SCIENTIFIC REPORT 2011

VALL D'HEBRON INSTITUTE OF ONCOLOGY

Centres de recerca de Catalunya

VHIO

INDEX SCIENTIFIC REPORT 2011

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

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INTRODUCING VHIO

PRECLINICAL RESEARCH

TRANSLATIONAL RESEARCH

CLINICAL RESEARCH

CORE TECHNOLOGIES

VHIO CLINICAL TRIALS CORE SERVICES & UNITS

Foreword

Josep Tabernero, Director

José Baselga, Scientific Director

Undertaking one of Spain's most dynamic cancer research programs, VHIO adopts a purely translational approach to research in order to realize the true promise of personalized medicine by turning research into more effective, targeted treatments and better practice for the care of our patients. Our efforts in 2011 have again resulted in significantly advancing cancer discovery by integrating translational science and clinical research within a multidisciplinary setting -- the winning formula behind what we do and how we do it at VHIO.

Importantly, the detailed study of individual patients and their particular cancer specificities is aided enormously by VHIO's location. Set within the campus of the Vall d'Hebron University Hospital (see page 8), we are privileged not only to have direct access to patients but also to catalyze daily collaboration between our preclinical, translational and clinical research teams with the Hospital's physician-scientists. Such cross-talk between oncology professionals within multidisciplinary teams allows us to rapidly advance personalized and targeted therapies against cancer.

While we are making encouraging progress, there are still numerous hurdles to be overcome in the battle against cancer. In last year's report we signaled our ambition to conduct more (and larger) clinical studies, better validate markers, and continue to unravel the vast amount of genetic and signaling pathway data and apply that knowledge clinically. Here, we will outline just a few of many VHIO highlights in 2011.

Dedicated to working on complex clinical trials with drugs in early development (Phase I and early phase II trials) focusing on novel targets, our Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa", inaugurated in June 2010 -- has already established itself as an international reference in developing new drugs based on identifying the molecular profile of each tumor and optimizing treatment regimes using combinations of new drugs with existing ones. In keeping with VHIO's translational model, clinical research at UITM is carried out by our Early Clinical Drug Development Group led by Jordi Rodón. Research is linked with various research areas carried out by other VHIO groups, connecting molecular biology and the best tumor models with pharmacology and innovative clinical research. Our scientists are collaborating closely in trials to facilitate biomarker development as well as research in mechanisms of resistance (see pages 44 - 45). Our Clinical Trials Office at the Vall d'Hebron University Hospital's Oncology Department also reports increased activity. In 2011, it coordinated more than 160 Phase I - Phase III studies – marking exciting growth in both the number of patients enrolled in trials as well as trials conducted (see pages 72 - 74).

One of VHIO's guiding principles both internally and externally is collaboration. In November we announced the creation of an international collaboration in partnership with the BBVA Foundation and The Massachusetts General Hospital Cancer Center (Boston, USA) -- the BBVA Foundation Biomarkers Research Program. Over the next five years, this program will develop personalized therapies for cancer patients through biomarker research, proceeding along two main lines: novel drug discovery and the improvement or optimized use of existing pharmaceutical therapies towards more effective, individually tailored treatments.

In view of the current financial climate, many would argue it to be a fool's errand to make predictions for the coming year. However, based on the facts some bets can be safely placed. Just as *Nature* predicted in its events from the research world in 2011, we will continue to witness further drops in the cost of clinical genome sequencing and improvements in our ability to identify the key driver mutations and genomic rearrangements in cancer patients. As such, we have been paving the way to incorporate novel technology platforms as well as attract outstanding new talent to our programs.

Firstly, we are delighted to announce that Aleix Prat will be joining us from C. M. Perou's lab (University of North Carolina at Chapel Hill, USA), in 2012 as Principal Investigator of VHIO's newly created Translational Genomics Group. He will lead the translation of genomic discovery by applying it at clinical level to better guide clinical trial design and biomarker marker development. Incorporating cutting edge Nanostring technology, Prat's team will participate in retrospective correlative science studies using tumor samples from clinical trials, validate predictive and/or prognostic genomic-based biomarkers in prospective clinical trials, as well as evaluate gene expression data as a tool to identify drug sensitivity/ resistance mechanisms.

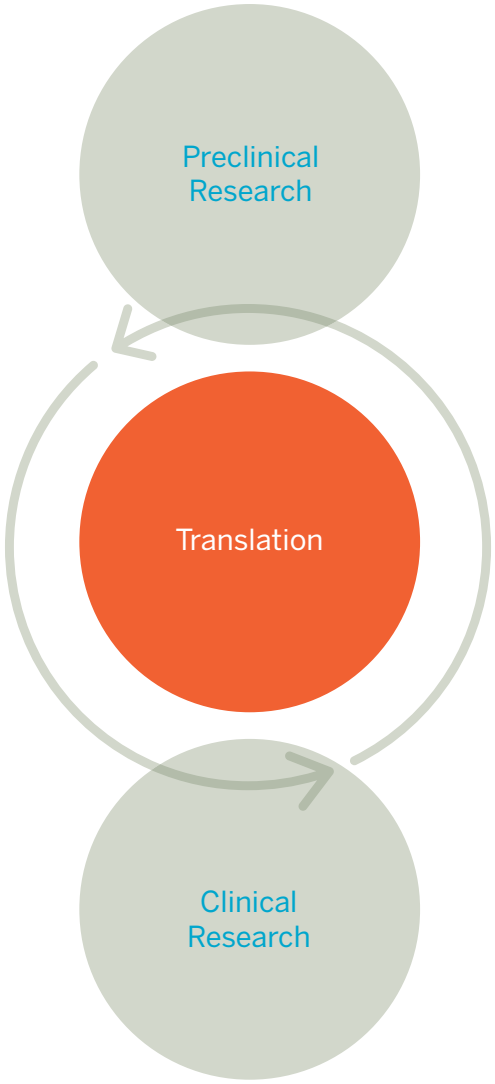
VHIO's Molecular Pathology Group represents a critical platform at the core of our activities including research involving the use of human tissue collected from patients including tissue banking and the development of primary xenograft models.

The group also plays an essential role in the design, implementation and evaluation of novel biomarker strategies. VHIO's molecular pathology par excellence, coupled with our thriving translational environment, have undoubtedly been decisive factors behind another young talent's decision to join forces with us in 2012. Paolo G. Nuciforo, currently Head of Molecular Pathology at Novartis Oncology (Basel, Switzerland), will head-up our Molecular Pathology Group to spur the development of new biomarkers and diagnostic tests for personalized medicine, leveraging more than eight years of experience in clinical and translational oncology.

Another important development in 2011 was the creation of VHIO's Scientific Advisory Board (SAB). The SAB is comprised of 10 leading experts, each internationally renowned for their excellence in the oncology field (see page 10). Nominated by VHIO's Board of Trustees, this expert panel will formally meat at least once a year and will assume an important role in evaluating our scientific activities, monitoring the quality of scientific output as well as advising on the scientific management and structure of VHIO.

Finally, as we noted in last year's Report, we have now finalized all the necessary strategic planning for VHIO's new home -- the Cellex Building. With construction commencing early next year, the new building will not only provide the necessary space and amenities to expand upon our research activities, but will also foster the already existing multidisciplinary cross-talk and connectivity by bringing all VHIO teams together under the same roof. The clock will consequently continue to tick in our favor – against cancer.

Josep Tabernero	José Baselga
Director	Scientific Director



Who we are, what we do and (just some) of how we did it in 2011

VHIO'S PURELY TRANSLATIONAL RESEARCH MODEL

Cancer treatment and care can and will only advance through the equal involvement and cross-talk between all oncology professionals as multidisciplinary cancer teams within an environment that provides the appropriate infrastructure, expertise, and interconnectivity.

From the very outset VHIO – under the scientific direction of José Baselga and the expert leadership of Josep Tabernero - has adopted a purely translational research model. VHIO is proof of the bench-bedside-bench principle, whereby laboratory discoveries are directly applied to patients and from the clinical side, tumor samples are analyzed in the laboratory.

Our translational approach facilitates the detailed study of each patient and each tumor. Aided by direct access to patients thanks to its location set within the Vall d'Hebron University Hospital, our translational research model and multidisciplinary setting, VHIO has become one of the few comprehensive cancer centers to translate research findings for the benefit of patients in record time.

Research at VHIO focuses on understanding all relevant aspects of cancer biology from cellular and molecular biology and genetics through to therapeutics. Our optimal patient care is made possible by our innovative programs in preclinical, translational, and clinical research, our cutting edge core technologies, whereby researchers collaborate closely with Vall d'Hebron University Hospital physician-scientists, a partnership that helps accelerate the application of key research findings to the benefit of our patients.

It is only through the continued and generous support received from our patrons, private institutions, companies, individuals, funding entities and agencies (please see pages 12 - 14 for further details) that our cancer teams continue to improve survival and quality of life for our patients today, and in so doing turn research into more effective, personalized treatments and better clinical practice for the future.

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

SCIENTIFIC DIRECTION

Josep Tabernero
Director

José Baselga
Scientific Director

Preclinical Research Program

Experimental Therapeutics

Growth Factors

Mouse Models of Cancer Therapies

Tumor Biomarkers

Proteomics

Translational Research Program

Gene Expression & Cancer

Stem Cells & Cancer

Cancer Genomics

Core Techonologies

Cancer Genomics

Molecular Pathology

Proteomics

Clinical Research Program

Clinical Trials Core Services & Units:

Clinical Trials Office

Clinical Research Oncology Nurses

Clinical Research Oncology Pharmacy Unit

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

Databases and Statistics

Molecular Pathology

Groups:

Breast Cancer & Melanoma

Early Clinical Drug Development

Gastrointestinal & Endocrine Tumors

Genitourinary, Central Nervous System (CNS) Tumors, Sarcoma & Cancer of Unknown Primary Site

Head and Neck & Gynecological Tumors

High Risk & Cancer Prevention

Oncogenetics

Radiation Oncology

Thoracic Tumors

Research Group / Units

Core Groups classified according to their scientific reporting line

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

Vall d'Hebron
Hospital

THE VALL D'HEBRON UNIVERSITY HOSPITAL:

AN IDEAL BASE AND ENVIRONMENT FOR VHIO'S MULTIDISCIPLINARY CANCER TEAMS

VHIO is located in the privileged environment of one of the largest University Hospitals in the country, the Vall d'Hebron University Hospital.

Cancer treatment and care can and will only advance through the equal involvement and cross-talk between all oncology professionals form different specialties as dynamic, multidisciplinary cancer teams within a setting that provides the appropriate infrastructure, expertise, and interconnectivity.

The Vall d'Hebron University Hospital offers the ideal environment and base through which to foster and promote such essential collaboration:

- VHIO coexists with the day to day activity of the hospital with all the available clinical care state-of-the-art technology for the treatment and care of cancer patients.
- The campus naturally spurs multidisciplinary cooperation, thus permitting a more comprehensive approach to combating cancer.

  It is thanks to this environment that VHIO has been able to develop its multidisciplinary cancer teams to ensure patients are cared for by as many different specialties as required for their particular type of disease including surgeons, medical oncologists, radiation oncologists, radiologists, pathologists, psychiatrists, and nurses.

- The Vall d'Hebron University Hospital is a teaching hospital associated with the Universitat Autònoma de Barcelona.

In addition to the inspiring dedication, expertise and dedication of VHIO's faculty, the combination of these aforementioned factors have also been of major importance in uniting the talent required to allow our teams of researchers to produce such excellent cancer science from bench-bedside-bench.

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

CLINICAL TRIALS AT VHIO

Driving drug development and targeted therapies against cancer, VHIO has rapidly become a leading reference in drug discovery from concept to clinic.

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

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 as a new facility at VHIO 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 one year and a half since it was inaugurated, among many other successes, through the clinical research carried out by the Early Clinical Drug Development Group (see pages 44 - 45), 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.

For more information, please see pages 44 - 45, or consult our Scientific Report for more information at: http://memorias.vhio.net/2011/.

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 adminstrative staff, this Office reports exciting growth in both the number of patients enrolled in trials as well as trials conducted each year. 2011 is no exception - totaling 161 Phase I-II-III trials with 675 patients recruited.

To consult the full list of highlights and a summary of activity in 2011 (see pages 72 - 74). For a detailed listing of all clinical trials conducted in 2011 visit our Scientific Report 2011 online at: http://memorias.vhio.net/2011/.

CANCER RESEARCH AT VHIO: LEADING SCIENTIFIC DISCOVERY TO PROGRESS AGAINST CANCER

Commandeering research in the fight against cancer, our preclinical, translational and clinical researchers as corresponding/senior authors or co-authors, published 125 scientific articles with a Median Impact Factor of 8,35.

These figures reflect both the increasing quality of scientific productivity at VHIO as well as the importance of its research and contribution to the oncology field.

Please see pages 15 - 17 of this Scientific Report for more information as well as a selection of just some of the most relevant articles by VHIO researchers published in 2011.

To view papers published across VHIO's programs and research groups visit the expanded version of our Scientific Report 2011 online at: http://memorias.vhio.net/2011/.

THE CELLEX BUILDING: TO STRENGTHEN VHIO'S MULTIDISCIPLINARY CROSS-TALK AND CONNECTIVITY

Throughout 2011 we have been finalizing the plans and facilities for our new building and are delighted to report that construction will commence in early 2012 as envisaged. The CELLEX building will not only facilitate the necessary and future expansion of VHIO's preclinical, translational and clinical research programs, but will also bring all our teams even closer together - accelerating yet further our translational research for tomorrow's targeted therapy: the barometer of VHIO success.

Fundació Privada
CELLEX

VHIO'S SCIENTIFIC ADVISORY BOARD: A SHARED VHIO VISION

Established in the Fall of 2011, VHIO's Scientific Advisory Board, comprised of the following 10 renowned experts within the oncology field, will undoubtedly help VHIO to further deliver on its mission of developing and advancing translational research of excellence:

Carlos L. Arteaga, MD (Chair)
Donna S. Hall Chair in Breast Cancer
Professor of Medicine and Cancer Biology
Associate Director of Clinical Research, Vanderbilt-Ingram Cancer Center, Nashville, USA

René Bernards, PhD
Head of Molecular Carcinogenesis, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Julio E. Celis, PhD
Scientific Director, Institute of Cancer Biology, Danish Cancer Society, Copenhagen, Denmark

Andrés Cervantes, MD, PhD
Associate Professor of Medicine, Head of Section of the Hematology and Medical Oncology Department, University Hospital of Valencia, Valencia, Spain

Fortunato Ciardiello, MD, PhD
Full Professor of Medical Oncology, Head of Experimental Therapeutics, the Division of Medical Oncology, Seconda Universitá di Napoli, Naples, Italy

Stanley B. Kaye, MD, FRCP, FRCR
Head of the Drug Development Unit and Head of the Section of Medicine, The Royal Marsden Hospital and The Institute of Cancer Research, London, UK

Carlos López Otín, PhD
Professor, Department of Biochemistry and Molecular Biology, University of Oviedo, Spain

Richard Marais, PhD
Director,
Paterson Institute for Cancer Research,
Manchester, UK

Jorge Reis-Filho, MD, PhD
Professor, Team Leader, Breakthrough Breast Cancer Research Center, Institute of Cancer Research, London, UK

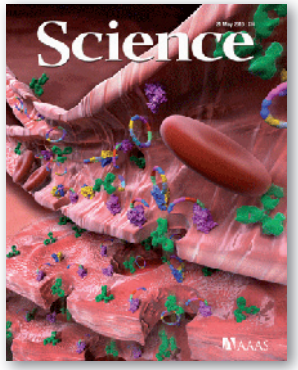
Jesús San Miguel Izquierdo, MD
Scientific Director,
Salamanca Institute of Biomedical Research,
Salamanca, Spain

LAUNCHED: VHIO *MEET THE EDITORS* SERIES OF PRESTIGIOUS TALKS

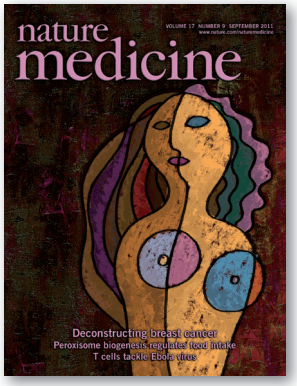
Launched this year with *Nature* journal's Senior Editor, cancer research, Barbara Marte on *Inside Nature* in October 2011, our annual series of VHIO Meet the Editors, provide oncology professionals of research institutes in Barcelona with unique opportunity to learn more about scientific publishing and cancer researcvh and put questions to the editors directly during the Q & A with the audience.

