Vall d'Hebron Institute of Oncology

Scientific Report 2008

VHIO

VALL D'HEBRON
Institute of Oncology

Centres de recerca de Catalunya

Funding sources

VHIO benefits from both public and private funding. Public funding comes from the Catalan Ministry of Health (Departament de Salut) and the Catalan Ministry of Innovation, Research and Enterprise (Departament de, Universitats, Innovació i Empresa), both of which belong to the Catalan Regional Government (Govern de Catalunya). Private initiative is a key source of VHIO funding, either by means of competitive support or philanthropic projects.

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FOT - Fundación Olga Torres

Fundación Científica de la Asociación Española Contra el Cáncer

FMMA - Fundación Mutua Madrileña Investigación Médica

International Foundations

EMBO - European Molecular Biology Organization

BCRF - The Breast Cancer Research Foundation

Summary

Foreword

It is a pleasure to present the second scientific report of the Vall d'Hebron Institute of Oncology (VHIO).

VHIO was born in 2006 out of the necessity to bring together the basic, clinical and translational oncology research activities at the Vall d'Hebron University Hospital campus. In these two years of life, VHIO has empowered its scientific programs, increased the number of principal investigators in the basic sciences, increased the number and complexity of our early clinical trials program and also expanded its collaborations with renowned institutions around the world.

As we enter into our third year, VHIO is building more basic research laboratories, completing the construction of a new Phase I facility, and consolidating the activities in its newly created Breast Cancer Center. Our investigators are testing in the clinic new and exciting compounds that are directed against molecular targets. These agents are used at times in combination with other agents and increasingly in a background of tumor-specific genomic alterations.

2008 has also witnessed the continuous support to our Center by the Government of Catalonia and the ministries of Health and Universities and Innovation. We are also thankful to the increased support of our activities by the Cellex Private Foundation, the FERO Foundation and the Welfare Projects "la Caixa" Foundation. Their continuous support is behind many of our newly created programs as well as facilities.

These are exciting times in oncology. The increasing knowledge on the molecular basis of cancer together with the availability of novel agents and improved diagnostic methods bring the promise of a future where the mortality due to cancer will drop. At the heart of our mission is to contribute to achieve these goals and to bring to our population the best cancer care possible. We are in an unique position within VHIO to contribute to this goal.

Dr. Josep Baselga
Director of VHIO

VHIO, Vall d'Hebron Institute of Oncology

A reference center for translational research in Oncology

The Vall d'Hebron Institute of Oncology (VHIO) was established in late 2006, as a non-profit foundation, on the premises of Vall d'Hebron University Hospital (VHUH), with the aim of responding to the challenges at the forefront of oncological research.

VHUH is the largest public teaching hospital in Barcelona and one of the most important hospitals in Spain. Because VHIO's organizational structure is part of VHUH, its researchers have exceptional access to multidisciplinary clinical facilities, a large body of patients, clinical samples and state-of-the-art health care technology, all of which set VHIO apart from other research centers.

This situation, in addition to the existing equipment and laboratory structure for basic research within VHUH and a consolidated and highly productive model in cancer research, defines the key elements of VHIO's success.

The VHIO mission

- To facilitate the transfer of scientific research to pioneering clinical practice, thus enabling our patients to benefit from the very latest advances in oncological research.
- To carry out scientific research of excellence in all areas, with specific emphasis on basic, translational and clinical research.
- To promote scientific cooperation among national and international cancer research centers.
- To promote all work in the field of cancer research that contribute to improving the quality of life of people suffering from the disease and of the public in general

An important novelty of VHIO is that the institute's emphasis on clinical research facilitates a flow of dialogue between basic research and clinical innovation.

Organization

The scientific structure of VHIO is similar to that of other leading international research centers. VHIO has fifteen different research lines, each of which is headed by a principal investigator (PI). They range from basic to clinical research, and all share a fundamental confidence in the value of translational research.

Basic research teams:

- Angiogenesis Laboratory
- Animal Models Laboratory
- Gene Expression and Cancer Laboratory
- Growth Factors Laboratory
- Proteomics Laboratory
- Stem Cells and Cancer Laboratory

Clinical research teams:

- Breast Cancer Program
- Experimental Therapies Program
- Gastrointestinal Tumors Program
- Genitourinary, CNS and Sarcoma Tumors Program
- Head, Neck and Gynecological Tumors Program
- High Risk and Cancer Prevention Program
- Lung Cancer Program
- Molecular Pathology Program
- Radiation Oncology Program

VHIO is governed by the following bodies:

The Board of Trustees is the highest decision-making, representative and administrative body. It consists of a president, a vice-president and board members. Board members include representatives of both the Department of Health and of the Department of Universities, Innovation and Enterprise of the Generalitat de Catalunya (Catalan Government). The remaining board members are private-sector representatives from affiliated supporting foundations, such as the Cellex Private Foundation, the Fero Foundation and the Welfare Projects "la Caixa" Foundation.

The Executive Committee is composed of seven members of the Board of Trustees. Its main responsibility is to ensure that action plans and programs approved by the Board of Trustees are duly put into practice.

The Director of VHIO is Josep Baselga, MD. He leads the project, assesses research outcomes resulting from VHIO research efforts and, together with the Scientific Committee, holds the ultimate responsibility for scientific and strategic decisions.

The Scientific Committee is formed by:

- Josep Baselga, MD. Director of the Vall d'Hebron Institute of Oncology (VHIO), Chairman of the Medical Oncology Service, Director of the Division of Medical Oncology, Hematology, and Radiation Oncology at the Vall d'Hebron University Hospital. Investigator. Experimental Therapies Group. Vall d'Hebron University Hospital. Barcelona, Spain.
- Paul Workman, PhD. Professor of Pharmacology & Therapeutics. Director, Cancer Research UK Center for Cancer Therapeutics. Institute of Cancer Research-Royal Marsden Hospital. London, UK.
- Carlos L. Arteaga, MD. Vice Chancellor's Chair in Breast Cancer Research. American Cancer Society Clinical Research Professor. Professor of Medicine and Cancer Biology. Director, Vanderbilt-Ingram Cancer Center Breast Cancer Program. Nashville, TN. USA.
- Charles L. Sawyers, MD. Professor of Medicine. Chair, Human Oncology and Pathogenesis Program; Marie-Josee and Henry R. Kravis Chair. Memorial Sloan-Kettering Cancer Center. New York, NY. USA. Investigator. Howard Hughes Medical Institute.
- Gordon B. Mills, MD, PhD. Chairman, Department of Molecular Therapeutics. Professor of Medicine. MD Anderson Cancer Center. Houston, TX. USA.
- Martine J. Piccart-Gebhart, MD, PhD. Professor of Oncology, Université Libre de Bruxelles (ULB). Director of the Medicine Department. Jules Bordet Institute. President, Breast International Group. Bruxells, Belgique.
- Mariano Barbacid, PhD. Director. Centro Nacional de Investigaciones Oncológicas (CNIO). Madrid, Spain.
- Daniel A. Haber, MD, PhD. Director, Massachusetts General Hospital. Cancer Center. Massachusetts General Hospital. Isselbacher/Schwartz Professor of Oncology. Harvard Medical School. Boston, MA. USA. Investigator. Howard Hughes Medical Institute.

The Managing Director of VHIO is currently Laura Pellisé, PhD. VHIO is truly grateful to Mr. Xavier Aragay for his excellent work while in the post in 2008.

The Hospital

Vall d'Hebron University Hospital (VHUH) is the largest hospital in Barcelona and the second largest in Spain; it covers various facilities that cover almost all medical and surgical specialities, has more than 1400 beds, and employs over 6000 people. It also houses various teaching centers, a medical school, public health facilities, research centers, laboratories and other complementary facilities.

This environment provides VHIO with one of the best health care platforms for carrying out oncological research:

- Excellent clinical environment for the treatment of cancer diseases.
- Multidisciplinary facilities.
- University health care teams specializing in clinical and translational research.
- Basic research equipment and laboratories.
- Technological platforms: Pathological Anatomy, Genomics, Proteomics and Molecular Imaging.

The Oncology Department at VHUH

The Oncology Department of VHUH was established in 1995 to meet the new requirements of oncology care and provide a focal point for the different services in order to produce fully interrelated multidisciplinary care teams.

Since its creation, it has undergone significant quantitative and qualitative growth in the areas of patient-care, teaching and research perspective, to become a gold-standard center in Europe.

VHUH Oncology Department's patient care and clinical research currently consists of several units, grouped by disease or knowledge area; breast, digestive, lung, gynecological and head and neck, genitourinary cancer and sarcomas and, finally, high risk patients and genetic counselling. The units work as a team and are managed by a section chief.

Vall d'Hebron University Hospital Health Care Data

(Department of Oncology, 2008)

First outpatient visits	3,520
Follow-up outpatient visits	37,856
Day Hospital Treatments	42,351

Additional services, increased quality and clinical excellence

- Functional Units
- Support and Palliative Care Unit
- Clinical Guides
- High Risk and Cancer Prevention Unit
- International Fellowship Program
- International Cancer Centers networking

Construction of new facilities

- Outpatient Medical Offices
- Day Hospital
- Pharmacy Unit
- Clinical Trials Unit
- Administrative department
- BCC (surgery, medical oncology, radiology, genetics and oncology day hospital)

Oncological research at VHUH: Vall d'Hebron Institute of Oncology

VHIO's objective is to close the gap between the results carried out in laboratories and their clinical application to patient care in a quick and efficient manner, by promoting the creation of bridges that connect the needs of doctors and patients to the basic science programs and translational research lines. Thus, VHIO unites basic, clinical and translational research at VHUH in order to improve prevention, early diagnosis and treatment of cancer.

The main focus of research in recent years has been on the development of molecularly targeted agents and the identification of biomarkers that predict sensitivity or resistance to these agents.

VHIO has been involved in the clinical development of several new agents including: gefitinib, erlotinib, lapatinib, pertuzumab, m-TOR inhibitors, PI3K inhibitors, TGFß inhibitors, SRC inhibitors, insulin-like growth factor receptor inhibitors and a variety of antiangiogenic agents. Many of these agents are now approved anti-cancer therapeutic agents.

Basic Research Program

In 2008, as an integral part of VHIO, the Basic Research Program designed a new competitive project financed by the Carlos III Health Institute of the Ministry of Science and Research, entitled "Transversal Action in Cancer" with the objective of producing advances in different translational projects, such as those relating to therapies aimed at breast cancer, and the characterization of trigger cells for different tumors including glioblastoma and colon cancer. In addition, VHIO has developed complex technologies, such as isolation of surrounding tumor cells and quantification of small molecules by mass spectrometry. These technologies have been very valuable to the different clinical research projects currently under way at Vall d'Hebron University Hospital.

- **Angiogenesis Laboratory.** This group focuses on the identification of specific substrates in distinct cellular microenvironments. PI J. Carlos Rodríguez-Manzaneque
- **Animal Models Laboratory.** This group focuses on the study of proteins that may play an important role in the development and progression of human melanoma. PI Juan A. Recio
- **Gene Expression and Cancer Laboratory.** This unit focuses on the study of molecular mechanisms involved in tumor genesis and progression, specifically, the study of multiform glioblastoma. PI Joan Seoane (ICREA)
- **Growth Factors Laboratory.** This team focuses on the study of certain signalling transduction pathways thought to play a role in cancer development. PI Joaquín Arribas (ICREA)
- **Proteomics Laboratory.** The objective of this laboratory is to provide state-of-the-art proteomic services to the other research groups and to implement new developments in order to keep abreast of new proteomic strategies and technologies. PI Francesc Canals
- **Stem Cells and Cancer Laboratory.** This group focuses on molecular mechanisms that regulate the initiation and progression of epithelial tumors. PI Héctor García-Palmer

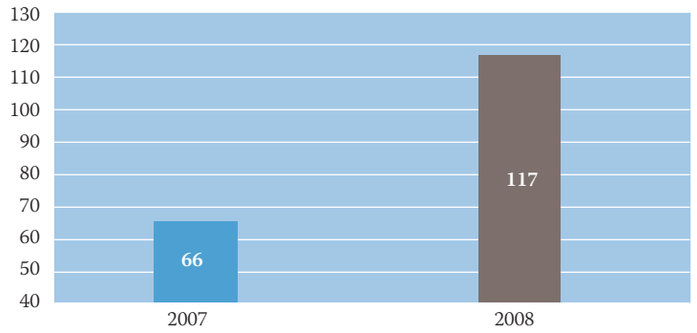
Clinical Research Program

The aim of the Clinical Research Program is to produce high-quality clinical research based on obtaining accreditation to conduct phase I, II and III clinical trials so that patients can gain access to new drugs being clinically assessed for efficacy.

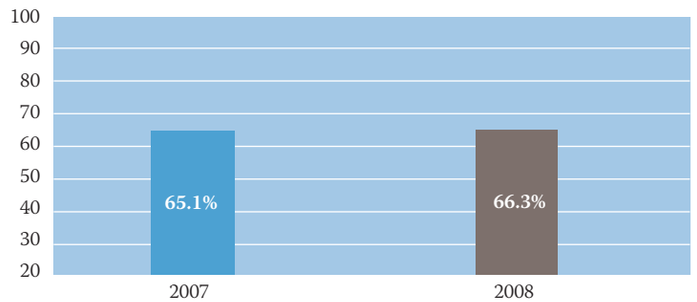
- **Breast Cancer Program.** As a clinical academic group, the Breast Cancer Program is committed to clinical practice, clinical and translational research, and a broad range of teaching. PI Javier Cortés
- **Experimental Therapies Program.** This research program is dedicated to the development of new therapies and preclinical studies, as well as early clinical studies with molecularly targeted agents. This program works closely with the other organ-based clinical research programs. PI Josep Baselga
- **Gastrointestinal Tumors Program.** This research program is dedicated to care, research, training and education in the field of gastrointestinal tumors. PI Josep Tabernero
- **Genitourinary, CNS and Sarcoma Tumors Program.** This group is dedicated to the study of tumors of the urinary tract and male genital tract. PI Joan Carles
- **Head, Neck and Gynecological Tumors Program.** The HNGT Program focuses primarily on research, and the development of new molecules. PI Josep M. del Campo
- **High Risk and Cancer Prevention Program.** This program focuses on identifying individuals at risk of hereditary cancer syndromes and offering genetic counseling, testing and advice for the early detection and prevention of cancer. PI Judith Balmaña and Orland Díez
- **Lung Cancer Program.** This program is dedicated to lung cancer research and research strategies. PI Enriqueta Felip
- **Molecular Pathology Program.** The Molecular Pathology Laboratory analyzes human tissue samples, cell pellets and mouse xenografts. It also performs immunohistochemistry, immunofluorescence, fluorescence in situ, hybridization for many key genes, tissue micro-array constructions, image analysis, nucleic acid extraction and quantification and gene sequencing. PI Santiago Ramon y Cajal
- **Radiation Oncology Program.** This research program is dedicated to concurrent chemotherapy and radiotherapy, clinical applications of targeted agents with radiation and clinical applications of new technology. PI Jordi Giralt

Scientific output

Publications



Publications in first quartile journals



The total impact factor in 2008 has been 715.467, with an average of 6.624.

Clinical Trials Program

The Oncology Department at Vall d'Hebron University Hospital is home to the largest medical unit for clinical trials in the Spain. Over the course of 2008, 103 clinical trials on new drugs were initiated, with 484 new subjects, and over 613 biopsies performed.

Clinical Trials Office Manager · Irene Marimón

Phase I Clinical Trials Coordinating Manager · Gemma Sala

Phase I Clinical Trials - Breast Cancer Unit Coordinating Manager · Susana Galtés

Clinical Trials Managing Coordinator · Yasmina Bernabé

Trials

	2007	2008
Phase I	20	26
Phase II	42	40
Phase III	31	37
Total	**93**	**103**

Patients

	2007	2008
Phase I	139	171
Phase II	170	133
Phase III	143	180
Total	**452**	**484**

Type of tumor

	2007	2008
Breast	125	162
Colon	90	52
Head and neck	20	10
Lung	32	19
Ovary	11	20
Sarcoma	1	0
Upper GI non-colon	13	44
Other	115	144
NET	3	15
Genitourinary	42	18

Biopsies

	2008
Abdominal mass	8
Breast	117
Eyebrow	39
Head and neck	13
Lymph node	4
Liver met.	68
Melanoma	16
Normal skin	348
Total	**613**

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Highlights 2008

Dr. Josep Baselga is distinguished with the Jaume I Clinical Research Award

The Director of VHIO, Josep Baselga, was awarded the Jaume I Award for Clinical Research in recognition of his important contribution to the progress of science in Spain. The jury was composed of eighteen Nobel Prize winners, renowned professors and scientists, who praised Dr. Baselga's translational research model.

Cellex Building

The Cellex Private Foundation, which is committed to the support of science, will provide VHIO with a state of the art Oncology Research Building.

The Cellex Building will host both, basic and clinical researchers. The building will bring together investigators who are currently dispersed in different VHUH buildings and enable VHIO to double its workspace.

Agreement for the construction of the Cancer Molecular Therapy Research Unit – Welfare Projects "la Caixa" Foundation

This Cancer Molecular Therapy Research Unit (UITM) will be engaged in Phase I trials of new drugs and therapeutic targets that improve the efficacy of pharmacological treatments against cancer and reduce toxicity.

This UITM will be located in the VHUH main building and will have an extension of over 1000 m^2.

ICREA-VHIO agreement

An agreement was signed with ICREA (Institució Catalana de Recerca i Estudis Avançats) to affiliate ICREA researchers with VHIO. Two professors-researchers are currently affiliated with VHIO:

- Dr. Arribas, head of the Growth Factors Study Group and coordinator of the VHIO Basic Research Program.
- Dr. Seoane, head of the Gene Expression and Cancer Study Group

FIR-VHIO agreement

VHIO research projects were originally conducted by both VHIO and the FIR (Fundació Institut de Recerca). The agreement between the institutes, signed in June 2008, establishes the timetable for the transfer of oncology research programs from the FIR to VHIO. It also gave VHIO the authority to manage any new basic oncology research programs undertaken within VHUH.

VHIO corporate website

An initial version of the VHIO corporate website (www.vhio.net) was launched in September 2008.

Comprehensive care for breast cancer: Breast Cancer Center

The VHUH Breast Cancer Center (BCC) has already become a reference center for breast cancer treatment. Oncologists, radiotherapists, geneticists, biologists, surgeons, pharmacy specialists, and radiologists work together at the BCC.

Inaugurated by HM Queen Sofia of Spain in May 2008, the BCC's main objective is to improve patient care by bringing together the breast-cancer diagnosis, treatment and research services.

Known as *Forward and Head On*, the BCC is located on two floors of the Maternity and Children's Building, which have been totally refurbished. The redevelopment work and the foundation of the BCC were made possible by the generous donation of Ms. Maria Angels Sanahuja, in memory of her parents.

The center houses the entire patient-care circuit, from medical offices with screening and full diagnostic equipment, to a day hospital with rooms for chemotherapy and pharmacy.

Breast cancer

Breast cancer is one of the most common forms of cancer and represents 30% of all tumors affecting women. In Catalonia, almost 5000 new cases are diagnosed every year, with a significantly increasing trend over the coming years.

One in eight women will suffer from breast cancer at some point in their lives, but early detection, research and improved treatments, have brought survival rates at five years close to 90%.

Breast cancer represents one-third of all the oncology activity at VHUH.

Breast Cancer Center Health Care Data 2008

First outpatient visits	1,665
Follow-up outpatient visits	11,161
Surgical activity (includes ambulatory surgery)	998
Day Hospital treatments	21,651

Scientific milestones

One of VHIO's priority objectives is to develop specific treatments to combat the mechanisms that cause specific tumors. To achieve this, the results obtained in the laboratory must be applied to patient care, and the responses of patients and other observations derived from clinical practice must return to the laboratory as a data source for formulating hypotheses and inspiring new lines of research.

At VHIO, this translational research means performing preclinical and clinical trials in patients and designing open research projects that allow data to flow freely between the laboratory and the clinic.

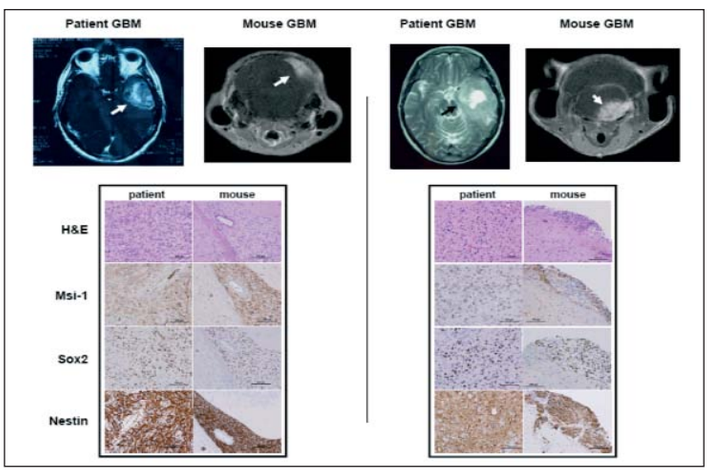
Following are three examples of this type of research; each project aims to proceed in this manner in order to rise to the pricipal challenge of designing personalized treatments for each patient.

VHIO identifies a therapeutic target for the most malignant brain tumor

TGF-beta increases glioma-initiating cell self-renewal through the induction of LIF in human glioblastoma.

Peñuelas S, Anido J, Prieto-Sánchez RM, Folch G, Barba I, Cuartas I, García-Dorado D, Poca MA, Sahuquillo J, Baselga J, Seoane J. Cancer Cell. 2009 Apr. 7; 15 (4): 315-27.

Multiform glioblastoma is one of the most malignant brain tumors and the one with the worst outcome. Research at VHIO has identified the molecular mechanisms involved in the appearance and recurrence of glioma. In brief, the study shows that the hormones TGFß and LIF induce the self-regenerating ability of the tumor-initiating-stem cells. According to the investigator, Joan Seoane, "these stem cells would be responsible for the brain tumor's origin, recurrence and resistance to conventional treatment. Inhibiting TGFß and/or LIF by pharmacologic means would encourage the elimination of the stem cells from the glioma and therefore its total eradication." To short-circuit this renewal process, we need to act on a link in the chain and thanks to our understanding of this mechanism, we have identified what could be the first therapeutic target in this type of tumor and its stem cells.

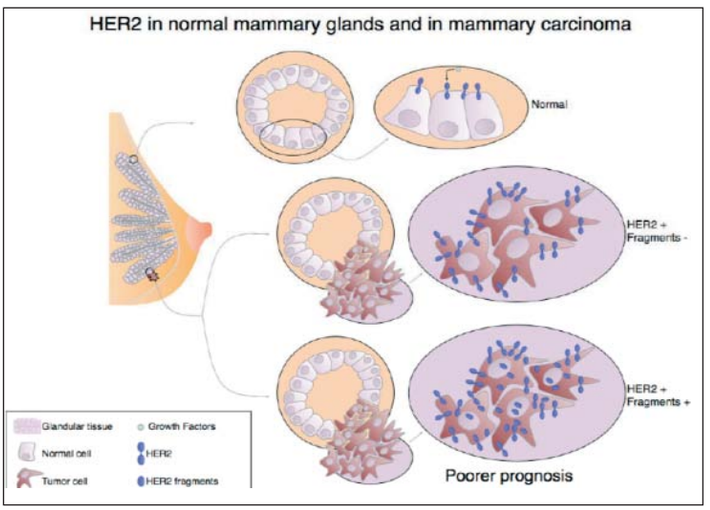


The success of this example of translational research is due to the close colaboration of the VHIO Gene Expression and Cancer Laboratory team, and the departments of Oncology and Neurosurgery at VHUH. A phase I clinical trial to test TGFß inhibitors is currently in progress.

VHIO pilots a new diagnostic test that detects HER2 fragments in breast cancer

A Naturally Occurring HER 2 Carboxy-Terminal Fragment Promotes Mammary Tumor Growth and Metastasis.

Pedersen K, Angelini PD, Laos S, Bach-Faig A, Cunningham MP, Ferrer-Ramon C, Luque-García A, García-Castillo J, Parra-Palau JL, Scaltriti M, Ramón y Cajal S, Baselga J and Arribas J. Molecular and Cellular Biology, June 2009.



Approximately 30% of all breast cancers currently diagnosed have a genetic abnormality that results in excess production of the protein HER2. Earlier studies carried out by Dr. Baselga's and Dr. Arribas' groups showed that approximately one-third of HER2-positive tumors present high levels of fragments of this protein. In comparison to tumors that present only the entire HER2 protein, the tumors with fragments have a worse outcome and are also resistant to treatment with trastuzumab, a drug used routinely to treat HER2-positive tumors.

For this reason, one of VHIO's most noteworthy achievements in 2008 was the work of the basic research group on growth factors, led by Joaquín Arribas, which resulted in the development of a new diagnostic test to detect fragments of HER2 in routine hospital clinical practice. This test will provide a better diagnosis in breast cancer patients and will make it possible to choose the most suitable treatment.

According to Arribas, "the result of this research is a unique example of the applicability of basic science to clinical practice, unlike in most published scientific studies, the results of which, over time, do not produce direct benefits in terms of diagnosis and/or treatment of patients". In this case, the study significantly determines the treatment of choice for some patients and suggests the utility of developing new molecules that act on the HER2 fragments.

VHIO tests a new combination of drugs for HER2-positive breast cancer without the adverse effects of conventional chemotherapy

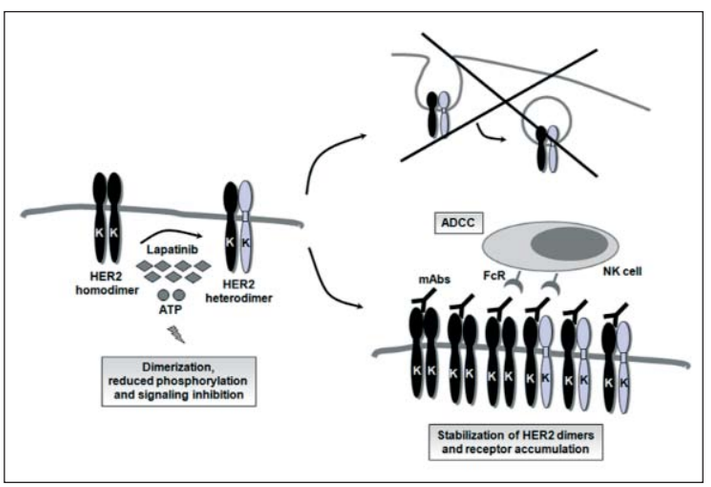
Lapatinib, a HER2 tyrosine kinase inhibitor, induces stabilization and accumulation of HER2 and potentiates trastuzumab-dependent cell cytotoxicity.

Scaltriti M, Verma C, Guzman M, Jimenez J, Parra JL, Pedersen K, Smith DJ, Landolfi S, Ramon Y Cajal S, Arribas J, Baselga J. Oncogene. 2008 Dec 8.

This research studied the action mechanisms of two drugs—lapatinib and trastuzumab—in combination for the treatment of HER2-positive breast cancer. Lapatinib is a molecule which, when combined with trastuzumab, neutralizes the activity of the HER2 receptor and improves the effect of the antibody. Although the results of preliminary studies have yet to be verified, we appear to have obtained the formulation of a new molecular therapy for the treatment of HER2-positive breast cancer. Another of the advantages of this combination is that it avoids the adverse effects of chemotherapy and it is therefore even more important to determine whether it may, indeed, replace conventional treatment in the future.

The new combination has been tested in mice, with highly positive and promising results: the interaction leads to the disappearance of the tumor with no recurrence in the short term.

The research is being carried out by the Experimental Therapies team at VHIO and the Breast Cancer research team, respectively. Both teams are currently conducting a phase III clinical trial in women with this primary HER2/ErbB2-positive breast cancer. The initial results may confirm the efficacy of the combination in curing HER2-positive breast cancer. The investigator Maurizio Scaltriti is cautiously optimistic as he believes we are dealing with "one of those cases where everything begins and ends well".



Basic research

"Research is an unstoppable engine that guides the fight against cancer."

Angiogenesis Laboratory

Juan Carlos Rodríguez-Manzaneque, group leader

Juan Carlos Rodríguez-Manzaneque graduated in pharmacy at the Universidad Complutense de Madrid (1991). His thesis project involved studies of gene transcriptional regulation by thyroid hormones and related nuclear receptors, under the direction of Dr. Angel Santos at the Facultad de Medicina, Universidad Complutense de Madrid (1991-1996). He worked with Dr. Luisa Iruela-Arispe at the Department of Pathology of Beth Israel Deaconess Medical Center/Harvard Medical School (Boston, USA) and at the University of California in Los Angeles (UCLA, Los Angeles, USA), where they concluded the identification of new antiangiogenic molecules, stressing the finding of members of a recently identified family of extracellular metalloproteases, named ADAMTS. During his postdoctoral training, he studied TSP1 actions during tumor progression. These studies provided relevant facts about the bioavailability of growth factors in the extracellular tumor microenvironment, mainly driven by proteolytic events.

In June 2002, Juan Carlos became a member of the Medical Oncology Research Program, leading the Angiogenesis Group. His research has focused on the role of proteases during extracellular remodeling processes, as a principal mechanism in the regulation of vascular homeostasis during tumor progression.

Angiogenesis Laboratory

ADAMTS1 belongs to a family of extracellular proteases that participate in a variety of biological events including inflammatory, angiogenic and developmental processes. In light of its properties, it is thought that its functions will depend on its catalytic activity, which, to date, has been limited to several matrix proteoglycans. A major goal of this laboratory is to identify those specific substrates in distinct cellular microenvironments. We have used several techniques to characterize some of these substrates, the functional relevance of which is currently under study.

The techniques used include DIGE (2D-fluorescence difference gel electrophoresis), ICPL (isotope-coded protein labelling), and the yeast two-hybrid system. Some of the identified substrates, especially relevant in an extracellular microenvironment, include the glycoproteins nidogen-1 and nidogen-2, major components of the vascular basement membrane, the transmembrane proteoglycan syndecan-4, implicated in adhesive and motility cellular properties, and the matrix-anchored tissue factor pathway inhibitor-2 (TFPI-2).

Group leader

Juan Carlos Rodríguez-Manzaneque PhD

Laboratory members

Post-doctoral Fellows
Carmen Casal PhD
Julie de Wever PhD
Antoni X. Torres-Collado PhD

Graduate Students
Estefanía Martino MD

Technician
María del Carmen Plaza-Calonge

Scientific activity

The extracellular matrix (ECM) provides an essential framework for cells to proliferate, migrate and differentiate to form a specific organ or tissue. The continuous remodelling of the ECM in coordination with proper cellular function is essential for the final development of an organism. Considerable advances have recently been made in the characterization of this dynamic ECM and its relevant role in maintaining vascular architecture has been remarked. Deficiencies in the strict control of ECM remodelling can entail the progression of various pathologies, such as tumorigenesis. Accordingly, the analysis of expression and catalytic activity of the responsible extracellular proteases has been used as a prognosis marker. Although the inhibition of these molecules became a high-priority line for the pharmaceutical industry, the disappointing results of clinical trials highlighted its complexity and the need for further. The family of matrix metalloproteases (MMPs) occupies a privileged place among the extracellular proteases involved in these processes,. More recently, members of the family of proteases related to adamalysin, ADAM and ADAMTS,have also been implicated, although their mechanism of action is not fully understood. All these families of metalloproteases are characterized by their multi-domain structure that consists of a catalytic sequence, partially conserved between all the members, accompanied by other domains with important roles in the interaction with other proteins and cellular components.

