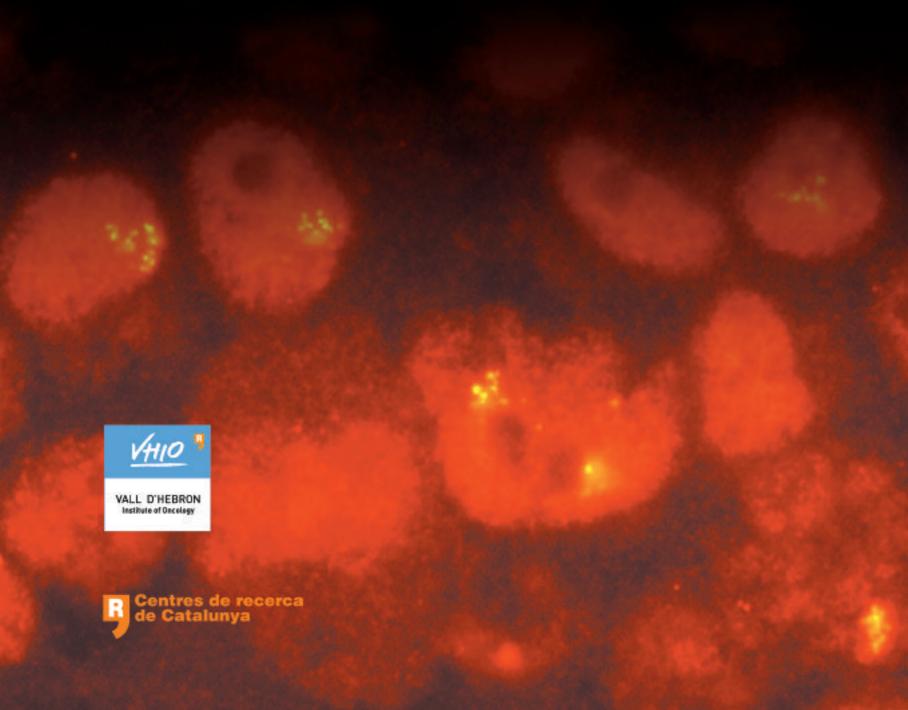
Vall d'Hebron Institute of Oncology

Scientific Report 2009



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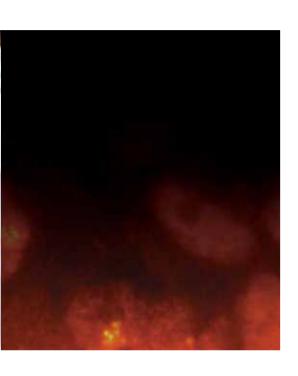


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Foreword



f a picture is worth a thousand words, the emerging landscape of oncology paints entire chapters. With the irrepressible explosion of novel data, the rapid advancement in new genomic technologies as well as exciting treatment modalities, the promise that lies ahead cannot be summarized in so few words!

Importantly, such progress can only be translated into real benefit for cancer patients within an environment that provides the appropriate infrastructure, combined expertise, essential interconnectivity and cross talk between all oncology specialists en force.

From the outset, VHIO has been organized and structured to do just that. By adopting a purely translational research model, VHIO is proof of the bench-bedside-bench principle – a term describing the process by which research from the laboratory is directly applied to patients and from the clinical side, patient samples are analyzed in the laboratory.

The translational approach is nothing new and clearly facilitates the detailed and direct study of each patient and each tumor. The strength of the VHIO is that it can do so more swiftly and dynamically. With direct access to our patients, our multidisciplinary teams strive to improve survival and quality of life for all our patients today, and in so doing turn research into more effective, personalized treatments and better practice for the future. To this end we also have one of the largest portfolios of novel targeted agents in our clinical trial unit.

In order to align the identification of the right therapy to the right patient, our preclinical cancer models have been developed to test new anti-cancer therapies, diagnostic and prognostic tools. These studies are not only critical in the design of novel strategies and approaches against cancer but also further insight into mechanisms that trigger and enable cancer survival. Recently discovered diagnostic tools have resulted in two licensing agreements with pharmaceutical companies in 2009 and we expect more novel tools to follow.

Our studies on the involvement of HER-2 and PI3K in mammary tumour growth and metastasis have triggered the development of new diagnostic tests in breast cancer. We have also identified new therapeutic targets for the most malignant brain tumor, glioblastoma. The research is based on the study of subsets of cancer stem cells that are responsible for tumor development and therapeutic resistance.

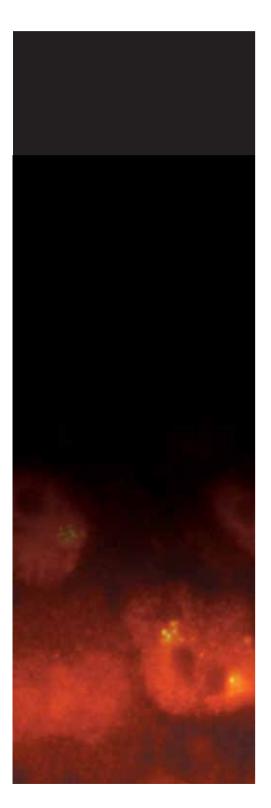
2010 marks a decade since the cracking of the human genome, a decade of talking about personalized medicine. Now we are practicing it. Genome sequencing is not only being used to identify cancer mutations but we are also starting to see it used on individual patients to guide treatment decisions.

VHIO is perfectly placed to help lead such efforts. In 2009, we established our genomics platform to sequence tumors of patients in situ and establish experimental personalized therapy for our cancer patients. The true promise of tailored therapy however can only be realized by accelerating the drug discovery process which is as complex as it is costly. Involving patients in early phase clinical trials is key. Our dedicated efforts in this respect have led to a consistent increase in patients enrolled in phase 1 and other trials at VHIO – furthering cancer treatment, care and cure.

Almost 40 years after President Nixon famously declared war on cancer, we have never been better equipped to win it. The thriving translational and multidisciplinary research environment of VHIO and the inspiring dedication and commitment of its faculty not only allow us to up the tempo in the race to combat cancer, but also accelerate the pace in advancing personalized and targeted therapies against cancer.

With continued support from the Government of Catalonia, the FERO Foundation, and the Welfare Projects "la Caixa", as well as the Cellex Private Foundation, we can and will do better.

Introduction



ancer is the principal cause of death in people of working age and one of the biggest challenges for modern medicine.

The Vall d'Hebron Institute of Oncology Foundation (from here on referred to as the VHIO) is a cancer research centre with the vision of becoming an international leader in the fight against cancer. Its day to day activities focus on understanding what cancer is; why it occurs; the mechanisms that make it function and how to diagnose it at the earliest stages with the objective of discovering how to cure it.

Despite recent advances, much work remains to be done.

"Advances in cancer research make us optimistic. The first step is to find less aggressive treatments that convert the most virulent cancers into chronic conditions; this will improve the quality of patients' lives. The following step is a cure." Josep Baselga, Director

Translational Research

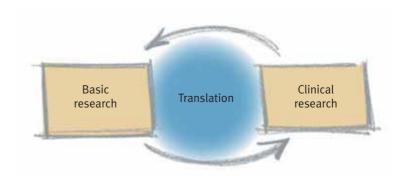
The VHIO was established in 2006, built on a model of translational research. Since then, studies carried out at the VHIO have produced several new treatments which are now used to treat patients around the world.

Translational research is the fastest route to offering effective treatments to patients. This type of research is only possible thanks to the coexistence of researchers from two distinct areas: clinical research, closely involved with the patients and their treatments; and basic research, carried out in laboratories.

"The main aim of the VHIO is to promote and develop independent studies of excellence into oncological diseases with a special emphasis on research which improves the prevention, early diagnosis and treatment of cancer."

Translational model creates synergies and establishes two-way exchanges of knowledge between those areas. From the basic research side, results of laboratory experiments are rapidly applied to patients and from the clinical side, samples from patients are analyzed and studied in the laboratory. This interaction gives rise to an effective and rapid response which may improve survival and quality of life for today's patients.

Translational research maximizes efficiency; cutting down on the non-productive periods, shortening the investigation process and enabling the detailed study of the peculiarities of each patient and each tumor.





The World of personalized therapy

Cancer is not a single disease but includes many diseases manifesting themselves differently in each patient. Researchers are very aware that the war will be won by means of a series of small discoveries; small changes that taken together will provide modern medicine with the tools and the strategies to outwit the disease. Instead of the magic bullet, we will need a whole range of weapons to fight this very complex adversary.

"Cancer is subject to the same Darwinian principles as all living things: it has a capacity to adapt to its environment and it surprises us every day."

We have advanced a great deal, it is now known that there is a repetitive pattern, among tumors with a finite repertoire of genes involved.

However, only the genes involved in 25% of the alterations detected have been identified and in this sense there is still a lot of work to be done.

We now know that the cure for cancer lies in the design of personalized therapies, where each person receives the treatment that best benefits him or her and produces the fewest side effects. This challenge requires meticulous, sophisticated and multi-disciplinary research systems with a quick response capability and organized in perfectly coordinated teams.

Models of predictive and personalized medicine will be able to sequence the complete genome of each individual; they will allow the ad hoc application of the correct drug according to the exact nature of the tumor of each patient.



Introduction





Currently there are molecular therapies approved for the treatment of some breast and colon tumors. Other medications, still at the experimental stage are giving promising results.

"Translational research allows us to evaluate patients, know their possibilities of responding positively to a treatment and seek out specific responses to resistances."

A unique player in the research arena

Talent and organization have been two of the outstanding characteristics of the VHIO from the outset. The VHIO is an integrated research center where cancer research is carried out by a multidisciplinary team of professionals with skills ranging from basic investigations through to translational and clinical research.

The VHIO is the result of a very personal vision of the concept of research. It is the product of converting translational research into an organizational structure where a complete team of professionals works together to unite efforts, examine problems from different angles and provide solutions; always with the same goal of understanding the mechanisms behind cancer and the best response to it.

Dr. Josep Baselga, director of the VHIO has promoted a working environment where scientific advances can generate improvements in clinical care, and where the experience of clinical work can consolidate scientific discoveries.

"We encourage teamwork because the results of teamwork are far superior to all the efforts of the individual researchers added together."

As well as those working directly in research, many institutions from the public and private sectors have participated in and supported the creation of the VHIO.

Backing to make our vision a reality

Translational research is extremely demanding and represents the most sophisticated way of caring for patients: it requires cutting edge technological equipment, excellent researchers and a constant supply of new therapies to investigate. The trustees understand the effort and the demands of such an ambitious project, they share with the VHIO the certainty that they are part of a historical challenge, one in which people suffering from the disease will find a medical solution, in some cases the cure.

From its inception and constitution the VHIO has had the support of:

- · The Ministry of Health, Generalitat de Catalunya
- The Ministry of Innovation, Universities and Enterprise, Generalitat de Catalunya
- $\cdot \ \text{Cellex Foundation}$
- · Fero Foundation
- "la Caixa" Social Work of the "la Caixa" Foundation

The VHIO is an organization requiring a tremendous responsibility, both institutional and personal; it demands that each and every person working here is conscientious in their work and gives of their absolute best.

"The trustees understand the power of ideas, of a vision and of a dream."



The University Hospital of Vall d'Hebron: an ideal environment for translational research

The environment of the University Hospital of Vall d'Hebron provides a magnificent base in which to develop cancer research.

- The VHIO coexists with the day to day activity of the hospital with all the available clinical care for the treatment of cancer patients
- The environment promotes professional relationships between experts from different areas thus permitting the multidisciplinary interactions of cancer specialists
- Equipment for basic research is readily available
- The University Hospital of Vall d'Hebron is a teaching hospital associated with the Universitat Autònoma de Barcelona

The combination of these factors has been of major importance in uniting the capacity for work and the talent required to allow the team of researchers of the VHIO to produce such excellent results to date.



2009 a year of consolidation for the VHIO

CIBOT; when research, university and the private sector unite efforts against cancer

The Translational Biomedicine and Oncology Research Consortium (CIBOT) is the product of an agreement between the VHIO, Novartis Pharmaceuticals, the University Hospital Vall d'Hebron and the Universitat Autonoma de Barcelona to create a flow of knowledge transfer. The work of CIBOT centers on access to tumor biobanks, for the identification and validation of therapeutic leads, strategies for selection of patients and the improved detection of the sensitivity of tumors to specific anticancer agents along with the mechanisms of resistance. During 2009 the consortium has developed two research projects.

Stand Up to Cancer - SU2C-International Dream Team

The VHIO is the only non-American center chosen to form part of the campaign Stand Up To Cancer-SU2C and it participates in the management of one of the research projects to discover the mechanisms to inactivate P13K in female cancers.

First licensing of a patent for the detection of a sub-type of breast cancer

For the first time the VHIO licensed a patent, jointly with the Fundació Institut de Recerca Vall d'Hebron (FIR-HUVH) and the Catalan Institution for Research and Advanced Studies (ICREA). The product patented will enable the development of a diagnostic kit to detect the mechanisms of resistance of HER2 positive breast tumors. VHIO and ICREA have also reached a second licensing agreement to develop any future diagnostic kits that may result from research in progress, which is supported by the Genoma España Foundation. Principal investigator: Dr. Joaquín Arribas Head of the VHIO Basic Research Program on Medical Oncology, Principal Investigator (PI) of the Growth Factor Laboratory and ICREA Professor.

Introduction



Tumor Biomarkers Team: PI Josep Villanueva, Olga Méndez, Laura Villarreal and Laura Córcoles



Genomics Cancer Pl Ana Vivancos

Josep Baselga appointed to the Board of Directors of the American Association of Cancer Research

The American Association of Cancer Research (AACR) appointed Dr. Josep Baselga to the Board of Directors for the next few years.

Dr. Joan Seoane receives the Banc de Sabadell Prize for Biomedical Research

The prize is awarded to young researchers with a career of excellence in the field of biomedicine.

Collaboration Agreement between the Fero Foundation and the VHIO

This agreement aims to define the future relationship between the two foundations and establish the terms and conditions for the financial backing which the FERO Foundation will provide for the VHIO.

Cancer Molecular Therapy Research Unit – "la Caixa"

A generous donation from the "La Caixa" Social Work of the "La Caixa" Foundation has made it possible to extend the Oncology Day Hospital to house the Cancer Molecular Therapy Unit (UITM). The new facilities will allow new studies on innovative drugs and therapeutic leads to be carried out to improve the pharmacological treatments for cancer and reduce their toxicity.

The construction work started in October 2009 and the new unit opened in June 2010.

Cellex Building

The Cellex Foundation will undertake the construction of a building to house the VHIO oncology research center. During 2009 the "Special Project" was passed by the City Council of Barcelona.

Modular Housing for Research (EMI)

The work for the new building of the Fundació Institut de Recerca de l'Hospital Universitari Vall d'Hebron (FIR-HUVH) started. The VHIO occupies five laboratories within the FIR-HUVH.

New Research Groups Start Work

The Tumor Biomarkers Group, led by Josep Villanueva, was set up in March 2009 with the principle objective of discovering new biomarkers to enable better diagnosis and monitoring of cancer treatments. The main task is to characterize samples from patients' tumors while also checking samples from unaffected individuals to identify significant differences and establish new molecular mechanisms for the detection and monitoring of cancer.

Also in 2009 a big step forward was taken with the creation of the Genomics Unit of the VHIO. Ana Vivancos directs the Cancer Genomics Group, whose main function is to sequence the genes involved in the tumors of each patient. Sequencing technology will allow for more accurate diagnostics. Introduction 10/11



The way forward

The VHIO teams are rigorously systematic in their daily work and apply accurately designed scientific protocols; this way they achieve results of a very high standard. They know that their purpose and work methods are rooted in the cure for cancer, they work fundamentally for patients.

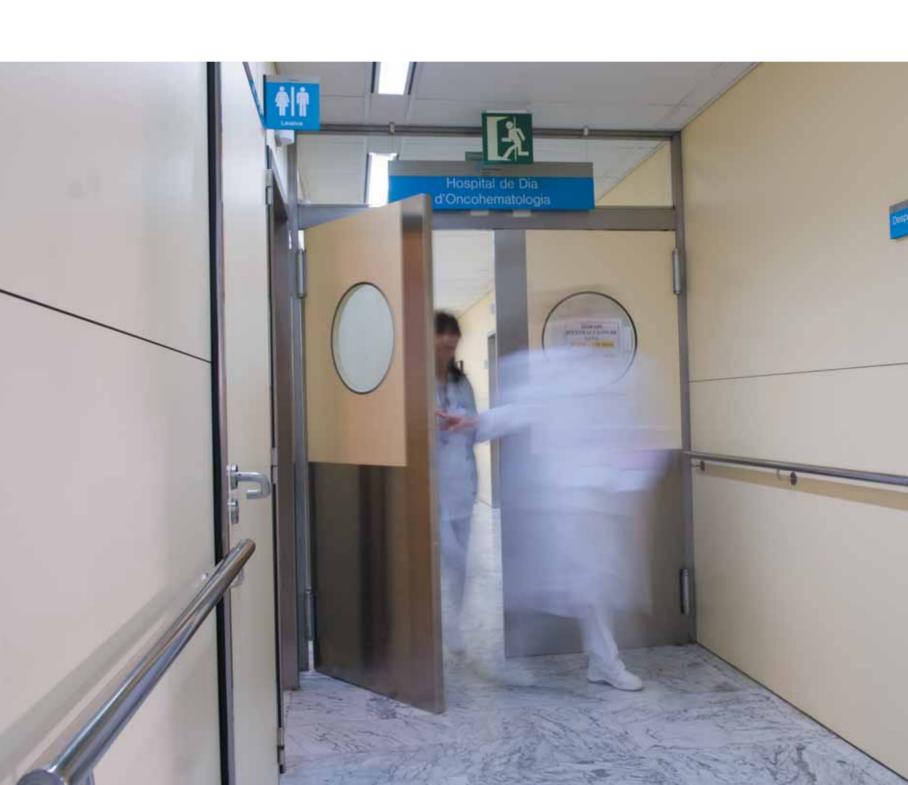
Cancer research has seen important advances in recent years. With the development of personalized therapies, the future of oncology will be the treatment of cancer case by case. In global terms, in the near future we will be able to avoid toxic treatments, early diagnosis will become the norm and surgical intervention will become more effective and less invasive. Great improvements will be made in radiotherapy and in general all treatments will be substantially improved.

In the future cancer will be curable and all the personnel of the VHIO will be proud to have invested their time and efforts, talent and daily work routines in contributing to reach this goal.

All quotes from speeches or publications by Dr. Josep Baselga, Director VHIO

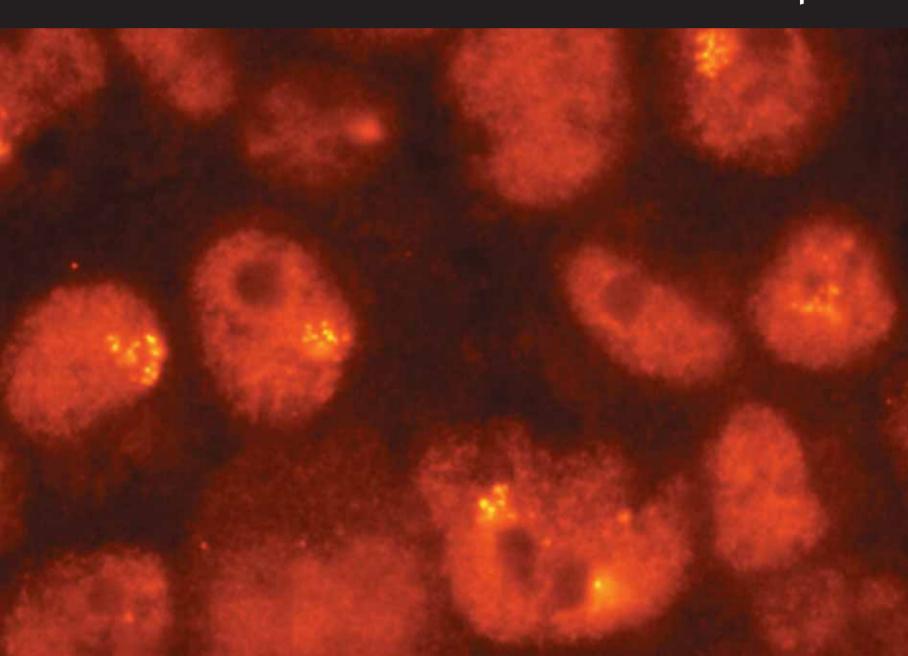


Prof. James D. Watson, Nobel laureate, and the VHIO Research Team: Maurizio Scaltriti, Hèctor García-Palmer, Joaquín Arribas, Francesc Canals, Josep Villanueva and J.A. Recio.

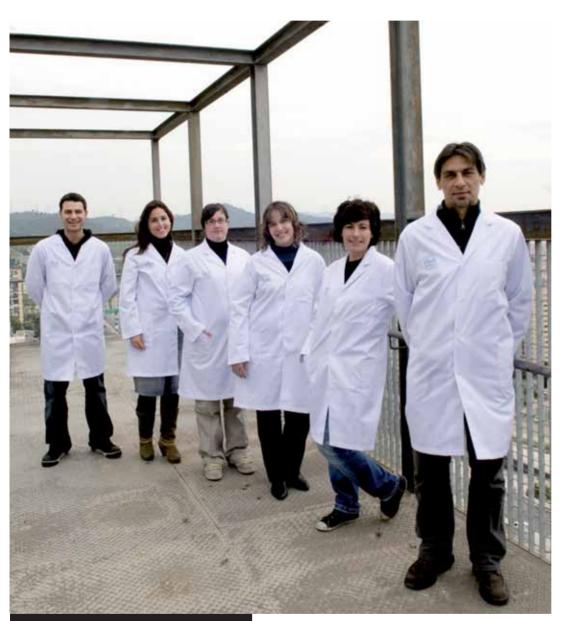


Research Groups and Clinical Support Services

Research Groups



Animal Models and Cancer Group



Juan Angel Recio

Pre-doctoral Fellows Pedro Andreu Pérez MS Rosaura Esteve Puig MS Marta López Fauqued MS

> *Technicians* Rosa Gil Judit Grueso Gragera

Strategic Goals

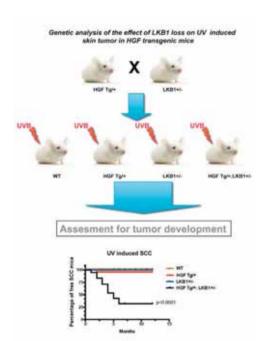
- 1 Role of LKB1 in tumor biology
- 2 Discovery of novel molecules involved in melanoma
- 3 Novel therapeutic strategies for melanoma treatment

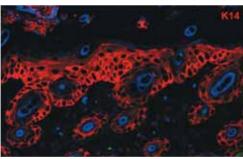
Achievements in 2009

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

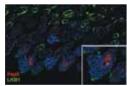
Our results indicated an important link between RAS pathway activation and the LKB1 kinase that belongs to the energy sensor pathway. Importantly, BRAF is mutated in 70% of melanomas. BRAF mutant melanoma cell lines showed constitutive levels of phosphorylated LKB1, indicating crosstalk between the RAS and LKB1 pathways and an unusual resistance to energy-stress conditions. Further investigations led us to discover that BRAF signaling was mediating the uncoupling of LKB1 and its downstream target AMPK by disconnecting the energy sensor pathway, thereby making these mutant cells resistant to low energy conditions. Importantly, the inhibition of BRAF signaling in combination with metabolic stress or activators of AMPK, leads the cells to apoptosis (Esteve-Puig et al. PLoS ONE (2009) 4(3): e4771).

We also assessed the in vitro and in vivo inhibition potential of the dual PI3K/MTOR inhibitor PI-103 and sorafenib, as single agents and in combination, in primary melanoma cell lines. Although PI-103 and sorafenib inhibited melanoma in vitro cell proliferation and viability, inhibition of the RAS pathway appeared to be more effective. The combination of the two agents in vitro showed a synergistic effect inhibiting RAS and PI3K pathways in a cell-line dependent manner. However, no cooperative effect was observed in blocking in vivo tumor growth in immunocompetent mice. Contrary to what was expected, the data indicate that PI-103 induced immunosuppression by inducing thymus atrophy and the upregulation of IL6, IL10 and VEGF, promoting in vivo tumor growth and inhibiting apoptosis.









Role of *LKB1* in UV induced DNA damage. Experimental approach to tests *LKB1* role in UV induced skin cancer. *LKB1* haploinsuficiency sensitizes to UVB induced skin cancer. Representative photographs of normal and pathological mouse skin after UVB irradiation.