Following each talk, the respective Editor spends the afternoon in closed sessions with VHIO PIs to discuss their research and present manuscripts 'in the pipeline'- an excellent opportunity to establish a personal relationship with the Editor as well as promote their research.

VHIO *MEET THE EDITORS*
CALENDAR 2012



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



Speaker: Victoria Aranda, Senior Editor, *Nature Medicine*
Talk: An In-Depth Look at Scientific Publishing, Criteria for Cancer Research Publications & Future Trends in Oncology
Date: 17 September 2012

The NEW ENGLAND JOURNAL of MEDICINE

Speaker: Bette Phimister, Deputy Editor, *New England Journal of Medicine*
Talk: Publishing Advances in Cancer Research
Date: 14 May 2012

Funding, Consortia & Accreditation

FUNDING

VHIO can and will only deliver on its goal of accelerating the pace in advancing personalized and targeted therapies against cancer thanks to the public funding it receives as well as the generous support from private institutions, companies and individuals. Furthermore, and as a direct reflection of VHIO's research of excellence, VHIO continues to secure essential funding through several International and National Competitive Grants.

Only with such continued support will the clock continue to tick in our favor - against cancer. VHIO would therefore like to express its immense gratitude to its following supporters, funding entities and agencies:

INSTITUTIONAL SUPPORTERS

Generalitat de Catalunya

fero Fundación de Investigación Oncológica

Obra Social "la Caixa"

Fundación BBVA

With the collaboration of:

Fundació Privada CELLEX

PRIVATE FUNDING

PUBLIC FUNDING

CONSORTIA

As a reflection of VHIO´s expertise in preclinical, translational and clinical research in oncology, it participated in the following Consortia of excellence in 2011:

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

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

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

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).

ACCREDITATION

In 2011 VHIO joined the Catalan Association of Research Centres (Associació Catalana d´Entitats de Recerca - ACER).

Scientific productivity: Research articles

ARTICLES PUBLISHED IN 2011

In 2011, 125 scientific articles were published by VHIO researchers as corresponding/ senior authors or co-authors with a Median Impact Factor (MIF) of 8,35. Both figures below 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

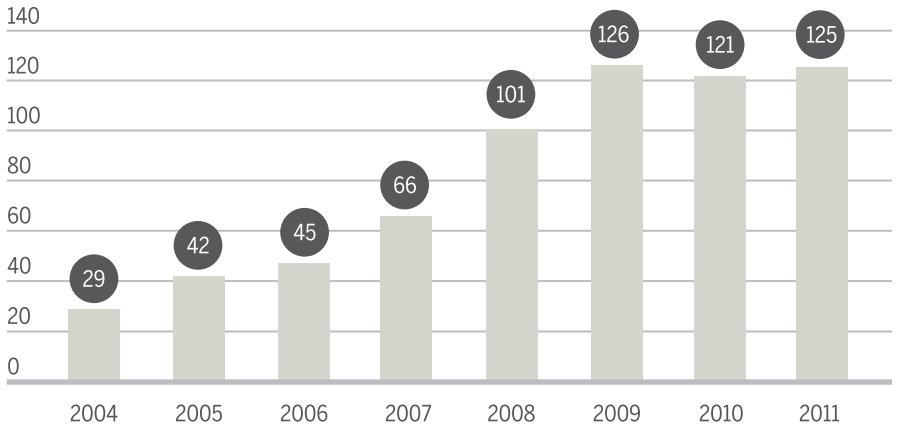


Figure 1: Number of articles published by VHIO researches from 2004-2011.

IMPACT FACTOR ARTICLES PUBLISHED IN 2011

Figure 2

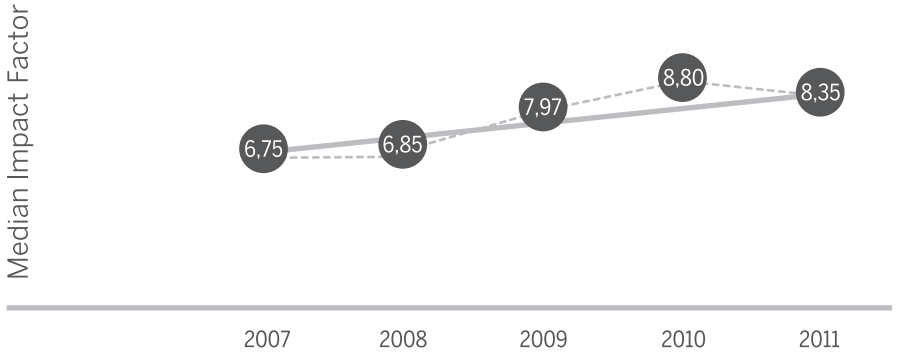


Figure 2: Median Impact Factor (MIF) of papers published by VHIO faculty from 2007-2011.

For a selection of most relevant articles by VHIO researchers published in 2011 please see pages 16 - 17 of this Scientific Report. To view all papers published per VHIO Group visit our Scientific Report 2011 online at: **http://memorias.vhio.net/2011/** (select tab "Publications, Projects & Awards").

Selection of most relevant articles by VHIO researchers published in 2011

Below is a **selected list** of articles published by VHIO researchers in 2011 with respective IFs:

Cortés, J; O'Shaughnessy, J; Loesch, D; Blum, JL; Vahdat, LT; Petrakova, K; Chollet, P; Manikas, A; Delozier, T; Vladimirov, V; Cardoso, F; Koh, H ; Bougnoux, P; Dutcus, CE; Seegobin, S; Mir, D; Meneses, N; Wanders, J; Twelves, C. (2011) A Phase III open-label randomised study (EMBRACE) of eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer. ***Lancet***, 377(9799), 914-923. IF: 38,278

Bass, AJ; Lawrence, MS; Brace, LE; Ramos, AH; Drier, Y; Cibulskis, K; Sougnez, C; Voet, D; Saksena, G; Sivachenko, A; Jing, R; Parkin, M; Pugh, T; Verhaak, RG; Stransky, N; Boutin, AT; Barretina, J; Solit, DB; Vakiani, E; Shao, W; Mishina, Y; Warmuth, M; Jimenez, J; Chiang, DY; Signoretti, S; Kaelin, WG; Spardy, N; Hahn, WC; Hoshida, Y; Ogino, S; Depinho, RA; Chin, L: Garraway, LA; Fuchs, CS; **Baselga, J**; **Tabernero, J**; Gabriel, S; Lander, ES; Getz, G; Meyerson, M. (2011) Genomic sequencing of colorectal adenocarcinomas identifies a recurrent VTI1A-TCF7L2 fusion. ***Nat Genet***, 3(10), 964-968. IF: 35,532

Haber, DA; Gray, NS; **Baselga, J.** (2011) The evolving war on cancer. ***Cell***, 145(1), 19-24. IF: 32,403

Chandarlapaty, S; Sawai, A; Scaltriti, M; Rodrik-Outmezguine, V; Grbovic-Huezo, O; Serra, V; Majumder, PK; **Baselga, J**; Rosen, N. (2011) AKT inhibition relieves feedbacksuppression of receptor tyrosine kinase expression and activity. ***Cancer Cell***, 19(1), 58-71. IF: 26,566

Gianni, L; Dafni, U; Gelber, RD; Azambuja, E; Muehlbauer, S; Goldhirsch, A; Untch, M; Smith, I; **Baselga, J**; Jackisch, C; Cameron, D; Mano, M; Pedrini, JL; Veronesi, A; Mendiola, C; Pluzanska, A; SemiglazoV, V; Vrdoljak, E; Eckart, MJ; Shen, Z; Skiadopoulos, G; Procter, M; Pritchard, KI; Piccart-Gebhart, MJ; Bell R; HerceptinAdjuvant (HERA) Trial Study Team. (2011) Treatment with trastuzumab for 1 year afteradjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. ***Lancet Oncol***, 12(3), 236-244. IF: 22,589

Henke, M; Alfonsi, M; Foa, P; **Giralt, J**; Bardet, E; Cerezo, L; Salzwimmer, M; Lizambri, R; Emmerson, L; Chen, MG; Berger, D. (2011) Palifermin decreases severe oral mucositis of patients undergoing postoperative radiochemotherapy for head and neck cancer: a randomized, placebo-controlled trial. ***J Clin Oncol***, 29(20), 2815-2820. IF: 18,372

Domchek SM, Mitchell G, Lindeman GJ, Tung NM, **Balmaña J**, Isakoff SJ, Schmutzler R, Audeh MW, Loman N, Scott C, Friedlander M, Kaufman B, Garber JE,Tutt A, Robson ME. Challenges to the development of new agents for molecularly defined patient subsets: lessons from BRCA1/2-associated breast cancer. ***J Clin Oncol***, 29(32), 4224-4226. IF: 18,372

Paz-Ares, LG; Gomez-Roca C, Delord JP, Cervantes A, Markman B, Corral J, Soria JC, Bergé Y, Roda D, Russell-Yarde F, Hollingsworth S, **Baselga J**, Umana P, Manenti L, **Tabernero J**. (2011) Phase I Pharmacokinetic and Pharmacodynamic Dose-Escalation Study of RG7160 (GA201), the First Glycoengineered Monoclonal Antibody Against the Epidermal Growth Factor Receptor, in Patients With Advanced Solid Tumors. ***J Clin Oncol***, 29(28), 3783-3790. IF: 18,372

Haller, DG; **Tabernero, J**; Maroun, J; de Braud, F; Price, T; Van Cutsem, E; Hill, M; Gilberg, F; Rittweger, K; Schmoll, HJ. (2011) Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. ***J Clin Oncol***, 29(11), 1465-1471. IF: 18,372

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Esteve, P., Sandonìs, A., Cardozo, M., Malapeira, J., Ibañez, C., Crespo, I., Gonzalez-Garcia, S., Marcos, S., Torribio, M. L., **Arribas, J.**, Shimono, A., Guerrero, I. and Bovolenta, P (2011) Secreted Frizzled-Related Proteins act as negative modulators of ADAM10 metalloproteinase activity during retinal neurogenesis. ***Nat Neurosci***, 14(5), 562-569. IF: 15,531

Higgins, MJ; **Baselga, J**. (2011) Targeted therapies for breast cancer. ***J Clin Invest***, 121(10), 3797-803. IF: 13,069

Cortés J, **Saura C**, Bellet M, **Muñoz-Couselo E**, Ramírez-Merino N, Calvo V, Pérez J, **Vidal M**. (2011) HER2 and hormone receptor-positive breast cancer-blocking the right target. ***Nat Rev Clin Oncol***, 8(5), 307-311 IF: 11,963

Cheok, CF; Verma, CS; **Baselga, J**; Lane, DP. (2011) Translating p53 into the clinic. ***Nat Rev Clin Oncol***, 8(1), 25-37. IF: 11,963

Kastrinos F, Steyerberg EW, Mercado R, **Balmaña J**, Holter S, Gallinger S, Siegmund KD, Church JM, Jenkins MA, Lindor NM, Thibodeau SN, Burbidge LA, Wenstrup RJ, Syngal S. (2011) The PREMM(1,2,6) model predicts risk of MLH1, MSH2, andMSH6 germline mutations based on cancer history. ***Gastroenterology***, 140(1),73-81. IF: 11,675

Sodir, NM; Swigart, LB; Anthony, N; Hanahan, KD; Evan, G; **Soucek, L**. (2011) Endogenous Myc maintains the tumor microenvironment. ***Gene Dev***, 25(9), 907-916. IF: 11,659

Scaltriti M, Eichhorn PJ, **Cortés J**, **Prudkin L**, **Aura C**, **Jiménez J**, Chandarlapaty S, **Serra V**, Prat A, **Ibrahim YH**, Guzmán M, Gili M, Rodríguez O, Rodríguez S, Pérez J, Green SR, Mai S, Rosen N, Hudis C, **Baselga J**. (2011) Cyclin E amplification/overexpression is a mechanism of trastuzumab resistance in HER2+ breast cancer patients. ***Proc Natl Acad Sci USA***, 108(9), 3761-3761. IF:9,681

Chakravarty, A; Shinde, V; **Tabernero, J**; Cervantes, A; Cohen, RB; Dees, EC; Burris, HA; Infante, JR; **Macarulla, T**: **Elez, E**; Andreu, J; Rodriguez-Braun, E; Roselló, S; von Mehren, M; Meropol, NJ; Langer, CJ; O'Neil, BH; Bowman, D; Zhang, M; Danaee, H; Faron-Yowe, L; Gray, G; Liu, H; Pappas, J; Silverman, L; Simpson, C: Stringer, B; Tirrell, S; Veiby, OP; Venkatakrishnan, K; Galvin, KM; Manfredi, MG; Ecsedy, JA. (2011) Phase I assessment of new mechanism-based pharmacodynamic biomarkers for MLN8054, a small-molecule inhibitor of Aurora A Kinase. ***Cancer Res***, 71(3), 675-685. IF:7,856

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VHIO MULTIDISCIPLINARY RESEARCH PROGRAMS

PRECLINICAL RESEARCH

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

DIRECTOR, PRECLINICAL RESEARCH PROGRAM

Joaquín Arribas

2011 has been truly exciting for our program. At the beginning of the year Laura Soucek, who finished an extremely successful project on the oncogene Myc as an anti-tumor target at G.I. Evan's Lab, the University of California at San Francisco (UCSF), USA, joined our program to lead VHIO's Mouse Models & Cancer Group (see page 26). Importantly, Laura was selected as the very top scientist within the Miguel Servet Call of the *Instituto de Salud Carlos III*. Furthermore, her research has also been awarded with the annual prize for translational research by the FERO Foundation. During her first year with us at VHIO, Laura has set up an exciting project on the effect of Myc on the tumor microenvironment that may expand therapeutic opportunities to target this oncogene.

Our Experimental Therapeutics Group led by José Baselga (see page 22), continued their work on understanding the HER2/PI3K pathway as a target to treat breast cancer. Through large-scale genomic analysis they identified cyclin E overexpression/amplification as a mechanism of resistance to anti-HER2 agents. They also identified the mechanism behind the resistance of some cancer cells to the inhibition of the PI3K-pathway and described novel therapeutic strategies for the treatment of HER2 breast cancer. Finally, they developed pharmacodynamic biomarkers and established novel patient tumor-derived breast cancer models to further explore combinatorial therapeutics in breast cancer.

Our Proteomics Group, headed by Frances Canals (see 'Core Technologies' on page 68), has continued to provide state-of-the-art proteomic technology and services to the laboratories of the Cancer Research Network and the *Plataforma de Proteómica en Red ProteoRed* (*Instituto de Salud Carlos III*). Regarding their own research, they have applied 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.

The Tumor Biomarkers Group led by Josep Villanueva (page 28) was awarded with a collaborative European Commission 7th Framework Programme of Research and Development (FP7) grant together with VHIO's Gastrointestinal & Endocrine Tumors Group headed by Josep Tabernero (page 44) as well as other European groups aimed at modeling and predicting resistance to molecular therapies in colorectal cancers. This grant has allowed VHIO's Tumor Biomarkers Group to start delivering on one of its initial strategic goals: to establish secreted response/resistance biomarkers to targeted drug therapy.

Finally, my own group, the Growth Factors Group, in collaboration with VHIO's Experimental Therapeutics Group, finished developing a robust test to analyze the levels of p95HER2, a biomarker that facilitates the identification of a particularly aggressive type of breast cancer. Importantly, the use of this test, which is based on specific monoclonal antibodies that recognize p95HER2, has been licensed to a large multinational pharmaceutical company.

We have also collaborated with VHIO's Proteomics Group in the study of the proteolytic remodeling of the extracellular matrix during malignant progression and identified a novel regulator of TGF-beta, a growth factor that determines several steps of the malignant progression pathway.

In summary, our groups have strengthened their respective collaboration in several markedly translational research projects that will undoubtedly contribute to improved cancer treatment in the near future.

PRECLINICAL RESEARCH

Experimental Therapeutics Group

Principal Investigator
José Baselga

Staff Scientist
Violeta Serra

Medical Oncologists
Jordi Rodón
Josep Tabernero

Post-Doctoral Fellows
Celina García
Yasir Ibrahim

Technicians
Pilar Antón
Maria Teresa Calvo
Patricia Cozar
Judit Grueso
Marta Guzmán
Olga Rodríguez

Strategic Goals

1. Unveil novel mechanisms of resistance against HER2- and PI3K-targeted therapies.
2. Study early molecular responses following PI3K inhibition to rationally design novel combination therapy in breast cancer.
3. Develop predictive and pharmacodynamic biomarkers of PI3K-pathway inhibitors.

