons for 2013, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2012

SUMMARY

We develop new targeted therapies for patients with hereditary breast and ovarian cancer. In this context we are participating in several Phase II clinical trials, some of which are expected to lead to registration trials in 2013. As theses targeted therapies tend to develop early mechanisms of resistance, we have initiated a collaboration with VHIO's Experimental Therapeutics and Cancer Genomics Groups, led by José Baselga and Ana Vivancos respectively, to study the genetic mechanisms of resistance and test new combinatorial therapies in patient-derived xenografts implanted in atymic mice.

As the clinical impact of genetic testing may differ among countries and relate to the cultural basis of each study population, we aimed to analyze the clinical and psychosocial impact of BRCA genetic testing in our setting. We recently finalized a longitudinal follow-up study ("IMASS Project": PI05/1491 entitled *Impacto clínico del asesoramiento y estudio genético en síndromes de predisposición hereditaria al cancer,* PI J. Balmaña), and published the analysis surrounding psychological well being further to BRCA testing in our setting (see figure).

We continue to collaborate in the international study IMPACT (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. We have also participated in a national study funded by FIS: *Densidad mamográfica, susceptibilidad genética y cáncer de mama en mujeres de alto riesgo* (Proyecto DM-BRCA, PS09/01024) in order to determine the role of breast density as a risk factor for breast cancer in women with mutations in BRCA1/2 genes.

In the field of genetic epidemiology, we are collaborating with VHIO's Oncogenetics Group, headed by Orland Díez, in next generation sequencing studies to search for mutations in new genes conferring predisposition to hereditary breast cancer.

We finalized our collaboration in an international project funded by the NIH, *Validation and extension of the PREMM model for mismatch repair gene mutations* (NIH grant #R1CA13829-01A1, PI: S. Syngal) to validate the PREMM1,2,6 predictive model for identification of Lynch Syndrome in international population and clinical-based cohorts.

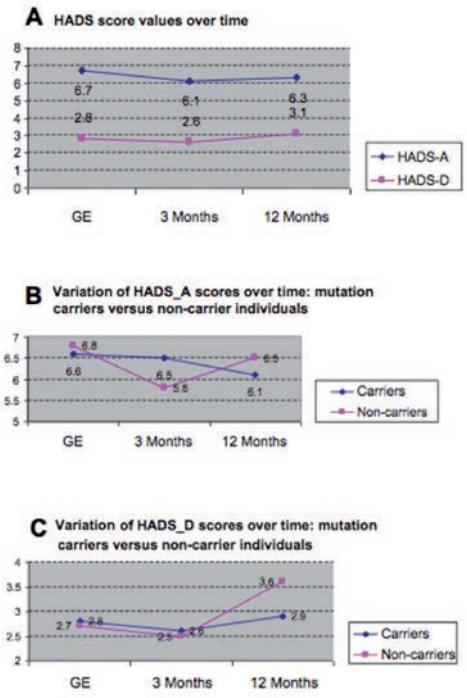


Figure: (A) Evolution of HADS-A and HADS-D over timer; (B and C) HADS-A and HADS-D scores over time based on genetic test result. Mean values are reflected.

Principal Investigator
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Post-Doctoral Fellow
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Anna Tenés

PhD Student
Gemma Montalban

Clinical Research
ONCOGENETICS GROUP

Strategic Goals

1. Application of massive sequencing to the diagnosis of hereditary cancer.
2. Characterization of large rearrangements and transcriptional effects of variants with unknown biological significance in breast cancer predisposition genes.
3. Identify variants of *PALB2*, *RAD51C*, *RAD51D*, and other genes of the Fanconi Anemia pathway.
4. Molecular analysis of new candidate breast/ovarian cancer genes.
5. Epidemiological analysis of *BRCA1* and *BRCA2* mutations in Spanish breast/ovarian cancer families.
6. Identify common low-penetrance alleles associated with breast cancer risk for *BRCA1* and *BRCA2* mutation carriers.
7. Study of irradiation-induced apoptosis and genetic variants associated to radio-sensitivity as predictors of late toxicity in breast cancer patients after radiotherapy.

Highlights in 2012

- We have developed methodologies of massive sequencing applied to the diagnosis of hereditary cancer.
- Identification of novel germ line sequence variants in *BRCA1*, *BRCA2*, *TP53*, *RAD51C* and *RAD51D* in cancer breast/ovarian cancer families. We have characterized large rearrangements and transcriptional effects in some of these genes.
- Collaboration with the Evidence Based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) International Consortium in the evaluation of methodologies for DNA/RNA analysis, and in the study of genetic variants of unknown clinical significance.
- Coordinated multicenter epidemiological research surrounding *BRCA1* and *BRCA2* mutations in more than 4.000 Spanish families with breast/ovarian cancer.
- We participated in the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) for the identification of new modifier alleles for *BRCA1/BRCA2* mutation carriers.
- The study of apoptosis and genetic variants in breast cancer patients treated with radiotherapy.

SUMMARY

Over the past few years our group has developed its research along to two main lines: 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. One main line of research is to search for other alleles which might predispose to these types of cancer. In particular, we are investigating *TP53*, *RAD51C*, *RAD51D*, *PALB2*, and some other genes whose products interact with *BRCA1/2* proteins.

To investigate mutation-negative families and individuals further, we are also developing projects based on the use of massive sequencing technologies to study panels of potentially predisposing genes. Moreover, we aim to study the whole exome to find new genes that could explain the presence of multiple cases of cancer in families and individual patients.

We also collaborate in wide case-control studies to identify low-penetrance alleles and genes that modify penetrance and expression of *BRCA1/2* mutations.

The *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 changes in untranslated regions in both genes constitute another area of intensive study. We carry out expression studies, in silico analyses, and collaborate with other laboratories in developing multifactorial studies to ascertain the effect of variants with unknown clinical significance.

Regarding genetic predisposition to radiotherapy-induced toxicity, we are investigating potential genetic and cellular markers for radiotherapy toxicity (allelic variants, cell apoptosis, and transcriptional profiles).

Figure: Electrophoresis of transcripts of the *BRCA1* gene in wild type and mutant lymphoblastoid cell lines.

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Principal Investigator
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Radiation Oncologists
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Meritxell Molla
Begoña Navaltropo
Mónica Ramos
Victoria Reyes
Ramona Verges

Clinical Research
RADIATION ONCOLOGY GROUP

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 2012

- We have implemented programs of image fusion for radiotherapy target delineation with the addition of PET.
- We have continued to increase the number of patients treated with IMRT. In 2012 we treated 245 patients with IMRT, representing a 21% annual increase.
- We have passed the quality control program and the "dummy run" in the Adaptive and innovative Radiation Treatment FOR improving Cancer treatment outcomE (ARTFORCE) project.
- We have conducted the theoretical studies to implement the total marrow irradiation technique in the context of bone marrow transplantation in multiple myeloma (see figure).

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 gynecology, pediatric and gastrointestinal tumors.
- Development of an estereotactic extracranial radiotherapy program in lung and liver metastases.
- Implementation of the total marrow irradiation program in bone marrow transplantation for patients with multiple myeloma.
- Achieving ISO 9001/2008 accreditation in the field of radiotherapy.
- The identification of factors associated with clinical response in advanced head and neck tumors treated with radiotherapy and cetuximab .