The protease ADAMTS1 was first found to display antiangiogenic properties but its mechanism of action is still being characterized. It has been suggested that this property depends on its catalytic activity so the identification of the substrate that causes the mentioned effect is still a priority. Further studies suggested a role for ADAMTS1 as a pro-metastatic protein. While it appears paradoxical that a protein described as antiangiogenic also displays a pro-metastatic capacity, it is reasonable to suggest that the final action will be determined by the microenvironment where the protease is available, considering every cell type and those candidate substrates that are present in a specific location. The potential proteolytic activity on endothelial cells may cause the displacement from the cell surface of growth factors and chemokines—molecules that are needed for the cell to proliferate—thus inhibiting their proliferation and consequently causing an antiangiogenic effect.

Cleavage of heparan-sulfate proteoglycans by ADAMTS

Among the targets of ADAMTS proteases, proteoglycans appear to be their most relevant substrates; these are multi-faceted molecules whose role in cancer and metastasis has been reported but is still the subject of debate. The biological functions of these proteoglycans vary, ranging from their participation as simple mechanical support to processes of adhesion, proliferation and cellular differentiation. These activities are mainly determined by the ability of these molecules to interact with multiple factors and act as reservoirs of soluble growth factors, chemokines, and a variety of proteolytic enzymes and coagulation-related molecules. Our recent findings include the fact that transmembrane syndecan proteoglycans are cleaved by ADAMTSs with consequences in adhesion and migration. Syndecan-4 is a cell-surface anchored heparan sulfate proteoglycan that participates in cell-cell and cell-matrix interactions of many cell types. Both its extracellular and cytoplasmic domains are involved in these actions, as the extracellular fragment cooperates with adhesion molecules and binds matrix components, and the short intracellular tail can interact with second messengers and initiate signaling events. Our close analysis of the cleavage of syndecan-4 revealed that other proteases widely recognized as sheddases did not induce the same proteolytic event as ADAMTS1 and ADAMTS4, indeed it appears similar to that induced by agonists suchas phorbol esters, cholesterol-depleting agents and cell density. Additional studies with different cell types showed that ADAMTS1 does not require the presence of GAGs anchored to the ectodomain of syndecan-4 to exert its actions. More importantly, this cleavage results in altered distribution of cytoskeleton components, changes

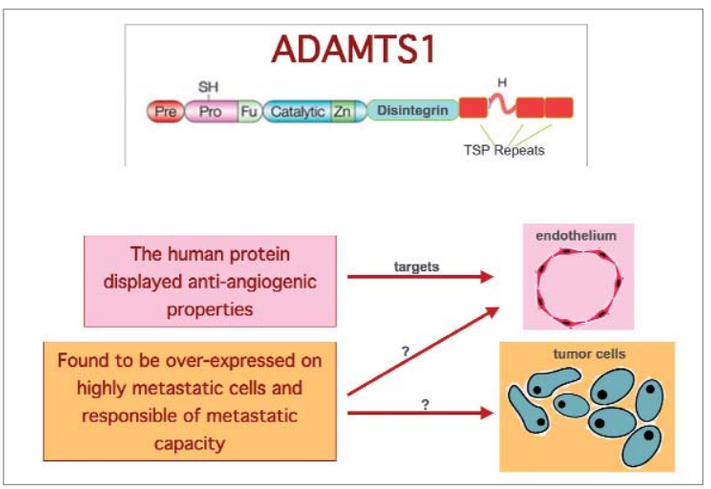


Figure 1. Schematic representation of ADAMTS1 protein showing its multi-domain structure. Studies with the human protein have shown its antiangiogenic activity on endothelial cells, although its potential role as a pro-metastatic gene has also been noted. The knowledge of specific substrates appears to be a key aspect to unraveling ADAMTS1 actions.

in the activity of the GTPase Rho, a functional loss of adhesion, alteration of focal adhesions, and a gain of migratory capacities. Our findings suggest that the shedding of syndecan-4 by ADAMTS1 is a relevant signal that disrupts cell adhesion and promotes cell migration during transformation events. Using syndecan-4 null cells, we also demonstrated that the ADAMTS1 proteolytic processing mimics the outcome of genetic deletion of this proteoglycan with regard to focal adhesion. The modification of syndecans by proteolysis reveals a complex system that requires a thorough characterization of the relationship between protease-proteoglycan-interacting factors during tumor and metastasis progression.

Characterization of TFPI-2 as a substrate of ADAMTS1 and its relevance in tumor plasticity/vasculogenic mimicry

In our attempt to unravel the functions of this extracellular protease we approached its actions using different biochemical and cellular models. These studies reported the identity of new ADAMTS1 substrates with functional implications (Torres-Collado et al., 2006; Canals et al., 2006). Tissue factor pathway inhibitor-2 (TFPI-2) was identified in a yeast two-hybrid screening as a direct substrate of ADAMTS1, with consequences for tumor progression. We performed xenograft assays with HT1080 fibrosarcoma cells. A detailed analysis of these tumors showed a significative decrease of vascularity when ADAMTS1 was present, and the periodic acid-Schiff (PAS) staining and localization of laminin showed the induction of a "vasculogenic-mimicry" (VM) phenotype in an ADAMTS1-dependent manner. Based on previous reports, we evaluated the presence of several genes that have been implicated in this phenomenon with the result that VE-cadherin, laminin and Tie1 appeared up-regulated in VM positive tumors. These data encouraged us to analyze HT1080 fibrosarcoma cells prior to injection into the flank of the mouse. Surprisingly, HT1080 parental cells are capable of forming pseudo-vascular structures in 3D matrices (matrigel, collagen), similar to endothelial cultures, and the evaluation of different markers showed that this cell line already express a set of genes that mimic an endothelial-like fate. Although the expression of further relevant genes was not altered, we are currently optimizing conditions to approach this analysis by immunolocalization. These data support a potential role of ADAMTS1 in the development of VM. Our molecular evaluations showed that HT1080 possesses the potentiality to form VM structures (given by its endothelial-like genetic pattern) but the presence of ADAMTS1 is required to finally be capable of forming them.

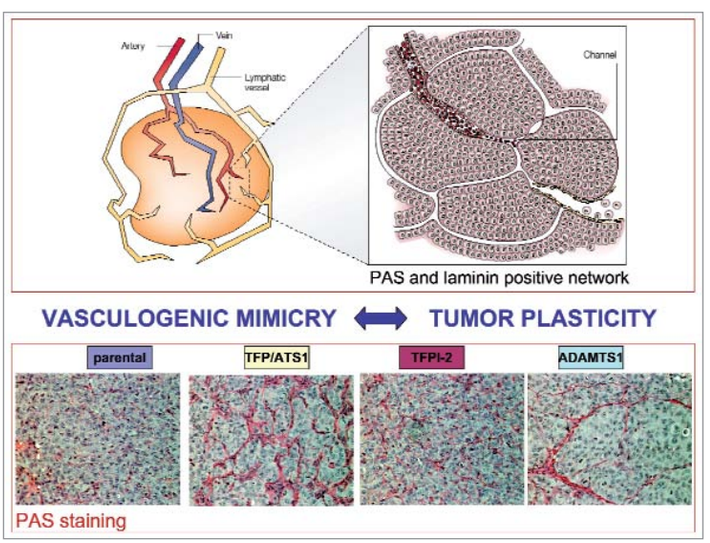


Figure 2. Representation of "vasculogenic-mimicry" phenomenon. Tumor cells possess the ability to acquire an endothelial-like phenotype that allows tumor growth independently of angiogenesis. In our model, ADAMTS1 overexpression provokes the appearance of this phenomenon, as visualized by PAS staining.

The concept of plasticity applied to tumorigenesis relates to the fact that some aggressive tumor cells share many characteristics with embryonic progenitors. A paradigm of tumor plasticity is the phenomenon of vasculogenic mimicry, defined as the ability of tumor cells to mimic neo-vascularization events by forming functional matrix-enriched networks, directly related to the acquisition of an endothelial-like molecular signature. This phenomenon was first characterized in cases of melanoma, but recent findings have provided signs of this mimicry in additional classes of tumors such as breast, ovarian and lung carcinomas, and in the more aggressive types of sarcomas. In addition, the main role of the matrix as controller of stem cell fate has been reported. Our more recent approaches have confirmed the presence of important markers of a stem-like tumor cell population, such as cd133 and cd44; we are therefore trying to characterize the potential relationship between VM-tumor plasticity-stemness capacity suggested by our findings.

Characterization of the relevance of additional substrates of ADAMTS1

We are using different cellular approaches with advanced techniques in proteomics to identify extracellular fragments generated by the catalytic activity of ADAMTS1. These analyses have been performed in collaboration with the Proteomics Laboratory, led by Dr. Canals.

To date, we have identified several substrates (Canals et al., 2006) that have been validated. Special attention has been paid to the family of nidogens (1 and 2)—main components of vascular basement membranes. The proteolysis of these proteins is being characterized in cell cultures and in human tumor samples. Our results show that both nidogen-1 and nidogen-2 proteolysis occurs under normal conditions and we therefore need to evaluate the importance of the generated fragments.

Research projects (2)

Funding agency: La Marató de TV3
Title: Cleaveage of proteoglycans by ADAMTS1 iroteases and its implications on angiogenesis.
PI: Dr. Juan Carlos Rodríguez-Manzaneque
Duration: 2005-May 2009

Funding agency: MEC
Title: Caracterización de la actividad catalinade metaloproteasa ADAMTS1 y relevancia en procesos tumorigénicos y metastásicos.
PI: Dr. Juan Carlos Rodríguez-Manzaneque
Duration: 2006-Sept 2009

Publications (1) / IF: 4.009

Rodríguez-Manzaneque JC, Carpizo D, **Plaza-Calonge MD**, **Torres-Collado AX**, Thai SN, Simons M, Horowitz A, Iruela-Arispe ML. Cleavage of syndecan-4 by ADAMTS1 provokes defects in adhesion. Int J Biochem Cell Biol. 2008 Aug 15. Epub ahead of print.
(IF: 4.009, 2 cuartil, biochemistry molecular biology)

Animal Models Laboratory

Juan Ángel Recio, group leader

Juan Ángel Recio graduated in biology and specialized in biochemistry at the Universidad Complutense de Madrid and holds a master's degree in Biotechnology. In 1997 he moved to Dr. Notarios's laboratory at the Lombardi Cancer Center, Georgertown University (Washington, DC), where he cloned the human and mouse genes of the protocph (pcph) oncogene, elucidated the ectonucleoside triphosphate diphosphohydrolase activity of the protein and its role in carcinogenesis.In 1999 he joined Dr. Merlino's lab at the National Cancer Institute (NCI, NIH, Bethesda, MD), where he contributed to the discovery of molecular mechanisms underlying signalling of the receptor tyrosine kinase c-MET and how those pathways subverted in malignant melanoma and rabdomyosarcoma. His achivements in the field of melanoma include the creation of a malignant melanoma mouse model which, is broadly used as a model for UV irradiation within the scientific community. The National Cancer Institute has recognized this line of work with several awards.

In December 2004 he joined to the Medical Oncology Program as a Group Leader (Ramon y Cajal Investigator) of the Animal Models and Cancer laboratory. The group has focused his interest on the discovery of novel molecular mechanisms involved in melanoma development and progression and the direct application of this knowledge to finding new therapeutical approaches.

Animal Models Laboratory

Our Lab is focused on the molecular basis of melanoma development and progression. By merging state-of-the-art technology with classical biochemical approaches and animal models, we are committed to contributing to the understanding of malignant melanoma development and progression. More specifically, our goal is the identification of novel molecules and molecular mechanisms involved in this aggressive disease to increase the options for therapeutic intervention. Our investigations also include testing new therapeutic approaches using novel drugs in the mouse melanoma model.

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Scientific activity

Novel molecules involved in Melanoma development

Melanoma is the most aggressive type of skin cancer. If metastatic, the median survival is limited to between 6 and 10 months, with no effective treatments available. The genetic, epigenetic and biochemical alterations acquired by melanocytes during tumor development and progression and specifically how they affect treatment response; remain major challenges in skin oncology.

The hepatocyte growth factor (HGF) transgenic malignant melanoma mouse model induced by ultraviolet (UV) radiation represents an interesting opportunity to study this disease. This unique model recapitulates etiologically, chronologically and histopathologically all the stages of the human counterpart including, molecular alterations such as the loss of the p16Ink4a/ARF locus, a relevant genetic mutation associated with human melanoma. The conjunction of these two factors, HGF overexpression and neonatal UV irradiation, were enough to mimic the appropriate context for melanoma development. Following this rationale, the identification of molecules participating in HGF signaling in the UV irradiated melanocytes could provide us with some novel proteins that might be responsible for melanoma development and maintenance. In the past two years we have identified some novel molecules involved in HGF signaling in melanoma neoplastic cell lines obtained from tumors grown in the UV irradiated mouse. Our goal is to focus on proteins that may play a role in human melanoma and whose activation in mice somehow mimics the human condition. We have already focused on two particular proteins that have led to two different subprojects:

Role of LKB1 in melanoma development

Among the molecules identified in the phospho-protein complexes specifically formed in response to HGF was Mo25, a scaffold protein necessary for the activity and correct localization of LKB1 kinase. We further identified LKB1 as a kinase modified in response to HGF and other cancer-related growth factors in a Ras pathway dependent manner. LKB1 is a multitask Serine/Threonine kinase with tumor suppressor activity that participates in a variety of biological processes involved in malignant transformation such as cell cycle control, energy metabolism sensor, gene regulation, apoptosis and cell polarity. However the biological role of LKB1 in response to growth factors is unknown. We recently discovered that oncogenic BRAF and Ras pathway activation by growth factors promotes the uncoupling of LKB1-AMPK complexes, conferring resistance to energy stress, and provides a mechanism to prevent inhibition of protein synthesis and cell growth in response to mitogenic stimulus.

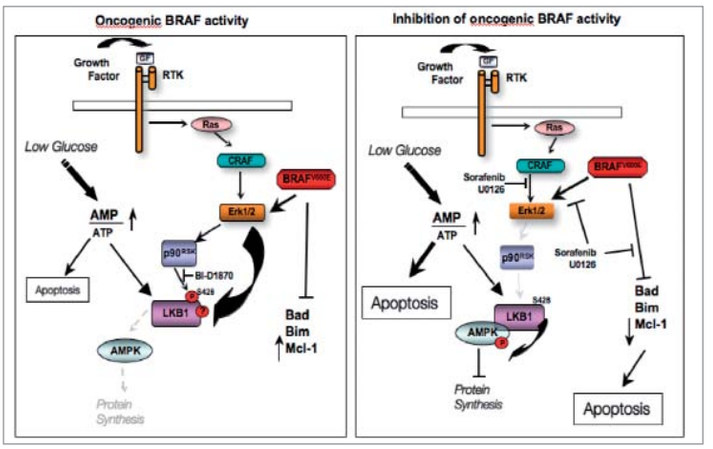

Figure 1. A model of the metabolic stress response regulation by oncogenic BRAF in melanoma cells. Resistance to stress conditions is essential for melanoma cell survival. We hypothesize that oncogenic BRAFV600E signaling (left panel) protects apoptosis by regulating BH3-family members and confers resistance to low energy conditions by promoting the uncoupling of LKB1 and AMPK through Erk1/2 and p90Rsk. Under these conditions, BRAF mutant cells have a limited response to low energy conditions. In the right panel inhibition of BRAF signaling allows the formation of the LKB1-AMPK complexes, restoring the energy stress pathway and promoting the downregulation of antiapoptotic proteins such as Mcl1. The activation of AMPK by metabolic stress conditions and the inhibition of BRAF signaling would have synergistic effects promoting apoptosis.

Role of LKB1 in UV-induced skin tumorigenesis.

Sporadic mutations in the lkb1 gene have been documented in cancers of the breast, pancreas, lung, prostate, cervix and ovary as well as in Peutz-Jeghers syndrome, a rare disorder characterized by the appearance of intestinal polyps and mucocutaneous melanocytic macules. More importantly, lkb1 mutations have been described in melanoma, and based on this information, we determined whether LKB1 could function as a potential link between an activated RAS pathway and dysfunctional c-Met signaling, and play a role in melanoma development and progression. According to this rationale we have generated several animal models to study the role of LKB1 in UV induced melanoma development and progression.

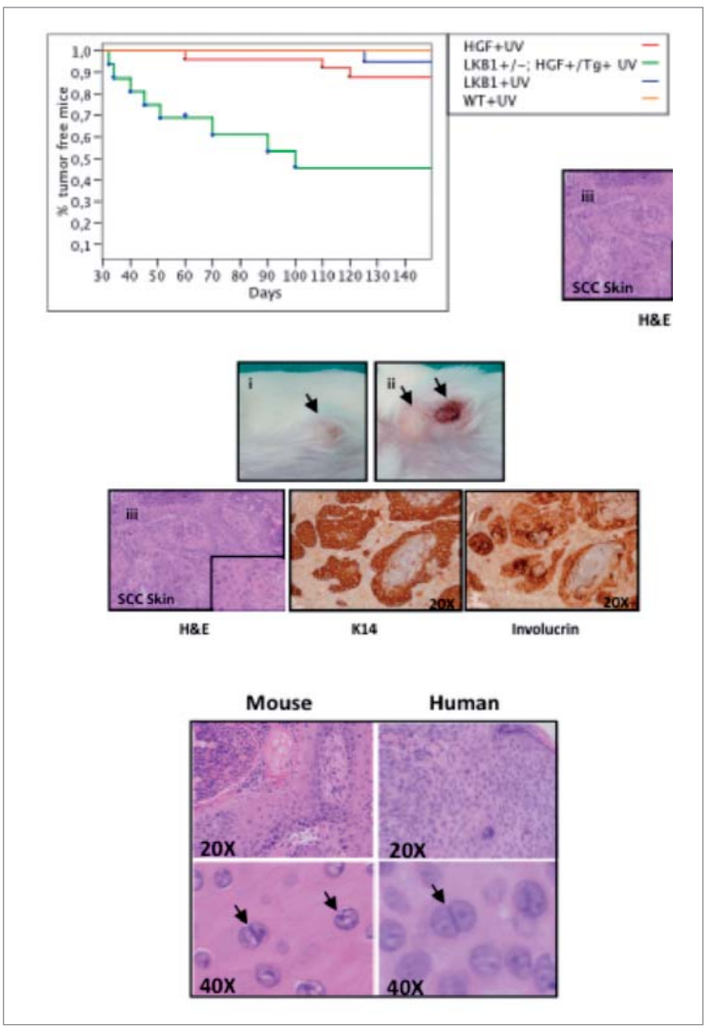

Figure 2. LKB1 haploinsufficiency sensitizes to UVB-induced skin tumorigenesis.

Arginine methylation: a post-translational modification modulating signal transduction

We identified arginine methylation as a post-translational modification responsible for the modulation of signal transduction. It is known that several growth factors activate the same signaling pathway. However the biological responses to theses ligands are quite different. Arginine methylation seems to modulate the signal amplitude in order to achieve the appropriate biological response elicited by a particular growth factor. We investigated the fine mechanism involved in this process, identifying the methylase involved in the process. This discovery adds a new level of signal transduction regulation and new candidates for therapeutic intervention.

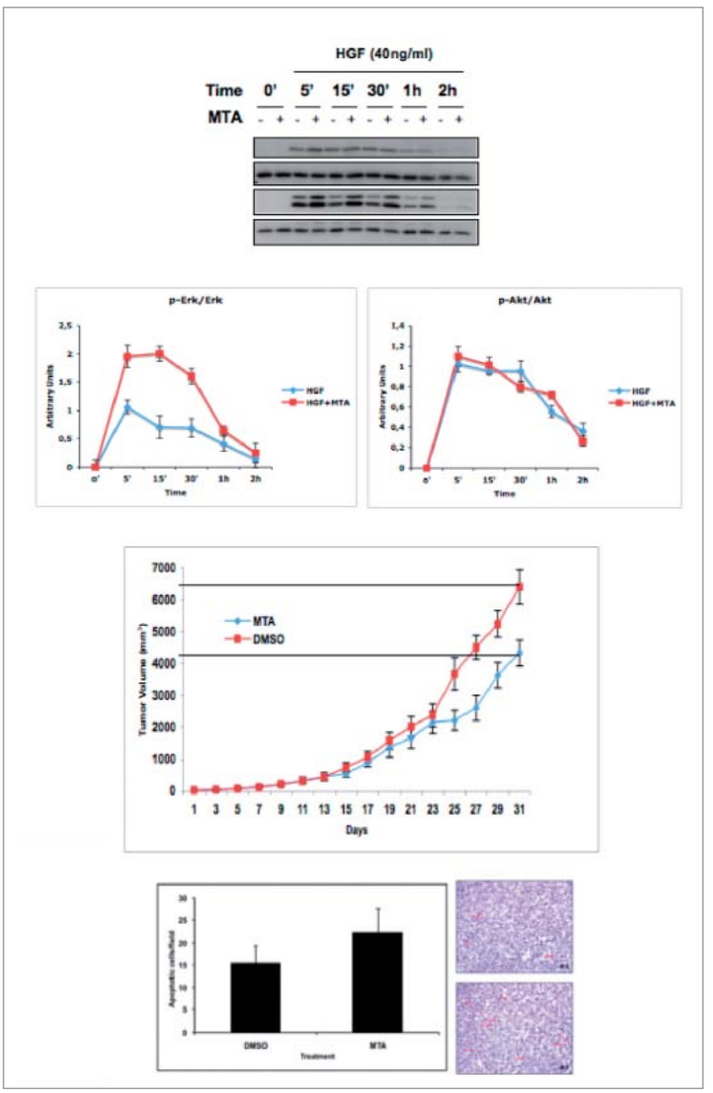

Figure 3. Modulation of the specific ligand dependent Erk1/2 signal amplitude by MTA treatment. MTA treatment reduces tumor growth in an immunocompetent mouse model without detectable systemic alterations.

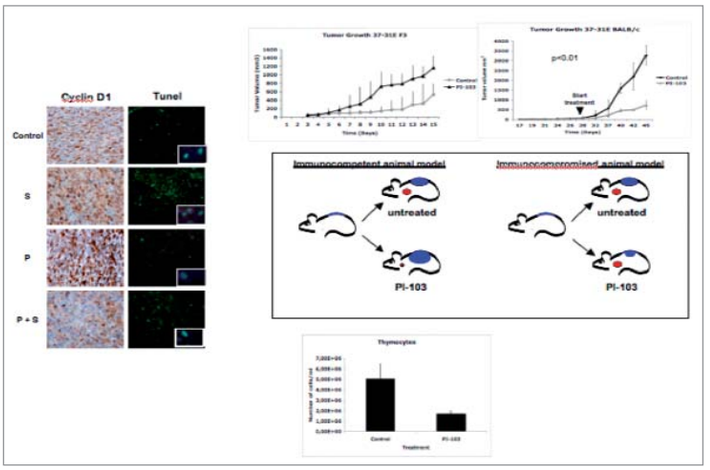

Figure 4. Important systemic effects induced by drug administration can be detected in further physiological animal models.

Preclinical study using PI3K and BRAF specific inhibitors

Recent results indicate the PI3K and Ras pathways are particularly relevant in human melanoma development and progression. The use of BRAF specific inhibitors (Sorafenib) as a monotherapy agent has been shown to be ineffective for melanoma treatment. We are combining different inhibitors targeting important pathways in melanoma development and progression to test their efficacy as combined agents in melanoma treatment, in an immunocompetent model. Importantly, this immunocompetent animal model revealed unexpected systemic effects that ultimately modify tumor behavior.

Research projects (4)

Funding agency: European Community (Marie Curie Reintegration Grant)
Title: Caracterization of novel mechanisms of HGF signaling in melanoma.
PI: Juan A. Recio
Duration: 2006-July 2008

Funding agency: ISCIII (FIS)
Title: Mecanismos de actuación del Factor de Crecimiento Hepático (HGF) en la adquisición y progresión del melanoma cutáneo: aplicación del modelo animal de melanoma maligno basado en ratones transgénicos del HGF.
PI: Juan A. Recio
Duration: 2006-February 2009

Funding agency: FMMA
Title: Papel de LKB1 en melanoma maligno.
PI: Juan A. Recio
Duration: 2007-July 2010

Funding agency: ISCIII (FIS)
Title: Papel de LKB1 en respuesta a factores de crecimiento y en el desarrollo y progresión del melanoma.
PI: Juan A. Recio
Duration: 2009-2011

Publications (2) / IF: 5.581

Callejas-Valera JL, Guinea-Viniegra J, Ramírez-Castillejo C, **Recio JA**, Galan-Moya E, Martínez N, Rojas JM, Ramón y Cajal S, Sánchez-Prieto R. E1a gene expression blocks the ERK1/2 signaling pathway by promoting nuclear localization and MKP up-regulation: implication in v-H-Ras-induced senescence. J Biol Chem. 83(19):13450-8. Epub 2008 Mar 3. (IF: 5.581, 1 cuartil, biochemistry & molecular biology)

Esteve-Puig R, Canals F, Colomé N, Merlino G, **Recio JA**. Uncoupling of the LKB1-AMPK_ energy sensor pathway by growth factors and oncogenic. BRAFV600E. PLoS ONE. In press.

Gene Expression and Cancer Laboratory

Joan Seoane, group leader

Joan Seoane obtained his Ph. D. in biochemistry and molecular biology in 1998 from the University of Barcelona.

He joined the Memorial Sloan-Kettering Cancer Center (MSKCC), New York, as a post-doctoral fellow in 1998. From 1998 to 2001, he worked as a research fellow and then from 2001 to 2003 as a research associate. During this time, he determined the molecular pathways involved in the anti-proliferative response to TGF-beta in epithelial cells and discovered how these pathways are disrupted in cancer. His post-doctoral work was the subject of publications in high impact journals (Cell, Nature, Nature Cell Biology) and he was awarded with the Memorial Sloan-Kettering Cancer Center Research Fellow (2003) and the Catalan Society of Biology (Josep Maria Sala Trepat, 2004) awards for the work performed during his post-doctoral stage.

In 2004, he was appointed Research Professor by ICREA and established his own Group "Gene Expression and Cancer". His research objectives are the study of the molecular mechanisms involved in the genesis and progression of brain tumors. His work is considered an example of translational research linking basic and clinical research.

In 2007, he joined the Young Investigator EMBO programme and was the recipient of an European Research Council grant.

In 2008, his work was chronicled in an article in Nature on biomedical research in Barcelona ("Catalonian powerhouse" Nature 454, 248-9, 2008).

Gene Expression and Cancer Laboratory

Our laboratory studies the molecular mechanisms involved in tumor genesis and progression. Due to the heterogeneity of cancer, our group has decided to study one particular tumor, glioma, and then assess whether we can extrapolate the acquired knowledge to other tumor types.

Very little is known about glioma genesis and progression at the molecular level and not much progress has been made in the treatment of this disease in recent years. Our main objective is to understand the molecular mechanisms involved in the biology of glioma in order to develop successful and rational therapeutic strategies. Our

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Technicians
Alexandra Arias
Isabel Cuartas
Carolina Raventós

approach is based on close collaboration with clinical researchers from our hospital and the study of patient-derived tumors. We are characterizing human glioma specimens, generating primary cultures of human tumor cells, and isolating the stem-cell-like population of patient-derived gliomas. In addition, we are generating mouse models for glioma based on the orthotopic inoculation of patient-derived glioma stem cells in the mouse brain. Glioma stem cells generate tumors in mice with the same characteristics as the original human tumor. This is an optimal model for the study of tumor development and preclinical research.

Scientific activity

Our studies are mostly based on the study of cells obtained from patient-derived tumortumors. We obtain tumor samples 30 minutes after surgery and we set up primary cultures and isolate cell populations from the tumor such as the cancer stem-cell-like pool. The study of those cells give us more reliable information about the original tumor than the study of established cell lines. Moreover, we inoculate the patient-derived glioma stem cells into the brain of immunocompromised mice and we are able to generate tumortumors with the same characteristics as the original human tumor and which we can monitor by MRI. This mouse model for human glioma has a lot of interest for the study of the molecular mechanisms involved in cancer and for the evaluation of the efficiency of pharmacological compounds.

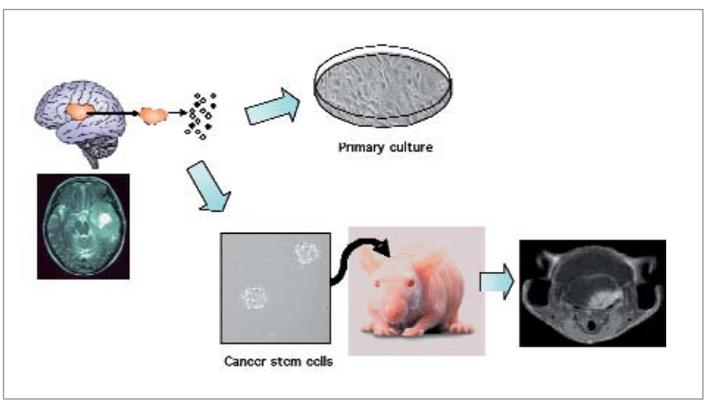

Figure 1. Disaggregated patient-derived tumor samples are plated to generate primary cultures and, at the same time, to obtain glioma stem cells that can, in turn, generate tumors in immunocompromised mice.

The TGF-beta signal transduction pathway in glioma

The best-characterized pathways involved in glioma are the tyrosine kinase receptor pathways (EGFR, PDGFR, FGFR) and many reports have shown that these pathways tend to be hyperactive and promote glioma genesis. However, other pathways such as the TGF-beta pathway have recently been shown to play a relevant role in glioma progression. Little is known about the mechanisms of signal transduction of the TGF-beta pathway and its role in oncogenesis. We are characterizing the activity and function of the TGF-beta pathway in human glioma and how it is interconnected with other pathways. We are studying how this pathway regulates glioma cell proliferation, invasion, motility, angiogenesis and differentiation. We aim to understand why and how the TGF-beta pathway is aberrantly regulated in cancer and we expect our results to contribute to the knowledge of the signal transduction mechanisms of TGF-beta in the context of cancer and normal development.

In 2007, we published part of this work in the Cancer Cell journal (Bruna et al. "High TGF-beta-Smad activity confers poor prognosis in glioma patients and promotes cell proliferation depending on the methylation of the PDGF-B gene" Cancer Cell, 2007). In that article we showed that the TGF-beta-Smad pathway is a poor prognostic factor in human glioma and discerned the molecular mechanisms of the oncogenic proliferative response to TGF-beta. The work was based on the study of patient-derived tumor cells and biopsies. The article has been chronicled in the Developmental Cell journal and was considered an example of translational research linking basic and clinical research.