Highlights in 2011

- Two additional mechanisms of resistance to trastuzumab-based therapy were identified. Both the amplification/overexpression of cyclin E and the loss of HER2 expression correlate to reduced clinical benefit in trastuzumab-treated HER2-positive breast cancer patients.
- Inhibition of Hsp90 is a valid strategy for the treatment of trastuzumab-resistant tumors.
- In collaboration with S. Chandarlapaty and N. Rosen, MSKCC, New York (USA), a novel mechanism of ERK-pathway compensatory activation following PI3K-based therapy was unveiled. Therapeutic strategies involving the combined targeting of PI3K and HER2 or of PI3K and MEK show enhanced antitumor activity in preclinical models.
- With VHIO's Growth Factors Group and the Molecular Pathology Group, we developed and validated an antibody for the detection of p95HER2 in clinical specimens.
- Development of a novel patient-derived tumor model that enables testing of novel hypothesis-based combined therapies in triple negative breast cancer.

Read more at www.vhio.net

SUMMARY

During 2011 our research focused on understanding the mechanisms of resistance to targeted therapy in breast cancer, with special emphasis on the blockade of the HER2/PI3K pathway. Our major aim has been to provide hypothesis-based strategies to combine targeted therapy and, in so doing, improve outcomes for patients.

Large-scale genomic analysis helped us to identify cyclin E overexpression/amplification as a targetable mechanism of resistance to trastuzumab, a therapeutic antibody against HER2. These findings were confirmed in the clinical setting since breast cancer patients with overexpressed/amplified cyclin E had reduced clinical benefit to trastuzumab-based therapies (see figure).

Insight into the biochemical adaptation following PI3K-pathway blockade 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 PI3K-pathway and HER2.

Further efforts were initiated to identify novel candidates of PI3K resistance through overexpression of an ORF 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 collaborative effort involving translational and clinical VHIO groups (Molecular Pathology, Cancer Genomics, and Breast Cancer & Melanoma) led us to identify pharmacodynamic markers of PI3K-pathway inhibition that can be exploited in the clinical development of these inhibitors. Importantly, these efforts have also enabled the development of novel patient tumor-derived breast cancer models *in vivo*. These preclinical models have shown to faithfully resemble the clinical setting and will be extremely useful in the study of targeted therapy resistance.

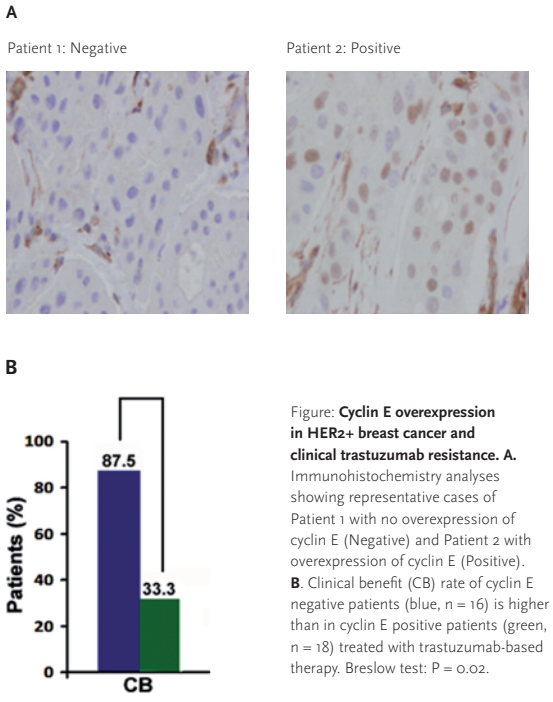

Figure: **Cyclin E overexpression in HER2+ breast cancer and clinical trastuzumab resistance. A.** Immunohistochemistry analyses showing representative cases of Patient 1 with no overexpression of cyclin E (Negative) and Patient 2 with overexpression of cyclin E (Positive). **B**. Clinical benefit (CB) rate of cyclin E negative patients (blue, n = 16) is higher than in cyclin E positive patients (green, n = 18) treated with trastuzumab-based therapy. Breslow test: P = 0.02.

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PRECLINICAL RESEARCH

Growth Factors Group

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Technicians

Marta Escorihuela
Cristina Ferrer
Antoni Luque

Associate Scientist

Aniello Cerrato

Strategic Goals

1. Characterize the proteolytic remodeling of the cell surface during malignant transformation.
2. Develop novel therapies against HER2-positive breast cancers.
3. Establish and characterize models that reproduce the different types of breast cancer.

Highlights in 2011

- Identification of a novel mechanism of regulation of TGF-beta signaling through the proteolytic cleavage of a cell surface TGF-beta trap.
- Characterization of the regulation of the metalloprotease ADAM10 by secreted frizzled-related proteins.
- Characterization of the role of p95HER2 in breast cancer progression and treatment.

Read more at www.vhio.net

SUMMARY

During malignant transformation a profound remodeling of the cell surface takes place. This remodeling includes the cleavage of a variety of transmembrane molecules such as receptors, growth factors and cell adhesion molecules. As a result, cell proliferation and migration increases.

We have recently shown that a variety of breast cancer cells express a transmembrane protein known as vasorin. When anchored to the plasma membrane vasorin is inactive. However, a metalloprotease known as ADAM17 has the ability to cleave vasorin from the cell surface and soluble vasorin is a potent inhibitor of TGF-beta, a growth factor that regulates many aspects of malignant progression. In early stages of tumor progression, TGF-beta, exerts an anti-proliferative and, hence, anti-tumor effect. By contrast, in advanced stages, TGF-beta promotes metastasis. Therefore, the inhibition of the cleavage of vasorin may increase the activity of TGF-beta and, hence, tumor suppression at early stages of tumor progression and the activation of the cleavage of vasorin may decrease TGF-beta activity and, thus, tumor progression.

In collaboration with P. Bovolenta's group, at the *Instituto Cajal*, the Spanish National Research Council (*CSIC*), Madrid, we have identified and characterized the secreted frizzled-related protein as inhibitors of ADAM10, a cell surface metalloprotease similar to ADAM17, that also plays a crucial role in the remodeling of the cell surface.

It is presently unclear how many types of breast cancer there are. Our research focuses on a type of breast cancer characterized by the presence of excessive levels of a cell surface receptor named HER2. HER2-positive tumors account for approximately 20% of all breast cancers. In recent years we showed that HER2-positive tumors are heterogeneous, a subtype of these tumors is characterized by the presence of fragments of HER2 collectively known as p95HER2. To facilitate the detection of p95HER2 in clinically relevant tumor samples, we have recently developed monoclonal antibodies against this HER2 fragment that have been patented and licensed for diagnostic use.

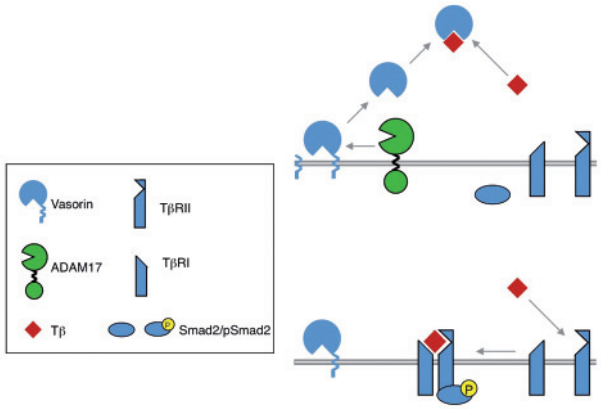

Figure: ADAM17 regulates TGF-beta signaling through the cleavage of VASN. Schematic showing the cleavage of VASN by ADAM17. Upper panel, the proteolytic release of the extracellular domain of VASN generates sVASN that binds TGF-beta, preventing the interaction of the growth factor with TbRII. Lower panel, in the absence of ADAM17 activity, TGF-beta binds T-betaRII, which recruits T-betaR. The complex recruits and phosphorylates Smad2.

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PRECLINICAL RESEARCH

Mouse Models of Cancer Therapies Group

Principal Investigator
Laura Soucek

Graduate Student
Antonio Jauset

Technician
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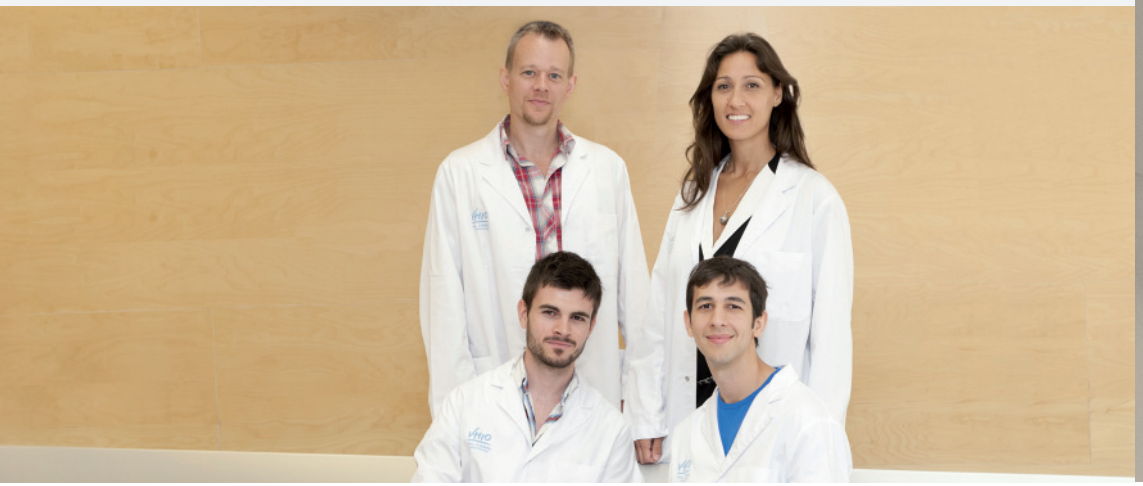
Staff Scientist
Jonathan Whitfield



Strategic Goals

1. Validation of Myc inhibition as therapeutic strategy in various mouse models of cancer.
2. Development of pre-clinical models of cancer therapy.
3. Defining the role of Myc inflammatory effectors in tumorigenesis.

Highlights in 2011

- Laura Soucek received a fellowship from the Miguel Servet Programme and the FERO Fellowship, awarded by the Her Royal Highness the Princess of Asturias.
- Endogenous Myc is shown to be responsible for the maintenance of tumor microenvironment.
- Blockade of mast cell function by Ibrutinib in a mouse model of insulinoma proves to be an efficacious strategy against this type of cancer and possibly other pancreatic cancers.

Read more at www.vhio.net

SUMMARY

Current new, targeted cancer therapies are directed against only a tiny proportion of targets within the cancer cell, most of which are restricted to only certain cancer types. While there have been some major successes using such agents, most prominently with kinase inhibitors, they have often not realized their true promise. This is largely because such targets reside in the most degenerate, redundant, plastic and adaptive parts of the aberrant signaling networks that drive cancer.

Tumor cells can adapt, either directly or evolutionarily, to such inhibitors easily, often 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, in principle, 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. Unfortunately, targeting nuclear targets such as Myc is technically challenging and has hitherto lacked any preclinical validation. However, over the past few years, we have shown that Myc inhibition can have a dramatic therapeutic impact in many, if not all cancers.

We are now interested in Myc's role in the coordination of programs downstream of different oncogenic signals and in different tissues, especially in relationship to the cross-talk between tumor and microenvironment, which could present some non-redundant and tractable targets for cancer therapy. We also intend to extend our studies to the therapeutic impact of Myc inhibition in metastasis, whereby Myc's role is still debated.

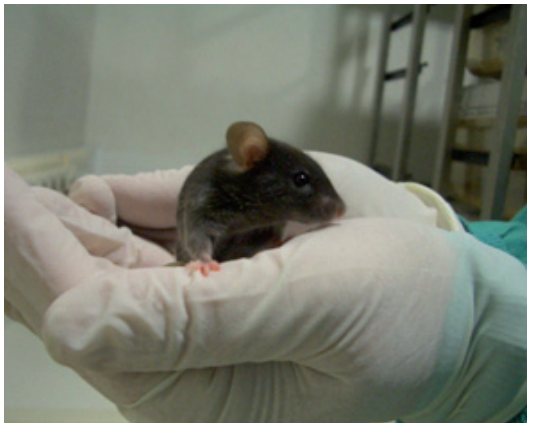


Figure: Mouse models have significantly contributed to our understanding of normal tissue and cancer biology, facilitating the temporary control of initiation, progression and evolution of physiological and pathological events.

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PRECLINICAL RESEARCH

Tumor Biomarkers Group

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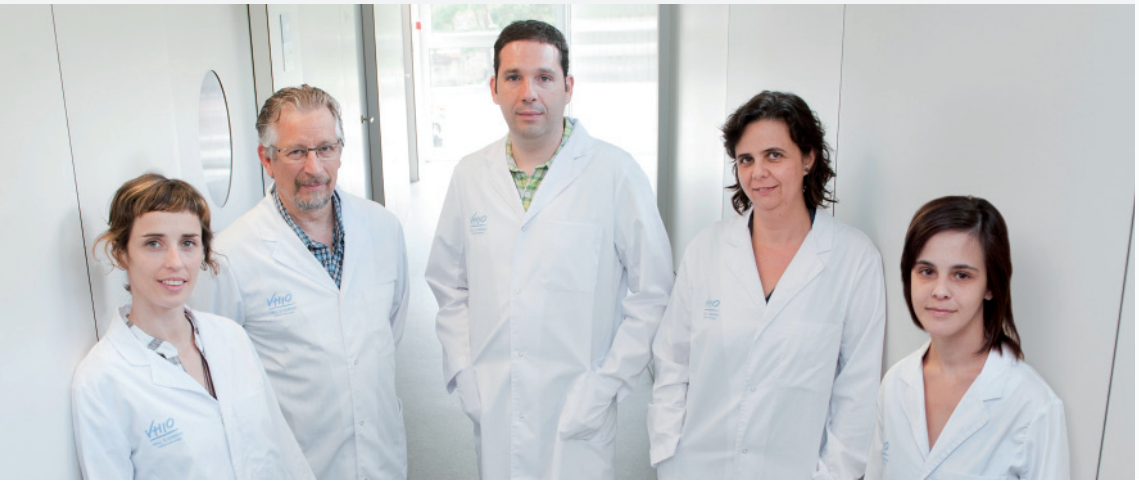

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Strategic Goals

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 2011

- Along with VHIO's Gastrointestinal & Endocrine Tumors Group led by Josep Tabernero as well as other European groups, we were awarded with a collaborative grant by the European Commission's 7th Framework Programme of Research and Development to work on modeling and predicting resistance to molecular therapies in colorectal cancers. This grant has allowed us to start working on one of our initial strategic goals: to establish secreted response/resistance biomarkers to targeted drug therapy.
- Our efforts towards investigating the secretome linked to tumor invasion in breast cancer have unmasked a number of previously unknown secreted candidate biomarkers. One of them is already undergoing functional validation.

Read more at www.vhio.net

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 advantageously 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 put 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.

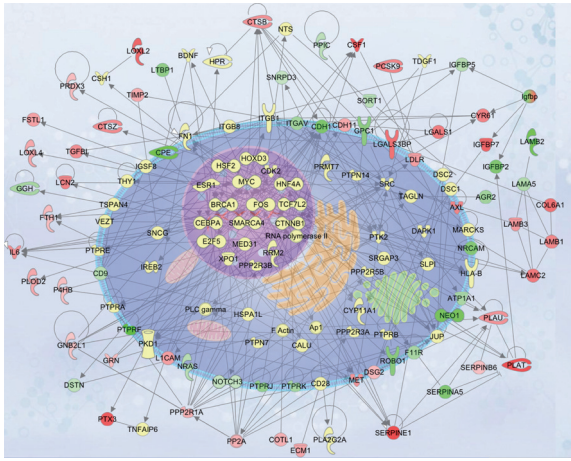

Figure: We and others aim to exploit the cancer secretome as a strategy for the proteomics interrogation of tissue-derived proximal fluids and cancer cell lines in the search for secreted tumor markers. The figure illustrates the secretome profiling of two different cell lines representing two of the major molecular subtypes in breast cancer. The proteins marked with red and green are growth factors, proteases, and other proteins previously linked to cancer, which are differentially secreted in the two cell lines. Additionally, the differentially secreted proteins have been connected to intracellular pathways using pathway analysis software. (Figure taken from reference: Journal of Proteome Research. 2009, 8 (3), 1489-1503).

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VHIO MULTIDISCIPLINARY RESEARCH PROGRAMS

TRANSLATIONAL RESEARCH


VHIO

DIRECTOR, TRANSLATIONAL RESEARCH PROGRAM

Joan Seoane

The overarching goal of VHIO's Translational Research Program is to improve and accelerate 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 possible 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. Each patient should therefore be treated with the optimal compound or combination of compounds for their particular disease. In addition, optimal treatment is determined by the specific molecular make up of the tumor. The challenge is therefore to identify which treatment should be linked to which patient and develop personalized medicine.