Furthermore, in vitro studies examining the effects of the *PI3K/MTOR* inhibitor in tumorderived cell lines indicated that *PI-103* induced the activation of *STAT3* and the upregulation of the anti-apoptotic *BH3* family proteins *McL1*, *BcL2* and *BcLxL*, favoring the in vitro survival of melanoma cells treated with sorafenib. These data make an argument for investigating unexpected effects of rational drug combinations on immunocompetent animal models prior to conducting clinical studies (Lopez-Fauqued et al. (2009) Int. J. Cancer (126) 7, 1549-1561).

Objectives for 2010

LKB1 role in UVB-induced
 DNA damage response
 Our own results and the previous literature
 revealed the role for LKB1 as a tumor suppressor involved in cell cycle control, and transcription regulation. In view of this, we wanted to investigate the possible interaction of LKB1 with proteins involved in the cell cycle and in the response to DNA damage. We have discovered a novel LKB1 binding protein involved in the cell cycle and DNA damage responses. The aim is to elucidate the role of LKB1 in DNA damage responses in skin cancer and its mutational status in human tumors as a predictor of risk

 Protein arginine methylation and signal transduction

Through our proteomic screening, we revealed a novel regulation in signal transduction mediated by arginine methylation. Our data indicate that this post-translational modification is coordinated with phosphorylation to promote the appropriate biological response. This regulation is ligand-dependent and growth factor specific, adding a novel possible mechanism to explain how the activation of one pathway by different growth factors within the same system leads to a different biological response. We have identified the protein methyltransferase responsible for this modulation and the protein kinase activity regulated by this

enzyme. We are currently investigating the role of methylation reactions in different biological responses and the possible deregulation of this mechanism in cancer. We are also investigating the therapeutic capabilities of the methyl-inhibitor Methylthioadenosine (MTA) in melanoma treatment

Projects

Plo50227

Characterization of novel mechanisms of HGF signaling in melanoma: Bring in to play the HGF mouse model for malignant melanoma. Funded by: Spanish Health Department (Instituto de Salud Carlos III) (FIS) Duration: 01/01/2006 to 01/01/2009.

Plo80653

Role of LKB1 in the response to growth factors and in the development and progression of melanoma

Funded by: Spanish Health Department (Instituto de Salud Carlos III) (FIS)
Duration: 01/01/2009 to 01/01/2011.

Fundacion MUTUA MADRILEÑA (FMM) Role of LKB1 in malignant melanoma Funded by: Mutua Madrileña Foundation Duration: 04/01/2007 to 04/01/2009.

Publications

Esteve-Puig R, Canals F, Colomé N, Merlino G, Recio JA. Uncoupling of the *LKB1-AMPK* alpha energy sensor pathway by growth factors and oncogenic *BRAF*. PloS One. 2009;4(3):e4771. Epub 2009 Mar 10.

López-Fauqued M, Hernandez J, Pujol A, Fernandez N and **Recio JA**. The dual *PI3K/mTOR* inhibitor (*PI-103*) promotes immunosupression, in vivo tumor growth and increases survival of sorafenib treated melanoma cells. Int J Cancer. 2009;(126)7:1549-61.

Animal Models and Cancer Group

Principal Investigator
Juan Angel Recio

Current positions

 Head of the Animal Models and Cancer Program

Academic Qualifications

- Degree in Biology from the Complutense University of Madrid, 1989.
- · Master's Degree in Biotechnology from the Complutense University of Madrid, 1989-1991.
- Doctorate in Cell Biology, Department of Morphology and Histology, Autonomous University of Madrid, 1997.



Areas of Research

- Identification of novel molecules involved in melanoma tumor development
- LKB1 role in UVB-induced DNA damage response
- · LKB1 role in skin tumor biology
- · Protein arginine methylation and signal transduction
- Preclinical study using Methylthioadenosine (MTA) for melanoma treatment

Prizes and Scholarships

· National Institutes of Health, Bethesda, USA (1997-1999)

Most relevant scientific publications

Uncoupling of the LKB1-AMPK ≈ Energy Sensor Pathway by Growth Factors and Oncogenic BRAF^{V600E}. Esteve-Puig R, Canals F, Colomé N, Merlino G, Juan A. Recio. PLoS ONE (2009) 4(3): e4771. doi:10.1371/journal.pone.000477.

The dual PI3K/MTOR inhibitor (PI-103) promotes immunosupression, in vivo tumor growth and increases survival of sorafenib treated melanoma cells. (2009) Marta López-Fauqued, Javier Hernandez, Anna Pujol, Nohelia Fernandez and Juan A. Recio. Int J Cancer (126) 71549-1561.

INK4A/ARF deficiency promotes UV-induced melanomagenesis. Juan A. Recio, Frances Noonan, Hisashi Takayama, Miriam R Anver, Paul Duray, Walter L. Lush, Gerd Linder, Edward C. de Fabo, Ronald A DePinho and Glenn Merlino (2002) Cancer Res. 62, 6724-6730.

Neonatal sunburn and melanoma in Mice. Frances P. Noonan, Juan A. Recio, Hisashi Takayama, Paul Duray, Miriam R. Anver, Walter L. Rush, Edward C. de Fabo, and Glenn Merlino (2001). Nature: 413:217-272.



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Strategic Goals

- 1 Optimization of the treatment of breast cancer with the incorporation of new drugs aimed at biological targets
- 2 Optimization of multidisciplinary treatment in patients with stage I-III breast cancer, incorporating studies with translational objectives.
- 3 Participation in the development of new chemotherapy drugs
- 4 Incorporation of proteomics and genomics platforms and platforms of circulating tumor cells in breast cancer studies

Achievements in 2009

In 2009, we played an active role in the development of several phase I, II and III clinical trials, from design to execution.

Biological therapies: Our group has been actively involved in developing several drugs aimed at different molecular targets, especially *HER2*, *PI3K/MTOR*, antiangiogenic agents, src and *IGFR*. In addition to the studies published this year, our group has developed its own important studies that are pioneers in their field, such as the double inhibition of *MTOR* and *IGFR*, and the combination of tyrosine kinase molecules with chemotherapy, with very promising results.

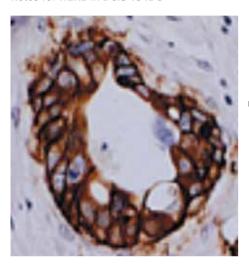
New chemotherapy agents: The results obtained with new chemotherapy drugs, which we have played an essential part in developing, has led to the leadership of our group in the fight against breast cancer using chemotherapy. As a result of this effort, this year the results of a new chemotherapy drug, eribulin, was presented at *ASCO*; this is the first drug to show increased survival with a single therapeutic agent in patients previously treated with taxanes and anthracyclines.

Optimization of studies. Our group is also involved in optimizing clinical studies to achieve positive objectives. The implementation of statistical tools aimed at clinical practice, the optimization of biological sampling and the selection of patients with better possibilities of showing positive results in phase I studies are a good example of this.

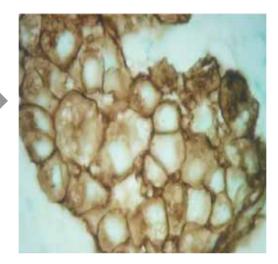
Participation in complex studies. One of the priorities of our group is carrying out complex studies to search for pharmacodynamic targets. This type of study requires both a sophisticated research team and an optimum interrelationship between all the departments responsible for patient care (multidisciplinary teams). This collaboration was optimized in 2009 from the perspective of both patient care and research.

Breast Cancer Group

Roles for HER2 in DCIS vs IDC



Ductal carcinoma in situ (DCIS) (50% amplify HER2)



Invasive ductal carcinoma (IDC) (22% amplify *HER2*)

Objectives for 2010

- · Implement sequencing of tumors in patients with breast cancer
- Study the efficacy of inhibitors of the *PI3K/mTOR* pathway and their relationship with the mutational state
- Continue investigating the factors involved in resistance to anti-HER2 treatments and strategies aimed at reversing them
- Study the efficacy of PARP inhibitors in breast cancer
- Implement therapeutic strategies and clinical trials differentiated by tumor subtype

Clinical Trials

CA180-004 Phase I Study of Dasatinib (BMS-354825) and Capecitabine for Advanced Breast Cancer

CHSP990A2101 A Phase I Dose Escalation, Multi-center, Open-label Study of HSP990 Administered Orally in Adult Patients With Advanced Solid Malignancies

3144A1-2206-WW A Phase 1/2, Open-label Study of Neratinib (*HKI-272*) in Combination With Capecitabine in Subjects With Solid Tumors and ErbB-2 Positive Metastatic or Locally Advanced Breast Cancer

Do102Co0003 A Phase I/II Multi-centre Study of *AZD8931* in Combination With Weekly Paclitaxel to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy in Patients With Advanced Solid Tumours and in a Selected Population With Low *HER2*-expressing Locally Recurrent and/or Metastatic Breast Cancer

Do81oCoo21 (fase I) A Phase I/II, Open Label, Multi-centre Study of *AZD2281* Administered Orally in Combination with Cisplatin, to Assess the Safety and Tolerability in Patients with Advanced Solid Tumours, and to Assess Efficacy in the Neoadjuvant Setting for Patients with Triple Negative Breast Cancer

MK0646-013 Study to Establish Proof-of-Biology for *MK0646* in Breast Cancer

MK-8669/004 A Phase I Study of Ridaforolimus (*MK8669*) and *MK0646* in Patients With Advanced Cancer

CRADoo1J2101 A Phase Ib/II Study Investigating the Combination of Everolimus With Trastuzumab and Paclitaxel in Patients With *HER2*-overexpressing Metastatic Breast Cancer

CAUY922A2101 A Phase I Dose Escalation, Multicenter, Open-label Study of *AUY922* Administered IV on a Once Weekly Schedule in Adult Patients With Advanced Solid Malignancies Including Phase II Expansion Arms in Patients With Either *HER2* Positive or ER Positive Locally Advanced or Metastatic Breast Cancer.

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

EMR 200027-051 Randomized Phase II Trial With Cetuximab and Cisplatin in the Treatment of ERnegative, PgR-negative, *HER2*-negative Metastatic Breast Carcinoma ("Basal Like")

SOLTIO701 A Phase II, Open-Label, Multicenter Clinical Trial of Pegylated Liposomal Doxorubicin (Caelyx®) as Primary Treatment for Patients With Breast Cancer and a History of Heart Disease or Age Over 65 Years.

BRCA trial A Randomized Phase II Pilot Trial of Carboplatin Compared to Docetaxel for Patients With Metastatic Genetic Breast Cancer [BRCA Trial

BO22495 A Phase Ib/II, Open-Label Study of the Safety, Tolerability, and Efficacy of Trastuzumab-*MCC-DM1* in Combination With Pertuzumab Administered Intravenously to Patients With *HER2*-Positive Locally Advanced or Metastatic Breast Cancer Who Have Previously Received Trastuzumab

IV-ERT-BC-o3 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

CTKI258A2202 A Multi-center, Open Label Phase II Trial of *TKI258* in *FGFR1* Amplified and Non-amplified Metastatic or Advanced *HER2* Negative Breast Cancer

BO22280 A Study of Pertuzumab in Combination With Herceptin and Chemotherapy in Patients With *HER2*-Positive Breast Cancer

IPI-504-07 A Phase 2 Multicenter Study Evaluating the Efficacy and Safety of IPI-504 in Combination With Trastuzumab in Patients With Pretreated, Locally Advanced or Metastatic Human Epidermal Growth Factor Receptor 2 (HER2) Positive Breast Cancer

3160A6-2206-WW (Fase I) A Phase 1 Study of *PKI-587* Administered as an Intravenous Infusion to Subjects With Solid Tumors

CA180-261 A Randomized, Double-Blind, Multi-Center Phase II Trial of Exemestane (Aromasin®) Plus Dasatinib Versus Exemestane Plus Placebo in Advanced ER+ Breast Cancer After Disease Progression on a Non-Steroidal Aromatase Inhibitor

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

CA163100 A Randomized Phase II Biomarker Neoadjuvant Study of Sequential AC Followed by Ixabepilone Compared to Sequential AC Followed by Paclitaxel in Women with Early Stage Breast Cancer Not Overexpressing *HER-2* and Estrogen Receptors

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

Breast Cancer Group

VEG108838 A Randomized, Multicenter, Phase III Study Comparing the Combination of Pazopanib and Lapatinib Versus Lapatinib Monotherapy in Patients With *ERBB2* Overexpressing Inflammatory Breast Cancer

EGF111438 Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in *ERBB2* (*HER2*) Positive Metastatic Breast Cancer

BO21977 An Open-Label Study of Trastuzumab-MCC-DM1 (T-DM1) vs. Capecitabine + Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer (EMILIA)

Looo7oIN3o5BO A phase III trial of vinflunine + capecitabine versus capecitabine alone in patients with advanced breast cancer previously treated with or resistant to an anthracycline and who are taxane resistant

Looo7oIN308BO A phase III trial of IV vinflunine versus an alkylating agent in patients with metastatic breast cancer previously treated with or resistant to an anthracycline, a taxane, an antimetabolite and a vinca-alkaloid

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

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

NEOALTTO A randomised, multicentre, openlabel, phase III study of neoadjuvant lapatinib, trastuzumab, and their combination plus paclitaxel in women with *HER2/ERBB2* positive primary breast cancer

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

SOFT Suppression of Ovarian Function Plus Either Tamoxifen or Exemestane Compared With Tamoxifen Alone in Treating Premenopausal Women With Hormone-Responsive Breast Cancer.

E7389-Gooo-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

MINDACT 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 Breast Cancer With 0 to 3 Positive Nodes

Publications

Cortés J, Saura C, Atzori M. *Risk of venous thromboembolism with bevacizumab in cancer patients.* JAMA 2009; 301:1434-5;

Cortés J, Baselga J. How to Treat Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Amplified Breast Cancer. J Clin Oncol (in press).

Cortes J, DiCosimo S, Climent MA, Cortés-Funes H, Lluch A, Gascón P, Mayordomo JI, Gil M, Benavides M, Cirera L, Ojeda B, Rodríguez CA, Trigo JM, Vazquez J, Regueiro P, Dorado JF, Baselga J; Spanish Breast Cancer Cooperative Group SOLTI. Nonpegylated liposomal doxorubicin (TLC-D99), paclitaxel, and trastuzumab in HER-2-overexpressing breast cancer: a multicenter phase I/II study. Clin Cancer Res. 2009 Jan 1;15(1):307-14.

Di Cosimo D. *Controversies in breast cancer:* the mammalian target of rapamycin as a target for breast cancer therapy. Breast Cancer Res. 2009;11 Suppl 3:S25.

Martín M, González Palacions F, Cortés J, de la Haba J, Schneider J. Prognostic and predictive factors and genetic analysis of early breast cancer. Clin Transl Oncol. 2009 Oct; 11 (10): 634-42.

Principal Investigator Javier Cortés

Current positions

- · Deputy Director of the Breast Cancer Program
- · Head of the Melanoma Program
- Specialist physician at the Oncology Department of Vall d'Hebron University Hospital
- Tutor of residents in Medical Oncology of Vall d'Hebron Hospital
- Member of the Board of Directors and Scientific Committee of the SOLTI Cooperative Group
- Member of the Scientific Committee of the International Congress on Anti-Cancer Treatment (ICACT)



Academic Qualifications

- · Degree in Medicine and Surgery, 1996
- Doctorate in Medicine and Surgery from the University of Navarra, 2002

Areas of Research

- · New microtubules in breast cancer
- · New forms and contents in HER2+ breast cancer
- Integration of antiangiogenic agents in current breast cancer treatment
- · New targeted agents in breast cancer

Prizes and Scholarships

· Scholarship from ASCO, AACR and from EORTC

Most relevant scientific publications

Nonpegylated Liposomal Doxorubicin (TLC-D99), Paclitaxel, and Trastuzumab in HER-2-Overexpressing Breast Cancer: A Multicenter Phase I/II Study

Cortes J, DiCosimo S, Climent MA, et al. Clinical Cancer Research, Volume: 15, Issue: 1, Pages: 307-314, Published: JAN 1 2009

How to Treat Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Amplified Breast Cancer Cortes J, Baselga J

Journal of Clinical Oncology, Volume: 27, Issue: 33, Pages: 5492-5494, Nov 20 2009

Experimental Therapeutics Group



José Baselga

Staff Scientist Maurizio Scaltriti PhD

Medical Oncologists Josep Tabernero MD Jordi Rodon MD Post-doctoral Fellows Violeta Serra PhD Pieter Eichhorn PhD Yasir Ibrahim PhD Celina Garcia PhD

Visiting Scholars
Michelangelo Russillo MD

Clinical Fellow Ben Markman MD

Technicians Marta Guzman Olga Rodriguez Magui Gili Pilar Anton

Strategic Goals

- 1 Discovering novel mechanisms of anti-*HER2* therapy resistance
- 2 Identifying mechanisms of resistance to PI3K/AKT/MTOR inhibitors
- 3 Hypothesis-based testing of new therapeutic strategies

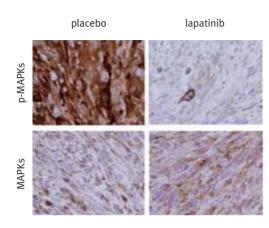
Achievements in 2009

In 2009, we identified cyclin E amplification/overexpression as a novel mechanism of resistance to the anti-*HER2* antibody trastuzumab. Preclinical data indicates that *CDK2* inhibition may be a successful therapeutic strategy for cyclin E overexpressing breast cancer patients.

Another important achievement was the discovery that inhibition of the *PI3K* pathway in *HER2* positive cells results in activation of the *ERK* pathway and its downstream effectors. This effect is reverted by both *MEK1/2* inhibition and *HER2* blockade with tyrosine kinase inhibitors. Finally, we tested several therapeutic approaches to revert/prevent anti-*HER2* therapy resistance. We proved that, by preventing *HER2* degradation, lapatinib induces the formation of inactive *HER2* dimers at the cell surface, which in turn leads to increased trastuzumab binding and a greater trastuzumab-mediated immune response.

Another efficacious strategy may be the use of *Hsp90* inhibitors. In fact, we found that *Hsp90* inhibitors, administered alone or in combination with trastuzumab, effectively inhibit *in vitro* proliferation and tumor growth of both parental and trastuzumab resistant cells.

Moreover, we found that either lapatinib or *Hsp90* inhibitors are active in *P95HER2*-expressing breast cancer tumors.



Lapatinib inhibits MAPK phosphorylation in *P95HER2* positive cells

Objectives for 2010

- Translate to clinical practice the use of *CDK2* and *Hsp90* inhibitors
- · Study the efficacy of novel Aκτ/MTOR inhibitors
- Predict genes/pathways responsible for resistance to PI3K/Aκτ/MTOR inhibitors
- Study new therapeutic combinations such as PI3K/AKT/MTOR inhibitors with MEK inhibitors or MTOR inhibitors with anti-IGF-IR agents
- Develop preclinical models based on tumor explants in immunocompromised mice

Projects

Overcoming Resistance to anti-HER2 therapy

Duration: 2010-2014 Funded by: ERC

Estrategias de Reversión de la Resistencia

a Terapias Anti-Her2 Duration: 2010-2014 Funded by: ISCIII

Targeting PI3K in Women's Cancer

Duration: 2009-2012 Funded by: AACR

Overcoming resistance to anti-HER2 therapy with PI3K inhibitors. Anticipating emerging resistance

to PI3K pathway inhibition Duration: 2009-2012 Funded by: Novartis-CIBOT

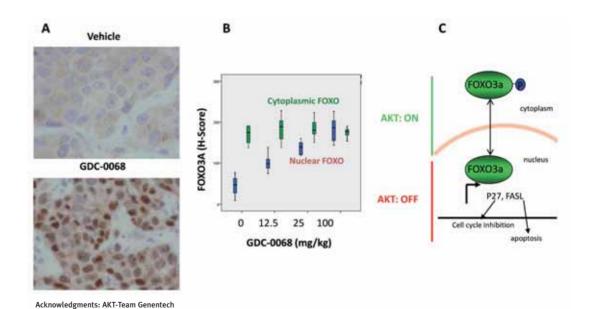


Figure 1. AKT inhibition in HER2 positive xenografts results in FOXO3a nuclear relocalization. A. Immunohistochemistryof BT474-trastuzumab resistant xenografts treated with either vehicle or 100mg/kg of GDC-0068. B. The cytoplasmicand nuclear staining of FOXO3a was quantified by H-Score in the same xenograftstreated with increasing doses of GDC-0068. C. AKT mediated phosphorylation of FOXO3a regulates its nuclear translocation and its activity targeting the transcription of genes associated with cell cycle inhibition and apoptosis.

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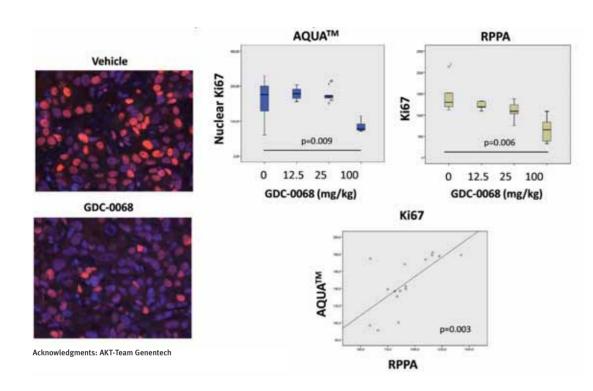


Figure 2. Comparison of two different platforms to quantify the proliferation biomarker Ki67 in tumor xenografts treated with an AKT inhibitor. A. Reduced Ki67 immunofluorescentstaining in BT474-trastuzumab resistant xenografts treated with the AKT inhibitor GDC-0068 (100mg/kg). B. Quantification by AQUA™ of the same xenografts treated with increasing doses of the inhibitor. C. Similar data was obtained by reverse phase protein array (RPPA) and quantified.

D. Correlation between AQUA™ and RPPA quantifications of the proliferation biomarker Ki67.

Towards Personalized Medicine in Cancer Acquisition of a Sequenom MassARRAY Platform to match the right patient with the right anti-cancer therapy.

Duration: 2009-2010

Novel Cancer Therapies to overcome resistance to anti-HER2 and PI3ĸ inhibitors in breast can-

cer

Duration: 2009-2010 Funded by: BCRF

Overcoming resistance to Anti-HER2 and PI3K inhibitors therapies in breast cancer

Duration: 2008-2009 Funded by: BCRF Truncated intracelular HER2 C-Terminal fragments and trastuzumab resistance

Duration: 2007-2009 Funded by: ISCIII

Ajuts de Suport a la Recerca. Grup de Recerca Consolidat Duration: 2009-2014

Funded by: AGAUR

Red Temática de Investigación Cooperativa del Cancer Duration: 2007-2011 Funded by: ISCIII

Clinical Trials

H9H-MC-JBAH Phase 1 Dose-Escalation Study of *LY2157299* in Patients with Recurrent Gliobastoma Multiforme.

MKo646-013 A Study to Establish Proof-of-Biology for *MK0646* in Breast Cancer

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

20070411 A Phase 1b/2 Open Label, Dose Escalation Study of *AMG 655* in Combination With *AMG 479* in Subjects With Advanced, Refractory Solid Tumors

26854165CAN1001 A phase I study to Determinate the safety, Pharmacology and Pharmacodynamics of *JNJ-26854165* in Subjects with Advanced Satge and/or refractory Solid Tumors or Lymphoma.

XL765-001 A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of *XL765* Administered Orally Daily to Subjects With Solid Tumors

MK0646-001 An Open-Label, Dose Escalation Phase I Trial of *MK0646* Given as a Weekly, Every Other Week, or Every Three Week Infusion in Patients With Advanced Solid Tumors and Multiple Myeloma

XL147-001 A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of *XL147* Administered Orally Daily to Subjects With Solid Tumors or Lymphoma

CBEZ235A2101 A Phase I/II, Multi-center, Openlabel Study of *BEZ235*, Administered Orally on a Continuous Daily Dosing Schedule in Adult Patients With Advanced Solid Malignancies Including Patients With Advanced Breast Cancer

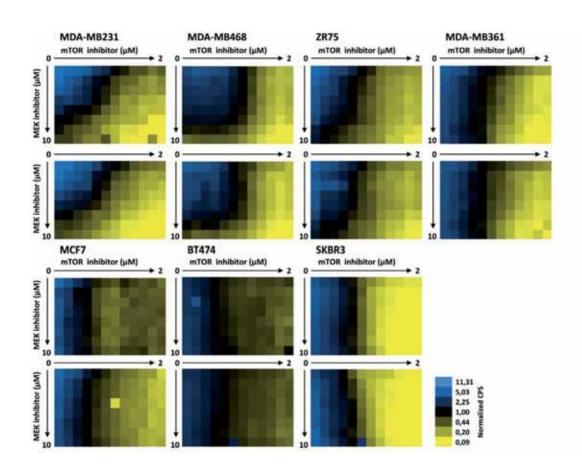


Figure 3. Inhibition of viability by a mTOR inhibitor and a MEK inhibitor in a panel of breast cancer cell lines. Quantification of cell viability with the CellTiterGlo $^{\circ}$ Luminescent Cell Viability Assay (Promega Biotech) after 6 days of treatment with increasing dosis of a mTOR inhibitor (0-2 μ M) and/or increasing dosis of aMEK inhibitor (010 μ M). The lower panel is an independent duplicate of the experiment. Results are presented as normalized CPS.