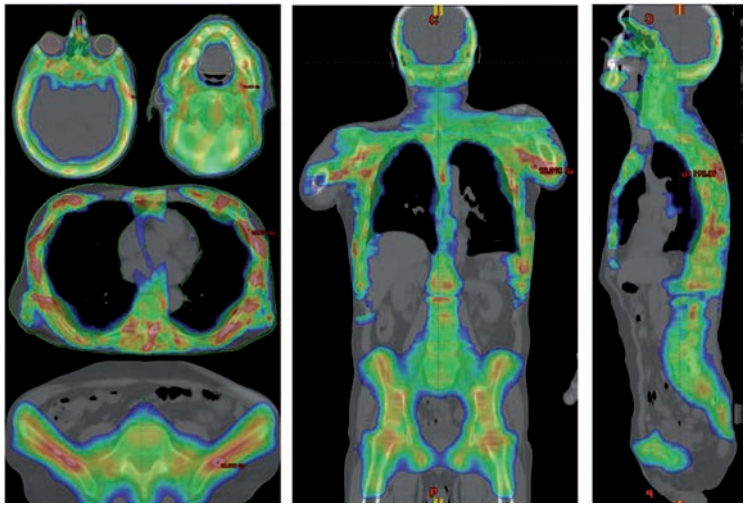

Figure: Dose distribution for total marrow irradiation and bone marrow transplant in patients with multiple myeloma.

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Principal Investigator
Enriqueta Felip

Medical Oncologists
Susana Cedrés
Alex Martínez
Pablo Martínez

Clinical Research
THORACIC TUMORS GROUP

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. Consolidation of the translational research program.
5. Contribution to early-drug development in lung cancer.
6. Collaboration with other research groups dealing with thoracic malignancies.

Highlights in 2012

- > 450 new lung cancer pts, approx 15 mesotheliomas, 5 thymomas.
- Close multidisciplinary collaboration; we have established a lung cancer tumors committee which convenes every two weeks.
- Implementation of pharmacogenomic approaches in advanced NSCLC pts (EGFR-mut, ALK, Sequenom in EGFR-wt/ALK-wt) in collaboration with VHIO's Cancer Genomics Group (Ana Vivancos) and the Vall d'Hebron University Hospital's Molecular Pathology Group (Javier Hernández and Irene Sansano).
- Top level inclusion in the phase I LDK378 study (ALK inhibitor): an oral presentation at the 2012 Annual Meeting of American Society of Clinical Oncology (ASCO), June 01 - 05, Chicago, USA, and at the European Society for Medical Oncology (ESMO) 2012 Congress, September 28 - 02 October, Vienna, Austria.
- Main investigators in the phase II study with AUY922 in NSCLC: an oral presentation also at the European Society for Medical Oncology (ESMO) 2012 Congress, September 28 - 02 October, Vienna, Austria.

SUMMARY

The main activity of the Thoracic Tumors Group is to deal with different aspects of lung cancer, one of the most frequent tumors diagnosed to-date. Our group concentrates on a number of areas: lung cancer prevention, early detection, more accurate techniques in diagnosis and staging, and a program for the rapid diagnosis of lung cancer.

In lung cancer patients with early-stage disease, we collaborate closely with thoracic surgeons and radiation therapists to better optimize the different treatment approaches in a truly multidisciplinary setting. Lung cancer patients suffer from sometimes severe symptoms associated with the disease; in order to ameliorate these symptoms we also work closely with a number of professionals from other disciplines. In patients with advanced-stage disease, personalized therapy is now the standard approach and our main objective is the early implementation of molecular determinants to better select treatment options.

We are actively involved in/contribute to our early drug development program and also deal with other less common thoracic malignancies such as small-cell lung cancer, mesotheliomas, thymomas, and neuroendocrine tumors.

To find out more about us, our research, publications and even our group's horizons for 2013, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2012

VHIO 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 function as scientific dependence groups, pursuing, implementing and developing independent research projects. In this context, Cancer Genomics is situated within the frame of our Translational Research Program directed by Joan Seoane, Proteomics forming part of our Preclinical Program, led by Joaquín Arribas, and Molecular Oncology and Translational Genomics under our Clinical Research Program directed by Josep Tabernero.

The PI Pages

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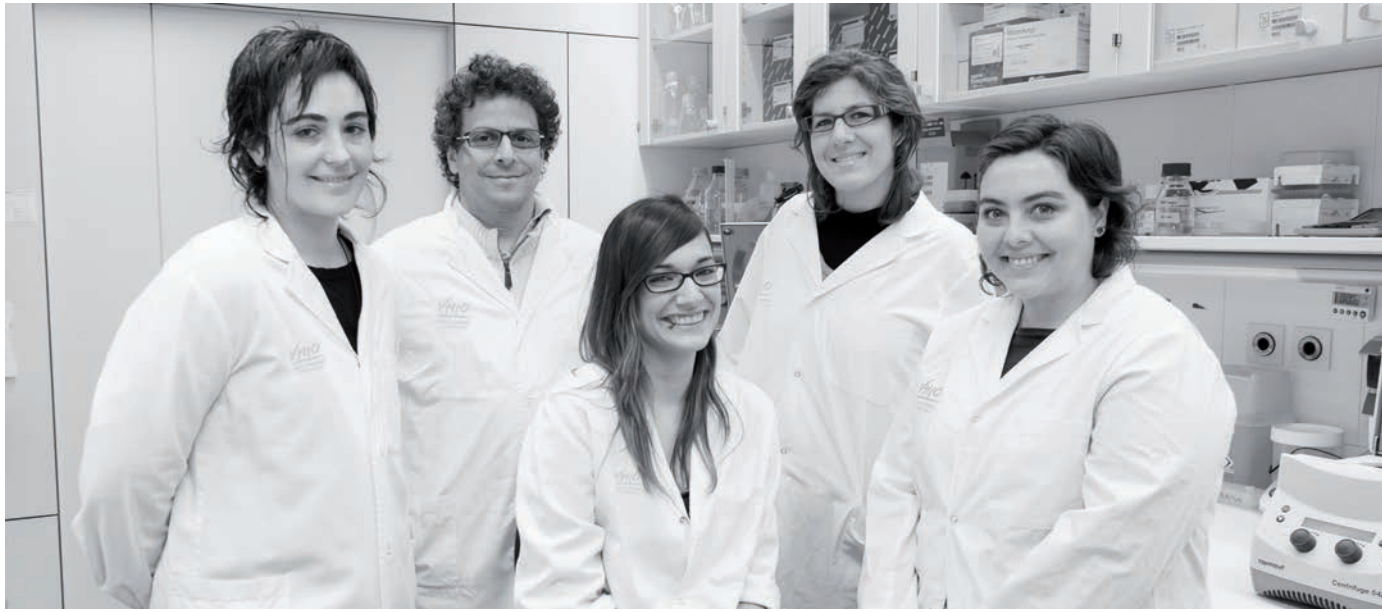
Core Technologies
CANCER GENOMICS GROUP



Strategic Goals

1. Provide cutting-edge applications in cancer genomics through the use of new technologies and protocol development.
2. Develop and implement improved strategies for routine patient pre-screening.

Highlights in 2012

- We have developed a routine prescreening testing with MassARRAY to profile frequent mutations in oncogenes. We have implemented several critical QC measures that ensure the high level quality of our results.
- We have developed and validated a panel of over 500 assays to interrogate mutations in oncogenes as well as tumor suppressor genes with the MassARRAY platform and adapted their use to NextGen sequencing.
- Setup of protocols and QC development that allow efficient and robust exome capture from FFPE-derived DNA.