It is also critical to understand the nature of intratumoral heterogeneity in order to improve cancer treatment through the combination of compounds targeting all cell types within a tumor. Among the different cell types forming intratumoral heterogeneity, some cells with stem cell characteristics have been identified. These cells, known as Cancer Stem Cells (CSCs), 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.

In order to study the two levels of cancer heterogeneity, we need to research cancer as closely as possible to that of a real tumor from an actual patient. For this very reason, we 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 colon and brain cancer respectively.

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 (see 'Core Technologies', pages 64-65).

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 improving cancer treatment and catalyzing the transfer of new insight generated by scientific research into the true benefit for patients.

TRANSLATIONAL RESEARCH

Gene Expression & Cancer Group

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Anna Cascante
Isabel Huber
Mª del Mar Inda
Dermot O'Sullivan
Andrea Saez

Technicians

Alexandra Arias
Isabel Cuartas
Rosa Gil
Carolina Raventós

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 and Cancer Stem Cells (CSCs).
3. Develop specific treatments for each of the different cellular entities present within a tumor.

Highlights in 2011

Through a thorough, unbiased screening, searching for novel therapeutic targets to tackle glioblastoma, 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. This work has been accepted for publication by *Nature Medicine* in 2012.

Read more at www.vhio.net

SUMMARY

Our group's research focuses on the study of glioma, the most common and aggressive brain tumor, and works with cell cultures and mouse models of glioma. Gliomas are the most common primary tumors of the brain, the most malignant form of glioma (glioblastoma multiforme), and one of the most aggressive of all human cancers. Treatment for these malignancies remains elusive and progress in this area of research is therefore critical. Gliomas share morphologic and gene-expression characteristics similar to glia, the support cells of the brain. Gliomas can be divided into four clinical grades on the basis of their histology and prognosis. Grade IV gliomas (glioblastoma multiforme, GBM) are highly malignant, usually recalcitrant to radio- and chemotherapy and have a median survival of 1-2 years.

Until recently, radiation has been the main standard-of-care treatment with a minimal role for systemic chemotherapy. Concurrent treatment with temozolomide with radiation improved median survival by 2.5 months compared with radiation therapy alone. Thus, temozolomide has become a standard adjuvant therapy for gliomas although offering modest clinical benefits.

Novel molecularly-targeted therapies against these devastating tumors are required. 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 give us 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 monitor by MRI. This mouse model is of great interest for the study of the molecular mechanisms involved in cancer and for evaluating the efficacy of pharmacological compounds (see figure below).

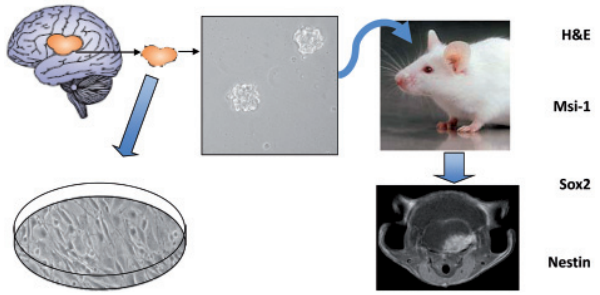

Figure : Animal model. Getting close to the real tumor.

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TRANSLATIONAL RESEARCH

Stem Cells & Cancer Group

Principal Investigator
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Graduate Student
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Post-Doctoral Fellows
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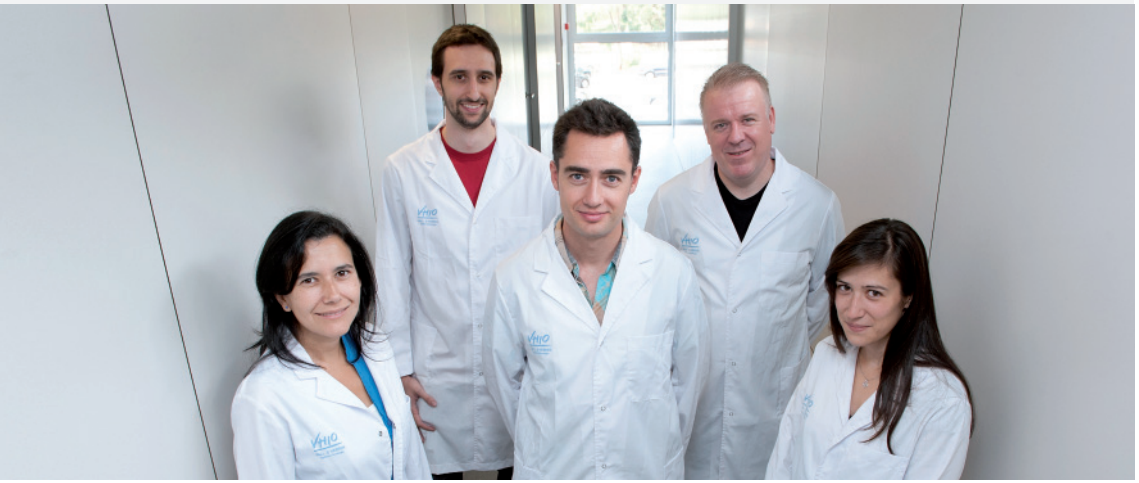
Stephan Tenbaum

Technician
Irene Chicote



Strategic Goals

1. Describe the key molecular mechanisms that confer Colon Cancer Stem Cells (CoCSCs) their capacity to self-renew and resist conventional or target-directed therapies.
2. Reveal the molecular drivers of CSC quiescence and its clinical relevance in cancer progression.
3. Identify the central molecules responsible for the development of metastasis in colon cancer.
4. Test the efficacy of both known and new drugs on CoCSCs, paying special attention to those molecular mechanisms involved in chemo-resistance and metastasis.

Highlights in 2011

- We have described the capacity of PI3K/AKT and Wnt/beta-catenin signalling pathways cooperating to induce colon cancer metastasis.
- The identification of one of the first mechanisms of resistance to PI3K and AKT inhibitors currently tested in multiple clinical trials.
- We are showing the anti-tumoral capacity of new experimental drugs that specifically inhibit the Wnt/beta-catenin pathway.
- The identification of new populations of CoCSCs with enhanced drug-resistance.

Read more at www.vhio.net

SUMMARY

The main interest of our laboratory is to understand the molecular mechanisms that allow tumors to self-renew, resist therapy, relapse and metastasise - all of which represent definitive factors in patient survival. In particular, we study the consequences of intra-tumoral cell heterogeneity for tumor evolution and patient survival. Among the different cell populations that build an heterogeneous tumor, Cancer Stem Cells (CSCs) 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. CSCs can compose the small reservoir of drug-resistant cells that are responsible for relapse after chemotherapy-induced remission, or can give rise to distant metastasis. It is therefore becoming increasingly evident that cancer treatment that fails to eliminate cancer stem cells may allow re-growth of the tumor. Colorectal cancer is a disease of high social impact and the prime focus of our research activities. At the molecular level we are analyzing the role of those oncogenic pathways that control the fate of Colon Cancer Stem Cells (CoCSCs). 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.

Research developed over the last few years has recently led to the description of a new mechanism of resistance to PI3K and AKT inhibitory drugs conferred by beta-catenin in colorectal cancer. This discovery is of major clinical relevance since many patients in clinical trials are not responding to these drugs and previously there was no molecular explanation behind such resistance. These new findings will allow 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 deaths of patients.

Recently, new experimental data support the capacity of new Wnt/beta-catenin inhibitors to eliminate colon cancer cells in combination with other targeted therapies. This project is a paradigmatic example of close collaboration with clinical research and pharma as well as a successful model of translational research.

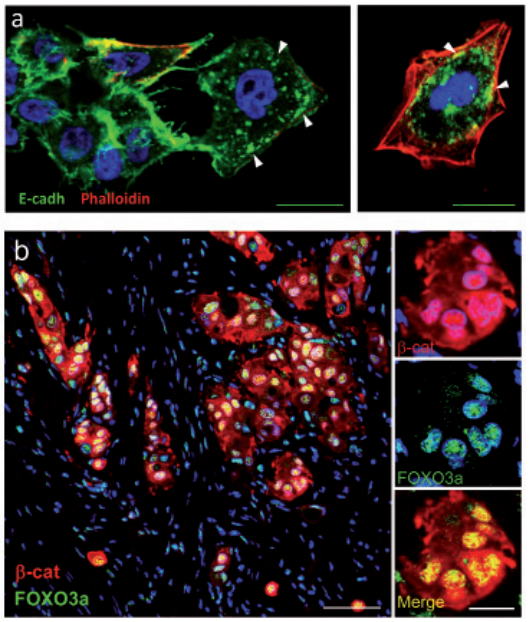


Figure: (a) Immunofluorescent images E-cadherin relocation in human colon cancer cells that acquire an invasive phenotype after concomitant activation of FOXO3a and beta-catenin protein expression. (b) Immunofluorecent staining of tumor cells accumulating nuclear FOXO3a and beta-catenin at the invasive front of a human colon carcinoma.

To find out more about us, our research, publications and even our group's horizons for 2012, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2011/

VHIO MULTIDISCIPLINARY RESEARCH PROGRAMS

CLINICAL RESEARCH

DIRECTOR, CLINICAL RESEARCH PROGRAM

Josep Tabernero

VHIO's Clinical Research Program, incorporating multidisciplinary cancer teams, is dedicated to developing both novel agents directed to specific signaling pathways in cancer and new/redefined tools to diagnose cancer earlier and better predict response to treatment. We are pioneering important studies involving both preclinical and early-drug development research studies, leading to several clinical trials designed to identify more effective cancer therapies tailored to individual patients. A hallmark of our program is the study of biomarkers that can distinguish between groups of patients who will respond to the designed therapy, and those unlikely to benefit (or worse, will respond negatively to the drug).

At the preclinical level, we are working with our other VHIO programs and groups to develop new 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 2011, these collaborations led to the development of new projects for the study of various different types of cancer: i.e. NSCLC (lung), pancreatic cancer, or metastasis in colorectal cancer (projects awarded with grants at national level). It has also resulted in tremendous cross-border collaboration, in which our internationally renowned groups (breast cancer and glioblastoma in particular) are in some cases the only non-American group participating in various consortia.

Given that each tumor has an independent genetic identity, we also participate in the development of molecular therapies targeting specific oncoproteins to obtain personalized therapies for patients displaying specific genetic lesions or deregulated signaling pathways (a partial list of oncoprotein targets includes among others EGFR, HER2, HER3, BRAF, MEK, PI3K, Akt, mTOR and IGF1-R.). We are also striving to identify new predictive markers of response to diverse treatments and markers of primary (de novo) and secondary resistance after treatment. To achieve this, we are analyzing the expression of receptors and intracellular effector proteins and the mutational status, as well as the copy number of oncogenes and established tumor suppressor genes (in tumor samples obtained prior to treatment and after resistance has built up).

Our work in collaboration with VHIO's Cancer Genomics Group is also very important. The molecular characterization of tumors facilitates 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.

We are also leading a program (with very encouraging preliminary results) devoted to the study of circulating biomarkers – the detection and genotyping of circulating free DNA (cfDNA). The goal of this project is to establish the role of plasma cfDNA as a predictor of response for anti-EGFR drugs and assess the prognostic value that quantitative and/or qualitative alterations in plasma cfDNA may have in metastatic patients.

In short, we are making dramatic progress in 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.

CLINICAL RESEARCH

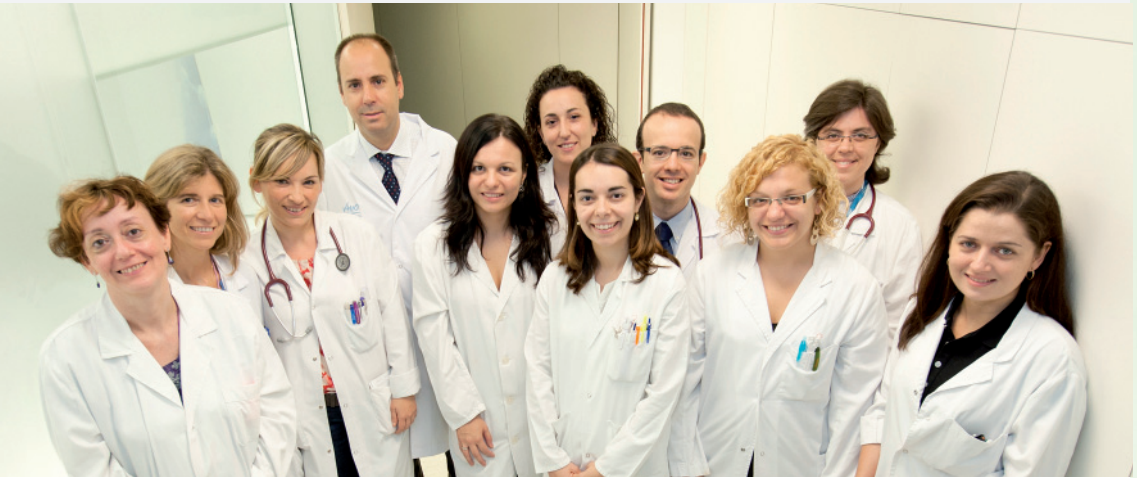
Breast Cancer & Melanoma Group

Principal Investigator

Javier Cortés

Medical Oncologists and Clinical Fellows

Judith Balmaña
Meritxell Bellet
Serena di Cosimo
Patricia Gómez
Leticia de Mattos
Eva Muñoz
Mafalda Oliveira
Vanesa Ortega
José Pérez
Cristina Saura
Mª Jesús Vidal



Strategic Goals

1. Optimizing treatment in those patients with HER2-positive tumors.
2. Leading clinical trials to reverse mechanisms of resistance to standard treatments.
3. Incorporate new drugs tested in early studies carried out by VHIO's Experimental Therapeutics Group (from phase I to more advanced studies) in our clinical trials.
4. Consolidate the implementation of personalized medicine using genetic tools.
5. Strengthen links yet further between our Group and VHIO's Experimental Therapeutics Group to provide "smarter" treatments to our patients as soon as possible.

Highlights in 2011

- Furthered insight into the mechanisms that render cells resistant to specific therapies, and then develop reversal strategies with special emphasis on HER2-overexpressing cells and the PI3k –AKT-mTOR signaling pathway.
- Research with new chemotherapy agents in patients with heavily-pretreated metastatic breast cancer.
- Developed new pharmacologic combinations that may increase efficacy against breast cancer.
- Explored different breast cancer tumors and identified specific molecular targets based on genetic profiling.

Read more at www.vhio.net

SUMMARY

Our breast cancer program has become one of the most active in Europe, both in terms of number of publications as well as participation in active projects. Main areas of interest include the continued development of new treatments and the search for mechanisms of resistance to current ones. The multidisciplinary collaboration and management with surgeons, pathologists, radiologists and radiotherapists, among others, makes it possible to incorporate the most innovative treatments in clinical practice and optimizes therapeutic alternatives. In clinical research four main areas of particular growth include:

1. Optimizing the treatment of patients with HER2-positive breast cancer, an especially aggressive tumor group.

2. Improving treatment of patients with highly advanced tumors by incorporating clinical studies with novel chemotherapy drugs that are not yet commercially available.

3. Application of new biological agents in order to reverse the mechanisms of resistance to classical drugs, both chemotherapy and hormone therapy.

4. The possibility of using drugs that have been tested in very early studies and that have shown sufficient activity to expand studies in patients with breast cancer.

Daily collaboration with the VHIO's Experimental Therapeutics Group makes our group pioneering not only in implementing new treatments but also in applying those which at least theoretically, prove the most active.

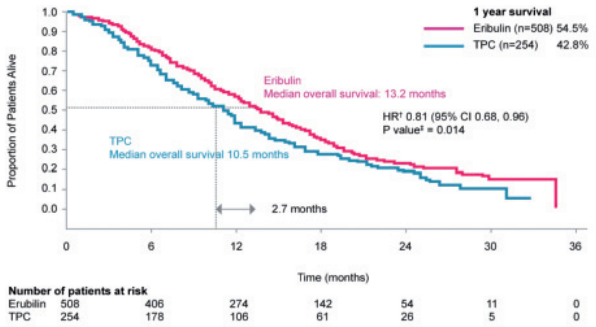


Figure: Eribulin is an synthetic analog of halichondrin B, a natural product found in marine sponges. When compared with the best physician's choice, eribulin improved overall survival in heavily pretreated patients with metastatic breast cancer (Cortes J, et al. Lancet 2011).