CLDE225X2101 A Phase I, Multicenter, Open-label, Dose-escalation Study of Oral *LDE225* in Patients With Advanced Solid Tumors

CBKM120X2101 A Phase IA, Multicenter, Open-label Dose Escalation Study of *BKM120*, Administered Orally in Adult Patients With Advanced Solid Malignancies

Publications

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, 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. 2009 Jun 1;27(16):2630-7.

Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer. 2009 Jul;9(7):463-75.

Baselga J, Zambetti M, Llombart-Cussac A, Manikhas G, Kubista E, Steger G, Biakhov M, Khasanov R, Machson A, Tjulandin S, Ludwig H, Verrill M, Ciruelos E, Egyhazi S, Xu L, Zerba K, Lee H, Clark E, Galbraith S. *Phase II genomics study of ixabepilone as neoadjuvant treatment for breast cancer.* J Clin Oncol. 2009 Feb 1;27(4):526-34.

Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, Raben D, **Baselga J**, Spencer SA, Zhu J, Youssoufian H, Rowinsky EK, Ang KK. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol. 2009 Nov 6.

Cedrés S, Prat A, Martínez P, Pallisa E, Sala G, Andreu J, del Campo JM, Quispe I, **Baselga J**, Felip E. *Clinical surrogate markers of survival in advanced non-small cell lung cancer (NSCLC) patients treated with second-third line erlotinib*. Lung Cancer. 2009 Nov; 66(2):257-61.

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Ciruelos EM, Cortés J, Cortés-Funes H, Mayordomo JL, Bermejo B, Ojeda B, García E, Rodríguez CA, Muñoz M, Gómez P, Manso L, Andrés R, Lluch A, Saura C, Mendiola C, **Baselga** J. *Gemcitabine and capecitabine in previously anthracycline-treated metastatic breast cancer: a multicenter phase II study (SOLTI 0301 trial)*. Ann Oncol. 2009 Nov 25.

Experimental Therapeutics Group

Cortes J, Baselga J. How to treat hormone receptor positive, HER2 amplified breast cancer? J Clin Oncol. 2009 Nov 20;27(33):5492-4.

Di Cosimo S, Baselga J. Phosphoinositide 3kinase mutations in breast cancer: a "good" activating mutation? Clin Cancer Res. 2009 Aug 15;15(16):5017-9.

Ellis MJ, Lin L, Crowder R, Tao Y, Hoog J, Snider J, Davies S, Deschryver K, Evans DB, Steinseifer J, Bandaru R, Liu W, Gardner H, Semiglazov V, Watson M, Hunt K, Olson J, Baselga J. Phosphatidyl-inositol-3-kinase Alpha catalytic subunit kinase domain mutations impart a favorable prognosis on estrogen receptor positive breast cancer through a mechanism that is independent of responsiveness to endocrine treatment. Breast Cancer Res Treat. 2009 Oct 21.

Garcia-Castillo J, Pedersen K, Angelini PD, Bech-Serra JJ, Colome N, Cunningham MP, Parra Palau JL, Canals F, Baselga J, Arribas J. HER2 carboxy terminal fragments regulate cell migration and cortactin phosphorylation. J Biol Chem. 2009 Sep 11;284(37):25302-13.

Gianni L, Baselga J, Eiermann W, Guillem Porta V, Semiglazov V, Lluch A, Zambetti M, Sabadell D, Raab G, Llombart Cussac A, Bozhok A, Martinez-Agullo A, Greco M, Byakhov M, Lopez Lopez J J, Mansutti M, Valagussa P, Bonadonna G. Addition of Paclitaxel to Doxorubicin Followed by Cyclophosphamide, Methotrexate and Fluorouracil, as Adjuvant or Primary Systemic Therapy: Results of a Randomized Phase III European Cooperative Trial in Operable Breast Cancer (ECTO). J Clin Oncol. 2009 May 20;27(15):2474-81.

Lennon S, Barton C, Banken L, Gianni L, Marty M, Baselga J, Leyland-Jones B. The Utility of Serum HER2 Extracellular Domain (ECD) Assessment in Clinical Decision Making: Pooled Analysis of Four Trials of Trastuzumab in Metastatic Breast Cancer. J Clin Oncol. 2009 Apr 1;27(10):1685-93.

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Markman B, Atzori F, Pérez-García J, Tabernero J, Baselga J. Status of PI3K inhibition and biomarker development in cancer therapeutics. Ann Oncol. 2009 Aug 27.

Mittendorf EA, Wu Y, Scaltriti M, Meric-Bernstam F, Hunt KK, Dawood S, Esteva FJ, Buzdar AU, Chen H, Eksambi S, Hortobagyi GN, Baselga J, Gonzalez-Angulo AM. Loss of HER2 amplification following trastuzumab-based neoadjuvant systemic therapy and survival outcomes. Clin Cancer Res. 2009 Dec 1;15(23):7381-8. Epub 2009 Nov 17. PubMed PMID: 19920100; PubMed Central PMCID: PMC2788123.

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Pedersen K, Angelini PD, Laos S, Bach-Faig A, Cunningham MP, Ferrer-Ramón C, Luque-García A, García-Castillo J, Parra-Palau JL, Scaltriti M, Ramón y Cajal S, Baselga J, Arribas J. A naturally occurring HER2 carboxy-terminal fragment promotes mammary tumor growth and metastasis. Mol Cell Biol. 2009 Jun;29(12):3319-31. Epub 2009 Apr 13. PubMed PMID: 19364815; PubMed Central PMCID: PMC2698729.

Peñuelas S, Anido J, Prieto-Sánchez RM, Folch G, Barba I, Cuartas I, García-Dorado D, Poca MA, Sahuquillo J, Baselga J, Seoane J. TGFß increases glioma-initiating cell self-renewal through the induction of LIF in human glioblastoma. Cancer Cell. 2009 Apr 7;15(4):315-27.

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Scaltriti M, Verma C, Guzman M, Jimenez J, Parra JL, Pedersen K, Smith DJ, Landolfi S, Ramon 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. 2009 Feb 12;28(6):803-14. Epub 2008 Dec 8. PubMed PMID: 19060928.

Tabernero J, Ciardiello F, Rivera F, Rodriguez-Braun E, Ramos FJ, Martinelli E, Vega-Villegas ME, Roselló S, Liebscher S, Kisker O, Macarulla T, Baselga J, Cervantes A. Cetuximab administered once every second week to patients with metastatic colorectal cancer: a two-part pharmacokinetic/pharmacodynamic phase I dose-escalation study. Ann Oncol. 2009 Nov 25.

Principal Investigator
José Baselga



Current positions

- Director of the Vall d'Hebron Institute of Oncology (VHIO)
- Head of the Experimental Therapeutics Program
- Head of the Oncology Department of Vall d'Hebron University Hospital, Barcelona
- Chair of Medicine at Universitat Autònoma de Barcelona (UAB)
- · Chairman of the European Society for Medical Oncology (ESMO), 2008-2009.
- Member of the editorial board of the following journals: Cancer Cell, Journal of Clinical Oncology, Annals of Oncology, Clinical Cancer Research
- Member of the board of directors of the American Society of Clinical Oncology
- Permanent member of the Scientific Council of the American Association for Cancer Research (AACR) and of the Ludwig Cancer Institute

Academic Qualifications

- · Chair of Medicine (2008), UAB
- · Doctorate in Medicine and Surgery, 1992
- Degree in Medicine from the Autonomous University of Barcelona, 1982

Areas of Research

- · Promoter of research into new treatments for cancer.
- Study of new molecular targets and research on molecular therapies to develop new, more efficient and less toxic treatments.
- Development of initial-stage clinical trials with therapies aimed at growth-factor receptors and intracellular-pathway signaling molecules

Prizes and Scholarships

- Elected member of the American Society for Clinical Investigation
- Distinguished Alumnus of the Memorial Sloan-Kettering Cancer Center
- Rosenthal Award of the American Association for Cancer Research
- · Jaime I Prize in Medical Research
- · Induction into the Civil Order of Health Care in the category of Merit with Plaque in Spain.

Most relevant scientific publications

J Clin Oncol, (1996)14 (3): 737-44. F.I.: 17.157 Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. Baselga J, Tripathy D, Mendelsohn J, Baughman S, Benz CC, Dantis L, Sklarin NT, Seidman AD, Hudis CA, Moore J, Rosen PP, Twaddell T, Henderson IC, Norton L

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J Clin Oncol, (2003)21 (12): 2237-46. F.I.: 17.157 Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, Nishiwaki Y, Vansteenkiste J, Kudoh S, Rischin D, Eek R, Horai T, Noda K, Takata I, Smit E, Averbuch S, Macleod A, Feyereislova A, Dong RP, Baselga J.

J Natl Cancer Inst. 2007 Apr 18; 99 (8):628-38 F.l.: 14.933. Expression of p95HER-2, a Truncated Form of the HER-2 Receptor, and Response to Anti-HER-2 Therapies in Breast Cancer.

Scaltriti M, Rojo F, Ocaña A, Anido J, Guzman M, Cortes J, di Cosimo S, Matias-Guiu X, Ramon y Cajal S, Arribas J, Baselga J.

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Neoadjuvant chemotherapy with Trastuzumab
followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with
HER2-positive locally advanced breast cancer
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Gianni L, Eiermann W, Semiglazov V, Manikhas A,
Lluch A, Tjulandin S, Zambetti M, Vazquez F,
Byakhow M, Lichinitser M, Climent MA, Ciruelos
E, Ojeda B, Mansutti M, Bozhok A, Baronio R,
Feyereislova A, Barton C, Valagussa P, Baselga J.

Gastrointestinal Tumors Group



Josep Tabernero

Medical Oncologists
Maria Alsina MD
Irene Braña MD
Jaume Capdevila MD
Maria Elena Elez MD
Teresa Macarulla MD
Manuel Ruiz MD

Strategic Goals

- 1 Clinical research with more translational endpoints
- 2 Early clinical research with innovative targets
- 3 Collaboration with International Groups for translational research within the context of EUFP7 and/or IMI calls but also in other settings
- 4 Collaboration with the Proteomics, Genomics, Tumor Stem Cells and Circulating Tumor Cells Groups at VHIO

Achievements in 2009

In 2009, we carried out basic research in collaboration with the Cell Signaling and Cancer Laboratory of the VHIO, and with other international research groups: The Weizman Institute, Rehovot, Israel; The Broad Institute, Cambridge, MA, US; University of Michigan, Ann Arbor, MI, US; and University Hospital Gasthuisberg, Leuven, Belgium). We have provided the rationale for several research studies, collecting clinical samples for validation of experimental endpoints and the discussion and manuscripts for these studies. We are also collaborating with several international institutions on projects partially funded by the European Union Framework Project 6.

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

Molecular Markers in Gastrointestinal Malignancies: The broad objective of this research project is devoted to improving the knowledge of prognostic and predictive factors for response and efficacy with targeted agents in the different gastrointestinal malignancies. In this regard, this research activity has contributed to narrowing the targeted population of patients by identifying mechanisms of resistance (either primary or secondary) and there by increasing the cost-efficacy ratio.

Clinical research: Our patients are enrolled in clinical trials devoted to specific malignancies—such as colorectal, gastric, pancreatic and esophageal cancer—with the objective of demonstrating improvements in the care of these diseases (the majority are phase II and phase III clinical trials). We have designed several investi-

gator-initiated clinical trials trying to answer this very relevant question. We have participated and contributed to the design of many clinical trials many of them developed in the context of national and international cooperative groups and some sponsored directly by pharmaceutical companies. In this regard, our group has pioneered the consecution of clinical trials that have leaded to the approval by the European Agency (EMEA) of targeted drugs. The most renowned are the case of cetuximab and panitumumab in colorectal cancer for the particular population of KRAS-wild type tumors and trastuzumab in gastric and gastroesophageal cancer with HER-2/neu overexpression.

Objectives for 2010

Clinical research: The development plans for the near future in the Gastrointestinal Tumors
Program consider a as a key feature the integration of more translational endpoints in our clinical research. In this regard the group is participating in clinical trials mainly being carried out by collaborative groups (including the EORTC, the European Gastrointestinal Consortium and preliminary collaborations with US NCI-sponsored groups). The ultimate goal of this approach is to develop new strategies that could help in delimiting which populations of patients would benefit more from new therapeutic strategies with in the vision of "personalized medicine".

Early Clinical Research: The development plans for the next 3-5 years in this setting include preclinical and clinical development of new drugs targeting different cancer properties.

- a.- Growth signals, including receptors and downstream effectors: EGFR FAMILY, HGF/cMET FGFR, PI3K-AKT-MTOR
- pathway, Ras-Raf-MEK-MAPK pathway, dual PI3K and MAPK pathway inhibition.
- b.- Apoptotic signaling: *HDM2* (*MDM2*) inhibition
- c.- Angiogenesis inhibitors: VEGFR pathway inhibition

Molecular Markers in Gastrointestinal Malignancies: Our main achievement is this area is the set-up of European Consortium leaded by University Hospital Gasthuisberg in Leuven, Belgium and our institution to integrate different platforms for the development of prognostic and predictive biomarkers. This approach includes gene expression signatures as well that ultimately may allow us to define different populations of patients within each tumor type. This population may have different molecular characteristics that could be treated with different therapeutic strategies. In this setting we have applied to different EU calls for the continuation of this Consortium:

- EUFP7 Health 2010 call
- IMI call. We are applying under different Consortiums to two IMI Efficacy Pillars, Oncology – Molecular Biomarkers and Oncology
- Imaging Biomarkers

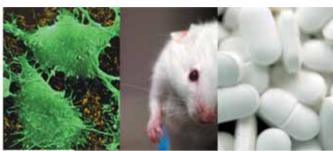
Basic Research in collaboration with the Cell Signaling and Cancer Laboratory of the VHIO, as well with other International Research Groups: The goals for the next 5 years are to consolidate our research laboratories and the collaborative projects we have with other Basic and Translational Research Groups. In this regard we are currently doing some experimental projects with the following Investigators/Institutions:

- Yossef Yarden at The Weizman Institute, Rehovot, Israel
- Jordi Barretina and Mathew Meyersson at The Broad Institute, Cambridge, US
- Eduardo Vilar and Stephen B. Gruber at The University of Michigan, Ann Arbor, US
- · Sabine Tejpar at The University of Leuven, Belgium
- · Iris Simon and Renè Bernards at the NKI/Agendia, Amsterdam, Holland
- · John Freshley and Arul Chinnaiyan at Compendia, Ann Arbor, US
- \cdot Steve Shak at GenomicHealth, Redwood City, US

Gastrointestinal Tumors Group

The targeted therapy revolution







Cellular activities are regulated by signaling networks
These networks are radically altered (deregulated) in cancer cells

In considering our Cell Signaling and Cancer Laboratories at VHIO, besides the preclinical studies devoted to better characterize new targeted agents in different cancer models we have contributed to setting up three different basic and translational research laboratories with special devotion to gastrointestinal malignancies:

- Cancer stem cells: The main interest of this laboratory is to understand 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 long term source of cancer self-renewal. The project is leaded by Hector Garcia-Palmer, PhD, previously working at MCRC, London, UK.
- · Proteomics: The main focus of this laboratory is the discovery of biomarkers and drug targets using the proteomic profiling of sub-proteomes, rather than whole tissues or plasma/serum. By using a new proteomics approach capable of the quantitative profiling of the secreted sub-proteome ('secretome') of cells, we will generate secretome signatures in different cancer model systems; particularly from the primary culture of tumors. The project is lead by Josep Villanueva, PhD, previously working at MSKCC in New York, US.
- Circulating Tumor Cells (CTCs) and Circulant DNA (cDNA) specimens: we are setting-up a platform for collecting CTCs and cDNA for the development of prognostic and predictive biomarkers, with special emphasis on filtration collection techniques.

Clinical Trials

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

1199.51 A Phase I-II Study of *BIBF 1120* and *FOLFOX* Compared to Bevacizumab and *FOLFOX* in First Line Metastatic Colorectal Cancer Patients

E7107-044-102 A Phase I Open-Label, Single-Arm, Dose Escalation Study of E7107 Administered IV (Bolus) on Days 1, 8, and 15 Every 28 Days to Patients with Solid Tumours

PM104A-001-04 "Phase I multicenter, open-label, dose-escalating study of *PM00104* administered as 1 and 3 hours intravenous infusion every 3 weeks in subjects with advanced solid tumors or lymphoma"

CBGT226A2101 A Phase I/II, Multi-center, Openlabel Study of *BGT226*, Administered Orally in Adult Patients With Advanced Solid Malignancies Including Patients With Advanced Breast Cancer

Po5670 A Pharmacodynamic Study of *SCH 900105* in Subjects With Advanced Solid Tumors Who Have Liver Metastases

CNTO328STM2001 A Phase 1/2, Multiple-dose, Dose-escalation Study to Assess the Safety, Efficacy, and Pharmacokinetics of Intravenous *CNTO 328*, an Anti-Interleukin 6 (IL-6) Monoclonal Antibody, in Subjects with Solid Tumors

PM1183-A-001-08 Phase I, Multicenter, Open-label, Dose-escalating, Clinical and Pharmacokinetic Study of *PM01183* in Patients With Advanced Solid Tumors

26854165CAN1001 A Phase I Study to Determine the Safety, Pharmacology, and Pharmacodynamics of *JNJ-26854165* in Subjects with Advanced Stage and/or Refractory Solid Tumors or Lymphoma

XL765-001 A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of *XL765* Administered Orally Daily to Subjects With Solid Tumors

C14002 A Phase I Clinical and Pharmacodynamic Study of *MLN8237*, A Novel Aurora A Kinase Inhibitor, in Patients With Advanced Malignancies

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

20070411 A Phase 1b/2 Open Label, Dose Escalation Study of AMG 655 in Combination With *AMG 479* in Subjects With Advanced, Refractory Solid Tumors

TTD-08-06 Open, Multicenter Phase II Study to Evaluate the Efficacy and Safety of the Combination of Panitumumab With Irinotecan in Patients With Wild-Type KRAS Metastatic Colorectal Cancer Refractory to Irinotecan Based Chemotherapy

EMR 62242-004 An Open-label, Randomized, Controlled, Multicenter, Phase I/II Trial Investigating *2 EMD 525797* Doses in Combination With Cetuximab and Irinotecan Versus Cetuximab and Irinotecan Alone, as Second-line Treatment for Subjects With K-ras Wild Type Metastatic Colorectal Cancer.

20070820 Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild Type KRAS and Refractory to Oxaliplatin-or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab

Gastrointestinal Tumors Group

20060579 A Phase 2, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of FOLFIRI in Combination With *AMG 479* or *AMG 655* Versus FOLFIRI for the Second-line Treatment of KRAS-mutant Metastatic Colorectal Carcinoma

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

13162 Phase 2b, DB, Randomized Study Evaluating Efficacy & Safety of Sorafenib Compared With Placebo When Administered in Combination With Modified FOLFOX6 for the Treatment of Metastatic CRC Subjects Previously Untreated for Stage IV Disease

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.

ML18147 A Randomized, Open-label Phase III Intergroup Study: Effect of Adding Bevacizumab to Cross Over Fluoropyrimidine Based Chemotherapy (CTx) in Patients With Metastatic Colorectal Cancer and Disease Progression Under First-line Standard CTx /Bevacizumab Combination PROTOCOL ML18147 (Formerly AIO 0504)

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

EFC10262 A Multinational, Randomized, Doubleblind 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

TTD-o6-o2 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

TTD-08-02 Phase II Study of Adjusted-dose Docetaxel-oxaliplatin-capecitabine in Patients With Advanced Gastric Adenocarcinoma and Intermediate General Status.

TEL0805 A Phase 2 Open-Label Study Evaluating the Efficacy and Safety of Telatinib in Combination With Chemotherapy as First-Line Therapy in Subjects With Advanced Gastric Cancer

DOCOX-C-00082 A randomized phase ii study of docetaxel in combination with oxaliplatin With or without 5-fu or capecitabine In metastatic or locally recurrent gastric cancer Previously untreated with chemotherapy for advanced disease.

PEPo2o6 A Randomized Phase II Study of PEPo2, Irinotecan or Docetaxel as a Second Line Therapy in Patients With Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

CRADoo1CDE16 A Single Arm, Multicenter Single Stage Phase II Trial of *RAD001* as Monotherapy in the Treatment of Metastatic Non Syndromic Neuro-endocrine Tumors

2-55-52030-726 Phase III, Randomised, Doubleblind, 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 **CRADoo1C2324** A Randomized Double-blind Phase III Study of *RADO01* 10 mg/d Plus Best Supportive Care Versus Placebo Plus Best Supportive Care in the Treatment of Patients With Advanced Pancreatic Neuroendocrine Tumor (NET)

2008002 A Global, Multi-center, Open-label, Phase 2 Study of *AGS-1C4D4* Given in Combination With Gemcitabine in Subjects With Metastatic Pancreatic Cancer

A6181111 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.

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

EFC10547 A Multinational, Randomized, Doubleblind Study, Comparing the Efficacy of Aflibercept Once Every 2 Weeks Versus Placebo in Patients Treated With Gemcitabine for Metastatic Pancreatic Cancer

TTD-08-05 Phase II Randomized Study to Compare Capecitabine + Bevacizumab Concomitantly With Radiotherapy Versus Capecitabine Concomitantly With Radiotherapy, as Neoadjuvant Treatment for Patients With Localized and Resectable Rectal Cancer

Publications

Capdevila J, Ramos FJ, Macarulla T, Elez E, **Tabernero J**. *The role of salvage treatment in advanced colorectal cancer*. Crit Rev Oncol Hematol 2009;71:53-61.

Sastre J, Aranda E, Massutí B, **Tabernero J**, Chaves M, Abad A, Carrato A, Reina JJ, Queralt B, Gómez-España A, González-Flores E, Rivera F, Losa F, García T, Sanchez-Rovira P, Maestu I, Díaz-Rubio E. *Elderly patients with advanced colorectal cancer derive similar benefit without excessive toxicity after first-line chemotherapy with oxaliplatin-based combinations: Comparative outcomes from the 03-TTD-01 phase III study.* Crit Rev Oncol Hematol 2009;70:134-44.

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Schöffski P, Guillem V, Garcia M, Rivera F, Tabernero J, Cullell M, Lopez-Martin JA, Pollard P, Dumez H, del Muro XG, Paz-Ares L. *Phase II randomized study of Plitidepsin (Aplidin), alone or in association with L-carnitine, in patients with unresectable advanced renal cell carcinoma*. Mar Drugs 2009;7:57-70.

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Markman B, Atzori F, Pérez-García J, **Tabernero J**, Baselga J. *Status of PI3K inhibition and biomarker development in cancer therapeutics*. Ann Oncol 2009 Aug 27. [Epub ahead of print].

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Espallargues M, Almazán C, Tebé C, Pla R, Pons JM, Sánchez E, Mias M, Alomar S, Borrás JM; ONCOrisc Study Group. *Management and outcomes in digestive cancer surgery: design and initial results of a multicenter cohort study*. Rev Esp Enferm Dig. 2009 Oct;101(10):680-96. English, Spanish

Forner A, Ayuso C, Isabel Real M, Sastre J, Robles R, Sangro B, Varela M, de la Mata M, Buti M, Martí-Bonmatí L, Bru C, **Tabernero J**, Llovet JM, Bruix J. *Diagnosis and treatment of hepatocellular carcinoma*. Med Clin (Barc). 2009 Feb 28;132(7):272-87.

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Goldberg RM, Meropol NJ, **Tabernero J**. *Accomplishments in 2008 in the treatment of advanced metastatic colorectal cancer*. Gastrointest Cancer Res 2009;3(5Supplement 2):S23-7.