SUMMARY

VHIO's Cancer Genomics Groups serves as a Core Technology Lab as part of its Translational Research Program. Our activities bridge the preclinical and clinical fields of cancer research.

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 HiSeq2000, Illumina (see figure).

The lab is part of a prescreening program, performing somatic mutation profiling with our genotyping platform in patients that are candidates to be enrolled in Phase I clinical trials. Such trials use targeted therapies such as PIK3CA, AKT1, BRAF or MEK inhibitors and include patients with specific molecular or genetic alterations.

We are also involved in a number of translational projects using Next-generation sequencing (NGS), such as identifying mechanisms of resistance to targeted therapies, studying clonal populations, using non-invasive approaches to profile somatic mutations in collaboration with both prelcinical and clinical researchers in several tumor types.

Protocol development and improving NextGen Sequencing are also a focus of our research activities as well developing efficient strategies for our prescreening program, involving FFPE-derived DNA and NextGen sequencing.

Figure: Instruments at Cancer Genomics Lab: MassARRAY (Sequenom), HiSeq 2000 (Illumina), MiSeq (Illumina).

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Principal Investigator
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Mª Alejandra Iglesias

Core Technologies
MOLECULAR ONCOLOGY GROUP

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 2012

- Development and validation in preclinical models of predictive and pharmacodynamic biomarkers of response to cMET, FGFRs, and AXL pathway inhibition.
- Exploration of new assays to detect biomarker/s expression at protein and RNA levels on CTC isolated with new filtration methods.
- Implementation of a quality assurance system within the laboratory for running tissue-based analyses on clinical samples.
- Over 1,500 molecular determinations on samples for patient inclusion into clinical trials.
- Supported over 100 clinical trials for sample management and analyses activities.
- Performed ~1000 IHC staining and ~1200 nucleid acid extractions (DNA and RNA) as a central laboratory in clinical studies.
- Supported basic and translation research programs with over 14,000 tests performed.

SUMMARY

The Molecular Oncology Group is one of VHIO's Core Technology Platforms. Its main goal 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 personalized therapies. Given the translational and multidisciplinary nature of research at VHIO, the Molecular Oncology Group represents a critical element at the core of all activities. It actively participates in all research projects involving the use of human tissues collected from patients including tissue banking and development of primary xenograft models.

The number of clinical trials at Vall d'Hebron in which the Molecular Oncology Group participates either as a local or central laboratory, has greatly increased over the last 5 years with up to 100 open studies in 2012, spanning 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 2012, we have performed over 1,500 molecular determinations on samples for patient inclusion into clinical trials and over 14,000 tests to support basic and translation research programs. We have also implemented a quality assurance system within the laboratory for running tissue-based analyses on clinical samples.

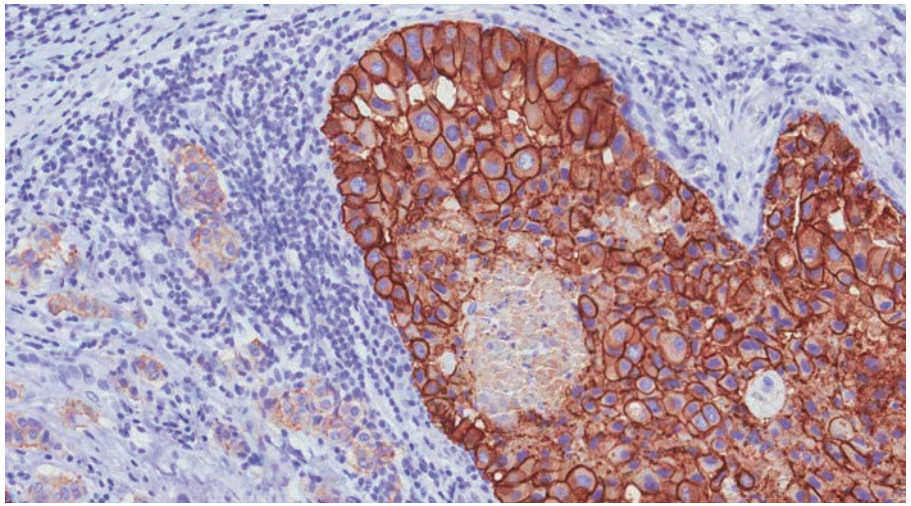

Figure: Heterogeneity of HER2 expression between ductal carcinoma in situ and adjacent invasive component in breast cancer.

To find out more about us, our research, publications and even our group's horizons for 2013, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2012

Principal Investigator
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Post-Doctoral Fellows
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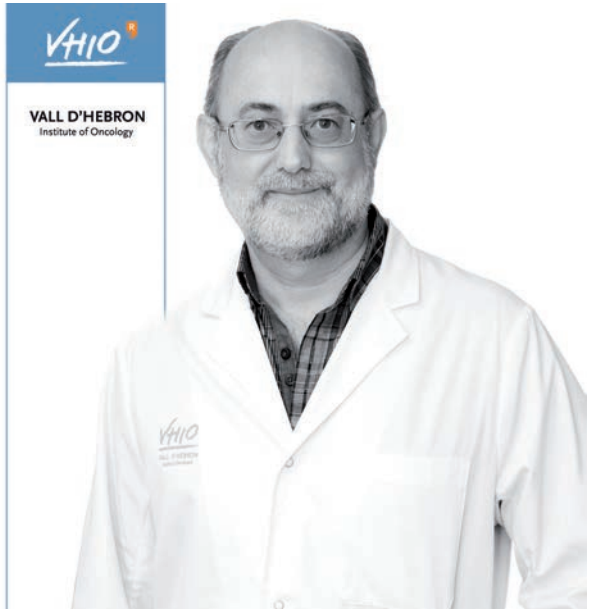
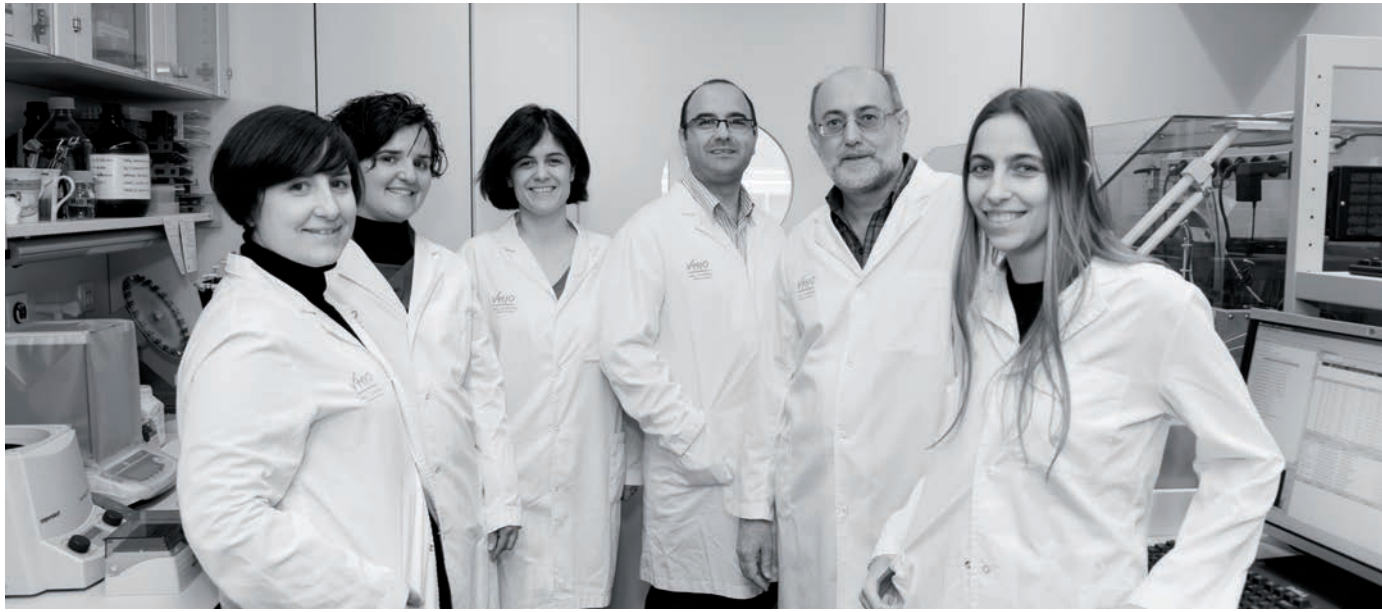
Marta Monge
Gemma Reverter

