VALL D'HEBRON INSTITUTE OF ONCOLOGY

SCIENTIFIC REPORT 2010

Centres de recerca de Catalunya

Vall D´Hebron Institute of Oncology (VHIO)
Passeig Vall d´Hebron 119
Edifici Maternoinfantil, planta 14
08035 Barcelona, Spain
Tel: +34 93 489 30 21
email: info@vhio.net
www.vhio.net

Direction	VHIO Communications
Design	Eureca Media (UOC GROUP)
Printing	AGPOGRAF, SA
Photography	Katherin Wermke

VHIO SCIENTIFIC REPORT 2010

FROM JOSÉ BASELGA

Scientific Director

As VHIO embraces this new decade, committed to realizing the true promise of personalized medicine - a reality well within reach I believe - it is hard to believe that the term 'translational' in cancer research has only relatively recently entered the oncology lexicon. The translational approach to research - a virtuous cycle of knowledge whereby laboratory discoveries are directly applied to patients and from the clinical side, tumors are analyzed at the molecular level in the laboratory - has rapidly been accepted as the only way forward in turning research into more effective, targeted treatments and better practice for the future care of our patients.

What makes VHIO special is that we can do this more rapidly and effectively than most. In order to do so, VHIO relies on direct access to patients thanks to its privileged location set within the Vall d'Hebron University Hospital, as well as the collaborative, multidisciplinary mindset of its outstanding teams and physician-scientist partnerships, without which such advancement could and would not be possible (please see '*Who we are, what we do and how we do it*', pages 7-11).

Integrating translational science and clinical research within a multidisciplinary setting is what we do at VHIO. This past year has marked significant progress in this respect, thanks to a series of exciting new developments based on key strengths that have firmly established VHIO as an international leader in cancer discovery

spanning basic molecular biology to clinical and translational research:

As a direct reflection of this exciting growth founded on a bedrock of research of excellence, VHIO's scientific structure has been reorganized - a necessary transition for yet faster 'translation'. The institute is now structured across four major programs: Preclinical Research, Translational Research, Clinical Research and Core Technologies. This move will suitably equip VHIO to deliver on its next essential phase of expansion.

In 2009 I announced the set up of VHIO's Tumor Biomarkers Group led by Josep Villanueva (see **page 60**) as well as the Cancer Genomics division headed by Ana Vivancos (refer to **page 56**). I am pleased to report that Josep has since implemented the sophisticated equipment necessary to identify novel cancer biomarkers to ultimately enable better diagnosis and disease monitoring. Fully embracing the 'omics' era and beyond, Ana's group is not only applying next-generation sequencing to identify novel cancer mutations, but is also collaborating in multidisciplinary projects at VHIO to apply it to individual patients and therefore better guide treatment decisions.

While the stunning new technologies in genomics, transcriptomics and the like are profoundly changing the face of cancer understanding and therapeutics, the true promise of tailored therapy can only be realized by accelerating the drug discovery process. One major step in this direction has been the opening of our Research Unit for Molecular Therapy of Cancer (UITM) - "La Caixa" - thanks to the generous support received from the Welfare Projects Division of the "la Caixa" Foundation (see **pages 10-11, 68-69**).

The Unit has been set up to conduct complex clinical trials with drugs in early development (Phase I and early Phase II), focusing on novel targets. In line with VHIO's translational ethos and practice, clinical research at the UITM is tightly linked with the different research areas carried out by our various groups - key to connecting molecular biology and the best tumor models with pharmacology and innovative clinical research.

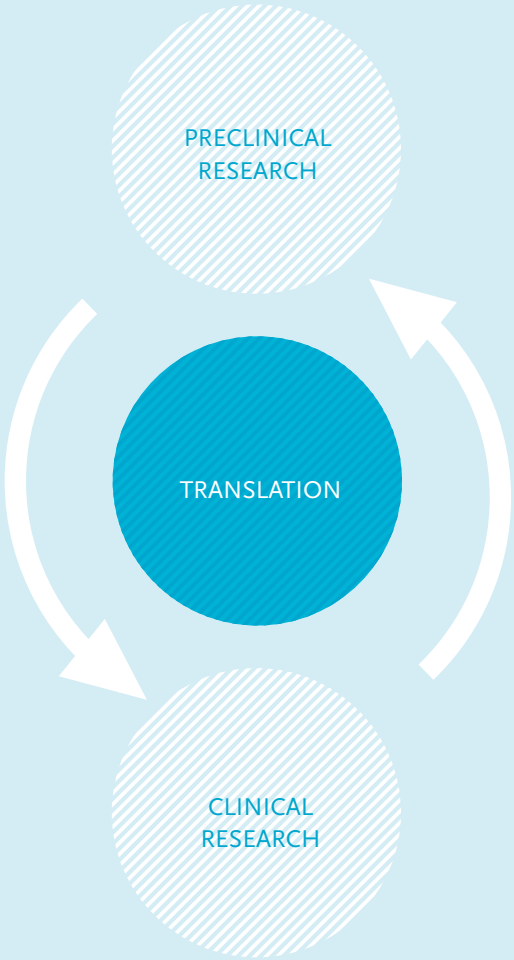
VHIO scientists will collaborate closely in the trials to facilitate biomarker development as well as research in mechanisms of resistance. Further, in partnership with molecular pathologists and VHIO's Cancer Genomics Group, the UITM team will perform molecular analysis of patients' tumors to select the best possible treatment for the individual patient with the experimental therapeutics available.

Sharing the same VHIO dedication to unmasking the basic mechanisms of cancer as well as improving patient care, I am delighted to announce the arrival of Laura Soucek next Spring. Thanks to the support received from the FERO Foundation, Laura will move to VHIO from Gerard Evan's lab at the University of California, San Francisco, to head up the Mouse Models and Cancer Group. While her expertise in the design and use of immune-competent mouse models of cancer will add tremendous value to our activities, she will also continue with her research on the role of the Myc oncogene in cancer progression.

Where to next? As I reflect on just how far translational research has led us, we still have a long way to travel. While the quality and depth of today's research is certainly reducing the serendipity of cancer science, we must all embrace a fundamental turnaround in the scale of our ambitions. In collaboration, larger scale studies should, can, and will be conducted. Only then will we be able to better validate markers, unravel the vast amount of genetic and pathway data to apply it clinically: the acme in advancing personalized and targeted therapies against cancer for the benefit of our patients today, the future of those tomorrow.

José Baselga
Scientific Director

WHO WE ARE, WHAT WE DO AND HOW WE DO IT



'FOUND' IN TRANSLATION

The translational approach facilitates the detailed and direct study of each patient and each tumor. Aided by direct access to patients thanks to its privileged location set within the Vall d'Hebron University Hospital, its purely 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.

Undertaking one of Spain's most dynamic cancer research programs, research at VHIO focuses on understanding all relevant aspects of cancer biology from cellular and molecular biology and genetics through to therapeutics. Our extraordinary 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 private institutions, companies, individuals, funding entities and agencies (please see **page 12** for further details) that our multidisciplinary teams continue to improve survival and quality of life for all our patients today, and in so doing turn research into more effective, personalized treatments and better clinical practice for the future.

VHIO'S PURELY TRANSLATIONAL RESEARCH MODEL

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

Research Group / Units

Core Groups classified according to their scientific reporting line

SCIENTIFIC DIRECTION

PRECLINICAL RESEARCH PROGRAM

- EXPERIMENTAL THERAPEUTICS
- GROWTH FACTORS
- TUMOR BIOMARKERS
- ANIMAL MODELS & CANCER
- PROTEOMICS

TRANSLATIONAL RESEARCH PROGRAM

- GENE EXPRESSIONS AND CANCER
- STEM CELLS & CANCER
- CANCER GENOMICS

CORE TECHNOLOGIES PROGRAM

- 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 "LA CAIXA"
- DATABASES AND STATISTICS

- MOLECULAR PATHOLOGY

- BREAST CANCER & MELANOMA
- GASTROINTESTINAL & ENDOCRINE TUMORS
- GENITOURINARY, CENTRAL NERVOUS SYSTEM (CNS) TUMORS, SARCOMA & CANCER OF UNKNOWN PRIMARY SITE
- HEAD, NECK & GYNECOLOGICAL TUMORS
- HIGH RISK & CANCER PREVENTION
- ONCOGENETICS
- RADIATION ONCOLOGY
- THORACIC TUMORS

TRANSITION FOR FASTER TRANSLATION: CELLEX BUILDING

Fundació Privada
CELLEX

Future expansion of VHIO's preclinical, translational and clinical research activities is paramount to be able to build on the milestones marked by VHIO to-date.

Further to the City Hall's approval of the project in 2009, we are carefully working on the strategic planning behind the new Cellex building which will not only provide the necessary space and amenities for VHIO to further develop its programs, but will also foster the already existing multidisciplinary cross-talk and connectivity by bringing all VHIO teams together under the same roof. We aim to have the plans for the building and facilities finalised over the coming year so that construction can begin in early 2012.

THE VALL D'HEBRON UNIVERSITY HOSPITAL

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

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.

FACILITIES & CLINICAL TRIALS

Enabling VHIO to further deliver on all its research, translational and clinical trial objectives, our Institute collaborates closely with the Vall d'Hebron University Hospital's Oncology Department, driven by a shared determination to both advance and accelerate personalized and targeted therapies against cancer.

The **Breast Cancer Center** was set up at Vall d'Hebron in 2008 in memoriam of Roman Sanahuja and Francisca Pons thanks to the Hospital's breast pathology and oncology teams of excellence. Dedicated to the care of patients with breast cancer, we combine forces and pool expertise across specialties in order to work in tightly connected multidisciplinary teams focused on achieving better, more effective treatments and ultimately cure.

The Breast Cancer Center: providing optimal care for breast cancer patients

THE RESEARCH UNIT FOR MOLECULAR THERAPY OF CANCER (UITM) - "LA CAIXA"

Knowledge of the molecular biology of cancer has grown exponentially over the last decade and this in turn has meant the identification of a host of therapeutic leads for the development of selective drugs. Directed by José Baselga and Josep Tabernero, under the clinical coordination of Jordi Rodón, the Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa" was inaugurated in June this year 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 already existing ones (see **pages 68-69**). >>

Obra Social "la Caixa"

Mirroring the multidisciplinary model of VHIO, research at the Unit incorporates an expert team of medical oncologists, specialists in molecular pathology, pharmacists exclusively dedicated to this field, experts in imaging and diagnostics, nurses specialized in molecular treatments and study coordinators. Such a multidisciplinary approach ensures that patients enrolled in the various Phase I and early Phase II Clinical Trials at the Unit - a crucial first-step in developing and accelerating new ways to combat cancer, receive the full range of expertise for his/her illness as well as detailed advice on the characteristics of his/her particular treatment.

This new 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 and individualized way - getting the right drug to the right patient at the right time. For more detailed information surrounding the Unit's strategic goals and a summary of successes to-date as well as information about all VHIO's Clinical Trial Services and activities, please see **pages 64 -66** or visit our Scientific Report online at: www.vhio.net.

Inauguration of the Research Unit for Molecular Therapy of Cancer (UITM)
"la Caixa", 23 June 2010.

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 through the generous support received 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

Patrons:

Generalitat de Catalunya

fero Fundación de Investigación Oncológica

Obra Social "la Caixa"

With the collaboration of:

Fundació Privada CELLEX

PRIVATE COMPETITIVE/ NON COMPETITIVE FUNDING

COMPETITIVE FUNDING: INTERNATIONAL GRANTS

NATIONAL GRANTS

To consult the list of specific projects funded in 2010 please visit our Scientific Report online at: www.vhio.net.

CONSORTIA

As a reflection of VHIO´s expertise in preclinical, translational and clinical research in oncology, it was invited to join the following Consortia of excellence in 2010:

- 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.

For more information and a full list of projects supported by our other funding organizations, companies and entities please visit our Scientific Report online at: www.vhio.net.