Principal Investigator
Josep Tabernero



Current positions

- · Director of Clinical Research Program at VHIO
- · Head of the Gastrointestinal Tumors Program
- · Section Head at the Oncology Department of Vall d'Hebron University Hospital
- Specialist physician at the Oncology Department of Vall d'Hebron University Hospital, 1997-2005
- Specialist physician at the Oncology
 Department of Hospital de la Santa Creu i Sant
 Pau, 1993-1997
- · Visiting physician at the M.D. Anderson Cancer Center, University of Texas, Houston (USA).
- Member of the board of directors of the Spanish Group for studying the treatment of digestive tumors (TTD)
- Member of the Expert Committee of the Program for Practical Clinical Guides on Cancer in Catalonia - Oncoguías

Academic Qualifications

- Degree in Medicine and Surgery from the Universitat de Barcelona, 1987
- · Specialization at Hospital de la Santa Creu i Sant Pau, 1989-1992
- Specialist in Medical Oncology, Universitat Autònoma de Barcelona, 1994

Areas of Research

- Development of prognostic and predictive biomarkers
- · Early drug development
- Therapeutic optimization in gastrointestinal tumors

Most relevant scientific publications

Oxaliplatin, 5? Fluorouracil and Leucovorin in Adjuvant Colon Cancer: Results of the International Randomized MOSAIC Trial.

André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A, on behalf of the MOSAIC investigators. N Engl J Med 2004;350:2343-2351.

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The Landscape of copy number alterations across multiple human cancers. Beroukhim R, Mermel CH, Porter D, Wei G, Raychaudhuri S, Donovan J, Barretina J, Boehm JS, Dobson J, Urashima M, McHenry KT, Pinchback R, Ligon AH, Cho YJ, Haery L, Greulich H, Reich M, Winckler W, Lawrence MS, Weir BA, Tanaka KE, Chiang DY, Bass AJ, Loo A, Hoffman C, Prensner J, Liefeld T, Yecies D, Signoretti S, Maher E, Kaye FJ, Sasaki H, Tepper JE, Fletcher JA, Tabernero J, Baselga J, Tsao M, DeMichelis F, Rubin MA, Janne PA, Daly MJ, Nucera C, Levine RL, Ebert BL, Gabriel S, Rustgi AK, Antonescu CR, Ladanyi M, Letai A, Garraway LA, Loda M, Beer DG, True LD, Okamoto A, Pomeroy SL, Singer S, Golub TR, Lander ES, Getz G, Sellers WR, Meyerson M. Nature 2010;463:899-905.

Gene Expression and Cancer Group



Joan Seoane

Post-doctoral Fellows Judith Anido Folgueira PhD Rosa Maria Prieto Sánchez PhD Andrea Sáez Borderías PhD

Graduate Students Gerard Folch Codera Alba González Juncà Laura Rodon Ahnert Francisco Miguel Torres Grande

> Technicians Alexandra Arias Piñeiro Isabel Cuartas Maza Carolina Raventós Bernal

Strategic Goals

- 1 Molecular mechanisms involved in the genesis and progression of glioma
- 2 Study of glioma-initiating cells, the cells responsible for the initiation, recurrence and resistance to conventional therapies in tumors
- 3 Study of the *TGFB* pathway as a therapeutic target in glioma

Achievements in 2009

We have discerned the mechanisms implicated in the oncogenic response to $TGF\beta$ in glioma. We have found that LIF is induced by $TGF\beta$ in glioma and mediates the pro-tumorogenic effect of $TGF\beta$.

Our results have shown that *LIF* is a cytokine that induces the self-renewal of glioma-initiating cells. We have found that *LIF* is a therapeutic target against glioma and confers poor prognosis in glioma patients.

We have also studied the effect of the *PI3K* inhibitors on glioma and glioma-initiating cells and the role of the forkhead transcription factor, *FoxG1*, in glioma.

Objectives for 2010

- · Study the role of the TGFBeta Shh, Notch and Wnt pathways in glioma
- Extrapolate our discoveries in glioma to other tumor types
- Characterize glioma-initiating cells, find new markers to identify them and study their regulation and biology

Role of FoxG1 in glioma
June, 2006- June, 2009
Association for International Cancer Research
(AICR)

EMBO Young Investigator October, 2007-2010 European Molecular Biology Organization (EMBO)

Projects

Consolider RNAREG
An Integrated approach to post-trasncriptional regutation of gene expression and its role in human disease
2009-2014
Ministerio de Ciencia e Innovación

2009SGR504 SGR Suport a Grups de Recerca de Qualitat 2009-2014 Agencia de Gestió d'Ajuts Universitaris i de Recerca

205819-Glioma Molecular mechanisms of glioma genesis and progression July, 2008- July, 2013 European Research Council

Plo70648
Papel del TGF-beta en la capacidad de autoregenración de las células madre de glioma
January, 2008- December, 2010
Spanish Ministry of Health
(FIS- Instituto Carlos III)

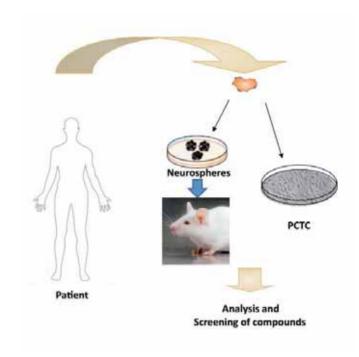
Publications

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Santamaria-Martínez A, Barquinero J, Barbosa-Desongles A, Hurtado A, Pinós T, **J. Seoane**, Poupon MF, Morote J, Reventós J, Munell F. *Identification of multipotent mesenchymal stromal cells in the reactive stroma of a prostate cancer xenograft by side population analysis*. Exp Cell Res (2009) 15, 3004-13 IF:3,948

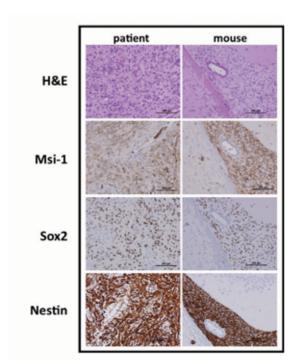
S. Peñuelas, J. Anido, R. M. Prieto-Sánchez, G. Folch, I. Barba, I. Cuartas, D. García-Dorado, M. A. Poca, J. Sahuquillo, J. Baselga, J. Seoane *TGF-beta increases glioma-initiating cell self-renewal through the induction of LIF in human glioblastoma*. Cancer Cell (2009) 15, 315-27 IF: 24,962

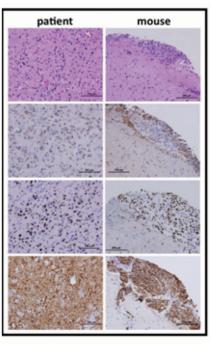
Gene Expression and Cancer Group



Patient GBM Mouse GBM Patient GBM Mouse GBM

| International Content of the Conte





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Principal Investigator Joan Seoane



Current positions

- Head of the Gene Expression and Cancer Program
- · ICREA Research Professor, 2004
- Professor at Universitat Autònoma de Barcelona
- Coordinator of the National Agency for Evaluation and Prospective Studies (ANEP)
- Member of the Executive Committee of the European Association for Cancer Research
- Member of the Neuro-Oncology Committees of Vall d'Hebron University Hospital and scientific advisor for the Genome platform of the Vall d'Hebron Research Institute
- Member of the Spanish Society of Biochemistry and the European Association for Cancer Research

Academic Qualifications

- Degree in Chemical Sciences from the Universitat de Barcelona, 1993
- Doctorate in Biochemistry and Molecular Biology from the University of Barcelona, 1998
- · ICREA Research Professor, 2004

Areas of Research

- · Study of the molecular mechanisms implicated in brain tumors
- · Study of tumor stem cells

Prizes and Scholarships

- Memorial Sloan-Kettering Cancer Center Research Fellow (2003)
- Catalan Biology Society (Josep M. Sala Trepat)
 (2004)
- · EMBO Young Investigator (2007)
- · Banc de Sabadell Biomedical Research Prize (2009)
- Beckman-Coulter award of the Spanish Society of Biochemistry and Molecular Biology (2009)
- · ERC, European Research Consortium
- · Association for International Cancer Research (AICR)
- European Comission, Marie Curie International Reintegration Grant
- · Ministry of Education and Science (FPU)
- · British Royal Society
- Ministry of Education and Science (Foreign travel award)
- · Ministry of Education and Science (FPI)

Most relevant scientific publications

TGF-beta increases glioma-initiating cell self-renewal through the induction of LIF in human glioblastoma. S. Peñuelas, J. Anido, R. M. Prieto-Sánchez, G. Folch, I. Barba, I. Cuartas, D. García-Dorado, M. A. Poca, J. Sahuquillo, J. Baselga, J. Seoane. Cancer Cell (2009) 15, 315-27[see Preview, Cancer Cell (2009) 15, 247-8]

High TGFbeta-Smad activity confers poor prognosis in glioma patients and promotes cell proliferation depending on the methylation of the PDGF-B gene. A. Bruna, R.S. Darken, F. Rojo, A. Ocaña, S. Peñuelas, A. Arias, R. Paris, A. Tortosa, J. Mora, J. Baselga, J. Seoane. Cancer Cell (2007) 11, 147-160 [see Preview, Dev. Cell (2007) 12, 324-5]

Genitourinary, Central Nervous System (CNS) tumors, Sarcoma and Cancer of Unknown Primary Site Program



Joan Carles

Medical Oncologists Claudia Valverde MD Jordi Rodón MD

> Clinical Fellows Rafael Morales Cristina Suárez

Strategic Goals

- 1 Implementation of a Urologic Oncology Functional Unit (Vall d'Hebron Urologic Tumors Center)
- 2 Consolidation of the Committee on Nervous System Tumors
- 3 Consolidation of the Bone and Soft Tissue Sarcoma Committee
- 4 Development of a translational platform in prostate cancer

Achievements in 2009

In 2009, we have consolidated the Genitourinary Program.

The program has developed an intense collaboration with the Urology Department, which has made it possible to publish several reviews and to draft a chapter of a book on genitoutinary tumors at the national level.

This close collaboration has allowed the implementation of clinical studies on different stages of the disease in a continuous way, making it easier for our patients to benefit from novel treatments. We are currently able to offer our patients studies on early-stage prostate cancer with chemotherapy, or targeted therapies including antiangiogenics and immunotherapy for advanced disease, together with the standard treatments in each situation.

One of the members of our group has spent 2 months at one of the most prestigious sarcoma centers in the World, the Dana Farber Cancer Institute (DFCI, Boston). This opportunity has allowed us to provide a better-quality care to our patients and to establish lines of collaboration with this center.

Objectives for 2010

- Design and development of clinical trials for genitourinary malignancies with the active participation of investigators from the Urology, Radiation Therapy and Medical Oncology Departments
- Creation of a translational research platform for Urologic Cancer
- Collaboration of physicians from the different disciplines involved in the Urologic cancer Board for the carrying out of doctoral theses of fellows belonging to each department
- Consolidaton of the CNS Committee with the delopment of several multidisciplinary clinical trials
- Collaboration with the Spanish Sarcoma Group (GEIS) in order to conduct clinical trials at different stages of the disease with emphasis in a histologic-tailored design

Genitourinary, Central Nervous System 40/41 (CNS) tumors, Sarcoma and Cancer of Unknown Primary Site Program

- · Creation of a translational platform for Sarcomas and Basic Research in close collaboration with the Biomedical Research Institute of Bellvitge (IDIBELL) and the Cancer Research Center of Salamanca (CIC)
- · The option for every member of the group to spend a minimum of 3 months in centers of acknowledged prestige in a specific area. In the following years, the program will promote shorter stays for joint projects development

Clinical Trials

Prostate

Phase II randomized study in high risk locally advanced prostate cancer comparing radiotherapy and hormonotherapy vs chemoradiotherapy and hormonotherapy.

Phase III double blind randomized study of ZD4054 in PSA relapse hormone-resistant prostate cancer

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

Multicenter, randomized, double-blind study to compare the efficacy and safety of aflibercept with a placebo administered every 3 weeks in patients with hormone-resistant metastatic prostate cancer treated with docetaxel/prednisone.

A multicenter, randomized, double-blind, phase 3 study of sunitinib plus prednisone versus prednisone in patients with progressive metastatic hormone-refractory prostate cancer after failure of a docetaxel-based chemotherapy regimen Protocol CA184043: A Randomized, Double-Blind, Phase 3 Trial Comparing Ipilimumab vs. Placebo Following Radiotherapy in Subjects with Castration Resistant Prostate Cancer that Have Received Prior Treatment with Docetaxel Phase III, randomized, double-blind, placebo-controlled trial of abiraterone acetate (CB7630) with prednisone in asymptomatic patients or patients with mild symptoms who are suffering from castration-resistant metastatic prostate cancer. Phase III multicenter, randomized, double-blind trial with multiple doses of alpharadin in the treatment of patients with hormone-resistant prostate cancer and bone metastasis.

Bladder cancer

Randomized trial of Larotaxel + cisplatin (LC) versus gemcitabine + cisplatin (GC) in first-line treatment of locally advanced/metastatic urothelial or bladder cancer.

PDX-o11 protocol. Phase II, single-arm study of pralatrexate in patients with advanced or recurrent metastatic transitional cell carcinoma of the bladder.

Renal cancer

A6181038. Treatment protocol with SU011248 of patients with metastatic renal cells refractory carcinoma or cytokines and that cannot be selected to participate in other SU011248 protocols, but that can benefit from treatment with SU011248,

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.

SOGUG 07-02. Phase I study of metronomic therapy with gemcitabine, capecitabine and sunitinib in patients with metastatic renal cancer. An open-label multicenter expanded access study of RAD001 in patients with metastatic carcinoma of the kidney who have progressed despite vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy Axitinib (AG-013736) as second-line treatment of renal cell cancer, etastásocp: Axis Trial.

Central nervous system

A Phase 1 dose-escalation study of LY2157299 in patients with recurrent glioblastoma Cilengitide for subjects with newly diagnosed glioblastoma multiforme and methylated MGMT gene promoter - a multicenter, open-label, controlled Phase III study, testing cilengitide in combination with standard treatment (temozolomide with concomitant radiation therapy, followed by temozolomide maintenance therapy) versus standard treatment alone (CENTRIC).

Genitourinary, Central Nervous System (CNS) tumors, Sarcoma and Cancer of Unknown Primary Site Program

Sarcoma

Phase III study comparing doxorubicin vs doxorubicin plus ifosfamide in metastatic sarcoma.

A Five-Tier, Phase 2 Open-Label Study of *IMC-A12* Administered as a Single Agent Every 2 Weeks in Patients With Previously- Treated, Advanced or Metastatic Soft Tissue and Ewing's Sarcoma/PNET

Open-label multicenter, expanded-access trial of imatinib mesylate as adjuvant therapy in adult patients with GIST following Ro resection.

Publications

Alvarado-Miranda A, Arrieta O, Gamboa-Vignolle C, Saavedra-Perez D, Morales-Barrera R, Bargallo-Rocha E, Zinser-Sierra J, Perez-Sanchez V, Ramirez-Ugalde T, Lara-Medina F. Concurrent chemo-radiotherapy following neoadjuvant chemotherapy in locally advanced breast cancer. Radiat Oncol. 2009 Jul 11;4:24.

Bellmunt J, Carles J, Albanell J. *Predictive modelling in hormone-refractory prostate cancer* (*HRPC*). Clin Transl Oncol. 2009 Feb;11(2):82-5. PubMed PMID: 19211372.

Bellmunt J, Macià F, Malmusi D, Llorente JA, Carles J, Lloreta J, Foro P, Gelabert A, Albanell J, Castells X. *Impact of PSA implementation and combined radiation and hormonal therapy (RT+HT) on outcome of prostate cancer patients*. Eur J Cancer. 2009 Nov;45(16):2804-9. Epub 2009 Jul 20. PubMed PMID: 19625182.

Bellmunt J, Théodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, Caty A, Carles J, Jagiello-Gruszfeld A, Karyakin O, Delgado FM, Hurteloup P, Winquist E, Morsli N, Salhi Y, Culine S, von der Maase H. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with

advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol. 2009 Sep 20;27(27):4454-61. Epub 2009 Aug 17. Erratum in: J Clin Oncol. 2010 Jan 1;28(1):182. Winquist, Eric [added]. PubMed PMID: 19687335.

Carles J, Morales R, Perez JM, Suárez C, Rodón J, Valverde C. *Management and interpretation of novel toxicities of molecular targeted therapies: renal toxicities*. Eur J Cancer. 2009 Sep;45 Suppl 1:309-17. Review. PubMed PMID: 19775627.

Carles J, Nogue M, Sole JM, Foro P, Domenech M, Suarez M, Gallardo E, García D, Ferrer F, Gelabert-Mas A, Gayo J, Fabregat X. *Phase II Study of Vinorelbine and Estramustine in Combination with Conformational Radiotherapy for Patients with High-Risk Prostate Cancer*. Int J Radiat Oncol Biol Phys. 2009 Jul 3. [Epub ahead of print] PubMed PMID: 19577864.

Lin CC, Calvo E, Papadopoulos KP, Patnaik A, Sarantopoulos J, Mita AC, Preston GG, Mita MM, Rodón J, Mays T, Yeh IT, O'Rourke P, Takimoto CH, Dancey JE, Chen H, Tolcher AW. *Phase I study of cetuximab, erlotinib, and bevacizumab in patients with advanced solid tumors*. Cancer Chemother Pharmacol. 2009 May;63(6):1065-71. Epub 2008 Sep 16. PubMed PMID: 18795291.

Rodón J, Iniesta MD, Papadopoulos K. *Development of PARP inhibitors in oncology. Expert Opin Investig Drugs*. 2009 Jan;18(1):31-43. Review. PubMed PMID: 1905;3880.

Tolcher AW, Sarantopoulos J, Patnaik A, Papadopoulos K, Lin CC, Rodón J, Murphy B, Roth B, McCaffery I, Gorski KS, Kaiser B, Zhu M, Deng H, Friberg G, Puzanov I. *Phase I, pharmacokinetic, and pharmacodynamic study of AMG 479, a fully human monoclonal antibody to insulin-like growth factor receptor 1.* J Clin Oncol. 2009 Dec 1;27(34):5800-7. Epub 2009 Sep 28. PubMed PMID: 19786654.

Abstracts

Diaz C, Olvera N, Martínez H, Mtz Cedillo J, Cuellar M, Morales R, Álvarez M, Segura B, de la Garza J, Aguilar P. *Paclitaxel plus carboplatin* (*PC*) in patients with metastatic melanoma (*MM*): Experience in a single institution. ASCO Meeting Abstracts. 2009 May 20: e20019.

Martinez P, Valverde C, Morales R, Rodón J, Suárez C, Baselga J, **Carles J**. *Docetaxel activity in second line treatment for urothelial carcinoma: a retrospective analysis*. European Journal of Cancer Supplements. 2009 September;7(2):448.

Morales R, Valverde C, Rodón J, Perez J, Maldonado X, Suárez C, Trilla E, **Carles J**. *Bilateral testicular germ cell tumors – a single hospital experience*. European Journal of Cancer Supplements. 2009 September;7(2):446.

Serrano C, Suárez C, Andreu J, **Carles J**. *Acuteaortic dissection during sorafenib-containing therapy*. J.Ann Oncol. 2010 Jan; 21(1):181-2.

Genitourinary, Central Nervous System 42/43 (CNS) tumors, Sarcoma and Cancer of Unknown Primary Site Program

Principal Investigator **Joan Carles**

Current positions

- · Head of the Genitourinary, CNS and Sarcoma Tumors Program.
- · Associate Professor of Medicine at Universitat Autònoma de Barcelona
- · Coordinator of the Medical Oncology (UDIMAS)
- · Active member of the European Society of Medical Oncology, the American Society of Clinical Oncology and the Spanish Research Group on Sarcoma (GEIS)
- · Vice-president of the Spanish Genitourinary **Tumor Group**



Academic Qualifications

- · Degree in Medicine and Surgery from the University of Barcelona, 1986
- · Specialist in Medical Oncology at Hospital Germans Trias i Pujol, 1990
- · Doctorate in Medicine from the Autonomous University of Barcelona, 1992

Areas of Research

Genitourinary clinical oncology, sarcoma and early clinical and translational research.

Prizes and Scholarships

· European qualification in Medical Oncology from the European Society for Medical Oncology, 1996

Most relevant scientific publications

Weekly administration of Docetaxel in combination with estramustine and celecoxib in patients with advanced hormone-refractory prostate cancer: final results from a phase II study Carles J, Font A, Mellado B, Domenech M, Gallardo E, González-Larriba JL, Catalan G, Alfaro J, Gonzalez Del Alba A, Nogué M, Lianes P, Tello JM. Br J Cancer. 2007 Nov 5;97(9):1206-10. Epub 2007 Oct 23.

Gemcitabine and oxaliplatin combination: a multicenter phase II trial in unfit patients with locally advanced or metastatic urothelial cáncer Carles J. Esteban E. Climent M. Font A. Gonzalez-Larriba JL, Berrocal A, Garcia-Ribas I, Marfa X, Fabregat X, Albanell J, Bellmunt J; Spanish Oncology Genito Urinary Group Study Group. Ann Oncol. 2007 Aug;18(8):1359-62.

Management and interpretation of novel toxicities of molecular targeted therapies: renal toxicities

Carles J, Morales R, Perez JM, Suárez C, Rodón J, Valverde C.

Eur J Cancer. 2009 Sep;45 Suppl 1:309-17. No abstract available.

Phase II Study of Vinorelbine and Estramustine in Combination with Comformational Radiotherapy for Patients with High Risk Prostate Cancer

Carles J., Nogue M., Sole JM., Foro P., Domenech M., Suarez M, Gallardo E, García D, Ferrer F, Gelabert-Mas A, Gayo J, Fabregat X. Int J Radiat Oncol Biol Phys. 2009 Jul 3.

Growth Factors Group



Joaquín Arribas

Post-doctoral Fellows Kim Pedersen PhD Josep Lluís Parra-Palau PhD Jordi Malapeira Argilaga PhD Beatriz Morancho Armisen PhD

> Graduate Students Cristina Bernadó Morales Pier Davide Angellini

Technicians
Antoni Luque Garcia
Marta Escorihuela Baez
Cristina Ferrer Ramón

Strategic Goals

- 1 To identify novel mechanisms and factors leading to breast cancer progression
- 2 To develop novel anti-tumor therapies and improve current ones
- 3 To identify novel biomarkers to better manage breast cancer patients

Achievements in 2009

In 2009 we continued to focus on the role of the carboxy terminal fragments of the protooncogene *HER2* in breast cancer progression and treatment. As a result, we have shown that one of these fragments, *611-CTF*, plays a causal role in the progression of a subgroup of breast cancers with bad prognosis that are resistant to some anti-*HER2* therapies such as Herceptin, a monoclonal anti-*HER2* antibody.

Objectives for 2010

 To identify novel factors and mechanisms involved in the progression of HER2-positive breast cancers

Projects

SGR Suport a Grups de Recerca de Qualitat Funded by: AGAUR-Generalitat de Catalunya Duration: 2010-2014

Desarrollo tecnológico de anticuerpos monoclonales con interés diagnóstico y/o terapéutico contra el receptor HER2 y/o sis variantes truncadas

Funded by: Genoma España Duration: 2009-2011

Fragmentos carboxilo terminals (CTFS) en la progresion y tratamiento del cancer de mama Funded by: ISCIII

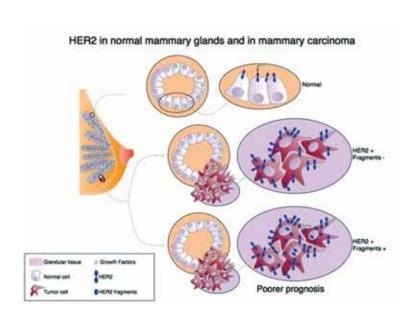
Duration: 2009-2013

Novel factors and mechanisms mediating the oncogenic activity of HER2 Funded by: Breast Cancer Research Foundation

Duration: 2009-2010

Metastasis in Breast Tumors expressing 611-CTF of HER2: mechanisms and therapeutic strategies

Funded by: Breast Cancer Research Foundation Duration: 2008-2009



Identificación de mecanismos y factores involucrados en la sobreexpresión y tráfico intracelular de ADAM17 (TACE). Relevancia para el desarrollo de tumores de mama Funded by: Fundación Mutua Madrileña Duration: 2007-2009

Red Temática de Investigación Cooperativa del Cáncer Funded by: ISCIII (Subdirección General de Redes y Centros de Investigación Cooperativa) Duration: 2007-20011

Publications

Arribas J, Esselens C. *ADAM17 as a therapeutic target in multiple diseases*. Curr Pharm Des. 2009;15(20):2319-35. Review.

Chandarlapaty S, Scaltriti M, Angelini P, Ye Q, Guzman M, Hudis CA, Norton L, Solit DB, **Arribas** J, Baselga J, Rosen N. *Inhibitors of HSP90 block P95-HER2 signaling in Trastuzumab-resistant tumors and suppress their growth*. Oncogene. 2010 Jan 21;29(3):325-34. Epub 2009 Oct 26.

Esselens C, Malapeira J, Colomé N, Casal C, Rodríguez-Manzaneque JC, Canals F, **Arribas J.** *The cleavage of semaphorin 3C induced by ADAMTS1 promotes cell migration.* J Biol Chem. 2010 Jan 22;285(4):2463-73. Epub 2009 Nov 13.