Technicians
Núria Colomé
Luna Martín
Carolina de la Torre

Core Technologies
PROTEOMICS GROUP





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 assist cancer therapeutics.

Highlights in 2012

- Proteomics services to VHIO and the Vall d'Hebron University Hospital groups, as well as ProteoRed-Instituto Salud Carlos III network.
- Work in progress towards the validation of a biomarker signature to help selection of patients and monitoring of the TGFbeta inhibitor-based treatment of glioma.
- Set up of new methodology, based on glycoprotein capture, for the proteomic screening of proteins shed by metalloproteases in cancer cells.
- Launch of the Spanish Consortium Chromosome 16 HPP, integrated in the HUPO Human Proteome Project.

To find out more about us, our research, publications and even our group's horizons for 2013, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2012

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. Nowadays, 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.

Our main line of research focuses 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. We employ mass spectrometry-based proteomic strategies to search for new substrates of these proteases and explore their role in tumor progression. We also pursue the use of proteomic techniques for screening and validation of biomarkers for cancer diagnostics, personalized treatment and monitoring (see figure).

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

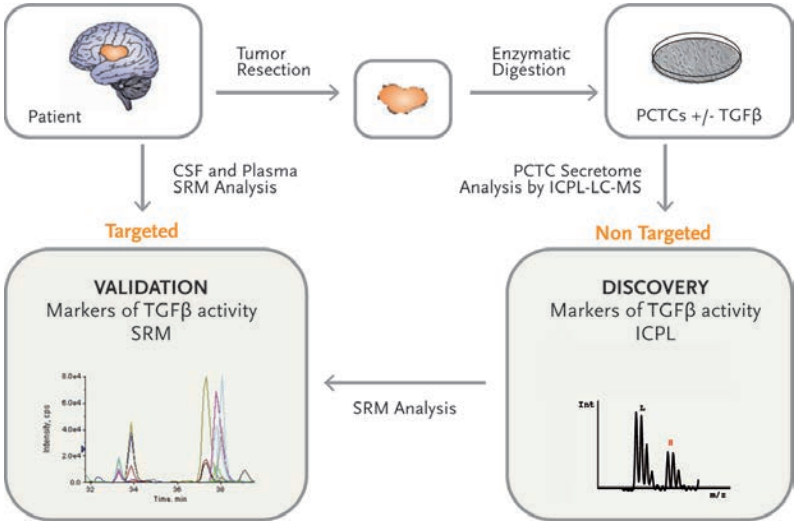


Figure: Schematics of a workflow directed to the identification of protein biomarkers for the management of TGFbeta responsive glioma patients. Proteomic discovery phase is conducted on the secretomes from tumor-derived primary cultures. Methods for mass spectrometry targeted analysis are developed for selected protein candidates. Verification and validation of these proteins as biomarkers is then undertaken on cerebrospinal fluid and plasma samples from a selected cohort of patients.

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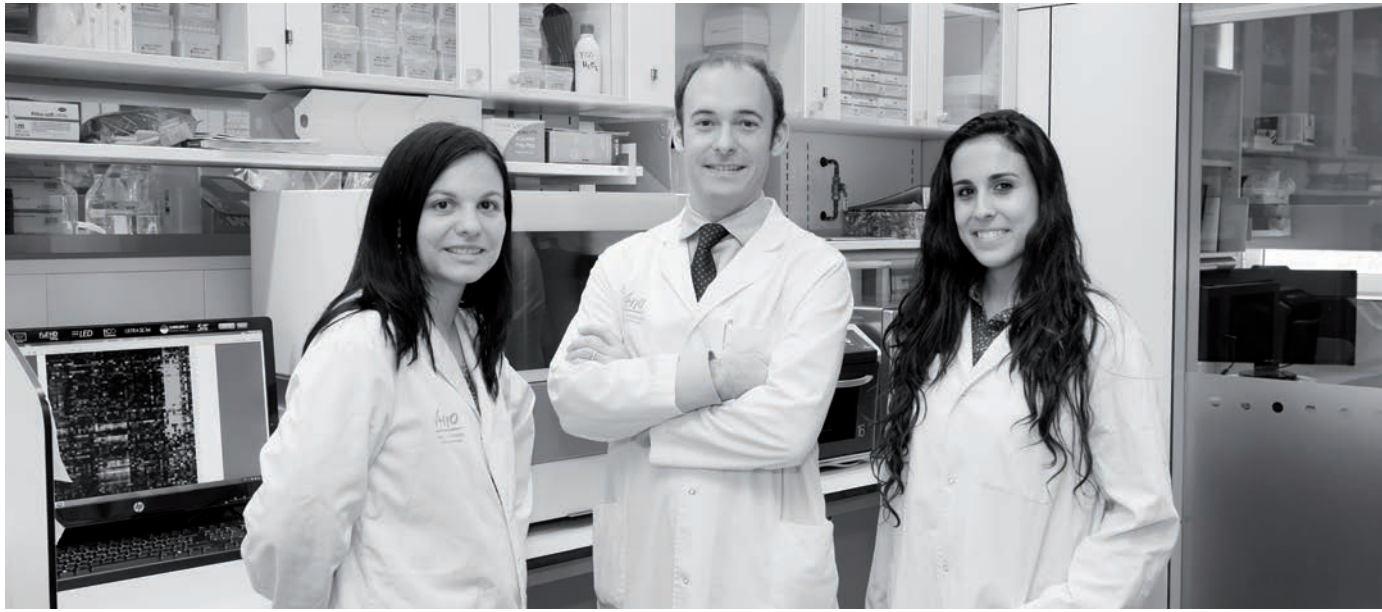
Clinical Research Technician
Patricia Galván

Specialist Physician in Breast Cancer (collaboration)
Maria Jesus Vidal Losada

Core Technologies

TRANSLATIONAL GENOMICS GROUP



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 cancer types.
3. Help implement gene expression-based tests in the clinical setting.

Highlights in 2012

- Implementation of the nCounter Nanostring platform.
- Creation of VHIO's first breast cancer gene expression-based dataset.
- Participation in the NEOERIBULIN clinical trial.
- Comparing gene expression-based predictors in breast cancer.
- Genomic characterization of breast cancer.