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CLINICAL RESEARCH

Early Clinical Drug Development Group and the Research Unit for Molecular Therapy of Cancer UITM - "la Caixa"

Director of Clinical Research at VHIO
Josep Tabernero

Principal Investigator, Early Clinical Drug Development Group

Medical Coordinator, UITM
Jordi Rodón

Head of Clinical Trials Office
Gemma Sala

Clinical Research Fellows
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Analía B. Azaro
Cristina Cruz
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Associated Investigators
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Joan Carles
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Investigators
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Judith Balmaña
Jaume Capdevila
Maria Elena Élez
Patricia Gómez
Teresa Macarulla
Pablo Martínez
Leticia de Mattos
Eva Muñoz
Mafalda Oliveira
Jose Manuel Pérez
Cristina Saura
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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

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 UITM facility 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 2011

- We have rapidly become one of the leading institutes worldwide with the most expertise in several areas of drug development such as PI3K/akt/mTOR inhibitors, FGFR inhibitors or drugs targeting developmental pathways such as TGFbeta, SHH, WNT, and NOTCH.
- We have performed several clinical trials with novel-novel combinations - combining several PI3K inhibitors with MEK inhibitors, IGF1R inhibitor with mTOR inhibitor, and NOTCH inhibitor with mTOR inhibitor.
- We have performed 17 clinical trials with patients selected based 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 prolactin receptor).
- We have co-developed several molecular tests for patient screening such as disease-oriented mutation panels for Sequenom.
- We have performed some of the most complex phase I trials, including those focused on rare 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.

Read more at www.vhio.net

SUMMARY

Early Clinical Drug Development Group

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 in mechanisms of resistance) for selected projects.

In addition, we have collaborated with VHIO's Molecular Pathology Group 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 personalized medicine.

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

Obra Social "la Caixa"

Inaugurated in June 2010 as a new facility - 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.

The UITM team is composed of Oncologists, Clinical Trial Coordinators and Data Managers, Nurses and Nurse Technicians, Pharmacists, as well as administrative personnel. With regards to both patient treatment and care as well as the research carried out at UITM, we collaborate with many other oncology professionals including Pathologists from the Vall d'Hebron Hospital's Molecular Pathology Department, Radiologists and Interventional Radiologists, as well as the Clinical Trials Office, Database Management as well as many other specialists (Dermatologists, Cardiologists, Ophthalmologists).

For more information about our Clinical Trials Office, Clinical Research Oncology Nurses and Oncology Pharmacy Unit, please see pages 72 - 80.

To find out more about us, our research, publications and even our group's horizons for 2012, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2011/

CLINICAL RESEARCH

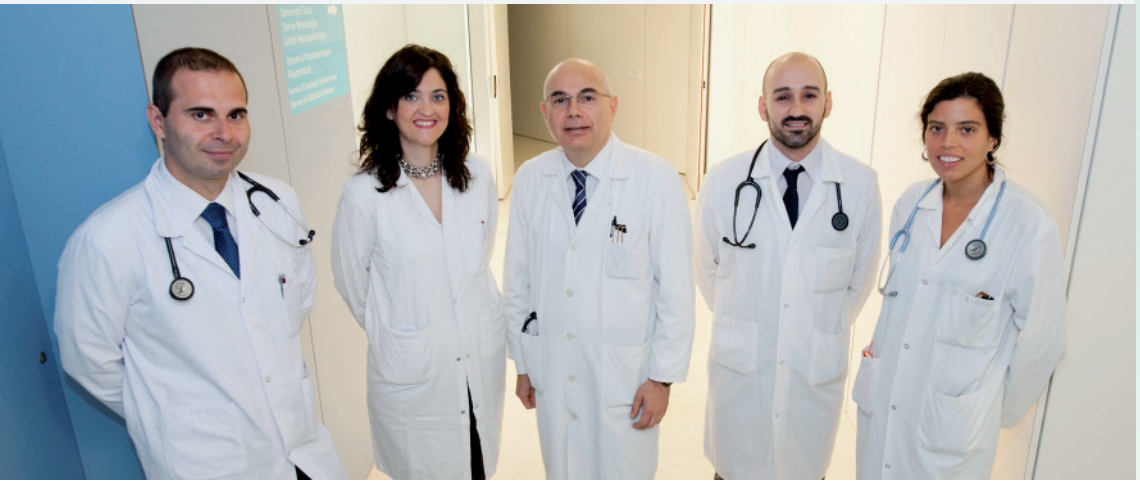
Gastrointestinal & Endocrine Tumors Group

Principal Investigator

Josep Tabernero

Medical Oncologists and Clinical Fellows

Maria Alsina
Guillem Argilés
Irene Braña
Jaume Capdevila
Maria Elena Élez
Mª Rosa Gallego
Teresa Macarulla



Strategic Goals

1. Clinical research in late stage with more translational endpoints, focusing on the identification of prognostic/predictive biomarkers.
2. Early clinical research with innovative targets.
3. Collaboration with international groups for translational research within the scope of the 7th European Commission Framework Programme as well as other contexts.
4. Collaboration with other VHIO groups including Proteomics, Genomics, and Stem Cells & Cancer.

Highlights in 2011

- Collaboration with several international research groups of excellence as well as participation in FP7 supported projects.
- 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 several investigator-initiated clinical trials as well as participation in many 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).

Read more at www.vhio.net

SUMMARY

In 2011, we carried out basic research in collaboration with VHIO's Stem Cells & Cancer Group led by Héctor G. Palmer as well as international research groups at the Weizman Institute, Rehovot (Israel), Broad Institute, Cambridge, MA (USA), University of Michigan, Ann Arbor, MI (USA), and the University Hospital Gasthuisberg, Leuven, (Belgium). We have provided the rationale for several research studies, collecting clinical samples for validation of experimental endpoints as well as the discussion and manuscripts for these studies. We are also collaborating with several international institutions on projects funded by the European Commission's 7th Framework Programme of Research & Development.

- Early Clinical Research: we have a strong interest in drug development and phase I clinical trials in solid tumors, especially focusing on the development of molecular targeted therapies with special emphasis on defining the optimal biological dose using pharmacokinetic/pharmacodynamic (*PK*;*PD*) modeling endpoints and the characterization of molecular biomarkers of clinical efficacy in the context of the phase I clinical trials.

- Molecular Markers in Gastrointestinal Malignancies: the overarching objective of this research project is to further insight into prognostic and predictive factors for response and efficacy with targeted agents in the different gastrointestinal malignancies. In this regard, our research has contributed to narrowing the targeted population of patients by identifying mechanisms of resistance (either primary or secondary) and thereby increasing the cost-efficacy ratio.

- Clinical research: Our patients are enrolled in clinical trials devoted to gastrointestinal-specific malignancies such as colorectal, gastric, pancreatic and esophageal cancer as well as endocrine tumors to demonstrate improved treatment of these diseases (the majority are phase II and phase III clinical trials). We have designed several investigator-initiated clinical trials aimed at responding to important, remaining questions. We have participated in - and contributed to - the design of many clinical trials, several of which have been developed in the context of national and international cooperative groups, and others sponsored directly by pharmaceutical companies. Our group has pioneered the consecution of clinical trials that have led to the approval of targeted drugs by the European Medicines Agency (EMA). The most renowned are cetuximab and panitumumab in colorectal cancer for the particular population of KRAS-wild type tumors and trastuzumab in gastric and gastroesophageal cancer with *HER*-2/neu overexpression.

To find out more about us, our research, publications and even our group's horizons for 2012, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2011/

CLINICAL RESEARCH

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

Principal Investigator

Joan Carles

Medical Oncologists and Clinical Fellows

Rafael Morales
Isaac Núñez
Jordi Rodón
Cesar Serrano
Cristina Suarez
Claudia Valverde

Strategic Goals

1. Design and development of clinical trials for all the malignancies covered by our group. Providing our patients with 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. Expand our translational research for glioblastoma in collaboration with VHIO's Gene Expression and Cancer Group.
4. 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 2011

- New drugs in GU malignancies: we have participated in the most important trials with different drugs that, throughout 2010/2011, have shown that they will change the prognosis of patients with prostate cancer including: Abiraterone acetate, MDV 3100, Cabazitaxel or Radium 223, and other novel immunotherapy drugs (Ipilimumab) that may also 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.
- Our research in CNS tumours has been consolidated with the development of new clinical trials and the creation of an expert panel comprised of experts in neurosurgery, radiology, radiotherapy, translational research and medical oncology.

Read more at www.vhio.net

SUMMARY

Our group is interested in both clinical and translational research. We have 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), and the Biomedical Research Institute of Bellvitge (IDIBELL), Barcelona (Spain). Results from this collaboration will be presented at the First Cleveland Vall d'Hebron Meeting in renal cell carcinoma taking place in July next year.

Another key area is the development of several multidisciplinary clinical trials in CNS tumors and the close collaboration with neurosurgery, radiation therapy, as well as the consolidation of a translational research platform for glioblastoma in collaboration with VHIO's Gene Expression and 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 a European Commission 7th Framework Programme of Research and Development grant.

We are also working with the Spanish Sarcoma Group (GEIS) in order to conduct clinical trials at different stages of the disease with emphasis on a histology-tailored design, and are currently involved in setting up a translational platform for sarcomas and basic research in partnership with the Biomedical Research Institute of Bellvitge (IDIBELL) and the Cancer Research Center of Salamanca (CIC).

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 2012, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2011/

CLINICAL RESEARCH

Head and Neck & Gynecological Tumors Group

Principal Investigator

Josep Maria del Campo

Medical Oncologists

Isabela Díaz de Corcuera
Ana Oaknin
Víctor Rodríguez Freixinós

Strategic Goals

1. Our main focus is clinical research. We are therefore active members of some of the most important cooperative groups in both Head and Neck and Gynecological Tumors, with contacts in the pharmaceutical industry. Such collaboration allows us to participate in the development of new drugs and also in Phase III clinical trials that are expected to change the standard of care of these pathologies.
2. To keep fully updated on the most interesting clinical research within the field with a view to increasing our participation in key projects as well as maintaining our established leadership within our field.

Highlights in 2011

- In 2011 we have achieved two important goals. We have joined the Gynecologic Oncology Group (GOG) - a non-profit organization promoting excellence in the quality and integrity of clinical and basic scientific research in the field of Gynecologic malignancies, as Co- Investigators in a cervical cancer trial. The GOG is the most important cooperative group worldwide in gynecological research. Secondly, as Principal Investigators, we have led a Phase III clinical trial that will run in many European gynecologic cooperative groups.

Read more at www.vhio.net

SUMMARY

Our group focuses on state-of-the-art patient care as well as clinical research with particular emphasis on the research and development of new molecules.

We have actively participated in the development of guidelines for patient care as well as served on tumor Boards at the Vall d'Hebron University Hospital; such collaboration has led to an annual increase in the number of patients that we follow-up.

Concerning our clinical activity we place great importance on our weekly meetings dealing with head and neck and gynecological tumors since these interdisciplinary meetings result in the establishment of diverse protocols and clinical guidelines.

Our multidisciplinary committees incorporate other specialties such as surgeons, radiotherapists, pathologists and radiologists which is critical for improved patient diagnosis, treatment and follow-up as well as to promote and collaborate in trials. Such collaboration results in a constantly increasing number of patients (20% yearly) for standard treatments as well as clinical trials. We are currently involved in more than fifteen ongoing trials as Principal Investigators.

Our group has also participated as main investigators or collaborators with several other departments from the Vall d'Hebron University Hospital as well as other Spanish and international groups. Various departments including maxillofacial, oral, gynecological and pathology teams actively collaborate with us for several of our projects. We have also actively participated in international conferences, given several presentations, and published key findings (see section 'Publications, Projects & Awards' of our Scientific Report 2011 online at: http://memorias.vhio.net/2011/.)

To find out more about us, our research, publications and even our group's horizons for 2012, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2011/

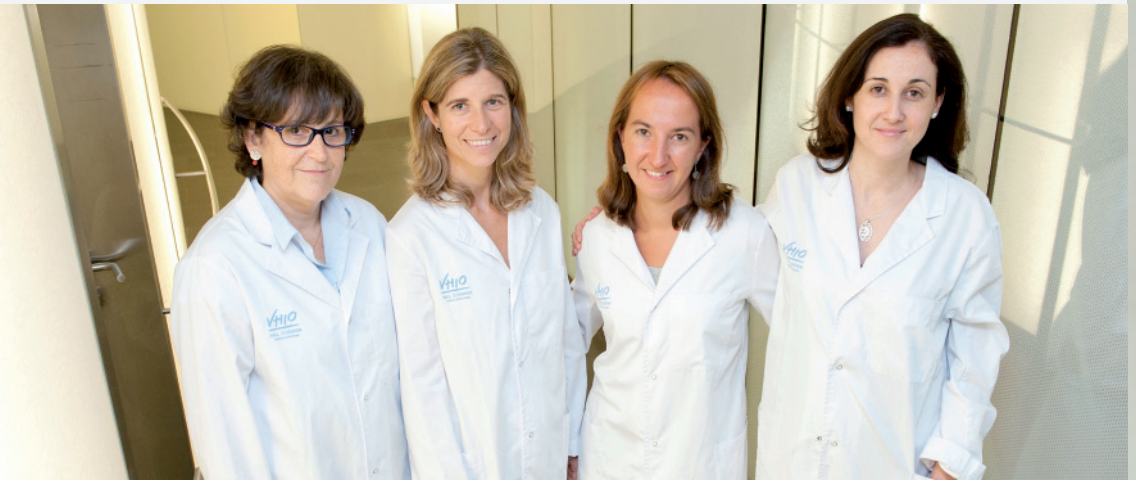
CLINICAL RESEARCH

High Risk & Cancer Prevention Group

Principal Investigator
Judith Balmaña

Clinical Nurse Specialist
Neus Gadea

Staff Scientists
Nina Bosch
Begoña Graña



Strategic Goals

1. Clinical development of specific therapeutic strategies for tumors associated with hereditary genetic alterations.
2. Analysis of the clinical impact of genetic testing in hereditary breast cancer.
3. Early detection of prostate cancer in 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 2011

- Participation in international clinical trials with PARP inhibitors for BRCA-associated tumors.
- Participation 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.

Read more at www.vhio.net

SUMMARY

We are committed to developing specific new targeted therapies for patients with hereditary cancer, as well as patients with triple negative breast cancer. In this context we are participating in several phase I-II clinical trials with PARP inhibitors in patients with early and advanced breast and ovarian cancer.

As the clinical impact of genetic testing might differ among countries and be related 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 that assessed the psychological well-being of individuals undergoing *BRCA* genetic testing ("IMASS Project": PI05/1491 with the title "Impacto clínico del asesoramiento y estudio genético en síndromes de predisposición hereditaria al cancer", PI Judith Balmaña). In this field, we recently finalized our analysis surrounding psychological well being post-BRCA testing in our setting.

We maintain our active collaboration in the international study IMPACT (Identification of Men with a genetic predisposition to ProstAte Cancer : Targeted Screening in *BRCA*1/2 mutation carriers and controls, MREC 05/MRE07/25, Chief Investigator: Dr. Rosalind Eeles MA; PhD;FRCR.FRCP) to analyze the efficacy of early detection of prostate cancer in patients with a mutation in the *BRCA*1/2 genes and we participated in a national study funded by FIS (Project title: "Densidad mamográfica, susceptibilidad genética y cáncer de mama en mujeres de alto riesgo (Proyecto DM-BRCA)", PS09/01024) with the aim of determining the role of breast density as a risk factor for breast cancer in women with mutations in the *BRCA*1/2 genes. We also participated in delineating the clinical features and molecular phenotype of breast cancer associated to germline p53 mutations as part of an international consortium.

In the field of genetic epidemiology, we have initiated next generation studies to search for mutations in new genes conferring predisposition to familial cancer and hereditary breast cancer.

We are participating 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: Sapna Syngal) to validate the PREMM1,2,6 predictive model for identification of Lynch syndrome in population and clinical-based cohorts.

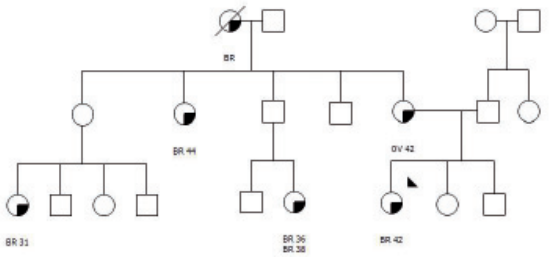


Figure: Graph depicting family with hereditary breast and ovarian cancer.