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

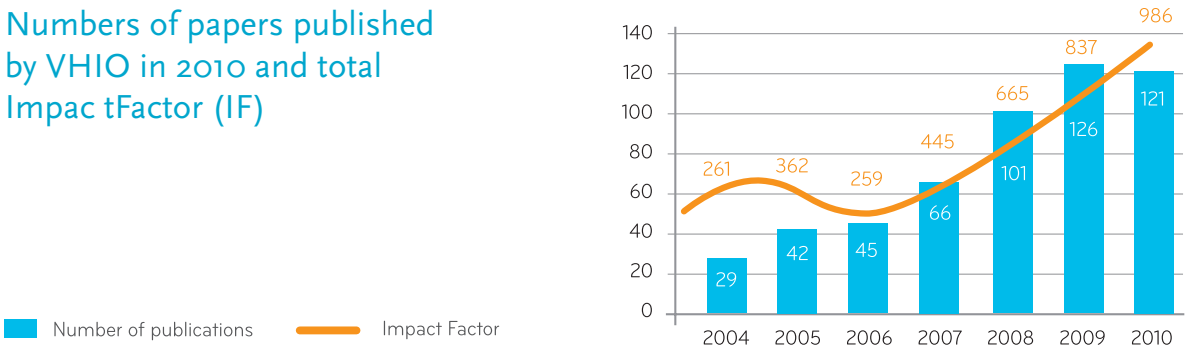
In 2010 VHIO joined the CERCA Institute of Research Centres of Catalunya - Institució CERCA Centres de Recerca de Catalunya.

SCIENTIFIC PRODUCTIVITY: RESEARCH ARTICLES

PAPERS PUBLISHED IN 2010

In 2010, 121 scientific articles were published by VHIO faculty as corresponding/senior author with the Impact Factor (IF) averaging at 8.15. As the table below demonstrates, VHIO continues to increase overall IF reflecting both the quality and importance of its reasearch and contribution to the oncology field:

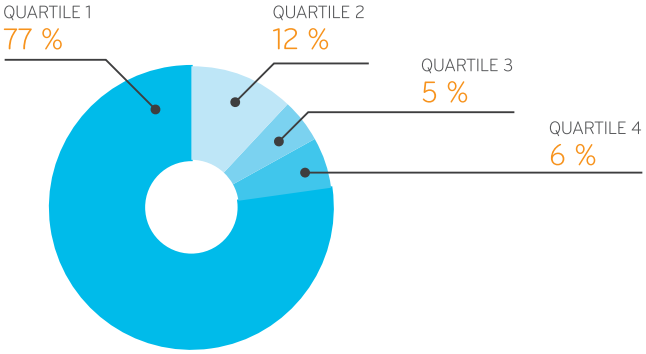
Numbers of papers published by VHIO in 2010 and total Impac tFactor (IF)



PUBLICATION IN THE TOP-TIER SCIENTIFIC JOURNALS

As reflected by the pie chart below, the majority of VHIO articles produced in 2010 were published the highest-ranking scientific publications in oncology:

VHIO
Scientific Articles 2010
Impact Factor (IF) distribution per quartiles*



* Q1 denotes top 25% of the IF distribution, Q2 medium-high (between top 25 -50%), Q3 a medium-low (top 50 -75%) and Q4 lowest (bottom 25% of the IF distribution).

SELECTION OF MOST RELEVANT VHIO ARTICLES PUBLISHED IN 2010

Below is a **selected list** of articles published by VHIO in 2010 with respective IFs:

The Landscape of copy number alterations across multiple human cancers. Beroukhim, R; Tabernero, J; Baselga, J; Meyerson M et al (2010) ***Nature***, 463, 899-905. IF: 36.104

Neoadjuvant chemotherapy with Trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Gianni, L., Baselga, J. et al (2010) ***Lancet***. 375, 377-384. IF: 33.633

TGF-β Receptor Inhibitors Target the CD44(high)/=d1(high) Glioma-Initiating Cell Population in Human Glioblastoma. Anido, J., Saez-BorderÌas, A., Gonzalez-Junca, A., Rodon, L., Folch, G., Carmona, M.A., Prieto-Sanchez, R.M., Barba, I., MartÌnez-Saez, E., Prudkin, L., Cuartas, I., Raventós, C., Martínez-Ricarte, F., Poca, M.A., GarcÌa-Dorado, D., Lahn, M.M., Yingling, J.M., Rodon, J., Sahuquillo, J., Baselga, J., Seoane, J. (2010) ***Cancer Cell***. 18, 655-668. IF: 26.925

NO Signals from the Cancer Stem Cell Niche. Seoane, J. (2010) ***Cell Stem Cell***, 5, 6(2) 97-98. IF: 25.943

Tirapazamine, Cisplatin and Radiation Versus Cisplatin And Radiation For Advanced Squamous Cell Carcinoma Of The Head And Neck (TROG 02.02, HeadSTART): A Phase III Trial Of The Trans-Tasman Radiation Oncology Group. Rischin, D; Peters, LJ; O'Sullivan, B; Giralt, J; Fisher, R; Yuen, K; Trotti, A; Bernier, J; Bourhis, J; Ringash, J; Henke; Kenny, L. (2010) ***J Clin Oncol***, 28(18), 2989-2995. IF: 18.970

Phase II proof-of-concept study of pazopanib monotherapy in treatment-naive patients with stage I/II resectable non–small-cell lung cancer. Altorki, N., Felip, E., Yankelevitz, D. F. et al (2010) ***J Clin Oncol***. 28, 3131-3137. IF: 18.970

Preoperative Chemotherapy Plus Surgery Versus Surgery Plus Adjuvant Chemotherapy Versus Surgery Alone in early-Stage Non-Small-Cell Lung Cancer. Felip, E., Massuti, B et al (2010) ***J Clin Oncol***. 28, 3138-3145. IF: 18.970

Towards efficient trials in colorectal cancer: The ARCAD Clinical Trials Program. De Gramont, A; Haller, D; Sargent, D; Tabernero, J; Matheson, A; Schilsky, R. (2010) ***J Clin Oncol***, 28, 527-530. IF: 18.970

Trastuzumab-DM1: Building a Chemotherapy-Free Road in the Treatment of Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer. Isakoff, S.J., Baselga, J. (2010) ***J Clin Oncol***, 29(4),351-354. IF:18.970

A phase II study of halichondrin B analog eribulin mesylate (E7389) in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline, a taxane, an capecitabine. Cortés, J; Allison, MA. et al (2010) ***J Clin Oncol***, 28, 3922-3928. IF: 18.970

Phase III Study of Bevacizumab plus Docetaxel Compared with Placebo plus Docetaxel for the First-line Treatment of HER2-negative Metastatic Breast Cancer. Miles, M; Cortés, J; Romieu, G et al (2010) ***J Clin Oncol***, 28, 3239-3247. IF: 18.970

An Intensive Loading Dose of Trastuzumab Achieves Higher Than Steady-State Serum Concentrations and Is Well Tolerated. Leyland-Jones, B; Colomer, R; Trudeau, M; Wardley, A; Latreille, J; Cameron, D; Cubedo, R; Al-Sakaff, N; Feyereislova, A; Catalani, O; Fukushima, Y; Brewster, M; Cortés, J. (2010) ***J Clin Oncol***, 28, 960-966. IF: 18.970

A Phase II Trial of Pertuzumab and Trastuzumab in Patients with HER2-Positive Metastatic Breast Cancer That Had Progressed During Prior Trastuzumab Therapy. Baselga, J; Cortés, J; Gianni, L. et al (2010) ***J Clin Oncol***, 28, 1138-1144. IF: 18.970

Critical Impact of Radiotherapy Protocol Compliance And Quality In The Treatment Of Advanced HeadAnd Neck Cancer – Results From Trog 02.02. Peters, LJ; O'Sullivan, B; Giralt, J; FitzGerald, TJ; Trotti, A; Bernier, J; Bourhis, J; Yuen, K (2010) ***J Clin Oncol***, 28(18), 2996-3001. IF: 18.970

Pharmacogenomic and pharmacoproteomic studies of cetuximab in metastatic colorectal cancer: biomarker analysis of a Phase I dose-escalation study. Tabernero, J., Cervantes, A., Rivera, F., Martinelli, E., Rojo, F., Von Heydebreck, A., Macarulla, T., Rodriguez-Braun, E., Vega-Villegas, M.E., Senger, S., Ramos, F.J., Roselló, S., Celik, I., Stroh, C., Baselga, J., Ciardiello, F. (2010) ***J Clin Oncol***. 28, 1181-1189. IF: 18.970

Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. Douillard, JY; Siena, S; Cassidy, J; Tabernero, J; Gansert, J et al. (2010) ***J Clin Oncol***, 28(31), 4697-4705. IF: 18.970

Multigene assays to improve assessment of recurrence risk and benefit from chemotherapy in early-stage colon cancer: has the time finally arrived, or are we still stage locked? Tabernero, J; Baselga, J et al (2010) ***J Clin Oncol***, 28(25), 3904-3907. IF: 18.970

Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. Baselga, J., Gelmon, K.A., Verma, S., Wardley, A., Conte, P., Miles, D., Bianchi, G., Cortes, J., McNally, V.A., Ross, G.A., Fumoleau, P., Gianni, L. (2010) ***J Clin Oncol.*** 28, 1138-1144. IF: 18.970

Open-label Phase II multicenter randomized study of the efficacy and safety of two dose levels of Pertuzumab a human epidermal growth factor receptor 2 dimerization inhibitor in patients with human epidermal growth factor receptor 2-negative metastatic breast cancer. Gianni, L., Lladó, A., Bianchi, G., Cortes, J., Kellokumpu-Lehtinen, P.L., Cameron, D.A., Miles, D., Salvagni, S., Wardley, A., Goeminne, J.C., Hersberger, V., Baselga, J. (2010). ***J Clin Oncol***. 28,1131-1137. IF: 18.970

Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErB2- positive trastuzumab-refractory metastatic breast cancer. Blackwell, K.L., Burstein, H.J., Storniolo, A.M., Rugo, H., Sledge, G., Koehler, M., Ellis, C., Casey, M., Vukelja, S., Bischoff, J., Baselga, J., O'Shaughnessy, J. (2010) ***J Clin Oncol***. 28, 1124-1130. IF: 18.970

HER2 Signatures in Breast Cancer: Ready to go to print? Eichhorn, P.J., Baselga, J. (2010) ***J Clin Oncol***. 28,1809-1810. IF: 18.970

Activity of a multitargeted chemo-switch regimen (Sorafenib, Gemcitabine, and metronomic capecitabine) in metastatic renal-cell carcinoma: A phase 2 study (SOGUG-02-06) Bellmunt, J; Trigo, JM; Calvo, E; Carles, J; Pérez-Garcia, JL; Rubio, J; Virizuela, JA; López, R N; Lázaro, M; Albanell, J (2010) ***Lancet Oncol***, 11(4), 350-357. IF: 17.764

Radiotherapy plus cetuximab for locoregionally advancevd head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Bonner, J.A., Giralt, J., Baselga, J., Ang, K.K. et al (2010) ***Lancet Oncol***. 11, 21-28. IF: 17.764

Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. De Roock, W; Tabernero, J; Macarulla, T; Tejpar, S. et al (2010) ***Lancet Oncol***, 11, 753-762. IF: 17.764

Deregulation of the PIK3CA and KRAS signaling pathways determines cancer cells' response to everolimus" Di Nicolantonio, F., Arena, S., Tabernero, J., Grosso, S., Molinari, F., Macarulla, T., Russo, M., Cancelliere, C., Zecchin, D., Mazzucchelli, L., Sasazuki, T., Shirasawa, S., Geuna, M., Frattini, M., Baselga, J., Gallicchio, M., Biffo, S., Bardelli, A. (2010) ***J Clin Invest***. 120, 2858-2866. IF: 14.152

Strand-specific deep sequencing of the transcriptome. Vivancos, AP; Güell, M; Dohm, JC; Serrano, L; Himmelbauer, H. (2010) ***Genome Res***, 20(7), 989-999. IF: 13.588

Management of breast cancer with targeted agents: importance of heterogenicity. Di Cosimo, S., Baselga, J. (2010) ***Nat Rev Clin Oncol***. 7, 139-147. IF: 10.787