Patient-derived glioma stem cells

Recently, a subpopulation of tumor cells with stem-cell-like properties have been identified in gliomas. This pool of cells, called glioma stem cells, is considered to be responsible for the initiation, propagation and recurrence of tumors indicating that more effective therapies will result from approaches aimed at targeting the stem-cell-like component of gliomas. Glioma stem cells are characterized by their self-renewing capacity, their multilineage differentiation properties, their high oncogenic potential, and their ability to generate detached spherical cellular structures (neurospheres) when cultured in a serum-free medium. Several markers, most of them previously described for neuroprogenitor cells, have been reported to identify glioma stem cells. Specifically, it has been shown that a glioma subpopulation of cells expressing the cell surface protein, CD133, is enriched for cancer stem cells. Still, little is known regarding the molecular characteristics, and regulatory mechanisms that control glioma stem cell biology.

We have studied glioma stem cells derived from patients, comparing their molecular characteristics with the rest of the tumor cells in order to obtain biomarkers of glioma stem cells and elucidate the oncogenic aberrations present in this type of cells. We have studied how the TGF-beta pathway controls the self-renewal capacity, proliferation and differentiation of these cells. We have found that TGF-beta induces the self-renewal and prevents the differentiation of glioma stem cells through the induction of a extracellular cytokine, LIF. This phenomenon promotes tumor progression and recurrence (Figure 2). Part of this work has recently been accepted for publication in Cancer Cell, (Peñuelas et al. "TGF-beta increases glioma-initiating cell self-renewal through the induction of LIF in human glioblastoma" Cancer Cell in press). This work revealed therapeutic targets against glioma and glioma stem cells and identified molecular biomarkers of prognosis and response to therapy. There is an ongoing phase I clinical trial in our hospital using TGF-beta inhibitory compounds. Our work improved the design of the clinical trial and provided biomarkers in order to stratify the patients that enter the clinical trial and have a higher chance of success.

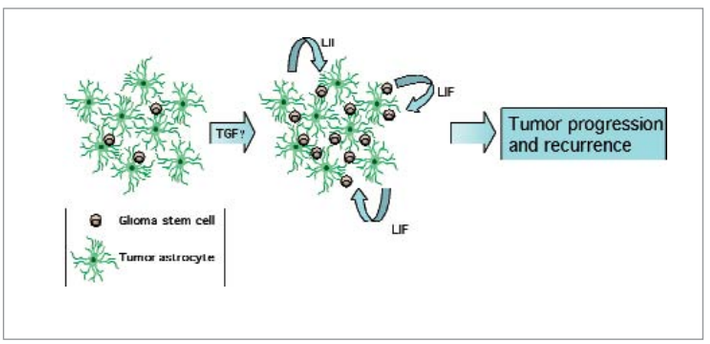

Figure 2. TGF-beta induces glioma stem cell self-renewal through the induction of LIF.

Role of the forkhead transcription factor FoxG1 in glioma

In addition, we are studying a transcriptional factor that can have a crucial role in the genesis of glioma. FoxG1 (previously known as BF1) is a transcription factor of the forkhead family and is the cellular homolog of Qin, the oncogene of the avian sarcoma virus 31. Importantly, FoxG1 is expressed in the neuroprogenitors of the telencephalon but not in differentiated cells and is essential for forebrain formation. Its ablation causes premature differentiation and cell cycle arrest of neuroprogenitors, impairing the development of the telencephalon. Interestingly, data from our laboratory have shown that FoxG1 is expressed in human high grade gliomas as well as in glioma cell lines and we have some indications that FoxG1 might be relevant in glioma genesis and progression as a putative new oncogene.

We are studying FoxG1 transcriptional regulation and determining why FoxG1 is aberrantly expressed in gliomas. We study the regulation of its activity identifying FoxG1 post-transcriptional modifications. In addition, we are identifying the set of genes regulated by FoxG1.

Research projects (5)

Funding agency: AICR (Association for International Cancer Research)
Title: Role of FOX G1 in glioma.
PI: Dr. Joan Seoane
Duration: 2006-June 2009

Funding agency: Eli Lilly
Title: Preclinical studies with the TGF-beta receptor I inhibitor LY02109761.
PI: Dr. Joan Seoane
Duration: July 2006-October 2008

Funding agency: ISCIII (FIS)
Title: Papel del TGF-beta en la capacidad de auto-regeneración de las células madre de glioma.
PI: Dr. Joan Seoane
Duration: 2008-December 2010

Funding agency: ERC
Title: Molecular Mechanisms of Glioma Genesis and Progression (GLIOMA).
PI: Dr. Joan Seoane
Duration: 2008-August 2013

Funding agency: EMBO
Title: EMBO YIP Member.
PI: Dr. Joan Seoane
Duration: 2008-December 2010

Publications (5) / IF: 33.508

Baselga J, Rothenberg ML, Tabernero J, **Seoane J**, Daly T, Cleverly A, Berry B, Rhoades SK, Ray CA, Fill J, Farrington DL, Wallace LA, Yingling JM, Lahn M, Arteaga C, Carducci M. TGF-beta signalling-related markers in cancer patients with bone metastasis. Biomarkers. 2008 Mar; 13(2):217-36.
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Seoane J. The TGFBeta pathway as a therapeutic target in cancer. Clin Transl Oncol. 2008 Jan;10(1):14-9. Review.

Peñuelas S, **Anido J**, **Prieto-Sánchez RM**, **Folch G**, Barba I, **Cuartas I**, García-Dorado D, Poca MA, Sahuquillo J, Baselga J, **Seoane J**. TGF-beta increases glioma-initiating cell self-renewal through the induction of LIF in human glioblastoma. Cancer Cell. In press.
(IF: 23.858, 1 cuartil, oncology)

Eichhorn PJ, Gili M, Scaltriti M, Serra V, Guzman M, Nijkamp W, Beijersbergen RL, Valero V, **Seoane J**, Bernards R, Baselga J. Phosphatidylinositol 3-kinase hyperactivation results in lapatinib resistance that is reversed by the mTOR/phosphatidylinositol 3-kinase inhibitor NVP-BEZ235. Cancer Res. 2008;68:9221-30.
(IF: 7.672, 1 cuartil, ONCOLOGY)

Seoane J, TGF-beta signaling in homeostasis and cancer. TGF-beta in Cancer Therapy. 1:23-35. Humana Press 2008.

Growth Factors Laboratory

Joaquín Arribas, group leader

Joaquín Arribas graduated in biochemistry at the Autonomous University of Madrid in 1987. He received a Ph. D. in biology in 1991. He joined the Memorial Sloan-Kettering Cancer Center (New York, USA) as a postdoctoral fellow to work with Joan Massagué on the proteolytic processing of transmembrane growth factors. In 1997, he joined the oncology department at Hospital Vall d'Hebron in Barcelona as a group leader to investigate the role of certain growth factors and their receptors in breast cancer progression and treatment and head of the Medical Oncology Basic Research Program. He was appointed Research Professor by ICREA (Institució Catalana de Recerca i Estudis Avançats) in 2007.

His research has been recognized with an EMBO Young Investigator Programme (YIP) award and the Beckman Coulter award to the Best Young Spanish Investigator in Biochemistry and Molecular Biology. He is a member of the Editorial Board of the Journal of Biological Chemistry.

He is also member of the Spanish and American Societies of Biochemistry and Molecular Biology and chairman of the Committee for the Evaluation of research project on Cancer of the Carlos III Health Institute.

Growth Factors Laboratory

Our lab studies the regulation of different intracellular signal transduction pathways as well as the remodeling of the extracellular matrix during the progression of breast cancers. We use as models the epidermal growth factor (EGF) signaling pathway and transmembrane metalloproteases of the ADAM (a disintegrin and metalloprotease") family. The receptor for EGF (EGFR) is the prototype of a family that includes three additional receptors: HER2 (ErbB2, neu), HER3 (ErbB3) and HER4 (ErbB4). HER2 is involved in the progression of a subgroup of particularly aggressive breast tumors. The ADAM metalloproteases are a group of more than 30 metalloproteases. Some of them, such as ADAM17 and ADAM10, participate in the progression of a variety of tumors.

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Technicians
Cristina Ferrer
Antonio García
Sandra Paola Mancilla
Marta Escorihuela

Scientific activity

Breast cancer is the most common cancer among women, According to the World Health Organization, more than 1.2 million women will be diagnosed with breast cancer each year worldwide and over 500,000 will die from the disease.

Approximately 30% of patients with breast cancer express excessive levels of the tyrosine kinase receptor HER2. The prognosis of these patients is clearly worse than that of patients with normal levels of the receptor. HER2 (ErbB2) belongs to the family of the epidermal growth factor receptor (EGFR), which also includes HER3 (ErbB3) and HER4 (ErbB4). We are currently investigating the relevance of novel isoforms of HER2 in tumor progression and treatment.

The HER signaling pathway

Dimerization of the extracellular domains leads to interaction between the intracellular kinases of the HER receptors and subsequent transphosphorylation of certain tyrosine residues in the C-terminal tail. These phosphotyrosines act as docking sites for a group of intracellular phosphotyrosine-binding proteins that transduce signals from the plasma membrane to the nucleus via different signaling pathways, including the mitogen activated protein kinases (MAPKs), PI(3)K-activated Akt, Src and phospholipase C gamma (PLCgamma) pathways. These signaling circuits control the expression of target genes that act in coordination to modify key aspects of cellular biology, including proliferation, migration, survival and differentiation.

Novel signaling abilities of HER receptors and fragments of them

In addition to the canonical mode, HER receptors or fragments of them seem to be endowed with direct signaling abilities. HER2 is a substrate of metalloproteases collectively known as alpha-secretases, which release the extracellular domain, leaving behind the transmembrane-cytoplasmic fragment, known as P95 (Fig. 1). By analogy with other transmembrane proteins also cleaved by alpha-secretases, it has been suggested that P95 can also be subsequently achieved by gamma-secretases, which release the intracellular domain in a process known as RIP (regulated intramembrane proteolysis). Although P95 has been poorly characterized, partly because it is produced at very low levels in cultured cell lines, it has been suggested that it is active. However, since P95 lacks the extracellular domain, it is not predicted to form hetero- or homodimers. Thus, the mechanism of activation of P95 remains unexplained.

We have recently identified alternative initiation of translation as an additional mechanism that generates CTFs of HER2 similar, but not identical, to P95. Initiation of translation from methionine codons, located upstream or downstream of the transmembrane domain, leads to the generation of two different CTFs (Fig. 1). Although preliminary evidence suggests that CTFs generated by translation are active, as in the case of P95, the mechanism of activation is unknown.

In summary, at least four different HER2 CTFs are generated by two independent mechanisms: proteolytic processing and alternative initiation of translation (Fig. 1). Two HER2 CTFs contain the transmembrane and cytoplasmic domains while two are predicted to be soluble intracellular proteins encompassing most of the cytoplasmic domain (Fig. 1).

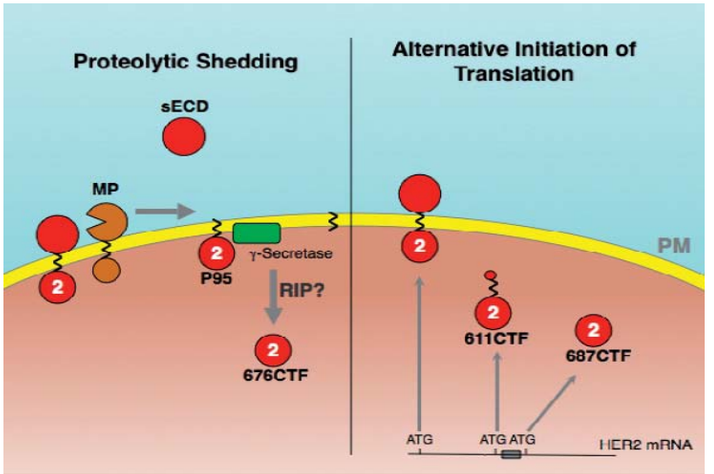


Figure 1. Generation of HER2 Carboxy Terminal Fragments (CTFs). HER2 CTFs are generated either by proteolytic processing of by alternative initiation of translation. The first mechanism consists in the sequential cleavage by metalloproteases (MP), that generate a transmembrane cytoplasmic fragment known as P95, and gamma-secretases, that produce the soluble intracellular cytoplasmic fragment. The second consists in alternative initiation of translation from two methionines located upstream or downstream the transmembrane domain.

HER2 fragments and breast cancer progression and treatment

Breast cancer patients expressing CTFs of HER2 are more likely to develop nodal metastasis and have worse prognosis than those expressing predominantly the full-length receptor. Furthermore, the presence of CTFs seems to be relevant for tumor treatment. Currently, two types of drugs targeting HER2 are used in clinical practice: monoclonal antibodies against the extracellular domain and small-molecule inhibitors that block the kinase activity of the receptor. We have recently shown that approximately 90% of breast cancer patients expressing CTFs are resistant to treatment with the anti-HER2 antibody Herceptin (trastuzumab). However, the CTFs expressed in tumors have not been characterized in detail and it is not known if these fragments arise in tumors by proteolysis and/or alternative initiation of translation. Furthermore, since the activity of the different CTFs has not been analyzed individually, their relative contribution to the malignant phenotype has not been determined.

Characterization of HER2 fragments

In 2008 we finished a comprehensive analysis of the different CTFs of HER2 expressed in breast cancers. The characterization of cells lines individually expressing different CTFs showed that the activity of P95 is comparable to that of full-length HER2. In contrast, the product of alternative initiation of translation from methionine 611 is hyperactive and specifically controls the expression of genes involved in malignant transformation and metastasis (Fig. 2). In contrast, CTFs devoid of a transmembrane domain appear to be inactive. Finally, we have established transgenic mouse models to show that expression of 611-CTF leads to the generation of tumors far more aggressive than those generated by full-length HER2 (Fig. 3).

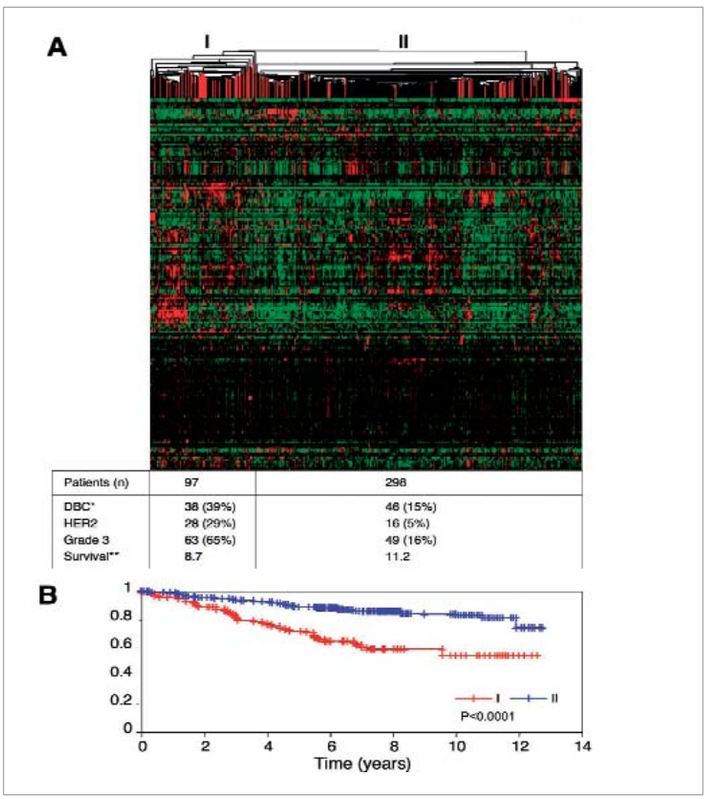


Figure 2. A. Unsupervised hierarchical clustering of 395 primary breast tumors from two independent publicly available studies, on the basis of expression levels of the 76-gene signature of 611-CTF (see Fig. S11). * Patients that Died from Breast Cancer. ** Mean survival time (years). B. Kaplan-Meier survival plots of the two patient groups classified in "A".

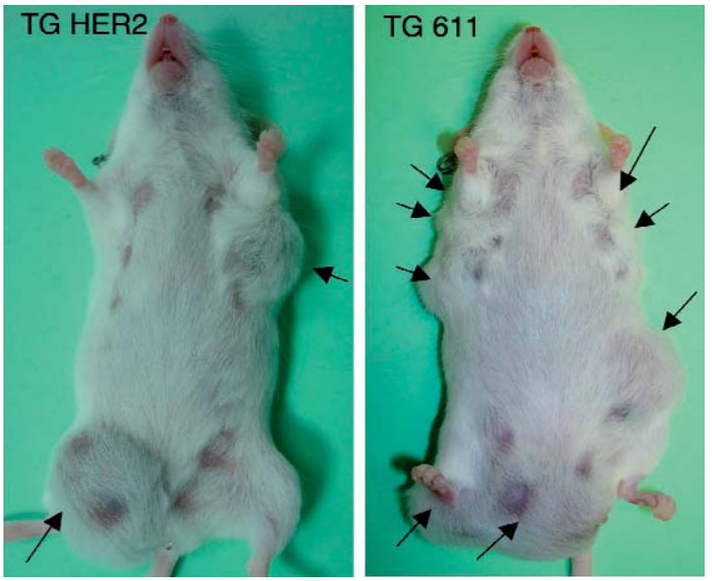


Figure 3. Representative TG HER2 (35 weeks old) and 611-CTF (25 weeks old) mice.

Research projects (10)

Funding agency: Asociación Española Contra el Cáncer
Title: Caracterización funcional y estructural contra el cáncer de un nuevo producto del proto-oncogén HER2. Implicaciones terapéuticas en cáncer de mama.
PI: Joaquín Arribas
Duration: April 2005-April 2008

Funding agency: Fundació "la Caixa"
Title: Identificación del degradoma de la metaloproteasa desintegrina TACE: relevancia en el desarrollo de tumores de mama.
PI: Joaquín Arribas
Duration: 2005-August 2008

Funding agency: Ministerio de Educación y Ciencia
Title: Generación y caracterización de ratones transgénicos expresando Fragmentos C-Terminales del oncogén HER2 en glándulas mamarias.
PI: Joaquín Arribas
Duration: 2005-October 2008

Funding agency: Fundació La Marató de TV3
Title: Identificació i caracterització dels mecanismes de tumorogenesis mediats pels fragments carboxiterminals de HER2.
PI: Joaquín Arribas
Duration: 2006-December 2008

Funding agency: Fundacion Mutua Madrileña (FMM)
Title: Identificación de mecanismos y factores involucrados en la sobreexpresión y tráfico intracelular de ADAM17(TACE). Relevancia para el desarrollo de tumores de mama.
PI: Joaquín Arribas
Duration: 2007-July 2010

Funding agency: Instituto Carlos III (Subdirección General de Redes y Centros de Investigación Cooperativa)
Title: Red Temática de Investigación Cooperativa del Cáncer.
PI: Joaquín Arribas
Duration: 2007-2010

Funding agency: Generalitat de Catalunya (AGAUR)
Title: SGR Suport a Grups de Recerca de Qualitat.
PI: Joaquín Arribas
Duration: 2006-December 2008

Funding agency: Genoma España
Title: Proteored.
PI: Joaquín Arribas
Duration: 2005-2010

Funding agency: The Breast Cancer Research Foundation
Title: Identification of factors and mechanisms leading to metastasis in breast tumors expressing HER2 Carboxy Terminal Fragments.
PI: Joaquín Arribas
Duration: 2007-2008

Funding agency: The Breast Cancer Research Foundation
Title: Metastasis in tumors expressing 611-CTF of HER2: mechanisms an d therapeutics strategies.
PI: Joaquín Arribas
Duration: 2008-2009

Publications (4) / IF: 21.587

Esselens C, **Malapeira J**, Canals F, Moss M and **Arribas J**. Metastasis-associated C4.4A, a GPI-anchored proteína cleaved by ADAM10 and ADAM17. Biol Chem. 2008 Aug;389(8):1075-84.
(IF: 2.840, 2 cuartil, biochemistry molecular biology)

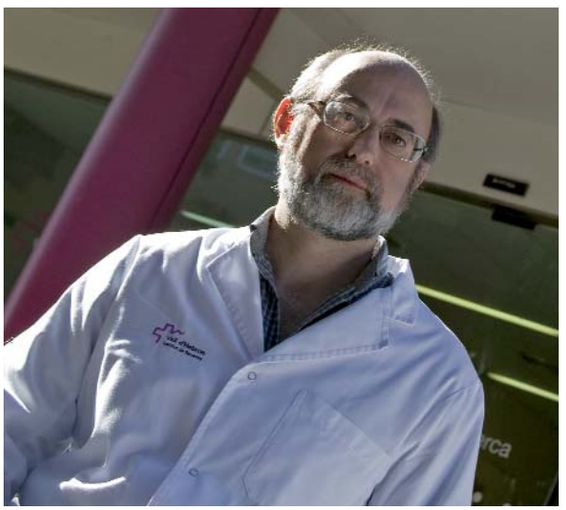
Scaltriti M, Verma C, Guzman M, Jiménez J, **Parra JL**, **Pedersen K**, Smith DJ, Landolfi S, Ramón y Cajal S, **Arribas J**, Baselga J. Lapatinib, a HER2 tyrosine kinase inhibitor, induces stabilization and accumulation of HER2 and potentiates trastuzumab-dependent cell cytotoxicity. Oncogene. In press.
(IF: 6.440, 1 cuartil, oncology)

Vilar E, Scaltriti M, Balmaña J, Saura C, Guzman M, **Arribas J**, Baselga J, Tabernero J. Microsatellite instability due to hMLH1 deficiency is associated with increased cytotoxicity to irinotecan in human colorectal cancer cell lines. Br J Cancer. 2008 Nov 18;99(10):1607-12. Epub 2008 Oct 21.
(IF: 4.635, 1 cuartil, oncology)

Serra V, Markman B, Scaltriti M, Eichhorn PJ, Valero V, Guzman M, Botero ML, Llonch E, Atzori F, Di Cosimo S, Maira M, Garcia-Echeverria C, **Parra JL**, **Arribas J**, Baselga J. NVP-BEZ235, a dual PI3K/mTOR inhibitor, prevents PI3K signaling and inhibits the growth of cancer cells with activating PI3K mutations. Cancer Res. 2008 Oct 1;68(19):8022-30.
(IF: 7.672, 1 cuartil, oncology)

Proteomics Laboratory

Francesc Canals, group leader



Francesc Canals graduated in organic chemistry at the Institut Químic de Sarrià, Barcelona, in 1982, where he also obtained his PhD in 1989 in the field of organic photochemistry. He also obtained a degree in biochemistry at the Universitat Autònoma, Barcelona, in 1987.

He worked as a postdoctoral fellow in the laboratory of Prof. Jack Kyte, at the University of California San Diego (USA) where he performed protein chemistry studies on the signaling mechanism of the epidermal growth factor receptor, showing that the tyrosine kinase of the receptor is activated after its dimerization.In 2003 he joined the Medical Oncology Research program as head of the Proteomics Laboratory. Since then, he has set up the different separation and mass-spectrometry based proteomic technologies provided by the facility. His research focuses on the development and application of proteomic strategies to characterize the substrate repertoire - degradome - of metalloproteases of the ADAM and ADAMTS families, involved in tumor progression.

Proteomics Laboratory

Our research work focuses on the application of proteomic techniques in 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 of the substrates of these proteases in the context of tumor cells is needed to elucidate their role in tumor growth and metastasis, to evaluate their potential use as therapeutic targets. Our laboratory uses mass-spectrometry based proteomic strategies to search new substrates of these proteases and explore their role in tumor progression. In parallel, as a core facility, the objective of the laboratory is to provide services to research groups in state-of-the-art proteomic methodologiesand to implement new developments to keep up to date with new proteomic strategies and technologies.

Group leader

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Laboratory members

Post-doctoral Fellow
Joan Josep Bech PhD

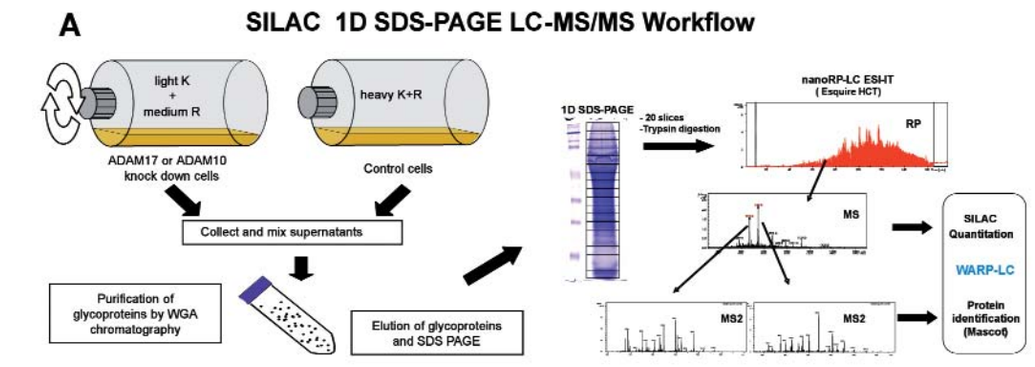
Technicians
Núria Colomé MSc
Marta Monge MSc

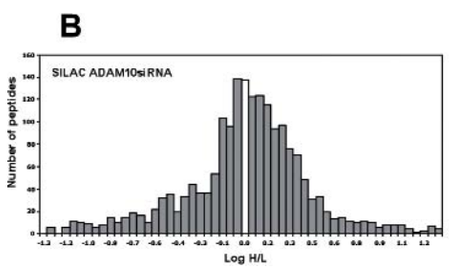
Scientific activity

The importance of the interaction between tumor cells and their microenvironment in malignant progression has been recently highlighted. Different metalloproteases play a crucial role in the regulation of the tumor microenvironment by mediating the remodeling of the extracellular matrix and the processing of extracellular and membrane proteins. Knowledge of the substrate repertoire (degradome) of these proteases is needed to elucidate their role in tumor growth and metastasis, in order to evaluate their potential use as therapeutic targets. We have demonstrated the utility of proteomic techniques to explore these degradomes. The present focus of our research is to extend these studies, incorporating new proteomic analysis techniques, to study metalloproteases known to play key roles in tumor progression. Metalloproteases of the ADAM family (ADAM10, ADAM17/TACE) and of the ADAMTS family (ADAMTS1), will be the object of study. TACE and ADAM10 are involved in the proteolytic cleavage of the transmembrane forms of EGFR ligands (shedding), required for the activation of the receptor, and are also involved in regulation of cell migration and adhesion. Several metalloproteases of this family are overexpressed in different types of tumors. The thrombospondin-domain containing protease ADAMTS1 has been recently found to be highly overexpressed in highly invasive mammary tumor cells, suggesting a major role for this protease in metastatic processes. The proposed proteomic studies aim to the identification and characterization of new substrates of these proteases in the context of cancer cells. The putative substrates identified will then be validated through characterization in vitro. The importance of the newly identified substrates in tumor development will be analyzed in preclinical models and their expression and shedding will be determined in mammary tumor samples.

Identification of substrates of ADAM10 and ADAM17 proteases using SILAC analysis

In order to search for substrates of the ADAM10 and ADAM17 metalloproteases, we have used model breast cancer cells in which conditional expression has been introduced, using the tet-off system, of either the protease or siRNA to knock down specifically the protease of interest. The comparison between conditions where the protease is either inactive or active can be then carried out in the same cell





ADAM10siRNA SILAC	Mean H/L	St. error	n	IPI
E-Cadherin	5.17	/	1	IPI00000513
Desmoglein-2	5.11	/	1	IPI00028931
PTP Receptor-type kappa	2.52	0.09	16	IPI00015756
C4.4A	**1.96**	**0.07**	**29**	**IPI00004310**
Dystroglycan-1	1.46	0.14	11	IPI00028911
LISCH protein	1.32	0.06	59	IPI00789912

Figure 1. Protease substrate screening using SILAC LC-MS analysis. A) Conditioned media SILAC-labeled glycoproteins from parental (Heavy label) and ADAM10 or ADAM17 knock down cells (light label) are collected. Analysis of the mixture of both samples is carried out by separating first by 1D-SDS-PAGE. The gel lane is cut into 20 slices which are digested with trypsin. Each peptide mixture is then analyzed by reverse phase LC coupled to ESI-Ion Trap MS. Quantitation of relative abundances for each peptide is made on the basis of the ratio of H/L intensities in the MS spectra. Proteins are identified trough database search from the MS/MS spectra. B) Distribution of H/L ratios for the 2001 peptides identified, corresponding to 658 different proteins on a ADAM10 SILAC experiment. C) Candidate substrates detected in the analysis. E-cadherin, desmoglein-2 and PTP receptor are known substrates of ADAM10.

clone. Differential proteomic analysis of the conditioned culture media of these cells has been performed using a SILAC (stable isotope labeling through aminoacids in culture) approach, and an analytical workflow comprising 1D-SDS-PAGE fractionation followed by liquid-chromatography coupled to electrospray mass spectrometry (LC-MS). Labeling is accomplished supplying specific labeled amino acids in the cell culture medium, thus allowing the labeling of all the proteins in the cell through its own metabolic processes. In this way, quantitative information can be obtained for all the proteins detected in the analysis.

A number of known substrates of both proteases were identified as such in the analysis, showing the expected decrease of the shed extracellular domain abundance in the medium upon knock down of the protease (Figure 1). In addition, several new candidate substrates of both proteases were identified. Among them, the GPI-anchored protein C4.4A, was identified and further validated as substrate of both ADAM10 and ADAM17 proteases. According to the identified peptides, both proteases cleave this protein close to the juxtamembrane region, releasing a soluble form devoid of the GPI-anchor. C4.4A protein, homologous to the urokinase-type plasminogen activator receptor, has been related to tumor invasion and metastasis. Cleavage of this protein by ADAMs constitutes a previously unknown level of regulation of its function. Work is in progress to validate and further characterize other proteins identified as potential substrates of these proteases.

Identification of ADAMTS1 substrates using DIGE and SILAC proteomic analysis

We have applied two complementary proteomic approaches, 2D electrophoresis DIGE and SILAC LC-MS analysis, to the search of substrates of the metalloprotease ADAMTS1, in a model breast cancer cell line were conditional overexpression of the protease was introduced.

Glycoproteins of the conditioned media from parental and ADAMTS1 overexpressing cells were purified and analyzed using a 2D-DIGE electrophoresis approach (Figure 2) and a SILAC methodology similar to the one described above for the ADAM10 and ADAM17 experiments.

Both approaches led to the identification of trombospondin-1 as a substrate of ADAMTS1, which has been reported recently by others, and shown to play a role in modulating angiogenesis.

Semaphorin 3C was also identified by both methodologies, and further validated as a substrate of both ADAMTS1 and ADAM17. This family of extracellular matrix proteins plays different roles in cell axon guidance in the nervous system, as well as in angiogenesis and tumor progression. The role of Semaphorin 3C in cancer cell migration is currently being investigated.

Other collaborative projects with VHIO groups

- Signaling through C-terminal fragments of HER-2 in breast cancer (with J. Arribas Lab.): SILAC proteomic analysis was used to analyze protein-protein interaction partners of HER-2. Several potential mediators of HER-2 signaling, as well as previously unreported phosphorylation sites have been identified.
- Screening for surface marker proteins of glioma-initiating stem-cells (with J. Seoane Lab.): Several candidate proteins have been identified has putative surface markers of glioma neurosphere forming cells through cell-surface proteome analysis.
- Biomarkers to monitor response to Hsp-90 inhibitor IPI-504 treatment (with M. Scaltriti - J. Baselga Lab.): Several candidate biomarkers of IPI-504 action have been identified by SILAC proteomic analysis of model cells.