SUMMARY

During most of 2012, I shared my Principal Investigator position at VHIO with a Postdoctoral Research Fellow position at C. M. Perou's Laboratory at the University of North Carolina (USA). Throughout 2012, I set up VHIO's Translational Genomics Group and implemented the technology, equipment, and the various protocols to facilitate the production of gene expression data in a timely and efficient manner. In addition, our group has already created the first breast cancer gene expression-based dataset from ~300 breast samples, which will allow the correct identification and characterization of future samples. We have started analyzing samples and provide scientific advice to several collaborators at VHIO and abroad.

In 2012, one of our major findings was that the current immunohistochemical (IHC)-based definition of Luminal A breast cancer is suboptimal to identify those patients that do not need adjuvant chemotherapy. At the same time, we have proposed an improved version of the current IHC-based definition of Luminal A breast cancer by using the progesterone receptor expression levels. These findings might have important clinical implications. Furthermore, we have shown in two additional articles that the different gene expression-based tests available for breast cancer management provide similar information but are not the same. This is important since there is widespread belief among our community that these genomic tests can be used interchangeably. I have also contributed to 8 high-impact articles (6 from international collaborators and 2 from VHIO) by providing scientific advice and/or performing gene expression analyses. One example being my participation in The Cancer Genome Atlas Project (TCGA) in breast cancer through my position at C. M. Perou's Lab.

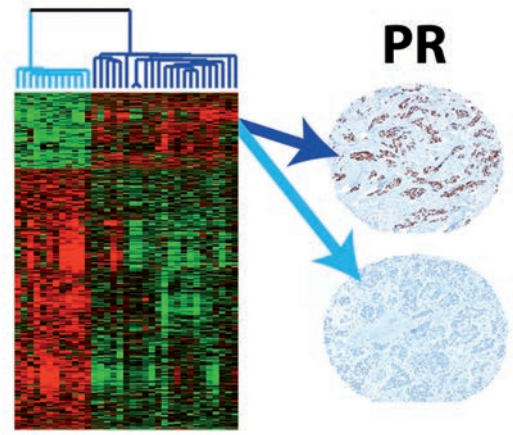


Figure 1: Summary of gene expression and pathological findings regarding the current IHC-based definition of Luminal A breast cancer.

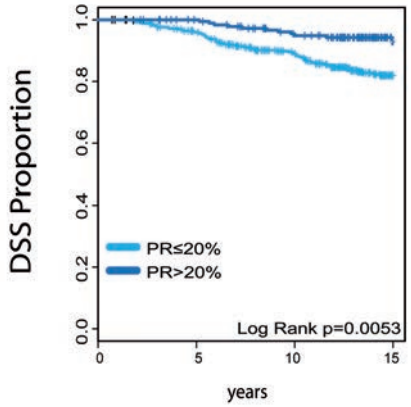


Figure 2: Kaplan-Meier survival analysis within immunohistochemical-based luminal A tumors (hormone receptor positive/HER2 negative/Ki-67 < 14%) based on the percentage of progesterone receptor (PR) –positive tumor cells.

To find out more about us, our research, publications and even our group's horizons for 2013, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2012

VHIO MULTIDISCIPLINARY RESEARCH PROGRAMS

VHIO TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

Head, Clinical Trials Office for Phase I Trials
Gemma Sala

Study Coordinators
Meritxell Baño
Marta Beltrán
Maria Herranz
Lidia Martínez de Arenzana
Laura Maynés
Adelaida Piera
Elisabet Sicart

Data Managers
Beatriz Blanco
Laia Cano
Gloria García
Isabel Rico
Cristina Viaplana

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

Study Coordinators
Lluïsa Carbonell
Cristina González
Neus Marqués
Oriol Nualart
Olga Padrós
Iratxe Puebla
Mireia Sanchís

Data Managers
Anna Aguilar
Soraya Fernández
Marta Malo
Xavier Martínez
Sergio Pérez
Andrea Retter
Montserrat Solà

Natalia Verde

Head, Clinical Trials Office for Phase I-III Cancer Trials (Breast, GU, CNS, Sarcoma and Gist)
Susana Muñoz

Study Coordinators
Judith Alonso
Raquel Espallargas
Violeta Esteban
Beatriz García
Jordi Humbert
Thaïs Miquel

Data Managers
Julia Esteban
Belén García
Àngels Porras
Rosa María Romero
Albert Torrent

Assistants
Núria Carballo
Angel Marín

Database Managers Office
Débora Moreno
Núria Murtra
Gessamí Sánchez Ollé

VHIO Transversal Clinical Trials Core Services & Units
CLINICAL TRIALS OFFICE

Strategic Goals

1. Contribute to the development of new treatments for 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 this period.
4. Provide high quality data adhering to deadlines.
5. Facilitate the work and communication between the different staff involved in the trial (oncologists, nurses, pharmacists, pathologists, etc.).
6. Ensure that the protocol is appropriately conducted from the initiation to the close of the respective trial.

Highlights in 2012

- Increase in the number of patients enrolled in clinical trials Phase I,II and III.
- Increase in the number of clinical trials performed.
- 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.
- Conducted 11 sponsor audits and 1 FDA inspection with satisfactory results.

For the full list of clinical trials at VHIO (Phases I - III) in 2012 please visit the VHIO Scientific Report online at: http://memorias.vhio.net/2012 (simply select the main tab 'Clinical Trials' and click on the Clinical Trials Office icon).

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, it is of little surprise that we have witnessed an important growth in the number of patients currently starting a new treatment in clinical trials in our department (see figures 1 & 2).

- 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. We have also organized a 36-hour postgraduate course (a new edition for 2012).

Figure 1: Total Annual Recruitment in Clinical Trials (Phase I-II-III)

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

Figure 2: Annual Recruitment Evolution (Phase I-II-III Trials)

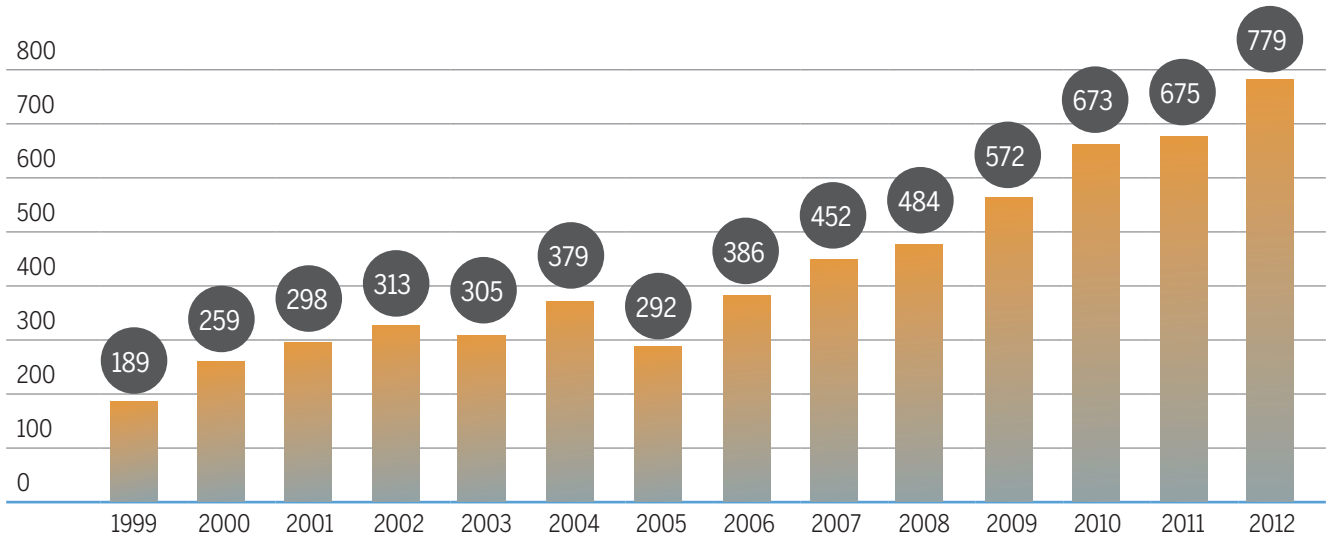


Figure 2: Increase in number of patients recruited in clinical trials from 1999 to 2012.