Lifespan extension by calorie restriction relies on the Sty1 MAP kinase stress pathway. Zuin, A; Carmona, M; Morales-Ivorra, I; Gabrielli, N; Vivancos, AP; Ayté, J; Hidalgo, E. (2010) EMBO J, 29 (5), 981-991. IF: 10.124

Analysis of the 10q11 cancer risk locus implicates MSMB and NCOA4 in human prostate tumorigenesis. Pomerantz, M.M., Tabernero, J., Baselga, J., Freedman, M.L. et al (2010) PLoS Genet. 6, e1001204. IF: 9.543

The ups and downs of Myc biology. Soucek, L; Evan, GI. (2010) Curr Opin Genet Dev, 20(1) 91-95. IF: 9.381

A major role of p95/611-CTF, a carboxy-terminal fragment of HER2, in the down-modulation of the estrogen receptor in HER2-positive breast cancers. Parra-Palau JL, Pedersen K, Peg V, Scaltriti M, Angelini PD, Escorihuela M, Mancilla S, SánchezPla A, Ramón y Cajal S, Baselga J, Arribas J. (2010) ***Cancer Res***. 70, 8537-8546. IF: 8.234

p95HER2 and breast cancer. Arribas, J., Baselga, J., Pedersen, K. and Parra-Palau, J. Ll. (2010) ***Cancer Res***. 71(5), 1515-1519. IF: 8.234

ADAMTS1 Contributes to the Acquisition of an Endothelial-like Phenotype in Plastic Tumor Cells. Casal, C; Torres, AX, Plaza, MD; Martino, E; Ramon Y Cajal, S; Rojo, F; Griffioen, AW; Rodriguez-Manzaneque. (2010) ***Cancer Res***, 70(11), 4676-4686. IF: 8.234

MLH1 founder mutations with moderate penetrance in Spanish Lynch syndrome families. Borràs, E; Balmaña, J; Capellá, G et al (2010) ***Cancer Res***, 1,70(19),7379-7391. IF: 8.234

PI3K inhibition results in enhanced HER signaling and acquired ERK dependency in HER2 overexpressing breast cancer. Serra, V., Scaltriti, M., Prudkin, L., Eichhorn, P., Ibrahim, Y. H., Chandarlapaty, S., Markman, B., Rodriguez, O., Guzman, M., Rodriguez, S., Gili, M., Russillo, M., Parra, J. Ll., Singh, S., Arribas, J., Neal Rosen, R., and Baselga, J. (2010) ***Oncogene***. 30(22), 2547-2557. IF: 7.414

Inhibitors of:SP90 block p95-HER2 signaling in Trastuzumab-resistant tumors and suppress their growth. Chandarlapaty, S., Scaltriti, M., Angelini, P., Ye, Q., Guzman, M., Hudis, C.A., Norton, L., Solit, D.B., Arribas, J., Baselga, J., Rosen, N. (2010) ***Oncogene***. 29, 325-334. IF: 7.414

SPROUTY-2 and E-cadherin regulate reciprocally and dictate colon cancer cell tumourigenicity. Barbáchano, A; Ordóñez-Morán, P; García, JM; Sánchez, A; Larriba, MJ; Martínez, N; Hernández, J; Landolfi, S; Bonilla, F; Pálmer, HG; Rojas, JM; Muñoz, A. (2010) ***Oncogene***, (29)34, 4800-4813. IF: 7.414

ADAM17 (TACE) regulates TGFBeta signaling through the cleavage of vasorin. Malapeira, J., Esselens, C., Bech-Serra, J. J. Canals, F., Arribas J. (2010) Oncogene, 30(16), 1912-1922. IF: 7.414

Phase I safety, pharmacokinetics and inhibition of Src activity study of saracatinib in patients with solid tumors. Baselga, J; Cervantes, A; Tabernero, J. et al (2010) ***Clin Cancer Res***, 16(19), 4876-4883. IF: 7.338

HER2 fragmentation and breast cancer stratification. Arribas, J; Parra-Palau, JL; Pedersen, K. (2010) ***Clin Can Res***, 16(16), 4071-4073. IF: 7.338

Aprataxin tumor levels predict response of colorectal cancer patients to irinotecan-based treatment. Dopeso, H; Mateo, S; Elez, E; Landolfi, S; Ramos, FJ; Tabernero, J; Schwartz, S; Arango, D et al (2010). ***Clin Cancer Res*** 16(8), 2375-2382. IF: 7.338

Clinical Benefit of lapatinib-based therapy in patients with human epidermal growth factor receptor-2-positive breast tumors coexpressing the truncated p95HER2 receptor. Scaltriti, M; Chandarlapaty, S; Prudkin, L; Aura, C; Jimenez, J; Angelini, PD; Sánchez, G; Guzman, M; Parra, JL; Ellis, C; Gagnon, R; Koehler, M; Gomez, H; Geyer, C; Cameron, D; Arribas, J; Rosen, N; Baselga, J. (2010) ***Clin Cancer Res***, 16(9), 2688-2695. IF: 7.338

New pathogenic candidates for diabetic macular edema detected by proteomic analysis. Hernández, C., García-Ramírez, M., Colomé, N., Villarroel, M., Corraliza, L., García-Pacual, L., Casado, J., Canals, F., Simó, R. (2010) ***Diabetes Care***, 33(7), 92. IF: 7.141

Germline mutations in CDH1 are infrequent in women with early-onset or familial lobular breast cancers. Schrader, KA; Balmaña, J; Huntsman, DG et al (2010) ***J Med Genet***, Oct 4. IF: 7.037

For the full list of publications per VHIO group please visit the 2010 Scientific Report online at: www.vhio.net.

VHIO Multidisciplinary Research Programs

PRECLINICAL RESEARCH

Director,
Preclinical Research Program

Joaquín Arribas

Our program continues to thrive within an environment that promotes and fosters collaboration and interconnectivity between all VHIO groups. VHIO's Experimental Therapeutics Group led by José Baselga focuses on understanding the mechanisms of resistance to certain personalized therapies - more specifically on a type of breast tumor characterized by the presence of high levels of a cellular component named HER2.

HER2 is not only a biomarker that defines this type of breast cancer, not surprisingly known as HER2-positive breast cancer, but is also the target of anti-cancer drugs. The most widely used anti-HER2 drug is a monoclonal antibody known as trastuzumab or herceptin. Despite the undeniable success that these drugs have had in the treatment of breast cancer, many HER2-positive tumors develop resistance against them. Baselga's group identified a novel mechanism by which cancer cells resist to anti-HER2 therapies: the amplification or overexpression of the cell cylce regulator cyclin E. This seminal finding will translate in better management of HER2-positive breast cancers.

Our Proteomics Group headed by Francesc Canals, has continued to provide services to the laboratories of the Cancer Research Network and of the *Plataforma de Proteómica en Red ProteoRed* (*Instituto de Salud Carlos III*). During 2010, the group has collaborated with more than 25 research groups - not only from the Vall d'Hebron University Hospital, but also from the main hospitals, research centers and universities in Spain. In addition to being a core proteomics facility, VHIO's Proteomics Group has actively participated in different research projects carried out by other VHIO groups such as the identification of novel substrates of the metalloprotease ADAMTS1 involved in tumor invasion and metastasis, in collaboration with my own Growth Factors Group, as well as the validation of a biomarker signature that will allow the selection of patients with glioma to be treated with TGFbeta inhibitors, in collaboration with the Gene Expression and Cancer Group led by Joan Seoane.

The Tumor Biomarkers Group implemented the sophisticated equipment necessary to carry out different projects on the identification of novel cancer biomarkers. This technology included the mass spectrometer LTQ Orbitrap Velos (our mass spectrometer).

Finally, the Growth Factors Group published findings that will allow a better diagnosis of HER2-positive breast cancers. Several years ago, in collaboration with the Experimental Therapeutics Group, the Growth Factors Group showed that a subgroup of particularly aggressive HER2-positive breast cancers were characterized by the presence of fragments of HER2 known as p95HER2. In addition to being aggressive, these tumors were resistant to treatment with trastuzumab. In 2010 we developed specific antibodies that allow the rapid and robust identification of p95HER2-positive tumors. These antibodies will soon lead to optimization of therapies used to treat p95HER2 tumors.

In 2011 we plan to expand our program through the incorporation of Laura Soucek (envisaged next Spring). Laura will join us from the laboratory of Gerard I. Evan at the University of California, San Francisco (USA), where she has performed outstanding research surrounding the role of the oncogene Myc in cancer progession.

PRECLINICAL RESEARCH
EXPERIMENTAL THERAPEUTICS GROUP

PRINCIPAL INVESTIGATOR
José Baselga

STAFF SCIENTIST
Maurizio Scaltriti

MEDICAL ONCOLOGISTS
Jordi Rodón
Josep Tabernero

POST-DOCTORAL FELLOWS
Pieter Eichhorn
Celina Garcia
Yasir Ibrahim
Violeta Serra

TECHNICIANS
Pilar Anton
Magui Gili
Marta Guzman
Olga Rodriguez

STRATEGIC GOALS

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

HIGHLIGHTS IN 2010

1. Blockade of HER2 kinase activity with lapatinib or inhibition of Hsp90 are valid strategies for the treatment of p95HER2 expressing tumors.
2. Two additional mechanisms of resistance to trastuzumab-based therapy are 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.
3. In collaboration with VHIO's Growth Factors Group led by Joaquín Arribas, we developed an antibody for the detection of p95HER2 in clinical specimens.

JOSÉ BASELGA

Principal Investigator
Experimental Therapeutics Group

SUMMARY

During 2010 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 data were confirmed in breast cancer patients whereby patients with overexpressed/amplified cyclin E had reduced clinical benefit to trastuzumab-based therapies.

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 as well as the Breast Cancer & Melanoma Group which is headed by Javier Cortés) led us to identify reliable predictive and pharmacodynamic markers of PI3K-pathway inhibition that can be exploited in the clinical development of these inhibitors.

Finally, we established 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.

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

PRECLINICAL RESEARCH
GROWTH FACTORS GROUP

PRINCIPAL INVESTIGATOR
Joaquín Arribas

POST-DOCTORAL FELLOWS
Verónica Calvo
Mathew Paul Cunningham
Jordi Malapeira
Beatriz Morancho
Josep Luis Parra-Palau
Kim Pedersen
Mariano Zacarias

GRADUATE STUDENTS
Pier Davide Angelini
Cristina Bernadó

TECHNICIANS
Marta Escorihuela
Cristina Ferrer
Antoni Luque

STRATEGIC GOALS

1. Develop and characterize the use of specific anti-p95HER2 antibodies to stratify breast cancer patients.
2. Establish mouse models to study the heterogeneity of HER2-positive breast tumors (i.e. breast cancer patient derived xenografts).
3. Characterize the link between premature senescence and breast cancer progression.

HIGHLIGHTS IN 2010

1. The generation of specific anti-p95HER2 antibodies. The use of these antibodies for diagnostic purposes has already been licensed.
2. We have established a collection of breast cancer patient derived xenografts.
3. We have linked the establishment of premature senescence driven by HER2 with tumor invasion.

JOAQUÍN ARRIBAS

Principal Investigator,
Growth Factors Group

SUMMARY

Breast cancer is a heterogeneous disease. Through molecular profiling at least five distinct types of breast cancer have been identified. Our group has focused on a type of breast cancer which accounts for 20-30% of all cases namely, HER2-positive. We are currently interested in both refining the diagnosis of HER2-postive breast cancers as well as discovering novel mechanisms by which this type of tumor progresses and invades other tissues. To tackle these questions we use a variety of cell-based and animal models as well as breast cancer patient samples obtained from the Vall d'Hebron University Hospital.

One of our research lines deals with resistance to anti-HER2 therapies. We have shown that approximately 30% of HER2-positive tumors are characterized by the presence of a HER2 species called p95HER2. These tumors tend to be resistant to treatment with monoclonal antibodies against HER2, which are routinely used to treat HER2-postive breast tumors. It would therefore be desirable to develop a robust test to determine the presence of p95HER2 in advance.