Facility and collaborative work

The Proteomics Laboratory has continued providing services as a member of the Instituto de Salud Carlos III Cancer Research Network, and of the Instituto Nacional de Proteómica ProteoRed, funded by Fundación Genoma España. This year, the laboratory has provided services to more than 30 research groups, not only from the Vall Hebron Hospital, but also from the main hospitals, research centers and universities in the area. In summary, the analysis performed include 40 2D-DIGE gels, 20 quantitative ICPL or SILAC experiments, representing a total of more than 450 LC-MS runs, and around 500 protein identifications by peptide mass fingerprint.

In conjunction with the services provided, the laboratory has actively participated in several projects involving proteomic analysis. The main contributions have been: in collaboration with Dr. R. Simó, of the Endocrinology Unit at the VHUH Research Institute we have continued to apply DIGE technology to study alterations in the protein contents of vitreous fluid of proliferative diabetic retinopathy patients subjected to vitrectomy (Fig. 3). Together with the Department of Immunology at the Universitat Autònoma, Barcelona, led by Dr. Dolores Jaraquemada, we have been working on the analysis of repertoires of HLA associated peptides of cell lines related to autoimmune diseases or cancer.

In the framework of the ProteoRed network, the laboratory has coordinated a multicentric study to evaluate reproducibility of a 2D-DIGE differential proteomic experiment. The results of the study show the robustness of the methodology used, and demonstrate the feasibility of across-lab validation schemes, pointing towards development of inter-lab QC strategies for proteomics research. The results were presented at the ABRF'09 Meeting, the 3rd SEPROT-LAHUPO Congress, and on the HUPO special meeting on reproducibility studies as preliminary requirements to launch HUPO Human Proteome Project.

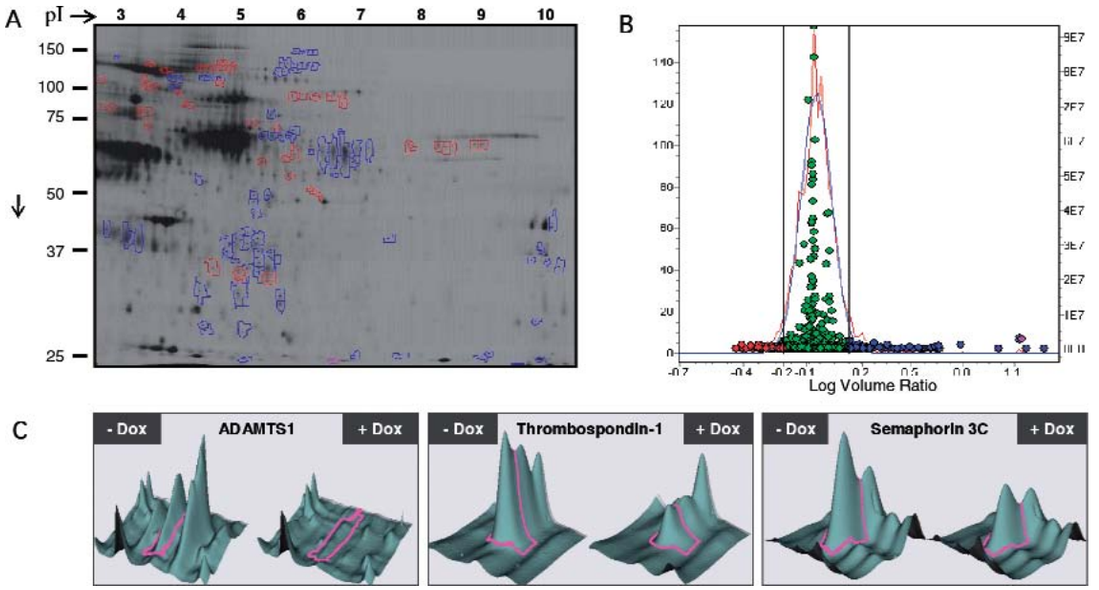


Figure 2. 2D-DIGE proteomic screening for ADAMTS1 substrates. A) 2D-DIGE gel image of conditioned medium glycoproteins. Proteins up-regulated in the ADAMTS1 overexpressing condition are marked in blue, proteins down-regulated in red. B) Frequency distribution of the volume ratios measured for the spots observed in the 2D-DIGE experiment. C) 3D image view of gel spots corresponding to ADAMTS1, Thrombospondin-1 and Semaphorin 3C, both showing an increase in the conditioned media of cells overexpressing ADAMTS1.

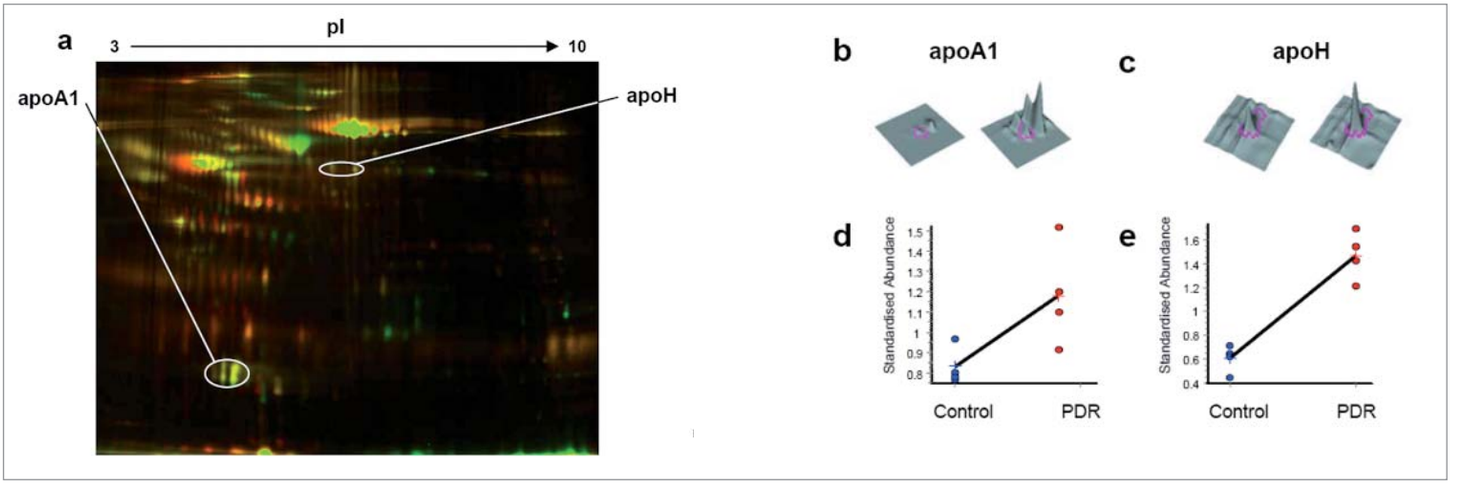


Figure 3. 2D-DIGE analysis of vitreous fluid proteins from control (non diabetic macular hole) versus Proliferative Diabetic Retinopathy patients (n=4) showing elevation of apolipoproteins A1 and H in PDR.

Research projects (1)

Funding agency: ISCIII (FIS)
Title: Identificación mediante análisis proteómico de nuevos sustratos de metaloproteasas implicadas en cáncer y caracterización de su papel funcional.
PI: Dr. Francesc Canals
Duration: January 2008-December 2010

Publications (5) / IF: 16.300

Álvarez I, Collado J, Daura X, **Colomé N**, Rodríguez-García M, Gallart T, Canals F, Jaraquemada D. The rheumatoid arthritis–associated allele HLA–DR10 (DRB1*1001) shares part of its repertoire with HLA–DR1 (DRB1*0101) and HLA–DR4 (DRB*0401). Arthritis & Rheumatism. 2008;58:1630-1639.
(IF: 7.677, 1 cuartil, rheumatology)

Esselens C, Malapeira J, **Colomé N**, **Canals F**, Arribas, J. Metastasis-associated C4.4A, a GPI-anchored protein cleaved by ADAM10 and ADAM17. Biological Chemistry. 2008 Aug;389(8):1075-84.
(IF: 2.840, 2 cuartil, biochemistry & molecular biology)

Simó R, Higuera M, García-Ramírez M, **Canals F**, García-Arumí J, Hernández C. Elevation of apolipoprotein A-I and apolipoprotein H levels in the vitreous fluid and overexpression in the retina of diabetic patients. Arch Ophthalmol. 2008 Aug;126(8):1076-81.
(IF: 2.984, 1 cuartil, ophthalmology)

Esteve-Puig R, **Canals F**, **Colomé N**, Merlino G, Recio JA. Uncoupling of the LKB1-AMPK-energy sensor pathway by growth factors and oncogenic BRAFV600E. PLoS ONE. In press.

Doll A, Abal M, Rigau M, **Monge M**, González M, Demajo S, Colás E, Llauradó M, Alazzouzi H, Planagumá J, Lohmann MA, Garcia J, Castellvi J, Ramón y Cajal S, Gil-Moreno A, Xercavins J, Alameda F, Reventós J. Novel molecular profiles of endometrial cancer-new light through old windows. J Steroid Biochem Mol Biol. 2008 Feb;108(3-5):221-9. Epub 2007 Sep 15. Review.
(IF: 2.799, 2 cuartil, biochemistry molecular biology science)

Stem Cells and Cancer Laboratory

Héctor G. Palmer, group leader

In 2001, Héctor G. Palmer obtained his PhD in biochemistry and molecular biology from the Universidad Autónoma de Madrid.

While working at the Instituto de Investigaciones Biomedicas in Madrid as a postdoctoral fellow, he described the role of Wnt pathway, vitamin D receptor (VDR) and snail transcription factors controlling human colon cancer progression.

In 2003, he was awarded with the Marie Curie Intra European Fellowship and in 2004, he joined the Cancer Research UK (UK) as a postdoctoral fellow under the leadership of Prof. Fiona M. Watt, where he described VDR as a novel transcriptional effector of the Wnt pathway that controls the fate of stem cells in adult epidermis. He also discovered that the central role of the Wnt signalling in tumor initiation depends on VDR function, opening a new opportunity for the use of Vitamin D based drugs to prevent cancer development.

In 2008 Héctor returned as an independent researcher and became group leader of the Stem Cells and Cancer Laboratory. He has continued his work on the role of Wnt/beta-catenin pathway driving normal and cancer stem cell fate in epithelial tissues and its relevance in tumor initiation, progression and self-renewal.

Stem Cells and Cancer Laboratory

The main interest of our laboratory is in understanding the molecular mechanisms that control the initiation and progression of colorectal cancer. In particular, we focus on studying how rare populations of cancer stem cells retain the ability to perpetuate tumors and how they become the drug-resistant, and studying the long-term source of tumor self-renewal. At the molecular level, we are analyzing the role of the Wnt/beta-catenin pathway controlling the fate of normal and cancer stem cells. We are specifically inter-

Group leader

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Laboratory members

Post-doctoral Fellow
Stephan Tenbaum PhD

Technician
Irene Chicote

ested in novel mechanism of gene transcription regulation dependent on Wnt signalling and its relevance in driving stem cell decisions: self-renewal versus differentiation.

Our technical approaches include cellular and molecular biology, as well as mouse models and most importantly the analysis of live human tissue directly provided from patients with colorectal tumors. This last line of work is extremely exciting because it permits us to work directly with human cancer stem cells, which is a privileged opportunity in the field of cancer research.

Scientific activity

- Characterization of new molecular features of the Wnt/beta-catenin signalling pathway and their relevance in normal and cancer stem cells physiology.
- Study of the contribution of cancer stem cells to the initiation, progression and self-renewal of epithelial tumors.
- Testing the specific sensitivity of human colon cancer stem cells to anti-tumoral agents.
- Understanding the mechanisms that govern somatic stem cell physiology in tissue homeostasis and regeneration.

Stem cells (SC) have the unique capacity to self-renew and the potential to differentiate into the multiple cell lineages that are present in adult tissues, sustaining their permanent renewal and their ability to regenerate upon injury. Interestingly, many molecules and signalling pathways that control SC fate are abnormal in the initiation of cancer in the same tissues. The Wnt/beta-catenin pathway is one of these driving forces that direct stem cell fate, controlling self-renewal and selecting cell lineages throughout development and tissue homeostasis. Abnormal activation of Wnt/beta-catenin signalling leads to tumor formation, affecting the balance of SC self-renewal versus differentiation.

We study novel molecular mechanisms of the Wnt pathway that control the physiology of normal and cancer SC. We are developing new mouse models and analyzing isolated SC from human tumors to study the role of novel Wnt signalling mechanisms in cancer initiation and self-renewal.

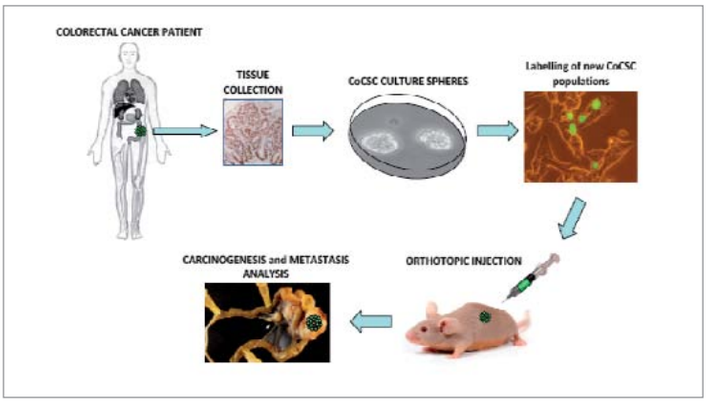


Figure 1. Experimental workflow.

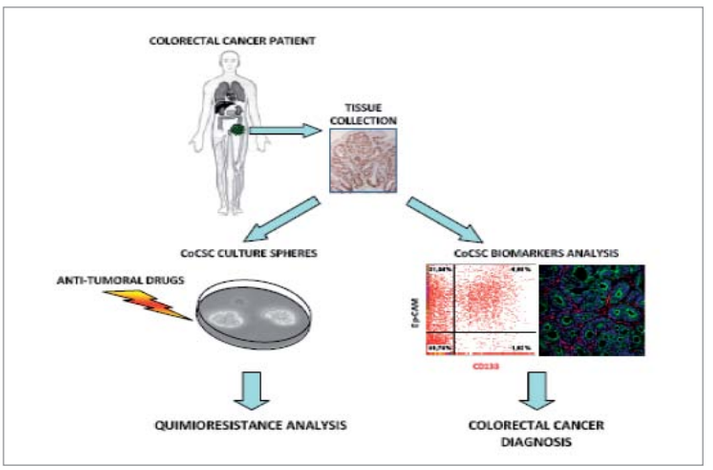


Figure 2. Identification of rare cancer stem cell populations.

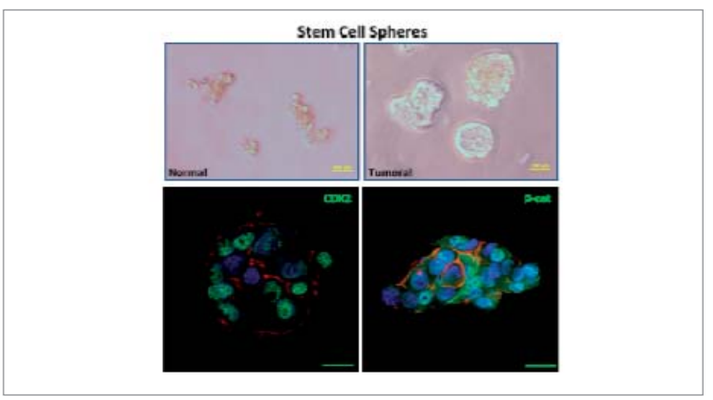


Figure 3. Stem cell spheres.

Research projects (2)

Funding agency: ISCIII (FIS)
Title: Células madre tumorales de colon y la ruta de Wnt/Beta-Catenina.
PI: Dr. H. Palmer
Duration: 2009-2011

Funding agency: Fundació Olga Torres
Title: Células Madre de Cáncer de Colon.
PI: Dr. H. Palmer
Duration: 2009-2011

Publications (5) / IF: 22.162

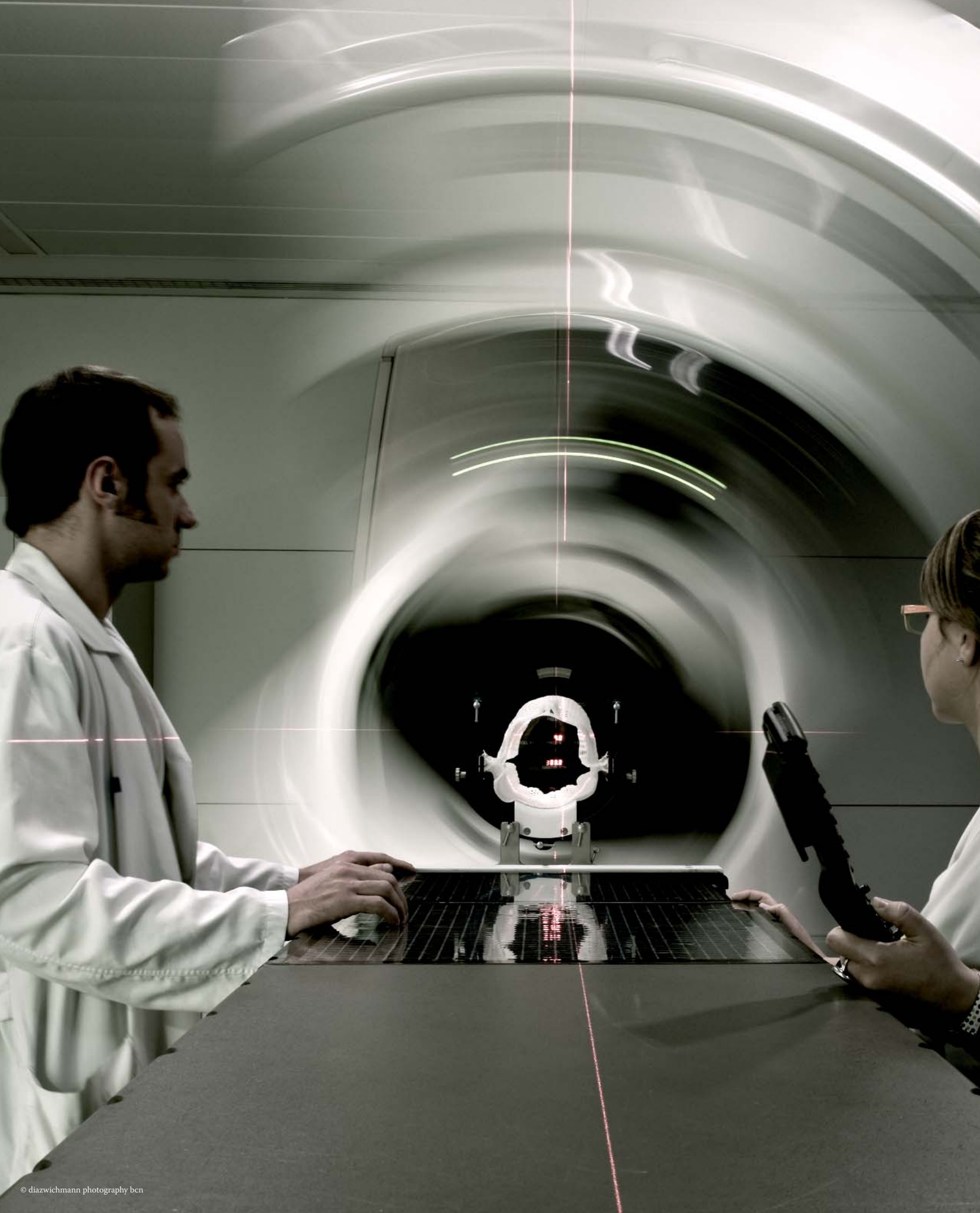
Pendás-Franco N, García JM, Peña C, Valle N, **Palmer HG**, Heinäniemi M, Carlberg C, Jiménez B, Bonilla F, Muñoz A, González-Sancho JM. DICKKOPF-4 is induced by TCF/beta-catenin and upregulated in human colon cancer, promotes tumour cell invasion and angiogenesis and is repressed by 1alpha,25-dihydroxyvitamin D(3). Oncogene. 2008 Jul 24;27(32):4467-77. Epub 2008 Apr 14.
(IF: 6.440, 1 cuartil, oncology)

Palmer HG, Martínez D, Carmeliet G, Watt FM. The vitamin D receptor is required for mouse hair cycle progression but not for maintenance of the epidermal stem cell compartment.
J Invest Dermatol. 2008 Aug;128(8):2113-7.
(IF: 4.829, 1 cuartil, dermatology)

Palmer HG, Anjos-Afonso F, Carmeliet G, Takeda H, Watt FM. The vitamin D receptor is a Wnt effector that controls hair follicle differentiation and specifies tumor type in adult epidermis. PLoS ONE. 2008 Jan 23;3(1):e1483.

Ordóñez-Morán P, Larriba MJ, **Palmer HG**, Valero RA, Barbáchano A, Duñach M, de Herreros AG, Villalobos C, Berciano MT, Lafarga M, Muñoz A. RhoA-ROCK and p38MAPK-MSK1 mediate vitamin D effects on gene expression, phenotype, and Wnt pathway in colon cancer cells. J Cell Biol. 2008 Nov 17;183(4):697-710.
(IF: 9.598, 1 cuartil, cell biology)

Martin Hübner A, **Tenbaum SP**. Complete remission of palmoplantar psoriasis through Helicobacter pylori eradication: a case report. Clin Exp Dermatol. 2008 May;33(3):339-40.
(IF: 1.295, 2 cuartil, dermatology science)



Clinical research

"Our obligation is to understand why an agent works and to select the right patients for treatment."

Breast Cancer Program

Javier Cortés, group leader

Javier Cortés obtained his degree in medicine and surgery at the Autonomous University of Madrid (1996) before specializing in medical oncology. He is the deputy director of the VHIO Breast Cancer Program, he has been an attending physician in Medical Oncology at Vall d'Hebron University Hospital since 2003 and he is the coordinator of the Resident Oncology Teaching and Training Program. He is a clinical investigator in the Breast Cancer and Melanoma programs and is the head of the Melanoma Program.

He is the author of more than 24 peer-review publications, specifically in the areas of breast and lung cancer, as well as new drugs. He actively participates in the development of national and international clinical studies, especially related with agents aimed at molecular targets and new chemotherapy drugs, and is an ad hoc reviewer of several oncology journals.

He is the recipient of a grant from the American Oncology Association (ASCO & AACR) and the European Organisation for Research and Treatment of Cancer (EORTC) in the "6th International Workshop in Clinical Cancer Research", held out in Flims, Switzerland, where he developed the project "A phase I study of everolimus (RAD001) in combination with gefitinib in anthracycline- and taxane- pretreated patients with metastatic breast cancer".

Breast Cancer Program

The VHIO Breast Cancer Program is dedicated to the care of patients with breast cancer, as well as research, training and education. As a clinical academic unit, we are committed to clinical experience, clinical and translational research, and a broad range of teaching.

Our approach is based on the principle that clinicians provide the best quality care to cancer patients. We are members of a multidisciplinary cancer team, meeting regularly to discuss the most appropriate treatment and management of each individual patient.

Group leader

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Meritxell Bellet MD
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Marta Guix MD
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Fellow
Francesco Atzori MD

Clinical Trials Coordinators
Olga Vidal MD
Raquel Espallargas MD
Violeta Esteban MD
Beatriz García MD

Over 12,600 patients were visited in 2008, including over 600 new patients. We are committed to bringing the best novel agents to our patients via a comprehensive program of clinical trials. Every year, the number of patients included in clinical trials increases. Last year, 162 patients were enrolled in breast cancer clinical trials, in addition to breast cancer patients participating in phase I trials.

Clinical activity

Our primary objective is to provide the best clinical care to breast cancer patients, including adequate family support. We divide our clinical activity into two major categories:

1. Outpatient care: In 2008 we visited more than 12,600 patients, of which over 600 were new patients. These numbers represent a 5% increase in new patients over the previous year, making us the leading hospital for breast cancer clinical activity in Spain.

Outpatient care includes the following:

- New patient visits.
- Visiting patients undergoing chemotherapy treatment.
- Follow-up visits.

2. Inpatient care: We visit on a daily basis patients hospitalized with breast cancer, perform follow-up visits, and if necessary place them in in-house continual care.

Our commitment to our patients is evidenced by the fact that our team has been able to eliminate the concept of waiting lists for breast cancer patients. Moreover, all patients are visited within one week, once they have been scheduled for a first visit.

Other activities include developing protocols to follow in different diagnostic and therapeutic processes in clinical practice guidelines. We have actively participated in drawing up the breast cancer oncology guidelines.

2008 was a particularly important year for all of us because the construction of the new Breast Cancer Center became a reality. This ambitious project was completed at the beginning of the year and is now fully equipped for work. The first floor houses surgery and radiology, and the primary use of the second floor is oncology. The services it provides include outpatient visits, day hospital, radiology and biopsies and molecular diagnosis procedures.

The new centre covers two main objectives:

- First and foremost, it provides care in a multi-disciplinary fashion to breast cancer patients, with the possibility of being visited on the same day by surgeons, radiologists and oncologists, within the same functional unit.
- The new facility is spacious, making patients more comfortable, in a similar way to the best American centers.

All of the above makes us believe that 2009 will be an exciting year full of opportunities for physicians as well as for patients, and we expect to excel in our care with the help of new medical, technical and logistics facilities.

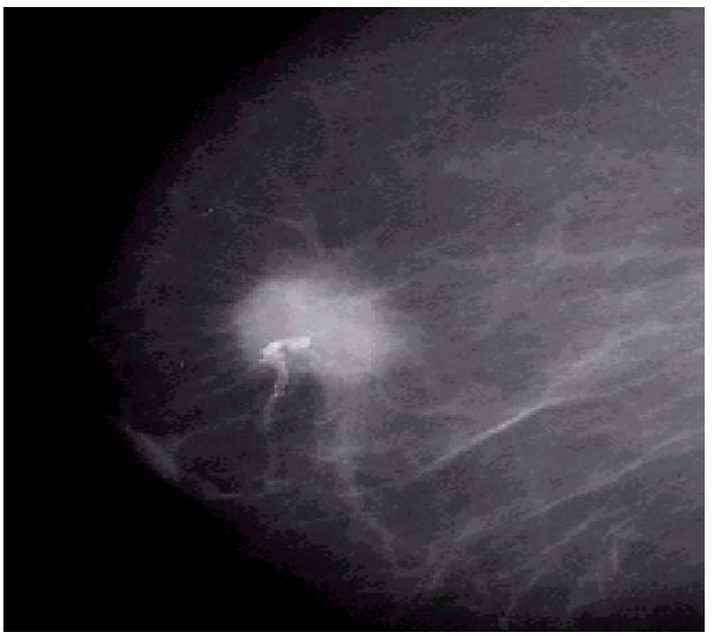

Figure 1. Mammography showing breast mass.

Scientific activity

Another important focus of the Breast Cancer Program is clinical research. We have developed a wide program of applied clinical research that gives patients the opportunity to receive novel treatments while participating in research.

We are developing phase I, II and III clinical trials, and our main goal is to add new molecules to the therapeutic arsenal against breast cancer.

The priorities of our program are:

- To understand the mechanisms that make cells overexpressing the HER2 receptor resistant to specific therapies, and then to develop strategies to revert it by incorporating new drugs or by developing strategies to avoid the mechanisms of resistance.
- Clinical investigation with agents that use new pathways as a target related to the aggressiveness of breast cancer, such as new anti-angiogenic agents.
- Research with new chemotherapy agents.
- Development of new pharmacologic combinations that may increase efficacy against breast cancer, often combining "classical" cytotoxic drugs with targeted agents.

To reach our objectives, all physicians are aware of the importance of including patients in clinical trials.