Figure 3: Annual Distribution of Phase I,II and III Trials

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

Figure 4: Number of Clinical Trials per year (Phase I-II-III Trials)

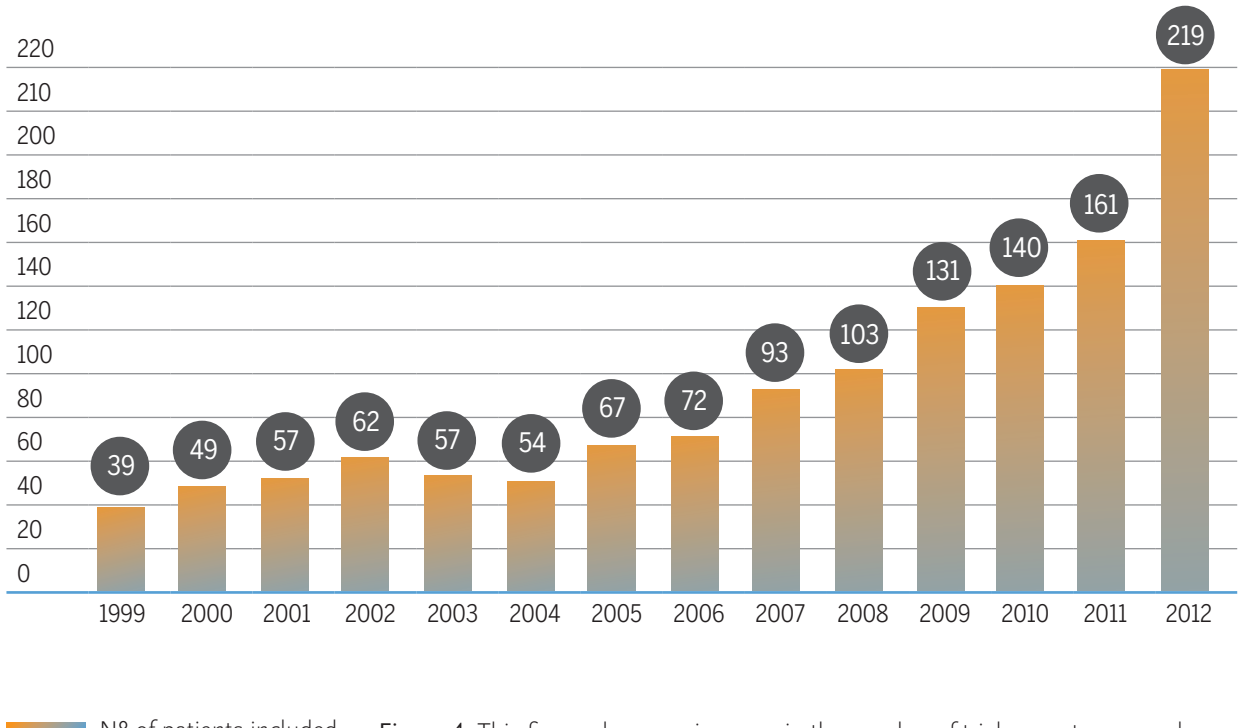


Figure 4: This figure shows an increase in the number of trials run at our oncology department, in particular Phase I trials.

SUMMARY

Set up in 1997, the Clinical Trials Office comprises an operational team conducting clinical trials at the Vall d'Hebron University Hospital's Oncology Department with more than 30 professionals including study coordinators, data managers and administrative staff working on more than 219 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: Phase I, Breast Cancer, and Phase II-III. Our Office has conducted 219 actively recruiting trials and succeeded in recruiting and coordinating a total of 779 patients included in clinical trials. In addition, we are following up all patients that were recruited prior to 2012 who are still enrolled and receiving study treatment.

For more information about Phase I and early Phase II trials, please see pages 42 - 43, Early Clinical Drug Development Group, and the Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa", pages 74 - 75.

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Principal Investigator, Early Clinical Drug Development Group Medical Coordinator
Jordi Rodón

Head Of Clinical Trials Office
Gemma Sala

Clinical Research Fellows
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Guillem Argilés
Analía B. Azaro
Cristina Cruz Rodrigo
Dienstmann

Associated Investigators
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Josep Maria del Campo
Javier Cortés
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Investigators
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Judith Balmaña
Maria Elena Élez
Jaume Capdevila
Patricia Gómez
Teresa Macarulla
Alex Martínez
Pablo Martínez
Leticia de Mattos
Eva Muñoz
Ana Oaknin
Mafalda Oliveira
Jose Manuel Pérez
Víctor Rodríguez
Cristina Saura
Tamara Sauri
Cristina Suarez
Claudia Valverde

Clinical Coordinators
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Laura Maynes
Adelaida Piera
Elisabet Sicart

Data Entries
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Laia Cano
Isabel Rico
Gloria Garcia
Cristina Viaplana

Pharmacist
Maribel Magaña

Nurse Supervisor
Ángeles Peñuelas

Nurse Coordinator
Sonia Valverde

Nurses
Meritxell Cucurell
Margarida Marcos
Isabel Muñoz
Lydia Vélez

Nurses' Assistant
Alicia López

Secretary
Teresa Mendoza

VHIO Transversal Clinical Trials Core Services & Units
RESEARCH UNIT FOR MOLECULAR THERAPY OF CANCER (UITM) - "la Caixa"

Strategic Goals

1. To further expand our broad portfolio of the most promising novel therapies for cancer.
2. Perform molecular analysis of patient tumors in order to select the best possible treatment with the experimental treatments available.
3. To treat patients in Phase I trials within an optimal environment incorporating highly experienced and multidisciplinary cancer teams.
4. 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 (phase I units, academic centers, international consortia of excellence, pharmaceutical companies).
5. Understand the mechanism of action of targeted therapies and to find predictive markers to better select in which cases these treatments work better.

Highlights in 2012

- Our Unit continues to report an annual increase in both the number of Phase I trials carried out as well as number patients enrolled in the trials.
- We have performed some of the most complex phase I trials, including those focused on rarer diseases including medulloblastoma, glioblastoma, basal cell carcinoma, lymphoma, thyroid medullar cancer, as well as those focusing on complex pharmacokinetics or biomarkers such as molecular imaging, tumor pharmacodynamic markers etc.
- In collaboration with VHIO's Cancer Genomics and Translational Cancer Genomics groups, we are now benefiting from the implementation of two cutting-edge technology platforms: the MiSeq sequencing system and nCounter Nanostring platform.
- We are currently applying for ISO accreditation which will further endorse the quality and excellence epitomizing our Unit and activities.

SUMMARY

Inaugurated in June 2010, thanks to the support received from the Welfare Projects Division of the "la Caixa" Foundation, 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 1,000 m² our Unit is located within the General Area of the Vall d'Hebron University Hospital.