We are also interested in analyzing the cellular heterogeneity of HER2-positive breast cancer in order to identify and purify the most aggressive and metastatic cells. Once purified, we will then test novel therapies to target these cells.

A third project concerns the link between premature cellular senescence and breast cancer progression. Cellular senescence is a process by which old or damaged cells stop dividing so they can be substituted by fresh cells. In normal conditions, cellular senescence is also used to prevent tumor initiation: potentially malignant cells are forced to senesce so they are rapidly cleared. However, advanced tumors pervert normal cellular senescence and use this mechanism to expand the tumor. We are currently analyzing how HER2-positive senescent cells contribute to breast cancer metastasis.

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

PRECLINICAL RESEARCH
TUMOR BIOMARKERS GROUP

PRINCIPAL INVESTIGATOR
Josep Villanueva

POST-DOCTORAL FELLOWS
Olga Méndez
Laura Villarreal

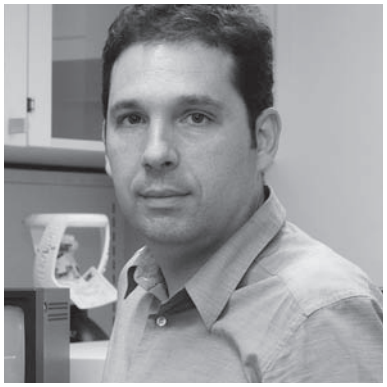
TECHNICIAN
Laura Córcoles

STRATEGIC GOALS

1. Characterize the mechanisms used by tumor cells to communicate with their microenvironment during tumorigenesis and exploit this 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 2010

1. The Tumor Biomarkers Group was established in 2009 with the key goal of discovering new biomarkers to enable better diagnosis and monitoring of cancer. We were granted our lab space in the Summer of 2010 housed in the new Collserola Building of the *Vall d'Hebron Institut de Recerca* (*VHIR*).
2. LTQ Orbitrap Velos (our mass spectrometer) was installed in Februrary 2010 - acquired in December 2009 thanks to the generous support received from the *Fundació Josep Botet* through the FERO Foundation. The Orbitrap LC/MS technology is the recognized standard for quantitative proteomics. This instrumentation is the optimal platform for protein identification, characterization and quantitation. The LTQ Orbitrap Velos is the essential and central element to our methodological approach.



JOSEP VILLANUEVA

Principal Investigator,
Tumor Biomarkers Group

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 among 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 can potentially 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 among each other and with their microenvironment. Since they are secreted they are most probably present in biological fluids such as blood. Our final goal is to identify tumor-specific secreted proteins that can be used to develop blood-based diagnostic tests for cancer detection and monitoring.

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

PRECLINICAL RESEARCH
ANIMAL MODELS & CANCER GROUP

PRINCIPAL INVESTIGATOR
Juan A. Recio

POST-DOCTORAL FELLOWS
Rosaura Esteve
Marta López
Pedro Andreu Pérez

TECHNICIANS
Rosa Gil
Judith Grueso

STRATEGIC GOALS

1. Role of LKBI in tumor biology.
2. Discovery of novel molecules involved in melanoma.
3. Novel therapeutic strategies for melanoma treatment.

JUAN A. RECIO

Prinicipal Investigator
Animal Models & Cancer Group

SUMMARY

Using proteomic screening (*OIGE*, *SILAC*) applied to tumor cell lines obtained from primary tumors grown in relevant animal models that recapitulate human disease (such as the *HGF* mouse melanoma model), we have isolated and identified 56 novel phospho-proteins in response to growth factors that participate in tumor progression and maintenance. Among the molecules identified was the *LKB1* energy sensor kinase. This molecule is deleted or mutated in different types of tumors (lung, colon, melanoma, etc.).

Our research established an important link between *RAS* pathway activation and the *LKB1* kinase that belongs to the energy sensor pathway. Importantly, *BRAFis* mutated in 70% of melanomas. *BRAF mutant* melanoma cell lines showed constitutive levels of phosphorylated *LKB1*, indicating crosstalk between the *RAS* and *LKB1* pathways and an unusual resistance to energy-stress conditions. Further investigations led us to discover that *BRAF signaling* was mediating the uncoupling of *LKB1* and its downstream target *AMPK* by disconnecting the energy sensor pathway, thereby making these mutant cells resistant to low energy conditions. Importantly, the inhibition of *BRAF* signaling in combination with metabolic stress or activators of *AMPK*, leads the cells to apoptosis.

We have also assessed the in vitro and in vivo inhibition potential of the dual *PI3K/MTOR* inhibitor *PI-103* and sorafenib, as single agents and in combination, in primary melanoma cell lines. Although *PI-W3* and sorafenib inhibited melanoma in vitro cell proliferation and viability, inhibition of the *RAS* pathway appeared to be more effective. The combination of the two agents in vitro showed a synergistic effect inhibiting *RAS* and *PI3K* pathways in a cell-line dependent manner. However, no cooperative effect was observed in blocking in vivo tumor growth in immunocompetent mice. Contrary to what was expected, the data indicated that PI-103 induced immunosuppression by inducing thymus atrophy and the upregulation of *IL6*. *IUO* and *VEGF*, promoting in vivo tumor growth and inhibiting apoptosis.

In vitro studies examining the effects of the *PI3K/MTOR* inhibitor in tumor derived cell lines indicated that *PI-103* induced the activation of *STAT3* and the upregulation of the anti-apoptotic *BH3* family proteins *MCL1*, *BCL2* and *BCLXL*, favoring the in vitro survival of melanoma cells treated with sorafenib. These data favor investigating unexpected effects of rational drug combinations on immunocompetent animal models prior to conducting clinical studies .

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

VHIO Multidisciplinary Research Programs

TRANSLATIONAL RESEARCH

Director,
Translational Research Program

Joan Seoane

VHIO's Translational Research Program promotes and strengthens the integration of basic and clinical research. Our main objective is to advance the treatment of cancer by 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 a disease with two levels of heterogeneity - intertumoral and intratumoral:

Firstly, tumors from different patients are molecularly diverse. 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 disease. Moreover, 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 treatments.

Secondly, cells within a tumor are different. Tumors are formed by cells with diverse states of proliferation, differentiation, motility, and, importantly, differential sensitivity to treatments. This could explain tumor resistance to treatments through the selection of resistant clones. It is thus 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, 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. Cancer stem cells 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 described to target cancer stem cells.

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.

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 Héctor G. Palmer's group, and my group have developed these types of models of brain and colon cancer.

Eradicating cancer can only be achieved through vastly improved insight into the molecular mechanisms involved in the dual heterogeneity of cancer. VHIO's Translational Research Program is consequently dedicated to studying both inter and intra-tumoral heterogeneity towards better, more effective treatments and ultimately cure.

TRANSLATIONAL RESEARCH
GENE EXPRESSION & CANCER GROUP

PRINCIPAL INVESTIGATOR
Joan Seoane

POST-DOCTORAL FELLOWS
Judith Anido
Mª Angels Carmona
Anna Cascante
Andrea Saez
Dermot O'Sullivan

GRADUATE STUDENTS
Gerard Folch
Alba González
Laura Rodón
Francisco M. Torres

TECHNICIANS
Alexandra Arias
Isabel Cuartas
Rosa Gil
Carolina Raventós

STRATEGIC GOALS

1. **Identify novel biomarkers to develop a personalized medicine based on the characteristics of each tumor.**
Using our patient-derived models, we study brain tumors in vitro and in vivo. Thanks to the thorough study of the molecular mechanisms involved in brain tumors, we are identifying novel therapeutic targets relevant for a subset of patients. We are identifying molecular markers to select the patients to benefit from each specific treatment helping to develop novel tailored treatments against brain tumors.

2. **Develop specific treatments against each of the different cellular entities present within a tumor.**
We are identifying, isolating and studying the different cellular entities present in tumors obtained from patients treated in our Hospital. We are developing novel treatments against the different cell types within the tumor with special interest in cancer stem cells which are responsible for the resistance to chemo- and radiotherapies as well as tumor recurrence.

HIGHLIGHTS IN 2010

1. In 2010 we published an article in *Cancer Cell* (Anido et al. Cancer Cell 2010), identifying a cellular entity with cancer stem cell properties in glioblastoma (GBM) and we observed that the cytokine TGFβ was critical for its behaviour.
Importantly, we showed that TGFβ inhibitors, currently under clinical development, target cancer stem cells in GBM providing a new therapeutic avenue against this cell type and we also identified the transcription factor Id1 as a therapeutic target against cancer stem cells in GBM and other tumor types.

2. We were awarded with an *Asociación Española Contra el Cáncer* (AECC) program grant which supports the multidisciplinary research that we perform at the Vall d'Hebron University Hospital and allows our group to undertake the most challenging and ambitious projects.

JOAN SEOANE

Principal Investigator,
Gene Expression & Cancer Group

SUMMARY

VHIO's Gene Expression and Cancer Group studies tumor heterogeneity and cancer stem cells with the aim of improving diagnosis and treatment of cancer. The group focuses on the study of brain tumors extrapolating discoveries to other tumor types to ultimately uncover the molecular mechanisms involved in the genesis and progression of cancer. Research is carried out in a multidisciplinary manner in close collaboration with oncologists, neurosurgeons, pathologists, radio-therapists, radiologists and other medical specialties involved in brain tumor treatment and care.

Glioma is the most common of all brain tumors and has morphologic and gene-expression characteristics similar to glia, the support cells of the brain. The most malignant form of glioma - glioblastoma (GBM) - is one of the most aggressive human cancers. GBM is usually recalcitrant to radio- and chemotherapy, with an extremely poor prognosis. Treatment for these malignancies remains elusive and progress in this area of research is paramount.

Our studies are mostly based on cells obtained from patient-derived tumors. We obtain tumor samples 30 minutes after surgery and set up primary cultures as well as isolate cell populations from the tumor such as the cancer stem-cell-like pool. The study of patient-derived cells provides us with much 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 for human glioma is of great interest for the study of the molecular mechanisms involved in cancer and evaluating the efficacy of pharmacological compounds.

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

TRANSLATIONAL RESEARCH
STEM CELLS & CANCER GROUP

PRINCIPAL INVESTIGATOR
Héctor G. Palmer

POST-DOCTORAL FELLOWS
Isabel Puig
Stephan Tenbaum

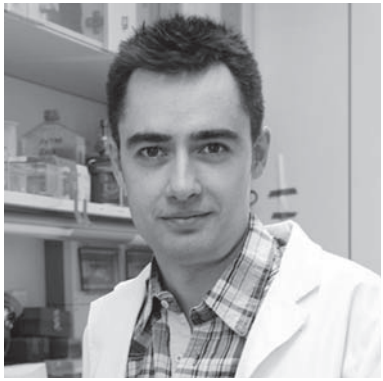
TECHNICIAN
Irene Chicote

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 Cancer Stem Cells (CSCs) 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 2010

1. Revealing the physiological role of Vitamin D receptor as an essential factor to block Wnt/beta-catenin oncogenic activity in colon cancer progression.
2. We described the capacity of PI3K/AKT and Wnt/beta-catenin signalling pathways cooperating to induce colon cancer metastasis.
3. The identification of one of the first mechanisms of resistance to PI3K and AKT inhibitors currently being tested in multiple clinical trials.
4. Discovering new populations of CoCSCs with enhanced drug-resistance.



HÉCTOR G. PALMER

Principal Investigator,
Stem Cells & Cancer Group

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 promote re-growth of the tumor.

Colorectal cancer is a disease of high social impact and is therefore 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. The benefit of PI3K and AKT inhibitors is currently being evaluated in several clinical trials. We are studying the efficacy of blocking these pathways as a new frontier in cancer treatment that aims to eliminate CSCs and achieve complete tumor remission, minimizing relapse.

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

VHIO Multidisciplinary Research Programs

CLINICAL RESEARCH

Director,
Clinical Research Program

Josep Tabernero

Since VHIO was established in 2006, we have addressed our best efforts in developing high-quality translational & clinical research that could translate into the benefit of cancer patients. Our Clinical Research Program (which integrates highly multidisciplinary cancer teams) is committed to developing novel agents directed to specific signaling pathways in cancer. Over the last few years, we have pioneered and accomplished important multinational studies involving both preclinical and early-drug development research studies as well as phase III clinical studies.