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CLINICAL RESEARCH

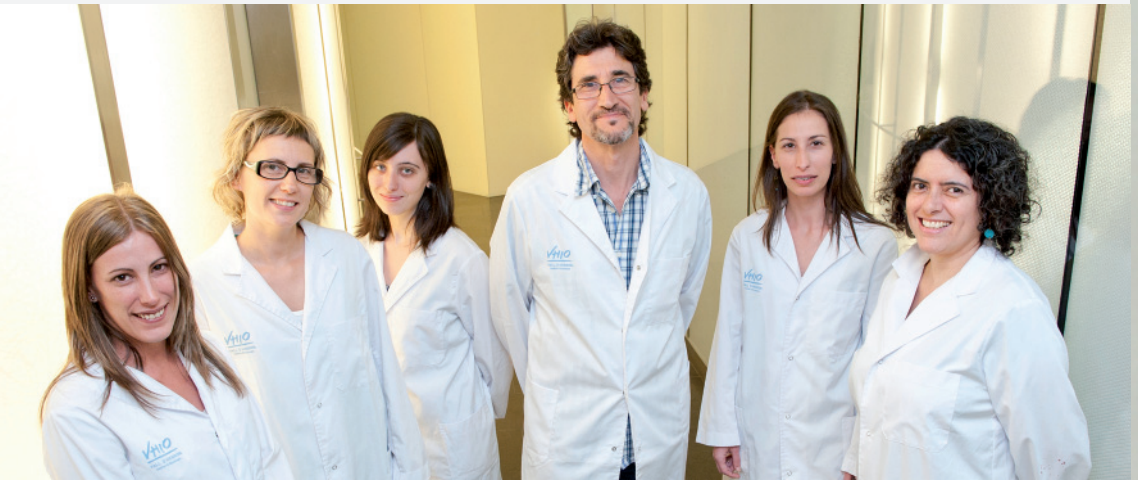
Oncogenetics Group

Principal Investigator
Orland Díez

Technicians
Miriam Masas
Anna Tenés

Graduate Student
Gemma Montalbán

Staff Scientists
Sandra Bonache
Sara Gutiérrez



Strategic Goals

1. Molecular analysis of germ line *BRCA1*, *BRCA2*, and *TP53* mutations in cancer families, and characterization of variants with unknown biological significance or potential transcriptional effects.
2. Analysis of the role of other genes (*RAD51C*, *RAD51D*, *ATM*, *PALB2*) in familiar breast cancer predisposition.
3. Next generation sequencing approaches to discover novel cancer susceptibility genes.
4. Identification of genes for susceptibility to radiotherapy side-effects.

Highlights in 2011

- Characterization of large rearrangements and transcriptional effects of variants with unknown biological significance in breast cancer predisposition genes.
- Identification of variants of *RAD51C* and *ATM* genes.
- Epidemiological analysis of *BRCA1* and *BRCA2* mutations in Spanish breast/ovarian cancer families.
- Study of transcriptional profiles and apoptosis in breast cancer patients after radiotherapy.

Read more at www.vhio.net

SUMMARY

Over the last five years our group has developed its research activity along to two main lines: genetic predisposition to hereditary breast/ovarian cancer, and genetic predisposition to radiotherapy-induced toxicity.

Inherited predisposition to breast and ovarian cancer is caused in part by mutations in the *BRCA1* and *BRCA2* genes, but only about one third of families with a strong family history of breast cancer carry mutations in these genes. One main research line is to search for other genes which might predispose to these types of cancer, testing high-risk families to identify high/moderate penetrance genes.

In particular, we are investigating *ATM*, *RAD51C*, *RAD51D*, and *PALB2*, whose products interact with *BRCA1/2* proteins. To investigate mutation negative families and individuals further, we are also developing a project based on the use of next generation sequencing technologies.

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 case-control studies to identify low-penetrance genes 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.

Regarding genetic predisposition to radiotherapy-induced toxicity, we are investigating DNA repair capacity of cells with *BRCA1* or *BRCA2* mutations, and putative genetic and cellular markers for radiotherapy toxicity (SNPs, apoptosis, transcriptional profiles).

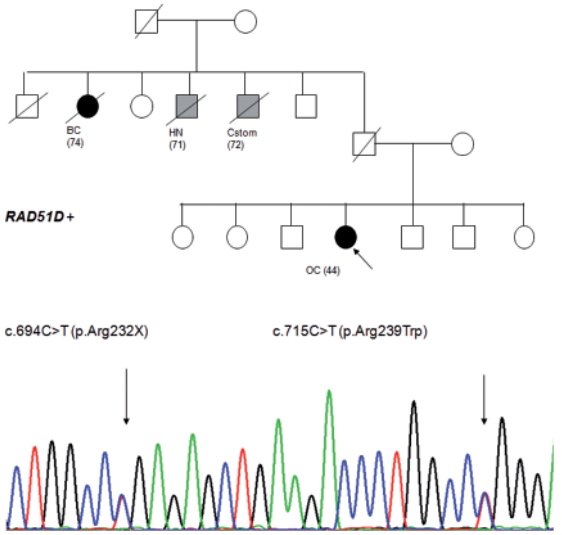


Figure: Mutations in breast/ovarian cancer susceptibility genes.

To find out more about us, our research, publications and even our group's horizons for 2012, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2011/

CLINICAL RESEARCH

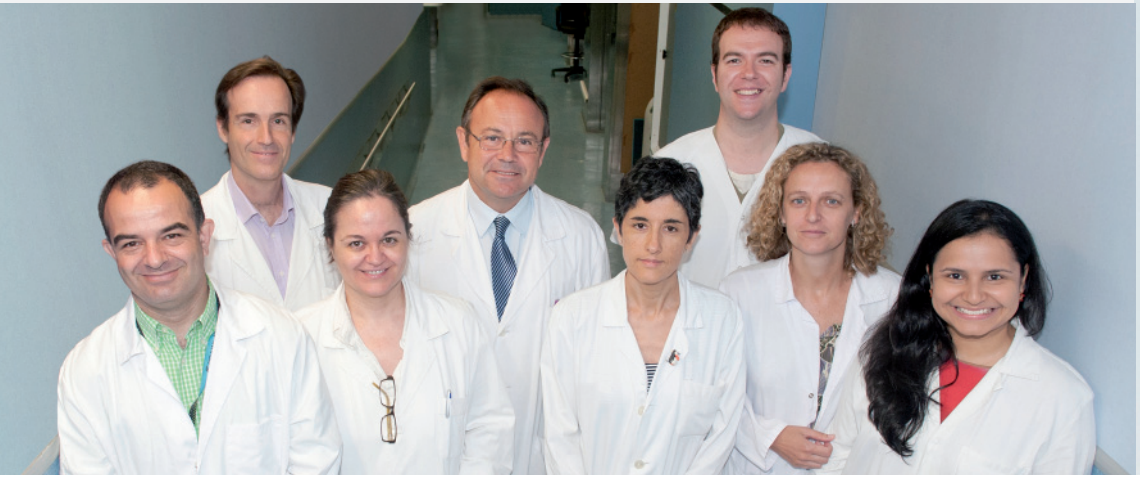
Radiation Oncology Group

Principal Investigator

Jordi Giralt

Radiation Oncologists

Sergi Benavente
Ramón Bodi
Xavier Maldonado
Meritxell Molla
Begoña Navaltropo
Mónica Ramos
Victoria Reyes
Ramona Verges



Strategic Goals

1. Technological development: the acquisition of new equipment to implement the most modern treatment techniques clinically such as rotational radiotherapy - Intensity Modulated Arc Therapy (IMAT) radiotherapy and adaptive Image-Guided Radiotherapy (IGRT).
2. Translational research: the application of biological knowledge of both cancerous and healthy tissue in order to tailor treatment to the characteristics of each patient and each tumor.

Highlights in 2011

- Intensity modulation radiotherapy (IMRT): we are currently dealing with IMRT patients who require dose escalation for prostate tumors, head and neck or re-irradiation, and patients who clearly benefit from dose reduction in healthy tissue such as patients with breast cancer, pediatric tumors, digestive and gynecological tumors. This year we have treated 202 patients and will continue to increase the number of patients treated with this technique.
- Radiosurgery and Fractionated Sterotactic Radiotherapy: this year we have treated 81 patients, a number which is gradually rising. We are progressing more innovative treatments for retinoblastoma or postoperative radiosurgery in single metastases.

Read more at www.vhio.net

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 important clinical trials, translational research projects, as well as technology development programs.

Childhood cancers are highly complex and require a specialized approach. Pediatric radiotherapy treatments are therefore performed in specialized centers. The Radiation Oncology Department at the Vall d'Hebron University Hospital is a reference center for radiotherapy treatment of pediatric patients in Spain. Treating more than 60 children each year, we have all the infrastructure to make such specialised treatment possible as well as the expertise and resources to participate in international clincial trials.

To find out more about us, our research, publications and even our group's horizons for 2012, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2011/

Treatment Planning

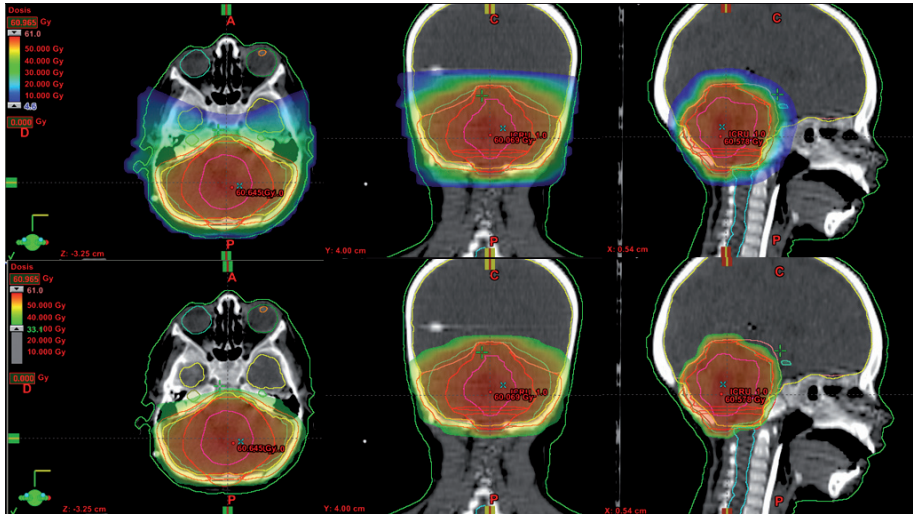


Figure: Dose distribution with IMRT and Boost-integrated technique in a child with medulloblastoma. This technique allows us to protect the cochlea and thus prevent deafness.

CLINICAL RESEARCH

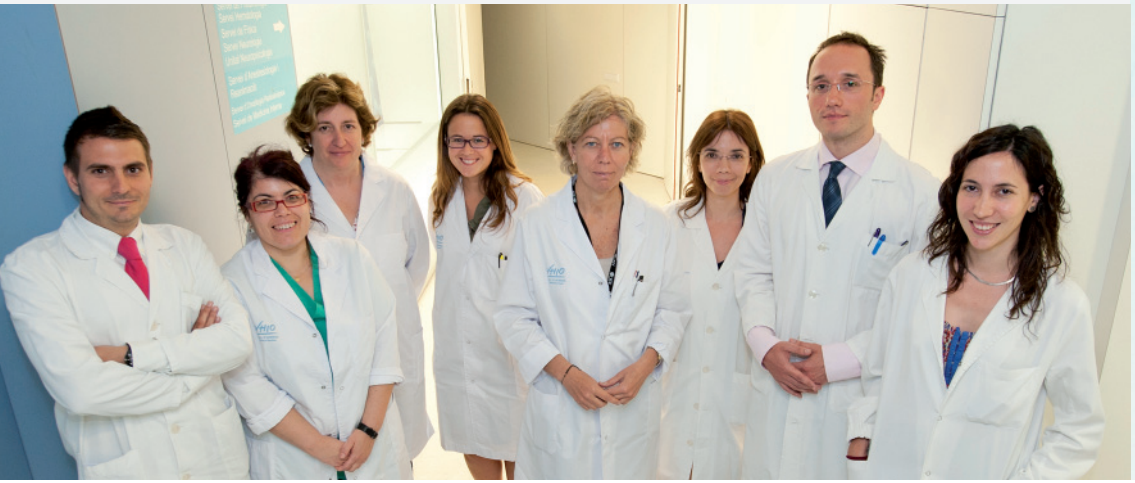
Thoracic Tumors Group

Principal Investigator

Enriqueta Felip

Medical Oncologists

Susana Cedrés
Alex Martínez
Pablo Martínez



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 2011

- Translational research achievements in lung cancer (ALK, ERBB2 and ERBB3 determinations, prognostic and predictive value) and in mesothelioma (PI3K pathway determinations). Presentations at the Annual Meeting of the American Society of Clinical Oncology (ASCO), June 3 - 7, 2011, Chicago, and at the IASLC meeting (Amsterdam 2011) related to these research areas.
- International presence, invited speaker (discussant) at the 2011 Annual Meeting of the American Society of Clinical Oncology, Chicago, the 14th World Conference on Lung Cancer (International Association for the Study of Lung Cancer - IASLC), Amsterdam 2011, the ECCO 16 - ESMO 36 - ESTRO 30 European Multidisciplinary Cancer Congress, Stockholm 2011, among others.
- Collaboration with a European multidisciplinary research group (European Thoracic Oncology Platform, ETOP).
- Publication of the ESMO Consensus Conference in Lung Cancer conclusions (Lugano, 2010).
- Grant obtained for pharmacogenomic determinations in lung cancer patients.

Read more at www.vhio.net

SUMMARY

The main activity of the Thoracic Cancer 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 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 collaborate 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.

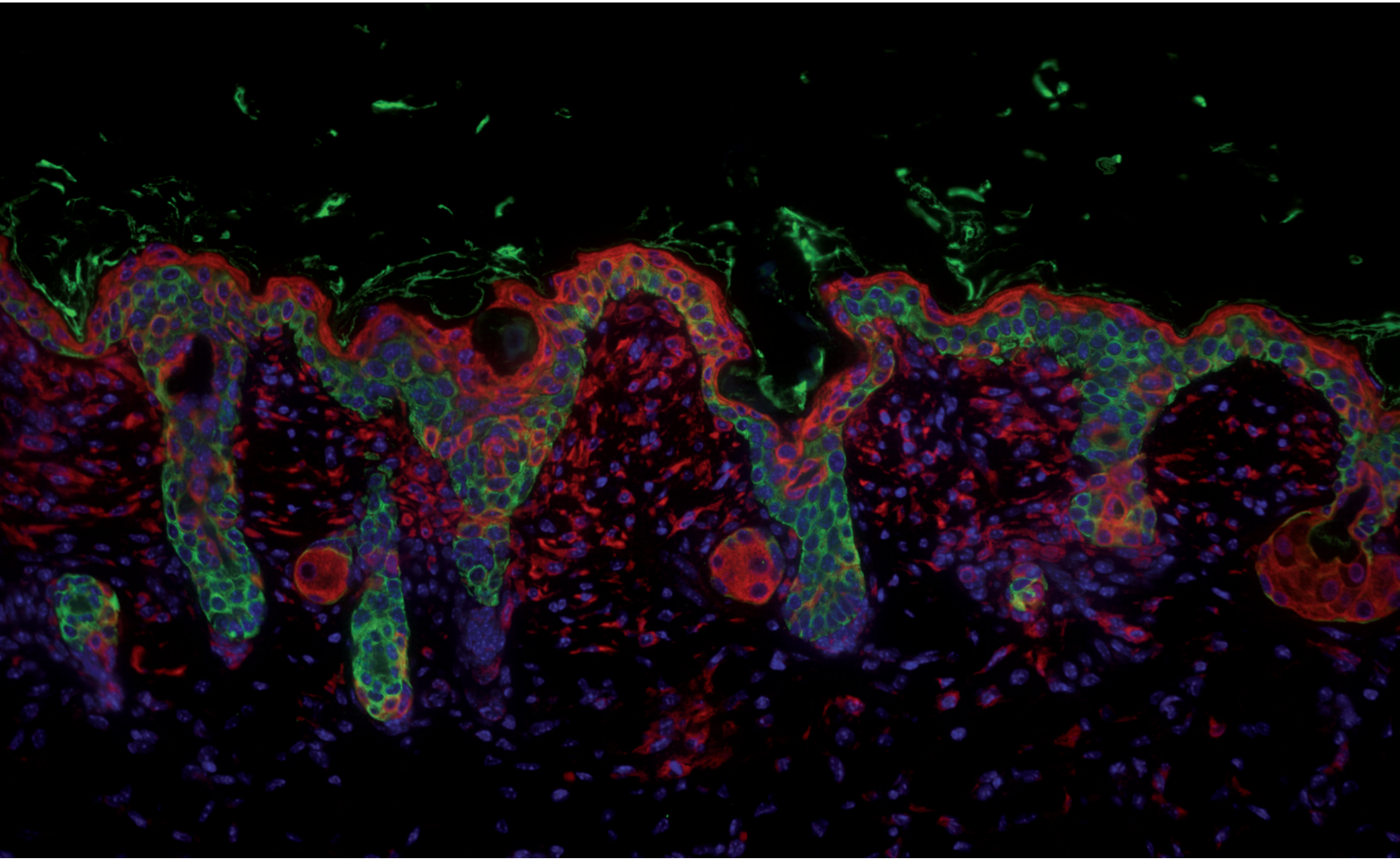
We are also contributing to the program of early drug development, and also deal with other less common thoracic malignancies such as small-cell lung cancer, mesotheliomas, thymomas, and neuroendocrine tumors.