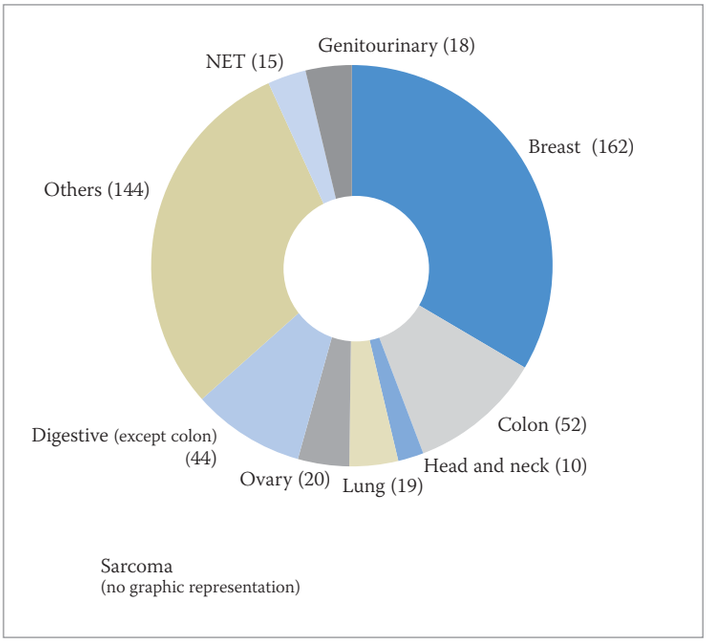

Figure 2. *In 2008-2009, almost 300 patients were included in breast cancer clinical trials; and the number of clinical studies continues to grow. Patients included in breast cancer trials represent 30% of the total number of patients included in clinical trials in the Oncology Department.*

Clinical trials (20)

A6181077 A Randomized Phase 2 Study Of SU011248 Versus Standard-of-Care For Patients With Previously Treated, Advanced, Triple Receptor Negative (ER, PR, HER2) Breast Cancer. Included patients: 1

CA180-088 Phase II Study of Dasatinib (BMS-354825) for Advanced Estrogen/Progesterone Receptor-Positive or Her2/Neu-Positive Breast Cancer. Included patients: 0

IV-ERT-BC-03 Phase II study for repeated dosing of the trifunctional bispecific anti-HER-2/neu x anti-CD3 antibody ertumaxomab in patients with HER-2/neu 1+ or 2+/FISH negative expressing advanced or metastatic breast cancer (stage IIIb/IV) progressing after endocrine treatment. Included patients: 4

EGF105485 A Randomized, Double-blind, Multicenter, Placebo-controlled Study of Adjuvant Lapatinib (GW572016) in Women With Early-Stage ErbB2 Overexpressing Breast Cancer. Included patients: 1

A6181064 A Randomized Phase 3 Study Of Docetaxel In Combination With Sunitinib Versus Docetaxel In The First-Line Treatment Of Advanced Breast Cancer Patients. Included patients: 9

CA180-004 Phase I Study of Dasatinib (BMS-354825) and Capecitabine for Advanced Breast Cancer. Included patients: 8

E7389-G000-301 A Phase III Open Label, Randomized Two-Parallel-Arm Multicenter Study of E7389 Versus Capecitabine in Patients With Locally Advanced or Metastatic Breast Cancer Previously Treated With Anthracyclines and Taxanes. Included patients: 2

E7389-G000-305 The "EMBRACE" Trial: Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389. A Phase III Open-Label, Randomized, Parallel, Two-arm, Multi-center Study of E7389 Versus "Treatment of Physician's Choice" in Patients With Locally Recurrent, Metastatic Breast Cancer, Previously Treated With At Least Two and a Maximum of Five Prior Chemotherapy Regimens, Including an Anthracycline and a Taxane. Included patients: 20

WO20698 A Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated Her2-Positive Metastatic Breast Cancer. Included patients: 1

VEG108838 A Randomized, Multicenter, Phase III Study Comparing the Combination of Pazopanib and Lapatinib Versus Lapatinib Monotherapy in Patients With ErbB2 Over-expressing Inflammatory Breast Cancer. Included patients: 3

AVF3693g A Phase III, Multicenter, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination With Chemotherapy Regimens in Subjects With Previously Treated Metastatic Breast Cancer. Included patients: 3

ALTTO A Randomised, Multi-centre, Open-label, Phase III Study of Adjuvant Lapatinib, Trastuzumab, Their Sequence and Their Combination in Patients With HER2/ErbB2 Positive Primary Breast Cancer. Included patients: 6

SOFT Ensayo en fase III para evaluar el papel de la supresión de la función ovárica y el papel de exemestano como tratamientos adyuvantes para mujeres premenopáusicas con cáncer de mama endocrino sensible. Included patients: 21

EMR 200027-051 Randomized Phase II Trial With Cetuximab and Cisplatin in the Treatment of ER-Negative, PgR-Negative, HER2-Negative Metastatic Breast Carcinoma ("Basal Like"). Included patients: 10

SOLTI0701 Estudio multinacional fase 2b, doble ciego y aleatorizado para evaluar la eficacia y seguridad de sarafenib frente a placebo administrados junto con capecitabina en pacientes con cáncer de mama localmente avanzado o metastásico. Included patients: 12

MINDACT (Microarray In Node-negative Disease May Avoid Chemotherapy): A Prospective, Randomized Study Comparing the 70-Gene Signature With the Common Clinical-Pathological Criteria in Selecting Patients for Adjuvant Chemotherapy in Node-Negative Breast Cancer. Included patients: 18

BO20289 An Open Label 2-arm Study to Evaluate the Impact of Adjuvant Bevacizumab on Invasive Disease Free Survival in Triple Negative Breast Cancer. Included patients: 2

CA163100 Estudio fase II, aleatorizado, para analizar biomarcadores asociados al tratamiento neoadyuvante y secuencial de AC seguido de ixabepilona en comparación con AC seguido de paclitaxel en mujeres con estadios iniciales de cáncer de mama sin sobreexpresión de HER-2 ni receptores estrogénicos. Included patients: 6

EGF107671 A Phase II Study of Lapatinib Plus Topotecan or Lapatinib Plus Capecitabine in the Treatment of Recurrent Brain Metastases From ErbB2-Positive Breast Cancer Following Cranial Radiotherapy. Included patients: 0

3144A1-2206-WW Estudio de fase 1/2, abierto, de neratinib (HKI-272) en combinación con capecitabina en pacientes con tumores sólidos y en pacientes con cáncer de mama metastásico o localmente avanzado positivo para ErbB-2. Included patients: 1

Publications (10) / IF: 60.147

Caralt M, Bilbao I, **Cortés J**, et al. Hepatic resection for liver metastases as part of the "oncosurgical" treatment of metastatic breast cancer. Ann Surg Oncol 2008;15:2804-10.
(IF: 3.917, 2 cuartil, oncology)

Cortés J, **Di Cosimo S**, Climent M, et al. Non-pegylated Liposomal Doxorubicin (TLC-D99), Paclitaxel and Trastuzumab in HER2 Overexpressing Breast Cancer: A Multicenter Phase I/II Study. Clin Cancer Res.In press.
(IF: 6.250, 1 cuartil, oncology)

Marty M, Sotiriou C, **Cortés J**, et al. Defining new strategies for the use of anthracyclines in the management of breast cancer. The Oncologist. In press.
(IF: 4.876, 1 cuartil, oncology)

Gradishar W, **Cortés J**. Clinical efficacy and emerging therapeutic utilization of novel taxanes. Eur J Cancer. In press.
(IF: 4.454, 1 cuartil, oncology)

Di Cosimo S, Baselga J. Targeted therapies in breast cancer: where are we now? Eur J Cancer. 2008 Dec;44(18):2781-90. Epub 2008 Nov 14. Review.
(IF: 4.454, 1 cuartil, oncology)

Serra V, Markman B, Scaltriti M, Eichhorn PJ, Valero V, Guzman M, Botero ML, Llonch E, **Atzori F**, **Di Cosimo S**, Maira M, Garcia-Echeverria C, Parra JL, Arribas J, Baselga J. NVP-BEZ235, a dual PI3K/mTOR inhibitor, prevents PI3K signaling and inhibits the growth of cancer cells with activating PI3K mutations. Cancer Res. 2008 Oct 1;68(19):8022-30.
(IF: 7.672, 1 cuartil, oncology)

Fabi A, Metro G, Ferretti G, Giannarelli D, **Di Cosimo S**, Papaldo P, Mottolese M, Carlini P, Felici A, Russillo M, Cognetti F. Do HER-2 positive metastatic breast cancer patients benefit from the use of trastuzumab beyond disease progression? A mono-institutional experience and systematic review of observational studies. Breast. 2008 Oct;17(5):499-505. Epub 2008 May 1. Review.
(IF: 2.155, 2 cuartil, oncology science)

Vilar E, Scaltriti M, Balmaña J, **Saura C**, Guzman M, Arribas J, Baselga J, Tabernero J. Microsatellite instability due to hMLH1 deficiency is associated with increased cytotoxicity to irinotecan in human colorectal cancer cell lines. Br J Cancer. 2008 Nov 18;99(10):1607-12. Epub 2008 Oct 21.
(IF: 4.635, 1 cuartil, oncology)

Felip E, Rojo F, Reck M, Heller A, Klughammer B, Sala G, Cedres S, Peralta S, Maacke H, Foernzler D, Parera M, Möcks J, **Saura C**, Gatzemeier U, Baselga J. A phase II pharmacodynamic study of erlotinib in patients with advanced non-small cell lung cancer previously treated with platinum-based chemotherapy. Clin Cancer Res. 2008 Jun 15;14(12):3867-74.
(IF: 6.250, 1 cuartil, oncology)

Baselga J, Semiglazov V, Van Dam P, Manikhas A, **Bellet M**, Mayordomo J, Campone M, Kubista E, Greil R, Bianchi G, Steinseifer J, Molloy B, Tokaji E, Gardner H, Phillips P, Stumm M, Lane HA, Dixon JM, Jonat W and Rugo HS. Phase II randomized neoadjuvant study of the mTOR inhibitor everolimus (RAD001) in combination with letrozole versus placebo and letrozole in patients with ER+ breast cancer. J Clin Oncol. 2008. In press.
(IF: 15.484, 1 cuartil, oncology)

Experimental Therapies Program

Josep Baselga, group leader

Josep Baselga is the director of the Vall d'Hebron Institute of Oncology (VHIO), chairman of the Medical Oncology Service, director of the Division of Medical Oncology, Hematology and Radiation Oncology at Vall d'Hebron University Hospital in Barcelona, Spain. He is also president of the Spanish Breast Cancer Cooperative Group, SOLTI and is a member of the editorial boards of Cancer Cell, Journal of Clinical Oncology, Clinical Cancer Research and Annals of Oncology. He has published over 200 peer-reviewed articles and over 300 abstracts and book chapters.

He sits on several committees of the American Association for Cancer Research (AACR) and is a member of the AACR Research Council. He is a former member of the board of directors of the American Society of Clinical Oncology (ASCO), a former member of the board of directors of the European Organization of Research on Treatment of Cancer (EORTC) and a member of the Scientific Advisory Committee of the Ludwig Institute for Cancer Research. He is currently the President of the European Society of Medical Oncology (ESMO).

His research interests are clinical breast cancer and translational early clinical research in the area of growth-factor receptors and downstream molecules as targets for breast cancer therapy. He conducted the initial clinical trials with the monoclonal antibodies cetuximab and trastuzumab. He was also involved in the clinical development of several new agents, including gefitinib, erlotinib, lapatinib, pertuzumab, m-TOR inhibitors, PI3K inhibitors, TGFß inhibitors, and a number of antiangiogenic agents.

In 2008, Dr. Baselga was awarded the Civil Order of Health in Spain, the AACR-Rosenthal Family Foundation Award and The Rey Jaime I Award in Medical Research in Spain.

Experimental Therapies Program

The Experimental Therapies Program is aimed at developing new therapies for patients with cancer and focuses on pre clinical studies as well as early (phase I) studies with molecularly targeted agents.

Our program works closely with the other organ-based research units. It is common for some of our phase I studies to evolve into organ-based phase II and phase III trials.

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Technicians
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Maria Luisa Gili
Olga Rodríguez

Database
Gesamí Sánchez MSc

Clinical activity

Our goal for 2009 is to consolidate our clinical research program in collaboration with the other organ-based units. Our program will benefit markedly from the construction of the new Cancer Molecular Therapy Research Unit "la Caixa", which will be located in the main building of the Vall d'Hebron Hospital and will be a facility dedicated solely to phase I clinical trials.

This facility will have state-of-the-art consultation rooms, treatment facilities, a dedicated pharmacy, a pharmacokinetics laboratory, and an area for study coordinators. In terms of new molecules we will start a series of clinical trials with Hsp90-chaperone inhibitors and will continue to expand our clinical trials with rationally based combination trials.

In 2008 we had a total of 20 active phase I clinical trials and close to 170 patients were enrolled in these early clinical trials. In terms of new molecules we have started a series of clinical trials with novel therapies such as inhibitors of the Hsp90 chaperone, an inhibitor of the spliceosome, a glycosylated antibody against EGFR and an Inhibitor of Smoothened (targeting the Sonic Hedgehog pathway). Among them, an early clinical trial of the combination of a PARP inhibitor with cisplatin stands out for a subset of patients with breast cancer. We continue to expand our early clinical trial program, both with novel drugs and with rationally-based combination trials. We recently signed an agreement with Novartis to collaborate on the development of some of the most promising agents in their pipeline, and similar agreements with other drug companies are under discussion.

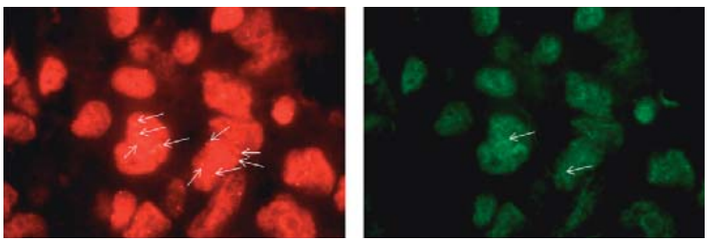

Figure 1. Example of cyclin E amplification in a HER2 positive breast Cancer, showing FISH for cyclin E (red) and chromosome 19 (green). Each white arrow indicates a copy of the gene hybridized with the respective probes.

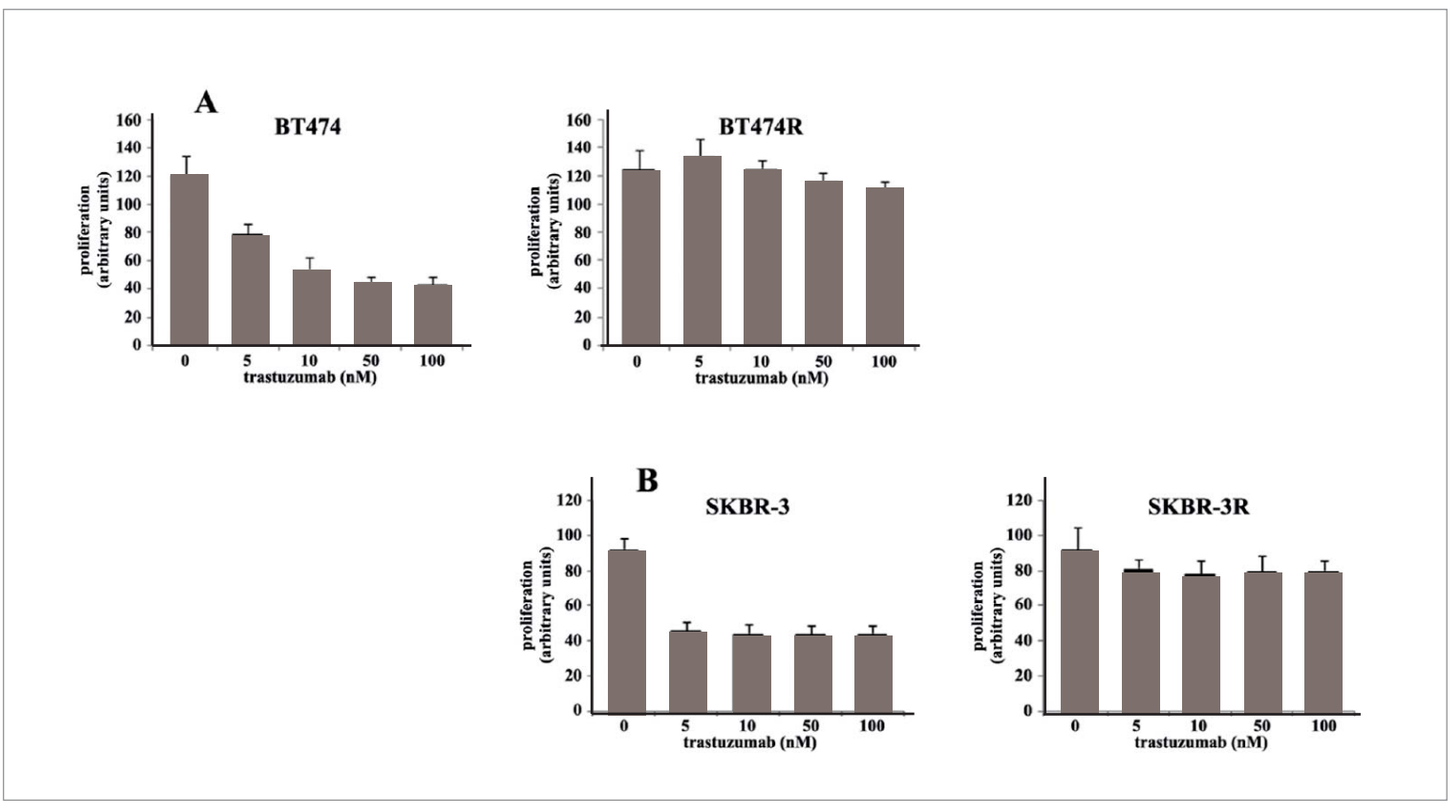

Figure 2. Establishment of trastuzumab-resistant BT474 and SKBR-3 cell lines. A. Comparison of proliferation of parental BT474 (left) and resistant BT474R (right) cells in response to increasing concentrations of trastuzumab. B. Comparison of proliferation of SKBR-3 (left) and SKBR-3R (right) cells in response to increasing concentrations of trastuzumab.

Scientific activity

Our research lines focus on understanding the molecular mechanisms of resistance to molecularly targeted treatments for HER2-overexpressing breast cancer and on identifying novel alternative compounds capable of overcoming these resistances.

Truncated p95HER2 receptor and novel anti-HER2 therapies

We showed that truncated forms of the HER2 receptor, (p95HER2), correlate with a lack of response to the anti-HER2 antibody trastuzumab. Lapatinib, a HER2 tyrosine kinase inhibitor, has proven to be efficacious in p95HER2-expressing cells in our preclinical models. We have now interrogated clinical samples from patients treated with lapatinib and found that patients with p95HER2-overexpressing tumors were as sensitive to this agent as p95HER2 negative tumors. This finding represents an additional step toward a rational subclassification of HER2-positive disease and a better selection of therapy for these patients.

In addition, we are exploring new combinations of anti-HER2 therapies. We identified a novel mechanism that may explain the enhanced anti-tumor effects obtained by combining trastuzumab with lapatinib. In particular, we showed that lapatinib induces HER2 accumulation at the plasma membrane, which results in enhanced immune-mediated trastuzumab-dependent cytotoxicity (Scaltriti et al.). This mechanism can be exploited in the treatment of patients with HER2-positive tumors, and clinical trials of this combination are under way.

Additional mechanisms of resistance to anti-HER2 therapies

As with the majority of anticancer agents, acquired resistance to anti-HER2 agents becomes an unavoidable phenomenon. On the other hand, identifying potential "escape" mechanisms could, in principle lead to improved therapeutic strategies aimed at preventing or delaying the development of acquired resistance.

Under these premises and in order to identify resistance mechanisms, we used a molecular barcode-screen approach to identify mediators of lapatinib resistance. We showed that deregulation of the PI3K pathway, either through PTEN down-modulation or by overexpression of the two most frequent breast cancer mutations in PI3KCA (E545K and H1047R), confers resistance to trastuzumab and lapatinib. We then confirmed these observations by showing that PI3K-mediated trastuzumab and lapatinib resistance can be abrogated with the PI3K/mTOR inhibitor NVP-BEZ235 (Eichhorn et al., Serra et al.).We are now testing, both at preclinical and clinical level, the efficacy of combining anti- HER2 compounds with PI3K/mTOR inhibitor agents to revert/delay trastuzumab or lapatinib resistance.

Using a different approach, we also generated cells with acquired resistance to either trastuzumab or lapatinib (Figure 1). These cells represent a powerful tool for gaining a better understanding of the molecular mechanisms at the root of their acquired resistance and, hence, testing novel compounds that may overcome it. To identify the genetic aberrations responsible for trastuzumab and lapatinib resistance exhibited by these cell lines, we performed both microarray (Luminex) and genome-wide single nucleotide polymorphism (SNPs) analysis using an Affymetrix 500K SNP array.

These analyses have shown that cyclin E is upregulated in our resistant cell lines. We have established protocols to analyze cyclin E gene amplification by FISH and cyclin E expression in paraffin embedded tissue by IHC. Initial analyses of 25 tissue samples indicate that cyclin E amplification/overexpression may be present in approximately 30% of HER2-positive breast cancers (unpublished data and Figure 2).We hypothesize that deregulation of cyclin E expression may play a causative role in the acquisition of trastuzumab resistance in breast cancer patients and we will test it at both preclinical and clinical level.

To overcome anti-HER2 therapy resistance, we will study several hypothesis-driven pharmaceutical combinations with signal transduction inhibitors, including the combination of different anti-HER2 compounds and the use of alternative agents targeting downstream/parallel pathways. Among the novel targeted therapies being studied, we plan to use PI3K/mTOR (mentioned above), Akt, CDK2 and Hsp90 inhibitors. We expect any promising preclinical leads to result in designing and carrying out studies in clinical practice.

While these agents are highly active in our experimental models, we are also gathering evidence that blockade of these pathways may result in activation of compensatory signalling that could, in turn, reduce the antitumor effects of these agents. Recent results from our laboratory indicate that inhibition of the PI3K pathway in HER2-positive cells results in activation of the MAPK pathway and its downstream effectors. This effect is reverted by both MEK1/2 inhibition and HER2 blockade with tyrosine kinase inhibitor. We are interested in understanding the precise mechanisms by which PI3K inhibition results in receptor tyrosine kinase transactivation. Finally, we will perform genome-wide screenings with cDNA and shRNA libraries in order to identify novel genes that mediate PI3K-inhibitor resistance.

Research projects (8)

Funding Agency: ISCIII (FIS)
Title: Truncated intracellular HER2 C-Terminal Fragments and Trastuzumab resistance.
PI: Dr. J. Baselga
Duration: 2006-2008

Funding Agency: ISCIII (Subdirección General de Redes y Centros de Investigación Cooperativa)
Title: Red Temática de Investigación Cooperativa del Cáncer.
PI: Dr. J. Baselga
Duration: 2007-2010

Funding Agency: AGAUR GENERALITAT DE CATALUNYA
Title: SGR Suport a Grups de Recerca de Qualitat.
PI: Dr. J. Baselga
Duration: 2005-2008

Funding Agency: European Comision
Title: Simulation modelling of the MAP kinase pathway.
PI: Dr. J. Baselga
Duration: 2003-2008

Funding Agency: ISCIII (Eurosalud)
Title: Simulation modelling of the MAP kinase pathway.
PI: Dr. J. Baselga
Duration: 2008-2011

Funding Agency: BCRF2007-2008
Title: Acquired resistance to Anti-HER2 and PI3K therapies in Breast Tumors: biomarkers and signalling pathways involved.
PI: Dr. J. Baselga
Duration: 2007-2008

Funding Agency: BCRF2008-2009
Title: Overcoming resistance to Anti-HER2 and PI3K inhibitors therapies in breast cancer.
PI: Dr. J. Baselga
Duration: 2008-2009

Funding Agency: European Comission
Title: Translating molecular knowledge into early breast cancer management: building on the BIG (Breast International Group) network for improved treatment tailoring
PI: Dr. J. Baselga
Duration: 2004-2011

Clinical trials (20)

WO17299 An Open-label Study of the Effect of First-line Herceptin Alone or in Combination With a Taxane on Tumor Response and Disease Progression in Patients With Metastatic Breast Cancer Who Relapsed After Receiving Adjuvant Herceptin for HER2-positive Early Breast Cancer. Included patients: 0

NEOALTTO Estudio fase III, aleatorizado, multicéntrico, abierto, de tratamiento neoadyuvante con lapatinib, trastuzumab y su combinación más paclitaxel en mujeres con cáncer de mama primario HER2/ErbB2 positivo. Included patients: 15

CA180-059 Phase II Study of Dasatinib (BMS-354825) for Advanced 'Triple-Negative' Breast Cancer. Included patients: 0

EORTC62012 Randomised Trial Of Single Agent Doxorubicin Versus Doxorubicin Plus Ifosfamide In The First Line Treatment Of Advanced Or Metastatic Soft Tissue Sarcoma. Included patients: 0

XL765-001 A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of XL765 Administered Orally Daily to Subjects With Solid Tumors. Included patients: 5

26854165CAN1001 A Phase I study to determine the safety, pharmacology and pharmacodynamics of JNJ26854165 in subjects with advanced stage and/or refractory solid tumors. Included patients: 13

XL147-001 A phase 1 dose-escalation study of the safety and pharmacokinetics of XL147 administered orally daily to subjects with solid tumors. Included patients: 3

STM01-102 A Phase III Randomized, Controlled Trial of Myocet, Trastuzumab and Paclitaxel Versus Trastuzumab and Paclitaxel for First-Line Therapy of Metastatic Breast Cancer. Included patients: 4

20040235 Estudio de búsqueda de dosis, abierto y multicéntrico, para evaluar la seguridad y tolerabilidad de AMG 706, panitumumab y una combinación de AMG 706 y panitumumab cuando se administra con quimioterapia de inducción (QI) y/o quimiorradioterapia (QRT) en el tratamiento de sujetos con carcinoma de células escamosas loco-regionalmente avanzado de cabeza y cuello (SCCHN). Included patients: 0

H9H-MC-JBAH Estudio fase I de escalado de dosis de LY2157299 en pacientes con cáncer avanzado o metastásico. Included patients: 9

BO17929 Estudio de fase II exploratorio, multicéntrico, con un colo grupo de tratamiento, para evaluar la eficacia y seguridad de la combinación de OmnitargTM (pertuzumab) y Herceptin (trastuzumab) en pacientes con cáncer de mama metastásico HER2-positivo. Included patients: 5

D8480C00015 An Exploratory, Open-Lael Study to Assess the Effects of AZD2171 on Tumors and Biomarkers in Patients With Previously Untreated or Recurrent Non-small Cell Lung Cancer (NSCLC) or Patients With Metastatic or Recurrent Head and Neck Cancer (HNC). Included patients: 4

CBEZ235A2101 A Phase I/II, Multi-Center, Open-Label Study of BEZ235, Administered Orally on a Continuous Daily Dosing Schedule in Adult Patients With Advanced Solid Malignancies Including Patients With Advanced Breast Cancer. Included patients: 12

CA187-002 A Phase I Dose Escalation Study of BMS-690514 in Patients With Advanced or Metastatic Solid Tumors. Included patients: 2

EGF103659 An Open-Label Expanded Access Study of Lapatinib and Capecitabine Therapy in Subjects With ErbB2 Overexpressing Locally Advanced or Metastatic Breast Cancer. Included patients: 3

FM-B04-01 Estudio Cooperativo Esuropeo de Terapia Sistémica Primaria en Mujeres con Cáncer de Mama Operable y T>2cm. Included patients: 0

MK0646-001 An Open-Label, Dose Escalation Phase I Trial of MK0646 Given as a Once Weekly Infusion in Patients With Advanced Solid Tumors and Multiple Myeloma. Included patients: 21

MK0646-013 A Study to Establish Proof-of-Biology for MK0646 in Breast Cancer. Included patients: 5

CBGT226A2101 A Phase I/II, Multi-center, Open-label Study of BGT226, Administered Orally in Adult Patients With Advanced Solid Malignancies Including Patients With Advanced Breast Cancer. Included patients: 13

MK-8669/004 Phase I Combination Study of Deforolimus (Ridaforolimus/MK8669) and MK0646 in Patients With Advanced Cancer. Included patients: 3

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Gastrointestinal Tumors Program

Josep Tabernero, group leader

Josep Tabernero graduated summa cum laude in medicine and Surgery from the Autonomous University of Barcelona. He is the head of the VHIO Gastrointestinal Tumors Program. Since 2003 he has been an attending physician at the Oncology Department of Vall d'Hebron University Hospital and is currently Section head at the Medical Oncology Department of the Vall d'Hebron University Hospital.

He is a member of several medical societies, hospital committees and workgroups as well as foreign committees and workgroups.

He has been a member of the Hospital Tumors Committee of Vall d'Hebron University Hospital since its creation, in colorectal cancer, gastric esophageal cancer, pancreatic cancer, and liver tumors and liver metastases.

He also performed clinical practice revisions of the Colon and Rectum Cancer Oncoguide developed by the Technology and Medical Research Evaluation Agency and the Oncology Steering Plan on 2003 and 2007 and of the Clinical Practice Guide for Colorectal Cancer Prevention developed by the Spanish Family and Community Medicine Society, the Ibero-American Cochrane Center and the Spanish Gastroenterology Society in 2003.

Gastrointestinal Tumors Program

The Gastrointestinal Tumors Program of the Medical Oncology Department is an integrated component of the multidisciplinary team of the Vall d'Hebron Gastrointestinal Tumors Project, which consists of gastrointestinal surgeons, medical oncologists, radiation oncologists, pathologists, radiologists, palliative care and clinical trial specialists. The program is dedicated to patient care, research, training and education in gastrointestinal tumors. As a clinical academic unit, it is committed to clinical excellence, clinical and translational research, and a broad range of teaching.

Group leader

Josep Tabernero MD
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Clinical members

Attending Physicians
Teresa Macarulla MD
Francisco Javier Ramos MD
Jaume Capdevila MD
M. Elena Élez MD
Manuel Ruiz MD
Sergio Peralta MD

Clinical Trials Coordinators
Elisabeth Sicart MD
Adelaida Piera Chem. Eng.
María Herranz MD

The Gastrointestinal Tumors Program approach is based on the principle that clinicians provide the best quality cancer care when they are members of a multidisciplinary cancer center, meeting regularly as at team to discuss the most appropriate management of each individual patient.

Clinical activity

Over 10,000 patients with gastrointestinal malignancies have been visited during year 2008, including 620 new patients. Proportionally, patients with colorectal cancer constitute the group of patients most frequently treated in our group, followed by patients with gastric cancer, pancreatic cancer and esophageal cancer. Year by year, the number of patients included in clinical trials have increased. During last year, more than 100 patients have been enrolled in clinical trials.

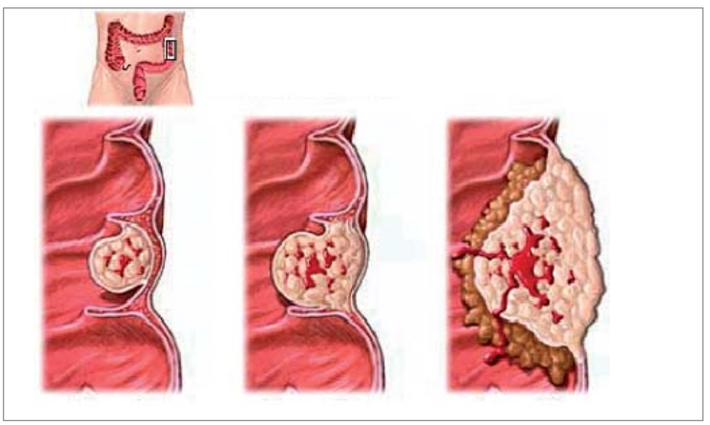

Figure 1. Colon cancer stages.

Figure 2. Virtual colonoscopy.

Scientific activity

The scientific activities of this program comprise three different fields of research:

- Clinical research: Patients are included in clinical trials devoted to specific malignancies—colorectal, gastric, pancreatic, esophageal cancer—with the aim of demonstrating improvements in best management (phase II or phase III clinical trials).
- Translational research devoted to improving knowledge of prognostic and predictive factors of response and efficacy in the different gastrointestinal malignancies.
- Basic Research in collaboration with the VHIO Stem Cells and Cancer Laboratory, and with other international research groups (University of Michigan, Vanderbilt University, Weizman Institute).

The clinical trials conducted by this group can be classified in three major areas:

- Phase II and III clinical trials aimed at demonstrating clinical benefit with new chemotherapy schedules and targeted agents in gastrointestinal malignancies: colorectal, esophageal, gastric, pancreatic and belier cancers.
- Phase I pharmacokinetic and pharmacodynamic studies with targeted agents directed to different critical signal transduction pathways. We have been involved in the development of targeted agents directed to the EGFR, either monoclonal antibodies like cetuximab, matuzumab, panitumumab and BO21495 (GA201) or tyrosine kinase inhibitors, like gefitinib, erlotinib, EKB-569 and AEE788. Another pathway of interest where we have been very actively involved is the angiogenesis pathway, with clinical studies with the following AEE788, Sunitinib and AG-013736. Other cellular targets where we have developed the same pharmacokinetic/pharmacodynamic approach include mTOR with the drug Everolimus; PI3K and mTOR with XL-147, XL-765, BEZ235 and BGT226; and PI3K with BKM120; Ras with BMS-214662; Hdm2 with JNJ-26854165; Aurora kinase A with MLN8054 and MLN8237.
- Phase I pharmacokinetic and pharmacodynamic studies with cytotoxic agents including Aplidin, ES-285, PM-104, Kahalalide, BO17687 and EPO906.

During 2008 this group has included 111 patients in clinical trials of the digestive therapy area (52 patients with colorectal cancer) and 87 patients in phase I trials.

Research project (1)

Simulation modelling of the MAP kinase pathway (SIMAP)
Duration: 2006-2008

The objective of SIMAP is to develop a comprehensive simulation of a biochemical model of the EGFR-MAP kinase pathway in connection with the clinical phenotype. SIMAP will rely on the OMICS revolution by combining mechanistic modelling of cancer-related pathway behavior, accompanied by new mining techniques and integrated with clinical data. Use of the SIMAP simulation will allow a drastic decrease in costs and timescales of treatments and support better patient cancer treatment and diagnosis.