One of our main strengths is undoubtedly the tight connectivity and cooperation between basic and clinical researchers. As a result of such partnership we are accelerating important research findings from the laboratory to the bedside. Our programs also incorporate surgeons, radiotherapists, pathologists and molecular biologists to better optimize the different treatment approaches in a truly multidisciplinary setting. This approach, coupled with the excellent reputation of our professionals, has encouraged the participation of our teams in a number of international cooperative projects during 2010. As testament to the solidness of such collaborations and our own individual projects, we have also witnessed an important increase in publications in high-impact scientific journals covering cancer-related disciplines.

In terms of clinical studies, VHIO leads a significant number of clinical trial programs (over 100 in 2010) designed to identify more effective cancer therapies. Our pathologists have developed considerable expertise in employing pioneering new techniques to diagnose cancer accurately, based in cutting-edge technologies in our research facilities. At a preclinical level, we have gained significant expertise in developing xenograft models with explant tumors from patients ("xenopatients") in mice, in order to mimic the patient's disease and study tumor development in optimized research models.

In 2010 we also initiated an ambitious program devoted to the study of circulating biomarkers (detection and genotyping of circulating free DNA). As part of this project, we aim to establish the role of plasma cfDNA as a predictor of response for anti-EGFR drugs and demonstrate that the measurement of plasma cfDNA quantitative and qualitative alterations may have a prognostic value in metastatic patients.

Looking ahead, we will keep on strengthening our commitment to searching for better personalized and targeted therapies against cancer, gain further insight into the key elements involved in cancer development, and ensure that this knowledge be promptly translated into the tools that will allow us to better prevent the disease.

CLINICAL RESEARCH
BREAST CANCER & MELANOMA GROUP

PRINCIPAL INVESTIGATOR
Javier Cortés

MEDICAL ONCOLOGISTS AND CLINICAL FELLOWS
Meritxell Bellet
Serena di Cosimo
Patricia Gómez
Eva Muñoz
José Pérez
Cristina Saura
Leticia de Mattos
Maria Jesús Vidal

STRATEGIC GOALS

1. Gain further insight into the mechanisms that make cells resistant to specific therapies, and then develop reverting strategies, with special emphasis on HER2-overexpressing cells and the PI3K –AKT-mTOR signaling pathway.
2. Research with novel chemotherapy agents in patients with heavily-pretreated metastatic breast cancer.
3. Develop new pharmacologic combinations that may increase efficacy against breast cancer.
4. Explore different breast cancer tumors and identify specific molecular targets based on genetic profiling.

HIGHLIGHTS IN 2010

1. We have studied different mechanisms of resistance of the HER2 signaling pathway.
2. We have indentified new chemotherapeutic agents for the treatment of metastatic breast cancer.
3. We have developed different approaches based on angiogenesis, PARP inhibitors, combination of different targeted agents, etc.

JAVIER CORTÉS

Principal Investigator,
Breast Cancer and Melanoma Group

SUMMARY

Our principal interest focuses on translational research and novel breast cancer drugs, especially new chemotherapy agents and therapies targeted against growth factor receptors and intracellular signaling molecules.

1. HER2 oncogene:

With the development of trastuzumab, treatment of HER2-positive breast tumors has evolved markedly. We have participated in projects aimed at optimizing treatment with trastuzumab (Cortés J, et al. *J Clin Oncol* 2009; Leyland-Jones B, et al. *J Clin Oncol* 2010). However, our knowledge continues to expand about many mechanisms of resistance that lead to disease progression and ultimately death of many patients. We discovered how truncated forms of the HER2 receptor (Scaltriti M, et al. *J Natl Cancer Inst* 2007) and quantitative alterations of cyclin E (Scaltriti M, et al. *Proc Natl Acad Sci USA* 2011) are associated with resistance to trastuzumab. We observed how complete blockage of the HER2 receptor with trastuzumab and pertuzumab (a monoclonal antibody directed against the HER2 receptor domain II) shows benefits in patients previously resistant to trastuzumab (Baselga J, et al. *J Clin Oncol* 2010). Our group was also the driving force behind a new theory regarding biological drugs, namely, "the combination of two or more drugs may be active even though patients have progressed through each of them separately." We were the first to observe this phenomenon in patients.

2. Intracellular signaling molecules:

We have been actively involved in the development of "small molecules" directed against various intracellular therapeutic targets. Among the most interesting projects is that which is aimed at inhibitors of SRC, a molecule involved in cell proliferation. Our work in this field has led us to develop dasatinib, not only in monotherapy, but also in combination with capecitabine (Somlo G., Cortés J. submitted), and to the development of numerous PI3K and mTOR inhibitors (Saura C, et al. ASCO 2010), AKT inhibitors and others.

3. Angiogenesis:

We have been extremely involved in the development of drugs against tumor angiogenesis, especially bevacizumab, an antibody directed against VEGF (Miles D, et al. *J Clin Oncol* 2010), and sunitinib, a small molecule particularly active against the VEGFR (Bergh J, et al., *J Clin Oncol* 2010 (in press)). We have led several studies to better define the toxicity of bevacizumab in breast cancer (Cortes J, et al. *Ann Oncol* (In press)). We believe that this toxicity not only depends upon the drug but also on the tumour type against which it is used (Cortés J, et al. *JAMA* 2009).

4. New chemotherapeutic agents:

We have headed the clinical development of several chemotherapeutic drugs for the treatment of breast cancer. We have actively participated in the clinical development of eribulin, a new antitubulin drug with a novel mechanism of action. The phase II study results were recently published (Cortés J, et al. *J Clin Oncol* 2010) and the EMBRACE study results (Cortés J, et al. Lancet in press), have led to the approval of this drug for the treatment of patients with metastatic breast cancer by the FDA.

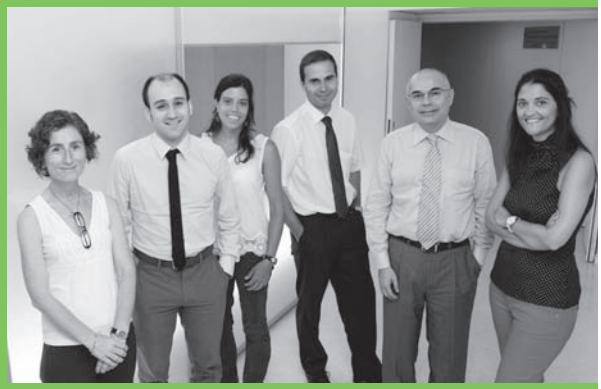
We are also Principal Investigators of different international registry studies with new chemotherapeutic drugs.

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:
www.vhio.net

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 Elez
Mª Rosa Gallego
Teresa Macarulla
Manuel Ruiz



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 Union Framework Calls as well as other contexts.
4. Collaboration with other VHIO groups including Proteomics, Genomics, and Stem Cells and Cancer.

HIGHLIGHTS IN 2010

1. Collaboration with several international research groups of excellence as well as participation in FP7 supported projects.
2. Early Clinical Research: drug development & phase I clinical trials in solid tumors with particular emphasis on developing molecular targeted therapies.
3. Molecular Markers in Gastrointestinal Malignancies: furthered insight into prognostic and predictive factors for response and efficacy with targeted agents in different gastrointestinal malignancies.
4. 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 by the European Medicines Agency (EMA) of targeted drugs.

JOSEP TABERNERO

Principal Investigator
Gastrointestinal & Endocrine Tumors Group

SUMMARY

In 2010, we carried out basic research in collaboration with VHIO´s Growth Factors Group as well as other internationally renowned research institutes and universities including the Weizman Institute, Rehovot (Israel); Broad Institute, Massachusetts (USA); University of Michigan, Ann Arbor (USA); and University Hospital Gasthuisberg, Leuven (Belgium). We have provided the rationale for several research studies, collecting clinical samples for validation of experimental endpoints and the discussion and manuscripts for these studies. We are also collaborating with several international institutions on projects partially funded by the 7th European Union Framework Project (FP7).

Early Clinical Research: we are particularly interested in drug development and phase I clinical trials in solid tumors and especially focused on the development of molecular targeted therapies aimed at 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 phase I clinical trials.

Molecular Markers in Gastrointestinal Malignancies: the overarching objective of our research is to increase 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 down 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 with the objective of demonstrating improvements in the care of these diseases (the majority are phase II and phase III clinical trials). We have designed several investigator-initiated clinical trials aimed at answering many unresolved, critical questions. We have participated and contributed to the design of several clinical trials - many of which have been developed in the context of national and international cooperative groups and some sponsored directly by pharmaceutical companies. In this regard, our group has pioneered the consecution of clinical trials that have leaded to the approval by the European Medicines Agency (EMA) of targeted drugs. The most renowned being the case of 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 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

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

PRINCIPAL INVESTIGATOR
Joan Carles

MEDICAL ONCOLOGISTS AND CLINICAL FELLOWS
Jordi Rodón
Claudia Valverde
Rafael Morales
César Serrano
Cristina Suárez

STRATEGIC GOALS

1. Design and development of clinical trials for all the malignancies covered by our group.
2. Conduct clinical trials at different stages of the disease with emphasis on a histology-tailored design.
3. Active collaboration of physicians from the different disciplines involved in GU (pathologists, urologists, radiotherapists and medical oncologists) to advise fellows and to develop doctoral theses.
4. Consolidation of a translational research platform for glioblastoma, in collaboration with VHIO's Gene Expression and Cancer Group led by Joan Seoane.
5. Creation of a translational platform for sarcomas and basic research in partnership with the Biomedical Research Institute of Bellvitge (IDIBELL), Barcelona, and the Cancer Research Centre of Salamanca (CIC).

HIGHLIGHTS IN 2010

1. Consolidation of clinical trials with new drugs for most GU malignancies.
2. Consolidation of the Committee on Nervous System (CNS) Tumours, with the development of several multidisciplinary clinical trials.

JOAN CARLES

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

SUMMARY

Our group is interested in both clinical and translational research with broad experience and 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 in the treatment of renal cell carcinoma, such as the Cleveland Clinic, Cleveland (USA). We are conducting an observational clinical study in renal cell carcinoma and also collaborating with the Biomedical Research Institute of Bellvitge (IDIBELL), Barcelona (Spain), in a translational research study of angiogenesis resistance mechanisms in renal cell carcinoma.

Another key area is the development of several multidisciplinary clinical trials in CNS tumors as well as the consolidation of our translational research platform for glioblastoma in collaboration with VHIO's Gene Expression & Cancer Group led by Joan Seoane.

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 close collaboration with the Biomedical Research Institute of Bellvitge (IDIBELL), Barcelona, and the Cancer Research Center of Salamanca (CIC - Spain).

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 excellence 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 2011 visit the VHIO Scientific Report 2010 online at:

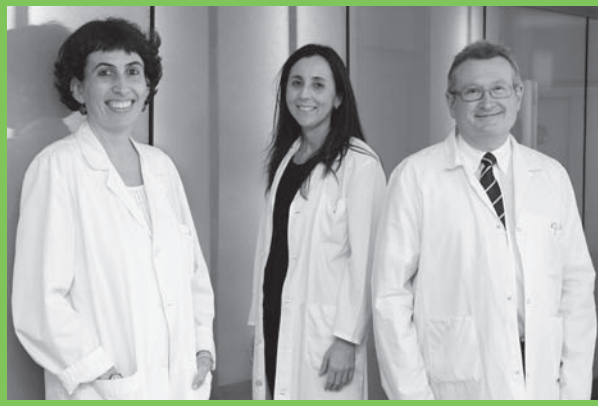
www.vhio.net

CLINICAL RESEARCH

HEAD, NECK & GYNECOLOGICAL TUMORS GROUP

PRINCIPAL INVESTIGATOR
Josep Maria del Campo

MEDICAL ONCOLOGISTS
Isabela Diaz de Corcuera
Ana Oaknin



STRATEGIC GOALS

1. Our main focus is clinical research. We are therefore dedicated to being active members in the most important cooperative groups in Head, 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 2010

1. In 2010 we have achieved two important goals. The first has been to join 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 be run in many European Gynecologic Cooperative Groups.