To find out more about us, our research, publications and even our group's horizons for 2012, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2011/

CORE TECHNOLOGIES

VHIO's Molecular Pathology Service, its Cancer Genomics Group headed by Ana Vivancos and Proteomics Group led by Francesc Canals, function as key research groups pursuing, implementing and developing independent research projects.

Reporting directly to VHIO's Scientific Director, they are also responsible for developing VHIO's core technologies. All these activities belong to VHIO's Core Technologies Program with Josep Tabernero, Director of Clinical Research, Joan Seoane, Director of Translational Research, and Joaquín Arribas, Director of Preclinical Research, acting in a scientific advisory capacity in Molecular Pathology, Cancer Genomics, and Proteomics respectively.



PROTEOMICS GROUP

Joaquín Arribas

Director, Preclinical Research Program

It is becoming increasingly clear that the current classification of cancer subtypes, based on the determination of the few currently available biomarkers, is insufficient to best select therapy against individual tumors. The future identification and validation of novel biomarkers will result in improved tumor classification and, therefore, better treatment. In addition, useful biomarkers should enable the monitoring of disease progression, regression or recurrence, as well as the assessment of response to therapy.

Over the last decade, this area of research has advanced dramatically in part due to the unprecedented development of novel proteomic technologies. Querying biomarkers in both very small cancer samples as well as surrogate samples including blood, cerebrospinal fluid or expectorations, is now a reality.

VHIO's Proteomics Group headed by Francesc Canals, a leader in the field, is equipped with state-of-the-art proteomic technology. In collaboration with other groups at Vall d'Hebron, his group has made important contributions during 2011 including the discovery of novel regulatory mechanisms of the TGF-beta and the RAS pathways and the validation of a biomarker signature to select the patients most likely to respond to inhibitors of the TGF-beta pathway. Undoubtedly, the Proteomics Group, along with our Molecular Pathology Group, enable VHIO to drive cutting edge discovery in the cancer biomarker field.

CANCER GENOMICS GROUP

Joan Seoane

Director, Translational Research Program

Recent advancements in sequencing technologies have led to a whole new world in terms of our understanding of cancer, shedding much light on the complexities of this multifaceted disease. Due to the thorough and in-depth analysis of the cancer genome, we are beginning to 'take down the enemy' by identifying its weaknesses little by little. Seminal discoveries have unmasked genetic abnormalities associated with cancer, facilitating the development of new molecular, targeted therapies that can interfere and revert tumor initiation and progression. While this is just the tip of the iceberg, we can rightfully expect a tremendous influx of knowledge over the coming years, set to definitively impact and advance cancer treatment and care.

VHIO's Cancer Genomics Group develops technology for the molecular characterization of tumors allowing patient stratification for the rational exploration of targeted cancer therapeutics. Moreover, the exhaustive study of cancer genomes is permitting us to better understand the biology of cancer as well as facilitating the discovery of novel mutations to be considered as therapeutic targets and markers to determine sensitivity or resistance to pharmacological compounds.

The Cancer Genomics Group is uniquely positioned to deliver personalized treatment since VHIO is leading a large number of early clinical studies with molecular targeted agents, with direct access to our patients' tumors.

MOLECULAR PATHOLOGY GROUP

Josep Tabernero

Director, Clinical Research Program

The Molecular Pathology 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 Pathology Group represents a critical element at the core of all its activities. It participates in research projects involving the use of human tissues collected from patients including tissue banking and development of primary xenograft models. The group designs, implements, and evaluates novel biomarker strategies to enable more efficient targeted therapy approaches and also runs numerous assays in clinical trials for real-time patient inclusion as well as pharmacodynamic monitoring and dose-finding.

In addition to its independent research, the group provides high-quality histopathology services to internal investigators and, externally, it serves as central and local laboratory in multiple clinical trials and international projects.

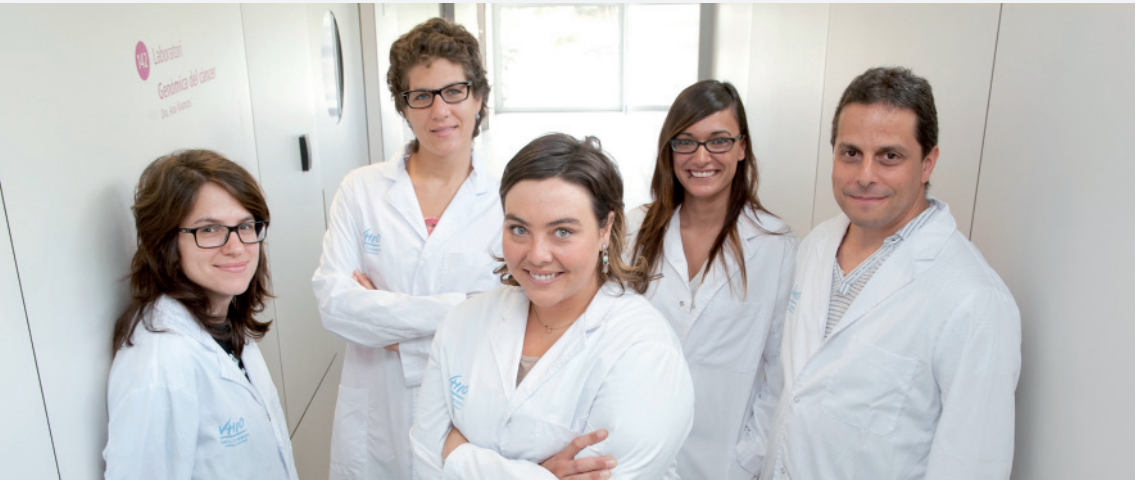
CORE TECHNOLOGIES

Cancer Genomics Group

Principal Investigator
Ana Vivancos

Bioinformatic
Daniel Silberschmidt

Technicians
Ginevra Caratù
Leire Mendizabal



Strategic Goals

1. Provide cutting-edge applications in cancer genomics through new technologies and protocol development. This will benefit basic research projects since new and more complex biological issues will be tackled and eventually solved.
2. Improved decision-making regarding targeted therapies through the genomic characterization of patient's tumors.
3. Implementation of non-invasive methods for genotyping somatic mutations in patients, such as circulating-free DNA.

Highlights in 2011

- Design and implementation of panels to detect somatic mutations using MassARRAY technology.
- Established protocols that allow efficient and robust exome capture from FFPE-derived DNA.
- Use of cfDNA to detect somatic mutations in patients.

Read more at www.vhio.net

SUMMARY

The Cancer Genomics is a Core Technology and translational laboratory, bridging basic and clinical cancer research.

We provide services to basic 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 a NextGen sequencer (HiSeq2000, Illumina).

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 may benefit from including patients with specific molecular or genetic alterations.

Our group is 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, and the use of non-invasive approaches to profile somatic mutations in collaboration with both basic and clinical researchers in several tumor types.

Protocol development and improvement in Next-Gen Sequencing is an active area of research in the lab as well as development of new assays to test mutations with iPlex chemistry (MassARRAY, Sequenom). 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.

MassARRAY (Sequenom)

HiSeq2000 (Illumina)

Figure: Technologies at our Cancer Genomics Core Lab, MassARRAY (Sequenom) MALDI-TOF MS and HiSeq2000 (Illumina) 2nd generation sequencer.

To find out more about us, our research, publications and even our group's horizons for 2012, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2011/

CORE TECHNOLOGIES

Molecular Pathology Group

Attending Physicians
Claudia Aura
Ludmila Prudkin

Laboratory Supervisor
Jose Jiménez

Laboratory Assistant
Mª Ángeles Díaz

Technicians
Elisabeth Llonch
Sandra Paola Mancilla
Paola Martínez
Nerea Peiró
Sonia Rodríguez
Gertrudis Sánchez

Administration
Mª Alejandra Iglesias

Strategic Goals

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

Highlights in 2011

- Ran a paraffin block archive with over 30,000 tumors and other relevant pathological specimens, as well as a tumor bank with over 6,600 high quality frozen samples.
- Participated in 85 clinical trials, acting as central laboratory in many of them.
- Performed over 7000 stainings, and sample material belonging to more than 400 patients have been included in either clinical trials or examined in a pre-screening setting.
- Explored HER family pathways in depth as well as many downstream targets including PI3K-Akt, mTOR, FGFR1 and 2, HGF-cMET pathways, among others.
- Evaluated pathway inhibition and downstream target behavior using preclinical models, and/or resistance, in the quest for biomarkers that anticipate prognosis or drug-response.
- Furthered our experience in using the Veridex's platform Cell SearchTM.
- Explored alternative ways to isolate and characterize circulating tumor cells.
- Nucleic acid extraction (DNA and RNA) in over 120 patient samples.

Read more at www.vhio.net

SUMMARY

The Molecular Pathology Group translates findings from basic research to the clinic. As pathologists, we collaborate closely with both basic researchers and oncologists in order to extract as much information as possible from tissue samples. Such knowledge ultimately serves to better guide clinicians' decision making in the clinic to directly benefit patients.

Our group is physically located within the Pathology Department of the Vall d'Hebron University Hospital, with access to a magnificent paraffin block archive with over 30,000 tumors and other relevant pathological specimens, as well as a tumor bank with over 6,600 high quality frozen samples routinely used for mRNA and protein studies.

During 2011 we have participated in 85 clinical trials, acting as central laboratory for many. Routinely, we perform immunohistochemistry studies with antibodies used as diagnostic markers (proliferation, angiogenesis, oncogenes, lack of suppressor genes, mutated genes) as well as characterize new therapeutical targets for the development of new specific inhibitors (more than 100 optimized antibodies).

This year we have performed over 7,000 stainings and sample material belonging to more than 400 patients has been included in either clinical trials or examined in a pre-screening setting. We also perform multiple-target immnuofluorescence, fluorescence in-situ hybridization for many key genes, tissue micro-array constructions, image analysis, nucleic acid extraction and quantification, and gene sequencing. Our work has been essential in translating findings from the laboratory bench to clinical trials.

We have explored HER2 pathways in depth as well as many downstream targets, including PI3K-Akt, mTOR, FGFR 1 and 2, HGF-c-MET pathways, among others. Using preclinical animal models we evaluated pathway inhibition and downstream target behavior, and/or resistance, in the quest for biomarkers that anticipate prognosis or response to treatment. These models serve as the ideal resource to identify such biomarkers in order to use them in further clinical trials.

In 2011 we have also gained further experience using the Veridex's platform Cell SearchTM that allows the detection and characterization of circulating tumor cells from patients' blood samples. This innovative technology should help to follow up on treatment and identify patients with a high risk of recurrence.

We have also explored other methods to isolate circulating tumor cells using filters specifically designed for this purpose that can detect these cells in the cellular size. Using this method we have been able to isolate cells that can later be characterized immunohistochemically as well as genetically.

As part of our role as a central laboratory, we have also successfully extracted DNA and RNA material from tumor samples from more than 120 patients using trizol and commercial kits.

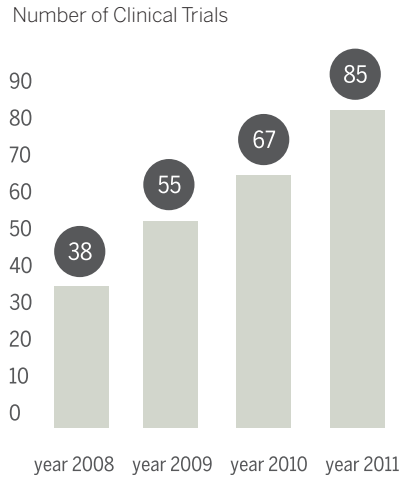


Figure: VHIO's Molecular Pathology Group's involvement in clinical trials - annual evolution.

To find out more about us, our research, publications and even our group's horizons for 2012, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2011/

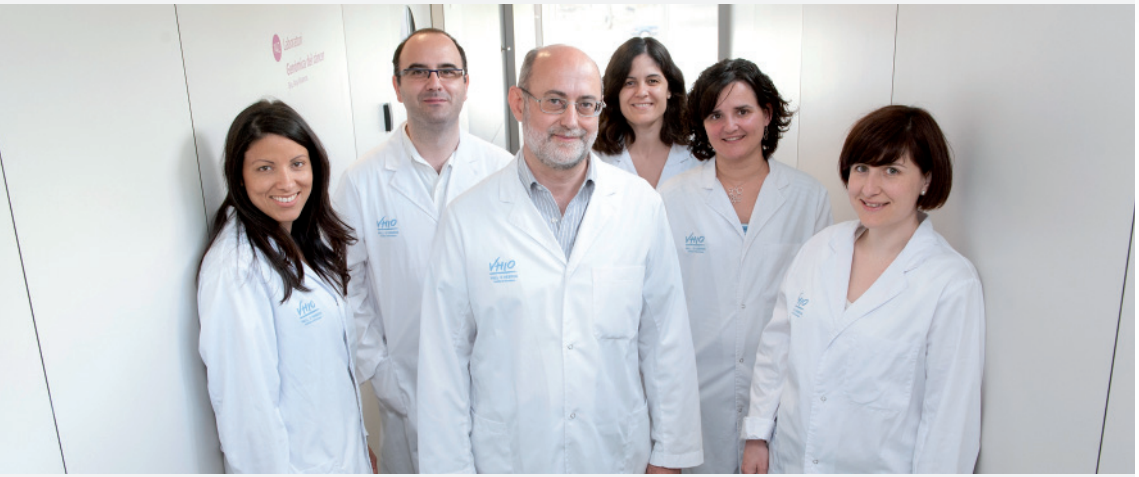
CORE TECHNOLOGIES

Proteomics Group

Principal Investigator
Francesc Canals

Post-Doctoral Fellows
Joan Josep Bech
Marta Monge
Gemma Reverter

Technicians
Núria Colomé
Carolina de la Torre



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 2011

- Proteomics services to VHIO and Vall d'Hebron Hospital groups, Instituto Salud Carlos III Cancer Research and ProteoRed networks.
- Discovery of a new regulatory mechanism of TGFbeta pathway involving the action of ADAM17 protease on the protein vasorin, with a potential role in tumor metastasis.
- Work in progress towards the validation of a biomarker signature to help selection of patients for TGFbeta inhibitor based treatment of glioma.
- Characterization of a new regulatory mechanism of the RAS pathway by specific arginine methylation, a potential new therapeutic target in cancer.

Read more at www.vhio.net

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. Our laboratory uses mass spectrometry-based proteomic strategies to search for new substrates of these proteases and explore their role in tumor progression. The laboratory also pursues the use of proteomic techniques for screening and validation of biomarkers for cancer diagnostic, treatment personalization and monitoring.

In parallel, as a core facility, we provide 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.

