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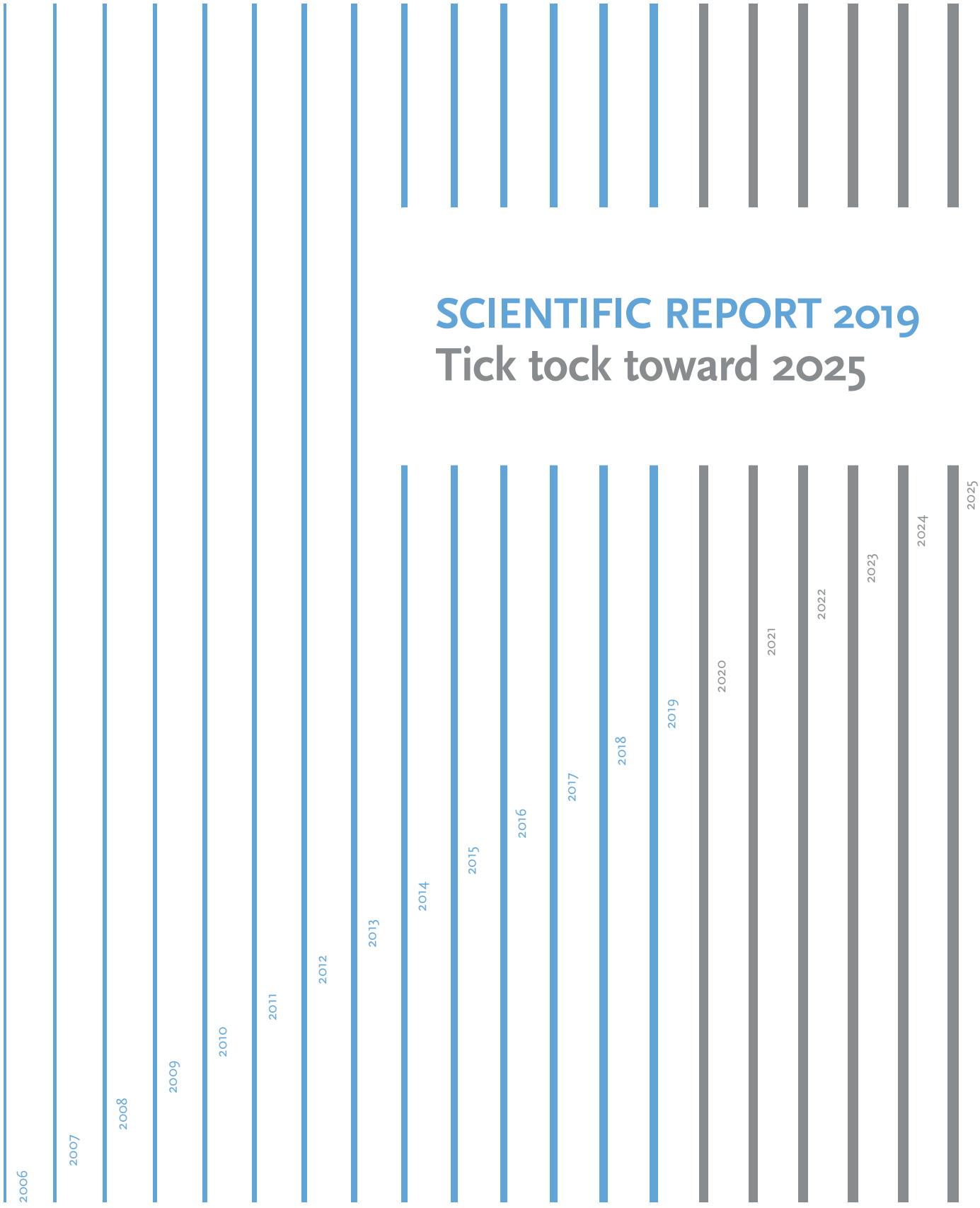
SCIENTIFIC REPORT 2019
Tick tock toward 2025



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VHIO's CELLEX CENTER: translation toward precision oncology

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VHIO Scientific Report 2019

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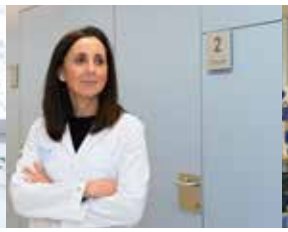

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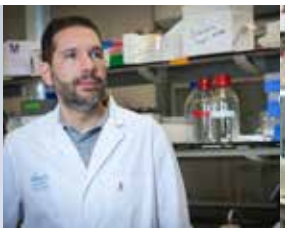

JOSEP VILLANUEVA

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VHIO's Scientific Report 2019: tick tock toward 2025

Championed by VHIO's Director, Josep Tabernero, our Program Directors, Principal Investigators, and Heads of our Transversal Clinical Trials Core Services & Units, spearhead efforts aimed at solving cancer sooner. They lead their respective groups and teams to turn current obstacles in oncology into opportunities, and look ahead to the future to anticipate the challenges ahead.

With the year 2025 rapidly approaching – the deadline to attain the World Health Organization's 9 voluntary global targets for noncommunicable diseases – they continue to drive and accelerate research advancements that will ultimately contribute to meeting target 1 in cancer, namely, a 25% relative reduction in overall mortality from this disease.

Introducing VHIO
Foreword

Josep Tabernero
Director, Vall d'Hebron Institute of Oncology (VHIO)

VHIO in 2019: tick tock toward 2025

To mark the 25th anniversary of *Nature Medicine* in 2019, the journal's editorial team invited me and ten other experts in biomedicine to contribute to a special news feature by answering the question: *What will shape the next 25 years of medical research?* [1]. As part of my response, I began by arguing that sweeping statements would be imprudent. Indeed, who would have predicted that the future of biomedicine, research and the treatment and care of patients suffering from serious diseases such as cancer, would be compromised by the rapid and global explosion of COVID-19?

I strongly believe in joining forces, nurturing and developing partnerships, and exchanging data to overcome the many challenges that hamper our efforts in solving cancer sooner. Alongside like-minded experts in oncology, we have forged numerous international consortia and multi-center studies that continue to drive spectacular advances against this disease. As importantly, we have learned from each other's experiences, successes and failures in order to avoid costly duplication and accelerate progress.

As this report goes to press, an article in *The Lancet* [2] caught my attention. Sadly, the piece sheds a glaring light on the lack of collaboration and synergy between nations in tackling the COVID-19 catastrophe. Not only has this pandemic destroyed the foundations for protecting and advancing health, but also it is threatening the aims set out in the Millennium Development Goals and (since 2016) the Sustainable Development Goals. Simply put, the clock is ticking.

This brings me back to the number 25. It is in fact the focus of this year's Scientific Report cover; a VHIO time bar towards 2025.

Here's why:
The year 2025 is the deadline to attain the World Health Organization's (WHO) nine voluntary global targets for noncommunicable diseases (NCDs) and mental health. Target 1 promises a 25% relative reduction in overall mortality from cardiovascular diseases, cancer, diabetes, and chronic respiratory diseases. Progress in implementing the *NCD Global Action* plan is tracked by WHO's *Global monitoring framework on NCDs* in order to monitor and report on the attainment of its nine global targets for NCDs by 2025. While COVID-19 is threatening our collective efforts to achieve this ambition in cancer, I believe that together – along with the vital funding and necessary support networks firmly in place -- achieving this target might be within reach.

One of the major European funding programs, *Horizon Europe*, was announced in 2019 and succeeds the European Commission's Horizon 2020 funding program for research for research and innovation. Within Horizon Europe's framework, five key research and innovation missions have been identified to increase the effectiveness of funding by pursuing clearly defined targets, 'Missions', including cancer. The Cancer Board, chaired by Walter Ricciardi (Rome, Italy), is flanked by its respective Assembly, on which I am truly honored to serve. The Board and Assembly Members will collectively seek to deliver on Mission's goals. They are: to ensure that more people live without cancer, more cancer patients are diagnosed earlier, suffer less and have a better quality of life after treatment.

But it's not just a matter of strengthening and securing vital funding for cancer research of

excellence. To deliver on these aforementioned ambitions, we must also seek to address many other serious concerns. As an example, The European Society for Medical Oncology (ESMO) -- for which I have had the privilege to serve as President throughout the 2018-2019 term -- has taken the lead in driving EU level action to tackle the serious shortages of essential cancer medicines. These identified shortages obviously have a direct impact on patient care across Europe. To ensure that this issue remains a top priority on the EU policy agenda, ESMO collaborated with the European Parliament to organize a cross-partisan event entitled *Shortages of Inexpensive, Essential Medicines: Calling for Tangible Political Commitments in the EU*, 09 April, Brussels (Belgium).

During my ESMO Presidency, The Economist Intelligence Unit and ESMO prepared a series of reports on medicine shortages in five countries – Germany, Bulgaria, Romania, Belgium, and Finland. The resulting country profiles show that unfortunately there is a lack of data on the magnitude of the issue and that European and international collaborations are key to facilitate the exchange of products in short supply. To further expose this growing public health emergency, which requires concerted and collaborative action at the EU level, members of ESMO's European Policy Committee co-authored a commentary [3] to report on these shortages and signal next steps to tackle this alarming reality.

In this context, I am delighted to announce that the role of ESMO's Magnitude of Clinical Benefit Scale (ESMO-MCBS) as a screening tool to identify cancer treatments that have potential therapeutic value (warranting full evaluation for the WHO's Essential Medicines List) was acknowledged by WHO's Expert Committee on Selection and Use of Medicines in the 22nd WHO Expert Committee on the 2019 Selection and Use of Medicines Report. Specifically, the Committee stated that *'all new EML cancer medicines, in general, should have a score on the ESMO-MCBS of A or B in the curative setting and of 4 or 5 in the non-curative setting. These scores would support a medicine being evaluated by the Expert Committee for inclusion in the EML through a full application'*.

The ESMO-MCBS major value-based framework, launched in 2015, continues to undergo finely-tuning in order to incorporate additional features and criteria. Under constant internal peer review, it has also recently been enriched with newly designed forms, a factsheet and booklet to facilitate the understanding of criteria, grading and outcomes. These resources should help to clarify certain misconceptions reported in the literature this year – addressed by members of ESMO's Cancer Medicines Committee [4].

Importantly, ESMO is not alone in these policy-orientated efforts. the European Association for Cancer Research (EACR), American Society of Clinical Oncology (ASCO), and the American Association for Cancer Research (AACR) – as well as many others – are all working shoulder to shoulder with other specialties, policy makers, as well as patient advocacy groups across the globe, to overcome the obstacles thwarting the optimal treatment and care for all cancer patients. One patient is one too many.

At VHIO, we are dedicated to advancing translational cancer science and medicine toward significantly improving outcomes for our patients. As VHIO's Director, I'm honored to highlight some of the many important contributions made by our multidisciplinary research teams in 2019, often in partnership with colleagues across the globe as well as leading European and international consortia. For an additional pick of papers please refer to From the Directors pages, 50-59.

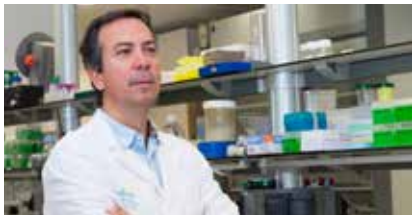
Impactful cancer science and medicine at VHIO

In 2019, VHIO researchers and clinical scientists published an impressive 333 scientific articles in leading journals as corresponding, senior, or co-authors (see full listing, pages 130-147). Many of these were published in the world's most prestigious scientific and medical journals.

Here is just a small sample of our studies that deservedly made headlines in 2019:

Driving transformative research closer to the clinic

Novel agent reactivates an immune call by LIF blockade



Joan Seoane, Co-Program Director of Preclinical and Translational Research at VHIO and ICREA Research Professor.

Building on previous VHIO research pioneered by our Gene Expression & Cancer Group (page 70), results from a study[5], led by Joan Seoane, Co-Program Director of Preclinical and Translational Research, and ICREA Research Professor, have shown that the blockade of the multi-functional cytokine LIF

induces tumor-infiltrating T cells to target and eliminate cancer.

Developed by VHIO, novel agent MSC-1 inhibits LIF and has now been shown to have a dual mechanism of action. First, in tumors expressing high levels of LIF, this protein promotes the proliferation of cancer stem cells. LIF blockade eliminates these tumor-initiating stem cells, putting the brakes on metastatic cell spread and cancer recurrence. Additionally, elevated LIF expression disables the anti-tumor alarm system and stops the immune system from thwarting cancer's plans. Blocking LIF reactivates the alarm to call an anti-tumoral immune response.

This research, carried out in collaboration with other VHIO groups and departments at the Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus (page 22), has now shown that LIF inhibits the *CXCL9* gene, which acts as a signal to lure immune system T cells. LIF blockade induces these immune system soldiers to invade, attack and destroy tumors. The study also showed that combining LIF inhibition with anti-PD1 therapy delivers powerful blows against cancer. Once the T cells infiltrate the tumors, they are activated by anti-PD1 immunotherapy. In animal models the pairing of both agents not only halted tumor growth but also, in some cases, made tumors disappear.

Pushing Myc inhibition closer to the clinic

Laura Soucek, PI of VHIO's Mouse Models of Cancer Therapies Group (right), ICREA Research Professor, and Co-Founder of Peptomyc S.L.

Another translational VHIO study from 2019 [6] represents an important forward step in driving the Omomyc mini-protein closer to the clinic. Findings led by Marie-Eve Beaulieu, CSO and co-founder of VHIO-born spin-off Peptomyc, directed by Laura Soucek, PI of our Mouse Models of Cancer Therapies Group (page 74), ICREA Research Professor and Co-Founder and CEO of Peptomyc, provided evidence for Omomyc as the first efficient and tolerable MYC inhibitor for the treatment of non-small cell lung cancer (NSCLC).

For the first time, the authors establish that Omomyc can be purified and administered *in vivo*, rapidly reaching the tumor site. Results showed that it successfully inhibits its target, leads to reduced tumor grade and promotes regression of existing disease. Thanks to Marie-Eve's particular expertise in peptide design and production, the team succeeded in scaling up the purification process of the mini-protein and re-assessing its therapeutic activity via intravenous administration. Its systemic delivery unleashes the anti-cancer potential of Omomyc and extends its application to the treatment of other tumors and metastases.

Omomyc may attack tumors not only through the blocking of proliferation and the induction of apoptosis, but also by triggering an immune response. The inhibitor can alter the profile of molecules released by cancer to trick the immune system, and may increase the infiltration of T lymphocytes into the tumor. This is relevant as immunotherapy is showing increasing promise in the treatment of several tumor types, but not all. The potential capacity of Omomyc to recruit immune cells at the tumor site, 'spoilered' in the study, indicates that it could also synergize and resensitize resistant tumors to immune-based therapies.

The promise of novel chimeric antigen receptor (CAR) T-cell immunotherapy

Co-Program Director of VHIO's Preclinical and Translational Research and ICREA Research Professor.

In 2019, our Growth Factors Group (page 72), led by Joaquin Arribas, Co-Program Director of Preclinical & Translational Research (page 52) at VHIO and ICREA Research Professor, initiated a new line of research focused on generating novel chimeric antigen receptors (CARs), as a strategy to use the immune system of patients to eradicate tumors. This approach has been enabled by the insights they previously gained by developing and characterizing bispecific antibodies. Specifically, these CARs are directed against the p95HER2 protein which is only found in some breast and gastric tumors, though completely absent in normal tissues.

Also this year, the group's expanding platform of breast and pancreatic cancer patient-derived experimental models has led them to identify novel mechanisms of resistance to anti-cancer therapies [7], as well as seek out biomarkers of sensitivity to precision therapies [8], in collaboration with national and international groups.

Gauging response to target-directed therapies for the more precise stratification of patients

VHIO's Stem Cells & Cancer Group (page 76), directed by Héctor G. Palmer, continues to make important progress

Héctor G. Palmer, Principal Investigator of VHIO's Stem Cells & Cancer Group.

in identifying molecular mechanisms conferring sensitivity or resistance to therapies in order to more precisely stratify patients for enrollment in clinical trials. Working in close collaboration with other VHIO groups and pharmaceutical companies, they seek to identify the molecular culprits that are responsible for the sensitivity or resistance to therapies blocking Wnt/beta-catenin, Notch, PI3K/AKT, EGFR/LGR5 or BRAF/MEK/ERK oncogenic signals.

As an example this year, and in collaboration with other Spanish investigators and VHIO teams including our Gastrointestinal & Endocrine Tumors Group (PI: Teresa Macarulla - page 88), Cancer Genomics (PI: Ana Vivancos – page 112), Molecular Oncology Group (PI: Paolo Nuciforo - page 114), Early Clinical Drug Development Group (PI: Elena Garralda – page 84), they have studied epigenetic EGFR gene repression and the conference of sensitivity to therapeutic BRAFV600E blockade in colon neuroendocrine carcinomas. Based on this published research [9], they are now designing new prescreening tests for a genetic-guided enrolment of patients in clinical trials. Importantly, their findings are helping to define new rational drug combinations to treat cancer patients with progressive disease.

Unmasking mechanisms of resistance in triple-negative breast cancer

One of the main challenges in more effectively treating triple-negative breast cancer (TNBC) is the acquisition of resistance to conventional chemotherapeutics. Research led by Sandra Peiró, Principal Investigator of our Chromatin Dynamics in Cancer Group (page 66), promises novel weaponry to more effectively combat cancer drug resistance in this particular tumor type.

Sandra Peiró, Principal Investigator, Chromatin Dynamics in Cancer Group.

This multi-center, Spanish study[10], also carried out in collaboration with VHIO's Growth Factors (PI: Joaquin Arribas, page 72) and Molecular Oncology Groups (PI: Paolo Nuciforo, page 114) shows that, when compared to other breast cancer subtypes, the DNA of TNBC cells is much more compacted which renders it resistant to therapy. Results also indicate that chromatin decompaction could help to potentiate current therapies.

More specifically, the investigators identified oxidation of histone H3 as a key element in the induction of DNA compaction as well as discovered an association between compaction and resistance to anticancer agents. They also discovered that LOXL2 inhibition could prevent chromatin compaction from occurring. This is particularly relevant since this compaction seems to frequently occur in TNBC, which hinders therapies from accessing the nucleus of cancer cells. While this occurs in other types of breast cancer, they found that in those patients with the triple-negative subtype who show most resistance to conventional therapies, LOXL2 is present in high quantities, suggesting its role as a mechanism of resistance.

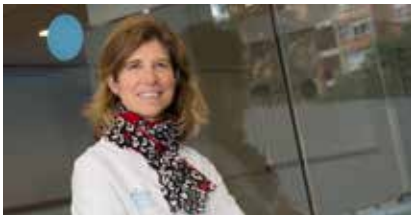
RAD51 as a biomarker in extending PARP inhibitors to additional tumor subtypes

Violeta Serra, Principal Investigator, Experimental Therapeutics Group.

Our Experimental Therapeutics Group, led by Violeta Serra (page 68), continues to mark important progress in gauging response to PARP Inhibitors (PARPi). Crucially, they have initiated the clinical validation of their *RAD51predict* test which is an immune-based assay performed on FFPE tumor sections. Reflective of its promise in better gauging efficacy of PARPi in individual patients and eventual implementation as a diagnostic test, these efforts have most recently been awarded by the ERA PerMed progam – an ERA-Net Cofund. This international project counts on the expertise of 32 partners from 23 countries, and is co-supported by the European Commission (Coordinator: *Instituto de Salud Carlos III* – ISCIII). The test is also being developed thanks to additional funding received this year from the *CaixaImpulse* Consolidate 2019 program.

Directed by Violeta Serra, and led by Alba Llop, post-doctoral fellow in our Experimental Therapeutics Group, the project not only centers on using RAD1 protein as a biomarker to help personalize cancer therapy, more precisely and rapidly predicting those patients who would be most likely to benefit from PARPi,

better guide stratification in clinical trials, as well as extend PARPi for the treatment of additional tumor types beyond breast and ovarian cancers. This present research builds on the successes of several previous projects, including the previous PARPiPRED (which was also funded by *CaixaImpulse*), aimed at identifying clinical biomarkers of sensitivity to PARP inhibitors, and is spearhead by Violeta Serra's Experimental Therapeutics Group, in collaboration with Judith Balmaña's Hereditary Cancer Genetics Group at VHIO (page 94), and our Breast Cancer Group (PI, Cristina Saura – page 82).



Judith Balmaña, Principal Investigator, Hereditary Cancer Genetics Group.

Cristina Saura, Principal Investigator, Breast Cancer & Melanoma Group.

Reflective of VHIO's expertise in the PARPi field, VHIO faculty, including Violeta Serra, Judith Balmaña, Marta Castroviejo, Ana Oaknin (PI of VHIO's Gynecological Malignancies Group (page 92), co-authored an elegant review [11] on a decade's development of these therapies, where we now stand, and where to next. This publication was first authored by Joaquin Mateo, PI of our Prostate Cancer Translational Research Group (page 98), who leads research aimed at potentiating PARPi in the treatment of prostate cancer.

Targeted multiplex proteomics towards more precisely matching patients to novel anti-cancer medicines

Paolo Nuciforo, Principal Investigator, Molecular Oncology Group.

Research led by Paolo Nuciforo, Principal Investigator of our Molecular Oncology Group (page 114), also co-authored by VHIO PIs Ana Vivancos (Cancer Genomics, page 112), Rodrigo Dienstmann (Oncology Data Science Group – ODysSey, page 96), explored the promise of using targeted multiplex proteomics (TMP) as a novel approach to simultaneously measure a panel of proteins implicated in oncogenic processes, tumor suppression, drug metabolism and resistance. Also including tumor differentiation markers, this tool could guide standard diagnostic decision-making as well as render the selection of new targeted therapies and immune-based therapeutics for patients with metastatic colorectal cancer (mCRC) more precise.

In the article [12], the authors concisely review the strengths and limitations of the current 'gold standard' in accurately measuring multi-proteins in experimental samples, immunoassay, and outlines the downside of applying targeted proteomics using selected reaction monitoring mass spectrometry (SRM-MS). The researchers, also counting on the expertise of other VHIO investigators as well as the Vall d'Hebron University Hospital (HUVH) Pathology Department (directed by Santiago Ramón y Cajal), describe their findings by sub-chaptering each stage of their analyses.

Representing the very first study to measure the impact of quantitative targeted proteomics in precision oncology against mCRC, they analyzed protein biomarker profiles and integrated the results obtained with the available clinical, pathological and genomic data towards advancing precious insights into predictive and prognostic markers. Not only do they signpost that proteomics-steered drug development will expand treatment options for patients who are eligible to participate in early phase clinical trials, particularly considering the increasing emergence of promising antibody-drug conjugates (ADCs) and immune-based treatments, but also ring in the repurposing of proteomics as powerful anti-cancer armory in precision oncology.

Developing kinder & less disruptive treatments

As I reflect on our contributions made at the clinical level, here I select potentially practice-changing studies, including advances in novel clinical trial design that VHIO clinical investigators led or co-authored in 2019.

First, a trio of papers published in *The New England Journal of Medicine* that reported important advances against colorectal, ovarian, and pancreatic cancers, respectively.

Novel treatment combination for patients with BRAF-mutant metastatic colorectal cancer

Josep Tabernero, Director of Clinical Research at VHIO.

Led by our Gastrointestinal & Endocrine Tumors Group (see page 88), findings presented on the ground at the 2019 Congress of the European Society of Medical Oncology (ESMO) here in Barcelona, showed that the triplet combination of the BRAF inhibitor, encorafenib, MEK inhibitor, binimetinib, and EGFR inhibitor, cetuximab, not only significantly improves overall survival but also increases objective response rates compared with standard of care in patients with BRAF V600E-Mutated Colorectal Cancer.

Published in parallel [13], the BEACON CRC phase III multicenter study, also counting on the expertise of co-author Elena Élez, Medical Oncologist and Clinical Investigator of VHIO's Gastrointestinal & Endocrine Tumors Group, included patients with BRAF V600E-mutant metastatic colorectal cancer who had disease progression after one or two previous regiments. Seeking to potentiate BRAF-directed therapy in this patient population, study participants were randomly assigned to receive triplet therapy with encorafenib, binimetinib and cetuximab, or the investigator's choice of either cetuximab and irinotecan or cetuximab and FOLFIRI.

Results showed significant clinical benefits with median overall survival of 9.0 months in the triplet group, 8.4 months in the doublet, and 5.4 months in the control arm. Regarding response rates, the researchers confirmed 26% in the triplet and 2% in the control. Importantly, tolerability of this novel combination was favorable.

These findings point to a potential paradigm shift in the treatment of this disease and warrant further investigation to better define the benefits of both the triplet and doublet combinations.

The promise of prolonged progression-free survival in newly diagnosed patients with high-grade ovarian cancer

Ana Oaknin, Principal Investigator, Gynecological Malignancies Group.

Also reported during the ESMO Congress 2019 and simultaneously published in *NEJM*, findings from the multinational phase III VELIA/GOG-3005 trial [14] led by Robert L. Coleman, University of Texas MD Anderson Cancer Center (USA), showed that the use of the poly (ADP-ribose) polymerase inhibitor veliparib plus first-line chemotherapy and as maintenance therapy improved progression-free survival (PFS) in patients with stage III or IV high-grade serous ovarian carcinoma versus induction chemotherapy alone.

The researchers, including Ana Oaknin, Principal Investigator of our Gynecological Malignancies Group (page 92), sought to establish whether PFS could be increased by adding veliparib as maintenance therapy in patients with newly high grade HGSC with and without germline *BRCA* mutations, and homologous recombination deficiency (HRD).

The trial included 1,140 patients from 210 sites in 10 countries who were randomly assigned to receive first-line induction chemotherapy with carboplatin/paclitaxel plus placebo followed by placebo maintenance of chemotherapy plus veliparib followed by veliparib maintenance.

Compared with the control group, the veliparib-throughout group had significantly prolonged PSF in the *BRCA* mutation and homologous recombination-deficiency cohorts, as well as the intention-to-treat population. This novel treatment approach shows that adding veliparib to standard chemotherapy and followed as maintenance therapy is able to statistically and clinically prolong PSF for patients recently diagnosed with high-grade ovarian cancer.

PARPi maintenance therapy against *BRCA*+ Metastatic Pancreatic Cancer

Teresa Macarulla, Principal Investigator, Gastrointestinal & Endocrine Tumors Group.

Headlining during the 2019 Annual Meeting of the American Society of Clinical Oncology (ASCO), 31 May-04 June (Chicago, USA), results from the POLO phase III study [15] co-authored by Teresa Macarulla, Medical Oncologist and Principal Investigator of our Gastrointestinal & Endocrine Tumors Group (page 88), also published in parallel in *NEJM*, and were selected to feature in ASCO's Media Program.

This international trial, led by Hedy L. Kinder (University of Chicago), was designed to evaluate the efficacy of maintenance therapy with a PARP inhibitor olaparib in patients with germline *BRCA*-mutated metastatic pancreatic cancer. Showing that this approach significantly improved progression-free survival (PFS) compared with placebo among

these patients, these findings could represent new hope and open up new treatment avenues for this patient population.

Specifically, approximately 6-8% of patients with pancreatic cancer are carriers of this mutation and could stand to benefit from this therapeutic approach. Expanding the group of patients who might also gain from Olaparib, beyond those who have a germline *BRCA*1 or *BRCA*2 mutation, could also be of interest.

Prolonging PFS in previously untreated PD-L1-positive metastatic renal cell carcinoma patients

Cristina Suarez, Medical Oncologist and Clinical Investigator, Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site Group.

Results of the phase III IMmotion151 trial presented by Brian Rini, Taussig Cancer Institute, Cleveland Clinic (USA) at ASCO 2019, which published simultaneously [16], show promise in improving progression-free survival (PFS) by combining monoclonal antibodies atezolizumab and bevacizumab versus sunitinib alone in patients with previously untreated, programmed cell death ligand (PD-L1)-positive, metastatic renal cell carcinoma.

The trial enrolled 915 patients from 152 sites in 21 countries who were randomly assigned to receive atezolizumab plus bevacizumab or sunitinib. The investigators, including Cristina Suarez, Medical Oncologist and Clinical Investigator of our Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site directed by Joan Carles (page 90), reported that not only did the combinatorial therapy prolong PSF in this patient population, if also showed a favorable safety profile, pointing to this approach as a first-line treatment option for selected patients with advanced renal cell carcinoma.

Clinical trial design in the era of precision oncology

WIN Worldwide Innovative Networking in personalized cancer medicine

In 2019, results of WINTHER clinical trial, *Genomic and transcriptomic profiling expands precision medicine* -the first study pioneered by the WIN Consortium (see page 29) published in *Nature Medicine* [17]. Led by VHIO, findings showed that RNA profiling together with DNA testing matches more patients with advanced cancer to personalized anti-cancer therapies than DNA profiling for tumor mutations alone.

Carried out in collaboration with other leading members of WIN, co-authors including Jordi Rodón, Clinical Investigator at the MD Anderson Cancer Center and Associate Investigator of VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 122), and Irene Braña, Phase I Investigator of the same Unit, showed that patients treated with a drug or regimen more closely matched to the molecular profile of their respective tumors, do better. By assessing RNA as an important adjunct to DNA profiling for determining precision treatments, WINTHER rings in a new era for personalized medicine in oncology.

Cancer Core Europe

Endorsed by the Cancer Core Europe Consortium (CCE), page 28, and officially launched during its 4th Annual Meeting, hosted by VHIO in 2019, the Basket of Baskets (BoB) two-stage clinical trial study promises a more flexible and adaptive model in order to significantly accelerate patients' access to an array of novel therapeutics. As the first European multi-modular academic trial, BoB integrates molecular prescreening, the development of novel diagnostic tests including ctDNA, with the assessment of targeted therapies matched to those patients who will be most likely to benefit from them.

BoB is divided into two separate parts: advanced molecular diagnosis or screening, i-Profiler, and the therapeutic phase, i-Basket. In the former patient tumor samples are analyzed for genetic profiling to identify the specific alterations of each individual tumor, followed by bioinformatics analyses to gauge the clinical relevance of a particular treatment tailored to these alterations, with the option of adding extra modules with other anti-cancer medicines currently under development.

Patients identified with the alteration/s included in BoB's i-Basket phase, and who meet the inclusion criteria, enter this second part. Each module focuses on a different treatment (either as monotherapy or in combination), and will have a different sponsor/coordinator. The first module is evaluating atezolizumab in a molecularly-selected population recruited this year, and funding to assess FGFR inhibition in specific patients has been secured.

Elena Garralda, Director of VHIO's Molecular Therapy of Cancer (UITM) - "la Caixa".

At VHIO, this novel trial is being carried out at our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 122), directed by Elena Garralda, and counts on the expertise of several VHIO investigators including Jordi Rodón and Irene Braña, Associate Investigator and Phase I Investigator of the same Unit, respectively, as well as Rodrigo Dienstmann, PI of VHIO's Oncology Data Science Group (ODysSey – page 96), and Ana Vivancos who leads our Cancer Genomics Group (page 112).

Ana Vivancos, Principal Investigator, Cancer Genomics Group.

Rodrigo Dienstmann, Principal Investigator, Oncology Data Science Group (ODysSey).

Ana's group is also appointed as co-lead of CCE's Genomics Taskforce, responsible for the alignment of genomic testing across all member institutions.

In addition to my pick of practice changing data and projects here, please also see an additional selection detailed in my introductory pages as Director of VHIO's Clinical Research Program (see pages 56-59), as well as the Paper pick section of each particular group; selected by our respective Principal Investigators.

The power of cross-border collaboration

In addition to our participation in the WIN Consortium and Cancer Core Europe, we also belong to several other important collaborations (see pages 151-157). 2019 celebrated the launch of an additional five pioneering projects:

The OPTIMISTICC Grand Challenge -Opportunity To Investigate the Microbiome's Impact on Science and Treatment In Colorectal Cancer- is a five-year consortium funded by Cancer Research UK's Grand Challenge, led by Matthew Meyerson, the Dana-Farber Cancer Institute-Harvard Medical School, and Wendy Garrett, Harvard T.H. Chan School of Public Health (USA).

Aimed at better understanding the difference between a healthy microbiome and a microbiome associated with the development of colorectal cancer, the co-investigators from the US, Canada, the UK, Netherlands, and Spain, are seeking to identify ways to manipulate this collection of microorganisms to better prevent and treat cancer. The project partners, including VHIO, are exploring this through clinical trials of new interventions based on the research results (see page 29).

EUCanCAN – the European-Canadian Cancer Network, led by the Barcelona Supercomputing Center - BSC (Spain), comprises a total of eighteen partners, including VHIO, to pursue the homogeneous analysis, management and exchange of genomic-driven oncology data to advance precision medicine in cancer.

Jointly funded by the European Union's Horizon 2020 research and innovation programme and the Canadian Institutes of Health, this four-year project is coordinated by David Torrents at the BSC, and strives to provide a functional platform for federated genome analysis systems towards efficiently analyzing, managing, sharing and reusing mass genomic data at the global level (page 30).

Immune-Image is a twenty two stakeholder-strong consortium incorporating public and private partners, including VHIO and the Vall d'Hebron Institute of Research (VHIR). Powered by the Innovative Medicines Initiative Joint Undertaking (IMI 2 JU), this initiative is led by Roche and coordinated by Albert Windhorst, Amsterdam University Medical Center (VUmC), The Netherlands.

Set to run for an initial duration of five years, this project is entitled Specific imaging of immune cell dynamics using novel tracer strategies, and seeks to develop a novel non-invasive imaging strategy for assessing immune cell activation and dynamics in oncology and inflammatory disease (page 30).

Funded by the European Union's Horizon 2020 research and innovation programme, the CELAC and European

Consortium for a Personalized Medicine Approach to Gastric Cancer (LEGACy) is a four-year project spearhead by Andrés Cervantes, the INCLIVA Health Research Institute (Spain), in partnership with ten other members including VHIO.

Focused on advancing personalized medicine against gastric cancer, this project aims to improve diagnosis and treatment by using data obtained through extensive research in four EU countries and four countries within the Community of Latin American and Caribbean States (CELAC) States, by applying personalized medicine at the three levels of prevention (page 30).

RADprecise

RADprecise - Personalized radiotherapy: Incorporating cellular response to irradiation in personalized treatment planning to minimise radiation toxicity, is supported by funding received through ERAPerMed's co-funded Joint Translational Call 2018 and was founded by seven leading organisations, including VHIO. This three-year project aims to render radiotherapy more precise by incorporating data from finely-tuned predictive models to pre-identify toxicity based on insights from multiple biomarkers of radiosensitivity in individual patients.

Led by Principal Investigator, Jenny Chang-Claude from the German Cancer Research Center (DKFZ), project partners are applying findings at the clinical level by integrating a treatment planning system (page 30).

The Last Word

As VHIO's Director, I am honored and privileged to lead and work with our many research talents and dedicated healthcare professionals in oncology. Without our multidisciplinary and translational teams, cross-border collaborations and partnerships, and the passion and drive that unite us all in our ambition to solve cancer sooner, our Institute would cease to exist.

That same sustained devotion and belief is also shared in equal measure by our wonderful institutional supporters – the Generalitat de Catalunya, Fundació Privada CELLEX, Fundación FERO, "la Caixa" Foundation, and the Fundación BBVA (pages 17-20), as well as VHIO's many other funding entities, agencies, and individuals (see pages 148-150, and 158-163). They all share the same intense desire as we do: to reduce the devastating burden that this disease has on society

Regarding the amazing support that we receive from individuals, I am very sad to report the passing of Pau Donés, singer, songwriter, guitarist and leader of the renowned Spanish rock group Jarabe de Palo, who, having been diagnosed with colorectal cancer in 2015, succumb to his disease in June 2020. Receiving treatment at our Vall d'Hebron University Hospital (HUVH), and cared for by our medical teams and specialists, particularly Elena Élez, Medical Oncologist and Clinical Investigator of our Gastrointestinal & Endocrine Tumors Group, he was a treasured patient, friend, and an ardent believer in the importance of research against cancer.

On behalf of VHIO, I take this opportunity to gratefully thank him for his support of research in oncology, his enormous generosity, commitment and boundless positivity, creativity, zest and zeal.

To raise funds for research at VHIO, he not only organized four sell-out concerts, but also valiantly spoke out to raise awareness on and around cancer. He really was a true inspiration to us all.

The promotional poster for Pau Donés' final fundraising concert, December 2019.

As this report goes to press, the latest statistics issued by the European Commission's Joint Research Centre [18] estimate that the cancer burden in EU-27 countries has risen to 2.7 million cases (all types, excluding non-melanoma cancer) and 1.3 million deaths in 2020.

Regarding the tick-tock to 2025 and the current COVID-19 pandemic (page 6 of my Foreword), I believe that we will overcome this global virus and progress to even bigger success in our efforts to combat cancer through 2025 and beyond. We can, and will, do even better.

Josep Tabernero
Director, Vall d'Hebron Institute of Oncology (VHIO).

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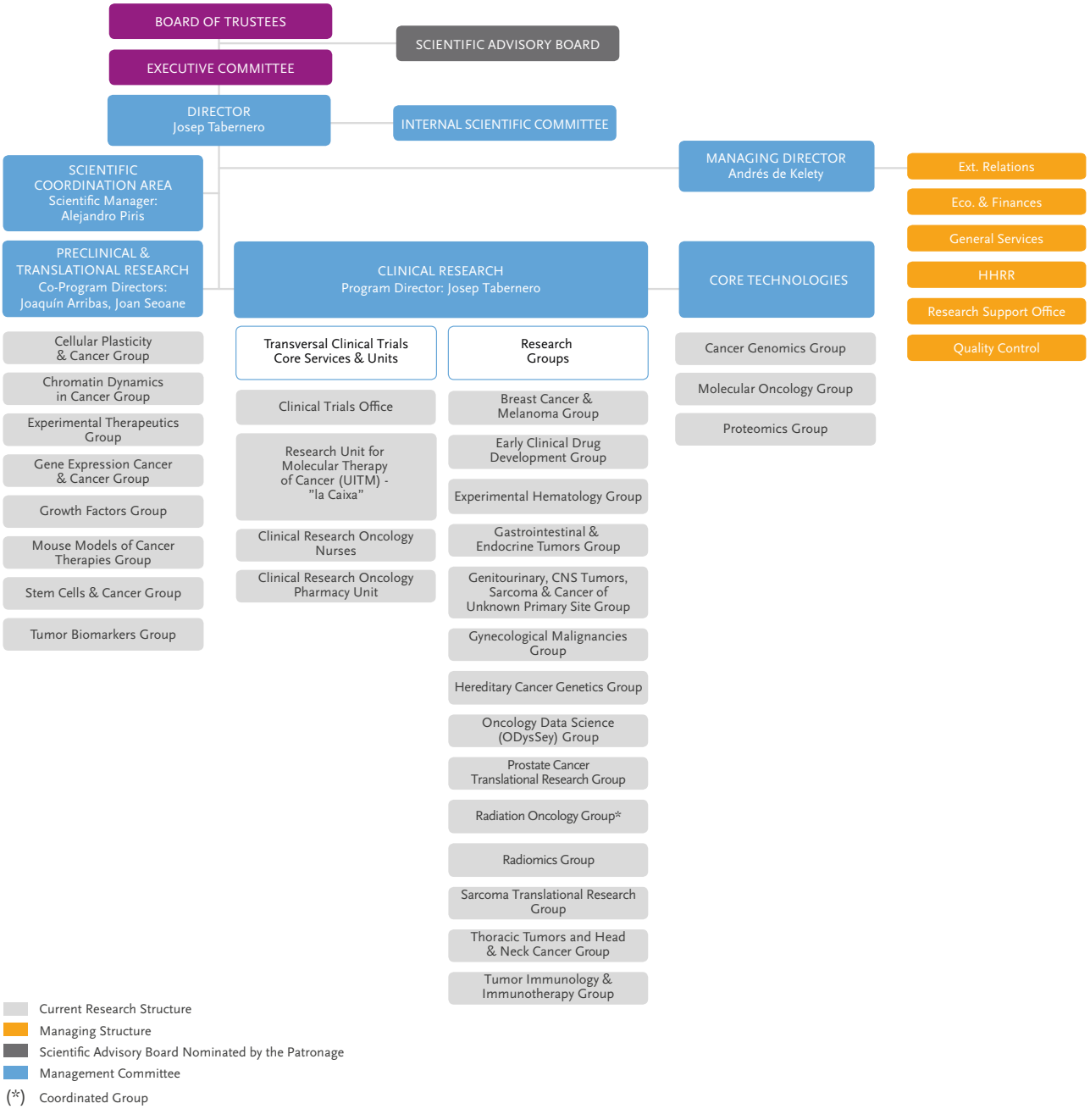
Introducing VHIO
Who we are and what we do

VHIO's Organigram 2019

In order to translate cancer discovery into real benefits for an increasing number patients, VHIO adopts a purely translational, multidisciplinary research model. Organized into three 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 talents to continue to both anticipate and tackle the many unresolved questions in ultimately outsmarting the multifaceted, heterogeneous and complex disease that is cancer:



VHIO in 2019: tick tock toward 2025

VHIO's translation toward precision oncology: a little more on how we did it in 2019

VHIO's Director, Josep Tabernero: welcoming all stakeholders in oncology to our CELLEX building – the home and heart of the Vall d'Hebron Institute of Oncology (VHIO).

Under the leadership of Josep Tabernero, the Vall d'Hebron Institute of Oncology (VHIO), created in 2006, has established itself as a comprehensive cancer center of proven excellence internationally. It is thanks to the devotion of our Principal Investigators and their teams, coupled with VHIO's optimal organizational structure based on a purely multidisciplinary and translational model that VHIO talents continue to anticipate and tackle the many unresolved questions in combatting this multifaceted and heterogeneous disease.

That said, our Institute would cease to exist without the generous support it receives from its Institutional Supporters, public funding, private institutions, companies, and individuals, as well as International and National Competitive Grants (see pages 148-150).

Special mention here highlights the tremendous belief and backing that we continue to receive from our dedicated patrons: the *Generalitat de Catalunya, Fundació Privada CELLEX, FERO Fundación de Investigación Oncológica,"la Caixa" Foundation,* and the *Fundación BBVA*.

Just some of their respective, major contributions include the following:

Generalitat de Catalunya

Our public patron, the *Generalitat de Catalunya* (the Government of Catalonia) – together with the Vall d'Hebron University Hospital (HUVH) – represented by its Departments of Health (*Departament de Salut*), and Industry and Knowledge (*Departament de Empresa I Coneixement*), has from the very outset been a dedicated supporter of VHIO's cancer science and medicine.

As a devoted ambassador of VHIO and our various research programs and projects, it has been institutionally and financially supporting us throughout our first decade and now, beyond, with the Catalan Minister of Health as the President of our Board of Trustees.

At 'home' VHIO's translational and multidisciplinary approach to cancer research is greatly facilitated through the connectivity and tremendous collaboration we have with the entire spectrum of oncology professionals at HUVH, and the rest of the Catalan Public Health System.

The Catalan Department of Health has played an essential role in integrating VHIO's research activity into the Catalan Health System,

representing a successful example of how the public and private sectors can work closely together for the benefit of science, patients and society.

As an active member of the CERCA Institute of Research Centers of Catalonia (*Institució CERCA–Centres de Recerca de Catalunya*), this collaboration affords us access to the Catalan Research System and the fiscal and legal benefits that this represents.

The financial support it has provided has consequently contributed majorly to VHIO's structural overheads, allowing us to center our efforts on our core research activities. Additionally our groups also receive funding from various Calls promoted and supported by the *Generalitat de Catalunya*. For further details see: *New funding and projects in 2019* (page 158-163).

Fundació Privada
CELLEX

It is thanks to one of our private patrons, the *Fundació Privada* CELLEX (CELLEX Foundation), that we have been able to build new facilities that have subsequently spurred our efforts aimed at advancing precision oncology and providing optimal patient treatment and care.

As a first example, it is thanks to this Foundation that the Vall d'Hebron University Hospital's Oncology Department's Oncology Day Hospital and Outpatients Facility opened its adjoining doors in 2008, with a subsequent and final phase of reforms in 2012. This carefully planned expansion and integration of various units and services, resulted in uniting all specialties and disciplines involved in the treatment and care of our patients in the same place and in so doing, now promotes the purely translational and multidisciplinary model for which VHIO is famed.

CELLEX also financed the construction and infrastructures of our state-of-the-art building – the CELLEX Center – that was completed in 2015. Marking a new VHIO chapter, our premises provided the necessary space and amenities to expand our research activities and further foster our multidisciplinary connectivity and exchange by bringing all VHIO research teams together under the same roof.

Providing the valuable space through which to grow, the CELLEX Center has not only further enhanced collaborations and accelerated our dedicated efforts to combat cancer, it has also allowed us to expand our groups in order to pursue new emerging research areas including immunology & immunotherapies, as well as fortify our research structure.

As importantly, thanks to CELLEX, our cutting-edge Animal Facility has spurred the more precise development of our predictive cancer models. Incorporating the latest platforms and technologies for analyzing small animals of human disease, this facility that we share with other colleagues across the Vall d'Hebron Barcelona Hospital Campus, has enabled us to further establish VHIO as a European reference in cancer modelling.

We take this opportunity to congratulate CELLEX as a most worthy recipient of one of the Government of Catalonia's *Josep Trueta* medals in 2019. Awarded to healthcare professionals and organizations that have significantly contributed to the advancement of healthcare, this recognition honors CELLEX's many initiatives that have accelerated biomedical research and improved healthcare across Catalonia.

fundación fero
Investigando por un futuro sin cáncer

Support received from the *Fundación FERO* (FERO Foundation), has, from the very beginning, enabled science of excellence at VHIO as well as promoted the careers of up-and-coming talents in oncology through its annual Fellowships. Concerning the former, the labs of Josep Villanueva, PI of our Tumor Biomarkers Group, Laura Soucek, PI of VHIO's Mouse Models of Cancer Therapies Group and ICREA Professor, Violeta Serra, PI of VHIO's Experimental Therapeutics Group, Joaquín Arribas, Co-Director of our Preclinical and Translational Program and ICREA Professor, who also heads our Growth Factors Group, and Sandra Peiró, who leads our Chromatin Dynamics Group, have been able to grow their groups and advance their pioneering research lines thanks to FERO.

FERO has also contributed to the expansion of our facilities. As an example, the Foundation was a sponsor of our Breast Cancer Center *Endavant i de Cara*, along with a personal donation received from Maria Angels Sanahuja. Funding received from FERO also enables us to develop our Droplet Digital PCR (ddpCR) Bio-Rad Technology platform and advancing research into the more effective and less invasive tracking of cancer by liquid biopsy.

Regarding its Annual Awards for Translational Research, a total of ten of our research scientists have been honored with this prize: Laura Soucek (2011), Héctor G. Palmer (2012), Ibrahim Yasir – formerly an investigator of VHIO's Experimental Therapeutics Group directed by Violeta Serra (2013), César Serrano (2015), Beatriz Morancho (2016), María Abad (2017), Alena Gros (2018), and Joaquin Mateo, Violeta Serra and Judith Balmaña (2019).

More specifically, VHIO's 2019 awardees have been prized to continue to develop the liquid biopsy of cancer; pioneered by our Institute – also driven by the VHIO-FERO's Institutional Advanced Molecular Diagnostics Program (DIAMAV). For more information about these innovative undertakings spearhead by VHIO's Joaquin Mateo, PI of our Prostate Cancer Translational Research Group, Violeta Serra, PI of our Experimental Therapeutics Group, and Judith Balmaña, PI of Hereditary Cancer Genetics, see page 33.

The aforementioned DIAMAV Program powered by FERO, enables VHIO's clinical investigators and cancer researchers to identify specific molecular risk factors better predict the potential efficacy of specific agents tailored to each particular tumor, further advance insights into the more effective and less invasive tracking of disease by liquid biopsy, and develop cancer diagnostics for the early detection of disease. More information on page 27.

Lastly, but by no means least, FERO also promotes the importance of cancer research through the organization of several public engagement and annual fundraising initiatives and events. As an example in 2019, it organized a 'swimathon', *Marnaton 4 FERO*, to raise money for research led by Héctor G. Palmer (PI of VHIO's Stem Cells & Cancer Group) into the early detection of cancer recurrence by liquid biopsy.

"la Caixa" Foundation

Thanks to the support received from the "la Caixa" Foundation, VHIO's Research Unit for Molecular Therapies of Cancer (UITM) – "la Caixa" opened its doors in 2010 to pioneer early drug discovery and clinical studies tailored to the specificities of patients. Research at this Unit has contributed to the development of several tumor cell targeted agents including trastuzumab, pertuzumab, cetuximab, panitumumab, ramucirumab, trifluridine/tipiracil, gefitinib, osimertinib, ceritinib, crizotinib, loratinib and everolimus, among others. Current focus also centers on accelerating and advancing immunotherapies including atezolizumab, nivolumab and pembrolizumab.

The UITM, under the co-direction of Josep Tabernero, VHIO's Director -who also heads our Clinical Research Program- and Elena Garralda, PI of our Early Clinical Drug Development Group (page 84), has subsequently established itself as a leading reference in developing novel therapies based on the molecular profile of each tumor and optimize treatment strategies using combinations of new agents with already existing ones. For more information see page 122.

Furthermore, in addition to various grants supporting several VHIO groups, the Foundation also fuels one of VHIO's three major institutional programs. Building on the successes of the two previous VHIO-"la Caixa" Institutional 3-year Programs, at the end of 2019 we announced a new 4-year VHIO-"la Caixa" Advanced Oncology Research Program (2020-2023). Marking the UITM turning ten in 2020 as well as the ringing in of a new VHIO decade, support received will further spur our purely translational and multidisciplinary teams to develop more potent and precise anti-cancer medicines, fortify existing research lines as well as initiate new projects to lead frontier research in some of the most relevant and rising focus fields in precision oncology. See page 27 for more details.

Also thanks to the "la Caixa" Foundation, our Clinical Research Oncology Pharmacy Unit's new home was completed in 2019. Providing the much needed additional space and equipped with the very latest technologies, the Molecular Therapy of Cancer (UITM) – "la Caixa" (page 122) – Clinical Research Onco-Hematology Unit will enable Maria Queralt Gorgas' team (page 126) to provide even higher quality pharmaceutical care and services, as well as continue to meet all regulatory requirements.

Finally, 2019 also celebrated the launch of our VHIO –"la Caixa" Scientific Seminars Series. This educational program welcomes internationally renowned researchers and clinical investigators to VHIO to share, discuss and debate latest insights, discovery and next directions in oncology with our students, postdocs and senior faculty from our preclinical, translational and clinical research groups. More information on page 38.

Fundación BBVA

Also driving programs to spur VHIO's avant-garde translational research in precision oncology, the *Fundación* BBVA (BBVA Foundation), financed our Tumor Biomarkers Research Program back in 2011. This five-year major framework agreement fueled collaborative science centering on the development of personalized therapies for cancer patients through biomarker research.

Building on the successes of this first program, our second BBVA-VHIO Institutional Program: the BBVA Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI) - page 28, represents an important forward step in advancing agents that inhibit checkpoint regulation of the immune system, better understanding mechanisms of resistance and response to these therapies, and prioritizing the early development of those drugs showing most promise. It also supports various research lines across other VHIO groups. Leading these research efforts are Alena Gros and Elena Garralda, PIs of our Tumor Immunology & Immunotherapy (page 108), and Early Clinical Drug Development (page 84) Groups, respectively.

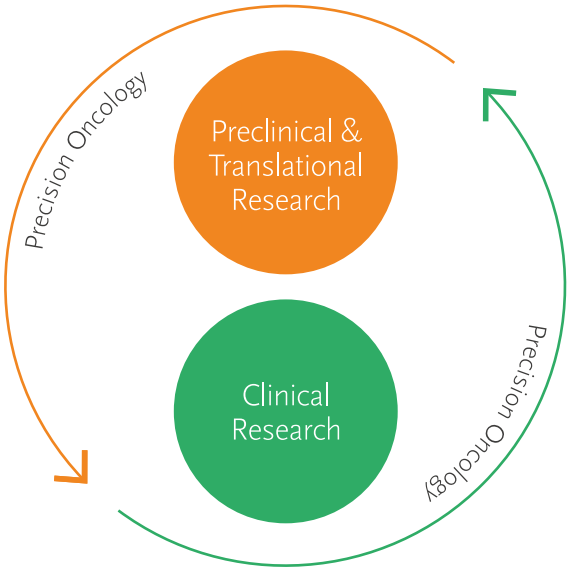
VHIO has co-founded various translational projects linked to the early clinical development phases of immunotherapy. These pioneering research endeavors are currently underway. Focus areas this year include the characterization of hyperprogressive disease with immunotherapy to advance insights into this phenomenon, as well as establishing a radiomic signature to predict response to immunotherapy; carried out in collaboration with Raquel Perez-Lopez, PI of our Radiomics Group (page 102).

Shining a light on the BBVA Foundation's dedication to spurring of progress against cancer, and indeed advances in cardiovascular disease, neurodegenerative diseases, as well as metabolic disorders, it received a prized bestowed by the national periodical *ABC*'s Health Section under the category of *Foundation of the Year*. Specifically, this *Premio ABC Salud* recognizes the Foundation's support of biomedical research programs of excellence, including VHIO and our aforementioned BBVA CAIMI program.

For a full listing of all VHIO's funding sources and entities see pages 148-157, and, for new funding and corresponding projects awarded in 2019, please refer to pages 158-163.

Located within the Vall d'Hebron Barcelona Hospital Campus, our researchers closely collaborate and interact with Vall d'Hebron University Hospital (HUVH) physician-scientists. Translational science and clinical research are therefore tightly connected which promotes superb interaction and teamwork which, in turn, accelerates the bench-bedside-bed cycle of knowledge. This privileged environment affords VHIO direct access to patients as well as the entire spectrum of oncology professionals who care for them, and a second-to-none appreciation of how cancer science can translate into more powerful, targeted treatments and better practice for the care of patients.

VHIO's pioneering model and programs, coupled with its belief in combining strengths through cross-border collaborations, continue to spur advances in reversing cancer resistance, halting metastatic spread, and more effectively treating even the most undruggable tumor types.



VHIO's multidisciplinary and translational model: the seamless, unrestricted flow of discovery in oncology.

Areas of cancer research at VHIO: at a glance

- Preclinical humanized models (PDXs – Avatars – and Organoids).
- Mechanisms of sensitivity, and primary and acquired resistance.
- Molecular and clinical Big Data to characterize subtypes of diseases.
- Early drug development.
- Clinical trials with innovative agents (phase I & II) and first-in-human studies.

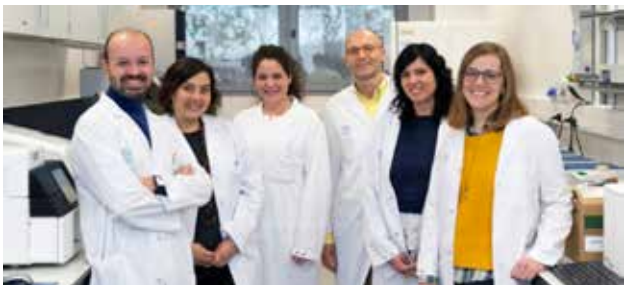
Driving and applying powerful technology platforms

At the core of VHIO's research activities are our suite of cutting-edge core technology platforms which allow our expert teams to apply next-generation whole-genome sequencing for precision oncology as well as develop and improve existing applications to drive faster results.

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 better predict the potential efficacy of specific agents matched to the specificities of individual patients.

VHIO's Cancer Genomics Group (page 112), headed by Ana Vivancos, serves as a Core Technology laboratory and provides cutting-edge applications in cancer genomics through state-of-the-art technologies and the development of novel, fully validated tests that are used in the clinical research setting (Prescreening Program). Her lab is equipped with an n-Counter (Nanostring) platform, two digital PCR platforms (BEAMing Sysmex and ddPCR, BIO-RAD), and three NextGen Sequencers; MiSeq, NextSeq and HiSeq2500, Illumina.

Our Prescreening Program, pioneered by Ana's Group in collaboration with VHIO's Molecular Oncology Group (page 114) led by Paolo Nuciforo, Early Clinical Drug Development Group headed by Elena Garralda, and Oncology Data Science (ODysSey) Group directed by Rodrigo Dienstmann (page 96), together with Susana Aguilar and Jenifer Gonzalez, performs molecular profiling in up to 1500 patients each year as potential candidates for enrollment in our Phase I clinical trials led by VHIO's Research Unit for Molecular Therapy of Cancer (UITM – "la Caixa", page 122, also championed by Elena Garralda.



VHIO's Prescreening team (left to right): Paolo Nuciforo, Ana Vivancos, Elena Garralda, Rodrigo Dienstmann, Susana Aguilar and Jenifer Gonzalez.

Patients' suitability for inclusion in any given clinical trial is assessed based on their respective genomic or pathologic profile. Ana's group has developed and routinely implemented several tests for this program. Two are based on NGS: an Amplicon-seq approach to sequence 67 genes as well as a 450-gene capture panel (Illumina)

The group uses nCounter (Nanostring) for their RNA-based gene fusion panel, with the capacity of detecting over 100 recurrent gene fusions (also enabling the assessment of of gene expression patterns in tumors), and Copy Number Alterations panel evaluating a 59 panel for genes with frequent gains or losses in cancer. Reflective of excellence and quality, they have attained ISO 15189 flexible accreditation for the Amplicon-seq testing method, and will soon obtain this accreditation for their large 450-gene capture panel.

Importantly, our prescreening efforts have established VHIO as one of the few centers in Europe to run such a comprehensive program. We will continue to extend our

efforts to an increasing number of patients thanks to expanded collaborations with other centers.

At the preclinical and translational level, VHIO was the first academic test center to incorporate in-house BEAMING liquid biopsy RAS biomarker technology (2015). As highlighted throughout the pages of this Scientific Report, we continue to make significant progress in validating and developing liquid biopsy technologies for the more effective, less invasive monitoring of cancer in real time.

"la Caixa" Foundation

The hub and heart of VHIO's early clinical drug development: our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa"

VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa". Middle image: Elena Garralda, UITM's Director.

VHIO continues to establish itself as a leading reference in progressing drug development and targeted therapies against cancer. Since its inauguration in 2010, the UITM, under the direction of Elena Garralda as Executive Director, alongside Josep Tabernero, has rapidly become as one of the few comprehensive facilities in Europe to up the tempo in transforming latest discovery into improved outcomes for patients.

It has been able to do so not only through the bridging and tight connectivity between health care professionals, VHIO researchers and clinical investigators, but also by identifying novel predictive markers of response to anti-cancer therapies and markers of primary resistance (de novo) and secondary treatment.

Research at the UITM is driven by Elena's Early Clinical Drug Development Group (page 84), and focuses on the development of novel agents based on the molecular profile of each tumor as well as the optimization of therapies using combinations of new drugs with existing ones.

In 2019, this Unit participated in 162 ongoing phase I clinical trials, 23 of which were Basket trials. UITM's facilities, coupled with its multidisciplinary clinical teams, enable VHIO to continuously expand its portfolio of early phase studies including complex trials such as 'baskets'. As an example, this year Elena's team initiated a novel academic study endorsed by the Cancer Core Europe (CCE) Consortium (page 28), and co-funded by pharmaceutical companies. The Basket of Basket (BoB) trial –designed and led by VHIO- integrates cutting-edge molecular prescreening the development of new diagnostic tests such as circulating DNA with the testing of targeted therapies in populations of patients with identified molecular alterations in their tumors and a high probability of benefiting from the selected treatments. For more detailed information see page 29.

This year we opened 46 new trials; 6 as Baskets. 499 patients were recruited, 241 of whom were enrolled in immunotherapy clinical studies. Our Clinical Trials Office (page 120), directed by Gemma Sala and also located in the patient environment of the Vall d'Hebron University Hospital (HUVH), coordinates a large portfolio of Phase I, Baskets, Phase II & III clinical trials. In 2019 the number of patients included in these trials totaled at 1122 across 425 actively recruiting trials.

Research at our Unit has contributed to the development of several tumor cell targeted agents including trastuzumab, pertuzumab, cetuximab, panitumumab, ramucirumab, trifluridine/tipiracil, gefitinib, osimertinib, ceritinib, crizotinib, loratinib and everolimus, among others. Current focus also centers on accelerating and advancing immunotherapies including atezolizumab, nivolumab and pembrolizumab.

Concerning novel immunotherapeutics, our Unit's Taskforce spearheads the early drug development of these agents and cell signaling. Specifically, we focus on second generation immunotherapies, including new cytokines, bispecifics, intratumoral agents, immunomodulatory agents and immune checkpoint inhibitors and combinations, as well as translational research in immuno-oncology in collaboration with several VHIO groups.

Vall d'Hebron Barcelona Hospital Campus | Vall d'Hebron Hospital | VHIO Vall d'Hebron Institute of Oncology

The Vall d'Hebron University Hospital (HUVH): the largest hospital complex in Catalonia and one of the most important in Spain.

VHIO's direct access to cancer patients: crucial to our purely translational research model

Located within the Vall d'Hebron Barcelona Hospital Campus, which also incorporates a trio of research institutes of international reference; Vall d'Hebron Institute of Research (VHIR), CEMCAT – Multiple Sclerosis Center of Catalonia, and VHIO, the Vall d'Hebron University Hospital (HUVH), affords VHIO direct access to patients as well as the entire spectrum of oncology professionals who care for them.

Organized into multidisciplinary and integrated teams, our researchers 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.

Transformative cancer research of excellence

2019 celebrated a record-breaking year in terms of the impact of our cancer science. 333 scientific articles were published by VHIO researchers as corresponding/senior or co-authors with a cumulative Impact Factor (IF) totaling at 3806.

This figure reflects an increase in the importance of VHIO's contribution to the oncology field. To view our selection of top papers in 2019 please refer to pages 43-49 of this Scientific Report. For the complete list of articles published by VHIO researchers and clinical investigators in 2019 see pages 130-147.

Predictive powers, promising biomarkers & novel drug targets

As documented throughout our Preclinical & Translational Program pages (see 62-79) within this Scientific Report, several VHIO studies and research lines continue to mark important progress in advancing cancer modelling, rendering predictive biomarkers more precise, and bringing new drug-targets closer to the clinic.

A few highlights in 2019:

Building on previous VHIO research pioneered by our Gene Expression & Cancer Group (page 70), results from another study* led by Joan Seoane, Co-Program Director of Preclinical and Translational Research at VHIO, and ICREA Research Professor, have shown that the blockade of the multi-functional cytokine LIF induces tumor-infiltrating T Cells to hone in on and eliminate cancer.

Novel agent MSC-1 reactivates an immune call by LIF blockade.

Developed by VHIO, novel agent MSC-1 inhibits LIF and has now been evidenced to have a dual mechanism of action. First, in tumors expressing high levels of LIF, this protein promotes the proliferation of cancer stem cells. LIF blockade eliminates these tumor-initiating stem cells, putting the brakes on metastatic cell spread and cancer recurrence. Additionally, elevated LIF expression disables the anti-tumor alarm system and stops the immune system from thwarting cancer's plans. Blocking LIF reactivates the alarm to call an anti-tumoral immune response.

This research, carried out in collaboration with other VHIO groups and departments at the Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus (page 22), has now culminated in a Phase I clinical trial currently assessing the safety and efficacy of LIF inhibitors in patients across three sites: HUVH, Memorial Sloan Kettering Cancer Center (MSKCC – New York, USA), and the Princess Margaret Cancer Center (Toronto, Canada).

* Pascual-García M, Bonfill-Teixidor E, Planas-Rigol E, Rubio-Perez C, Iurlaro R, Arias A, Cuartas I, Sala-Hojman A, Escudero E, Martínez-Ricarte F, Huber-Ruano I, Nuciforo P, Pedrosa L, Marques C, Braña I, Garralda E, Vieito M, Squatrito M, Pineda E, Graus F, Espejo C, Sahuquillo J, Tabernero J, Seoane J. LIF regulates CXCL9 in tumor-associatedmacrophages and prevents CD8 + T cell tumor-infiltration impairing anti-PD1 therapy. *Nat Commun.* 2019 Jun11;10(1):2416.

In 2019, our Growth Factors Group (page 72), led by Joaquin Arribas, Co-Program Director of Preclinical & Translational Research (page 52) at VHIO and ICREA Research Professor, has initiated a new line of research focused on generating novel chimeric antigen receptors (CARs), as a strategy to use the immune system of patients to eradicate tumors. This approach has been enabled by the insights they previously gained by developing and characterizing bispecific antibodies. Specifically, these CARs are directed against the p95HER2 protein which is only found in some breast and gastric tumors, though completely absent in normal tissues.

Also this year, the group's expanding platform of breast and pancreatic cancer patient-derived experimental models has led them to identify novel mechanisms of resistance to anti-cancer therapies*, as well as seek out biomarkers of sensitivity to precision therapies **, in collaboration with national and international groups.

*Lambies G, Micelio M, Martínez-Guillamon C, Olivera-Salguero R, Peña R, Frías CP, Calderón I, Atanassov BS, Dent SYR, ArribasJ, García de Herreros A, Díaz VM. TGFß-activated USP27X deubiquitinase regulates cell migration and chemoresistance via stabilization of Snail1. *Cancer Res.* 2019.Jan 1;79(1):33-46.

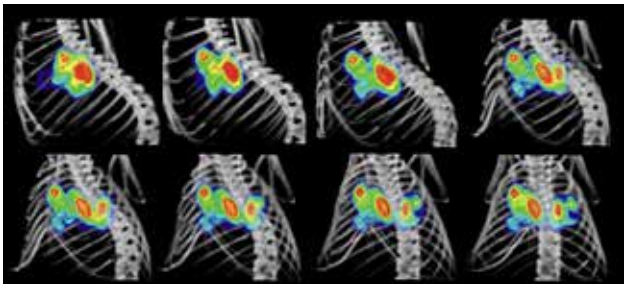
** Kang SA, Guan JS, Tan HJ, Chu T, Thike AA, Bernadó Morales C, Arribas J, Wong CY, Tan PH, Gudi M, Putti TC, Sohn J, Lim SH, Lee SC, Lim YP. Elevated WBP2 expression in HER2-positive breast cancers correlates with sensitivity to trastuzumab based neo-adjuvant therapy: A

Retrospective and Multicentric Study. *Clin Cancer Res.* 2019 Apr 15;25(8):2588-2600.

One translational VHIO study published in 2019* represents an important forward step in driving the Omomyc mini-protein closer to the clinic. Findings first authored by Marie-Eve Beaulieu, CSO and Co-Founder of VHIO-born spin-off Peptomyc, directed by Laura Soucek, PI of our Mouse Models of Cancer Therapies Group (page 74), ICREA Research Professor and Co-Founder and CEO of Peptomyc, evidence the Omomyc mini-protein as the first efficient and tolerable MYC inhibitor for the treatment of non-small cell lung cancer (NSCLC).

For the very first time the authors establish that the Omomyc mini-protein can be purified and administered *in vivo*, rapidly reaching the tumor site. Results show that it successfully inhibits its target, leads to reduced tumor grade and promotes regression of existing disease.

Thanks to Marie-Eve's particular expertise in peptide design and production, the team succeeded in scaling up the purification process of the mini-protein and re-assessing its therapeutic activity via intravenous administration. Its systemic delivery unleashes the anti-cancer potential of Omomyc and extends its application to the treatment of other tumors and metastases.



3D rendering of microPET/CT imaging of lungs of a tumor-bearing mouse 24 hours after intranasal administration of 2.37 mg/kg Omomyc-DFO-89Zr. CT data are displayed in gray scale and Omomyc-DFO-89Zr microPET data in color scale. The color scale is expressed as %ID/g for Omomyc-DFO-89Zr uptake.

The authors suggest that Omomyc may attack tumors not only through the blocking of proliferation and the induction of apoptosis, but also by triggering an immune response. The inhibitor can alter the profile of molecules released by cancer to trick the immune system, and may increase the infiltration of T lymphocytes into the tumor. This is relevant since immunotherapy is showing increasing promise in the treatment of several tumor types, but not all. The potential capacity of Omomyc to recruit immune cells at the tumor site, 'spoilered' in the study, indicates that it could also synergize and resensitize resistant tumors to immune-based therapies.

* Beaulieu ME, Jauset T, Massó-Vallés D, Martínez-Martín S, Rahl P, Maltais L, Zacarias-Fluck MF, Casacuberta-Serra S, Serrano Del Pozo E, Fiore C, Foradada L, Cano VC, Sánchez-Hervás M, Guenther M, Romero Sanz E, Oteo M, Tremblay C, Martín G, Letourneau D, Montagne M, Morcillo Alonso MÁ, Whitfield JR, Lavigne P, Soucek L. Intrinsic cell-penetrating activity propels Omomyc from proof of concept to viable anti-MYC therapy. *Sci Transl Med.* 2019 Mar 20;11(484):eaar5012.

VHIO's Stem Cells & Cancer Group (page 76), directed by Héctor G. Palmer, has made important progress in identifying molecular mechanisms conferring sensitivity or resistance to therapies in order to more precisely stratify patients for enrollment in clinical trials.

More specifically, working in close collaboration with other VHIO groups and pharmaceutical companies, they seek to identify the molecular culprits that are responsible for the sensitivity or resistance to therapies blocking Wnt/beta-catenin, Notch, PI3K/AKT, EGFR/LGR5 or BRAF/MEK/ERK oncogenic signals.

As an example, in collaboration with other Spanish investigators and VHIO teams including our Gastrointestinal & Endocrine Tumors Group (PI: Teresa Macarulla - page 88), Cancer Genomics (PI: Ana Vivancos – page 112), Molecular Oncology Group (PI: Paolo Nuciforo - page 114), Early Clinical Drug Development Group (PI: Elena Garralda – page 84), they have studied epigenetic EGFR gene repression and the conference of sensitivity to therapeutic BRAFV600E blockade in colon neuroendocrine carcinomas; results of which were published this year*.

Based on this research, they are now designing new prescreening tests for a genetic-guided enrolment of patients in clinical trials. Importantly, their findings are helping to define new rational drug combinations to treat cancer patients with progressive disease.

*Capdevila J, Arqués O, Hernández Mora JR, Matito J, Caratù G, Mancuso FM, Landolf S, Barriuso J, Jimenez-Fonseca P, Lopez Lopez C, Garcia-Carbonero R, Hernando J, Matos I, Nuciforo P, Hernández-Losa J, Esteller M, Martínez-Cardús A, Tabernero J, Vivancos A, Palmer HG. Epigenetic EGFR Gene Repression Confers Sensitivity to Therapeutic BRAFV600E Blockade in Colon Neuroendocrine Carcinomas. *Clin Cancer Res.* 2020 Feb 15;26(4):902-909. Epub 2019 Oct 31.

Instituto de Salud Carlos III

Our Experimental Therapeutics Group, led by Violeta Serra (page 68), continues to mark important progress in gauging response to PARP Inhibitors (PARPi). Crucially, they have initiated the clinical validation of their *RAD51predict* test which is an immune-based assay performed on FFPE tumor sections.

Reflective of its promise in better gauging efficacy of PARPi in individual patients and eventual implementation as a diagnostic test, these efforts have most recently been awarded by the ERA PerMed progamme – an ERA-Net Cofund. This international project counts on the expertise of 32 partners from 23 countries, and is co-supported by the European Commission (Coordinator: *Instituto de Salud Carlos III* – ISCIII). The test is also being developed thanks to additional funding received this year from the la Caixa Foundation's *CaixaImpulse* Consolidate 2019 program.

CaixaImpulse

Directed by Violeta Serra, and led by Alba Llop, Post-Doctoral Fellow of our Experimental Therapeutics Group, the project not only centers on using

RAD1 protein as a biomarker to help personalize cancer therapy, more precisely and rapidly predicting those patients who would be most likely to benefit from PARPi, better guide stratification in clinical trials, as well as extend PARPi for the treatment of additional tumor types beyond breast and ovarian cancers.

This present research builds on the successes of several previous projects, including the previous PARPiPRED (which was also funded by *CaixaImpulse*), aimed at identifying clinical biomarkers of sensitivity to PARP inhibitors, and is spearhead by Violeta Serra's Experimental Therapeutics Group, in collaboration with Judith Balmaña's Hereditary Cancer Genetics Group at VHIO (page 94), and our Breast Cancer Group (PI, Cristina Saura – page 82).

Reflective of VHIO's expertise in the PARPi field, VHIO faculty, including Violeta Serra, Judith Balmaña, Marta Castroviejo, Ana Oaknin (PI of VHIO's Gynecological Malignancies Group (page 92), co-authored an elegant review* on a decade's development of these therapies, where we now stand, and where to next. This publication was first authored by Joaquin Mateo, PI of our Prostate Cancer Translational Research Group (page 98), who leads research aimed at potentiating PARPi in the treatment of prostate cancer.

*Mateo J, Lord CJ, Serra V, Tutt A, Balmaña J, Castroviejo-Bermejo M, Cruz C, Oaknin A, Kaye SB, de Bono JS. A decade of clinical development of PARP inhibitors in perspective. *Ann Oncol.* 2019. Sep 1;30(9):1437-1447.

One of the main challenges in more effectively treating triple-negative breast cancer (TNBC) is the acquisition of resistance to conventional chemotherapeutics. Research led by Sandra Peiró, Principal Investigator of our Chromatin Dynamics in Cancer Group (page 66), promises novel weaponry to more effectively combat cancer drug resistance in this particular tumor type.

This multi-center, Spanish study*, also carried out in collaboration with VHIO's Growth Factors Group (PI: Joaquin Arribas, page 72) shows that, when compared to other breast cancer subtypes, the DNA of TNBC cells is much more compacted which renders it resistant to therapy. Results also indicate that chromatin decompaction could help to potentiate current therapies.

More specifically, the investigators identified oxidation of histone H3 as a key element in the induction of DNA compaction as well as discovered an association between compaction and resistance to anticancer agents.

They also discovered that LOXL2 inhibition could prevent chromatin compaction from occurring. This is particularly relevant since this compaction seems to frequently occur in TNBC, which hinders therapies from accessing the nucleus of cancer cells. While this occurs in other types of breast cancer, they found that in those patients with the triple-negative subtype who show most resistance to conventional therapies, LOXL2 is present in high quantities, suggesting its role as a mechanism of resistance.

* Cebrià-Costa JP, Pascual-Reguant L, Gonzalez-Perez A, Serra-Bardenys G, Querol J, Cosín M, Verde G, Cigliano RA, Sanseverino W, Segura-Bayona S, Iturbide A, Andreu D, Nuciforo P, Bernado-Morales C, Rodilla V, Arribas J, Yelamos J, de Herreros AG, Stracker TH, Peiró S. LOXL2-mediated H3K4 oxidation reduces chromatin accessibility in triple-negative breast cancer cells. *Oncogene.* 2020 Jan;39(1):79-121. Epub 2019 Aug 28 2019.

Teaching an old protein new tricks, VHIO's Tumor Biomarkers Group (page 78), directed by Josep Villanueva, has continued to pursue the potential of the HMGA1 protein as novel biomarker and drug target in breast cancer. Notably, his team has focused on developing monoclonal antibodies against this protein that could be used in the near future in cancer diagnostics and therapeutics.

Their expertise in this field led to a review article this year* exploring the future clinical implications of the unexpected secretion of HMGA1 in triple-negative breast cancer (TNBC).

* Méndez O, Pérez J, Soberino J, Racca F, Cortés J,Villanueva J. Clinical Implications of Extracellular HMGA1 in Breast Cancer. *Int J Mol Sci.* 2019. 20(23), 5950.

VHIO's Core Technologies Program (pages 110-117), incorporates our Cancer Genomics, Molecular Oncology, and Proteomics Groups led by Ana Vivancos, Paolo Nuciforo, and Francesc Canals respectively. They 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.

As an example in 2019, research led by Paolo Nuciforo, Principal Investigator of our Molecular Oncology Group (page 114), co-authored by our Director, Josep Tabernero, and VHIO PIs Ana Vivancos (Cancer Genomics Group, page 112) and Rodrigo Dienstmann (Oncology Data Science Group – ODysSey, page 96), explored the promise of using targeted multiplex proteomics (TMP) as a novel approach to simultaneously measure a panel of proteins implicated in oncogenic processes, tumor suppression, drug metabolism and resistance. Also including tumor differentiation markers, this tool could guide standard diagnostic decision-making as well as render the selection of new targeted therapies and immune-based therapeutics for patients with metastatic colorectal cancer (mCRC) more precise.

In the article*, the authors concisely review the strengths and limitations of the current 'gold standard' in accurately measuring multi-proteins in experimental samples, immunoassay, and outlines the downside of applying targeted proteomics using selected reaction monitoring mass spectrometry (SRM-MS). The researchers, also counting on the expertise of other VHIO investigators as well as the Vall d'Hebron University Hospital (HUVH) Pathology Department (directed by Santiago Ramón y Cajal), describe their findings by sub-chaptering each stage of their analyses.

Representing the very first study to measure the impact of quantitative targeted proteomics in precision oncology

against mCRC, they analyzed protein biomarker profiles and integrated the results obtained with the available clinical, pathological and genomic data towards advancing precious insights into predictive and prognostic makers.

Not only does this signpost that proteomics-steered drug development will expand treatment options for patients who are eligible to participate in early phase clinical trials, particularly considering the increasing emergence of promising antibody-drug conjugates (ADCs) and immune-based treatments, but also rings in the repurposing of proteomics as powerful anti-cancer armory in precision oncology.

*Serna G, Ruiz-Pace F, Cecchi F, Fasani R, Jimenez J, Thyparambil S, Landolfi S, Elez E, Vivancos A, Hembrough T, Tabernero J, Dienstmann R, Nuciforo P. Targeted multiplex proteomics for molecular prescreening and biomarker discovery in metastatic colorectal cancer. *Sci Rep.* 2019 Sep 19;9(1):13568.

VHIO's practice-changing data in 2019: at a glance

In addition to the myriad clinical highlights documented throughout this report, along with our various programs and units highlighted in the pages that follow this chapter, just some of the practice-changing data has been hand-picked by our Director, Josep Tabernero. First, five studies highlighted in his Foreword to this report (see sub-section *Developing kinder & less disruptive treatments*, pages 10-13), and second, his additional selection featuring in his *From the Program Director* (page 56).

Concerning the former, here is a sample of our Clinical Research Program (80-109) studies that made the headlines in 2019:

Novel treatment combination for patients with BRAF-mutant metastatic colorectal cancer (page 10), led by our Gastrointestinal & Endocrine Tumors Group (page 88), headed by Teresa Macarulla and directed by Josep Tabernero:
Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, Wasan H, Ciardiello F, Loupakis F, Hong YS, Steeghs N, Guren TK, Arkenau HT, Garcia-Alfonso P, Pfeiffer P, Orlov S, Lonardi S, Elez E, Kim TW, Schellens JHM, Guo C, Krishnan A, Dekervel J, Morris V, Calvo Ferrandiz A, Tarpgaard LS, Braun M, Gollerkeri A, Keir C, Maharry K, Pickard M, Christy-Bittel J, Anderson L, Sandor V, Tabernero J. 2019. *N Engl J Med.* 381(17): 1632 – 1643.

The promise of prolonged progression-free survival in newly diagnosed patients with high-grade ovarian cancer (page 11), co-authored by Ana Oaknin, Principal Investigator of our Gynecological Malignancies Group (page 92):
Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, Okamoto A, Moore KN, Efrat Ben-Baruch N, Werner TL, Cloven NG, Oaknin A, DiSilvestro PA, Morgan MA, Nam JH, Leath CA, Nicum S, Hagemann AR, Littell RD, Cella D, Baron-Hay S, Garcia-Donas J, Mizuno M, Bell-McGuinn K, Sullivan DM, Bach BA, Bhattacharya S, Ratajczak C°K, Ansell PJ, Dinh MH, Aghajanian C, Bookman MA. 2019. *N Engl J Med.* 381(25): 2403 - 2415.

PARPi maintenance therapy against BRCA+ Metastatic Pancreatic Cancer (page 11), co-authored by Teresa Macarulla, Principal Investigator of our Gastrointestinal & Endocrine Tumors Group (page 88):
Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. Golan T; Hammel P; Reni M; Van Cutsem E; Macarulla T; Hall MJ; Park JO; Hochhauser D; Arnold D; Oh DY; Reinacher-Schick A; Tortora G; Algül H; O'Reilly EM; McGuinness D; Cui KY; Schlienger K; Locker GY; Kindler HL. 2019. *N Engl J Med.* 381(4): 317 - 327.

Prolonging PFS in previously untreated PD-L1-positive metastatic renal cell carcinoma patients (page 12), co-authored by Cristina Suarez, Medical Oncologist and Clinical Investigator of our Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site directed by Joan Carles (page 90):
Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. Rini BI, Powles T, Atkins MB, Escudier B, McDermott DF, Suarez C, Bracarda S, Stadler WM, Donskov F, Lee JL, Hawkins R, Ravaud A, Alekseev B, Staehler M, Uemura M, De Giorgi U, Mellado B, Porta C, Melichar B, Gurney H, Bedke J, Choueiri TK, Parnis F, Khaznadar T, Thobhani A, Li S, Piault-Louis E, Frantz G, Huseni M, Schiff C, Green MC, Motzer RJ, IMmotion151 Study Group. 2019. *Lancet.* 393(10189): 2404 – 2415.

Clinical trial design in the era of precision oncology (page 12), led by VHIO and co-authored by Tabernero, VHIO's Director, Jordi Rodón, Associate Investigator of VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 122), and Irene Braña, Phase I Investigator at the same Unit:
Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial. Rodon J, Soria JC, Berger R, Miller WH, Rubin E, Kugel A, Tsimberidou A, Saintigny P, Ackerstein A, Braña I, Loriot Y, Afshar M, Miller V, Wunder F, Bresson C, Martini JF, Raynaud J, Mendelsohn J, Batist G, Onn A, Tabernero J, Schilsky RL, Lazar V, Lee JJ, Kurzrock R. 2019. *Nat Med.* 25(5): 751 - 751.

And there's a lot more >>>

For more 2019 highlights selected by our Preclinical & Translational Research Co-Program Directors and Director of Clinical Research Program, led by Joaquin Arribas, Joan Seoane, and Josep Tabernero, respectively, see pages 50-59, as well as this year's Foreword compiled by Josep Tabernero - pages 6-15.

Please also refer to our Core Technologies Program (pages 110-117) as well as our individual VHIO group pages. Compiled by each respective Principal Investigator, they provide a summary of strategic goals, current research lines, as well as their most important developments/contributions and pick of papers for 2019.

VHIO's trio of institutional programs: delivering on the promise of precision medicine and potentiating novel therapies and approaches

Among the many studies spearhead by VHIO investigators, several are supported thanks to our three institutional programs fueled by our private patrons, the FERO Foundation, "la Caixa" Foundation, and BBVA Foundation (for more information on all our patrons and institutional supporters see pages 17-20).

These three essential programs are set to significantly impact on our ongoing research efforts across many different VHIO groups that collectively seek to solve cancer sooner. They are as follows:

fundación fero
Investigando por un futuro sin cáncer

FERO Foundation: driving advanced molecular diagnostics against cancer

Co-led by VHIO's Director, Josep Tabernero in collaboration with Ana Vivancos, Paolo Nuciforo, and Rodrigo Dienstmann, Principal Investigators of our Cancer Genomics (page 112), Molecular Oncology (page 114), and Oncology Data Science (ODysSey- page 96) Groups, respectively, our VHIO-FERO Advanced Molecular Diagnostics Program (DIAMAV), is powered by the essential support received from one of our patrons, the FERO Foundation. This program seeks to advance molecular profiling in patients in order to more effectively match personalized treatment strategies based on the genomic or pathologic profile of each individual patient and the molecular makeup of their disease.

It is thanks to the backing received from FERO that VHIO has both established itself as a reference in prescreening and oncogenomics in Europe, and continues to extend its enabling technologies and platforms to an increasing number of individuals. More specifically, driven by VHIO's Prescreening Program which also counts on the expertise of Elena Garralda, Principal Investigator of Early Clinical Drug Development (page 84), along with Susana Aguilar and Jenifer Gonzalez, molecular profiling is performed in up to 1500 patients each year.

Our researchers and clinical investigators identify specific molecular risk factors and better predict the potential efficacy of specific agents tailored to each particular tumor. Additionally, this knowledge better guides our multidisciplinary teams to assess and establish patients' suitability for inclusion in early phase clinical trials led by VHIO's Research Unit for Molecular Therapy of Cancer (UTIM) – "la Caixa", also headed by Elena Garralda.

Our VHIO-FERO DIAMAV Program enables us to lead one of the few centers in Europe to run such a comprehensive program, ensure that more of our patients can ultimately benefit from our powerful technology programs and approaches, further advance research into the more effective and less invasive tracking of cancer by liquid biopsy, as well as develop cancer diagnostics for the early detection of disease.

"la Caixa" Foundation

"la Caixa" Foundation: advancing research toward rendering anti-cancer medicines more precise

Building on the successes of the two previous VHIO-"la Caixa" Institutional 3-year Programs, at the end of 2019 we announced a new 4-year VHIO-"la Caixa" Advanced Oncology Research Program (2020-2023). Marking the UITM turning ten in 2020 as well as the ringing in of a new VHIO decade, support received will further spur our purely translational and multidisciplinary teams to develop more potent and precise anti-cancer medicines, fortify existing research lines as well as initiate new projects to lead frontier research in some of the most relevant and rising focus fields in precision oncology.

More specifically, our transformative research lines will continue to center of those areas showing particular promise in solving multiple questions that stand in the way of more effectively combating cancer. Just some of these scientific directions will include our continued unpicking of the complex role that the microbiome plays in cancer development, driving 'big data'-derived insights, and devise and integrate cutting-edge platforms incorporating bioinformatics, biostatistics and machine learning applications in cancer prognosis and prediction, as well as harness the potential of Artificial Intelligence (AI) in the development of individually matched therapies.

In parallel with our plans to expand VHIO's portfolio of clinical trials performed at our Research Unit for Molecular Therapy of Cancer – "la Caixa", directed by Elena Garralda (page 122), that have led and/or contributed to the approval of some 30 anti-cancer agents by the U.S. Food and Drug Administration (FDA), this Program will enable us to further advance and apply novel anti-cancer approaches and armory including liquid biopsy, RNA expression analysis, immune-based therapies, bispecific antibodies, oncolytic virus, and intratumoral therapy.

These efforts are driven thanks to the expertise of several VHIO groups and teams including our Early Clinical Drug Development (page 84), Cancer Genomics (page 112), Molecular Oncology (page 114), Oncology Data Science (ODysSey – page 96) Groups, led by Elena Garralda, Ana Vivancos, Paolo Nuciforo, and Rodrigo Dienstmann, respectively.

The matched dedication of our clinical and translational investigators across all VHIO groups, as well as VHIO's Clinical Trial Office (page 120), headed by Gemma Sala, Clinical Trials Support Office (page 129), managed by Susana Muñoz, Clinical Research Oncology Nurses (page 124), spearhead by Nines Pañuelas, and Clinical Research Oncology Pharmacy Unit (page 126), led by Maria Queralt Gorgas, has also made the past decade's total of 1060 Phase I and 1076 Phase II insightful studies possible.

Engineered to support education, trigger essential debate and promote data exchange across borders, the program is also dedicated to organizing expert seminars and international scientific meetings to come. As an example, our VHIO –"la Caixa" Scientific Seminars Series (page 38), launched in 2019. This educational program welcomes internationally renowned researchers and clinical investigators to VHIO to share, discuss and debate latest insights, discovery and next directions in oncology with our students, postdocs and senior faculty from our preclinical, translational and clinical research groups.

Fundación BBVA

BBVA Foundation: driving powerful programs to spur VHIO's avant-garde translational research in precision oncology

Considering the tremendous successes of the very first VHIO-BBVA Foundation Program on Tumor Biomarkers Research that launched back in 2011, VHIO and the BBVA Foundation renewed their agreement in in 2017. Building on the achievements of the first program, our Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI), represents an important forward step in advancing agents that inhibit checkpoint regulation of the immune system, better understanding mechanisms of resistance and response to these therapies, and prioritizing the early development of those drugs showing most promise.

Under the leadership of our Director, Josep Tabernero, this ambitious project counts on the expertise of VHIO's Elena Garralda (PI of VHIO's Early Clinical Drug Development and Director of our Research Unit for Molecular Therapy of Cancer (UITM) – pages 84 and 122), who heads up CAIMI's clinical research, Alena Gros (PI, VHIO's Tumor Immunology and Immunotherapy – page 108), who takes the lead on translational research, and Ana Vivancos (PI of our Cancer Genomics – page 112) who directs our internationally recognized Prescreening Program in collaboration with Paolo Nuciforo (PI of VHIO's Molecular Oncology Group – page 114), and Rodrigo Dienstmann (PI of our Oncology Data Science – ODysSey Group, page 96), along with Susana Aguilar and Jenifer Gonzalez.

VHIO has co-founded various translational projects linked to the early clinical development phases of immunotherapy. These pioneering endeavors are currently underway. Just some focus areas include the development of cell-based therapies such as killer T cells for non-responders to current immunotherapies, characterizing hyperprogressive disease with immunotherapy to advance insights into this phenomenon, as well as establishing a radiomic signature to predict response to immunotherapy, in collaboration with Raquel Perez-Lopez, PI of our Radiomics Group (page 102).

At 'home' and away: advancing cancer science and medicine in collaboration

Accelerating progress through team science

VHIO's expert and interdisciplinary taskforces, coordinated by Alejandro Piris (page 128), our Scientific Manager, comprise comprehensive teams of oncologists, pathologists, other MD disciplines, preclinical and translational researchers, clinical research nurses, data curators and miners as well as study coordinators, and project managers, among others.

Currently counting nine groups covering colorectal, breast, lung, gynecologic, prostate, melanoma, pancreatic, gastric tumor types as well as immunotherapy and onco-imaging, our taskforces regularly convene to synergize efforts, boost collaborations among groups and between specialists, and continuously revise respective circuits and ethics toward advancing cancer science and medicine.

VHIO's translational task-forcing.

Updating on VHIO's participation in international consortia of excellence

Cancer Core Europe

Cancer Core Europe (CCE) is a unique partnership aimed at addressing the cancer care research continuum. Launched in 2014, this working consortium represents a critical mass of activity for the successful integration of all cancer care information, clinical research and outcome research, led by the 6 founding partners and European comprehensive cancer centers of excellence: the Gustave Roussy Cancer Campus Grand Paris (Villejuif, France), Cambridge Cancer Centre (Cambridge, UK), Karolinska Institute (Stockholm, Sweden), Netherlands Cancer Institute – NKI (Amsterdam, The Netherlands), National Center for Tumor Diseases – DKFZ-NCT (Heidelberg, Germany), The National Cancer Institute of Milan (Italy), and VHIO.

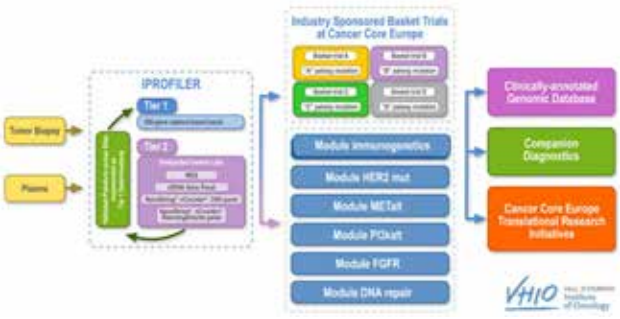
CEE promotes the pooling and exchange of expertise, research findings, common platforms and processes, and empowers researchers and clinicians to rapidly exploit this trove of biological insights and clinical data for the benefit of patients.

Endorsed by CCE and officially launched during its 4th Annual Meeting, hosted by VHIO, the Basket of Baskets (BoB) two-stage clinical trial study promises a more flexible and adaptive model in order to significantly accelerate patients' access to an array of novel therapeutics. As the

first European multi-modular academic trial, BoB integrates molecular prescreening, the development of novel diagnostic tests including ctDNA, with the assessment of targeted therapies matched to those patients who will be most likely to benefit from them.

BoB is divided into two separate parts: advanced molecular diagnosis or screening, i-Profiler, and the therapeutic phase, i-Basket. In the former patient tumor samples are analyzed for genetic profiling to identify the specific alterations of each individual tumor, followed by bioinformatics analyses to gauge the clinical relevance of a particular treatment tailored to these alterations, with the option of adding extra modules with other anti-cancer medicines currently under development.

Patients identified with the alteration/s included in BoB's i-Basket phase, and who meet the inclusion criteria, enter this second part. Each module focuses on a different treatment (either as monotherapy or in combination), and will have a different sponsor/coordinator. The first module is evaluating atezolizumab in a molecularly-selected population recruited this year, 2019, and funding to assess FGFR inhibition in specific patients has been secured.



Pioneering multi-modular trial design in oncology: the two-part Basket of Baskets (BoB) clinical study.

At VHIO, this novel trial is being carried out at our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 122), directed by Elena Garralda, and counts on the expertise of several VHIO investigators including Jordi Rodón and Irene Braña, Associate Investigator and Phase I Investigator of the same Unit, respectively, as well as Rodrigo Dienstmann, PI of VHIO's Oncology Data Science Group (ODysSey – page 96), and Ana Vivancos who leads our Cancer Genomics Group (page 112). Ana's group is also appointed as co-lead of CCE's Genomics Taskforce and is responsible for the alignment of genomic testing across all member institutions.
www.cancercoreeurope.eu

Worldwide Innovative Networking in personalized cancer medicine

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 39 leading organizations representing all stakeholders in personalized cancer medicine covering 21 countries and 4 continents, united by their vision to deliver on the promise of effective, personalized cancer medicine to patients worldwide.

Under the tagline WINning together, WIN was formed on the premise that members can accomplish more together than each organization can achieve working alone. Aimed at improving cancer patients' survival and quality of life, WIN members also collaboratively design and carry out global studies designed to achieve breakthroughs for cancer patients across the globe.

In 2019, results of WINTHER clinical trial, Genomic and transcriptomic profiling expands precision medicine -the first study pioneered by the WIN Consortium- published in *Nature Medicine**. Led by VHIO, findings showed that RNA profiling together with DNA testing matches more patients with advanced cancer to personalized anti-cancer therapies than DNA profiling for tumor mutations alone.

Carried out in collaboration with other leading members of WIN, co-authors including Josep Tabernero, VHIO's Director, Jordi Rodón, Clinical Investigator at the MD Anderson Cancer Center and Associate Investigator of VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 122), and Irene Braña, Phase I Investigator of the same Unit, showed that patients treated with a drug or regimen more closely matched to the molecular profile of their respective tumors, do better. By assessing RNA as an important adjunct to DNA profiling for determining precision treatments, WINTHER rings in a new era for personalized medicine in oncology.

Rodon J, Soria JC, Berger R, Miller WH, Rubin E, Kugel A, Tsimberidou A, Saintigny P, Ackerstein A, Braña I, Loriot Y, Afshar M, Miller V, Wunder F, Bresson C, Martini JF, Raynaud J, Mendelsohn J, Batist G, Onn A, Tabernero J, Schilsky RL, Lazar V, Lee JJ, Kurzrock R. Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial. *Nat Med.* 2019. 25(5): 751 - 751.
www.winconsortium.org

New in 2019

CANCER RESEARCH UK | GRAND CHALLENGE OPTIMISTICC

Announced at the beginning of 2019, the OPTIMISTICC Grand Challenge -Opportunity To Investigate the Microbiome's Impact on Science and Treatment In Colorectal Cancer- is a 5-year consortium funded by Cancer Research UK's Grand Challenge, led by Matthew Meyerson, the Dana-Farber Cancer Institute-Harvard Medical School, and Wendy Garrett, Harvard T.H. Chan School of Public Health (USA).

Aimed at better understanding the difference between a healthy microbiome and a microbiome associated with the development of colorectal cancer, the co-investigators from the US, Canada, the UK, Netherlands, and Spain, are seeking to identify ways to manipulate this collection of microorganisms to better prevent and treat cancer. They are exploring this through clinical trials of new interventions based on the research results.

It is thanks to the Grand Challenge Funding that the project partners, including VHIO, are able to pool the necessary expertise in order to establish how the microbiome influences a cancer's response to treatment, develop new treatments that alter the microbiome, and

decipher how an individual's external environment may affect their microbiome.
www.optimisticc.org

EUCanCAN – the European-Canadian Cancer Network, led by the Barcelona Supercomputing Center - BSC (Spain), comprises a total of 18 partners from 5 different countries to pursue the homogeneous analysis, management and exchange of genomic-driven oncology data to advance precision medicine in cancer.

Jointly funded by the European Union's Horizon 2020 research and innovation programme and the Canadian Institutes of Health, this 4-year project is coordinated by David Torrents at the BSC, and strives to provide a functional platform for federated genome analysis systems towards efficiently analyzing, managing, sharing and reusing mass genomic data at the global level.

The participating reference nodes, including VHIO, seek to process, store and share between 30-35 thousand patient samples across various tumor types. This consortium also promises to drive discovery into robust and clinically-relevant patterns of genomic variation in cancer, including predictive biomarkers.

Using existing and newly generated genomic and clinical insights within the consortium, the feasibility of EUCanCAN infrastructures and their interoperability are being tried and tested. This analysis is being carried out in partnership with some of the most active centers throughout Europe and Canada in genomic oncology across locally selected sites.

As an indicator of both the quality and promise of this project, the Global Alliance for Genomics and Health (GA4GH), selected it as one among seven world leading genomic data initiatives as its new Driver Projects for 2019
www.eucancan.com

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825835.

Immune-Image is a 22 stakeholder-strong consortium incorporating public and private partners across 9 countries, including VHIO and the Vall d'Hebron Institute of Research (VHIR) from Spain. Powered by the Innovative Medicines Initiative Joint Undertaking (IMI 2 JU), this initiative is led by Roche and coordinated by Albert Windhorst, Amsterdam University Medical Center (VUmC), The Netherlands. Set to run for an initial duration of five years, this project is entitled Specific imaging of immune cell dynamics using novel tracer strategies, and seeks to develop a novel non-invasive imaging strategy for assessing immune cell activation and dynamics in oncology and inflammatory disease.

Main deliverables include developing clinically validated radio-and optical immunotracers for the monitoring and measurement of immune cell presence, activation status and trafficking, and designing and implementing a ready-to-use sustainable molecular imaging platform, incorporating standardized protocols, best practices, quantitative image analyses, immune-based tracking design and development.

By establishing a sustainable and flexible platform for molecular imaging of immune cells dynamics using a wide range of new tracer approaches, the team aims at potentiating immune-based therapies in precision oncology by enabling the 'smart' monitoring of these novel anti-cancer medicines.
www.immune-image.eu

Funded by the European Union's Horizon 2020 research and innovation programme, the CELAC and European Consortium for a Personalized Medicine Approach to Gastric Cancer (LEGACy) is a 4-year project spearhead by Andrés Cervantes, the INCLIVA Health Research Institute (Spain), in partnership with 10 other members across 9 different countries including VHIO.

Focused on advancing personalized medicine against gastric cancer, this project aims to improve diagnosis and treatment by using data obtained through extensive research in four EU countries and four countries within the Community of Latin American and Caribbean States (CELAC) States, by applying personalized medicine at the three levels of prevention. This consortium seeks to implement a personalized medicine strategy at the first level of prevention, improve early gastric cancer detection at the second level of prevention, and improve treatment through the identification of high-risk populations.

Partners from Argentina, Belgium, Chile, Germany, Mexico, The Netherlands, Paraguay, Portugal and Spain are working together to design a cost-effective algorithm based on tumor biology data. Analysing more than 3 thousand cases in total, the project will also bring new insights into gastric cancer subtyping.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825832.

RADprecise

RADprecise - Personalized radiotherapy: Incorporating cellular response to irradiation in personalized treatment planning to minimise radiation toxicity, is supported by funding received through ERAPerMed's co-funded Joint Translational Call 2018* and was founded in 2019 by 7 leading organisations from Spain, Italy, Germany and France. This 3-year project aims to render radiotherapy more precise by incorporating data from finely-tuned predictive models to pre-identify toxicity based on

insights from multiple biomarkers of radiosensitivity in individual patients.

Led by Principal Investigator, Jenny Chang-Claude from the German Cancer Research Center (DKFZ), project partners are applying findings at the clinical level by integrating a treatment planning system. Using parametric models and machine learning, clinical investigators from academia and health research, in collaboration with small and medium enterprises as well as patient advocates, are applying new biological data as well as readily available genomic information to develop models that can more precisely envisage adverse effects from radiotherapy to be validated in independent samples.

At preclinical level, RADPrecise's predictive models will be key to tailoring therapy to each patient's sensitivity. Given that an estimated 5-10 per cent of all patients receiving radiotherapy either as primary treatment or in combination will suffer severe adverse effects, with a further fifty per cent thought to experience less severe yet burdensome ones, this project prioritizes the identification of radiosensitive patients.
www.erapermed.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 779282.

For a complete overview of VHIO's participation in several Consortia of excellence see pages 151-158.

Strengthening our research, growing teams & fortifying facilities

As our Institute goes from strength to strength, and further develop its research lines and projects based on defined strategic directions, we continue to expand our scientific faculty as well as scientific support units and teams.

Illustrative of this growth, César Serrano who is a Medical Oncologist and Clinical Investigator of our Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site Group (directed by Joan Carles, page 90), took the reins as Principal Investigator of VHIO's new Sarcoma Translational Research Group (page 104).

His group will seek to identify the critical molecular mediators of oncogenic signaling sarcomas, characterize response and resistance mechanisms to targeted therapies against these tumor types, as well as preclinically model and validate therapeutic strategies toward improving outcomes for patients in the clinic.

César Serrano, PI of VHIO's Sarcoma Translational Research Group which launched in early 2019.

Alejandro Piris, Scientific Manager, VHIO's Scientific Coordination Area.

Since it was established back in 2010, VHIO's Scientific Coordination Area (see page 128) has evolved from an office providing basic support to a highly professional team with experience in both cancer research and project management. Directed by Alejandro Piris, his scientific coordination teams offer a range of personalized and professional support services to all VHIO groups, including identifying projects and helping to prepare proposals – all of which enable our researchers to file successful applications.

Also incorporating our Clinical Trials Support Office, led by Susana Muñoz, efforts center on identifying key opportunities, requirements and elements that should be taken into account, establish project deadlines, lead and coordinate proposal writing, and devise and implement contingency plans.

In 2019 Alejandro's Area was awarded by the Catalonian Department of Health's Strategic Plan for Research and Innovation in Health (PERIS). Newly introduced to PERIS' Call this year, his team has received a *Go Europe* grant which promote international R&D&I (see page 160). This funding awards research support units of accredited research institutes and centers belonging to the CERCA Institute (*Institució CERCA Centres de Recerca de Catalunya*), in order to extend their global reach, increase participation in international projects -EU's Horizon 2020 Research and Innovation programme in particular- as well as improve their success rate and returns achieved through competitive grants.

Completed in 2019: the building of our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" – Clinical Research Onco-Hematology Unit. Pictured here, Maria Queralt Gorgas, Clinical Director of VHIO's Clinical Research Oncology Pharmacy Unit.

It is thanks to the additional support received from the "la Caixa" Foundation (see page 19) that the building of the new home of our Clinical Research Oncology Pharmacy Unit was completed in 2019. Providing the much needed additional space and equipped with the very latest technologies, the Molecular Therapy of Cancer (UITM) – "la Caixa" (page 122) – Clinical Research Onco-Hematology Unit will enable Maria Queralt Gorgas' team (page 126) to provide even higher quality pharmaceutical

care and services, as well as continue to meet all regulatory requirements.

Awards & Recognitions 2019

International

The Web of Science Group announced its who's who on the annual and global Highly Cited Researchers list for 2019, curated by the Institute for Scientific Information. Featuring among the 6216 top drawer leading researchers across the main 21 fields of the sciences and social sciences covered by the Essential Science Indicator (ESI), are VHIO's Director, Josep Tabernero, and Enriqueta Felip, Principal Investigator of our Thoracic Tumors & Head and Neck Cancer Group.

For the fourth consecutive year Josep was selected for his exceptional advancements in cancer research under the category of Clinical Medicine that lists a total of 436 named leaders this year. Moving from her first listing under the Cross-Field category in 2018, Enriqueta joined Josep under the same field.

European

European Commission | Horizon 2020 European Union funding for Research & Innovation

Just as our Director, Josep Tabernero, was completing his two-year term as President of the European Society of Medical Oncology (ESMO), 2018-2019, his renowned expertise and leadership as an international trailblazer in cancer science and medicine was called upon by EU's Horizon 2020 program.

Succeeding the European Commission's Horizon 2020 funding program for research and innovation, Horizon Europe is an ambitious €100 billion undertaking consisting of three main pillars – Excellent Science, Global Challenges and European Industrial Competitiveness, Innovative Europe, as well as the overarching ambition of Widening Participation and Strengthening the European Research Area.

Within Horizon Europe's framework, five key research and innovation missions have been identified to increase the effectiveness of funding by pursuing clearly defined targets. They are: Adaptation to climate change including societal transformation, Cancer, Climate-neutral and smart cities, Healthy oceans, seas, coastal and inland waters, oil health and food.

Each mission has an appointed Board comprised of acclaimed leaders to shape and spur new research and innovation. All missions are also flanked by their respective Assemblies consisting of up to 30 high-level experts. The main role of these bodies is to help guide the Board members and provide an additional pool of ideas and knowledge to contribute to the successes of the respective missions. The Cancer panel consists of 26 members, including our Director, Josep Tabernero.

National

Josep Tabernero (left). Francesc Bosch (right).

In 2019 both VHIO's Director, Josep Tabernero, and Francesc Bosch, Principal Investigator of our Experimental Hematology Group, featured among the Spanish edition of Forbes magazine's pick of the 100 most influential leaders in healthcare across Spain.

Spanning 25 different specialties, Josep and Francesc were recognized under the categories of oncology and hematology, respectively. This accolade salutes their determined efforts aimed at advancing cancer research, precision medicine and care.

SEOM
Sociedad Española de Oncología Médica

VHIO's Enriqueta Felip, Vice President of SEOM.

Announced at SEOM2019 -the annual Congress of the Spanish Society of Medical Oncology (SEOM), 22-25 October (Pamplona, Spain), Enriqueta Felip, Principal Investigator of VHIO's Thoracic Tumors & Head and Neck Cancer Group, and her #SEOM2Punto0 team, were elected to join SEOM's Board of Directors 2019-2021 under the presidency of Álvaro Rodríguez-Lescure, Head of the Medical Oncology Service of the Hospital General Universitario de Elche (Alicante, Spain).

Led by Enriqueta, now Vice President of SEOM (to serve as President 2021-2013), her elected team will work alongside Álvaro and other Board Members to help expand the Society, its educational programs, innovation and relations with key stakeholders, and in collaboration with its expert working groups and supporters.

fundación fero
Investigando por un futuro sin cáncer

Presided by Sol Daurella who took up the reins as FERO Foundation's President in 2019, FERO's community gathered once again at the stunning Oval Room of Catalonia's National Museum of Art (MNAC) for its annual fundraising gala dinner, sponsored by Andbank, and the 10th edition of FERO's Annual Awards for Translational Research to promote cancer science of excellence and grow the careers of up-and-coming talents in oncology. This year, FERO honored three more VHIO investigators who now join VHIO's previous seven Annual Award recipients.

Chaired by Andrés Cervantes, Director of Oncology at the Institute of Health Research INCLIVA (Valencia, Spain), the Foundation's expert selection committee backed two pioneering VHIO projects aimed at developing the liquid biopsy of cancer. This year's three prizes were presented to Joaquin Mateo, Violeta Serra and Judith Balmaña, Principal Investigators of VHIO's Prostate Cancer Translational Research, Experimental Therapeutics, and Hereditary Cancer Genetics Groups, respectively, and Asís Palazón, Investigator at CIC bioGUNE (Bilbao, Spain).

Concerning VHIO's duo of FERO Awards, one was jointly supported by the Ramón Areces Foundation, and the other by the hair care and styling company, GHD.

Andrés Cervantes (left) and Paloma Garcia Peña, Member of the Board of Trustees, the Ramón Areces Foundation (far right), present VHIO's Joaquin Mateo with one of FERO's Annual Awards for Translational Research 2019.

Since VHIO incorporated in-house BEAMing liquid biopsy RAS biomarker technology back in 2015, the first academic test center to do so, our Institute continue to make significant progress in validating and developing liquid biopsy and Droplet Digital PCR Bio-Rad technologies to better guide treatment decisions for our patients and less invasively 'police' disease over time, in real time.

VHIO's contributions to-date have largely been possible thanks to the continued backing and belief received from FERO (see page 18). These two most recent accolades will enable our scientists to further develop this approach towards ultimately delivering a more precise and rapid diagnosis of cancer, steering treatment decision making, and monitoring the course of cancer and response to therapy.

Specifically, Joaquin was awarded for his project that is set to test whether this novel approach can also help to predict the evolution of prostate cancer and in so doing, potentially detect disease relapse earlier as well as more 'smartly' monitor cancer's next moves.

Left to right: José Baselga, FERO's Honorary President, Thys Niermeyer, Director General, ghd Spain, presented VHIO's Violeta Serra and Judith Balmaña with the first joint FERO-GHDproject Award.

To be spearhead by VHIO's Violeta Serra and Judith Balmaña, the very first joint FERO-GHD project – a new initiative launched in 2019– will also develop liquid biopsy to monitor response to therapy and establish sensitivity of breast cancer patients with BRCA1/2 mutations to treatment with PARP inhibitors. The goal is to more effectively tailor personalized treatment regimens to the unique specificities of each particular cancer, more effectively tackle cancer drug resistance, as well as establish which patients would be most likely to benefit from these targeted therapies.

Projecting a live fundraising counter on the big screens during the event, FERO invited donations for a project aimed at more precisely monitoring the course of medulloblastoma – the most frequent of all pediatric brain tumors and a leading cause of cancer-related deaths in children.

Project lead Joan Seoane, Co-Program Director of Preclinical and Translational Research at VHIO and ICREA Professor, was invited to take center stage and provide a synopsis about this critical line of research. Building on his previous studies showing proof-of-concept that cerebrospinal fluid (CSF) can be exploited to characterize brain tumors as it contains ctDNA, Joan will seek to advance and apply this approach in order to better gauge the aggression of disease in these young patients, more faithfully guide treatment decisions, and use liquid biopsy-driven insights to develop and accelerate more precise and potent therapies against brain cancer.

frA | FUNDACIÓN RAMÓN ARECES

Joan Seoane, Co-Program Director of Preclinical and Translational Research at VHIO and ICREA Research Professor.

Presented at a special award ceremony hosted by the Ramón Areces Foundation in Madrid, and presided by Ángeles Heras, Spanish Secretary of State for University Research, Development and Innovation, and President of the Foundation's Board of Trustees, Florencio Lasaga, VHIO's Joan Seoane, was also honored as recipient of one of its Annual National Awards, now in its XIX edition. These recognitions spur 'home-grown' science led by researchers of international excellence.

In the treatment of patients with metastatic non-microcytic lung cancers and melanoma, immune checkpoint inhibitors represent the 'go to' in systemic immunotherapy. Unfortunately, however, not all patients respond to these novel immune-based therapies, with the tumor microenvironment as a crucial and determining factor. Interestingly, intracranial lesions respond differently to these inhibitors than extracranial ones. This could suggest that the microenvironment modulates response to therapy in these patients.

Joan's team, in collaboration with Enriqueta Felip, Principal Investigator of VHIO's Thoracic Tumors & Head and Neck Cancer Group, and Eva Muñoz-Couselo, Medical Oncologist and Clinical Investigator of our Breast Cancer & Melanoma Group (PI: Cristina Saura), will analyze these patients' brain metastases and compare them with their respective primary tumors in order to advance insights into the factors governing clinical response to immune checkpoint blockade in individual patients.

"la Caixa" Foundation

Left to right: Hector Peinado (CNIO), Maria Abad (VHIO), Teresa Macarulla (VHIO), Bruno Costa Silva (Champalimaud Foundation).

Maria Abad, Principal Investigator of our Cellular Plasticity & Cancer Group was awarded under the "la Caixa" Health Research Call 2018 for a project entitled *Defining the Role of Exosome-Secreted Micropeptides in Pancreatic Cancer.*

Led by Maria, and jointly coordinated by Hector Peinado, Head of the Microenvironment and Metastasis Group, the Spanish National Cancer Research Centre (CNIO – Madrid), and Bruno Costa Silva, Head of Systems Oncology, Champalimaud Foundation (Lisbon, Portugal), the study will count on their renowned expertise in micropeptides, exosomes, and liver pre-metastatic niches, respectively, as well as a team comprised of leading pancreatic cancer clinical investigators including VHIO's Teresa Macarulla, PI of our Gastrointestinal & Endocrine Tumors Group, and specialists in proteomics and biocomputing.

Based on the hypothesis that tumor cells use these micropeptides as cancer messengers inside exosomes, the investigator will strive to establish just how they promote cancer progression and disease spread towards developing novel therapies and ultimately improving outcomes for patients.

aecc Contra el Cáncer

WORLD CANCER RESEARCH DAY

VHIO's Director, Josep Tabernero, presenting during the *Asociación Española Contra el Cáncer* (Spanish Association against Cancer – AECC) Annual Awards Ceremony 2019, celebrated on the occasion of World Cancer Research Day (WCRD), 24 September. This World Day was launched back in 2016 by AECC to encourage the active involvement of researchers, citizens, institutions and leaders across the globe to support the advancement of research against cancer.

Marking World Cancer Research Day (WCRD), the *Asociación Española Contra el Cáncer* (Spanish Association against Cancer – AECC) announced its 2019 awardees during a special ceremony in Madrid presided by Her Majesty the Queen Letizia of Spain, its Honorary President, alongside Pedro Duque, Spanish Minister of Science, Innovation and Universities, and Ignacio Muñoz, AECC's President.

Roundtable debate session during World Cancer Research Day 2019.

Among the many internationally renowned cancer scientists and clinical investigators who were invited to attend this auspicious occasion were VHIO's Director, Josep Tabernero, who delivered a talk highlighting Europe's dedicated efforts aimed at solving cancer sooner, followed by a roundtable debate which counted on the expertise of VHIO's Joaquin Arribas, Co-Program Director of Preclinical & Translational Research and ICREA Research Professor, alongside Eva Ciruelos, President of SOLTI and Medical Oncologist at the *12 de Octubre* Hospital in Madrid, Carmen Vela, Director of EUROFIN-INGENASA collaborative projects and Member of the EU's Health and Food Mission, Javier Garcia, Founder of Columbus Venture Partners, and Cristóbal Belda, Sub-General Director of Evaluation and Research Funding, Carlos III Health Institute (ISCIII).

Elena Élez, Medical Oncologist and Clinical Investigator of our Gastrointestinal & Endocrine Tumors Group (PI:Teresa Macarulla), was among the Award recipients who received funding as an AECC Senior Clinician. This particular category provides experienced medical

professionals in oncology with support to develop and consolidate research at the clinical level.

Elena's awarded project will enable her to continue developing minimally and non-invasive approaches for the early detection and/or progression of colorectal cancer including the study of prognostic and predictive values of circulating tumor DNA (ctDNA in advanced disease. Given that cancer relapse and metastatic cell spread are responsible for between 50-70% of colorectal cancer mortality, the need to bring these exciting methods closer to the clinic is critical.

Miriam Sansó, Post-Doctoral Fellow of our Cancer Genomics Group directed by Ana Vivancos, received an AECC Investigator's Award. These grants support postdoctoral talents to pursue their respective scientific careers towards establishing their own research lines. Miriam's project will center on the comprehensive molecular profiling of multiple primary tumors in lung cancer patients to elucidate common genetic origins.

Around 12% of lung cancer patients at Vall d'Hebron suffer multiple primary tumors (MPTs). When a second tumor is diagnosed in a patient with a previous history of cancer, the challenge is to evaluate whether the second lesion is a metastasis of the first or a new primary tumor. The genomic analysis of different MPTs could identify possible coincident genetic alterations in these patients, and integrative analysis will aim at seeking out genomic signatures of MPT risk.

Under the same category of AECC Investigator, Post-Doctoral Fellow of our Stem Cells & Cancer Group, Isabel Puig, received renewed funding this year for her development of novel therapeutics against colon cancer recurrence. Almost 50% of patients with colorectal cancer will relapse with a new, more aggressive tumor which reduces the survival of these patients.

The group, directed by Héctor G. Palmer, has identified a subpopulation of drug-resistant slow-cycling cancer cells with enhanced capacity to reinitiate tumors thus being responsible for disease relapse. They have identified TET2 gene as a relevant factor for slow-cycling cancer cells survival, which could therefore serve as a potential drug-target for their elimination, and also shown that 5-hydroxymethylcytosine, generated by TET2 enzymatic activity, is a valuable biomarker to predict relapse in colorectal cancer patients.

Another VHIO project, awarded under the category of AECC Seed Ideas, is led by Pere Barba, Clinical Investigator of our Experimental Hematology Group directed by Francesc Bosch. His research will focus on optimizing checkpoint inhibitors to improve outcomes for patients with lymphoproliferative neoplasms who receive allogneneic hematopoietic cell transplantation (allo-HCT).

PD-1 inhibition could be damaging in patients who undergo stem cell transplantation, resulting in an increased risk of graft-versus-host disease and other immune-mediated complications. VHIO investigators will study PD-1 inhibitors in patients who have received a transplant and identify strategies to prevent damaging side effects in these patients.

VHIO would like to acknowledge AECC's invaluable contribution to promoting cancer discovery and translational research of excellence, and the support it gives to countless researchers and groups across Spain and beyond.

For a full listing of AECC-funded projects awarded in 2019, please refer to pages 161-162.

Left to right: VHIO's Josep Maria Miquel (Senior Project Manager), Elena Élez (Clinical Investigator & Medical Oncologist), Josep Tabernero (VHIO's Director), Cristina Saura (PI: Breast Cancer & Melanoma Group), César Serrano (PI: Sarcoma Translational Research Group), Sandra Porta (Project Management Coordinator).

The third edition of the Catalonian Department of Health's Strategic Plan for Research and Innovation in Health (*Pla Estratègic de Recerca i Innovació en Salut,* PERIS), announced 66 award recipients in 2019. The selected projects, recognized for their promise to yet further strengthen research throughout the region, are set to deliver on PERIS' ambitions of promoting health and wellbeing among Catalonia's citizens, increase international competitiveness to reaffirm the community as a leading hub of research and innovation of excellence, as well as further establish health as a key driver of social and economic development.

VHIO picked up recognitions in each of the three defined categories, namely, professional development, the incorporation of new research talents and technicians in existing groups, and support to drive and engage in international scientific activities.

First, PERIS funding will facilitate the recruitment of an additional group member which will enable Elena Élez (Clinical Investigator of our Gastrointestional & Endocrine Tumors Group), to dedicate the necessary time to implement and lead a project for detecting relapse in advanced colon cancer patients by longitudinally following a personalized molecular signature liquid biopsy.

Newly introduced this year, PERIS' *Go Europe* grants award research support units of accredited research institutes and centers belonging to the CERCA Institute, in order to extend their global reach, increase participation in international projects -EU's Horizon 2020 Research and Innovation programme in particular- as well as improve their success rate and returns achieved through competitive grants.

Specifically, this funding will strengthen VHIO's international grant application processes and consolidate our European Projects Office directed by Alejandro Piris, Scientific Manager, VHIO's Scientific Coordination Area (see page 128).

Since it was established back in 2010, this specialized unit has evolved from an office providing basic support to a

highly professional team with experience in both cancer research and project management. *Go Europe* support will further enable Alejandro's department to centralize all identified proposals and projects presented by VHIO researchers and management teams, match them to existing and future calls across various funding sources, and tailor them to the requirements of the respective calls.

Regarding the incorporation of new research faculty and technicians in existing groups, Cristina Saura, Joaquin Mateo, and César Serrano, PIs of our Breast Cancer & Melanoma, Prostate Cancer Translational Research, and Sarcoma Translational Research Groups, respectively, also received funding to incorporate new talents within their teams.

Celebrating the 16th edition of the *Fundación Mutua Madrileña*'s Health Research Awards 2019, VHIO's Maria Abad, Principal Investigator of our Cellular Plasticity & Cancer Group, was prized for her research to seek out micropeptides that are implicated in pancreatic cancer, and functionally characterize their role and relevance towards targeting these molecular messengers as markers of disease progression and metastases.

Recipients of the *Fundación Mutua Madrileña*'s Health Research Awards 2019.

Micropeptides are tiny proteins that, due to their size, have gone largely unnoticed under the lens. Up until now, that is. While the microproteome remains a relatively unexplored area, it is already showing promise in advancing discovery against cancer.

Out of the mere handful of micropeptides that have been characterized to-date, three have been linked to cancer. Considering that there are thousands of these micro proteins in our cells, it is plausible that many of them, yet to be discovered, could assume important roles in tumor formation and metastatic cell spread.

This support will further enable Maria Abad's team to investigate the microproteome of pancreatic cancer and identify novel micropeptides that can be used as therapeutic targets as well as biomarkers of disease. They have previously unmasked several micropeptides implicated in cancer; some halt tumor growth, while others prevent cancer cells from invading other tissues and metastasizing. This funding will help the group to navigate this new world of micropeptides in greater depth toward translating their therapeutic promise at the clinical level.

The 2019 FIDEM Award winners at the ceremony hosted by CaixaForum.

Celebrated at the CaixaForum center for culture in Barcelona, the *Fundación Internacional Dona Emprenedora* (International Foundation for Women Entrepreneurs - FIDEM) announced the 2019 recipients of its annual prizes that honor exceptional examples of pioneering entrepreneurship led by women. Now in its 22nd edition, this recognition also applauds those companies and initiatives that spur economic development and promote societal enrichment.

Among the eight winners, who were each selected from a short list of five nominees/companies per category, VHIO's Laura Soucek, Principal Investigator of our Mouse Models of Cancer Therapies Group and ICREA Research Professor, was prized under *Innovation* for her research centered on translating Omomyc-based therapy into clinical application, which subsequently led to the creation of a VHIO-born spin-off, Peptomyc S.L, back in 2014.

1- The 20 awardees of the 2019 Catalunya la Pedrera Foundation's Pedrera Talents prizes. 2- VHIO's Managing Director, Andrés de Kelety presents VHIO's Iosune Baraibar with her Award certificate.

The la *Fundació Catalunya La Pedrera* (Catalunya la Pedrera Foundation) Pedrera Talents prizes launched in 2012 to recognize and promote the careers of young talents in healthcare who work at hospital across Catalonia.

In 2019, 20 prizes were awarded to young professionals who have completed their specialty training, to support their continued development at their respective hospitals or research centers as healthcare providers and researchers.

The ceremony counted on the official presence of panelists Lluis Farrés, Director of the Foundation's Knowledge & Research Area, Anna Meseguer, Head of Operations & Institutional Relations of the *Dirección General de Investigación e Innovación en Salut* (General Direction of Health Research and Innovation), Jordi Ara, *General Manager of the Instituto Calalán de la Salud* (ICS) - *Área Metropolitana Norte* (Catalan Institute of Health – North Metropolitan Health Service), Josep Maria Campistol, Director General of the Hospital Clínic de Barcelona, and Andrés de Kelety, VHIO's Managing Director.

Iosune Baraibar, the first to have received a Pedrera Talents Prize from VHIO, was awarded for her project *Identification of response biomarkers to anti-TGFβ anti-LIF treatments in cancer patients.* Iosune, a Clinical Investigator of our Gastrointestinal & Endorcine Tumors Group's translational research program, directed by Teresa Macarulla, was also one of the six awardees who were selected to deliver a brief talk on her prized project-*elevator pitch*- during the event.

The Ceremony also included roundtable sessions; one of which, *Women in Science*, included Elena Garralda, Director of VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", and PI of our Early Clinical Drug Development Group, as an Invited Speaker.

VHIO's Elena Garralda as Invited Speaker of the round table session on Women in Science.

Fundació La Marató de TV3

VHIO's recipients of La Marató funding awarded in 2019.

Thanks to the fundraising efforts of the 2018 annual telethon *La Marató* organized and led by media channels, *TV3* and *Catalunya Ràdio*, dedicated that year to cancer research, seven VHIO-led projects, as well as one more in which VHIO will participate as a partner, were selected and prized this year.

Elena Élez, Medical Oncologist and Clinical Investigator of our Gastrointestinal & Endocrine Tumors Group, headed by Teresa Macarulla, will advance liquid biopsy as an approach to less invasively and more precisely track, monitor and evaluate individual patients suffering from colorectal cancer. She will seek to establish whether this technique can more effectively predict response to anti angiogenic therapies that can stop tumors from growing their own blood vessels, and thus slow and even shrink tumor growth.

Violeta Serra, who directs VHIO's Experimental Therapeutics Group, received *Marató* funding to investigate mechanisms of resistance to therapy with PARP inhibitors (PARPi). By liquid biopsy, Violeta's team will aim to establish whether the RAD51 biomarker, that can predict sensitivity to PARPi, can more effectively identify the patients who will be most likely to benefit.

Raquel Perez-Lopez, Principal Investigator of Radiomics at VHIO, received funding to analyze the use of molecular diffusion nuclear magnetic resonance imaging in the monitoring of patients with bone metastases. This new approach might ultimately help to better guide treatment decision making and improve outcomes for patients – particularly those with advanced prostate and breast cancers.

Alena Gros, Principal Investigator of our Tumor Immunology & Immunotherapy Group was awarded for research centered on developing more effective and personalized immune-based therapies for the treatment of patients suffering from advanced endometrial carcinoma. This project will focus on the characterization of immune cells that reside in the tumors, the expansion of tumor-infiltrating lymphocytes (TIL) from tumors, and the development of mouse models of patients' immune systems.

Laura Soucek, Principal Investigator of VHIO's Mouse Models of Cancer Therapies Group and ICREA Research Professor, heads up research aimed at developing viable, non-toxic pharmacological options for Myc targeting in the clinic. Her group also received *Marató* funding to validate novel Omomyc-based cell penetrating peptides for cancer therapy.

Specifically, her group seeks to establish that Omomyc can put the brakes on tumor progression and achieve a change in the immunosuppressive tumor microenvironment and promote the immune control of tumors. They will also combine Omomyc with current immunotherapies to assess the potential efficacy of this therapeutic approach, as well as study the impact of MYC inhibition in KRAS-driven lung cancer, along with other mutations that inactivate tumor suppressor genes.

VHIO's Francesc Bosch, Principal Investigator of Experimental Hematology, also received *Marató* funding to better understand the specific changes that promote the clinical progression of chronic lymphocytic leukemia (CLL) which leads to the decline in function of the immune system. These insights would help to more precisely predict the course of this disease.

Thanks to *Marató* funding this year, Sandra Peiró, who directs our Chromatin Dynamics in Cancer Group, will study cholangiocarcinoma; a less common yet difficult-to-treat tumor type, which is generally diagnosed at late stage with a high risk of recurrence after surgery. Sandra's group will study the IDH1/2 mutation that is present in 20% of these tumors. This mutation generates an oncometabolite that alters the epigenetic pattern of mutated IDH1 cells. By better understanding the genetics

and epigenetics of this disease, they hope to ultimately improve outcomes for patients.

In addition to these seven funded projects, Josep Villanueva, Principal Investigator of VHIO's Tumor Biomarkers Group, will participate in a project coordinated by Virgina Amador, the August Pi Sunyer Institute for Biomedical Research (IDIBAPS) in Barcelona. The team will study the tumor immune microenvironment and the pathogenesis and control of mantle cell lymphoma (MCL). Josep will lead the research focused on the secretome of these tumors.

For a full listing of new projects awarded in 2019, please refer to pages 158-166.

VHIO-organized events: sharing the latest insights & developments in cancer science and clinical investigation

VHIO is dedicated to organizing events of the highest caliber to present and debate the very latest in cancer discovery – from the bench to bedside and back. These educational opportunities often lead to new research collaborations that continue to accelerate our collective efforts aimed at solving cancer sooner.

VHIO -"la Caixa" Scientific Seminars Series

Launched in 2019, our VHIO –"la Caixa" Scientific Seminars Series educational program welcomes internationally renowned researchers and clinical investigators to VHIO to share, discuss and debate latest insights, discovery and next directions in oncology with our students, postdocs and senior faculty from our preclinical, translational and clinical research groups.

Taking place in VHIO's state-of-the-art CELLEX Building Auditorium, each seminar consists of a 30-45minute talk followed by a Q&A round with the audience. Chaired be each respective VHIO host, these expert talks are typically scheduled to take place on Fridays.

Scientific Co-Chairs: María Abad, PI, Cellular Plasticity & Cancer Group (page 64), Laura Soucek, PI, Mouse Models of Cancer Therapies Group (page 74), and Elena Élez, Medical Oncologist and Clinical Investigator, Gastrointestinal & Endocrine Tumors Group (PI: Teresa Macarulla, directed by Josep Tabernero – page 88).

Scientific Coordinator: Josep Maria Miquel, VHIO's Project Manager (Scientific Coordination Area directed by Alejandro Piris, Scientific Manager – page 128).

Inaugural Seminar from left to right: Scientific Co-Chairs - Elena Élez, Maria Abad, Laura Soucek, Co-Host - Josep Villanueva, Invited Speaker - Ángela Nieto, and VHIO's Director, Josep Tabernero.

Inaugural Seminar

Speaker: Ángela Nieto, Research Professor, Institute of Neurosciences, Miguel Hernández University (UMH) – Spanish National Research Council (CSIC).
Talk title: *Epithelial plasticity in health and disease (the Ins and Outs of the EMT).*
Date: 20 September.
Co-hosts: VHIO's Director Josep Tabernero & Josep Villanueva, PI of our Tumor Biomarkers Group.

VHIO-"la Caixa" Scientific Seminar Series 2019

Speaker: Antonio Maraver, Team Leader of the Oncogenic Pathways in Lung Cancer Group, Institute de Research en Cancérologie de Montpellier (ICRM), Montpellier, France.
Talk title: *Role of the Notch pathway in lung adenocarcinoma: beyond the KrasG12V mouse model.*
Date: 08 November.
Host: Maria Abad, PI, Cellular Plasticity & Cancer Group.

Speaker: Justin Odegaard, Vice President of Clinical Development, Guardant Health, Redwood City, California, USA.
Talk title: *The current utility and future promise of liquid biopsy.*
Date: 21 November.
Co-hosts: VHIO's Director, Josep Tabernero, and Ana Vivancos, PI, Cancer Genomics Group.

Speaker: Julio Aguirre-Ghiso, Director of Head and Neck Cancer Basic Research, Director of Solid Tumor and Metastasis Research, Division of Hematology and Oncology, Department of Medicine and Otolaryngology, Mount Sinai School of Medicine, New York, USA.
Talk title: *Role of adult stem cell niches and primed pluripotency programs in early DCC dormancy*
Date: 28 November.
Host: Héctor G. Palmer, PI, Stem Cells & Cancer Group.

Speaker: Nuria López Bigas, Group Leader of the Biomedical Genomics Research Group, Institute for Research in Biomedicine Barcelona – IRB, Barcelona, Spain.
Talk title: *Tumor genomes shed light on mutational processes and cancer vulnerabilities.*
Date: 13 December.
Host: María Abad, PI, Cellular Plasticity & Cancer Group.

More information:
www.vhio.net/en/scientific-seminar-series.

Building on the successes of our previous annual series of VHIO *Meet the Editors*, we continue to welcome the editors of some of the most prestigious journals within our field. In 2019, we had the pleasure of hosting I-Mei Siu, Senior Editor of *Cancer Discovery*, who met with our PIs, groups and research teams, and toured our state-of-the-art building – the CELLEX Center.

I-Mei Siu, Senior Editor of *Cancer Discovery* with our Director, Josep Tabernero, in front of VHIO's CELLEX Center.

Ad-hoc courses, workshops & observerships

Based on specific lines and research areas that continue to position VHIO as a leading international reference, we share our expertise, learn from eminent guest speakers, discuss and debate our latest findings through the organization of VHIO ad-hoc courses and workshops.

Exchanging latest discovery in cancer science and medicine, VHIO organized and hosted a total of 50 Courses, Workshops, Observerships and Perceptorships in 2019.

1. Preceptorship on Locally Advanced Melanoma, 31 January-01 February. Coordinator: Eva Muñoz Couselo. 2. Inmunoterapia y Tratamientos Dirigidos en Cáncer del Pulmón, 28 February – 01 March. Course Director: Enriqueta Felip. 3. Sharing Experiences: from Molecular Biology to Clinical Management, 09 -10 May. Director: Francesc Bosch. 4. II Reuniones Regionales de GIST, 16 May. Meeting Organizer: César Serrano. 5. Advanced Management of Gastroenteropancreatic Neuroendocrine Tumors, 16 – 17 May. Director: Josep Tabernero. 6. 14º Curs de Formació d'Assaigs Clínics en Oncologia i Hematologia, November. Organizer: VHIO's Clinical Trials Office.

Our series of *Benchstoming Seminars* represent an excellent educational opportunity for junior faculty at VHIO to both present and exchange on and around their respective research interests across VHIO's various research programs.

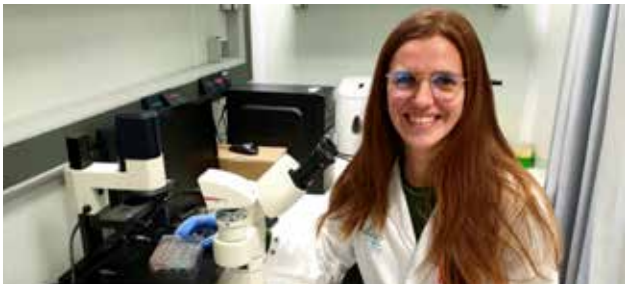
Not only do our young researchers learn more about their other colleagues and research lines, they can also express their ideas surrounding a given topic presented at each seminar. The specially crafted informal format of these meetings favours free thought, flow, and interaction between the speakers and participants.

Current Benchstorming Co-Chairs, Elena Senís (left) and Chiara Bellio (right).

As the Benchstormings turned three years old in 2019, Elena Senís, Post-Doctoral Fellow of VHIO's Cellular Plasticity & Cancer Group (PI: Maria Abad) and Benchstorming Co-Chair, announced that Chiara Bellio, Post-Doctoral Fellow of VHIO's Tumor Biomarkers Group (PI: Josep Villanueva), had taken over the reins from previous Co-Chair Toni Jauset, formerly a graduate student of VHIO's Mouse Models of Cancer Therapies Group and researcher at VHIO-born spin-off Peptomyc S.L. We take this opportunity to thank Toni for his hard work and dedication.

In 2019, they organized 16 Benchstorming Sessions during which researchers discussed and 'benchstormed' their research areas. Each session is graded by all attendees and one presenter is announced as winner of the best presentation for each season.

Faiz Bilal, Post-Doctoral Fellow of our Growth Factors Group (PI: Joaquín Arribas), was announced as the best presenter for January-June's series for his talk on *Overcoming resistance to targeted therapies in MAPK dependent tumors.*



Andrea García, Graduate Student, VHIO's Tumor Immunology & Immunotherapy Group (PI: Alena Gros), was announced as the winner of the September-December series for her talk on *Development of personalized minimally-invasive T-cell therapies targeting the tumor mutanome.*

Building on the success of the 'spin-off' *Techstorming* sessions to present on novel technologies and latest lab approaches in cancer research, Elena and Chiara introduced an additional sister Benchstorming series with especially paired preclinical-clinical expert sessions on a selected hot topic.

Elena Élez, Medical Oncologist and Clinical Investigator of our Gastrointestinal & Endocrine Tumors Group (PI: Teresa Macarulla, Director: Josep Tabernero), joined together with Laura Escudero, Post-Doctoral Fellow of VHIO's Gene Expression & Cancer Group (PI: Joan Seoane), to present on Liquid Biopsy. Irene Rius, Post-Doctoral Fellow of our Growth Factors Group (PI: Joaquín Arribas), and Pere Barba, Hematologist and Clinical Investigator of Experimental Hematology (PI: Francesc Bosch), reported on CAR T-cells. Tackling the topic of Immunotherapy were Elena Garralda, PI of VHIO's Early Clinical Drug Development and Director of our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", and Andrea García, Graduate Student of VHIO's Tumor Immunology & Immunotherapy Group (PI: Alena Gros).

We also take this opportunity to highlight a special session presented by Marie-Eve Beaulieu, Co-Founder & CSO, of VHIO-born spin-off, Peptomyc S.L., Alba Llop, Leader of VHIO's RAD51 predict test project and Post-Doctoral Fellow of VHIO's Experimental Therapeutics Group (PI: Violeta Serra), and Carlos López, Business Development Manager at VHIO (Scientific Coordination Area directed by Alejandro Piris, Scientific Manager), entitled *Bringing your great ideas to market.*

More information
www.vhio.net/en/benchstorming-seminars.

VHIO's public engagement & outreach

VHIO supports and organizes activities to increase public interest in cancer research and promote the important advances reported by our scientists and clinical investigators. These efforts are aimed at patients, youngsters and non-specialized adult audiences to enrich scientific culture as well as promote science as a stimulating career path for young people – the future of our research.

Importantly, some of these initiatives have resulted in considerable funding for research at VHIO. We will continue to identify, lead and participate in all these precious initiatives and launch new ones based on identified opportunities.

In 2019, VHIO led and/or participated in over 40 public outreach events, programs and fundraising initiatives including:

- II Reunión Regional de GIST (II Regional GIST Meeting)
- 48H Open House BCN – open days for the general public.
- III *Mocador Solidari* presentation
- Spanish Association against Cancer (AECC) conference:
- *El tumor cerebral: una visión integral* - An integral vision of brain cancer
- *Carrera por el Càncer de Páncreas* - runathon to support research against pancreatic cancer
- *Jarabe y amigos contra el cáncer* - Pau Donés' cancer research fundraising rock concerts
- *El Paseico de la mama* – strollathon for breast cancer
- *Festival de la Ciencia* (Science Festival)
- *Festival de cine de Alicante* (Alicante Film Festival) - Dones en Actiu
- *Marnaton 4 FERO* – swimathon organized by the FERO Foundation
- *Pink Run Mir* – runathon fundraiser for breast cancer research
- *Una palabra. Una Mujer. Una vida* - exhibition and workshop dedicated to raising awareness about breast cancer
- The Youth Mobile Festival: YoMo
- VHIO's *Escuela y Ciencia* Program - see sub-section
- VHIO-HUVH's annual series of workshops for patients suffering from breast cancer
- II VHIO-IDIBELL-ICO Workshop on Prostate Cancer
- VHIO's Running for Research (R4R) – in collaboration with the FERO Foundation - see sub-section
- MBA BCN Global - student visits to VHIO
- Visit by Portugal's Minister for Science, Technology and Higher Education, Manuel V. Heitor
- Visit to the *Escuela de Administración Pública de Catalunya*
- Visit to the *Escuela FEDAC Montcada*
- Visit to the *Escuela Virolai*
- ProstateNet Workshop
- World Cancer Research Day institutional presentation & open meeting
- *Zumba Solidario* – Zumba workouts to support research against cancer

escolaciència

In 2019 VHIO's education program, Schools and Science, welcomed a total of over 490 under-twelves from 6 local primary schools to meet our faculty, tour our laboratories and learn more about cancer biology and research.

The main objectives of this outreach program are to teach young and inquisitive minds about the importance of research in solving cancer sooner, how we at VHIO conduct

our investigation, and to hopefully inspire some to ultimately become the next generation of cancer scientists.

During their half day visits our young visitors participated in junior masterclasses and hands-on activities to explain the origins and development of cancer, led and supervised by VHIO faculty. In view of the tremendous success and excellent feedback received from the students and teachers, we will continue to open our doors to all primary schools who wish to participate in this program, with dates already in the diary for 2020.

VHIO Vall d'Hebron Institute of Oncology
RUNNING FOR RESEARCH
www.vhio.net

Inspired by Daniel Massó Vallés, formerly a Postdoc of our Mouse Models of Cancer Therapies Group, and now researcher of VHIO spin-off Peptomyc S.L., and Irene Rius, Post-Doctoral Fellow of our Growth Factors Groups, VHIO's Running for Research (R4R) currently comprises a team of some 20 researchers who are participating in several half and full marathons to mix and mingle with the general public and spread the word about who we are, what we do, and promote the value and importance of supporting cancer research.

Our dedicated runners, who officially enter sports events in the name of VHIO, are kitted out with R4R-branded baseball caps and t-shirts to increase visibility and trigger conversation with fellow runners and other members of the public present.

R4R participated in several 'runathons' in 2019, including the 5K and 10K races of the third annual Barcelona-based fundraiser of the Spanish Association against Cancer's (AECC), Run against Cancer, Move for Multiple Sclerosis - the Granollers half marathon, the Barcelona marathon, the 5k Carrera de las Ciudades against Pancreatic Cancer, and the 12.5K Portlligat trail.

VHIO's R4R rallying for research against cancer: 1- At the Spanish Association against Cancer's (AECC) *Run against Cancer*. 2- The *Carrera de las Ciudades* to support research against pancreatic cancer. 3- Participating at the mountain race *Portlligat trail*.

fundación fero
Investigando por un futuro sin cáncer

One of our Institutional Supporters and Patrons, the FERO Foundation (see page 18) also promotes the importance of cancer research through the organization of several public engagement and annual fundraising initiatives and events.

As examples in 2019, it organized a 'swimathon', *Marnaton 4 FERO*, to raise money for research led by Héctor G. Palmer (PI of VHIO's Stem Cells & Cancer Group) into the early detection of cancer recurrence by liquid biopsy.

Marnaton 4 FERO, Cadaqués (Girona, Barcelona).

Another FERO crowdfunding initiative surrounded its participation at the *41st Zurich Marató Barcelona*, which also counted on several runners from VHIO's Running for Research team. Funds raised were allocated to support molecular diagnostics at VHIO to help extend the more precise characterization of individual tumors and matching of anti-cancer therapies to an increasing number of patients.

VHIO's Twitter account launched at the end of January 2019 and has since attracted over 3000 followers. To discover what we are excited about, our latest news, and other tweets that are catching our attention elsewhere, we invite you to follow us @VHIO and join the conversation today.

VHIO WREN'S LENS

Celebrating its second birthday in December 2019, *Wren's Lens*, our internal monthly newsletter, was devised to update all VHIO faculty on highlights covered in our news and/or media program along with special newsletter extras: *Talent Tidbits,* special features and dates in the diary that might be of interest.

The branding, inspired by our Communications Director's surname, incorporates a silhouette of the Wren species perched on top of a lens accentuating VHIO's logo. Reflective of its popularity and keen VHIO following, *Wren's Lens* has since become more of an internal blog spot than a 'news desk' update.

For all the latest information about VHIO, our Principal Investigators, research programs and groups, latest news and headlines please visit: www.vhio.net.

Scientific Productivity: research articles

Articles published in 2019

In 2019, 333 scientific articles were published by VHIO researchers as corresponding/senior or co-authors with a cumulative Impact Factor (IF) totaling at 3806 and a Median Impact Factor (MIF) of 11,43. These figures reflect both the scientific impact and importance of VHIO's research and contributions to the oncology field:

Figure I
Number of articles published by VHIO researchers from 2007 - 2019

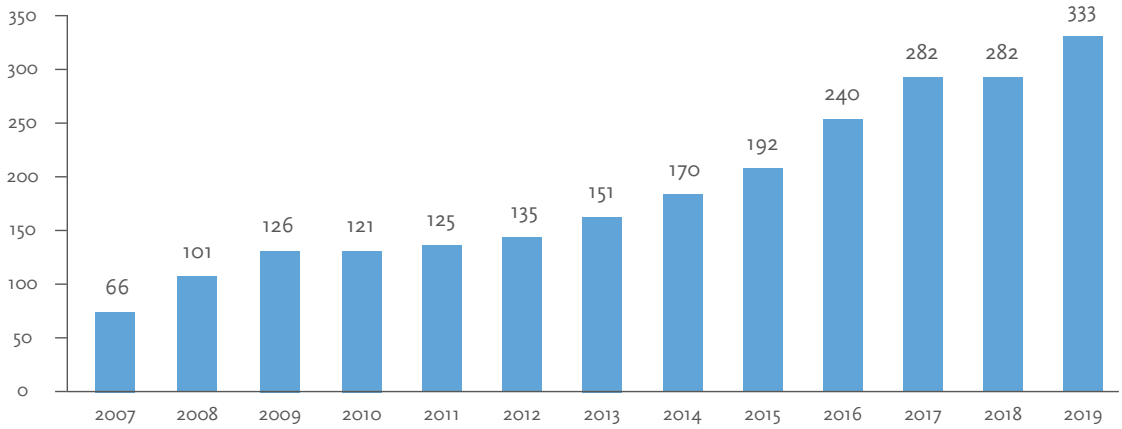
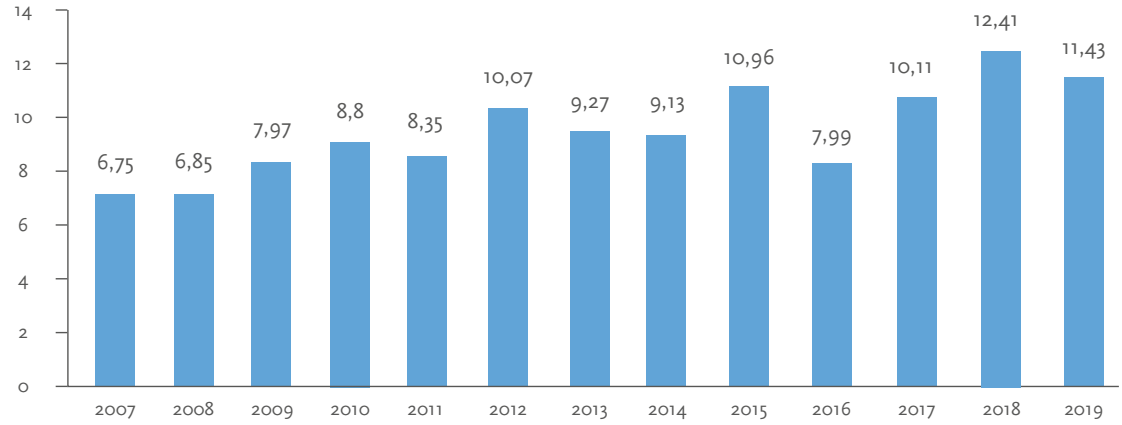


Figure II
Median Impact Factor of papers published by VHIO faculty from 2007 - 2019



For the complete list of VHIO scientific articles published in 2019 in journals with allocated Impact Factor please see pages 130-147. To browse our selection of most relevant articles by VHIO researchers published in 2019 please refer to pages 43-49 of this Scientific Report.

To view our Principal Investigators' selection of a maximum of 4 top papers per group please see respective team pages (sub-section *PI paper pick*). To access each group's full list of publications in 2019, as compiled by our Principal Investigators, visit the extended version of our Scientific Report online at: **http://memorias.vhio.net/2019**

Selection of some of the most relevant articles by VHIO researchers published in 2019

Below is a selected list of articles published by VHIO researchers in 2019 with respective Impact Factors. For the complete list of VHIO scientific articles published in 2019 in journals with allocated Impact Factor please see pages 130-147.

Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. de Wit R; de Bono J; Sternberg CN; Fizazi K; Tombal B; Wülfing C; Kramer G; Eymard JC; Bamias A; Carles J; Iacovelli R; Melichar B; Sverrisdóttir Á; Theodore C; Feyerabend S; Helissey C; Ozatilgan A; Geffriaud-Ricouard C; Castellano D; CARD Investigators. 2019. *N Engl J Med.* 381(26): 2506 - 2518. IF:70,670.

Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. Fizazi K; Shore N; Tammela TL; Ulys A; Vjaters E; Polyakov S; Jievaltas M; Luz M; Alekseev B; Kuss I; Kappeler C; Snapir A; Sarapohja T; Smith MR; ARAMIS Investigators. 2019. *N Engl J Med.* 380(13): 1235 - 1246. IF:70,670.

Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. Kopetz S; Grothey A; Yaeger R; Van Cutsem E; Desai J; Yoshino T; Wasan H; Ciardiello F; Loupakis F; Hong YS; Steeghs N; Guren TK; Arkenau HT; Garcia-Alfonso P; Pfeiffer P; Orlov S; Lonardi S; Elez E; Kim TW; Schellens JHM; Guo C; Krishnan A; Dekervel J; Morris V; Calvo Ferrandiz A; Tarpgaard LS; Braun M; Gollerkeri A; Keir C; Maharry K; Pickard M; Christy-Bittel J; Anderson L; Sandor V; Tabernero J. 2019. *N Engl J Med.* 381(17): 1632 - 1643. IF:70,670.

Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. Loriot Y; Necchi A; Park SH; Garcia-Donas J; Huddart R; Burgess E; Fleming M; Rezazadeh A; Mellado B; Varlamov S; Joshi M; Duran I; Tagawa ST; Zakharia Y; Zhong B; Stuyckens K; Santiago-Walker A; De Porre P; O'Hagan A; Avadhani A; Siefker-Radtke AO; BLC2001 Study Group. 2019. *N Engl J Med.* 381(4): 338 - 348. IF:70,670.

Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. Golan T; Hammel P; Reni M; Van Cutsem E; Macarulla T; Hall MJ; Park JO; Hochhauser D; Arnold D; Oh DY; Reinacher-Schick A; Tortora G; Algül H; O'Reilly EM; McGuinness D; Cui KY; Schlienger K; Locker GY; Kindler HL. 2019. *N Engl J Med.* 381(4): 317 - 327. IF:70,670.

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JOAQUÍN ARRIBAS
Preclinical & Translational Research
Co-Program Director

JOAN SEOANE
Preclinical & Translational Research
Co-Program Director

JOSEP TABERNERO
Clinical Research
Program Director

VHIO Scientific Report 2019

From the Program Directors

Extended version online: memorias.vhio.net/2019
PDF version: memorias.vhio.net/2019/SR-VHIO-2019.pdf

From the Co-Program Director

JOAQUÍN ARRIBAS
Preclinical & Translational Research
Co-Program Director

Preclinical research at VHIO focuses on establishing new ways to halt and revert the progression of highly aggressive tumors, including those affecting the breast, pancreas, colon, lung, and brain.

Considering the extensive inter- and intra-tumoral heterogeneity of human cancers, this is a complex challenge. To achieve this, we investigate novel anti-cancer therapeutic approaches tailored to each tumor type. We apply these therapies in increasingly faithful experimental models. Using these predictive models, we also anticipate the resistance of tumors to anti-cancer drugs.

As I reflect on just some of the many research highlights reported by our program this year, 2019 has been a particularly fruitful one. These advances have undoubtedly been driven by our purely collaborative approach to cancer science and teamwork with other VHIO groups and leading institutes in oncology. As Co-Program Director it is a pleasure and privilege to update on few important developments in 2019:

Tumor Biomarkers Group

VHIO's Tumor Biomarkers Group, headed by Josep Villanueva (page 78), has continued to pursue their studies to demonstrate the potential of HMGA1 as a biomarker and drug target in breast cancer. Notably, his team has focused on the development of monoclonal antibodies against HMGA1 that could be used in the near future in cancer diagnostics and therapeutics.

Their expertise in this field led to a review article this year exploring the future clinical implications of the unexpected secretion of HMGA1 in triple-negative breast cancer (Méndez et al. *Int J. Mol. Sci.* 2019), and has also resulted in several fruitful collaborations with academic groups and the pharmaceutical industry. As an example, they have recently participated in a project led by Arkaitz Carracedo at the CIC BioGUNE (Bizkaia, Spain), that studied the induction of senescence by the gene PML (Revandkar et al. *Cell Death Differ.* 2019).

Experimental Therapeutics Group

Our Experimental Therapeutics Group (page 68), directed by Violeta Serra, has made important progress this past year. Crucially, they initiated the clinical validation of the *RAD51predict* test, an immune-based assay performed on FFPE tumor sections, to predict response to PARP inhibitors across multiple tumor types. This is an international project funded by the ERA PerMed program - an ERA-Net Cofund, supported by 32 partners from 23 countries, and co-funded by the European Commission (Coordinator: *Instituto de Salud Carlos III* - ISCIII).

Thanks also to the support received this year from the *CaixaImpulse Consolidate* program ("la Caixa" Foundation and Caixa Capital Risk), this test will be further developed towards its implementation as a diagnostic test.

Additionally, her group has unveiled novel mechanisms of resistance to targeted therapies in hereditary BRCA1/2 breast

cancer and in estrogen receptor (ER)-positive breast cancer. These findings have been reported as publications in renowned journals including *Nature Communications* and *Molecular Cancer Therapeutics*. Finally, with funding received from the Breast Cancer Now Foundation, a novel strategy to treat ER+ tumors based on targeting the androgen receptor will be widely tested in patient-derived tumor models. Again, the close collaboration and connectivity with other VHIO groups are key to these important achievements.

Mouse Models of Cancer Therapies Group

Laura Soucek's Mouse Models of Cancer Therapies Group (page 74), has continued to contribute to groundbreaking science by reporting definitive advances in bringing the Myc inhibitor mini-protein, Omomyc, closer to the clinic (Beaulieu et al. *Sci Transl Med*. 2019). The relevance of this publication was attested by a comment in *Nature Reviews Cancer,* and *Nature Reviews Drug Discovery* by the journal's Editor, Teresa Villanueva.

Laura's group has also collaborated with Rajeev Vibhakar, the University of Colorado Health Sciences Center (USA), to demonstrate the therapeutic potential of Myc inhibition in childhood rhabdoid tumors. As a result of another collaboration with Esther Vázquez and Antonio Villaverde, *Universitat Autònoma de Barcelona* (UAB), and Ibane Abasolo, Vall d'Hebron Research Institute (VHIR), Barcelona, her group has shown the therapeutic potential of therapeutic proteins delivered in the form of inclusion bodies to treat breast cancer.

Finally, alongside Jordi Alcaraz, University of Barcelona (UB), Laura's team has also evidenced that epigenetic SMAD3 repression in tumor-associated fibroblasts reduces fibrosis and sensitivity to the antifibrotic drug nintedanib in lung squamous cell carcinoma.

Growth Factors Group

My own Growth Factors Group (page 72), has embarked on a novel line of research to generate novel CARs (chimeric antigen receptors) as the state-of-the-art strategy to use the immune system of patients to eradicate tumors.

With the insights gained during the development and characterization of bispecific antibodies, we have been able to develop our CARs in a highly efficient manner. They are directed against a protein, named p95HER2, which is only found in some mammary and gastric tumors and completely absent in normal tissues. Of note, this project has been funded by the Spanish Association Against Cancer (AECC), for the next five years.

Our expanding platform of breast and pancreatic cancer patient-derived experimental models has allowed us to establish a series of fruitful collaborations with several national and international groups. These partnerships have enabled us to identify novel mechanisms of resistance to anti-tumor therapies (Lambies et al., Diaz-Rodriguez et al., and Gomez-Miragaya et al.) and biomarkers of sensitivity to precision therapies (Kang et al., Blasco-Benito et al.).

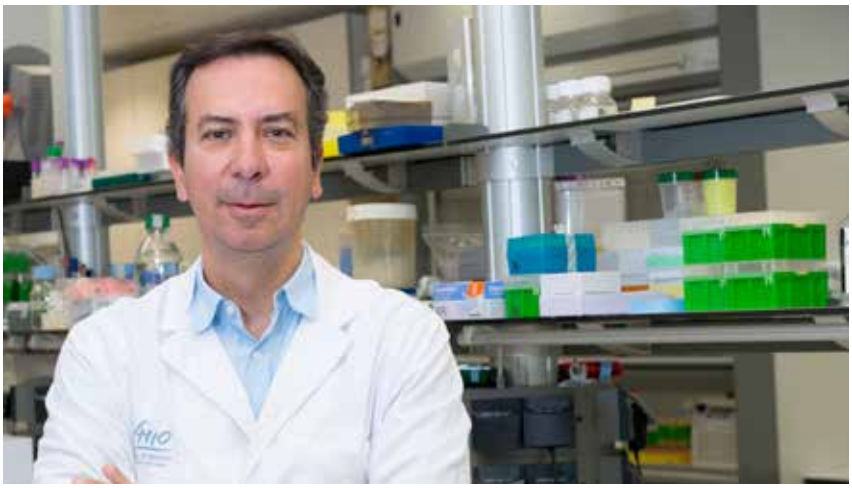
We have also contributed to characterizing a novel antibody drug conjugate that has proven effective against some pancreatic tumors and triple negative breast cancers (Merlino et al.). In addition, we have helped to identify drugs targeting senescent cells which, under certain circumstances, have an important role in tumor progression. Within VHIO, we have joined forces with Sandra Peiró's Chromatin Dynamics in Cancer Group (page 66), to unveil mechanisms that govern gene expression in triple negative breast cancer (Cebria Costa et al.).

In 2019 Veronica Rodilla was awarded with a *Stop Fuga de Cerebros* grant from Roche aimed at retaining talent 'at home', and Irene Rius and Faiz Bilal both defended their PhDs on novel therapies against breast and pancreatic cancers, respectively.

Lastly, it has been an extremely productive year for the *Centro de Investigación Biomédica en Red* (CIBERONC- *Instituto de Salud Carlos III* (ISCIII): Center for the Biomedical Research Network in Oncology), under the expert leadership of Anna Bigas, Hospital del Mar Medical Research Institute - IMIM (Barcelona).

This network, which I had the pleasure of leading from 2016-2019, comprises several of the most active cancer research groups across Spain, including my own group, VHIO's Gene Expression (page 70), and Gastrointestinal & Endocrine Tumors Groups (PI: Teresa Macarulla, page 88), directed by Joan Seoane and Josep Tabernero, respectively.

From the Co-Program Director



JOAN SEOANE
Preclinical & Translational Research
Co-Program Director

To develop and enhance anti-cancer therapies targeting all cell types within a tumor, we must achieve a deeper understanding of intratumoral heterogeneity. Among the different cell types forming this complex landscape, cancer stem cells (CSCs) have been characterized by their self-renewing capacity, multi-lineage differentiation properties, high oncogenic potential, and ability to replicate the heterogeneity of original human tumors in mouse models.

They are also responsible for the initiation, recurrence and chemo- and radio-resistance of tumors, indicating that more effective therapies could be identified via strategies targeting the stem-cell-like component of tumors. To-date, few pharmacological compounds have proven successful.

VHIO's preclinical and translational researchers investigate cancer as closely as possible to the actual tumor and generate patient-derived *in vitro* and *in vivo* cancer models. Tumor specimens are obtained shortly upon surgical resection and we then study their respective tumor cells and cancer stem cells. Mouse models are then developed to recapitulate the characteristics of patients' tumors as faithfully as possible.

Both VHIO's Stem Cells & Cancer Group (page 76), led by Héctor G. Palmer, and my own Gene Expression & Cancer Group (page 70), have helped to develop these models for brain cancer as well as CRC, neuroendocrine, hepatic tumors, and peritoneal pseudomyxoma, respectively.

Stem Cells & Cancer Group

In 2019, Héctor G. Palmer's Group has also continued to explore novel strategies to combat cancer cell dormancy and discover new therapeutic targets. Building on their previous findings (Puig et al. *J Clin Invest.* 2018), evidencing TET2 as a controller of chemo-resistant slow-cycling cancer cell survival and tumor recurrence, his group is now investigating the function of TET2, DPPA3, and other epigenetic factors governing dormancy in further depth.

They are making important progress in developing therapies that modulate these dormancy drivers and defining biomarkers to detect chemo-resistant dormant tumor cells (DTCs).

His team explores molecular mechanisms conferring sensitivity or resistance to therapies in order to more precisely stratify patients for enrollment in clinical trials. As an example, in collaboration with other Spanish groups and VHIO teams including Gastrointestinal & Endocrine Tumors (PI: Teresa Macarulla - page 88), Cancer Genomics (PI: Ana Vivancos - page 112), Molecular Oncology (PI: Paolo Nuciforo - page 114), Early Clinical Drug Development (PI: Elena Garralda – page 84), they have studied epigenetic EGFR gene repression and the conferrence of sensitivity to therapeutic BRAFV600E blockade in colon neuroendocrine carcinomas; results of which were published this year

(Capdevila et al. *Clin Cancer Res*. 2020. Epub 2019).

Cellular Plasticity & Cancer Group

VHIO's Cellular Plasticity & Cancer Group headed by Maria Abad (page 64), continues to mark important progress in identifying and characterizing novel cancer micropeptides involved in cancer cell plasticity that could represent novel actors in carcinogenesis. Not only could these tumor-micropeptides be crucial in advancing insights into cancer physiopathology, but they could also serve as novel cancer biomarkers for early detection of disease.

To-date Maria's team have discovered six new cancer micropeptides and shown evidence *in vitro* and *in vivo* that four of them act as novel tumor suppressors, triggering cell cycle arrest, differentiation, or inhibition of mesenchymal traits in cancer cells. During 2019 her group's research has expanded to identify novel secreted micropeptides that act as crucial cellular messengers for pancreatic metastasis. Watch this space!

Chromatin Dynamics in Cancer Group

Research carried out by Sandra Peiró's Chromatin Dynamics in Cancer Group (page 66), continues to advance insights in deciphering the 3D chromatin structure and dynamics in cancer, as well as identify biomarkers and epigenetic mechanisms of drug resistance in ER+ breast cancer, cholangiocarcinomas, and NUT-midline carcinomas.

Alongside other groups including VHIO's Growth Factors Group (PI: Joaquín Arribas, page 72), her group has recently reported findings (Cebrià-Costa el al. *Oncogene* 2020. Epub 2019), that could represent a forward step in more effectively combating cancer drug resistance in triple-negative breast cancer (TNBC).

When compared to other breast cancer subtypes, they have discovered that the DNA of TNBC cells is much more compacted which renders it resistant to therapy. Their results indicate that chromatin decompaction could potentiate current therapies.

They have also shown that LOXL2 inhibition could prevent chromatin compaction from occurring. This is particularly relevant since it seems to frequently occur in TNBC, which hinders therapies from accessing the nucleus of cancer cells. In patients with the triple-negative subtype who show most resistance to conventional therapies, LOXL2 is present in high levels. This finding points to its role as a mechanism of resistance.

Gene Expression & Cancer Group

My group has continued to pioneer and develop liquid biopsy to disentangle the complexity and heterogeneity of brain tumors. Our analysis of ctDNA in cerebrospinal fluid has opened up new avenues for research aimed at achieving a better understanding of central nervous system cancers.

Reflective of our expertise in this field, we recently analyzed various studies on the use of liquid biopsy in primary and metastatic brain tumors for diagnosis and follow-up of disease as well as the identification of mechanisms or resistance or susceptible mutations (Seoane et al. *Ann Oncol*. 2019). Not yet ready for 'prime time', our group will continue to lead research in liquid biopsy to bring this novel approach closer to the clinic.

We are as equally committed to exploring the tumor microenvironment which, in the case of brain tumors, plays a key role in cancer progression. Importantly, we have reported that the cytokine LIF assumes an essential role in the tumor microenvironment and is thus a promising therapeutic target.

Building on our previous research, where we established a link between LIF and cancer as well as showed that its blockade eliminates cancer stem cells and prevents disease progression and recurrence, our group has now evidenced that LIF regulates CXCL9 in tumor-associated macrophages and prevents CD8 + T cell tumor-inflation impairing anti-PD1 therapy (Pascual-García et al. *Nat Commun*. 2019).

Finally, we have embarked on two new multidisciplinary projects in 2019. First, in collaboration with Enriqueta Felip, PI of VHIO's Thoracic Tumors & Head and Neck Cancer Group (page 106), and Eva Muñoz, Clinical Investigator of our Breast Cancer & Melanoma Group (PI: Cristina Saura, page 82), we will analyze patients' brain metastases and compare them with respective primary tumors to identify 'governers' of clinical response to immune checkpoint blockade.

Secondly, in partnership with Francesc Bosch, PI of VHIO´s Experimental Hematology Group (page 86), our research in liquid biopsy will extend to CNS lymphoma patients for the early and real-time detection of disease recurrence and brain metastases.

It is thanks to such a strong VHIO ethos of teamwork and purely multidisciplinary approach to cancer science that preclinical and clinical research at our Institute are tightly connected. Our teams collectively strive to accelerate the transformative, robust science that can translate into clinical benefits for our patients.

From the Program Director

JOSEP TABERNERO
Clinical Research
Program Director

VHIO's multidisciplinary and translational approach to team science tightly connects its cancer scientists with our clinical investigators. From the very outset, this model has enabled our program to spearhead cooperative preclinical, early phase studies aimed at developing novel anti-cancer therapies, as well as new or redefined prognostic/diagnostic tools and techniques to better detect disease, track progression and more accurately predict response to treatments.

As our Institute goes from strength to strength, and further develop its research lines and projects based on defined strategic directions, we continue to expand our scientific faculty as well as scientific support units and teams. As an example in 2019, César Serrano, Medical Oncologist and Clinical Investigator of our Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site Group (directed by Joan Carles, page 90), set up our Sarcoma Translational Research Group (page 104).

His group aims to identify the critical molecular mediators of oncogenic signaling sarcomas, characterize response and resistance mechanisms to targeted therapies against these tumor types, as well as preclinically model and validate therapeutic strategies toward improving outcomes for patients in the clinic.

Many research lines at VHIO are fueled thanks to our three institutional programs; the VHIO-FERO Foundation's Advanced Molecular Diagnostics Program (DIAMAV- page 27), VHIO- "la Caixa" Foundation Advanced Oncology Research Program (page 27), and the VHIO-BBVA Foundation Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI – page 28). We also continue to advance cancer science and medicine thanks to the tremendous support that we receive from all of our Institutional Supporters (pages 17-20), international and national funding bodies, associations and entities, as well as companies, patient advocay groups, charities, and individual donors (see pages 148-150).

Concerning clinical trial design in the era of precision oncology, our program pioneers novel study design including Baskets and first-in-human trials. As an example, results from the WINTHER clinical trial, *Genomic and transcriptomic profiling expands precision medicine*, co-authored by Jordi Rodón, Clinical Investigator at the MD Anderson Cancer Center (Texas, USA), and Associate Investigator of VHIO's Research Unit for Molecular Therapy of Cancer (UITM) (page 122), and Irene Braña, Phase I Investigator of the same Unit, published in 2019 (Rodon J et al. *Nat Med*. 2019).

Led by VHIO's Early Clinical Drug Development Group directed by Elena Garralda (page 84), and carried out in collaboration with other leading members of the WIN Consortium (page 29), findings showed that RNA profiling together with DNA testing matches more patients with advanced cancer to personalized anti-cancer therapies than DNA profiling for tumor mutations alone. For more information please see my Foreword (page 12).

Additionally, our Basket of Baskets (BoB) two-stage clinical trial study that promises a more flexible and adaptive model in order to significantly accelerate patients' access to an array of novel therapeutics, officially launched in 2019. Endorsed by the Cancer Core Europe Consortium – CCE (page 28), BoB is the first European multi-modular academic trial that integrates molecular prescreening, the development of novel diagnostic tests including ctDNA, with the assessment of targeted therapies matched to those patients who will be most likely to benefit from them.

This novel trial is being carried out at our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 122), directed by Elena Garralda, and counts on the expertise of several VHIO investigators including Rodrigo Dienstmann, PI of VHIO's Oncology Data Science Group (ODysSey – page 96), and Ana Vivancos who leads our Cancer Genomics Group (page 112). For more updates on BoB please also see my Foreword (page 12).

In addition to our participation in the WIN Consortium and Cancer Core Europe, we also belong to several other important cross-

border collaborations. Covered in detail in my Foreword to this report, 2019 celebrated the launch of an additional five pioneering projects.

In addition to my pick of additional practice changing studies highlighted in my Foreword, I also take this opportunity to mention a few more that made the headlines in 2019:

Good news for the treatment landscape of HER2+ refractory metastatic breast cancer

Data from a phase II study, that were presented on the ground at the 2019 San Antonio Breast Cancer Symposium – SABCS (10-14 December, San Antonio, USA), driven in collaboration with VHIO, promise new hope for the treatment of metastatic HER2-postive breast cancer.

The phase II DESTINY-Breast01 study (Modi S et al. *N Engl J Med*. 2019), co-authored by VHIO's Cristina Saura, Principal Investigator of our Breast Cancer Group (page 82), also in collaboration with Javier Cortés, Translational Investigator of the same group this study built on findings from the phase I safety results (Tamura K et al. *Lancet Oncol*. 2019) of this second generation antibody drug conjugate; trastuzumab deruxtecan against advanced HER2 positive breast cancer previously treated with trastuzumab emtansine.

Findings showed that 60.9% of those patients treated with this novel therapy had an objective response, with progression free survival at more than 16 months. These results are particularly important considering that these patients had progressed after an average of 6 other previous lines of therapy. Importantly, the investigators showed that trastuzumab deruxtecan achieves lasting results and significant anti-cancer activity. As such, this novel approach could provide fresh hope for those patients with refractory disease who have limited treatment options.

Gene-targeted olaparib delivers powerful blows against BRCA1/2 mutated prostate cancer

First authored by Joaquin Mateo, Principal Investigator of VHIO's Prostate Cancer Translational Research Group (page 98), results from the TOPARP-B multi-center phase II trial, published ahead of print in 2019 (Mateo J et al. *Lancet Oncol*. 2020), confirmed the anti-tumor activity of single agent PARP inhibitor, olaparib, against metastatic castration-resistant prostate cancer (mCRPC).

Designed as an open-label single arm study, the second in this two part adaptive trial sought to establish the efficacy of treating mCRPC patients with DNA-damage repair (DDR) alterations, who had previously received chemotherapy and were no longer responding to standard treatments. TOPARP-B drew on the promising results reported from TOPARP-A where the association between DNA repair defects and response to olaparib in 49 molecularly unselected patients was first described.

The investigators performed targeted screening and identified those patients whose prostate cancers had faulty DNA repair genes. 98 patients from across a total of 17 UK hospitals were randomly assigned and treated in the study. Results showed that overall, 47% of patients with these DNA repair defects responded to olaparib, putting the brakes on disease progression for an average of 5.5 months. The most common defects were *BRCA* mutations, although various others were also identified in other genes including PALB2 and ATM, among others.

Importantly, those men with *BRCA1/2* mutated disease responded the best, with 80% responding and 40% free of cancer progression for over a year. The high and durable responses observed in the subpopulation of patients with mCRPC support the implementation of genomic stratification of metastatic castration-resistant prostate cancer in clinical practice based on tumor sequencing. This gene-targeted approach could help guide treatment decisions as well as match more effective therapies to the molecular make up of individual patients' tumors.

Encouraging responses were also observed in patients carrying PALB2 mutations, ATM mutations, and other DNA repair gene alterations – totaling at 50, 37, and 20% respectively. These findings might also point to PARPi having a role as monotherapy or in combination to more effectively tackle other subtypes of metastatic prostate cancer.

Driving the development of pioneering cell therapies for non-responders to current immunotherapies

Research led by Alena Gros, Principal Investigator of our Tumor Immunology & Immunotherapy Group (page 108) signposts a new, less invasive approach to identify killer T lymphocytes in patients with gastrointestinal tumors with low mutational burden who are refractory to approved immune-based treatments. Importantly, killer T cells identified in blood that can hone in on mutations uniquely expressed in cancer cells pave the way for an alternative and personalized therapeutic avenue.

More specifically, those patients with gastrointestinal tumors with low mutational burden, so-called 'cold' tumors, constitute a current challenge for immunotherapy. Novel cell therapies based on the administration of killer T cells that can recognize neoantigens, have shown promising antitumor activity in a small number of patients with cold tumors.

Findings reported by Alena's Group (Gros A et al. *J Clin Invest*. 2019), in collaboration with colleagues at the National Cancer Institute (NCI-NIH) and other leading institutes, break new ground within the field by promoting the development of these treatments towards ultimately providing new hope for patients with metastatic disease who do not respond to treatment with approved cancer immunotherapies. Additionally, the investigators described a less invasive, blood-based method to identify, measure and track lymphocytes against neoantigens expressed in advanced gastrointestinal cancers including pancreas, gastroesophageal, bile duct, colon and rectum.

While the investigators did not initially expect to find killer T lymphocytes in the blood of these patients with cold tumors, with low mutational burden, they showed that these cells can be identified and selected in blood. This study will promote the identification of neoantigen-specific T lymphocytes derived from blood towards ultimately offering a new array of personalized and more promising anti-cancer immunotherapeutic for these patients.

Screening *BRCA1/2* deep intronic regions to reveal the missing links in HBOC susceptibility

Dedicated to unmasking variants toward improved genetic diagnosis, research spearhead by Judith Balmaña's Hereditary Cancer Genetics Group (page 94), first co-authored by Gemma Montalban (former Graduate Student of the group), and Senior Scientists, Sara Gutiérrez-Enríquez and Orland Díez (Montalban G. *J Med Genet*. 2019), builds on their efforts to more precisely explore the genetic epidemiology of hereditary breast and ovarian cancer (HBOC).

This research has shed important light on the characterization of new pathogenic variants in HBOC genes, and provided discriminatory tools to interpret variants of uncertain significance in *BRCA* genes.

Genetic analysis of *BRCA1* and BRCA2 for the diagnosis of hereditary breast and ovarian cancer (HBOC) generally focuses on coding regions and exon-intron boundaries. Although germline pathogenic variants in these regions explain around 20% of HBOC cases, there is still an important fraction that remains undiagnosed.

Aimed at identifying potential spliceogenic variants that could explain part of the missing HBOC susceptibility, the investigators screened *BRCA1/2* deep intronic regions by targeted gene sequencing in 192 high-risk HBOC families testing negative for *BRCA1/2* during conventional analysis.

This research identified the first *BRCA1* deep intronic variant associated with HBOC by pseudoexon activation. While the frequency of deleterious variants in these regions appeared to be low, their study highlights the importance of studying non-coding regions and performing comprehensive RNA assays to both complement and improve genetic diagnosis.

lorlatinib and the more precise treatment of non-small-cell lung cancer

Research co-authored by Enriqueta Felip, Principal Investigator of our Thoracic Tumors & Head and Neck Cancer Group (page 106), represents an important advance in more effectively treating patients suffering from anaplastic lymphocyte kinase (*ALK*) -positive non-small-cell lung cancer who have failed therapy with one or more second-generation *ALK* tyrosine kinase inhibitors – TKIs (Shaw AT et al. *J Clin Oncol*. 2019).

Considering the body of preclinical data that suggest *ALK* resistance mutations may represent a biomarker of response in previously treated patients, the investigators sought to advance insights into the molecular determinants of response to lorlatinib, a third-generation *ALK*-TKI, to more effectively identify those patients who are more likely to derive clinical benefit.

Plasma and tumor tissue samples were collected from 198 patients with ALK-positive non-small-cell lung cancer. The researchers analyzed plasma DNA for *ALK* mutations and studied tumor tissue DNA using an *ALK* mutation-focused next-generation sequencing assay. Results showed that lorlatinib is more effective in patients with *ALK* mutations compared with those without.

Tumor genotyping for *ALK* mutations after failure of a second-generation TKIs may more precisely identify patients who are most likely respond to this therapy.

BRCA reversion mutations: key players in resistance to PARP inhibitors

Ana Oaknin, Principal Investigator of VHIO's Gynecological Malignancies Group (page 108), has co-authored research evidencing that *BRCA* reversion mutations in circulating tumor DNA (ctDNA) predict primary and acquired resistance to the PARP Inhibitor (PARPi) rucaparib in high-grade ovarian carcinoma – HGOC (Lin KK et al. *Cancer Discov*. 2019).

A key resistance mechanism to platinum-based chemotherapies and PARPi in BRCA-mutant cancers is the acquisition of *BRCA* reversion mutations that restore protein function. To estimate the prevalence of *BRCA* reversion mutations in HGOC, the authors of this study performed deep liquid biopsy analysis on patients' blood samples collected during their participation in the ARIEL2 international, multicenter, two-part, phase II study.

By targeted next-generation sequencing of circulating cell-free DNA (cfDNA) extracted from pretreatment and postprogression plasma in patients with deleterious germline or somatic *BRCA* mutations treated with PARPi rucaparib, *BRCA* reversion mutations were identified in pretreatment cfDNA from 18% of platinum-refractory and 13% of platinum-resistant cancers,

compared with 2% of platinum-sensitive cancers.

Patients without *BRCA* reversion mutations detected in pretreatment cfDNA had significantly longer rucaparib progression-free survival than those with reversion mutations. To study acquired resistance, they sequenced 78 postprogression cfDNA, identifying eight additional patients with *BRCA* reversion mutations not found in pretreatment cfDNA.

Adding to our increasing insights into PARPi and mechanisms of resistance, results show that *BRCA* reversion mutations are detected in cfDNA from platinum-resistant or platinum-refractory HGOC, and are associated with decreased clinical benefit from rucaparib treatment. Sequencing of cfDNA can detect multiple *BRCA* reversion mutations, demonstrating the capture of multiclonal heterogeneity.

Seeking out more effective and less toxic treatment approaches against prostate cancer

First authored by Joan Carles, Principal Investigator of our Genitourinary, CNS Tumors, Sarcoma and Cancer of Unknown Primary Site Group (page 90), in collaboration with Jordi Giralt's Radiation Oncology Group (page 100), a phase II randomized study (Carles J et al. *Int J Radiat Oncol Biol Phys*. 2019) assessed the activity of radiation therapy and 3-year androgen deprivation with or without chemotherapy in patients with high-risk localized prostate cancer.

Chemotherapy with docetaxel improves survival in patients with metastatic prostate cancer. The investigators aimed to establish the efficacy of combining docetaxel with radiation therapy (RT) plus androgen deprivation in this patient population by examining the benefit of 9 weekly docetaxel administrations to RT plus three years of luteinizing hormone-releasing hormone analogues.

A total of 132 patients included in the trial received either the standard-of-care control arm with luteinizing hormone-releasing hormone analogues plus RT (arm A) or the experimental arm (RT + 9 weekly cycles of docetaxel + 3 years of androgen deprivation therapy, arm B). The primary objective was to achieve a high percentage of patients who were free of biochemical recurrence within 5 years of randomization. Secondary endpoints included biochemical recurrence-free survival (BRFS), progression-free survival (PFS), overall survival (OS), clinical response rate, biochemical response rate, and toxicity.

Results showed that concurrent weekly docetaxel can be administered safely with standard doses of RT without a significant increase in the toxicity profile. While no statistically significant differences for 5-year BRFS, PFS, and OS were observed when docetaxel was added to conventional treatment, long-term follow-up has not yet been enough to meet median PFS and OS.

Predicting risk of distant dissemination in early-stage colorectal cancer

Led by Rodrigo Dienstmann, Principal Investigator of VHIO's Oncology Data Science – ODysSey Group (page 96), results from a study (Dienstmann R et al. *Ann Oncol*. 2019) assessing the relative contribution of clinicopathological variables, genomic markers, transcriptomic subtyping and microenvironment features for outcome prediction in stage II/III colorectal cancer, confirm tumor microenvironment infiltration patterns as powerful predictors of the risk for distant dissemination in early-stage colorectal cancer (CRC).

The investigators sought to establish whether consensus molecular subtype (CMS) groups and immune-stromal infiltration patterns can better predict outcomes over tumor-node-metastasis (TNM) staging and microsatellite instability (MSI) status in early-stage CRC.

Results showed that in multivariable models, only ClinPath and MicroCells remained significant prognostic factors, with both CytoLym and CAF infiltration scores improving survival prediction beyond other markers. Patients whose tumors were CytoLym high/CAF low had better DFS than other strata. Microsatellite stable tumors had the strongest signal for improved outcomes with CytoLym high scores and the poor prognosis linked to high CAF scores was limited to stage III disease.

These findings show that tumor microenvironment infiltration patterns represent potent determinants of the risk of cancer cell spread in patients with early-stage CRC. Multivariable models suggest that the prognostic value of MSI and CMS groups is largely explained by CytoLym and CAF infiltration patterns.

In addition to the many original research articles published this year, our investigators have also authored several reviews, commentaries, opinion pieces, and invited perspectives.

As an example, Francesc Bosch, Principal Investigator our Experimental Hematology Group (page 86), co-authored a superb review (Bosch F, Dalla-Favera R. *Nat Rev Clin Oncol*. 2019), exploring novel insights into the genetic lesions involved in the pathogenesis of chronic lymphocytic leukemia (CLL), the most frequent type of leukemia in adults, and how these discoveries are influencing the clinical management and the development of new therapeutic strategies against this disease.

Importantly, my selection of the clinical science that has shaped our year offers a mere snapshot of the many contributions driven by VHIO talents. These accomplishments have only been possible in collaboration with other VHIO groups, and thanks to strong cross-border partnerships.

Together, we can and will do better.


VHIO
VALL D'HEBRON
Institut d'Oncologia

VHIO Scientific Report 2019

Programs

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VHIO Scientific Report 2019

Preclinical & Translational Research

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PRECLINICAL & TRANSLATIONAL RESEARCH

Cellular Plasticity & Cancer Group

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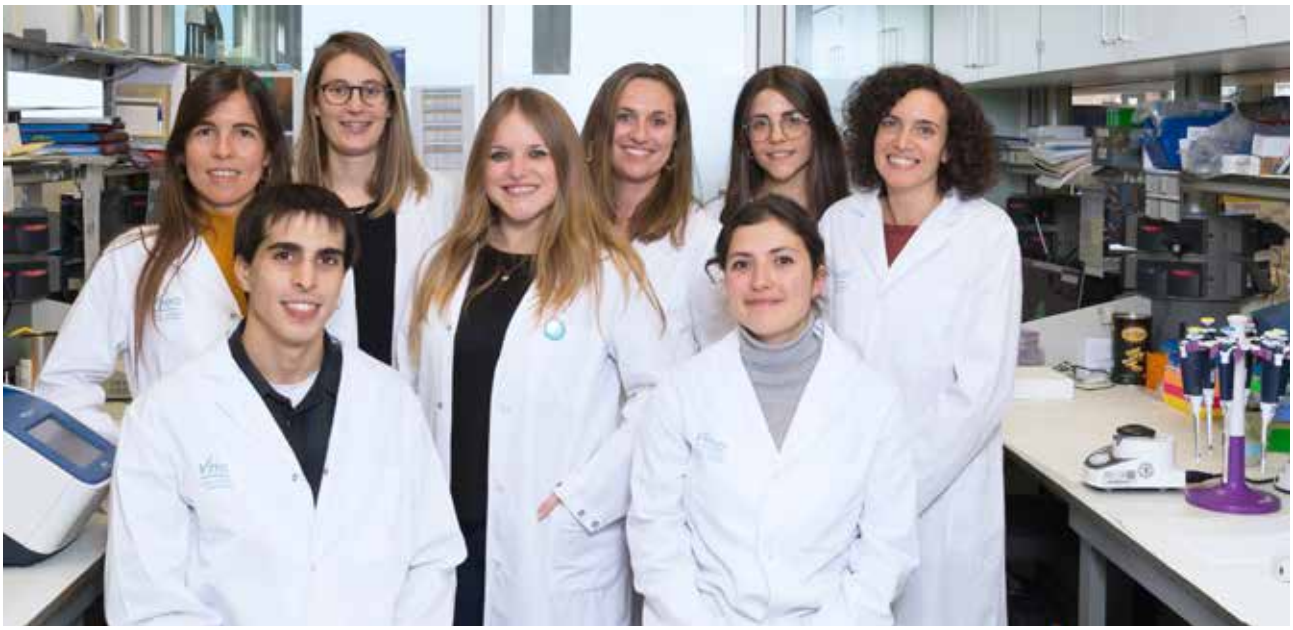

Strategic goals

- Discover and characterize novel micropeptides involved in cancer cell plasticity.
- Generate new patient-stratification tools based on cancer micropeptides.
- Develop new therapeutic-agents based on novel micropeptides.
- Decipher the molecular mechanisms governing the acquisition of stem cell properties during tumorigenesis.
- Develop new anti-cancer therapies based on the inhibition of cancer cell plasticity.

Highlights

- We were awarded with the Health Research Grant 2018 from the "la Caixa" Foundation.
- We also received the Health Research Grant from *La Mutua Madrileña Foundation*.
- María Abad was invited as a guest editor for the first ever special issue on small-ORF encoded microproteins published in *Experimental Cell Research*.
- María Abad co-devised and launched the VHIO–"la Caixa" Scientific Seminars Series as Scientific Co-Chair alongside Laura Soucek (PI, Mouse Models of Cancer Therapies Group, page 74), and Elena Élez (Medical Oncologist and Clinical Investigator, Gastrointestinal & Endocrine Tumors Group, page 88).

Summary

Our group focuses on the interplay between cellular plasticity, stem cells and cancer. Cellular plasticity is recognized today as a critical feature of cancer cells that enables them to transit between different cellular states, including reversible transitions between mesenchymal and epithelial phenotypes, or stem cell-like and differentiated states. In tumors, the acquisition of stem cell properties correlates with increased malignancy and poor prognosis, and Cancer Stem Cells (CSCs) sustain the tumor bulk and contribute to treatment resistance and disease relapse post-therapy.

In this respect, we have reported that inducing dedifferentiation with the so-called Yamanaka factors can lead to the development of a variety of tumors. We have also demonstrated that tissue damage, as the main driver of cancer, triggers cell dedifferentiation and the acquisition of stem cell properties *in vivo*.

These observations have important therapeutic implications given that chemotherapy and radiotherapy – cornerstones for the treatment of most cancers – could have the side effect of inducing stemness in non-stem cancer cells and, in turn, possibly contribute to tumor recurrence and metastasis.

Our main objective is to better understand the mechanisms and players implicated in this process, with the ultimate goal of developing novel therapies based on the inhibition of cancer cell plasticity.

Recent findings have demonstrated that some genomic regions, previously considered as non-coding (including lncRNAs), contain small open reading frames encoding for evolutionary conserved, unannotated micropeptides. The few that have been identified to-date play key functions in elemental cellular processes, leading to a new level of complexity with major implications – from basic research to the clinical setting.

Over the past three years we have focused on identifying and characterizing novel cancer micropeptides that could represent novel actors in carcinogenesis.We have discovered six new cancer micropeptides and have obtained compelling evidence *in vitro* and *in vivo* that four of them act as novel tumor suppressors, inducing cell cycle arrest, differentiation or inhibition of mesenchymal traits in cancer cells.

The identification of tumor-micropeptides could be crucial in advancing insights into cancer physiopathology. Moreover, they could also serve as new cancer biomarkers for the early detection of disease and patient stratification for tailored therapies, as well as therapeutic targets.

In 2019, we have expanded our micropeptides studies and embarked on a new project that aims to identify novel secreted micropeptides that act as crucial cellular messengers for pancreatic cancer metastasis.

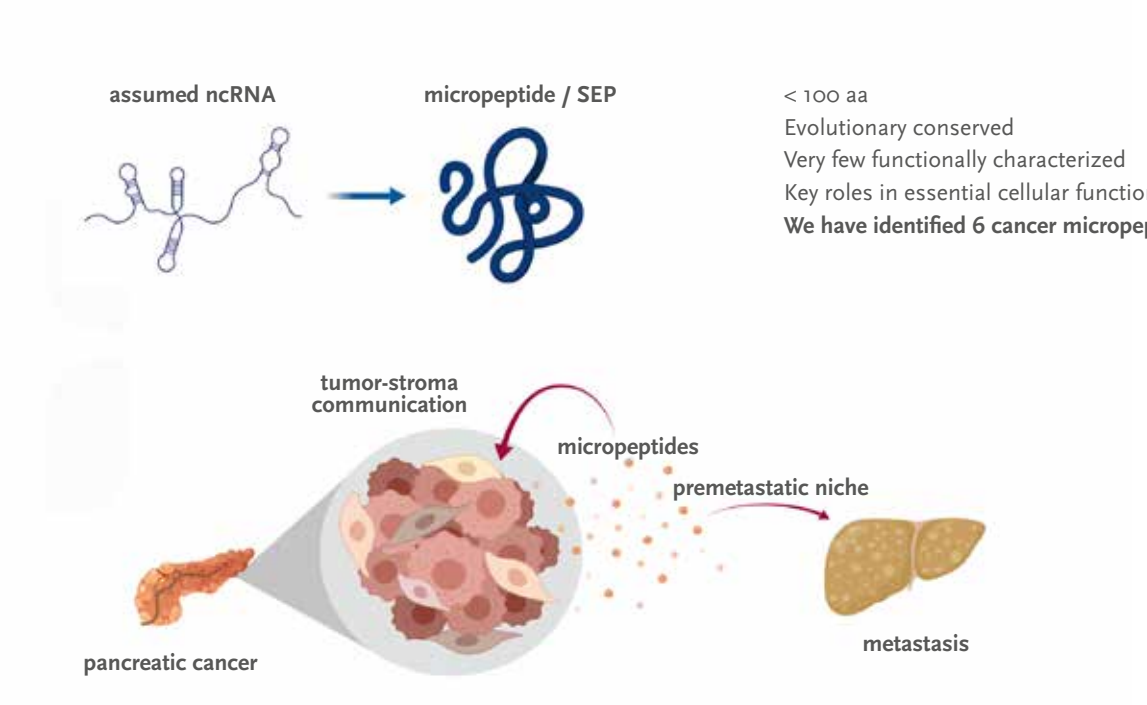

Figure: Upper panel, recent findings have revealed that many genomic regions previously considered as non-coding in fact code for unannotated micropeptides; some of them have been shown to be important for cancer. Lower panel, we are investigating if cancer cells use unannotated secreted microproteins as intercellular messengers to promote tumor growth and metastasis.

PRECLINICAL & TRANSLATIONAL RESEARCH

Chromatin Dynamics in Cancer Group

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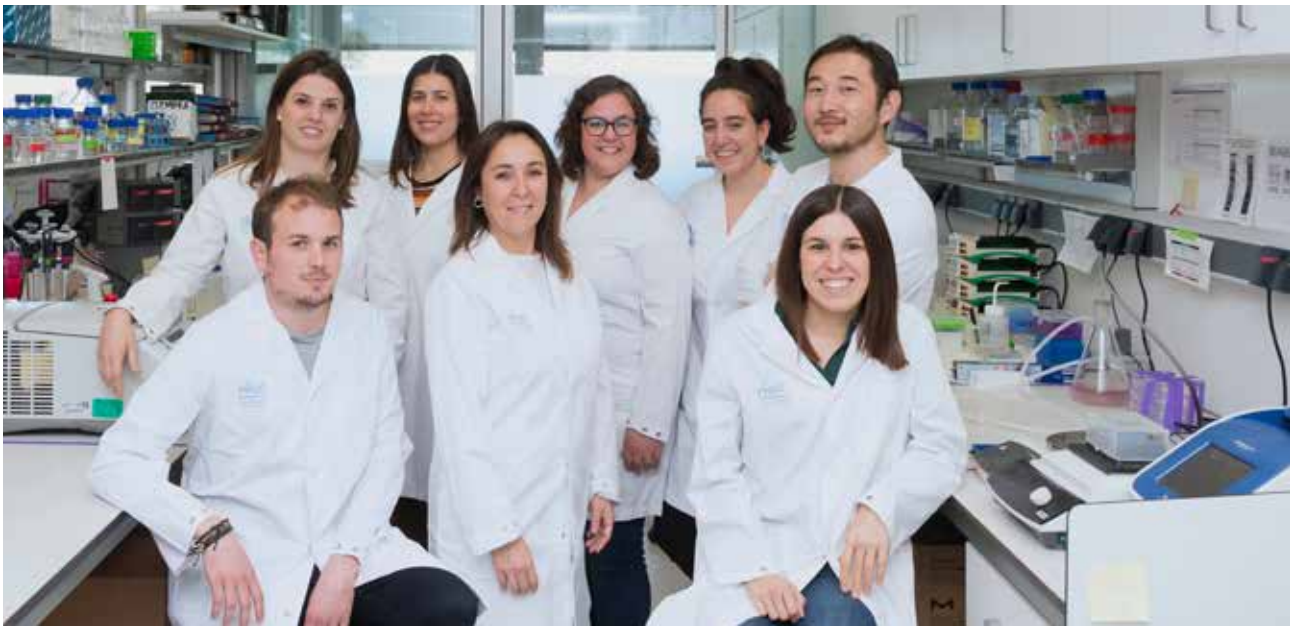

Strategic goals

The laboratory has two main goals:

1. Understand the 3D chromatin structure and dynamics in cancer from a basic research perspective;
2. Identify biomarkers and epigenetic mechanisms of drug response and resistance in ER+ breast cancer, cholangiocarcinomas, and NUT-midline carcinomas.

Specifically:

1.1. Which molecular events direct chromatin movements?
1.2. Are these events due to the specific binding of a subset of transcription factors?
1.3. To what extent are chromatin architecture changes reversible?
1.4. During the process of metastasis cells go through an intermediate state. Does this state possess a specific and genomic architecture that determines the metastatic fate? Could we blockthis ?
1.5. What is the role of oxidized H3 in other tumor types? Could we inhibit this oxidation using a peptide-based therapy?
2.1. Identification of key epigenetic components using PDXs, Cas9–cholangiocarinoma cell lines, and organoids with epigenetic drugs currently used in clinical trials.
2.2. Can we combine different drugs (based on results from 2.1) to overcome resistance?
2.3. Which are the biomarkers that will enable us to stratify patients for more effective treatments?

Highlights

- We have discovered the molecular function of oxidize Histone H3 in TNBC.
- We have consolidated our collaboration with VHIO's Gastrointestinal & Endocrine Tumors Group (PI: Teresa Macarulla, page 88) through a grant received from *La Marató TV3* Foundation.
- Gemma Serra obtained her PhD from the Pompeu Fabra University, Barcelona, with magna cum laude.

Summary

Our laboratory seeks to better understand how epigenetics and chromatin structure and dynamics affect cell behavior, with a specific focus on cancer. Through our comprehensive studies, we aim to dissect the role of epigenetic changes in cancer, identify mechanisms of response and resistance to anti-cancer medicines, and explore new therapeutic opportunities.

Over the last few years, we have elucidated epigenetic changes during EMT and cancer progression, and discovered a new histone H3 modification (oxidized H3) enriched in heterochromatin that is implicated in chromatin condensation and the transition to a metastatic cell fate (published in *Mol. Cell,* FEBS J., and *Oncogene*). We have also discovered an important role for lamin B1 in the reorganization of 3D chromatin structure during EMT (published 2018, *Nat. Commun.*).

Dedicated to fully applying these insights to the epigenetic landscape and 3D structure during this malignant transformation, we have adopted chromosome conformation–based techniques together with ChIP-seq, ATAC-seq and RNA-seq. By combining these data with excellent computational and statistical tools in standard cancer models, such as cancer cell lines, and in a large and unique collection of patient-derived xenograft (PDX) models, we will continue to navigate this largely uncharted area which shows great promise in the early diagnosis of disease.

We are equally committed to describing the association of chromatin conformation modifications with the acquisition of malignant traits and evaluating the functional consequences of these developments in genes and pathways. Next steps will involve deciphering how these alterations occur at the molecular level and more precisely identifying these putative culprits for future targeted therapy

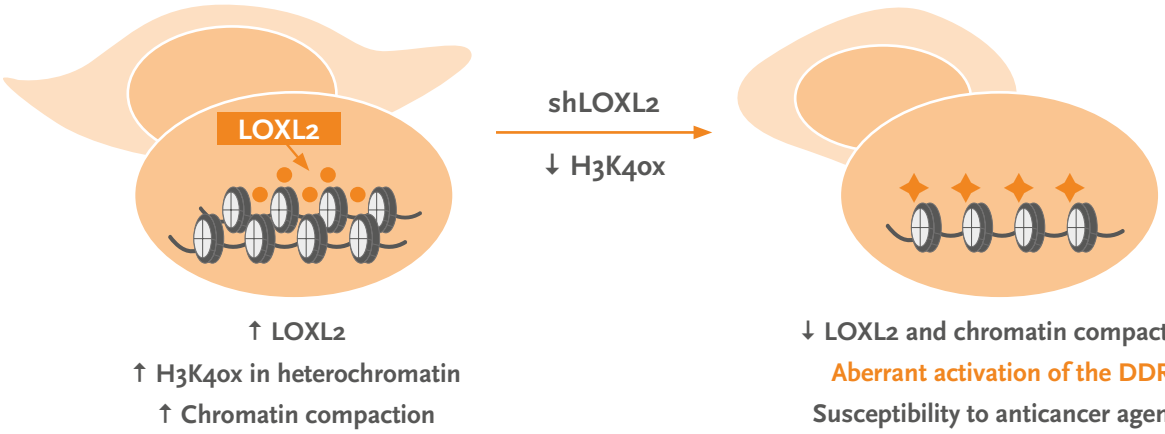

Figure: Triple negative breast cancer cells.

PI paper pick

Cebrià-Costa JP, Pascual-Reguant L, Gonzalez-Perez A, Serra-Bardenys G, Querol J, Cosín M, Verde G, Cigliano RA, Sanseverino W, Segura-Bayona S, Iturbide A, Andreu D, Nuciforo P, Bernado-Morales C, Rodilla V, Arribas J, Yelamos J, de Herreros AG, Stracker TH, Peiró S. LOXL2-mediated H3K4 oxidation reduced chromatin accessibility in triple negative breast cancer cells. *Oncogene.* 2020 Jan;39(1):79-121. Epub 2019 Aug 28.

PRECLINICAL & TRANSLATIONAL RESEARCH

Experimental Therapeutics Group

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Strategic goals

- Developing predictive biomarkers of targeted treatments in ER+ and TN breast cancers, including inhibitors directed against the DNA damage repair protein PARP and against signaling/cell cycle kinases (CDK4/6, PI3K/AKT or FGFR).
- Exploring novel treatment combinations for ER+ and TN breast cancers.
- Contributing to personalized medicine by developing a diagnostic test to better guide treatment strategies based on PARP inhibitors.
- Establishing patient tumor-derived breast cancer preclinical models to explore hypothesis-based combinatorial therapies.

Highlights

- We have contributed towards a better understanding of the mechanisms underlying BRCA1 restoration that confer resistance to PARP inhibitors.
- We described that the natural inhibitor of CDK4/6, p16, alters target engagement of CDK4/6 inhibitors, implying that high levels of p16 may impede drug binding.
- We have obtained funding from the *ERA PerMed* as well as the *CaixaImpulse* programs to clinically validate and further implement a diagnostic test to identify PARP inhibitor sensitive tumors.
- Our group has established a panel of over one hundred ER+ and TN breast cancer PDXs, mainly from the metastatic disease setting. We especially focus on models that recapitulate the progression to CDK4/6 inhibitors and *BRCA1/2*-associated tumors.

Summary

VHIO's Experimental Therapeutics Group conducts bench-to-bedside preclinical research in breast cancer to advance insights into biomarkers of response to targeted therapies. To do so, we generate preclinical models such as patient-derived xenografts (PDXs) and patient-derived cultures (PDCs) from breast cancer patient samples.

Our group has significantly contributed to the field of PI3K inhibitor resistance and we continue to explore mechanisms of resistance to CDK4/6 inhibitors, FGFR inhibitors, AKT inhibitors and AR modulators (SARMs) in breast tumors in greater depth.

Using clinically relevant PDXs we provided data to further support that loss of G1-cell cycle checkpoint control, such as mutation/loss of *RB1* or *CCND1*-amplification, is associated with lack of response to CDK4/6 blockade in estrogen receptor positive breast cancer. We have also generated a collection of PDXs containing FGFR amplification to study biomarkers of sensitivity to FGFR inhibitors; both pan-FGFR1-4 and Multi-targeted Tyrosine Kinase Inhibitors (MTKIs).

Encouraged by the early success of DNA damage repair inhibitors in germline *BRCA1/2* mutated tumors, we initiated a project aimed at identifying response biomarkers of PARP inhibitors (PARPi) as well as other DNA damage repair inhibitors including those targeting WEE1 or ATR.

Our studies underpin the capacity of germline *BRCA* mutant tumors to recover HRR functionality and develop resistance to PARPi. We have developed an assay, the RAD51predict test, which accurately identifies germline *BRCA* tumors that have restored HRR functionality and become resistant to these drugs. Importantly, this test also identifies tumors that are sensitive to PARPi through HRR alterations beyond the germline *BRCA* condition. We filed a patent (EU application in 2017 and PCT in 2018), and we are currently validating the use of this test in tumor samples from breast, ovarian and prostate cancer patients.

Finally, we are also studying the effects of PARPi on the tumor immune environment. HRR-deficient tumors have been shown to accumulate cytosolic DNA, which can elicit an innate immune signal (the STING pathway) and upregulate interferon-related genes, leading to lymphocytic infiltration and PD-L1 expression. We are testing the hypothesis that treatment of HRR-deficient tumors with PARPi elicits a DNA damage response that results in upregulation of PD-L1 and might limit the antitumor immune-mediated cytotoxicity by lymphocytes, but sensitizes to anti-PD-L1 treatments.

In short, working closely together with Cristina Saura's Breast Cancer Group (page 82), and Judith Balmaña's Hereditary Cancer Genetics Group (page 94), our team has significantly advanced the understanding of the mode of action of novel targeted therapies, identified new response biomarkers and developed a biomarker-based assay with potential clinical application. We have also demonstrated the efficacy of hypothesis-based drug combinations.

Reflective of VHIO's purely multidisciplinary and translational approach, our research is also carried out through collaborations with other groups including VHIO's Molecular Oncology (page 114), and Oncology Data Science – OdysSey (page 96) Groups directed by Paolo Nuciforo and Rodrigo Dienstmann, respectively.

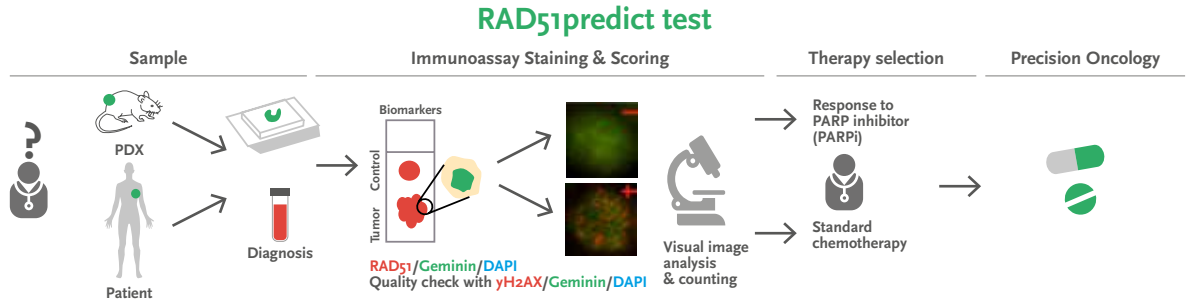

Figure 1: RAD51predict (predictor of PARPi response) is an immune-based assay, performed on FFPE tumor sections, that identifies nuclear biomarkers and determines the functionality of the HRR DNA-damage pathway and the response to PARPi therapy. It has been validated in PDX models and we are currently extending the clinical validation to several tumor types.

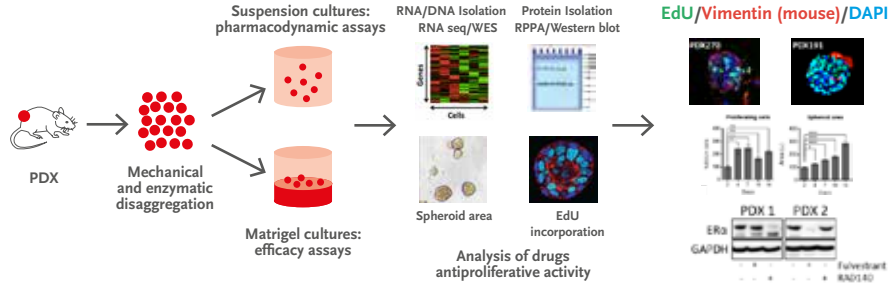

Figure 2: Generation of patient-derived culture cells (PDCs) coming from BC PDXs: after mechanical and enzymatic disaggregation, cells are seeded in suspension or matrigel cultures for pharmacodynamic analysis and for drug efficacy assay (spheroid area and EdU incorporation). Representative images and data of each approach are shown.

PI paper pick

Pellegrino B, Mateo J, Serra V, Balmaña J. Controversies in oncology: are genomic tests quantifying homologous recombination repair deficiency (HRD) useful for treatment decision making? *ESMO Open*. 2019 May 9;4(2):e000480.

Mateo J, Lord CJ, Serra V, Tutt A, Balmaña J, Castroviejo-Bermejo M, Cruz C, Oaknin A, Kaye SB, de Bono JS. A decade of clinical development of PARP inhibitors in perspective. *Ann. Oncol*. 2019 Sep 1;30(9):1437-1447.

Gourley C, Balmaña J, Ledermann JA, Serra V, Dent R, Loibl S, Pujade-Lauraine E, Boulton SJ. Moving From Poly (ADP-Ribose) Polymerase Inhibition to Targeting DNA Repair and DNA Damage Response in Cancer Therapy. *J. Clin. Oncol*. 2019 Sep 1;37(25):2257-2269.

Green JL, Okerberg ES, Sejd J, Palafox M, Monserrat L, Alemayehu S, Wu J, Sykes M, Aban A, Serra V, Nomanbhoy T. Direct CDKN2 Modulation of CDK4 Alters Target Engagement of CDK4 Inhibitor Drugs. *Mol. Cancer Ther.* 2019 Apr;18(4):771-779.

PRECLINICAL & TRANSLATIONAL RESEARCH

Gene Expression & Cancer Group

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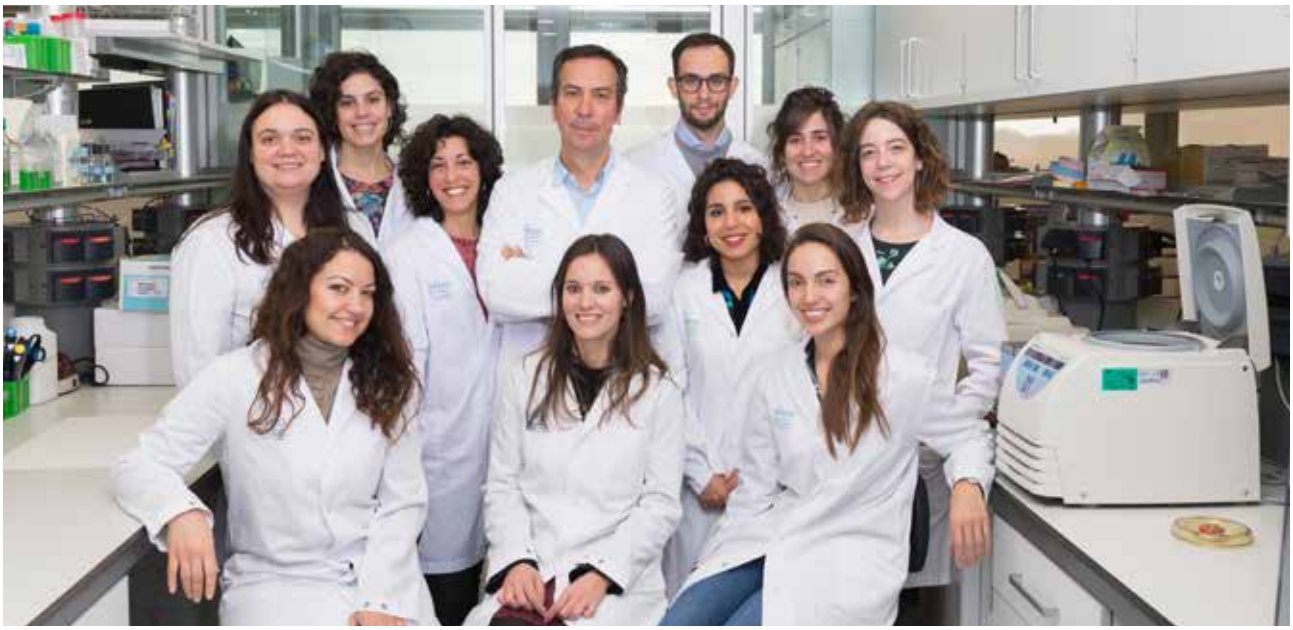

Strategic goals

- Identify new therapeutic targets against brain tumors and novel biomarkers to more precisely predict response to therapy.
- Study intratumor heterogeneity.
- Investigate the tumor microenvironment.
- Develop methods for non-invasive molecular diagnosis through the study of circulating biomarkers.
- Generate patient-derived mouse models of brain cancers.

Highlights

- We have successfully translated our discoveries into a clinical trial. Having initiated a first-in-human and first-in-class clinical trial last year with a novel compound, MSC-1 – designed by our group and developed by the VHIO born spin-off, Mosaic Biomedicals, that Joan Seoane founded in 2012 - we have now completed the Phase I study.
- We continue to develop liquid biopsies based on the analysis of cell free circulating tumor DNA in cerebrospinal fluid for the diagnosis, prognosis and monitoring of patients with brain tumors.
- Building on our previous research showing the superiority of CSF over plasma, we have embarked on a joint project funded by the Spanish Association against Cancer (AECC). In partnership with colleagues at the *Hospital 12 de Octubre* (Madrid), and *Hospital Clinic de Barcelona*, we will develop this concept and determine how it could be implemented in clinical practice.
- Joan Seoane was awarded by the Ramón Areces Foundation in 2019 to seek out novel immunotherapeutic targets in brain metastases.

  In multidisciplinary collaboration with Enriqueta Felip, PI of VHIO's Thoracic Tumors & Head and Neck Cancer Group (page 106), and Eva Muñoz, Clinical Investigator of our Breast Cancer & Melanoma Group (PI: Cristina Saura, page 82), he will analyze patients' brain metastases and compare them with respective primary tumors to reveal factors governing clinical response to immune checkpoint blockade.

Summary

We study primary brain tumors and brain metastasis; some of the most aggressive of all cancers. Both glioblastoma and brain metastasis are dismal diseases with limited therapeutic options. Advancing progress in this field towards improving outcomes for these patients is therefore critical.

Evolving heterogeneity is among one of the major challenges that are currently hampering our efforts aimed at more effectively treating brain cancers. We focus on inter-tumor heterogeneity and evolution that includes genomic heterogeneity, cancer initiating cells and stroma/immune cell heterogeneity – including the study of TGF-β and LIF.

Tumors are composed of a mosaic of cell subclones that differ in their genomic alterations. Our group explores the genomic diversity present in glioblastoma and analyzes intratumor genomic heterogeneity as it evolves over time in response to therapy. We are designing tools to monitor evolving genomic heterogeneity, and studying the use of liquid biopsies for brain cancer through the study of circulating cell free tumor DNA in cerebrospinal fluid from patients.

Specifically, we are driving cerebrospinal fluid as liquid biopsy for the real time policing of brain cancer closer to the clinic. Reflective of our expertise in developing this novel approach, we recently first-authored an article (Seoane et al. *Ann Oncol*. 2019), analyzing several studies on the use of liquid biopsy in primary and metastatic brain tumors for the diagnosis and follow-up of disease as well as the detection of mechanisms of resistance or susceptible mutations.

While no biomarker derived from liquid biopsy against these tumor types has yet been validated and integrated into clinical practice, there is an increasing body of evidence in the literature, including our findings, that points to its efficacy in the real time evaluation of malignant disease and potential in better guiding the therapeutic management of patients.

We are as equally committed to furthering insights into the role of the tumor microenvironment which, in the case of brain cancers, assumes a crucial role in cancer progression. Advancing discovery into the tumor microenvironment promises a way of combating cancer independently of its heterogeneity.

By eliminating the niche where tumors reside and thrive should help us to develop more effective anti-cancer compounds. In this context, we have reported that the cytokine LIF assumes an essential role in the tumor microenvironment and is consequently a promising therapeutic target.

Building on our previous LIF studies, where we were the first to establish a link between this multi-functional protein and cancer, as well as show that LIF blockade eliminates cancer stem cells and prevents disease progression and recurrence, subsequent research has led to the publication of a further article this year directed by our Group (Pascual-García et al. *Nat Commun*. 2019.)

We have now shown that the novel agent MSC-1, developed by VHIO, inhibits LIF and has now been shown to have a dual mechanism of action. In tumors expressing high levels of LIF, this protein promotes the proliferation of cancer stem cells. LIF blockade eliminates these tumor-initiating stem cells, putting the brakes on metastatic cell spread and cancer recurrence.

Additionally, elevated LIF expression disables the anti-tumor alarm system and stops the immune system from thwarting cancer's plans. Blocking LIF reactivates the alarm to call an anti-tumoral immune response.

Figure: Novel agent MSC-1 reactivates an immune call by LIF blockade.

PI paper pick

Pascual-García M, Bonfill-Teixidor E, Planas-Rigol E, Rubio-Perez C, Iurlaro R, Arias A, Cuartas I, Sala-Hojman A, Escudero E, Martínez-Ricarte F, Huber-Ruano I, Nuciforo P, Pedrosa L, Marques C, Braña I, Garralda E, Vieito M, Squatrito M, Pineda E, Graus F, Espejo C, Sahuquillo J, Tabernero J, Seoane J. LIF regulates CXCL9 in tumor-associated macrophages and prevents CD8 + T cell tumor-infiltration impairing anti-PD1 therapy. *Nat Commun*. 2019 Jun 11;10(1):2416.

Seoane J, De Mattos-Arruda L, Le Rhun E, Bardelli A, Weller M. Cerebrospinal fluid cell-free tumour DNA as a liquid biopsy for primary brain tumours and central nervous system metastases. *Ann Oncol*. 2019 Feb 1;30(2):211-218.

Siravegna G, Mussolin B, Venesio T, Marsoni S, Seoane J, Dive C, Papadopoulos N, Kopetz S, Corcoran RB, Siu LL, Bardelli A. How liquid biopsies can change clinical practice in oncology. *Ann Oncol*. 2019 Oct 1;30(10):1580-1590.

De Mattos-Arruda L, Sammut SJ, Ross EM, Bashford-Rogers R, Greenstein E, Markus H, Morganella S, Teng Y, Maruvka Y, Pereira B, Rueda OM, Chin SF, Contente-Cuomo T, Mayor R, Arias A, Ali HR, Cope W, Tiezzi D, Dariush A, Dias Amarante T, Reshef D, Ciriaco N, Martinez-Saez E, Peg V, Ramon Y Cajal S, Cortes J, Vassiliou G, Getz G, Nik-Zainal S, Murtaza M, Friedman N, Markowetz F, Seoane J, Caldas C. The Genomic and Immune Landscapes of Lethal Metastatic Breast Cancer. *Cell Rep*. 2019 May 28;27(9):2690-2708.

PRECLINICAL & TRANSLATIONAL RESEARCH

Growth Factors Group

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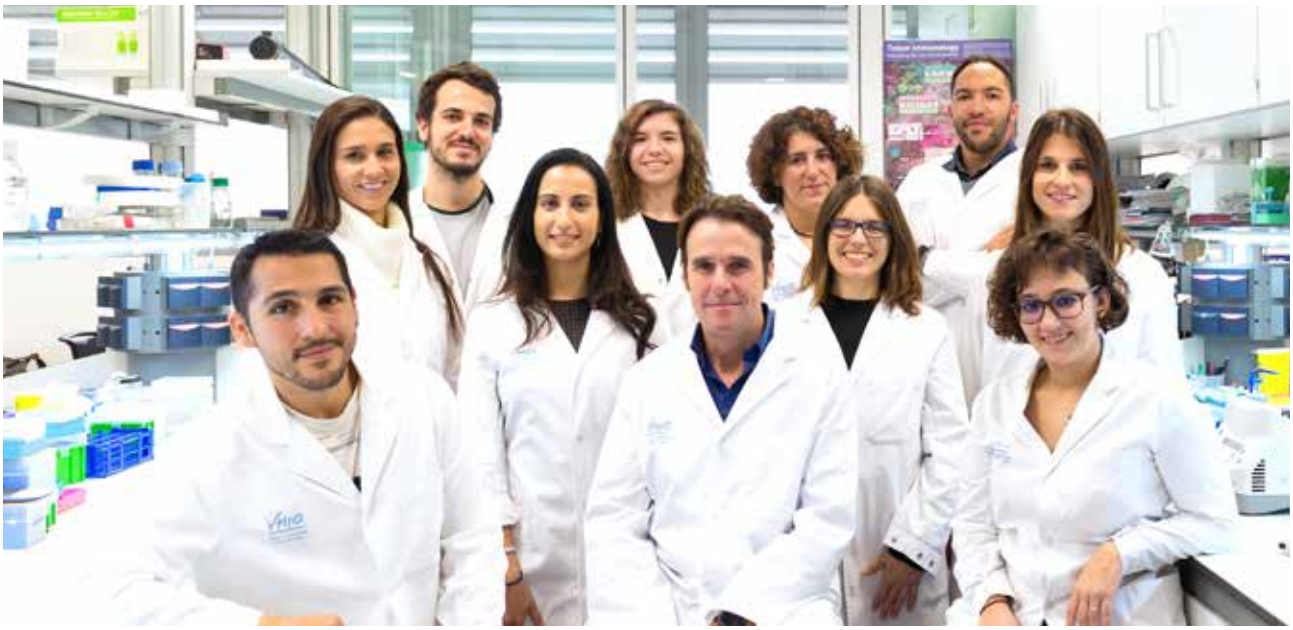

Strategic goals

- Generation and characterization of CARs against a subset of HER2 positive tumors.
- Development of an ADC against p95HER2.
- Determine the role of cellular senescence in breast cancer progression and treatment.
- Identification of new mechanisms of resistance to targeted therapies against pancreatic cancer.

Highlights

- We have initiated the development of a novel T-cell based therapy against p95HER2 positive breast cancer, p95HER2-CARs.
- Our group has characterized mechanisms of resistance against anti-HER2 therapies in breast cancer.
- We have identified novel factors implicated in pancreatic cancer resistance to MEK inhibitors.
- We have collaborated in the characterization of novel senolytic compounds.

Summary

During 2019, we continued our research line on novel immune therapies by generating novel CARs (chimeric antigen receptors). With the knowledge accumulated during the development and characterization of bispecific antibodies, we have been able to efficiently develop our CARS that are directed against the p95HER2 protein; only present in some mammary and gastric tumors, and completely absent in normal tissues. Importantly, this project has been funded by the Spanish Association Against Cancer (AECC) for the next five years.

In addition, our ever-expanding platform of breast and pancreatic cancer patient-derived experimental models led to us establishing several fruitful collaborations with several national and international groups. These partnerships have enabled us to identify novel mechanisms of resistance to anti-cancer therapies (Lambies et al., Diaz-Rodriguez et al., and Gomez-Miragaya et al.) as well as biomarkers of sensitivity to precision medicines (Kang et al., and Blasco-Benito et al.).

Our group has also contributed to the characterization of a novel antibody drug conjugate that is effective against some pancreatic tumors and triple negative breast cancers (Merlino et al.). Finally, we have also collaborated in identifying drugs targeting senescent cells which, under certain circumstances, majorly contribute to tumor progression. At VHIO, we have worked with several groups on research led by Sandra Peiró, Principal Investigator of our Chromatin Dynamics in Cancer Group (page 66), to unveil mechanisms that govern gene expression in triple negative breast cancer (Cebria Costa et al.).

Our highly collaborative approach has also allowed us to participate in several large-scale projects funded by the European Union this year, including the Immune-Image project supported by the Innovative Medicines Initiative (IMI). This large-scale consortium aims to develop novel tracers to monitor the immune response to anti-tumor therapies for research into patient-derived cancer xenografts. We are also participating in the COLOSSUS multi-center European Commission Horizon 2020-supported project; *Advancing a Precision Medicine Paradigm in metastatic Colorectal Cancer: Systems based patient stratification solutions*, for which our group is developing humanized mouse models.

Mention must also be made regarding the continued backing and support received from the Breast Cancer Research Foundation (BCRF), for which we are extremely grateful.

Several of our young talents have been awarded in 2019 including Veronica Rodilla who received a *Stop Fuga de Cerebros* grant from Roche, and Irene Rius and Faiz Bilal who defended their PhD theses on novel therapies against breast and pancreatic cancers, respectively.

Lastly, it has been an extremely productive year for the *Centro de Investigación Biomédica en Red* (CIBER-ONC: Center for the Biomedical Research Network in Oncology), under the scientific direction of our Principal Investigator, Joaquín Arribas. This recently established network is comprised of several of the most active cancer research groups across Spain, including three at VHIO.

PI paper pick

Triana-Martínez F, Picallos-Rabina P, Da Silva-Álvarez S, Pietrocola F, Llanos S, Rodilla V, Soprano E, Pedrosa P, Ferreirós A, Barradas M, Hernández-González F, Lalinde M, Prats N, Bernadó C, González P, Gómez M, Ikonomopoulou MP, Fernández-Marcos PJ, García-Caballero T, Del Pino P, Arribas J, Vidal A, González-Barcia M, Serrano M, Loza MI, Domínguez E, Collado M. Identification and characterization of Cardiac Glycosides as senolytic compounds. *Nat. Commun.* 2019 Oct 21;10(1):4731.

Blasco-Benito S, Moreno E, Seijo-Vila M, Tundidor I, Andradas C, Caffarel MM, Caro-Villalobos M, Urigüen L, Diez-Alarcia R, Moreno-Bueno G, Hernández L, Manso L, Homar-Ruano P, McCormick PJ, Bibic L, Bernadó Morales C, Arribas J, Canals M, Casadó V, Canela EI, Guzmán M, Pérez-Gómez E, Sánchez C. Therapeutic targeting of HER2-CB2R heteromers in HER2-positive breast cancer. *Proc Natl Acad Sci U S A.* 2019 Feb 26;116(9):3863-3872.

Kang SA, Guan JS, Tan HJ, Chu T, Thike AA, Bernadó Morales C, Arribas J, Wong CY, Tan PH, Gudi M, Putti TC, Sohn J, Lim SH, Lee SC, Lim YP. Elevated WBP2 expression in HER2-positive breast cancers correlates with sensitivity to trastuzumab-based neo-adjuvant therapy:A Retrospective and Multicentric Study. *Clin. Cancer Res.* 2019 Apr 15;25(8):2588-2600.

Lambies G, Miceli M, Martínez-Guillamon C, Olivera-Salguero R, Peña R, Frías CP, Calderón I, Atanassov BS, Dent SYR, Arribas J, García de Herreros A, Díaz VM. TGFβ-activated USP27X deubiquitinase regulates cell migration and chemoresistance via stabilization of Snail1. *Cancer Res.* 2019 Jan 1;79(1):33-46.

PRECLINICAL & TRANSLATIONAL RESEARCH

Mouse Models of Cancer Therapies Group

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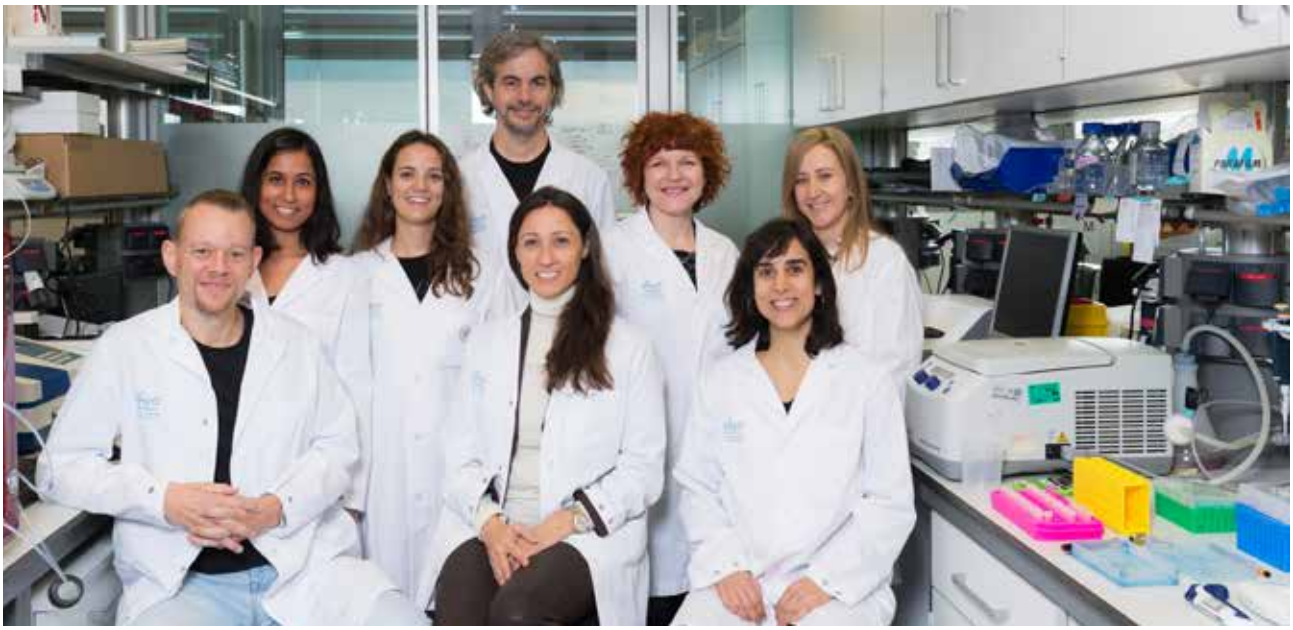
Fulbright Scholar
Jessica Lee Chambers



Strategic goals

- Validation of new Omomyc-based cell penetrating peptides for cancer therapy.
- Preclinical validation of novel anti-Myc therapies in breast, brain, lung, neuroblastoma, melanoma, colorectal cancer and multiple myeloma.
- Define the role of Myc in promoting cancer immune evasion.
- Elucidate the role of the Myc network in Max-defective gastrointestinal stromal tumors (GISTs), Small-Cell Lung Cancer (SCLC) and Pheochromocytomas (PCC).

Highlights

- The publication by Beaulieu et al. in *Science Translational Medicine* showing that the Myc inhibitory peptide Omomyc can penetrate cancer cells and act against tumors in vivo, demonstrating its potential for clinical development, has generated a great deal of media coverage.
- Laura Soucek and Jonathan Whitfield were guest editors of a special edition of *Current Opinion in Pharmacology* on *Peptides in Cancer*.
- Additional new funding granted, notably from La Marató and FIS (ISCIII).
- 2 new patent applications were filed by Laura Soucek's laboratory.

Summary

Our group focuses on the pleiotropic and ubiquitous Myc oncoprotein, whose deregulation is implicated in almost all human cancers. The technical challenges of targeting nuclear transcription 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 strategy.

Over the past few years, we have demonstrated in several mouse models that Myc inhibition has a dramatic therapeutic impact across several tumor types, with very mild and reversible side effects in normal tissue.

Encouraged by our results in mice, we are now interested in developing viable, non-toxic pharmacological options for Myc targeting in the clinic. To do so, we have created a spin-off company, Peptomyc S.L., for the development of Myc-inhibiting peptides for cancer therapy. Our laboratory in partnership with Peptomyc is currently validating our novel approach against notoriously difficult-to-treat cancers that are resistant to standard treatments and in dire need of new therapeutic avenues (i.e. KRAS-driven Non-Small Cell Lung Cancer, glioblastoma, and metastatic triple negative breast cancer).

Our group has continued to contribute to groundbreaking science by publishing in journals of international prestige. One particular highlight for 2019 is a paper describing key studies for advancing our Myc inhibitor mini-protein Omomyc towards the clinic (Beaulieu et al. *Intrinsic cell-penetrating activity propels Omomyc from proof of concept to viable anti-Myc therapy. Sci Trans Med.* 2019). This publication was very well received by the scientific community and highlighted in *Nature Reviews Cancer* and *Nature Reviews Drug Discovery* as a potential seminal milestone towards the clinical application of our first-in-class Myc inhibitor.

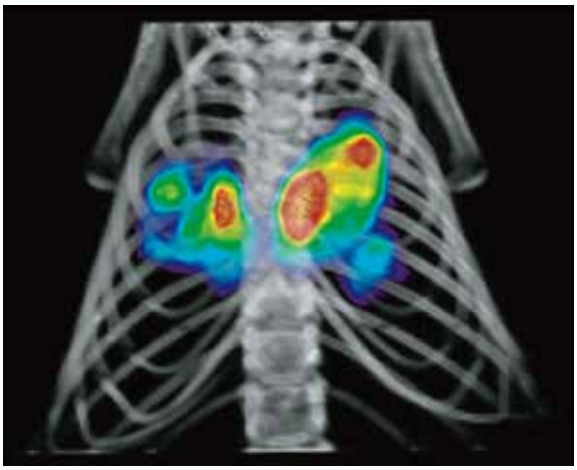
Laura Soucek and first author Marie-Eve Beaulieu also had the opportunity to add their authors' views regarding this important achievement thanks to a publication in *Molecular & Cellular Oncology*, in which they summarized the main take-home messages of their publication in *Science Translational Medicine* on Myc biology and inhibition.

This year has also celebrated several collaborative successes:

Our work with Rajeev Vibhakar's laboratory led to a publication in *International Journal of Cancer*, demonstrating the therapeutic potential of Myc inhibition in childhood rhabdoid tumors. In addition, results of our collaborative studies with teams led by Esther Vazquez, Ibane Abasolo and Antonio Villaverde, were published in *Advanced Science* and demonstrate the potential of therapeutic proteins delivered in the form of inclusion bodies to treat breast cancer.

Last but not least, we contributed to an excellent manuscript headed by Jordi Alcaraz and published in *Cancer Research*, showing that epigenetic SMAD3 repression in tumor-associated fibroblasts reduces fibrosis and sensitivity to the antifibrotic drug nintedanib in lung squamous cell carcinoma.

We have also had the privilege of hosting a Fulbright Scholar (as part of the U.S. Department of Education's International Exchange Program), Jessica Chambers, who graduated from Princeton University.



Omomyc-DFO-^{89}Zr

Figure: **Adapted from Beaulieu et al., 2019:** 3D rendering of mPET/mCT imaging of lungs of a tumor-bearing mouse 24 hours after intranasal administration of Omomyc-DFO-89Zr. CT data are displayed in gray scale and Omomyc-DFO-89Zr mPET data in color scale. The color scale is expressed as %ID/g for Omomyc-DFO-89Zr uptake.

PI paper pick

Beaulieu ME, Jauset T, Massó-Vallés D, Martínez-Martín S, Rahl P, Maltais L, Zacarias-Fluck MF, Casacuberta-Serra S, Serrano del Pozo E, Fiore C, Foradada L, Castillo Cano V, Guenther M, Romero Sanz E, Oteo M, Tremblay C, Martín G, Letourneau D, Montagne M, Morcillo Alonso MA, Whitfield JR, Lavigne P, Soucek L. Intrinsic cell-penetrating activity propels Omomyc from proof of concept to viable anti-Myc therapy. *Sci Trans Med.* 2019 Mar 20;11(484).

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Pesarrodona M, Jauset T, Díaz-Riascos ZV, Sánchez-Chardi A, Beaulieu ME, Seras-Franzoso J, Sánchez-García L, Baltà-Foix, Sandra Mancilla R, Fernández Y, Rinas U, Schwartz Jr S, Soucek L, Villaverde A, Abasolo I, Vázquez E. Targeting antitumoral proteins to breast cancer by local administration of functional inclusion bodies. *Adv Sci.* 2019 Jul 24.

Whitfield JR, Soucek L. Editorial Overview: Peptides in Cancer. *Curr Opin Pharmacol.* 2019 Jun 27. pii: S1471-4892(19)30045-1.

PRECLINICAL & TRANSLATIONAL RESEARCH

Stem Cells & Cancer Group

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Lorena Ramirez

Student
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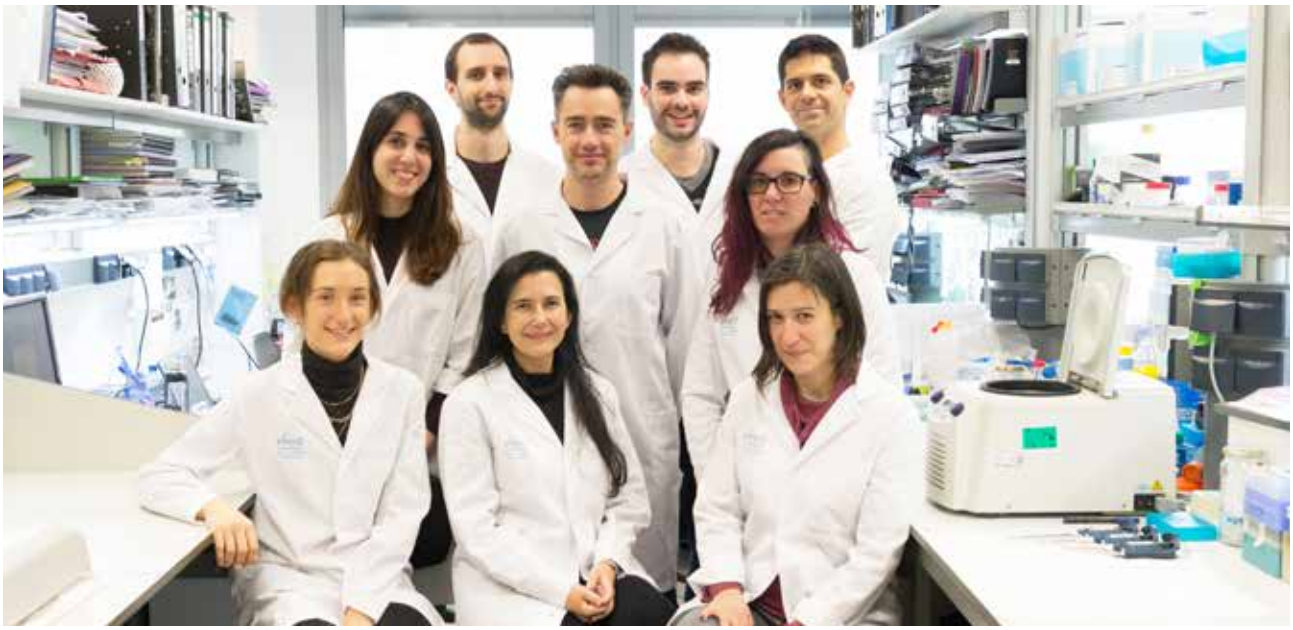

Strategic goals

- Understanding Tumor Dormancy
  Studying the role of epigenetic factors ruling dormancy in chemoresistance, minimal residual disease, relapse, dissemination and metastasis.
- ONIRIA - modulating cell dormancy to fight cancer
  Developing small drugs modulators of cancer cell dormancy to block cancer progression.
- Matching targeted therapies
  Revealing the mechanisms of response to drugs targeting EGFR, BRAF, MEK, ERK, LGR5, Wnt or PARP.
- Refining advanced cancer models
  Expanding our collection of PDXs and developing new orthotopic models and live imaging techniques.

Highlights

- Cancer cell dormancy
  We have revealed key epigenetic factors ruling cancer cell dormancy, hypoxia, chemoresistance and tumor recurrence and developed effective small drugs targeting some of them.
- Matched therapies
  Our group has described relevant determinants of response to BRAF and Notch inhibitors, and demonstrated the efficacy of new rational drug combinations and evaluated the minimal residual disease of RET fused tumors.
- Advanced cancer models
  We have generated and refined new cancer models of colorectal cancer in collaboration with several European funded networks.

Summary

Hector G. Palmer and his Stem Cells & Cancer Group are studying the mechanisms that permit tumors to escape from effective treatments and progress to advanced stages, when patients' lives are at risk.

His team uses multi-omic approaches for revealing unexpected alterations related with tumor phenotypes. The group also pairs gene editing (CRISPR/Cas) with classical signalling biochemistry in cancer cell lines as well as genetically modified mice, patient-derived organoids and xenografts (PDX) to study the functional relevance of these newly identified alterations in patients' response to therapies.

The group is also part of a global multidisciplinary task force that includes oncologists, surgeons, radiologists and nurses. This strong collaboration means that laboratory results have a rapid clinical interpretation and translation to the bedside.

Main research lines include:

Tumor cell dormancy

We study the intriguing biology of cancer cell dormancy that is responsible for chemoresistance, formation of minimal residual disease and relapse of patients. The team discovered a core epigenetic network governing dormancy of tumor cells (*J Clin Invest*. 2018), and is now studying the function of TET2, DPPA3 and other epigenetic factors governing dormancy in further depth. Importantly, we are rapidly progressing in developing drugs that modulate dormancy drivers including TET2 and defining novel biomarkers to detect chemo-resistant dormant tumor cells (DTC).

Response to target-directed drugs

Our group works in close collaboration with oncologists and pharmaceutical companies to identify molecular mechanisms responsible for the sensitivity or resistance to drugs blocking Wnt/beta-catenin, Notch, PI3K/AKT, EGFR/LGR5 or BRAF/MEK/ERK oncogenic signals (*Nat Med*. 2012; *Clin Can Res*. 2014; *Clin Can Res*. 2019). Based on our discoveries we are designing new pre-screening tests for a genetic-guided enrolment of patients in clinical trials. Crucially, our findings are helping to define new rational drug combinations to treat cancer patients with progressive disease.

Advanced pre-clinical models of cancer

We are expanding and characterizing our PDX collections (CRC, neuroendocrine, hepatic tumors and peritoneal pseudomyxoma), and improving their potential to evaluate drug efficacy and metastasis by orthotopic injection and live imaging (TC, PET and Echography).

We are developing ambitious projects through the EuroPDX Consortium (page 151), a collaboration that VHIO co-founded incorporating the main reference groups working with PDX in Europe.

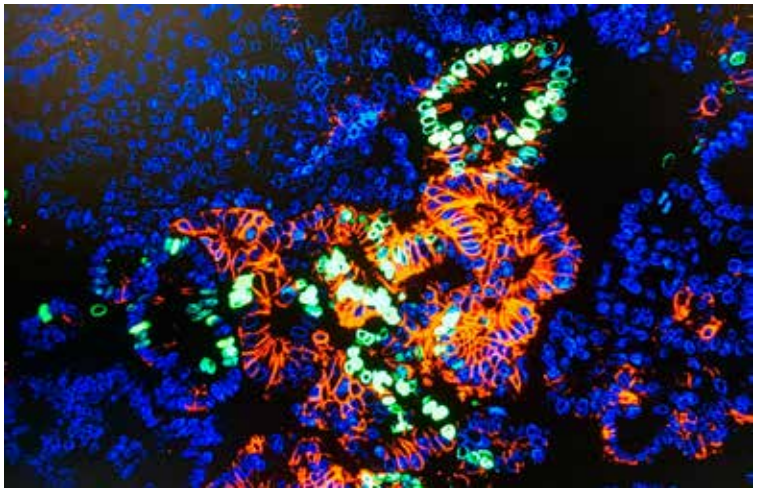

Figure: Chemoresistant dormant tumor cells (green nuclei) hide within hypoxic niches (red) in growing carcinomas.

PI paper pick

Capdevila J, Arqués O, Hernández Mora JR, Matito J, Caratù G, Mancuso FM, Landolfi S, Barriuso J, Jimenez-Fonseca P, Lopez Lopez C, Garcia-Carbonero R, Hernando J, Matos I, Nuciforo P, Hernández-Losa J, Esteller M, Martínez-Cardús A, Tabernero J, Vivancos A, Palmer HG. Epigenetic EGFR Gene Repression Confers Sensitivity to Therapeutic BRAFV600E Blockade in Colon Neuroendocrine Carcinomas. *Clin Cancer Res*. 2020 Feb 15;26(4):902-909. doi: 10.1158/1078-0432.CCR-19-1266. Epub 2019 Oct 31.

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Selenica P, Raj N, Kumar R, Brown DN, Arqués O, Reidy D, Klimstra D, Snuderl M, Serrano J, Palmer HG, Weigelt B, Reis-Filho JS, Scaltriti M. Solid pseudopapillary neoplasms of the pancreas are dependent on the Wnt pathway. *Mol Oncol*. 2019 Aug;13(8):1684-1692. doi: 10.1002/1878-0261.12490. Epub 2019 Jul 3.

PRECLINICAL & TRANSLATIONAL RESEARCH

Tumor Biomarkers Group

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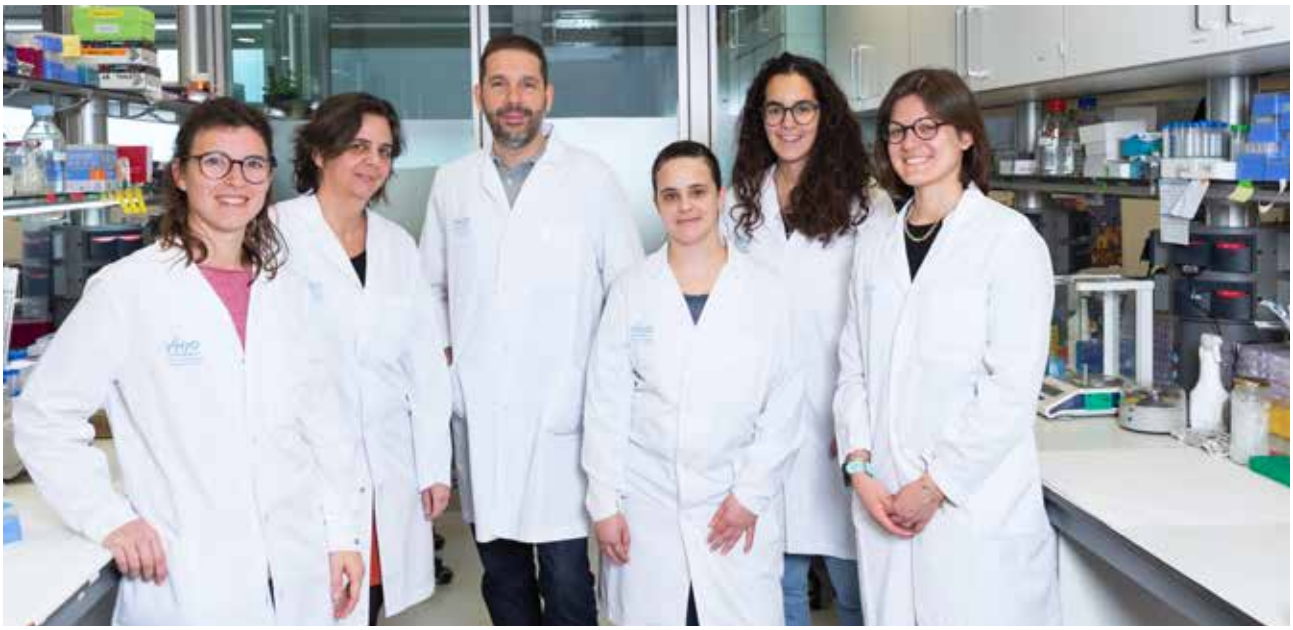
Candida Salvans
Gabriel Tamayo



Strategic goals

- Exploit the role of non-classical secretion linked to tumor invasion and metastasis to identify biomarkers and therapeutic targets against breast cancer.
- Characterize the role of extracellular HMGA1 in breast cancer invasion and metastasis.
- The characterization of mechanisms adopted by tumor cells to communicate with their microenvironment during treatment to establish secreted response/resistance biomarkers to cancer drug therapies.

Highlights

- We have recently generated monoclonal antibodies (mAbs) against HMGA1 and now validating them *in vitro*. The results obtained using the antibodies in migration, invasion and cancer signaling assays are very promising. We foresee to continue validating them as biomarkers predicting metastasis in breast cancer, and as drugs that could block invasion and metastasis in Triple-Negative Breast Cancer (TNBC).

Summary

Tumor cell communication with its microenvironment plays an important role in tumor initiation and progression. Cancer 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 these cells to communicate amongst themselves as well as with their microenvironment during tumorigenesis. We aim to exploit these data to advance biomarker and drug target discovery.

Our team's working hypothesis is that cellular signaling pathways undergo alterations during the tumorigenesis process and that these changes are translated into differential protein secretion, which can also potentially be used to identify secreted markers. Furthermore, 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 representing potential therapeutic targets.

The methodological focus of our group centers on profiling the secreted sub-proteome ('secretome') of cells by quantitative mass spectrometry. Most secreted proteins contain a signal peptide that directs their sorting to the extracellular space through the endoplasmic reticulum (ER)–Golgi secretory pathway. One of the most striking observations when secretome profiles are carefully produced and analyzed is that they contain hundreds of theoretical intracellular proteins.

Recent reports showing intracellular proteins with alternative extracellular functions suggest that new protein functions associated with alternative subcellular localizations could implicated in tumorigenesis. In line with this notion, our recent efforts within the context of therapeutics and tumor invasion have led us to hypothesize that the characterization of non-classical protein secretion could lead to the development of novel anti-cancer therapies.

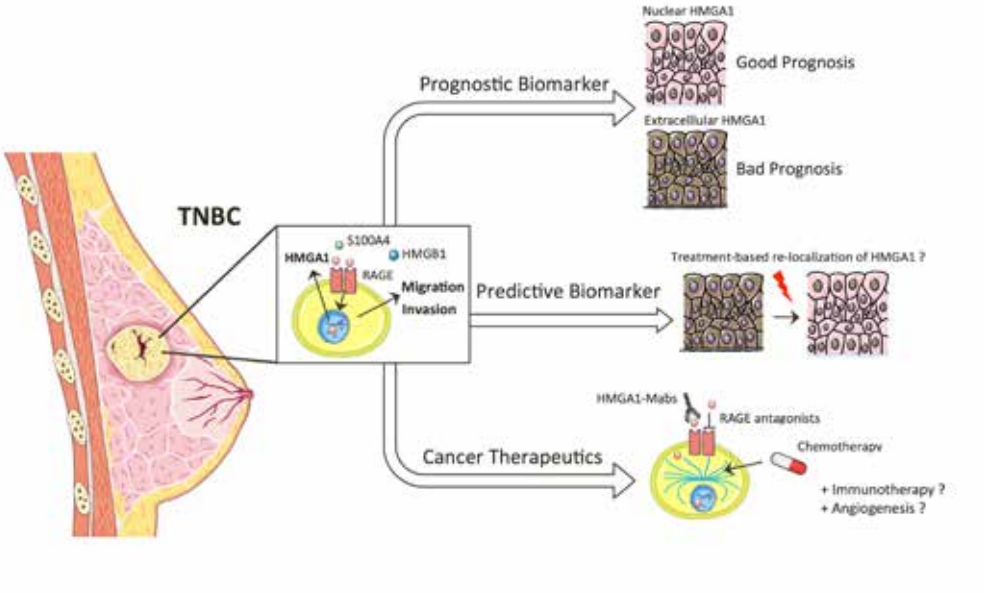


Figure: Clinical applications of extracellular HMGA1 in Triple-Negative Breast Cancer (TNBC). The secretion of HMGA1 and the alteration of its subcellular localization in metastatic TNBC has potential diagnostic and therapeutic implications in the management of TNBC patients. Reproduced from Méndez et al. *Int J Mol Sci*. 2019. 20(23), 5950.

PI paper pick

Méndez O, Pérez J, Soberino J, Racca F, Cortés J, Villanueva J. Clinical Implications of Extracellular HMGA1 in Breast Cancer. *Int J Mol Sci*. 2019. 20(23), 5950.

VHIO Scientific Report 2019

Clinical Research

Extended version online: memorias.vhio.net/2019
PDF version: memorias.vhio.net/2019/SR-VHIO-2019.pdf

CLINICAL RESEARCH

Breast Cancer & Melanoma Group

Principal Investigator
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Medical Oncologists and Clinical Fellows
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Miriam Arumi
Judith Balmaña
Meritxell Bellet
Marta Capelan
Santiago Escriva
Laia Garrigos
Patricia Gomez
Eva Muñoz
Mafalda Oliveira
Carolina Ortiz
Isabel Pimentel
Esther Zamora

Clinical Nurse Specialist
Anna Suñol

Nutritionist
Nuria Duran

Strategic goals

Breast:

- Optimize therapies by introducing novel anti-cancer treatments and adding rational combinations to combat mechanisms of resistance.
- Incorporate proteomics, genomics, and cfDNA platforms in translational research to advance insights into tumor biology.
- Apply preclinical and predictive data to help guide innovative clinical trial design in advanced disease.

Melanoma:

- Our Melanoma Unit spearheads one of the largest networks in Spain and across Europe, and is also one of the most active in metastatic and adjuvant clinical trials in melanoma and other skin tumors. Each trial is tightly connected with the corresponding translational research lines led by VHIO scientists.

Highlights

- Relevant contributions in drug approval: thanks to the leadership position of our investigators we have contributed to the approval of drugs including neratinib in the advanced setting. We are currently involved in the development of some of the most promising therapies that will be approved in the near future including tucatinib and DS8201.
- Precision medicine: thanks to VHIO's in-house prescreening program we continue to identify potential patients with molecular alterations as an enrichment strategy for clinical trials with PI3K, ESR1 or HER2 mutations. Our Institute's proteomics and cfDNA platforms have also helped us to advance insights into tumor biology.

Summary

The main area of expertise of the Breast Cancer Group led by Cristina Saura is clinical research focused on drug development and associated translational research. In addition to high patient recruitment in our studies, we also play a leading role in many of the clinical trials that we run. This enables us to have a direct impact in applying translational data to guide and accelerate drug development:

- *HER2-positive disease*: we are participating in the major trials testing novel therapies and the most promising agents in our field including DS8201, tucatinib, neratinib and SYD985. In collaboration with VHIO's Growth Factors Group, led by Joaquín Arribas (page 72), we explore cancer drug resistance to these agents through VHIO's in-house established PDX models. Alongside Paolo Nuciforo's Molecular Oncology Group (page 114), we are aiming to validate more precise methods to quantify HER2 expression.
- *Luminal disease*: In partnership with VHIO's Experimental Therapeutics Group, headed by Violeta Serra (page 68), we have developed several PDX models to advance our understanding of mechanisms of resistance to several drugs, and how they may be reversed through treatment with PI3K, AKT, CDK4/6, and BET inhibitors, as well as novel oral SERDs and different PARP inhibitors.
- *Triple negative disease*: In additon to our participation in clinical trials testing combinations of immunotherapies, we are collaborating in pioneering projects focused on cell-based therapies directed by Alena Gros, PI of VHIO's Tumor Immunology and Immunotherapy Group (page 108), to develop novel personalized T-cell therapies against cancer.
- *cfDNA*: In collaboration with VHIO's Cancer Genomics Group, led by Ana Vivancos (page 102), we have analyzed concordance of genomic alterations in synchronous tumor biopsies and ctDNA from metastatic breast cancer patients. We are now participating in various projects to address the challenging scenario of early disease and the identification of cfDNA in unexplored biological samples including breast milk.

Our Melanoma and other skin tumors Group is led by Eva Muñoz. She has actively participated in several phase I, II and III trials focused on melanoma and other skin tumors to study various emerging therapies for the treatment of these diseases. This group leads it own research program incorporating clinical investigators, dermatologists and cancer investigators at VHIO.

The team's studies focus on new target therapies and resistance to immunotherapy by conducing purely translational research centered on melanoma, skin squamous and basocelular carcinoma resistance acquisition and disease progression. Their efforts also center on mapping new therapeutic avenues, follow up standards and identifying biomarkers for a more precise treatment selection matched to the specificities of our patients.

PI paper pick

Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, Andre F, Iwata H, Ito Y, Tsurutani J, Sohn J, Denduluri N, Perrin C, Aogi K, Tokunaga E, Im SA, Lee KS, Hurvitz SA, Cortes J, Lee C, Chen S, Zhang L, Shahidi J, Yver A, Krop I; DESTINY-Breast01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N Engl J Med.* 2020 Feb 13;382(7):610-621. doi: 10.1056/NEJMoa1914510. Epub 2019 Dec 11.

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Prat A, Saura C, Pascual T, Hernando C, Muñoz M, Paré L, González Farré B, Fernández PL, Galván P, Chic N, González Farré X, Oliveira M, Gil-Gil M, Arumi M, Ferrer N, Montaño A, Izarzugaza Y, Llombart-Cussac A, Bratos R, González Santiago S, Martínez E, Hoyos S, Rojas B, Virizuela JA, Ortega V, López R, Céliz P, Ciruelos E, Villagrasa P, Gavilá J. Ribociclib plus letrozole versus chemotherapy for postmenopausal women with hormone receptor-positive, HER2-negative, luminal B breast cancer (CORALLEEN): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol.* 2020 Jan;21(1):33-43. doi: 10.1016/S1470-2045(19)30786-7. Epub 2019 Dec 11.

Hamid O, Molinero L, Bolen CR, Sosman JA, Muñoz-Couselo E, Kluger HM, McDermott DF, Powderly JD, Sarkar I, Ballinger M, Fassò M, O'Hear C, Chen DS, Hegde PS, Hodi FS.Safety, Clinical Activity, and Biological Correlates of Response in Patients with Metastatic Melanoma: Results from Phase I trial of Atezolizumab. *Clin Cancer Res.* 2019 Oct 15;25(20):6061-6072. doi: 10.1158/1078-0432.CCR-18-3488. Epub 2019 Jul 29.

CLINICAL RESEARCH

Early Clinical Drug Development Group

Director of Clinical Research at VHIO
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Elena Garralda

Associate Investigators
Senior Consultants
Judith Balmaña
Joan Carles
Enriqueta Felip
Elena Garralda
Teresa Macarulla
Ana Oaknin
Cristina Saura
Josep Tabernero

Phase I Investigators
Guzman Alonso
Maria Alsina
Guillermo Argiles
Analia Azaro
Irene Braña
Meritxell Bellet
Ana Callejo
Jaume Capdevila
Marta Capelan
Susana Cedres
Elena Elez
Santiago Escriva
Lorena Fariñas
Vladimir Galvao
Patricia Gomez
Itziar Gardeazabal
Macarena Gonzalez
Alberto Hernando
Jorge Hernando
Juan Martin
Alexandre Martinez
Joaquin Mateo
Ignacio Matos
Rafael Morales
Eva Muñoz
Alejandro Navarro
Mafalda Oliveira
Nuria Pardo
Omar Saavedra
Cesar Serrano
Cristina Suarez
Claudia Valverde
Helena Verdaguer
Maria Vieito
Esther Zamora

Data Manager
Roger Berche

Clinical Nurse Specialists
Andrea Martinez
Patricia Prieto
Natassia Wornham

Highlights

- As a leading reference in drug development at global level we clinically test the best in-class drugs. We have expanded our expertise to other cell-signaling pathway inhibitors, such as immunotherapeutics and second generation immunotherapies as well as intratumoral agents.
- We have carried out many clinical trials with novel-novel combinations including the pairing of targeted therapies (novel/novel) and, in immuno-oncology, coupling checkpoint inhibitors with either chemotherapy, targeted therapies, or other immunomodulatory agents.
- Within the scope of the VHIO-"la Caixa" Advanced Oncology Research Program (page 27), we have performed several clinical trials with patients selected on molecular alterations: mutations in AKT1, EGFR, PIK3CA, PIK3CB, PTEN, IDH1, ALK, ROS1, BRAF, NRAS, KRAS, FGFR1 and 2, MET, HER2, HER3, RET; amplifications in HER2, AKT 1, 2, and 3, FGFR1, MET, NOTCH1-4, rearrangements of NTRK1-3 ROS1, ALK, BRAF, RSPO2/3, RET and FGFR1-3, and alteration in protein expression of PTEN, or overexpression of PDL1, CEA and FAP.
- Secured funding for a program to explore primary and acquired resistance to targeted therapies. This project integrates patient-derived xenografts and the analysis of next-generation sequencing of multiple tissue samples and circulating-free tumor DNA. In collaboration with VHIO's Ana Vivancos, Violeta Serra, Héctor G. Palmer, and Joaquín Arribas – PI's of our Cancer Genomics (page 112), Experimental Therapeutics (page 68), Stem Cells & Cancer (page 76), and Growth Factors (page 72) Groups, respectively we are focusing on the fibroblast growth factor and the RET pathway.
- Co-development of molecular tests for patient screening (disease-oriented mutation panels for NGS platforms and Nanostring nCounter).
- As part of our VHIO-BBVA Foundation Comprehensive Program of Cancer Immunotherapy & Immunology - CAIMI (page 28), we have continued our line of work to characterize hyperprogressive disease with immunotherapy and are involved in a collaboration with the European Organisation for Research and Treatment of Cancer (EORTC), to advance our understanding of this phenomenon.
- We have continued our collaboration with Rodrigo Toledo, one of VHIO's Translational Investigators, to monitor the cfDNA of patients receiving immunotherapy and characterize the clonal evolution of these patients.
- Also within the context of our VHIO-BBVA Foundation's CAIMI program, we are working with Raquel Perez-Lopez, PI of our Radiomics Group (page 102), to establish a radiomic signature to predict response to immunotherapy.
- We have secured funding to add a new module to the Basket of Basket (BoB) trial, to explore FGFR inhibition (TAS120) in genomically selected populations).
- Initiated in 2019, we are evaluating the role of specific imaging of immune cell dynamics using novel tracer strategies, supported by the Innovative Medicines Initiative (IMI).
- We have started our program for advanced therapies in solid tumors, as well as implemented our own academic TILs program in collaboration with Alena Gros, PI of VHIO's Tumor Immunology & Immunotherapy Group (page 108), our CAR-T cell project funded through a grant received from the Spanish Association against Cancer (AECC) in 2019), and NK cells, research in collaboration with colleagues at the *Clínica Universitaria de Navarra*, in addition to other cell-based therapies.

Strategic goals

- Early clinical development of the best-in-class targeted therapies, determining the optimal schedule and patient population that would most likely benefit most from these drugs by participating in novel clinical trials.
- Analyze patients' tumors for molecular aberrations that may predict the efficacy of targeted agents and enable a more precise selection of the most appropriate treatment matched to the specificities of individual patients with advanced cancer.
- Link clinical research at the UITM with the various preclinical and translational research groups at VHIO, and foster powerful collaborations with different partners involved in drug development and translational research (phase I units, academic centers, consortia, pharmaceutical companies).

Summary

We focus on proof-of-concept and proof-of-mechanism trials with targeted therapies, with particular emphasis on cell signaling, cancer stem cells, and immuno-oncology. These include first-in-human studies of targeted therapies, rational combinations of targeted therapies, biomarker-driven trials, and studies in molecularly selected populations.

We link clinical research at the Research Unit for Molecular Therapy of Cancer (UITM) –"la Caixa" (page 122), with different areas of investigation carried out at VHIO, following a truly translational model. For selected projects, we match molecular biology and optimal tumor models with pharmacology and innovative clinical research by involving VHIO scientists in our trials (biomarker development, profound understanding of mechanisms of action and resistance).

We have collaborated with VHIO's Molecular Oncology (page 114) and Cancer Genomics (page 112) Groups, led by Paolo Nuciforo and Ana Vivancos, as well as Rodrigo Dienstmann, PI of our ODysSey Group (page 96), together with Susana Aguilar and Jenifer Gonzalez, to perform molecular analysis of patients' tumors. This enables us to select the optimal treatment for our patients with the experimental therapies available in our portfolio of clinical trials.

Importantly, in relation to precision oncology, VHIO is a founding member of both the WIN (Worldwide Innovative Networking in personalized cancer medicine) -page 29, and the Cancer Core Europe (CCE) – page 28, consortia. Both are non-governmental organizations that connect international (WIN) and/or European (CCE) cancer centers, including VHIO, to advance cancer diagnostics and therapeutics.

This year, our group and VHIO's UITM, have continued to lead the Basket of Baskets (BoB) trial, securing funding to add new modules to the multi-modular trial. This academic study, endorsed by Cancer Core Europe (page 28), integrates molecular prescreening, the development of new diagnostic tests such as circulating DNA, with the assessment of targeted therapies in populations of patients who, matched to specific molecular alterations, will be most likely to benefit from these treatments.

Our Early Drug Development Group and Phase I Unit (UITM), continues to establish VHIO as a leading reference in driving drug development and targeted therapies in oncology. Testament to this is the number of patients who entrust us with their care (499 patients enrolled in phase I and basket studies in 2019), the portfolio of different trials available (162 phase I trials including 22 basket studies in 2019), and the novelty of our programs in precision medicine and immunotherapy drug development. This is also evidenced by our leading role in Cancer Core Europe's Clinical Trials Task Force.

We have also fostered important alliances with the pharmaceutical industry, including this year's Partner of Choice Initiative with MedImmune, and collaborate closely with other clinical research organizations and academic centers of excellence, as well as companies dedicated to advancing personalized cancer medicine and care.

PI paper pick

Rodon J, Soria, JC, Berger R, Miller, W H, Rubin E, Kugel A, Tsimberidou A, Saintigny P, Ackerstein A, Braña I, Loriot Y, Afshar M, Miller V, Wunder F, BressonC, Martini, JF, Raynaud, J, Mendelsohn, J, Batist, G, Onn, A, Tabernero, J, Richard L Schilsky, RL, Lazar, V, Lee, JJ, Kurzrock, R. Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial. *Nat Med.* 2019 May;25(5):751-758.

Pascual-García M, Bonfill-Teixidor E, Planas-Rigol E, Rubio-Perez C, Iurlaro R, Arias A, Cuartas I, Sala-Hojman A, Escudero L, Martínez-Ricarte F, Huber-Ruano I, Nuciforo P, Pedrosa L, Marques C, Braña I, Garralda E, Vieito M, Squatrito M, Pineda E, Graus F, Espejo C, Sahuquillo J, Tabernero J, Seoane J. LIF regulates CXCL9 in tumor-associated macrophages and prevents CD8+ T cell tumor-infiltration impairing anti-PD1 therapy. *Nat Commun.* 2019 Jun 11;10(1):2416.

Hierro C, Matos I, Martin-Liberal J, Ochoa de Olza M, Garralda E. Agnostic-Histology Approval of new drugs in Oncology: are we already there? *Clin Cancer Res.* 2019 Jun 1;25(11):3210-3219.

CLINICAL RESEARCH

Experimental Hematology Group

Principal Investigator
Francesc Bosch

Translational Research Coordinator
Marta Crespo

Clinical Research Coordinator
Pau Abrisqueta

Lab Manager
Júlia Carabia

Hematologists/Lead Investigators
Pere Barba
David Beneitez
Gael Roue
Amparo Santamaria
David Valcárcel

Hematologists/Lab Specialists
Adoracion Blanco
Sabela Bobillo
Olga Benitez
Maria Cerda
Cecilia Carpio
Sally Franco
Maria Laura Fox
Laura Gallur
Mercedes Gironella
Gloria Hidalgo
Gloria Iacoboni
Macarena Izuzquiza
Marta Julia
Ana Marin
Maria Martinez
Alba Mesa
Antonieta Molero
Julia Montoro
Mayda Navarrete
Margarita Ortega
Guillem Orti
Ana Ortuño
Carles Palacio
Gloria Passarelli
Olga Salamero
Silvia Saumell
Milagros Suito
Barbara Tazon
Gustavo Robayo
Elisa Roldan
Marta Villalba

Post-Doctoral Scientists
Juan Camilo Nieto
Diana Reyes
Marcelo Lima Ribeiro

Phd Students
Cristina Hernandez
Isabel Jimenez
Daniel Medina
Carlota Pages

Technicians
Marc Antoni Armengol
Sergio Manresa
Magdalena Munuera
Lluis Puigdefabregas

Strategic goals

- We translate preclinical findings into clinical benefit by developing early phase clinical trials and defining new prognostic and predictive factors.

Main research lines currently focus on:

- Deciphering the mechanisms involved in pathogenesis and progression of hematological neoplasms.
- The preclinical study of new therapeutic regimens in experimental models that mimic the tumoral microenvironment using primary cells and patient-derived xenograft (PDX) models.
- Defining new biomarkers for a more rational and precise treatment of patients.

Highlights

- In 2019 we have participated in the publication of 45 scientific papers, and as principal authors (first, last or corresponding) of 12 of these. 60% of these articles are published in journals in the first quartile, with an accumulative Impact Factor of 95.
- This year we have initiated six new projects, four of which are supported through grants received from competitive calls, including *La Fundació La Marató de TV3*.

Summary

VHIO's Experimental Hematology Group conducts translational, pre-clinical and clinical research on hematological neoplasms of both lymphoid and myeloid origin. Our research team is composed of hematologists and biological scientists who work closely together to design, conduct and lead our programs. Our projects are always based on the unmet medical needs identified by hematologists, with the ultimate goal of translating our results to patients by developing early phase clinical trials and defining novel biomarkers to improve diagnosis, prognosis and outcomes.

We aim to provide new therapeutic options for our patients by deciphering the mechanisms involved in the pathogenesis and progression of hematological malignancies. We also conduct pre-clinical studies of new therapeutic proposals for patients diagnosed with hematological malignancies. Our group fosters the definition of new biomarkers in hematology that will lead to a more rational and precise diagnosis, prognosis and treatment of our patients.

Finally, the Hematology Clinical Trials Unit is currently participating in more than 103 clinical studies, including phase I clinical trials (n=25) and first-in-human studies of targeted therapies, both in lymphoid and myeloid malignancies. Last year 146 patients were included in our clinical trials, with 53 patients enrolled in phase I studies.

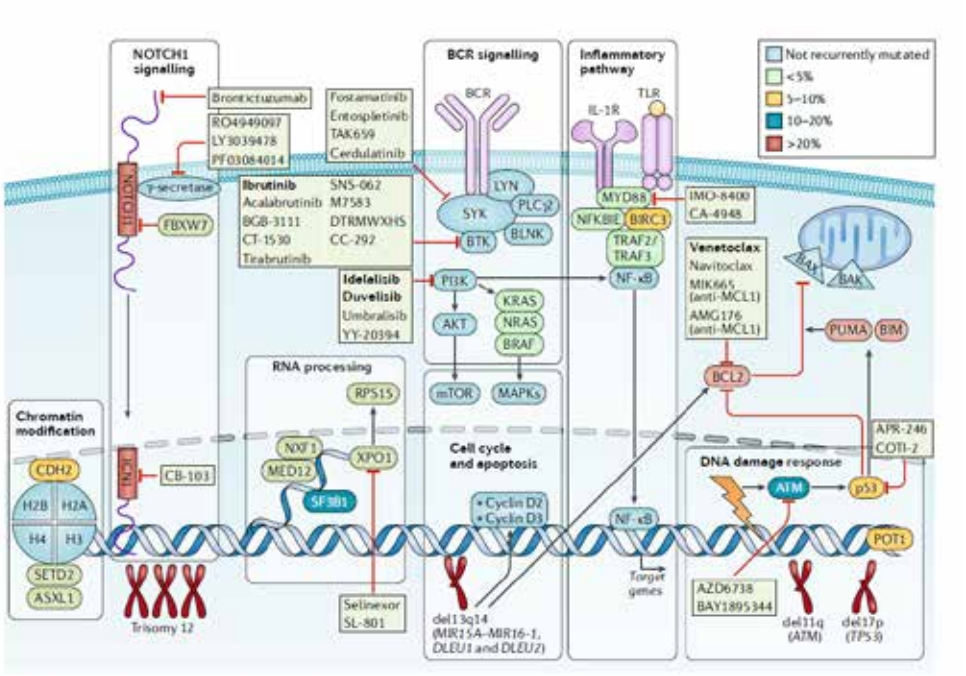


Figure: CLL genetic landscape and currently tested targeted drugs. Bosch F, Dalla-Favera R. *Nat Rev Clin Oncol.* 2019.

PI paper pick

Bosch F, Dalla-Favera R. Chronic Lymphocytic Leukaemia: From Genetics to Treatment. *Nat Rev Clin Oncol.* 16 (11), 684-701, Nov 2019.

Bosch F, Cantin G, Cortelezzi A, Knauf W, Tiab M, Turgut M, Zaritskey A, Merot J-L, Tausch E, Trunzer K, Robson S, Gresko E, Böttcher S, Foà R, Stilgenbauer S, Leblond V. Obinutuzumab plus fludarabine and cyclophosphamide in previously untreated, fit patients with chronic lymphocytic leukemia: a subgroup analysis of the GREEN study. *Leukemia*, 34 (2), 441-450. 2019.

CLINICAL RESEARCH

Gastrointestinal & Endocrine Tumors Group

Director
Josep Tabernero

Principal Investigator
Teresa Macarulla

Medical Oncologists and Clinical Fellows
Daniel Alejandro Acosta
Maria Alsina
Guillermo Argiles
Iosune Baraibar
Elvira Buxo
Jaume Capdevila
Jose Luis Cuadra
Marc Diez
Elena Elez
Jorge Hernando
Nuria Mulet
Javier Ros
Remedios Segura
Helena Verdaguer

Clinical Nurse Specialist
Ariadna Maria Garcia

Translational Investigator
Rodrigo A. Toledo

Bioinformatician
Pol Cusco

Translational Technician
Ana Belen Moreno

Translational Graduate Student
Carlota Arenillas

Masters Students
Davide Ciardiello
Giulia Martini

Strategic goals

- Discovery of novel biomarkers and validation of new prognostic/predictive biomarkers for GI/Endocrine malignancies.
- Development of relevant preclinical models in vitro (2D/ 3D cell cultures) and in vivo (i.e. PDX) with emphasis on the identification of predictive/ response markers.
- Molecular characterization of GI cancers: colorectal, gastric, pancreatic, biliary tract.
- Study of (targetable) molecular subtypes.
- Early clinical development with novel targets.
- Clinical research in later stage including translational research endpoints, focusing on the identification of prognostic/ predictive biomarkers.
- Design, leadership and development of investigator-initiated trials (IIT), including Basket studies.
- Participation in multidisciplinary/ multinational consortia and collaborative research programs of excellence.
- Validation of repurposed drugs or candidate drugs, in partnership with pharma companies or academic groups.
- Expansion of research lines in GI cancers including the study of microbiota & immunology/ immunotherapy.
- Further validation of liquid biopsies for monitoring and diagnostics of GI tumors.

Highlights

- We have advanced insights into prognostic and predictive factors for response and efficacy with targeted agents across various gastrointestinal malignancies.
- Our group has launched a non-invasive genomic platform for monitorization and discovery of resistance mechanisms for colorectal cancer using whole-exome sequencing of sequential samples of tumor and circulating tumor DNA samples
- Establishment of MAF (Mutant Allele Fraction) of BRAFV600E in plasma as a tool for the therapeutic monitoring of patients with a poor prognosis.
- Understanding the colorectal cancer microbiome: implications in therapy (studies with Fusobacterium and other microbiota, such as OPTIMISTICC – page 29).
- Participation in ongoing EU Horizon 2020-funded projects and consortia including MoTriColor, IntraColor COLOSSUS, as Principal Investigators (pages 151-157). 2019 celebrated the launch of a Horizon 2020-supported consortium: LEGACY (page 30).
- Our group is partner of many national and international consortia and networks including Cancer Core Europe (CCE) – page 28, WIN – page 29, and the CIBERONC.
- Elena Élez was awarded by the Catalonian Department of Health's Strategic Plan for Research and Innovation in Health (*Pla Estratègic de Recerca i Innovació en Salut*, PERIS), to continue working on a personalized molecular signature for liquid biopsy.

Summary

Our Gastrointestinal and Endocrine Tumors Group has actively participated in the development of molecular therapies targeting altered signaling pathways of colorectal, pancreatic, gastric and neuroendocrine cancers, among others. We have pioneered early phase clinical trials to potentiate novel anti-cancer strategies against GI cancers, as well as translational studies associated to these novel therapeutic approaches, including biomarker discovery.

We focus on seeking out prognostic and predictive factors related to targeted and immune therapies as well as identifying new response and resistance markers. Our group has also made significant progress in validating and developing liquid biopsy technologies, including BEAMing, for the more effective, less invasive monitoring of cancer in real time. Moreover, our research has shown that genomic and transcriptomic profiling are both useful for guiding treatment decision making and improving patient outcomes.

Through our participation in the OPTIMISTICC Grand Challenge *-Opportunity To Investigate the Microbiome's Impact on Science and Treatment In Colorectal Cancer-* five-year consortium funded by Cancer Research UK's Grand Challenge (page 29), we are also studying the microbiome and it is role and relevance in the development of colorectal cancer. Within the same collaborative project we have launched a novel prospective cohort, the MICROCOSM cohort, to longitudinally analyze over 2500 patients and how current colon cancer treatments affect the microbiome.

In 2019, we have participated in several clinical and translational research collaborations. Our group was instrumental in the development of clinical research studies that could well be practice changing for the treatment of two gastrointestinal malignancies: 1) colorectal tumors bearing BRAF V600E mutations and 2) gBRCA1/2 mutated pancreatic cancer (see selected papers below).

The CELAC and European Consortium for a Personalized Medicine Approach to Gastric Cancer (LEGACy – see page 30), funded through the European Union's Horizon 2020 research and innovation program, launched in 2019. As a member of this project, we coordinate data integration and perform the molecular characterization of study samples. These efforts are led by María Alsina, Medical Oncologist and Clinical Investigator of our group, and Rodrigo Dienstmann, PI of our Oncology Data Science (ODysSey) Group – page 96.

Also funded by the European Union's Horizon 2020 research and innovation programme, NoCanTher–Nanomedicine upscaling for early clinical phases of multimodal cancer therapy is a multi-center–Consortium represents an important forward step in in utilizing nanoparticles than can better target and more precisely combat cancer cells. During its 8th General Assembly in London (UK) this year, researchers discussed the project's progress and defined the final steps for reaching the clinical setting, under the leadership of our group, expected to start during the next year.

Reflected by publications in some of the most prestigious scientific titles in 2019, our group has both directed and collaborated in important studies, just some of which include:

Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer (Kopetz S, et al. *N Engl J Med.* 2019). For more information about this study which was led by our Director, Josep Tabernero, please see his Foreword, page 10.

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer (Golan T, et al. *N Engl J Med*. 2019).

Metastatic pancreatic cancer is particularly refractory to treatment. Current standard-of-care first-line treatments are associated with a median progression-free survival of approximately 6 months, and fewer than 10% of patients are alive 5 years after the initial diagnosis. In POLO study, co-authored by our PI, Teresa Macarulla, patients with a germline BRCA1 or BRCA2 mutation make up a small subgroup of those with metastatic pancreatic cancer. The poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitor olaparib has had antitumor activity in this population. Among patients with this germline BRCA mutation and metastatic pancreatic cancer, results showed that progression-free survival was longer with maintenance olaparib than with placebo.

Biomarker analysis beyond angiogenesis: RAS/RAF mutation status, tumour sidedness, and second-line ramucirumab efficacy in patients with metastatic colorectal carcinoma from RAISE - a global phase III study (Yoshino T, et al. *Ann Oncol.* 2019).

The RAISE study, led by Josep Tabernero, showed that the addition of ramucirumab to FOLFIRI improved patient outcomes, regardless of RAS/RAF mutation status, and tumor sidedness. Ramucirumab treatment provided a numerically substantial benefit in BRAF-mutated tumors.

Second-line treatment with ramucirumab+FOLFIRI improved overall survival (OS) versus placebo+FOLFIRI for patients with metastatic colorectal carcinoma (CRC). Post hoc analyses of RAISE patient data examined the association of RAS/RAF mutation status and the anatomical location of the primary CRC tumour (left versus right) with efficacy parameters.

Phase I/II Trial to Evaluate the Efficacy and Safety of Nanoparticle Albumin-Bound Paclitaxel in Combination With Gemcitabine in Patients With Pancreatic Cancer and an ECOG Performance Status of 2. Macarulla T, et al. *J Clin Oncol.* 2019.

Led by our PI, Teresa Macarulla, this study was designed to evaluate the efficacy and tolerability of different gemcitabine plus nanoparticle albumin-bound (NAB) paclitaxel (GA) dosing regimens in patients with metastatic pancreatic ductal adenocarcinoma (PDAC) and a poor PS. NAB-paclitaxel administered at different doses in combination with gemcitabine on days 1, 8, and 15 every 28 days is well tolerated and results in acceptable safety and efficacy in patients with metastatic pancreatic ductal adenocarcinoma and a poor Karnofsky performance status (PS). Moreover, gemcitabine plus nanoparticle albumin-bound (NAB) paclitaxel GA significantly improved survival compared with gemcitabine alone in patients with PDAC and a PS of 70% or greater. Due to the low number of patients with reduced PS, the efficacy of this regimen in fragile patients remains unclear.

PI paper pick

Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, Wasan H, Ciardiello F, Loupakis F, Hong YS, Steeghs N, Guren TK, Arkenau HT, Garcia-Alfonso P, Pfeiffer P, Orlov S, Lonardi S, Elez E, Kim TW, Schellens JHM, Guo C, Krishnan A, Dekervel J, Morris V, Calvo Ferrandiz A, Tarpgaard LS, Braun M, Gollerkeri A, Keir C, Maharry K, Pickard M, Christy-Bittel J, Anderson L, Sandor V, Tabernero J. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. *N Engl J Med.* 2019 Oct 24;381(17):1632-1643.

Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, Park JO, Hochhauser D, Arnold D, Oh DY, Reinacher-Schick A, Tortora G, Algül H, O'Reilly EM, McGuinness D, Cui KY, Schlienger K, Locker GY, Kindler HL. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. *N Engl J Med*. 2019 Jul 25;381(4):317-327.

Macarulla T, Pazo-Cid R, Guillén-Ponce C, López R, Vera R, Reboredo M, Muñoz Martin A, Rivera F, Díaz Beveridge R, La Casta A, Martín Valadés J, Martínez-Galán J, Ales I, Sastre J, Perea S, Hidalgo M. Phase I/II Trial to Evaluate the Efficacy and Safety of Nanoparticle Albumin-Bound Paclitaxel in Combination With Gemcitabine in Patients With Pancreatic Cancer and an ECOG Performance Status of 2. *J Clin Oncol*. 2019 Jan 20;37(3):230-238.

Yoshino T, Portnoy DC, Obermannová R, Bodoky G, Prausová J, Garcia-Carbonero R, Ciuleanu T, García-Alfonso P, Cohn AL, Van Cutsem E, Yamazaki K, Lonardi S, Muro K, Kim TW, Yamaguchi K, Grothey A, O'Connor J, Taieb J, Wijayawardana SR, Hozak RR, Nasroulah F, Tabernero J. Biomarker analysis beyond angiogenesis: RAS/RAF mutation status, tumour sidedness, and second-line ramucirumab efficacy in patients with metastatic colorectal carcinoma from RAISE-a global phase III study. *Ann Oncol.* 2019 Jan 1;30(1):124-131.

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

Principal Investigator
Joan Carles

Medical Oncologists and Clinical Fellows
Macarena Gonzalez
Joaquin Mateo
Rafael Morales
Cesar Serrano
Cristina Suarez
Claudia Valverde
Maria Vieito

Clinical Nurse Specialist
Alexandre Sierra

Strategic goals

- Design and develop clinical trials covering all malignancies studied by our group. We seek to provide our patients with the most novel and optimal treatments including immune-based therapeutics, targeted therapies and new chemotherapies.
- Conduct clinical trials at different stages of disease with emphasis on a histology-tailored design and multidisciplinary approach.
- Develop new tools and techniques including liquid biopsy for our patients to more precisely tailor treatments against mCRPC, GIST and kidney cancer.
- Microbiota studies as a biomarker for immunotherapies to treat bladder and kidney cancers.
- Consolidate our biopsy program (mainly in bone), for patients with mCRPC to target genomic alterations including PI3K pathways, DNA repair genes, and androgen receptor alterations.
- Further consolidate our Kidney Cancer Task Force at VHIO in collaboration with researchers at the Vall d'Hebron Research Institute (VHIR) and Biomedical Research Institute of Bellvitge (IDIBELL).
- Expand our translational research platform for glioblastoma in collaboration with VHIO's Gene Expression & Cancer Group.
- Develop our translational platform for GIST and expand research in collaboration with the Spanish Sarcoma Group (GEIS), and other European referral centers. We are also an active member of the European References Network (ERN).

Highlights

- We have consolidated our Task Force and our Serum Bank in Prostate Cancer. This allows us to participate in different translational studies a sell as lead the IRONMAN Project in Spain.
- Expansion of our Phase I program across all tumor types studied by our group.
- Fostered and developed new collaborations with different VHIO as well as external research groups.

Summary

We are dedicated to advancing clinical and translational research against cancer and have extensive experience and expertise in treating various neoplasms. We design and develop clinical trials for genitourinary malignancies at different stages of disease in collaboration with urologists and radiation therapists.

During 2019 we continued to consolidate our expert Prostate Task Force. By closely connecting clinical and translational researchers at VHIO and the Vall d'Hebron Research Institute (VHIR), we have initiated translational projects focused on prostate cancer. We are also doing the same for kidney cancer in pursuit of similar goals in collaboration with other partners including Biomedical Research Institute of Bellvitge (IDIBELL).

Over recent years, several advances have been reported in the more effective treatment of GU malignancies. Immunotherapy (IO) is proving increasingly important against bladder and kidney cancers. Concerning the latter, immune-based therapies in combination with others or paired with antiangiogenics is considered the new standard treatment for first-line therapy. Both approaches have proven more effective compared with antiangiogenic therapy alone.

In bladder cancer immunotherapy has also been shown as superior to chemotherapy in second line and in first-line for ineligible patients. It has recently been shown that immunotherapy in combination with concurrent chemotherapy or as maintenance after 4/6 cycles of chemotherapy in first-line improves progression-free survival (PFS).

Our group –along with others- has observed that immunotherapy could also be effective for certain subgroups of patients with castration-resistant prostate cancer. We are currently participating in phase I studies to assess immune-based cancer medicines for the treatment of this patient population.

We have also participated in various clinical trials using checkpoint inhibitors for the adjuvant treatment of bladder and kidney cancers with high risk of recurrence. Working closely with our Vall d'Hebron University Hospital's Urology Department and other experts in high-risk tumors, we are currently running studies aimed at improving outcomes for patients with non-muscle- invasive bladder cancer.

We collaborate with various other renowned research centers including the Cleveland Clinic (Ohio, USA), University of California, San Francisco (California, USA). We also participate in studies carried out in partnership with the Gustave Roussy Institute (Paris, France), Barts Health NHS Trust – Hospital (London, UK), and Kantonsspital St. Gallen (Switzerland).

This year we have expanded our translational research program in prostate cancer working alongside VHIO's Prostate Cancer Translational Research Group, led by Principal Investigator Joaquin Mateo (pages 98-99). We have performed 20 biopsies (16 bone and 4 prostate biopsies) and aim to correlate blood samples with these tests.

Our main focus is metastatic castration-resistant prostate cancer and we are working on a project led by Joaquin, entitled: *Clinical Qualification of DNA Repair Defects as Biomarkers in Metastatic Prostate Cancer Using Integrated Genomics and Tissue-Based Functional Assays*. This research is supported by the US Department of Defense's (DoD) Congressionally Directed Medical Research Program. Additionally, we are participating in the IRONMAN project lead by the Memorial Sloan Kettering Cancer Center (MSKCC – New York, USA). Led by VHIO we collect patients' reported outcomes in parallel with serum. This research is supported by Movember and the FERO Foundation.

We are also partnering with VHIO's Radiomics Group headed by Raquel Perez-Lopez (pages 102-103), to analyze MRI alterations in patients who have started hormonal treatments for metastatic prostate cancer and correlate these data with bone biopsies performed in parallel.

This particular project, *iPROMET: a study for clinical validation of whole-body diffusion-weighed MRI as a response biomarker of bone metastases in patients with prostate cancer,* counts on the combined expertise of a urologist, radio-oncologist, radiologist and medical oncologist to establish a circuit for the systematic metastatic tissue acquisition from prostate cancer patients at our Hospital.

We have also expanded our avatar program for kidney cancer tumors in collaboration with IDIBELL and implanted more than 30 samples. Additionally, we continue to participate in the REVOLUTION project, pREdiction of niVOLUmab acTION metastatic renal cancer patients: Treg function, tumoral access and NK interactions as predictive biomarkers of immunotherapy, supported by TRANSCAN-2 ERA-NET, under the scope of the EU Framework Programme Horizon 2020.

In collaboration with other professionals in neurosurgery and radiation therapy, we lead and develop several multidisciplinary clinical studies and phase I trials in CNS tumors. Additionally, it is thanks to a project with our Gene Expression & Cancer Group led by Joan Seoane (pages 70-71), that we continue to develop VHIO's translational research platform for glioblastoma. We analyze cfDNA in blood and cephaloraquidic liquid for assessing primary CNS tumors and metastases.

Our group also collaborates in a project directed by the European Organisation for Research and Treatment of Cancer (EORTC, Brussels, Belgium), against several tumor types, working on CNS tumors: *Cancer Patients for Efficient Clinical Trial Access* (SPECTA). The main objective is to screen patients and develop academic clinical trials based on molecular stratification. This initiative is supported by the European Cancer Research Fund (ECRF) and Walgreens Boots Alliance (WBA). We are also active at the national level in a medulloblastoma platform to better define and classify these cancers.

We continue to work closely with the Spanish Sarcoma Group (GEIS) on clinical trials at different stages of disease with emphasis on a histology-tailored design and are currently setting up a translational platform for sarcomas and basic research in partnership with IDIBELL and the Cancer Research Center of Salamanca – CIC (Spain). For GIST tumors we are working with Jonathan Fletcher's lab at the Brigham and Women's Hospital (Boston, USA).

Importantly, we have been recognized by the Spanish Ministry of Health as a Spanish National Health System Reference Service (*Centros, Servicios y Unidades de Referencia del Sistema Nacional de Salud* - CSUR), to treat sarcoma patients. This accreditation enables us to participate in the European References Network (ERN) for sarcoma tumors and other rare diseases.

One of our group members, César Serrano, who carried out a three-year fellowship at the Dana Farber Cancer Institute (Boston, USA), has established an independent line of experimental research on sarcomas. Notably, his translational studies have led to novel treatment strategies against sarcoma, including the design of a phase Ib clinical trial to assess – for the first time in oncology – a rapid-alternation drug schedule of targeted therapies (NCT02164240). In 2019 he set up his own research group, VHIO's Sarcoma Translational Research (pages 104-105).

During this year we have consolidated different clinical trials with new drugs in GIST by leading and participating in phase I-II-III studies. As this report went to print, one of these studies led to the U.S. Food and Drug Administration's (FDA) January 2020 approval of Avapritinib for the treatment of adult patients harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including D842V mutations.

Our Serum Bank now incorporates the majority of tumor types that we study (CNS tumors, GIST; renal cell carcinoma and CRPC), and we will continue to collect samples from our patients.

Dedicated to promoting education and exchange, in 2019 we welcomed six fellows from in (5) and outside (1) of Spain for three-month short stays.

PI paper pick

De Wit R, De Bono J, Sternberg CN, Fizazi K, Tombal B, Wulfing C, Kramer G, Eymard JC, Bamias A, Carles J, Iacovelli R, Melichar B, Sverrisdottir A, Theodore C, Feyerabend S, Helissey C, Ozatilgan A, Geffriaud-Ricouard C, Castellano D, CARD Investigators. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med.* 2019 Dec 26;381(26):2506-2518.

Gulley JL, Borre M, Vogelzang NJ, Ng S, Agarwal N, Parker CC, Pook, David W; Rathenborg P, Flaig TW, Carles J, Saad F, Shore ND, Chen L, Heery CR, Gerritsen WR, Priou F, Langkilde NC, Novikov A, Kantoff PW. Phase III Trial of PROSTVAC in asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. *J Clin Oncol.* 2019 May 1;37(13):1051-1061.

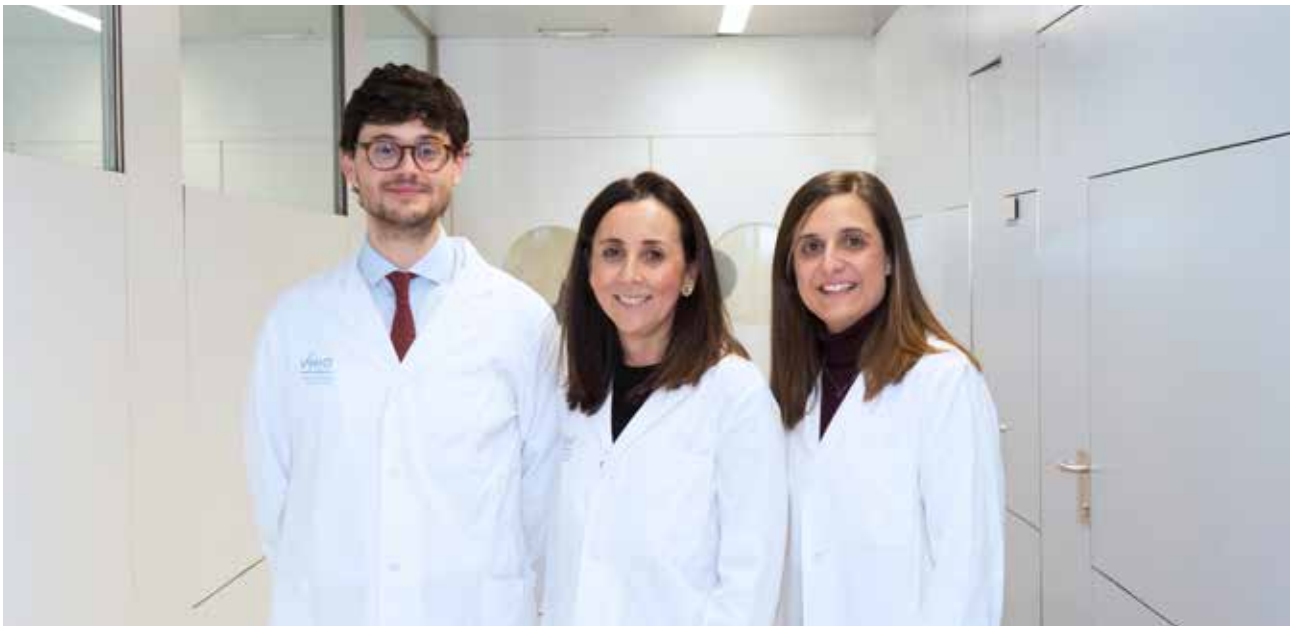
Carles J, Pichler A, Korunkova H, Tomova A, Ghosn M, El Karak F, Makdessi J, Koroleva I, Barnes G, Bury D, Ozatilgan A, Hitier S, Katolicka J. An observational, multicentre study of cabazitaxel in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel (CAPRISTANA). *BJU Int.* 2019 Mar;123(3):456-464.

Carles J, Gallardo E, Domenech M, Font A, Bellmunt J, Figols M, Mellado B, Saez MI, Suarez C, Mendez MJ, Maroto P, Luque R, de Portugal T, Aldabo R, Bonfill T, Morales-Barrera R, Garcia J, Macia, S, Maldonado X, Foro P. Phase 2 Randomized Study of Radiation Therapy and 3-Year Androgen Deprivation With or Without Concurrent Weekly Docetaxel in High-Risk Localized Prostate Cancer Patients. *Int J Radiat Oncol Biol Phys.* 2019 Feb 1;103(2):344-352.

Gynecological Malignancies Group

Principal Investigator
Ana Oaknin

Medical Oncologists
Lorena Fariñas
Francisco Grau



Strategic goals

- Determine the best treatment approaches against advanced gynecologic malignancies through optimally designed international clinical trials.
- Contribute to early drug development in gynecologic cancers.
- Expand our translational research program to advance precision medicine.
- Specifically, we strive to:
  - Further develop novel immunotherapeutics for the treatment of endometrial cancer and cervical cancer.
  - Apply cellular therapy to metastatic cervical cancer through the adoptive cell transfer of tumor infiltrating lymphocytes (TILs).
  - Consolidate our position as a reference site for clinical research in gynecologic malignancies.
  - Continue to be a referral center for patients who seek to participate in our clinical studies.

Highlights

Our group continues to take the lead on other clinical trials that might define the next generation of treatment regimens, including:

- Ana Oaknin signed the FDA filling of dostarlimab (PD-1 inhibitor) in MSI-H recurrent endometrial cancer after successfully presenting the results of the clinical trial included in the file at the Society of Gyencologic Oncology's (SGO) 2019 Annual Meeting (Honolulu, Hawaii, March 16-19).
- Ana is global lead of a phase III Investigator initiated trial for first line metastatic cervical cancer (the BEATcc trial) running in USA, EU and Japan. She is also the European lead investigator of the EMPOWER trial, a phase III study aimed at testing cemiplimab in recurrent cervical cancer. Both of these trials promise potentially practice-changing data.
- She is also the lead investigator of the ATOMICC Trial to investigate the role of dostarlimab as maintenance therapy in locally advanced cervical cancer.

These efforts have positioned Ana Oaknin as a Key Opinion Leader in our field which is also reflected by her participation at some of the largest, global oncology conferences and meetings.

Summary

Our clinical research group focuses on gynecological malignancies and the development of novel therapies against these tumor types. We are also members of some of the most relevant societies in gynecological oncology including the Gynecologic Cancer InterGroup (GCIG) for which we are appointed as the Spanish Representative on the Cervical Cancer as well as phase II trial Committees, the Gynecologic Oncology Group (GOG), as the Spanish clinical lead, as well as the European Network of Gynecological Oncology Trial Groups (ENGOT).

Our group contributes to the advancement of the treatment of gynecological malignancies. Over the past few years, we have participated in the development of a number of therapies that constitute the current standard of care in different malignancies. As an example, our PI, Ana Oaknin, is one of the co-authors of the SOLO-1 trial (Olaparib as maintenance therapy in BRCA mut Ovarian Cancer patients) – Moore et al. *N Engl J Med.* 2018. This clinical trial has changed first line therapy for those patients diagnosed with ovarian cancer harboring a BRCA mutation.

In 2019 we have participated in several important clinical trials that have generated new and compelling data in gynecologic malignancies. As an example, we co-authored a study showing that the addition of veliparib to standard chemotherapy based on paclitaxel/carboplatin, and as maintenance therapy, significantly prolonged progression free survival of all our patients recently diagnosed with high-grade ovarian cancer (Coleman RL et al. *N Engl J Med.* 2019).

As part of our evolving knowledge on PARPi and mechanisms of resistance, our deep liquid biopsy analysis performed on patients' blood samples collected during their participation in the ARIEL-2 study, has enabled us to identify BRCA reversion mutations as one of the key players (Lin KK et al. *Cancer Discov.* 2019).

While metastatic cervical cancer is a devastating disease, over recent years we have succeeded in broadening our therapeutic approaches which have mainly been driven by immunotherapy. We have been studying the role of the anti-PD1 molecule nivolumab in those patients who have progressed after failure to respond to platinum therapy. We have observed encouraging activity in this patient population with a notoriously poor prognosis which certainly warrants further investigation (Naumann RW et al. *J Clin Oncol.* 2019).

In addition, our Principal Investigator, Ana Oaknin, also serves on the Executive Board as Vice President for the *Grupo Español de Investigación en Cáncer de Ovario* – GEICO (the Spanish Ovarian Cancer Research Group), and as Faculty of the European Society for Medical Oncology's (ESMO) Annual Meeting's Gynecological Tumors Track, for which she was appointed as the Track Chair at the ESMO Congress 2019 (Barcelona, Spain, 27 September-01 October), where she discussed the selected presentations of the Track's Presidential Symposium.

PI paper pick

Lin KK, Harrell MI, Oza AM, Oaknin A, Ray-Coquard I, Tinker AV, Helman E, Radke MR, Say C, Vo LT, Mann E, Isaacson JD, Maloney L, O'Malley DM, Chambers SK, Kaufmann SH, Scott CL, Konecny GE, Coleman RL, Sun JX, Giordano H, Brenton JD, Harding TC, McNeish IA, Swisher EM. BRCA Reversion Mutations in Circulating Tumor DNA Predict Primary and Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma. *Cancer Discov.* 2019 Feb;9(2):210-219.

Naumann RW, Hollebecque A, Meyer T, Devlin MJ, Oaknin A, Kerger J, López-Picazo JM, Machiels JP, Delord JP, Evans TRJ, Boni V, Calvo E, Topalian SL, Chen T, Soumaoro I, Li B, Gu J, Zwirtes R, Moore KN. Safety and Efficacy of Nivolumab Monotherapy in Recurrent or Metastatic Cervical, Vaginal, or Vulvar Carcinoma: Results From the Phase I/II CheckMate 358 Trial. *J Clin Oncol.* 2019 Nov 1;37(31):2825-2834.

Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. *Lancet.* 2019 Jan 12;393(10167):169-182. Review.

Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, Okamoto A, Moore KN, Efrat Ben-Baruch N, Werner TL, Cloven NG, Oaknin A, DiSilvestro PA, Morgan MA, Nam JH, Leath CA 3rd, Nicum S, Hagemann AR, Littell RD, Cella D, Baron-Hay S, Garcia-Donas J, Mizuno M, Bell-McGuinn K, Sullivan DM, Bach BA, Bhattacharya S, Ratajczak CK, Ansell PJ, Dinh MH, Aghajanian C, Bookman MA. Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. *N Engl J Med.* 2019 Dec 19;381(25):2403-2415.

CLINICAL RESEARCH

Hereditary Cancer Genetics Group

Principal Investigator
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Senior Scientists
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Sara Gutiérrez Enríquez

Post-Doctoral Fellow
Sandra Bonache

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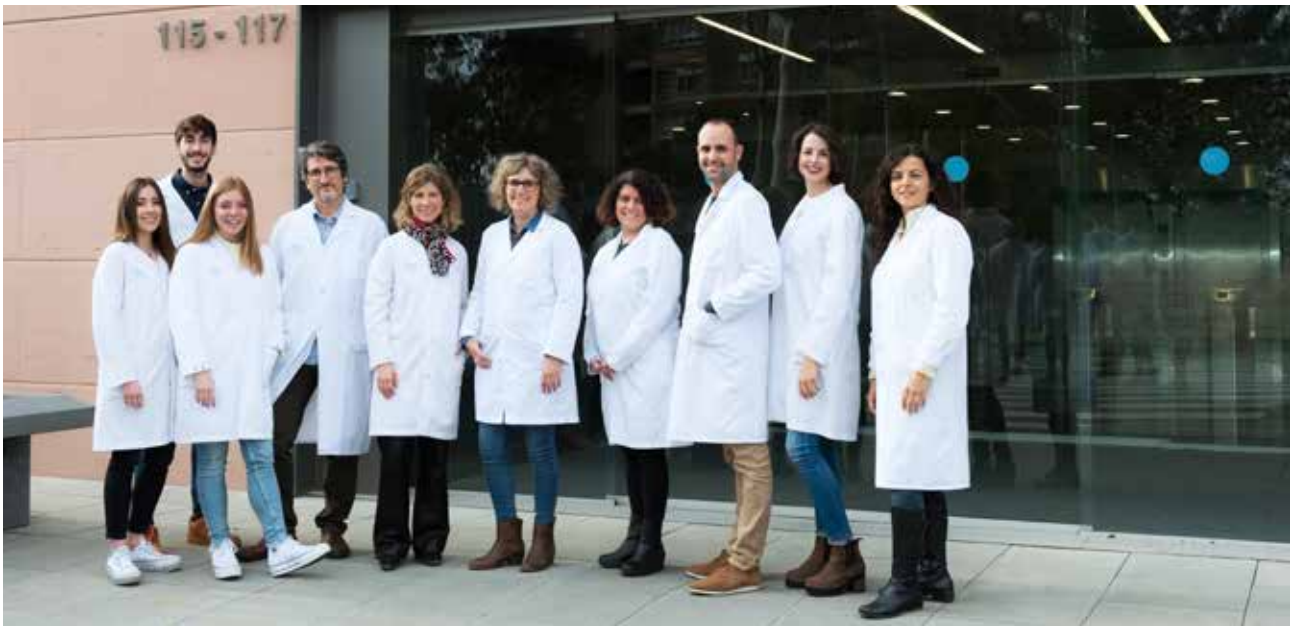
Alejandro Moles

Clinical Nurse Specialist
Neus Gadea

Genetic Counselors
Estela Carrasco
Adria Lopez

Auxiliary Clinician
Carmen Aguilar

Data Curator
Sara Torres



Strategic goals

- Characterization of new hereditary breast and ovarian cancer (HBOC) genes, psychological impact of multigene testing, and feasibility of Polygenic Risk Score (PRS) in HBOC.
- Targeting DNA damage response in breast cancer and implementing our RAD51 assay as a clinical biomarker for PARPi therapy.
- Evaluation of the preventive effect of denosumab on breast cancer prevention in *BRCA1* mutation carriers (BRCA-P trial).
- New disease models and diagnostic tools for head and neck squamous cell carcinoma in Fanconi Anemia patients.
- Unravel the genetic diagnosis of HBOC.
- Identify cellular and genomic biomarkers as predictors of late toxicity after radiotherapy.

Highlights

- In 2019 we published a part of our work analyzing the complexity of hereditary cancer susceptibility through multidimensional analysis in our population. As a result, phenotype-driven panels with opportunistic testing of BRCA1/2 and MMR genes have been implemented in our national health system. Simultaneously, we initiated our longitudinal registry of mutations carriers in new genes and are investigating personality traits as predictors of the psychological impact of multigene testing, especially regarding uncertainty.
- We have received funding through several competitive grants to study the RAD51Predict assay as a functional biomarker of homologous recombination repair deficiency and predictor of PARPi resistance.
- Our group has published findings on the role of spliceogenic variants and its pathogenicity in BRCA genes, and the incorporation of semi-quantitative analysis of splicing alterations for the clinical interpretation of variants in these genes. We have described the first pathogenic deep intronic *BRCA1* variant that results in loss of function explaining part of the missing genetic susceptibility to breast and ovarian cancer.
- We have developed a specific in silico predictor for BRCA1/2 to evaluate the effect of genetic variants with uncertain clinical significance. The predictive software is freely available online at: https://www.biotoclin.org/BRASS#about. Our computational algorithm was presented at the latest edition of the international CAGI Challenge (Critical Assessment of Genome Interpretation https://genomeinterpretation.org/content/BRCA1_BRCA2), and our methodology was ranked in second place.
- We are now participating in the RADprecise - Personalized radiotherapy: Incorporating cellular response to irradiation in personalized treatment planning to minimise radiation toxicity. This collaborative project launched in 2019 and is supported through funding received from ERAPerMed.
- We are leading the search for clinically relevant microRNAs as novel biomarkers for radiosensitivity.
- Two PhD theses were defended in 2019.

Summary

We focus on the clinical development of PARP inhibitors (PARPi) in early *gBRCA1/2* breast cancer and novel combinations in the advanced setting. The consolidation of our collaboration with VHIO's Experimental Therapeutics Group (page 68), led by Violeta Serra, has resulted in a large collection of *BRCA1/2*-associated patient-derived xenografts (PDX) implanted in athymic mice. We are using these murine models to identify mechanisms of resistance to targeted therapies, identify novel biomarkers, and assess new combinatorial treatments at progression. We have identified a functional biomarker for PARPi sensitivity that has been tested preclinically and in human samples, and we are now collecting samples for a larger clinical validation.

Our group is also interested in unravelling the challenges of implementing the advances in diagnosis of hereditary cancer susceptibility and applying these insights to clinical practice. In partnership with the hereditary cancer program at the Catalan Institute of Oncology (ICO), we are investigating the genetic complexity of hereditary cancer through the multidimensional analysis of a customized panel, as well as the psychological impact in our population.

Ongoing research centers on the role of personality traits in predicting the psychological impact of genetic results and the uptake of prevention strategies. We have recently received funding to assess genome-based cancer risk estimation and cancer-risk adapted approaches incorporating polygenic risk score (PRS) analysis. A longitudinal national-based registry of mutation carriers incorporates prospective data for the analysis of health outcomes.

We pursue our interest in the genetic epidemiology of hereditary breast and ovarian cancer (HBOC) in collaboration with Senior Scientist of our group, Sara Gutiérrez-Enríquez. This joint research has shed important light on the characterization of new pathogenic variants in HBOC genes, and provided discriminatory tools to interpret variants of uncertain significance in BRCA genes. Our group is devoted to deciphering the role of intronic, splicing, and missense variants in major HBOC genes and investigate the yield of long-read RNA-seq. Sara Gutiérrez-Enríquez is also independently leading research into predictive genetic and cellular markers for susceptibility to radiotherapy-induced clinical toxicity.

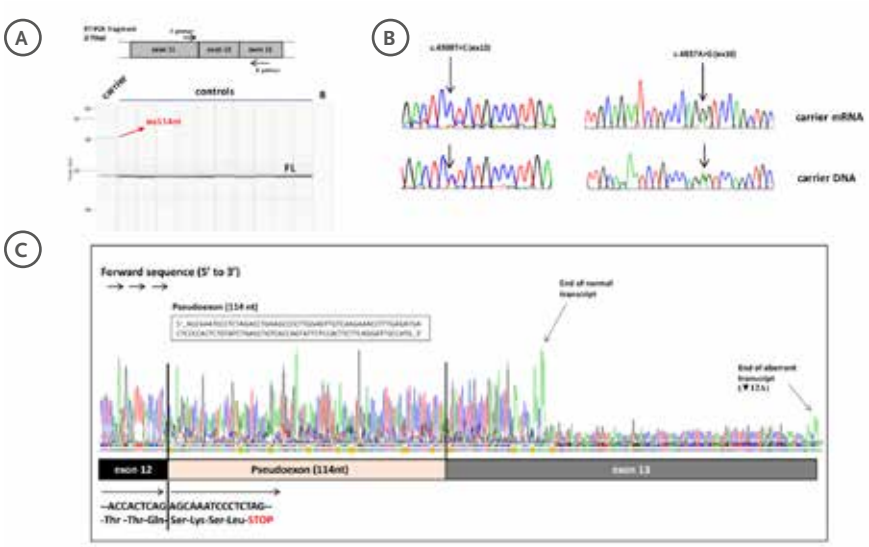


Figure: BRCA1 c.4185+4105C>T characterisation in patient RNA. (A): QIAxcel electrophoresis of RT -PCR assay covering exons 11–13 (275 bp). An extra band of ~400 bp was detected in variant carrier (ins114nt), not present in controls. (B): Sanger electropherogram showing allelic imbalance at polymorphisms c.4308T>C and c.4837A>G. (C): Sanger sequencing confirmed the insertion of 114 nucleotides (nt) between exons 12 and 13, generating a new transcript that we annotated as ▼12A (r.4185_4186ins4185+3990_4185+4103). This transcript is predicted to encode for a truncated BRCA1 protein (p.Gln1395_Gln1396insSerLysSerLeu*).

PI paper pick

Montalban G, Bonache S, Moles-Fernández A, Gisbert-Beamud A, Tenés A, Bach V, Carrasco E, López-Fernández A, Stjepanovic N, Balmaña J, Diez O, Gutiérrez-Enríquez S. Screening of BRCA1/2 deep intronic regions by targeted gene sequencing identifies the first germline BRCA1 variant causing pseudoexon activation in a patient with breast/ovarian cancer. *J Med Genet.* 2019 Feb;56(2):63-74.

Padilla N, Moles-Fernández A, Riera C, Montalban G, Özkan S, Ootes L, Bonache S, Díez O, Gutiérrez-Enríquez S, de la Cruz X. BRCA1- and BRCA2-specific in silico tools for variant interpretation in the CAGI 5 ENIGMA challenge. *Hum Mutat.* 2019 Sep;40(9):1593-1611.

Montalban G, Bonache S, Moles-Fernández A, Gadea N, Tenés A, Torres-Esquius S, Carrasco E, Balmaña J, Diez O, Gutiérrez-Enríquez S. Incorporation of semi-quantitative analysis of splicing alterations for the clinical interpretation of variants in BRCA1 and BRCA2 genes. *Hum Mutat.* 2019 Dec;40(12):2296-2317. (Editor's Choice).

Feliubadaló L, López-Fernández A, Pineda M, Díez O, Del Valle J,Gutiérrez-Enríquez S, Teulé A, González S, Stjepanovic N, Salinas M, Capellá G,Brunet J, Lázaro C, Balmaña J; Catalan Hereditary Cancer Group. Opportunistic testing of BRCA1, BRCA2 and mismatch repair genes improves the yield of phenotype-driven hereditary cancer gene panels. *Int J Cancer.* 2019 Nov15;145 (10): 2682-2691..

CLINICAL RESEARCH

Oncology Data Science (ODysSey) Group

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Biomedical Engineer
Anna Pedrola

Data Curators
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Magdalena Guardiola
Fiorella Ruiz
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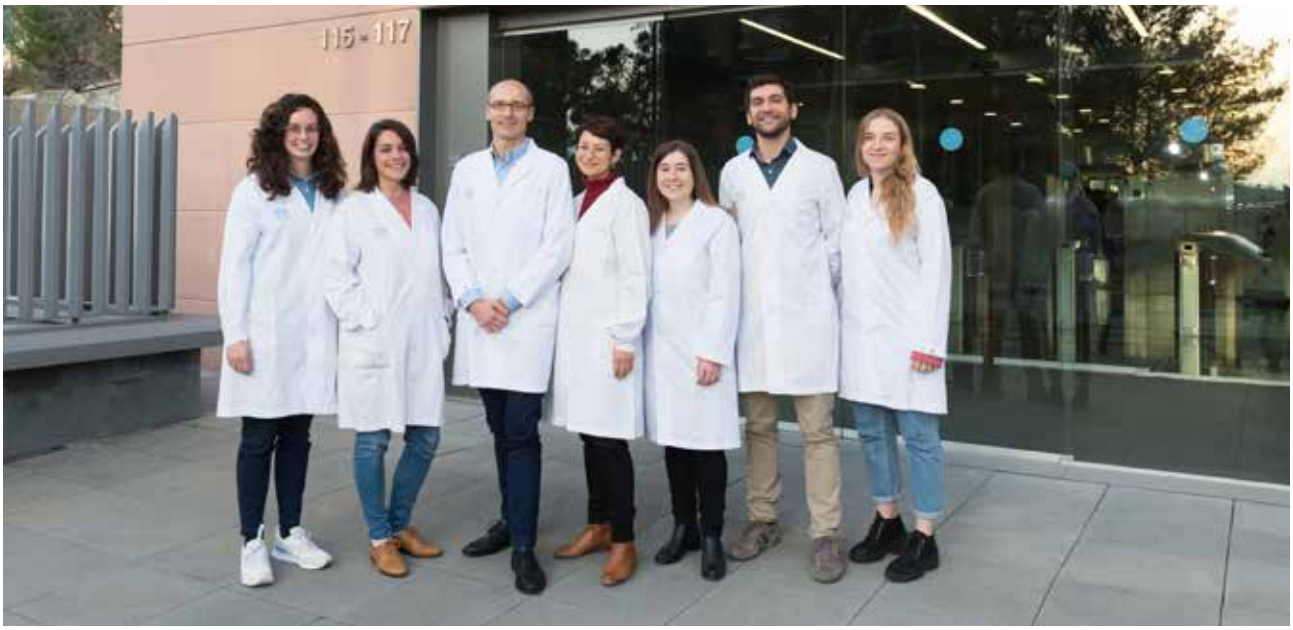
Cristina Viaplana



Strategic goals

Facilitate clinical-molecular correlative studies at VHIO:

- Development and maintenance of clinical-molecular databases as a resource for clinicians, molecular pathologists and translational investigators.
- Provide guidance to medical oncologists and cancer biologists during the design and interpretation of biomarker correlative studies, as well as development and validation of omics-based tests that have direct clinical application.

Promote evidence-based medicine:

- Continued medical education with standardized reports of genomic alterations and weekly Molecular Tumor Boards. We facilitate data exchange among a wide range of experts for the review of patients' medical histories and cancer molecular profiles in order to more precisely guide treatment decisions.

Collaborative research on Big and Real-World Data:

- Encourage interactions among computational oncology scientists and preclinical-clinical researchers to promote the identification of cancer subtypes and druggable drivers.
- Generate large databases that allow the study of complex associations between tumor omics, drug sensitivities and patient outcome.

Highlights

- We have provided support to VHIO's investigators working on clinical and preclinical research. This has resulted in several impactful publications in the field, oral presentations at top oncology conferences and statistical leadership in multiple phase 2 and 3 trials.
- We have developed and explored tools that help translate the strong biological dependencies of colorectal cancer subtypes into druggability opportunities. We have also studied the impact of driver genes, transcriptomic subtypes and microenvironment features on prognosis of colorectal cancer patients.
- Active member of the AACR Genomics Evidence Neoplasia Information Exchange (GENIE) project, a multi-phase, multi-year, international study that catalyzes precision oncology through the development of a regulatory-grade registry aggregating and linking clinical-grade cancer genomic data with clinical outcomes from tens of thousands of cancer patients treated at the participating institutions.
- Co-development of the Molecular Tumor Board portal (MTBP), a clinical decision support system to select the most appropriate treatment for cancer patients based on genomics data, including clinical trial opportunities. The portal employs a variety of state-of-the-art tools to interpret the biological and clinical significance of tumor and germline alterations. The MTBP is regularly used in the Cancer Core Europe (CCE) Consortium's Basket of Basket (BoB) trial, which is the first European multi-modular academic clinical trial in Europe and set to significantly advance basket trial design to-date by integrating molecular prescreening, the development of novel diagnostic tests including ctDNA, and assessing targeted therapies matched to those patients who will be most likely to benefit from them.

An open access version of our MTBP technology, developed under CCE's umbrella, is available at: http://mtbp.org.

Summary

VHIO's ODysSey Group promotes translational research in precision oncology by integrating cancer molecular profiling data with clinical outcomes of oncology patients treated at the Vall d'Hebron University Hospital (HUVH).

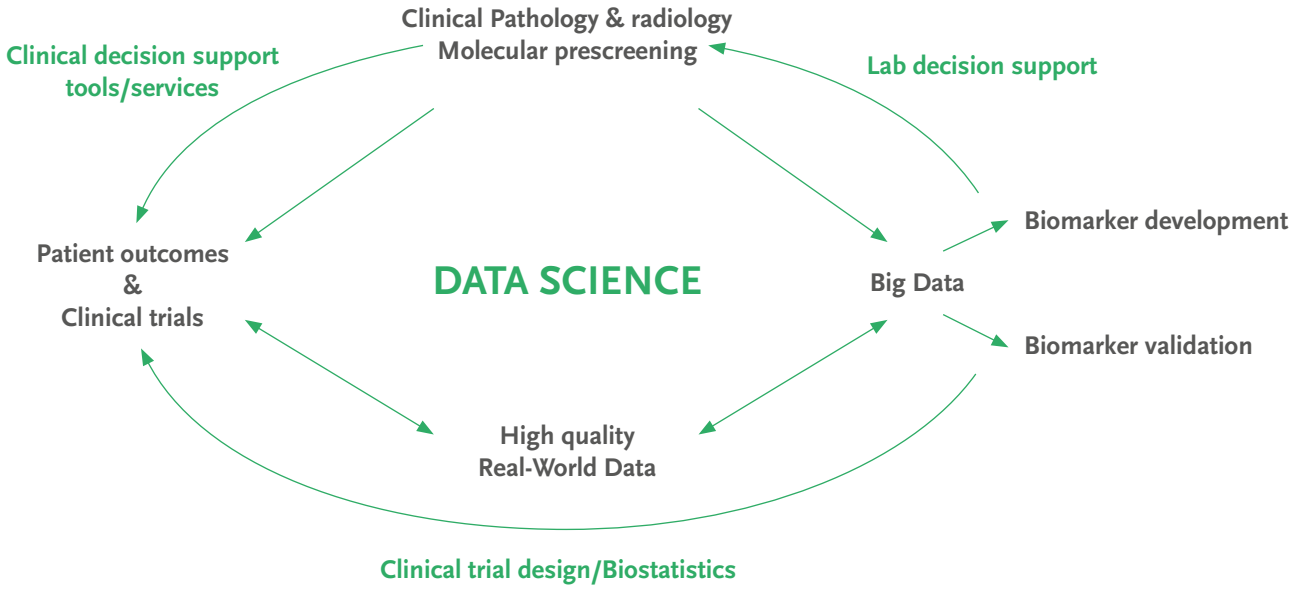
To explore big and real-world data, we design and maintain comprehensive clinical-molecular databases and provide operational support to investigators interested in correlative analyses for hypothesis-generation and biomarker validation. We also assist investigators in sample size calculation, clinical trial design and downstream statistical analyses.

Our team also participates in international multi-omic data analyses projects and foster collaborative research in computational oncology. We are dedicated to connecting cancer researchers working on predictive and prognostic modelling, the identification of cancer drivers, molecular subtyping, primary-metastasis heterogeneity, microenvironment signatures and druggability in solid tumors.

Molecular Prescreening Program

In 2019, our group, together with Susana Aguilar and Jenifer Gonzalez, and in collaboration with VHIO's Cancer Genomics Group led by Ana Vivancos (page 112), and Molecular Oncology Group, directed by Paolo Nuciforo (page 114), have performed tumor molecular profiling in over 1,100 cancer patients as candidates for enrollment in clinical trials. In total, 151 patients were treated with biomarker-matched innovative therapies as a result of this effort.

Interpretation of next-generation sequencing tests and educating clinicians on emerging biomarkers is another of our priority areas. During our Molecular Tumor Board meetings, we promote precision oncology by providing guidance regarding inclusion in early clinical trials with biomarker-guided targeted agents or immunotherapies.



PI paper pick

Dienstmann R, Villacampa G, Sveen A, Mason MJ, Niedzwiecki D, Nesbakken A, Moreno V, Warren RS, Lothe RA, Guinney J. Relative contribution of clinicopathological variables, genomic markers, transcriptomic subtyping and microenvironment features for outcome prediction in stage II/III colorectal cancer. *Ann Oncol.* 2019 Oct 1;30(10):1622-1629.

Rodriguez-Freixinos V, Fariñas-Madrid L, Gil-Martin M, Barretina-Ginesta P, Romeo M, Villacampa G, Pardo B, Ahmed H, Recalde S, Piulats JM, Gómez-Plaza MC, Gil-Moreno A, Sala E, Martínez-Román S, Ponce J, Meléndez C, Carballas E, Dienstmann R, Oaknin A. Chemotherapy and PARP inhibitors in heavily pretreated BRCA1/2 mutation ovarian cancer patients. *Gynecol Oncol.* 2019 Feb;152(2):270-277.

Serna G, Ruiz-Pace F, Cecchi F, Fasani R, Jimenez J, Thyparambil S, Landolfi S, Elez ME, Vivancos A, Hembrough T, Tabernero J, Dienstmann R, Nuciforo P. Targeted multiplex proteomics for molecular prescreening and biomarker discovery in metastatic colorectal cancer. *Sci Rep.* 2019 Sep 19;9(1):13568.

CLINICAL RESEARCH

Prostate Cancer Translational Research Group

Principal Investigator
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Senior Investigator
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Post-Doctoral Fellows
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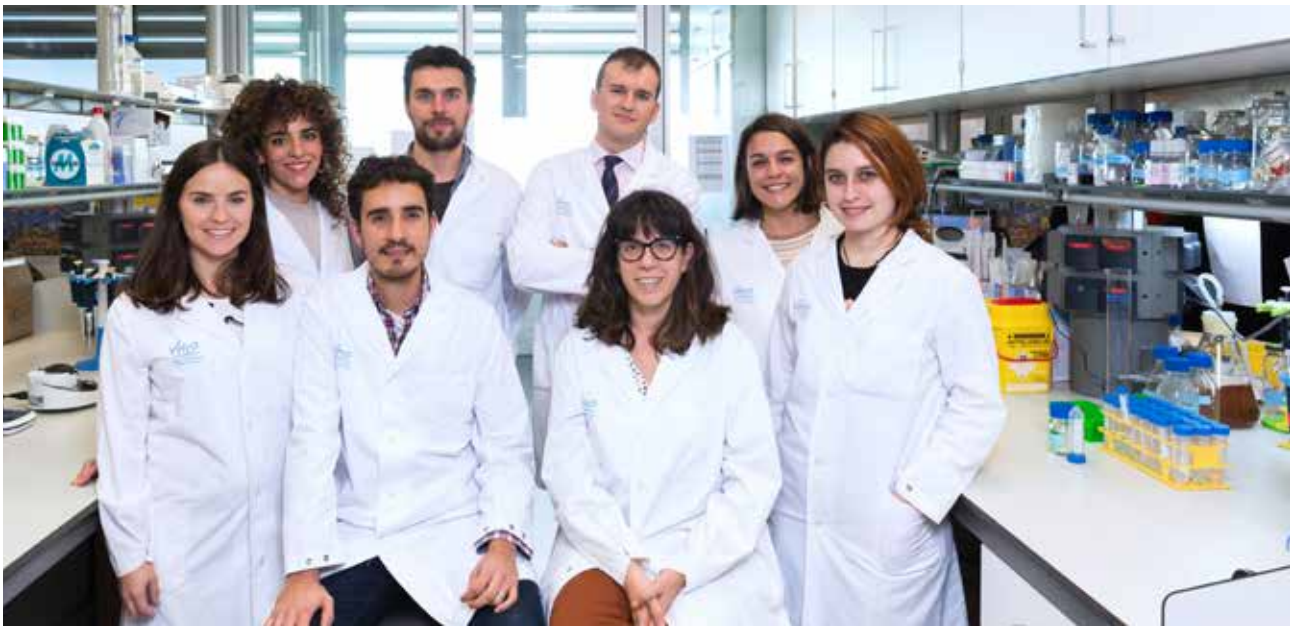
Irene Casanova

PhD Student
Sara Arce

Technicians
Teresa Casals
Sarai Cordoba



Strategic goals

- To establish a clinically relevant re-classification of metastatic prostate cancer integrating genotypic and phenotypic data with functional assays.
- Develop prostate cancer molecular stratification assays based on tumor tissue and circulating biomarkers.
- Optimize the combination of DNA repair-targeting drugs with androgen receptor inhibitors.
- Build a precision medicine core for prostate cancer patients treated at the Vall d'Hebron University Hospital (HUVH).

Highlights

- Launch of the IRONMAN Registry in Spain. This project is driven by academic team-science and collects clinical data and biospecimens for correlative analysis from patients with advanced prostate cancer.
- Participation in the PROfound study, the first-ever positive biomarker-driven clinical trial in prostate cancer, which has confirmed the efficacy of PARP inhibitors in DNA repair defective prostate cancer.
- The setting up of our first investigator-initiated clinical trial co-targeting AR and PARP in metastatic hormone-naïve prostate cancer; the study will initiate recruitment in 2020.
- We were granted the 2019 FERO Foundation Award (page 33), to develop liquid biopsy assays in advanced prostate cancer.

Summary

Over the last decade, we have witnessed a revolution in the treatment of metastatic castration-resistant prostate cancer (mCRPC) which is an advanced and lethal form of prostate cancer. A deeper understanding of its underlying biology has led to the development of compounds targeting the androgen signaling pathway and the immune system, as well as taxanes and radiopharmaceuticals.

Despite these advances in more effectively managing mCRPC, it remains a fatal disease resulting in significant morbidity and mortality globally. Arguably, the most critical need in drug development against CRPC is treatment molecular stratification. In parallel efforts must continue to center on identification of robust predictive biomarkers of response and the development of targeted anti-cancer therapies. The advent of these novel treatments has driven tumor evolution towards a shift in the genomic landscape observed in patients with advanced disease.

We embrace a purely comprehensive and integrative approach to research. As such, our group encompasses molecular biology, tumor genomics, clinical trials and computational sciences in order to develop precision medicine strategies to treat advanced prostate cancer based on predictive biomarkers of response.

Defects in DNA repair genes -particularly in double-strand breaks- are present in 20-25% of mCRPC cases, and allow us to study how we can deliver more precise cancer treatment and care. Some of these mutations have prognostic and predictive implications which are crucial in delivering on the promise of personalized medicine in oncology.

We use a range of tools (CRISPR gene editing, shRNA, siRNA and pharmacological inhibitors) to induce loss-of-function of key DNA repair genes in prostate cancer in-vitro models to establish how tumors adapt their DNA repair machinery, and how this is affected by modulation of oncogenic AR signaling. Our interest in cell cycle modulation by DNA damage has also led us to study the senescence-like phenotype observed after exposure to targeted agents, which we hypothesize is a mechanism of drug resistance, and how to target it therapeutically.

Aiming at translating our findings into benefits for patients as rapidly as possible, we study the same genomic and transcriptomic signatures in biopsies from patients with metastatic prostate cancer. In parallel, we collect longitudinal liquid biopsies to study how a tumor evolves during response and progression to targeted agents.

Our research focuses on optimal patient stratification strategies for clinical care, with particular emphasis on combining DNA repair targeting agents with those that inhibit androgen signaling.

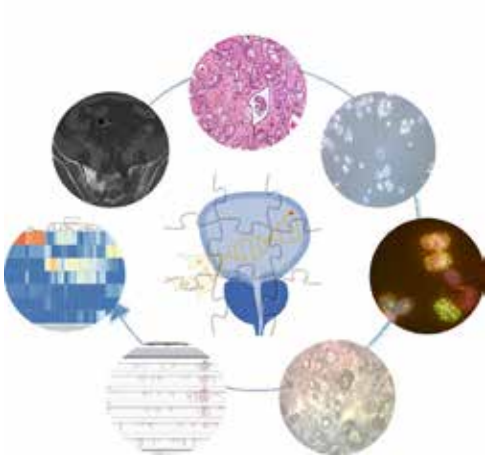


Figure: Our comprehensive approach to prostate cancer research aims to encompass data from molecular biology assays in preclinical experiments with genomics, immunohistochemistry and immunofluorescence data in patient tumor biopsies and patient-derived laboratory models to optimize the development of precision medicine strategies to then be tested in clinical trials.

PI paper pick

Mateo J, Seed G, Bertan C, Rescigno P, Dolling D, Figueiredo I, Miranda S, Nava Rodrigues D, Gurel B, Clarke M, Atkin M, Chandler R, Messina C, Sumanasuriya S, Bianchini D, Barrero M, Petremolo A, Zafeiriou Z, Fontes MS, Perez-Lopez R, Tunariu N, Fulton BA, Jones R, McGovern UB, Ralph C, Varughese M, Parikh O, Jain S, Elliott T, Sandhu S, Porta N, Hall E, Yuan W, Carreira S, de Bono JS. Genomics of lethal prostate cancer at diagnosis and castration-resistance. *J Clin Invest.* 2019 Dec 24. pii: 132031.

Mateo J, Porta N, Bianchini D, McGovern U, Elliott T, Jones R, Syndikus I, Ralph C, Jain S, Varughese M, Parikh O, Crabb S, Robinson A, McLaren D, Birtle A, Tanguay J, Miranda S, Figueiredo I, Seed G, Bertan C, Flohr P, Ebbs B, Rescigno P, Fowler G, Ferreira A, Riisnaes R, Pereira R, Curcean A, Chandler R, Clarke M, Gurel B, Crespo M, Nava Rodrigues D, Sandhu S, Espinasse A, Chatfield P, Tunariu N, Yuan W, Hall E, Carreira S, de Bono JS. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol.* 2020 Jan;21(1):162-174.

Athie A, Arce S, Gonzalez M, Morales R, Suarez C, Casals T, Hernandez G, Carles J, Mateo J. Targeting DNA Repair Defects for Precision Medicine in Prostate Cancer. *Curr Oncol Rep.* 2019 Mar 27;21(5):42.

Abida W, Cyrta J, Heller G, Prandi D, Armenia J, Coleman I, Cieslik M, Benelli M, Robinson D, Van Allen EM, Sboner A, Fedrizzi T, Mosquera JM, Robinson BD, De Sarkar N, Kunju LP, Tomlins S, Wu YM, Nava Rodrigues D, Loda M, Gopalan A, Reuter VE, Pritchard CC, Mateo J, Bianchini D, Miranda S, Carreira S, Rescigno P, Filipenko J, Vinson J, Montgomery RB, Beltran H, Heath EI, Scher HI, Kantoff PW, Taplin ME, Schultz N, deBono JS, Demichelis F, Nelson PS, Rubin MA, Chinnaiyan AM, Sawyers CL. Genomic correlates of clinical outcome in advanced prostate cancer. *Proc Natl Acad Sci U S A.* 2019 Jun 4;116(23):11428-11436.

CLINICAL RESEARCH

Radiation Oncology Group

Principal Investigator
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Radiation Oncologists
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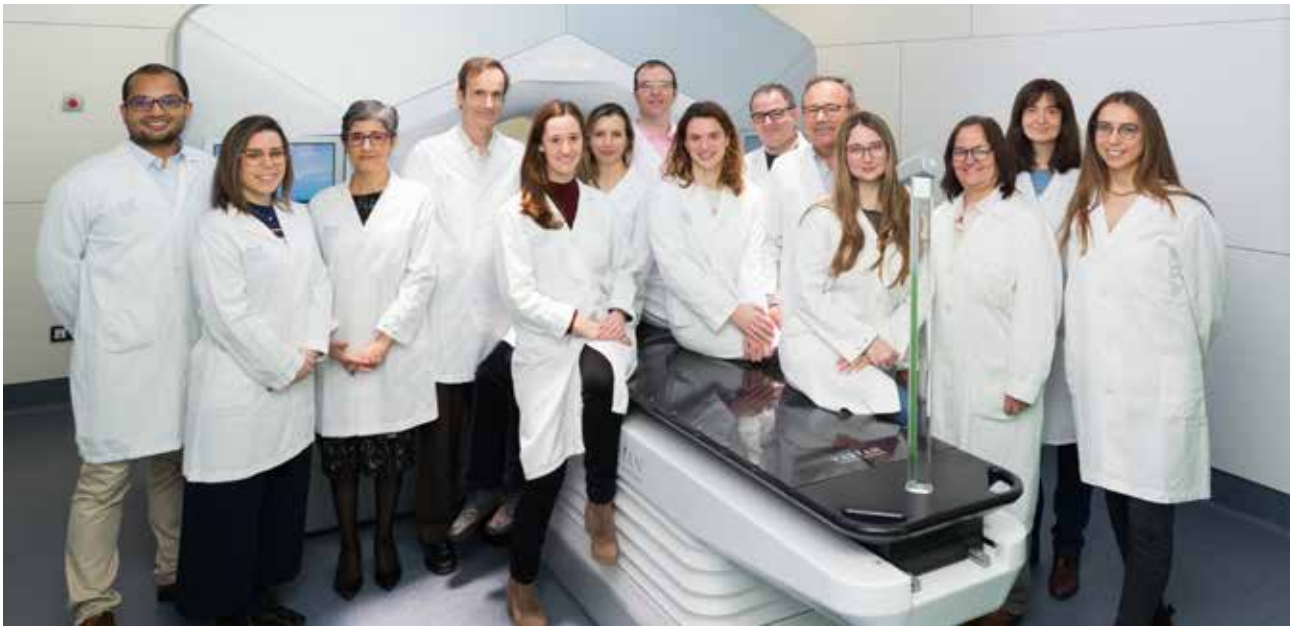
Alexandra Giraldo
Raquel Granado
Beatriz Gutierrez
Begoña Navalpotro
Maria Magdalena Marti
Xavier Maldonado
Soraya Mico
Monica Ramos
Victoria Reyes



Strategic goals

- Technology development: acquisition of new equipment to implement cutting edge clinical techniques such as rotational radiotherapy - with intensity modulated arc therapy (VMAT), adaptive radiotherapy, respiratory control radiotherapy (RT4D), and image-guided radiotherapy (IGRT).
- Translational research: application of insights into cancer biology as well as healthy tissue in order to personalize therapy matched to the characteristics and specificities of each patient, each individual tumor.
- Quality. Continue to obtain the ISO 9001/2008 recertification in the field of radiation oncology.
- Clinical research. To accelerate and advance clinical research into combined radio-immunotherapy therapy.

Highlights

- Over 90% of our patients treated with radical radiotherapy have received highly complex techniques.
- We now started therapy using our Halcyon linac - the first ever to be installed in Spain.
- Our group has initiated a project for combined radiotherapy and nanoparticles in head and neck cancer.
- We have implemented the `breath hold' technique, with the first of our patients having already received this treatment approach.
- We participate as national heads of radiotherapy quality control procedures in the International Society of Paediatric Oncology (SIOP) trials for medulloblastoma (PNET5), ependymoma (EP2), and Wilms (umbrella).

Summary

VHIO's Radiation Oncology Group is integrated within the Radiation Oncology Department of the Vall d'Hebron University Hospital (HUVH), and is actively involved in the multidisciplinary treatment of patients with malignant tumors. We also participate either as Principal Investigators or research collaborators in a number of pioneering clinical trials, translational research projects, as well as technology development programs.

In 2019 we have renewed three linacs thanks to a donation received from the Amancio Ortega Foundation. The machines incorporate all the very latest technology and the implementation of these highly complex techniques requires additional expertise from our service, special trainings in order to establish the indications, administration procedures, quality control methods, as well as the implementation of the necessary tools for the measurement of results. These include:

- Breathing control for the treatment of tumors that are located in moving body regions such as the lungs and liver. Therapy is synchronized with respiratory rhythm. This technique is especially indicated in stereotactic body radiotherapy (SBRT).
- Deep inspiration breath hold (DIBH) is a radiation therapy technique where patients take a deep breath during treatment. The patient is asked to take a deep breath and hold this breath while the radiation is delivered. Deep breathing ensures that the heart moves away from the chest and thus receives a lower dose.
- Real-Time Tumor-Tracking Radiotherapy is used in the hypofractionated treatment of prostate cancer. Markers are placed on the prostate and during therapy the system recognizes them. If the prostate moves (e.g. bladder or rectum), the technique can detect this and indicates the correction.
- Adaptive radiotherapy is used for the treatment of gynecological and bladder tumors, which move and can change position. A three-dimensional image is taken before therapy is administered and indicates where the organ requires therapy, with a treatment plan that best adapts to the position of the organ at that precise moment.
- Radiosurgery of small lesions is applied for the treatment of small brain tumors and/or metastases, and for some non-oncological conditions such as trigeminal neuralgia that no longer responds to standard therapy, and some Parkinsonism conditions. A very high dose is administered in very small volume (5-10 mm in diameter), requiring extremely precise techniques.

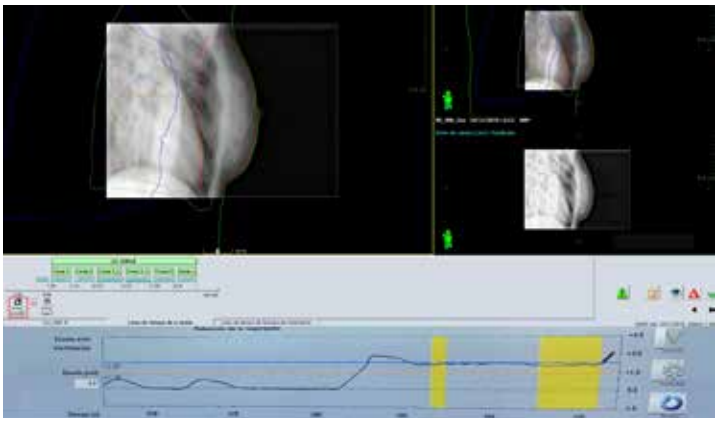


Figure: A patient being treated with the 'Breast hold' technique. The upper image shows the patient's CT scan. The orange line marks the contour of the heart, which moves away from the breast (in red). The light green line is the left lung, and the pink, the tumor bed.
The lower part of the figure shows breathing control. When the black line (volume of the lung), is between the orange and blue lines the treatment is on, if it goes out of this line the beam is off. The yellow area is when treatment is administered.

PI paper pick

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CLINICAL RESEARCH

Radiomics Group

Principal Investigator
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PhD Students
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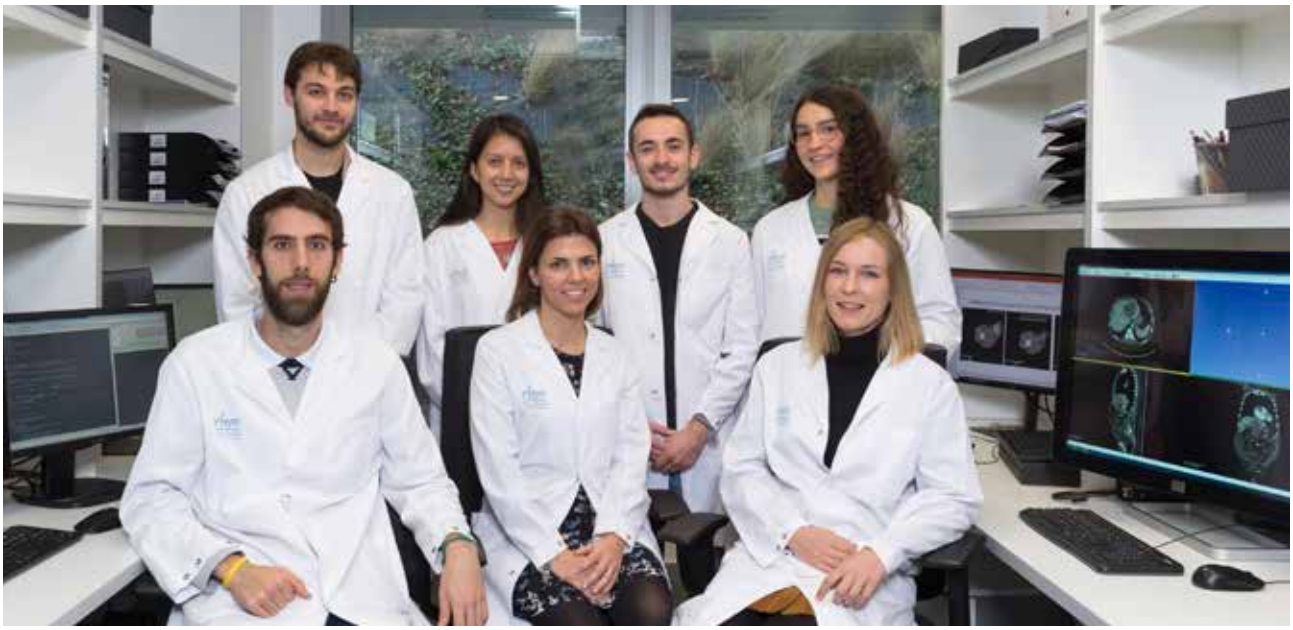
Eric Delgado
Maria Vittoria Raciti
Samantha Elizabeth Toinga



Strategic goals

- Provide expertise in engineering and bioinformatics for the development and clinical qualification of quantitative imaging biomarkers for precision medicine to improve outcomes for cancer patients.
- Use functional imaging for optimizing drug development through clinical trials.
- Integrate radiomics and genomics in translational studies towards a deeper understanding of tumor evolution and mechanisms of resistance to anti-cancer therapies.
- Optimize and standardize imaging acquisition protocols.
- Develop and implement computational models for advanced image processing.

Highlights

- Our group was awarded with a *Fundació La Marato de TV3* Grant and Raquel Perez-Lopez has just been granted a CRIS Foundation Research Talent Award.
- We have developed and validated a combined CT-radiomics and clinical signature with predictive value of response to immunotherapy. The preliminary results of this study were presented at the European Society for Medical Oncology (ESMO) Congress 2019 (manuscript currently under review).
- We have also developed a pipeline for semi-automatic robust quantification of residual tumor on the post-surgery MRI in patients with brain glioblastoma (manuscript under review).
- The continued expansion of existing partnerships with other groups as well as new collaborative projects in order to increase the incorporation of imaging studies within translational research lines.

Summary

Our Radiomics Group keeps growing; in 2019 Alonso Garcia and Marta Ligero started their PhD programs and Samantha Toinga joined us to carry out her MsC research project on imaging habitats towards evaluating tumor heterogeneity. Kinga Bernatowicz also joined the group as our new Post-Doctoral Scientist. We are also pleased to announce that we are currently recruiting for additional new talents and will soon incorporate another post-doctoral researcher to the group.

Over the last year, we have fostered further collaborations with additional leading imaging research groups including the Computing Vision Centre (CVC–*Universitat Autónoma de Barcelona*), and cutting-edge centres such as the Bellvitge Institute for Biomedical Research (IDIBELL), in Barcelona, the Institute of Cancer Research (ICR), London, UK, the Netherlands Cancer Institute (NKI), Amsterdam, and the Cancer Research UK (CRUK) Cambridge Institute. In partnership, we have designed various projects for which we have applied for funding through national and international grants.

Continuing our collaboration with VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" led by Elena Garralda (pages 122-123), we have developed a CT-radiomics signature towards better characterizing immunotherapy response (selected as an Oral Presentation at the ESMO Congress 2019, 27 September – 01 October, Barcelona; paper currently under review). Thanks to the support received through an AstraZeneca Proof of Concept Award, we will soon initiate the first prospective study of CT and multiparametric MRI-radiomics to quantify changes in tumor cellularity and vascularization as a biomarker of response to immune checkpoint inhibitors.

We are also delighted to report that the CRIS Cancer Foundation has recently awarded Raquel Perez-Lopez with a Research Talent Award. This will fuel her research aimed at improving cancer patient selection for immunotherapy and better understanding differential responses to immune-checkpoint inhibitors.

Thanks to the support of received from the Carlos III Institute of Health (ISCIII) and the Prostate Cancer Foundation Young Investigator Award, we have started a multi-center prospective study of whole-body diffusion-weighted MRI as a response biomarker of bone metastasis in prostate cancer patients. This study will soon be expanded to include breast cancer patients thanks to funding from *La Fundació La Marato de TV3* (PreciMet study).

We have also established interdisciplinary partnerships with various VHIO groups to work together on several translational research projects. Our ethos of team science is key for optimizing imaging and accelerating translational research against cancer.

Focused on applying imaging biomarkers and radiomics to cancer discovery, our efforts center on advancing precision imaging in personalized medicine towards ultimately improving outcomes for cancer patients.

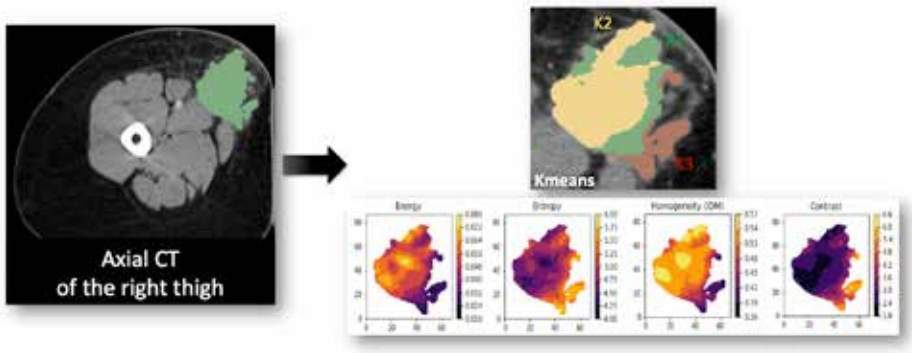


Figure: Unravelling tumor heterogeneity using advanced computational analysis of medical images.

PI paper pick

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CLINICAL RESEARCH

Sarcoma Translational Research Group

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Daniel Pilco Janeta

Student
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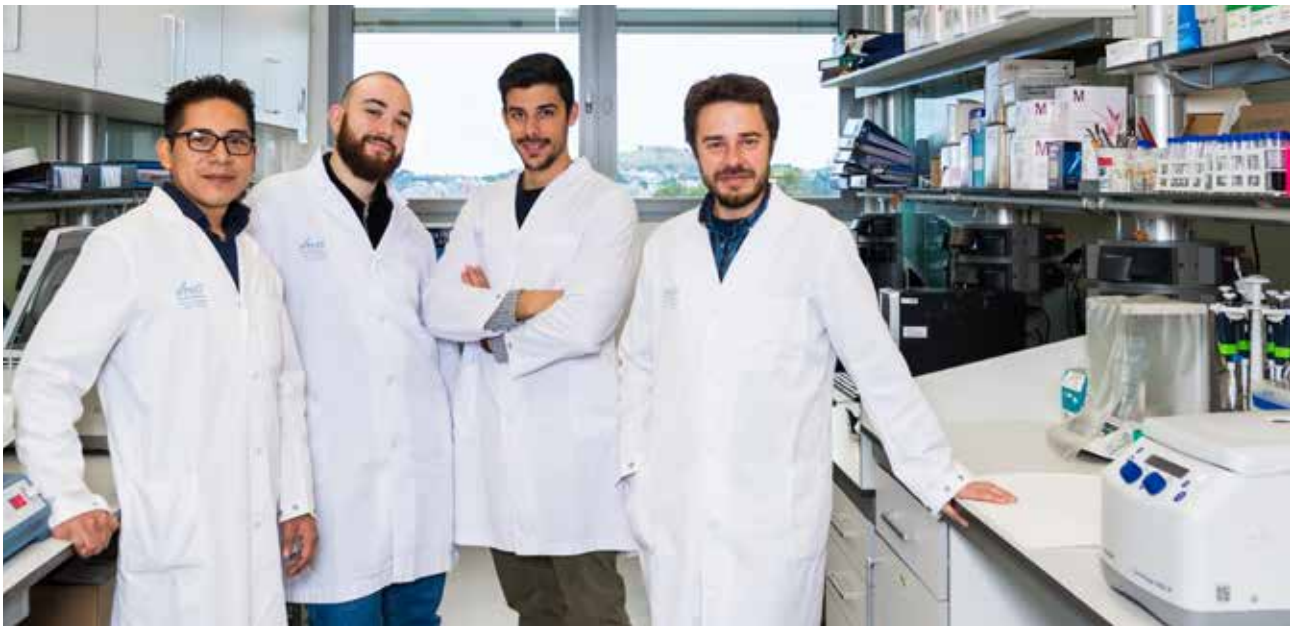

Strategic goals

- Identification of critical molecular mediators of oncogenic signaling in sarcomas.
- Characterization of response and resistance mechanisms to targeted therapies in sarcomas.
- Preclinical modelling and validation of therapeutic strategies to translate at the clinical level.

Highlights

- We have recently determined the molecular basis for the limited clinical benefit of TKIs in imatinib-resistant GIST.
- Our group has led high-level studies towards the clinical implementation of liquid biopsy in GIST patients.
- We have been awarded by the Spanish Ministry of Science and Innovation (FIS Program) to study the evolutionary landscape of resistance in GIST.
- César Serrano organized the first national symposium for sarcoma patients and advocacy groups.

Summary

Sarcoma encompasses >70 entities of mesenchymal origin, constituting 1-2% of all cancers. From a biological perspective sarcomas can be classified into two broad categories: genomically simple sarcomas driven by simple genetic alterations, such as translocations or specific activating mutations; and tumors with complex and unbalanced genomic aberrations. Each of these categories includes diverse sarcomas subtypes showing often profound differences in their molecular makeup, course of disease and therapeutic approach.

Our group focuses on the study of sarcomas with oncogenic dependency on specific drivers of disease. Among them, gastrointestinal stromal tumor (GIST) is the most common malignant mesenchymal neoplasm and constitutes a paradigmatic model to study oncogene addiction and identify structural and functional mechanisms for drug response and drug resistance.

Ongoing aim efforts aim at a deeper biological understanding of GIST and other sarcomas in order to advance drug development. One of the major hurdles with a direct impact on patients' outcomes, concerns the heterogeneity of mechanisms of resistance. Our overarching goal is therefore to identify crucial molecules and signaling mechanisms in GIST biology that can serve as therapeutic vulnerabilities.

We also continue to validate a core set of molecules co-regulated by KIT downstream pathways and identified through extensive whole transcriptome studies across several clinically representative human GIST models. Our group is particularly interested in those with pro-survival function to better understand cellular adaptation to driver inhibition, which may eventually be novel therapeutic targets.

We are as equally interested in performing high-throughput genomic and transcriptomic studies in order to decipher the evolving patterns of resistance in GIST throughout the course of disease, as well as researching liquid biopsy in sarcoma to provide robust evidence that will help to more precisely guide treatment decisions through plasma sequencing.

Our goal is to have a true impact clinically by improving the daily treatment and care of our sarcoma patients. We are proud to report that our Sarcoma Multidisciplinary Unit has been designated as an Expert National Sarcoma Center by the Spanish Ministry of Health, and thus constitutes an optimal setting to translate cancer discovery into true clinical outcomes.

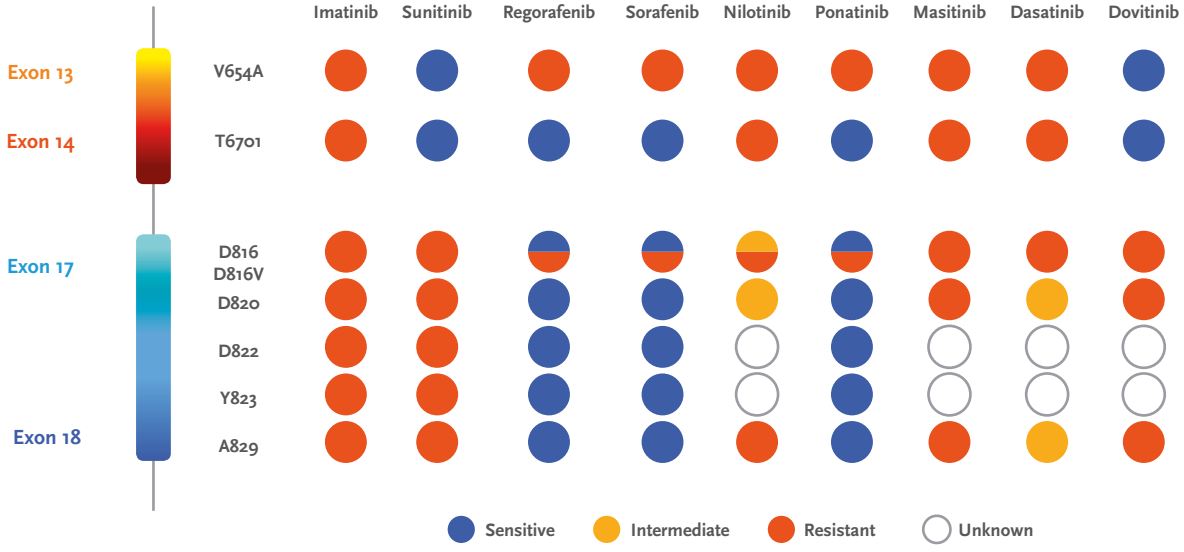

Figure: Gastrointestinal stromal tumor (GIST) is the most common malignant mesenchymal tumor and a successful and paradigmatic model to dissect mechanisms of response and resistance to molecularly targeted agents. Our group has recently discovered that small molecule KIT-inhibitor monotherapies have a drug-specific activity profile against a subset of the KIT secondary mutational spectrum, which constitutes the molecular basis for the modest clinical benefit observed with successive lines of treatment in imatinib-resistant GIST. This finding has a direct impact on the future of drug development in GIST and other diseases (Figure from Serrano & Fletcher, *Oncotarget* 2019; 10: 6286-6287.).

PI paper pick

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CLINICAL RESEARCH

Thoracic Tumors & Head and Neck Cancer Group

Principal Investigator
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Post-Doctoral Fellow
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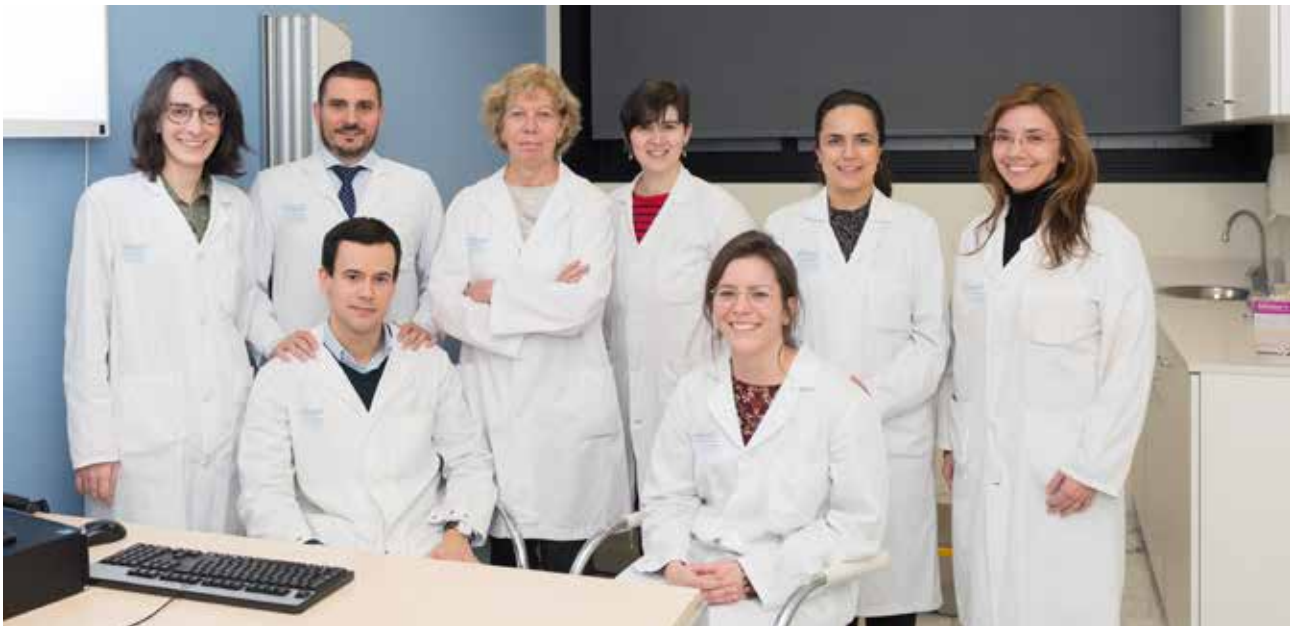
Victor Monton
Gisela Rodriguez



Strategic goals

- Consolidation of our translational thoracic cancer program in non-small-cell lung cancer, small-cell lung cancer and mestothelioma.
- Implementation of liquid biopsy determinations.
- Contribute to early drug development, targeted therapies and immunotherapy strategies for the treatment of thoracic and head and neck tumors.
- Advance precision medicine for lung cancer patients through translational research and the application of cutting-edge technologies and novel approaches.
- Potentiate new therapies including immunotherapeutics and targeted agents for the management of patients with thoracic and head and neck malignancies.
- Further strengthen multidisciplinarity for optimal patient care.

Highlights

- Consolidation of our translational thoracic cancer genomics unit, which counts on the expertise of Ramon Amat, Senior Scientist, Post-Doctoral Fellow, Caterina Carbonell, and a Bioinformatician, Joan Frigola. By integrating genomics, molecular biology and clinical data, this team collaborates closely with our clinical investigators to better understand lung cancer physiology and response to therapy.

Summary

VHIO's Thoracic Tumors & Head and Neck Cancer Group is dedicated to advancing cancer treatment and care for patients suffering from thoracic malignancies, including lung cancer, mesothelioma and thymic malignancies, and head and neck cancers. We focus on disease prevention, early detection and the more precise diagnosis and staging of disease toward improving clinical outcomes.

Our group strives to match currently available targeted therapies with specific molecular alterations identified in patients, identify molecular mechanisms of acquired resistance, and optimize novel immunotherapy strategies.

For our patients with early-stage thoracic malignancies, we collaborate closely with a multidisciplinary team incorporating thoracic surgeons, radiation therapists, radiologists, pulmonologists, pathologists and biologists. In so doing, we are potentiating several treatment approaches and modalities. Given that our patients can suffer from severe symptoms we are also deeply committed to ameliorating clinical outcomes by working in tight connectivity with professionals across other disciplines.

Precision medicine for the treatment advanced lung cancer is no longer an ambition. It is a guiding principle. We establish molecular determinants of disease in individual tumors and circulating-free DNA (cfDNA) by liquid biopsy, to more effectively tailor therapies to the specificities of each patient's disease.

For patients with head and neck tumors we work alongside expert surgeons, radiotherapists, radiologists, pathologists, and nutritionists, and also lead a clinical trial program to assess novel immunotherapeutics and targeted agents in this particular setting.

Immune-based strategies have a role in the treatment algorithm for the management of non-small cell lung cancer; a number of protocols are now ongoing at our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 122). We contribute to VHIO's early clinical drug development efforts, led by Elena Garralda (page 84), and also manage other less common thoracic malignancies including head and neck cancer, small-cell lung cancer, mesothelioma, thymoma and neuroendocrine tumors.

PI paper pick

Shaw AT, Solomon BJ, Besse B, Bauer TM, Lin CC, Soo RA, Riely GJ, Ou SI, Clancy JS, Li S, Abbattista A, Thurm H, Satouchi M, Camidge DR, Kao S, Chiari R, Gadgeel SM, Felip E, Martini JF. ALK Resistance Mutations and Efficacy of Lorlatinib in Advanced Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2019 Jun 1;37(16):1370-1379.

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Dziadziuszko R, Smit EF, Dafni U, Wolf J, Wasąg B, Biernat W, Finn SP, Kammler R, Tsourti Z, Rabaglio M, Ruepp B, Roschitzki-Voser H, Stahel RA, Felip E, Peters SJ. Afatinib in NSCLC With HER2 Mutations: Results of the Prospective, Open-Label Phase II NICHE Trial of European Thoracic Oncology Platform (ETOP). *Thorac Oncol*. 2019 Jun;14(6):1086-1094.

CLINICAL RESEARCH

Tumor Immunology & Immunotherapy Group

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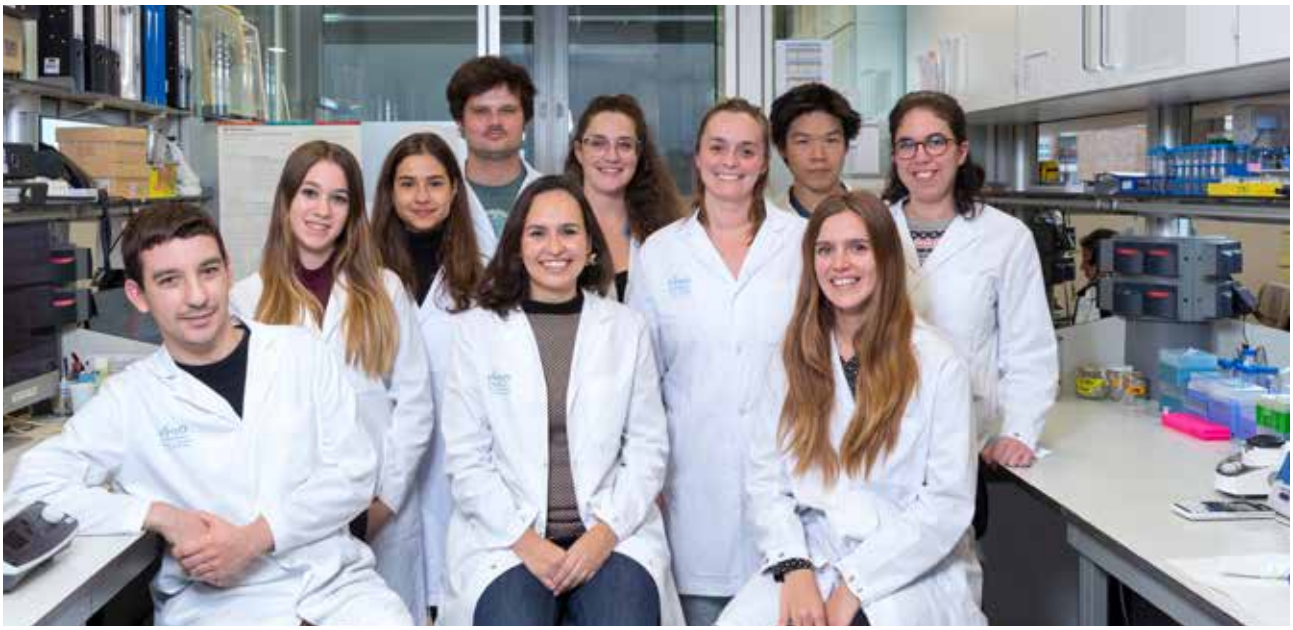

Strategic goals

- Characterize the personalized anti-tumor T-cell response in cancer patients.
- Mine the personalized repertoire of tumor-reactive lymphocytes for potential biomarkers of response to cancer immunotherapy.
- Investigate novel strategies to more swiftly identify tumor-reactive lymphocytes as well as the target antigens driving this response.
- Study the tumor cell intrinsic mechanisms of resistance to T cell mediated cytotoxicity
- Develop personalized T-cell-based cancer immunotherapies for patients with solid tumors.

Highlights

- We have performed the clinical grade validations of TIL expansion for the treatment of patients in collaboration with our hospital's Blood and Tissue Bank, and thanks to funding received from the BBVA Foundation and its Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI - page 28) at VHIO Elena Garralda, Principal Investigator of VHIO's Early Clinical Drug Development (page 84) and Director of our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 122), is designing the clinical protocol to treat patients with epithelial cancers with TILs enriched for neoantigen recognition.
  We estimate that we will submit the investigational new drug application (IND) and clinical protocol to the *Agencia Española de Medicamentos y Productos Sanitarios* (AEMPS) by October 2020. Our aim is to treat patients by mid-2021.
- Our group is now collaborating with Holger Heyn, Team Leader at the National Center for Genomic Analysis (CNAG-CRG), Barcelona, to study the T cells infiltrating endometrial cancers with unprecedented detail, at the single cell level. These studies will guide the identification of T cells with superior traits for adoptive cell transfer.

Summary

The immune system can recognize, hone in on and eliminate cancer. Through multiple mechanisms however, tumors can evade and dodge the immune response. Immunotherapies against cancer exploit the immune system to more effectively attack disease. Clinical studies have shown that immune checkpoint inhibitors and T cell-based therapies can mediate tumor regression in cancer patients with metastatic disease. Thus, in addition to surgery, radiation therapy and chemotherapy, immunotherapy is increasingly representing the fourth pillar of anti-cancer therapy across a variety of tumor types.

Despite encouraging antitumor responses, currently only a fraction of patients treated with immune-based therapies respond and some unfortunately report autoimmune-related adverse events. There is therefore a critical need to develop and personalize these promising treatments.

To do so, and thanks to the support received from the BBVA Foundation's Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI) at VHIO (see page 28), we study mechanisms of response, toxicity and resistance to cancer immunotherapeutics in patients at the Vall d'Hebron University Hospital (HUVH). We aim to identify biomarkers of response in liquid biopsies.

One correlative biomarker described to-date is mutation burden. Tumor-specific somatic mutations are optimal targets for cancer immunotherapy and render tumors immunogenic; some of these can bind to the patients' human leukocyte antigen (HLA) molecules and elicit T-cell responses.

We adopt a highly personalized approach to screen for T-cell mediated recognition of mutated antigens as well as shared antigens using autologous antigen presenting cells that can process and present in all the potential HLA restriction elements.

Following this strategy, we aim to establish whether the presence of lymphocytes recognizing these antigens is associated with response. In parallel, we plan to advance personalized T-cell therapies to treat metastatic colorectal cancer, which is largely resistant to current anti-cancer strategies. We plan to file an IND to the Spanish Regulatory Agency in October 2020 that will enable us to treat patients with metastatic epithelial cancers with neoantigen-reactive TILs using this personalized approach. By enriching for neoantigen-reactive lymphocytes, we hope to enhance the efficacy of TIL therapy in epithelial cancers.

In summary, our group focuses on better understanding the naturally occurring T-cell response to cancer and establishing ways to exploit these antitumor responses to develop more effective, powerful, and precise immunotherapies against cancer.

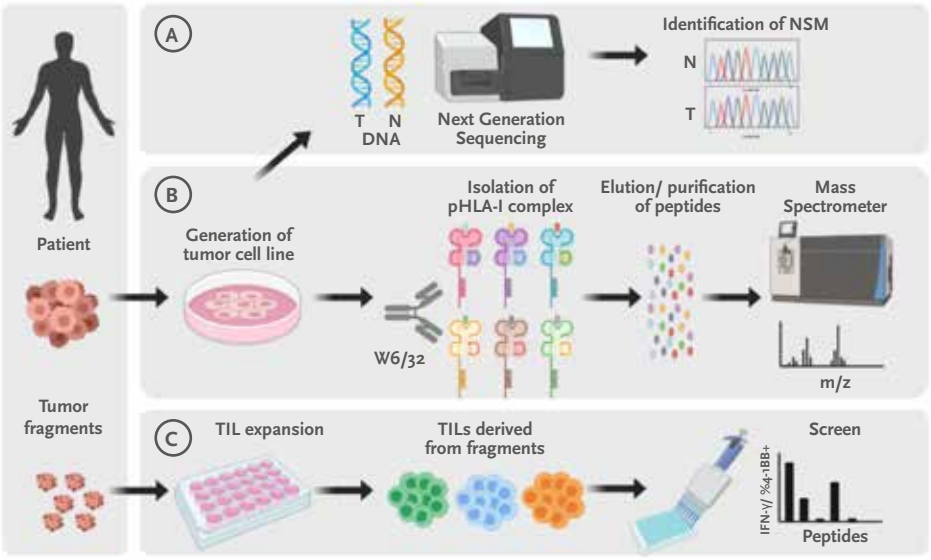

Figure: **Personalized approach to identify tumor and neoantigen-specific TILs**. a) We sequence normal and tumor DNA to identify all the non-synonymous mutations. b) In parallel we attempt to generate a tumor cell line. When generated, we isolate the peptide-MHCI complexes and we identify the peptides presented by MHCI by the tumor cell line by Mass spectrometry. c) Finally, we screen the TILs expanded from the tumor cell line for recognition of the candidate neoantigen peptides identified in a) or elluted from MHCI in b).

PI paper pick

Gros A, Tran E, Parkhurst MR, Ilyas S, Pasetto A, Groh EM, Robbins PF, Yossef R, Garcia-Garijo A, Fajardo CA, Prickett TD, Jia L, Gartner JJ, Ray S, Ngo L, Wunderllich JR, Yang JC, Rosenberg SA. Recognition of human gastrointestinal cancer neoantigens by circulating PD-1+ lymphocytes. *J Clin Invest.* 2019 Nov 1;129(11):4992-5004.

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PFRS
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VHIO Scientific Report 2019

Core Technologies

Extended version online: memorias.vhio.net/2019
PDF version: memorias.vhio.net/2019/SR-VHIO-2019.pdf

CORE TECHNOLOGIES

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Laia Ramos

Bioinformatician
Francesco M. Mancuso

Bioinformatics Technical Auxiliary
Marina Gómez
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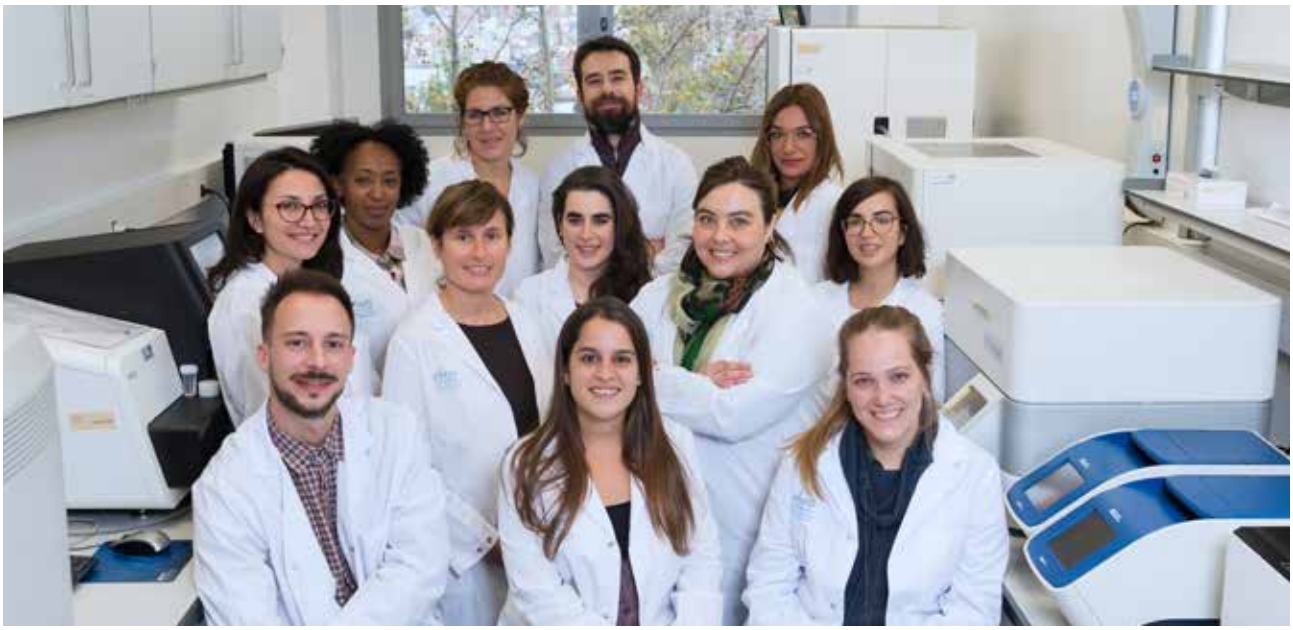

Strategic goals

- Develop and implement improved strategies for routine patient prescreening with a large pan-cancer panel in a setting of excellence (ISO 15189 flexible accreditation).
- Provide cutting-edge applications in cancer genomics through the use of novel technologies and protocol development.
- Prioritize translational projects and partnerships that reinforce VHIO's renowned excellence in oncology.

Highlights

- VHIO is one of the six founding partners of the Cancer Core Europe Consortium (CCE - see page 28) alongside the Gustave Roussy Cancer Campus Grand Paris (Villejuif, France), Cambridge Cancer Centre (Cambridge, UK), Karolinska Institute (Stockholm, Sweden), Netherlands Cancer Institute – NKI (Amsterdam, The Netherlands), and the National Center for Tumor Diseases–DKFZ-NCT (Heidelberg, Germany), and, most recently incorporating the National Cancer Institute of Milan (INT). Our group is appointed co-leader of the Consortium's Genomics Taskforce and is responsible for the alignment of genomic testing across all member institutions
- We have validated our 450 gene capture panel for Tumor Mutational Burden and for Copy Number Alterations be used in our Prescreening Program (see page 21).
- In liquid biopsy, we are developing Copy Number Alteration analysis through the use of shallow Whole Genome Sequencing to provide data along with our custom NGS test with Unique Molecular Identifiers (UMI) chemistry and envision that this will be our first disease tracking test in the clinical setting.
- Driven by our Advanced Molecular Diagnostics Program - DIAMAV, supported by the FERO Foundation (page 18, page 27), VHIO is one of the few centers in Europe to run such a comprehensive prescreening program. Molecular profiling in around 1100 patients per year as candidates for enrollment in our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 122) early clinical trials, enables our teams to more precisely match an increasing number of individual patients with a particular study.

Summary

VHIO's Cancer Genomics Group serves as a Core Technology laboratory. We are also dedicated to translational research as well as novel genomic test development.

Our group provides cutting-edge applications in cancer genomics through state-of-the-art technologies and the development of novel, fully validated tests that are used in the clinical research setting (Prescreening Program). Our lab is equipped with an n-Counter (Nanostring) platform, two digital PCR platforms (BEAMing Sysmex and ddPCR, BIO-RAD) and three NextGen Sequencers; MiSeq, NextSeq and HiSeq2500, Illumina. We are also starting to work with Minion Oxford Nanopore technology.

VHIO's Prescreening Program (page 21), is nucleated around the activity of two VHIO groups – Cancer Genomics and Molecular Oncology, led by Paolo Nuciforo (page 114), in collaboration with VHIO's Elena Garralda (PI of our Early Clinical Drug Development Group – page 84), and Rodrigo Dienstmann (PI, Oncology Data Science – ODysSey Group), together with Susana Aguilar and Jenifer Gonzalez. Our Advanced Molecular Diagnostics Program - DIAMAV, is supported by the FERO Foundation (page 18, page 27).

We perform molecular profiling in over 1100 patients each year as potential candidates for enrollment in our Phase I clinical trials led by VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 122), directed by Elena Garralda.

Patients' suitability for inclusion in any given clinical trial is assessed based on their respective genomic or pathologic profile. Our Group has developed and routinely implemented several tests for our Prescreening Program. Two are based on NGS: an Amplicon-seq approach to sequence 67 genes as well as a 450-gene capture panel (Illumina). We use nCounter (Nanostring) for our RNA-based gene fusion panel, with the capacity of detecting over 100 recurrent gene fusions (also enabling us to assess gene expression patterns in tumors), and our Copy Number Alterations panel, evaluating a 59 gene panel for genes with frequent gains or losses in cancer.

As a reflection of our dedication to excellence and quality in the services we provide, we have attained ISO 15189 flexible accreditation for our Amplicon-seq testing method and will soon obtain it for our large 450-gene capture panel.

Research activities focus on developing novel multiplexed tests that are optimized to FFPE-derived nucleic acids. Once developed, they are validated and used in both clinical and translational research.

We are also involved in a number of translational research projects including the identification of mechanisms of resistance to targeted therapies, as well as predictive biomarkers for immunotherapeutics. Our group is particularly interested in liquid biopsy and on RNA-based analysis of tumors for microenvironment profiling.

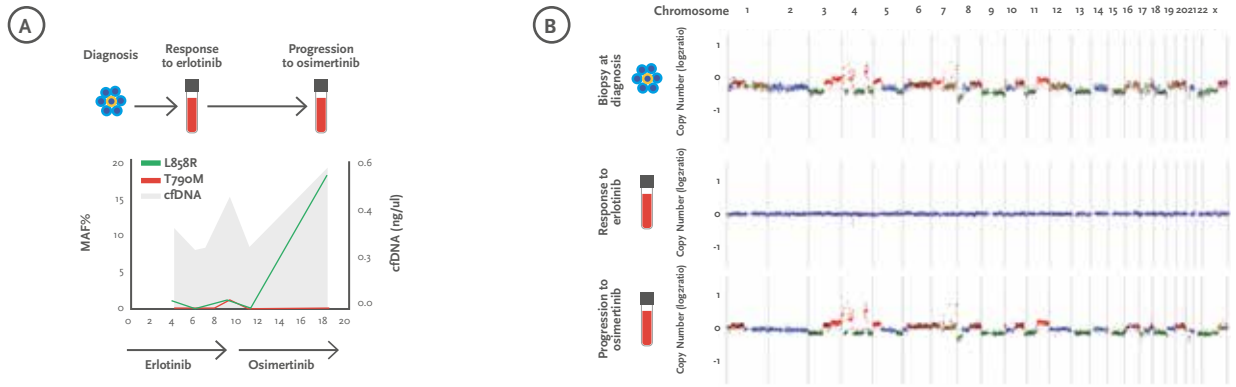

Figure: Genome-wide Copy Number Alteration (CNA) by shallow whole genome sequencing (shWGS) analysis of solid and liquid biopsies to follow residual disease and progression of a patient with lung adenocarcinoma. A. Samples collected from a patient with EGFR L858R mutated NSCLC depicted at the top of the plot, lines of treatments at the bottom of x axis, and results of liquid biopsy follow-up by ddPCR of a EGFR mutation panel. Mutant allelic fractions (MAF%) for L858R and T790M EGFR mutations (left y axis), cell free DNA concentration (right y axis) . B. Results from shWGS for the biopsy at diagnosis (upper panel), from the plasma collected at response to erlotinib (middle panel) and from the plasma collected at progression disease (bottom panel).

PI paper pick

Capdevila J, Mayor R, Mancuso FM, Iglesias C, Caratú G, Matos I, Zafón C, Hernando J, Petit A, Nuciforo P, Cameselle-Teijeiro JM, Álvarez CV, Recio JA, Tabernero J, Matias-Guiu X, Vivancos A, Seoane J. Early evolutionary divergence between papillary and anaplastic thyroid cancers. *Ann Oncol.* 2019 Nov 1;30(11):1843.

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Vivancos A, Aranda E, Benavides M, Élez E, Gómez-España MA, Toledano M, Alvarez M, Parrado MRC, García-Barberán V, Diaz-Rubio E. Comparison of the Clinical Sensitivity of the Idylla Platform and the OncoBEAM RAS CRC Assay for KRAS Mutation Detection in Liquid Biopsy Samples. *Sci Rep.* 2019 Jun 20;9(1):8976.

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CORE TECHNOLOGIES

Molecular Oncology Group

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Lidia Sanchez
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Esther Farell
Kristiana Plamenova

Strategic goals

- Discovery and validation of novel biomarkers using tissue-based technologies.
- Identification of targetable alterations as part of VHIO's Prescreening Program (page 21).
- Application of molecular pathology strategies to support early clinical drug development programs.
- Resolve spatial interaction of tumor-associated microbiota, tumor cells, and immune cells in the tumor microenvironment.
- Better define molecular target epidemiology to render treatment strategies more precise.
- Act as a central and local laboratory in clinical trials.
- Serve as a Core Facility for VHIO research programs.

Highlights

- Application of targeted multiplex proteomics for molecular prescreening and biomarker discovery in metastatic colorectal cancer (*Scientific Reports 2019*).
- Work-package leader and central laboratory for the Horizon 2020-supported COLOSSUS - Advancing a Precision Medicine Paradigm in metastatic Colorectal Cancer: Systems based patient stratification solutions (page 151).

Summary

The mission of VHIO's Molecular Oncology Group 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 medicine in oncology.

Together with VHIO's Cancer Genomics Group (PI Ana Vivancos, page 112), and Oncology Data Science - ODysSey Group (PI Rodrigo Dienstmann), along with Susana Aguilar and Jenifer Gonzalez, our group participates in VHIO's Molecular Prescreening Program. We molecularly profile over 1100 patients per year as candidates for enrolment in early phase clinical trials at our Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" (page 122). We also serve as one of VHIO's Core Technology Platforms and our laboratory is therefore key to our translational research lines and programs.

We actively participate in all projects involving the use of human tissue collected from patients, including biomarker analyses for patient stratification and inclusion in clinical trials, digital pathology, tissue banking and the development of primary patient-derived xenograft (PDX) models. Our contribution is reflected by several high-impact factor collaborative papers published throughout 2019.

Our group also continues to work both independently as well as in partnership to establish the impact of microbiome in colorectal cancer development and progression. In particular, we are developing a *Fusobacterium nucleatum* diagnostic assay that permits the simultaneous visualization and quantification of bacteria within tumors.

As a Core Facility we have provided support for approximately 280 clinical studies conducted at Vall d'Hebron, representing around 70% of all currently open trials at our institution. Our involvement in clinical trials ranges 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 2019 we performed more than 4000 molecular determinations on samples for patient inclusion in clinical trials, and over 23,000 tests to support basic and translation research. We have also served as the central laboratory of choice for 10 international studies, and successfully maintained the prestigious ISO15189 accreditation that endorses quality and competence.

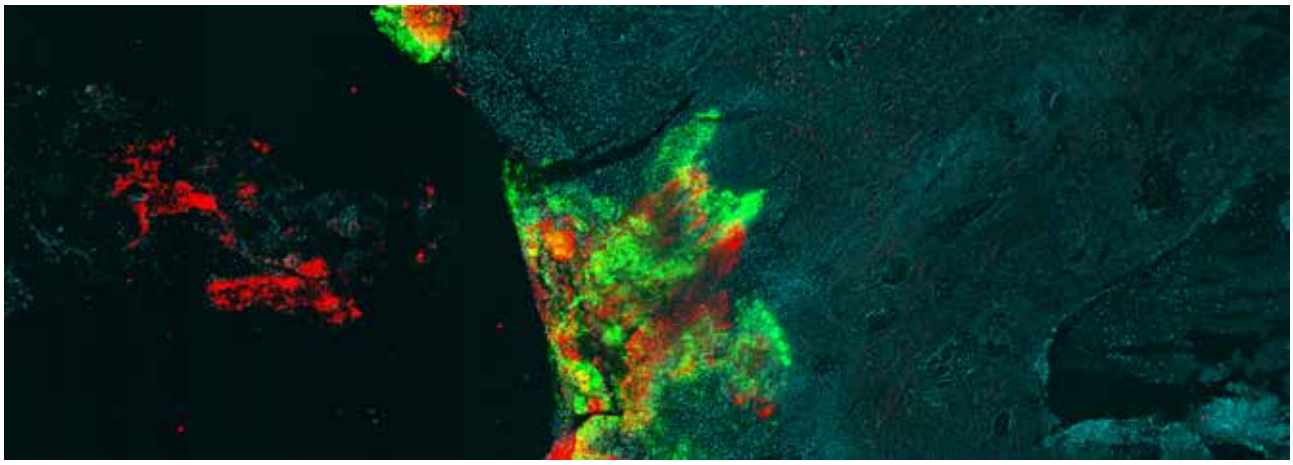

Figure: Intratumoral bacteria visualization by in situ hybridization stainings using bacteria-specific RNA probes (virtual image reconstruction, green for *Fusobacterium nucleatum* and red for *Propionibacterium acnes*).

PI paper pick

Serna G, Ruiz-Pace F, Cecchi F, Fasani R, Jimenez J, Thyparambil S, Landolfi S, Elez E, Vivancos A, Hembrough T, Tabernero J, Dienstmann R, Nuciforo P. Targeted multiplex proteomics for molecular prescreening and biomarker discovery in metastatic colorectal cancer. *Sci Rep*. 2019 Sep 19;9(1):13568.

Saura C, Hlauschek D, Oliveira M, Zardavas D, Jallitsch-Halper A, de la Peña L, Nuciforo P, Ballestrero A, Dubsky P, Lombard JM, Vuylsteke P, Castaneda CA, Colleoni M, Santos Borges G, Ciruelos E, Fornier M, Boer K, Bardia A, Wilson TR, Stout TJ, Hsu JY, Shi Y, Piccart M, Gnant M, Baselga J, de Azambuja E. Neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with oestrogen receptor-positive, HER2-negative, early-stage breast cancer (LORELEI): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2019 Sep;20(9):1226-1238. doi: 10.1016/S1470-2045(19)30334-1.

Oliveira M, Saura C, Nuciforo P, Calvo I, Andersen J, Passos-Coelho JL, Gil Gil M, Bermejo B, Patt DA, Ciruelos E, de la Peña L, Xu N, Wongchenko M, Shi Z, Singel SM, Isakoff SJ. FAIRLANE, a double-blind placebo-controlled randomized phase II trial of neoadjuvant ipatasertib plus paclitaxel for early triple-negative breast cancer. *Ann Oncol*. 2019 Aug 1;30(8):1289-1297.

CORE TECHNOLOGIES

Proteomics Group

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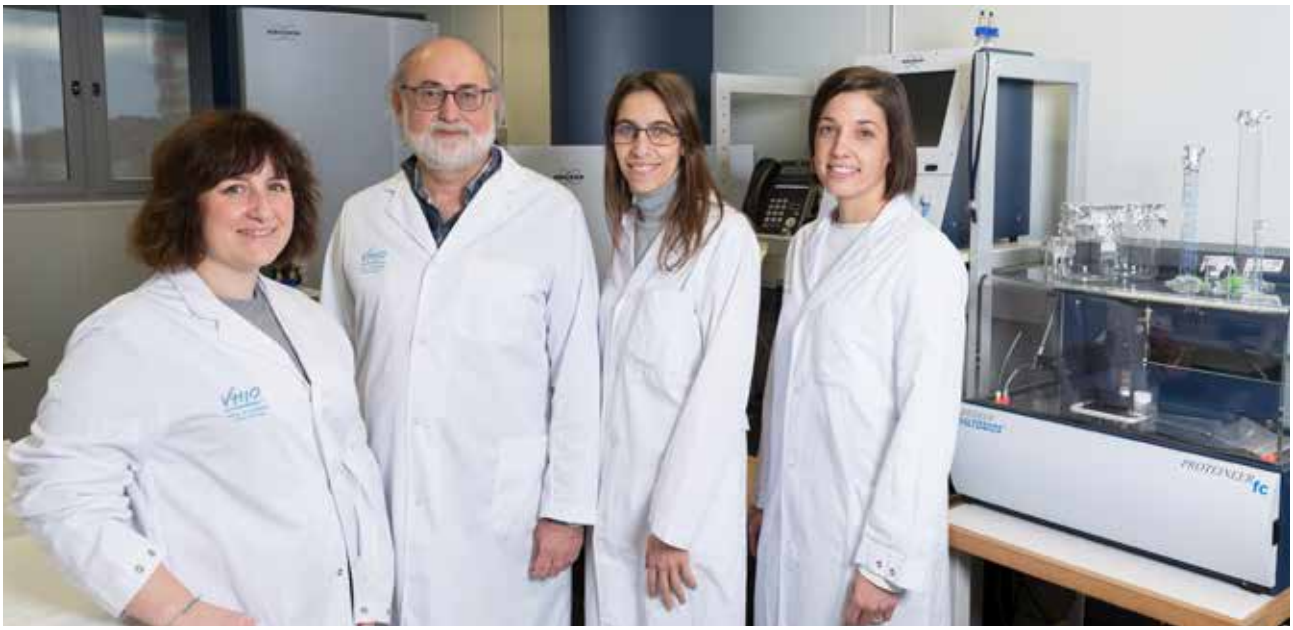
Technicians
Luna Martín
Anna Sabé



Strategic goals

- Provide services in proteomic techniques to other research groups as a Core Facility.
- Proteomic screening for new biomarkers to help develop cancer therapeutics.
- Development of mass spectrometry-based assays for the analysis of biomarkers in clinical samples.
- Contribute to mapping the Chromosome 16 proteome as part of the Human Proteome Project.

Highlights

- The provision of proteomic services to VHIO groups, oncology professionals at the Vall d'Hebron University Hospital (HUVH), and members of the *ProteoRed-Instituto Salud Carlos III* network.
- Application of proteomic and phosphoproteomic screening to the characterization of CRC PDX models
- Setting up mass spectrometry based analytical methods to monitor specific drugs in plasma and tumor tissue, to monitor preliminary pharmacokinetics in preclinical mouse models.
- Participation in the Spanish Consortium Chromosome 16 HPP, the HUPO Human Proteome Project.

Summary

VHIO's Proteomics Group serves as a Core Technology Platform, provides state-of-the-art proteomic methodologies to VHIO researchers, and incorporates new developments within the field to offer the very latest strategies and technologies in the field.

We employ mass spectrometry-based proteomic strategies for the screening and validation of biomarkers for cancer diagnostics, precision therapy and the closer monitoring of disease.

One of our research lines focuses on the development of mass spectrometry-based assays for the analysis of biomarkers in clinical samples. We have been developing immune-MS based assays with improved selectivity and accuracy in the analysis of low abundance biomarker proteins in plasma or CSF samples.

Our group also develops MS based assays for marker proteins in FFPE tissue samples, aimed at providing accurate quantitative measurements that can translate in superior stratification compared with routine IHC scoring methods.

We have set up workflows for the proteomic and phosphoproteomic characterization of patient-derived xenograft (PDX) models of colorectal cancer. PDX constitute an ideal platform for the molecular characterization at the proteomic level of this tumor type. Complementary to genomic classification, we are exploring the suitability of this characterization as a tool for tumor subtype classification.

VHIO's Proteomics Group is a member of the Spanish Consortium Chromosome 16 HPP which forms part of the HUPO Human Proteome Project. Following a chromosome-centric strategy, this multicenter and international project seeks to develop an entire map of the proteins encoded by the human genome to advance our understanding of human biology in health and disease.

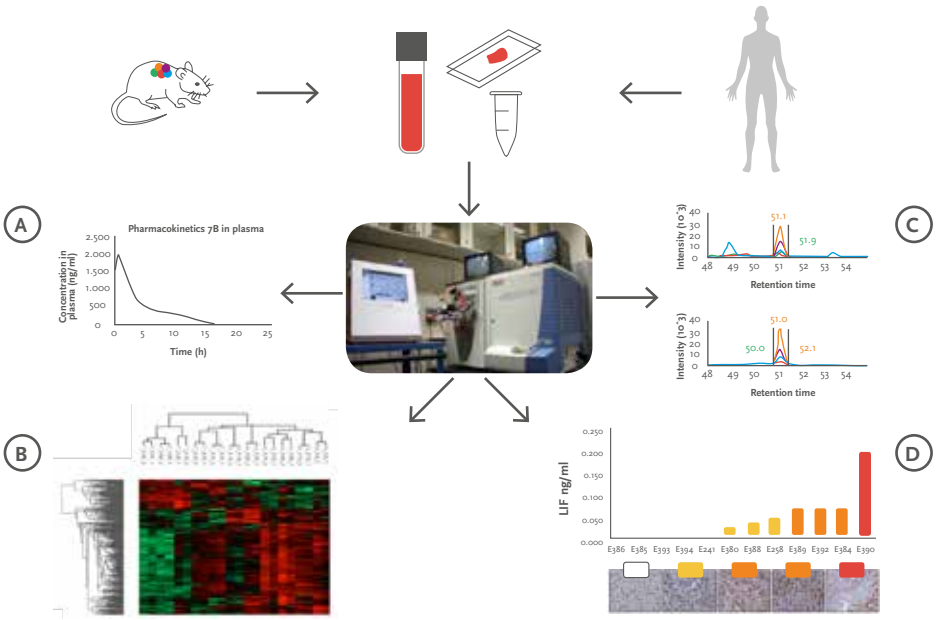


Figure: **Proteomics in preclinical and translational research.** Our laboratory provides mass spectrometry based analysis of plasma, tissue or FFPE samples for: A) monitoring small drugs in plasma or tissue of model animals for pharmacokinetic characterization. B) Profiling of total proteome and phosphoproteome of PDX tumor models to explore pathways involved in therapeutic response. C) targeted LCMS analysis and D) immune-MS analysis, to measure levels of biomarkers in clinical samples for patient stratification or treatment monitoring.

PI paper pick

Arreal L, Piva M, Fernández S, Revandkar A, Schaub- Clerigué A, Villanueva J, Zabala-Letona A, Pujana M, Astobiza I, Cortazar AR, Hermanova I, Bozal-Basterra L, Arruabarrena-Aristorena A, Crespo JR, Valcarcel-Jimenez L, Zúñiga-García P, Canals F, Torrano V, Barrio R, Sutherland JD, Alimonti A, Martin-Martin N, Carracedo A. Targeting PML in triple negative breast cancer elicits growth suppression and senescence. *Cell Death Differ.* 2019 Oct 1.

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3
Consulta

VHIO Scientific Report 2019

VHIO's Transversal Clinical Trials Core Services & Units

Extended version online: memorias.vhio.net/2019
PDF version: memorias.vhio.net/2019/SR-VHIO-2019.pdf

VHIO's TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

Clinical Trials Office

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Alejandro Lahire
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Isabel Maria Miquel
Soraya Peralta
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Nuria Torra

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Gemma Pruna
Cristina Resina
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Clinical Trials Office Administrative Support
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Marc Palomar

Clinical Trials Office Assistant
Alexandre Valle

Clinical Trials Quality Assurance Management
Francisco Javier Fonts
Silvia Garcia
Isabel Gonzalez

Strategic goals

- Contribute to the development of novel therapies against cancer.
- Consolidation as an international reference for clinical trials in oncology.
- Guide patients enrolled in trials to comply with the protocol requirements and help them with daily life throughout the duration of their participation. Ensure that protocols are managed and followed from initiation to the close of the respective clinical study.
- Standardize clinical trial processes to ensure optimal quality and the compliance of Good Clinical Practice (GCP).

Highlights

- Our Clinical Research Support Unit, which was set up in 2016, continues to guide investigators with the start-up and management of independent research lines.
- We continue to report important numbers of clinical trials performed and respective patient recruitment.
- Optimal management of the complexity of protocols which are increasingly demanding.
- We have provided tailored training for our staff in order to further improve the quality of our work and expand related skill sets.
- Implemented new tools and procedures aimed at increasing the quality and efficacy of research.
- Continued optimal quality and procedures achieved through the Inspection for Accreditation of our phase I Unit, the Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa", by the *Generalitat de Catalunya*, carried out in 2016. We received reaccreditation in 2019.
- New patient monitoring system employing electronic medical records.
- Increased office space for the management and coordination of our activities.

Summary

Launched in 1997, our Clinical Trials Office incorporates experts conducting clinical trials at the Vall d'Hebron University Hospital's (HUVH) Medical Oncology Department, the Vall d'Hebron Barcelona Hospital Campus. Headed by VHIO's Director, Josep Tabernero, our team comprises study coordinators, data managers, sample managers, administrative as well as quality control staff, who coordinate phase I–IV clinical studies and also participate in several translational research projects at VHIO.

Organized into three groups, covering all tumor types and studies, our personnel are managed by the Clinical Trials Office Director, Gemma Sala.

In 2019 we managed 1 phase 0, 139 Phase I, 23 Basket studies, 141 phase II, and 121 phase III clinical trials with active recruitment throughout the year (see Figure), with patient enrolment totaling at 1122. 150 new trials were initiated, including 8 post-authorization trials and rollover studies. In addition, we continue to follow up patients who were recruited prior to 2019 and are still enrolled and receiving study treatment (more than 900 patients in total, and more than 1400 in follow up).

More than half of our patients included in our Phase I Clinical Trials have been referred to us from other Hospitals, which has consequently positioned our Unit as leading reference in early clinical studies.

As a reflection of our continued expansion as well as recognition of excellence, we have undergone 16 audits with positive results and VHIO's Research Unit for Molecular Therapy of Cancer (UITM) –"la Caixa", directed by Elena Garralda (page 122), has been reaccredited by the *Generalitat de Catalunya*.

As we continue to render personalized medicine more precise by matching therapies to respond to the specificities of each individual patient, each individual tumor, the requirements and selection criteria for inclusion in certain studies are also becoming more complex.

While we are dedicated to expanding our portfolio of trials in order to ultimately establish new treatment models with highly selective drugs, we continue to fine-tune patient selection criteria in order to best identify those patients who are most likely to benefit from novel therapies, including emerging immune-based therapies, tailored to individual patients' molecular 'measurements'.

The prestige of our Hospital's Medical Oncology Department is increasingly recognized by pharmaceutical as well as biotechnology companies. It has also become a reference program and selected by the industry to carry out complex clinical trials for which the number of participating centers is highly restricted.

Clinical sites are selected based on the highest standards of quality and capacity for carrying out state-of-the-art research. We have participated in early phase trials of different drugs, ultimately enabling the pharmaceutical industry to market novel anti-cancer medicines. We are involved in studies promoted by the pharmaceutical industry as well as those developed by us in collaboration with other hospitals. We have also conducted more than 10 Investigator-Initiated Trials (IITs).

Annual recruitment of patients enrolled in Clinical Trials (Phases 0, I + Baskets - II–III)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Included in Phase 0																					1
Included in Phase I	35	59	57	110	130	120	108	132	139	171	222	245	277	290	345	303	370	453	445	508	499
Included in Phase II	59	72	66	94	91	130	73	165	170	133	161	207	180	253	257	302	327	333	323	361	337
Included in Phase III	95	128	175	109	84	129	111	85	143	180	189	221	218	236	241	166	282	343	328	329	285
N° of patients included	**189**	**259**	**298**	**313**	**305**	**379**	**292**	**382**	**452**	**484**	**572**	**673**	**675**	**779**	**843**	**771**	**979**	**1.129**	**1.096**	**1.198**	**1.122**
Post Authorization & Rollovers trials																20	56	50	80	184	164

Annual Distribution of Phases 0, I + Basket, II and III Trials

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Phase 0 trials																					1
Phase I + Basket trials	6	10	12	14	17	15	16	19	20	26	31	37	48	66	75	83	106	129	137	161	162
Phase II trials	19	22	23	23	22	19	30	32	42	40	55	54	57	85	96	99	94	117	107	131	141
Phase III trials	14	17	22	25	18	20	21	21	31	37	45	49	56	68	61	64	89	108	111	107	121
N° of clinical trials	**39**	**49**	**57**	**62**	**57**	**54**	**67**	**72**	**93**	**103**	**131**	**140**	**161**	**219**	**232**	**246**	**289**	**354**	**355**	**399**	**425**
Post-authorisation & Rollover Trials																5	14	16	19	33	34

VHIO's TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

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

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Director
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Medical Coordinator
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Susana Maria Cedres
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Lorena Fariñas
Vladimir Galvao De Aguiar
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Patricia Gomez
Macarena Gonzalez
Jorge Hernando
Alberto Hernando
Ana Mafalda Antunes
Alexandre Martinez
Juan Jesus Martin
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Ignacio Matos
Rafael Morales
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Margarida Marcos
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Tania Sanchez
Alba Silverio

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Nursing Assistant
Maria Teresa Ferreras
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Alicia Lopez
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Cristina Resina

Inventory Manager
Cristina Resina

Secretary
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Laura Maños

Pharmacist
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Maria Alcalde
Montserrat Carreres
Isabel De La Paz
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Toni Lozano
Javier Martinez
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Pablo Piera
Eugenia Serramontmany

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Maria Hidalgo
Roser Klimt
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Alba Serrano
Isabel Perez
Marta Pozo
Alan Paul Thompson
Silvia Torralba
Ester Vilaro
Noemi Visus

Pharmacy Logistics Managers
Maria Hidalgo
Sara Pizarro

Strategic goals

- Early drug development and translational research led by UITM physician-researchers and VHIO scientists: expansion of our broad portfolio of promising novel anticancer therapies, across a balanced spectrum of studies, with special focus on first-in-human studies, novel-novel combinations, best-in-class compounds, and a new class of drugs.
- Perform complex trials such as organ dysfunction trials, Octopus as well as Basket studies, and link clinical research at UITM to VHIO's preclinical and translational projects. Our Unit also collaborates with the various partners involved in drug development and translational research.
- Genomic medicine trials in early drug development: perform molecular analysis of patients' tumors in order to select the best possible treatment with the experimental treatments available, co-develop medical informatics applied to genomic medicine, and integrate preclinical and clinical research by incorporating novel drugs, new insights, and study design together with customized molecular diagnostics.
- Immunotherapy: our Unit's taskforce in early drug development of immunotherapeutics and cell signaling focuses on second generation immunotherapies, including new cytokines, bispecifics, intratumoral agents, immunomodulatory, and immune checkpoint inhibitors and combinations, as well as translational research in immuno-oncology.

"la Caixa" Foundation

Highlights

- We have performed some of the most complex phase I trials, including those focused on molecularly-selected patient populations (trials in complex molecularly-selected patient populations Basket/Octopus trials) as well as trials in immuno-oncology.
- We have expanded our expertise in drugs targeting developmental pathways, cell signaling (ERK, MET, FGFR, RET, NOTCH, NTRK), and immunotherapy (LAG3, TIGIT, OX40, CD40, IDO, arginase inhibitors and engineered antibodies).
- Developed by VHIO's Cancer Genomics Group, PI: Ana Vivancos, page 112, we benefit from applications for faster results including an n-Counter (Nanostring) platform, two digital PCR platforms (BEAMing Sysmex and ddPCR, BIO-RAD), and two NextGen Sequencers; MiSeq and HiSeq2500 (Illumina). We also co-develop customized molecular tests for VHIO's Prescreening Program, page 21 (disease-oriented mutation panels for our NGS platforms).
- We have developed alliances with many pharma companies as the preferred site for testing their novel and most relevant therapies, including GlaxoSmithKline OCTC, Roche ImCORE, and AstraZeneca/MedImmune, Partners of Choice.
- We have successfully implemented the Basket of Baskets (BoB) trial which is a novel study in personalized medicine integrating cutting-edge molecular prescreening, the development of new diagnostic tests such as circulating DNA or Nanostring, with the testing of targeted therapies in populations of patients with identified molecular alterations in their tumors and a high probability of benefiting from the selected treatments. This is an academic study, endorsed by the Cancer Core Europe (CCE) consortium, and co-funded by pharmaceutical companies. The first module evaluating atezolizumab in a molecularly-selected population recruited this year, and we have secured funding to evaluate FGFR inhibition in specific populations. We are engaged in ongoing and advanced negotiations with other pharmaceutical companies.
- We have introduced Molecular Tumor Board meetings to discuss the most relevant genomic features of complicated cases to evaluate possible treatment options.
- We have started an advanced cell-based therapy program, and are participating in several pharma sponsored trials to evaluate the role of TIL therapy as well as exploring an academic TIL product in collaboration with Alena Gros, PI of VHIO's Tumor Immunology & Immunotherapy Group (page 108).
- In collaboration with several other VHIO groups, we head the VHIO-"la Caixa" Advanced Oncology Research Program (2020-2023) (page 27).

Summary

Inaugurated in June 2010, thanks to the support received from 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 (HUVH), the Vall d'Hebron Barcelona Hospital Campus.

This privileged environment with direct access to patients, coupled with VHIO's translational approach to research and superb scientific framework, has enabled our Unit to rapidly establish itself as one of the few comprehensive facilities in Europe to rapidly transform latest discovery into benefits for patients.

By promoting tight connectivity between oncology care and research we establish novel treatment models for patients with highly selective drugs, and advance insights into tumor diseases and how to treat them in an individualized way – getting the right therapy to the right patient at the right time. As the figures show, we are gradually doing so for an increasing number of patients.

In 2019, also thanks to the support received from the "la Caixa" Foundation, the building of VHIO's Clinical Research Oncology Pharmacy's Unit's (led by Maria Queralt, page 126), new Facility, the Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa"- Clinical Research Onco-Hematology Unit was completed. Equipped with all with all the very latest technologies, this will enable them to provide even higher quality pharmaceutical care and continue to respond to all regulatory requirements.

This year, our Unit has participated in 162 ongoing phase I clinical trials, 23 of which are Basket trials. Our facilities, coupled with our multidisciplinary clinical teams, enable us to continue to expand our portfolio of phase I studies. This year we opened 46 new trials; 6 as Baskets. 499 patients were recruited, 241 of whom were enrolled in immunotherapy clinical trials

Research carried out at our Unit by VHIO's Early Clinical Drug Development Group directed by Elena Garralda (page 84), centers on the development of new drugs based on the molecular profile of each tumor as well as the optimization of treatment regimens using combinations of new agents with those that already exist.

Reflective of VHIO's purely translational model, our studies are also linked to several research lines led by other VHIO groups, thus connecting molecular biology and optimal tumor models with pharmacology and innovative clinical research. VHIO scientists also collaborate closely in our trials to facilitate biomarker development, a deep understanding of the mechanism of action, as well as research into mechanisms of cancer drug resistance.

In partnership with VHIO's Cancer Genomics (PI Ana Vivancos), Molecular Oncology (PI Paolo Nuciforo), and Oncology Data Science - ODysSey (PI Rodrigo Dienstmann), together with Susana Aguilar and Jenifer Gonzalez, we perform molecular analyses of patients' tumors to select the best possible treatment with the experimental therapeutics available. Thanks to our Cancer Genomics Group's development of existing applications for faster results including an n-Counter (Nanostring) platform, two digital PCR platforms (BEAMing Sysmex and ddPCR, BIO-RAD), and two NextGen Sequencers; MiSeq and HiSeq2500 (Illumina) we continue to drive faster and more precise mutational analyses of tumor suppressor genes as well as translocations and gene amplifications.

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 of many other oncology professionals including our team of Clinical Research Oncology Nurses led by Mª Angeles Peñuelas (page 124), pathologists from the Vall d'Hebron University Hospital's Molecular Pathology Department, radiologists and interventional radiologists, as well as our Clinical Trials Office and Database Management, directed by Gemma Sala (page 120), Clinical Research Oncology Pharmacy Unit headed by Maria Queralt (page 126), and other healthcare specialists including dermatologists, cardiologists, and ophthalmologists.

VHIO's TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

Clinical Research Oncology Nurses

Nurse Supervisor
Mª Angeles Peñuelas

Nurse Coordinators
Sonia Valverde
Lydia Velez

Nurses
Irene Calzado
Anna Maria Carro
Cristina Casal
Mª Elena De Cabo
Begoña Fargas
Sandra Jara
Carla Junyent
Margarida Marcos
Marta Mate
Nuria Membrives
Mireia Milan
Mireia Moral
Isabel Muñoz
Silvia Oliver
Judith Olivera
Silvia Puyalto
Tania Sanchez
Alba Silverio
Patricia Suarez

Nurse Supervisor's Assistant
Juan Manuel Garcia

Nursing Assistants
Alicia Lopez
Thalia Maldonado
Mª Ascension Martin
Ana Belen Ortiz
Cristina Resina

Summary

Clinical trials in oncology are essential for the identification of novel, more effective targeted therapies against cancer as well as improving survival, side effect profiles and the quality of life of patients. Advances in oncology care and the development of more powerful anti-cancer medicines are driven by optimal processes in clinical trials.

Our expert clinical research oncology nurses assume a central role by undertaking a variety of roles including identifying trends in side effects, closely collaborating with multidisciplinary teams to develop and evaluate patient management, contributing to clinical studies by collating samples and quality data, as well as providing excellence in nursing care and symptom management for all patients enrolled in clinical trials.

VHIO's Clinical Research Oncology Nurses, specialized in molecular therapies, are headed by Angeles Peñuelas and represent an important element of the multidisciplinary teams involved in the studies performed and coordinated at VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa" and Clinical Trials Office, directed by Elena Garralda and Gemma Sala, respectively (see pages 120-123).

Supporting these teams comprised of medical oncologists, molecular pathologists, oncology pharmacists, clinical researchers, and study coordinators, VHIO's oncology nurses are key to ensuring the delivery of optimal care for patients who receive the full range of expertise, guidance, and the necessary follow-up throughout the course of their participation in a clinical study.

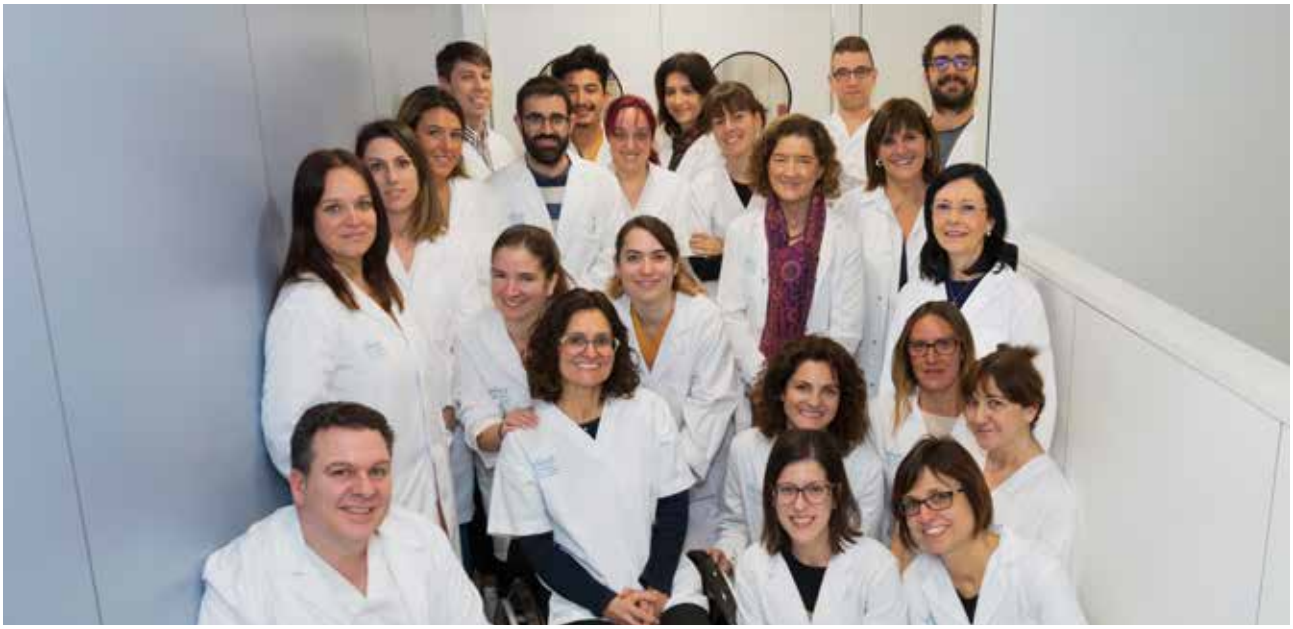
As importantly is the psychological support they provide, alongside the other superbly trained oncology care givers and specialists including psychologists. Our nurses also provide patients and their families with the information and professional guidance they need to make fully informed decisions concerning their treatment options.

In 2019, across the 425 actively recruiting trials patient enrollment totaled at 1122. Our clinical teams also continue to follow up patients that were recruited prior to 2019 who are still enrolled and receiving treatment.

As VHIO continues to expand its portfolio of clinical trials to ultimately establish novel treatments with highly selective drugs, and fine-tune patient selection criteria in order to identify those patients who are most likely to benefit from them, we can expect a steady increase in patient recruitment across our clinical studies in the future.

VHIO's TRANSVERSAL CLINICAL TRIALS CORE SERVICES & UNITS

Clinical Research Oncology Pharmacy Unit



Clinical Director of the Clinical Research Oncology Pharmacy Unit
Maria Queralt Gorgas

Coordinators of the Clinical Research Oncology Pharmacy Unit
David Lopez
Jana Vidal

Senior Pharmacists
Maria Josep Carreras
Laura Maños

Pharmacists
Faten Ahmad
Angela Alcala
Maria Alcalde
Montserrat Carreres
Isabel De La Paz
Carla Esteban
Pablo Latorre
Toni Lozano
Javier Martinez
Pablo Montejano
Pablo Piera
Eugenia Serramontmany

Technicians
Laura Blanch
Romina Bellini
Esther Carabantes
Ismael Delgado
Rafael Diaz
Maria Hidalgo
Roser Klimt
Sergi Mengual
Susana Mulet
Isabel Perez
Marta Pozo
Alba Serrano
Alan Thompson
Silvia Torralba
Ester Vilaro
Noemi Visus

Secretary
Isabel Mª Alerany

Strategic goals

- Excellence in the services we provide to clinical oncology research programs through optimal efficacy, efficiency and safety.
- Management, dispensing, preparation and administration of clinical study drugs according to protocol specifications. Ensure traceability of the entire circuit with the development and implementation of new software.
- Maximized control of storage temperature of samples and preparations.
- Optimal use of a computerized program, IPharma-FUNDANET®, for the management of clinical trial supplies.
- Provision of a pharmaceutical care program for patients in phase I studies treated with orally administered medicines to improve safety, compliance and efficacy of these therapies.
- Provide instructions and indications to patients for orally administered therapies in phase II and III studies.
- Successful sponsor audits as well as inspections carried out by regulatory authorities.

"la Caixa" Foundation

Highlights

- In 2019, thanks to the support received from the "la Caixa" Foundation, the building of our new facility, the Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa"- Clinical Research Onco-Hematology Unit was completed. Equipped with all with all the very latest technologies, this will enable us to provide even higher quality pharmaceutical care and continue to respond to all regulatory requirements.
- Replacing paper medical orders, we have implemented electronic prescription ordering for IV administration medication in our site prescription software.
- We have developed new traceability software that includes global pharmacotherapeutic processes; the prescription, validation, dispensing, preparation and administration of drugs in the oncology and hematology clinical trial setting.
- Our Unit has provided clinical and technical support for the prescription, preparation, and administration of cytostatics in clinical trials, providing e-records of usage and timings.
- Qualitative and quantitative quality control of all parenteral anticancer preparations to guarantee patient safety and protocol compliance.
- ISO9001:2015 certification renewed. Successful sponsor audits, regulatory inspections, and participation in the renewal of VHIO's Phase I Unit reaccreditation.

Summary

Our Unit is ISO 9001:2015 certified and affiliated with the Medical Oncology Service of the Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus. As noted in our Highlights section above, thanks to the support received from the "la Caixa" Foundation, the building of our new Facility, the Research Unit for Molecular Therapy of Cancer (UITM) – "la Caixa"- Clinical Research Onco-Hematology Unit was completed. Equipped with all with all the very latest technologies, this will enable us to provide even higher quality pharmaceutical care and continue to respond to all regulatory requirements.

We focus on two main areas of clinical research in oncology:

Oncology Pharmaceutical Care Program

Our team of pharmacists specialized in hospital pharmacy and oncology pharmacy and our laboratory technicians prepare cytostatics and other parenteral therapies used in clinical trials. They also monitor and follow-up patients.

Pharmacological Research in Oncology Support Program

This program is led by our team of pharmacists and laboratory technicians specialized in clinical trials, who are responsible for study supplies management, storage, dispensation, and traceability control.

In 2019 we managed drugs used in 591 active clinical trials in oncology & hematology, and 7.426 resupply deliveries/clinical trials supplies receptions. We continue to benefit from our cutting-edge system for controlling storage temperature which, performing electronic temperature recordings every 5 minutes daily, displays readings on computers equipped with audiovisual alarms as well as an around-the-clock SMS alert system to monitor and report temperature deviations.

Regarding the design and validation of our drug preparation process traceability system, we ensure qualitative and quantitative quality control of our computerized system.

In 2019 our dispensing staff actively participated in 113 pre-study visits, 185 initial visits, 1,841 monitoring visits, 111 close-out visits. We have also successfully passed 21 audits, 1 mock inspection, 1 ISO inspection, and 1 inspection by local regulatory authorities for reaccreditation of our Oncology Phase I Unit.

Additionally, 39,055 clinical trial drugs have been dispensed and validated by our pharmacists, 13,782 of which were for oral administration, 1,017 for IM/subcutaneous administration, and 24,256 for IV administration. A total of 214 Standardized Dispensing Procedures for clinical trials have been drawn up and we have performed 892 updates of these procedures due to subsequent amendments to protocols or pharmacy manuals. 156 storage temperature data reports have also been prepared by our dispensing team.

Preparations of cytostatics, monoclonal antibodies and other parenteral antitumor drugs for clinical trials totaled at 24,122. We also included 432 antineoplastic therapeutic schedules in our prescription software.

Our Pharmaceutical Care Program for patients enrolled in phase I clinical trials: we performed 1,205 visits, 253 screenings, 238 C1D1s, and 221 follow-ups, also compiling patient diaries and/or instructions for patients (in the absence of documentation provided by the respective sponsor).

We have also compiled 15 different diaries and 15 instruction manuals for patients enrolled in the phase I studies involving orally administered drugs by our preparation staff. We also prepared 23 diaries and patient manuals for phase II and phase III clinical trials in 2019 for patients enrolled in all phase II and III studies involving orally administered drugs by our dispensing staff.

SCIENTIFIC COORDINATION AREA & CLINICAL RESEARCH SUPPORT UNIT (CRSU) - Academic CRO

Scientific Coordination Area

Head of Area
Alejandro Piris Giménez

Senior Project Managers
Neus Bayó
Elena Chavarria
Javier Gonzalo
Josep Maria Miquel
Sandra Porta
Isabel Vallvé
Xenia Villalobos

Junior Project Managers
Berta Colldeforns
Eric Delgado
Nacho Sánchez

Area Summary:

VHIO's Scientific Coordination Area has consolidated itself as a Unit to support VHIO's Direction, Management, and research groups for the development of research proposals and programs, monitoring and follow up. We also provide support to our various Task Forces (page 28), that strengthen and promote multidisciplinary connectivity and spur joint research programs with other oncology teams at the Vall d'Hebron University Hospital, Vall d'Hebron Barcelona Hospital Campus (page 22).

Our managerial responsibilities include both financial and scientific support, as well as the implementation of institutional actions to various areas including education, ethics & regulatory issues, scientific dissemination, consortia and coordinated research. These cover competitive grant application processes, dissemination of national and international funding opportunities for our researchers, assessment of the preparation and writing of competitive project proposals, as well as the monitoring and coordination of awarded research projects.

We aim to optimize opportunities for the internationalization of groups through a personalized plan for VHIO groups, centralize ideas from taskforces and match selected research priorities with competitive calls, as well as support highly innovative technological project proposals to increase VHIO's success rate in terms of Innovative Medicines Initiative (IMI), and H2020 and Horizon Europe framework approved projects as coordinators and partners through the proactive search and evaluation of opportunities, as well as potentiate our area's organizational structure and optimize our project management processes.

Strategic goals

- Identify and promote new research opportunities involving academic and industry partners.
- Write, coordinate and manage scientific proposals.
- Manage, monitor and follow up institutional programs.
- Promote intramural research through education, networking and driving force.

Highlights

- In 2019, VHIO's success rate was 30%, out of 207 grant (competitive) applications.
- This year, our Unit managed more than 9 million EUR obtained from competitive funds.
- Our research support to VHIO groups has been recognized through our co-authorship of two publications: *How I treat gastric adenocarcinoma* (Alsina M et al. *ESMO Open*. 2019); *New clinical trial designs in the era of precision medicine* (Garralda E et al. *Mol Oncol*. 2019).
- We co-launched, together with VHIO's Educational Committee, our VHIO-"la Caixa" Foundation VHIO Scientific Seminars Series (see page 38).
- Our Unit co-leads major EU consortia, including MoTriColor (H2020), page 152, COLOSSUS (H2020), page 151, the Basket of Baskets trial (Cancer Core Europe – CCE, page 28), and participates in numerous project boards and work packages.
- We have provided support to our Scientific Direction through the management of scientific data, documents and actions required for the elaboration and development of research proposals and projects at VHIO.

SCIENTIFIC COORDINATION AREA & CLINICAL RESEARCH SUPPORT UNIT (CRSU) - Academic CRO

Clinical Research Support Unit (CRSU) - Academic Cro

CRS Unit Head
Susana Muñoz

Lead CRA and Project Manager
Marta González

Clinical Research Associates
Darío López
Júlia Molina
Lídia Piquet
Amaya González

Area Summary:

Our academic Contract Research Organization (CRO) has extensive experience in conducting sponsored trials and investigator-initiated trials. The CRO offers a complete package of start-to-end management services required to perform clinical trials and studies. Thanks to our multidisciplinary team, we can operate as a full service CRO in clinical studies from phase I to IV studies. We also offer guidance to all researchers and sponsors on how to achieve the best experimental design and logistical advice in order to maximize their resources. With a team of 6 professionals, our CRO provides medical writing support, full regulatory activities, monitoring, project management, e-CRF creation, statistics, drug management, insurance management, and pharmacovigilance activities. We seek to expand the our Unit's structure with a clinical project manager and a CRA to be able to even more effectively manage current and future clinical trials, optimize CRO digital tools to allow for working remotely, as well as continue to bring out the best in each team member to enhance our newly created Facility.

Strategic goals

- Clinical project management support to awarded R&D projects (European/Pharma funded), academic Oncology Clinical Trials lead by our Medical Oncologists and Clinical Investigators at VHIO and the Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus (page 22).
- Academic CRO for Investigator initiated trials.

Highlights

- In 2019 our academic CRO successfully managed a number of major projects including COMBAT, TOPIC, IRONMAN, MONEO, among others. Most of these are led the Vall d'Hebron University Hospital (HUVH) oncology teams, at the Medical Oncology Department headed by Josep Tabernero, VHIO's Director.
- During 2019, we successfully met the the regulatory requirements of all of our trials (first submissions and amendments).
- Our CRA team were able to monitor more than 150 patients in several hospitals throughout Spain.
- We managed clinical trials drug requirements in more than 25 national hospitals.
- We have also evidenced sufficient benefits to cover CRO activities for non-funded academic trials.

Full listing of articles published by VHIO investigators in 2019

Articles published by VHIO Investigators in 2019 with allocated Impact Factor (IF):

Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. de Wit R; de Bono J; Sternberg CN; Fizazi K; Tombal B; Wülfing C; Kramer G; Eymard JC; Bamias A; Carles J; Iacovelli R; Melichar B; Sverrisdóttir Á; Theodore C; Feyerabend S; Helissey C; Ozatilgan A; Geffriaud-Ricouard C; Castellano D; CARD Investigators. 2019. *N Engl J Med.* 381(26): 2506 - 2518. IF:70,670.

Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. Fizazi K; Shore N; Tammela TL; Ulys A; Vjaters E; Polyakov S; Jievaltas M; Luz M; Alekseev B; Kuss I; Kappeler C; Snapir A; Sarapohja T; Smith MR; ARAMIS Investigators. 2019. *N Engl J Med.* 380(13): 1235 - 1246. IF:70,670.

Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. Kopetz S; Grothey A; Yaeger R; Van Cutsem E; Desai J; Yoshino T; Wasan H; Ciardiello F; Loupakis F; Hong YS; Steeghs N; Guren TK; Arkenau HT; Garcia-Alfonso P; Pfeiffer P; Orlov S; Lonardi S; Elez E; Kim TW; Schellens JHM; Guo C; Krishnan A; Dekervel J; Morris V; Calvo Ferrandiz A; Tarpgaard LS; Braun M; Gollerkeri A; Keir C; Maharry K; Pickard M; Christy-Bittel J; Anderson L; Sandor V; Tabernero J. 2019. *N Engl J Med.* 381(17): 1632 - 1643. IF:70,670.

Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. Loriot Y; Necchi A; Park SH; Garcia-Donas J; Huddart R; Burgess E; Fleming M; Rezazadeh A; Mellado B; Varlamov S; Joshi M; Duran I; Tagawa ST; Zakharia Y; Zhong B; Stuyckens K; Santiago-Walker A; De Porre P; O'Hagan A; Avadhani A; Siefker-Radtke AO; BLC2001 Study Group. 2019. *N Engl J Med.* 381(4): 338 - 348. IF:70,670.

Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. Golan T; Hammel P; Reni M; Van Cutsem E; Macarulla T; Hall MJ; Park JO; Hochhauser D; Arnold D; Oh DY; Reinacher-Schick A; Tortora G; Algül H; O'Reilly EM; McGuinness D; Cui KY; Schlienger K; Locker GY; Kindler HL. 2019. *N Engl J Med.* 381(4): 317 - 327. IF:70,670.

Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. González-Martín A; Pothuri B; Vergote I; DePont Christensen R; Graybill W; Mirza MR; McCormick C; Lorusso D; Hoskins P; Freyer G; Baumann K; Jardon K; Redondo A; Moore RG; Vulsteke C; O'Cearbhaill RE; Lund B; Backes F; Barretina-Ginesta P; Haggerty AF; Rubio-Pérez MJ; Shahin MS; Mangili G; Bradley WH; Bruchim I; Sun K; Malinowska IA; Li Y; Gupta D; Monk BJ; PRIMA/ENGOT-OV26/GOG-3012 Investigators. 2019. *N Engl J Med.* 381(25): 2391 - 2402. IF:70,670.

Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. Coleman RL; Fleming GF; Brady MF; Swisher EM; Steffensen KD; Friedlander M; Okamoto A; Moore KN; Efrat Ben-Baruch N; Werner TL; Cloven NG; Oaknin A; DiSilvestro PA; Morgan MA; Nam JH; Leath CA; Nicum S; Hagemann AR; Littell RD; Cella D; Baron-Hay S; Garcia-Donas J; Mizuno M; Bell-McGuinn K; Sullivan DM; Bach BA; Bhattacharya S; Ratajczak CK; Ansell PJ; Dinh MH; Aghajanian C; Bookman MA. 2019. *N Engl J Med.* 381(25): 2403 - 2415. IF:70,670.

Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. Rini BI; Powles T; Atkins MB; Escudier B; McDermott DF; Suarez C; Bracarda S; Stadler WM; Donskov F; Lee JL; Hawkins R; Ravaud A; Alekseev B; Staehler M; Uemura M; De Giorgi U; Mellado B; Porta C; Melichar B; Gurney H; Bedke J; Choueiri TK; Parnis F; Khaznadar T; Thobhani A; Li S; Piault-Louis E; Frantz G; Huseni M; Schiff C; Green MC; Motzer RJ; IMmotion151 Study Group. 2019. *Lancet.* 393(10189): 2404 - 2415. IF:59,102.

Cervical cancer. Cohen PA; Jhingran A; Oaknin A; Denny L. 2019. *Lancet.* 393(10167): 169 - 182. IF:59,102.

Actively personalized vaccination trial for newly diagnosed glioblastoma. Hilf N; Kuttruff-Coqui S; Frenzel K; Bukur V; Stevanovic S; Gouttefangeas C; Platten M; Tabatabai G; Dutoit V; van der Burg SH; Thor Straten P; Martínez-Ricarte F; Ponsati B; Okada H; Lassen U; Admon A; Ottensmeier CH; Ulges A; Kreiter S; von Deimling A; Skardelly M; Migliorini D; Kroep JR; Idorn M; Rodon J; et al. 2019. *Nature.* 565(7738): 240 - 245. IF:43,070.

Atezolizumab with or without cobimetinib versus regorafenib in previously treated metastatic colorectal cancer (IMblaze370): a multicentre, open-label, phase 3, randomised, controlled trial. Eng C; Kim TW; Bendell J; Argilés G; Tebbutt NC; Di Bartolomeo M; Falcone A; Fakih M; Kozloff M; Segal NH; Sobrero A; Yan Y; Chang I; Uyei A; Roberts L; Ciardiello F; IMblaze370 Investigators. 2019. *Lancet Oncol.* 20(6): 849 - 861. IF:35,386.

ESMO-MCBS: setting the record straight. Cherny NI; Tabernero J; de Vries EGE. 2019. *Lancet Oncol.* 20(4): 192 - 192. IF:35,386.

NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue sarcoma (Act. In. Sarc): a multicentre, phase 2-3, randomised, controlled trial. Bonvalot S; Rutkowski PL; Thariat J; Carrère S; Ducassou A; Sunyach MP; Agoston P; Hong A; Mervoyer A; Rastrelli M; Moreno V; Li RK; Tiangco B; Herraez AC; Gronchi A; Mangel L; Sy-Ortin T; Hohenberger P; de Baère T; Le Cesne A; Helfre S; Saada-Bouzid E; Borkowska A; Anghel R; Co A; Gebhart M; Kantor G; Montero A; Loong HH; Vergés R; et al... 2019. *Lancet Oncol.* 20(8): 1148 - 1159. IF:35,386.

PET or MRI to improve response evaluation in clinical trials? Deroose CM; Gheysens O; Perez-Lopez R. 2019. *Lancet Oncol.* 20(8): 1060 - 1062. IF:35,386.

Ramucirumab plus pembrolizumab in patients with previously treated advanced non-small-cell lung cancer, gastro-oesophageal cancer, or urothelial carcinomas (JVDF): a multicohort, non-randomised, open-label, phase 1a/b trial. Herbst RS; Arkenau HT; Santana-Davila R; Calvo E; Paz-Ares L; Cassier PA; Bendell J; Penel N; Krebs MG; Martin-Liberal J; Isambert N; Soriano A; Wermke M; Cultrera J; Gao L; Widau RC; Mi G; Jin J; Ferry D; Fuchs CS; Petrylak DP; Chau I. 2019. *Lancet Oncol.* 20(8): 1109 - 1123. IF:35,386.

Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFALL): a double-blind, randomised, placebo-controlled, phase 3 trial. Fuchs CS; Shitara K; Di Bartolomeo M; Lonardi S; Al-Batran SE; Van Cutsem E; Ilson DH; Alsina M; Chau I; Lacy J; Ducreux M; Mendez GA; Alavez AM; Takahari D; Mansoor W; Enzinger PC; Gorbounova V; Wainberg ZA; Hegewisch-Becker S; Ferry D; Lin J; Carlesi R; Das M; Shah MA; RAINFALL Study Group. 2019. *Lancet Oncol.* 20(3): 420 - 435. IF:35,386.

Rogaratinib in patients with advanced cancers selected by FGFR mRNA expression: a phase 1 dose-escalation and dose-expansion study. Schuler M; Cho BC; Sayehli CM; Navarro A; Soo RA; Richly H; Cassier PA; Tai D; Penel N; Nogova L; Park SH; Schostak M; Gajate P; Cathomas R; Rajagopalan P; Grevel J; Bender S; Boix O; Nogai H; Ocker M; Ellinghaus P; Joerger M. 2019. *Lancet Oncol.* 20(10): 1454 - 1466. IF: 35,386.

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Funding & Consortia

FUNDING

VHIO can and will only deliver on its goal of accelerating the pace in advancing personalized and targeted therapies against cancer thanks to the public funding it receives as well as the generous support from institutional supporters, private institutions, companies, associations, societies, and individual donors. As a direct reflection of VHIO's research of excellence, VHIO also continues to secure essential funding through several International and National Competitive Grants. Regarding the latter, we would like to also recognize the *Asociación Española Contra el Cáncer* (AECC) for its longstanding support of several VHIO groups and researchers (page 34).

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

INSTITUTIONAL SUPPORTERS

Generalitat de Catalunya

Fundació Privada CELLEX

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Investigando por un futuro sin cáncer

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SEVENTH FRAMEWORK PROGRAMME

European Commission
Horizon 2020
European Union funding for Research & Innovation

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imi innovative medicines initiative

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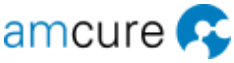


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GRIFOLS


GETNE
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WN

worldwide
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CONSORTIA

As a reflection of VHIO's expertise in preclinical, translational and clinical research in oncology, we participated in the following Consortia of excellence in 2019:

Cancer Core Europe (CCE) is a unique partnership aimed at addressing the cancer care - cancer research continuum challenge. Launched in 2014, this working consortium represents a critical mass of activity for the successful integration of all cancer care information, clinical research and outcome research, led by the 6 founding partners and European comprehensive cancer centers of excellence: the Gustave Roussy Cancer Campus Grand Paris (Villejuif, France), Cambridge Cancer Centre (Cambridge, UK), Karolinska Institute (Stockholm, Sweden), Netherlands Cancer Institute – NKI (Amsterdam, The Netherlands), National Center for Tumor Diseases – DKFZ-NCT (Heidelberg, Germany), VHIO, as well as The National Cancer Institute of Milan (Italy). CEE promotes the pooling and exchange of expertise, research findings, common platforms and processes, and empowers researchers and clinicians to rapidly exploit this trove of biological insights and clinical data for the benefit of patients.
Endorsed by CCE, 2019 celebrated the official launch of the Basket of Baskets (BoB) two-stage clinical trial study, promising a more flexible and adaptive model in order to significantly accelerate patients' access to an array of novel therapeutics – see page 28 for more information.
www.cancercoreeurope.eu

COLOSSUS–*Advancing a Precision Medicine Paradigm in metastatic Colorectal Cancer: Systems based patient stratification solution*s, is a multi-center European Commission Horizon 2020-supported project powered by 14 leading clinical investigators and researchers spanning 8 European countries, with expertise in cancer immunology, systems biology, computational modelling, bioinformatics, omics analysis, clinical oncology/pathology, preclinical research, medical imaging, clinical trials, health economics and patient management.
This 5-year undertaking aims at better classifying and treating metastatic colorectal cancer (mCRC).
Focused on microsatellite stable RAS mutant (MSS RAS mt) disease–a genetically identified type of CRC with very few therapeutic options available once patients develop resistance to existing chemotherapies, the COLOSSUS team will strive to both expand and refine the classification of this particular subset of colorectal cancer.
www.colossusproject.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 754923.

The **EuroPDX Consortium**–*Translating Knowledge in Oncology,* launched in 2013 to create a network of clinically relevant models of human cancer, and in particular patient-derived xenograft (PDX) models. Connecting 18 cancer centers across 13 countries that are developing PDX cancer models, this initiative promotes the sharing and exchange of findings on promising therapeutics as well as leads multicenter preclinical studies.
EuroPDX strives to reduce the duplication of efforts in oncology drug development and ultimately improve the quality of life and overall survival of cancer patients.
Supported by the European Union's Horizon 2020 research and innovation programme and launched in 2018, EDIReX – EuroPDX Distributed Infrastructure for Research on patient-derived cancer Xenografts, is led by the EuroPDX Consortium counting on the research excellence of 19 entities -including VHIO- spanning 13 European countries. The main aims of this project are to facilitate data exchange among academic and industrial preclinical and translational cancer professionals and, to spur and consolidate scientific collaborations in PDX research across Europe.
www.europdx.eu

The EDIReX project has received funding from the European Union's Horizon 2020 research and innovation programme, grant agreement no. #731105.

Intracolor

Initiated in 2016, **INTRACOLOR** (Evolution of resistant clones to novel target-directed drugs in colorectal tumors: a genetic and epigenetic study of intratumoural heterogeneity dynamics), is supported by EU Horizon 2020 funding and led by VHIO.
Running in parallel with the Phase I/II MoTriColor trials, it incorporates 6 of MoTriColor's members to assesses three novel targeted therapies for mCRC, each matched to distinctive gene expression signatures.
Representing a comprehensive framework for translational research, emerging molecular data is prospectively integrated in preclinical models and proof-of-concept clinical trials in mCRC. This project is carried out in collaboration with SPECTAcolor–Screening Platform for Efficient Clinical Trials Access in Colorectal Cancer, which is an initiative of the EORTC, supported by Alliance Boots.
www.motricolor.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 643638.

MESI-STRAT

MESI-STRAT combines the expertise of 14 partners from 6 European countries to establish the interplay of breast cancer metabolism and oncogenic signaling (Metabolic Signaling) by systems medicine approaches. Aimed at developing new models for knowledge-based STRATification of patients into subgroups with different endocrine therapy resistance mechanisms, this pan-European 57-month project, supported by the European Union's Horizon 2020 research and innovation programme, represents an important forward step towards improving outcomes for these patients.
The team pioneers breast cancer metabolism as a novel approach for the stratification of patients, tracking of resistance and better guiding clinical decision-making throughout the course of endocrine therapy. Through the development of new computational models in combination with network analyses, pharmacogenomics and integrated multi-omics data, MESI-STRAT will play a decisive role in better deciphering the metabolic and signaling networks that drive resistance to endocrine-based therapies.
www.mesi-strat.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 754688.

MOTRICOLOR

Spurred by Horizon 2020's European Union funding for Research and Innovation funding, **MoTriColor** (Molecularly guided Trials with specific treatment strategies in patients with advanced newly molecular defined subtypes of Colorectal cancer), led by VHIO, is powered by 8 clinical research centers of excellence, spanning Spain, Italy, The Netherlands and Belgium, as well as a European organization in cancer research and a diagnostic/prognostic SME.
Dedicated to conducting multi-center early phase clinical trials to establish the anti-tumor activity of novel experimental therapies for patients with metastatic or advanced colorectal cancer, patients are stratified based on their gene expression profiles according to recently established predictive signatures.
This pioneering approach aims at identifying sensitivity of individual patients to the proposed experimental therapies towards ultimately developing more precise anti-cancer therapies for these patients.
www.motricolor.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 635342.

NoCanTher

Funded through a grant received from the European Union's Horizon 2020 research and innovation programme, the **NoCanTher–Nanomedicine upscaling for early clinical phases of multimodal cancer therapy is a multi-center–Consortium** is led by IMDEA Nanoscience and represents an important forward step in utilizing nanoparticles than can better target and more precisely combat cancer cells.
It builds on the preclinical successes reported by the former FP7-funded MultiFun Consortium that evidenced the efficacy of a multi-modal therapeutic approach based on functionalized magnetic nanoparticles and magnetic hyperthermia for the intra-tumoral treatment of breast and pancreatic tumors
Connecting 11 leading European research centers, including industry partners, NoCanTher assesses this nano-based approach and provide preliminary data on its efficacy in humans and aim to translate these preclinical findings into early clinical development for the treatment of pancreatic cancer.
www.nocanther-project.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 685795.

Phd PI3K biology in health & disease

The **PhD PI3K biology in health & disease Network** incorporates 10 academic, clinical and industrial partners with renowned expertise in research focused on PI3K signaling. Leading a unique training network, this collaboration connects complementary expertise and brings additional value, novel tools and leadership of excellence in order to train talented early stage researchers and suitably equip them for leading roles in cancer science and drug discovery in European industry and academia.
This research training programe not only represents unparalleled educational opportunity for these young scientists, but also aims to increase the international competitiveness of European research in PI3K discovery and drug development.
www.pi3k-phdproject.eu

SPECTAcolor The EORTC Biobank Project
EORTC Alliance Boots

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 in 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.
https://www.eortc.org/blog/category/spectacolor

TRANSCAN-2

The Spanish Association against Cancer (AECC), and the *Institute of Health Carlos III* (ISCIII) through the *ERA-NET*: *Aligning national/regional translational cancer research activities* awarded VHIO with two **TRANSCAN-2** projects funded by the EU's Horizon 2020 framework program in 2017.
Supported through the TRANSCAN Joint Translational Call on *Minimally and non-invasive methods for early detection and/or progression of cancer*, the first will establish non-invasive prognostic markers for resected early-stage non-small cell lung cancer (NSCLC) by assessing the role of circulating and exosomal miRNAs and free circulating DNA (fcDNA); as well as characterize blood-based tumor-educate platelets (TEPs) for the evaluation of patients treated with immune checkpoint inhibitors using novel sequencing technologies.
The second project will focus on the early detection of relapse in advanced colon cancer patients by longitudinally following a personalized molecular signature by liquid biopsy. This proof-of-concept, prospective, multi-center study will primarily seek to evaluate the clinical feasibility of tracking tumor progression by dynamically detecting a molecular and personalized signature from a blood test.
www.transcanfp7.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 643638.

Announced in 2018, one of the **U.S. Department of Defense's (DoD) Innovative Minds in Prostate Cancer (IMPaCT)** Awards funds a three- year collaborative partnership to advance precision medicine against metastatic prostate cancer (mPC). This coalition will count on the multidisciplinary expertise of investigators at VHIO, the Spanish National Cancer Research Centre–CNIO (Madrid, Spain), and the University of Washington (USA). Aimed at more precisely gauging response in patients to standard therapies, the team seeks to develop new, more effective and tailored treatment strategies, as well as design a clinical trial to assess the performance of a DNA damaging platinum chemotherapy, carboplatin, that is already used to treat other tumor types including ovarian and breast cancer.
https://cdmrp.army.mil/pcrp

Worldwide Innovative Networking in personalized cancer medicine

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 39 leading organizations representing all stakeholders in personalized cancer medicine covering 21 countries and 4 continents, united by their vision to deliver on the promise of effective, personalized cancer medicine to patients worldwide.
Under the tagline WINning together, WIN was formed on the premise that members can accomplish more together than each organization can achieve working alone. Aimed at improving cancer patients' survival and quality of life, WIN members also collaboratively design and carry out global studies designed to achieve breakthroughs for cancer patients across the globe.
For updates in 2019 see page 29.
www.winconsortium.org

NEW CONSORTIA – officially launched in 2019

Announced at the beginning of 2019, the **OPTIMISTICC Grand Challenge – Opportunity** To Investigate the Microbiome's Impact on Science and Treatment In Colorectal Cancer- is a 5-year consortium funded by Cancer Research UK's Grand Challenge, led by researchers at the Dana-Farber Cancer Institute-Harvard Medical School, and Harvard T.H. Chan School of Public Health (USA).
Aimed at better understanding the difference between a healthy microbiome and a microbiome associated with the development of colorectal cancer, the co-investigators from the US, Canada, the UK, Netherlands, and Spain, are seeking to identify ways to manipulate this collection of microorganisms to better prevent and treat cancer.
It is thanks to the Grand Challenge Funding that the project partners, including VHIO, are able to pool the necessary expertise in order to establish how the microbiome influences a cancer's response to treatment, develop new treatments that alter the microbiome, and decipher how an individual's external environment may affect their microbiome (also see page 29).
www.optimisticc.org

EUCanCAN – the European-Canadian Cancer Network, led by the Barcelona Supercomputing Center (Spain), comprises a total of 18 partners from 5 different countries to pursue the homogeneous analysis, management and exchange of genomic-driven oncology data to advance precision medicine in cancer.
Jointly funded by the European Union's Horizon 2020 research and innovation programme and the Canadian Institutes of Health, this project strives to provide a functional platform for federated genome analysis systems towards efficiently analyzing, managing, sharing and reusing mass genomic data at the global level. The participating reference nodes seek to process, store and share between 30-35 thousand patient samples across various tumor types.
This consortium also promises to drive discovery into robust and clinically-relevant patterns of genomic variation in cancer, including predictive biomarkers. See page 30 for more information.
www.eucancan.com

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825835.

Immune-Image is a 22 stakeholder-strong consortium incorporating public and private partners across 9 countries, including VHIO and the Vall d'Hebron Institute of Research (VHIR) from Spain. Powered by the Innovative Medicines Initiative Joint Undertaking (IMI 2 JU), this initiative is led by Roche and coordinated by the Amsterdam University Medical Center (VUmC), The Netherlands. Set to run for an initial duration of five years, this project is entitled *Specific imaging of immune cell dynamics using novel tracer strategies*, and seeks to develop a novel non-invasive imaging strategy for assessing immune cell activation and dynamics in oncology and inflammatory disease.
Main deliverables include developing clinically validated radio-and optical immunotracers for the monitoring and measurement of immune cell presence, activation status and trafficking, and designing and implementing a ready-to-use sustainable molecular imaging platform, incorporating standardized protocols, best practices, quantitative image analyses, immune-based tracking design and development. See page 30 for additional information.
www.immune-image.eu

Funded by the European Union's Horizon 2020 research and innovation programme, the CELAC and European Consortium for a Personalized Medicine Approach to Gastric Cancer (LEGACy) is a 4-year project spearhead by INCLIVA Health Research Institute (Spain), in partnership with 10 other members across 9 different countries including VHIO.
Focused on advancing personalized medicine against gastric cancer, this project aims to improve diagnosis and treatment by using data obtained through extensive research in four EU countries and four countries within the Community of Latin American and Caribbean (CELAC). States outcomes by applying personalized medicine at the three levels of prevention. This consortium will seek to implement a personalized medicine strategy at the first level of prevention, improve early gastric cancer detection at the second level of prevention, and improve treatment through the identification of high-risk populations.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825832.

RADprecise

RADprecise - Personalized radiotherapy: Incorporating cellular response to irradiation in personalized treatment planning to minimise radiation toxicity, is supported by funding received through ERAPerMed's co-funded Joint Translational Call 2018* and was founded in 2019 by 7 leading organisations from Spain, Italy, Germany and France. This 3-year project will render radiotherapy more precise by incorporating data from finely tuned predictive models to pre-identify toxicity based on insights from multiple biomarkers of radiosensitivity in individual patients.
Led by colleagues at the German Cancer Research Center (DKFZ), Germany, project partners will apply findings at the clinical level by integrating a treatment planning system. Using parametric models and machine learning, clinical investigators from academia and health research, in collaboration with small and medium enterprises as well as patient advocates, will apply new biological data as well as readily available genomic information to develop models that can more precisely envisage adverse effects from radiotherapy to be validated in independent samples. More information on page 30 of this Report.
www.erapermed.eu.

*This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No. 779282

Other collaborations:

The **AstraZeneca VHIO Alliance** announced in 2015, and the **MedImmune VHIO Alliance** launched in 2018, drive advancements at preclinical, clinical and translational research levels across the AstraZeneca's oncology portfolio. Combining VHIO's strengths in promoting cancer discovery through the integration of translational science and clinical research with AstraZeneca's promising early stage oncology pipeline, the alliance focuses on areas including DNA damage repair, drug resistance, new drug combinations and molecular profiles for patient selection.
Bookmark and visit VHIO's website for forthcoming updates:
www.vhio.net

The **SCITRON** *Consorcio público-privado de Investigación Científica y Translacional en Oncología* (Consortium for Scientific Translational Research in Oncology) is a scientific program established in collaboration with Novartis in 2017 as a new model of R&D collaboration. This initiative connects expertise from Novartis and VHIO in applied and translational research to increase the impact of basic research in clinical practice.
The specific areas of interest include the development of a technology platform that analyses tumor clonal evolution and resistance mechanisms to targeted immunotherapy.
www.novartis.com

Launched by Roche in 2016, the **imCORE - immunotherapy Centres of Research Excellence Network** - a 21-strong academic powerhouse set to progress discovery in cancer immunotherapy, brings together internationally renowned scientific and clinical experts in cancer immunotherapy to collaborate in investigating the most promising novel treatment approaches. Working in collaboration with scientists from Roche and Genentech, researchers and physician-scientists in cancer immunotherapy from across the globe aim to drive the application and extension of immune-based strategies to more tumor types, as well as advance research into the cellular and molecular mechanisms modulating immune response to cancer.
This Network was designed to significantly advance anti-cancer immunotherapeutics and accelerate discovery towards benefiting patients who may stand to gain from novel immune agents as mono therapy or in combination.
www.roche.com/research_and_development/what_we_are_working_on/oncology/cancer-immunotherapy/collaboration-in-cancer-immunotherapy.htm

The OCTC - Oncology Clinical and Translational Consortium, a collaborative scientific research network comprised of 6 renowned comprehensive cancer centers, was launched by GSK in 2013. While GSK gains OCTC's expertise in preclinical, translational and clinical development of novel anticancer therapeutics, the participating centers 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

ACCREDITATION

In 2017 VHIO underwent evaluation for accreditation of the CERCA Institute of Research Centres of Catalunya (*Institució CERCA–Centres de Recerca de Catalunya*) for the period 2013–2016. In recognition of VHIO's progress, performance in knowledge transfer activities and management of excellence, VHIO was awarded the maximum qualification of an A grading.

The European Commission's Human Resources for Research (HRS4R) strategy enables research institutions of excellence to actively implement and uphold the requisites of The European Charter for Researchers and Code of Conduct for the Recruitment of Researchers for their HR policies and practices.
VHIO's comprehensive analysis and action plan was officially approved by HRS4R assessors in 2018 and our Institute was consequently granted permission to use the HR Excellence in Research Award logo as demonstration of its stimulating and favorable work environment.
www.vhio.net/en/hr-excellence-research

Also reflecting our dedication to excellence and the quality of our services and procedures, our Cancer Genomics and Molecular Groups are both ISO 15189 accredited for their testing methods and technologies. Similarly, we continue to meet the high standards in quality and procedures in the audit of our clinical trials Units, carried out by the *Generalitat de Catalunya*. Our Research Management is also endorsed by ISO 9001 Certification.

New funding and projects in 2019

For a complete listing of all our current supporters and funding sources see section Funding & Consortia (pages 148-157).

INSTITUTIONAL SUPPORTERS

VHIO patrons (more information see pages 17-20)

Departament de Salut: Budgetary support
Departament d'Empresa i Coneixement: Budgetary support

VHIO's CELLEX Building & Infrastructure

Advanced Molecular Diagnostics Program (DIAMAV), and other VHIO investigators, groups and projects

Research Unit for Molecular Therapy of Cancer (UITM) - "la Caixa", and "la Caixa" International Program for Cancer Research and Education

Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI)

INTERNATIONAL SUPPORT

Innovative Medicine Initiative (IMI) – International Consortium (page 30) Immune-Image: Specific Imaging of Immune Cell Dynamics Using Novel Tracer Strategies
PI VHIO: Josep Tabernero
Gastrointestinal and Endocrine Tumors Group
SC1-BHC-10-2019 Pre-Commmercial Procurement (PCP)– INTERNATIONAL CONSORTIUM
oncNGS: NGS diagnostics in 21st century oncology: the best, for all, at all times
PI VHIO: Josep Tabernero
Gastrointestinal and Endocrine Tumors Group
Marie Skiodowska-Curie Individual Fellowships
AR-DDR: Co-targeting androgen receptor signalling and DNA damage repair for precision therapy
Granted to Joaquín Mateo
Prostate Cancer Translational Research Group

Grand Challenge International Consortium
OPTIMISTICC: OPportunity To Investigate the Microbiome's Impact on Science and Treatment In Colorectal Cancer (see page 29)
PI VHIO: Josep Tabernero
Gastrointestinal and Endocrine Tumors Group

Breast Cancer Now Catalyst Programme
Modulation of androgen receptor signaling as a therapeutic strategy for oestrogen receptor-positive metastatic breast cancer
PI: Violeta Serra
Experimental Therapeutics Group

Clinical Unit Visit
Granted to Joao Pedro de Almeida Moreira Pinto
Mentor: Teresa Macarulla
Gastrointestinal and Endocrine Tumors Group
Clinical/ Research Fellowship
Evaluation of Immunological Activity Markers in Patients with Metastatic Cancer receiving checkpoint inhibitors
Granted to Vladimir Galvao
Mentor: Elena Garralda
Early Clinical Drug Development Group

BCRF BREAST CANCER RESEARCH FOUNDATION

Breast Cancer Research Foundation Grant
Novel therapies against HER2-positive breast tumors: targeting oncogene-induced senescence and the immune system
PI: Joaquín Arribas
Growth Factors Group

NIH National Institutes of Health Turning Discovery Into Health

Specialized Programs of Research Excellence (SPOREs) in Human Cancers
SPORE in Breast Cancer
PI: Violeta Serra
Experimental Therapeutics Group

SECRETARÍA DE EDUCACIÓN, CIENCIA, TECNOLOGÍA EN INNOVACIÓN

Beca Internacional de Posgrado
Granted to Daniel Pilco
Mentor: César Serrano
Sarcoma Translational Research Group

NATIONAL FUNDING

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Ajuts per a xarxes d'R+D+I per a dur a terme programes de valorització i transferencia dels resultats de recerca Catalan Consortium
Valorització de l'Arxiu Europeu de Genoma-Fenoma (EGA) per la Indústria i la Societat (VEIS)
PI VHIO: Rodrigo Dienstmann
Oncology Data Science Group (ODysSey)
Beatriu de Pinos:
In-depth profiling of neoantigen specific-lymphocyte subsets with superior traits for personalized T cell therapies
Granted to Jara Palomero
Tumor Immunology & Immunotherapy Group
FI-Predoctoral DGR:
Modulació de la senyalització del receptor d'androgen com a estratègia terapèutica pel càncer de mama metastàsic estrogen-positiu resistent a inhibidors de CDK4/6 i PI3K
Granted to Laia Monserrat
Experimental Therapeutics Group
FI-Predoctoral DGR:
Identification of Novel Micropeptides Involved in Lung Cancer Stemness: New Cancer Players for New Therapies
Granted to Olga Boix
Cellular Plasticity and Cancer Group

Institució CERCA Centres de Recerca de Catalunya

CERCA Accreditation's associated program incentives

Generalitat de Catalunya

DEPARTAMENT DE SALUT
Intesificació de Professionals amb formació Sanitaria Especialitzada
Impacte del seguiment longitudinal en càncer colorrectal estadi III i avançat mitjançant una signatura molecular personalitzada en biòpsia líquida
PI: Elena Élez
Gastrointestinal and Endocrine Tumors Group
Joves Investigadors Doctors
Nou anàlisi combinat de biopsia liquida per a monitoritzar l'evolució genómica tumoral i la resposta a tractaments dirigits en cáncer de prostata
Granted to Irene Casanova
Prostate Cancer Translational Research Group
Projectes de Recerca en Medicina Personalitzada (ERA PerMed) INTERNATIONAL CONSORTIUM
Personalized radiotherapy: incorporating cellular response to irradiation in personalized treatment planning to minimize radiation toxicity (RADprecise)
PI VHIO: Sara Gutiérrez Enríquez
Hereditary Cancer Genetics Group

Consolidació de les unitats de promoció de projectes de R+D+I Internacionals (Go Europe)
Implementación de mejoras en la solicitud de ayudas internacionales. Consolidación de la Oficina de Proyectos UE de VHIO. MATCH Program: Ideas - Oportunidades
PI: Alejandro Piris

Proyectos I+D Retos
Explotando el Microproteoma para Encontrar Nuevas Dianas Moleculares contra el Cáncer
PI: Maria Abad
Cellular Plasticity and Cancer Group
Ayudas para la Contratos Juan de la Cierva Formación
Granted to Laura Escudero
Gene Expression and Cancer Group
Ayudas para la Contratación de Personal Técnico de Apoyo (PTA)
Granted to Agatha Martín
Cancer Genomics Group

VHIO projects managed through the *Instituto de Investigación Sanitaria Acreditdo Institut de Recerca* (Accredited Research Institute - Vall d'Hebron)

Proyectos de Investigación en Salud
Immunotherapy against HER2 positive tumors / Inmunoterapia contra tumores HER2 positivos
PI: Joaquín Arribas
Growth Factors Group
Proyectos de Investigación en Salud
Understanding the Immunosuppressive Tumor Microenvironment in Brain Cancer
PI: Joan Seoane
Gene Expression and Cancer Group
Proyectos de Investigación en Salud
Validación de una nueva terapia anti-Myc en melanoma
PI: Laura Soucek
Mouse Models of Cancer Therapies Group
Proyectos de Investigación en Salud
Diagnostic and Therapeutic implications of the HMGA1-RAGE signaling pathway in Triple Negative Breast Cancer
PI: Josep Villanueva
Tumor Biomarkers Group
Proyectos de Investigación en Salud
Towards an accurate estimation of cancer risk and individualization of medical management by applying the Polygenic Risk Score (PRS) in hereditary breast and ovarian cancer
PI: Judith Balmaña
Hereditary Cancer Genetics Group
Proyectos de Investigación en Salud
Comprehensive RNA expression and DNA repair functional analysis of clinically actionable hereditary breast/ovarian cancer genes in patients with uninformative multi-gene panel result
PI: Sara Gutiérrez-Enríquez
Hereditary Cancer Genetics Group
Proyectos de Investigación en Salud
Comprehensive RNA expression and DNA repair functional analysis of clinically actionable hereditary breast/ovarian cancer genes in patients with uninformative multi-gene panel result
PI: César Serrano
Sarcoma Translational Research Group
Proyectos de Programación Conjunta Internacional INTERNATIONAL CONSORTIUM ERAPERMED
Patient stratification based on DNA repair functionality for cancer precision medicine (RAD51predict)
COORDINATOR VHIO: Violeta Serra
Experimental Therapeutics Group
Miguel SERVET
Exploiting senescence in a two-step approach to treat metastatic Prostate Cancer
Granted to Nicolás Herranz
Prostate Cancer Translational Research Group

Miguel SERVET Tipo II
Granted to Violeta Serra
Experimental Therapeutics Group
Ayudas para la Intensificación de la Actividad Investigadora
Granted to Pau Abrisqueta
Experimental Hematology Group
Ayudas para Contratos Predoctorales de Formación en Investigación en Salud
Granted to Sara Arce
Prostate Cancer Translational Research Group
Ayudas para Contratos Predoctorales de Formación en Investigación en Salud
Granted to Miranda Fernandez
Experimental Hematology Group

Convocatoria para Adjudicación de Ayuda para Proyectos de Investigación en Salud
Identificación y Análisis del Microproteoma del Cáncer de Páncreas: Los Micropéptidos como Nuevas Dianas Terapéuticas y Biomarcadores Tumorales
PI: Maria Abad
Cellular Plasticity and Cancer Group

Ayudas Predoctorales InPhinit Incoming
Granted to Flaminia Pedretti
Mentor: Violeta Serra
Experimental Therapeutics Group
Ayudas Predoctorales InPhinit Incoming
Granted to Queralt Serra
Mentor: Sandra Peiró
Chromatin Dynamics in Cancer Group

PRIVATE FUNDING

Health Research_NATIONAL CONSORTIUM:
Defining The Role of Exosome-Secreted Micropeptides in Pancreatic Cancer
Coordinator VHIO: Maria Abad
Cellular Plasticity and Cancer Group

Beca FERO en Investigación Oncológica Traslacional
Novel approaches to liquid biopsy in prostate cancer to inform precision medicine
PI: Joaquin Mateo
Prostate Cancer Translational Research Group
Proyectos FERO-GHD en Cáncer de Mama
Development of a liquid biopsy test to assess the homologous recombination function status in BRCA1/2 mutation carriers with breast cancer to inform therapy selection
PI: Violeta Serra
Experimental Therapeutics Group
Pronóstico precoz de la recaída tumoral en una gota de sangre – Marnaton
PI: Héctor G. Palmer
Stem Cells and Cancer Group

ERAPERMED - INTERNATIONAL CONSORTIUM
Patient stratification based on DNA repair functionality for cancer precision medicine
Coordinator VHIO: Violeta Serra
Experimental Therapeutics Group
ACCELERATOR - INTERNATIONAL CONSORTIUM
PREDICT-Meso: PRE-malignant Drivers Combined with Target-Drug validation in Mesothelioma
PI VHIO: Susana Cedrés
Thoracic Tumors & Head and Neck Group
ACCELERATOR - INTERNATIONAL CONSORTIUM
SMART Experimental Cancer Medicine Trials eNABLED
PI VHIO: Elena Garralda
Early Clinical Drug Development Group

ACCELERATOR - INTERNATIONAL CONSORTIUM
Pseudomyxoma peritonei: building a European multicentric cohort to accelerate new therapeutic perspectives
PI VHIO: Héctor G. Palmer
Stem Cells and Cancer Group
Grupos Coordinados AECC – NATIONAL CONSORTIUM
Redirección de células T contra tumores dirigidos por HER2
Coordinator VHIO: Joaquín Arribas
Co-PI VHIO: Elena Garralda
Co-PI VHIO: Francesc Bosch
Growth Factors Group
Early Clinical Drug Development Group
Experimental Hematology Group
Ideas Semilla
Optimización del uso de inhibidores de checkpoint en pacientes con neoplasias linfoides que reciben un trasplante alogénico de progenitores hematopoyético
PI: Pere Barba
Experimental Hematology Group
Clínico Senior AECC
Métodos mínimamente invasivos y no invasivos para la detección precoz y / o progresión del cáncer colorrectal incluyendo el estudio del pronóstico y predictivo del ADN tumoral circulante en la enfermedad avanzada.
Granted to Elena Élez
Mentor Josep Tabernero
Gastrointestinal and Endocrine Tumors Group
Investigador AECC
Tumores primarios múltiples en pacientes con cáncer de pulmón: elaboración de un perfil molecular integral para elucidar orígenes genéticos comunes
Granted to Miriam Sansó
Mentor Ana Vivancos
Cancer Genomics Group

FUNDACIÓN RAMÓN ARECES

Concurso Nacional para la adjudicación de Ayudas a la Investigación en Ciencias de la Vida y de la Materia
Identification of novel immunotherapeutic targets in lung and melanoma brain metastases
PI: Joan Seoane
Gene Expression and Cancer Group

GILEAD

Becas Gilead a la Investigación Biomédica
Understanding the tumor immune microenvironment in diffuse large B-cell lymphoma for the development of immunotherapeutic strategies that target each individual's immune biology
PI: Francesc Bosch
Experimental Hematology Group

Fundació Catalunya La Pedrera

Programa Joves i Ciència
PI: Violeta Serra
Experimental Therapeutics Group
Programa Joves i Ciència
Mentor: Joan Seoane
Gene Expression and Cancer Group

SEOM Sociedad Española de Oncología Médica

Ayuda para proyectos de Investigación de Secciones y Grupos de Trabajo
Registro prospectivo Sección de Cáncer Hereditario SEOM de personas portadoras de variantes en nuevos genes de susceptibilidad al cáncer
PI: Judith Balmaña
Hereditary Cancer Genetics Group

Fundació La Marató de TV3

Convocatoria d'Ajuts a la Investigació Oncològica
Caracterització epigenètica dels colangiocarcinomes
PI: Sandra Peiró
Chromatin Dynamics in Cancer Group
Convocatoria d'Ajuts a la Investigació Oncològica
Immunoteràpia personalitzada per a càncer d'endometri
PI: Alena Gros
Tumor Immunology & Immunotherapy Group
Convocatoria d'Ajuts a la Investigació Oncològica
Estudi i implicacions translacionals de l'evasió del sistema immunitari en la leucèmia limfàtica crónica
PI: Francesc Bosch
Experimental Hematology Group

Convocatoria d'Ajuts a la Investigació Oncològica
El microambient immune tumoral en la patogènesi i control del limfoma de cèl·lules del mantell
PI: Josep Villanueva
Tumor Biomarkers Group

Convocatoria d'Ajuts a la Investigació Oncològica
Superant la resistència a les immunoteràpues a través de la inhibició de Myc en càncer de pulmó mutat en KRAS amb perfils mutacionals diversos
PI: Laura Soucek
Mouse Models of Cancer Therapies Group

Convocatoria d'Ajuts a la Investigació Oncològica
Implementació de la biòpsia líquida més enllà de les aplicacions actuals: estudi prospectiu del valor pronòstic i predictiu de l'ADN tumoral circulant en càncer colorectal metastàtic
PI: Elena Élez
Gastrointestinal and Endocrine Tumors Group

Convocatoria d'Ajuts a la Investigació Oncològica
PrecIMet: imatge de precisió per a l'avaluació de metàstasis òssies
PI: Raquel Pérez-López
Radiomics Group

Convocatoria d'Ajuts a la Investigació Oncològica
Biòpsies líquides per a la identificació de mecanismes de resistència als inhibidors de PARP en càncers associats a BRCA1/2
PI: Violeta Serra
Experimental Therapeutics Group

STOP FUGA DE CEREBROS
Senescent cells as a therapeutic target against breast cancer
Granted to Verónica Rodilla
Mentor Joaquín Arribas
Growth Factors Group

Beca Junior Getne Proyecto de Investigación 2018
Análisis de marcadores pronósticos y predictivos de respuesta a inhibidores de tirosina quinasa en cáncer diferenciado de tiroides a partir de patrones de metilación del ADN
PI: Jorge Hernando
Gastrointestinal and Endocrine Tumors Group

IRONMAN-ES: Estudio prospectivo observacional de parámetros clinicos y biomarcadores en cáncer de próstata avanzado en hospitales de España
PI: Joaquín Mateo
Prostate Cancer Translational Research Group

Topological Radiomics (TOPiomics): Early Detection of Genetic Abnormalities in Cancer Treatment Evolution
PI: Raquel Pérez-López
Radiomics Group

Pronóstico y control de peso en pacientes con cáncer de mama mediante una intervención de dieta y ejercicio (PREDICOP)
PI: Cristina Saura
Breast Cancer and Melanoma Group

BRCA-P: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, International Phase 3 Study to determine the Preventive Effect of Denosumab on Breast Cancer in Women carrying a BRCA1 Germline Mutation
PI: Susana Muñoz

Donacions Campanya Mocador Solidari
PI: Cristina Saura
Breast Cancer and Melanoma Group

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