Clinical trials (28)

A6181122 A Multicenter, Randomised, Double-Blind, Phase 3 Study Of Sunitinib In Metastatic Colorectal Cancer Patients Receiving Irinotecan, 5-Fluorouracil And Leucovorin (FOLFIRI) As First Line Treatment. Included patients: 3

A6181114 An Open-Label Sunitinib Malate (SU011248) Continuation Protocol For Patients Who Have Completed A Prior Sunitinib Study And Are Judged By The Investigator To Have The Potential To Benefit From Sunitinib Treatment. Included patients: 1

BO20904 Double-Blind, Randomised, Multicenter, Phase III Study of Bevacizumab in Combination With Capecitabine and Cisplatin Versus Placebo in Combination With Capecitabine and Cisplatin, As First-Line Therapy in Patients With Advanced Gastric Cancer. Included patients: 4

2-55-52030-726 Phase III, Randomised, Double-blind, Stratified Comparative, Placebo Controlled, Parallel Group, Multi-centre Study to Assess the Effect of Deep Subcutaneous Injections of Lanreotide Autogel 120mg Administered Every 28 Days on Tumour Progression Free Survival in Patients With Non-functioning Entero-pancreatic Endocrine Tumour. Included patients: 1

A6181111 A Phase I Clinical and Pharmacodynamic Study of MLN8237, A Novel Aurora A Kinase Inhibitor, in Patients With Advanced Malignancies. Included patients: 1

C14002 A Phase I Clinical and Pharmacodynamic Study of MLN8237, A Novel Aurora A Kinase Inhibitor, in Patients With Advanced Malignancies. Included patients: 17

IMCL CP11-0602 Estudio de fase 2 abierto, multicéntrico para evaluar la eficacia y tolerancia del IMC-11F8 en combinación con 5-FU/FA y Oxaliplatino (Folfox-6 modificado) en pacientes con un cáncer colorectal no tratado, localmente avanzado o matastasico. Included patients: 8

TTD-06-02 Phase II, Multicentre, Uncontrolled Pilot Study to Evaluate Safety and Efficacy of the Combination of Cetuximab and Chemotherapy (Docetaxel, Cisplatin, 5-fluorouracil) as Neoadjuvant Therapy Followed Concomitant Chemoradiotherapy (Cisplatin) Plus Cetuximab in Patients With a Locoregional Esophageal Carcinoma. Included patients: 6

TTD-05-02 Randomized, Multicenter, Phase III Study, to Evaluate the Efficacy and Safety of Bevacizumab Alone or Combined With Capecitabine and Oxaliplatin as Support Therapy After Initial Chemotherapy Treatment With Capecitabine, Oxaliplatin and Bevacizumab in Metastatic Colorectal Cancer Patients. Included patients: 6

DOCOX-C-00082 Estudio randomizado de fase II de docetaxel en combinación con oxaliplatino con o sin 5-FU o capecitabina, en cáncer gástrico metastásico o en recurrencia local que no haya sido tratado previamente para la enfermedad avanzada con quimioterapia. Included patients: 10

WX-60/004 Randomized, Open Label, Phase II Proof of Concept Study of WX-671 in Combination With Gemcitabine vs.Gemcitabine Alone in Patients With Locally Advanced, Non Resectable Pancreatic Cancer in Order to Evaluate the Anti-Tumor Activity of the Combination Therapy. Included patients: 4

EFC6596 A Randomized, Open Label Multi-Center Study Of Single Agent Larotaxel (XRP9881) Compared To Continuous Administration of 5-FU For The Treatment Of Patients With Advanced Pancreatic Cancer Previously Treated With A Gemcitabine-Containing Regimen. Included patients:

E7107-044-102 Estudio clínico fase I de búsqueda de dosis, abierto, no randomizado, con E7107 en administración intravenosa (bolus IV) los días 1, 8 y 15 de cada ciclo de 28 días, en pacientes con tumores neoplásicos sólidos. Included patients: 13

PETACC-8 Adjuvant Treatment of Fully Resected Stage III Colon Cancer With FOLFOX-4 Versus FOLFOX-4 Plus Cetuximab. Included patients: 8

PM104-A-003-05 Estudio de fase I multicéntrico, abierto, clínico y farmacocinético de escalada de dosis de PM00104 administrado cada 3 semanas, por vía intravenosa, durante 24 horas, a sujetos con tumores sólidos malignos avanzados o linfomas. Included patients: 15

20050203 A Randomized, Multicenter, Phase 3 Study to Compare the Efficacy of Panitumumab in Combination With Oxaliplatin/ 5-fluorouracil/ Leucovorin to the Efficacy of Oxaliplatin/ 5-fluorouracil/ Leucovorin Alone in Patients With Previously Untreated Metastatic Colorectal Cancer. Included patients: 0

CRAD001C2241 A Single Arm, Multicenter Phase II Study of Everolimus in Patients With Metastatic Colorectal Adenocarcinoma Whose Cancer Has Progressed Despite Prior Therapy With an Anti-EGFR Antibody (if Appropriate), Bevacizumab, Fluoropyrimidine, Oxaliplatin, and Irinotecan-based Regimens. Included patients: 6

EXPERT-C A Multicentre Randomised Phase II Clinical Trial Comparing Oxaliplatin (Eloxatin), Capecitabine (Xeloda) and Pre-Operative Radiotherapy With or Without Cetuximab Followed by Total Mesorectal Excision for the Treatment of Patients With Magnetic Resonance Imaging (MRI) Defined High Risk Rectal Cancer. Included patients: 5

C10002 A Phase 1 Trial of Extended MLN8054 Dosing in Patients With Advanced Malignancies. Included patients: 3

PEP0206 A randomized phase II study of PEP02, irinotecan or docetaxel as a second line therapy in patients with locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma (PEP0206), eudraCT number: 2006-006452-35. Included patients: 3

EFC10262 VELOUR A Multinational, Randomized, Double-Blind Study, Comparing the Efficacy of Aflibercept Once Every 2 Weeks Versus Placebo in Patients With Metastatic Colorectal Cancer (MCRC) Treated With Irinotecan / 5-FU Combination (FOLFIRI) After Failure of an Oxaliplatin Based Regimen. Included patients: 8

BO21495 An Open Label, Dose-escalation Study to Evaluate Safety, Pharmacokinetics and Tumor Growth Control Rate of RO5083945, a Glycoengineered Antibody Against EGFR, in Patients With Metastatic and/or Locally Advanced Malignant EGFR+ Solid Tumors. Included patients: 8

20060447 A Randomized, Phase 1b/2 Trial of AMG 102 or AMG 479 in Combination With Panitumumab Versus Panitumumab Alone in Subject With Wild-Type KRAS Metastatic Colorectal Cancer. Included patients: 1

MK0646-004 A Phase II III Study of MK0646 Treatment in Combination With Cetuximab and Irinotecan For Patients With Metastatic Colorectal Cancer. Included patients: 6

A4061028 A Randomized, Double-Blind Phase 3 Study Of Gemcitabine Plus AG-013736 Versus Gemcitabine Plus Placebo For The First-Line Treatment Of Patients With Locally Advanced, Unresectable Or Metastatic Pancreatic Cancer. Included patients: 8

TTD-08-02 Phase II Study of Adjusted-Dose Docetaxel-Oxaliplatin-Capecitabine in Patients With Advanced Gastric Adenocarcinoma and Intermediate General Status. Included patients: 0

CRAD001C2324 EA Randomized Double-blind Phase III Study of RAD001 10 mg/d Plus Best Supportive Care Versus Placebo Plus Best Supportive Care in the Treatment of Patients With Advanced Pancreatic Neuroendocrine Tumor (NET). Included patients: 9

GETNE0801 Ensayo clínico de fase II, multicéntrico, abierto, no controlado para evaluar la eficacia de la combinación de sorafenib y bevacizumab en el tratamiento de pacientes con tumor neuroendocrino avanzado y/ o metastásico. Included patients: 5

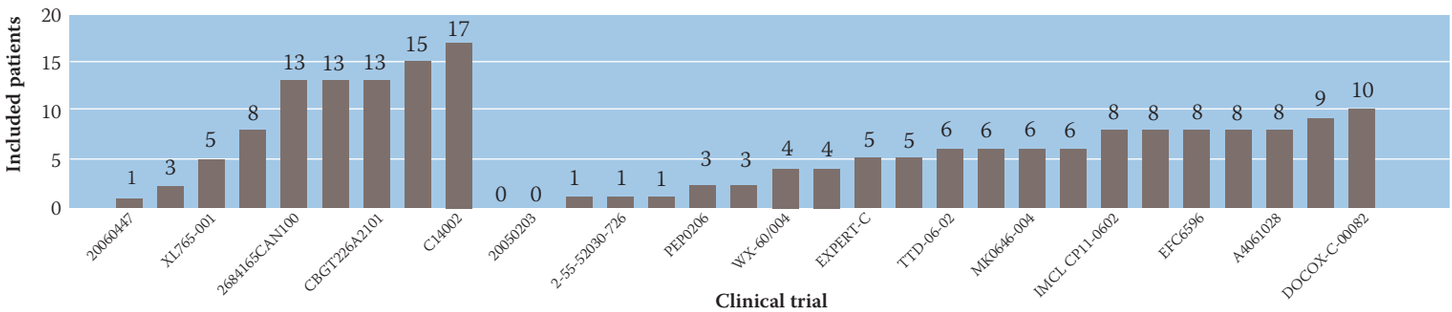

Figure 3. Included patients in the clinical trials of the Gastrointestinal Tumors Program in 2008.

Publications (22) / IF: 193.322

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(IF: 6.250, 1 cuartil, oncology)

Baselga J, Rothenberg ML, **Tabernero J**, Seoane J, Daly T, Cleverly A, Berry B, Rhoades SK, Ray CA, Fill J, Farrington DL, Wallace LA, Yingling JM, Lahn M, Arteaga C, Carducci M. TGF-beta signalling-related markers in cancer patients with bone metastasis. Biomarkers 2008;13:217-36.
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Pardo B, Paz-Ares L, **Tabernero J**, Ciruelos E, García M, Salazar R, López A, Blanco M, Nieto A, Jimeno J, Izquierdo MA, Trigo JM. Phase I clinical and pharmacokinetic study of kahalalide F administered weekly as a 1-hour infusion to patients with advanced solid tumors. Clin Cancer Res 2008;14:1116-23.
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(IF: 4.876, 1 cuartil, oncology)

Tabernero J, Rojo F, Calvo E, Burris H, Judson I, Hazell K, Martinelli E, Ramon y Cajal S, Jones S, Vidal L, Shand N, **Macarulla T**, **Ramos FJ**, Dimitrijevic S, Zoellner U, Tang P, Stumm M, Lane HA, Lebwohl D, Baselga J. Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamic study in patients with advanced solid tumors. J Clin Oncol 2008;26:1603-10.
(IF: 15.484, 1 cuartil, oncology)

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Bouchahda M, **Macarulla T**, Spano JP, Bachet JB, Lledo G, Andre T, Landi B, **Tabernero J**, Karaboué A, Domont J, Levi F, Rougier P. Cetuximab efficacy and safety in a retrospective cohort of elderly patients with heavily pretreated metastatic colorectal cancer. Crit Rev Oncol Hematol. 2008 Sep;67(3):255-62. Epub 2008 Apr 8.
(IF: 4.632, 1 cuartil, hematology)

Haller DG, Cassidy J, Clarke SJ, Cunningham D, Van Cutsem E, Hoff PM, Rothenberg ML, Saltz LB, Schmoll HJ, Allegra C, Bertino JR, Douillard JY, Gustavsson BG, Milano G, O'Connell M, Rustum Y, **Tabernero J**, Gilberg F, Sirzén F, Twelves C. Potential regional differences for the tolerability profiles of fluoropyrimidines. J Clin Oncol 2008;26:2118-23.
(IF: 15.484, 1 cuartil, oncology)

Firestein R, Bass AJ, Kim SY, Dunn IF, Silver SJ, Guney I, Freed E, Ligon AH, Vena N, Ogino S, Chheda MG, Tamayo P, Finn S, Shrestha Y, Boehm JS, Jain S, Bojarski E, Mermel C, Barretina J, Chan JA, Baselga J, **Tabernero J**, Root DE, Fuchs CS, Loda M, Shivdasani RA, Meyerson M, Hahn WC. CDK8 is a colorectal cancer oncogene that regulates beta-catenin activity. Nature 2008;455:547-51.
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Capdevila J, **Elez E**, **Peralta S**, **Macarulla T**, **Ramos FJ**, **Tabernero J**. Oxaliplatin-based chemotherapy in the management of colorectal cancer. Expert Rev Anticancer Ther 2008;8:1223-36.
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Vilar E, Scaltriti M, Balmaña J, Saura C, Guzman M, Arribas J, Baselga J, **Tabernero J**. Microsatellite instability due to hMLH1 deficiency is associated with increased cytotoxicity to irinotecan in human colorectal cancer cell lines. Br J Cancer 2008;99:1607-12.
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(IF: 2.274, 2 cuartil, Oncology)

Genitourinary, CNS and Sarcoma Tumors Program

Joan Carles, group leader

Joan Carles is the head of the VHIO Genitourinary, CNS and Sarcoma Tumors Program. He graduated in medicine at the University of Barcelona in 1986.

He has published more than 100 works, in Spain and abroad, including scientific articles, oncology book chapters and conference lectures, particularly on genitourinary tumors. He is a reviewer of several oncology journals and an active member of the Spanish Medical Oncology Society, the European Society of Medical Oncology and the American Society of Clinical Oncology. He is also Secretary of the Spanish Genitourinary Group (SOGUG) and member of the board of directors of the UDIMAS.

Genitourinary, CNS and Sarcoma Tumors Program

Our experts in the Genitourinary Tumors Program treat cancers of the urinary tract and male genital tract with the shared goals of controlling cancer and preserving quality of life after treatment. Patients with CNS tumors and sarcoma are treated in the same Unit with the same goals.

Our program includes teaching residents and medical students, and clinical research and includes the following services: Multi-specialty consultation; Rapid diagnosis anddevelopment of a treatment plan; State-of-the-art treatment options; Follow-up care after initial treatment; Opportunity to enroll in clinical trials of new and promising forms of treatment.

Working together in our weekly multidisciplinary committees, our surgeons (urologist, neurosurgeons and traumatologist), oncologists and radiation therapists help patients choose the most appropriate

Group leader

Emiliano Calvo MD
(until September 2008)

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Clinical members

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Rafael Morales MD
Cristina Suárez MD

Clinical Trials Coordinators
Oriol Olivé MD
Mireia Centelles MD

treatment. The complete range of cancer treatment choices available for our patients, including access to clinical trials of new therapies, means that every patient's care plan is individualized to their diagnosis and special needs. Additionally, we work closely with physicians from other services, nursing and social services to provide excellence in these areas. This multidisciplinary activity thus promotes a coordinated approach to clinical care, education for both the patient and resident physician, and research.

Clinical activity

The Genitourinary Tumor Group has driven the multidisciplinary care of the patient through coordinated action of the Urology and Radiotherapy services, which are coordinated by the Urological Tumors Committee, which meets every week.

Two Committees were also set up in 2008: the Sarcoma and Bone Tumors Committee that brings together traumatologists, radiotherapists, radiologists, medical oncologists and pathologists, and decide the best strategy for treating primary tumors and bone metastases and for preventing complications such as pathological fractures.

A CNS Committee has also been created. In this Committee, neurosurgeons, radiologists, neurologists, radiotherapists and medical oncologists participate and decided the best sequential treatment for patients.

In 2008, a total of 4.865 consultations were held with oncology patients at our department, 279 of which (5.7%) were first consultations. These figures show a stabilization in relation to last year.

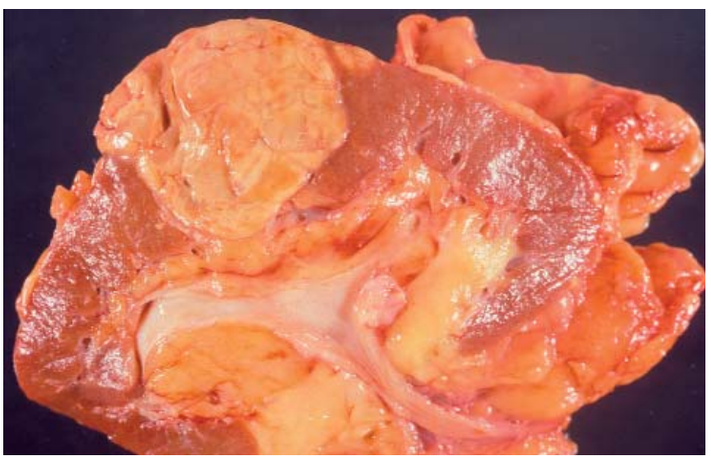

Figure 1. Renal tumor affecting middle part of the kidney.

Scientific activity

At international level, since 1997 we have been a full member of the European Organization for Research and Treatment of Cancer (EORTC), a genitourinary cancer group.

Furthermore, we were assigned the roles of Faculty Member and Committee member of the scientific program to select presentations at the conference of the American Society of Clinical Oncology (ASCO) for 2003-2004 and 2004-2005.

Finally, since 2007, we have been had the Faculty Member role of the Educational Committee of the European Society of Medical Oncology (ESMO), as part of the expert group Principles of Clinical Trials and Systemic Therapy.

One example of the participation in national groups was the creation, alongside the Service Coordinator, Dr. Josep Baselga, of the Spanish Urological Tumors Treatment Group (SOGUG) in September 1999. The Group has also participated actively since 1996 in the Germinal Group (GG) and in the Spanish Sarcoma Research Group" (GEIS).

This year we concluded important phase III trials and began new trials in different pathologies such as sarcoma or CNS. This year has been a year of adaptations, with the incorporation of new members and pathologies.

Due to these changes, we have different clinical trials in different pathologies. We are trying to offer different clinical trials for different stages of the disease.

Below is a list of the trials initiated in recent years in our group. As can be seen, they include early evaluation of innovative drugs through the study of the activity and efficiency of antitumoral medication in patients with diagnosed genitourinary tumors:

Phase I, pharmacokinetic and pharmacodynamic trials of cytostatic drugs and medication targeted to block or inhibit specific molecular targets in tumoral cells, whether as sole agents or combined with others. Some of these drugs are being administered for the first time to humans.

Phase II trials for preliminary observation of oncological drug activity on oncological pathologies of the genitourinary area, whether evaluating drugs aimed at molecular targets or new cytotoxic agents, as sole or combined agents.

Phase III trials of new chemotherapy drug combinations aimed at demonstrating the benefits of innovative therapy strategies in the treatment of tumors, essentially of the genitourinary area, but also in other areas such as sarcoma and CNS tumors.

Results analysis of the Phase II randomized trial on advanced unfit urothelial cancer (EORTC 30986).

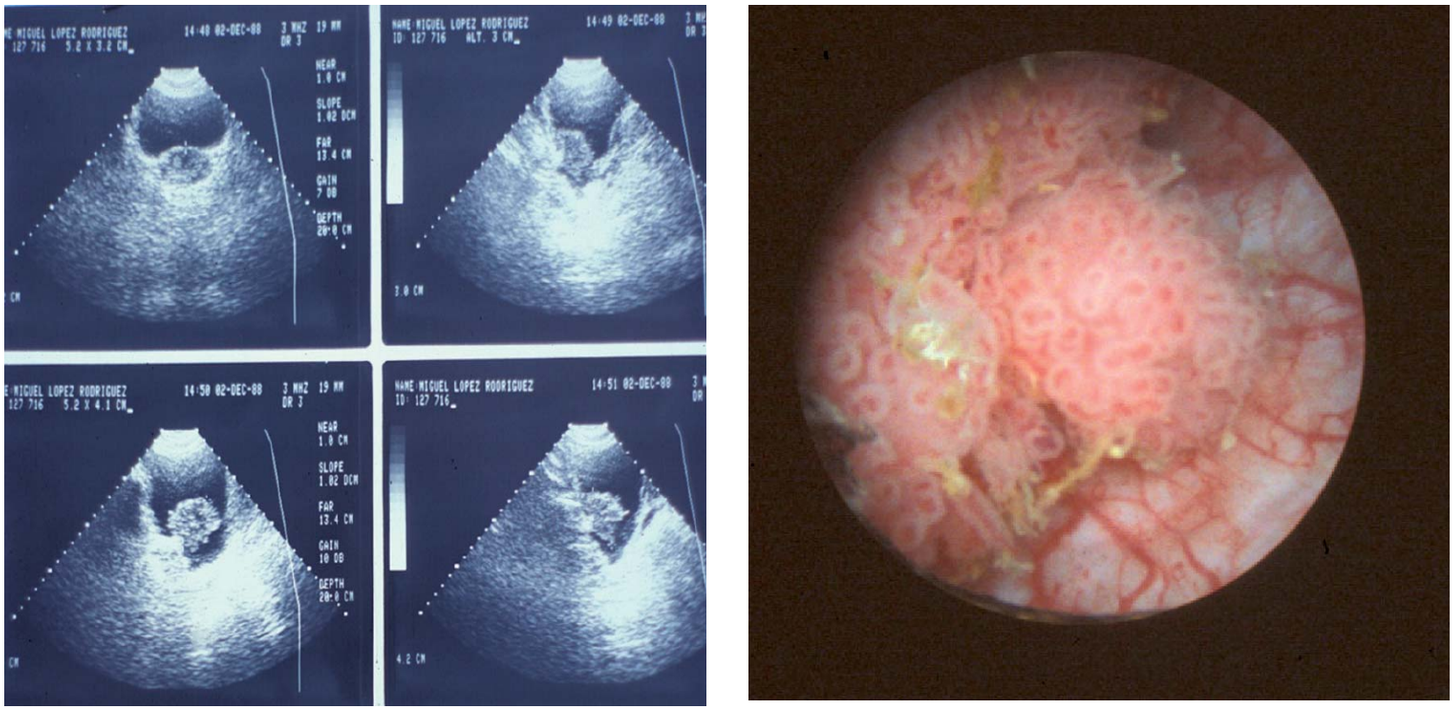

Figure 2. Bladder cancer: Exophytic tumor localized in the lateral wall. A. Ultrasonography excam. B. Cystoscopic view.

Clinical trials (10)

Phase I studies

L00070 GE 102Q0. Phase I trial of dosage escalation of vinflunine on hard capsules administered twice a day during 2 consecutive days per week on patients with advanced/metastatical solid tumors. Included patients: 7

XL147-001. A dose escalating and pharmacokinetic First in Human Phase I study of XL147, an oral PI3K inhibitor, in patients with advanced solid tumors. Included patients: 3

SOGUG07-02. A dose escalating Phase I study of combined gemcitabine, capecitabine and sunitinib in patients with advanced renal cell carcinoma. Included patients: 1

Prostate cancer

A4021011. A randomized non-comparative open label Phase II study of CP-751.871, a monocolonal antibody anti-IGFR, in combination with docetaxel/prednisone in patients with hormone refractory prostate cancer with or without previous chemotherapy. Included patients: 7

Phase II randomized study in high risk locally advanced prostate cancer comparing radiotherapy and homronotherapy vs chemoradiotherapy and hormonotherapy. (Open December 2008)

Phase III double blind randomized study of ZD4054 in PSA relapse hormonoresistant prostate cancer. Included patients: 3

Bladder cancer

EORTC30986. A randomized Phase II/III study of gemcitabine/carboplatin versus methotrexate/carboplatin/vinblastin in first line of therapy of patients with advanced urothelial càncer that are non-eligible for cisplatin-based chemotherapy. Included patients: 1

Renal cancer

IMA901-202. A multicenter open label Phase II study of intradermal IMA901 and GM-CSF with or without low dose cyclophosphamide in patients with advanced renal cell carcinoma. Included patients: 3

CNS

H9H-MC-JBAH: A Phase 1 dose-escalation study of LY2157299 in patients with recurrent glioblastoma. Included patients: 9

Sarcoma

EORTC62012: Phase III study comparing doxorubicin vs doxorubicin plus ifosfamide in metastatic sarcoma. Included patients: 0

Grants (2)

2007. First grant given by the Sarcoma Spanish Research Group for the project Predictive molecular factors in GIST: Study of the expression of the cellular pointing ways through tissue microarrays, mutation study and its correlation with the response to STI-571.

2008. Sarcoma Spanish Research Group for the project Critical role of different molecules implicated in DNA repair as prognostic factor in sarcoma tumors.

Publications (9) / IF: 66.134

Foro P, Valls A, **Carles J**, Lynd F, Sanz X, Rodríguez de Dios N,Reig A, Lacruz M, Lozano J, Mambrive I, Algara M. Randomized clinical trials with two palliative radiotherapiy regimens in painful bonemestatase: 30 GY in 10 Fractions compared with 8 GY in single fraction. Radiotherapy and Oncology 89. 2008:150-155.
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(IF: 1.429, 2 cuartil, oncology SCIENCE)

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(IF: 2.499, 2 cuartil, clinical neurology science)

Prat A, Serrano C, **Valverde C**, **Calvo E**. Acute severe hypothyroidism induced by sunitinib. Radiother Oncol. 2008 Oct;89(1):124-5. Epub 2008 May 24.
(IF: 4.074, 2 cuartil, oncology)

Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A, Lebwohl D, Ravaud A; RECORD-1 Study Group. Colaboradors: **Calvo E**, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008 Aug 9;372(9637):449-56.
(IF: 28.638)

Head, Neck and Gynecological Tumors Program

Josep Maria del Campo, group leader

Josep Maria del Campo MD is currently leader of the Head and Neck and Gynecological Cancer Program in the Oncology Department at the Vall d'Hebron University Hospital. He holds a degree in medicine and surgery from the University of Barcelona, Spain (1975). He is currently a member of many comittes and workgroups, and a representative of the Spanish Group on Ovarian Cancer Research at the ENGOT (European Network on Gynecological Oncology Trials).

Head, Neck and Gynecological Tumors Program

Our program is aimed at state-of-the-art patient care as well as clinical research, mainly focusing on research and development of new molecules. Our multidisciplinary committees involve other specialties such as surgeons, radiotherapists, pathologists and radiologists for patient diagnosis, treatment and follow-up, and to promote and collaborate on trials in these areas. This collaboration leads to a constant increase in the number of patients (20% per year) for standard treatments and for clinical trials. Our program currently contributes to more than ten ongoing trials as principal investigators.

Group leader

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Clinical members

Attending Physicians
Marta Parera MD
Isabela Díaz MD

Clinical Trials Coordinators
Cristina González MD
Mireia Sanchis MD

Clinical activity

Our group has actively participated in the development of guidelines for patient care as well as tumor boards at Vall d´Hebron University Hospital. These collaborations have allowed us to increase the number of patients that we follow up yearly.

The Head and Neck Tumors Unit had 150 first visits in 2008 and more than 2000 visits in total; the Gynecological Tumor Unit visited 80 new patients and a total of more than 1200 in 2008.

We have spearheaded the creation of the following clinical protocols:

- Head and neck tumors
- Ovarian tumors
- Endometrial tumors
- Cervical tumors

In our clinical activity, we place special emphasis on weekly meetings of Head and Neck and Gynecological Tumors because these interdisciplinary meetings are often the source of different protocols and clinical guidelines.

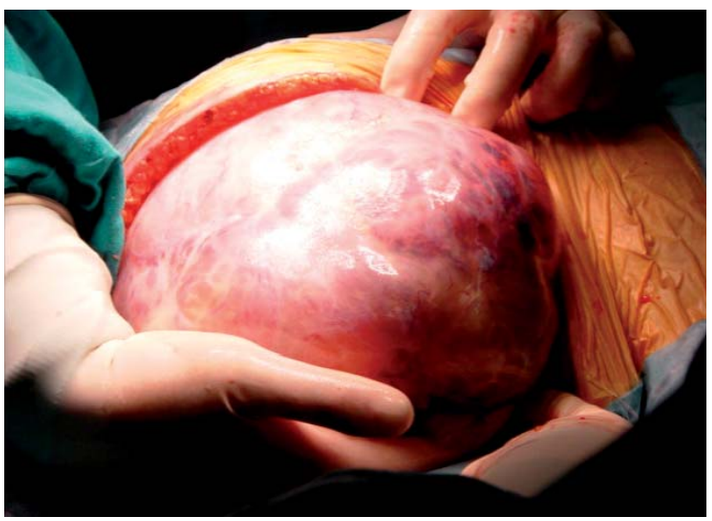

Figure 1. Advanced ovarian carcinoma.

Scientific activity

- Clinical investigation is a field of special interest to us. Our group has participated mainly as principal investigators but also as collaborators with other departments of Vall d´Hebron University Hospital and with other Spanish and international groups.
- Maxillofacial, ORL, GYN and the Pathology Departments actively participate with us in our different projects.
- We are members of several cooperative groups (SGHNC, GEICO, GCIC, ENGOT) and participate in the development of new clinical studies specifically aimed at developing new molecules.
- We actively participate in conferences, presentations and publications.
- The number of patients that we include in clinical studies has been growing constantly. In the 2006-2007 period, approximately 100 patients were included.

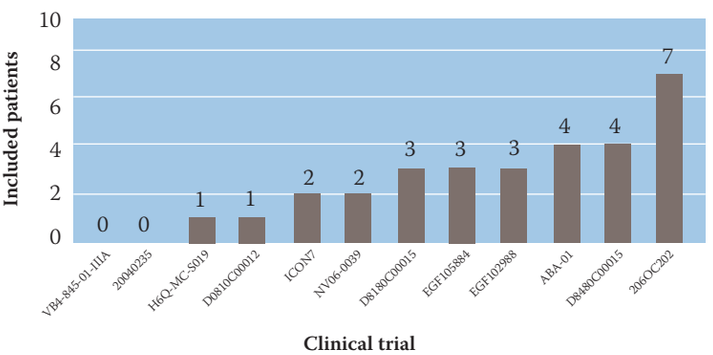

Figure 2. Included patients in the clinical trials of the Head, Neck and Gynecological Tumors Program in 2008.