García-Castillo J, Pedersen K, Angelini PD, Bech-Serra JJ, Colomé N, Cunningham MP, Parra-Palau JL, Canals F, Baselga J, **Arribas J**. *HER2 carboxylterminal fragments regulate cell migration and cortactin phosphorylation*. J Biol Chem. 2009 Sep 11;284(37):25302-13. Epub 2009 Jul 8. PubMed

Pedersen K, Angelini PD, Laos S, Bach-Faig A, Cunningham MP, Ferrer-Ramón C, Luque-García A, García-Castillo J, Parra-Palau JL, Scaltriti M, Ramón y Cajal S, Baselga J, **Arribas J**. *A naturally occurring HER2 carboxy-terminal fragment promotes mammary tumor growth and metastasis*. Mol Cell Biol. 2009 Jun;29(12):3319-31. Epub 2009 Apr 13. Article Recommended by Faculty of 1000.

Scaltriti M, Verma C, Guzman M, Jimenez J, Parra JL, Pedersen K, Smith DJ, Landolfi S, Ramon 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. 2009 Feb 12;28(6):803-14. Epub 2008 Dec 8.

Growth Factors Group

Principal Investigator
Joaquín Arribas



Current positions

- · Director of Basic Research Program at VHIO
- · Head of the Growth Factors Program
- · ICREA Research Professor, 2007
- Member of the Executive Committee of the Territorial Network for Cooperative Cancer Research (RTICC)
- Chairman of the Committee for the Evaluation of Research Projects on Cancer (Cancer Research Fund) of the Carlos III Health Institute
- Member of the Spanish and American Society of Biochemistry and Molecular Biology (SEBBM)
- Member of the Editorial Board of the Journal of Biological Chemistry

Academic Qualifications

- Degree in Biochemistry from the Universidad Autónoma de Madrid, 1987
- · Doctorate in Biology, 1991

Areas of Research

- · Study of the role of signal transduction pathways in the development of cancer
- Role of the EGF receptors in breast cancer progression

Prizes and Scholarships

- · EMBO Young Investigator Programme (YIP)
- Beckman-Coulter award of the Spanish Society of Biochemistry and Molecular Biology

Most relevant scientific publications

A Naturally Occurring HER2 Carboxy-Terminal Fragment Promotes Mammary Tumor Growth and Metastasis. Pedersen, K., Angelini, P.-D., Laos, L., Bach-Faig, A., Cunningham, M.-P., Ferrer-Ramón, C., Luque-García, A., García-Castillo, J., Parra-Palau, J.-Ll., Scaltriti, M., Ramón y Cajal, S., Baselga J. and Arribas, J. (2009) Mol Cell Biol 29, 3319-3331.

Biosynthesis of tumorigenic HER2 C-terminal fragments by alternative initiation of translation. Article Recommended by Faculty of 1000. Anido, J., Scaltriti, M., Bech Serra, J. J., Federico Rojo, F. Baselga, J. and Arribas, J. (2006) EMBO J. 25, 3234-3244.

TACE is required for the activation of the EGFR by TGF-alpha in tumors. Borrell-Pagès, M., Rojo, F., Albanell, J., Baselga, J., and Arribas, J. (2003) EMBO J 22, 1114-1124.



Josep Maria del Campo

Medical Oncologists Ana Oaknin MD Isabela Diaz de Corcuera MD

Strategic Goals

- 1 Reference Center in Patient Care and Clinical Research
- 2 Highly specialized in treatment
- a. Training in Gynecological Oncology
- b. Fellowships
- 3 International projection
- 4 Potentiate scientific activity
- a. Publications in impact journals
- b. Communications in international conferences

Achievements 2009

The research program has expanded considerably in 2009. Our group has directed the following studies as principal investigator: 17 phase I, II and III clinical trials with new drugs aimed at treating head and neck cancer, ovarian and endometrial cancer. More than 60 patients have been enrolled in these trials.

This activity has required close collaboration with other departments of Vall d'Hebron University Hospital and with international cooperative groups.

The Gynecological Oncology, Maxillofacial, ENT and Anatomical Pathology departments have collaborated actively in developing these projects. A program of clinical trials has been initiated, designed and led by our group with the aim of participating from the outset in the development of new molecules.

The research activity of the group has meant that it has begun to be a reference point for other hospitals in the region, with an increase in the number of patients referred from these hospitals.

A large part of the research activity has been carried out in close collaboration with other national and international cooperative groups (GEICO, AGO, ENGOT, GOG, GCIG) to develop new molecules. The activity of the group has allowed its members to form part of the executive committees and subcommittees of these groups.

Objectives for 2010

- Our team aims to consolidate itself as a reference center by creating high-level multidisciplinary teams. To this end, we will encourage training of specialists involved in gynecological and head and neck tumors by means of a Fellowship in International Reference Hospitals
- We will create a regional network of hospitals to facilitate patient access to novel treatments in clinical trials that are currently limited to reference centers
- We aim to form part of the management structures of the cooperative groups of greatest international relevance (ENGOT, GCIG) and strengthen relations with highly specialized centers in our areas of interest (NCIC, Peter McCallum CC, Irvine MC, HSK Wiesbaden)
- We will develop our own database for each disease, which allows for exhaustive reviews of practical interest and of publishing potential
- We will increase communications in international forums and publications in impact journals

Clinical trials

1200.28 A Randomized, Open-label Phase II Study of *BIBW 2992* Versus Cetuximab (Erbitux) in Patients With Metastatic or Recurrent Head and Neck Squamous Cell Carcinoma (HNSCC) After Failure of Platinum-containing Therapy With a Cross-over Period for Progressing Patients

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)

AP23573-07-205 A Randomized Phase II Trial of Ridaforolimus (AP23573; MK-8669) Compared to Progestin or Chemotherapy in Female Adult Patients With Advanced Endometrial Carcinoma

CA163-196 A Phase III, Open Label, Randomized, 2 Arm Study of Ixabepilone Administered Every 21 Days Versus Paclitaxel or Doxorubicin Administered Every 21 Days in Women With Advanced Endometrial Cancer Who Have Previously Been Treated With Chemotherapy

H6Q-MC-So19 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

ABA-o1 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

Do81oCooo12 Phase II, Open-Label, Randomised, Comparative, International Multicentre Study to Assess the Safety and Efficacy of Different Doses of *AZD2281* Given Orally Twice Daily Versus Intravenous Liposomal Doxorubicin Given Monthly in Patients With Advanced BRCA1- or BRCA2-Associated Ovarian Cancer Who Have Failed Previous Platinum-based Chemotherapy

IP-CAT-AC-o3PRo2 Two-arm, randomized, openlabel, phase IIIb study investigating the safety of a 3 hour i.p. infusion of catumaxomab with and without prednisolone premedication in patients with malignant ascites due to epithelial cancer"

D8180Cooo15 A Phase II, Double-blind, Placebocontrolled, Multi-centre, Randomised Study of *AZD0530* in Patients With Advanced Ovarian Cancer Sensitive to Platinum-based Chemotherapy

SHH4489g A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Efficacy and Safety of *GDC-0449* As Maintenance Therapy in Patients With Ovarian Cancer in a Second or Third Complete Remission

Do81oCooo19 Phase II Randomised, Double Blind, Multicentre Study to Assess the Efficacy of *AZD2281* in the Treatment of Patients With Platinum Sensitive Serous Ovarian Cancer Following Treatment With Two or More Platinum Containing Regimens

MO22225 A Study of First Line Treatment With Avastin (Bevacizumab) in Combination With Carboplatin and Weekly Paclitaxel in Patients With Ovarian Cancer

NVo6-0039 Multi-Center, Randomized, Double-Blind, Phase III Efficacy Study Comparing Phenoxodiol in Combination With Carboplatin Versus Carboplatin With Placebo in Patients With Platinum-Resistant or Platinum-Refractory Late-Stage Epithelial Ovarian, Fallopian or Primary Peritoneal Cancer Following at Least Second Line Platinum Therapy

MORAb-003-004 A Randomized, Double-blind, Placebo-Controlled, Phase 3 Study to Assess the Efficacy and Safety of Weekly MORAb-003 in Combination With Carboplatin and Taxane in Subjects With Platinum-sensitive Ovarian Cancer in First Relapse

ICON7 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

MO22224 AURELIA: A Multi-center, Open-label, Randomised, Two-arm Phase III Trial of the Effect on Progression Free Survival of Bevacizumab Plus Chemotherapy Versus Chemotherapy Alone in Patients With Platinum-resistant, Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

VEG110655 A Phase III Study to Evaluate the Efficacy and Safety of Pazopanib monotherapy Versus Placebo in Women Who Have not Progressed after First Line Chemotherapy for Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer.

Publications

Cedrés S, Prat A, Martínez P, Pallisa E, Sala G, Andreu J, **del Campo JM**, Quispe I, Baselga J, Felip E. *Clinical surrogate markers of survival in advanced non-small cell lung cancer (NSCLC) patients treated with second-third line erlotinib*. Lung Cancer. 2009 Nov;66(2):257-61. Epub 2009 Feb 23. PubMed PMID: 19231023.

Del Campo JM, Roszak A, Bidzinski M, Ciuleanu TE, Hogberg T, Wojtukiewicz MZ, Poveda A, Boman K, Westermann AM, Lebedinsky C; Yondelis Ovarian Cancer Group. *Phase II randomized study of trabectedin given as two different every 3 weeks dose schedules (1.5 mg/m2 24 h or 1.3 mg/m2 3 h) to patients with relapsed, platinum-sensitive, advanced ovarian cancer.* Ann Oncol. 2009 Nov;20(11):1794-802. Epub 2009 Jun 25. PubMed PMID: 19556318.

Prat A, Parera M, Adamo B, Peralta S, Perez-Benavente MA, Garcia A, Gil-Moreno A, Martinez-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. 2009 Feb;20(2):294-7. Epub 2008 Sep 26. PMID: 18820245 [PubMed - indexed for MEDLINE]

Vergote I, Finkler N, del Campo JM, Lohr A, Hunter J, Matei D, Kavanagh J, Vermorken JB, Meng L, Jones M, Brown G, Kaye S; ASSIST-1 Study Group. *Phase 3 randomised study of canfosfamide (Telcyta, TLK286) versus pegylated liposomal doxorubicin or topotecan as third-line therapy in patients with platinum-refractory or -resistant ovarian cancer.*Eur J Cancer. 2009 Sep;45(13):2324-32. Epub 2009 Jun 8. PMID: 19515553 [PubMed - indexed for MED-LINE]

Principal Investigator

Josep Maria

del Campo



Current positions

- Head of the Head & Neck and Gynecological Tumors Program
- · Staff Physician at Department of Oncology
- Head of the Medical Oncology Service of the Head and Neck Tumors Committee (ORL)
- Head of the Medical Oncology Service of the Head and Neck Tumors Committee (MF)
- Head of the Medical Oncology Service of the Gynecological Tumors Committee
- Active member of the American Society of Clinical Oncology (ASCO)
- · Member of the Catalan Oncology Society
- Vice-president of the Spanish Research Group on Ovarian Cancer (GEICO)
- Representative of the Spanish Research Group on Ovarian Cancer in the Gynecological Intergroup (GCIG), Endometrial Cancer Section
- Representative of the Spanish Research Group on Ovarian Cancer in the European Network on Gynecological Oncology Trials (ENGOT)

Academic Qualifications

- Degree in Medicine and Surgery from the Universitat de Barcelona, 1975
- · Staff physician at the Oncology Department of Vall d'Hebron University Hospital, 1977

Areas of Research

Clinical Research and Development of new drugs to treat gynecological and head and neck tumors

Most relevant scientific publications

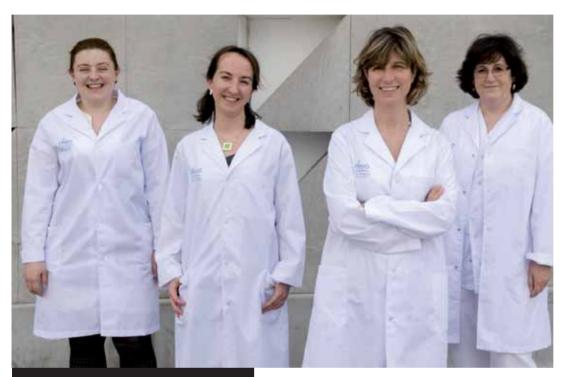
Conclusiones de la Evaluación Oncológica postquirúrgica en 272 enfermas afectas de Cáncer de Mama en Estadíos I a III. L.A. Solé, D.Rubio, J.M. del Campo. Rev. Esp. Oncol. 26: 581-584, 1979.

Estudio Estadístico en un grupo de 700 enfermas afectas de Cáncer de Mama. D. Rubio, L.A. Solé, R. Bodi, J.M. del Campo. Rev. Esp. Oncol. 26: 513-515. 1979.

Combinación de Quimioterapia y Hormonoterapia en el Cáncer Avanzado de Mama. J.M. del Campo et al. Oncología 80, no 3: 7-13, 1980.

Asociación quimioterapia-hormonoterapia en el tratamiento del Cáncer Avanzado de Ovario, (Estadíos III-IV, F.I.G.O.). J.M. del Campo et al. Oncología 80, vol V: 113, 1981.

Tratamiento del Cáncer de Ovario. En Tratamiento actual del Cancer-II. **J.M. del Campo**. Jano 528: 50-53, 1982.



Judith Balmaña

Staff scientist Nina Bosch PhD

Clinical Nurse Specialist Neus Gadea

> **Graduate Students Daniel Fortuny** Irene Valenzuela

Strategic Goals

- 1 Development of the clinical and molecular tools to identify people with suspected Lynch syndrome or hereditary breast and ovarian cancer syndrome associated with BRCA
- 2 Analysis of the medical and psychosocial impact of the genetic study of hereditary cancer (BRCA and Lynch syndrome)
- 3 Development of specific therapeutic strategies for tumors associated with hereditary genetic alterations
- 4 Identification of new genes causing predisposition to hereditary breast cancer
- 5 Evaluation of the risk of cancer of adult patients with Fanconi anemia and survivors of other childhood syndromes with genetic predisposition to cancer

Achievements in 2009

In 2009, a doctoral thesis was defended, focusing on the development and validation of a predictive model to identify carriers of mutations in Lynch syndrome.

Doctoral Thesis: Development and Validation of a Predictive Model for Identification of MLH1 and MLH2 Mutation Carriers in Lynch Syndrome. Directors: Joan Brunet and José Baselga Supervised by: Sapna Synga, MD, MPH

Furthermore, collaboration has continued with the Dana Faber Cancer Institute and the Erasmus Medical Center to expand the predictive model to new genes. We are also leading a Phase I clinical trial jointly led a phase I clinical trial with a specific drug (PARP inhibitor) in combination with chemotherapy for solid tumors.

We have continued to analyze the clinical and psychosocial impact of genetic studies in hereditary syndromes and we took part in studies searching for mutations in new genes conferring predisposition to hereditary breast cancer. We concluded the comparative analysis of two molecular techniques for studying the instability of microsatellites in tumors preserved in paraffin for the identification of patients with suspected Lynch syndrome.

Objectives for 2010

· We the PREMM1,2,6 predictive model in a cohort of patients with populational endometrial cancer and validate the model in different populations of patients with colon cancer internationally, including a Spanish cohort. We are continuing with the process of developing specific new therapies for patients with hereditary cancer or patients with sporadic cancer and molecular abnormalities similar to those of hereditary cancer. We are expanding the analysis of the long-term psychosocial impact of genetic studies in hereditary syndromes,

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specifically in the male population. We are taking part in an international study to analyze the efficacy of early detection of prostate cancer in patients with a mutation in the *BRCA2* gene and a national study to determine the role of breast density as a risk factor for breast cancer in women with mutations in the *BRCA1/2* genes. We are scheduled to carry out ultrasequencing studies studies to search for mutations in new genes conferring predisposition to hereditary breast cancer

Projects

SEOM -Sociedad Española de Oncología Médica Comparison of different molecular screening techniques for Lynch syndrome in colorectal cancer patients. 2007-2009

Ro1CA132829-01A1 NIH Grant. Validation and extension of the PREMM model. 2008-2012

Clinical Trials

Do81oCoo21 A Phase I/II, Open Label, Multi-centre Study of AZD2281 Administered Orally in Combination with Cisplatin, to Assess the Safety and Tolerability in Patients with Advanced Solid Tumours, and to Assess Efficacy in the Neoadjuvant Setting for Patients with Triple Negative Breast Cancer

Publications

Balmaña J, Díez O, Castiglione M; ESMO *Guidelines Working Group. BRCA in breast cancer: ESMO clinical recommendations*. Ann Oncol. 2009 May;20 Suppl 4:19-20. Review.

Díez O, Gutiérrez-Enríquez S, **Balmaña J**. Heterogeneous prevalence of recurrent BRCA1 and BRCA2 mutations in Spain according to the geographical area: implications for genetic testing. Fam Cancer. 2009 Nov 26.

Díez O, Gutiérrez-Enríquez S, Mediano C, Masas M, Saura C, Gadea N, **Balmaña J**. *A novel de novo BRCA2 mutation of paternal origin identified in a Spanish woman with early onset bilateral breast cancer. Breast Cancer Res Treat*. 2009 Aug 1.

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 among individuals undergoing BRCA1/2 genetic testing in a multicentre Spanish cohort*. Hum Reprod. 2009 Apr;24(4):1000-6. Epub 2008 Dec 26. Erratum in: Hum Reprod. 2009 Jul;24(7):1772.

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Kastrinos F, Allen JI, Stockwell DH, Stoffel EM, Cook EF, Mutinga ML, Balmaña J, Syngal S. Development and validation of a colon cancer risk assessment tool for patients undergoing colonoscopy. Am J Gastroenterol. 2009 Jun;104(6):1508-18. Epub 2009 Apr 28.

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Quispe I, **Balmaña J**. *Predictive models for identification of germline mutation carriers in Lynch syndrome*. Med Clin (Barc). 2009 May 12.

Sanz J, Ramón y Cajal T, Torres A, Darder E, Gadea N, Velasco A, Fortuny D, López C, Fisas D, Brunet J, Alonso MC, **Balmaña J**. *Uptake of predictive testing among relatives of BRCA1 and BRCA2 families: a multicenter study in northeastern Spain*. Fam Cancer. 2009 Dec 20.

Principal Investigator
Judith Balmaña



Current positions

- · Head of the High Risk and Cancer Prevention Program
- Specialist in Medical Oncology at the Vall d'Hebron University Hospital
- Certificate of the ECFMG (Educational Commission for Foreign Medical Graduates), 1999
- Member of the Spanish Society of Medical Oncology (SEOM)
- Member of InSiGHT (International Society for Gastrointestinal Hereditary Tumors)
- Member of the board of the SEOM Hereditary Cancer Section
- Coordinator of the family cancer module of the 1st Master's Degree in Genetic Counselling at Pompeu Fabra University (UPF).
 Member of ESMO

Academic Qualifications

- Degree in Medicine and Surgery from the Universitat de Barcelona, 1995
- Doctorate in Medicine from the Universitat Autònoma de Barcelona, 2009

Prizes and Scholarships

- Scholarship to study at the Risk and Prevention Clinic at Dana Farber Cancer Institute, Boston, Mass. USA
- Participant in the exchange program organized by the International Federation of Medical Students Association

Most relevant scientific publications

Opinion about reproductive decision making among individuals undergoing BRCA1/2 genetic testing in a multicentre Spanish cohort. 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. Hum Reprod. 2009 Apr;24(4):1000-6. Epub 2008 Dec 26. Erratum in: Hum Reprod. 2009 Jul;24(7):1772.

Comparison of predictive models, clinical criteria and molecular tumour screening for the identification of pactients with Lynch syndrome in a population-based cohort of colorectal cancer patients. Balmaña J, Balaguer F, Castellví-Bel S, Steyerberg EW, Andreu M, Llor X, Jover R, Castells A, Syngal S; Gastrointestinal Oncology Group of the Spanish Gastroenterological Association. J Med Genet. 2008; 45 (9): 557-63. Epub 2008 Jun25.

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Santiago Ramón y Cajal

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Josep Castellví MD

Laboratory Supervisor José Jiménez

> Technicians Sonia Rodríguez Elisabeth Llonch Nerea Peiró Gertrudis Sánchez

Assistant Mª Angeles Díaz

NEO-ALTTO Central Lab Coordinator
Laurence Lebreton

Strategic Goals

- 1 To serve as translator between basic and clinical research
- 2 Molecular pathology strategies serving clinical oncology needs
- 3 Discovery of biomarkers
- 4 Participate as central and local laboratory in clinical trials performing pharmacodynamic studies

Achievements in 2009

The Molecular Pathology Program is physically located within the Pathology Department, with access to 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, which are routinely used for mRNA and protein studies.

During 2009, our group has participated in 55 clinical trials, acting as central laboratory in many of them. We routinely perform immunohistochemistry studies with antibodies used as diagnosis markers (proliferation, angiogenesis, oncogenes, lack of suppressor genes, mutated genes) and to characterize new therapeutic targets for developing new specific inhibitors (more than 100 optimized antibodies with this technique). We also perform multiple-target immunofluorescence, fluorescence insitu hybridization for many key genes, tissue micro-array constructions, image analysis, nucleic acid extraction and quantification and gene sequencing. The work performed by this laboratory has been essential in translating findings from the laboratory bench to clinical trials. We have explored HER2 pathways well as many downstream targets. including the PI3K-AKT pathway. Using preclinical animal models, we evaluated pathway inhibition and downstream target behavior resistance in the quest for biomarkers that anticipate prognosis or drug-response. These models serve as the ideal resource for identifying these biomarkers in order to use them in further clinical trials.

In 2009 we also implemented new technologies that include the use of automated image analysis based on immunofluorescence (Aqua™ HistoRx); this platform has the capacity to quantify immunofluorescent intensities, avoiding intra- and interobserver variation and, more importantly, to mask only the population of interest and exclude other cell types from the analyses. We are also developing the use of the Veridex platform, Cell Search™ that allows the detection and characterization of circulating tumor cells from patients´ blood samples; this innovative technology would make it possible to follow up treatments and identify patients with high risk of recurrence.

Objectives for 2010

- · As central laboratory we will analyze tissue samples from various clinical trials, including the NEO-ALTTO trial that explores whether treatment with lapatinib, trastuzumab (Herceptin®), or their combination, together with traditional chemotherapy (paclitaxel), can reduce the size of breast tumors prior to surgery. This global trial will recruit 450 women with HER2 (ERBB2)-positive breast cancer at about 130 sites in 32 countries
- Preclinical animal models exploring novel Akt/mTOR inhibitors as well as new therapeutic combinations such as PI3K/Aκτ/MTOR inhibitors with MEK inhibitors or mTOR inhibitors with anti-IGF-IR agents
- Generate a DNA extraction platform from archival tissue in order to perform high through-put gene sequencing, profiling tumoral samples from diverse sources

Projects

Overcoming Resistance to anti-HER2 therapy
Duration: 2010-2014

Funded by: ERC

Overcoming resistance to anti-HER2 therapy with PI3K inhibitors. Anticipating emerging resistance to PI3K pathway inhibition

Duration: 2009-2012 Funded by: Novartis

Sequenom MassArray Platform Duration: 2009-2010

Células Tumorales circulantes en Cáncer de mama Fundación Rafael del Pino 2009-2011

Clinical Trials

CA180-004 Phase I Study of Dasatinib (*BMS-354825*) and Capecitabine for Advanced Breast Cancer.

CHSP990A2101 A Phase I Dose Escalation, Multicenter, Open-label Study of *HSP990* Administered Orally in Adult Patients With Advanced Solid Malignancies.

MKo646-o13 Study to Establish Proof-of-Biology for *MK0646* in Breast Cancer.

MK-8669/004 A Phase I Study of Ridaforolimus (*MK8669*) and *MK0646* in Patients With Advanced Cancer.

CRADoo1J2101 A Phase Ib/II Study Investigating the Combination of Everolimus With Trastuzumab and Paclitaxel in Patients With *HER2*-overexpressing Metastatic Breast Cancer.

CAUY922A2101 A Phase I Dose Escalation, Multicenter, Open-label Study of AUY922 Administered IV on a Once Weekly Schedule in Adult Patients With Advanced Solid Malignancies Including Phase II Expansion Arms in Patients With Either *HER2* Positive or ER Positive Locally Advanced or Metastatic Breast Cancer.

EMR 200027-051 Randomized Phase II Trial With Cetuximab and Cisplatin in the Treatment of ERnegative, PgR-negative, HER2-negative Metastatic Breast Carcinoma ("Basal Like").

BO22495 A Phase Ib/II, Open-Label Study of the Safety, Tolerability, and Efficacy of Trastuzumab-*MCC-DM1* in Combination With Pertuzumab Administered Intravenously to Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer Who Have Previously Received Trastuzumab.

CTKI258A2202 A Multi-center, Open Label Phase II Trial of *TKI258* in *FGFR1* Amplified and Non-amplified Metastatic or Advanced *HER2* Negative Breast Cancer.

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IPI-504-07 A Phase 2 Multicenter Study Evaluating the Efficacy and Safety of IPI-504 in Combination With Trastuzumab in Patients With Pretreated, Locally Advanced or Metastatic Human Epidermal Growth Factor Receptor 2 (HER2) Positive Breast Cancer.

CA180-261 A Randomized, Double-Blind, Multi-Center Phase II Trial of Exemestane (Aromasin®) Plus Dasatinib Versus Exemestane Plus Placebo in Advanced ER+ Breast Cancer After Disease Progression on a Non-Steroidal Aromatase Inhibitor.

CA163100 A Randomized Phase II Biomarker Neoadjuvant Study of Sequential AC Followed by Ixabepilone Compared to Sequential AC Followed by Paclitaxel in Women with Early Stage Breast Cancer Not Overexpressing *HER-2* and Estrogen Receptors.

BO21977 An Open-Label Study of Trastuzumab-MCC-DM1 (*T-DM1*) vs. Capecitabine + Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer (EMILIA).

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

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.

NEOALTTO A randomised, multicentre, openlabel, phase III study of neoadjuvant lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2/ErbB2 positive primary breast cancer.

SOFT Suppression of Ovarian Function Plus Either Tamoxifen or Exemestane Compared With Tamoxifen Alone in Treating Premenopausal Women With Hormone-Responsive Breast Cancer.

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 Breast Cancer With 0 to 3 Positive Nodes.

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.

1199.51 A Phase I-II Study of BIBF 1120 and FOLFOX Compared to Bevacizumab and FOLFOX in First Line Metastatic Colorectal Cancer Patients.

PM104A-001-04

CBGT226A2101 A Phase I/II, Multi-center, Openlabel Study of BGT226, Administered Orally in Adult Patients With Advanced Solid Malignancies Including Patients With Advanced Breast Cancer.

Po5670 A Pharmacodynamic Study of SCH 900105 in Subjects With Advanced Solid Tumors Who Have Liver Metastases.

CNTO328STM2001 A Phase 1/2, Multiple-dose, Dose-escalation Study to Assess the Safety, Efficacy, and Pharmacokinetics of Intravenous *CNTO 328*, and Anti-Interleukin 6 (IL-6) Monoclonal Antibody, in Subjects with Solid Tumors.

PM1183-A-001-08 Phase I, Multicenter, Openlabel, Dose-escalating, Clinical and Pharmacokinetic Study of *PM01183* in Patients With Advanced 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.

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

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.

20070411 A Phase 1b/2 Open Label, Dose Escalation Study of *AMG 655* in Combination With *AMG 479* in Subjects With Advanced, Refractory Solid Tumors.

TTD-o8-o6 Open, Multicenter Phase II Study to Evaluate the Efficacy and Safety of the Combination of Panitumumab With Irinotecan in Patients With Wild-Type KRAS Metastatic Colorectal Cancer Refractory to Irinotecan Based Chemotherapy.

EMR 62242-004 An Open-label, Randomized, Controlled, Multicenter, Phase I/II Trial Investigating 2 *EMD 525797* Doses in Combination With Cetuximab and Irinotecan Versus Cetuximab and Irinotecan Alone, as Second-line Treatment for Subjects With K-ras Wild Type Metastatic Colorectal Cancer.

20070820 Phase 2 Study of Panitumumab Plus Irinotecan Followed by Panitumumab Plus AMG 479 in Subjects With Metastatic Colorectal Carcinoma Expressing Wild Type KRAS and Refractory to Oxaliplatin-or Irinotecan- and Oxaliplatin-containing Regimens to Evaluate Mechanisms of Acquired Resistance to Panitumumab.

20060579 A Phase 2, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of FOLFIRI in Combination With AMG 479 or AMG 655 Versus FOLFIRI for the Second-line Treatment of KRAS-mutant Metastatic Colorectal Carcinoma.

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.

IMCL CP12-0709 An opel label, multicenter, phase 2 study evaluating the safety and efficacy of IMC-1121B in combination with 5-FU/FA and oxaliplatin (modified FOLFOX-6) as first-line therapy in patients with metastatic colorectal cancer.

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

TTD-o6-o2 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.

2-55-52030-726 Phase III, Randomised, Doubleblind, 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.

CRADoo1C2324 A Randomized Double-blind Phase III Study of RADoo1 10 mg/d Plus Best Supportive Care Versus Placebo Plus Best Supportive Care in the Treatment of Patients With Advanced Pancreatic Neuroendocrine Tumor (NET).

XL147-001 A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of XL147 Administered Orally Daily to Subjects With Solid Tumors or Lymphoma.

CBEZ235A2101 A Phase I/II, Multi-center, Openlabel Study of *BEZ235*, Administered Orally on a Continuous Daily Dosing Schedule in Adult Patients With Advanced Solid Malignancies Including Patients With Advanced Breast Cancer.

MK0646-001 An Open-Label, Dose Escalation Phase I Trial of MK0646 Given as a Weekly, Every Other Week, or Every Three Week Infusion in Patients With Advanced Solid Tumors and Multiple Myeloma.

CBKM120X2101 A Phase IA, Multicenter, Openlabel Dose Escalation Study of BKM120, Administered Orally in Adult Patients With Advanced Solid Malignancies.

CLDE225X2101 A Phase I, Multicenter, Openlabel, Dose-escalation Study of Oral *LDE225* in Patients With Advanced Solid Tumors. **H9H-MC-JBAH**

EMD121974-011 Cilengitide for Subjects With Newly Diagnosed Glioblastoma Multiforme and Methylated MGMT Gene Promoter - A Multicenter, Open-Label, Controlled Phase III Study, Testing Cilengitide in Combination With Standard Treatment (Temozolomide With Concomitant Radiation Therapy, Followed by Temozolomide Maintenance Therapy) Versus Standard Treatment Alone.

BAY43-9006/12782 A Phase II, Randomized, Open-label, Multicenter, Study Evaluating the Efficacy of Sorafenib Alone and Sorafenib in Combination With Low Dose Interferon Alpha-2a as Second-line Treatment of Sunitinib Failure in Patients With Metastatic Renal Cell Carcinoma.

A4021011 A Phase 2, Randomized, Non-Comparative, Two-Arm Open Label, Multiple-Center Study Of *CP-751,871* In Combination With Docetaxel/Prednisone In Chemotherapy- Naive (Arm A) And Docetaxel/Prednisone Refractory (Arm B) Patients With Hormone Insensitive Prostate Cancer.

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)

H6Q-MC-So19 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

XL765-003 A Phase 1 Dose-Escalation Study of *XL765* in Combination With Erlotinib in Subjects With Solid Tumors.

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.

CA187-017 A Double-Blind, Randomized, Parallel Two-Arm Phase II Trial of *BMS-690514* Versus Erlotinib in Previously Treated NSCLC Patients.

VEG111128 An Open-label, Multicentre, Randomised Phase II Study of Pazopanib in Combination With Pemetrexed in First-line Treatment of Subjects With Predominantly Nonsquamous Cell Stage IIIBwet/IV Non-small Cell Lung Cancer.

GECPo6/o1 Phase III, Multicenter, Open-Label, Randomized Trial of Tarceva [®] vs Chemotherapy in Patients With Advanced NSCLC With Mutations in the TK Domain of the EGFR.

Publications

Romero J, Esteves M, Landolfi S, Hernández-Losa J, Castaño J, Wilson AJ, **Ramon y Cajal S**, Mariadason JM, Schwartz S Jr, Arango D. *The receptor tyrosine kinase EPHB4 has tumor suppressor activities in intestinal tumorigenesis*. Cancer Res. 2009 Sep 15;69(18):7430-8. Epub 2009 Sep 8.

Monge M, Doll A, Colas E, Gil-Moreno A, Castellvi J, García A, Colome N, Perez-Benavente A, Pedrola N, Lopez-Lopez R, Dolce X, **Ramon y Cajal S**, Xercavins J, Matias-Guiu X, Canals F, Reventos J, Abal M. J. *Substractive proteomic approach to the endometrial carcinoma invasion front*. Proteome Res. 2009 Oct; 8(10): 4676-84

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Castellvi J, Garcia A, Ruíz-Marcellan C, Hernández-Losa J, Peg V, Salcedo M, Gil A and Ramon y Cajal S. Cell signaling in endometrial carcinoma: Phosphorylated 4E-Binding Protein-1 expression in endometrial cancer correlates with aggressive tumors and prognosis. Hum Pathol. 2009 Oct; 40(10): 1418-26. Epub 2009 May 9.

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Benavente S, Vergés R, Hermosilla E, Fumanal V, Casanova N, Garcia A, Ramon y Cajal S and Giralt J. Overexpression of phosphorylated 4E-BP1 predicts for tumor recurrence and reduced survival in cervical carcinoma treated with postoperative radiotherapy. Int J Radiat Oncol Biol Phys. 2009 Apr 11. [Epub ahead of print]

Artero Castro, H. Kondoh, P.J. Fernández-Marcos, M. Serrano, S. Ramón y Cajal, M.E. Lleonart. *RPLP1 bypasses replicative senescence and contributes to transformation*. Exp Cell Res. 2009 May 1;315(8):1372-83. Epub 2009 Feb 20.

Scaltriti M, Verma C, Guzman M, Jimenez J, Parra JL, Pedersen K, Smith DJ, Landolfi S, **Ramon y Cajal S**, Arribas J and Baselga J. *Lapatinib, a HER2 tyrosine kinase inhibitor, induces stabilization and accumulation of HER2 and potentiates trastuzumab-dependent cell cytotoxicity.* Oncogene. 2009 Feb 12;28(6):803-14. Epub 2008 Dec 8.

López-Vicente L, Armengol G, Pons B, Coch L, Argelaguet E, Lleonart M, Hernánez-Losa J, de Torres I, **Ramón y Cajal S**. *Regulation of replicative and stress-induced senescente by RSK4, which is down-regulated in human tumors*. Clin Cancer Res. 2009 Jul 15;15(14):4546-53. Epub 2009 Jul 7.

GGuillen-Marti J, Diaz R, Quiles MT, Lopez-Cano M, Vilallonga R, Huguet P, Ramon y Cajal S, Sanchez-Niubo A, Reventós J, Armengol M, Arbos MA.J. *MMPs/TIMPs and inflammatory signalling de-regulation in human incisional hernia tissues.* J Cell Mol Med. 2009 Nov-Dec;13(11-12):4432-43. Epub 2008 Dec 29.PMID: 19397782

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Ivanova AV, Ivanov SV, **Prudkin L**, Nonaka D, Liu Z, Tsao A, Wistuba I, Roth J, Pass HI. *Mechanisms of FUS1/TUSC2 deficiency in mesothelioma and its tumorigenic transcriptional effects*. Molecular Cancer. 2009 Oct 24;8(1):91.

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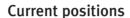
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Prudkin Ludmila, Diane Liu, Natalie C. Ozburn, Menghong Sun, Carmen Behrens, Xi Ming Tang, Kathlynn C. Brown, B. Nebiyou Bekele, Cesar Moran and Ignacio I. Wistuba. *Epithelial-Mesenchymal Transition in Non-Small Cell Lung Cancer Development and Progression*. Modern Pathology, March 2009.

Prudkin Ludmila, Ximing Tang, Ignacio I. Wistuba. *Germ-Line and Somatic Presentations of the EGFR T790M Mutation in Lung Cancer* Journal of thoracic oncology, January 2009. Principal Investigator
Santiago Ramon
y Cajal



- · Head of the Molecular Pathology Program
- · Chairman of the Pathology Department at Vall d'Hebron University Hospital
- Full Professor of Pathology at Universitat Autònoma de Barcelona (UAB)

Academic Qualifications

- Degree in Medicine and Surgery from the Universidad de Zaragoza, 1982
- Doctorate in Medicine and Surgery from the Faculty of Medicine, Universidad de Zaragoza
- Specialization in Histopathology at the Jiménez Díaz Foundation, Madrid

Prizes and Scholarships

- · Rhone-Poulenc-Rorer Award of the Association for Cancer Research, 1996
- Ernesto Seco Award of the Royal National Academy of Medicine, 1996
- Member of Honor of the College of Physicians of Zaragoza, 1997
- National Award for Research in Oncology for young investigators (1997), International Research Promotion Council (IRPC) Award for "Eminent Scientist of the Year 1999"
- · IRPC Gold Medal
- · Corresponding Academic of the Royal National Academy of Medicine, 2001

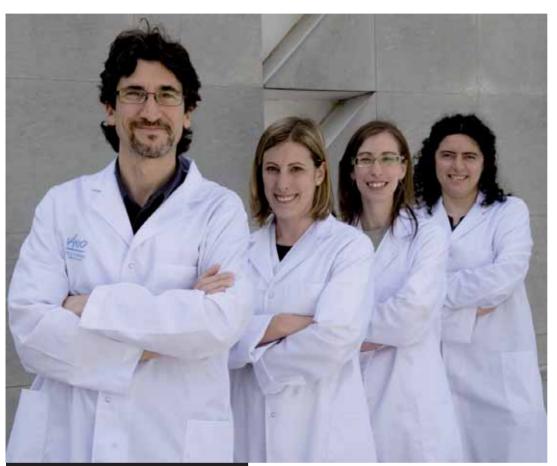
- Honorary Academic of the Royal Academy of Medicine of Andalusia, 2006
- Scholarship from the National Training Plan for Research Personnel, 1983 and 1984
- · Scholarship from the Social Security Health Care Research Fund, 1989-1990. Postdoctoral Fellow at the Pathology Department of Yale University (USA), 1989-90

Areas of Research

- · Tumor pathology
- · Study of new diagnostic and prognostic markers in cancer
- · Molecular pathology
- · Study of Cell Signalling pathway in human tumors. Identification of funnel factors
- · Study of gene expression of senescence in human tumors



Oncogenetics Group



Orland Díez

Staff scientist Sara Gutierrez Enríquez PhD

> Technicians Miriam Masas Castro Anna Tenés Felipe

Strategic Goals

- 1 Molecular study of the genetic predisposition to hereditary breast/ovarian cancer
- 2 Identification and characterization of mutations and molecular alterations of genes of genetic predisposition to familiar breast/ovarian cancer of (BRCA1 and BRCA2, TP53, among others)
- 3 Identification of new genes for predisposition to familiar breast/ovarian cancer
- 4 Analysis of genetic modifiers of risk in BRCA1/BRCA2 breast/ovarian cancer families
- 5 Study of DNA repair capacity of cells with mutations in *BRCA1* or *BRCA2* genes

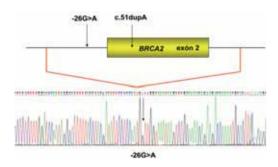
Achievements in 2009

In 2009, the Oncogenetics laboratory group carried out the following activities in collaboration with the Clinical group:

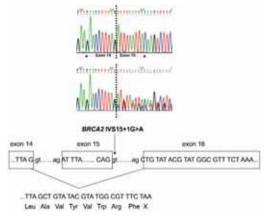
We performed the identification and molecular characterization of new and complex alterations in BRCA1 and BRCA2 genes, which had not previously been described. We developed a database with molecular data of more than 3000 families analyzed for BRCA genes in 14 centers in Spain. The purpose of this is to determine the spectrum and frequency of the mutations in our population and the clinical variables that better predict the presence of mutations to improve the selection criteria of the families for genetic studies. We also identified TP53, CHEK2 and PALB2 mutations in women with familial breast cancer and no BRCA mutation. We studied genomic expression of genes that predict susceptibility to secondary effects of radiotherapy in breast cancer.

Objectives for 2010

- Analysis of variants with unknown biological significance and changes in untranslated regions in BRCA1 /BRCA2 genes
- We also aim to identify and characterize germ line sequence variants en the BRCA1, BRCA2 and TP53 genes in breast cancer families



Study of the de novo mutation c.51dupA, identified in a woman with breast cancer and no family history of the disease



Splicing alteration caused by the BRCA2 mutation IVS15+G>A in a woman with hereditary breast cancer

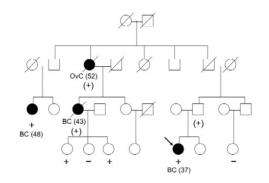
Projects

Desarrollo de un modelo predictivo de detección de mutaciones en los genes BRCA1 y BRCA2 en población española con sospecha de cáncer de mama familiar.

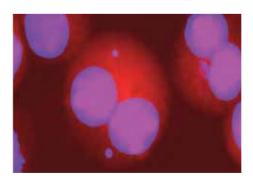
2008-2009.

Fundación de Investigación Médica Mútua Madrileña.

Cáncer de mama y ovario hereditario: estudio de perfiles de expresión génica y proteómica de linfocitos irradiados como factor predictivo. 2008-2010. Fundación de Investigación Médica Mútua Madrileña.



Family with breast cancer (BC) and ovarian cancer (OC): Carriers (+) and non-carriers (-) of mutations of the BRCA1 gene



Micronuclei induced by mitomycin C in cells carrying a mutation in the BRCA2 gene

Publications

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 2009;117:461-5.

Rosa-Rosa JM, Pita G, Llort G, Brunet J, Lázaro C, Blanco I, Ramon y Cajal T, **Díez O**, de la Hoya M, Caldés T, Tejada I, González-Neira A, Benitez J. *A Genome wide linkage scan reveals three new loci for familial breast cancer susceptibility*. Am J Hum Genet 2009; 84:115-22.

Díez O . *Molecular pathology of hereditary breast cancer*. Clin Transl Oncol 2009: (11) sup 1:24-26.

Díez O, Gutiérrez-Enríquez S. *BRCA2 splice site* mutations in an Italian breast/ovarian cancer family. Ann Oncol 2009; 20:1285.

Balmaña J, **Díez O**, Castiglione M. *BRCA in breast cancer: ESMO Clinical Recommendations*. Ann Oncol 2009; Supp 4: iv19-iv20.

Díez O, Gutiérrez-Enríquez S, Mediano C, Masas M, Saura C, Gadea N, Balmaña J. *A novel de novo BRCA2 mutation of paternal origin identified in a Spanish woman with early onset bilateral breast cancer*. Breast Cancer Res Treat 2010; 121:221-5.

Díez O Gutiérrez.Enríquez S, Balmaña J. Heterogenic prevalence of recurrent BRCA1 and BRCA2 mutations in Spain according to the geographical area: implications for genetic testing. Fam Cancer 2010;9:187-91.

Balmaña J, **Díez O**, Rubio I, Castiglione M; ESMO Guidelines Working Group. *BRCA in breast cancer: ESMO Clinical Practice Guidelines*. Ann Oncol 2010; Supp 5: v20-v22.

Oncogenetics Group

Principal Investigator Orland Díez



Current positions

- · Head of the Oncogenetics Program
- Staff member of the Molecular Biology Laboratory at Vall d'Hebron University Hospital.

Academic Qualifications

- Degree in Biology from the Universitat de Barcelona, 1982
- Specialist in Clinical Biochemistry (B.I.R.) from the Ministry of Health and Consumer Affairs, 1992
- Doctorate in Biology from the Universitat de Barcelona, 1999

Areas of Research

- Identification and characterization of mutations and molecular alterations of genes causing genetic predisposition to familial breast and ovarian cancer (including BRCA1 and BRCA2).
- · Identification of new genes causing predisposition to hereditary breast cancer.
- Identification of low-penetrance genes and genetic risk modifiers for breast and ovarian cancer
- Study of the repair capacity of DNA in cells carrying a mutation in the BRCA1 or BRCA2 genes.

Prizes and Scholarships

 Accreditation in Human Genetics from the Spanish Association of Human Genetics, 2002

Most relevant scientific publications

Differences in the phenotypic expression of a new BRCA1 mutation in identical twins. Díez O, Brunet J, Sanz J, del Río E, Alonso MC, Baiget M. The Lancet 1997; 9079: 713.

The R71G BRCA1 is a founder Spanish mutation and leads to aberrant splicing of the transcript. Vega A, Campos B, Bressac de Paillerets B, Bond PM, Janin N, Douglas FS, Domènech M, BaenaM, Pericay C, Alonso C, Carracedo A, Baiget M, **Díez O**. Hum Mutat 2001; 17: 520-1

Analysis of BRCA1 and BRCA2 genes in Spanish breast/ovarian cancer patients: a high proportion of mutations unique to Spain and evidence of founder effect. Díez O, Osorio A, Durán M, Martinez-Ferrandis JI, de la Hoya M, Salazar R, Vega A, Campos B, Rodríguez-López R, Velasco E, Chaves J, Díaz-Rubio E, Cruz JJ, Torres M, Esteban E, Cervantes A, Alonso C, San Román JM, González-Sarmiento R, Miner C, Carracedo A, Armengod ME, Caldés T, Benítez J, Baiget M. Hum Mutat 2003; 22: 301-12.

Immunohistochemical expression of DNA repair proteins in familial breast cancer differentiate BRCA2-associated tumors. Honrado E, Osorio A, Palacios J, Milne RL, Sánchez L, Díez O, Cazorla A, Syrjakoski K, Huntsman D, Heikkilä P, Lerma E, Kallioniemi A, Rivas C, Foulkes WD, Nevanlinna H, Benítez J. J Clin Oncol 2005; 23: 7503-11.

A Genome wide linkage scan reveals three new loci for familial breast cancer susceptibility. Rosa-Rosa JM, Pita G, Llort G, Brunet J, Lázaro C, Blanco I, Ramon y Cajal T, **Díez O**, de la Hoya M, Caldés T, Tejada I, González-Neira A, Benitez J. Am J Hum Genet 2009; 84:115-22.



Francesc Canals

Post-doctoral Fellows Joan-Josep Bech PhD Marta Monge PhD

> Technicians Núria Colomé MSc

Strategic Goals

- 1 Exploring the role of ADAM and ADAMTS metalloproteases in cancer through proteomic analysis
- 2 Proteomic screening for new biomarkers to assist cancer therapeutics
- 3 Providing services in proteomic techniques to other research groups as core facility

Achievements in 2009

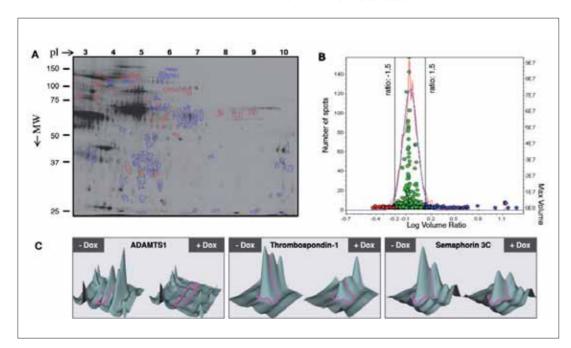
In a collaborative project with Dr. J. Arribas laboratory, using a combined DIGE and SILAC proteomic approach, we identified Semaphorin 3C as a new substrate of the metalloprotease *ADAMTS1* (Figure 1). The specific cleavage product of S₃C is able to promote the migration of breast cancer cells. This newly discovered mechanism can thus be involved in the induction of metastasis by ADAMTS1 overexpression in breast cancer.

We have used ICPL and label-free based liquidchromatography- mass spectrometry analysis to analyze the proteins secreted by glioma cell lines or primary cultures of cells derived from gliomas, in response to TGF-beta stimulation (in collaboration with Dr. J. Seoane). These experiments led to the identification of several proteins as candidate biomarkers to select glioma types suitable for therapies targeted at the TGF-beta pathway. Other contributions to projects of VHIO research groups that involved proteomic analysis include exploring the mechanism of the induction of cell migration by HER-2 activity in breast cancer through phosphorylation of cortactin (with Dr. Arribas lab), exploring the mechanisms of HGF signaling in melanoma (with Dr. JA Recio), and searching for cell-surface markers of glioma initiating cells (with Dr. J Seoane).

The Proteomics Laboratory has continued to provide services as a member of the Carlos III Health Institute Cancer Research Network, and of the ProteoRed National Proteomics Institute. During this year, the laboratory has provided services in several proteomic techniques to more than 25 research groups, not only from the Vall d'Hebron Hospital but also from the main hospitals, research centers and universities in the area. In several cases, the laboratory has been participating actively in collaborative projects with these groups, including projects relating to endometrial cancer and diabetic retinopathy.

Proteomics Group

Figure 1. 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.

Objectives for 2010

- Continue to explore the role of ADAM and ADAMTS metalloproteases in tumor progression
- Screening for new cell-surface markers of glioma-initiating cells to aid characterization of tumor heterogeneity and specific features of stem-like cells, such as tumor initiation ability or drug susceptibility
- Implementing new quantitative proteomic analysis methodologies, such as iTRAQ and label-free strategies
- Continuing to provide service on state-of-theart proteomic methodologies to other research groups

Projects

Identificación mediante análisis proteómico de nuevos sustratos de metaloproteasas implicadas en cáncer y caracterización de su papel funcional

Duration: 2008-2010 Funded by: ISCIII (FIS)

Instituto Nacional de Proteómica. ProteoRed

Duration: 2006-2010

Funded by: Fundación Genoma España

Red Temática de Investigación Cooperativa

del Cancer
Duration: 2007-2011

Funded by: ISCIII (Subdirección General de Redes y Centros de Investigación Cooperativa)

Publications

Alonso-del-Rivero M, Trejo SA, Rodríguez de la Vega M, González Y, Bronsoms S, **Canals F**, Delfín J, Diaz J, Aviles FX, Chávez MA. *A novel metallo-carboxypeptidase-like enzyme from the marine annelid Sabellastarte magnifica - a step into the invertebrate world of proteases*. FEBS J. 2009 Sep;276(17):4875-90. Epub 2009 Aug 4.

Bech-Serra JJ, Borthwick A, Colomé N; ProteoRed Consortium, Albar JP, Wells M, Sánchez del Pino M, Canals F. A multi-laboratory study assessing reproducibility of a 2D-DIGE differential proteomic experiment. J Biomol Tech. 2009 Dec;20(5):293-6.

Doll A, Gonzalez M, Abal M, Llaurado M, Rigau M, Colas E, Monge M, Xercavins J, Capella G, Diaz B, Gil-Moreno A, Alameda F, Reventos J. *An orthotopic endometrial cancer mouse model demonstrates a role for RUNX1 in distant metastasis*. Int J Cancer. Jul 15;125(2):257-63, 2009.

Esselens C, Malapeira J, Colomé N, Casal C, Rodríguez-Manzaneque JC, **Canals F**, Arribas J. *The cleavage of semaphorin 3C induced by ADAMTS1 promotes cell migration*. J Biol Chem. 2010 Jan 22;285(4):2463-73. Epub 2009 Nov 13.

Esteve-Puig R, Canals F, Colomé N, Merlino G, Recio J. A. *Uncoupling of the LKB1-AMPKalpha energy sensor pathway by growth factors and oncogenic BRAF*. PloS One. 2009;4(3):e4771. Epub 2009 Mar 10.

García-Castillo J, Pedersen K, Angelini PD, Bech-Serra JJ, Colomé N, Cunningham MP, Parra-Palau JL, Canals F, Baselga J, Arribas J. *HER2 carboxylterminal fragments regulate cell migration and cortactin phosphorylation*. J Biol Chem. 2009 Sep 11;284(37):25302-13. Epub 2009 Jul 8.

Garcia-Ramírez M, Hernández C, Villarroel M, Canals F, Alonso MA, Fortuny R, Masmiquel L, Navarro A, García-Arumí J, Simó R. *Interphotoreceptor retinoid-binding protein* (*IRBP*) is downregulated at early stages of diabetic retinopathy. Diabetologia. 2009 Dec;52(12):2633-41. Epub 2009 Oct 13.

Hellin JL, Bech-Serra JJ, Moctezuma EL, Chocron S, Santin S, Madrid A, Vilalta R, **Canals F**, Torra R, Meseguer A, Nieto JL. *Very low-molecular-mass fragments of albumin in the plasma of patients with focal segmental glomerulosclerosis*. Am J Kidney Dis. 2009 Nov;54(5):871-80. Epub 2009 Sep 25.

Lyakhovich A, Bech-Serra JJ, Canals F, Surralles J. Quick two-dimensional differential in gel electrophoresis-based method to determine length and secondary structures of telomeric DNA. Anal Biochem. 2009 Jan 15;384(2):356-8. Epub 2008 Oct 5.

Monge M, Colas E, Doll A, Gil-Moreno A, Castellvi J, Diaz B, Gonzalez M, Lopez-Lopez R, Xercavins J, Carreras R, Alameda F, Canals F, Gabrielli F, Reventos J, Abal M. *Proteomic approach to ETV5 during endometrial carcinoma invasion reveals a link to oxidative stress*. Carcinogenesis. 2009 Aug;30(8):1288-97. Epub 2009 May 14. PubMed PMID: 19443906.

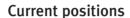
Monge M, Doll A, Colas E, Gil-Moreno A, Castellvi J, Garcia A, Colome N, Perez-Benavente A, Pedrola N, Lopez-Lopez R, Dolcet X, Ramon y Cajal S, Xercavins J, Matias-Guiu X, Canals F, Reventos J, Abal M. Subtractive proteomic approach to the endometrial carcinoma invasion front. J Proteome Res. 2009 Oct;8(10):4676-84.

Rodríguez CE, Arranz JA, Colomé N, Bech-Serra JJ, Canals F, Del Toro M, Riudor E. *Proteomic analysis in cerebrospinal fluid of patients with atypical nonketotic hyperglycinemia and pulmonary hypertension - a pilot study.* Proteomics – Clinical Applications, 12: 1430-9, 2009.

Trejo SA, López LM, Caffini NO, Natalucci CL, Canals F, Avilés FX. Sequencing and characterization of asclepain f: the first cysteine peptidase cDNA cloned and expressed from Asclepias fruticosa latex. Planta. 2009 Jul;230(2):319-28. Epub 2009 May 20.

Proteomics Group

Principal Investigator
Francesc Canals



- · Head of the Proteomics Program
- Collaborations with research groups from VHIO, UAB, CNIC and Genyo.

Academic Qualifications

- Degree in Organic Chemistry from Institut Químic de Sarrià, 1982
- Doctorate in Organic Chemistry from Institut Químic de Sarrià, 1989
- Science degree studies in the specialty of biochemistry at the Autonomous Universitat de Barcelona, 1987



Areas of Research

- Application of proteomics techniques to the identification and characterization of metalloprotease substrates implicated in tumor progression and metastasis
- Proteomic analysis using the latest MALDI-TOF and ESI-ion trap mass spectrometry techniques, 2D-DIGE two-dimensional electrophoresis, liquid chromatography coupled to ESI-MS, and quantitative techniques based on isotope markers (ICPL, SILAC)
- Development of new strategies for proteomic analysis

Prizes and Scholarships

- F.P.I. doctoral scholarship from the Ministry of Education and Science, 1985-1989
- · M.E.C. postdoctoral scholarship, 1989-1991
- · CIRIT-DGU postdoctoral scholarship, 1991-1992
- MEC Contract for the Reincorporation of Investigators, 1992-1995

Most relevant scientific publications

Identification of substrates of the extracellular protease ADAMTS1 by DIGE proteomic analysis. Canals, F., Colomé, N., Ferrer, C., Plaza-Calonge, M.C., Rodríguez-Manzaneque, J.C. Proteomics, 6, S28-S35, 2006

Proteomic Identification of Desmoglein-2 and ALCAM as substrates of ADAM17 and ADAM10 by Difference Gel Electrophoresis. Bech-Serra, J., Santiago-Josefat, B., Esselens, C., Saftig, P., Baselga, J., Arribas, J., Canals, F. Mol. Cell. Biol., 26, 5086-5095, 2006

The cleavage of semaphorin 3C induced by ADAMTS1 promotes cell migration. Esselens C, Malapeira J, Colomé N, Casal, C, Rodríguez-Manzaneque JC, Canals F, Arribas J J. Biol. Chem., 285(4): 2463-73, 2010



Achievements in 2009

In 2009 we started the IMRT program in prostate, head and neck and breast cancer. We also developed the stereotactic radiotherapy program in pediatrics, especially focused on brain tumors and retinoblastoma.

We participated in a quality control program in radiotherapy for Head and neck cancer. This study showed that patients with a major deviation in volume delineation or dose delivery had a statistically significant reduction in loco-regional control. This study has been accepted for publication in the *Journal of Clinical Oncology*.

We showed that a combination of panitumumab and radiotherapy is feasible and has a similar toxicity profile to that of cetuximab plus radiotherapy. Results on efficacy will be analyzed in 2010.

We also showed that, in patients with earlystage cervical carcinoma, a low p4E-BP1 expression was associated with a significantly higher of failure of standard treatments and can be used as a prognostic factor.

Jordi Giralt

Radiation Oncologists
Sergi Benavente MD
Ramón Bodi MD
Xavier Maldonado MD
Meritxell Molla, MD PhD
Begoña Navalpotro MD
Mónica Ramos MD
Victoria Reyes MD
Ramona Verges MD

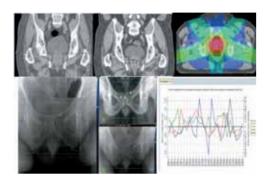
Strategic Goals

- 1 Technology developments: Highly conformal radiotherapy
- 2 Translational research: EGFR inhibitors plus radiotherapy

Objectives for 2010

- · Continue with the IMRT program in pediatric, gynecology and gastrointestinal tumors
- Develop the extracranial stereotactic radiotherapy program in lung cancer and liver metastases
- Improve quality control programs and develop new techniques
- Study new therapeutic combinations with radiotherapy and EGFR inhibitors in head and neck cancer and gastrointestinal tumors

Radiation Oncology Group



Dose distribution and verification for a IMRT treatment plan with fiducials

Clinical Trials

Head and Neck Tumors

- · A Randomized, 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. Study Identifier (*EGF102988*).
- Radiotherapy plus panitumumab versus chemoradiation in unresectable locally advanced head and neck cancer (AMG 20062079).
- · A randomized, double-blind, placebo-controlled parallel-group phase III clinical study to assess the efficacy and safety of soluble beta-1,3/1,6-glucan (SBG) on oral mucositis in head and neck cancer patients undergoing radiotherapy with or without chemotherapy (SBG-2-03).
- Randomized Phase III trial on postoperative chemoradiation in combination with anti EGFR-antibody versus postoperative chemoradiation in head and neck squamous cell carcinomas (HNSCC) with high risk of locoregional recurrence. (EORTC Protocol 22071-24071)

Genitourinary Tumors

- · Phase III randomized multicenter trial of adjuvant androgen deprivation in combination with high-dose three-dimensional conformal radiation therapy in intermediate-to-low-risk localized prostate cancer (DART o1/o5).
- · Phase IV-III randomized, parallel-arm, openlabel prospective 36-month multicenter clinical trial to evaluate the efficacy of intermittent versus continuous androgen blocking treating biochemical recurrence of prostate cancer treated with radiation therapy. PROST_INTERMIT. AC/I(AG) 82/2006 (1905)
- Phase IIIb non-randomized, open-label multicenter trial to monitor the safety of monthly doses of degarelix in patients with prostate cancer". FE 200 486 CS34

- · A randomized, parallel-arm, open-label trial comparing degarelix with goserelin plus antiandrogen flare protection (bicalutamide), in terms of prostate size reduction in prostate cancer patients of intermediate-to-high risk, who require neoadjuvant hormone therapy prior to radiotherapy (curative intent) FE 200486 CS30 · Phase II randomized clinical trial of radiation
- · Phase II randomized clinical trial of radiation therapy, hormone therapy and chemotherapy with docetaxel versus radiation therapy and hormone therapy in patients with high-risk localized prostate cancer (stage III and IV). QT_RT SOGUG

Brain Tumors

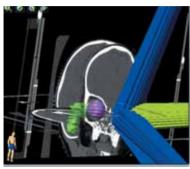
- Phase III trial to evaluate primary chemotherapy with temozolomide versus radiation therapy in patients with low-grade gliomas, stratified by loss of 1p" EORTC 22033-26033
- · Gilencetida in patients with recently-diagnosed multiform glioblastoma and with methylation promotor of the gene MGMT- multicenter, openlabel controlled phase III trial to evaluate gilencetida in combination with conventional treatment (temozolomide with concomitant radiation therapy, followed by maintenance treatment with temozolomide) versus conventional treatment alone. (CENTRIC).

Digestive Tumors

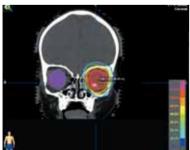
- · Phase II open-label non-controlled ,multicenter pilot study to evaluate the efficacy and safety of the combination of cetuximab and chemotherapy (docetaxel, cisplatin, 5-fluorouracilo) as neoadjuvant treatment followed by concomitant chemotherapy and radiation therapy (cisplatin) combined with cetuximab in patients with locoregional esophageal cancer (TTD-o6-o2).
- · Phase II randomized study of Capecitabine + Bevazucimab + external radiation therapy versus Capecitabine + external radiation therapy as preoperative treatment in patients with locally advanced resectable rectal cancer (TTD-08-05).

Breast Cancer

· A randomized, parallel arm, open-label trial of Selective Use of Postoperative Radiotherapy after Mastectomy: SUPREMO (EORTC 22051).







Esteroatactic radiotherapy far a retinoblastoma

Pediatric Tumors

- · A prospective randomized controlled trial of hyperfractionated versus conventionally fractionated radiotherapy in standard risk medulloblastoma, a SIOP trial (PNET 4).
- · Localized Non-Rhabdomyosarcoma Soft Tissue Sarcomas: European paediatric Soft Tissue Sarcoma Study Group (EpSSG NRSTS 2005).
- EuroNet-Paediatric Hodgkin's Lymphoma Group, international Inter-Group Study for classical Hodgkin's Lymphoma in Children and Adolescents (EuroNet-PHL-C1)

Projects

Use of PET to delimit the volume of treatment in

children with Hodgkin disease Duration: 2008-2009

Funded by: HUVH

Impact of anatomical changes during treatment with radiation therapy on dose distribution in patients with locally advanced head and neck cancer

Duration: 2009-2010 Funded by: HUVH

RF ablation of tumor resection margins to reduce the incidence of reoperation and improve local control in patients with breast cancer. PI 08/90536

Breast irradiation in ventral decubitus position: comparison dosimetry comparison and analysis of reproducibility

Duration: 2009-2011 Funded by: HUVH

Publications

Benavente S, Vergés R, Hermosilla E, Fumanal V, Casanova N, García A, Ramón Y Cajal S, **Giralt J**. *Overexpression of Phosphorylated 4E-BP1 Predicts for Tumor Recurrence and Reduced Survival in Cervical Carcinoma Treated with Postoperative Radiotherapy*. Int J Radiat Oncol Biol Phys. (2009) Dec 1;75(5):1316-22

Guarner J, Navalpotro B, Molero X, **Giralt J** and Malagelada JR. *Management of painful chronic pancreatitis with single dose radiotherapy*. Am J Gastroenterol 2009 Feb;104:349-55

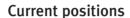
Antolin M, Varela E, Verges R, Guarner F, **Giralt J**, and Malagelada JR. *Faecal DNA and calprotectin as biomarkers of acute intestinal toxicity in patients undergoing pelvic radiotherapy*. Aliment Pharmacol Ther. 2009;30(2):175-85

Benavente S, Huang S, Armstrong EA, Chi A, Hsu KT, Wheeler DL, Harari PM. *Establishment and characterization of a model of acquired resistance to epidermal growth factor receptor targeting agents in human cancer cells*. Clin Cancer Res, 2009;15(5):1585-92.

Rivera F, Galán M, Tabernero J, Cervantes A, Vega-Villegas ME, Gallego J, Laquente B, Rodríguez E, Carrato A, Escudero P, Massutí B, Alonso-Orduña V, Cardenal A, Sáenz A, **Giralt J**, Yuste AL, Antón A, Aranda E; on Behalf of the Spanish Cooperative Group for Digestive Tumor Therapy (TTD). *Phase II Trial of Preoperative Irinotecan-Cisplatin Followed by Concurrent Irinotecan-Cisplatin and Radiotherapy for Resectable Locally Advanced Gastric and Esophagogastric Junction Adenocarcinoma*. Int J Radiat Oncol Biol Phys. 2009 Jun 17.

Radiation Oncology Group

Principal Investigator Jordi Giralt



- · Head of Radiation Oncology Program
- Chairman of the Radiation Oncology Service at Vall d'Hebron University Hospital
- · Professor of Radiation Oncology

Academic Qualifications

- Degree in Medicine at Universitat de Barcelona, 1981
- Residency in Radiation Oncology at Vall d'Hebron University Hospital
- Doctorate in Medicine from Universitat
 Autònoma de Barcelona, 1989



Areas of Research

- · Pediatric tumors
- · Head and Neck Cancer
- · Technology Developments

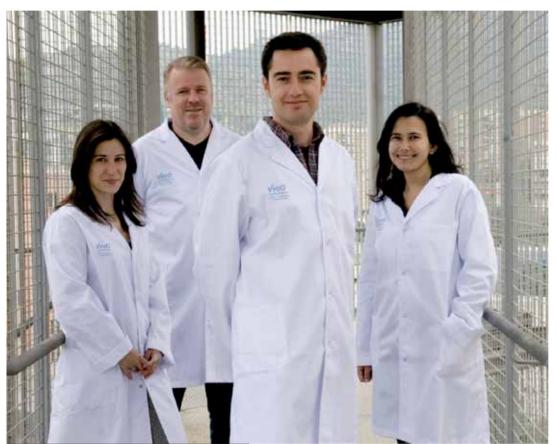
Most relevant scientific publications

Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. Bernier J, Domenge C, Ozsahin M, Matuszewsña K, Lefebvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A, van Glabbeke M; European Organization for Research and Treatment of Cancer Trial 22931. N Engl J Med. 2004 May 6; 350(19):1945-52 The expression of epidermal growth factor receptor results in a worse prognosis for patients with rectal cancer treated with preoperative radiotherapy: a multicenter, retrospective analysis. Giralt J, de las Heras M, Cerezo L, Eraso A, Hermosilla E, Velez D, Luján J, Espín E, Roselló J, Majó J, Benavente S, Armengol M, de Torres I; Grupo Español de Investigación Clínica en Oncología Radioterápica (GICOR). Radiother Oncol. 2005 Feb; 74(2):101-8

Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, Jones CU, Sur R, Raben D, Jassem J, Ove R, Kies MS, Baselga J, Youssoufian H, Amellal N, Rowinsky EK, Ang KK. N Engl J Med. 2006 Feb 9; 354(6):567-78.

Radiotherapy Protocol Compliance And Quality In The Treatment Of Advanced Head and Neck Cancer – Results From Trog 02.02. Peters LJ, O'Sullivan B, Giralt J, FitzGerald TJ, Trotti A, BernierJ, BourhisJ, Yuen K, Fisher R, and Rischin D. J Clin Oncol. J Clin Oncol. 2010 Jun 20;28(18):2996-3001

Stem Cells and Cancer Group



Héctor G. Palmer

Post-doctoral Fellows Stephan Tenbaum PhD Isabel Puig PhD

Technicians
Irene Chicote

Strategic Goals

- 1 To describe the key molecular mechanisms responsible for the self-renewal of colon cancer stem cells (CoCSC)
- 2 To identify the central molecules responsible for the development of metastasis in colon cancer
- 3 To investigate the relevance of novel transcription factors as nuclear effectors of Wnt/betacatenin signal in colon cancer
- 4 To test the efficacy of known and new drugs on CoCSC, with special attention to the molecular mechanisms involved in chemoresistance and metastasis

Achievements in 2009

In 2009, the Stem Cells and Cancer group has focused on studying the distinct properties of colon cancer stem cells and the mechanisms responsible for tumor metastasis.

In particular, we have established novel functional stem cell markers that permit to identify and isolate new CoCSC populations. These markers correlate with populations of cancer cells with enhanced resistance to antitumor drugs.

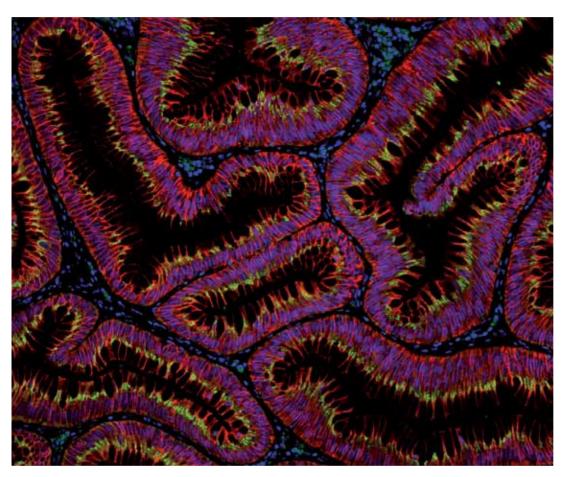
We have also discovered unexpected cooperation between the Wnt/beta-catenin pathway and PI3K/Aκτ/FOXO signaling in promoting colon cancer metastasis. Interaction between their mutual nuclear effectors drives cancer cells towards motility and invasion. This phenomenon appears to occur in colon cancer patients as well, leading us to propose new biomarkers to predict tumor metastasis and clinical response to PI3K/Aκτ inhibitors.

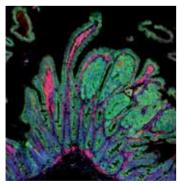
Objectives for 2010

Our objectives for next year are:

- To characterize the gene expression profile specific to the new CoCSC populations described in our laboratory. This screening approach will allow us to identify new molecules specifically expressed by CoCSC, which could become effective biomarkers for predicting tumor progression and response to therapy
- We plan to finish our first project relating to Wnt/beta-catenin and PI3K/AKT/FOXO pathways in colon cancer metastasis
- Following our results with beta-catenin and FOXO molecular interplay, we will study the relevance of these mechanisms in the acquisition of stem cell properties and resistance to Akt inhibitors

Stem Cells and Cancer Group





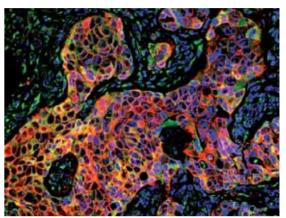
Projects

Human Colon Cancer Stem Cells and Wnt pathway Funded by: Fundació Vall d´Hebrón Institut d´Oncología (VHIO)

Duration: FROM January 2008 TO present

Human Colon Cancer Stem Cells and Wnt/beta-catenin pathway Funded by: Instituto de Salud Carlos III. Proyecto FIS - Plo81356. Duration: From 2009 TO 2012

Human Colon Cancer Stem Cells Funded by: Olga Torres Foundation Duration: From 2009 TO 2011



Publications

Barbáchano A, Ordóñez-Morán P, García JM, Sánchez A, Larriba MJ, Martínez N, Hernández J, Landolfi S, Bonilla F, **Palmer HG**, Rojas JM, Muñoz A. *SPROUTY-2 represses E-cadherin and* associates with malignancy in colon cancer. Second Round Revision in Oncogene.

Martínez-Iglesias O, Garcia-Silva S, Tenbaum SP, Regadera J, Larcher F, Paramio JM, Vennström B, Aranda A. *Thyroid hormone receptor beta1 acts as a potent suppressor of tumor invasiveness and metastasis*. Cancer Res. 2009 Jan 15;69(2):501-9.

Puig I, Champeval D, De Santa Barbara P, Jaubert F, Lyonnet S, Larue L. *Deletion of Pten in the mouse enteric nervous system induces ganglioneuromatosis and mimics intestinal pseudoobstruction*. J Clin Invest. 2009 Dec;119(12):3586-96. doi: 10.1172/JCl39929. Epub 2009 Nov 2.

Puig I, Yajima I, Bonaventure J, Delmas V, Larue L. *The tyrosinase promoter is active in a subset of vagal neural crest cells during early development in mice*. Pigment Cell Melanoma Res. 2009 Jun;22(3):331-4. Epub 2009 Feb 11.

Principal Investigator Héctor G. Palmer



Current positions

· Head of the Stem Cells and Cancer Program

Academic Qualifications

- Degree in Biological Sciences from the Universitat Autònoma de Barcelona, 1997
- Doctorate in Biochemistry and Molecular Biology from the Universidad Autónoma de Madrid, 2001
- Postdoctoral studies at the Biomedical Research Institute (CSIC-UAM, Madrid), 2001-2003, and at the London Research Institute-Cancer Research UK, 2004-2008

Areas of Research

- New molecular mechanisms of action of the Wnt/beta-catenin pathway in colon cancer
- Role of cancer stem cells in initiation, progression, metastasis and resistance to anti-tumor agents in colon cancer
- Key signalling pathways in induction and maintenance of quiescence and chemoresistance of normal and cancer stem cells

Prizes and Scholarships

- · Marie Curie Intra-European (2004)
- · Cancer Research UK (2005)

Most relevant scientific publications

The Vitamin Receptor is a Wnt effector that control hair follicle differentiation and specifies tumor type in adult epidermis.

Palmer HG, Anjos-Afonso F, Carmeliet G, Takeda H, Watt FM.

PLoS ONE. 2008 Jan 23;3(1):e1483.

The transcription factor SNAIL represses vitamin D receptor expression and responsiveness in human colon cancer.