Due to such a privileged environment with direct access to patients, coupled with VHIO's translational approach to research and superb scientific framework, our Unit has rapidly established itself as one of the few comprehensive facilities in Europe to 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. We are gradually doing so for an increasing number of patients. In 2012, 66 phase I clinical trials were performed at the Unit with a total of 290 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 42 - 43), 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.

Obra Social "la Caixa"

In partnership with VHIO's Molecular Oncology and Cancer Genomics Groups (see Core Technologies, pages 60 - 67) 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 in 2012 by VHIO's Cancer Genomics and Translational Cancer Genomics groups - MiSeq and nCounter Nanostring respectively, we will now up the tempo 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 70 - 80.

For more specific information about our clinical trials please visit our extended Scientific Report online at: http://memorias. vhio.net/2012

Supervisor
Ángeles Peñuelas

Nurse Coordinators
Sonia Valverde
Lydia Vélez

Nurses
Anna Aliau
Mª Elena de Cabo
Meritxell Cucurell
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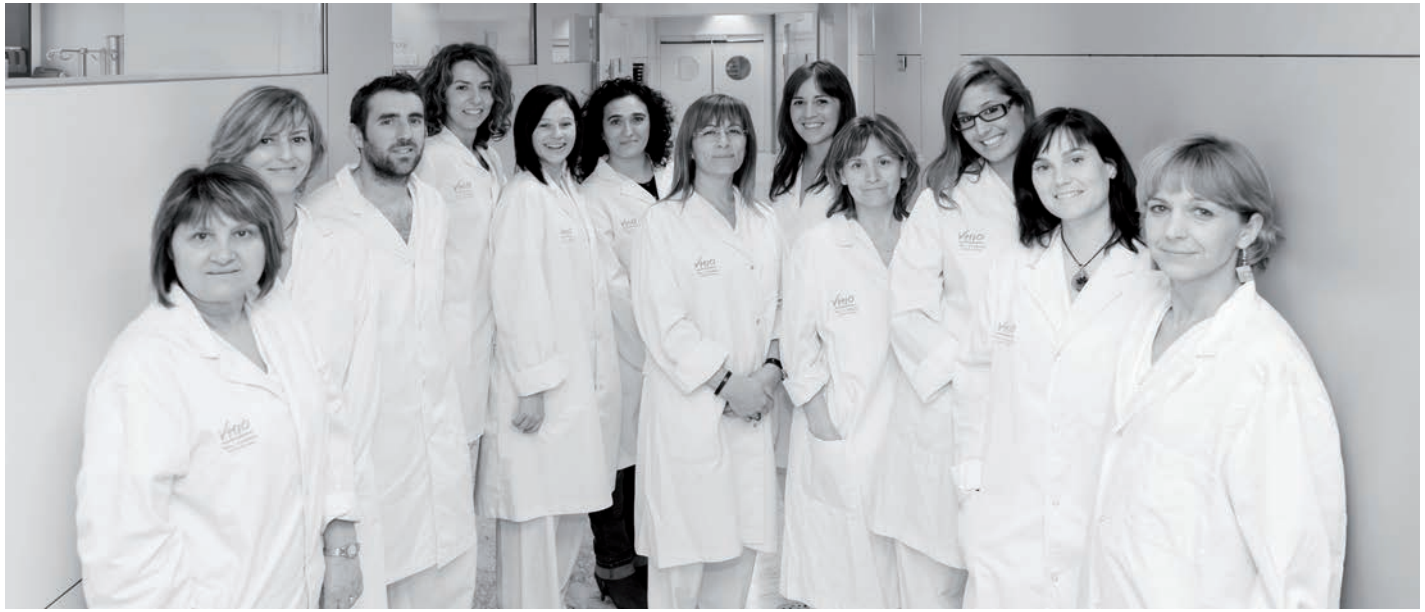
Mireia Milán
Isabel Muñoz
Raquel Muriel
Tania Sánchez
Alex Sierra
Ariadna Torrella

Nursing Assistants
Purificación Cardenete
Alicia López
Mª Ascensión Martín
Elena Oller

VHIO Transversal Clinical Trials Core Services & Units
CLINICAL RESEARCH ONCOLOGY NURSES



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 74 for more information) and the Clinical Trials Office (see page 71). Incorporating medical oncologists, specialists in molecular pathology, pharmacists exclusively dedicated to this field (see VHIO's Clinical Research Oncology Pharmacy Unit on page 78), 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.

To visit VHIO's extended Scientific Report online visit: http://memorias.vhio.net/2012

Coordinator of the Clinical Research Oncology Pharmacy Unit

Maria Josep Carreras Soler

Coordinator of Pharmacological Research in Oncology Support Unit

Laura Mañós Pujol

Pharmacists

Patricia Díez Duran
Anna Farriols Danés
Elena López Montero
Maribel Magaña Pintado
Maria Oliveras Arenas
Berta Renedo Miró
Carol Valdivia Vadell

Clinical Trials Re-Supplies Manager

Carol Herrero

Technicians

Romina Bellini Martínez
Hugo Cortina Colás
Maria Hidalgo Casas
Susana Mulet Lozano
Sara Pizarro López

VHIO Transversal Clinical Trials Core Services & Units

CLINICAL RESEARCH ONCOLOGY PHARMACY UNIT

Strategic Goals

1. Achieve excellence in the quality of the service we provide to the different clinical oncology research programs through optimal efficacy, efficiency and safety. - Ensure traceability of management and preparation of drugs for clinical trials.
2. Provide and ensure excellent control of the storage temperature of samples and prepared products.
3. Increase documented control of the accounting of drugs returned by patients.
4. Provide instructions and indications to patients for orally administered treatments.
5. Implementation of traceability program in clinical trial supplies management (storage, dispensation and accountability) to be enhanced through an interphase with the traceability program used in the Cytostatics and monoclonal antibodies preparation Unit: ISISH-TRI program.

Highlights in 2012

- Centralization of all preparations in clinical trials with the opening of the pharmacy unit.
- Implementation 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 document the traceability of the relevant documentation on the trials in digital format and documentation on 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.
  - Clinical and technical support of the process of prescription/ preparation/administration of cytostatics in clinical trials, providing an electronic record of all actions, users, dates and times. Batches and expiry dates of the products used. Use of electronic technologies and computerized processes: voice technology (Voice-Directed Work, Vocollect).The master database of the traceability project for study drug dispensation and storage is currently being designed.
- Design of electronic medical order prescription for study drugs of oral and iv administration for Phase I clinical trials.
- Implementation of the qualitative and quantitative quality control system for cytostatic preparations in clinical trials, which will guarantee the preparation of the correct trial drugs at the right dosage, without medication errors.
- Improvement of pharmaceutical care program providing written information extracted from the Infowin program during the interviews to select and/or polymedicated patients.

SUMMARY

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

Our clinical research activities are carried out through two programs:

- The Oncology Pharmaceutical Care Program is responsible for preparing cytostatics, monoclonal antibodies, biological products and other parenteral antitumor drugs used in clinical trials in oncology, and for monitoring the clinical activity in oncology patients. It incorporates a team of pharmacists specializing in hospital pharmacy and oncology pharmacy, as well as laboratory technicians.
- The Pharmacological Research in Oncology Support Program comprises a team of pharmacists, biologists, nurses and laboratory technicians specializing in clinical trials. The program is dedicated to managing, storing, issuing and controlling samples for clinical trials in oncology.