Clinical trials (10)

VB4-845-01-IIIA A Randomized, Multicentre Therapeutic Confirmatory Study to Evaluate the Efficacy and Safety of Proxinium Plus Best Supportive Care Versus Best Supportive Care Alone in Patients With Advanced Squamous Cell Carcinoma of the Head and Neck Who Have Received at Least One Anti-Cancer Treatment Regimen for Advanced Disease. Included patients: 0

H6Q-MC-S019 A Randomized, Phase 2, Placebo-Controlled, Double-Blinded Study With and Without Enzastaurin in Combination With Paclitaxel and Carboplatin as First-Line Treatment, Followed by Maintenance Treatment in Advanced Ovarian Cancer. Included patients: 1

NV06-0039 Multi-center, randomized, double-blind, phase III efficacy study comparing phenoxodiol (oral dosage form) in combination with carboplatin versus carboplatin with placebo in patients with platinum - resistant or platinum - refractory late-stage ephitelial ovarian, fallopian or primary peritoneal cancer following at least second line platinum therapy. Included patients: 2

EGF102988 A Randomised, Double-Blind, Placebo-Controlled, Multi-centre, Phase III Study of Post-Operative Adjuvant Lapatinib or Placebo and Concurrent Chemoradiotherapy Followed by Maintenance Lapatinib or Placebo Monotherapy in High-Risk Subjects with Resected Squamous Cell Carcinoma of the Head and Neck (SCCHN). Included patients: 3

ABA-01 A Randomised,Double Blind, Placebo Controlled, Multicentre Trial of Abagovomab Maintenance Therapy in Patients With Epithelial Ovarian Cancer After Complete Response to First Line Chemotherapy. Included patients: 4

D0810C00012 A phase II, open-Label, randomised, comparative, international multicentre study to asses the safety and efficacy of three different doses of AZD2281 given orally once or twicw daily and intravenous liposomal doxorubicin given monthly in patients with advanced BRCA1- or BRCA2- associated ovarian cancer who have previous platinu- based chemotherapy. Included patients: 1

D8180C00015 A Randomised,Double Blind, Placebo Controlled, Multicentre Trial of Abagovomab Maintenance Therapy in Patients With Epithelial Ovarian Cancer After Complete Response to First Line Chemotherapy. Included patients: 3

EGF105884 A Randomized, Double-blind, Placebo Controlled, Multicentre, Phase II Study of Oral Lapatinib in Combination With Concurrent Radiotherapy and Cisplatin Versus Radiotherapy and Cisplatin Alone, in Subjects With Stage III, IVA, B Squamous Cell Carcinoma of the Head and Neck (SCCHN). Included patients: 3

206OC202 Phase 2, Open-Label, Randomized Study of Liposomal Doxorubicin With/Without Volociximab for Treatment of Subjects With Advanced Epithelial Ovarian Cancer or Primary Peritoneal Cancer Relapsed After Prior Therapy With Plat/Taxane-Based Chemo. Included patients: 7

ICON7 A Randomised, Two-Arm, Multi-Centre Gynaecologic Cancer InterGroup Trial of Adding Bevacizumab to Standard Chemotherapy (Carboplatin and Paclitaxel) in Patients With Epithelial Ovarian Cancer. Included patients: 2

Publications (7) / IF: 34.353

Gil-Moreno A, Díaz-Feijoo B, Pérez-Benavente A, **del Campo JM**, Xercavins J, Martínez-Palones JM. Impact of extraperitoneal lymphadenectomy on treatment and survival in patients with locally advanced cervical cancer. Gynecol Oncol. 2008 Sep;110(3 Suppl 2):S33-5. Epub 2008 Jun 5.
(IF: 2.919, 2 cuartil, oncology)

Prat A, **Parera M**, **del Campo JM**. Prognostic role of CA-125 nadir in stage IV epithelial ovarian cancer. J Clin Oncol. 2008 Apr 1;26(10):1771-2; author reply 1772.
(IF: 15.484, 1 cuartil, oncology)

Prat A, **Parera M**, Reyes V, Peralta S, Cedrés S, Andreu J, Huguet P, del Campo JM. Successful treatment of pulmonary metastatic salivary ductal carcinoma with trastuzumab-based therapy. Head Neck. 2008 May;30(5):680-3.
(IF: 2.007, 2 cuartil, surgergy)

Prat A, **Parera M**, Adamo B, Peralta S, Perez-Benavente MA, Garcia A, Gil-Moreno A, Martínez-Palones JM, Baselga J, del Campo JM. Risk of recurrence during follow-up for optimally treated advanced epithelial ovarian cancer (EOC) with a low-level increase of serum CA-125 levels. Ann Oncol. 2008 Sep 26.
(IF: 4.875, 1 cuartil, oncology)

Gil-Moreno A, Franco-Camps S, Díaz-Feijoo B, Pérez-Benavente A, Martínez-Palones JM, **del Campo JM**, **Parera M**, Verges R, Castellví J, Xercavins J. Usefulness of extraperitoneal laparoscopic paraaortic lymphadenectomy for lymph node recurrence in gynecologic malignancy. Acta Obstet Gynecol Scand. 2008;87(7):723-30.
(IF: 1.274, 2 cuartil, obstetrics & gynecology)

Del Campo JM, Prat A, Gil-Moreno A, Pérez J, **Parera M**. Update on novel therapeutic agents for cervical cancer. Gynecol Oncol. 2008 Sep;110(3 Suppl 2):S72-6. Epub 2008 Jun 9. Review.
(IF: 2.919, 2 cuartil, obstetrics & gynecology)

Prat A, **Parera M**, Peralta S, Pérez-Benavente MA, Garcia A, Gil-Moreno A, Martínez-Palones JM, Roxana I, Baselga J, **del Campo JM**. Nadir CA-125 concentration in the normal range as an independent prognostic factor for optimally treated advanced epithelial ovarian cancer. Ann Oncol. 2008 Feb;19(2):327-31. Epub 2007 Dec 6.
(IF: 4.875, 1 cuartil, oncology)

High Risk and Cancer Prevention Program

Judith Balmaña, clinical group leader

Judith Balmaña is the head of the High Risk and Cancer Prevention Program at the Medical Oncology Department of Vall d'Hebron University Hospital. She graduated in medicine and surgery in 1995 at the University of Barcelona. While at the cancer genetic clinic at Hospital Sant Pau, Barcelona.

She has published over 30 peer-reviewed articles and over 50 abstracts and book chapters. She is the coordinator of the Familial Cancer core in the Postgraduate Program in Genetic Counseling at Universitat Pompeu Fabra, Barcelona. Her research interests center on genetic predisposition to cancer, and more specifically the identification of individuals at risk, clinical impact of genetic testing, and genetic epidemiology of hereditary cancer syndromes. She is working on validation of prediction models for identification of mutation carriers in Lynch syndrome, development of molecular strategies for screening of individuals at risk of Lynch syndrome, genetic epidemiology of hereditary breast cancer in Spain, and clinical development of specific therapeutic strategies for individuals with a genetic susceptibility to breast and ovarian cancer. She was awarded a grant for a clinical fellowship at the Risk and Prevention Clinic at Dana Farber Cancer Institute, Boston, MA.

High Risk and Cancer Prevention Program

The High Risk and Cancer Prevention Program is focused on recognizing individuals at risk of a hereditary cancer syndrome and offering genetic counseling, testing, and recommendations for early detection and prevention of cancer. Our multidisciplinary unit includes medical oncologists, a specialized nurse, clinical research fellows, and geneticists working in the laboratory. The unit works closely with other specialized departments such as gynecology, surgery, gastroenterology, pathology, radiology, and pediatric oncology.

Working together, our goal is to help identify individuals at high risk of developing cancer because of a genetic predisposition, recommend specific surveillance measures for early detection and/or prevention of cancer, and provide counseling regarding genetic testing. Additionally, the clinical and laboratory units are working together on scientific research projects in order to translate scientific knowledge into the best specialized care for patients.

Clinical group leader

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Clinical members

Oncologic Clinical Nurse Specialist
Neus Gadea

Clinical Research Fellow
Daniel Fortuny MD

Laboratory group leader

Orland Díez PhD
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Laboratory members

Sara Iliana Gutiérrez PhD

Technicians
Miriam Masas
Anna Tenés

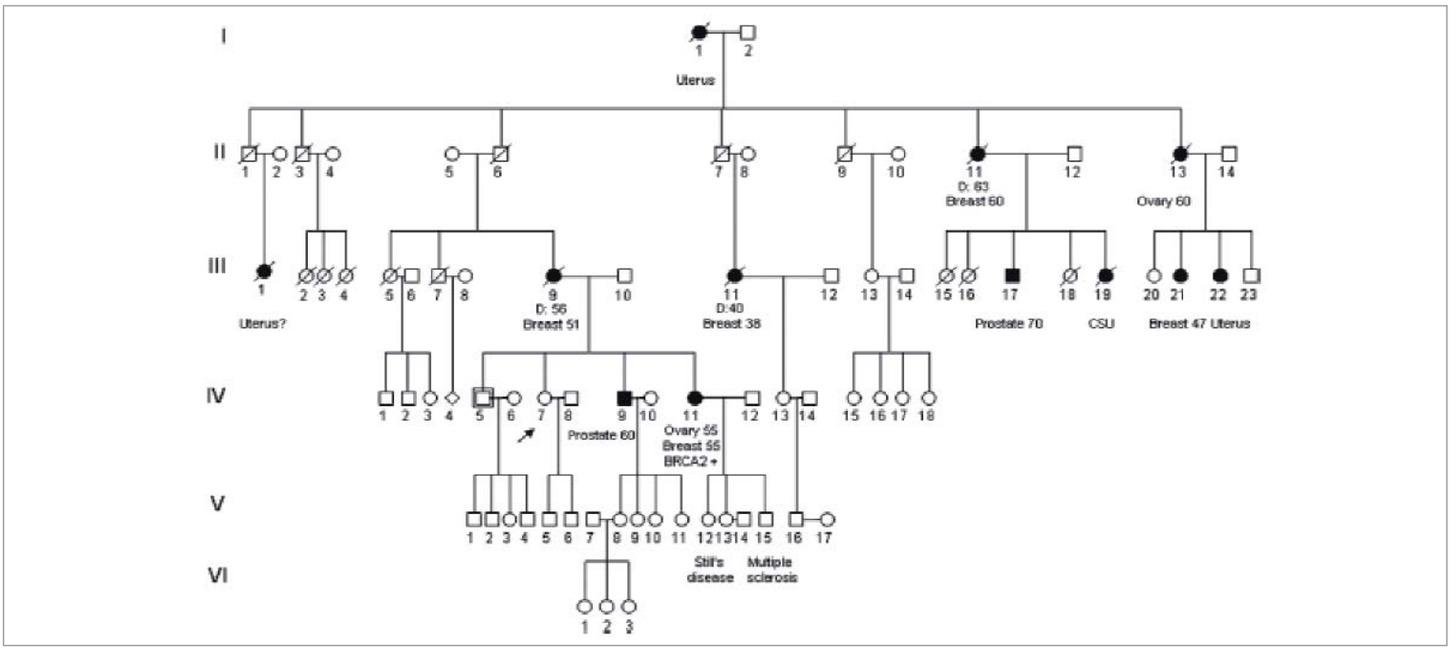

Figure 1. Pedigree of the family with the two BRCA2 mutations. The arrow indicates the disease-free proband. Filled symbols indicate subjects affected by cancer. The number after cancer sites indicate the age at diagnosis. The age of death is reported if known Subject (IV 11) is a BRCA2 mutation carrier. CSU, cancer site unknown; D, deceased.

Clinical activity

The High Risk and Cancer Prevention Program at Vall d'Hebron University Hospital began clinical activity in June 2005. Since then, more than 1,400 individuals and more than 1,000 families have been visited. Patients are referred from the same hospital and from other centers in Catalonia. During this period specific protocols have been implemented with each specific department for referral of individuals at risk of digestive, gynecology, breast, urological and pediatric hereditary cancers to the high risk unit. Implementation of a screening protocol for early detection of breast cancer in women at high risk has been agreed in a multidisciplinary team. A protocol for molecular screening of individuals at risk of hereditary predisposition to colorectal cancer has also been developed in collaboration with the pathology department. A novel protocol for the follow-up of adults with Fanconi Anemia has been implemented since 2008.

Scientific activity

The following research lines and projects have been developed and/or are ongoing in clinical research:

- Impact of genetic testing in hereditary cancer syndromes (IMASS Project).
- Efficacy and comparison of two different molecular strategies for screening of individuals at risk of Lynch syndrome.
- Identification of mutations in the ATM gene in families with hereditary breast families and no mutation identified in the BRCA genes.
- Extension and validation of the PREMM1,2 model and validation of other predictive models for Lynch syndrome.
- Validation of Lynch predictive models in the Spanish population.
- Development of a prevalence table of BRCA mutations in the Spanish population. In collaboration with Orland Díez and Sara Gutiérrez, the project is ongoing with the aim of developing an easy-to-use tool for prediction of BRCA mutation carriers in our country and has been funded by a private grant.
- Identification of novel targets in basal-like breast cancer.

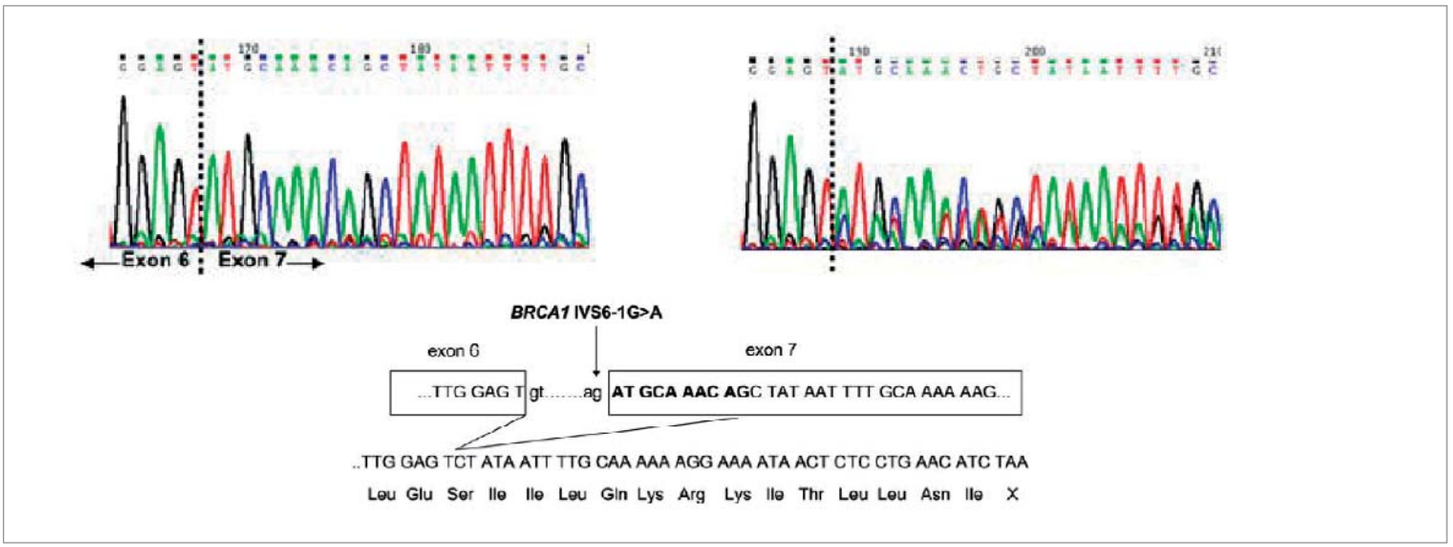

Figure 2. Partial sequence of the RT-PCR products of the wild type and mutated alleles from a BRCA1 IVS6-1G>A (c. 302-1G>A) carrier, and schema of the region of exon 6–exon 7 junction of BRCA1 gene. Sequencing anyalysis revealed a 10-base frameshift deletion at the beginning of exon 7 (c. 302_311del10) and a predicted premature stop codon.

Clinical trials (2)

D0810C0021 Ensayo Fase I/II, abierto, multicéntrico, de AZD2281 oral en combinación con Cisplatino, para valorar la seguridad y tolerabilidad en pacientes con tumores sólidos avanzados, y para valorar la eficacia neoadyuvante en pacientes con cáncer de mama triple negativo. Included patients: 12

BRCA: A phase II randomized trial to compare the efficacy of carboplatin versus taxotere in advanced BC patients with BRCA1/2 mutation.

Grants (3)

Sociedad Española de Oncología Médica 2006-2008

Prevalence and risk of cancer in breast cancer families with heterozygous mutation carriers in ATM gene. The aim of this project is to determine whether heterozygous ATM mutations may play a role in familial breast cancer not associated with BRCA1 or BRCA2 mutations. Role: Co-investigator.

Sociedad Española de Oncología Médica 2007-2009

Comparison of different molecular screening techniques for Lynch syndrome in colorectal cancer patients. The goal of this project is to compare the sensitivity and specificity of two different techniques for microsatellite instability in colorectal cancer patients at risk of Lynch syndrome. Role: Principal investigator.

NIH grant #R01CA132829-01A1
Validation and extension pf the PREMM model for mismatch repair gene mutations. Role: Co-investigator.

Orland Díez, laboratory group leader

Orland Díez graduated in biology from the University of Barcelona in 1983 and specialized in clinical biochemistry at the Hospital Universitari de Bellvitge in Barcelona (1992). He has been head of the VHUH laboratory for molecular analysis of hereditary cancer since April 2007.

He is the author of more than 80 publications, particularly in hereditary breast/ovarian cancers, including scientific articles, oncology and genetics book chapters, monographic pieces, and his doctoral thesis on molecular analysis of BRCA1 and BRCA2 genes.

His research interests are mainly in cancer predisposition genes. He actively participates in the development of methodological strategies for the analysis of hereditary breast cancer genes and in the description of their recurrent genetic alterations in the Spanish population.

He specializes in Human Genetics at VHUH and is an investigator in the area of hereditary breast and ovarian cancer.

Scientific activity

The following research lines and projects have been developed or are in progress, with the close collaboration of Sara Gutiérrez, a postdoctoral biologist specializing in molecular analysis of hereditary cancer.

- Study of the prevalence of point mutations and large rearrangements in the BRCA1 and BRCA2 genes.
- Development of a prevalence table of BRCA mutations in the Spanish population and their relation with familial phenotype.
- Study of breast cancer predisposition genes in patients with early onset breast cancer, with or without family history of the disease.
- Identification of mutations in the ATM gene in families with hereditary breast cancer and no mutation identified in the BRCA genes.
- Identification of biological markers of breast cancer predisposition by genomic characterization of the response to mutagenic agents in peripheral blood lymphocytes in familial breast cancer.
- Identification of genes that predict susceptibility to adverse effects of radiotherapy in breast cancer by the analyzing their genetic variants and genomic expression.

Research projects (4)

Funding agency: FIS (04/1832)
Title: Molecular diagnosis of breast cancer predisposition by the genomic characterization of the response to mutagenic agents in peripheral blood lymphocytes.
PI: Dr. Orland Díez

Funding agency: FMM
Title: Development of a predictive model of BRCA1 and BRCA2 mutation detection in the Spanish population with familial breast cancer.
PI: Dr. Orland Díez

Funding agency: FIS (05/2181)
Title: Identification of genes that predict susceptibility to adverse effects of radiotherapy in breast cancer by studying their genetic variants and genomic expression.
Collaborating investigator: Dr. Orland Díez

Funding agency: SEOM
Title: Study of the prevalence and cancer-associated risk of ATM heterozygotic mutations in families with breast cancer negative for BRCA1 and BRCA2 genes.
Collaborating investigator: Dr. Orland Díez
Duration: 2006-2008

Publications (12) / IF: 57.018

Fortuny D, **Balmaña J**, Graña B, Torres A, Ramón Y Cajal T, Darder E, **Gadea N**, Velasco A, López C, Sanz J, Alonso C, Brunet J. Opinion about reproductive decision making in individuals undergoing BRCA genetic testing in a multicentre Spanish cohort. Human Reproduction 2008, Dec 26.
(IF: 3.543, 1 cuartil, reproductive biology, science)

Vilar E, Scaltriti M, **Balmaña J**, Saura C, Guzman M, Arribas J, Baselga J, Tabernero J. Microsatellite instability due to hMLH1 deficiency is associated with increased cytotoxicity to irinotecan in human colorectal cancer cell lines. Br J Cancer, 2008 Nov 18;99(10):1607-12. Epub 2008 Oct 21.
(IF: 4.635, 1 cuartil, oncology)

Balmaña J, Balaguer F, Castellví-Bel S, Steyerberg EW, Andreu M, Llor X, Jover R, Castells A and Syngal S, for the Gastrointestinal Oncology Group of the Spanish Gastroenterological Association. Comparison of predictive models, clinical criteria and molecular tumor screening for the identification of patients with Lynch syndrome in a population-based cohort of colorectal cancer patients. J Med Genet 2008 Sep;45(9):557-63. Epub 2008 Jun 25.
(IF: 5.535, 1 cuartil, genetics & heredity)

Gutiérrez-Enríquez S, Coderch V, **Masas M**, **Balmaña J**, **Díez O**. The variants BRCA1 IVS6-1G>A and BRCA2 IVS15+1G>A lead to aberrant splicing of the transcripts. Breast Cancer Res Treat. 2008 Aug 19.
(IF: 4.453, 2 cuartil, oncology)

Kastrinos F, Stoffel EM, **Balmaña J**, Steyerberg EW, Mercado R, Syngal S. Phenotype comparison of MLH1 and MSH2 mutation carriers in a cohort of 1,914 individuals undergoing clinical genetic testing in the United States. Cancer Epidemiol Biomarkers Prev. 2008 Aug;17(8):2044-51.
(IF: 4.642, 1 cuartil, oncology science)

Balaguer F, **Balmaña J**, Castellví-Bel S, Steyerberg EW, Andreu M, Llor X, Jover R, Syngal S, Castells A; Gastrointestinal Oncology Group of the Spanish Gastroenterological Association. Validation and extension of the PREMM1,2 model in a population-based cohort of colorectal cancer patients. Gastroenterology. 2008 Jan; 134(1):39-46. Epub 2007 Oct 26.
(IF: 11.673, 1 cuartil, gastroenterology & hepatology)

Balmaña J, Steyerberg EW, Syngal S. Quantification of risk for carrying mutations in Lynch syndrome genes. ASCO 2008 Educational manuscript.

Gutiérrez-Enríquez S, Balmaña J, Baiget M, **Díez O**. Detection of the CHEK2 1100delC mutation by MLPA BRCA1/2 analysis: a worthwhile strategy for its clinical applicability in 1100delC low-frequency populations?. Breast Cancer Res Treat 2008; 107:455-7.
(IF: 4.453, 2 cuartil, oncology)

Milne RL, Osorio A, Ramón y Cajal T, Vega A, Llort G, de la Hoya M, **Díez O,** Alonso C, Lazaro C, Blanco I, Sánchez de Abajo A, Caldés T, Blanco A, Graña B, Chirivella I, Garcés V, Tejada MI, Beristain E, Miramar MD, Calvo MT, Durán M, Velasco E, Martínez E, Guillén C, Salazar R, Antoniou AC, Urioste M, Benítez J. The average cumulative risks of breast and ovarian cancer for carriers of mutations in BRCA1 and BRCA2 attending genetic counselling units in Spain. Clin Cancer Res 2008;14:2861-9.
(IF: 6.250, 1 cuartil, oncology)

Osorio A, Pollán M, Pita G, Schmutzler RK, Versmold B, Engel C, Meindl A, Arnold N, Preisler-Adams S, Niederacher D, Hofmann W, Gadzicki D, Jakubowska A, Hamman U, Lubinski J, Toloczko-Grabarek A, Cybulski C, Debniak T, Llort G, Yannoukakos D, **Díez O**, Peissel B, Peterlongo P, Radice P, Heikkinen T, Nevanlina H, Mai PL, Loud JT, McGuffog L, Antoniou A, Benitez J. An evaluation of the polymorphisms Ins16bp and Arg72Pro in p53 as breast cancer risk modifiers in BRCA1 and BRCA2 mutation Carriers. Br J Cancer 2008;99:974-7.
(IF: 4.635, 1 cuartil, oncology)

Brunet J, **Gutiérrez-Enríquez S**, Torres A, Bérez V, Sanjosé S, Galceran J, Izquierdo A, Menéndez JA, Gumà J, Borrà J. ATM germline mutations in Spanish early-onset breast cancer patients negative for BRCA1/BRCA2 mutations. Clinical Genetics 2008;73:465-73.
(IF: 3.181, 2 cuartil, genetics & heredity)

Febrer E, Mestres M, Caballín MR, Barrios L, Ribas M, **Gutiérrez-Enríquez S**, Alonso C, Ramón y Cajal T, Francesc Barquinero J. Mitotic delay in lymphocytes from BRCA1 heterozygotes unable to reduce the radiation-induced chromosomal damage. DNA Repair 2008; 7:1907-11.
(IF: 4.018, 2 cuartil, genetics & heredity science)

Lung Cancer Program

Enriqueta Felip, group leader

Enriqueta Felip is the head of the Lung Cancer Program. She received her medical degree from the Universitat Autònoma de Barcelona, where she also completed her studies for a PhD in medical oncology. She is a member of the Steering Committee of the Spanish Lung Cancer Group and a member of the Spanish Society of Medical Oncology Executive Committee.

She is currently a member of ESMO, ASCO and IASLC and was a member of the Scientific Committee of the IASLC 2005. She is the coordinating author of Minimum Clinical Recommendations for Diagnosis, Treatment and Follow-up in Lung Cancer for the European Society of Medical Oncology. She has published many peer-review articles and book chapters in this field and is and has been a member of many committees and workgroups.

Lung Cancer Program

The Lung Cancer Program at Vall d'Hebron University Hospital takes care of patients with lung cancer diagnosed at our Institution. Each year more than 400 patients are diagnosed with lung cancer in our hospital and all new cases are discussed weekly in a multidisciplinary setting by the Tumors Committee. Research lines of the Lung Cancer Program include the optimization of chemotherapy in early-stage disease, evaluation of new drugs and the use of pharmacogenomic approaches.

Group leader

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Clinical members

Attending Physicians
Susana Cedrés MD
Pablo Martínez MD

Head of Study Coordinator
Irene Marimón MD

Clinical Trials Coordinators
Oriol Nualart MD
Meritxell Soler MD
Marta Beltrán PhD

Clinical activity

The Lung Cancer Program is at present dealing with several clinical activities:

- The Program has been involved in a program dealing with rapid diagnosis in patients with suspected lung carcinoma. There is continuous work with nurses, pneumologists, pathologists and radiologists to carry out the whole diagnosis and staging process in less than 4 weeks.
- Each year more than 420 new lung cancer patients are diagnosed in our Institution and are seeing by our program. We aim to see these patients within 2-3 days of diagnosis and staging.
- Members of the Program play an essential role in the Lung Cancer Committee meeting. In this forum, all new lung cancer cases are discussed in a multidisciplinary environment.
- The program is working to incorporate the most recent findings in lung cancer research into clinical practice.
- A close relationship is maintained with doctors working in primary health care and several information sessions have already taken place.
- The program works closely with nurses and psychologists in order to provide better support for patients.

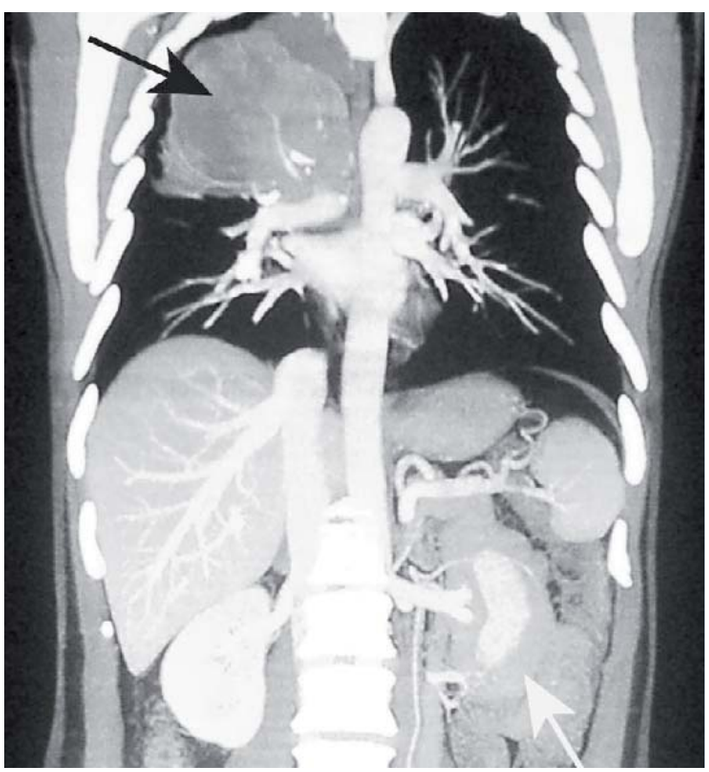

Figure 1. Patient diagnosed of non-small cell lung cancer tumor with vascular invasion.

In recent years, the Lung Cancer Program has carried out a clinical research program with participation in multicenter clinical research trials. We have led and participated in national and international cooperative groups. We have driven the clinical sessions program of the Service, which promotes multidisciplinary, integrated care of lung cancer. Members of the program have also sat on the boards of of Spanish and European oncologic societies.

Scientific activity

The Lung Cancer Program has been closely involved in clinical research in areas such as new chemotherapy agents, drugs targeting EGFR, angiogenesis-inhibiting drugs, multidisciplinary treatments for patients with early stage lung cancer, and analysis of predictive factors for response/survival.

The main contribution in the past year has been the following:

- The excellent relationship between the members of the Tumors Committee has encouraged the development of clinical research protocols with the participation of several services, with participation in the NATCH trial, in which 620 surgical lung cancers were included and in which the role of complementary chemotherapy and possible molecular prediction factors of clinical benefits to chemotherapy was analyzed. Vall d'Hebron University Hospital has been the main recruiter study coordinator in this European multicenter trial.
- The Program also participates in an international trial analyzing the possible contribution of a new drug (Pazopanib) in preoperative treatment of surgery patients. This study has involved collaboration between members of a number of different departments Preliminary data on this trial were presented at the conference of the American Society of Clinical Oncology (ASCO)-08 and the final results have been submitted for publication in the Journal of Clinical Oncology.
- Knowledge of genetic and molecular alterations is highly relevant to improving treatment results in lung neoplasia. The research on predictive survival factors/response factors to drugs is a priority line in lung cancer. In this area we have established work collaborations with the Pathological Anatomy Service of Vall d'Hebron University Hospital and with the Research Laboratory of the Oncology Service at Germans Trias i Pujol Hospital, Badalona, which have resulted in communications and publications of clinical relevance.

- We have led the national-wide establishment of a database of women diagnosed with lung cancer to define the epidemiological specifics of our country. This project has been carried out as part of our participation in the international group National Lung Cancer Partnership.
- We have participated in phase I-II trials with new drugs in lung cancer. Specifically, over the past year we have worked with the following drugs/combinations: EPO 906, pertuzumab/erlotinib, SU011248, pazopanib, ZD6474, erlotinib, BMS 690514 and MK0646-001. We have also authored several studies with these drugs in lung cancer, the results of which will be presented at ASCO-2008.

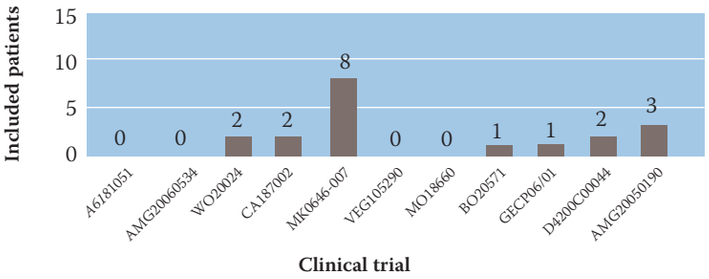

Figure 2. Included patients in the clinical trials of the Lung Cancer Program in 2008.