JOSEP MARIA DEL CAMPO

Principal Investigator
Head, Neck & Gynecological Tumors Group

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 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 Hospital as well as other Spanish and international groups. Various departments including maxillofacial, oral, gynecological and pathology teams actively participate with us in our many projects.

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

CLINICAL RESEARCH
HIGH RISK AND CANCER PREVENTION GROUP

PRINCIPAL INVESTIGATOR
Judith Balmaña

STAFF SCIENTISTS
Nina Bosch
Begoña Graña

CLINICAL NURSE SPECIALIST
Neus Gadea

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 and prevention of hereditary breast cancer.
4. Early detection of prostate cancer in *BRCA* mutation carriers.
5. Development of a clinical and molecular database for adult survivors of Fanconi Anemia and evaluation of their cancer risk.
6. Identification of new genes involved in hereditary cancer through application of next generation sequencing.
7. Validation of prediction models in Lynch syndrome.

HIGHLIGHTS IN 2010

1. Participation in international clinical trials with PARP inhibitors for *BRCA*-associated tumors.
2. Participation in an international study for early detection of prostate cancer in *BRCA* mutation carriers (IMPACT).
3. Participation in a national study to assess the role of breast density as a risk factor for breast cancer in *BRCA* mutation carriers.
4. Participation in the development of PREMM1,2,6 model for Lynch syndrome.

JUDITH BALMAÑA

Principal Investigator,
High Risk and Cancer Prevention Group

SUMMARY

We are committed to developing specific new targeted therapies for patients with hereditary cancer, as well as for 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 may 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: *Impacto clínico del asesoramiento y estudio genético en síndromes de predisposición hereditaria al cancer*, PI Judith Balmaña). We also analyzed the intake of prophylactic surgeries among BRCA mutation carriers in our setting through analysis of our own Clinical Database.

We are collaborating in the international study IMPACT (Identification of Men with a genetic predisposition to ProstAte Cancer : Targeted Screening in BRCA1/2 mutation carriers and controls) to analyze the efficacy of early detection of prostate cancer in patients with a mutation in the *BRCA1/2* genes and are participating in a national study to determine the role of breast density as a risk factor for breast cancer in women with mutations in the *BRCA1/2* genes.

In the field of genetic epidemiology, we have participated in two studies to determine the prevalence of PALB2 mutations in familial breast cancer. We have also 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 National Institutes of Health (NIH - USA): Validation and extension of the PREMM model for mismatch repair gene mutations, to validate the PREMM1,2,6 predictive model for identification of Lynch syndrome in population and clinical-based cohorts.

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

CLINICAL RESEARCH
ONCOGENETICS GROUP

PRINCIPAL INVESTIGATOR
Orland Díez

STAFF SCIENTISTS
Sara Gutierrez,
Sandra Bonache

TECHNICIANS
Miriam Masas
Anna Tenés

GRADUATE STUDENT
Gemma Montalbán

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 2010

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

ORLAND DÍEZ

Principal Investigator,
Oncogenetics Group

SUMMARY

Over the last five years our group has developed its research activity in two main areas: 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.

In the area of 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).

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

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. Integrate programs, with quality and efficiency criteria, for patients suffering from cancer in the areas of expertise of the Vall d'Hebron University Hospital (with special emphasis on patient care in radiation oncology).
2. Contribute, streamline and enhance all aspects related to improving prevention, diagnosis, treatment, monitoring, education and cancer research.

HIGHLIGHTS IN 2010

1. The development of the Intensity Modulated Radiation Therapy (IMRT) program. We have successfully implemented it for prostate, breast, and head and neck cancer.
2. Development of the stereotactic radiotherapy program in pediatrics, specially focused on brain tumors and retinoblastoma.

JORDI GIRALT

Principal Investigator,
Radiation Oncology Group

SUMMARY

Our group is composed of specialists in radiation oncology working on specific areas of tumors, each of whom carry out their own respective line of research. We collaborate with the Vall d'Hebron Hospital's Department of Physics to develop quality control programs and also for clinical research projects associated with new technologies such as PET planning, adaptive radiation therapy for head and neck tumors or Intensity Modulated Radiation Therapy (IMRT).

Our three main areas of interest surround concurrent chemo radiotherapy, clinical applications of targeted agents with radiation, and clinical application of new technology and quality control.

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

CLINICAL RESEARCH THORACIC TUMORS GROUP

PRINCIPAL INVESTIGATOR
Enriqueta Felip

MEDICAL ONCOLOGISTS
Susana Cedrés
Victor Freixinós
Pablo Martínez

CLINICAL TRIAL COORDINATOR
Oriol Nualart

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

HIGHLIGHTS IN 2010

1. Translational research achievements in lung cancer (ALK, ERBB2 and ERBB3 determinations, prognostic and predictive value) and in mesothelioma (PI3K pathway determinations).
2. Collaboration with a European multidisciplinary research group (European Thoracic Oncology Platform, ETOP).
3. Publication of the ESMO Consensus Conference in Lung Cancer (Lugano 2010) conclusions.

ENRIQUETA FELIP

Principal Investigator,
Thoracic Tumors Group

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 also contribute to early drug development as well as 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 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

VHIO Multidisciplinary Research Programs

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, Joan Seoane, and Joaquín Arribas acting in a scientific advisory capacity in Molecular Pathology, Cancer Genomics, and Proteomics respectively.

PROTEOMICS GROUP

JOAQUÍN ARRIBAS

Director, Preclinical Research Program

Cancer biomarker research aims to develop non-invasive tests to score cancer risk, allow early cancer detection and better management of cancer patients. An appropriate tumor classification ensures the selection of the most appropriate therapy. In addition, useful biomarkers should enable the monitoring of disease progression, regression or recurrence as well as the assessment of response to therapies.

This area of research has recently experienced a dramatic acceleration due to the unprecedented development of proteomic technologies among other factors. Querying biomarkers in very small cancer samples as well as in surrogate samples including blood or expectorations is now possible.

The 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 already made important contributions, as shown by the more than a dozen publications in high-impact factor journals. In addition, the Proteomics Laboratory is a founding partner of *Proteored*, the Spanish Network of Proteomic Laboratories. Undoubtedly, the Proteomics Group, along with our Pathology Department, places VHIO in the best position to conduct cutting edge discovery in the cancer biomarker field.

GENOMICS GROUP

JOAN SEOANE

Director, Translational Research Program

In recent years seminal discoveries have revealed genetic abnormalities associated with cancer, such as HER2, BRAF, ALK, EGFR. The identification of key cancer genes has led to the development of new molecular targeted therapies that interfere, and revert, tumor initiation and progression processes. While these advances are highly encouraging, our current bottleneck in the field of cancer therapeutics is in the translation of the available knowledge on genetic alterations into therapeutic benefit.

The matching of specific genetic alterations with the most appropriate therapy is a major step forward towards the goal of personalized medicine in cancer. VHIO's Cancer Genomics Group develops technology that allows the application of mutation profiling approaches to facilitate patient stratification for the rational exploration of targeted cancer therapeutics. In addition, the thorough study of cancer genomes performed by the group is facilitating the discovery of novel mutations that determine sensitivity or resistance to pharmacological compounds as well as implementing the molecular diagnosis of cancer.

Our Cancer Genomics Group is uniquely positioned to test this personalized approach to therapy since VHIO is leading a large amount of early clinical studies with molecular targeted agents and we have access to the tumors of all our patients. Ana's team is therefore successfully linking molecular diagnosis with better treatment.

MOLECULAR PATHOLOGY GROUP

JOSEP TABERNERO

Director, Clinical Research Program

The Molecular Pathology Group is one of VHIO's Core Technology Platforms incorporating highly qualified professionals including pathologists and technicians with extensive experience in molecular diagnostics.

Regarding sample management, several techniques are employed including immunohistochemistry, fluorescence in situ hybridization (FISH), immunofluorescence (direct, indirect); "CellSearch" technology (to detect CTCs in peripheral blood by isolation and enumeration); image analysis; tissue bank management and maintenance; DNA and RNA extraction, quantification and quality assessment; tissue microarrays; building of blocks (of cell pellets), as well as other routine techniques in pathology.

The group provides state-of-the-art diagnostics through complex and high quality testing, following accepted ethical guidelines and adopting accepted validation criteria for assay development. As a reference laboratory, the group also participates in numerous multilateral and international projects.

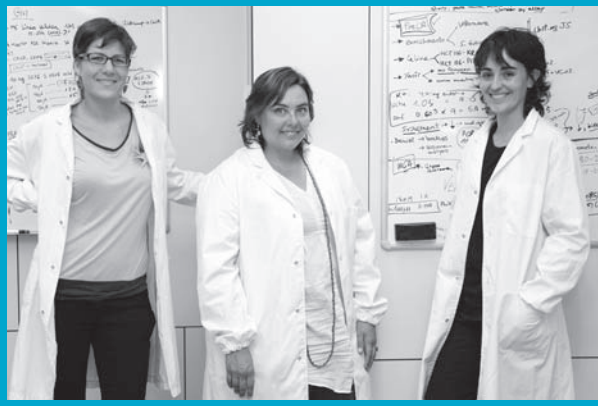
Given the translational and multidisciplinary nature of research at VHIO, the Molecular Pathology Group represents a critical element at the core of our activities. It actively participates in all research projects involving the use of human tissues collected from our patients including the development of xenograft models to study the evolution of the disease in an optimal model.

We will continue to implement the most innovative techniques required to ensure that molecular pathology at VHIO continues to operate as a reference laboratory contributing and collaborating with other VHIO groups and projects for the benefit of our patients.

CORE TECHNOLOGIES
CANCER GENOMICS GROUP

PRINCIPAL INVESTIGATOR
Ana Vivancos

TECHNICIANS
Ginevra Caratú
Leire Mendizibal



STRATEGIC GOALS

1. Provide cutting-edge applications in Cancer Genomics by means of new technologies and protocol development.

   Tumor samples have been fixed in formalin and embedded in paraffin (FFPE) historically, which means there are thousands of samples conserved in this way in pathology departments. While this is useful for long-term conservation and IHC, DNA is heavily modified and fragmented. We aim to develop protocols and techniques that allow us to extract the maximum amount of genomic data from FFPE-derived DNA.

HIGHLIGHTS IN 2010

1. Design and implementation of cancer-type specific panels of assays to detect somatic mutations with MassARRAY technology.
2. The lab has developed and validated a panel of 500 assays to be used with MassARRAY (Sequenom) interrogating most frequent mutations observed in oncogenes as well as in tumor suppressor genes (source, COSMIC db).
3. The establishment of protocols that allow efficient and robust exome capture from FFPE-derived DNA.

ANA VIVANCOS

Principal Investigator
Cancer Genomics Group

SUMMARY

The Cancer Genomics Group is a translational laboratory, bridging the basic and clinical fields of research.

We are actively collaborating in multidisciplinary projects, such as prescreening of somatic mutations in patients that are candidates to be enrolled in Phase I clinical trials with targeted therapies, e.g. PIK3CA, AKT1, BRAF or MEK inhibitors. We are also involved in profiling somatic mutations and identifying driver mutations, studying clonal populations etc. in several tumor types.

Protocol development and improvements in Next-Gen Sequencing is a key research area in our lab, as well as developing new assays to test mutations with iPlex chemistry (MassARRAY, Sequenom).

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

CORE TECHNOLOGIES

MOLECULAR PATHOLOGY GROUP

ATTENDING PHYSICIANS
Claudia Aura
Ludmilla Prudkin

LABORATORY SUPERVISOR
José Jiménez

LABORATORY ASSISTANT
Mª Ángeles Díaz

TECHNICIANS
Elisabeth Llonch
Sandra Paola Mancilla
Nerea Peiró
Sonia Rodríguez
Gertrudis Sánchez

STRATEGIC GOALS

1. Molecular pathology strategies serving clinical oncology.
2. Act as a 'translator' between basic and clinical research.
3. Biomarker discovery.
4. Participate as a central and local laboratory in clinical trials performing pharmacodynamic studies.