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VHIO MULTIDISCIPLINARY RESEARCH PROGRAMS

VHIO CLINICAL TRIALS CORE SERVICES & UNITS

Clinical Trials Office

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
Meritxell Soler

Data Managers

Beatriz Blanco
Gloria García
Isabel Rico
Cristina Viaplana

Head, Clinical Trials Office for Phase II-III

Isabel Grau
Irene Marimon

Study Coordinators

Judith Alonso
Cristina González
Jordi Humbert
Neus Marqués
Oriol Nualart
Olga Padrós
Iratxe Puebla
Mireia Sanchís
Alba Vilarrasa

Data Managers

Anna Aguilar
Marta Malo
Xavier Martínez
Sergio Pérez
Andrea Retter
Montserrat Solà

Head, Clinical Trials Office for Breast Cancer Trials

Susana Muñoz

Study Coordinators

Raquel Espallargas
Violeta Esteban
Beatriz García
Olga Vida

Data Managers

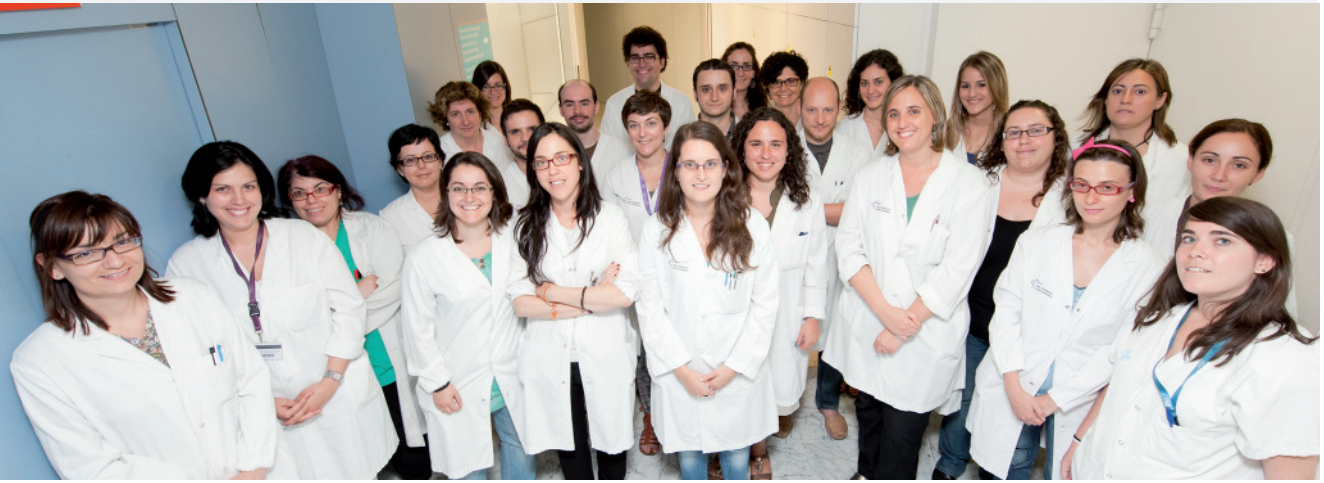
Julia Esteban
Belén García
Àngels Porras
Rita Ramadas
Rosa María Romero

Assistants

Núria Carballo
Angel Marín

Database Managers Office

Débora Moreno
Núria Murtra
Gessamí Sánchez Ollé



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 2011

- 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.

Read more at www.vhio.net

- 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 figure 1 and figure 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 and junior CRAs. We have also organized a 36-hour post-graduate course (a new edition for 2011).

Figure 1: Total Annual Recruitment in Clinical Trials

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Included in Phase I	8	9	35	59	57	110	130	120	108	132	139	171	222	245	277
Included in Phase II	50	70	59	72	66	94	91	130	73	165	170	133	161	207	180
Included in Phase III	85	82	95	128	175	109	84	129	111	85	143	180	189	221	218
Total nº. of patients included	**143**	**161**	**189**	**259**	**298**	**313**	**305**	**379**	**292**	**382**	**452**	**484**	**572**	**673**	**675**

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

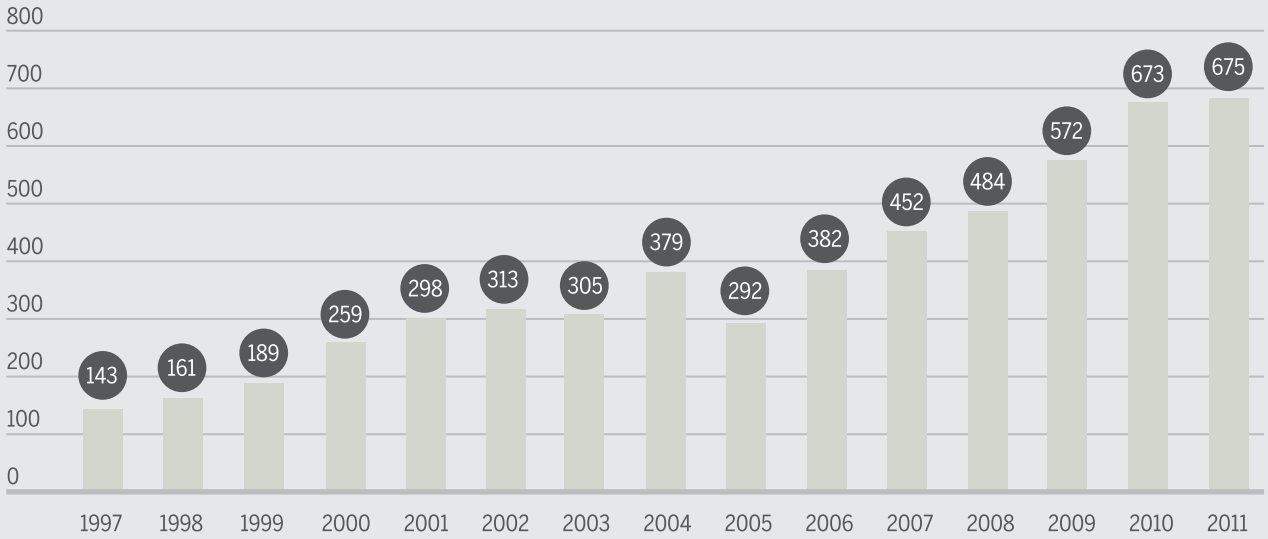


Figure 2: Increase in number of patients recruited in clinical trials from 1997 to 2011.

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

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Phase I trials	1	1	6	10	12	14	17	15	16	19	20	26	31	37	48
Phase II trials	11	18	19	22	23	23	22	19	30	32	42	40	55	54	57
Phase III trials	10	13	14	17	22	25	18	20	21	21	31	37	45	49	56
Nº of clinical trials	**22**	**32**	**39**	**49**	**57**	**62**	**57**	**54**	**67**	**72**	**93**	**103**	**131**	**140**	**161**

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 160 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 separate teams: Phase I, Breast Cancer, and Phase II-III.

Our Office has conducted 161 actively recruiting trials and succeeded in recruiting and coordinating a total of 675 patients in these trials. In addition, we are following up all patients that were recruited prior to 2011 who are still enrolled and receiving study treatment.

For more information about Phase I and early Phase II trials, please see pages 44 - 45, Early Clinical Drug Development Group and the Research Unit for Molecular Therapy of Cancer UITM - "la Caixa" .

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Clinical Research Oncology Nurses

Supervisor

Ángeles Peñuelas

Nurse Coordinators

Sonia Valverde
Lydia Vélez

Nurses

Anna Aliau
Mª Elena de Cabo
Meritxell Cucurell
Miriam García
Margarida Marcos
Marta Mate
Núria Membrives
Mireia Milán
Isabel Muñoz
Tania Sánchez
Alex Sierra

Nursing Assistants

Purificación Cardenete
Alicia López
Mª Ascensión Martín
Elena Oller

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 45 for more information) and the Clinical Trials Office (see page 72).

Incorporating medical oncologists, specialists in molecular pathology, pharmacists exclusively dedicated to this field (see VHIO's Clinical Research Oncology Pharmacy Unit on page 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 find out more about us, our research, publications and even our group's horizons for 2012, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2011/

Clinical Research Oncology Pharmacy Unit

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Maria Hidalgo Casas
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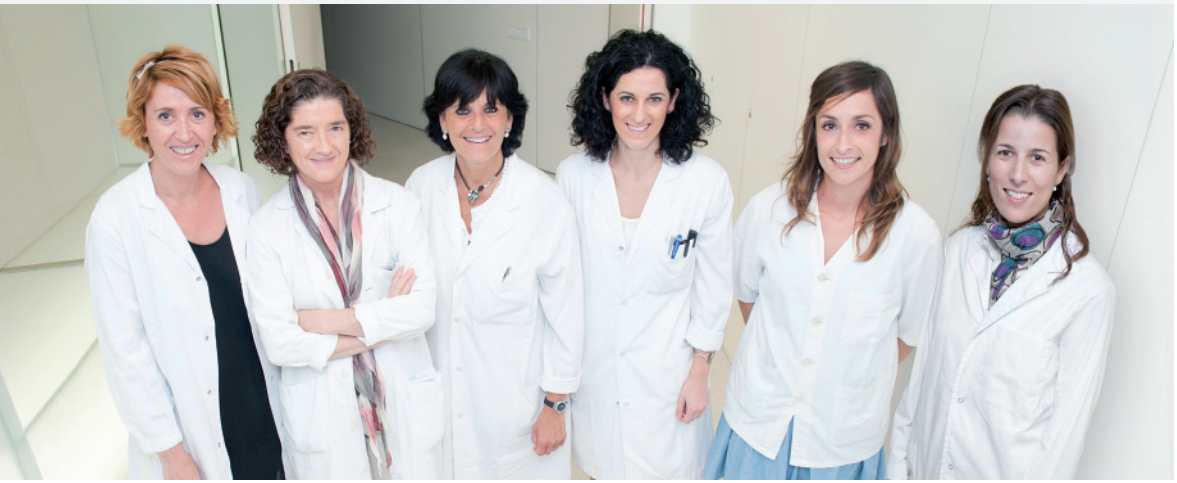

Strategic Goals

1. Achieve excellence in the quality of the service we provide to the different clinical oncology research programs through optimal efficacy, efficiency and safety.
2. Ensure traceability of management and preparation of drugs for clinical trials.
3. Provide and ensure excellent control of the storage temperature of samples and products prepared.
4. Increase documented control of the accounting for drugs returned by patients.
5. Provide instructions and indications to patients for orally administered treatments.
6. Implementation of traceability program in clinical trial supplies management (storage, dispensation and accountability) and enhance through an interphase with the traceability program used in the cytostatics and monoclonal antibodies preparation Unit. ISISH-TRI program.
7. Prepare trial drugs for parenteral administration through integrating all phases of prescription, preparation and administration in computerized systems to prevent errors in medication.
8. Provide pharmaceutical care to patients enrolled in Phase I clinical trials to achieve optimal study treatment and increased patient safety during treatment.

Read more at www.vhio.net

Highlights in 2011

- Opening of new facilities: our Clinical Research Oncology Pharmacy Unit is now located closer to the Research Unit of Molecular Therapy of Cancer (UITM) - "la Caixa", and now incorporates new computerized and technological systems for the management, control and storage of IV clinical trial drugs infusions. We aim to optimize the service and facilitate integration with the rest of the research team.
- 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 relating to the supplies from their reception at the unit until they are dispensed (oral medication or drug 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 for the 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. Use of voice technology (Voice-Directed Work, Vocollect).The master database of the traceability system for study drug dispensation and storage is currently under design.
- 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.

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 anti-tumor drugs used in clinical trials in oncology, as well as monitoring 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, monitoring, issuing and controlling samples for clinical trials in oncology and its delivery to SC (oral medication) or to the Oncology Pharmacy Unit (IV infusion medication).

In 2011 our activity has focused on the following key areas:

- *Management of clinical trial drugs*: we have managed clinical trial drugs for 161 active trials in oncology. The number of clinical trial supplies deliveries totaled at 1.685.

- *Updating a novel system for controlling storage temperature*: with electronic temperature recordings every 5 minutes displayed on the program's computers including an audio and visual alarm as well as a system for sending an alarm via SMS to 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 to perform drug accountability or the sponsor to 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 transparent and sealed bag. Our unit has managed drug accountability for drugs returned by patients from 52 clinical trials in 2011.

- *Ensuring traceability of storage management, custody and dispensing of clinical trial drugs*: the design of a computerized storage area for controlling samples, 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 (Vocollect Voice-Directed Work system).

- *Support for, and liaison with, the trial sponsors*: The Pharmacological Research in Oncology support Unit's Pharmacists have taken part in 25 pre-study visits, 87 initial visits, 651 monitoring visits and 35 final visits and successfully passed 10 audits. Preparation staff have participated in 4 pre-study visits, 77 initial visits, 114 follow up visits, 4 training visits and 2 audits.

- *Dispensing*: a total of 11.662 clinical trial drugs have been dispensed with the validation of a pharmacist. 4.626 of these were for orally administered clinical trial drugs. The conditioning and re-labeling of the primary packaging containers for clinical trial drugs to be taken by the patient only on site, have also been carried out. A total of 96 Standardized Dispensing Procedures have also been drawn up and updated. 111 storage temperature data reports have been compiled.

- *Preparations*: a total of 6.128 preparations of cytostatics, monoclonal antibodies and other parenteral anti-tumor drugs for clinical trials. A total of 88 Standardized Preparation Procedures have been drawn up.

- *Collateral*: the 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 corresponding forms for patients. In 2011 we compiled 35 standard operating procedures and 11 documents for patients. Our dispensing unit has also prepared 14 diaries and instructional documents for patients.

- *Development of our pharmaceutical care program for 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 2011 we carried out a total of 813 visits to patients in Phase I clinical trials, 98 pre-screening visits, 173 screening visits, 507 follow-up visits, and 35 end study visits.

- *Improved 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.*

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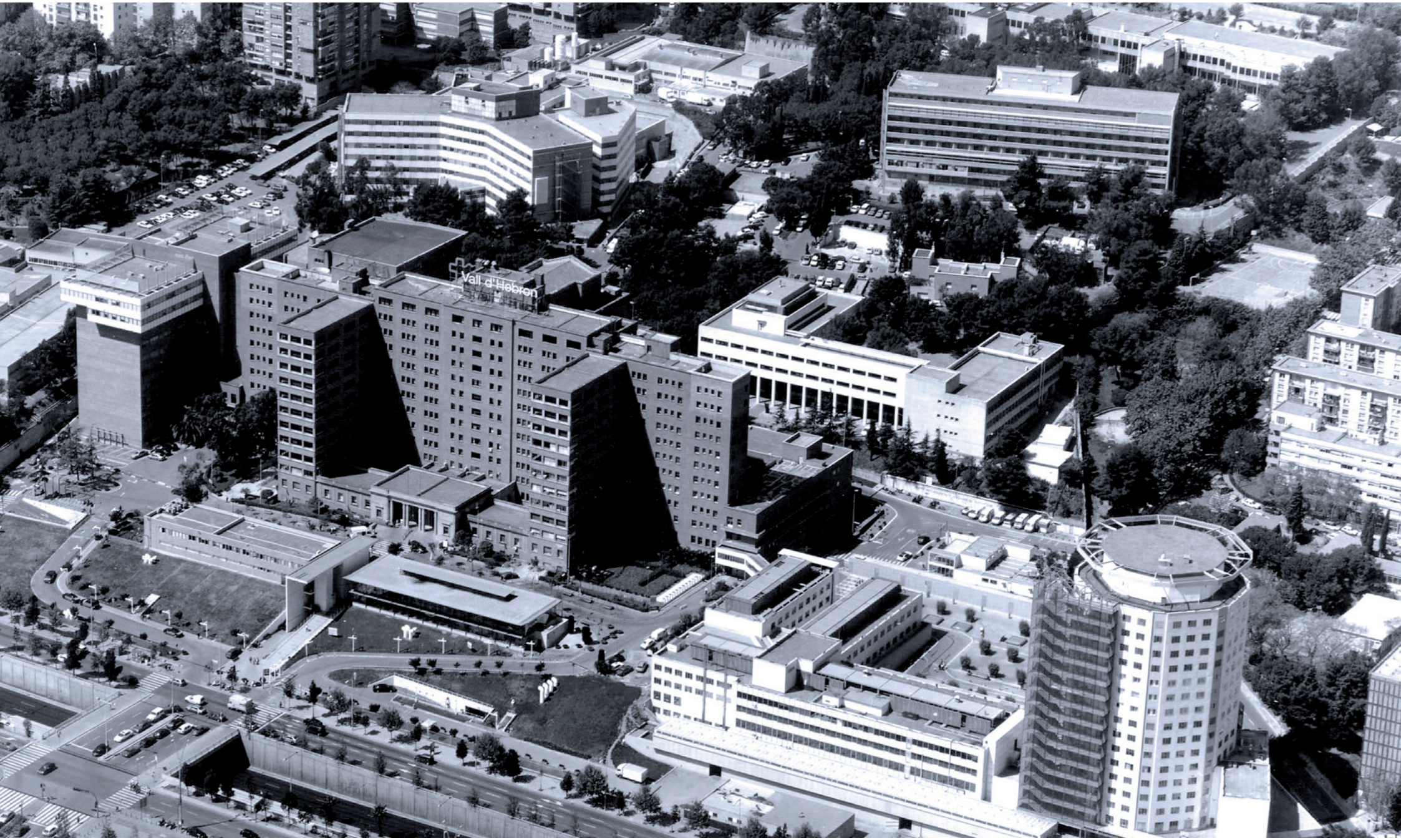

The Vall d'Hebron University Hospital: the ideal base and environment for VHIO's multidisciplinary cancer teams.

Patrons:

With the collaboration of: