Scientific Report

2013

VALL D’HEBRON INSTITUTE OF ONCOLOGY
Following more than a decade of extraordinary developments in cancer research — from molecular mechanisms to clinical care to new enabling technologies — we are poised to deliver a much more personalized form of cancer treatment and care to our patients. In 2013, we made tremendous progress in both fine-tuning diagnosis and treatment strategies to the unique molecular make-up of an increasing number of patients, as well as key advancements in our understanding of basic cancer biology and the approval of new tailored therapies. While these efforts span basic, translational and clinical research, they share one unified goal: to outsmart the camouflage and trickery employed by this despicable disease that too often allows it to go undetected, dodge powerful anti-cancer therapeutics, and spread its havoc.

We still have a very long road to travel if we are to conquer cancer. To succeed, we simply must raise the bar and set our ambitions higher than ever. By furthering research, implementing new tools and building integrative platforms, combining our strengths and overcoming current obstacles en force, I believe we can outwit cancer, jump several moves ahead in what can be considered as a biomedical game of chess. This undertaking is undeniably challenging, but, to paraphrase Albert Einstein, in the middle of every challenge lies opportunity.

Considering the developments over the past year, we have good reason to be optimistic.

**PDX and optimal preclinical study design**

A critical asset in our translational model is our direct access to cancer patients — only possible because of our privileged location within the heart of the Vall d’Hebron University Hospital. This helps us excel in translating research findings for the benefit of patients in record time. It also reduces the risk of costly failures at clinical level, as only a small proportion of initially promising drug candidates ultimately make their way through the clinic and gain approval.

In order to accelerate the development of potent new targeted cancer therapies, our researchers carry out a host of preclinical studies, testing potential agents in combinations as well as rigorously assessing mechanisms of resistance. The goal is to predict success in the clinic and lessen the attrition of new drug entities as they progress through the development pipeline into the clinic. A vital tool in our armory is the development of patient-derived tumor xenograft (PDX) mouse models that faithfully recapitulate cancer. These models help us understand the nuances of tumor development and shape the
design of subsequent clinical studies and therapeutic strategies.

Importantly, 2013 marked the launch of a collaboration between VHIO and 14 cancer centers across 9 European countries, called the EuroPDX European Consortium: *Translating Knowledge in Oncology*. This consortium connects research entities of excellence that are developing clinically relevant PDX cancer models, helping to share key findings on promising therapeutics as well as carry out multi-center preclinical studies.

**Teaching anticancer agents new tricks**

In our efforts to optimize the appropriate drug at the right dose for each individual patients, we are beginning to reap rewards from clinical studies, building on preclinical studies on novel combination therapies, in larger cohorts of patients. In parallel, we are also seeking out new applications for available chemotherapeutics. The high-throughput screening of previously FDA-approved agents can identify therapeutics that could be rapidly moved to the clinic for new applications.

This so-called ‘drug repurposing’ could accelerate the development of alternative therapies for cancers that notoriously fail to respond to standard therapies. Furthermore, as we already know a huge amount about any adverse effects, these repurposed compounds are naturally more quickly fit for purpose than their novel, unproven counterparts.

In the Fall of 2013, replacing the European Union Framework Programmes, *Horizon 2020* was implemented with the emphasis on frontier and interdisciplinary research. One of the initial topics favors novel studies and clinical approaches supporting the optimization of available therapies, specifically drug repurposing. This represents further opportunity for VHIO to advance current efforts in this arena.

**Cancer immunotherapy: a dynamic contender in dismantling cancer's armory**

Despite its great promise, the battle to establish immunotherapy as a legitimate cancer therapeutic agent has been messy. There have been several casualties along the way -- failed vaccines, small companies and even careers along a roller coaster of promise and disappointment. Excitement surrounding early phase trial successes has generally evaporated in quick and cruel succession by disappointing and costly failures in late-stage clinical trials.

Thanks to the remarkable dedication of the pioneers and other researchers in this field, we have a new suite of cancer vaccines and promising novel experimental therapies in the pipeline. The new momentum in cancer immunotherapy is incredibly exciting for preclinical and clinical researchers – maybe even game-changing. Apparently the editors of the prestigious journal *Science* agree: it ranked cancer immunotherapy as number one in its *Top 10 Breakthroughs of 2013*. We are seeing that immunological strategies really work and should impact the way we treat cancer in the future -- using novel immune agents as mono therapy or in combination, depending on the patient’s tumor.

Looking ahead, we eagerly anticipate the application and extension of immunotherapies to more tumor types, as well as combining powerful immunotherapeutic agents with the current cornerstones of cancer -- chemotherapy and radiation. We will also need to better understand the cellular and molecular mechanisms modulating immune response to cancer as well as learn from the outcomes of current and future trials.

At VHIO, we have initiated a campaign to attract principal investigators in cancer immunology and immunotherapy to implement and lead novel research focused on areas such as immuno-oncology, the tumor microenvironment, and the development of immune-based personalized therapeutics. I fully expect that VHIO’s multidisciplinary cancer teams will feature new expertise in cancer immune-therapeutics in the year to come.

**Oncogenomics data goes ‘inter’**

Spurred by remarkable developments in DNA sequencing technology that have brought us to the brink of the “$1,000 genome,” whole-genome sequencing for precision oncology has been heralded as a trail blazer in cancer research and is already benefiting patients in clinical practice. By sequencing panels of genes or entire genomes in cancer patients, we are now better equipped than ever before to identify specific molecular risk factors and gauge the potential efficacy of specific agents for individual patients.

Despite such progress, we have not yet solved how to harness and store the overwhelming wealth of data generated through oncogenomics. How can we empower researchers and clinicians to exploit this trove of biological knowledge and clinical data? And how can these insights become truly integrated into mainstream healthcare?

To help resolve these challenges, we have been engineering new medically-driven platforms that will ultimately advance precision medicine in oncology by delivering exploitable omics data – genomics, transcriptomics, proteomics and more -- to potential end-users. Our
multidisciplinary team of experienced bioinformaticians, experimental and clinical scientists, seeks to design and assess integrative bioinformatics applications, building a platform for the sustainable exploitation of these tools and services for the benefit of patients.

**Trial design: efficacy, effectiveness in real time**

There is much debate surrounding ways we can improve the design of clinical trials, balancing speed and safety with real-time assessment of data and making fluid adjustments in dosage and treatment as needed. We are excited to drive advances in clinical trial design, to complement the innovation we are seeing at the bench and in our translational research.

During 2013, VHIO has participated in a number of innovative clinical trials in conjunction with centers around the world. While we continue to work closely with industry, we are committed to leading novel academic trials of excellence, supported through public funding.

One such example is the WINThER (WINTherapeutics) trial, promoted within the scope of the Worldwide Innovative Networking in personalized cancer medicine (WIN) Consortium (supported through a European Union Framework Program 7 grant). This exquisite trial investigates DNA and RNA from dual biopsies of tumor and matched normal tissue for each patient. The gene data are examined by advanced bioinformatics tools to provide a predictive efficacy score for potential drugs for each patient. WINThER is an exciting response to the call from oncologists for a more aggressive, speedy application of personalized therapy to larger populations of patients.

Another promising partnership is our role in the POSEIDON metastatic breast cancer trial, which investigates a novel PI3K inhibitor. Launched this year (supported by the RATHER and EurocanPlatform consortia in collaboration with Genentech), we are joined by the Netherlands Cancer Institute (NKI, Amsterdam), Cambridge University Hospitals and Cancer Research UK Cambridge Institute. The POSEIDON trial represents Genentech’s first ever investigator-led multi-national study in Europe.

In a similar vein, we are trying to improve our understanding of the distinct molecular subtypes in colorectal cancer, which have different biological hallmarks and -- not surprisingly -- varying responses to therapy. The COLThERES project funded by the European Commission’s 7th Framework Programme, is a consortium incorporating European clinical research centers of excellence including VHIO. 2013 has marked notable progress in identifying and validating a number of gene signatures that may be used to establish distinct molecular subgroups of CRC patients. These results have led to the design of various novel clinical trials which are currently enrolling patients with a poor prognosis. This project represents an academically led success story.

**Locking the shackles on metastatic spread**

For treatment-resistant cancers with a desperately poor prognosis, such as those driven by mutations in the Ras gene (including colon, lung, and pancreatic cancer), we must continue to unmask more specific genomic links as well as study new approaches in treating these patients.

We must also maintain our efforts aimed at checking the mechanisms that cancer cells use to spread and establish metastatic offshoots. Urgent research is still required to counteract and halt tumor cell spread factors with targeted therapies designed with a 'Rolls Royce' sophistication combined with a finale roar of a Ferrari!

Many studies have shown that the shotgun approach often leads to regression of disease, with a more fast and furious return than the original cancer.

At the research level, we need to get much smarter at tracking down circulating tumor cells that drive metastasis. The early detection of these sinister cells is imperative. Sophisticated nanotechnologies are already promising the quantification of biomarkers expressed on cancer cells which will help us to distinguish between the devil cancer cells and the deep-blue sea of healthy cells.

We are now upon the eve of moving into our new home, the CELLEX building. By bringing all our preclinical, translational and clinical research teams under the same roof, for an even faster exchange of ideas and results, we will undoubtedly be better equipped to spur this vital future research into paralyzing metastatic activity that currently threatens the lives of countless cancer patients every year. One patient is one too many.

At VHIO, we determinedly translate current challenges in winning the war on cancer into opportunities towards victory.

Josep Tabernero
Director
The Vall d’Hebron Institute of Oncology (VHIO)
WHO WE ARE AND WHAT WE DO

VHIO’s Organigram 2013

In order to translate research findings for the benefit of patients in record time, VHIO adopts a purely translational, multidisciplinary research model. Organized into four main programs – Preclinical, Translational, Clinical, and Core Technologies, our research focuses on understanding the fundamental biology of human cancer, from cellular and molecular biology and genetics through to therapeutics.

Its optimal organizational structure allows VHIO to relentlessly tackle the many unresolved questions in ultimately outsmarting the multifaceted, heterogeneous and complex disease that is cancer:

VHIO in 2013: opportunity towards checkmating cancer

BOARD OF TRUSTEES

EXECUTIVE COMMITTEE

DIRECTOR
Josep Tabernero

SCIENTIFIC ADVISORY BOARD

SCIENTIFIC COMMITTEE
President: José Baselga

MANAGING DIRECTOR
Andrés de Kelety

CORE TECHNOLOGY PROGRAM

- Cancer Genomics
- Proteomics
- Molecular Oncology
- Translational Genomics
- Scientific Equipment Unit

DIRECTION PRECLINICAL RESEARCH PROGRAM
Joaquín Arribas

- Growth Factors
- Experimental Therapeutics
- Tumor Biomarkers
- Mouse Models of Cancer Therapies

DIRECTION TRANSLATIONAL RESEARCH PROGRAM
Joan Seoane

- Gene Expression Cancer
- Stem Cells & Cancer

DIRECTION CLINICAL RESEARCH PROGRAM
Josep Tabernero

- Transversal Clinical Services/Units
  - Clinical Trials Office
  - Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa"
  - Research Nurses
  - Clinical Trial Pharmacists
  - Databases & Statistics
- Research Groups
  - Breast Cancer & Melanoma
  - Early Clinical Drug Development
  - Gastrointestinal & Endocrine Tumors
  - Genitourinary, CNS & Sarcoma Tumors
  - Head and Neck & Gynecologic Cancer
  - High Risk & Cancer Prevention
  - Thoracic Tumors
  - Oncogenetics
  - Radiotherapy*

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  - Thoracic Tumors
  - Oncogenetics
  - Radiotherapy*

CORE TECHNOLOGY PROGRAM

- Cancer Genomics
- Proteomics
- Molecular Oncology
- Translational Genomics
- Scientific Equipment Unit

Current Research Structure
Managing Structure
Scientific Advisory Board Nominated by the Patronage
Management Committee
Coordinated Group

Ext. Relations
Eco. & Finances
General Services
HHRR
Research Support Office

more info at www.vhio.net
VHIO’s direct access to cancer patients: a critical asset in VHIO’s purely translational research model

At the preclinical, translational and clinical research levels VHIO continues to drive key advancements in cancer science and medicine (see pages 81 - 87 for our full list of publications in 2013, and an overview of Scientific Productivity as well as selected articles on pages 13 - 15). Our research endeavors largely benefit from VHIO’s privileged location within the heart of the Vall d’Hebron University Hospital, affording direct access to patients as well as the entire spectrum on oncology patients who care for them. Organized into multidisciplinary integrated teams, our researchers can closely collaborate and interact with Vall d’Hebron physician-scientists. Translational science and clinical research are therefore tightly connected, accelerating the bench-bedside-bed cycle of knowledge.

A LITTLE OF HOW WE DID IT IN 2013

Oncogenomics at VHIO: accelerating discovery translating to cures

At the heart of VHIO’s research activities lies our suite of cutting-edge core technology platforms which enable us to apply next-generation whole-genome sequencing for precision oncology. By sequencing panels of genes or entire genomes in cancer patients, we are now better equipped than ever before to identify specific molecular risk factors and gauge the potential efficacy of specific agents for individual patients. In parallel, these technologies immensely benefit and accelerate the research efforts of our preclinical, translational and clinical scientists, including the identification of mechanisms of resistance to targeted therapies, the study of clonal populations, as well as defining novel therapeutic opportunities based on mutation profiles.

Our Cancer Genomics Group (see pages 60 - 61 of this report), equipped with a genotyping platform (MassARRAY sequenom) and two NextGen sequencers: MiSeq and HiSeq2500, Illumina, provides a pre-screening program of mutations in patients who are candidates for our portfolio of phase I clinical trials (please refer to our Research Unit for Molecular Therapy of Cancer (UITM) – “la Caixa” for more information, pages 74 - 75).

The molecular profile of each patient indicates his/her suitability for inclusion in a given clinical trial aimed at testing the usefulness of novel targeted therapies, such as PIK3CA, AKT1, BRAF or MEK inhibitors. These endeavors are not only revolutionizing tumor classification but also increasingly impacting on how cancer treatment decisions are made.

As a reflection of our commitment to excellence, one key development in 2013 has been obtaining ISO 15189:2007 certification for both our Cancer Genomics and Molecular Oncology Groups (pages 62 - 63). VHIO has consequently become one of the first research institutes in Spain to meet this standard, demonstrating its technical competencies, level of quality, standardization, validation of processes and staff training. Such accreditation is highly valued by the companies and institutions that seek to collaborate with us – in recognition that quality is key to competitiveness.

Incorporated only last year, our Translational Genomics Group (pages 66 - 67) has successfully implemented the technology, equipment and protocols to facilitate gene expression data in both the nCounter Nanostring and RNAseq platforms. Concerning the former, incidentally ranking 4th in The Scientist’s Top 10 Innovations for 2013, the group is one of the first to provide this commercial assay in Europe. Using this assay, the group has this year shown that HER2+ breast cancer can be classified into four different subtypes, one of which demonstrates both a greater response to and increased benefit from chemotherapy and anti-HER2 therapy. Such newly, refined classification of different tumor subtypes will ultimately facilitate more effective treatment tailored to a specific tumor as well as advance targeted therapy against HER2+ breast cancer.

By bringing more detailed prognostics directly to the clinical setting, and further developing and validating the next generation of tests, VHIO will significantly contribute
Clinical Trials at VHIO: driving drug development and targeted therapies against cancer

VHIO has increasingly established itself as a leading reference in drug discovery from concept to clinic:

• Research Unit for Molecular Therapies of Cancer (UITM) “la Caixa”: fighting cancer’s biology, one patient at a time

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

This Unit, a pioneering project at national level, also benefits from the same privileged environment enjoyed by VHIO; located in the patient care environment of the Vall d’Hebron University Hospital and set within the research context. This excellent bridging and tight connectivity between health care and research enables us to establish new treatment models for patients with highly selective drugs, expanding the knowledge of tumor diseases and how to treat them in an individualized way - getting the right drug to the right patient at the right time.

In the space of just three years since it was inaugurated, among many other successes, through the research carried out by VHIO’s Early Clinical Drug Development Group (see pages 42 - 43) the Unit has firmly established itself as a leading reference in various areas of drug development including PI3K/akt/mTOR inhibitors, FGFR inhibitors or drugs targeting developmental pathways such as TGF beta, SHH, WNT, and NOTCH.

Thanks to the Unit’s outstanding facilities coupled with the excellent multidisciplinary clinical teams of professionals, 2013 witnessed a further increase in phase I trials numbering at 75 and enrolling a total of 345 patients.

While we continue to expand our portfolio of phase I trials, adding new targeted therapies against novel, promising targeted therapies and best-in-class therapies, the technology platforms provided by VHIO’s Cancer Genomics (pages 60 - 61), and Translational Cancer Genomics Groups (pages 66 - 67), such as the MiSeq sequencing system and nCounter Nanostring platform respectively, will drive faster and more precise mutational analysis of tumor-suppressor genes as well as translocations and gene amplifications.

It’s not only about speed and precision. Importantly this year, both our Cancer Genomics, and Molecular Oncology Groups received ISO accreditation – further endorsing the quality and excellence epitomizing our activities.

Obra Social “la Caixa”

Established in 1997, the Clinical Trials Office at the Vall d’Hebron University Hospital coordinates studies from Phase I to Phase III and is organized in three separate teams: Phase I, Breast Cancer, and Phase II - III. Thanks to the dedication and drive of more than 30 professionals including study coordinators, data managers and administrative staff, this Office reports exciting growth in both the number of patients enrolled in trials as well as trials conducted each year. 2013 continues the trend - totaling 232 Phase I-II-III trials with 843 patients recruited.

To consult the full list of highlights and a summary of activity in 2013 see pages 70 -73. For a detailed listing of all clinical trials conducted in 2013 visit our Scientific Report online at: http://memorias.vhio.net/2013/.

To discover more please see pages 74 - 75, or consult our Scientific Report online at: http://memorias.vhio.net/2013/.

• Clinical Trials Office

VHIO’s participation in International Consortia of excellence

We can only hope to accelerate discovery and thus improved cancer treatment and care by combining our strengths and overcoming current obstacles in collaboration. 2013 has marked the launch of several unique, cross-border opportunities which will ultimately avoid duplication of research efforts but also spur advancements making personalized medicine more precise and accessible for an increasing number of patients:

The EuroPDX Consortium – Translating Knowledge in Oncology (see page 4 of the Foreword to this...
PDX and optimal preclinical study design), was launched in 2013 with the common goal of creating a network of clinically relevant models of human cancer, and in particular patient-derived xenograft (PDX) models. Connecting 14 cancer centers across 9 European countries that are developing PDX cancer models, this initiative will promote the sharing and exchange of findings on promising therapeutics as well as lead multi-center preclinical studies.

EuroPDX will strive to reduce the duplication of efforts in oncology drug development and ultimately improve the quality of life and overall survival of cancer patients.

For forthcoming information please bookmark VHIO’s website: www.vhio.net.

Announced in 2013, The MErCuRIC Consortium, funded by the European Commission’s 7th Framework Programme of Research and Development, incorporates 13 partners in eight different European countries to lead and pioneer a multicentre phase Ib/II clinical trial. This study will assess a novel therapeutic strategy aimed at combating metastasis, improving survival and developing new approaches to treat patients with colorectal cancer. http:/ /mercuric.eu.

Launched in 2011 (VHIO joined in 2013), supported by the IMI Innovative Medicines Initiative – a Joint Undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA), OncoTrack, Methods for systematic next generation oncology biomarker development, is an international consortium of over 80 scientists and constitutes one of Europe’s largest collaborative academic-industry efforts aimed at developing and assessing novel approaches for the identification of new markers for colon cancer.

Incorporating a network of 27 research entities spanning 10 countries, SPECTAcolor - Screening Platform for Efficient Clinical Trials Access in Colorectal cancer, is an initiative within the framework of the research program of the EORTC, supported by Alliance Boots. Launched this year, 2013, this is the first prospective fully annotated tumor samples Biobank and Biomarker analysis platform for genetic profiling of patients suffering from advanced colorectal cancer. http://spectacolor.eortc.org.

In addition to these new opportunities embraced in 2013, VHIO continues to participate in on-going Consortia of excellence including: RATHER – Rational Therapy for Breast Cancer, EurocanPlatform, COLThERES – Colon Therapy Research Consortium, and WIN – Worldwide Innovative Networking in personalized cancer medicine. Just some of the exciting developments resulting from these four collaborations in 2013 have been suitably highlighted in the Foreword to this Scientific Report (see page 6: Trial design: efficacy, effectiveness in real time).

For the full list of Consortia and respective project overviews, please see pages 90 - 91 of this report.

Other collaboration:

Cancer research at VHIO: dismantling cancer’s armory

Leading scientific discovery against cancer. in 2013 our preclinical, translational and clinical researchers published 151 scientific articles as corresponding/
senior or co-authors, with a Median Impact Factor (MIF) of 9.27. These figures reflect an increase in scientific productivity — witnessed year in, year out, a maintained MIF score, as well as the importance of VHIO’s research and contribution to the field.

For the complete list of articles published by VHIO researchers and physician-scientists in 2013 see pages 81 - 87. To view this year’s selection of just some of the most relevant articles by VHIO Faculty published in 2013 refer to pages 14 - 15.

The CELLEX building: connecting and expanding VHIO’s multidisciplinary research teams — the drivers behind more effective, targeted therapies against cancer

With the invaluable support:

**Fundació Privada CELLEX**

2013 has witnessed the completion of the construction of VHIO’s new home: the CELLEX building. In the space of just one year since we compiled our 2012 Scientific Report, we are now in the throes of planning towards equipping its interior.

Importantly, to further develop our research of excellence involving patient-derived tumor xenograft (PDX) mouse models that faithfully recapitulate cancer (please see the Foreword to this report, page 4: *PDX and optimal preclinical study design*), we have been finalizing the plans for our new Animal Facility. With a capacity of over 5000 cages, adopting a state-of-the-art recycling system, this facility will benefit the endeavors of VHIO scientists and our colleagues at the Vall d’Hebron Research Institute (VHIR), as well as those belonging to other CERCA-accredited research centers (CERCA - Institute of Research Centers of Catalonia), such as the Institute of Photonic Sciences (ICFO).

Marking an exciting new era towards precision oncology, we are upon the eve of the final completion of the CELLEX building. This will not only provide VHIO with the space it desperately requires to be able to expand its programs and activities, but will also bring all our research teams under the same roof, for an even faster exchange and application of data — the key to better serving cancer science and medicine, and most importantly of all, ultimately improve the lives of those touched and affected by cancer.

**VHIO-organized events: debate and exchange of the highest degree**

In 2013 VHIO opened its doors to participants at the following events:

- **VHIO Meet the Editors**

Our 2013 annual series of VHIO Meet the Editors prestigious talks provided oncology professionals of research institutes of excellence in Barcelona with unique opportunity to learn more about scientific publishing and cancer research and put questions and comments to the editors directly during the Q & A with the audience. They also continued to provide valuable opportunity to get to know the editors of the highest impact factor journals personally:

**VHIO’s Meet the Editors in 2013:**

**Cancer Cell**

**Speaker:** Li-Kuo Su, Editor-in-Chief
**Talk:** Cancer Cell and the Cancer Research Community
**Date:** 14 January 2013

**THE LANCET Oncology**

**Speaker:** David Collingridge, Editor-in-Chief
**Talk:** Insights on editorial decision-making and peer review
**Date:** 26 July 2013

As this Scientific Report goes to print, we are pleased to announce the following dates in the diary for 2014:

**CANCER DISCOVERY**

**Speaker:** Judy Quong, Executive Editor of Cancer Discovery
**Talk:** Cancer Discovery: Looking Back, Moving Forward
**Date:** 24 February 2014

**Speaker:** Jean-Charles Soria, Editor-in-Chief, Annals of Oncology
**Date:** 08 September 2014

**Speaker:** Alexander M. M. Eggermont, Editor-in-Chief, EJC
**Date:** 15 December 2014
As we advanced in our 2012 VHIO Scientific Report, in collaboration with the Fritz Bender Foundation, VHIO co-organized and hosted the 17th Fritz Bender Foundation International Symposium on Progress towards Individualized Cancer Treatments, 07-09 November 2013, here at the Vall d’Hebron University Hospital campus.

Established by the Fritz Bender Foundation, and expertly engineered by Kurt S. Zaenker (the Fritz Bender Foundation, and University of Witten/Herdecke, Germany), and Enrico Mihich (the Dana Farber Cancer Institute, Boston, USA), the main aim of these symposia is to provide a unique platform for up and coming young researchers and physician-scientists to interact, exchange, and debate with current thought-leaders within the oncology field.

Secondly, these meetings seek to promote the latest advances within the field at international level in order to also impact at local level. This is achieved by identifying the most suitable research institute as co-organizer to host in the respective country selected for each symposium.

For 2013, VHIO was honored to host and co-organize the 17th in the symposium series, with the support of an educational grant received through the “la Caixa” Foundation:

Incorporating an outstanding panel of internationally renowned speakers, and attracting some 250 participants, the symposium ran for two and a half days organized into five main sessions: 1) Genetic Profiling of Patients, 2) Tumor Characterization, 3) Tumor-Host Relationships, 4) Therapeutic Targets I, and 5) Therapeutic Targets II.

In addition to the main scientific program, which delivered on addressing some of the many remaining questions in our efforts to change the face of cancer through precision cancer treatment and care, we all discovered yet more relevant and recent advances within the oncology field throughout the poster sessions. In recognition of these contributions, in collaboration with VHIO, both Nature Reviews Cancer and Nature Reviews Clinical Oncology each sponsored a poster prize awarded to the two top posters.

The 2013 edition of these Symposia both matched and celebrated the successes of past Fritz Bender Foundation International meetings, elegantly captured in a special meeting report published in Molecular Oncology, Volume 8, Issue 1, February 2014, Pages 1–8, News and Views, Towards individualized cancer therapy: Challenges and prospects, authored by Ezzie Hutchinson.
Scientific Productivity: research articles

ARTICLES PUBLISHED IN 2013

In 2013, 151 scientific articles were published by VHIO researchers as corresponding/senior authors or co-authors with a Median Impact Factor (MIF) of 9.27. These figures reflect an increase in scientific productivity, maintained MIF score, as well as the importance of VHIO’s research and contribution to the oncology field.

Figure I: Number of articles published by VHIO researchers from 2007 – 2013.

IMPACT FACTOR ARTICLES PUBLISHED IN 2013

For the complete list of VHIO Scientific articles published in 2013 in journals with allocated Impact Factor please see pages 81 - 87. To view a selection of most relevant articles by VHIO researchers published in 2013 please see pages 14 - 15 of this Scientific Report.

To consult publications per group as selected by our Principal Investigators, visit our Scientific Report online at: http://memorias.vhio.net/2013/ (select tab ‘Publications & Awards).

Figure II: Median Impact Factor (MIF) of papers published by VHIO faculty from 2007 – 2013.
Selection of some of the most relevant articles by VHIO researchers published in 2013

Below is a selected list of articles published by VHIO researchers in 2013 with respective Impact Factors indicated. For the complete list of VHIO scientific articles published in 2013 in journals with allocated Impact Factor please see pages 81 - 87 of this Scientific Report.


Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy. Ryan CJ; Smith MR; de Bono JS; Molina A; Logothetis CJ; de Souza P; Fizazi K; Mainwaring P; Piulats JM; Ng S; Carles J; Mulders PF. Basch E; Small EJ; Saad F; Schrijvers D; Van Poppel H; Muhkerjee SD; Suttmann H; Gerritsen WR; George DJ; Yu EY; Efstathiou E; Pantuck A; Winquist E; Higano CS; Park Y; Kheoh T; Griffin T; Scher HI; Rathkopf DE. 2013. *N Engl J Med* 368: 138-148. IF: 51,658

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine. Von Hoff DD; Ervin T; Arena FP; Chiorean EG; Infante J; Moore M; Seay T; Tjulandin SA; Ma WW; Saleh MN; Harris M; Reni M; Dowden S; Laheru D; Bahary N; Ramanathan RK; Tabernero J; Hidalgo M; Goldstein O; Van Cutsem E; Wei X; Iglesias J; Renschler MF. 2013. *N Engl J Med* 369: 1691-1703. IF: 51,658

Panitumumab-FOLFOX4 Treatment and RAS Mutations in Colorectal Cancer. Douillard JY; Oliner KS; Siena S; Tabernero J; Burkes R; Barugel M; Humblet Y; Bodoky G; Cunningham D; Jassem J; Rivera F; Kocákova I; Ruff P; Blasinska-Morawiec M; Šmakal M; Canon JL; Rother M; Williams R; Rong A; Wiezorek J; Sidhu R; Patterson SD. 2013. *N Engl J Med* 369: 1023-1034. IF: 51,658

Panitumumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma ( REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Grothey A; Cutsem EV; Sobrero A; Siena S; Falcone A; Ychou M; Humblet Y; Bouché O; Mineur L; Barone C; Adenis A; Tabernero J; Yoshino T; Lenz HJ; Goldberg RM; Sargent DJ; Cihon F; Cupit L; Wagner A; Laurent D. 2013. *Lancet* 381: 303-312. IF: 39,060


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VHIO MULTIDISCIPLINARY RESEARCH PROGRAMS

PRECLINICAL RESEARCH
VHIO’s Preclinical Program focuses on how critical signaling pathways affect the progression of breast, lung, pancreatic, and brain tumors. These pathways, including the MEK-ERK and the PI3K-mTOR, both activated by receptor tyrosine kinases, converge on Myc, a central regulator of gene expression. We are also interested in how malignant cells modify extracellular media and normal neighbor cells to generate the environment that fosters tumor growth. We are constantly searching for components and mechanisms against which to develop drugs to block malignant progression.

To deliver on our objectives, we generate sophisticatedly genetically modified mice to model tumor progression. In addition, we implant tumor pieces resected at the Vall d’Hebron University Hospital into immunodeficient mice. Once established in mice, these tumors, known as patient-derived xenografts (PDX), constitute a model that closely resembles the original tumors allowing our groups to test their novel therapies and discover mechanisms of resistance to current anti-cancer therapies. In addition, we have a keen interest in proteomic techniques that allow the analysis of thousands of factors simultaneously.

Our Mouse Models of Cancer Therapies Group, headed by Laura Soucek, has continued to focus on the Myc oncogene. They have shown Myc as a therapeutic target in different tumor types. Importantly in 2013, Soucek’s group reported that inhibition of Myc eradicates Non-Small-Cell-Lung Cancer in mice. As therapeutic strategies aimed at inactivating Myc, they are investigating cell-penetrating peptides.

VHIO’s Experimental Therapeutic’s Group led by Violeta Serra is dedicated to understanding the role of the PI3K/mTOR pathway as well as that of the mechanisms of DNA repair in tumor progression and therapy. In particular, they have identified that the activation of the receptor tyrosine kinase c-KIT impairs the anti-tumor activity of PI3K inhibitors in a subset of breast cancers, providing a rationale to combine PI3K and c-KIT inhibitors in these tumors.

Our Tumor Biomarkers Group under the leadership of Josep Villanueva, investigates how the factors secreted by cancer cells modify the tumor environment. They have shown that a large number of proteins are released from cells via non-classical secretory pathways that are used by transformed cells. Some of these proteins could be used as tumor biomarkers. His group has also developed various methods that greatly improve the reproducibility and statistical power of proteomic data.

Finally, my own Growth Factors Group has continued to characterize the response to treatment of a subtype of breast cancer known as HER2-positive. We have described novel components of the signaling pathway activated by the receptor tyrosine kinase HER2 that are relevant to the progression of breast cancers. We have also shown that the premature senescence of breast cancer cells results in the modification of the extracellular environment and, as a consequence, an increased ability of tumor cells to invade healthy tissue.

Our groups’ results have been published in several journals of excellence including Cancer Discovery, Genes & Development, The Journal of Clinical Investigation, and Cancer Research. Furthermore, as a direct reflection of the high caliber of cancer science that we conduct, our groups are supported through International and National Competitive Grants from the Association for International Cancer Research (AICR), the Breast Cancer Research Foundation (BCRF), Instituto de Salud Carlos (Institute of Health Carlos III, ISCIII), and the Spanish Association Against Cancer (AECC).
STRATEGIC GOALS

2. Developing predictive and pharmacodynamic biomarkers of PI3K-pathway inhibitors.
4. Establishing a patient tumor-derived breast cancer preclinical model to explore hypothesis-based combinatorial therapies.

HIGHLIGHTS IN 2013

- We have identified two mechanisms that lead to activation of mTORC1 signaling and impair sensitivity to PI3K inhibitors. This preclinical observation has been linked with limited activity of these agents in the clinic and proposes combination therapeutic strategies to improve the activity of this class of agents.
- Robust Akt inhibition in tumors from patients treated with GDC-0068 is achievable, supporting the clinical development of this compound in defined patient populations.
- Molecular characterization and clinical response to a lapatinib-based therapy for the tumors of a Li-Fraumeni patient shows prevalence of HER2 and EGFR genomic alterations.

SUMMARY

During 2013 our research has advanced insight into the mechanisms of sensitivity and resistance to targeted therapy in breast cancer, focusing on two main areas: the blockade of the HER2/PI3K-pathway as well as therapies targeting homologous recombination deficiency. Our ultimate goal is to provide hypothesis-based strategies to combine targeted therapy and, in so doing, improve outcomes for patients.

Insight into the biochemical adaptation following PI3K pathway blockade had revealed the presence of a FOXO/HER3-mediated ERK activation that limits the activity of PI3K inhibitors in HER2 positive breast cancer. Further studies have identified c-KIT and IGF-1R as important players mediating the PI3K-compensatory response in some subsets of triple negative breast cancer and in luminal B breast cancer, respectively. Since targeting these membrane receptors in vivo results in therapeutic benefit when combined with PI3K-pathway inhibitors in certain models, predictive biomarkers are required.

We are further exploring potential predictive biomarkers in PI3K-targeting therapies by dissecting single agent PI3K inhibitor responder patients' genotypes. Specifically, we have analyzed differences in the genome between tumors that have become resistant to single-agent PI3K-pathway inhibitors, following a significant clinical response. To study the impact of PI3K activation in other cancers we have dissected potential predictive biomarkers for dual PI3K/MEK-targeting in colorectal cancer. We have also demonstrated sensitization of chemotherapy-resistant breast cancer tumors to combined PI3K-therapeutic regimens, a study resulting in the activation of a Phase Ib international clinical trial led by VHIO.

Our group has established novel patient tumor-derived breast cancer models in vivo. These preclinical models faithfully resemble the metastatic disease and have been extremely useful in studying sensitivity and resistance to targeted therapy. Specifically, we have expanded the use of these models to study the predictive biomarkers of response and resistance to PARP inhibitors in hereditary breast cancers with BRCA1/2 mutations.
PRECLINICAL RESEARCH

GROWTH FACTORS GROUP

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Junjie Zhang
STRATEGIC GOALS

2. Develop novel therapeutic strategies to treat HER2-positive tumors and identify mechanisms of resistance to current therapies.
3. Initiate research into pancreatic cancer in close collaboration with VHIO’s Clinical Research Program, directed by Josep Tabernero.

HIGHLIGHTS IN 2013

• We have identified and characterized a dominant-negative N-terminal Fragment of HER2 frequently expressed in HER2-positive breast cancers.
• We have discovered PELO to be a novel regulator of the signals transduced by HER2.
• We have shown the pro-metastatic effect of the secretome of HER2-induced senescent breast cancer cells.

SUMMARY

Continuing our focus on breast cancer and receptor tyrosine kinases, during 2013 we completed the characterization of the role of fragments of the HER2 receptor that modulate its activity and, hence, its oncogenic activity. One of these fragments, known as HER2 NTF, acts as a weak dominant negative and is present in a high percentage of breast cancers of the HER2-positive subtype. In addition, we have identified PELO as a negative regulator of the signaling pathways initiated by HER2. Importantly, the knock down of PELO increases the metastatic ability of breast cancer cells. Finally, we have shown that constitutively activated HER2 leads to premature senescence. These senescent cells remain metabolically active and display a remarkable secretory phenotype enriched in prometastatic and protumorogenic factors. As a result, we have established the prometastatic effect of the secretome of HER2-induced senescent cells.

We have also been collaborating with other VHIO groups, particularly with Experimental Therapeutics led by Violeta Serra. This work has focused on the identification of mechanisms of resistance to inhibitors of the PI3K pathway and the description of a novel mutation that activates HER2 in patients with Li-Fraumeni Syndrome.

We are extremely grateful to the Spanish Association Against Cancer (AECC), the Breast Cancer Research Foundation (BCRF) and the AVON Cosmetics Foundation, for their continued, critical support of our research – now more important than ever given the current economic climate.

Lastly, but by no means least, we continue to coordinate the Breast Cancer Program within the Red Territorial de Investigación Cooperativa en Cáncer, supported by the Instituto de Salud Carlos III (ISCIII).

Figure: The Knockdown of PELO results in increased metastatic phenotype. Breast cancer cells expressing firefly luciferase or the same cells genetically modified to inhibit the expression of PELO were injected into the mammary fat pad of nude mice and tumors were allowed to grow until they reached 600 mm³, at which point the tumors were removed. Two months after removal of the primary tumor, metastatic growth was detected by in vivo imaging of total photon flux. The mice were then sacrificed and luminescence was analysed in axillary lymph node and lungs. Identical settings and scale (shown) were used in image preparation for all panels.
STRATEGIC GOALS

1. Validation of Myc inhibition by small molecules as a therapeutic strategy in lung cancer.
2. Pre-clinical validation of new therapeutic approaches against pancreatic, brain, and lung cancer.
3. Defining the role of Myc inflammatory effectors in pancreatic tumorigenesis and tumor maintenance.
4. Design and characterization of new cell penetrating peptides for cancer therapy.

HIGHLIGHTS IN 2013

• Myc inhibition is shown to eradicate KRas driven Non-Small-Cell-Lung-Cancer in mice, without any emergence of resistance, even after long term treatment.
• We collaborated with Margaret McGee, University College Dublin (Ireland), to identify the mechanism of death in cells treated with microtubule-damaging chemotherapeutic agents such as Taxol.
• Laura Soucek was awarded the prestigious Association for International Cancer Research (AICR) grant to develop anti-cancer therapies through Myc inhibition, as well as the Grants4Targets from Bayer to develop Myc inhibitory drugs.
• Daniel Massó Vallés, a post-graduate student in the lab, received a PhD fellowship from the Biochemistry, Molecular Biology and Biomedicine Program of the Universidad Autónoma de Barcelona. Project title: Targeting Myc in Breast Cancer Metastasis. He was also awarded the 7th Jornada Científica VHIR Poster Prize 2013.

SUMMARY

Current targeted cancer therapies are directed against a limited number of molecules, frequently restricted only to particular tumor types and often residing in the most degenerate, redundant, plastic and adaptive parts of the aberrant signaling networks that drive cancer. Hence, tumors often adapt to such inhibitors, evolving into more aggressive cancers as a consequence of the imposed selective pressure. Hence, we seek instead to establish the therapeutic utility of targeting an essential common signaling conduit that is shared by some - if not all - cancers. The main focus of our group is the pleiotropic and ubiquitous Myc oncoprotein, whose deregulation is implicated in almost all human cancer types. The technical challenges of targeting nuclear transcriptional factors such as Myc – and the concern regarding potential side effects – had until recently precluded any preclinical validation of Myc inhibition as a possible therapeutic approach. However, over the past few years, we have demonstrated in several mouse models that Myc inhibition has a dramatic therapeutic impact in different types of cancer, with very mild and reversible side effects in normal tissues.

We are currently expanding our studies to cancer metastasis, where Myc could play a crucial role in the coordination of the cross-talk between tumor and microenvironment, and the instruction of the metastatic soil. We are also interested in pushing Myc inhibition towards the clinic by developing viable, non-toxic options for its targeting in vivo.

Concerning the latter, we hired a new postdoc, Marie-Eve Beaulieu, an expert in structural biology and peptide design, from Quebec (Canada). Since she joined our group, Marie-Eve has been working on developing, producing and purifying Omomyc-based cell penetrating peptides for direct delivery to cancer cells and tumors, then proceeding to their validation in vitro and in vivo. Thanks to preliminary results, VHIO has filed an application for a European patent (nº EP133821678: Methods and composition for the treatment of cancer) for the use of Omomyc-based peptides and their variants in the treatment of various types of cancer. Studies to assess their therapeutic impact are underway.

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

TUMOR BIOMARKERS GROUP

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STRATEGIC GOALS

1. The characterization of mechanisms adopted by tumor cells to communicate with their microenvironment during tumorigenesis. We then use this data for biomarker discovery.

2. Discovery of secreted signaling pathway-based tumor biomarkers and therapeutic targets using quantitative proteomics.

3. To establish secreted response/resistance biomarkers to targeted drug therapy, measurable through non-invasive methods.

HIGHLIGHTS IN 2013

- We have shown that a large number of proteins that had never previously been detected in the extracellular space, are specifically secreted using non-classical secretion pathways and could be used as tumor markers. We hypothesize that tumor cells use unconventional or alternative protein secretion pathways during tumorigenesis.

- Our group has developed and implemented a statistical filter for quantitative proteomics data that increases the reproducibility of statistical results. This filter increases the number of true positives, decreases the number of false positives as well as the false discovery rate of the proteomics data sets.

- We have developed a proteomic methodology based on 3D-spheroids to analyze the action of anti-EGFR targeted drugs. The methodology is compatible for both cell-based assays and 3D-secretome proteomics. We have proved that the 3D-culture methodology developed, recapitulates the observed sensitivity/resistance to anti-EGFR targeted drugs in colorectal cancer patients.

SUMMARY

Tumor cell communication with its microenvironment performs an important role in tumor initiation and progression. Tumor cells hijack the tumor microenvironment ecosystem via paracrine signaling to promote a pro-oncogenic microenvironment that is crucial for the development of primary and metastatic tumors.

Our main aim is to characterize the mechanisms adopted by cancer cells to communicate amongst themselves as well as with their microenvironment during tumorigenesis, and exploit this to advance biomarker discovery. Our group’s working hypothesis is that cellular signaling pathways undergo changes during the tumorigenesis process and that such alterations are translated into differential protein secretion, which can also potentially be exploited to identify secreted markers. In addition, some of the differentially regulated proteins could be direct extracellular messengers of intracellular signaling pathways contributing to fundamental stages implicated in cancer initiation and progression, therefore becoming potential therapeutic targets.

Proteomic technologies facilitate a genome-scale search for tumor-specific biomarkers and drug targets and could therefore revolutionize early detection and molecular characterization of cancer through non-invasive methods. The methodological focus of our group centers on a new proteomic approach capable of quantitatively profiling the secreted sub-proteome (‘secretome’) of cells. Secretome signatures in different breast cancer model systems - as well as from clinical samples, will be generated and analyzed using differential expression statistics, and then set within the context of intracellular signaling transduction using bioinformatic tools.

The cancer secretome contains secreted proteins that tumor cells use as molecular SMS to communicate to each other and with their microenvironment. Since they are secreted they have a high probability of being present in biological fluids such as blood. Our final goal is to identify tumor-specific secreted proteins that can be used to develop blood-based diagnostic tests for cancer detection and monitoring.

Figure: Schematic representation of classical and non-classical protein secretion pathways. The top part of the diagram shows the classical ER-Golgi secretory pathway. The rest of the illustration depicts different non-classical protein secretion pathways.

To find out more about us, our research, publications and even our group’s horizons for 2014, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2013/
VHIO MULTIDISCIPLINARY RESEARCH PROGRAMS

TRANSLATIONAL RESEARCH
VHIO’s Translational Research Program is dedicated to improving and accelerating the integration of preclinical and clinical research. We consequently strive to translate advances in molecular research to patient care as rapidly as possible by tackling the disease from all angles and generating synergies between molecular and clinical cancer research.

One of the main challenges we all face in our collective battle to combat cancer is tumor diversity. Cancer is an extremely complex and heterogeneous disease given that tumors are molecularly diverse. Moreover, tumors are formed by cells with multifarious states of proliferation, differentiation, motility, and, importantly, varying sensitivity to treatment. In short, each patient has a unique tumor with a particular combination of genomic aberrations. Our patients should therefore be treated with the optimal compound/combination of compounds to respond to the specificities of their respective disease. Since the selection of the most appropriate treatment depends on the specific molecular taxonomy of the tumor, the challenge is to identify which treatment should be linked to which patient and in so doing, further advance precision medicine in oncology.

In order to improve cancer treatment through the combination of compounds targeting all cell types within a tumor, it is also imperative to better understand the nature of intratumoral heterogeneity. Among the different cell types forming intratumoral heterogeneity, some cells with stem cell characteristics have been identified. Known as Cancer-Initiating Cells (CICs) or Cancer Stem Cells (CSCs), these cells are characterized by their self-renewing capacity, their multi-lineage differentiation properties, their high oncogenic potential, and ability to replicate the heterogeneity of original human tumors in mouse models. CICs are also considered responsible for the initiation, recurrence and chemo- and radio-resistance of tumors indicating that more effective therapies will result from strategies aimed at targeting the stem-cell-like component of tumors. Few pharmacological compounds have yet been shown to successfully do so.

In order to effectively explore the two levels of cancer heterogeneity, we investigate cancer as faithfully as possible to that of a real tumor and generate patient-derived models both in vitro and in vivo. Tumor specimens are obtained shortly upon surgical resection and the tumor cells including cancer stem cells are studied. The next step is to generate mouse models reproducing the characteristics of the tumor from the patient. Both VHIO’s Stem Cells & Cancer Group led by Héctor G. Palmer, and my own Gene Expression & Cancer Group have developed these types of models of brain and colon cancer respectively, work which has led to important findings published in top tier journals.

Since tumor diversity and heterogeneity are due to variations in the genome or the epigenome of cancer, genomic and epigenomic studies are paramount. Serving as a Core Technology, our Cancer Genomics Group headed by Ana Vivancos, leads VHIO’s ‘omics’. Ana’s lab is equipped with a genotyping platform (MassARRAY, Sequenom) and two NextGen sequencers (MiSeq and HiSeq2500, Illumina), providing cutting-edge applications in cancer genomics through the use of new technologies and protocol development (see ‘Core Technologies’, pages 58 - 67). It is thanks to the dedicated work of her group that tumor genomic analysis will be used to steer cancer treatment and management decisions for an increasing number of patients.

Providing optimal treatment tailored to individual patients relies on team work, studying cancer as closely as possible to the real patient, and tackling cancer heterogeneity head-on. VHIO’s Translational Research Program is devoted to delivering on this promise by catalyzing the transfer of new insight generated by scientific research into the true benefit for patients.
GENE EXPRESSION & CANCER GROUP

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STRATEGIC GOALS

2. The study of intratumoral heterogeneity.
3. Identification of novel biomarkers to develop precision onco-medicine based on the particularities and characteristics of each tumor.
4. To better understand the molecular mechanisms implicated in cancer stem cells.
5. Develop methods for non-invasive molecular diagnosis through the study of circulating biomarkers.

HIGHLIGHTS IN 2013

• Resulting in two publications (Serra et al. Cancer Discovery, and De Mattos-Arruda et al. Molecular Oncology – for all our group’s publications please visit the 2013 VHIO Scientific Report online), for which Joan Seoane is co-corresponding author, we have studied the genomic heterogeneity of tumors of the same patient and have achieved a greater understanding of the biology of the tumors and identified the optimal treatment precisely tailored to the individual patient.
• Joan Seoane received the prestigious Dr. Josef Steiner Cancer Research Award.

SUMMARY

Our group’s research focuses on the study of brain tumors, glioblastoma and brain metastasis in particular. These are some of the most aggressive cancers and advancing progress within the field is consequently critical. Our studies are largely based on research into patient-derived tumors. We generate animal models that recapitulate the tumor of the patient at genomic and gene expression levels. We inoculate the patient-derived tumor cells into the brain of immunocompromised mice and they generate tumors with the same characteristics as the original human tumor, which we can then monitor by MRI. This mouse model for human glioma is of major interest in the study of the molecular mechanisms involved in cancer as well as the evaluation of the efficacy of pharmacological compounds.

One of the most important challenges in cancer is tumoral heterogeneity of tumors (see figure), which we are studying at both the level of genomic alterations and that of cell differentiation state. Regarding the latter, we are analyzing a subpopulation of undifferentiated cells responsible for tumor initiation and relapse. These cells have stem cell-like characteristics and are known as cancer-initiating cells (CICs) or cancer stem cells. CICs are considered to be responsible for the initiation, recurrence and chemoresistance of tumors. CICs are, therefore, crucial therapeutic targets and achieving a better understanding of the molecular mechanisms involved in this type of cells, is paramount. We aim to identify novel markers for CICs, further knowledge regarding the signaling pathways and molecular mechanisms involved in CICs, and design novel therapeutic approaches to target CICs.

Finally, during 2013, we have initiated a new line of research based on the study of circulating tumor cells and circulating tumor DNA. Tumors shed cells and DNA into the bloodstream and the analysis of these circulating markers allows for the accurate, non-invasive molecular diagnosis of the tumor. These circulating markers facilitate the monitoring of tumor progression. Moreover, they will also contribute to improved methods for the early detection of cancer since the analysis of tumor cells or mutated DNA in blood is more sensitive compared with certain imaging techniques.

Figure: One of the most important challenges in cancer treatment: intratumoral heterogeneity.
STRATEGIC GOALS

1. Describe the key molecular mechanisms that confer CoCSC their capacity to self-renew and resist conventional or target directed therapies.
2. Unmask the molecular drivers of CSC quiescence, clinical relevance in cancer progression and evaluate their potential inhibition to eradicate CoCSC.
3. Study the efficacy and mechanism of action of new Wnt/beta-catenin inhibitory drugs for the treatment of CRC patients.
4. Identify the genetic determinants of sensitivity or resistance to the novel generation of Wnt/beta-catenin inhibitors.
5. Implement predictive biomarkers of response to therapeutic Wnt/beta-catenin inhibitors and other targeted therapies.

HIGHLIGHTS IN 2013

- We have revealed the molecular mechanisms governing the delicate link between stemness and quiescence in chemoresistant colon cancer cells. Many of the genes and proteins that play a central role in this process are epigenetic chromatin remodelers. The activity of these factors can potentially be inhibited as a new therapeutic approach to eliminate CoCSC.
- We have accumulated evidence regarding the efficacy and mechanisms of action of a new generation of Wnt/beta-catenin inhibitory drugs on CRC. We are also identifying potential biomarkers to predict response to these inhibitors.

SUMMARY

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

In particular, we are dedicated to studying the consequences of intra-tumoral cell heterogeneity for tumor evolution and patient survival. Among the different cell populations that build an heterogeneous tumor, Cancer Stem Cells (CSC) are at the apex of a differentiation process within the cancerous tissue somewhat reminiscent of the hierarchy present in the normal tissue from which they originate. Furthermore, CSC can compose the small reservoir of drug-resistant cells that are responsible for relapse after chemotherapy-induced remission, or give rise to distant metastasis. It is therefore becoming evident that a cancer treatment that fails to eliminate cancer stem cells may allow re-growth of the tumor.

As a hideous disease with such a devastating impact on society, colorectal cancer is our prime focus of study. At molecular level, we are analyzing the role of those oncogenic pathways that control the fate of Colon Cancer Stem Cells (CoCSC). RAS/PI3K/AKT and Wnt/beta-catenin pathways are two such driving forces that direct cancer stem cell fate and lead the progression of many tumor types.

Over recent years we have succeeded in describing a new mechanism of resistance to PI3K and AKT inhibitory drugs conferred by beta-catenin in colorectal cancer. Such discovery is of great clinical relevance since many patients in clinical trials are not responding to these drugs and no molecular explanation behind resistance had previously been described. These new findings will facilitate the selection of sensitive patients based on their expression of particular biomarkers that predict drug-response.

We are currently leading research focusing on a new generation of Wnt/beta-catenin inhibitory drugs in close collaboration with several major pharmaceutical companies. We have already produced experimental evidence regarding the efficacy and mechanisms of action of such drugs in pre-clinical models of colorectal cancer with patient-derived xenografts. This marks an important milestone in the field, since colorectal cancer was described as a paradigmatic tumor addicted to the oncogenic Wnt/beta-catenin pathway many decades ago. We are also identifying the molecular determinants of response to these drugs that could become robust biomarkers to select sensitive patients and guide the design of new clinical trials in the future. Some of these predictive biomarkers are mutations affecting components of the Wnt/beta-catenin pathway, whose identification can be perfectly standardized in clinical practice for patient selection.

Our collaboration with the Oncology Service at the Vall d’Hebron University Hospital and pharmaceutical companies will accelerate the translation of our findings into clinical practice and hopefully revert the long-stalled scenario of CRC therapies.

Figure: Molecular prescreening and selection of colorectal cancer patients to be included in precise clinical trials with target directed drugs.
VHIO MULTIDISCIPLINARY RESEARCH PROGRAMS

CLINICAL RESEARCH
From the Director

The PI Pages

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

As a direct reflection of VHIO’s purely translational research model, our clinical research groups work hand-in-hand with scientists from our Preclinical, Translational, Core Technology Programs. In relation to our Core Technologies, in 2013 we obtained ISO certification for VHIO’s Cancer Genomics and Molecular Oncology Groups. This not only recognizes VHIO’s technical competencies, optimal quality, standardization, validation of processes and staff training, but also positions our institute as one of the very first in Spain to have met this rigorous standard.

Importantly this year, we have also been paving the way to incorporate BEAMing digital PCR/flow cytometry technology as a further tool through which to detect drug resistance mediated by specific mutations such as that of the KRAS oncogene which is massively implicated in metastatic disease across various tumor types. Set to empower our current suite of technologies, this accurate, sensitive and non-invasive approach to detect mutations in circulating tumor DNA in blood, shows great promise in next-generation companion diagnostics and the mutational profiling of individual tumors.

In Colorectal Cancer (CRC) we have developed a combined oncogenic pathway signature that allows the identification of patients with an active epidermal growth factor receptor (EGFR)-signaling pathway that could benefit from downstream pathway inhibition. We are exploring whether KRAS-, BRAF- or PIK3CA profiles might be useful in predicting the response to the EGFR pathway inhibitors rather than mutation status alone. We are also pioneering important studies involving both preclinical and early-drug development, leading to clinical trials designed to identify more effective cancer therapies tailored to individual patients.

Current efforts focus on the role of plasma cfDNA as a predictor of response for novel targeted therapies and demonstrating that the measurement of plasma cfDNA quantitative and qualitative alterations may have a prognostic value in metastatic patients. The results of these determinations have been correlated with those of tumor biopsies to determine whether the former data may substitute the information obtained from the latter. Therefore, tumor-derived somatic mutation profiling in plasma, if feasible and reproducible, may represent an alternative to tumor-tissue, providing real-time insights into tumor dynamics, and consequently lead to a better understanding of the pathways that drive cancer metastasis.

While we have undoubtedly marked important progress this year in fine-tuning diagnosis and treatment strategies to the unique molecular make-up of an increasing number of patients, we still have a long way to go in combating cancer. We must therefore continue to share our expertise – and benefit from the experiences of many others – through international collaboration. Such pan-global exchange spanning basic, translational and clinical research is critical not only in accelerating discovery but also avoiding the costly duplication of efforts. It is through such partnership that we are currently driving important advances in trial design -- examples in 2013 being the WINTHER (WINTherapeutics) study and the POSEIDON trial (page 6).

Similarly, this year has marked the launch of several unique opportunities in the form of consortia of excellence (pages 90 - 91), which will spur advancements to make personalized medicine more precise and accessible for an increasing number of individuals whose lives are threatened by cancer.

At VHIO, as we demonstrate year in, year out, we can and will do better.
BREAST CANCER & MELANOMA GROUP

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Vanesa Ortega
José Manuel Pérez
Aleix Prat
Cristina Saura
Jesús Soberino
Mª Jesús Vidal
STRATEGIC GOALS

1. Optimize treatment options in patients with resistant HER2-positive tumors and triple negative breast cancer, with particular focus on new targeted agents which overcome resistance to standard anti-HER2 agents, or better therapeutic strategies to be explored in preclinical models prior to using them in patients. We hope to expand these efforts to other scenarios, such as chemo or endocrine resistant tumors.

2. To continue to lead Phase I-based Phase II trials, and closely collaborate with VHI O’s Experimental Therapeutics Group, transitioning to more advance studies with data obtained from early drug development.

3. Implement “omic” tools to better design clinical trials.

4. To continue working with VHO’s Preclinical Groups to ultimately provide “smarter” treatments to our patients as rapidly as possible.

5. Advance onco-immunology towards improved management of patients with breast cancer, specifically HER2 and triple negative.

6. Establish our group as a leader in the field of melanoma. During 2010-2012 we began working with melanoma patients to try and provide them access to the best clinical trials. In 2013, we have offered more than 10 different new molecules in close collaboration with VHO’s Experimental Therapeutics Group. More than 50% of our patients with metastatic melanoma have entered clinical trials.

7. To consolidate our leadership in melanoma in Spain and expand our expertise at European level (envisaged 2014-2016).

HIGHLIGHTS IN 2013

1. We have observed that combining eribulin with PI3K inhibitors might enhance the activity of both drugs, which has opened new options and opportunities for our patients. A phase Ib/II trial will commence in 2014, led by VHI O investigators.

2. We continued our development of patient-derived xenografts in close collaboration with the VHI O’s Preclinical Research Program. We currently have the most important collection at European level.

3. We have been involved in the steering committees of the most relevant randomized Phase II and III clinical trials, and participated in some of the most important clinical trials, which has previously led to the approval of drugs such as pertuzumab and eribulin. In 2014, the first Phase Ib/II trial will be initiated, led by our group and sponsored by Novartis.

4. Application of new biological agents to reverse mechanisms of resistance to classical drugs, not only to anti-HER2 therapy, but also to endocrine therapy.

5. We collaborate closely with VHO’s Early Drug Development Group headed by Jordi Rodóin which allows us to consider drugs that have been tested in very early studies and that have shown sufficient activity to expand studies in patients with breast cancer. In 2013, we have initiated clinical trials based on the preliminary efficacy results we observed in early clinical trials.

6. Triple Negative Breast Cancer. We have started an ambitious clinical research program focusing on this tumor type and now have a few specific clinical trials underway. We are dedicated to leading this field of research over the next 4-5 years.

SUMMARY

Our Breast Cancer Program continues to be one of the most active in Spain and one of the most renowned across Europe. In 2013, 32 publications (25 of them in the first quartile), totaled an impact factor of 384.08, with a mean IF of 12. Interestingly, we published a newly proposed concept surrounding cancer research in January 2014 (epub ahead of print, Nov. 2013), in the highest impact factor journal, CA: A Cancer Journal for Clinicians (IF: 153.46). In addition, we have initiated more than 25 new clinical trials and studies. We are not only committed to participating in clinical and preclinical studies, but we also lead several -- reflected by our representation of Steering Committees for some, and appointed international leaders for others.

Our main areas of interest continue to center on the development of new treatments and the search for mechanisms of resistance to current ones. Multidisciplinary collaboration and management with surgeons, pathologists, radiologists and radiotherapists, among others, facilitates the incorporation of the most innovative treatments in clinical practice and optimizes therapeutic alternatives. In clinical research, our key areas of activity include:

1. HER-positive breast tumors. Over recent years, new targeted therapies against HER2 have become available. We are particularly proud to lead one of them, pertuzumab, which has improved outcomes of our patients. In close collaboration with VHO’s Growth Factors and Experimental Therapeutics Groups, led by Joaquín Arribas and Violeta Serra respectively, different mechanisms of resistance to this therapy and other strategies are currently under study. We are particularly interested in the design of new strategies to overlap such mechanisms. There are two interesting new compounds which are now being tested in Phase II trials; Neratinib and TDM-1. We are leading the clinical development of the former. Importantly, we have observed that TDM-1 activity, although impressive, is not very significant during the first week of administration. For this reason, we have initiated a Phase Ib trial of TDM-1 in combination with chemotherapy.

2. To optimize chemotherapy-based strategies. The majority, if not all, of our patients with metastatic breast cancer will at some point require treatment with chemotherapy, and, unfortunately, they will become resistant to it. For this reason, we strongly believe that overcoming mechanisms of resistance to chemotherapy will enhance the activity of these drugs. In collaboration with VHO’s Experimental Therapeutics Group, we aimed to improve the efficacy of eribulin, a new chemotherapeutic agent, with targeted agents, based on a new mechanism of resistance. We demonstrated (as presented at the San Antonio Breast Cancer Symposium - SABCS, 10 – 14 December 2013), that the efficacy of eribulin depends on PI3K status. This resistance might be overcome by the addition of different PI3K inhibitors (see figure). In 2014, the first Phase Ib/II trial will be initiated, led by our group and sponsored by Novartis.

3. Application of new biological agents to reverse mechanisms of resistance to classical drugs, not only to anti-HER2 therapy, but also to endocrine therapy.

4. We collaborate closely with VHO’s Early Drug Development Group headed by Jordi Rodóin which allows us to consider drugs that have been tested in very early studies and that have shown sufficient activity to expand studies in patients with breast cancer. In 2013, we have initiated clinical trials based on the preliminary efficacy results we observed in early clinical trials.

5. Triple Negative Breast Cancer. We have started an ambitious clinical research program focusing on this tumor type and now have a few specific clinical trials underway. We are dedicated to leading this field of research over the next 4-5 years.

To find out more about us, our research, publications and even our group’s horizons for 2014, visit the VHI O Scientific Report online at: http://memorias.vhio.net/2013/
STRATEGIC GOALS

1. Clinical early development of the best-in-class targeted therapies, determining the optimal schedule and patient population to benefit most from these drugs by participating in novel clinical trials.

2. Analyze patients’ tumors for molecular aberrations that may predict the efficacy of targeted agents, in order to select the most appropriate treatment for each individual with advanced cancer.

3. Link clinical research at the Research Unit for Molecular Therapy of Cancer (UITM) - “la Caixa” with the various preclinical and translational research groups at VHIO, and collaborate with the different partners involved in drug development and translational research (phase I units, academic centers, consortia, pharmaceutical companies).

HIGHLIGHTS IN 2013

• As one of the leading institutes worldwide with expertise in areas of drug development such as PI3K/akt/mTOR inhibitors, MAPK inhibitors or drugs targeting developmental pathways such as TGFbeta, SHH, WNT, and NOTCH, we have been clinically testing the best-in-class drugs. We have also expanded our expertise to other cell-signaling pathway inhibitors such as MET and FGFR.

• We have performed several clinical trials with novel-novel combinations - combining several PI3K inhibitors with MEK inhibitors. IGF1R inhibitor with PI3K or MEK inhibitors, Smo inhibitor with a PI3K inhibitor, and a NOTCH inhibitor with mTOR inhibitor.

• We have performed many clinical trials with patients selected on molecular alterations (mutations in AKT, PIK3CA, PTEN, ALK, BRAF, NRAS, KRAS, FGFR1 and 2, MET; amplifications in HER2, AKT1,2, and 3, FGFR1, MET, and alteration in protein expression of PTEN, or overexpression of PDL1, GCC or of prolactin receptor).

• We have co-developed several molecular tests for patient screening such as disease-oriented mutation panels for Sequenom.

SUMMARY

Our main interest surrounds proof-of-concept and proof-of-mechanism trials with targeted therapies, especially those aimed at cell signaling and cancer stem cells. These include first-in-human studies of targeted therapies, rational combinations of targeted therapies, biomarker-driven trials and trials in molecularly selected populations.

We try to link clinical research at the UITM with the different areas of research carried out by VHIO’s research groups, following a truly translational model: linking molecular biology and the best tumor models with pharmacology and innovative clinical research. We are therefore dedicated to involving VHIO scientists in the trials (biomarker development, profound understanding of the mechanism of action, research into mechanisms of resistance) for selected projects. In addition, we have collaborated with VHIO’s Molecular Oncology Group, headed by Paolo Nuciforo, as well as the Cancer Genomics Group led by Ana Vivancos, and the Translational Genomics Group directed by Aleix Prat to perform molecular analysis of patients’ tumors in order to select the best possible treatment for our patients with the experimental treatments available in our portfolio of clinical trials - one step closer to realizing the true promise of precision medicine.

Importantly, in relation to precision oncology, VHIO is a founding member of the WIN (Worldwide Innovative Networking in personalized cancer medicine) Consortium, initiated by the Institut Gustave Roussy (IGR), Paris, (France) and University of Texas MD Anderson Cancer Center, Texas (USA). WIN is a non profit, non-governmental organization that brings together 22 cancer centers including VHIO and industry partners from five continents to address the challenge of increasing the efficacy of cancer diagnostics and therapeutics.

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

To find out more about us, our research, publications and even our group’s horizons for 2014, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2013/
CLINICAL RESEARCH

GASTROINTESTINAL & ENDOCRINE TUMORS GROUP

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Medical Oncologists and Clinical Fellows
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Guillem Argilés

Jaume Capdevila
María Elena Élez
Teresa Macarulla
Tamara Sauri
STRATEGIC GOALS

1. Discovery of new biomarkers in gastrointestinal tumorigenesis.
2. Validation of new prognostic biomarkers.
3. Development of relevant preclinical models in vitro and in vivo with a special emphasis on the identification of predictive markers.
4. Early clinical research with innovative targets.
5. Clinical research in late stage with more translational endpoints, focusing on the identification of prognostic/predictive biomarkers.
6. Participation in multidisciplinary/multinational consortia and research programs.

HIGHLIGHTS IN 2013

- Early Clinical Research: drug development & Phase I clinical trials in solid tumors with particular emphasis on developing molecular targeted therapies.
- Molecular Markers in Gastrointestinal Malignancies: advance insight into prognostic and predictive factors for response and efficacy with targeted agents in different gastrointestinal malignancies.
- Clinical Research: design of investigator-initiated clinical trials as well as participation in numerous trials developed in the context of national and international cooperative groups.

SUMMARY

In 2013, we have led and participated in numerous cooperative and singular research projects related to Gastrointestinal Malignancies. In addition to our key participation in international consortia of excellence including the WIN (Worldwide Innovative Networking in personalized cancer medicine) Consortium and other initiatives funded by the European Commission’s 7th Framework Program (e.g. EurocanPlatform, COLTHERES, MErCuRIC – see pages 90 - 91 of this report), at both preclinical and clinical levels, we have continued to further strengthen our purely multidisciplinary and translational approach to research.

Reflected by publications in the most prestigious scientific titles in 2013, our group has participated in many studies with important clinical impact including:

- The first-in-human trial of an RNA interference (RNAi) therapeutic targeting VEGF and KSP in cancer patients with liver involvement. Importantly, the results showed safety, mechanism of action, and clinical activity with a novel first-in-class LNP-formulated RNAi therapy in patients.
- Studies analyzing RAS mutations in colorectal cancer (CRC) such as the combination of Panitumumab-FOLFFOX4 treatment and its implication in the lack of response in patients with additional RAS mutations (other than KRAS). Patients with metastatic CRC without RAS mutations, showed improvements in overall survival with this combinational therapy.
- A Phase III trial validating the importance of VEGFR-2 signaling as a therapeutic target in advanced gastric cancer (Ramucirumab monotherapy – REGARD study).
- A Phase III study in patients with metastatic pancreatic adenocarcinoma proving that the combination of nab-paclitaxel plus gemcitabine significantly improves overall survival, progression-free survival, and response rate vs. gemcitabine monotherapy.
- The CORRECT study evidencing a continuing role of targeted treatment after disease progression in previously treated metastatic CRC. The therapy studied, Regorafenib (a multikinase inhibitor), is the first small-molecule multikinase inhibitor with survival benefits in mCRC patients who progressed after all standard therapies.
- The development of a combined oncogenic pathway signature allowing the identification of patients with an active EGFR-signalling pathway that could benefit from downstream pathway inhibition.
- A study establishing colorectal cancer intrinsic subtypes that predict chemotherapy benefit, deficient mismatch repair and epithelial-to-mesenchymal transition. Classification based on molecular subtypes allowed us to expand and improve CRC classification beyond standard molecular and immunohistochemical assessment, promising better guided treatment and management of these patients in the future.

Other research lines this year have included the use of validated biomarkers and their respective reference isogenic cell lines to develop next generation, non-invasive, diagnostics that can monitor the burden of disease, its respective molecular features, and response to novel targeted therapies.

We have also participated in several pre-clinical and clinical studies on predicted responsive patient subsets using genetically annotated tumor surgical specimens (‘Xenopatients’) in mice, expanding our collaboration with VHIO’s Stem Cells & Cancer Group, led by Héctor Palmer. Further, in partnership with pharmaceutical companies or academic groups, dedicated efforts continue to focus on the validation of re-profiled drugs or candidate drugs.

For more info at www.vhio.net

To find out more about us, our research, publications and even our group’s horizons for 2014, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2013/
CLINICAL RESEARCH

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

Principal Investigator
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Medical Oncologists and Clinical Fellows
Rafael Morales
Núria Mulet
Jordi Rodón
Cristina Suárez
Claudia Valverde
STRATEGIC GOALS

1. Design and develop clinical trials for all the malignancies covered by our group. We strive to provide our patients with the newest and optimal treatments for their respective disease, including immunotherapeutics, targeted therapies or new chemotherapeutics.
2. Conduct clinical trials at different stages of disease with emphasis on a histology-tailored design.
3. Develop new tools such as liquid biopsy for our patients for tailored treatment in CRPC.
4. Expand our translational research platform for glioblastoma in collaboration with VHIO’s Gene Expression & Cancer Group led by Joan Seoane.
5. Creation of a translational platform for sarcomas and basic research in partnership with the Biomedical Research Institute of Bellvitge (IDIBELL) and the Cancer Research Centre of Salamanca (CIC).

HIGHLIGHTS IN 2013

• New drugs in GU malignancies: we have participated in the most important trials with different drugs that, throughout 2012/2013, have demonstrated that they will change the prognosis of patients with prostate cancer including: Vaccines (Prostvac), Enzalutamide, Cabazitaxel or Radium 223. All these new drugs have demonstrated that they may improve the survival of our patients. Furthermore, in other GU malignancies we are participating in clinical trials to show the utility of adjuvant treatment in renal cancer, or new drugs in second and third line treatment. In bladder cancer we are participating in new clinical trials that combine classical chemotherapy with novel targeted agents and second line treatments. We will also start with agents that are able to modulate the host immune response and combat cancer. During this year, we have participated in Phase I clinical trials to test new therapies and immunotherapeutics for bladder and prostate cancer.

• Our research in Central Nervous System (CNS) tumours has been further consolidated with the development of additional clinical trials and the creation of a Board comprised of experts in neurosurgery, radiology, radiotherapy, translational research, and medical oncology.

SUMMARY

Our group is interested in both clinical and translational research with broad experience and grounded expertise in treating tumors since we are involved in the treatment of different neoplasms.

We focus on the design and development of clinical trials for genitourinary malignancies at different stages of the disease with the active participation of urologists, radiation therapists and medical oncologists. Over recent years, many developments have been reported in GU tumors; particularly in prostate and kidney cancer. Close collaboration between all specialists involved in the treatment of these tumors is therefore mandatory. It is also important to continue with our translational research platform for urologic cancer as well as conduct clinical trials in early, adjuvant as well as metastatic disease.

We also collaborate with other research centers of excellence including the Cleveland Clinic (USA), University of California San Francisco (USA), Gustave Roussy Hospital (France), and the Biomedical Research Institute of Bellvitge (IDIBELL), here in Barcelona (Spain). Results from these collaborations have been presented at the Castrate-Resistant Prostate Cancer (CRPC) meeting that took place May 24, 2012. Further research updates and new insights will be presented at the Second Cleveland-Vall d’Hebron meeting that will take place at the end of next year, 2014.

Another key area is the development of several multidisciplinary clinical trials and Phase I trials in CNS tumors, in close collaboration with professionals in neurosurgery and radiation therapy. We are also focused on consolidating the translational research platform for glioblastoma in collaboration with VHIO’s Gene Expression & Cancer Group led by Joan Seoane. We have consolidated a collaborative study with different centers in Europe to develop a vaccine for patients with glioblastoma. This project is supported by the European Commission’s 7th Framework Programme of Research and Development.

Our group is also working with the Spanish Sarcoma Group (GEIS), to conduct clinical trials at different stages of disease with emphasis on a histology-tailored design. We are currently involved in setting up a translational platform for sarcomas and basic research in partnership with the Biomedical Research Institute of Bellvitge (IDIBELL) and the Cancer Research Center of Salamanca (CIC – Spain). For GIST tumors we have developed a close relationship with J. Fletcher’s lab at Brigham and Women’s Hospital (USA). In this context, further research updates and discovery will also be reported at the New Insights in GIST meeting that will take place April 04, next year.

The serum bank dedicated to various tumor types such as CNS tumors, renal cell carcinoma and CRPC, will continue to recruit samples from our patients.

Lastly, but by no means least, we promote education and exchange by offering our group members the exciting opportunity to spend a minimum of 3 months in research centers of prestige within a specific field. In the near future we envisage that this program will promote shorter stays for joint project development. Importantly, in terms of education and exchange, two fellows spent a total of 6 months with us in 2013.
STRATEGIC GOALS

1. We are focused on clinical and translational research and are members of the most relevant international cooperative groups in Gynecological and Head & Neck Tumors. Such collaboration allows us to participate in the initial development of new drugs, from Phase I to Phase III trials.

2. Further expand our recognized expertise in clinical research within our field and continue to lead an increasing number of international projects.

HIGHLIGHTS IN 2013

• As a result of our collaboration with the Gynecologic Oncology Group (GOG), established in 2011, we are authors of pivotal studies in cervical cancer as well as ovarian cancer, both presented at the 2013 Annual Meeting of the American Society of Clinical Oncology (ASCO), May 31 – 04 June, Chicago (USA).

• In 2012 we were nominated as International Coordinator of a new Phase III trial in recurrent ovarian cancer. This study is currently being planned and under discussion in Europe (ENGOT group), as well as in the US (GOG group).

SUMMARY

Our group focuses on standard patient care as well as clinical research. Continuous development and research into new anticancer drugs represent a major area of our activity. Notably, based on our expertise, we have also actively participated in the revision of all Spanish guidelines in gynaecological cancer.

We are either members or affiliate members of some of the most relevant societies in oncology including the Gynecologic Cancer Inter Group (GCIG), European Network of Gynaecological Oncology Trial Groups (ENGOT), Grupo Español de Investigación en Cáncer de Ovario (Spanish Gynecological Group - GEICO), Gynecologic Oncology Group (GOG). In addition our group is involved in developing new strategies, approaches, and optimal trial design for research.

With regards to clinical activities at the Vall d’Hebron University Hospital, we play a central, key role as members of multidisciplinary committees and teams in Head and Neck and Gynecological Cancer Tumors. Our contribution, in close connectivity and collaboration with other professionals and specialties (including surgeons, radiotherapists, radiologists and pathologists), leads to the establishment of new treatment protocols and clinical guidelines to further advance clinical practice within our Hospital.

As a reference group for other specialties as well as several research centers of excellence, we have steadily increased the number of patients treated in clinical trials with new drugs. Currently we are involved in more than twenty trials as either Principal Investigators and/or Coordinators of National and International investigational studies.

We are continuously contributing to international conferences of excellence through the delivery of presentations, invited lectures, and the sharing and debating of key findings with colleagues and peers across the globe (for more information please select the ‘Publications, Projects & Awards’ tab of our Scientific Report 2013 online at: http://memorias.vhio.net/2013/).
STRATEGIC GOALS

3. Testing new combination therapies for BRCA-associated PDX’s that have progressed to PARP inhibitors.
4. Early detection of prostate cancer in BRCA mutation carriers.
5. Identification of new genes involved in hereditary breast cancer through the application of next generation sequencing.

HIGHLIGHTS IN 2013

• Active participation in international Phase II clinical trials with targeted therapies for BRCA-associated tumors.
• Establishing a large collection of BRCA-associated patient-derived xenografts implanted in athymic mice.
• Recruitment of 30 patients and controls in the IMPACT study (an international study for early detection of prostate cancer in BRCA mutation carriers).
• Participation in a national study to assess the role of breast density as a risk factor for breast cancer in BRCA mutation carriers.

SUMMARY

We are committed to developing new targeted therapies for patients with hereditary breast cancer. In this context, during 2013, patients with advanced breast cancer and a BRCA mutation could participate in a Phase II trial with a specific DNA binding agent, or enrol in a randomized Phase II trial with a PARP inhibitor in combination with chemotherapy. In addition, two years after initiating our collaboration with VHIO’s Experimental Therapeutics Group and the Cancer Genomics Group led by Violeta Serra and Ana Vivancos respectively, we are starting to see the benefits of such teamwork which has already resulted in a collection of BRCA-associated patient-derived xenografts implanted in athymic mice. These murine models will be used to study genetic mechanisms of resistance to targeted therapies and test new combinatorial treatments at progression.

This year we have also begun to analyze data collected in the national study funded by FIS: Densidad mamográfica, susceptibilidad genética y cáncer de mama en mujeres de alto riesgo (Proyecto DM-BRCA, PS09/01024) in order to determine the role of breast density as a risk factor for breast cancer in women with mutations in BRCA1/2 genes.

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

Figure: A baseline blood sample, a biopsy pre-treatment, and a biopsy at progression after a targeted therapy, are obtained. Next generation sequencing is performed to analyze genetic mechanisms of resistance.

To find out more about us, our research, publications and even our group’s horizons for 2014, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2013/
CLINICAL RESEARCH

ONCOGENETICS GROUP

Principal Investigator
Orland Diez

Staff Scientist
Sara Gutiérrez

Post-Doctoral Fellow
Sandra Bonache

Technicians
Miriam Masas
Anna Tenés

PhD Student
Gemma Montalban
STRATEGIC GOALS

1. Application of massive sequencing to the diagnosis of hereditary cancer.
2. Establish the prevalence in Spanish population of genetic variants of known breast/ovarian cancer genes conferring high to moderate penetrance.
4. Characterization of large rearrangements and transcriptional or functional effects of variants with unknown biological significance in breast cancer predisposition genes.
5. Identification of common low-penetration alleles that modify breast cancer risk for BRCA1 and BRCA2 mutation carriers.
6. To study the combination of apoptosis assay and genetic markers as predictive tests for late toxicity after radiotherapy.

HIGHLIGHTS IN 2013

• We performed exome sequence analysis of affected relatives from breast cancer families negative for BRCA1/2 mutations in order to unmask new potential predisposing genes.
• Our group has analyzed a panel of more than 40 predisposition breast/ovarian cancer genes by massive sequencing in a control group of BRCA1/2 patients to finely-tune the given methodology.
• We have led a multicenter study to determine the prevalence of RAD51D disease-causing variants in Spanish breast/ovarian cancer families.
• We collaborated with the working groups of the Evidence Based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) International Consortium in the evaluation of methodologies for DNA/RNA analysis, and alternative transcripts in BRCA1 and BRCA2 genes.
• We have also participated in the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), which identified new modifier alleles for BRCA1/BRCA2 mutation carriers.
• We confirmed that severe, late side effects induced by radiotherapy of breast cancer are associated to low levels of irradiation-induced apoptosis.
• In collaboration with the International Radiogenomics Consortium we participated in a meta-analysis on the association between fibrosis or overall toxicity and TGFB1 SNP rs1800469 c.-1347T>C in breast cancer patients.

SUMMARY

Our work focuses on two main lines of research: 1) genetic predisposition to hereditary breast/ovarian cancer, and 2) genetic predisposition to radiotherapy-induced toxicity.

Inherited predisposition to breast and ovarian cancer is caused by the BRCA1 and BRCA2 genes, but only about one fourth of families carry mutations in these genes. We search for other alleles which might predispose to these types of cancer and use massive sequencing technologies to study panels of potentially predisposing genes in families tested negative for BRCA1 and BRCA2. Moreover, we are sequencing whole coding regions (exome) to discover new genes that might explain the presence of multiple cases of cancer in families and individual patients.

BRCA1/2 genes have an extraordinary high allelic heterogeneity and many results of genetic testing are variants with unknown biological significance. The analysis of these variants and other alterations in untranslated regions in both genes constitutes another area of intensive study. We carry out splicing studies, in silico analyses, and collaborate with other laboratories to develop multifactorial studies aimed at ascertaining the effect of variants with unknown clinical significance.

Radiotherapy represents the most effective non-surgical modality in the curative treatment of cancer. Around half of all cancer patients receive radiotherapy at some point during their treatment. While around 3-5% of individuals suffer from severe long-term side-effects, more experience moderate toxicity. There is now good evidence for the heritability of radiosensitivity as a trait as well as a growing interest in identifying the genetic variants associated with increased sensitivity to radiation. To identify those patients who will develop toxicity, we are investigating potential genetic and cellular markers for radiotherapy toxicity (allelic variants, cell apoptosis, and transcriptional profiles).
Principal Investigator
Jordi Giralt

Radiation Oncologists
Sergi Benavente
Xavier Maldonado
Meritxell Molla
Begoña Navaltropo
Mónica Ramos
Victoria Reyes
Ramona Verges
SUMMARY

Our group is integrated within the Radiation Oncology Department of the Vall d’Hebron University Hospital and is actively involved in the multidisciplinary treatment of patients with malignant tumors. We also participate as principal investigators or research collaborators in a number of important clinical trials, translational research projects, as well as technology development programs.

Current and future research priorities include the following main areas:

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

STRATEGIC GOALS

1. **Technology development.** Acquisition of new equipment to implement clinically the most modern treatment techniques such as rotational radiotherapy - with intensity modulated arc therapy (IMAT), adaptive radiotherapy and image-guided radiotherapy.

2. **Translational research.** Application of biological knowledge of both cancer and healthy tissue in order to individualize treatment to the characteristics of each patient and each tumor.

HIGHLIGHTS IN 2013

- We achieved an increase in the number of patients treated with IMRT. In 2013 we treated 326 patients with IMRT, representing a 33% increase.
- The Adaptive and innovative Radiation Treatment FOR improving Cancer treatment outcomE (ARTFORCE) project was initiated in 2013. At present we have included 6 patients (see Figures).
- We started a dose escalation program using Image Guided RadioTherapy (IGRT), with fiducials.

To find out more about us, our research, publications and even our group’s horizons for 2014, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2013/
STRATEGIC GOALS

1. Close multidisciplinary collaboration with the different professionals involved in thoracic malignancies diagnosis, management, and research.
2. Optimization of different treatment approaches to the management of early-stage lung cancer patients.
3. Implementation of personalized medicine using pharmacogenomic tools.
4. Consolidation of a translational research program.
6. Collaboration with other research groups dealing with thoracic malignancies.

HIGHLIGHTS IN 2013

• 450 new lung cancer patients including 20 cases of mesothelioma and 5 thymomas.
• We continue to foster close multidisciplinary collaboration through our established lung cancer tumors committee which convenes twice a week.
• Implementation of pharmacogenomic approaches in advanced NSCLC (EGFR-mut, ALK, ROS1, FGFR1, Sequenom in EGFR-wt/ALK-wt), in collaboration with VHIO’s Cancer Genomics Group led by Ana Vivancos, and the Vall d’Hebron University Hospital’s Pathology Service working with Javier Hernández and Irene Sansano.
• Involvement in exome sequencing in NSCLC patients which resulted in a presentation at the 2013 Annual Meeting of the American Association of Clinical Oncology (ASCO), May 31 - 04 June, Chicago (USA).
• Enriqueta Felip presented on Women in oncology, how to develop an academic career, as invited speaker at the 2013 Annual Meeting of the American Association of Clinical Oncology (ASCO), May 31 - 04 June, Chicago (USA).
• The organization of the European Multidisciplinary Conference in Thoracic Oncology (EMCTO), 09 – 11 May 2013, Lugano (Switzerland).

SUMMARY

The main focus of the Thoracic Tumors Group is to tackle various aspects of lung cancer, one of the most frequently diagnosed tumors to-date. Our group concentrates on a number of areas ranging from disease prevention, early detection, more accurate techniques in diagnosis and staging, to advancing precision medicine and treatment of lung cancer. We are also highly dedicated to our program which centers on the rapid diagnosis of this tumor type.

In lung cancer patients with early-stage disease, we collaborate closely with thoracic surgeons and radiation therapists to better optimize the different treatment approaches and modalities set within a truly multidisciplinary setting. Since lung cancer patients sometimes suffer from severe symptoms associated with the disease, we strive to ameliorate these symptoms working in close connection with a number of professionals from other disciplines. In patients with advanced-stage disease, personalized therapy is now the standard approach and our key objective is the early implementation of molecular determinants to better select treatment options tailored to individual patients.

We actively contribute to VHIO’s efforts aimed at early clinical drug development, and also deal with other less common thoracic malignancies such as small-cell lung cancer, mesotheliomas, thymomas, and neuroendocrine tumors.
VHIO MULTIDISCIPLINARY RESEARCH PROGRAMS

CORE TECHNOLOGIES
VHIO’s Cancer Genomics, Molecular Oncology, Proteomics, and Translational Genomics Groups led by Ana Vivancos, Paolo Nuciforo, Francesc Canals, and Aleix Prat respectively, are responsible for the development of VHIO’s cutting-edge core technologies and platforms. These groups also pursue, implement, and develop their own independent research lines and projects.
STRATEGIC GOALS

1. We develop and implement improved strategies for routine patient pre-screening. We are actively developing NGS techniques to be used in our pre-screening program that facilitate increasingly cost-efficient mutation detection.
2. We provide cutting-edge applications in cancer genomics through the use of new technologies and protocol development.

HIGHLIGHTS IN 2013

- We received International Standarization Organization ISO 15189:2007 accreditation for our MassARRAY platform. This reflects our commitment to generating high quality results for our patients. This accreditation covers the whole process from sample reception up to the delivery of data surrounding mutations in BRAF, EGFR, KRAS and EGFR oncogenes in particular.
- We have developed and validated a panel of over 500 amplicons in 56 genes that allow the interrogation of mutations in oncogenes as well as tumor suppressor genes. The amplicon panel, VHIO-Card, can be used with both the MassARRAY platform as well as the NextGen sequencing platforms.

SUMMARY

Our Cancer Genomics Group serves as a Core Technology at VHIO and is dedicated to bridging preclinical and clinical cancer science and discovery.

We provide services to preclinical and clinical researchers as well as lead our own research lines and projects in technology development and translational research. The lab is equipped with a genotyping platform (MassARRAY, Sequenom) and two NextGen sequencers: MiSeq and HiSeq2500, Illumina (see figure).

Our group is involved in VHIO’s pre-screening program and performs somatic mutation profiling with our genotyping platform in patients that are candidates to be enrolled in Phase I clinical trials. The molecular profile of each patient indicates his/her suitability for inclusion in a given clinical trial aimed at testing the usefulness of novel targeted therapies, such as PIK3CA, AKT1, BRAF or MEK inhibitors.

As a reflection of our commitment to excellence, we successfully met the requirements of the ISO 15189:2007 accreditation process in 2013. Our lab, along with VHIO’s Molecular Oncology laboratory led by Paolo Nuciforo, were both accredited with ISO 15189:2007 certification and we have consequently become one of the first research institutes in Spain to meet this standard. Issued by the Spanish National Accreditation Entity (ENAC), such accreditation situates VHIO in a privileged position, demonstrating its technical competencies, level of quality, standardization, validation of processes and staff training.

In collaboration with preclinical and clinical researchers working across several tumor types, we are also involved in a number of translational projects using next-generation sequencing (NGS), such as identifying mechanisms of resistance to targeted therapies, studying clonal populations, and defining novel therapeutic opportunities based on mutation profiles.

Protocol development and improving NextGen Sequencing also represent an important focus of our research activities, including the development of efficient strategies for our pre-screening program, involving FFPE-derived DNA and NextGen sequencing.

To find out more about us, our research, publications and even our group’s horizons for 2014, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2013/
CORE TECHNOLOGIES

MOLECULAR ONCOLOGY GROUP

Principal Investigator
Paolo Nuciforo

Attending Physicians
Claudia Aura
Roberta Fasani
Ludmila Prudkin

Laboratory Supervisor
Jose Jiménez

Laboratory Assistant
Mª Ángeles Díaz

Technicians
Mª del Carmen Díaz
Paola Martinez
Nerea Peiró
Gertrudis Sánchez

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

HIGHLIGHTS IN 2013
• ISO 15189:2007 quality accreditation to conduct tissue-based analyses on clinical samples.
• Development of a laboratory information management system (VHIOPAT).
• Central laboratory for biorepository, biomarkers and CTC analyses in different national and international studies.
• Over 1,900 molecular determinations on samples for patient inclusion into clinical trials.
• Supported over 140 clinical trials for sample management and analyses.
• Supported basic and translation research programs with over 17,000 tests performed.

SUMMARY
The Molecular Oncology Group’s mission is to apply state-of-the-art tissue-based technologies to basic, translational, and clinical research with a clear focus on developing and validating novel tumor biomarkers for precision cancer medicine. Our group is one of VHIO’s Core Technology Platforms and is therefore central to VHIO’s research activities. We actively participate in all research projects involving the use of human tissue collected from patients including tissue banking, the development of primary xenograft models, and circulating tumor cells (CTC) analyses.

We currently provide support to more than 140 clinical trials conducted at Vall d’Hebron, which represents an increase of more than 35% compared to 2012. Our activities relating to clinical trials range from the coordination of sample collection, storage and shipment, developing and running multiple assays for real-time patient inclusion, as well as pharmacodynamic monitoring and dose finding.

In 2013, our laboratory successfully obtained the prestigious ISO 15189:2007 quality accreditation for running tissue-based analyses on clinical samples. During this year, we have performed over 1,900 molecular determinations on samples for patient inclusion into clinical trials and almost 17,000 tests to support basic and translation research programs, with a ~20% overall increase in activity as compared to 2012. We have also been the central laboratory for 5 international studies.

To find out more about us, our research, publications and even our group’s horizons for 2014, visit the VHIO Scientific Report online at: http://memorias.vhio.net/2013/
CORE TECHNOLOGIES PROTEOMICS GROUP

Principal Investigator
Francesc Canals

Post-Doctoral Fellows
Joan Josep Bech
Núria Colomé
Marta Monge
Gemma Reverter

Technician
Luna Martín

Pre-Doctoral Student
Marta Vilà
STRATEGIC GOALS

1. Provide services in proteomic techniques to other research groups as a core facility.
2. Explore the role of ADAM and ADAMTS metalloproteases in cancer through proteomic analysis.
3. Proteomic screening for new biomarkers to help develop cancer therapeutics.
4. Contribute to mapping the Chromosome 16 proteome as part of the Human Proteome Project.

HIGHLIGHTS IN 2013

• The provision of proteomic services to VHIO and Vall d’Hebron University Hospital groups as well as to members of the ProteoRed-Instituto Salud Carlos III network.
• Work in progress towards the validation of a biomarker signature to facilitate patient selection and the monitoring of TGF-beta inhibitor-based treatment of glioma.
• Characterization of proteins shed by metalloproteases in breast cancer cells, using a new, highly efficient, proteomic methodology developed in our laboratory.
• Participation in the Spanish Consortium Chromosome 16 HPP (forming part of the HUPO Human Proteome Project).

SUMMARY

Proteomics is directed to the characterization of the entire set of proteins - proteome - expressed by a particular cell or tissue under specific physiological or pathological conditions. The application of proteomic technologies to cancer research is a rapidly expanding field - not only for basic research but also for the discovery of diagnostic or disease-progression biomarkers. We mainly focus on the application of proteomic techniques to the identification and characterization of substrates of metalloproteases involved in tumor progression. Metalloproteases of the ADAM and ADAMTS families are known to play a crucial role in the regulation of the tumor microenvironment by mediating the remodeling of the extracellular matrix and the cleavage of specific extracellular and membrane proteins.

Knowledge surrounding the substrates of these proteases in the context of tumor cells is required in order to elucidate their role in tumor growth and metastasis as well as evaluate their potential use as therapeutic targets. Our group employs mass spectrometry-based proteomic strategies to search for new substrates of these proteases and analyze their involvement in tumor progression. We also use proteomic techniques for screening and the validation of biomarkers for cancer diagnostics, personalized treatment and monitoring (see figure).

Our laboratory is a member of the Spanish Consortium Chromosome 16 HPP which forms part of the HUPO Human Proteome Project. This multicenter, international project aims to develop an entire map of the proteins encoded by the human genome following a chromosome-centric strategy to advance our understanding of human biology in health and disease. Focusing on important aspects of biology, this project is set to impact on ongoing disease-oriented research.

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

![Figure: Schematics of a workflow directed to the identification of protein biomarkers for the management of TGFbeta responsive glioma patients.](http://memorias.vhio.net/2013/)

To find out more about us, our research, publications and even our group’s horizons for 2014, visit the VHIO Scientific Report online at: [http://memorias.vhio.net/2013/](http://memorias.vhio.net/2013/)
CORE TECHNOLOGIES

TRANSLATIONAL GENOMICS GROUP

Principal Investigator
Aleix Prat

Clinical Research Technician
Patricia Galván

Specialist Physician in Breast Cancer (collaboration)
María Jesús Vidal Losada
STRATEGIC GOALS

1. Use genomic data to guide clinical trial design and biomarker development in order to identify more optimal treatment regimens for cancer patients.
2. Use gene expression data to better characterize different cancer types and better understand cancer biology.
3. Help implement gene expression-based tests in the clinical setting.

HIGHLIGHTS IN 2013

• Implementation of the nCounter Nanostring and RNA-seq platforms.
• Implementation of the PROSIGNA® breast cancer test.
• Refinement of the pathology-based definition of the Luminal A subtype.
• Identification of subsets of patients with advanced HER2+ disease with high sensitivity to anti-HER2 therapies.
• Participation in the NEOERIBULIN clinical trial.
• Initiation of the PAMELA clinical trial.

SUMMARY

2013 has witnessed the arrival and establishment of VHIO’s Translational Genomics Group. In almost record time, we have successfully implemented the necessary technology, equipment and the various protocols to facilitate production of gene expression data in two different platforms (nCounter and RNAseq). In addition, we have completed two breast cancer gene expression-based datasets of 400 and 50 breast samples using the nCounter Nanostring and RNA-seq Illumina platforms, respectively. These two datasets will allow the correct identification and characterization of future breast samples. We have already started analyzing samples and providing scientific guidance and advice to several collaborators both at VHIO and overseas.

One of our major findings in 2013 was that the current immunohistochemical (IHC)-based definition of Luminal A breast cancer is suboptimal to identify those patients who do not need adjuvant chemotherapy. At the same time, we have proposed an improved version of the current IHC-based definition of Luminal A breast cancer using progesterone receptor expression levels. These findings have been incorporated in the 2013 St. Gallen International Consensus Guidelines for the systemic treatment of primary breast cancer and thus might have important clinical implications.

In two separate articles, we have provided new data regarding one of the intrinsic subtypes of breast cancer known as Basal-like. More specifically, in an analysis across 6 cancer types, we first showed Basal-like breast cancer to be a unique molecular entity that is more similar to squamous cell lung cancer than other breast tumors. This result actually suggests that Basal-like breast cancer might have a distinct cell-type of origin. Furthermore, we showed in another study that the current pathology-based triple-negative definition of the Basal-like subtype is still biologically heterogeneous and that gene expression data can help us to identify the different groups found within triple-negative disease.

Our group has participated in 24 articles providing scientific advice and/or performing gene expression analyses. Among them, we participated in 1 letter, 1 editorial, 8 original research articles: 5 as first author (and 2 of them as correspondent), 2 as second author and 1 as third author. The total Impact Factor of our group in 2013 totaled at 175.81.

Figure: Identification of a cancer type-specific 126-gene signature. GBM, glioblastoma multiforme; SQCLC, squamous cell lung cancer; LUAD, lung adenocarcinoma; CCR, colorectal adenocarcinoma.
VHIO MULTIDISCIPLINARY RESEARCH PROGRAMS

VHIO TRANSVERSAL CLINICAL TRIALS

CORE SERVICES & UNITS
Clinical Trials Office
Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa"

Clinical Research Oncology Nurses
Clinical Research Oncology Pharmacy Unit
VHIO TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

CLINICAL TRIALS OFFICE

Head, Clinical Trials Office for Phase I Trials
Gemma Sala

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

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

Study Coordinators
Lúïsa Carbonell
Cristina González
Marta Malo
Olga Padrós
Iratxe Puebla
Mireia Sanchís
Montserrat Solà

Data Managers
Anna Aguilar
Anna Casas
Soraya Fernández
Xavier Martínez
Sergio Pérez

Andrea Retter
Natalia Verde

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

Study Coordinators
Judith Alonso
MªAlba Calamardo
Raquel Espallargas
Violeta Esteban
Beatriz García
Jordi Humbert
Thaïs Miquel
Oriol Nualart

Data Managers
David Álvarez
Julia Esteban
Belén García
Bruno García

Mariona Pocarull
Angels Porras
Rosa Maria Romero
Anna Serrano
Albert Torrent

Assistants
Núria Carballo
Angel Marin

Database Managers Office
Alba Meire
Débora Moreno
Núria Murtra
STRATEGIC GOALS

1. Contribute to the development of new treatments for cancer.
2. Consolidation as an international reference hospital for clinical trials in oncology.
3. Guide patients taking part in a trial to comply with the requirements of the protocol and to help them with daily life throughout this period.
4. Provide high quality data adhering to deadlines.
5. Facilitate the work and communication between the different staff involved in the trial (oncologists, nurses, pharmacists, pathologists, etc.).
6. Ensure that the protocol is appropriately conducted from the initiation to the close of the respective trial.
7. Standardize clinical trials process to assure quality and the compliance of Good Clinical Practice (GCP).
8. Organize an annual post-graduate course on clinical trials in oncology to train study coordinators, data managers, nurses and CRAs.

HIGHLIGHTS IN 2013

• Increase in the number of patients enrolled in clinical trials Phase I, II and III.
• Increase in the number of clinical trials performed.
• Provided tailored training to our staff in order to improve the quality of their work and expand upon skills.
• Implemented new tools and procedures aimed at increasing the quality and efficacy of research.
• Conducted 13 sponsor audits with satisfactory results.
• Implementation of new software for clinical trial management.
• Organization of a new GCP training course for all oncology staff.

Clinical trials are one of the best treatment options since they compare current state-of-the-art treatment with a potentially superior treatment and may even offer new drugs to patients for whom there are no alternative treatments. All patients in our oncology department are therefore considered as potential candidates for inclusion in our clinical trials. Although all patients may not be eligible or do not agree to take part in a clinical trial, we offer this option to all who meet the necessary criteria as per the different research protocols.

As a highly established center in cancer treatment, it is of little surprise that we have witnessed an important growth in the number of patients currently starting a new treatment in clinical trials in our department (see figures I & II).

• The Vall d’Hebron University Hospital’s Oncology Department has gained much prestige which has been acknowledged by the pharmaceutical industry. It has consequently become a reference center selected by the industry to carry out complex clinical trials for which the number of participating centers is highly restricted - chosen for their high standards of quality and capacity to carry out state-of-the-art research. Hence, our hospital has taken part in phase I trials of different drugs and allowed the pharmaceutical industry to market novel therapies aimed at cancerous cells.

We take part in clinical trials promoted by the pharmaceutical industry as well as those developed in our department in collaboration with other hospitals.

• Finally, the Clinical Trials Office has been involved in training future study coordinators, data managers, nurses, and junior CRAs. Since 2005, we have continued to organize a 36-hour postgraduate course -- 2013 marked the 8th edition.

For more specific information about our clinical trials please visit our extended Scientific Report online at: http://memorias.vhio.net/2013/

FIGURE I: TOTAL ANNUAL RECRUITMENT IN CLINICAL TRIALS (PHASE I-II-III)

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FIGURE II: ANNUAL RECRUITMENT EVOLUTION (PHASE I-II-III TRIALS)

FIGURE III: ANNUAL DISTRIBUTION OF PHASE I,II AND III TRIALS

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SUMMARY

Set up in 1997, the Clinical Trials Office comprises an operational team conducting clinical trials at the Vall d’Hebron University Hospital’s Oncology Department with more than 30 professionals including study coordinators, data managers and administrative staff working on more than 230 trials. They are responsible for the logistics, coordination, data management and also the start-up process for new studies.

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

The Clinical Trials Office coordinates studies from Phase I to Phase III and is divided into three teams to cover all tumor groups and all trial phases. Our Office has conducted 232 actively recruiting trials and succeeded in recruiting and coordinating a total of 843 patients included in clinical trials. In addition, we are following up all patients that were recruited prior to 2013 who are still enrolled and receiving study treatment.

This year we have also organized a Good Clinical Practice (GCP) course with the aim of ensuring that all our staff involved in clinical trials is properly trained in GCP. Considering that they participate in several clinical trials from different sponsors, we wanted to offer a unique GCP training course independent of any sponsor in particular. This course has been certified by the Consell Català de Formació Continuada de Professions Sanitàries (CCFCPS) and La Comisión...
FIGURE IV: NUMBER OF CLINICAL TRIALS PER YEAR (PHASE I-II-III TRIALS)

during 2012-2013. Our course has recently been audited and successfully fulfills all the required criteria as an official GCP training.

**COMPARATIVE PATIENTS RECRUITED 2012-2013**

- Phase I: 345 (41%)
- Phase II: 257 (30%)
- Phase III: 241 (29%)

**Total:** 8,2% Increase

**COMPARATIVE DISTRIBUTION OF TRIALS 2012-2013**

- Phase I: 13,6% Increase
- Phase II: 12,9% Increase
- Phase III: 10,3% Decrease

**Total:** 5,9% Increase

**Phase I trials:** 75 (32%)

**Phase II trials:** 96 (42%)

**Phase III trials:** 61 (26%)
VHIO TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

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

Director of Clinical Research at Vhio
Josep Taberner

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

Head Of Clinical Trials Office
Gemma Sala

Clinical Research Fellows
Barbara Adamo
Guillem Argilés
Ana B. Azaro
Cristina Cruz

Associated Investigators
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Josep Maria del Campo
Javier Cortés
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Investigators
Maria Alsina
Judith Balmaña
Maria Elena Elez
Jaume Capdevila
Patricia Gómez
Teresa Macarulla
Alex Martinez
Pablo Martínez
Leticia de Mattos
Eva Muñoz
Ana Oaknin
Mafalda Oliveira
Jose Manuel Pérez
Víctor Rodríguez
Cristina Saura
Tamarás Sauri
Cristina Suárez
Davis Torrejón
Claudia Valverde

Clinical Coordinators
Meritxell Baño
Marta Beltrán
Maria Herranz
Lidia Martínez de Arenzana
Laura Maynes
Adelaida Péra
Elisabet Sicart

Data Entries
Beatriz Blanco
Laia Cano

Isabel Rico
Gloria García
Cristina Viaplana

Pharmacist
Maribel Magaña

Nurse Supervisor
Ángeles Peñuelas

Nurse Coordinator
Sonia Valverde

Nurses
Meritxell Cucurell
Margarida Marcos
Isabel Muñoz
Lydia Vélez

Nurses’ Assistant
Alicia López

Secretary
Teresa Mendoza
In collaboration with VHIO’s Cancer Genomics and •

We have performed some of the most complex phase

Our Unit continues to report an annual increase in

HIGHLIGHTS IN 2013

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

STRATEGIC GOALS

SUMMARY

Inaugurated in June 2010, thanks to the support received from the Welfare Projects Unit of the “la Caixa” Foundation, the Research Unit for Molecular Therapy of Cancer (UITM) - “la Caixa”, is dedicated to complex clinical trials with drugs in early development (Phase I and early Phase II trials), focusing on novel targets. Occupying a total surface area of 1000 m² our Unit is located within the General Area of the Vall d’Hebron University Hospital.

Due to such a privileged environment with direct access to patients, coupled with VHIO’s translational approach to research and superb scientific framework, our Unit has rapidly established itself as one of the few comprehensive facilities in Europe to transform latest discovery into benefits for patients in record time.

UITM promotes tight connectivity between healthcare and research which enables us to establish new treatment models for patients with highly selective drugs, expanding the knowledge of tumor diseases and how to treat them in an individualized way - getting the right drug to the right patient at the right time. As the figures show, we are gradually doing so for an increasing number of patients. In 2013, 75 phase I clinical trials were performed at the Unit with a total of 345 patients enrolled. It is thanks to the Unit’s facilities coupled with the excellent multidisciplinary clinical teams, that we continue to expand our portfolio of phase I trials.

Research carried out at our Unit by VHIO’s Early Clinical Drug Development Group ( see pages 42 - 43), focuses on the development of new drugs based on the molecular profile of each tumor as well as the optimization of treatment regimes using combinations of new drugs with those already existing. In line with VHIO’s translational model, research is also linked with other research areas carried out by VHIO groups, connecting molecular biology and optimal tumor models with pharmacology and innovative clinical research. VHIO scientists also collaborate closely in the trials to facilitate biomarker development, a profound understanding of the mechanism of action, as well as research into mechanisms of resistance.

In partnership with VHIO’s Molecular Oncology, and Translational Cancer Genomics groups (see Core Technologies, pages 58 - 67) we perform molecular analysis of the patients’ tumors in order to select the best possible treatment with the experimental therapeutics available. Furthermore, thanks to the technology platforms provided by VHIO’s Cancer Genomics and Translational Cancer Genomics groups including MiSeq and nCounter Nanostring respectively, we will continue to up the tempo in driving faster, more precise mutational analysis of tumor-suppressor genes as well as translocations and gene amplifications.

The UITM incorporates a multidisciplinary team comprised of medical oncologists, clinical trial coordinators and data managers, nurses and nurse technicians, pharmacists, as well as administrative personnel. Excellent patient treatment and care as well as pioneering research is also made possible thanks to the collaboration with many other oncology professionals including pathologists from the Vall d’Hebron University Hospital’s Molecular Pathology Department, radiologists and interventional radiologists, as well as the Clinical Trials Office, Database Management, and healthcare specialists (dermatologists, cardiologists, ophthalmologists).

To find out more about the full spectrum of clinical trials (Phases I - III) at Vall d’Hebron, as well as our Transversal Clinical Trials Services and Units, please see pages 70 - 73 and pages 76 - 80.

For more specific information about our clinical trials please visit our extended Scientific Report online at: http://memorias.vhio.net/2013/
VHIO TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

CLINICAL RESEARCH ONCOLOGY NURSES

Supervisor
Ángeles Peñuelas

Nurse Coordinators
Sonia Valverde
Lydia Vélez

Nurses
Anna Aliau
Mª Elena de Cabo
Meritxell Cucurell
Ana Gil de Avalle
Margarida Marcos
Marta Mate
Núria Membrives

Nursing Assistants
Alicia López
Mª Ascensión Martín

Mireia Milán
Isabel Muñoz
Raquel Muriel
Tania Sánchez
Alex Sierra
Lidia Vegas
SUMMARY

Clinical trials in oncology are essential for both the identification of new, more effective therapies for cancer as well as improving outcomes such as survival, side effect profiles, combination therapies and quality of life.

Such advances in cancer care and the development of more effective cancer therapeutics depend on an optimal clinical trial process.

Clinical Research Oncology Nurses play a key role in that process by assuming a variety of roles including identifying trends in side effects, collaborating with the multidisciplinary team to develop and evaluate patient management, contributing to the scientific process by collating quality data as well as providing excellence in nursing care and symptom management of trial participants.

VHIO’s Clinical Research Oncology Nurses, specialized in molecular treatments, are headed by Angeles Peñuelas and represent a critical and expert element of the multidisciplinary oncology team involved in clinical trials managed by VHIO’s Research Unit for Molecular Therapy of Cancer (UITM) - “la Caixa” (see page 74 - 75 for more information) and the Clinical Trials Office (see page 70 - 73). Incorporating medical oncologists, specialists in molecular pathology, pharmacists exclusively dedicated to this field (see VHIO’s Clinical Research Oncology Pharmacy Unit on page 78), clinical research oncology nurses and study coordinators, VHIO’s multidisciplinary approach means that the patient receives the full range of expertise for his/her illness as well as detailed advice on the characteristics of his/her particular treatment.
Coordinator of the Clinical Research Oncology Pharmacy Unit
Maria Josep Carreras Soler

Coordinator of Pharmacological Research in Oncology Support Unit
Laura Mañós Pujol

Pharmacists
Patricia Díez Durán
Anna Farriols Danés
Inés Jiménez Lozano
Elena López Montero
Marta Munné García

María Oliveras Arenas
Berta Renedo Miró
Carol Valdivia Vadell
Jana Vidal Otero

Technicians
Romina Bellini Martínez
Hugo Cortina Colás
María Hidalgo Casas
Susana Mulet Lozano
Pedro Nestal Romero

Sara Pizarro López
Gemma Tomás Alonso
Sílvia Tomalba Bernal

Clinical Trials
Re-Supplies Manager
Carol Herrero Endrino
STRATEGIC GOALS

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

HIGHLIGHTS IN 2013

- Opening of new facilities: the Clinical Research Oncology Pharmacy Unit is located in close proximity to the Research Unit for Molecular Therapy of Cancer (UITM) - “la Caixa” (please see pages 74 - 75 of this Scientific Report), with the incorporation of new computerized and technological systems for the management, control and storage of clinical trial drugs. We have optimized the service by bringing it physically closer to the UITM, thereby facilitating integration with the rest of the research team.
- Centralization of all preparations in clinical trials with the opening of the pharmacy unit.
- Implementation of the traceability system: ISISH-TRI program.
- CFMTrials computerized system: traceability system for the management, control and storage of clinical trial supplies to both ensure and record the traceability of the relevant documentation of both the trials in digital format and the supplies upon reception until they are dispensed (oral medication or drugs for intravenous infusion). Documentation is transferred electronically to the traceability system of the preparation unit, thereby minimizing the possibility of medication errors.
- Clinical and technical support of the process of prescription/preparation/administration of cytostatics in clinical trials, providing an e-record of all actions, users, dates and times.
- Batches and expiry dates of the products used. Use of electronic technologies and computerized processes: voice technology (Voice-Directed Work, Vocollect). The master database of the traceability project for study drug dispensation and storage is currently under design.
- Design of electronic medical order prescriptions for study drugs of oral and iv administration for phase I clinical trials.
- Implementation of the qualitative and quantitative quality control system for cytostatic preparations in clinical trials, which will guarantee the preparation of the correct trial drugs at the right dosage, without medication errors.
- Improvement of our pharmaceutical care program by providing written information extracted from the Infowin program during the interviews to select and/or polymedicate patients.

SUMMARY

Our Unit is ISO 9001:2008 certified and associated with the Medical Oncology Programs of the Vall d’Hebron University Hospital.

Our clinical research activities are carried out through two different programs:

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

In 2013 our activity centered on the following main areas:

- Management of clinical trial drugs: we have managed clinical trial drugs for 242 active clinical trials in oncology. The number of deliveries of clinical trial supplies totaled at 2,886 in 2013.
- Maintenance of a novel system for controlling storage temperature: performing electronic temperature recordings every 5 minutes. These readings are displayed on the program’s computers equipped
with an audio and visual alarm as well as a system for sending an alert via SMS to the pharmacist on duty, continuously for 24 hours in case of temperature deviations.

• **Maintenance and improved efficiency of a new safety drug accountability procedure for drugs returned by patients:** this allows either our unit’s personnel or that of the sponsor to perform drug accountability and verify treatment compliance safely using a Cabin Vertical Laminar FLOW (CVLF). The study drug returned by the patient is accounted for by pharmacy personnel in Cabin Vertical Laminar Flow (CVLF) and the pills are kept in a transparent and sealed bag. This year, our unit has carried out drug accountability for drugs returned by patients from 85 clinical trials.

• **Ensuring and implementing traceability of the management of storage, custody and dispensing of clinical trial drugs:** the design of a computerized storage area for controlling samples, their location, expiry dates and traceability using a barcode reader. ISISH-TRI program system.

• **Design and validation of the drug preparation process traceability system:** qualitative and quantitative quality control of the computerized system that incorporates barcode technology, electronic scales and voice technology (Verbio Speech Technologies-Directed Work system).

• **Support for, and liaison with, the trial sponsors:** dispensing personnel have participated in 25 pre-study visits, 95 initial visits, 991 follow-up visits, 44 final visits, as well as successfully passing 14 audits. In addition, preparation staff has participated in 3 pre-study visits, 96 initial visits, 122 follow-up visits, and 9 audits.

• **Dispensing:** a total of 15,775 clinical trial drugs have been dispensed with the validation of a pharmacist. 6,518 of these are for orally administered clinical trial drugs. The conditioning and re-labeling of the primary containers for clinical trial drugs have also been performed. A total of 208 Standardized Dispensing Procedures have also been drawn up and updated. 216 storage temperature data reports have been compiled.

• **Preparations:** a total of 8,675 preparations of cytostatics, monoclonal antibodies and other parenteral antitumor drugs for clinical trials have been carried out. A total of 81 Standardized Preparation Procedures have been drawn up.

• **Collateral:** we have prepared documentation relating to each clinical trial for medical and nursing staff as well as for patients, ranging from standard operating procedures to instructions and related forms for patients. In 2013, 135 different antineoplastic therapeutic regimens were computerized, 22 standard operating procedures compiled, and 19 patient-orientated documents produced. Our dispensing unit has also prepared 12 diaries and Instructions for patients.

• **Development of our pharmaceutical care program for patients enrolled in Phase I clinical trials:** activity was extended to all Phase I clinical trials involving oral medication. The pharmacological history of patients was recorded and the usual treatment reconciled with that being studied. Patients and researchers were informed regarding potential drug-drug interactions of the study drug with others/concomitant complementary therapies and administration of the drug recorded through patient interviews as well as the subsequent accountability for medication returned. During 2013 we carried out a total of 808 visits to patients in Phase I clinical trials, 321 pre-screening visits, 278 screening visits, and 209 follow-up visits.

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

• **ISO 9001:2008 certification renewed.**
Full listing of articles published by VHIO Investigators in 2013

Articles published by VHIO Investigators in 2013 with allocated Impact Factor


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Funding & Consortia

FUNDING

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CONSORTIA

As a reflection of VHIO’s expertise in preclinical, translational and clinical research in oncology, it participated in the following Consortia of excellence in 2013:

**COLTHERES - Colon Therapy Research Consortium**

partners European clinical research centers as well as translational researchers who have received core funding from the European Commission’s 7th Framework Programme of Research and Development to define and perform biomarker driven clinical trials to improve cancer therapy outcomes. Launched in 2011, this 4-year programme uses comprehensively molecularly-annotated colon cancers as a ‘test-bed’ to define specific biomarkers of response or resistance to signalling pathway agents. [http://www.coltheres.eu](http://www.coltheres.eu).

Aimed at improved outcomes for cancer patients and reduced mortality across Europe through prevention, early detection and improved treatments, **EurocanPlatform**, founded in 2011, is funded by the European Commission’s 7th Framework Programme and comprises 28 European leading cancer Institutions and organisations working together in a unique collaboration. The centers share infrastructures and collaborate on projects to help advance cancer research and treatment. [http://eurocanplatform.eu](http://eurocanplatform.eu).

**The EuroPDX Consortium – Translating Knowledge in Oncology**, was launched in 2013 with the common goal of creating a network of clinically relevant models of human cancer, and in particular patient-derived xenograft (PDX) models. Connecting 14 cancer centers across 9 European countries that are developing PDX cancer models, this initiative will promote the sharing and exchange of findings on promising therapeutics as well as lead multi-center preclinical studies. EuroPDX will strive to reduce the duplication of efforts in oncology drug development and ultimately improve the quality of life and overall survival of cancer patients. For forthcoming information please bookmark VHIO’s website: [www.vhio.net](http://www.vhio.net).

**Announced in 2013, The MErCuRIC Consortium**, funded by the European Commission’s 7th Framework Programme of Research and Development, incorporates 13 partners in eight different European countries to lead and pioneer a multicentre phase Ib/II clinical trial. This study will assess a novel therapeutic strategy aimed at combating metastasis, improving survival and developing new approaches to treat patients with colorectal cancer. [http://mercuric.eu](http://mercuric.eu).
Launched in 2011 (VHIO joined in 2013), supported by the IMI Innovative Medicines Initiative – a Joint Undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA). OncoTrack, Methods for systematic next generation oncology biomarker development, is an international consortium of over 80 scientists and constitutes one of Europe’s largest collaborative academic-industry efforts aimed at developing and assessing novel approaches for the identification of new markers for colon cancer.

RATHER - Rational Therapy for Breast Cancer, is funded by the European Commission’s 7th Framework Programme of Research and Development. Representing an important step in delivering on precision oncology by developing tailored therapies using a rational approach, this project will focus on two specific difficult-to-treat subtypes of breast cancer. Involving the combined efforts of six research institutions and two biomedical companies this is a five-year project that commenced in January 2011. http://www.ratherproject.com.

Incorporating a network of 27 research entities spanning 10 countries, SPECTAcolor - Screening Platform for Efficient Clinical Trials Access in Colorectal cancer, is an initiative within the framework of the research program of the EORTC, supported by Alliance Boots. Launched this year, 2013, this is the first prospective fully annotated tumor samples Biobank and Biomarker analysis platform for genetic profiling of patients suffering from advanced colorectal cancer. http://spectacolor.eortc.org.

WIN - Worldwide Innovative Networking in personalized cancer medicine, initiated by the Institut Gustave Roussy (France) and The University of Texas, MD Anderson Cancer Center (USA) is a non profit, non-governmental organization incorporating 22 cancer centers and industry partners from five continents to address the challenge of increasing the efficacy of cancer diagnostics and therapeutics. Promoted within the scope of this Consortium, WINThER (WINTherapeutics) is a unique academic and international clinical trial (launched in 2012), aimed at better predicting drug sensitivity and optimizing individualized therapeutic decisions with improved clinical outcome for patients. http://www.winconsortium.org.

Other collaboration:

2013 marked the launch of the CIBOT Consorcio de Investigación Biomédica y Oncología Translacional (Consortium for Biomedical and Translational Research in Oncology), a new scientific program in collaboration with Novartis. This initiative will define and develop research aimed at: determining the etiopathogenic mechanisms of cancer as well as developing novel or more efficient diagnostic and therapeutic tools; investigating the therapeutic potential of new antineoplastic agents; and applying cutting-edge technologies and latest data to advance cancer research. Specific areas of interest include the effects of HER-2 amplification pattern and prior Herceptin/TDM-1 therapy on HER-2 expression, the therapeutic inhibition of the oncogenic Wnt/beta-catenin pathway, and targeting wild type c-KIT combination with PI3K pathway inhibition in basal-like PDXs. www.novartis.com.

The OCTC - Oncology Clinical and Translational Consortium, a collaborative scientific research network comprised of six renowned comprehensive cancer centers, was launched by GSK at the end of 2013. While GSK will gain OCTC’s expertise in preclinical, translational and clinical development of novel anticancer therapeutics, the participating centers will have access to studies with GSK’s early stage oncology pipeline and opportunities to accelerate and advance the next generation of novel oncology therapeutics. www.gsk.com.
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