HIGHLIGHTS IN 2010

1. Run a paraffin block archive with over 25,000 tumors and other relevant pathological specimens, as well as a tumor bank with over 6,000 high quality frozen samples.
2. Participated in 65 clinical trials, acting as central laboratory in many of them.
3. Performed over 5,800 stainings, and sample material belonging to more than 370 patients have been included in either clinical trials or examined in a pre-screening setting.
4. Explored HER2 pathways in depth as well as many downstream targets including PI3K-Akt, mTOR, FGFR, C-MET, Sonic-HedgeHog pathways, among others.
5. Evaluated pathway inhibition and downstream target behavior using preclinical models, and/or resistance, in the quest for biomarkers that anticipate prognosis or drug-response.
6. Improve the use of new technologies including automated image analysis based on immunofluorescence (AQUA™, HistoRx).
7. Increased experience in using the Veridex's platform Cell Search™.

SUMMARY

The Molecular Pathology Group translates findings from basic research to the clinic. Working in a multidisciplinary environment our work not only serves oncologists by offering patients newly discovered treatments as well as anticipating the response of patients, but also provides basic researchers with a means through which to validate their findings.

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 25,000 tumors and other relevant pathological specimens, as well as a tumor bank with over 6,000 high quality frozen samples, routinely used for mRNA and Protein studies.

During 2010 we have participated in 65 clinical trials, acting as a central laboratory for many of them. Routinely, we perform immunohistochemistry studies with antibodies used as diagnostic markers (proliferation, angiogenesis, oncogenes, lack of suppressor genes, mutated genes) as well as to characterize new therapeutic targets for the development of new specific inhibitors (more than 100 optimized antibodies).

This year we have performed over 5,800 stainings and sample material belonging to more than 370 patients have 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. The work performed by this laboratory has been essential in translating findings from the laboratory to clinical trials.

We have explored HER2 pathways as well as many downstream targets, including PI3K-AKT, mTOR, FGFR, C-MET, Sonic-HedgeHog 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 drug-response. These models serve as the ideal resource to identify these biomarkers in order to use them in further clinical trials.

In 2010 we have also improved the use of new technologies including automated image analysis based on immunofluorescence (AQUATM, HistoRx). This platform can quantify immunofluorescent intensities avoiding intra- and inter-observer variation and, more importantly, to mask the population of interest alone, excluding other cell types from the analyses.

We have also developed the use of the Veridex's platform Cell SearchTM that allows the detection and characterization of circulating tumor cells from patients' blood samples, this innovative technology will help in following up treatments and identifying patients with high risk of recurrence.

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

CORE TECHNOLOGIES
PROTEOMICS GROUP

PRINCIPAL INVESTIGATOR
Francesc Canals

POST-DOCTORAL FELLOWS
Juan Josep Bech
Marta Monge

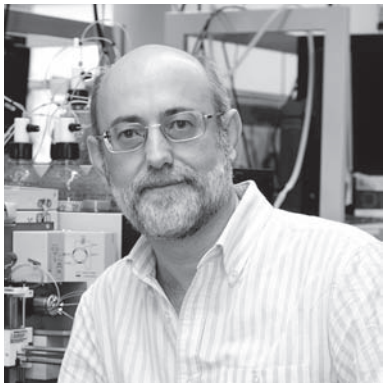
TECHNICIAN
Nuria Colomé

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 2010

1. Proteomics services to VHIO and Vall d'Hebron University Hospital groups, *Instituto Salud Carlos III* Cancer Research and *ProteoRed* networks.
2. Description of a new mechanism involved in metastasis of breast cancer through the ADAMTS1 proteolytic cleavage of the protein Semaphorin 3C.
3. 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.
4. Work towards the validation of a biomarker signature to help selection of patients for TGFbeta inhibitor based treatment of glioma.



FRANCESC CANALS

Principal Investigator,
Proteomics Group

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.

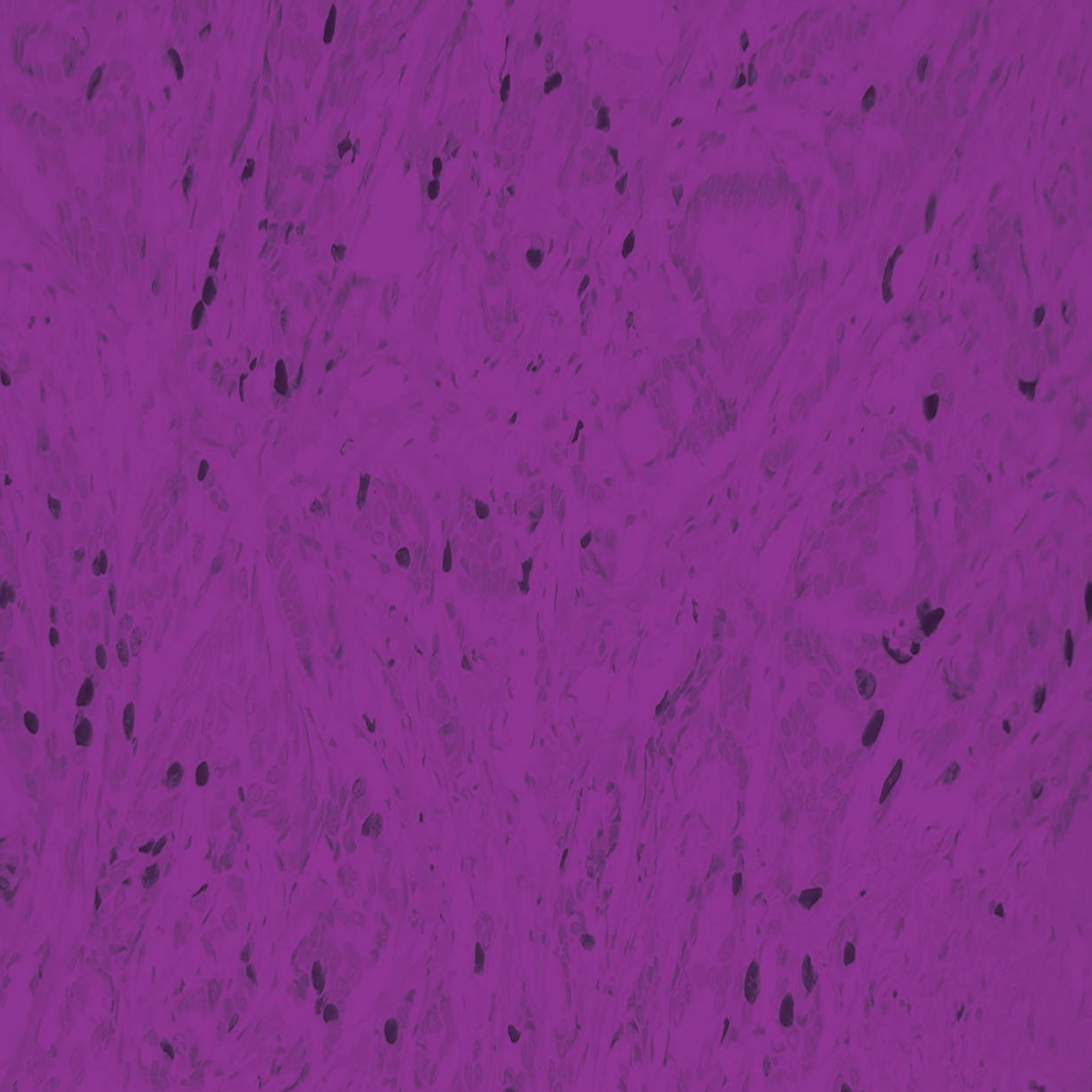
Our main line of research focuses on the application of proteomic techniques to the identification and characterization of substrates of metalloproteases involved in tumor progression. Metalloproteases of the ADAM and ADAMTS families are known to play a crucial role in the regulation of the tumor microenvironment 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.

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

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net



VHIO CLINICAL TRIALS CORE SERVICES & UNITS

VHIO
CLINICAL TRIALS
CORE SERVICES & UNITS
CLINICAL TRIALS OFFICE

HEAD, CLINICAL TRIALS OFFICE

Irene Marimon

HEAD, CLINICAL TRIALS OFFICE FOR BREAST TRIALS

Susana Muñoz

HEAD, CLINICAL TRIALS OFFICE FOR PHASE 1 TRIALS

Gemma Sala

CLINICAL TRIALS MANAGEMENT COOPRDINATOR

Yasmina Bernabé

CLINICAL TRIALS COORDINATORS

Marta Beltran, Raquel Espallargas, Violeta Esteban, Beatriz García, Cristina González, Maria Herranz, Jordi Humbert, Larua Maynés, Oriol Nualart, Oriol Olivé, Olga Padrós, Adelaida Piera, Mireia Sanchís, Elisabet Sicart, Meritxell Soler, Olga Vidal, Iratxe Puebla

DATA ENTRY

Judith Alonso, Meritxell Baño, Beatriz Blanco, Julia Esteban, Belen García, Gloria García,Lidia Martínez, Xavier Martínez, Sergio Pérez, Àngels Porras, Rita Ramadas, Andrea Retter, Isabel Rico, Rosa Maria Romero, Alba Vilarrasa

HEAD OF DATABASE MANAGERS OFFICE

Gessamí Sánchez-Ollé

DATABASE MANAGERS

Débora Moreno, Núria Murtra

ASSISTANTS

Núria Carballo, Angel Marín

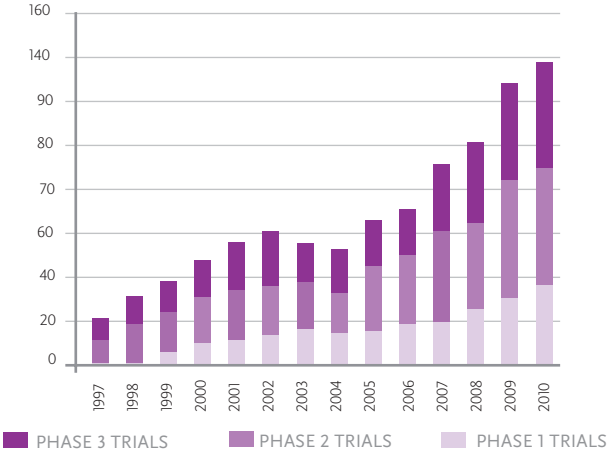
STRATEGIC GOALS

1. Consolidation as an international reference hospital for clinical trials in oncology.
2. Contribute to the development of new treatments for cancer.
3. Guide patients taking part in a trial to comply with the requirements of the protocol.
4. Ensure that the data is available on time and of high quality.
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 form initiation to close.

HIGHLIGHTS IN 2010

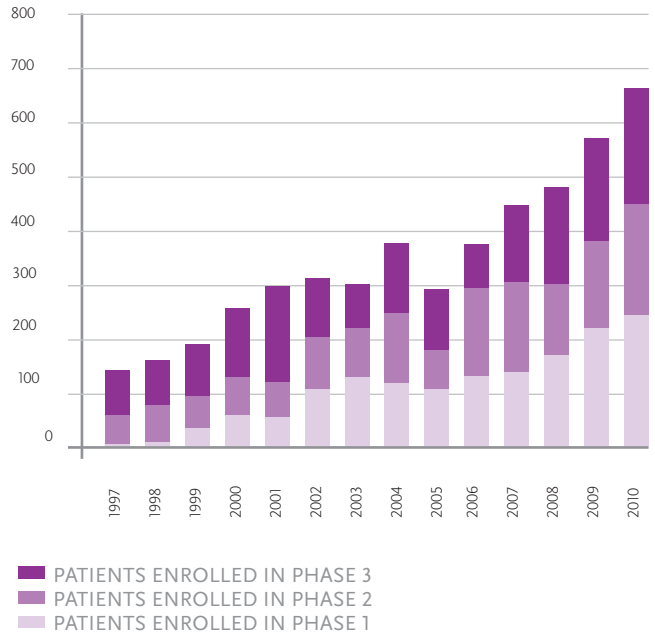
1. Increase in the nº of patients enrolled in clinical trials phase 1,2 and 3:

TOTAL ANNUAL RECRUITMENT IN CLINICAL TRIALS



2. Increase in the nº of clinical trials performed. We have also witnessed a steady increase in the number of trials run by our department, Phase I in particular (please see Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa" on **pages 10-11** and **68-69** of this Scientific Report for further information).