Palmer HG, Larriba MJ, Garcia JM, Ordonez-Moran P, Pena C, Peiro S, Puig I, Rodriguez R, de la Fuente R, Bernad A, Pollan M, Bonilla F, Gamallo C, de Herreros AG, Muñoz A. Nat Med. 2004 Sep;10(9):917-9.

Vitamin D3 promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of b-catenin signaling.

Palmer HG, Gonzalez-Sancho JM, Espada J, Berciano MT, Puig I, Baulida J, Quintanilla M, Cano A, de Herreros AG, Lafarga M, Muñoz A. J Cell Biol. 2001 Jul; 154:1-22.

Thoracic Tumors Group



Enriqueta Felip

Medical Oncologists
Susana Cedrés MD
Pablo Martínez MD

Graduate Students Marina Longo Mireia Cazorla Eva Checa

Strategic Goals

- 1 Optimization of multidisciplinary treatment in patients with stage I-III cancer
- 2 Early integration of genetic determinations to personalize treatments
- 3 Participation in the development of new drugs
- 4 Active intervention in the fight against smoking

Achievements in 2009

In 2009, we presented at ASCO and IASLC the results of a randomized trial in 624 patients with surgically treated lung cancer. In the study, we showed that preoperative chemotherapy does not increase perioperative mortality and that more patients are capable of receiving preoperative chemotherapy than adjuvant chemotherapy.

We confirmed that the development of skin toxicity during treatment with erlotinib correlates with clinical outcome. Furthermore, in the MERIT study, we showed that amplification of the EGFR region of chromosome 7 may be associated with the response to erlotinib.

We also presented data on efficacy and safety for new drugs (pazopanib, sunitinib, pertuzumab, *MK0646*, *BMS690514*) in patients with lung cancer.

Finally, we carried out a preliminary analysis of an epidemiologic study in women with lung cancer in Spain, in which we found that the most frequent histologic subtype is adenocarcinoma (76%), that the mean age (61.7 years) is somewhat lower than that observed in men, and that 40% of patients are non-smokers.

Objectives for 2010

- Implement the determination ALK translocation
- Study the efficacy of PI₃K/mTOR inhibitors in patients with lung cancer resistant to EGFR-TKIs
- Study the efficacy of PARP inhibitors in lung cancer
- · Analyze the epidemiologic/clinical characteristics of women diagnosed with lung cancer
- Play an active role in organizing a European consensus meeting on lung cancer

Clinical Trials

XL765-003 A Phase 1 Dose-Escalation Study of XL765 in Combination With Erlotinib in Subjects With Solid Tumors

MKo646-oo7 An Open Label, Randomized Phase I/IIa Trial Evaluating MKo646 in Combination With Erlotinib for Patients With Recurrent Non-Small Cell Lung Cancer

BO20571 A Randomized, Open-label Study Comparing the Anti-tumor Effect of Treatment With Tarceva Plus Avastin Versus Chemotherapy Plus Avastin in Patients With Advanced Nonsmall Cell Lung Cancer

CA187-017 A Double-Blind, Randomized, Parallel Two-Arm Phase II Trial of BMS-690514 Versus Erlotinib in Previously Treated NSCLC Patients

VEG111128 An Open-label, Multicentre, Randomised Phase II Study of Pazopanib in Combination With Pemetrexed in First-line Treatment of Subjects With Predominantly Nonsquamous Cell Stage IIIBwet/IV Non-small Cell Lung Cancer

GECPo6/o1 Phase III, Multicenter, Open-Label, Randomized Trial of TarcevaÃfÆ'ââ'¬-Ãfâ¤-Ã'® vs Chemotherapy in Patients With Advanced NSCLC With Mutations in the TK Domain of the EGFR

EMR 62240-506 Open, Randomized, Multinational Phase IIIb Trial Evaluating the Activity and Safety of Cetuximab as 250 mg/m2 Weekly and 500 mg/m2 Every Two Weeks Maintenance Therapy After Platinum-based Chemotherapy in Combination With Cetuximab as First-line Treatment for Subjects With Advanced Non-small Cell Lung Cancer (NSCLC).

GSK109493

20060534 Amgen Protocol 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

Publications

Briasoulis E, Pavlidis N, **Felip E**; ESMO Guidelines Working Group. *Cancers of unknown primary site: ESMO clinical recommendations for diagnosis, treatment and follow-up*. Ann Oncol. 2009 May;20 Suppl 4:154-5. Review.

Cedrés S, Prat A, Martínez P, Pallisa E, Sala G, Andreu J, del Campo JM, Quispe I, Baselga J, Felip E. *Clinical surrogate markers of survival in advanced non-small cell lung cancer (NSCLC) patients treated with second-third line erlotinib.* Lung Cancer. 2009 Nov;66(2):257-61. Epub 2009 Feb 23.

Chan AT, Felip E; ESMO Guidelines Working Group. Nasopharyngeal cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009 May;20 Suppl 4:123-5. Review.

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. 2009 May; 20 Suppl 4:68-70. Review.

Felip E, Garrido P, Trigo JM, López-Brea M, Paz-Ares L, Provencio M, Isla D; Spanish Society of Medical Oncology. *SEOM guidelines for the management of non-small-cell lung cancer (NSCLC)*. Clin Transl Oncol. 2009 May;11(5):284-9.

Thoracic Tumors Group

Ingelido AM, Abballe A, di Domenico A, Fochi I, lacovella N, Saragosa A, Spagnesi M, Valentini S, Felip E. Levels and profiles of polychlorinated dibenzofurans, and polychlorinated biphenyls in feedstuffs and milk from farms in the vicinity of incineration plants in Tuscany, Italy. Arch Environ Contam Toxicol. 2009 Aug;57(2):397-404. Epub 2008 Dec 16.

Licitra L, 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. 2009 May;20 Suppl 4:121-2. Review.

Lung Cancer OncoGuia Group, Manchon Walsh P, Manchon P, Borràs JM, Ferro T, Espinàs JA. Lung Cancer OncoGuia. Clin Transl Oncol. 2009 Dec;11(12):805-24.

Muñoz E, Cedrés S, Felip E. Rare tumours of the chest. Eur J Cancer. 2009 Sep;45 Suppl 1:400-1. PubMed PMID: 19775646.

Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, Majem M, Lopez-Vivanco G, Isla D, Provencio M, Insa A, Massuti B, Gonzalez-Larriba JL, Paz-Ares L, Bover I, Garcia-Campelo R, Moreno MA, Catot S, Rolfo C, Reguart N, Palmero R, Sánchez JM, Bastus R, Mayo C, Bertran-Alamillo J, Molina MA, Sanchez JJ, Taron M; Spanish Lung Cancer Group. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. 2009 Sep 3;361(10):958-67. Epub 2009 Aug 19.

Sørensen M, Felip E; ESMO Guidelines Working Group. Small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009 May; 20 Suppl 4:71-2. Review.

Stahel RA, Weder W, Felip E; ESMO Guidelines Working Group. Malignant pleural mesothelioma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009 May;20 Suppl 4:73-5. Review.

Principal Investigator
Enriqueta Felip



Current positions

- · Head of the Lung Cancer Program
- · Specialist physician in Medical Oncology at Vall d'Hebron University Hospital
- Head of the Medical Oncology Service of the Thoracic Tumors Committee at Vall d'Hebron Hospital since 1995
- European coordinator of the European Society of Medical Oncology Guidelines Task Force since 2001
- Member of the executive committee of the Spanish Lung Cancer Group (GECP)
- Member of the board of directors of the Spanish Society for Medical Oncology (SEOM)
- Spanish representative of the European Society for Medical Oncology (ESMO)
- Active member of the International Association for the Study of Lung Cancer (IASLC)

Academic Qualifications

- · Degree in Medicine and Surgery from the Universitat Autònoma de Barcelona, 1987
- Doctorate in Medicine and Surgery from the Universitat Autònoma de Barcelona, 1994

Areas of Research

- · Optimization of multidisciplinary treatments
- Early integration of genetic determinations to personalize treatments
- · Development of new drugs

Most relevant scientific publications

Phase II proof-of-concept study of pazopanib monotherapy in treatment-naive patients with stage I/II resectable non-small-cell lung cancer. Altorki N, Lane ME, Bauer T, Lee PC, Guarino MJ, Pass H, Felip E, Peylan-Ramu N, Gurpide A, Grannis FW, Mitchell JD, Tachdjian S, Swann RS, Huff A, Roychowdhury DF, Reeves A, Ottesen LH, Yankelevitz DF. J Clin Oncol. 2010 Jul 1;28(19):3131-7.

Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer.

Felip E, Rosell R, Maestre JA, Rodríguez-Paniagua JM, Morán T, Astudillo J, Alonso G, Borro JM, González-Larriba JL, Torres A, Camps C, Guijarro R, Isla D, Aguiló R, Alberola V, Padilla J, Sánchez-Palencia A, Sánchez JJ, Hermosilla E, Massuti B; Spanish Lung Cancer Group.

J Clin Oncol. 2010 Jul 1;28(19):3138-45.

A phase II pharmacodynamic study of erlotinib in patients with advanced non-small cell lung cancer previously treated with platinum-based chemotherapy. 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. Clin Cancer Res. 2008 Jun 15;14(12):3867-74.



Research Groups and Clinical Support Services

Clinical Support Services

Clinical Trials Office



Head of the Clinical Trials Office Irene Marimon

Head of the Clinical Trials Office for Phase I Trials Gemma Sala

Head of the Clinical Trials Office for Breast Trials Susana Muñoz

> Clinical Trials Management Coordinator Yasmina Bernabé

Clinical Trials Coordinators Marta Beltran Raquel Espallargas Violeta Esteban Beatriz García Cristina González Maria Herranz Jordi Humbert Laura Maynés Oriol Nualart Oriol Olivé Olga Padrós Adelaida Piera Mireia Sanchis Elisabet Sicart Meritxell Soler Olga Vidal

Data managers
Julia Esteban
Gloria García
Belen García
Lídia Martínez
Xavier Martínez
Àngels Porras

Rita Ramadas Andrea Retter Isabel Rico Rosa María Romero

Head of Database Managers Office Gessamí Sánchez-Ollé

> Database Managers Débora Moreno Núria Murtra

> > Assistants Nuria Carballo Angel Marin

Clinical trials play an essential role in the development of new therapies to combat cancer, as they constitute the methodological basis of scientifically recognized clinical research.

Clinical trials allow ethical and highly controlled experimental research in humans once the preclinical experimental development phase of a new drug has shown that the drug may represent an improvement on the available or standard treatment for patients at a given moment.

The desire to improve current cancer treatment and to offer new therapeutic choices to our patients has driven the development of the Clinical Trials Office in the Oncology Department of Vall d'Hebron Hospital.

The Clinical Trials Office is responsible for the logistics, coordination and management of the data from the clinical trials carried out in the Oncology Department of Vall d'Hebron Hospital. Our team is responsible for facilitating the administrative procedures required to obtain approval from the Clinical Research Ethics Committee of Vall d'Hebron Hospital for the different trials that are of interest to the department.

When the trial has been approved by the regulating authorities, the Clinical Trials Office is responsible for the correct logistical development of the trial by working together with the oncologists of the department who act as principal investigators or co-investigators, and with the rest of the research team.

A coordinator and a data managers are assigned to each clinical trial. The coordinator is the point of connection between the study sponsor and the research team and is responsible for managing the procedures required y the team in accordance with the protocol. The data manager provides the sponsor with all the necessary clinical data described in the protocol and, together with the sponsor's clinical trial monitor, monitors the quality of these data.



Nurse Supervisor Nines Peñuelas

Clinical Trials Coordinator Sonia Valverde

> Phase I Clinical Trials Coordinator Lydia Vélez

> > Nurses
> > Núria Membrives
> > Àlex Sierra
> > Mireia Milán
> > Marta Mate
> > Meritxell Cucurell
> > Isabel Muñoz

Nurse Technicians Alicia López Elena Oller This office was set up in 1997 with the incorporation of 2 clinical trial coordinators dedicated exclusively to implementing and carrying out the approximately 20 projects that were initiated that year. Over time, this group has grown along with the number of trials.

In 2009, work was carried out on the expansion of the Clinical Trials Office with the creation of a new area for phase I clinical trials; this area comprises consulting rooms, treatment rooms, a pharmacy and offices, and is located in the general clinical trials area of Vall d'Hebron Hospital. This new area will enter into operation in the first half of 2010.

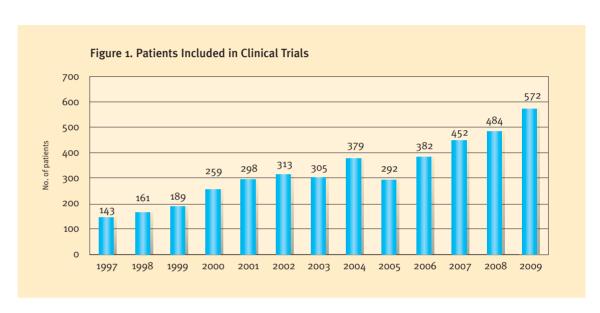
Clinical trials are one of the best choices of treatment, as they compare current state-of-the-art treatment with a potentially superior treatment and may even offer new drugs to patients for whom there are no alternative treatments; for this reason, all patients in our oncology department are considered as potential candidates for inclusion in the clinical trials available in the department. Although all patients are clearly not eligible or do not agree to take part in a clinical

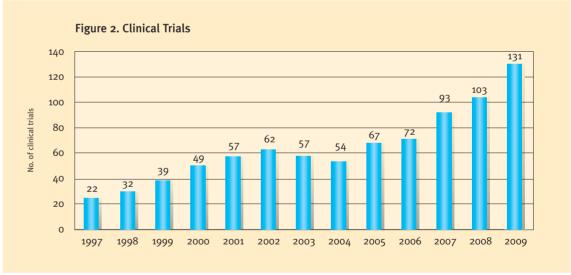


trial, we offer this option to all patients who meet the necessary criteria established in the different research protocols.

This, together with the will to be a world reference centre in cancer treatments makes it unsurprising that there has been a spectacular growth in the number of patients currently starting a new treatment in clinical trials in our department. This increase is clearly shown by the rising curve between 1997 and 2010 seen in Figure 1. In 2009, a total of 572 patients were enrolled in clinical trials.

Clinical Trials Office





Not only has there been an increase in the number of patients enrolled in the growing range of clinical trials (Figure 2 shows how the number of clinical trials has increased sixfold between 1997 and 2009) but there has also been a proportional increase in patients enrolled in phase I clinical trials.

Table 1

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Enrolled in phase I	8	9	35	59	57	110	130	120	108	132	139	171	222
Enrolled in phase II	50	70	59	72	66	94	91	130	73	165	170	133	161
Enrolled in phase III	85	82	95	128	175	109	54	129	111	85	143	180	189
No. of patients enrolled	143	161	189	259	298	313	305	379	292	382	452	484	572

As shown in Table 1, patients enrolled in phase I clinical trials have gone from 5.5% in 1997 to almost 40% of clinical trials available in our department in 2009.

Phase I clinical trials (involving filamentary toxicity studies and definition of the correct dosage for use in subsequent trials) involve highly complex studies that are often associated with pharmacodynamic studies of tissue samples from the patients enrolled in these trials. These pharmacodynamic studies require sequential biopsies of both cancerous and healthy tissue, with the aim of showing the inhibition of the targets by the drug and identifying the end affects on the intracellular signaling pathways, the cell cycle and apoptosis. Our oncology department provides added value phase I clinical trials by proposing and playing an active role in these pharmacodynamic studies associated with the clinical trials, thereby making it possible to obtain improved knowledge that can help to establish the optimum biological doses of the drug and to understand the intimate mechanisms of action of the drugs being studied.

Phase I clinical trials offer the opportunity to continue treating some cancer patients who have not responded to other currently available therapies.

The Vall d'Hebron Hospital Oncology Department has acquired the necessary prestige acknowledged by the pharmaceutical industry, which has allowed it to become a development center chosen by the industry in order to carry out complex phase I clinical trials, in which the number of participating centers is highly restricted and the centers are chosen for their high standards of quality and ability to carry out state-of-the-art research. Hence, our hospital has taken part in phase I trials of different drugs, such as Xeloda, Herceptin, Tarceva, etc.

Furthermore, our collaboration and participation in phase II clinical trials (studies on the effectiveness of a drug in certain cancers determined by the protocol) and phase III clinical trials (comparative studies of the efficacy of the new therapy on the most effective available therapy for a cell type and a specific stage) has allowed the pharmaceutical industry to market novel therapies aimed at cancerous cells, including drugs such as Cetuximab, Iressa, Xeloda, Herceptin, etc.

Not only do we take part in clinical trials promoted by the pharmaceutical industry, we have also developed our own clinical trials, which have been accepted and carried out in collaboration with other hospitals.

Finally, the Clinical Trials Office has been involved in training future coordinators and managers of clinical trial data and monitors. In 2004, we began a 36-hour course aimed at university students in the field of bio-health and nurses in order to train the personnel required in clinical trial units such as ours. In 2009, we taught the 4th edition of this course.

Oncology Pharmaceutical Care Program Unit



Head of the Oncology Pharmaceutical Care Unit Maria-Josep Carreras Soler

Coordinator of Pharmacological Research in Oncology Support Unit Laura Mañós Pujol

Pharmacists
Patricia Díez Duran
Anna Farriols Danés
Maria Oliveras Arenas
Maribel Magaña Pintiado

Clinical Trials Resupplies Manager Anna Martí Fabra

Technicians
Susana Mulet Lozano
Sara Pizarro López
Technicians team of Oncology
Pharmacy Unit

The Oncology Pharmaceutical Care Unit of the Pharmacy Department with ISO 9001:2008 certification, is associated with the Medical Oncology Programs of the Vall d'Hebron University Hospital.

The Oncology Pharmaceutical Care Program is responsible for preparing cytostatics, monoclonal antibodies and other parenteral antitumor drugs used in clinical trials in oncology, and for monitoring the clinical activity in oncology patients. It has a team of pharmacists specializing in hospital pharmacy and oncology pharmacy, and laboratory technicians.

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

Strategic Goals

To achieve excellence in the quality of the service we provide to the different clinical oncology research programs, in terms of efficacy, efficiency and safety.

- Ensuring traceability of management and preparation of drugs for clinical trials
- Providing and ensuring excellent control of the storage temperature of the samples and prepared products
- Increasing documented control of the accounting of drugs returned by patients in phase I trials
- Providing instructions and indications to patients for orally administered treatments
- Preparing trial drugs for parenteral administration by integrating all the phases of prescription, preparation and administration in computerized systems aimed at preventing errors in medication

Pharmaceutical activity

- 1- Management of clinical trial drugs: The program has managed clinical trial drugs for active 131 clinical trials in oncology. The total number of for clinical trial supplies deliveries was 874.
- 2- Installation of a novel system for controlling storage temperature: with electronic temperature recording every 5 minutes, which is shown on the program's computers and includes an audio and visual alarm as well as a system for sending an alarm via SMS to the cellphone of the pharmacist on duty, continuously for 24 hours, in case of temperature deviations.

Oncology Pharmaceutical Care Program Unit

- 3-Preparation of the project for ensuring traceability of the management of storage, custody and dispensing of clinical trial drugs: Design of a computerized storage area for controlling samples, their location, expiry dates and traceability by means of a barcode reader.
- 4- Design and validation of the drug-preparation process traceability system and qualitative and quantitative quality control of the process Computerized process that integrates the application of barcode technology, electronic scales and voice technology (Vocollect Voice-Directed Work system).
- 5- Support for and liaison with the sponsors of the clinical trials. Pharmacy Unit has taken part in 14 pre-study visits, 69 initial visits, 481 monitoring visits and 13 final visits. It has successfully passed 10 audits.

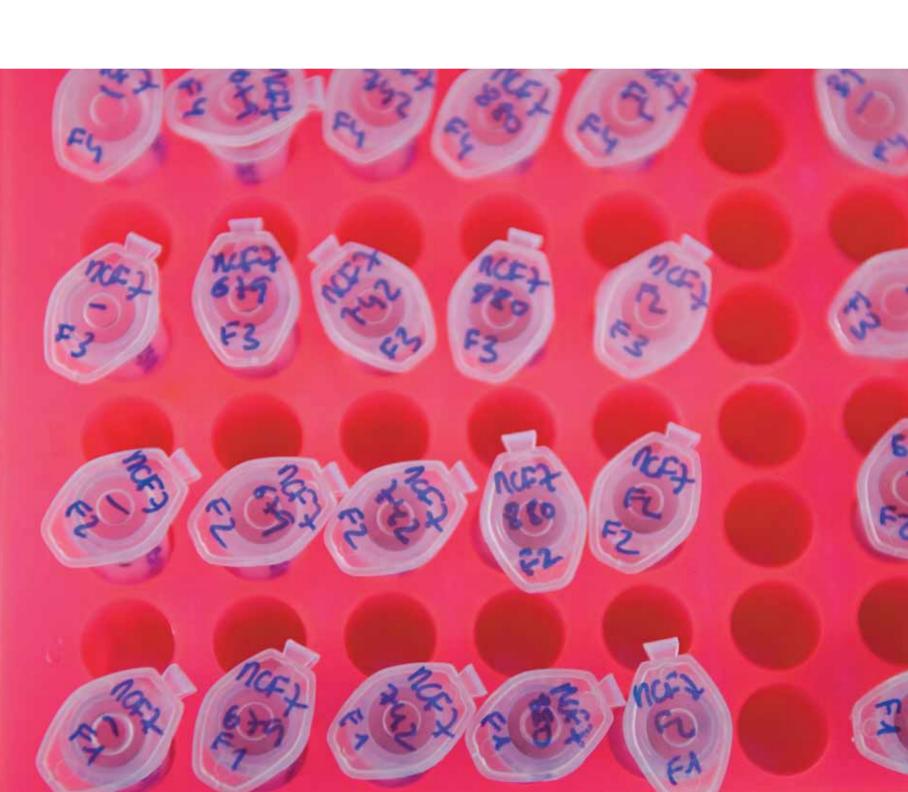
The ISO9001:2008 certification has been renewed for Pharmacy Dept.

- 6- Dispensing: A total of 7754 clinical trial drugs have been dispensed with the validation of a pharmacist. The conditioning and re-labeling of the primary containers for clinical trial drugs has also been carried out. A total of 108 Standardized Dispensing Procedures have also been drawn up and updated.
- 7- Preparations: A total of 8434 preparations of cytostatics, monoclonal antibodies and other parenteral antitumor drugs for clinical trials were carried out (7754 preparations with drugs provided by the sponsor and 680 with commercial drugs provided by the hospital). A total of 54 Standardized Dispensing Procedures have been drawn up.

Objectives and Projects

- 1- Opening of new facilities:
- The Oncologic Pharmacology Research Support, Unit of Pharmacy Dept in a new location closer to the new Phase I/II unit, with the incorporation of new computerized and technological systems for management, control and storage of clinical trial drugs in order to increase the quality and quantity of the service provided to the different clinical research programs in oncology
- Inauguration of the Unit for the Preparation of Cytostatics in clinical trials integrated into the Phase I/II Unit, with the aim of optimizing the service and bringing it as close as possible to the place where it is needed, thereby facilitating integration with the rest of the research team
- 2- Implementation of the traceability system:
- CFMTrials computerized system in:
- · Management, control and storage of clinical trial supplies that makes it possible to ensure and document the traceability of the relevant documentation on the trials in digital format and documentation relating to the supplies from their reception at the unit until they are dispensed (oral medication or drug for intravenous infusion); the documentation is transferred electronically to the traceability system of the preparation unit, thereby minimizing the possibility of medication errors
- · Clinical and technical support of the process of prescription/ preparation/administration of cytostatics in clinical trials, which will make it possible to have an electronic record of all actions, users, dates, times, batches and expiry dates of the products used. Use of electronic technologies and computerized processes. Use of voice technology (Voice-Directed Work, Vocollect)

- 3- Implementation of the qualitative and quantitative quality control system for cytostatic preparations in clinical trials, which will make it possible to guarantee the preparation of the correct trial drugs at the right dosage, without medication errors
- 4- Improvement of the process of pharmaceutical care of patients included in phase I/II trials by means of preparation of diaries and instructions for the patient for all trials (phase I, II and III) in which the clinical trial drugs are administered orally. The patients will be visited at the Pharmaceutical Care Consultation, where they will be provided with information on the form of administration of the trial drug; and their pharmacological history will be recorded and the usual treatment will be reconciled with the treatment being studied; patients and researchers will be informed of potential interactions of the study drug with other drugs/concomitant complementary therapies and administration of the drug will be recorded by means of patient interviews and accounting of the medication returned in subsequent visits



VHIO researchers contributed to oncological and biomedical discoveris through a total of 126 scientific publications in 2009. Total IF 2009: 836,991

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