Clinical trials (10)

D4200C00044 A phase III, International, randomised, double-blind, parallel-group, multicentre study to assess the efficacy of ZD6474 (ZACTIMA) plus best supportive care versus placebo plus best supportive care in patients with locally advanced or metastatic (satge IIIB-IV) non small cell lung cancer (NSCLC) after prior therapy with an epidermal growth factor tyrosine kinase inhibitor (EGFRTKI). Included patients: 2

GECP06/01 Phase III Study (Tarceva®) vs Chemotherapy to Treat Advanced Non-Small Cell Lung Cancer (NSCLC) in Patients With Mutations in the TK Domain of EGFR. Included patients: 1

VEG105290 A Phase II, Non-randomized, Multicenter Study to Evaluate the Safety and Efficacy of Pazopanib (GW786034) as Pre-Surgical Therapy in Treatment-Naive Subjects With Stage IA or IB, Resectable Non Small Cell Lung Cancer (NSCLC). Included patients: 0

A6181051 Estudio de Fase 1 de SU011248 en Combinación con Gentamicina y Cisplatino en Pacientes con cáncer de Pulmón no Microcítico en Estadío IIIb/IV. Included patients: 0

MO18660 Estudio en grupos paralelos, de fase II de Tarceva (Erlotinib) en pacientes con cáncer pulmonar no microcítico avanzado (estadíos IIIB/IV) no tratados previamente con quimioterapia incluyendo un escalado de dosis hasta toxicidad en ex fumadores y fumadores habituales. Included patients: 0

BO20571 A phase II study of Tarceva in Combination with Avastin versus chemotherapy plus Avastin in 1st line advanced NSCLC patients. Included patients: 1

MK0646-007 An Open Label, Randomized Phase I/IIa Trial Evaluating MK0646 in Combination With Erlotinib for Patients With Recurrent Non-Small Cell Lung Cancer. Included patients: 8

20050190 A Multicenter, Open Label, Randomized Study of AMG 951 in Subjects With Previously Untreated Stage IIIb/IV Non-Small Cell Lung Cancer (NSCLC) Treated With Chemotherapy With or Without Bevacizumab. Included patients: 3

20060534 A Phase 1b/2 Trial of AMG 479 or AMG 102 in Combination With Platinum-based Chemotherapy as First-Line Treatment for Extensive Stage Small Cell Lung Cancer. Included patients: 0

WO20024 Estudio de fase Ibmulticéntrico, abierto, de la combinación de Pertuzumab y Erlotinib en pacientes con CPNM localmente avanzado o metastásico (estadio IIIb/IV) en los que ha fracasado previamente al menos un régimen de quimioterapia. Included patients: 2

Scientific projects (7)

Pharmacodynamic study of erlotinib in advanced NSCLC, in collaboration with Grossansdorf University. Published in Clin Cancer Res-08

PI of the Phase I-II erlotinib/pertuzumab combination study in NSCLC. Presented at ASCO-08, ESMO-08 (Manuscript in preparation)

PI of the Phase II patupilone (EPO 906) study in advanced NSCLC. Presented at ESMO-08

Collaboration in the Phase I trial analyzing BMS 690514 in advanced NSCLC. Presented at ASCO-08, submitted to ASCO-09

PI of the Phase III NATCH trial in early-stage disease. Submitted to ASCO-09

Collaboration in the Phase I study analyzing erlotinib/MK0646 in advanced NSCLC. Submitted to ASCO-09

PI of an epidemiological study looking for clinical / molecular characteristics of Spanish women with lung cancer. Submitted to ASCO-0

Publications (12) / IF: 53.086

Felip E, Rosell R. Pemetrexed as second-line therapy for advanced non-small-cell lung cancer (NSCLC). Ther Clin Risk Manag. 2008 Jun;4(3):579-85

Bottomley A, Debruyne C, **Felip E**, Millward M, Thiberville L, D'Addario G, Rome L, Zatloukal P, Coens C, Giaccone. Symptom and quality of life results of an international randomised phase III study of adjuvant vaccination with Bec2/BCG in responding patients with limited disease small-cell lung cancer. Eur J Cancer. 2008 Oct;44(15):2178-84.
(IF: 4.454, 1 cuartil, oncology)

Felip E, Rojo F, Reck M, Heller A, Klughammer B, Sala G, **Cedres S**, Peralta S, Maacke H, Foernzler D, Parera M, Möcks J, Saura C, Gatzemeier U, Baselga J. A phase II pharmacodynamic study of erlotinib in patients with advanced non-small cell lung cancer previously treated with platinum-based chemotherapy. Clin Cancer Res. 2008 Jun 15;14(12):3867-74.
(IF: 6.250, 1 cuartil, oncology)

Chan AT, **Felip E**, ESMO Guidelines Working Group. Nasopharyngeal cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2008 May;19 Suppl 2:ii81-2.
(IF: 4.875, 1 cuartil, oncology)

Stahel RA, Weder W, **Felip E**, ESMO Guidelines Working Group. Malignant pleural mesothelioma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2008 May; 19 Suppl 2:ii43-4.
(IF: 4.875, 1 cuartil, oncology)

Pivot X, **Felip E**; ESMO Guidelines Working Group. Squamous cell carcinoma of the head and neck: ESMO clinical Recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2008 May;19 Suppl 2:ii79-80.
(IF: 4.875, 1 cuartil, oncology)

Sørensen M, **Felip E**; ESMO Guidelines Working Group. Small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2008 May;19 Suppl 2:ii41-2.
(IF: 4.875, 1 cuartil, oncology)

D'Addario G, **Felip E**; ESMO Guidelines Working Group. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis,treatment and follow-up. Ann Oncol. 2008 May;19 Suppl 2:ii39-40.
(IF: 4.875, 1 cuartil, oncology)

Briasoulis E, Pavlidis N, **Felip E**; ESMO Guidelines Working Group. Cancers of unknown primary site: ESMO clinical recommendation for diagnosis,treatment and follow-up. Ann Oncol. 2008 May;19 Suppl 2:ii106-7.
(IF: 4.875, 1 cuartil, oncology)

Prat A, Parera M, Reyes V, Peralta S, **Cedrés S**, Andreu J, Huguet P, del Campo JM. Successful treatment of pulmonary metastatic salivary ductal carcinoma with trastuzumab-based therapy. Head Neck. 2008 May;30(5):680-3.
(IF: 2.007, 2 cuartil, surgergy)

Folprecht G, Tabernero J, Köhne CH, Zacharchuk C, Paz-Ares L, Rojo F, Quinn S, Casado E, Salazar R, Abbas R, Lejeune C, **Marimón I**, Andreu J, Ubbelohde U, Cortes-Funes H, Baselga J. Phase I pharmacokinetic/pharmacodynamic study of EKB-569, an irreversible inhibitor of the epidermal growth factor receptor tyrosine kinase, in combination with irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) in first-line treatment of patients with metastatic colorectal cancer. Clin Cancer Res 2008;14: 215-23.

Felip, E. ESMO Guidelines Working Group. Small-cell lung cancer: ESMO Clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2008 May; 19 (5): 1027-9.
(IF: 4.875)

Molecular Pathology Program

Santiago Ramón y Cajal, group leader

Santiago Ramón y Cajal is the head of the Pathology Department at Vall D'Hebron University Hospital, Barcelona, Spain, and is Professor of Pathology at the Universidad Autónoma, Barcelona.

Dr. Ramón y Cajal has published over 175 peer-reviewed articles, in addition to over 320 abstracts and book chapters.

His research interests are mainly in tumor pathology, studying new and better diagnostic and prognostic markers in cancer, as well as molecular pathology, and describing the proteins and signaling cascades involved in carcinogenesis.

He is a corresponding academy member of the Spanish National Medical Royal Academy, Honor Academy Member of the Royal Medicine Academy of Granada, and the Medical College of Zaragoza, Spain. He received the Spanish National Young Investigator Award in 1999.

He won the Eminent Scientist of the year 1999 award for his work in pathology and the International Research Promotion Council (IRPC) Gold Medal in acknowledgment of his contribution to studies of the oncogenic and sensitizer capabilities of the adenovirus E1A protein in human cancer.

Molecular Pathology Program

The Molecular Pathology Program is part of the Pathology Department of the Vall d'Hebron University Hospital and is closely associated with the Medical Oncology Program of the Research Institute at Vall d'Hebron University Hospital. The Pathology Department is dedicated to diagnostic (clinical) and experimental pathology and cooperates with other services and Hospital Units. The Oncologic

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Research Pathology Laboratory is fully dedicated to analyzing human tissue samples, cell pellets and mouse xenografts—mandatory in our projects. This group is currently participating in approximately 40 clinical trials, acting as the central laboratory in some of them. We routinely perform immunohistochemistry (more than 100 optimized antibodies), immunofluorescence of multiple targets, 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 program is essential in translating findings from bench to bed.

Scientific activity

Activity in cancer pathology, transplants, inflammatory pathology and pediatric pathology is the highest in Catalonia and one of the highest of Europe, providing all of the diagnostic and prognostic services in tumor pathology, hematopathology, microorganism detection, human genetics and infectious diseases. Technical resources range from traditional tissue stainings and DNA hybridization methods to the most sophisticated technologies, including quantitative PCR (Polimerase Chain Reaction) and DNA sequencing, western blotting and other molecular biology techniques. The program is a leader in the field of molecular pathology and is continuously implementing new prognostic methods. For example, the Pathology department has recently been recognized as a reference center for the detection of K-Ras mutations, and it is collaborating closely with pharmaceutical companies and other Spanish hospitals in this regard.

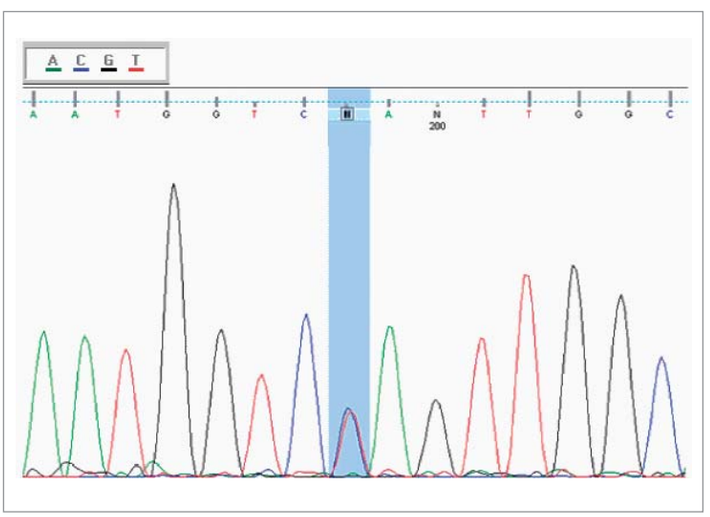

Figure 1. Direct sequencing: Mutational analysis for key genes.

Molecular and immunohistochemical diagnosis

The Pathology department has a magnificent paraffin block archive with over twenty thousand tumors and other relevant pathological specimens, as well as a tumor bank with over 6000 high quality frozen samples, routinely used for mRNA and Protein studies. Also, the majority of frozen and paraffin embedded tumor samples are included in clinical protocols and trials, which warrants their monitoring and clinical correlation.

Immunohistochemical studies with antibodies used as diagnosis markers are carried out on little differentiated tumors or tumors of unknown origin as prognosis markers (markers of proliferation, angiogenesis, oncogenes, lack of suppressor genes, mutated genes) as well as studies to characterize new therapeutical targets for the developing of new specific inhibitors. The Pathology Department has extensive experience in the optimization of immunohistochemical studies and the validation or confirmation of antibodies. The large historical archive of biopsies and protocolized tumors is very useful for creating tissue arrays of all kinds of normal and tumoral tissues, even for unusual cancers, in any location and any malignancy status.

The in situ hibridization studies routinely used are based on gene amplification, translocation studies and viral-sequence detection. New targets are also being detected, in close association with pharmaceutical companies, to preselect patients in clinical trials.

DNA and mRNA-based PCR studies are used to detect different viruses and genes. Depending on the gene, they are also sequenced afterwards to identify relevant mutations.

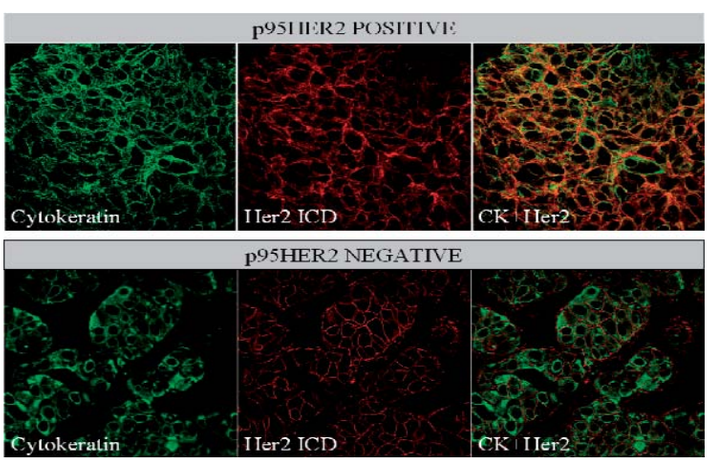

Figure 2. p95HER2 detection. (A) Tumor scored positive for p95HER2 expresion as the intracellular HER2 antibody staining (red) co-localizated with the pan-cytokeratin antibody stain (green). (B) Tumor scored negative.

In vitro new chemotherapy drug response studies

The group has a cellular biology laboratory with laminar flow cabinets and incubators, which allow them to perform explant studies from human biopsies, as well as cell line studies. In this regard, the pathology department has published a large number of peer-reviewed articles on the validation and characterization of new chemotherapy drugs in vitro, studying the signalling pathways involved.

The in vitro study of inhibitors and drugs on primary tumor explants is one of the main elements in the validation process, and they are carried out in technically complex studies, which can provide relevant added value when defining the applications of these molecules in clinical trials.

Molecular targets and new inhibitors: studies in tumor samples and other locations

Due to its close ties to the Oncology Service, where tens of clinical trials are carried out, extensive experience has been acquired in the validation of molecular targets on tumor samples from patients treated with several inhibitors, from growth factor receptors to the signalling cascades activated in response to extracellular signals.

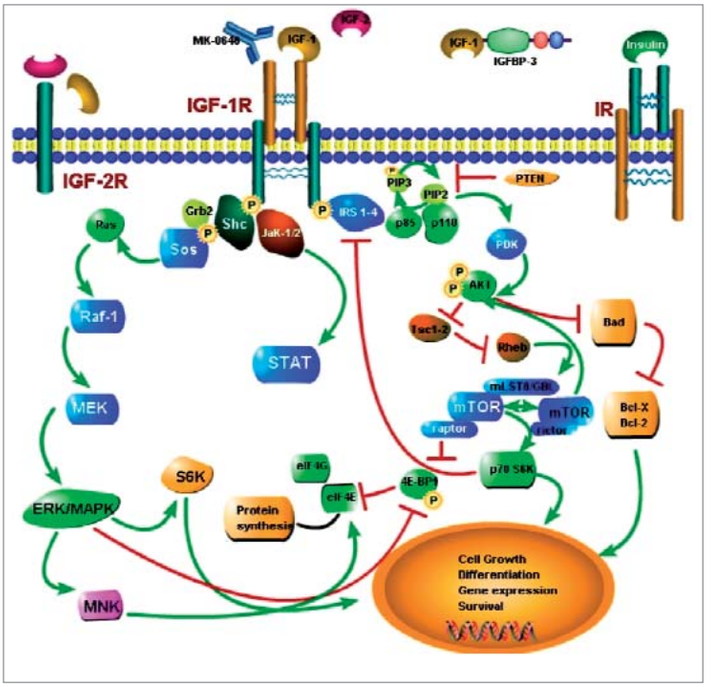

Figure 3. The IGF system.

Clinical trials (38)

20040235 Dosage research trial, open and multicenter, to evaluate the safety and tolerance of AMG 706, panitumumab and a combination of AMG 706 and panitumumab when administered with induction chemotherapy (QI) and/or chemoradiotherapy (QRT) in the treatment of individuals with squamous cell carcinoma head and neck locally-regionally advanced (SCCHN).

20050203 Randomized, multicenter, phase III trial to compare the efficiency of panitumumab combined with oxaliplatin/5-fluoracil/leucovorine against the efficiency of oxaliplatin/5-fluoracil/leucovorine alone on patients with metastatical colorectal cancer not previously treated.

2-55-52030-726 Phase III, randomised, double blind, stratified comparative, placebo controlled, parallel group, multicentre study to assess the effect of deep subcutaneous injections of lanreotide autogel 120 mg administered every 28 days on tumour progression free survival in patients with non functioning entero-pancreatic endocrine tumour.

26854165CAN1001 A Phase I study to determine the safety, pharmacology and pharmacodynamics of JNJ26854165 in subjects with advanced stage and/or refractory solid tumors.

A4021011 Phase II, randomized, non comparative, open, multicenter, two groups trial of CP-751, 871 combined with docetaxel/prednisone on patients with hormone resistant prostate cancer without prior chemotherapy (Group A) or refractory to docetaxel/prednisone (Group B).

ALTTO Phase III randomized, multicenter, open trial of lapatinib, trastuzumab, its sequential administration of both and the combined administration of both as adjuvant treatment on patients with HER-2/ErbB2 positive breast cancer.
BEATRICE Phase III multicentric, international trial, to evaluate adjuvant therapy with bevacizumab in triple negative breast cancer.

BO20571 A phase II study of Tarceva in Combination with Avastin versus chemotherapy plus Avastin in 1st line advanced NSCLC patients.

BMS690514 Phase I trial, with dosage increase of BMS-690514 on patients with advanced or metastatical solid tumors.

BO17929 Phase II exploratory, multicenter, single treatment group trial to evaluate the efficiency and safety the combination of OmnitargTM (pertuzumab) and Herceptin® (trastuzumab) on patients with metastatical HER-2 positive breast cancer.

BO20904 Phase III multicenter, double blind, randomized trial of bevacizumab combined with capacitabine and cisplatinum, for first line treatment on patients with advanced stomach cancer.

BO21495, Open-Label, multicenter, dose-escalation Phase I/II study to evaluate safety, pharmacokinetics and activity of RO5083945, a Glycoengineered Antibody against EGFR, in patients with metastatic and/or locally advanced malignant EGFR+ Solid Tumors. CA180-004 Phase I trial of dasatinib (BMS-354825) and capacitabine on advanced breast cancer.

CBEZ235A2101 Phase I/II, multicenter, open trial of BEZ235, daily and continuously orally administered on adult patients with advanced solid tumors, including patients with advanced breast cancer.

CRAD001C2241 Phase II, multicenter, single branch clinical trial, of RAD001 on patients with metastatical colorectal adenocarcinoma with tumor progression even with previous treatment with an anti-EGFR antibody (in appropriate cases), bevacizumab, fluoropirimidine, oxaliplatin and irinotecan-based patterns.

CRAD001C2324 A Randomized Double-Blind Phase III Study of RAD001 10 mg/d Plus Best Supportive Care Versus Placebo Plus Best Supportive Care in the Treatment of Patients With Advanced Pancreatic Neuroendocrine Tumor (NET).

D8480C00015 Exploratory, randomized, double blind trial to evaluate the effect of AZD2171 and gefitinib, alone or combined, on biomarkers and tumors of patients with non microcytic lung cancer (NMLC) not previously treated, evaluated before the usual treatment, or on patients with metastatical or recurrent head and neck cancer (HNC).

EGF102988 Phase III, multicenter, randomized, double blind, controlled with placebo trial of lapatinib or placebo for postoperative adjuvant treatment and concomitant chemotherapy followed by lapatinib or placebo single therapy, on patients with high risk resectable epidermal head and neck carcinoma (SCCHN).

EGF105485 (TEACH) Randomized, double blind, multicenter trial, controlled with placebo, of lapatinib in adjuvancy on women with initial tumor breast cancer that presented ErbB2 over expression in the primary tumor.

EMR200025-051 Phase II randomized trial with cetuximab and cisplatin in ER-negative, PR negative and HER2 negative (basal type) metastatic breast cancers.

EXPERT-C Phase II multicenter, randomized comparison trial of oxaliplatin (Elotaxin), capacitabine (Xeloda) and preoperative radiotherapy with or without cetuximab, followed with total excision of the mesorectum as treatment for patients with high risk rectum cancer defined by magnetic resonance.

FM-B04-01 Cooperative European Study on Systemic Primary Therapy on women with operable breast cancer and T>2cm.

GECP06/01 Phase III multicenter, open, randomized trial of treatment with erlotinib (Tarceva) against chemotherapy on patients with advanced non microcytic lung carcinoma that present mutations in the tyrosine kinase (TK) domain of the epidermis growth factor receptor (EGFR).

H9H-MC-JBAH, A Phase I LY2157299 dose-escalatio in patients with recurrent glioblastome multiforme.

IMC11F8 IMCL CP11-0602, Open label, multicenter, phase II study evaluating the efficacy and safety of IMC-11F8 in combination with 5-FU/FA and oxaliplatin (mFOLFOX-6) in patients with treatment-naïve, locally-advanced or metastatic colorectal cancer.

MINDACT Microarray in node negative disease may avoid chemotherapy trial. Conducted by The Netherlands Cancer Institute, funded by the European Organization for Research and Treatment of Cancer.

MK-0646-001 Phase I open trial of the increase of dosage of MK-0646 administered by infusion once a week on patients with advanced solid tumors and multiple myeloma.

MK0646-007 An Open Label, Randomized Phase I/IIa Trial Evaluating MK0646 in Combination With Erlotinib for Patients With Recurrent Non-Small Cell Lung Cancer.

MO18660 Parallel groups phase II trial of Tarceva (erlotinib) on patients with advanced non microcytic lung cancer (stages IIIB/IV) not previously treated with chemotherapy including an increase of dosage up to toxicity on ex smokers and regular smokers.

NEO-ALTTO A randomized, multicenter open/label phase III study of neoadjuvant lapatinib, trastuzumab and their combination plus paclitaxel in women with HER2 positive primary breast cancer.

PETACC-8 Adjuvant treatment with FOLFOX-4 against FOLFOX-4 + cetuximab for colon cancer on stage III completely extirpated.

SIMAP Simulation modeling of the MAP kinase pathway.

TTD06-01 Phase II, Multicentre, Uncontrolled Pilot Study to Evaluate Safety and Efficacy of the Combination of Cetuximab and Chemotherapy (Docetaxel, Cisplatin, 5-Fluorouracil) as Neoadjuvant Therapy Followed Concomitant Chemoradiotherapy (Cisplatin) Plus Cetuximab in Patients With a Locoregional Esophageal Carcinoma.

VEG105290 Phase I, open, multicenter trial to evaluate the safety and effectiveness of Pazopanib (GW786034) as neoadjuvant treatment on patients with non microcytic lung cancer, resectable, stage IA, IB, IIA or IIB (up to T") not previously treated.

W020024 Phase Ib multicenter, open trial, on the combination of pertuzumab and erlotinib on patients with locally advanced or metastatical NMLC (stage IIIb/IV) on which at least one chemotherapy treatment has previously failed.

WO206987TOC412 Phase II, randomized clinical trial, double-blided, to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel versus placebo + trastuzumab + docetaxel in patients with HER2 positive metastatic breast cancer, not previously treated.

XL147-001 A phase 1 dose-escalation study of the safety and pharmacokinetics of XL147 administered orally daily to subjects with solid tumors.

XL765-001 A phase 1 dose-escalation study of the safety and pharmacokinetics of XL765 administered orally daily to subjects with solid tumors.

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Radiation Oncology Program

Jordi Giralt, group leader

Jordi Giralt is the head of the Radiation Oncology Service at Vall d'Hebron University Hospital in Barcelona, Spain, and Associate Professor of Medicine at the Universidad Autónoma, Barcelona.

He is chairman of the Spanish Pediatric Cancer Group and a founder member of the Spanish Group for Clinical Research GICOR. He has published over 50 peer-reviewed articles, in addition to over 200 abstracts and book chapters. His research interests are in pediatric, gastrointestinal and head and neck cancer.

Dr. Giralt holds a Ph.D. from the Universidad Autonoma, Barcelona.

Radiation Oncology Program

The Radiation Oncology Program focuses on clinical research. There are 3 main areas of interest: concurrent chemo-radiotherapy, clinical applications of targeted agents with radiation and clinical application of new technology and quality control.

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Clinical activity

Novel targets for cancer therapy in combination with radiation and chemotherapy and prevention of radiation-induced toxicity were the two lines of clinical research in 2008. We are conducting a phase II study in esophageal cancer with Erbitux given concurrently with radiation and carboplatin and a second study of Erbitux, radiation and capecitabine in locally advanced rectal cancer. We have conducted a randomized double-blind trial with the aim of studying the use of probiotics in preventing radiation-induced enteritis. In head and neck we are participating in a phase III trial comparing radiation and cisplatin with lapatinib or placebo in the postoperative setting. We also are working on a KGF for the treatment of mucositis in combination. In breast cancer we have focused on the prevention of skin toxicity. In pediatric cancer we participated in a phase III trial comparing standard craniospinal irradiation versus hyperfractionated radiation therapy. This was a multi-institutional study conducted by the International Society for Pediatric Oncology (SIOP) and Dr Giralt was one of the members of the steering committee. In prostate cancer we are participating in 2 phase III studies, one in the intermediate risk group and one in the post-operative setting.

Scientific activity

New targets

- PanituPanitumumab plus radiotherapy in locally advanced head and neck cancer. Randomized phase II trial ongoing.
- Radiation plus cisplatin +/- lapatinib in the postoperative setting. Phase III trial ongoing.
- Cetuximab in the treatment of locally advanced esophageal cancer. Phase II trial ongoing.

Mucositis / epithelitis

- Palifermin (Recombinant Human Keratinocyte Growth Factor, rHuKGF) for the reduction of oral mucositis in patients receiving radiotherapy Presented at ESTRO 08, manuscript in preparation.
- Soluble Beta-1,3/1,6-glucan for mucositis prevention in patients receiving radiotherapy. Double blind phase III trial ongoing.
- 3% urea lotion prevents dehydration and desquamation after radiotherapy in breast cancer. Double blind phase III trial, presented at ESTRO 08, manuscript in preparation.

Others

- Selective use of postoperative radiotherapy after mastectomy. Phase III trial ongoing.
- Short course versus long course androgenic blockade combined with high-dose radiotherapy in intermediate and high-risk prostate cancer. Phase III trial ongoing.
- Intermittent androgenic blockade in biochemical relapse prostate cancer. Phase III trial ongoing.

Translational research

- Differential Activation of Protein Translation is Associated with Aggressive Phenotype of Cervical Cancers Presented at ASTRO 08, manuscript accepted at Int J Radiat Oncol Biol Phys.
- Radiotherapy versus temozolomide in low grade gliomas after stratification for genetic 1p loss. Phase III trial ongoing.

Technology developments

- Highly conformal radiotherapy in pediatric tumors: stereotactic techniques.
- IMRT in prostate and head and neck cancer (Fig. 1)
- Quality assurance: portal imaging guided treatment deviations (Fig. 2)
- Stereotactic radiotherapy in brain tumors (Fig. 3)
- New techniques under evaluation:
  - Breast cancer irradiation in prone position
  - Volume changes during RT in H&NC
  - Fiducial marks in prostate cancer for treatment guidance
  - PET imaging for target delineation in pediatric Hodgkin disease

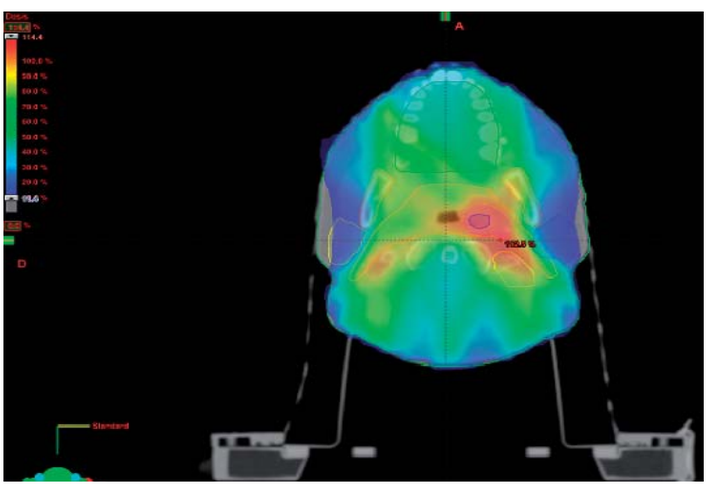

Figure 1. Dose distribution in a patient with a rhynopharynx tumor treated with IMRT.

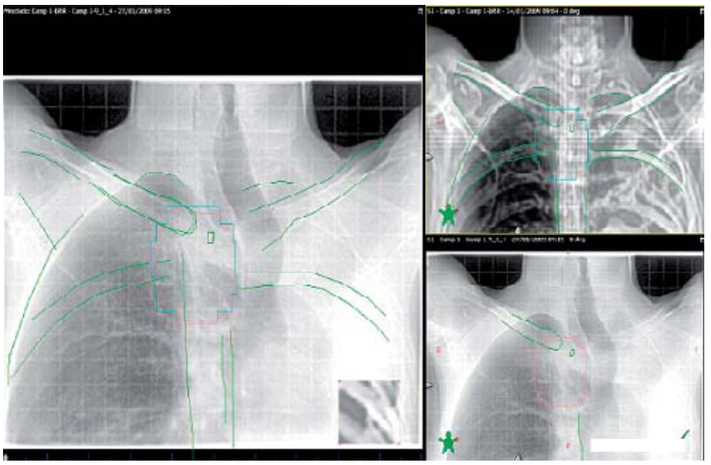

Figure 2. Portal film and matching for correction in a patient with lung cancer.

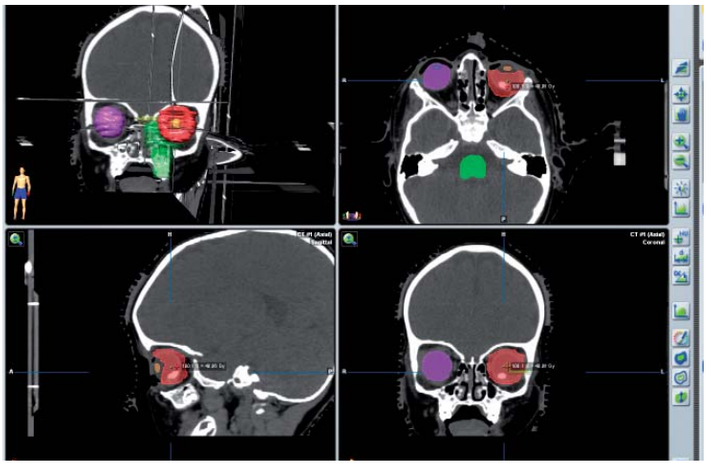

Figure 3. Treatment planning and dose distribution in the treatment of a child with a retinoblastoma.

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Publications

The database contains 117 publications. These are publications both with and without an impact factor. It also includes publications that were in press in 2008.

- Total publications: 117
- Publications with IF: 108
- Other publications: 9
- Total IF 2008: 715.467

IF: 52.589

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Coordination: VHIO Communication Department
with the valuable contribution of María Teresa Pamias

Production: Hores extraordinàries

Translation: Liam Orr

Photographs: Norberto Aliata
Díaz Wichmann Photography BCN
J.A. Recio (cover page)

Printing: Gràfiques Cuscó

Legal deposit: B-40.204-2009

November 2009

VHIO
VALL D'HEBRON
Institute of Oncology

Founded by:

Generalitat de Catalunya

With the collaboration of:

FUNDACION CELLEX

fero
Fundación de Investigación Oncológica

Welfare Projects
"la Caixa" Foundation