In 2012 our activity has involved the following key areas:

- *Management of clinical trial drugs*: we have managed clinical trial drugs for 219 active clinical trials in oncology. The number of clinical trial supplies deliveries totaled at 2,730.

- *Updating of a novel system for controlling storage temperature*: with electronic temperature recordings every 5 minutes - which is shown on the program's computers including an audio and visual alarm as well as a system for sending an alarm via SMS to the

cell phone of the pharmacist on duty, continuously for 24 hours in case of temperature deviations.

- *Implementation 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 safely using a Cabin Vertical Laminar FLOW (CVLF). The study drug returned by the patient is accounted for by pharmacy personnel in Cabin Vertical Laminar Flow (CVLF) and the pills are kept in a clear and sealed bag. This year, our unit has performed drug accountability for drugs returned by patients from 52 clinical trials.

- *Ensuring traceability of the management of storage, custody and dispensing of clinical trial drugs*: the design i 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 taken part in 25 pre-study visits, 99 initial visits, 968 monitoring visits and 44 final visits and successfully passed 14 audits. Preparation staff have participated in 5 pre-study visits, 98 initial visits, 130 monitoring visits, and 9 audits.

- *Dispensing*: a total of 14,865 clinical trial drugs have been dispensed with the validation of a pharmacist. 5,850 of these dispensations are for orally administration clinical trial drugs .The conditioning and re-labeling of the primary containers for clinical trial drugs have also been carried out. A total of 147 Standardized Dispensing Procedures have also been drawn up and updated. 169 storage temperature data reports have been generated.

- *Preparations*: a total of 8,807 preparations of cytostatics, monoclonal antibodies and other parenteral antitumor drugs for clinical trials have been carried out. A total of 91 Standardized Preparation Procedures have been drawn up.

- *Collateral*: preparation of documentation relating to each clinical trial for medical and nursing staff as well as for patients from standard operating procedures to instructions and relating forms for patients. In 2012, 140 different antineoplastic therapeutic regimens were computerized, we compiled 17 standard operating procedures and 46 patient-orientated documents. The dispensing unit has prepared 11 Diaries and Instructions for patients.

- *Development of pharmaceutical care program to patients included in Phase I clinical trials*: activity was extended to all Phase I clinical trials involving oral medication. The pharmacological history of patients was recorded and the usual treatment was reconciled with that being studied. Patients and researchers were informed regarding potential drug-drug interactions of the study drug with others/concomitant complementary therapies and administration of the drug recorded through patient interviews as well as the subsequent accountability for medication returned. During 2012 a total of 660 visits to patients in Phase I clinical trials were conducted and we carried out 250 pre-screening visits, 232 screening visits, 170 follow-up visits and 8 end study visits. 116 patient telephone consultations were also attended.

- *Improve d pharmaceutical care of patients included in Phase I/II trials*: through diaries and instructions for patients in all trials (Phase I, II i, III) that involved drugs being administered orally.

- *ISO9001:2008 certification renewed.*

To find out more about us, our research, publications and even our group's horizons for 2013, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2012

Full listing of articles published by VHIO investigators in 2012

Articles published by VHIO investigators in 2012 in journals with allocated impact factor

Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer. *Baselga, Jose*; Campone, Mario; Piccart, Martine; Burris, III, Howard A.; Rugo, Hope S.; Sahmoud, Tarek; Noguchi, Shinzaburo; Gnant, Michael; Pritchard, Kathleen I.; Lebrun, Fabienne; Beck, J. Thaddeus; Ito, Yoshinori; Yardley, Denise; Deleu, Ines; Perez, Alejandra; Bachelot, Thomas; Vittori, Luc; Xu, Zhiying; Mukhopadhyay, Pabak; Lebwohl, David; Hortobagyi, Gabriel N.. 2012. ***N Engl J Med*** 366: 520-529. IF: 53,298

Increased survival with enzalutamide in prostate cancer after chemotherapy. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS; *AFFIRM Investigators*. ***N Engl J Med*** 2012. 367(13):1187-1197. IF: 53,298

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. *Baselga, Jose*; *Cortes, Javier*; Kim, Sung-Bae; Im, Seock-Ah; Hegg, Roberto; Im, Young-Hyuck; Roman, Laslo; Pedrini, Jose Luiz; Pienkowski, Tadeusz; Knott, Adam; Clark, Emma; Benyunes, Mark C.; Ross, Graham; Swain, Sandra M.; CLEOPATRA Study Grp. 2012. ***N Engl J Med***. 366: 109-119. IF: 53,298

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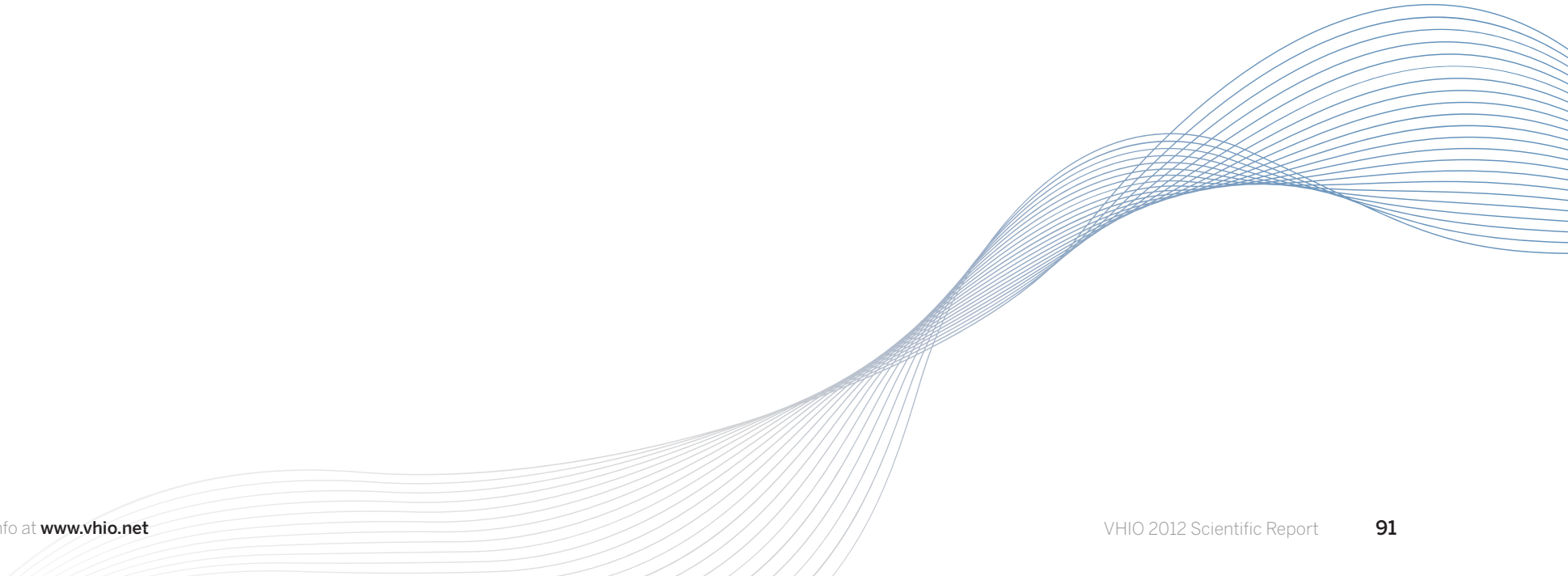

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