ANNUAL DISTRIBUTION OF PHASE 1,2 AND 3 TRIALS



3. Completion and inauguration of our new phase I Unit: Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa".

IRENE MARIMON
Head, Clinical Trials Office
SUSANA MUÑOZ
Head, Clinical Trials Office for Breast Trials
GEMMA SALA
Head, Clinical Trials Office for Phase 1 Trials
YASMINA BERNABÉ
Clinical Trials Management Cooprdinator

SUMMARY

Clinical trials play an essential role in the development of new therapies to combat cancer since they constitute the methodological basis of scientifically recognized clinical research. They involve ethical and highly controlled experimental research in humans once the preclinical experimental development phase of a new drug has shown that the drug may represent an improvement on the available or standard treatment for patients at a given moment. Our dedicated efforts aimed at both improving current cancer treatment as well as offering new therapeutic choices to our patients, represent the driving force behind the development of our Clinical Trials Office since it was established in 1997.

Clinical Trials 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 considered as potential candidates for inclusion in our trials. While some patients are not eligible/do not agree to take part in a clinical trial, we offer this option to all who meet the necessary criteria established in the different research protocols. This, coupled with our desire to become an international reference in cancer treatment, has spurred a significant increase in the number of our patients currently starting a new treatment in clinical trials (see table in ´Highlights´ section). In 2010, a total of 673 patients were enrolled in phase I,II and III clinical trials.

Our Clinical Trials Office comprises a team of thirty professionals including study coordinators, data managers and administrative staff working on more than 150 trials. They are responsible for the logistics, coordination, data management and also the start-up of new studies.

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

Our Office coordinates studies from phase I to phase III and is divided into three separate teams: Phase I, Breast Cancer and Phase II-III. Since June 2010, following the completion of the new Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa" (please see **pages 10-11** of this Scientific Report for further information), all early phase trials are conducted at this facility spanning 1000m2 with the capacity of administering treatment to 400 patients per year participating in early development clinical trials. The UITM facilitates essential new studies on innovative drugs and therapeutic leads aimed at improving the pharmacological treatments for cancer and reduce their toxicity.

The Vall d'Hebron University Hospital's Oncology Department is widely considered as prestigious by the pharmaceutical industry and has consequently established itself as a center of reference through which to conduct complex clinical trials involving a highly restricted number of participating centers selected for their outstanding quality and optimal ability to conduct state-of-the-art research. We have therefore taken part in phase I trials of different drugs including Xeloda, Herceptin, Tarceva etc., enabling the pharmaceutical industry to market novel therapies aimed at cancerous cells including drugs such as Cetuximab, Iressa, Xeloda, and Herceptin.

We also take part in clinical trials promoted by the pharmaceutical industry as well as those developed in our department as part of a collaboration with other hospitals. Lastly, the Clinical Trials Office has been involved in training future study coordinators, data managers and junior CRAs through the organization of a 36-hour post-graduate course, in its sixth edition in 2010.

To find out more about our Clinical Trials Office, our horizons for 2011 visit the VHIO Scientific Report 2010 online at:
www.vhio.net

For more information about our activities at the Research Unit for Molecular Therapy of Cancer (UITM) - "La Caixa", visit the VHIO Scientific Report 2010 online at:
www.vhio.net

ANGELES PEÑUELAS

Supervisor

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 **pages 10-11** and **68-69** for more information) and the Clinical Trials Office (see **page 70**). Incorporating medical oncologists, specialists in molecular pathology, pharmacists exclusively dedicated to this field (see VHIO´s Clinical Research Oncology Pharmacy Unit on **page 70**), 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.

VHIO CLINICAL TRIALS CORE SERVICES & UNITS

CLINICAL RESEARCH ONCOLOGY NURSES

SUPERVISOR
Ángeles Peñuelas

NURSE COORDINATORS
Lydia Vélez
Sonia Valverde

NURSES
Anna Aliau
Mª Elena de Cabo
Meritxell Cucurell
Marta Mate
Núria Membrives
Mireia Milán
Isabel Muñoz
Alex Sierra

NURSING ASSISTANTS
Purificación Cardenete
Alicia López
Elena Oller
Mª Ascensión Martín

VHIO CLINICAL TRIALS CORE SERVICES & UNITS

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

DIRECTOR OF CLINICAL RESEARCH AT VHIO
Josep Tabernero

CLINICAL COORDINATOR
Jordi Rodón

HEAD OF CLINICAL TRIALS OFFICE FOR PHASE I TRIALS
Gemma Sala

MEDICAL ONCOLOGISTS
Leticia de Mattos, Rodrigo Dienstmann, Maria Elena Élez, Teresa Macarulla, Cristina Saura

CLINICAL TRIAL COORDINATORS
Marta Beltran, Maria Herranz, Lidia Martínez de Arenzana, Laura Maynes, Adelaide Piera, Elisabet Sicart

DATA MANAGER
Lidia Martínez de Arenzana

PHARMACIST
Maribel Magaña

NURSE SUPERVISOR
Angeles Peñuelas

NURSES
Alicia López, Lydia Vélez

NURSE COORDINATOR
Sonia Valverde

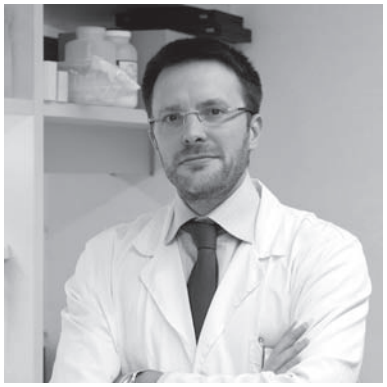
SECRETARY
Teresa Mendoza

STRATEGIC GOALS

1. To have a broad portfolio of the most promising novel therapies for cancer.
2. Perform molecular analysis of patient tumors in order to select the best possible treatment with the available experimental treatments.
3. To treat patients in Phase I trials in a safe environment, with an experienced and multidisciplinary team.
4. Understand the mechanism of action of targeted therapies and to find predictive markers to better select in which cases these treatments work better.

HIGHLIGHTS IN 2010

1. We have rapidly become one of the leading institutes worldwide with the most expertise in PI3K/akt/mTOR inhibitors.
2. 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.
3. We have performed 17 clinical trials with patients selected on molecular alterations (mutations in AKT, PIK3CA, PTEN, ALK, BRAF, NRAS, KRAS, FGFR1 and 2, MET; amplifications in HER2, AKT 1,2, and 3, FGFR1, MET, and alteration in protein expression of PTEN or prolactin receptor).
4. We have co-developed several molecular tests for patient screening such as disease-oriented mutation panels for Sequenom.



JORDI RODÓN

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

SUMMARY

Inaugurated in June 2010 - thanks to the support received from the Welfare Projects Division of the "la Caixa" Foundation (please see **pages 10-11** of this Scientific Report for more information), our Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa" is dedicated to working on complex clinical trials with drugs in early development (Phase I and early Phase II trials) focusing on novel targets. Our main interest surrounds proof-of-concept and proof-of-mechanism trials with targeted therapies, especially target therapies focusing on 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 the 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 therefore try to directly involve VHIO scientists in the trials (biomarker development, deep understanding of the mechanism of action, research in mechanisms of resistance) for selected projects.

In addition, we have collaborated with the Molecular Pathology and the Cancer Genomics groups to perform molecular analysis of the patients tumor in order to select the best possible treatment with the available experimental treatments one step closer to realizing the promise of personalized medicine.

Obra Social "la Caixa"

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at:

www.vhio.net

VHIO CLINICAL TRIALS
CORE SERVICES & UNITS

CLINICAL RESEARCH ONCOLOGY PHARMACY UNIT

COORDINATOR OF THE CLINICAL RESEARCH ONCOLOGY PHARMACY UNIT
Maria- Josep Carreras Soler

COORDINATOR OF PHARMACOLOGICAL RESEARCH IN ONCOLOGY SUPPORT UNIT
Laura Mañós Pujol

PHARMACISTS
Patricia Díez Duran,
Anna Farriols Danés,
Maribel Magaña Pintado,
Maria Oliveras Arenas,
Berta Renedo Miró

CLINICAL TRIALS RESUPPLIES MANAGER
Anna Martí Fabra

TECHNICIANS
Maria Hidalgo Casas,
Susana Mulet Lozano,
Sara Pizarro López

STRATEGIC GOALS

1. Achieve excellence in the quality of service we provide to the different clinical oncology research programs through optimal efficacy, efficiency and safety.
2. Ensure traceability of management and preparation of drugs for clinical trials.
3. Provide and ensure excellent control of the storage temperature of samples and prepared products.
4. Increase documented control of the accounting of drugs returned by patients in Phase I clinical trials.
5. Provide instructions and indications to patients for orally administered treatments.
6. Prepare trial drugs for parenteral administration through the integration of all phases of prescription, preparation and administration in computerized systems to prevent errors in medication.
7. Provide pharmaceutical care to patients enrolled in Phase I clinical trials to achieve optimal study treatment and increased patient safety during treatment.

HIGHLIGHTS IN 2010

In 2010 pharmaceutical activity has involved the following key areas:

1. *Management of clinical trial drugs*: we have managed clinical trial drugs for 182 active clinical trials in oncology. The number of clinical trial supplies´ deliveries totaled at 1.178.
2. *Installation of a novel system for controlling storage temperature*: 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 cell phone of the pharmacist on duty, continuously for 24 hours to check for temperature deviations.

3. *Implementation of a new safety drug accountability procedure for drugs returned by patients*: this allows either our unit´s personnel or that of the sponsor to perform drug accountability and verify treatment compliance safely, using a Cabin Vertical Laminar FLOW (CVLF).

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

5. *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).

6. *Support for, and liaison with, the trial sponsors*: dispensing personnel have taken part in 14 pre-study visits, 65 initial visits, 666 monitoring visits and 40 final visits and successfully passed 20 audits. Preparation staff have participated in 2 pre-study visits, 60 initial visits, 104 monitoring visits, 3 training visits and 11 audits.

7. *Dispensing*: a total of 9265 clinical trial drugs have been dispensed with the validation of a pharmacist. The conditioning and re-labeling of the primary containers for clinical trial drugs have also been carried out. A total of 119 Standardized Dispensing Procedures have also been drawn up and updated. 84 storage temperature data report s have been generated.

8. *Preparations*: a total of 7307 preparations of cytostatics, monoclonal antibodies and other parenteral antitumor drugs for clinical trials have been carried out . A total of 57 Standardized Preparation Procedures have been drawn up.

9. *Collateral*: preparation of documentation relating to each clinical trial for medical and nursing staff as well as for patients ranging from standard operating procedures to instructions and relating forms for patients.

10. *Implementation of a pharmaceutical care program through a pilot with six Phase I clinical trials* (*September to December* 2010): activity was extended to all Phase I clinical trials involving oral medication. During the pilot we conducted a total of 163 visits to patients in Phase I clinical trials and carried out 20 pre-screening visits, 56 screening visits, 93 follow-up visits and 5 end study visits.

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

12. *ISO9001*:2008 certification renewed.

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 and other parenteral antitumor drugs used in clinical trials in oncology, and for monitoring the clinical activity in oncology patients. It incorporates a team of pharmacists specializing in hospital pharmacy and oncology pharmacy, as well as laboratory technicians.

The Pharmacological Research in Oncology Support Program is made up of pharmacists, biologists and laboratory technicians specializing in clinical trials. The program is dedicated to managing, storing, issuing and controlling samples for clinical trials in oncology.

To find out more about us, our research, publications and even our group's horizons for 2011 visit the VHIO Scientific Report 2010 online at: www.vhio.net

Patrons:

With the collaboration of: