VHIO

VALL D'HEBRON
Institute
of Oncology

Turning 15 and driving continued, 'crystalized' progress against cancer during COVID-19 pandemic waves

SCIENTIFIC REPORT
2021

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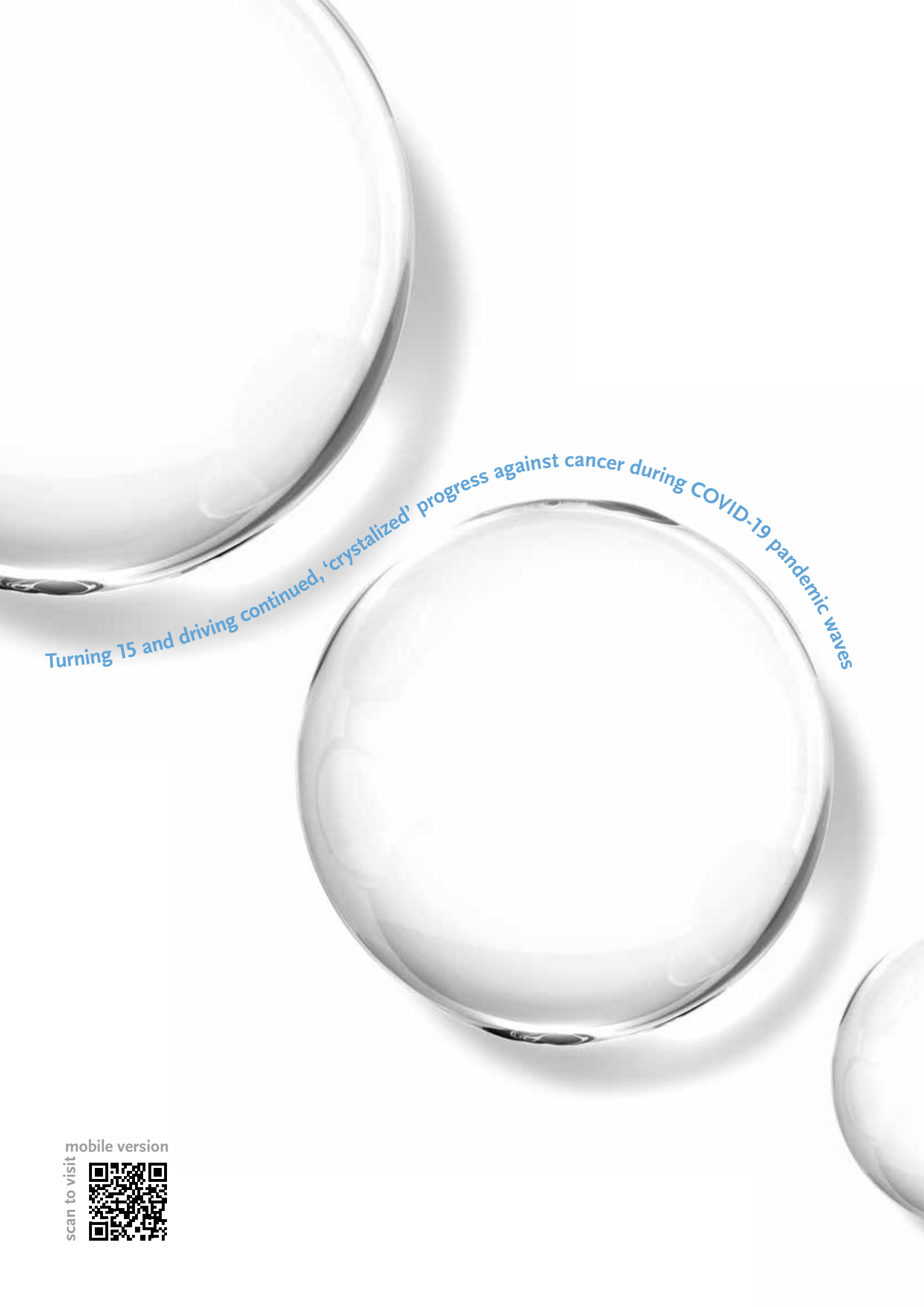

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VALL D'HEBRON INSTITUTE OF ONCOLOGY (VHIO)
SCIENTIFIC REPORT 2021

Turning 15 and driving continued, 'crystalized' progress against cancer during pandemic waves

This year's Scientific Report celebrates our Institute's 15th year of advancing cancer science and clinical oncology against this disease. The simple branding incorporating crystals is symbolic for three reasons:

First, in some cultures, crystals are associated with a 15-year anniversary. Second, as evidenced throughout this report, we continue to achieve greater clarity regarding the many complexities that still remain in more effectively combating cancer. Finally, the spherical crystals, emitting energy from all sides, represents VHIO's multidisciplinary and translational model – a seamless, unrestricted flow of discovery from the bench to bedside and back, for which our Institute is famed.

Championed by VHIO's Director, Josep Tabernero, our Principal Investigators as well as the Heads of our Transversal Clinical Trials Services, Units and Programs, spearhead efforts aimed at solving cancer sooner. They lead their respective groups and teams to turn obstacles into opportunities, and work tirelessly to resolve current and future challenges in beating this highly complex disease.

A seal of scientific leadership at global level: VHIO accredited as a Severo Ochoa Center of Excellence (2022-2026)

Announced at the end of 2021, and highlighted by our Director in his Foreword to this year's Scientific Report (see pages 6-25), our Institute has been accredited as a Severo Ochoa Center of Excellence. This prestigious distinction is granted within the subprogram of the Spanish Institutional Strengthening of the State Plan for Scientific and Technical Research & Innovation, and recognizes national research centers that demonstrate scientific leadership of excellence and impact at global level.

Conferring reputation and social and scientific recognition, this accreditation is awarded annually, managed and supported by Spain's State Research Agency* (*Agencia Estatal de Investigación* - AEI) - a body affiliated with the Spanish Ministry of Science and Innovation (*Ministerio de Ciencia e Innovación*). Valid for four years, this accreditation is renewable thereafter through re-application for the same rigorous evaluation carried out independently by an international scientific committee of renowned researchers.

From the 2020 call, VHIO is the only newly accredited Severo Ochoa Center of Excellence, alongside the other six re-awarded research centers. Set within the Vall d'Hebron Barcelona Hospital Campus, VHIO is also the first research institute linked to the national healthcare system to have received this distinction.

This accolade reflects our Institute's important contributions to cancer science and precision medicine in oncology at a global level. It also confirms VHIO's scientific leadership and proven capacity to advance frontier research, generate high-impact results, as well as attract and retain research talent.

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*Supported by the State Agency for Research - *Agencia Estatal de Investigación* - AEI (CEX2020-001024-S / AEI / 10.13039 / 501100011033).

FOREWORD

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

2021: Turning 15 and driving continued, 'crystalized' progress against cancer during COVID-19 pandemic waves

This year's Scientific Report celebrates our Institute's 15th year of advancing cancer science and clinical oncology against this disease that will affect an estimated 1 in 2 people during their lifetime.

The simple branding incorporating crystals is symbolic for three reasons. First, in some cultures, crystals are associated with a 15-year anniversary. Second, as evidenced throughout this report, we continue to achieve greater clarity regarding the many complexities that still remain in more effectively combating cancer. Finally, the spherical crystals, emitting energy from all sides, represents VHIO's multidisciplinary and translational model – a seamless, unrestricted flow of discovery from the bench to bedside and back.

This approach was pioneered by José Baselga, our Institute's founder and first director, who very sadly passed away at the age of 61 on 21 March, 2021.

The international scientific cancer community, along with all other stakeholders in oncology, continues to mourn his passing. José was a visionary scientific leader and trailblazer in cancer research and precision oncology who made tremendous contributions to improving outcomes for cancer patients worldwide. By integrating patient care within a multidisciplinary program connecting basic, clinical and translational science, he spearhead efforts to rapidly translate cancer discovery into clinical benefits for patients.

This unique research model emboldened him to create VHIO in 2006. From the outset, he had one guiding principle for our Institute. Namely, to seamlessly bridge preclinical and clinical research in order to foster a continuous virtuous cycle of knowledge from bench to bedside and back. This translational approach continues to be at the very core of VHIO's philosophy, which I, as VHIO's Director, passionately pursue alongside our multidisciplinary teams.

José was also an exceptionally generous mentor and a much-loved friend. Please refer to the close of this Foreword, *Honoring the life and legacy of the father of precision medicine in oncology* (page 21).

On behalf of all of us at VHIO, I dedicate this year's Scientific Report to the treasured memory of José Baselga.

José "Pepe" Baselga, MD, PhD (1959-2021): a visionary leader in translational science and precision oncology, and VHIO's founder and first director.

Another element of this year's design includes the fold-out section that opens this report. I am pleased to announce that our Institute received *Excelencia Severo Ochoa* accreditation in 2021, and is now recognized as a Severo Ochoa Center of Excellence (2022-2026). Granted as part of the subprogram of the Spanish Institutional Strengthening of the State Plan for Scientific and Technical Research and Innovation, this accolade recognizes national research centers demonstrating scientific leadership of excellence and impact at a global level.

This distinction not only reflects VHIO's important contributions to cancer science and precision medicine in oncology, but also confirms our capacity to advance frontier research, generate high-impact results, as well as attract and retain research talent. Set within the Vall d'Hebron Barcelona Hospital Campus, VHIO is the first research center closely linked to one of the Spanish National Healthcare System's Hospitals to have been endorsed by this prestigious seal of excellence.

For a second consecutive year, due to the safety issues brought about by COVID-19, we had to adjust our approach to this year's photography. With the exception of some of our larger groups, we have moved mountains to ensure that as many group members as possible have been included, and without masks. Each photograph was shot at a distance, in locations away from areas dedicated to the care of our cancer patients. For faculty working remotely, we invited them to submit their photos from home.

COVID-19: the impact on cancer patients, clinical research and oncology professionals

In our determined efforts to overcome the challenges posed by COVID-19 pandemic waves, VHIO's researchers and clinical investigators have continued to drive important advances in cancer discovery and improve the treatment and care of cancer patients.

For another year, we succeeded in weathering the COVID-19 storm. VHIO's multidisciplinary teams speedily adjusted to shifting circumstances and continued to balance physically working in the lab and/or clinical setting with remote working. In some instances, we continued to adapt conventional cancer care, deviate from existing protocols, and administer novel therapies including immunosuppressive treatment regimens.

Additionally, we have fine-tuned technology-based and remote interventions in patient care in order to minimize on-site monitoring visits and in-person consultations. These measures, which were rapidly adopted at the outbreak of the pandemic in 2020, are flanked by the application of telemedicine. This development is one of the few welcome offshoots of the pandemic. Remote patient care has subsequently stepped up in bringing crucial medical expertise to more patients.

Thanks to our discussions with the Spanish Agency of Medicines and Medical Products (AEMPS), the virtual monitoring of patients in clinical trials was first implemented in Spain. AEMPS subsequently supported this move which enabled us to continue conducting essential clinical research.

At VHIO, we firmly believe in turning challenges into opportunities. This ethos drives us to steadfastly pursue our preclinical, translational and clinical research to improve the early detection, diagnosis and treatment of cancer.

As importantly, like many other biomedical research institutes, we also joined the historic, scientific effort in the COVID-19 era by leading essential research into the real-world impact of the virus on our cancer patients, oncology professionals, and clinical studies (see page 33).

Spurring transformative cancer science and clinical research

I can report another record-breaking year in terms of our contributions to translational cancer science and clinical research. In partnership with many other leading research centers and groups, both nationally and internationally, VHIO teams and talents published 446 scientific articles in leading journals as corresponding, senior or co-authors in 2021. This is a remarkable achievement, particularly considering the turbulent pandemic waves.

I take this opportunity to highlight just a few of our studies that rightly made headlines this year, some of which were paradigm-shifting:

Calling the faithful: the predictability and reproducibility of cancer models

The validation of reliable preclinical cancer models

EurOPDX
Translating Knowledge in Oncology

One concern over the reliability and predictive powers of patient-derived cancer xenograft (PDXs) models is whether the mouse host influences tumor evolution during PDX engraftment and propagation, affecting the accuracy of PDX modeling in human cancer. The mouse microenvironment of the transplanted tumor has been suggested to induce selective pressures differing from those in humans, causing PDX tumors to adapt and change in ways that are not observed in patients.

The EurOPDX Consortium* partners (page 199), including VHIO as a founding member, collaborated with the US-based PDXNet Consortium to assess whether the PDX engraftment process in mice causes tumors to evolve, especially in ways that could affect their suitability for the testing of promising new cancer therapies.

Led by Enzo Medico, University of Torino, Candiolo Cancer Institute FPO-IRCCS (Turin, Italy), and Jeffrey Chuang, Jackson Laboratory for Genomic Medicine (Farmington, CT, USA), the researchers, including several VHIO investigators** with expertise in developing modelling systems including PDXs and organoids, exhaustively analyzed copy number alterations (CNAs) in 1,451 PDXs and matched patient tumor (PT) samples from more than 500 models.

Led by first author Xing Yi Woo (Jackson Laboratory), the findings of this study [1] showed that the differences between the CNA profiles of PDXs and matched patient tumors are generally marginal, randomly distributed and analogous to differences observed between the two pieces of the same patient tumor. These findings confirm that copy number evolution is not aberrantly driven by the mouse host environment.

By confirming that tumors engrafted and passaged in PDXs maintain a high degree of molecular fidelity to the original patient tumors, this research verifies their suitability for preclinical drug testing, and represents a step forward in further validating the reliability of robust preclinical models in cancer research.

* The EDIReX project has received funding from the European Union's Horizon 2020 research and innovation programme, grant agreement No. 731105.

** This study counted on the expertise of several VHIO preclinical and translational group leaders including co-author Violeta Serra (PI: Experimental Therapeutics Group), and collaborative authors Joaquin Arribas (PI: Growth Factors Group), Héctor G. Palmer (PI: Stem Cells & Cancer Group), Laura Soucek (PI: Models of Cancer Therapies Group), and Alejandro Piris (Head of VHIO's Scientific Management Area).

Organoid cancer models: promising accelerators of precision medicine

Jose A. Seoane, Principal Investigator, Cancer Computational Biology Group.

At VHIO, we are dedicated to accelerating robust preclinical data required to reliably guide the clinical development of innovative agents and approaches, as well as evidence reproducibility before moving into the clinic. An area of strength is in cancer modelling, with particular emphasis on the fine tuning of PDXs, avatar and organoid models to identify factors governing tumor progression and response to therapy.

To overcome certain limitations of murine models in faithfully recapitulating later stages of carcinogenesis in humans, research co-authored by VHIO's Jose A. Seoane reinforces the value of primary human organoids. These models of tumorigenesis mimic oncogenic transformation on a collective tissue scale and accurately replicate the *in vivo* biology of their original native tissues.

In a study [2] directed by Calvin J. Kuo, Stanford University School of Medicine (CA, USA), the investigators leveraged human gastric organoids to establish the first forward genetics human *ARID1A* transformation model. Multi-omic analysis revealed both the phenotypic and functional capture of several features of *ARID1A*-mutated gastric cancer.

This strategy revealed essential oncogenic transformation mechanisms of early *ARID1A*-deficient gastric cancer. This multi-tool method could be extended and applied to other tumor types to generate clinically relevant data on disease initiation and response to therapy.

Immunotherapy: stepping up across tumor types

Unveiled: a novel mechanism of resistance to T-cell bispecific antibodies & CAR-T targeting HER2 breast cancer

Joaquín Arribas, Principal Investigator, Growth Factors & Cancer Group.

Immunotherapy continues to show exciting promise in more effectively combating several tumor types. Many current strategies focus on ensuring the efficient delivery of active cytotoxic cells directly to tumors. Provided that inhibitory mechanisms are in check, it is thought that once the lymphocytes engage to cancer cells, they will unfailingly destroy them.

The redirection of lymphocytes, via T-cell bispecific antibodies (TCBs) and chimeric antigen receptors (CARs), is already approved as an approach to treat some hematologic malignancies. But in solid tumors, these immune-based strategies continue to fail. Research led by VHIO's Joaquín Arribas, revealed how HER2 breast cancer cells adopt a strategy to resist clearance by these redirected lymphocytes [3].

Findings evidenced that the disruption of interferon-gamma signaling enables cancer cells to escape death by lymphocytes, conferring resistance to immunotherapy and promoting disease progression.

These results could help to potentiate future immune-based strategies and more precisely identify those patients who would be most likely to benefit from them. Moving forward, the investigators hope to launch a clinical trial in 2024-25 to advance CAR-T targeting in breast cancer.

Machine learning for grading neoantigens as potential therapeutic targets

Alena Gros, Principal Investigator, Tumor Immunology & Immunotherapy Group.

Tumor neoepitopes are a class of major histocompatibility complex (MHC)-bounded peptides and represent the antigenic determinants of neoantigens. Recognized by tumor-infiltrating lymphocytes (TILs), they can trigger an immune response to cancer and are thus currently being targeted by adoptive T-cell therapies. Identifying mutant neoepitopes from tumor cells that can be detected by T cells could help to develop more effective tumor-specific, cell-based therapies, as well as advance important insights into antitumor responses.

In a study [4] directed by veteran cancer researcher Steven A. Rosenberg and Paul F. Robbins, co-led by Jared J. Gartner, National Cancer Institute, NIH (Bethesda, MD, USA), the researchers, including VHIO's Alena Gros, describe a novel machine learning model to assess a large dataset of verified tumor neoantigens, along with a corresponding dataset of matched negative candidates from the same samples.

As a ranking algorithm for class I candidate neoepitopes, this tool was developed using next-generation sequencing (NGS) data and a dataset of 185 identified neoepitopes that are recognized by HLA class I-restricted TILs from patients with metastatic cancer, across several tumor types. The scoring output provided a set of candidate neoantigens that could be used as therapeutic targets and facilitate *in vitro* and *in vivo* studies aimed at developing more effective immune-based therapies.

Immune checkpoint inhibitor atezolizumab as a potential game changer in early-stage non-small cell lung cancer

Enriqueta Felip, Principal Investigator, Thoracic Tumors & Head and Neck Cancer Group.

The IMpower010 multicenter, open-label, randomized trial was designed to compare the efficacy and safety of an immune checkpoint inhibitor, atezolizumab, compared with best supportive care as adjuvant therapy in patients with stage IB-stage IIIA non-small cell lung cancer (NSCLC), following resection and adjuvant chemotherapy.

Importantly, this was the first clinical trial to demonstrate that immunotherapy significantly improves disease-free survival compared with best supportive care alone, particularly in tumors expressing PD-L1. Building on these primary results, reported at the American Society of Clinical Oncology's virtual Annual Meeting (ASCO June 2021), data from the IMpower010 interim disease-free analysis were presented by lead investigator, VHIO's Enriqueta Felip at the European Society for Medical Oncology's virtual Congress 2021 (ESMO 2021), 16-21 September.

Results from exploratory analyses of sites of disease relapse and subsequent therapy with atezolizumab compared with best supportive care in patients with stage II and III NSCLC, showed significantly less disease recurrence and improved disease-free survival, particularly in those patients whose tumors expressed PD-L1. Reflective of the relevance of these findings, data from this study [5] published in parallel during the ESMO meeting.

This landmark study points to a potential paradigm shift in the treatment of patients with resected, early-stage NSCLC. Results also shine important light on more effectively combating high-risk cancer in the early-stage setting before it spreads, as well as potentially preventing disease recurrence.

Cemiplimab shows promise as the first immune-based therapy to improve overall survival in patients with recurrent and/or metastatic cervical cancer

Ana Oaknin, Principal Investigator, Gynecological Malignancies Group.

Data from the second interim analysis of the multi-center, international Phase III EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 trial, first authored on behalf of the Gynecologic Oncology Group (GOG) by Krishnansu S. Tewari, University of California, Irvine (CA, USA), were presented at ESMO 2021.

Co-led on behalf of the European Network of Gynecological Oncology Trial groups (ENGOT) by VHIO's Ana Oaknin, this study [6] assessed the efficacy of PD-1 inhibitor, cemiplimab, as monotherapy, compared with physician's choice chemotherapy in

improving clinical outcomes, measured by overall survival (OS) as the primary endpoint.

This study not only rings in the largest clinical trial to-date in this patient population, it also marks the advent of cemiplimab as the first immune-based therapy to show an improvement in overall survival in patients whose disease progressed on first line treatment with platinum-based chemotherapy. Strikingly, this improvement was observed in all patients irrespective of tumor histology.

The results show great promise in opening up new treatment avenues for these patients. Crucially, women suffering from cervical cancer are most frequently diagnosed between the ages of 35 and 44 years of age. Efforts will continue to center on more effectively combat this terrible disease by significantly extending the survival of these younger cancer patients.

And, in combination:

KEYNOTE-811: pembrolizumab combination as a potentially transformative treatment for HER2-positive gastric cancer

Josep Tabernero, VHIO's Director and Head of the Medical Oncology Department, Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus.

Previous phase II studies combining PD-1 antibody pembrolizumab with trastuzumab plus chemotherapy have shown increased clinical efficacy and a manageable safety profile in patients with HER2-positive advanced gastric or gastroesophageal junction adenocarcinoma (HER2+ GC).

Building on these encouraging results, the randomized, double-blind, global phase III KEYNOTE-811 trial, led by Yelena Y. Janjigian, Memorial Sloan Kettering Cancer Center - MSKCC (New York, USA), was designed to further assess this novel triplet. The initial findings, which were selected to first outing during ASCO 2021, led to the subsequent U.S. Food and Drug Administration (FDA) accelerated approval of the pembrolizumab combination for the first-line treatment of patients with locally advanced unresectable or metastatic HER2+ GC.

The KEYNOTE-811 investigators have most recently reported results from the interim analysis of the first patients who were randomly assigned to receive pembrolizumab or placebo in combination with trastuzumab and chemotherapy. Not only did the combination of pembrolizumab, trastuzumab plus chemotherapy significantly improve overall response rate, it also markedly reduced tumor size and induced complete responses in some patients. Their findings also support preclinical data suggesting a possible synergy between dual HER2 and PD-1 blockade.

This study [7] is the first to show the efficacy of a PD-1 immune checkpoint inhibitor in this particular patient population. Completion of this trial will confirm whether the data translates in improved progression-free survival as well as overall survival.

Immunotherapy plus selected targeted therapies in patients with previously treated advanced urothelial cancer: negatives into positives

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

Evaluating the efficacy of an anti-PD-L1 antibody, durvalumab, in combination with therapy targeted to tumor mutations in bladder cancer, the adaptive biomarker-directed platform and multi-arm BISCAY phase Ib study led by Thomas Powles, Cancer Research UK - Barts Cancer Centre, St. Bartholomew's Hospital (London UK), co-authored by VHIO's Joan Carles, failed to show increased activity for any of the combinations.

Previous studies had already demonstrated the efficacy of durvalumab in chemotherapy-refractory advanced urothelial cancer (AUC), achieving long-lasting remissions in a subset of these patients. Considering that urothelial cancer is characterized by several recurrent targetable genomic alterations, this ambitious trial combined durvalumab with three matched targeted therapies: FGFR, PARP, and TORC1/2 inhibitors. Of these, only FGFR inhibition had previously been tested with positive outcomes in this tumor type.

Eligible patients were assigned to one of six study arms, including durvalumab as monotherapy, to evaluate whether the addition of any of the three different families of inhibitors improved outcomes. Disappointingly, reported response rates did not meet efficacy criteria for further development, and published findings [8] did not provide data pointing to novel treatment approaches.

That said, the results raise important questions regarding the utility of targeted therapy plus immunotherapy in patients with AUC. First, future studies designed to assess the pairing of matched targeted therapies with immunotherapy, and in larger cohorts, could now be avoided, sparing patients' exposure to ineffective treatment approaches. Second, in their biomarker analyses, the investigators compared genomic profiling by liquid biopsy with traditional tissue biopsy. They observed a high consistency between the two, which further supports ctDNA as a non-invasive and real-time screening tool. Lastly, BISCAY's study

model could also positively inform biomarker-based multi-arm clinical trial design.

CheckMate 9ER: the promise of a novel immune-based combination in renal cell carcinoma

Cristina Suárez, Clinical Investigator & Medical Oncologist, Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site Group (PI: Joan Carles).

Results of the CheckMate 9ER open-label, randomized, phase III study [9] directed by Toni K. Choueiri, Dana-Farber Cancer Institute, Lank Center for Genitourinary Oncology (Boston, MA, USA), and co-authored by VHIO's Cristina Suárez, evaluated the efficacy of first-line immunotherapy with nivolumab plus targeted therapy with cabozantinib versus sunitinib in patients with previously untreated advanced clear cell renal cell carcinoma (ccRCC).

In this multicenter study, performed in 125 cancer centers, urology centers and hospitals across 18 countries, including VHIO and our Vall d'Hebron University Hospital (HUVH), patients were randomly assigned to receive first-line immunotherapy with nivolumab plus targeted therapy with cabozantinib, or sunitinib, until disease progression or toxicity. The primary end point of this investigation was progression-free survival with secondary end points including overall survival and objective response.

The CheckMate 9ER Investigators showed patients who received the nivolumab and cabozantinib combination had significantly better progression-free and overall survival, and a greater likelihood of response compared with those who were assigned to sunitinib. These promising findings point to a potential new therapeutic avenue for this patient population.

Advancing insights into the immune cell and tumor milieu

The immune microenvironment as a driver of disease progression in chronic lymphocytic leukemia

Francesc Bosch, Principal Investigator, Experimental Hematology Group.

Advancing insights into the underlying mechanisms that drive disease progression in chronic lymphocytic leukemia (CLL), results of a study [10] directed by VHIO's Francesc Bosch suggest that dynamic clonal evolution is not the main culprit. Pointing to the interaction with the immune microenvironment as a key influencer, this research sheds light on why some patients progress on treatment, while others do not.

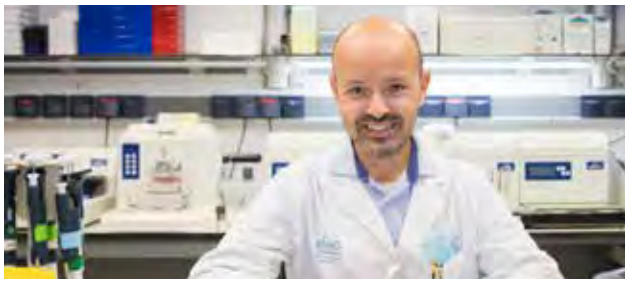
The investigators performed genetic and immunological longitudinal analysis pairing primary samples from untreated CLL patients with clinical progression, with sampling performed at the time of diagnosis and progression, and from patients with stable disease at diagnosis and long-term asymptomatic follow-up.

As the first comprehensive longitudinal analysis of the genetic and immunological processes implicated in CLL progression, results indicate that alterations in the immune microenvironment are highly significant. They assessed the changes occurring from diagnosis to clinical progression that were not associated with the passage of time but differed among patients with progressive disease compared with those with stable CLL.

Data showed that patients with progressive disease had a greater accumulation of terminally exhausted CD8+ T cells, which can be induced by interleukin 10 (IL-10) cytokine secreted by leukemic cells, and increased expression of some immune inhibitory receptors. All these changes lead to a more rapid deterioration of the immune system; reducing its capacity to hone in on and attack malignant cells.

In concordance with previous studies, these analyses showed that genetic alterations do not explain disease progression since they occurred randomly, and in both groups. Instead, the changes in immune cells reduce their capacity to recognize and kill cancer cells, and the alterations in cancer cells empower them to dodge the immune surveillance of tumors. These results could provide a rationale for the use of early immunotherapeutic intervention to help prevent or stall disease progression.

Exploring immune microenvironment dynamics during HER2-targeted treatment in breast cancer



Paolo Nuciforo, Principal Investigator, Molecular Oncology Group.

The host immune system assumes an important role in HER2-positive breast cancer (HER2+ BC). Around half of these tumors have more than 10% of stromal tumor-infiltrating lymphocytes (sTILS), which associates with better survival in both HER2+ early and advanced breast cancer, as well as higher complete response rates after

neoadjuvant anti-HER2-based chemotherapy. These immune cells therefore determine prognosis and might contribute to the efficacy of targeted treatments.

But the composition, localization and functional orientation of these cells within the tumor microenvironment the dynamics at play during anti-HER2 treatment, remain largely unknown. Research directed by VHIO's Paolo Nuciforo sought to decipher changes in the tumor-immune contexture by assessing sTILs during neoadjuvant treatment with lapatinib, a HER2 tyrosine kinase inhibitor, combined with trastuzumab targeted therapy in patients with early-stage HER2+ BC in the phase II PAMELA trial.

Findings of this study [11] showed that sTIL levels increased after two weeks' HER2 inhibition in HER-negative disease and the HER2-enriched subtype. Further, their immune contexture analysis revealed that immune cells spatially interacting with cancer cells have the strongest association with response to anti-HER treatment.

This research illuminates the importance of considering the tumor immunosuppressive microenvironment -- a key factor in response to immune checkpoint blockade and adoptive T-cell transfer therapies -- in the design and development of future strategies aimed at more effectively combating early-stage HER2+ BC.

The seeking out and application of robust biomarkers

RAD51 as a biomarker of homologous recombination deficiency & predictor of clinical outcomes in patients with triple-negative breast cancer

Violeta Serra, Principal Investigator, Experimental Therapeutics Group.

Based on DNA repair functionality, the RAD51 assay, pioneered and developed in-house by VHIO's Violeta Serra's team, has been proven to complement genomic testing in clinical practice. This was reaffirmed in 2021 for prostate cancer as evidenced by results of biomarker analysis [12] from the TOPARP-B study co-led by VHIO's Joaquin Mateo (PI: Prostate Cancer Translational Research Group).

Biomarker analysis from the GeparSixto randomized clinical trial [13], directed by Violeta, has validated RAD51 as a clinically relevant biomarker of homologous recombination-mediated DNA repair deficiency, and a predictive tool for selecting patients with primary triple-negative breast cancer who would most likely respond to treatment with platinum-based neoadjuvant chemotherapy.

Patients enrolled in the GeparSixto study received treatment with neoadjuvant non-pegylated liposomal doxorubicin plus paclitaxel with or without carboplatin. Results from their biomarker analysis demonstrated that the patients who benefited most from carboplatin were those with tumors with homologous repair deficiency by RAD51.

This study supports the clinical validity of their RAD51 assay as a functional test and an independent predictive biomarker of response to carboplatin in untreated triple-negative breasts cancer. Building on the positive results of earlier studies across other tumor types, these latest findings point to the future incorporation of RAD51 in the clinic.

Clinically qualifying predictive biomarkers of response to PARPi in prostate cancer patients

Joaquin Mateo, Principal Investigator, Prostate Cancer Translational Research Group.

PARP inhibitors (PARPi) are approved for treating advanced prostate cancers with various defective DNA repair genes, although not all patients derive the same benefit from this targeted therapy. Research led by Johann de Bono, The Institute for Cancer Research, Royal Marsden NHS Foundation Trust (London, UK), alongside VHIO's Joaquin Mateo -also co-authored by Violeta Serra- sought to clinically qualify predictive biomarkers of response to this class of molecularly stratified therapy.

Aimed at refining the predictive biomarker suite for patient stratification, the investigators analyzed samples from the aforementioned TOPARP-B phase II trial, results of which published in 2020, with Joaquin as a Co-senior author [14]. The results from this subsequent study [12] have now revealed a group of 'super-responders'. Findings showed that patients with complete *BRCA2* deletions responded exceptionally to PARPi with high and durable responses, and advanced insights into which patients carrying PALB or ATM mutations might also benefit from this therapy.

These data may enable the fine-tuning of patient stratification in clinical practice, and the more precise identification of those who could benefit from this class of targeted therapy, based on the molecular specificities of their respective disease.

As already highlighted, (see previous sub-section), this study also demonstrates how the RAD51 assay can help

to complement genomic testing in clinical practice, also in prostate cancer, by identifying alterations in the *BRCA* gene, as well as PALB2 mutations; discriminating between biallelic and monoallelic in the latter. This is particularly relevant since this research has also shown that only those patients with biallelic PALB2 mutations benefit from treatment with PARP inhibitor olaparib.

Combating cancer resistance, progression and disease recurrence

Busted: a driver of adaptive resistance to therapies targeting KIT mutations in gastrointestinal stromal tumors

César Serrano, Principal Investigator, Sarcoma Translational Research Group.

Over recent years, much progress has been made in more effectively treating gastrointestinal stromal tumors (GIST) thanks to the advent of a new generation of more potent and 'smarter' inhibitors that target the *KIT* proto-oncogene and dysregulated platelet-derived growth factor receptor (PDGFR). As an example, the tyrosine kinase inhibitor imatinib has shown clinical benefit in around 80-85% of patients with advanced GIST. However, these patients will unfortunately and inevitably develop secondary resistance.

The specific molecular events that ultimately lead to the adaptive resistance of GIST to the current array of agents that target KIT/PDGFRA mutations remain elusive and represent a major challenge in improving outcomes for these patients. Findings from a study [15] led by VHIO's César Serrano have illuminated the possible causes of resistance by unmasking the E3 ubiquitin ligase Atrogin-1 (*FBXO32*) protein as a mediator of resistance to KIT-targeted inhibition in GIST.

The investigators, including Joaquin Arribas (PI: VHIO's Growth Factors Group), assessed clinically representative *in vitro* and *in vivo* GIST models and GIST patients' samples. Using NGS and GIST-specific gene panels, they studied multiple genes and associated pathways in KIT GIST, and discovered that *FBXO32*, is one of the most critical genes differentially expressed in GIST upon inhibition of KIT and related pathways, irrespective of the type of KIT mutation.

Using different preclinical models, they observed that KIT-targeted inhibition leads to a significant increase in *FBXO32*. This overexpression is a specific survival mechanism of GIST cells, enabling the adaptation to KIT-directed inhibition by apoptosis evasion via cell quiescence.

Currently, there are no specific inhibitors targeting this protein, calling for the development of novel agents. Signposting next step directions, the authors proposed that potential new therapies could be used in combination with imatinib as a more effective treatment strategy. Performing *in vitro* and *in vivo* studies they assessed the efficacy of combining imatinib with the TAK-243 small-molecule inhibitor of the ubiquitin activating enzyme.

This novel therapeutic pairing effectively halted adaptation to treatment mediated by *FBXO32* and led to a significant increase in cancer cell death. This strategy could help to potentiate currently available therapies in this patient population.

First-in-class targeted therapy as a promising new contender against advanced cholangiocarcinoma

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

Aimed at improving outcomes for previously treated patients with unresectable or metastatic cholangiocarcinoma, whose tumors express an isocitrate dehydrogenase 1 mutation (*IDH1*), the phase III multicenter, randomized ClarIDHy clinical trial assessed the performance and safety of ivosidenib, a first-in-class targeted inhibitor of *IDH1*, that is already approved for the treatment of acute myeloid leukemia in some patients with this genetic variant.

Results from this double-blind, placebo-controlled study [16] reported the final overall survival and safety profile of ivosidenib in patients with *IDH1*-mutated CCA whose disease had progressed on one or two previous treatment lines with chemotherapy. By putting ivosidenib to the therapeutic test, the investigators sought to open up a new, more effective and less toxic treatment avenue to target this highly aggressive tumor type.

The ClarIDHy Investigators, led by Andrew X. Zhu, Massachusetts General Hospital Cancer Center, Harvard Medical School (Boston, USA), including VHIO's Teresa Macarulla, showed that ivosidenib numerically improved overall survival compared with placebo, despite a high crossover rate, maintained quality of life, and was well tolerated.

Moving forward, this targeted therapy could potentially respond to the unmet need for new therapies to more effectively combat *IDH1*-mutated CCA. Future studies will aim at achieving a deeper understanding of mechanisms of resistance, and additional translational studies are already under way to investigate disease relapse using circulating tumor DNA (ctDNA) analysis.

COSMIC-311: delivering a new standard of care for patients with thyroid cancer

Jaume Capdevila, Clinical Investigator and Medical Oncologist, Gastrointestinal & Endocrine Tumors Group (PI: Teresa Macarulla).

The double-blind phase III COSMIC-311 study evaluated the efficacy and safety of targeted therapy, cabozantinib, versus placebo in patients with radioiodine-refractory differentiated thyroid cancer (RAIR DTC) who had progressed during/after prior VEGFR-targeted therapy for whom there is no standard of care.

The interim results of this pivotal study [17], led by Marcia S. Brose, Abramson Cancer Center, University of Pennsylvania (PA, USA), and co-authored by VHIO's Jaume Capdevila, achieved the primary endpoint of progression-free survival in all randomized patients including those who had previously received lenvatinib, and cabozantinib showed clinical and statistical improvements over placebo, with no unexpected toxicities.

The final data of COSMIC-311 were subsequently presented by Jaume Capdevila during ESMO 2021. Results confirmed the superior efficacy and manageable safety profile of cabozantinib, as previously evidenced, with improved progression-free survival, irrespective of prior VEGFR-targeted therapy. Cabozantinib achieved a striking 80% reduction in the risk of disease progression in these patients.

Based on these results, the U.S. Food and Drug Administration (FDA), granted approval of this therapy as a new standard of care for this patient population in September 2021. The European Medicines Agency (EMA) recently followed suit with recommended approval of cabozantinib for the treatment of patients with locally advanced or metastatic DTC, refractory or not eligible to radioactive iodine who have progressed during or after prior systemic therapy (March 2022).

These regulatory approvals represent new hope for these patients who are in particular need of more effective treatment options.

PARPi prevents disease recurrence in BRCA-mutated high-risk, early-stage breast cancer

Judith Balmaña, Principal Investigator, Hereditary Cancer Genetics Group.

BRCA mutations are found in approximately 5% of breast cancer patients. Around 55-65% of women with a *BRCA1* mutation, and approximately 45% with a *BRCA2* mutation will develop breast cancer before the age of 70. Despite the many advances in developing more potent, targeted treatments, many patients with high-risk disease will unfortunately suffer relapse.

The OlympiA interventional Phase III study, directed by Andrew Tutt, Institute of Cancer Research and Kings College London (London, UK), and co-led by VHIO's Judith Balmaña, aimed at extending the personalized and targeted promise of olaparib to patients with early-stage, primary, high-risk HER2-negative breast cancer and a germline *BRCA1/2* mutation (gBRCAm), to improve clinical outcomes as well as prevent disease recurrence.

Selected to first outing during ASCO 2021, and published in parallel [18], data showed that targeted treatment with olaparib achieved a significantly superior reduced risk of disease relapse compared with the control group. Regarding the recurrence of invasive disease, analysis at three years revealed that over three quarters of patients in the placebo arm and over 80% of those receiving olaparib showed no relapse. Furthermore, as an orally administered therapy with low-level toxicity, this agent promises improved quality of life for these patients. Showing that patients with early-stage high-risk breast cancer with an inherited *BRCA1/2* mutation can be more effectively treated with targeted therapy, these results were heralded as potentially practice-changing.

The promise of powerful antibody-drug conjugates

Expanding the therapeutic arsenal against metastatic breast cancer

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

Presented at ESMO 2021, Cristina Saura revealed primary outcomes of the phase III TULIP study. This multi-center, open-label randomized clinical trial compared the efficacy and safety of the antibody-drug conjugate (ADC), [Vic-] trastuzumab duocarmazine, to physician's choice in the treatment of patients with HER2-positive, progressive metastatic breast cancer (MBC) who had received at least two previous lines of therapy or ado-trastuzumab emtansine treatment in the metastatic setting.

Conducted at 89 sites, including VHIO, the study's primary endpoint was progression-free survival.

The investigators reported a statistically significant improvement over physician's choice treatment, and observed a trend toward better overall survival for patients treated in the experimental arm.

While these results show promise, adverse events were reported. Moving forward, these manageable events will need to be considered in the development of this next generation ADC as a contender in the treatment of these patients.

Ringing in an antibody-drug conjugate in early breast cancer

Mafalda Oliveira, Clinical Investigator and Medical Oncologist, Breast Cancer & Melanoma Group (PI: Cristina Saura).

The first results of a window of opportunity trial, SOLTI-1805 TOT-HER3, were presented at ESMO 2021. Co-led by VHIO's Mafalda Oliveira and directed by Aleix Prat (Hospital Clínic Barcelona), TOT-HER3, is the first study to evaluate the HER3 directed antibody-drug conjugate (ADC), patritumab deruxtecan, in patients with early hormone-sensitive HR-positive/HER2-negative breast cancer. Prior to this clinical trial, this ADC had only demonstrated anti-tumor activity and a tolerable safety profile in patients with heavily pretreated metastatic high or low HER3 expression levels.

Preliminary results from the first patients included in this trial showed tumor reduction in just under half of cases. Over half of these enrolled patients showed increased immune infiltration and reduced tumor cellularity with just a single shot of the drug. In almost one out of two cases, this therapy achieved tumor shrinkage and even the disappearance of disease. As encouragingly, the treatment was tolerable and the safety profile was consistent with that previously reported for this ADC.

These promising findings could ultimately translate in benefits for patients with newly diagnosed early HER2-negative breast cancer.

DESTINY-Breast03: promising a new standard of care for HER2-positive metastatic breast cancer

Javier Cortés, an Associate Translational Investigator at VHIO.

Headlining at ESMO 2021, results from the DESTINY-Breast03 phase III trial were presented by lead investigator Javier Cortés, Associate Translational Investigator at VHIO. This study compared the efficacy and safety of a new-generation HER2-directed antibody-drug conjugate (ADC), trastuzumab deruxtecan-nxki, with the older-generation ADC, trastuzumab emtansine, in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and a taxane treatment.

The primary endpoint of this study was progression-free survival (PFS). Over 70% of patients treated with trastuzumab deruxtecan arm in the second line remained without progression or worsening of disease at 12 months, compared to 34% of patients treated with trastuzumab emtansine in standard treatment arm of this study. The data, heralded as spectacular, also showed an objective response rate of almost 80% versus 34% in the trastuzumab emtansine arm, further supporting the striking clinical activity of this new-generation ADC.

Based on the striking results from the previous phase II DESTINY-Breast01 trial, co-authored by Cristina Saura [19], Principal Investigator of our Breast Cancer Group, and Javier Cortés, the U.S. Food and Drug Administration (FDA) granted trastuzumab deruxtecan Breakthrough Therapy Designation (BTD) in the US for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.

Of note, further to the reported DESTINY-Breast03 data, new clinical practice guidelines for metastatic breast cancer were developed and published [20] by eminent leaders in this field, including Cristina and Javier, outlined that this new-generation ADC may be considered as second-line therapy in regions where the drug is available.

DESTINY-CRC01: exploratory biomarker analysis in tumor and liquid biopsy

Elena Élez, Medical Oncologist and Clinical Investigator, Gastrointestinal and Endocrine Tumors Group (PI: Teresa Macarulla).

Reported at ASCO 2021, results of the phase II, multicenter, open-label DESTINY-CRC01 trial [21] showed that treatment with the antibody-drug conjugate (ADC), trastuzumab deruxtecan-nxki, produced durable responses in patients with previously treated HER2-positive metastatic colorectal cancer refractory to standard treatment, with a safety profile consistent with that reported in previous trials assessing this therapy.

The DESTINY-CRC01 Investigators, including VHIO's Elena Élez, performed subsequent exploratory biomarker analysis by tumor and liquid biopsy to seek out potential mechanisms of resistance and response for the more precise matching of patients to this therapy. The results were presented by lead author Salvatore Siena, Università degli Studi di Milano (Milan, Italy) at ESMO 2021.

Biomarker data in paired ctDNA samples collected at baseline and disease progression from patients enrolled in this trial indicate that antitumor activity correlates with baseline HER2 expression or amplification in both tumor and liquid biopsy. In the paired ctDNA samples by liquid biopsy that were collected at the beginning of the study and during disease progression, acquired alterations were observed in several genes, but none were common across patients.

Further studies assessing the potential mechanisms of resistance and patient selection for this therapy in patients with HER2-positive metastatic colorectal cancer are warranted.

Dynamic designs, approaches, tools and platforms

Since VHIO incorporated in-house BEAMing liquid biopsy RAS biomarker technology in 2015, the first academic test center to do so, our teams have made great progress in validating and developing liquid biopsy and Droplet Digital PCR Bio-Rad technologies for the more effective, less invasive 'policing' of cancer over time, in real time.

Illustrative of these efforts are the following two VHIO research developments that also made headlines in 2021:

Immune cells in cerebrospinal fluid: predictors of response to immunotherapy against brain metastasis

Joan Seoane, Co-Director of Preclinical & Translational Research, Principal Investigator, Gene Expression & Cancer Group, and an ICREA Research Professor.

Results from previous studies [22],[23] led by Joan Seoane and other groups, have shown that cerebrospinal fluid can provide vital insights into the genomic characteristics of brain tumors and therefore be used as a minimally invasive liquid biopsy. Spurred by these findings, the investigators sought to establish whether they could effectively characterize the tumor microenvironment in brain metastasis.

By analyzing immune cells infiltrating cerebrospinal fluid for the characterization of the tumor microenvironment in brain metastases, latest research directed by Joan [24] confirms that these cells recapitulate the characteristics of those detected in brain metastases and could act as novel and non-invasive biomarkers to predict patient responsiveness to immune-based therapies.

Immune checkpoint inhibitors (ICIs), including anti-PD1, anti-PD-L1, and anti-CTLA4, have shown significant clinical benefits in patients with progressive or metastatic solid tumors, including some brain metastasis. Notably, these immune-based therapies have improved outcomes for some of those suffering from lung cancer and melanoma. Together, these tumor types along with breast cancer, are three common malignancies that lead to brain metastases.

One of the major challenges is that new lesions can differ immensely from the primary tumor, and thus respond in a different way to immune-based therapies. While some patients benefit from treatment with ICIs, the majority do not. To predict response to these therapies necessitates the characterization of tumor specimens. Due to the anatomical location of brain tumors and the risk of surgical procedures, accessing samples from brain malignancies is challenging.

Joan's team analyzed patients' samples and assessed the immune cells present in the brain metastases. In parallel, they performed immune cell profiling of cerebrospinal fluid to identify which cell types were present and compared them to those obtained from the metastatic lesions. They identified the T cells that recognize tumor cells, and those that are active in treatment.

By characterizing the individual sequences of immune cells the investigators established which cells are attacking the tumor, discerning how they evolve over time. This pioneering approach could help to more precisely guide clinical decision making in treating these patients with immune-based therapeutic strategies.

VHIO's suite of cutting-edge technologies: incorporating Guardant Health's liquid biopsy test

Ana Vivancos, Principal Investigator, Cancer Genomics Group.

Announced at the beginning of 2021, VHIO's Cancer Genomics Group, led by Ana Vivancos, has now incorporated the Guardant Health liquid biopsy. As the

first cancer research center to do so in Europe, this avant-garde platform provides complete genomic results in all solid tumors from a simple blood test in seven days and will therefore help to overcome the limitations associated with traditional tissue biopsy.

Guardant360 CDx technology -- the first liquid biopsy test for comprehensive genomic profiling to have received approval from the U.S. Food and Drug Administration (FDA) – will facilitate the non-invasive detection of an increasing number of mutations for the more precise selection of therapies matched to the molecular specificities of each individual patient's disease.

This tool will also enable VHIO's clinical investigators and medical oncologist to identify and select those patients who may be candidates for enrollment in clinical trial studies performed at our Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch, directed by Elena Garralda (page 149).

Integrating this new technology into VHIO's expanding suite of cutting-edge platforms will further spur our dedicated efforts aimed at developing and advancing next generation therapies and precise diagnostics in precision oncology. Watch this space!

Spearheading next generation clinical trials: Cancer Core Europe's design and development of data-rich, adaptive studies in oncology

Elena Garralda, Principal Investigator, Early Clinical Drug Development Group, and Director of VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – Caixa Research.

Incorporating experts from the seven European comprehensive cancer centers belonging to the Cancer Core Europe (CCE) Consortium (page 37), including VHIO, along with an additional four non-CCE partners, the EU-funded, multi-site EU Horizon 2020-funded project CCE Building Data Rich Clinical Trials (CCE-DART) officially launched in 2021.

As I mentioned in last year's report, CCE-DART, led by VHIO's Elena Garralda, seeks to become a groundbreaking example in driving a novel generation of clinical trials in the current era of precision oncology by developing interconnected tools to reduce the current complexity of investigator-initiated trials. This project also aims at better guiding clinical decision-making by integrating cutting-edge digital technologies and platforms.

To overcome the rigidity and limitations of traditional randomized controlled trials that do not allow for the 'real time' and necessary adaptation in tune with the rapid pace of cancer discovery – especially in the academic setting, novel clinical trial designs promote the optimization of biomarker-drug co-development towards more precisely tailoring therapies to each disease setting, each individual patient.

CCE-DART investigators will spur the design and development of a new generation of dynamic data-rich studies in oncology. Building on the CCE-developed Basket of Baskets (BoB) investigator-initiated and adaptive trial which launched in 2018, CCE-DART will further enhance BoB's harmonized, molecular multi-tier profiling platform to more precisely match patients to novel anti-cancer medicines. In parallel, they will continue to develop multiple treatments in genomically-selected populations.

By introducing new tools (or adapting existing ones) the project also seeks to elevate the management and decision-making of clinical studies to the digital age, and ultimately represent a groundbreaking example for driving a new generation of clinical trials in by leveraging novel technologies within existing clinical structures.

Common infrastructures and the wealth of experience gained through CCE sites' running of innovative academic studies will help the project partners to deliver on the four key objectives. Namely, to improve patient enrolment strategies and trial designs, accelerate the use of novel health technologies in the clinical setting, optimize clinical trial data management and analysis, and globalize the results of the project by promoting transparency of investigator-initiated studies.

This project has received funding from the European Union's Horizon 2020 framework programme research under grant agreement No: 965397.

Returning briefly to BoB, a new iBASKET therapeutic module was introduced in 2021. Also led by VHIO, this addition will focus on the targeting of fibroblast growth factor (FGFR) genomic alterations present in multiple tumor types. Incorporating four different arms, investigators will assess the anti-tumor activity and efficacy of FGFR inhibitor futibatinib in patients with FGFR-aberrant solid tumors.

CT-based radiomics signatures to predict response to immune checkpoint inhibitors in advanced solid tumors

Raquel Perez-Lopez, Principal Investigator, Radiomics Group.

Research spearhead by Raquel Perez-Lopez has culminated in the development of a new, non-invasive tool to predict response to immune checkpoint inhibitors in patients with solid tumors. This pioneering radiological model is based on the application of artificial intelligence in the assessment of pretreatment computed tomography images of tumors, where associations can be made between these images and molecular profiles correlating with immune response.

Predicting response prior to the administration of anti-PD-1 and PD-L1 immunotherapies, results of this study [25] showed up to 75% accuracy in patients treated at our Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch, directed by Elena Garralda (page 149).

By providing reliable predictive scoring, this non-invasive approach promises the more precise identification of those patients who would be most likely to benefit from immune checkpoint inhibitor monotherapy and enables a closer tracking of disease progression and response to treatment, over time. This tool can also capture tumors in their entirety as opposed to limited pictures obtained from the particular biopsy site which do not accurately reflect tumor heterogeneity.

The authors conclude that the integration of multidimensional data including radiomics, clinical variables and genomic characterization may be key to optimizing immune checkpoint inhibitor treatment selection toward ultimately improving survival and quality of life of cancer patients. Further, while their predictive radiomics signature shows promise for anti-PD1/PD-L1 patient selection, additional testing in other cohorts as newer immunotherapies emerge will be required.

PIPO: a web-based tool for patient selection in early phase clinical trials

VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – Caixa Research: a leading reference in early clinical drug development & clinical trials in oncology.

Research [26] headed by VHIO's Elena Garralda, Principal Investigator of VHIO's Early Clinical Drug Development Group & Director of VHIO's Research Unit for Molecular Therapy of Cancer (UITM)–Caixa Research, alongside co-corresponding author, Ignacio Matos, a Phase I Investigator of the same group, has led to the development a user-friendly online prognostic calculator, PIPO.

This VHIO Clinical Program core study, counting on the expertise of several other clinical investigators and medical oncologists at our Institute including Rodrigo Dienstmann, Principal Investigator of our Oncology Data Science–OdysSEy Group (page 118), was designed to tackle the well described challenge of patient selection in early phase clinical trials.

Using a training cohort with consecutive patients from our UITM–Caixa Research (page 149), the researchers built a prognostic model to predict overall survival outcomes of patients to be enrolled in phase I studies with immune checkpoint inhibitors or targeted therapies based on clinical parameters assessed at baseline.

Results of this study demonstrate that the PIPO calculator is a feasible, objective, and user-friendly interactive tool to gauge specific survival probabilities for each patient prior to enrolment in a phase I trial and is useful for both treatment types.

Spin-off successes

Peptomyc's Omomyc-based therapy put to the clinical test

Laura Soucek, Co-Director of Preclinical & Translational Research, Principal Investigator, Models of Cancer Therapies Group, an ICREA Research Professor, and Co-Founder & Chief Executive Officer of VHIO-born spin-off Peptomyc S.L.

PEPTOMYC

Co-founded back in 2014 by VHIO's Laura Soucek, CEO of the enterprise, and Marie-Eve Beaulieu, Chief Scientific Officer (CSO) of the company, VHIO-born spin-off Peptomyc received approval from the Spanish Agency of Medicines and Medical Devices for conducting clinical trials in Spain (AEMPS), to initiate the first-in-human Phase I/IIa clinical trial with its first compound – a disruptive Myc inhibitor, Omomyc (OMO-103).

Building on the proven preclinical efficacy and safety of the Omomyc cell-penetrating mini-protein in mouse models [27], and Peptomyc's company's successful development of anti-Myc peptides for the treatment of several tumor types, this latest milestone, celebrated in March 2021, represents a greatly anticipated leap into the clinical research setting and an important step forward in becoming the first ever clinically viable and direct inhibitor of Myc – a protein implicated in the formation of most tumor types.

MYC has been considered an 'undruggable' cancer target for many years. Laura's group has previously shown that Myc blockade has an excellent therapeutic effect in several mouse models, with mild side

effects that are well tolerated and reversible. Now that Laura and her Peptomyc team have received approval to initiate their early phase clinical trial, they can further progress in testing the safety and efficacy of this Omomyc-based therapy for the benefit of cancer patients.

Their Phase I/IIa Study to Evaluate Safety, PK and Efficacy of the MYC-Inhibitor OMO-103 in Solid Tumours - MYCure (NCT04808362), led by VHIO's Elena Garralda, Director of our Research Unit for Molecular Therapy of Cancer (UITM) –CaixaResearch (page 149) and Principal Investigator of Early Clinical Drug Development at our Institute, is now underway. For more information and to discover more about the MYCure early phase clinical trial, I invite you to turn to page 41.

As an aside, I would like to highlight a superb review [28] co-authored by Laura Soucek and Jonathan R. Whitfield, Senior Investigator of her Models of Cancer Therapies Group, that transports us on the long and often rocky road in bringing a Myc inhibitor closer to the clinic.

Sharing their personal views and hopes for the future, as well highlighting the scientific breakthroughs and multiple strategies aimed at successfully targeting Myc, they salute the extraordinary efforts of all the researchers focused on developing treatment for a target long deemed 'undruggable'. The final haul towards a first Myc inhibitor in the clinic? Based on this this review, inhibiting one of the most wanted targets in cancer therapy might be within reach.

Mosaic Biomedicals' MSC-1: transitioned to the clinic

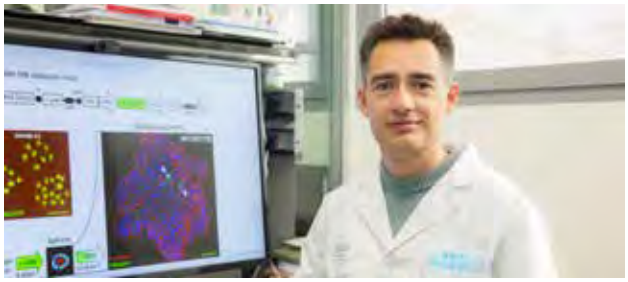
Joan Seoane, Co-Director of Preclinical & Translational Research, Principal Investigator, Gene Expression & Cancer Group, an ICREA Research Professor, and Co-Founder of Mosaic Biomedicals.

VHIO's Joan Seoane and his Gene Expression & Cancer Group previously established the role of leukemia inhibitor factor (LIF) in oncogenesis as a promoter of cancer progression by regulating the tumor microenvironment and inducing self-renewal in tumor-initiating cells. This research culminated in the development of MSC-1, a therapeutic LIF neutralizing antibody. MSC-1's transition to the clinic and translation into benefits for cancer patients promises an important addition to the current arsenal of powerful anti-cancer weaponry.

Joan co-founded VHIO-born spin-off Mosaic Biomedicals in 2012 for the design and development of this novel compound. In 2016, Mosaic merged with Northern Biologics Inc. (Toronto, Canada), and Northern-Mosaic announced the global acquisition of clinical-stage MSC-1 (now AZD0171) by MedImmune/AstraZeneca in 2020.

The phase II clinical trial of AZD0171 (in combination with durvalumab and chemotherapy) in solid tumors (NCT04999969) has initiated patient recruitment.

Setting out: spin-off ONIRIA Therapeutics to counteract cancer resistance and combat disease relapse



Héctor G. Palmer, Principal Investigator, Stem Cells & Cancer Group, Co-Founder and Chief Scientific Officer, ONIRIA Therapeutics.

Created in 2021, and officially launched as this scientific report goes to print, a new spin-off, ONIRIA Therapeutics (page 42), comprises three co-founding partners: VHIO, the *Universidad de Barcelona* (UB), and the ICREA Catalan Institution for Research, and is mainly funded by the "la Caixa" Foundation (page 30), *Asociación Española Contra el Cáncer* – AECC (Spanish Association Against Cancer), and the *Instituto de Salud Carlos III* – ISCIII (Institute of Health Carlos III).

By modulating cell dormancy to overcome cancer persistence, this spin-off will develop new anti-cancer armory to counteract resistance and prevent disease relapse in patients. Among various ongoing projects, ONIRIA Therapeutic's most advanced agent is a first-in-class molecule, ONR-001, that allosterically activates the TET2 master epigenetic enzyme, causing tumor cells to enter a dormant state and even die.

ONIRIA has already secured patent protection for its TET2 modulators and demonstrated efficacy in preclinical animal models by showing that ONR-001 promotes and sustains cancer cell dormancy and even causes cell death upon prolonged treatment. The investigators are now evaluating the efficacy of ONR-001 in several hematologic and solid tumor types, honing

in on those cancers that are hypermethylated as a consequence of TET2 loss-of-function.

Héctor G. Palmer is ONIRIA's Chief Scientific Officer, and Esther Riambau, a venture builder, serves as the company's Chief Executive Officer. The founding team also includes Isabel Puig, a Senior Investigator of Héctor's group, as the company's Scientific Advisor for new therapeutic targets; Xavier Barril, an ICREA investigator at UB, and ONIRIA's Scientific Advisor in computational chemistry; Carlos Galdeano, a Serra Hunter Lecturer Professor and Head of the Protein Degradation Laboratory at UB, who is appointed as its Scientific Advisor in drug discovery.

This pioneering project has also been possible thanks to the additional support received from *Agència de Gestió d'Ajuts Universitaris i de Recerca* – AGUAR (Agency for Management of University and Research Grants), *Fundación FERO* (FERO Foundation – page 29), and the *Fundació Privada CELLEX* (CELLEX Private Foundation – page 28).

The power of cross-border collaboration in precision oncology

In addition to our participation Cancer Core Europe, we also belong to several other important collaborations and partnerships. 2021 celebrated the launch of several new projects including the PERSIST-SEQ international Consortium:

PERSIST-SEQ is a five-year public-private partnership to provide the cancer research community with a new gold standard workflow for single-cell sequencing by developing and validating best practices as well as generating and analyzing high-quality FAIR data. Led by Principal Investigator Alexander van Oudenaarden, Hubrecht Institute (Utrecht, The Netherlands), PERSIST-SEQ connects 16 partners and is co-directed by the Oncode Institute (Utrecht) and AstraZeneca.

Funded by the Innovative Medicines Initiative (IMI), this project represents an important step forward in developing smarter, standardized and reproducible approaches to effectively predict, target, and combat drug-resistance in cancer. Leading experts in cancer modelling and the development of single-cell sequencing technologies will advance insights into the complexity and heterogeneous response of single-cell-derived persisters to anti-cancer therapies.

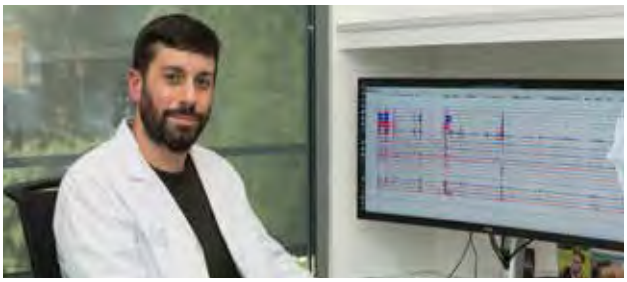
Led by Héctor G. Palmer, our investigators will provide clinical expertise and patients' samples (pre, post and on-treatment), develop sophisticated mouse models linked to clinical trials, and direct one of the defined work packages on single-cell acquisition from models of tumor plasticity.

PERSIST-SEQ receives funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 101007937.

For more information and updates on VHIO's leading participation in other international projects and consortia of excellence see pages 197-214.

Strengthening our programs and supporting VHIO's research talents

As our Institute goes from strength to strength, and seeks to further develop its research lines and projects based on strategic directions, we continue to expand our scientific faculty. 2021 celebrated the incorporation of two new VHIO team leaders:



Jose A. Seoane, Principal Investigator, Cancer Computational Biology Group.

Jose A. Seoane joined us to establish and lead VHIO's Cancer Computational Biology Group (page 78) which focuses on leveraging epi(genetic) cancer datasets to unmask the molecular mechanisms implicated in cancer initiation, progression, drug resistance and metastasis.

Jose's group aims at advancing insights into the role of chromatin regulatory elements in treatment response and metastasis, identifying new epigenetic biomarkers of drug response, and potentiating anti-cancer medicines by combining epigenetic therapies with other agents.

Lara Nonell, Head, Bioinformatics Unit.

Expanding our Core Technologies Program, Lara Nonell has set up VHIO's Bioinformatics Unit (page 128) to implement state-of-the-art pipelines and develop tools for the analysis and visualization of different omics datasets, including publicly available datasets.

Her team seeks to integrate and apply advanced bioinformatics approaches to identify and validate biomarkers for cancer diagnostics, generate

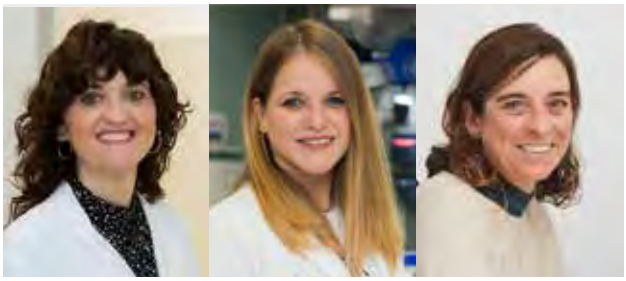
computational models to incorporate multi-omics data using classical or cutting-edge machine learning techniques, and establish collaborative research with VHIO groups to promote the use of advanced computational methods for data analysis, visualization and interpretation.

Susana Aguilar, Head, VHIOTECA Unit.

Our VHIOTECA Unit (page 158) was created in 2021 to support investigators for the obtention, registration and preservation of biological samples other than tumoral tissue (plasma, feces, saliva) from cancer patients, and facilitate the use of these samples in research projects. Joining our other transversal clinical trials core services, VHIOTECA's team is headed by Susana Aguilar and comprises clinical research oncology nurses specialized in specific tumor types, sample managers, and support technicians for sample logistics and database creation/maintenance.

Providing an optimal structure for the dynamization of circuits, this Unit seeks to consolidate, develop and improve existing circuits and processes, and help VHIO researchers to set up new projects and foster new collaborations requiring these types of samples. Spurring studies into the microbiome during tumor development and progression, especially in colorectal cancer, they will also focus on the collection, genomic and molecular analysis of stool samples. VHIOTECA also compliments our Molecular Prescreening Program (page 132), which is also coordinated by Susana alongside Jenifer González, a Research Support Technician.

VHIO ACADEMY



Left to right: VHIO Academy Co-Chairs, Elena Élez, Clinical Investigator and Medical Oncologist, Gastrointestinal & Endocrine Tumors Group, Maria Abad, Principal Investigator, Cellular Plasticity & Cancer Group, and Clara Caminal, Head of the Academy.

Launched this year, the VHIO Academy (page 40), manages, integrates and disseminates training opportunities in cancer research, educational initiatives for all VHIO personnel as well as programs tailored to patients and members of our community. Directed by Co-Chairs, Elena Élez and Maria Abad, and headed by Clara Caminal, its main objective is to provide a range of activities aimed at the career development of our faculty and foster a training environment of excellence.

Just some of these programs include institutional fellowships to attract and retain research talents in oncology, continuous learning opportunities such as complementary courses, workshops, seminars and educational events.

In 2021 our first institutional doctoral fellowships call included five four-year FPI-Severo Ochoa grants for national and international young researchers to carry out their doctoral thesis research at our Institute. Associated with our recent accreditation as a Severo Ochoa Center of Excellence (page 7), these opportunities are within the framework of the EU Pre-doctoral training contracts (FPI) 2021, and supported by the Spanish Ministry of Science and Innovation.

Honoring the life and legacy of the father of precision medicine in oncology

José Baselga, MD, PhD (1959-2021): a global trailblazer in oncology, pioneer of translational cancer research, and VHIO's founder and first director.

My Foreword to last year's report included my personal tribute to VHIO's founder and first director, José Baselga, who very sadly died at the age of 61 on 21 March, 2021. While José's untimely passing will continue to represent an unfillable void in cancer research treatment and care, he leaves a tremendous legacy for the scientific community; one that will continue to inspire present and future generations of cancer researchers and clinical investigators.

Reflective of the scale of our collective loss, tributes in his memory published in numerous leading scientific journals of excellence. Tragically, these included the first obituary published in *Cancer Discovery* [29], a journal of the American Association for Cancer Research (AACR), for which he served as a co-founding Editor-in-Chief. Several other touching tributes dedicated to José's memory [30],[31],[32], also captured his qualities as an iconic leader and chaptered his illustrious career trajectory devoted to improving outcomes for cancer patients worldwide.

In José's honor two special awards have recently launched. One of our Institutional Supporters, the *Fundación FERO* (page 29), that he founded in 2001, announced its Dr. Baselga Award to further promote translational research in oncology. This accolade will prize translational research of excellence carried out at research institutes in Spain by investigators of any nationality. In addition to FERO's Annual Awards for Translational Research, this grant will further spur the translation of scientific discovery into clinical benefits for our patients.

The AACR-AstraZeneca Career Development Award for Physician-Scientists, honoring his extraordinary life and scientific legacy, will foster the careers of promising physician-scientists and support impactful clinical research with the potential to markedly improve patient outcomes.

On a related note, a superb documentary supported by AstraZeneca, *José Baselga: Cancer's Fiercest Opponent*, beautifully chapters his life, career, charismatic persona and all the qualities that made him a visionary in oncology and a truly dedicated, generous mentor of countless talents in our field. This one-hour tribute, covering many defining periods of his life and illustrious career, also includes precious footage and family photos, personal reflections, memories and lesser-known facts that José's wife, Silvia, and their four children Marc, Clara, Alex, and Pepe, so generously share with the audience.

Alongside other colleagues who had the privilege of working with José and knowing him as an extraordinary person impassioned by everything he did, I am truly honored to have participated in this outstanding documentary.

At VHIO, we strive to honor José Baselga's legacy by applying the same dedication, determination, collaborative spirit and fight in combating cancer.

He will never be forgotten.

The Last Word

As VHIO's Director, I am extremely fortunate to lead and work with our many research talents and dedicated healthcare professionals in oncology. Without our multidisciplinary, translational and clinical teams, national and international collaborations and partnerships, coupled with our unified determination to solve cancer sooner, our Institute would cease to exist.

That same sustained devotion and belief is also shared in equal measure by our amazing Institutional Supporters and Patrons – the *Generalitat de Catalunya*, *Fundació Privada CELLEX*, *Fundación FERO*, "la Caixa" Foundation, and the *Fundación BBVA* (pages 27-31) as well as VHIO's many other funding entities, agencies, and individuals (pages 194-196). They all share the same sustained devotion and intense desire as we do: to reduce the devastating burden that this disease has on society.

Illustrated by the many research highlights and developments chaptered in the pages that follow, we continue to drive, 'crystalized' progress against cancer.

By doing what we do best, namely turning challenges into opportunities, I believe that we will report bigger success in more effectively targeting and thwarting this disease through 2022 and beyond.

We can, and will, do even better.

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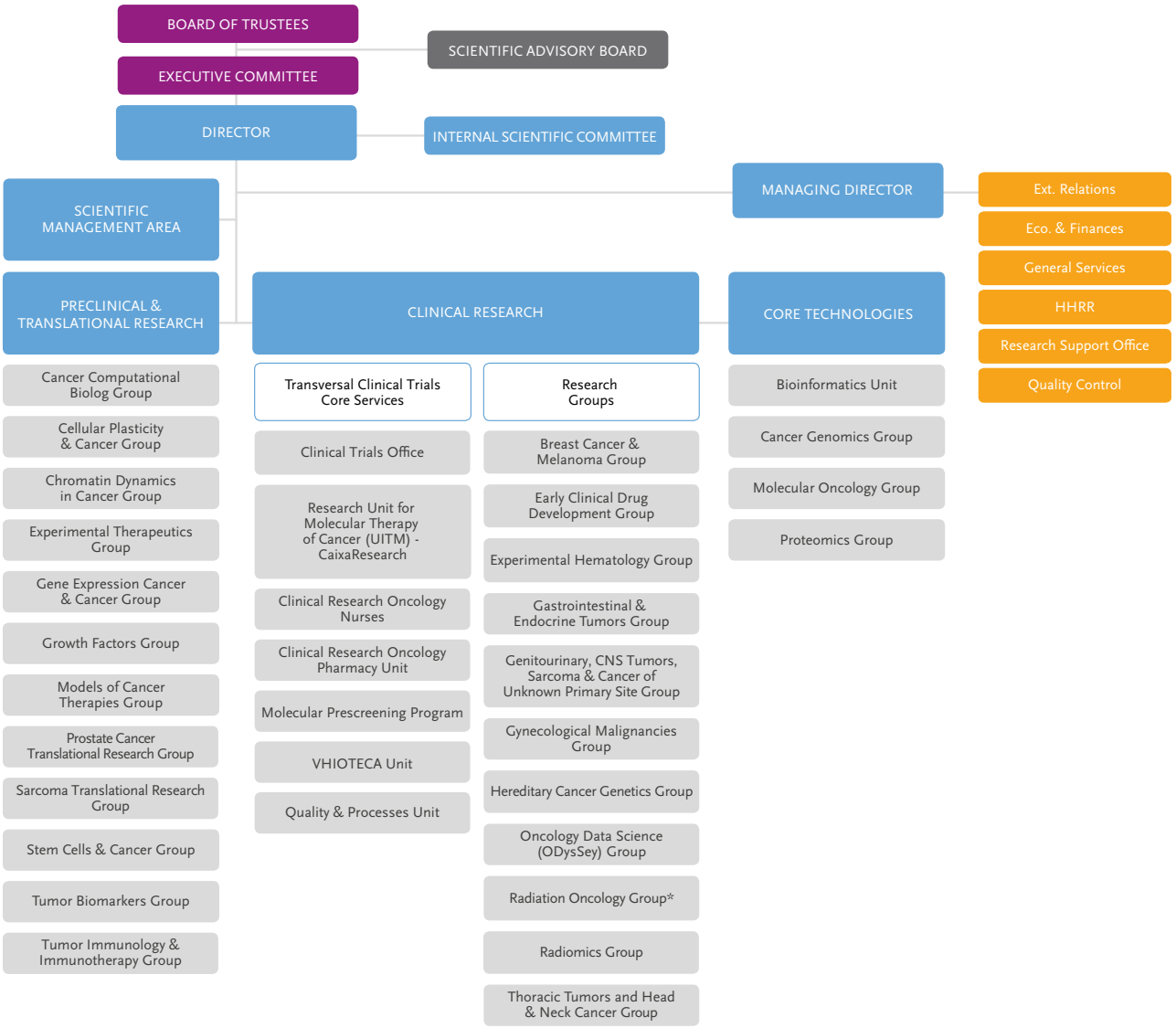
WHO WE ARE AND WHAT WE DO

VHIO's Organigram 2021

In order to translate cancer discovery into real benefits for an increasing number of our patients, we adopt a purely translational, multidisciplinary research model. Organized into three main programs – Preclinical & Translational, Clinical, and Core Technologies, our research focuses on achieving a deeper understanding of the fundamental biology of human cancer, from cellular and molecular biology and genetics through to therapeutics.

Our optimal organizational structure enables VHIO research talents to anticipate and tackle the many unresolved questions that currently hamper efforts aimed at solving cancer sooner.



VHIO IN 2021: TURNING 15 AND DRIVING CONTINUED, 'CRYSTALIZED' PROGRESS AGAINST CANCER DURING COVID-19 PANDEMIC WAVES

Josep Tabernero, VHIO's Director and Head of the Medical Oncology Department, Vall d'Hebron University Hospital – HUVH (Vall d'Hebron Barcelona Hospital Campus).

Under the leadership of Josep Tabernero, the Vall d'Hebron Institute of Oncology (VHIO) has established itself as a comprehensive cancer center of proven excellence internationally and continues to grow from strength to strength. It is thanks to VHIO's optimal organizational structure and multidisciplinary, translational research model that we continue to anticipate and tackle the many challenges posed by this multifaceted, heterogeneous and hugely complex disease.

This transformative approach was pioneered by José Baselga, our Institute's founder and first director, who very sadly passed away from Creutzfeldt-Jakob disease (CJD), a rapidly progressing, neurodegenerative disease, at the age of 61 on 21 March, 2021 (please see pages 6 and 21 of Josep's Foreword to this scientific report).

From the outset, José had one guiding principle for VHIO. Namely, to seamlessly bridge preclinical and clinical research in order to foster a continuous virtuous cycle of knowledge from bench to bedside and back. This translational approach continues to be at the very core of VHIO's philosophy and is passionately pursued by our multidisciplinary teams and research talents.

In honor of José Baselga's incredible legacy, we collectively strive to apply the same dedication and fight in beating cancer, each and every day.

Without the generous support we receive from our Institutional Supporters, public funding, private institutions, companies, and individuals, as well as through International and National Competitive Grants, our Institute would simply cease to exist. We are also truly grateful for the tremendous backing that we continue to receive from our dedicated patrons: the *Generalitat de Catalunya*, *Fundació Privada CELLEX*, *Fundación FERO*, "la Caixa" Foundation, and the *Fundación BBVA*.

Just some of their many contributions include the following:

Generalitat de Catalunya

Our public Patron, the *Generalitat de Catalunya* (Government of Catalonia) – together with the Vall d'Hebron University Hospital (HUVH) – represented by its *Departament de Salut* (Department of Health), and *Departament de Empresa I Coneixement* (Department of Industry and Knowledge), 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, the Vall d'Hebron Barcelona Hospital Campus, 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, through the Catalan Institute of Health (ICS), 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*.

In 2021, the Government of Catalonia's Department of Health awarded three new VHIO projects. Research led by Alena Gros, Principal Investigator of our Tumor Immunology & Immunotherapy Group (page 100), will focus on the development of personalized, non-invasive cell therapies targeting the cancer mutanome of metastatic endometrial cancer. Raquel Perez-Lopez, Principal Investigator of VHIO's Radiomics Group (page 122), will apply precision imaging and artificial intelligence to better characterize patients' response to cancer immunotherapy. Violeta Serra, Principal Investigator of our Experimental Therapeutics Group (page 108), will lead research to seek out predictive biomarkers of response to PARP inhibitors (PARPi) and platinum-based chemotherapy in hereditary breast and ovarian cancer.

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, helps to spur purely translational and multidisciplinary research for which VHIO is famed.

The CELLEX Center: the home, heart and hub of translational & transformative research at VHIO.

CELLEX also financed the construction and infrastructures of our state-of-the-art building – the CELLEX Center – that was completed back 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 out teams with 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 strengthen our teams, pursue and develop new emerging research areas, and fortify our research structure.

As importantly, thanks to CELLEX, our cutting-edge Animal Facility that we share with other colleagues across the Vall d'Hebron Barcelona Hospital Campus, enables our investigators to further develop and finely-tune our predictive cancer models. Incorporating the latest platforms and technologies, this facility has helped to establish VHIO as a reference in cancer modelling.

Support received from the *Fundación FERO* (FERO Foundation), has, from the very outset, enabled science of excellence at VHIO as well as promoted the careers of up-and-coming talents in oncology through its annual grants and 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 Research Professor, Violeta Serra, PI of VHIO's Experimental Therapeutics Group, Joaquín Arribas, PI of our Growth Factors Group, also an ICREA Research Professor, Sandra Peiró, PI of our Chromatin Dynamics Group, and most recently, César Serrano, PI of our Sarcoma and Translational Research 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 continue to develop the liquid biopsy of cancer and thus advance research into the more effective and less invasive tracking of disease. These investigations, spearhead by VHIO's Director, Josep Tabernero, are carried out within the scope of FERO's Institutional Advanced Molecular Diagnostics Program (DIAMAV), that fuels VHIO's Molecular Prescreening Program (page 156).

Regarding its Annual Awards for Translational Research in Oncology, a total of fourteen of our research scientists have been prized to date: 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), Joaquin Mateo, Violeta Serra and Judith Balmaña through the first FERO-ghd funded project (2019), Raquel Perez-López, Cristina Saura and Miriam Sansó – the second annual FERO-ghd award (2020), and Nicolás Herranz in 2021.

Specifically, Nicolas Herranz, Senior Investigator of our Prostate Cancer Translational Research directed by Joaquin Mateo (page 92), was awarded this year for his project entitled, *Exploiting therapy-induced senescence in a synthetic lethal approach to treat advanced prostate cancer*. This funding will enable him to seek out new therapies or drug combinations that neutralize senescent cells and prevent cancer resistance in prostate cancer (page 45). This FERO Grant is supported by the Ramón Areces Foundation.

In 2021, the FERO Foundation supported an additional two new VHIO projects. Our Director, Josep Tabernero, was awarded to explore new technologies for the identification of novel biomarkers of sensitivity and resistance to targeted therapies in metastatic colorectal cancer. This research will be carried out by our Gastrointestinal & Endocrine Tumors Group (page 110), led by Teresa Macarulla. VHIO's Joan Seoane, Principal Investigator of our Gene Expression & Cancer Group (page 86), has received FERO funding to further pursue his research into cerebrospinal fluid as liquid biopsy for the detection, characterization and treatment of brain cancer recurrence. Joan and his team have been awarded for their studies analyzing circulating DNA in the cerebrospinal fluid of pediatric patients with medulloblastoma.

"la Caixa" Foundation

Thanks to the support received from the "la Caixa" Foundation, VHIO's Research Unit for Molecular Therapies of Cancer (UITM) – CaixaResearch (page 149), 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 direction of Elena Garralda, Principal Investigator of our Early Clinical Drug Development Group (page 106), has subsequently established itself as a leading reference in developing novel therapies based on the molecular profile of each tumor and optimizing treatment strategies using combinations of new agents with already existing ones. It also pioneers the design and development of novel, adaptive clinical studies including the basket, multi-modular and umbrella trials. Elena's team is dedicated to studying the efficacy of treatment approaches and anti-cancer medicines by allowing for the 'real time' and necessary adaptation in tune with the rapid pace of cancer discovery - especially in the academic setting.

By advancing clinical trial study design in the current era of precision medicine, VHIO continues to make important contributions to tackling the current challenges in oncology including the globalization of clinical research, and the implementation of emerging health technologies in the clinical setting. One major development in these directions, was the launch of the EU-funded, multi-site project, Cancer Core Europe Building Data Rich Clinical Trials - CCE-DART (page 37), which is coordinated by Elena Garralda.

In addition to various grants supporting several VHIO groups and projects, 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 beginning of 2020, we launched a new 4-year VHIO – "la Caixa" program: CaixaResearch Advanced Oncology Research Program, 2020-2023 (page 139). This support further spurs 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 emerging focus fields in precision oncology.

It is also thanks to the "la Caixa" Foundation that VHIO's Clinical Research Oncology Pharmacy Unit's (page 154) 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) – CaixaResearch Clinical Research Onco-Hematology Unit enables Isabel Cidoncha's team to provide even higher quality pharmaceutical care and services, as well as continue to meet all the regulatory requirements.

Four new VHIO projects received funding from the "la Caixa" Foundation in 2021. First, thanks to an awarded Health Research "la Caixa" Project, Elena Élez, Medical Oncologist and Clinical Investigator of our Gastrointestinal & Endocrine Tumors Group (page 110), will lead the PROMISE study: *BioPrinted hydROgel MicrofluIdicS to mimic patient-specific tumor mEtastatic*.

Under the scope of the "la Caixa" INPhINIT Retaining and INPhINIT InComing funding programs, a trio of predoctoral projects have been granted. Concerning the former, Olivia Prior, a PhD student of our Radiomics Group (page 122), will aim to decipher spatial and temporal cancer heterogeneity with machine learning and precision imaging, under the mentorship of Principal Investigator Raquel Perez-Lopez.

Mentored by Maria Abad, Principal Investigator of VHIO's Cellular Plasticity & Cancer Group (page 80), a Graduate Student of her group, Marion Martínez will carry out her research project entitled, *OncoPeptides: mining the secreted microproteome for novel regulators of PDAC biology*. The IPhINIT InComing "la Caixa" Foundation fellowship, will support Ariadna Grinyó, a Graduate PhD Student of Joaquín Arribas' Growth Factors Group (page 88). Supervised by Joaquín, her research project centers on armoring a

p95HER2 CAR T for the controlled secretion of antitumor agents upon T-cell activation.

Finally, through our VHIO – CaixaResearch Scientific Seminars Series, launched in 2019, we continue to welcome 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. Naturally, due to the COVID-19 pandemic, these expert sessions were mostly hosted and conducted virtually. In 2021, a total of 23 VHIO - CaixaResearch Scientific Seminars took place (page 51).

Fundación BBVA

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 very first program, our second BBVA-VHIO Institutional Program: the BBVA Comprehensive Program of Cancer Immunotherapy & Immunology - CAIMI (page 140), 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.

Under the leadership of VHIO's Director, Josep Tabernero, these research efforts are headed by Alena Gros and Elena Garralda, Principal Investigators of our Tumor Immunology & Immunotherapy and Early Clinical Drug Development Groups (pages 100, and 106), respectively, in collaboration with VHIO's in-house Molecular Prescreening Program of excellence, (please also see: FERO Foundation's Advanced Molecular Diagnostics Program – DIAMAV, page 138).

Main objectives of the BBVA Foundation's CIAMI program include achieving a deeper understanding of naturally occurring T-cell response to cancer and establishing novel ways to exploit these anticancer responses to develop more effective, powerful and personalized immune-based strategies, approaches and therapies to combat this disease; across several tumor types.

Various pioneering translational projects linked to the early clinical development phases of immunotherapy are underway. Focus areas include the characterization of hyperprogressive disease with immunotherapy to advance insights into this phenomenon, led by Elena Garralda, Principal Investigator of VHIO's Early Clinical Drug Development Group (page 106). Carried out in collaboration with Raquel Perez-Lopez, PI of our Radiomics Group (page 122), a radiomic signature has been developed to more precisely predict response to immunotherapy.

Importantly, thanks to the funding received through CAIMI, Elena Garralda's team and Alena Gros' group have worked together to finalize the clinical grade validations of tumor-infiltrating lymphocytes (TILs) expansion for the treatment of certain cancer patients at the Vall d'Hebron University Hospital (HUVH). This work was carried out in collaboration with the *Banc de Sang i Teixits* - BST (Blood and Tissue Bank), a public agency of the Catalan Department of Health.

Alena's group, together with Elena Garralda's team, has received authorization from the AEMPS, and initiated patient recruitment for a phase I clinical study to test the safety and tolerability of neoantigen-selected TIL for patients with solid tumors refractory to standard therapies.

VHIO's TRANSLATION TOWARD PRECISION ONCOLOGY: A LITTLE MORE ON HOW WE DID IT IN 2021

Located within the Vall d'Hebron Barcelona Hospital Campus, our researchers and clinical investigators work together as multidisciplinary teams. Also incorporating physician-scientists and other professionals as well as disciplines in oncology at our Vall d'Hebron University Hospital (HUVH), translational science and clinical research are therefore tightly connected which promotes superb interaction and teamwork which, in turn, accelerates the bench to bedside and back 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 transformative model, 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: a snapshot

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

Advancing translational and transformative clinical research against cancer

The *Fundació Privada CELLEX* (CELLEX Foundation), one of VHIO's Patrons and Institutional Supporters (page 194), financed the construction of our state-of-the-art building – the CELLEX CENTER – that was completed back in 2015. Also supporting our infrastructures, the CELLEX Foundation enables us to advance translational cancer science through our purely multidisciplinary research model and interconnected facilities and platforms.

In 2021, 446 scientific articles were published by VHIO researchers as corresponding/senior or co-authors. For a selection of some of the most relevant articles by VHIO researchers published this year please see pages 63-73 (for our full listing, see pages 168-193).

To view each Principal Investigator's Paper Pick 2021 (highlighting a maximum of four selected contributions in 2021), please refer to their corresponding group pages, as well as our Director's selection of just some of the papers that made the headlines in 2021 (pages 7-18).

COVID-19 pandemic papers

Like many other biomedical research institutes in 2021, VHIO researchers also joined the historic, scientific effort in the COVID-19 era by (co) leading essential research into the impact of this virus on cancer patients as well as professionals in oncology.

Just some of our contributions included the following:

Presented at the virtual 2021 Annual Congress of the European Society for Medical Oncology (ESMO), updated analysis of the OnCOVID registry, directed by David J. Pinato, Imperial College London (UK), and co-authored by Juan Aguilar-Company, Internal Medicine & Infectious Diseases specialist at the Vall d'Hebron University Hospital's (HUVH) Medical Oncology Department, headed by Josep Tabernero, who also co-authored this study, evaluated the prevalence of COVID-19 sequelae and their impact on the survival of patients with cancer in Europe.

For this retrospective study, over 2,700 patients were enrolled from 35 centers who were diagnosed with SARS-CoV-infection between February 2020 – February 2021. Analysis focused on COVID-19 survivors who underwent clinical reassessment at each participating institution, including HUVH. The investigators documented the prevalence of COVID-19 sequelae and described factors implicated in their development and their association with post-COVID-19 survival, defined as the interval resumption of systemic anti-cancer medicines in patients treated within 4 weeks of a COVID-19 diagnosis.

Based on the data from over 1,500 patients who survived COVID-19, results from this study [1] show that sequelae post-COVID-19 compromise long-term survival and outcomes, affecting up to 15% of patients with cancer after recovery. The OnCovid study investigators concluded that adjustments to systemic anti-cancer therapy can be safely pursued in treatment-eligible patients.

Also presented during ESMO 2021, results from a study led by clinical researchers at VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch (page 149), directed by Elena Garralda, reported on the impact of the COVID-19 pandemic on Phase I studies at our Institute.

Presented by Maria Julia Lostes Bardaji, a phase I Investigator at our UITM-Caixa Research, and Silvia Perez-Pujol, Head of VHIO's Start Up Unit, while data showed an initial decrease in new clinical studies during 2020, digitalization and measures in place proved effective in maintaining activity; leading to an increase in the number of new proposals for phase I studies at the end of 2020 at this Unit. The investigators also observed a more significant increase in proposals from January to July 2021.

The researchers analyzed statistics relating to the initiation of phase I clinical trials from January 2019 to July 2021, including new study proposals, pre-selection and study initiation visits. Data showed that while there was a 9.6% decrease in new clinical trial proposals in 2020 compared with 2019, dropping from 146 to 132, the number of pre-selection as well as initiation site visits increased in 2020.

The investigators concluded that, despite the challenges posed by COVID19 and the subsequent, initial decrease of new studies observed during 2020, their findings demonstrated that the number of new proposals for phase I clinical trials increased in 2021. This trend supports the efficiency of remote pre-selection site visits as an alternative to on-site visits, and the efficacy of digitalization and measures in place to maintain clinical start up activity at VHIO during the pandemic.

Of note, as highlighted by Elena Garralda in her pages updating on the activities of our UITM-Caixa Research (page 149), clinical research activities and patient enrollment in our trials were successfully maintained throughout 2021. Our phase I Unit participated in 207 ongoing phase I studies, 27 of which are Basket trials (a 6% increase compared with 2020). In 2021, 66 new trials opened; 5 as Baskets, with 551 patients enrolled.

Led by Elena Élez, a Medical Oncologist and Clinical Investigator of VHIO's Gastrointestinal & Endocrine Tumors Group, a study [2] conducted on behalf of the Spanish Society of Medical Oncology (SEOM) and the +MIR SEOM Residents and Young Oncologists Committee, assessed the prevalence of burnout in junior medical oncologists in Spain - before and after the onset of the COVID-19 pandemic.

The investigators, including first author Pablo Jiménez Labaig, Member of +MIR SEOM and a Medical Oncologist at the Cruces University Hospital, Barakaldo (Bizkaia, Spain), conducted two online surveys aimed at residents and medical oncologists in their first five years post-residency.

Findings showed that almost one out of four young oncologists surveyed had doubts concerning their medical vocation. Results from the first survey revealed that 28% of respondents were affected by burnout, increasing to almost 36% in residents in their second year of training. It also identified other issues that can lead to professional exhaustion including the perceived lack of vacation and leisure time and struggle to strike a better work-life balance.

Almost 84% of survey participants confirmed that they had missed part of their training rotations and medical stays at other hospitals in Spain and abroad. Nearly three-quarters of respondents were reassigned to COVID-19 care in challenging work conditions, and 17% of them reported that they had contracted COVID-19.

Regarding mental health, 37% had scores indicating anxiety, 30% with moderate to severe depression, and 64% of survey participants confirmed that they had no access to psychological support at the workplace. These worrisome findings raise an alarm concerning the lack

of measures aimed at reducing burnout suffered by many of our younger medical oncologists.

VHIO's Elena Élez coordinates the +MIR SEOM Residents and Young Oncologists Committee. Her devotion to nurturing and growing the careers of young investigators and medical oncologists is also reflected by her co-leadership of VHIO's recently established Academy (page 40).

(1) Pinato DJ, Tabernero J, Bower M, Scotti L, Patel M, Colomba E, Dolly S, Loizidou A, Chester J, Mukherjee U, Zambelli A, Dalla Pria A, Aguilar-Company J, Ottaviani D, Chowdhury A, Merry E, Salazar R, Bertuzzi A, Brunet J, Lambertini M, Tagliamento M, Pous A, Sita-Lumsden A, Srikandarajah K, Colomba J, Pommeret F, Seguí E, Generali D, Grisanti S, Pedrazzoli P, Rizzo G, Libertini M, Moss C, Evans JS, Russell B, Harbeck N, Vincenzi B, Biello F, Bertulli R, Liñan R, Rossi S, Carmona-García MC, Tondini C, Fox L, Baggi A, Fotia V, Parisi A, Porzio G, Saponara M, Cruz CA, García-Illescas D, Felip E, Roqué Lloveras A, Sharkey R, Roldán E, Reyes R, Earnshaw I, Ferrante D, Marco-Hernández J, Ruiz-Camps I, Gaidano G, Patriarca A, Bruna R, Sureda A, Martinez-Vila C, Sanchez de Torre A, Cantini L, Filetti M, Rimassa L, Chiudinelli L, Franchi M, Krengli M, Santoro A, Prat A, Van Hemelrijck M, Diamantis N, Newsom-Davis T, Gennari A, Cortellini A; OnCovid study group. Prevalence and impact of COVID-19 sequelae on treatment and survival of patients with cancer who recovered from SARS-CoV-2 infection: evidence from the OnCovid retrospective, multicentre registry study. *Lancet Oncol*. 2021 Dec;22(12):1669-1680.

(2) Jiménez-Labaig P, Pacheco-Barcia V, Cebrià A, Gálvez F, Obispo B, Páez D, Quílez A, Quintanar T, Ramchandani A, Remon J, Rogado J, Sánchez DA, Sánchez-Cánovas M, Sanz-García E, Sesma A, Tarazona N, Cotés A, González E, Bosch-Barrera J, Fernández A, Felip E, Vera R, Rodríguez-Lescure Á, Élez E. Identifying and preventing burnout in young oncologists, an overwhelming challenge in the COVID-19 era: a study of the Spanish Society of Medical Oncology (SEOM). *ESMO Open*. 2021 Aug;6(4):100215.

The development and application of powerful platforms & empowering technologies

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 accelerate 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.

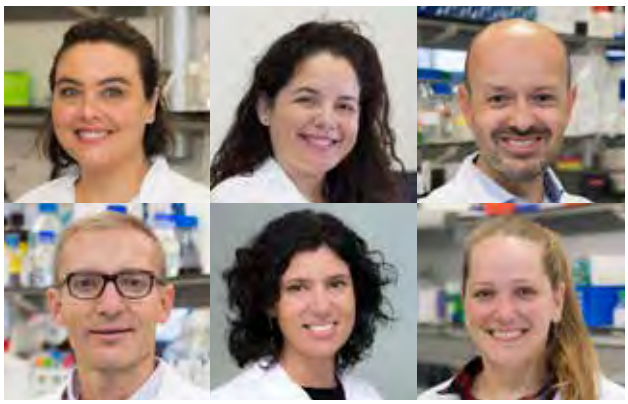
VHIO's Cancer Genomics Group (page 130), headed by Ana Vivancos, serves as a Core Technology laboratory and provides cutting-edge applications in cancer genomics through state-of-the-art technologies and the development of novel, fully validated tests that are used in the clinical research setting. Her lab is equipped with an n-Counter (Nanostring) platform, two digital PCR platforms (BEAMing Sysmex and ddPCR, BIO-RAD), and four NextGen Sequencers; MiSeq, NextSeq and HiSeq2500 from Illumina, and most recently, a MinION from Oxford Nanopore Technologies.

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, thanks to our multidisciplinary teams in collaboration with VHIO's Cancer Genomics Group and Paolo Nuciforo's Molecular Oncology Group (page 132) 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.

In 2021, we incorporated Guardant Health liquid biopsy. As the first cancer research center to do so in Europe, this avant-garde platform provides complete genomic results in all solid tumors from a simple blood test in seven days and will therefore help to overcome the limitations associated with traditional tissue biopsy. Guardant360 CDx technology -- the first liquid biopsy test for comprehensive genomic profiling to have received approval from the U.S. Food and Drug Administration (FDA) – will facilitate the non-invasive detection of an increasing number of mutations for the more precise selection of therapies matched to the molecular specificities of each individual patient's disease.

Integrating this new technology into VHIO's expanding suite of cutting-edge platforms will further accelerate progress in developing and advancing next generation therapies and precise diagnostics in precision oncology. Also in liquid biopsy, Ana's group has developed their custom NGS test with Unique Molecular Identifiers (UMIs) combined with Copy Number Alteration analysis using Shallow Whole Genome Sequencing (sWGS), that will be their first disease tracking test in the clinical setting.

Molecular Prescreening at VHIO: driving the clinical implementation of emerging cancer biomarkers



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

VHIO's Molecular Prescreening Program (page 156) is powered by one of our Institutional Programs, FERO Foundation's Institutional Advanced Molecular Diagnostics Program – DIAMAV (page 138), and

catalyzes precision medicine at VHIO. Over the past decade, molecular prescreening at VHIO has provided access to advanced molecular diagnostics to an increasing number of patients, and is critical in matching targeted therapeutic approaches with hundreds of clinical trial opportunities.

Molecular prescreening at VHIO also counts on the expertise provided through our Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch (pages 149-151), funded by the "la Caixa" Foundation and directed by Elena Garralda. Representing a key driver of clinical-molecular correlative research at our Institute, this program is co-led by VHIO's Ana Vivancos, Elena Garralda, Paolo Nuciforo, and Rodrigo Dienstmann. The team regularly convenes to explore existing molecular tests, developed in-house, and novel biomarkers of interest for the potential inclusion in the program.

Performing molecular profiling in over 1,100 patients each year, VHIO is one of the few centers in Europe to run such a comprehensive program.

In 2021, tumor molecular profiling was performed in 1,138 cancer patients who are candidates for enrolment in clinical studies. Our cancer researchers and genomicists participate in weekly tumor board meetings with VHIO's medical oncologists to provide guidance on the interpretation of NGS results as well as discuss new markers for clinical testing in patients eligible for inclusion in our early phase clinical studies performed at our UITM – CaixaResearch.

Further developments this year also include the validation of our Cancer Genomics Group's 450 gene capture panel for mutations, Tumor Mutational Burden and for Copy Number Alterations, to be used in our molecular prescreening, and research led by Paolo Nuciforo, Principal Investigator of VHIO's Molecular Oncology Group (page 132), continues to identify targetable alterations as part of this program.

Flanking these efforts, our VHIOTECA Unit (page 158) was created in 2021 to support investigators for the obtention, registration and preservation of biological samples other than tumoral tissue (plasma, feces, saliva) from cancer patients, and facilitate the use of these samples in research projects. Joining our other transversal clinical trials core services, VHIOTECA's team is headed by Susana Aguilar, who also coordinates our Molecular Prescreening Program in collaboration with Jenifer González, Research Support Technician of our Cancer Genomics Group.

We continue to extend our efforts to an increasing number of patients through collaborations with other research centers, across borders. As an example, VHIO participates in the AACR's Genomics Evidence Neoplasia Information Exchange project (GENIE) that catalyzes the sharing of integrated genomic and clinical datasets across multiple cancer centers worldwide.

Incorporating 20 consortium participants across the globe, VHIO is the only institution from Spain. This major international collaboration also counts on the expertise of its informatics partners, SAGE and cBioPortal, that serve as secure data repository and visualization portals.

The first set of cancer genomic data aggregated through AACR's GENIE was available to the global oncology community in January 2017. The ninth data set, GENIE 9.0-public, was released in February 2021, and the tenth, GENIE10.0 public, followed in June 2021. Most recently, this project has hit another important milestone. With the release of GENIE 11.0-public, the registry now contains over 136,000 sequenced samples from over 121,000 patients, making the AACR Project GENIE registry among the largest fully public cancer genomic data sets released to date.

Fulfilling an unmet need by providing the necessary statistical power to better guide clinical decision-making, particularly in the case of rare cancers and rare variants in common cancers, GENIE empowers novel clinical and translational research.

VHIO was invited to join this pioneering project in 2018 and our participation is led by Rodrigo Dienstmann, Principal Investigator of our Oncology Data Science (ODysSey) Group (page 118).

"la Caixa" Foundation

VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch: spearheading early clinical drug development and dynamic studies in precision oncology

VHIO's UITM - CaixaResearch: the heart and hub of our early clinical drug development.

Thanks to the support we receive from one of our Institutional Supporters and Patrons, "la Caixa" Foundation (page 30), VHIO continues to establish itself as a leading reference in progressing drug development and targeted therapies against cancer. Our Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch (page 149), founded back in 2010, has rapidly become one of the few comprehensive facilities in Europe to translate latest discovery into improved outcomes for patients, as rapidly as possible.

Directed by Elena Garralda, alongside our Director, Josep Tabernero, 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 this Unit is driven by Elena Garralda's Early Clinical Drug Development Group (page 106), 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. These efforts have 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.

As a direct result of clinical studies conducted at our UITM-CaixaResearch, more than 30 anti-cancer agents by either the U.S. Food and Drug Administration (FDA), or the European Medicines Agency (EMA), or both.

Current research centers on accelerating and advancing immunotherapies including atezolizumab, nivolumab and pembrolizumab. Concerning novel immunotherapeutics, we spearhead 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, including Alena Gros' Tumor Immunology & Immunotherapy Group (page 100).

Pioneering next generation, adaptive clinical studies

Our UITM-CaixaResearch facilities, coupled with VHIO's CaixaResearch Advanced Oncology Research Program, 2020-2023 (page 139), enable us to continuously expand our portfolio of early phase studies including complex trials such as basket studies, as well as spearhead next generation clinical trials in oncology.

Our participation in ongoing and new projects including the EU-funded Cancer Core Europe Consortium – Building Data Rich Clinical Trials (CCE-DART), that officially launched in 2021, also allows us to optimize biomarker-drug co-development to more precisely match tailored therapies to each disease setting, each individual patient. These 'smarter' study designs seek to more effectively identify the optimal treatment for the right patient, at the right time. They also promise to overcome the rigidity and limitations of traditional clinical trials.

Throughout 2021, despite the challenges posed by the COVID-19 pandemic, our Unit led 207 ongoing phase I plus Basket clinical trials – an increase over previous years. Similarly, more patients than ever before were enrolled in our phase I and basket studies. This year, 551 patients participated in these studies. It is thanks to the dedication of Elena Garrlda's Group, and all our expert professionals across VHIO's Transversal Clinical Trials Core Services and Units, that activity was successfully maintained, and in some instances even surpassed, in order to respond to the needs of our patients.

VHIO's Clinical Trials Office (page 146), directed by Marta Beltran, is also located in the patient environment of the Vall d'Hebron University Hospital (HUVH). Her team coordinates our phase I and Basket studies, and a large portfolio of phase II & III clinical trials. In 2021 a record total number of 1,326 patients were enrolled across our 511 actively recruiting trials. In addition, 280 patients were included in a total of 34 post authorization and rollover studies.

Overall, this increased activity was largely achieved by establishing adaptive circuits and approaches to ensure the optimal running of clinical studies, while delivering –as always- optimal patient care. Newly introduced measures in response to the pandemic, whenever and wherever possible, included remote monitoring as well as dispensation of medication for certain patients receiving orally administered therapies, and telematics clinical consultations. Additionally, the virtual monitoring of certain patients in clinical trials quickly emerged as a solution to some issues posed by COVID-19.

VHIO's direct access to cancer patients: at the center of our purely translational research model

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

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.

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

VHIO can only continue to accelerate the pace in advancing personalized and targeted therapies against cancer thanks to the generous support received from our Patrons and Institutional Supporters: the *Generalitat de Catalunya*, *Fundació Privada CELLEX*, *Fundación FERO*, "la Caixa" Foundation, and the *Fundación BBVA*. In addition to this precious funding, three of them also fuel our trio of Institutional Research Programs:

fundación fero
Investigando por un futuro sin cáncer

Advanced Molecular Diagnostics Program – DIAMAV. This program (page 138) supports molecular prescreening at VHIO as we seek to advance molecular profiling in patients 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. Our investigators aim to identify specific molecular risk factors to better predict the potential efficacy of specific agents tailored to each particular tumor, advance insights into the more precise and less invasive tracking of disease by liquid biopsy, and develop cancer diagnostics for the early detection of disease.

"la Caixa" Foundation

CaixaResearch Advanced Oncology Research Program. Building on the successes of the two previous VHIO – "la Caixa" institutional 3-year programs, our CaixaResearch program - 2020-2023 (page 139), enables our researchers and investigators to accelerate the development of more potent and targeted anti-cancer medicines, strengthen 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; those areas showing particular promise in solving the multiple questions that stand in the way of more effectively combating cancer.

Fundación BBVA

Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI). As a result of the achievements of the very first VHIO – BBVA Foundation Program on Tumor Biomarkers Research, the BBVA Foundation officially launched this second 4-year program (page 140) in 2018 to advance agents that inhibit checkpoint regulation of the immune system, achieve a deeper understanding of mechanisms of resistance and response to these therapies, and prioritize the early development of those agents showing most promise.

Our research efforts and activities are also supported by funding received from several private institutions, companies, associations, societies, and individual donors (pages 194-196). In addition, we continue to secure essential funding through several International and National Competitive Grants. Regarding the latter, we take this opportunity to also gratefully thank the *Asociación Española Contra el Cáncer* – AECC (Spanish Association against Cancer) for its longstanding support of several VHIO groups and researchers (page 47).

To browse the complete list of our newly funded projects in 2021 see pages 208-214.

Powerful cross border partnerships of excellence

At VHIO we are dedicated to fostering, developing and (co) leading multi-center collaborations that combine the necessary expertise and resources to more rapidly advance cancer discovery. Regarding our leadership of -and participation in- several existing international consortia and alliances (page 197), 2021 marked many important developments including the following:

Cancer Core Europe

The Cancer Core Europe Consortium – CCE (page 197), 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. It also spearheads next generation clinical trials by designing and developing data rich, dynamic studies in oncology.

Officially announced in 2021, multi-site EU Horizon 2020-funded Cancer Core Europe Consortium-Building Data Rich Clinical Trials (CCE-DART) incorporates experts from the seven European comprehensive cancer centers belonging to the CCE Consortium, including VHIO, along with an additional four non-CCE partners*. Led by VHIO's Elena Garralda, Principal Investigator of our Early Clinical Drug Development Group (page 106), and Director of VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch (page 149), this project is Illustrative of our collaborative efforts aimed at pioneering novel clinical trial design in the current era of precision oncology.

Building on the CCE-developed Basket of Baskets (BoB) investigator-initiated and adaptive trial which launched in 2018, which was also designed and co-developed by Elena's team at UITM-CaixaResearch, CCE-DART will further enhance BoB's harmonized, molecular multi-tier profiling platform to more precisely match patients to novel anti-cancer

medicines based on the genetic specificities of their individual tumors. In parallel, the researchers will continue to develop multiple treatments in genomically-selected populations.

By harnessing and incorporating powerful cutting-edge technologies, methods and platforms, CCE-DART investigators will spur the design, development, and ringing in of a new generation of data rich, dynamic studies in oncology. To overcome the rigidity and limitations of traditional randomized controlled trials that do not allow for the 'real time' and necessary adaptation in tune with the rapid pace of cancer discovery – especially in the academic setting, these novel clinical studies promote the optimization of biomarker-drug co-development toward more precisely tailoring therapies to each disease setting, each individual patient.

Common infrastructures and the wealth of experience gained through CCE sites' running of innovative academic studies will help the project partners to deliver on the four key objectives. Namely, to improve patient enrolment strategies and trial designs, accelerate the use of novel health technologies in the clinical setting, optimize clinical trial data management and analysis, and globalize the results of the project by promoting transparency of investigator-initiated studies.

www.cce-dart.com

This project has received funding from the European Union's Horizon 2020 framework programme research under grant agreement No. 965397.

*CCE-DART participants - CCE Consortium Members: VHIO, Karolinska Institute, (Stockholm, Sweden), Cambridge Cancer Center (Cambridge, UK), National Center for Tumor Diseases (Heidelberg, Germany), Netherlands Cancer Institute, (Amsterdam, The Netherlands), National Cancer Institute of Milan (Italy). Gustave Roussy Cancer Campus Grand Paris (Villejuif, France). Non-CCE Members: Digital Experimental Cancer Medicine Team (Manchester, UK), The Hyve (Utrecht, The Netherlands), DataRiver (Modena, Italy), Form Vision (Abcoude, The Netherlands).

Regarding the aforementioned CCE Basket of Baskets (BoB) modular, open-label, phase II, multicenter study evaluating targeted agents in molecularly selected populations with advanced solid tumors, a new iBASKET therapeutic module was introduced in 2021.

Also led by VHIO, this addition will focus on the targeting of fibroblast growth factor (FGFR) genomic alterations present in multiple tumor types. Incorporating four different arms, investigators will assess the anti-tumor activity and efficacy of FGFR inhibitor futibatinib in patients with FGFR-aberrant solid tumors.

www.basketofbaskets.eu

EU CAN

The European-Canadian Cancer Network (EUCANCan) Consortium (page 198) launched in 2019 to pursue the homogeneous analysis, management and exchange of genomic-driven oncology data for the advancement of precision medicine against cancer.

This four-year project, coordinated by David Torrents, ICREA Professor and Head of Computational Genomics at the Barcelona Supercomputing Center (Spain), is jointly fueled by the European Union's Horizon 2020 research and innovation programme and the Canadian Institutes of Health Research (CIHR).

As a federated network comprising interoperable infrastructures in Canada, Germany, the Netherlands, France, and Spain, leading experts in oncogenomics and cancer data science from 18 organizations, including VHIO's Rodrigo Dienstmann (PI: Oncology Data Science – ODysSey, page 118), swiftly apply and exchange genomic-generated intelligence and discovery.

VHIO's participation, also counting on the expertise of our Director, Josep Tabernero, and Elena Garralda (Director, UITM-CaixaResearch, page 149) focuses on standardizing clinical-genomics datasets for precision oncology and creating webtools that will expand patient access to biomarker-driven trials in Europe. These efforts (Work Package 5: *Standardized clinical reporting across sites*), are co-directed by Rodrigo Dienstmann and Jürgen Eils, Heidelberg University Hospital (UKL) – German Cancer Research Center (DKFZ).

www.eucancan.com

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

oncotrialstrack

As part of the EUCANCan project, VHIO's Onco Trials Track launched in 2021. Designed and developed by Rodrigo Dienstmann's team, this online resource empowers healthcare providers in the difficult and time-consuming task of finding the most suitable VHIO clinical trial for cancer patients and contacting investigators from recruiting sites for case discussion and referral.

Unlike many other available databases, Onco Trials Track offers a user-friendly interface with up-to-date catalogue of molecularly and semantically tagged clinical trials. This interactive VHIO clinical trial locator provides the very latest information on clinical trial recruitment and enables the easy identification

of clinical studies with unique biomarker criteria for precision cancer therapy.

Clinical studies can be filtered by tumor type, disease stage, investigational drug class phase of clinical development, among other indicators. This VHIO-developed hub also promotes the possible acceleration of patient referral processes by completing detailed contact e-forms. Discover more here: **www.oncotrialstrack.vhio.net**

Funded by the European Union's Horizon 2020 research and innovation programme, the NoCanTher – Nanomedicine upscaling for early clinical phases of multimodal cancer therapy – Consortium (page 201), launched in 2016, and is coordinated by IMDEA Nanociencia (Madrid, Spain). Connecting 11 leading European research centers, including VHIO, along with industry partners, this multi-center undertaking also counts on the expertise of the CIBBIM-Nanomedicine Group at the Vall d'Hebron Research Institute – VHIR (Barcelona, Spain).

NoCanTher focuses on the development of magnetic nanoparticles and magnetic hyperthermia for the intra-tumoral treatment of patients with unresectable, locally advanced pancreatic cancer that has not metastasized. Currently the only therapeutic alternative for these patients, who account for 20% of patients with pancreatic cancer, is palliative chemotherapy. This pioneering project represents an important step forward in applying nanoparticles for the more effective and direct targeting of cancer cells in this patient population.

Announced in 2021, NoCanTher has now rolled out the clinical phase of the project. The pilot trial, designed and developed by VHIO's Teresa Macarulla, Principal Investigator of our Gastrointestinal & Endocrine Tumors Group (page 110), is underway and shows promise in ultimately ringing in nanotechnology-based therapies at the clinical level.

This study is based on the results obtained in the preclinical phase of NoCanTher co-led by VHIR's CIBBIM-Nanomedicine Drug Delivery and Targeting Group, directed by Simo Schwartz Jr. This preclinical work verified the efficacy of nanoparticles in animal models with implanted patient-derived pancreatic tumors that were previously induced. The investigators showed that when magnetic iron oxide nanoparticles are injected directly into tumors, the generated hyperthermia achieves cancer shrinkage and alters the characteristics of tumors; facilitating the direct delivery of chemotherapy.

This strategy, now being put to the test in the clinical setting, allows heat to be exclusively applied to the area where the nanoparticles are located without harming the surrounding healthy tissues. Magnetic hyperthermia, together with the administration of standard chemotherapy, can transform electromagnetic energy into heat in order to destroy tumor cells and locally control cancer growth. The intracellular delivery also promises to reduce the adverse effects associated with chemotherapy.

Marking the final phase of the NoCanTher project, this clinical study could ultimately open new therapeutic avenues for patients with locally advanced pancreatic cancer, for whom there are no other treatment options available except chemotherapy.

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.

Launched in 2021, the PERSIST-SEQ (page 205), multi-center consortium is a five-year public-private partnership aimed at building a reproducible single-cell sequencing workflow to capture tumor drug persistence. This project aims to provide the cancer research community with a new gold standard workflow for single-cell sequencing by developing and validating best practices as well as generating and analyzing high-quality FAIR data.

Led by Principal Investigator Alexander van Oudenaarden, Hubrecht Institute (Utrecht, The Netherlands), PERSIST-SEQ connects 16 partners, including VHIO, and is co-directed by the Oncode Institute (Utrecht) and AstraZeneca. Funded by the Innovative Medicines Initiative (IMI), this project represents an important step forward in developing smarter, standardized and reproducible approaches to effectively predict, target, and combat drug-resistance in cancer.

Leading experts in cancer modelling and the development of single-cell sequencing technologies will advance insights into the complexity and heterogeneous response of single-cell-derived persisters to anti-cancer therapies. Our Institute will provide clinical expertise and patients' samples (pre, post and on-treatment), develop sophisticated mouse models linked to clinical trials, and Héctor G. Palmer, Principal Investigator of our Stem Cells & Cancer Group (page 96), will direct one of the defined work packages on single-cell acquisition from models of tumor plasticity.

This coalition comprises field-leading researchers as well as medical oncologists who will leverage their cancer modelling approaches and cutting-edge platforms to perform the sequencing of single tumour cells. Aimed at refining and standardizing a broadly applicable workflow for single-cell sequencing, PERSIST-SEQ teams will aim to advance insights into therapeutic resistance in cancer toward developing more effective therapies and prevent disease persistence.

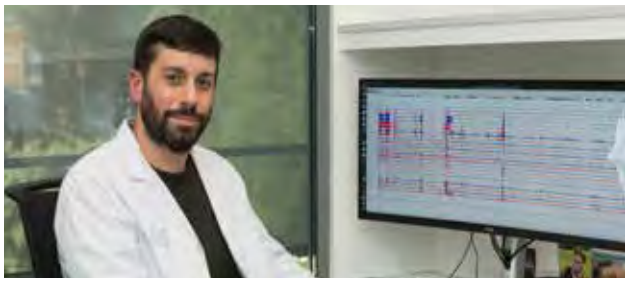
Importantly, PERSIST-SEQ will employ an open access model to build and sustain its benchmarking procedures and centralized European data infrastructure. This strategy will help to avoid costly duplication of efforts, promote collaboration across disciplines, and facilitate the adoption of state-of-the-art single cell technologies.

www.persist-seq.org

PERSIST-SEQ receives funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 101007937.

Strengthening our programs and supporting VHIO's research talents

As our Institute goes from strength to strength, and seeks to further develop its research lines and projects based on strategic directions, we continue to expand our scientific faculty. As highlighted in our Director's Foreword (page 20), to this scientific report, 2021 celebrated the incorporation of two new VHIO team leaders:

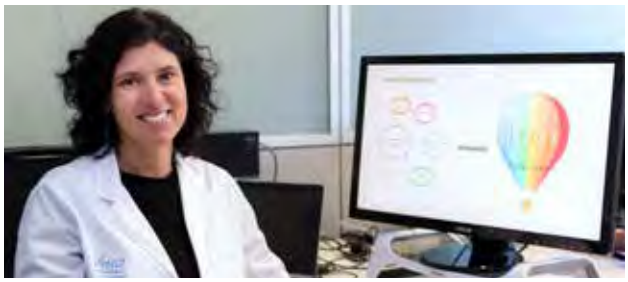


Jose A. Seoane, Principal Investigator, Cancer Computational Biology Group.

Jose A. Seoane joined us to establish and lead VHIO's Cancer Computational Biology Group (page 78) which focuses on leveraging epi(genetic) cancer datasets to unmask the molecular mechanisms implicated in cancer initiation, progression, drug resistance and metastasis.

Lara Nonell, Head, Bioinformatics Unit.

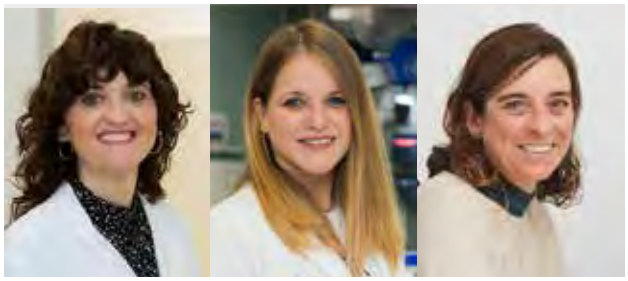
Expanding our Core Technologies Program, Lara Nonell has set up VHIO's Bioinformatics Unit (page 128) to implement state-of-the-art pipelines and develop tools for the analysis and visualization of different omics datasets, including publicly available datasets.



Susana Aguilar, Head, VHIOTECA Unit.

Our VHIOTECA Unit headed by Susana Aguilar (page 158), was created in 2021 to support investigators for the obtention, registration and preservation of biological samples other than tumoral tissue (plasma, feces, saliva) from cancer patients, and facilitate the use of these samples in research projects. This Unit also compliments VHIO's Molecular Prescreening Program (page 156), which continues to be coordinated by Susana, alongside Jenifer González, a Research Support Technician at VHIO's Cancer Genomics Group (PI: Ana Vivancos, page 130).

VHIO ACADEMY



Left to right: VHIO Academy Co-Chairs, Elena Élez, Clinical Investigator and Medical Oncologist, Gastrointestinal & Endocrine Tumors Group, Maria Abad, Principal Investigator, Cellular Plasticity & Cancer Group, and Clara Caminal, Head of the Academy.

Launched this year, the VHIO Academy manages, integrates and disseminates training opportunities in cancer research, educational initiatives for all VHIO personnel as well as programs tailored to patients and members of our community. Directed by Co-Chairs, Elena Élez and Maria Abad, and headed by Clara Caminal, its main objective is to provide a range of activities aimed at the career development of our faculty and foster a training environment of excellence.

Just some of these programs include institutional fellowships to attract and retain research talents in oncology, continuous learning opportunities such as complementary courses, workshops, seminars and educational events.

In 2021 our first institutional doctoral fellowships call included five four-year FPI-Severo Ochoa grants for national and international young researchers to carry out their doctoral thesis research at our Institute. Associated with our recent accreditation as a Severo Ochoa Center of Excellence (page 5), these

opportunities are within the framework of the EU *Pre-doctoral training contracts (FPI) 2021*, and supported by the Spanish Ministry of Science and Innovation.

Spin-off successes

Laura Soucek, Co-Director of VHIO's Preclinical & Translational Research Program, Principal Investigator of our Models of Cancer Therapies Group, an ICREA Research Professor, and Co-Founder & Chief Executive Officer of VHIO-born spin-off Peptomyc S.L.

Co-founded in 2014 by VHIO's Laura Soucek, CEO of the enterprise, and Marie-Eve Beaulieu, Chief Scientific Officer (CSO) of the company, VHIO-born spin-off Peptomyc has now received approval from the Spanish Agency of Medicines and Medical Devices for conducting clinical trials in Spain (AEMPS), to initiate the first-in-human Phase I/IIa clinical trial with its first compound – a disruptive Myc inhibitor, Omomyc (OMO-103).

Building on the proven preclinical efficacy and safety of the Omomyc cell-penetrating mini-protein in mouse models, and Peptomyc's company's successful development of anti-Myc peptides for the treatment of several tumor types, this latest milestone, celebrated in March 2021, represents a greatly anticipated leap into the clinical research setting, and an important step forward in becoming the first ever clinically viable and direct inhibitor of Myc – a protein implicated in the formation of most tumor types.

MYC has been considered an 'undruggable' cancer target for many years. Laura's group has previously shown that Myc blockade has an excellent therapeutic effect in several mouse models, with mild side effects that are well tolerated and reversible. Now that Laura and her Peptomyc team have received approval to initiate their early phase clinical trial, they can further progress in testing the safety and efficacy of this Omomyc-based therapy for the benefit of cancer patients.

Their Phase I/IIa Study to Evaluate Safety, PK and Efficacy of the MYC-Inhibitor OMO-103 in Solid Tumours - MYCure (NCT04808362), led by VHIO's Elena Garralda, Principal Investigator of our Early Clinical Drug Development Group (page 106), and Director of our Research Unit for Molecular Therapy of Cancer (UITM) –CaixaResearch (page 149), is now underway.

This study is an open label, two-part, FIH phase I/IIa dose-finding study designed to determine the safety, tolerability, PK, PD and proof-of-concept of OMO-103 in patients with advanced solid tumors:

Part I: Around 11 to 24 patients in total will be enrolled, covering 6 OMO-103 dose levels, with the primary objective of determining the safety and tolerability of OMO-103, and defining an appropriate dose for further evaluation in part IIa.

Part IIa: Dose expansion where at least 3 parallel groups of patients with advanced non-small cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC), and colorectal cancer (CRC), will be treated with the recommended phase II dose of OMO-103 to further characterize the safety, tolerability, PK, PD and anti-tumor activity of OMO-103. Approximately 18 patients will be enrolled in each of the 3 parallel groups of patients (NSCLC, PDAC, CRC).

Joan Seoane, Co-Director of VHIO's Preclinical & Translational Research Program, Principal Investigator of our Gene Expression & Cancer Group, an ICREA Research Professor, and Co-Founder of Mosaic Biomedicals.

VHIO's Joan Seoane and his Gene Expression & Cancer Group (page 86) previously established the role of leukemia inhibitor factor (LIF) in oncogenesis as a promoter of cancer progression by regulating the tumor microenvironment and inducing self-renewal in tumor-initiating cells. This research culminated in the development of MSC-1, a therapeutic LIF neutralizing antibody. MSC-1's transition to the clinic and translation into benefits for cancer patients promises an important addition to the current arsenal of powerful anti-cancer weaponry.

Joan co-founded VHIO-born spin-off Mosaic Biomedicals in 2012 for the design and development of this novel compound. In 2016, Mosaic merged with Northern Biologics Inc. (Toronto, Canada), and Northern-Mosaic announced the global acquisition of clinical-stage MSC-1 (now AZD0171) by MedImmune/AstraZeneca in 2020.

The phase II clinical trial of AZD0171 (in combination with durvalumab and chemotherapy) in solid tumors (NCT04999969) initiated patient recruitment in 2021.

At VHIO we are devoted to translating our research into improved clinical outcomes for the direct benefit of cancer patients. To do so, the creation of new spin-off companies is instrumental in developing potential new treatment avenues discovered in the laboratory, and further accelerating our drug discovery efforts.

Created in 2021, and officially launched as this scientific report goes to print, a new spin-off, ONIRIA Therapeutics (page 19), comprises three co-founding partners: VHIO, the *Universidad de Barcelona* (UB), and the ICREA Catalan Institution for Research, and is mainly funded by the "la Caixa" Foundation (page 30), *Asociación Española Contra el Cáncer* – AECC (Spanish Association Against Cancer), and the *Instituto de Salud Carlos III* – ISCIII (Institute of Health Carlos III):

Left to Right: Héctor G. Palmer, Principal Investigator, Stem Cells & Cancer Group, Co-Founder and Chief Scientific Officer, ONIRIA Therapeutics. Esther Riambau, Chief Executive Officer, ONIRIA Therapeutics.

By modulating cell dormancy to overcome cancer persistence, this spin-off will develop new anti-cancer armory to counteract resistance and prevent disease relapse in patients. Among various ongoing projects, ONIRIA Therapeutic's most advanced agent is a first-in-class molecule, ONR-001, that allosterically activates the TET2 master epigenetic enzyme, causing tumor cells to enter a dormant state and even die.

ONIRIA has already secured patent protection for its TET2 modulators and demonstrated efficacy in preclinical animal models by showing that ONR-001 promotes and sustains cancer cell dormancy and even causes cell death upon prolonged treatment. The investigators are now evaluating the efficacy of ONR-001 in several hematologic and solid tumor types, honing in on those cancers that are hypermethylated as a consequence of TET2 loss-of-function.

Héctor G. Palmer, Principal Investigator of VHIO's Stem Cells & Cancer Group (page 96), is ONIRIA's Chief Scientific Officer, and Esther Riambau, a venture builder, serves as the company's Chief Executive Officer. The founding team also includes Isabel Puig, a Senior Investigator of Héctor's group, as the company's Scientific Advisor for new therapeutic targets; Xavier Barril, an ICREA investigator at UB, and ONIRIA's Scientific Advisor in computational chemistry; Carlos Galdeano, a Serra Hunter Lecturer Professor and Head of the Protein Degradation Laboratory at UB, who is appointed as its Scientific Advisor in drug discovery.

Recognitions and prized research in 2021

Reflective of their exceptional contributions to cancer science, VHIO's Josep Tabernero, Enriqueta Felip & Javier Cortés featured among Clarivate's Highly Cited Researchers 2021

In addition to all our newly funded research lines and programs in 2021 (see pages 208-214), also driven through the backing received each year from our Institutional Supporters (pages 27-31), and public and private national, European, and International funding sources and entities (pages 194-196), VHIO investigators and teams have also been recognized through several prizes, accolades and recognitions.

Just some of which include the following:

VHIO's trio of Clarivate Highly Cited Researchers 2021. Left to Right: Josep Tabernero, Enriqueta Felip, and Javier Cortés.

For another consecutive year, our Director Josep Tabernero, Enriqueta Felip, Principal Investigator of VHIO's Thoracic Tumors & Head and Neck Cancer Group, and Javier Cortés, an Associate Translational Investigator at VHIO, featured among Clarivate's annual listing of some 6,600 Clarivate Highly Cited Researchers in 2021, curated by the Institute of for Scientific Information.

Josep Tabernero, also Head of the Medical Oncology Department, Vall d'Hebron University Hospital (HUVH), has for the sixth consecutive year been selected for significantly advancing cancer research under the category of Clinical Medicine that listed a total of 453 named leaders this year.

Joining Josep on the 2021 list of outstanding contributors to Clinical Medicine, is VHIO's Enriqueta Felip, Head of the Thoracic Cancer Unit at HUVH, President of the Spanish Society of Medical Oncology (SEOM), and Secretary of the International Association for the Study Lung Cancer (IASLC), who has been recognized for a third year running.

Included under the Cross-Field category last year, Javier Cortés, an Associate Translational Investigator at VHIO, featured as a Highly Cited Researcher 2021 under the same category.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE
European Society for Medical Oncology

In parallel with the publication of its 2025 Vision, the European Society for Medical Oncology (ESMO) finalized its 2021 composition of expert committees and working groups. These include several VHIO Investigators and Medical Oncologists who were (re) appointed as ESMO serving officers, faculty, committee and editorial board members.

Left to right: Maria Alsina, Judith Balmaña, Irene Braña, Javier Cortés, Elena Garralda, Teresa Macarulla, Ana Oaknin, César Serrano, Cristina Suárez, and Claudia Valverde.

In addition to their existing commitments including contributions at ESMO congresses and conferences as co-organizers, track chairs, expert speakers, discussants and panelists, newly appointed roles in 2021 include the following:

Maria Alsina, a Medical Oncologist and Clinical Investigator of VHIO's Gastrointestinal & Endocrine Tumors Group (PI: Teresa Macarulla), commenced her mandate as an ESMO Faculty Member, Gastrointestinal Tumours - Upper Digestive, and also serves on *Annals of Oncology*'s Editorial Board.

Judith Balmaña, Principal Investigator of VHIO's Hereditary Cancer Genetics Group, is now a Member of ESMO's Cancer Prevention Faculty. She also continues to serve as a Faculty Coordinator of ESMO's Cancer Genetics Group and collaborates in the compilation and updating of its Clinical Practice Guidelines.

Irene Braña, Clinical Investigator and Medical Oncologist of VHIO's Thoracic Tumors & Head and Neck Cancer Group (PI: Enriqueta Felip), is an appointed member of ESMO's Neck Cancer Faculty.

In addition to his membership of ESMO's Scientific Committee and chairmanship at several ESMO congresses meetings, and his appointment as Editorial Board Member of its top journal *Annals of Oncology*, Javier Cortés, Associate Translational Investigator at VHIO, also serves as Member of its Breast Cancer Faculty.

Elena Garralda, Principal Investigator of our Early Clinical Drug Development Group, and Director of our Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch, is now a Member of its Developmental Therapeutic Faculty, and continues to serve as a Core Member of ESMO's Women for Oncology Committee. Elena is also author of the *ESMO Perspectives* digital magazine's *On target* column. Further enriching the magazine's appeal and illuminating potentially controversial issues and emerging trends in cancer research and clinical practice, *On target* launched in 2021.

Teresa Macarulla, Principal Investigator, VHIO's Gastrointestinal & Endocrine Tumors Group, now serves as an Editorial Board Member of ESMO's flagship journal, *Annals of Oncology* .

Ana Oaknin, Principal Investigator of VHIO's Gynecological Malignancies Group is appointed as an ESMO Guidelines Committee Subject Editor, and also serves as a Gynecologic Cancer ESMO Faculty Member.

César Serrano, Principal Investigator of VHIO's Sarcoma Translational Research Group, and Claudia Valverde, Clinical Investigator and Medical Oncologist, VHIO's Genitourinary, CNS Tumors, Sarcoma & Cancer of Unknown Primary Site Group (PI: Joan Carles), are both Members of ESMO's Sarcoma Faculty.

Cristina Suárez, Medical Oncologist and Clinical Investigator, VHIO's Genitourinary, CNS Tumors & Cancer of Unknown Primary Site Group (PI: Joan Carles) has been appointed as a Member of ESMO's Genitourinary Tumors, Non-Prostate Faculty.

Expanding their commitments to ESMO, they join previously appointed VHIO faculty who are current members of ESMO Committees, Task Forces, and Editorial Boards, including our Director, Josep Tabernero, who is Past-President of ESMO (2018-2019), Member the Magnitude of Clinical Benefit Scale Working Group, Core Committee Member of ESMO's European Policy Committee, and an Associate Editor of *Annals of Oncology* and ESMO Open.

SEOM
Sociedad Española de Oncología Médica

Enriqueta Felip, Principal Investigator, VHIO's Thoracic Tumors & Head and Neck Cancer Group.

Having served as Vice-President of the Spanish Society of Medical Oncology's (SEOM) throughout its previous two-year term of governance, VHIO's Enriqueta Felip has now taken the reins as SEOM's new President (2021-2023). Officially announced at its Annual virtual SEOM Congress 2021, she continues to serve alongside its Board of Directors, expert committees,

working groups and supporters, to respond to the rapidly changing needs of its membership and further establish SEOM as a leading professional society in medical oncology.

Efforts led in tandem by Enriqueta and SEOM's Vice-President, César Rodríguez, Medical Oncologist, the Salamanca University Hospital, will also focus on promoting the multidisciplinary approach to the diagnosis and treatment of cancer, forging and nurturing key alliances with other professional societies, including the European Society for Medical Oncology (ESMO), and further strengthening SEOM's presence on the international oncology stage.

Also officially announced and Annual virtual Congress 2021, César Serrano, Principal Investigator of VHIO's Sarcoma Translational Research Group, now serves as a SEOM Board Member. Dedicated to identifying and responding to the needs of young oncologists in Spain, Elena Élez, Medical Oncologist and a Clinical Investigator of VHIO's Gastrointestinal & Endocrine Tumors Group, continues to coordinate the +MIR SEOM Residents and Young Oncologists Committee. Elena's devotion to nurturing and growing the careers of young investigators and medical oncologist is also reflected by her co-leadership of VHIO's recently established Academy (page 40).

Institut Català de la Salut

The 2020 and 2021 recpients of the prestigious ICS Research Awards.

Celebrated during the *Institut Català de la Salut* (Catalan Institute of Health - ICS) 2021 Annual Conference on research developments at ICS and around the world, the recipients of the 2020-2021 ICS Research Awards included our Director, Josep Tabernero, and Garazi Serna, a PhD Student of VHIO's Molecular Oncology Group (PI: Paolo Nuciforo, page 132). Due to the safety issues posed by COVID-19, in-person attendance was naturally limited to a minimum, and this year's meeting also included the 2020 ICS Research Award winners who were not presented with these prestigious recognitions last year due to the pandemic.

Josep Tabernero, Head of the Medical Oncology Department at the Vall d'Hebron University Hospital (HUVH), received the ICS 2020 Lifetime Achievement Award for Research in Hospitals of the Catalan Institute of Health. This accolade recognizes his outstanding contributions to advancing precision medicine in oncology, especially in colorectal cancer.

Under the predoctoral category, the 2021 ICS prize for the best research paper in Health Sciences was awarded jointly to VHIO's Garazi Serna and Juan Carrillo, a Student at the Childhood Liver Oncology Group, led by Carol Armengol, the Germans Trias i Pujol Institute, (IGTP).

Garazi Serna, a PhD Student of VHIO's Molecular Oncology Group (PI: Paolo Nuciforo).

Garazi Serna's awarded research*, carried out in collaboration with other VHIO investigators, advanced insights into the role of *Fusobacterium nucleatum*, an important pathogenic gut bacterium associated with colorectal cancer, in locally advanced rectal cancer (LARC). By quantifying *Fusobacterium nucleatum* in untreated and post-neoadjuvant chemoradiotherapy (nCRT) samples from LARC patients, the investigators sought to establish its association with response to therapy and survival. First authored by Garazi Serna, this study showed that *F. nucleatum* persistence post-nCRT is associated with high relapse rates, potentially linked to suppression of immune cytotoxicity. These findings could help to more precisely identify a higher risk of disease recurrence or metastasis in patients who do not show a complete response to treatment, and ultimately support clinical decision-making.

*Serna G, Ruiz-Pace F, Hernando J, Alonso L, Fasani R, Landolfi S, Comas R, Jimenez J, Elez E, Bullman S, Tabernero J, Capdevila J, Dienstmann R, Nuciforo P. *Fusobacterium nucleatum* persistence and risk of recurrence after preoperative treatment in locally advanced rectal cancer. *Ann Oncol*. 2020 Oct;31(10):1366-1375.

eco Fundación para la Excelencia y la Calidad de la Oncología

VHIO was prized with the I *Premio José Baselga a la Innovación Traslacional en Oncología* at the 9th annual edition of the *Fundación para la Excelencia y la Calidad de la Oncología* ECO Awards.

At the 9th annual edition of the *Fundación para la Excelencia y la Calidad de la Oncología* - ECO Awards (Foundation for Excellence and Quality in Oncology), celebrated at the Royal Academy of Medicine, Madrid

(Spain), VHIO received ECO's first *Premio José Baselga a la Innovación Traslacional en Oncología* (José Baselga Prize for Translational Innovation in Oncology). This prize, honoring the tremendous legacy of our founding and first director, José Baselga, who very sadly died at the age of 61 on 21 March 2021 (see pages 6 and 21), recognizes excellence in translational cancer research and precision oncology.

In his acceptance speech, broadcast live during the ceremony, our Director, Josep Tabernero, thanked the ECO Foundation for establishing this special Award as a tribute to José Baselga's extraordinary accomplishments and illustrious career. He also dedicated the prize to all VHIO Faculty who strive to honor José's legacy by applying the same dedication, determination, collaborative spirit and fight in solving cancer sooner.

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fundación fero
Investigando por un futuro sin cáncer

One of our Patrons and Institutional Supporters, the *Fundación FERO* (page 29) – whose founder and late Honorary President is José Baselga who tragically passed away this year (see our Director's Foreword, pages 6 and 21), announced its 2021 Annual Award winners back in May.

These prestigious accolades include FERO's Awards for Translational Research, now in their 21st edition in 2021, and the third FERO-ghd Award for breast cancer research. Most recently, as this scientific report goes to print, FERO announced its Dr. Baselga Award to further promote translational research in oncology. This prize, honoring the extraordinary life and scientific legacy of José Baselga, VHIO's founder and first director, will spur translational research of excellence carried out at research institutes in Spain by investigators of any nationality.

VHIO-led projects prized by FERO in 2021

In addition to FERO's championing of our Advanced Molecular Diagnostics Program – DIAMAV (page 138), and several other VHIO investigators and groups, the following projects will be fueled by FERO's support:

Nicolas Herranz, Senior Investigator of our Prostate Cancer Translational Research.

Nicolas Herranz, Senior Investigator of our Prostate Cancer Translational Research directed by Joaquin Mateo (page 92), was awarded by FERO this year for his project entitled, *Exploiting therapy-induced senescence in a synthetic lethal approach to treat advanced prostate cancer.* Thanks to this support received through this Award, Nicolas will pursue research aimed at identifying new therapies or drug combinations that neutralize senescent cells and prevent cancer resistance in prostate cancer.

Specifically, his project will focus on the modulation of prostate cancer evolution by harnessing the emergence of a senescence phenotype (via treatment with standard-of-care or targeted therapies) to then target with senolytic drugs under a synthetic susceptibility approach.

He will seek to characterize therapy-induced senescence (TIS) phenotype in response to androgen receptor signalling inhibition or targeted drugs in prostate cancer cell lines; identify senolytic drugs highly selective for TIS prostate cancer cells by screening customized drug libraries; validate the efficacy of the identified drug combinations in patient-derived xenograft (PDXs) models; evaluate TIS in patient biopsies collected on response to therapy; and pioneer the characterization of TIS signatures in PC by combining transcriptomic data of PC cell lines and patient samples.

This FERO Award was supported by the Ramón Areces Foundation. Due to the safety issues posed by the COVID-19 pandemic, FERO's XXI Annual Awards were officially announced via a live streamed special session.

Two additional VHIO projects received funding from the FERO Foundation in 2021:

Josep Tabernero, VHIO's Director and Head of the Medical Oncology Department, Vall d'Hebron University Hospital (HUVH).

Led by Josep Tabernero, a newly -funded project on *New technologies for the identification of markers of sensitivity and resistance to targeted therapies in metastatic colorectal cancer*, will seek out de novo and acquired sensitivity/resistance mechanisms in patients with metastatic colorectal cancer harboring a BRAF mutation. Aimed at developing new therapeutic strategies to more effectively treat this disease, this project will strive to improve cancer treatment selection in this patient population.

The investigators will also assess the value of BRAF V600E Mutant Allele Frequency (MAF), in circulating cell-free DNA (cfDNA) as a biomarker to predict treatment response, as well as a potential tool for the selection of the treatment.

Joan Seoane, Co-Director of VHIO's Preclinical & Translational Research Program, Principal Investigator of our Gene Expression & Cancer Group, an ICREA Research Professor.

Joan Seoane has received funding for his project entitled: *Liquid biopsy in pediatric brain cancer: circulating DNA analysis in cerebrospinal fluid in medulloblastoma pediatric patients with medulloblastoma to help in the detection, characterization and treatment of brain tumor recurrence.*

Focused on circulating DNA in cerebrospinal fluid in pediatric patients with medulloblastoma suspected of relapse, research could help to detect disease relapse earlier, differentiate recurrence from false progression, and facilitate the design of more effective therapies to improve patient outcomes.

Analyzing cerebrospinal fluid and tumor DNA in blood is a much less invasive and sequential way of studying these tumors, and allows for the more precise tracking of disease to better guide molecular diagnosis, prognosis and, above all, treatment decision making.

Joan and his team (page 86), will study 25 pediatric patients with progression by analyzing circulating DNA in cerebrospinal fluid. This research is based on the close monitoring of patients to detect possible disease relapse which is the main cause of mortality in these patients due to the complexities associated with obtaining tumor tissue samples.

"la Caixa" Foundation

In addition to its support of many other VHIO programs and initiatives, including our Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch (page 149), and our CaixaResearch Advanced Oncology Research Program (page 139), four new VHIO projects received funding in 2021 from one of our Institutional Supporters and patrons, the "la Caixa" Foundation (page 30):

Elena Élez, Medical Oncologist and Clinical Investigator of our Gastrointestinal & Endocrine Tumors Group.

First, thanks to an awarded Health Research "la Caixa" Project, Elena Élez will lead the PROMISE study: *BioPrinted hydROgel MicrofluIdicS to mimic patient-specific tumor mEtastatic*. Coordinated by the *Institut de Bioenginyeria de Catalunya* – IBEC (IBEC Institute for Bioengineering of Catalonia), this project will apply 3D bioprinting technology aimed at improving the survival of cancer patients.

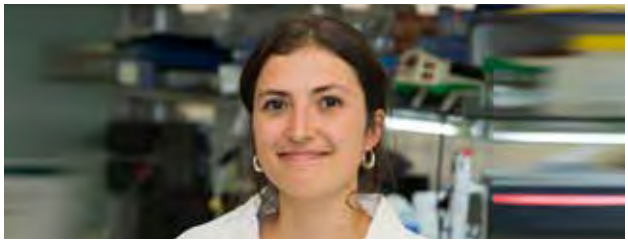
3D bioprinting techniques generate three-dimensional cell models that replicate human physiology to test new therapeutic strategies in the laboratory. These models can effectively mimic a patient's specific tumor and tumor microenvironment. By combining 3D bioprinting with advanced liquid biopsy technology in an organ-on-a-chip system, this novel approach will provide physicians with new tools to better understand and monitor disease evolution in patients with metastatic colorectal cancer, and improve survival rates.

Supported by the "la Caixa" INPhINIT Retaining and INPhINIT Incoming Fellowship Programs, a trio of predoctoral projects have also been granted this year.

INPhINIT Retaining:

Olivia Prior, PhD Student, VHIO's Radiomics Group.

Under the mentorship of Raquel Perez-Lopez, Principal Investigator of our Radiomics Group (page 122), Olivia Prior's project, *Deciphering spatial and temporal cancer heterogeneity by applying machine learning and precision imaging*, aims to accurately characterize the spatial-temporal landscape of intratumor heterogeneity by 3-dimensional (3D) computed tomography (CT) and magnetic resonance imaging (MRI) radiomics. Olivia will also integrate radiomics with molecular data from tumor samples and circulating tumor DNA, through the application of multi-omics. This approach may improve tumor characterization, response assessment and help to more precisely guide treatment selection.

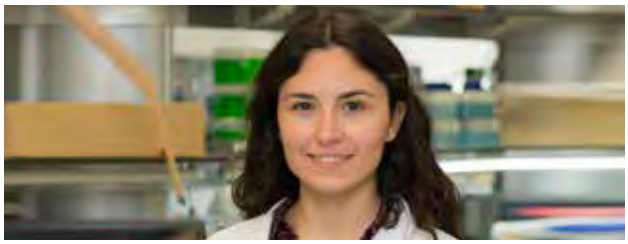


Marion Martínez, Graduate Student, VHIO's Cellular Plasticity & Cancer Group.

Mentored by Maria Abad, Principal Investigator of VHIO's Cellular Plasticity & Cancer Group (page 80), Marion Martínez will carry out her research project entitled, *OncoPeptides: mining the secreted microproteome for novel regulators of PDAC biology*, which is based on the hypothesis that exosome-packaged microproteins

are essential messengers for tumor communication both within the primary tumor site and distantly within the pre-metastatic niche, and thus regulate tumor progression and cancer cell spread. Focused on pancreatic adenocarcinoma (PDAC), Marion will seek to mine its exosome-secreted microproteome for novel regulators of cancer growth and metastasis.

INPhINIT Incoming:



Ariadna Grinyó, Graduate Student, VHIO's Growth Factors Group.

Under the mentorship of Joaquín Arribas, Principal Investigator of our Growth Factors Group (page 88), Ariadna Grinyó's research project, *Armoring a p95HER2 CAR T for the controlled secretion of antitumor agents upon T-cell activation*, will build on previous research of this group that led to the development of a second-generation CAR T against p95HER2, a tumor-specific antigen expressed in around 30% of HER2+ tumors.

Results demonstrated its high effectivity and specificity *in vivo* against p95HER2 positive cell line-derived tumors, but limited antitumoral effect in patient-derived xenograft (PDXs) models (unpublished). In addition, the general failure of second-generation CAR T s against solid tumors in the clinic illuminates the need to improve the design of therapies. Ariadna will focus on the design and testing of an armored p95HER2 CAR T for the controlled secretion of antitumor agents upon T-cell activation.

asociación española contra el cáncer

The *Asociación Española Contra el Cáncer* – AECC (Spanish Association against Cancer), is a longstanding supporter of several VHIO groups and researchers. We take this opportunity to salute and applaud AECC's invaluable contribution to promoting cancer discovery and translational research of excellence, as well as the essential backing that it provides to countless investigators and teams across Spain and beyond.

Additional VHIO researchers were awarded this year across four of AECC's many pioneering programs and initiatives. In 2021, VHIO's Maria Abad, Joaquin Mateo, and Raquel Perez-Lopez, received funding as an AECC Coordinated Group, Carolina Ortiz as an AECC Junior Clinician, Isabel Puig as an AECC Researcher, and Enrique Javier Arenas as an AECC Postdoc.

Left to right: María Abad, PI of VHIO's Cellular Plasticity & Cancer Group, Joaquin Mateo, PI of our Prostate Cancer Translational Research Group, and Raquel Perez-Lopez, PI of VHIO's Radiomics Group.

Awarded under the category of AECC Coordinated Group – National Consortium, María Abad, Joaquin Mateo, and Raquel Perez-Lopez, Principal Investigators of VHIO's Cellular Plasticity & Cancer (page 80), Prostate Cancer Translational Research (page 92), and Radiomics (page 122) Groups, respectively, will lead a project entitled, *Tumoral senescence induced by anti-cancer therapies constitutes a novel prognostic biomarker and a therapeutic target*.

This consortium comprises experts in preclinical, translational and clinical research to investigate therapy-induced senescence (TIS) as a new prognostic biomarker and therapeutic target, and develop novel therapeutic strategies and non-invasive diagnostic tools. This project focuses on pancreatic and prostate cancer; two tumor types with robust preclinical evidence of therapy-induced senescence, and in critical need for new, more effective therapeutic options.

Experts in cellular senescence, diagnostic medical imaging, and the development of new therapies, will work together to develop non-invasive imaging methods to detect senescence in tumors, and identify new targets and, eventually, new compounds or combinations that neutralize senescent cells to avoid their undesirable effects on residual tumors post-therapy. In short, the investigators will strive to drive the concept of cellular senescence closer to the clinic.

Carolina Ortiz, Clinical Investigator and Medical Oncologist, VHIO's Breast Cancer Group.

Awarded this year as an AECC Junior Clinician, Carolina Ortiz will investigate *Circulating tumor DNA (ctDNA) in breast milk for the early detection of pregnancy pregnancy-associated breast cancer*, led by Cristina Saura, Principal Investigator of our Breast Cancer Group (page 104).

Based on their previous studies showing that ctDNA could be isolated from breast milk in 10 patients with pregnancy-associated breast cancer, including patients with early-stage disease, and that tumor mutations were also present in ctDNA isolated from breast milk, the researchers propose that the detection of ctDNA

in breast milk can be used as a new non-invasive biomarker for the early diagnosis of breast cancer associated with pregnancy.

The main objectives of this new study are to quantify the ctDNA and the mutant allelic fraction in breast milk, and assess the sensitivity, specificity and precision of the detection of ctDNA in breast milk and blood. Directed by Cristina Saura, Carolina Ortiz will co-conduct a case-control study that includes patients with pregnancy-associated breast cancer (cases) and pregnant patients at a higher risk of developing breast cancer. For the detection of ctDNA, the researchers will combine state-of-the-art sequencing techniques and panels of specific *BRCA* genes. Mutations detected in breast milk will be compared with blood and tumor samples from the same patients.

Isabel Puig, Post-Doctoral Fellow, VHIO's Stem Cells & Cancer Group.

Isabel Puig was awarded under the category of AECC Investigator, for a project aimed at *Deciphering the molecular mechanisms of tumor cell resistance to cancer therapies,* directed by Héctor G. Palmer, Principal Investigator of VHIO's Stem Cells & Cancer Group (page 96).

The resistance of tumor cells to anti-cancer medicines represents a major challenge in more successfully combating cancer. This therapeutic failure is due to the multiple strategies that cancer cells adopt to dodge therapeutic blows. Disrupting multiple resistance strategies at once has emerged as a promising approach toward successfully eradicating these resistant malignant cells as major drivers of disease relapse.

This group has previously identified a new actor that can simultaneously regulate several of these resistance strategies. Isabel Puig's awarded project will seek to develop a novel therapy to more effectively thwart disease recurrence, and advance deeper insights into the molecular mechanisms that are implicated in tumor cell resistance to cancer therapies.

Enrique Javier Arenas, Post-Doctoral Fellow, VHIO's Growth Factors Group.

Selected under the AECC Postdoc funding category, VHIO's Enrique Javier Arenas will pursue research focused on *Overcoming cancer immunotherapy resistance: new combinatorial strategies to improve immunotherapies*, directed by Joaquín Arribas, Principal Investigator of our Growth Factors Group (page 88).

This group's previous studies have established models of resistance to T-cell based therapies and identified a novel mechanism of resistance. They evidenced that disruption in interferon-gamma signaling in cancer cells leads to intrinsic resistance to destruction by fully active, correctly engaged, T lymphocytes.

Based on these findings, this project aims at identifying novel strategies that could be rapidly applied in the clinic, further exploring the mechanistic biology of resistant cells and the interplay with interferon-gamma response and resistance to immunotherapy.

SEOM
Sociedad Española
de Oncología Médica

The 2021 *Sociedad Española de Oncología Médica* (SEOM) Award Ceremony.

In celebration of this year's awardees who were granted by the *Sociedad Española de Oncología Médica* – SEOM (Spanish Association of Medical Oncology), the in-person Award Ceremony took place but with a limited attendance due to the safety issues posed by the COVID-19 pandemic. Announced on the occasion of SEOM's virtual Annual Congress – SEOM2021, the 44 prized projects included a duo of VHIO proposals aimed at improving outcomes for breast cancer patients.

Left to right: VHIO's Cristina Saura and Mafalda Oliveira, recipients of SEOM Awards in 2021.

Cristina Saura, Principal Investigator of our Breast Cancer Group (page 104), was presented with the SEOM-Daiichi Sankyo Award for her project on *ctDNA in breast milk for the early detection of pregnancy-associated breast cancer*.

These patients generally have a poor prognosis since they are usually diagnosed at late-stage. The physiological changes that occur in the breast make it difficult to palpate to identify nodules. Furthermore, during pregnancy cancer is not usually actively searched for.

After analyzing samples of breast milk from patients who had been diagnosed with breast cancer, Cristina's team previously discovered the presence of circulating tumor DNA (ctDNA). Their hypothesis is that tumors in their earliest stages are very small and have not released enough ctDNA into the bloodstream. But, due to the proximity of the breast tissue to the tumor, there is a high amount ctDNA in breast milk for the early detection of pregnancy-associated breast cancer, which would improve the prognosis of these patients.

Reflective of the novelty of this approach, this VHIO-led research has also been awarded this year by the *Asociación Española Contra el Cáncer* – AECC (Spanish Association against Cancer), and also previously received funding through the joint *Fundación FERO* (FERO Foundation)-ghd annual Award in 2020.

Mafalda Oliveira, a Clinical Investigator and Medical Oncologist of Cristina Suara's Breast Cancer Group, received the SEOM – FECMA/MASET Award for research *Exploring the impact of breast and gut microbiome on breast cancer prognosis and response to immune checkpoint inhibitors*. This project is based on earlier research led by other VHIO groups that evidenced how the intestinal microbiota plays an important role in colorectal cancer.

Considering these results, research led by Mafalda will seek to establish if the mammary microbiota also plays a role in breast cancer. The investigators will study how, together with the gut microbiome, it can influence the response to treatment with immune checkpoint inhibitors (ICIs), considering that the microbiota plays essential roles in the immune response.

VHIO's Director, Josep Tabernero, receiving a 2021 Trifermed Award for Social Impact in Healthcare.

Trifermed Annual Awards recognize individuals and organizations that make significant contributions to improving the quality of healthcare in our society. Prized under the *Impulsor* category, our Director, Josep Tabernero, was recognized in 2021 for his outstanding achievements in advancing precision medicine in oncology and improving outcomes for cancer patients. This year's Trifermed Award Ceremony took place in person, with a limited attendance to comply with COVID-19 safety measures and regulations.

In his acceptance speech, Josep paid tribute to people who have lost their loved ones to COVID-19, as well as all healthcare professionals who worked tirelessly to overcome the major challenges that it posed throughout the pandemic waves. He dedicated this Award to all oncology professionals at the Vall d'Hebron University Hospital (HUVH), and VHIO's multidisciplinary research teams. He also gratefully thanked several other leaders within the field, including the eminent cancer researcher and trailblazing medical oncologist, José Baselga, VHIO's founder and first director, who very sadly died last year at the age of 61 (pages 6 and 21).

Fundación Merck Salud

Broadcast live during Merck's Research Awards Ceremony, our Director, Josep Tabernero, dedicated this recognition to all healthcare professionals in oncology at the Vall d'Hebron University Hospital (HUVH), as well as VHIO's researchers and clinical investigators.

Marking the 30th Anniversary of the *Fundación Merck Salud* (Merck Health Foundation), its annual *Ayudas Merck de Investigación* 2021 (Merck Research Awards) were presented at the Teatro Real in Madrid (Spain). These recognitions support pioneering research projects spanning endocrinology and/or cardiometabolic risk, rare diseases, multiple sclerosis, fertility, immune-oncology, and personalized precision medicine.

This year's Award Ceremony, celebrated in person albeit with a reduced participation due to the safety issues posed by COVID-19, also recognized five leading figures in Spanish healthcare and institutions of excellence including Josep Tabernero, VHIO's Director and Head of the Medical Oncology Department at the Vall d'Hebron University Hospital (HUVH).

Josep dedicated this important recognition to all healthcare professionals and teams who provide cancer patients with the very best treatment and care, as well as VHIO researchers who strive to improve patient outcomes by advancing cancer discovery and clinical researh. Most importantly, he recognized the generosity of patients and thanked them for their amazing support of - and belief in - our cancer research.

Fundación Pfizer

Laura Escudero, a Post-Doctoral Fellow of Joan Seoane's Gene Expression & Cancer Group.

Laura Escudero, a Post-Doctoral Fellow of VHIO's Gene Expression & Cancer Group (page 86), received a Scientific Innovation Award for Young Researchers from the *Fundación Pfizer* (Pfizer Foundation), for research focused on cerebrospinal fluid as liquid biopsy for the precise characterization and policing of medulloblastoma.

Building on previous research led by Joan Seoane, Laura first authored a proof-of-concept study* showing that the analysis of cerebrospinal fluid (CSF) circulating tumor DNA (ctDNA), allows for the more precise characterization, molecular diagnosis (including subtyping and risk stratification), and real time tracking of medulloblastoma – the most prevalent malignant brain tumor in childhood.

Carried out in collaboration with other VHIO groups and experts at the Vall d'Hebron University Hospital, the investigators showed that ctDNA from cerebrospinal fluid reveals genomic alterations during disease evolution (even prior to surgery) to more precisely guide treatment decision making. This approach also translates in less invasive sampling and better identification and characterization of disease relapse.

In recognition of this pioneering research, this *Fundación Pfizer* Prize will further support Laura Escudero to pursue her research and develop her career.

* Escudero L, Llort A, Arias A, Diaz-Navarro A, Martínez-Ricarte F, Rubio-Perez C, Mayor R, Caratù G, Martínez-Sáez E, Vázquez-Méndez É, Lesende-Rodríguez I, Hladun R, Gros L, Ramón Y Cajal S, Poca MA, Puente XS, Sahuquillo J, Gallego S, Seoane J. Circulating tumour DNA from the cerebrospinal fluid allows the characterisation and monitoring of medulloblastoma. *Nat Commun*. 2020 Oct 27;11(1):5376.

Left to right: Violeta Serra, VHIO's Violeta Serra, Principal Investigator of our Experimental Therapeutics Group. Violeta Serra presenting her prized Metapremio research project in the Auditorium of our CELLEX Building.

Research directed by VHIO's Violeta Serra, Principal Investigator of our Experimental Therapeutics Group (page 84), was prized with a 2021 *Metapremio* from the *Asociación de Cáncer de Mama Metastásico* (Spanish Association against Metastatic Breast Cancer) for a research project aimed at identifying biomarkers of response to a novel antibody-drug conjugate (ADC), using breast cancer patient-derived xenograft models (PDXs).

Violeta's research will further build on the first results of a window of opportunity trial, SOLTI-1805 TOT-HER3 (page 15), co-led by VHIO's Mafalda Oliveira, Clinical Investigator and Medical Oncologist of Cristina Saura's Breast Cancer Group. TOT-HER3 is the first study to evaluate the HER3-directed antibody-drug conjugate (ADC), patritumab deruxtecan, in patients with early hormone-sensitive HR-positive/HER2-negative breast cancer.

Aimed at identifying biomarkers of treatment response to better predict which patients would be most likely to benefit from this ADC, Violeta and her team will build on their preclinical studies that complemented the biomarker findings of TOT-HER3 using metastatic breast cancer patient-derived xenografts (PDXs) models. The investigators will now evaluate the activity of this ADC in clinically relevant PDX models, derived from patients who progressed on CDK4/6 or PARP inhibitors (PARPi). They will also aim to dissect its mode of action to help identify biomarkers for the selection of patients in clinical practice.

The Spanish Association against Metastatic Breast Cancer was created thanks to the dedication of Chiara Giorgetti, a former patient of VHIO's Cristina Saura, alongside other patients with metastatic breast cancer and their friends and families. When Chiara sadly passed away from metastatic breast cancer in December 2018, this Association established the Chiara Giorgetti Award in 2019, and later, the *Metapremios*, in her memory.

Joaquin Mateo, Principal Investigator, VHIO's Prostate Cancer Translational Research Group.

In 2021, Joaquin Mateo, Principal Investigator of our Prostate Cancer Translational Research Group (page 92), was announced as one of the six recipients of a *Fundación Cris contra el Cáncer* (CRIS Foundation against cancer) Clinical Talent Program Award. Aimed at

providing support and incentives for clinical researchers to develop their careers in Spain, this five-year funding program will enable Joaquin to develop and advance his research lines carried out at VHIO and the Vall d'Hebron University Hospital (page 36).

This funding will support research into *Prostate cancer genomic evolution and signatures of DNA damage repair deficiencies*. Building on his group's previous studies aimed at optimizing the use of PARP inhibitors (PARPi) in metastatic prostate cancer (mPC), Joaquin and his team will seek to further refine the optimal biomarker suite for patient stratification toward potentially expanding the target population who can benefit from these promising anti-cancer medicines.

At the genomic level, the investigators will study hundreds of samples of prostate tumors at different stages. They will assess how and when alterations appear that render these tumors vulnerable to PARPi. These efforts will help to more precisely identify those patients who would be most likely to respond to these treatments, and better guide clinical decision making.

Left to right: Francisco Javier Ros, Clinical Investigator and Medical Oncologist, VHIO's Gastrointestinal & Endocrine Tumors Group. Francisco upon receiving his Fundación Mutal Médica Award in 2021.

Now in their 31st annual edition, the *Fundación Mutal Médica* (Mutual Médica Foundation) Awards recognize the important contributions made by physicians, residents and students in developing innovative therapies, advancing diagnostic tools and platforms, and advancing the treatment and care of patients.

Under the mentorship of Elena Élez, Francisco Javier Ros, Clinical Investigator and Medical Oncologist of our Gastrointestinal & Endocrine Tumors Group (page 110), was awarded for a project entitled, *Identification and validation of response and resistance mechanisms to targeted therapies for BRAFV600E mutated metastatic colorectal cancer*.

Over recent years, research has greatly advanced insights into the molecular biology of colorectal cancer. While more effective, targeted treatments have improved outcomes for certain patients, a significant number of patients do not respond to treatment or whose disease rapidly progresses. In particular, patients with a *BRAFV600E* mutation, present in 8-10% of metastatic colorectal cancer (mCRC), have a poor prognosis with limited treatment options.

Carried out in collaboration with Héctor G. Palmer's Stem Cells & Cancer Group (page 96), at VHIO, results in preclinical models revealed that tissue remodelling and mucinous differentiation contribute to the acquisition of resistance to BRAF inhibitor-based therapies. Our investigators will now seek to unveil new vulnerabilities in these tumors, and develop models to test the efficacy of new treatment combinations. They will also evaluate new predictive biomarkers of response to treatment to help better guide the optimal selection of therapy matched to molecular specificities of patients with BRAF V600E-mutated mCRC.

In addition to the examples highlighted here – featuring just some of the many newly funded research lines, initiatives, and programs in 2021 – we invite you to browse our comprehensive listing under *New Funding and Projects in 2021* (pages 208-214), as well as view a complete listing of our Institutional Supporters, public and private national, European, and International funding sources and entities this year (pages 194-196).

To discover more about our dedicated Patrons, the *Generalitat de Catalunya*, *Fundació Privada CELLEX*, *Fundación FERO*, "la Caixa" Foundation, and the *Fundación BBVA*, as well as our Institutional Research Programs, please refer to pages 27-31, and 138-141, respectively.

VHIO-organized events: sharing the latest advances & 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.

Launched back in 2019, our VHIO – CaixaResearch 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.

These sessions take place in VHIO's state-of-the-art CELLEX Building Auditorium, although the majority in 2021, were hosted virtually due to the COVID-19 pandemic. Each seminar typically consists of a 30-45 minute talk followed by a Q&A round with the audience. Chaired be each respective VHIO host, these expert talks are usually scheduled to take place on Fridays.

Scientific co-Chairs (left to right): María Abad, PI, Cellular Plasticity & Cancer Group, Laura Soucek, PI, Models of Cancer Therapies Group, and Elena Élez, Medical Oncologist and Clinical Investigator, Gastrointestinal & Endocrine Tumors Group. Scientific Coordinator: Josep Maria Miquel (far right), Senior Project Manager, VHIO's Scientific Management Area.

In 2021, a total of 23 VHIO - CaixaResearch Scientific Seminars took place as follows:

Speaker: Arkaitz Carracedo, Principal Investigator of Cancer Cell Signaling & Metabolism Lab, CICbioGUNE, Bilbao, Spain

Talk title: Metabolic Intricacies of Prostate Cancer

Date: 15 January

VHIO Host: Maria Abad, PI, Cellular Plasticity & Cancer Group

Speaker: Chi Van Dang, Scientific Director, Ludwig Institute for Cancer Research. Professor, The Wistar Institute, Pennsylvania, USA

Talk title: MYC, Metabolism & the Circadian Clock in Tumorigenesis

Date: 05 February

VHIO Host: Laura Soucek, PI, Models of Cancer Therapies Group

Speaker: Elisa Espinet, German Cancer Research Center | DKFZ. Division of Stem Cells and Cancer, Heidelberg, Germany

Talk title: Cellular Cross-Talks, Heterogeneity and Cell of Origin of Human PDAC: Insights from the Transcriptome & Methylome of Isolated Cell Populations

Date: 05 March

VHIO Host: Maria Abad, PI, Cellular Plasticity & Cancer Group

Speaker: Benjamin Neel, Professor of Medicine, NYU Grossman School of Medicine, Director, Laura and Isaac Perlmutter Cancer Center, NY, USA

Talk title: New Combination Approaches to Targeting Cancer

Date: 19 March

Speaker: María Casanova-Acebes, Junior Group Leader at CNIO, Madrid, Spain

Talk title: Macrophage Determinants for the Initiation & Progression of Non-Small-Cell Lung Carcinoma

Date: 09 April

VHIO Host: Maria Abad, PI, Cellular Plasticity & Cancer Group

Speaker: Umberto Malapelle, Chief Supervisor, Predictive Molecular Pathology Laboratory, Department of Public Health, University Federico II of Naples, Italy

Talk title: Next Generation Sequencing in Predictive Molecular Pathology

Date: 23 April

VHIO Host: Paolo Nuciforo, PI, Molecular Oncology Group

Speaker: Geoff Lindeman, Joint Head, Cancer Biology & Stem Cells Division, Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

Talk title: Searching for Novel Therapeutic Targets for the Treatment & Prevention of Breast Cancer

Date: 07 May

VHIO Host: Judith Balmaña, PI, Hereditary Cancer Genetics Group

Special Session: VHIO Meet the Editors with Miguel Foronda, Associate Editor, Nature Cancer

Talk title: The Ins & Outs of *Nature Cancer*

Date: 20 May

VHIO co-Hosts: Joan Seoane, PI, Gene Expression & Cancer, and Maria Abad, PI, Cellular Plasticity & Cancer Group

Speaker: Yardena Samuels, Head, EKARD Institute for Cancer Diagnosis Research. Department of Molecular Cell Biology. Head, Weizmann-Brazil Tumor Bank, Rehovot, Israel

Talk title: Towards Deciphering the Immuno-Genomic Landscape in Melanoma

Date: 21 May

VHIO Host: Alena Gros, PI, Tumor Immunology & Immunotherapy Group

Speaker: Raquel Sánchez, Head, Service of Neurology, Hospital Clínic de Barcelona. Alzheimer's disease & other cognitive disorders group. IDIBAPS, University of Barcelona, Spain

Talk title: Creutzfeldt-Jakob Disease & Other Prion Diseases

Date: 28 May

VHIO Host: Laura Soucek, PI, Models of Cancer Therapies Group

Speaker: Mercedes Robledo, Group Leader, Hereditary Endocrine Cancer Group, Spanish National Cancer Research Center (CNIO), Madrid, Spain

Talk title: Genetics & Genomics of Pheochromocytomas. Searching for its Achilles Heel

Date: 04 June

VHIO Host: Judith Balmaña, PI, Hereditary Cancer Genetics Group

Speaker: Jean Yves Masson, Full Professor, Laval University Cancer Research Center, Quebec, Canada

Talk title: Functional Analysis of Missense Mutations in Homologous Recombination Proteins

Date: 18 June

VHIO Host: Sara Gutiérrez-Enríquez, Senior Investigator, Hereditary Cancer Genetics Group

Speaker: Toni Celiá-Terrassa, Group Leader, Cancer Stem Cells & Metastasis Dynamics Lab, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain

Talk title: Stem Cell Properties in Breast Cancer Metastasis

Date: 02 July

VHIO Host: Maria Abad, PI, Cellular Plasticity & Cancer Group

Speaker: Manuel Collado, Group Leader, Stem Cells in Cancer and Aging Laboratory, Health Research Institute of Santiago de Compostela (IDIS), A Coruña, Spain

Talk title: Cell Senescence in Development, Regeneration & Cancer

Date: 16 July

VHIO Host: Maria Abad, PI, Cellular Plasticity & Cancer Group

Speaker: Ephrat Levy-Lahat, Director, Medical Genetics Institute, Professor, Internal Medicine & Medical Genetics, Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel

Talk title: Hereditary Breast Cancer: From Families to the Population

Date: 30 July

VHIO Host: Judith Balmaña, PI, Hereditary Cancer Genetics Group

Speaker: Charles Swanton, Senior Group Leader, Francis Crick Institute & UCL Cancer Institute, London, UK

Talk title: Cancer Evolution, Immune Evasion & Metastasis

Date: 17 September

VHIO Host: César Serrano, PI, Sarcoma Translational Research Group

Speaker: Antonia Tomás, Group Leader, Circadian Rhythm and Cancer Laboratory, IMIB-UMU-Arrixaca, Murcia, Spain

Talk title: Circadian Rhythm & Cancer: an Approximation with Diurnal Animal Models

Date: 01 October

VHIO Host: Maria Abad, PI, Cellular Plasticity & Cancer Group

Speaker: Marie Arsenian, Professor, Molecular Tumor Biology, Karolinska Institutet (KI), Stockholm, Sweden

Talk title: MYCN & Differentiation Control in Childhood Neuroblastoma

Date: Friday 13th November, 12:00h

VHIO Host: Laura Soucek, PI, Models of Cancer Therapies Group

Speaker: Amanda Spurdle, NHMRC Investigator Fellow, Group Leader, Molecular Cancer Epidemiology, QIMR Berghofer Medical Research Institute, Brisbane, Australia

Talk title: Classification of Germline Variants in Hereditary Breast -Ovarian Cancer Genes: How to Specify Types & Weight of Evidence

Date: 15 October

VHIO Host: Sara Gutiérrez-Enríquez, Senior Investigator, Hereditary Cancer Genetics Group

Speaker: Teresa Palomero, Associate Professor of Pathology & Cell Biology (in the Institute for Cancer Genetics), Columbia University Irving Medical Center, New York, USA

Talk title: Mechanisms of Transformation in Peripheral T-Cell Lymphomas

Date: 11 November

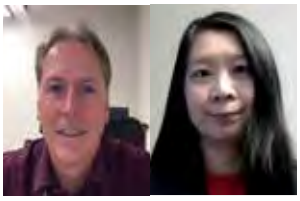
VHIO Host: Marta Crespo, Translational Research Coordinator, Experimental Hematology Group

Speaker: Jesús Bañales, Investigator Miguel Servet II and CIBEREHD (ISCIII), Ikerbasque Research Professor & Head, Liver Diseases Group, Biodonostia Health Research Institute – Donostia University Hospital, San Sebastian, Spain.

Talk title: The Role of Protein NEDDylation in the Pathogenesis of Cholangiocarcinoma: Novel Therapeutic Opportunities

Date: 26 November

VHIO Host: Sandra Peiró, PI, Chromatin Dynamics in Cancer Group



Speakers: Evon Poon, Senior Scientist, Institute of Cancer Research (ICR), and John Anderson, Professor, Experimental Pediatric Oncology, University College London (UCL) Great Ormond St. Institute of Child Health, London, UK

Talk title: Combined Small Molecular & Immune Strategies to Target MYC- Driven Pediatric Cancers

Date: 03 December

VHIO Host: Laura Soucek, PI, Models of Cancer Therapies Group

Speaker: Íñigo Martincorena, Group Leader, Sanger Institute, Cambridge, UK

Talk title: Somatic Mutations & Clonal Expansions in Normal Tissues

Date: 10 December

VHIO Host: César Serrano, PI, Sarcoma Translational Research Group

www.vhio.net/events/scientific-seminar-series

BENCH ST RMING SEMINARS

Established in 2016, our annual 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 currently underway, they can also express their ideas surrounding a given topic presented at each seminar; the specially

crafted informal format favors free thought, flow, and interaction between the speakers and participants.

Reflective of VHIO's purely translational and multidisciplinary research model, 2021 marked the launch of additional seminars that counted on the participation and expertise of our Clinical Investigators and Medical Oncologists.

Our Benchstorming Co-Chairs (left to right): Chiara Bellio, Associate Researcher of our Tumor Biomarkers Group (PI: Josep Villanueva), Sara Simonetti, Attending Physician of VHIO's Molecular Oncology Group (PI: Paolo Nuciforo), and Tian Tian, Senior Scientist of our Chromatin Dynamics in Cancer Group (PI: Sandra Peiró).

In 2021, 18 Benchstorming Sessions took place, mostly remotely online due to the COVID-19 pandemic. Each invited VHIO investigator(s) discussed and 'benchstormed' their respective research areas. For a full listing please visit the extended version of this scientific report online at: memorias.vhio.net/2021 (select the Education & Training tab).

www.vhio.net/events/benchstorming-seminars

Ad-hoc courses, workshops, perceptorships & observerships

1.EvolutIOn. Una nueva visión en el tratamiento del cáncer (7ª edición), 01 February. Coordinators: Enriqueta Felip, PI, VHIO's Thoracic Tumors & Head and Neck Cancer Group, Joan Carles, PI, VHIO's Genitourinary, CNS Tumors, Sarcoma & Cancer of Uknown Primary Site, and Eva Muñoz, Clinical Investigator & Medical Oncologist, VHIO's Breast Cancer and Melanoma Group. 2. Preceptorship en Genética del Cáncer Hereditario, 09 - 10 June. Coordinator: Judith Balmaña, PI, VHIO's Hereditary Cancer Genetics Group. 3. Preceptorship en Cáncer de Ovario, October - December. Coordinator: Ana Oaknin, PI, VHIO's Gynecological Malignancies Group. 4. Manejo del Cáncer de Mama en la era COVID-19, 14 October. Coordinator: Juan Aguilar-Company, Internal Medicine & Infectious Diseases Specialist, Vall d'Hebron University Hospital's Medical Oncology Department (headed by Josep Tabernero). 5.Gastrointestinal Cancer and Neuroendocrine Malignancies Program, 11 November. Coordinators: Josep Tabernero, VHIO's Director, and Teresa Macarulla, PI, VHIO's Gastrointestinal & Endocrine Tumors Group. 6. Lung Cancer Program, 02-03 December. Coordinator: Enriqueta Felip, PI, VHIO's Thoracic Tumors & Head and Neck Cancer Group.

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 18 Courses, Workshops, Observerships and Perceptorships in 2021. Naturally, due to the COVID-19 pandemic, the majority of these were hosted and conducted virtually, online.

In addition to these educational opportunities, we have organized and streamed several expert talks and presentations, as well as produced, published and disseminated various on-demand webinars covering a broad range of topics and tumor types.

For a full listing of these particular educational opportunities in 2021, please visit the extended version of this Scientific Report online at: http://memorias.vhio.net/2021.

www.vhio.net/events/workshops-courses

VHIO's patient engagement events, fundraising, and public outreach activities

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, as documented in this section of our scientific report. We will continue to seek out, lead and participate in all these precious initiatives and launch new ones based on identified opportunities.

In addition to VHIO's comprehensive lay media program, the invited participation of our researchers and clinical investigators across a broad range of communication channels, and campaigns tailored to our social media platforms and respective target audiences, VHIO led and/or participated in several public outreach events, programs and fundraising initiatives in 2021.

Due to the COVID-19 pandemic, many of our planned activities had to be cancelled or postponed. The majority of those that could go ahead were either conducted virtually, or carried out in strict compliance with the stipulated social distancing rules and required safety measures.

Illustrative of these efforts, we take this opportunity to mention just a few of the many highlights in 2021:

Connecting and conversing with cancer patients outside of the clinic

At VHIO we are committed to organizing and promoting educational programs especially tailored to those who matter most; our cherished patients.

Providing opportunity for debate and exchange among patients, their families and loved ones, and connecting them with our physician-scientists, cancer researchers, and other professionals in oncology, we co-organize an annual series of breast cancer workshops:

7th edition of our annual breast cancer workshops (October 2021 – June 2021)

HUVH-VHIO's annual breast cancer workshops for our cancer patients, their families and friends, as well as the general public.

Launched in 2015, these workshops are coordinated by Marta Capelan, a Medical Oncologist and Clinical Investigator of VHIO's Breast Cancer Group, directed by Cristina Saura, and organized in collaboration with the Vall d'Hebron University Hospital's (HUVH) Breast Cancer Unit, also led by Cristina Saura, and other expert teams across the Vall d'Hebron Barcelona Hospital Campus.

This year, these workshops were supported by Pfizer and icrom Clinical Research Office Management, in collaboration with the *Asociación Endavant Chic@s*. Due to the safety issues posed by the COVID-19 pandemic these events took place online.

In 2021, we launched a new monthly series of live online sessions covering several tumor types, that have been especially crafted for cancer patients and non-specialized audiences #VHIOATuLado.

#VHIOATuLado

Inaugurating this new series of special sessions, were VHIO's Enriqueta Felip, Principal Investigator of our Thoracic Tumors & Head and Neck Cancer Group, and Head of the Thoracic Cancer Unit at the Vall d'Hebron University Hospital (HUVH), and Alberto Jauregui, Head of the Thoracic Surgery Service at Vall d'Hebron. Discussing various aspects relating to the diagnosis of lung cancer, they presented on the recent developments in this field, including the latest advances in patient treatment and care.

Throughout each of these dedicated sessions, also including experts in preclinical, translational and clinical cancer research, participants are invited to post their comments and questions online to actively contribute and engage in the various topics that are discussed and debated.

For a full listing of these educational opportunities in 2021, we invite you to visit the extended version of this scientific report online at: http://memorias.vhio.net/2021 (select 'Education & Training').

Public fundraising in support of cancer research

Pau Donés and *Jarabe Contra el Cáncer*

Jordi Calvera

Left to right: One of the promotional posters for Pau's sell-out fundraising rock concerts, and Pau on stage with VHIO's Elena Élez.

We remain deeply saddened by 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, succumbed to his disease on 09 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.

To raise funds for research at VHIO, he not only organized various *Jarabe Contra el Cáncer* sell-out concerts with his band and several other renowned musicians, but also spoke out to raise awareness on and around cancer. As Pau prepared for his death, he contacted journalist Jordi Évole to discuss his own final fundraising initiative against cancer. *Eso que tú me das* –the title of one of his very last songs recorded with his band- was to be the title of the documentary and very final interview, which broadcast in cinemas across Spain, following his passing.

Directed by Ramón Lara and Jordi Évole, and produced by *Producciones del Barrio y Atresmedia*, all proceeds were donated to support several research projects at VHIO.

Vivir es Urgente 2021

The *Fundación CRIS contra el Cáncer*, *Jarabe Contra el Cáncer*, Pau's family including his brother Marc Donés, in collaboration with the *Help! Buenas Ideas* network, launched a new fundraising initiative in 2021: *La Camiseta Pau* (Pau's T-shirt). Marking the 1st anniversary

of his passing, these T-shirts went on sale in June to raise funds for research at VHIO. Within just one month, this initiative raised an incredible 350.000€, and by the close of the campaign in September, succeeded in raising a total of 524.581€.

This T-shirt, with the slogan *Vivir es urgente* (Life is urgent), was designed by Pau Donés and worn by him at another of his fundraising concerts that took place in Mexico City, October 2017. These three words became a mantra during his final years.

Pictured: the presentation of the first cheque for 350.000€ just one month after the campaign launched in June 2021, with Pau's brother Marc Donés, Marta Cardona, Director of the Fundación Cris Contra el Cáncer, Jorge Martínez and José Maria Piera from the Help! Buenas Ideas network, along with VHIO's Director, Josep Tabernero, Alejandro Piris, Elena Élez, Raquel Lopez-Perez, and Joaquin Mateo, whose research will be supported by this funding.

Pau Donés, you will never be forgotten.

el paseíco de la mama
10º aniversario

Left to right: Cristina Saura, Inés Gasén, and Meritxell Bellet.

El Paseíco de la Mama (loosely translated as strolling for breast cancer) began to take shape when Inés Gasén was diagnosed with breast cancer during her pregnancy – not only naturally provoking fear and uncertainty for her and her family, but also raising many questions and doubts concerning the health and the future ahead for her baby.

Triggering a call to action in her mother in-law, Elaine, and driven by the need to bring a positive out of the then challenging times, she decided to organize an annual sponsored walk to raise funds aimed at advancing insights into breast cancer. Rallying support among their family and circle of friends and acquaintances, Elaine and her two daughters Pili and Susan, and Inés, founded *El Paseíco de la Mama* in 2011.

From the very outset, *El Paseíco de la Mama* has been a tremendous supporter of research directed by Cristina Saura, Principal Investigator of our Breast Cancer Group and Head of the Vall d'Hebron University Hospital's Breast Cancer Unit, and continues to gain momentum year in, year out, with an increasing number of participants, donations and personal pledges.

While the 2020 sponsored 7.5 km walk along Zaragoza's canal had to be held later on that year due to the COVID-19 pandemic, this did not deter the fundraising efforts. This year, Inés Gasén presented Cristina Saura and Meritxell Bellet with a cheque for 38.485€. This support will fuel research aimed at reliably measuring blood estradiol in premenopausal women with breast cancer undergoing hormonal treatment, led by Meritxell Bellet.

Endavant Chic@s
Asociación Cáncer de mama

Left to right: Marta Capelan, Cristina Saura, Luisa Vázquez – President of the *Asociación Endavant Chic@s*, and Judith Balmaña.

Asociación Endavant Chic@s organizes several fundraising sports tournaments and other initiatives throughout the year. As a result of these efforts, it succeeded in raising 11.405,34€. This donation, presented to VHIO's Cristina Saura, Judith Balmaña, and Marta Capelan by the Association's President, Luisa Vázquez in 2021, will fund essential research aimed at improving outcomes and the quality of life of breast cancer patients at the Vall d'Hebron University Hospital's Breast Cancer Unit, headed by Cristina Saura.

Specifically, this donation will support a project led by Judith Balmaña, Principal Investigator of our Hereditary Cancer Genetics Group, aimed at better calculating the risk of developing breast cancer using predictive models toward more precisely anticipating and preventing disease in individual patients.

In addition, it will also co-fund research into the benefits of yoga in alleviating fatigue associated with breast cancer. A randomized study will include a group of patients undergoing neoadjuvant chemotherapy treatment who will participate in two weekly yoga classes online due to the issues posed by the COVID-19 pandemic, and a control group. This research is also supported by the aforementioned *Paseíco de la Mama*.

The not-for-profit *Em dones força* association presents VHIO's Cristina Saura and Meritxell Bellet with 10.000€ to advance breast cancer research and the treatment and care of patients.

Em dones força, created by a group of friends in Riudoms, Tarragona (Catalonia) to raise funds for breast cancer research through a variety of activities, presented VHIO's Cristina Saura, Principal Investigator of our Breast Cancer Group, and Meritxell Bellet, a Clinical Investigator and Medical Oncologist of Cristina's group, with a cheque for 10.000€ as a result of their fundraising efforts.

Meritxell Bellet was Elvira Mas' oncologist. Elvira was a co-founder of and President of *Em dones força*, who sadly recently passed away from breast cancer. The official presentation of this important donation took place at VHIO's CELLEX Building, and paid tribute to Elvira and her legacy. Fifty people, including her husband, children, family members, friends and neighbors in Riudoms, all of whom form part of *Em dones força*, attended this special event.

Funding will support Meritxell Bellet's project entitled: *Recruiting ERβ in the fight against triple negative breast cancer (TNBC)*.This research could potentially provide new treatment avenues for these patients.

Pañuelo Solidario': solidarity scarves for cancer research

The launch of the 4th 'Pañuelo Solidario' 2021 campaign at Vall d'Hebron.

'Pañuelo Solidario' is a fundraising campaign driven by the Vall d'Hebron University Hospital (HUVH), in collaboration with the lifestyle store Natura that produces and distributes these solidarity scarves in its shops and online. All proceeds will be donated to support cancer research carried out by two predoctoral researchers. They are Alejandra Cano of VHIO's Breast Cancer Group, and Carina Masferrer, the Gynecological Biomedical Research Group at the Vall d'Hebron Institute of Research (VHIR).

Established in 2017 by the campaign's ambassador, Judit Mascó, and designed each year by artist Clàudia Valsells, this fundraising initiative seeks to improve the treatment and wellbeing of women suffering with breast cancer and gynecological cancers. Timed to coincide with International Women's Day, held annually on 08 March, the official launch of this year's campaign took place at Vall d'Hebron in strict compliance with all the COVID-19 pandemic safety and control measures.

Alejandra Cano's research focuses on STEPS – therapeutic support for cancer survivors. This project is dedicated to providing more resources and psychological support for patients after their diagnosis and post-treatment to alleviate anxiety and emotional stress, as well as tools to facilitate their reincorporation into daily life, both at the personal and professional levels.

Carina Masferrer's research centers on developing new therapeutic strategies for the more effective treatment of endometrial cancer. She is currently assessing the efficacy of a targeted therapy with a small-molecule, ABTL0812, in combination with immunotherapy. This approach could open up new treatment avenues for patients, particularly for those with aggressive disease.

On the occasion of the *Associació Solidària Sosciathlon's* 6th annual public fundraiser, VHIO's Ramon Amat and Caterina Carbonell were presented with a donation of 10.000€ in support of research carried out by VHIO's Thoracic Tumors & Head and Neck Cancer Group.

Celebrating its 6th annual public fundraiser, that took place in La Pineda, Vila-seca (Tarragona, Catalonia), the *Associació Solidària Sosciathlon* (Solidarity Association Sosciathlon) raised a total of 20.000€, that was evenly split between VHIO and the *ENACH.ORG distrofia neuroaxonal infantil* (ENACH. ORG infantile neuroaxonal dystrophy). This year's sports event attracted some 1,000 participants and secured funding through sponsorship, event registrations, donations, and merchandise sales.

This donation will support research carried out by Enriqueta Felip's Thoracic Tumors & Head and Neck Cancer Group that focuses on disease prevention, early detection and staging of these tumor types toward improving clinical outcomes. On behalf of Enriqueta's team, Ramon Amat, Associate Researcher, and Caterina Carbonell, Post-Doctoral Fellow of her group, were presented with a donation of 10.000€ that will fuel essential research aimed at improving outcomes for

patients suffering from thoracic malignancies and head and neck tumors.

Established in 2014, the *Associació Solidària Sosciathlon* fosters value-based solidarity, volunteering, help and commitment, and donates the proceeds from their annual events between two different entities, while promoting health and culture through sport.

Advancing insights into sarcomas: SarcModel (ing)

Carlota Coloma and her family have this year donated 15.000€ to support translational research into sarcomas led by VHIO's César Serrano.

Sarcoma is a very rare tumor type; representing between 1-2% of all cancers. It is also a highly complex disease with more than 70 subtypes; each with a different biological makeup and clinical behavior. For these reasons, VHIO's César Serrano, who leads our Translational Sarcoma Research Group, initiated the SarcModel project that focuses on advancing cancer modelling against this disease.

In support of these efforts, Carlota Coloma, Director of the production company 15LFilms and *alma mater* of the documentary *Backstage. Hablemos de un sarcoma* (Backstage. Let's talk about sarcoma), set about raising funds. Alongside her family, and with the support received from various sponsors, this documentary was produced in honor of her mother who passed away from sarcoma, in order to help other families going through the same experience. It also superbly documents how researchers and oncologists work together to seek out more effective treatments against this disease.

Through the Migranodearena crowdfunding platform, they succeeded in raising 15.000€ to help advance sarcoma research at VHIO. Specifically, this donation will spur César's Group's SarcModel project that ultimately aims to extend the promise of precision medicine in oncology to sarcoma patients.

We also take this opportunity to gratefully thank the many other entities, organizations and individuals, including our cherished patients, who also dedicate their precious time, energy and efforts in supporting our public, national outreach program as well as raising funds for our research through individual as well as crowdfunding activities.

Public outreach and engagement

World Cancer Day (WCD), 04 February, is led by its founding and organizational body, the Union for International Cancer Control (UICC). To mark the occasion in 2021, VHIO's Director, Josep Tabernero, Enriqueta Felip (PI: Thoracic Tumors & Head and Neck Cancer Group), Elena Garralda (PI: VHIO's Early Clinical Drug Development Group), and Director of our Research Unit for Molecular Cancer Therapy of Cancer – UITM, CaixaResearch), Ana Vivancos (PI: Cancer Genomics Group), and Alena Gros (PI, Tumor Immunology & Immunotherapy Group), were among other leading experts in oncology across the Vall d'Hebron Barcelona Hospital Campus, who were invited as panelists and speakers.

Including the participation of cancer patients, and aimed at the general public at large, this special event addressed key topics including the latest advancements in oncology, cancer prevention, and important aspects regarding the wellbeing and care of people suffering from this disease.

World Cancer Day 2021 not only celebrated its 21st birthday but also the final year of its *'I Am and I Will'* 3-year global campaign. As importantly, it also recognized the extraordinary efforts of hospitals, cancer organizations, research institutes, cancer care professionals and providers, volunteers, advocates and individuals around the world who rapidly responded to the myriad challenges posed by the COVID-19 pandemic.

It praised the valiant actions of all stakeholders in oncology, including funding bodies, government agencies, regulatory authorities, and the pharmaceutical industry who continued to work together in maintaining progress in cancer research, treatment and care. Capturing just some of these amazing endeavors, the UICC launched a dedicated web page: *Adaptations and innovations in cancer care through COVID-19 and beyond*, that encapsulated the bravery and achievements of people living with cancer and their families, as well as the nurses, doctors, researchers, advocates and others who care for them throughout the COVID-19 crisis.

VHIO investigators joined together with other researchers and healthcare professionals in oncology at Vall d'Hebron to mark World Cancer Day 2021.

Coinciding with the International Day of Women and Girls in Science, celebrated annually on 11 February, several of our researchers participated in two different programs. The first, *CONÓCELAS*, was organized by the *Asociación Española de Investigación sobre el Cáncer* – ASEICA (Spanish Association of Cancer Research), in collaboration with the *Red de Asociaciones de Investigadores y Científicos Españoles en el Exterior* - RAICEX (Network of Associations for Spanish Researchers and Scientists Abroad), and the *Ciencia es Femenino* (Science is Feminine) organization in Galicia.

Taking place virtually this year due to the COVID-19 pandemic, the main objective of this event is to give visibility to the important contributions made by female researchers in combating cancer. *CONÓCELAS*, also supported by VHIO's María Abad (PI: Cellular Plasticity & Cancer Group) as a driving force, connected around 6,500 students throughout Spain with 150 investigators to discover more about the work of today's female rising stars in cancer research and oncology.

The second, *#100tífiques*, is a joint initiative of the *Fundació Catalana per a la Recerca i la Innovació – FCRI* (Catalan Foundation for Research and Innovation), and the Barcelona Institute of Science and Technology (BIST), in collaboration with the *Departament d'Educació de la Generalitat de Catalunya* (Deparment of Education, the Government of Catalonia).

The main goals of *#100tífiques* are to promote the relevance and role of women in science and technology, and foster collaboration between scientists from academia and enterprise. It also seeks to achieve a more direct and reciprocal relationship between science and society.

Now in its 3rd edition, 2021 counted on the participation of around 100 women in science (pre-doctoral students, postdocs, group leaders and directors of research from both the public and private sectors), including 13 VHIO scientists, who gave virtual talks to primary and secondary school students throughout Catalunya.

MOVEMBER

November, celebrated globally throughout the month of November, was established back in 2003. This public awareness movement has since gathered tremendous momentum worldwide; having financed over 1,250 projects in men's health globally.

Vall d'Hebron teams once again joined the Movember movement against prostate cancer in 2021.

For another year, physicians, investigators and healthcare professionals at the Vall d'Hebron University Hospital's – HUVH (page 36) Urology Service, Vall d'Hebron Institute of Research (VHIR), and VHIO's Prostate Cancer Translational Research Group (PI: Joaquin Mateo), joined together to support this campaign at the national level through the *Fundación Movember*, and the #MovemberTeam. By the year 2030, the Movember aims to reduce the number of men who die prematurely from prostate cancer through preventable causes by 25%.

This year, their official MOVEMBERVHIO/HUVH funding page invited donations, and encouraged the sporting of moustaches to mark the movement and promote via social media platforms #Movember2021, among other public awareness actions and activities.

One of the many Movember-supported projects includes the IRONMAN Registry, for which VHIO serves as the central laboratory in Spain, led by Joaquin Mateo, Principal Investigator of our Prostate Cancer Translational Research Group. IRONMAN is an international, population-based registry that will include 5000 men with advanced prostate cancer across ten countries, 500 of whom will be from Spain. It seeks to advance insights into the clinical outcomes associated with the management of this disease as well as better understand its biological and clinical diversity.

Nationally, this project is implemented by the *Fundación Movember* and co-funded by one of VHIO's Patrons and Institutional Supporters, *Fundación FERO* (page 29). Counting on the expertise of investigators at VHIO and colleagues at the Spanish National Cancer Research Center – CNIO (Madrid), who coordinate this program, along with a network of global data centers and their participating sites, this project represents an important step forward in advancing precision medicine against advanced prostate cancer.

Nit Europea de la Recerca

VHIO's Sandra Peiró presenting on epigenetics and cancer.

The *Nit Europea de la Recerca* (European Night of Research) is celebrated annually in more than 300 cities across 30 countries throughout Europe, including Barcelona. This event was established to enable members of the public to meet researchers, learn about their respective scientific disciplines, research lines and activities.

In 2021, this scientific soirée counted on the participation of a trio of VHIO investigators. Hosted by venues including the CosmoCaixa Barcelona, the "la Caixa" Foundation (page 30) Sandra Peiró, Principal Investigator of our Chormatin Dynamics in Cancer Group, talked about epigenetics and its role in cancer.

Carmen Escudero, a Graduate Student of Sandra's group, and Joana Domènech, a Graduate Student of our Hereditary Cancer Genetics Group, headed by Judith Balmaña, led a workshop on genetic mutations in cancer aimed at younger audiences. Using pieces of LEGO® they superbly simplified a complex topic.

Barcelona cultura

La Festa de la Ciència 2021

Left to right: VHIO's Carmen Escudero was invited to explain genetic mutations in cancer using pieces of LEGO®, and Marta Ligero presented on the promise of AI in advancing precision medicine in oncology.

Promoted by the *Ajuntament de Barcelona* (Barcelona City Council), 2021 celebrated the 14th annual edition of the *Festa de la Ciència* (Celebration of Science) that took place in person adhering to all the social distancing rules and restrictions posed by the COVID-19 pandemic. This public event was established as an educational forum to learn about, consider and update on the many challenges that are being tackled through research of excellence.

Universities, research centers, including VHIO, other scientific institutions and companies, and experts in scientific communication, joined together to devise a stimulating and informative program of matched excellence in 2021. The agenda included over 120 different talks, presentations and activities for people of all ages.

Regarding VHIO's contributions to this annual celebration of science, Carmen Escudero, a Graduate Student of our Chromatin Dynamics in Cancer Group led by Sandra Peiró, gave a talk on genetic mutations in cancer. Using pieces of LEGO®, she was able to creatively explain how faulty genes lead to cancer.

Marta Ligero, a PhD Student of VHIO's Radiomics Group, directed by Raque Perez-Lopez, gave a mini talk on Artificial Intelligence (AI), to decipher the secrets of medical images. Throughout her talk, Marta explained how AI can advance crucial insights into cancer, representing a step forward in precision medicine in oncology.

Several other researchers and experts from across the Vall d'Hebron Barcelona Hospital Campus also participated in this event including Paula Galvá from the Vall d'Hebron University Hospital (HUVH), who gave a talk on the importance of telemedicine in the COVID-19 era and how it has revolutionized certain aspects of healthcare delivery.

Open house: Vall d'Hebron's Science and Innovation Week

Welcoming visitors to discover more about VHIO's suite of Core Technologies.

In 2021 our Vall d'Hebron Barcelona Hospital Campus launched its first Science and Innovation Week, 15-19 November, that provided the general public with a great opportunity to learn more about cutting-edge platforms, tools and techniques on-campus that are shaping the future of healthcare, including augmented and virtual reality in healthcare, robotics, simulation, and 3D technologies. Including activities for faculty at Vall d'Hebron and other institutions, the week's educational program also offered an exciting range of events aimed at younger audiences.

Forming part of Vall d'Hebron's strategic plan to promote its innovation, driven and developed in-house, this event was also established to give researchers, clinical investigators, technicians and healthcare professionals who spur these stunning advances in medical technologies greater visibility in society.

The inaugural program also included five roundtable sessions covering healthcare and telemedicine in the digital age, as well as a series of presentations dedicated to spin-offs and start-ups at Vall d'Hebron. These included talks by VHIO's Joan Seoane and Laura Soucek, Co-Directors of our Preclinical and Translational Research Program -both ICREA Research Professors- who discussed the value of technology transfer in society and the promise of these companies in improving outcomes for patients. Illustrative of these efforts, they each introduced participants to their respective VHIO-born spin-offs, Mosaic Biomedicals (page 41), and Peoptomyc (page 41).

This dedicated VHIO educational program (established back in 2017), welcomes under-twelves from various local primary schools to meet our faculty, tour our laboratories and learn more about cancer biology and research.

The main objectives of our Schools and Science outreach program are to teach young and inquisitive minds about the importance of cancer research, and hopefully inspire some of them to ultimately become the next generation of cancer scientists.

During their half-day visits our young visitors participate in junior masterclasses and hands-on activities to explain the origins and development of cancer, led and supervised by VHIO faculty.

Unfortunately, due to the safety issues posed by the COVID-19 pandemic, we had to postpone our 2021 program of activities. In view of the excellent feedback that we receive from students and teachers alike, 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 2022 – pandemic restrictions permitting.

VHIO's social media channels & platforms

In addition to VHIO's comprehensive lay media program and the invited participation and presence of our researchers and clinical investigators across a broad range of communication channels, we continue to expand our outreach through news announcements, campaigns, images, and videos tailored to our social media platforms and respective target audiences.

To discover what we are excited about, our latest news, and other developments that are catching our attention elsewhere, we invite you to follow us, and join in on our 'conversation' today:

www.vhio.net

SCIENTIFIC PRODUCTIVITY: RESEARCH ARTICLES

Articles published in 2021

In 2021, 446 scientific articles were published by VHIO researchers as corresponding/senior or co-authors.

Figure I

Number of articles published by VHIO researchers from 2007 - 2021

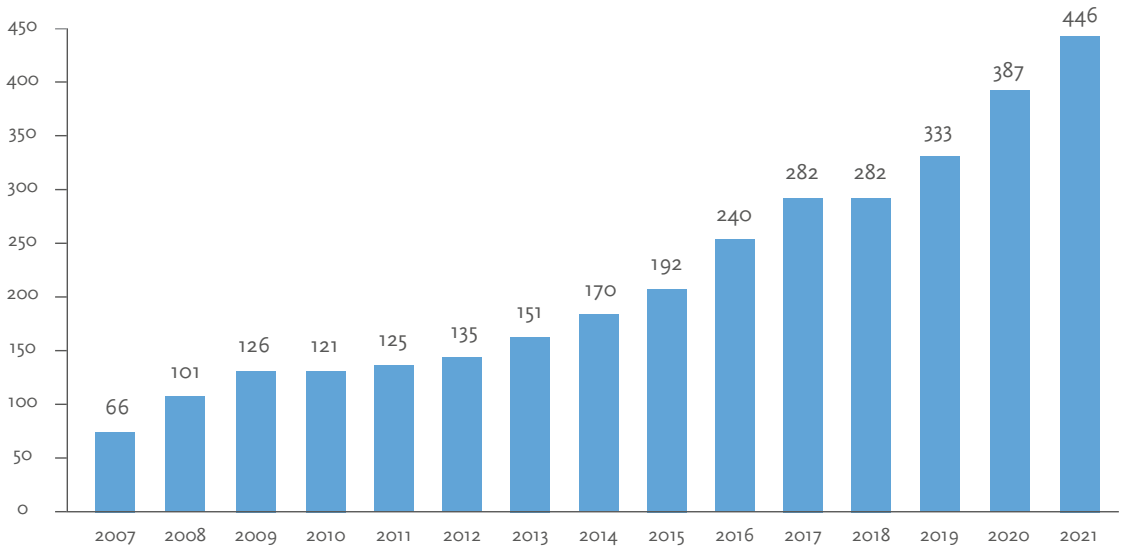
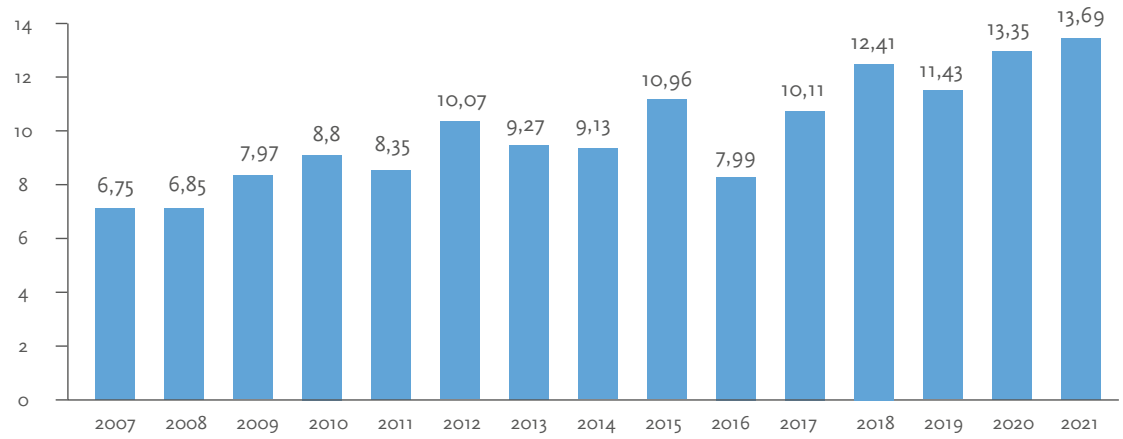


Figure II

Median Impact Factor of papers published by VHIO faculty from 2007 - 2021



For the complete list of VHIO scientific articles published in 2021 in journals with allocated Impact Factor please see pages 168-193. To browse our selection of most relevant articles by VHIO researchers published in 2021 please refer to pages 63-73 of this Scientific Report.

To view our Principal Investigators' selection of a maximum of 4 top papers per group in 2021 please see respective team pages (sub-section PI Paper Pick 2021). To access each group's full list of publications in 2021, as compiled by our Principal Investigators, visit the extended version of our Scientific Report online at: **http://memorias.vhio.net/2021**

INTRODUCING VHIO

SELECTION OF SOME OF THE MOST RELEVANT ARTICLES BY VHIO RESEARCHERS PUBLISHED IN 2021

Below is a selected list of articles published by VHIO researchers in 2021 with respective Impact Factors (IF) indicated. For the complete list of scientific articles published by VHIO Investigators in 2021 please see pages 168-193.

Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, Gelber RD, de Azambuja E, Fielding A, Balmaña J, Domchek SM, Gelmon KA, Hollingsworth SJ, Korde LA, Linderholm B, Bandos H, Senkus E, Suga JM, Shao Z, Pippas AW, Nowecki Z, Huzarski T, Ganz PA, Lucas PC, Baker N, Loibl S, McConnell R, Piccart M, Schmutzler R, Steger GG, Costantino JP, Arahmani A, Wolmark N, McFadden E, Karantza V, Lakhani SR, Yothers G, Campbell C, Geyer CE Jr; OlympiA Clinical Trial Steering Committee and Investigators. *N Engl J Med.* 2021 Jun 24;384(25):2394-2405. IF: 91.253.

Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, Oyervides Juárez VM, Hsieh JJ, Basso U, Shah AY, Suárez C, Hamzaj A, Goh JC, Barrios C, Richardet M, Porta C, Kowalyszyn R, Feregrino JP, Żołnierek J, Pook D, Kessler ER, Tomita Y, Mizuno R, Bedke J, Zhang J, Maurer MA, Simsek B, Ejzykowicz F, Schwab GM, Apolo AB, Motzer RJ; CheckMate 9ER Investigators. *N Engl J Med.* 2021 Mar 4;384(9):829-841. IF: 91.253.

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Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, Luft A, Akopov A, Martinez-Marti A, Kenmotsu H, Chen YM, Chella A, Sugawara S, Voong D, Wu F, Yi J, Deng Y, McCleland M, Bennett E, Gitlitz B, Wakelee H; IMpower010 Investigators. *Lancet.* 2021 Oct 9;398(10308):1344-1357. IF: 79.323.

Enhancing anti-tumour efficacy with immunotherapy combinations. Meric-Bernstam F, Larkin J, Tabernero J, Bonini C. *Lancet.* 2021 Mar 13;397(10278):1010-1022. IF: 79.323.

Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Sun JM, Shen L, Shah MA, Enzinger P, Adenis A, Doi T, Kojima T, Metges JP, Li Z, Kim SB, Cho BC, Mansoor W, Li SH, Sunpaweravong P, Maqueda MA, Goekkurt E, Hara H, Antunes L, Fountzilas C, Tsuji A, Oliden VC, Liu Q, Shah S, Bhagia P, Kato K; KEYNOTE-590 Investigators. *Lancet.* 2021 Aug 28;398(10302):759-771. IF: 79.323.

Precision oncology in metastatic colorectal cancer - from biology to medicine. Di Nicolantonio F, Vitiello PP, Marsoni S, Siena S, Tabernero J, Trusolino L, Bernards R, Bardelli A. *Nat Rev Clin Oncol.* 2021 Aug;18(8):506-525. IF: 66.675.

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CDK4/6 inhibitors in breast cancer: spotting the difference. Perez-Garcia JM, Cortes J, Llombart-Cussac A. *Nat Med.* 2021 Nov;27(11):1868-1869. IF: 53.440.

Endometrial cancer. Makker V, MacKay H, Ray-Coquard I, Levine DA, Westin SN, Aoki D,Oaknin A. *Nat Rev Dis Primers* 7, 88 (2021). IF: 52.329.

The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. Janjigian YY, Kawazoe A, Yañez P, Li N, Lonardi S, Kolesnik O, Barajas O, Bai Y, Shen L, Tang Y, Wyrwicz LS, Xu J, Shitara K, Qin S, Van Cutsem E, Tabernero J, Li L, Shah S, Bhagia P, Chung HC. *Nature.* 2021 Dec;600(7890):727-730. IF: 49.962.

Anthracyclines for Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Are We Ready to Let Them Go? Tarantino P, Tolaney SM, Harbeck N, Cortes J, Curigliano G. *J Clin Oncol.* 2021 Nov 10;39(32):3541-3545. IF: 44.544.

Cabozantinib in Combination With Atezolizumab for Advanced Renal Cell Carcinoma: Results From the COSMIC-021 Study. Pal SK, McGregor B, Suárez C, Tsao CK, Kelly W, Vaishampayan U, Pagliaro L, Maughan BL, Loriot Y, Castellano D, Srinivas S, McKay RR, Dreicer R, Hutson T, Dubey S, Werneke S, Panneerselvam A, Curran D, Scheffold C, Choueiri TK, Agarwal N. *J Clin Oncol.* 2021 Nov 20;39(33):3725-3736. IF:44.544.

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First-in-Human Phase I Study of MP0250, a First-in-Class DARPin Drug Candidate Targeting VEGF and HGF, in Patients With Advanced Solid Tumors. Baird RD, Linossi C, Middleton M, Lord S, Harris A, Rodón J, Zitt C, Fiedler U, Dawson KM, Leupin N, Stumpp MT, Harstrick A, Azaro A, Fischer S, Omlin A. *J Clin Oncol.* 2021 Jan 10;39(2):145-154. IF: 44.544.

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Pregnancy After Breast Cancer: A Systematic Review and Meta-Analysis. Lambertini M, Blondeaux E, Bruzzone M, Perachino M, Anderson RA, de Azambuja E, Poorvu PD, Kim HJ, Villarreal-Garza C, Pistilli B, Vaz-Luis I, Saura C, Ruddy KJ, Franzoi MA, Sertoli C, Ceppi M, Azim HA Jr, Amant F, Demeestere I, Del Mastro L, Partridge AH, Pagani O, Peccatori FA. *J Clin Oncol*. 2021 Oct 10;39(29):3293-3305. IF: 44.544.

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Chemotherapy de-escalation using an 18F-FDG-PET-based pathological response-adapted strategy in patients with HER2-positive early breast cancer (PHERGain): a multicentre, randomised, open-label, non-comparative, phase 2 trial. Pérez-García JM, Gebhart G, Ruiz Borrego M, Stradella A, Bermejo B, Schmid P, Marmé F, Escrivá-de-Romani S, Calvo L, Ribelles N, Martinez N, Albacar C, Prat A, Dalenc F, Kerrou K, Colleoni M, Afonso N, Di Cosimo S, Sampayo-Cordero M, Malfettone A, Cortés J, Llombart-Cussac A; PHERGain steering committee and trial investigators. *Lancet Oncol*. 2021 Jun;22(6):858-871. IF: 41.316.

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PROGRAMS

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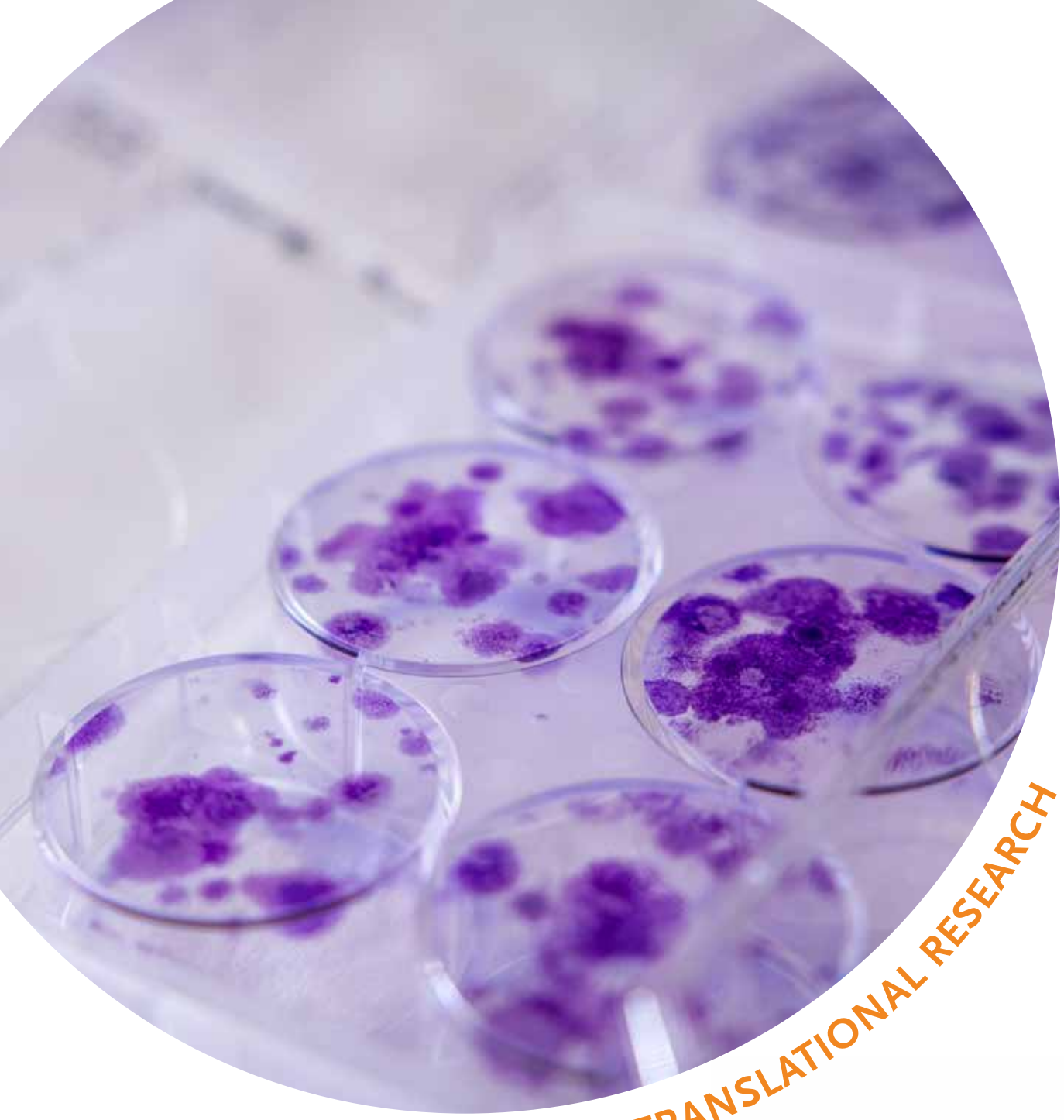
PROGRAMS



PRECLINICAL & TRANSLATIONAL RESEARCH

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VALL D'HEBRON INSTITUTE OF ONCOLOGY (VHIO)
SCIENTIFIC REPORT 2021

PRECLINICAL & TRANSLATIONAL RESEARCH

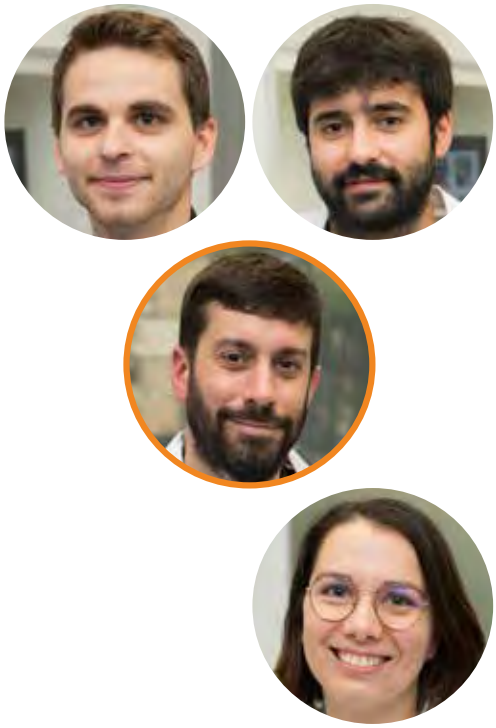
For another year, due to the safety issues brought about by COVID-19, we had to adjust our approach to this report's photography. With the exception of some of our larger groups*, we have ensured that as many group members as possible have been included, and without masks. Each individual picture was taken at a distance in locations away from areas dedicated to the care of our cancer patients. For faculty working remotely, we invited them to submit their photos from home.

*** Considering certain logistical and spatial issues, we have unfortunately had to repeat pictures of some of our larger groups and units from VHIO's Scientific Report 2019 - as indicated in the corresponding pages.**

PRECLINICAL & TRANSLATIONAL RESEARCH

CANCER COMPUTATIONAL BIOLOGY GROUP

Principal Investigator José A. Seoane **Postdoctoral Fellow** Silvana Maas **Graduate Student** José Liñares **Master's Degree Student** Arnau Llinàs



STRATEGIC GOALS

- Understand the role of chromatin regulatory elements in treatment response and metastasis.
- Discover new epigenetic biomarkers of drug response.
- Potentiate therapeutic options by combining epigenetic therapies with other agents.

HIGHLIGHTS

- VHIO's Cancer Computational Biology Group was established in May 2021.
- Jose A. Seoane's Ramon y Cajal Fellowship started this year.
- Jose A. Seoane received a grant from the *Ministerio de Ciencia e Innovación* to explore epigenetic synthetic lethality mechanisms.
- Our group joined the AURORA metastatic breast cancer consortium.
- José Liñares received his PhD in December 2021.

SUMMARY

Jose A. Seoane joined VHIO this year to set up the newly established Cancer Computational Biology Group. Our team leverages epi(genetic) cancer datasets to unmask the molecular mechanisms implicated in cancer initiation, progression, drug resistance and metastasis towards improved outcomes for patients.

We aim to advance insights into the role of chromatin regulatory elements in treatment response and metastasis, develop novel epigenetic synthetic lethality-based therapeutic options, improve patient stratification guided by multi-omics analysis, and seek out novel epigenetic biomarkers of treatment response.

We have previously shown how the genetic modifiers of chromatin structure are associated with chemotherapy resistance in breast cancer (Seoane et al. 2019)*. Our group aims to establish how these epigenetic alterations affect drug resistance and how epigenetic therapies can be used to target tumor suppressor genes.

We are also exploring how the machine learning-based integration of multi-omic datasets can facilitate the discovery of new cancer subgroups and biomarkers, as well as help to better predict treatment outcomes and drug response.

Our group has participated/participates in multiple international consortia including The Cancer Genome Atlas, the Human Tumor Atlas Network, Cancer Target Discovery and Development (CTD 2) Network, and, most recently, AURORA (metastatic breast cancer multi-omic cohort).

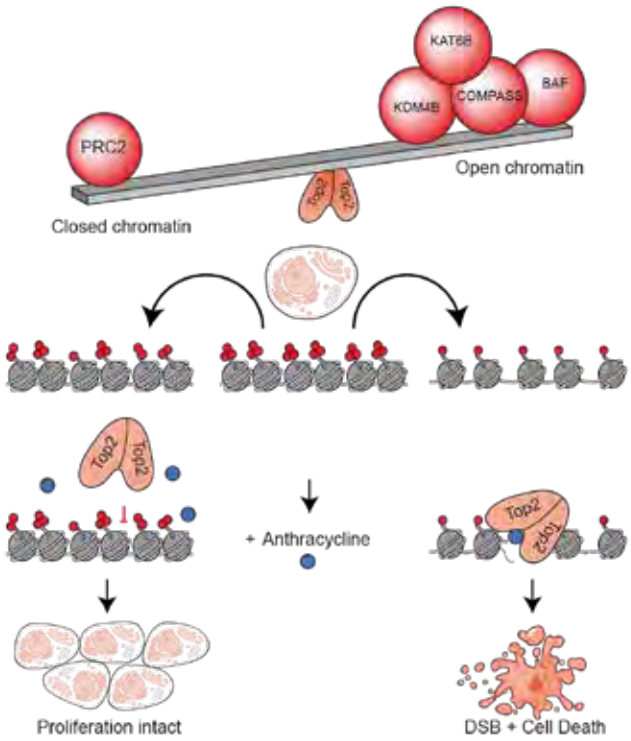


Figure: Epigenetic regulation of chromatin regulatory genes in response to anthracyclines. In presence of anthracycline, when chromatin regulatory genes are highly express the chromatin is compacted so the TOP2A protein cannot access to DNA so the drug does not work as it should. However, if the chromatin machinery genes that open the chromatin are highly expressed, the DNA is accessible, TOP2A binds DNA properly, anthracycline poison TOP2A causing double strand break and apoptosis.

PI PAPER PICK 2021

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PRECLINICAL & TRANSLATIONAL RESEARCH

CELLULAR PLASTICITY & CANCER GROUP

Principal Investigator Maria Abad **Post-Doctoral Fellow** Elena Senís **Research Assistants** Marta Gimenez, Lluis Palenzuela **Graduate Students** Olga Boix, Alba Escriche, Emanuela Greco, Marion Martinez, Iñaki Merino **Masters Student** Alejandro Bernardo **Visiting Student** Camilla Bertrani

STRATEGIC GOALS

- Advance insights into the interplay between therapy-induced senescence, cellular plasticity and cancer.
- Decipher the molecular mechanisms governing the acquisition of stem cell properties during tumorigenesis and after therapy.
- Discover and characterize novel microproteins involved in cancer cell plasticity.
- Develop novel anti-cancer therapies based on the inhibition of cancer cell plasticity.

HIGHLIGHTS

- Our PI, María Abad, organized the first symposium on microproteins at the 43rd virtual Annual Meeting of the Spanish Society of Biochemistry & Molecular Biology (SEBBM), 19-22 July, Barcelona, Spain.
- We published our work identifying pTUNAR, a novel microprotein that regulates neural differentiation.
- We published a book chapter describing a versatile toolbox to study the role of Myc in *in vivo* reprogramming.
- We were awarded with a coordinated grant from the *Asociación Española Contra el Cáncer* - AECC (Spanish Association Against Cancer), to study the therapy-induced tumoral senescence and its potential as a therapeutic target and prognostic biomarker.
- Our PhD student, Marion Martínez, was awarded with a "la Caixa" Foundation Doctoral Fellowship INPhINIT – RETAINING, 2021.

SUMMARY

We focus on the interplay between stress responses, cellular plasticity and cancer. Cellular plasticity is now recognized as a critical feature of cancer cells, enabling them to transit between different cellular states and promote tumor growth, disease progression after therapy, and metastasis.

Our group has previously 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 -the main driver of cancer- triggers the onset of cellular senescence which then induces dedifferentiation and the acquisition of stem cell properties *in vivo*.

These findings 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 cancer cell spread.

Our main objective is to advance insights into 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 results have demonstrated that some genomic regions, previously considered as non-coding (including lncRNAs), contain small open reading frames encoding for evolutionary conserved, unannotated microproteins. The few that have been identified to date assume 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 five years, our efforts have focused on identifying and characterizing novel cancer microproteins which could be novel actors in carcinogenesis. We have discovered five new cancer microproteins 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. In addition, using a peptidomics approach, we have identified a set of microproteins secreted by pancreatic tumors, either soluble or secreted in exosomes. These novel microproteins could be crucial cellular messengers for pancreatic cancer metastasis.

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

In 2021, we have continued to characterize our identified cancer microproteins and have published our work on pTUNAR, a microprotein that regulates neural differentiation through the modulation of calcium dynamics (Senís et al. 2021). In addition, we have contributed a book chapter on the role of Myc in *in vivo* reprogramming (Senís et al. 2021). Please see our paper pick for 2021 below.

Finally, we have embarked on a collaborative project to study therapy-induced tumoral senescence and its potential as a therapeutic target and prognostic biomarker, funded by the *Asociación Española Contra el Cáncer* - AECC (Spanish Association Against Cancer).

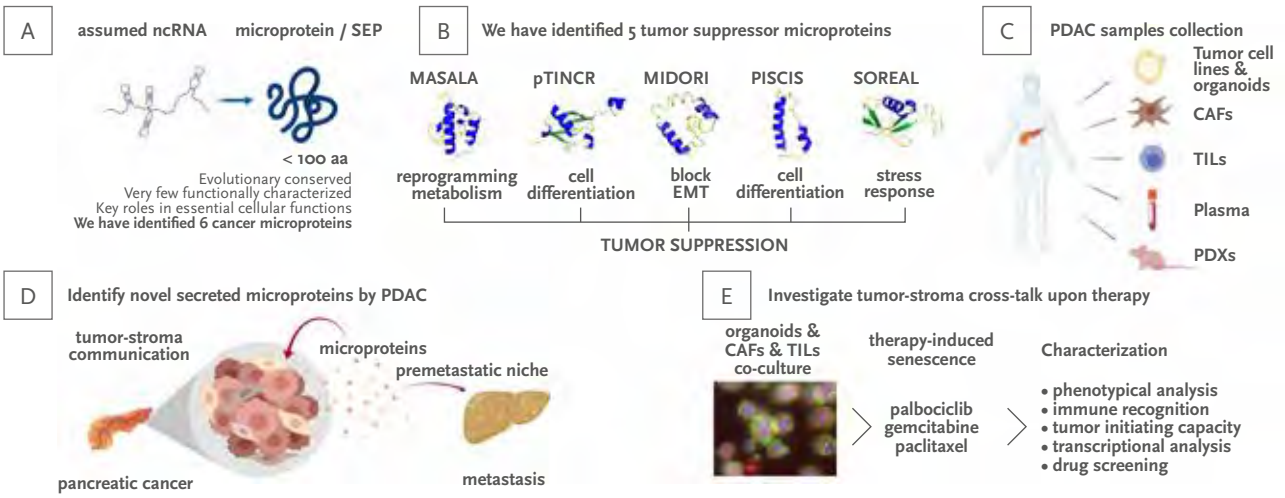

Figure: A) Recent findings have revealed that many genomic regions previously considered as non-coding in fact code for unannotated microproteins; some of them have been shown to be important for cancer. B) Our group has identified 5 novel microproteins with tumor suppressor activities. We have characterized them *in vitro* and *in vivo*. C) We have generated a comprehensive patient-match collection of pancreatic cancer samples, that is going to be instrumental for our research. D) We are investigating if cancer cells use unannotated secreted microproteins as intercellular messengers to promote tumor growth and metastasis. E) We are establishing co-cultures of organoids-CAFs-TILs to investigate the impact of therapy in the tumor-stroma cross-talk.

PI PAPER PICK 2021

Senís E, Esgleas M, Najas S, Jiménez-Sábado V, Bertani C, Giménez-Alejandre M, Escriche A, Ruiz-Orera J, Hergueta-Redondo M, Jiménez M, Giralt A, Nuciforo P, Albà MM, Peinado H, Del Toro D, Hove-Madsen L, Götz M, Abad M. TUNAR lncRNA Encodes a Microprotein that Regulates Neural Differentiation and Neurite Formation by Modulating Calcium Dynamics. *Front Cell Dev Biol*. 2021 Dec 31;9:747667.

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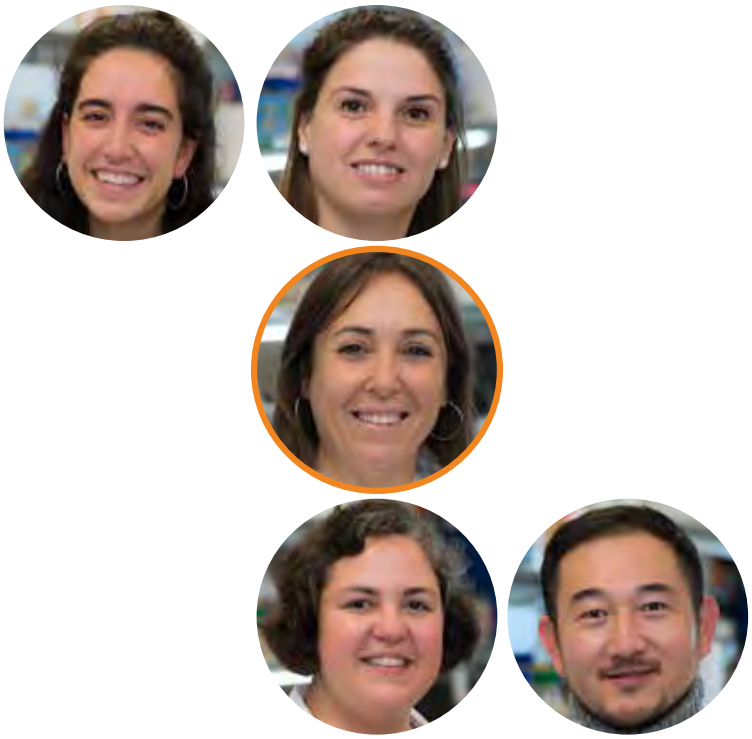
PRECLINICAL & TRANSLATIONAL RESEARCH

CHROMATIN DYNAMICS IN CANCER GROUP

Principal Investigator Sandra Peiró **Senior Scientist** Tian Tian **Graduate Students** Carmen Escudero, Queralt Serra **Students** Núria Lupión, Laia Montes **Technician** Jessica Querol



STRATEGIC GOALS

The two main goals of our laboratory are as follows:

- Understand the 3D structure of chromatin and its dynamics in cancer from a basic research perspective.
- Identify epigenetics features associated with diagnosis, treatment and drug resistance in ER+ breast cancer, gastrointestinal and hepatobiliary malignancies, and NUT-midline carcinomas.

Specifically:

- Which molecular events direct chromatin movements?
- Are these events due to the specific binding of a subset of transcription factors?
- What are the drivers associated with chromatin architecture reversible changes?
- During the process of metastasis cells go through an intermediate state. Does this state possess a specific and genomic architecture that determines metastatic fate? Could we use the underlying molecular mechanisms to inhibit metastasis?
- What is the role of oxidized H3 in solid tumors? Could we inhibit this oxidation using a peptide-based therapy?
- Are epigenetic dysregulations associated with gastrointestinal and hepatobiliary malignancies? Can Epidrug be applied to treat these malignancies?
- Which are the epigenetic biomarkers that will enable us to stratify gastrointestinal and hepatobiliary cancer patients for more effective treatments?

HIGHLIGHTS

- We have consolidated our collaboration with VHIO's Gastrointestinal & Endocrine Tumors Group (page 110) through a grant received from the *La Marató TV3* Foundation.
- Tian Tian received an *Asociación Española Contra el Cáncer* - AECC (Spanish Association against Cancer) Investigator Award for research focused on NUT-midline carcinoma.
- We have generated and fully characterized (molecularly and clinically) a unique collection of 19 advanced cholangiocarcinoma patient-derived xenograft (PDX) models.

SUMMARY

Our laboratory seeks to better understand how epigenetics and chromatin structure and dynamics affect cell behavior, with 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(Iturbide el al. 2015, Herranz et al. 2016, Cebrià-Costa et al. 2020)*. We have also discovered an important role for lamin B1 in the reorganization of 3D chromatin structure during EMT (Pascual-Reguant et al. 2018)**.

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 focus on deciphering how these alterations occur at the molecular level and more precisely identifying these putative culprits for future targeted therapy.

PI PAPER PICK 2021

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PRECLINICAL & TRANSLATIONAL RESEARCH

EXPERIMENTAL THERAPEUTICS GROUP

Principal Investigator Violeta Serra **Post-Doctoral Fellow** Alba Llop-Guevara **Graduate Students** Heura Domènech, Andrea Herencia Laia Monserrat, Andreu Òdena, Flaminia Pedretti **Visiting Students** Cristina Molina, Claudia Yáñez **Technicians** Judit Grueso, Marta Guzmán, Olga Rodríguez

STRATEGIC GOALS

- Develop predictive biomarkers of targeted treatments in ER+ and triple negative breast cancers, including inhibitors directed against the DNA damage repair protein PARP as well as signaling/ cell cycle kinases (CDK4/6, PI3K/AKT or FGFR).
- Explore novel treatment combinations for ER+ and triple negative breast cancers.
- Contribute 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

- Our group has contributed towards achieving a better understanding of the mechanisms underlying sensitivity to AKT inhibitors in breast cancer, as well as the clinical utility of diagnostic tools based on the identification of DNA repair deficiency.
- We have obtained funding from the "La Caixa" Foundation, *Asociación Española Contra el Cáncer* – AECC, *Agència de Gestió d'Ajuts Universitaris i de Recerca* – AGAUR (Agency for Management of University and Research Grants), and the *Instituto de Salud Carlos III* – ISCIII (Carlos III Health Institute), to develop a pre-commercial prototype of the RAD51 test for implementation into the Vall d'Hebron University Hospital's (HUVH) diagnostic programs.
- We have established a panel of over one hundred ER+ and triple negative breast cancer PDXs, mainly from the metastatic setting. We particularly focus on models that recapitulate progression on CDK4/6 inhibitors, and *BRCA1/2*-associated tumors.

SUMMARY

Our 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 including patient-derived xenografts (PDXs) and patient-derived cultures (PDCs) from breast cancer patient samples.

We have significantly contributed to the field of PI3K inhibitor resistance and continue to more deeply explore mechanisms of resistance to CDK4/6 inhibitors, FGFR inhibitors, AKT inhibitors and AR modulators (SARMs) in breast tumors.

Additionally, we are exploring the potential of a novel HER3-targeted antibody-drug conjugate (ADC) as a therapeutic strategy for advanced breast cancers that have developed resistance to the current standard of care treatments.

Using clinically relevant PDXs, we have provided data to further support that the loss of G1-cell cycle checkpoint control, such as mutation/loss of *RB1* or *CCND1*-amplification, is associated with the lack of response to CDK4/6 blockade in estrogen receptor-positive breast cancer. Additionally, we 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 DNA repair functionality and develop resistance to PARPi. We have developed an assay, the RAD51 test, which accurately identifies germline *BRCA* tumors that have restored DNA repair functionality and become resistant to these drugs. Importantly, this test also identifies tumors that are sensitive to PARPi through its alterations in DNA repair by homologous recombination 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 investigating the effects of PARPi on the tumor immune environment. DNA repair-deficient tumors 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 DNA repair-deficient tumors with PARPi elicits a DNA damage response, resulting in upregulation of PD-L1 that might limit the antitumor immune-mediated cytotoxicity by lymphocytes, but sensitizes to anti-PD-L1 treatments.

Our group works closely together with Cristina Saura's Breast Cancer Group (page 104), and Judith Balmaña's Hereditary Cancer Genetics Group (page 116). Reflective of VHIO's purely multidisciplinary and translational approach, our research is also carried out in collaboration with other groups including VHIO's Molecular Oncology Group (page 132), and Oncology Data Science – OdysSey Group (page 118), directed by Paolo Nuciforo and Rodrigo Dienstmann, respectively.

Our team has significantly advanced insights into 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.

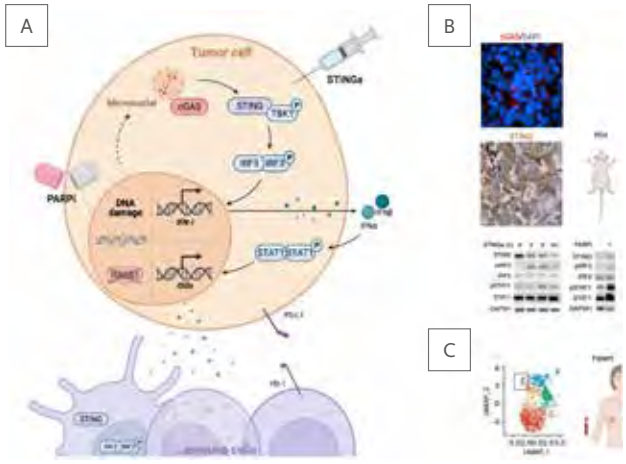

Figure: A) Schematic representation of the activation of the STING pathway in response to PARP inhibitors in tumor cells. In the absence of double strand break repair by homologous recombination, PARPi-induced DNA damage leads to micronuclei formation and cGAS activation, which triggers the STING pathway and the interferon response. B) Representative images of data showing formation of cGAS-positive micronuclei, STING expression in tumor cells and STING pathway activation upon treatment with a STING agonist or a PARP inhibitor. C) Representation of the peripheral immune populations in a patient receiving a PARPi as anti-cancer treatment.

PI PAPER PICK 2021

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PRECLINICAL & TRANSLATIONAL RESEARCH

GENE EXPRESSION & CANCER GROUP

Principal Investigator Joan Seoane **Staff Scientist** Ignasi Barba **Medical Fellow** Simona Casalino **Post-Doctoral Fellows** Ester Bonfill-Teixidor, Laura Escudero, Raffaella Iurlaro, Lidia Mateo, Ester Planas-Rigol, Gonçalo Rodrigues **Graduate Students** Ester Arroba, María López **Masters Student** Alba Díaz **Lab Manager** Alexandra Arias **Technicians** Alexandra Arias, Isabel Cuartas, Laura García, Iris Marcote, Alba Martínez

STRATEGIC GOALS

- Identify new therapeutic targets against brain tumors and novel biomarkers to more precisely predict response to therapy.
- The study of 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

- By scRNAseq analysis, we have discovered that the immune cells present in the cerebrospinal fluid of brain metastasis patients can provide biomarkers to predict response to immunotherapy (Rubio-Perez et al. 2021).
- We have participated in the elaboration of the EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis (Le Rhun et al. 2021).
- We discovered a parallelism between the inflammation occurring in SARS-CoV-2 placenta infection and cancer, and found that SARS-CoV-2 infection can impact neonatal outcome (Cribiù et al. 2021).
- A phase II clinical trial (NCT04999969) to test MSC-1(now AZD0171), initiated patient recruitment in 2021.This novel compound was designed and developed by the VHIO born spin-off, Mosaic Biomedicals, founded by Joan Seoane in 2012. Mosaic Biomedicals was acquired by Medimmune/Astrazeneca in 2020.

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 toward improving outcomes for these patients is therefore critical.

Our group is designing tools to monitor and characterize brain tumors, with specific focus on brain metastasis and central nervous system lymphomas. By analyzing immune cells in cerebrospinal fluid, we discovered that we could obtain predictive biomarkers of response to immunotherapy without having to perform a majorly invasive intracranial biopsy (Rubio-Perez et al. 2021). Moreover, we have shown that cell free circulating tumor DNA in cerebrospinal fluid facilitates the monitoring and early detection of tumor relapse in central nervous system lymphomas (Bobillo et al. 2021).

While no biomarker derived from liquid biopsy against these tumor types has yet been integrated into clinical practice, mounting evidence reported in the literature, including our findings, points to its efficacy in the real-time evaluation of malignant disease and potential to better inform and guide the therapeutic management of patients. Reflective of our work in the field, we were invited to help elaborate the EANO – ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with brain metastasis (Le Rhun et al. 2021). It has been a privilege for us to collaborate alongside other renowned scientists and clinicians specialized in brain metastasis to set out these European clinical guidelines for the management of this dismal disease.

We are as committed to advancing research into the role of the tumor microenvironment which, in the case of brain cancers, assumes a crucial role in cancer progression. Advancing insights into the tumor microenvironment promises powerful weaponry in combating cancer, regardless of heterogeneity.

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

We are now testing a novel agent MSC-1 (now AZD0171), a LIF neutralizing antibody, developed by VHIO spin-off, Mosaic Biomedicals, founded by Joan Seoane in 2012. Mosaic Biomedicals was acquired by Medimmune/Astrazeneca in 2020. A phase II clinical trial (NCT04999969) to test MSC-1 initiated patient recruitment in 2021.

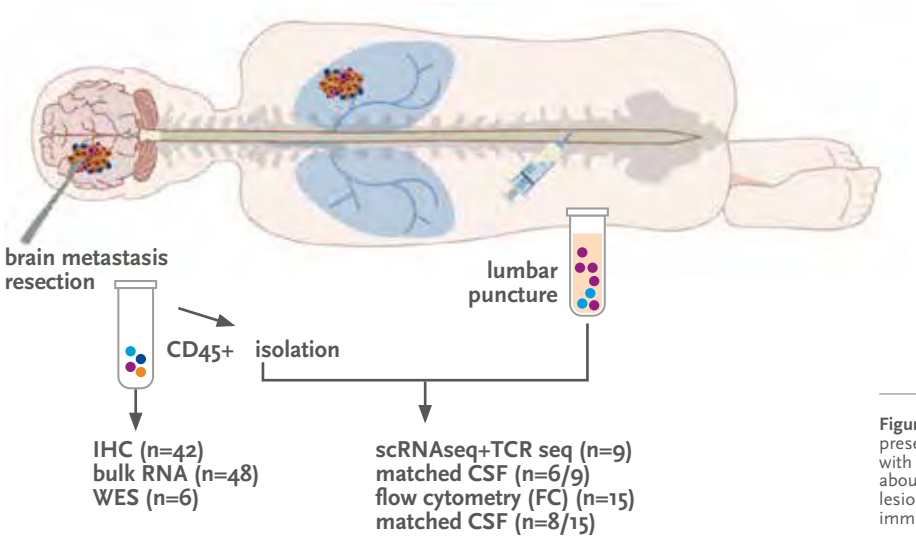

Figure: The characterization of immune cells present in the cerebrospinal fluid of patients with brain metastasis facilitates information about the immune system in the metastatic lesion and provides biomarkers of response to immunotherapies.

PI PAPER PICK 2021

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PRECLINICAL & TRANSLATIONAL RESEARCH

GROWTH FACTORS GROUP

Principal Investigator Joaquín Arribas **Post-Doctoral Fellows** Enrique Javier Arenas, Vanesa Nogales **Graduate Students** Ariadna Grinyó, Marta Lalinde, Macarena Román Alonso **Technicians** Marta Escorihuela, Sandra Perez **Visiting Scientists** Marta Bort, Santiago Duro, Alex Martínez-Sabadell, Andrea Miro

STRATEGIC GOALS

- Generation and characterization of CARs against tumor specific antigens.
- 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.

HIGHLIGHTS

- We have generated a next generation CAR T Cell that showed very promising results in *in vitro* and *in vivo* experiments.
- We have generated a new ADC against p95HER2 for potential use in combinatorial therapy.
- We obtained preliminary results showing differential role of cellular senescence in cancer according to the stage of tumor progression.
- We identified a novel mechanism of resistance to targeted therapies, involving INF-γ.

SUMMARY

2021 has been the second year of conciliation with the contingent limitations caused by COVID. However, our group has managed to continue working on all our research lines and we have produced significant results.

We have advanced insights into new mechanisms of resistance to targeted therapies. Firstly, we have demonstrated the role of the transcription factor SLUG in resistance to therapies directed against the RAF-MEK1/2-ERK1/2 pathway in pancreatic cancer (Bilal et al. 2021) Secondly, we have described a novel mechanism of acquired cancer cell resistance to T cell bispecific antibodies and CAR T targeting HER2 through JAK2 down-modulation (Arenas et al. 2021; Martínez-Sabadell et al. 2021).

Our group has also collaborated with VHIO's Sarcoma Translational Research Group (page 94), directed by César Serrano, in the study of E3 ubiquitin ligase Atrogin-1 as a mediator of adaptative resistance to KIT-targeted inhibition in gastrointestinal stromal tumor (García-Valverde et al. 2021).

Other collaborations have led to the following discoveries reported this year:

1) DNA hypomethylating agent (HMA) treatment can directly modulate the anti-tumor response and effector function of CD8+ T cells (Loo Yau et al. 2021), 2) the genetic activation of MAPK as a recurrent mechanism of anti-HER2 therapy resistance that may be effectively counteracted with MEK/ERK inhibitors (Smith E. et al. 2021), iii) CAF-derived NRG1 mediates trastuzumab resistance through HER3/AKT, which might be reverted by pertuzumab (Guardia et al. 2021), iv) RANK signaling increases after anti-HER2 therapy contributing to the emergence of resistance in HER2-positive breast cancer (Sanz-Moreno et al. 2021), and v) PI3K activation promotes resistance to eribulin in HER2-negative breast cancer (Gris-Oliver et al. 2021).

For all these studies published in 2021 see PI Paper Pick plus footnotes* below.

Regarding unpublished results:

In the generation and characterization of CARs against tumor specific antigens, we have produced a fourth-generation CAR T cell that has shown promising results in vitro and in vivo. Once we have validated its efficacy and safety, this therapy will be tested in a first phase clinical trial.

Our group has continued to pursue research into the role of senescent cells in tumor progression. We have obtained significant results on how this differs according to tumor stage. This project has received funding from the Breast Cancer Research Foundation (BCRF) for two years.

Ariadna Grinyo, a PhD student supported by a "la Caixa" Foundation INPhINIT Doctoral Fellowship-Incoming, joined our group in 2021. Ariadna has previous experience as a researcher of immune response at the biotechnology company Integral Molecular in Philadelphia (PA, USA), and has started her thesis on the generation of fourth-generation CARs against solid tumors.

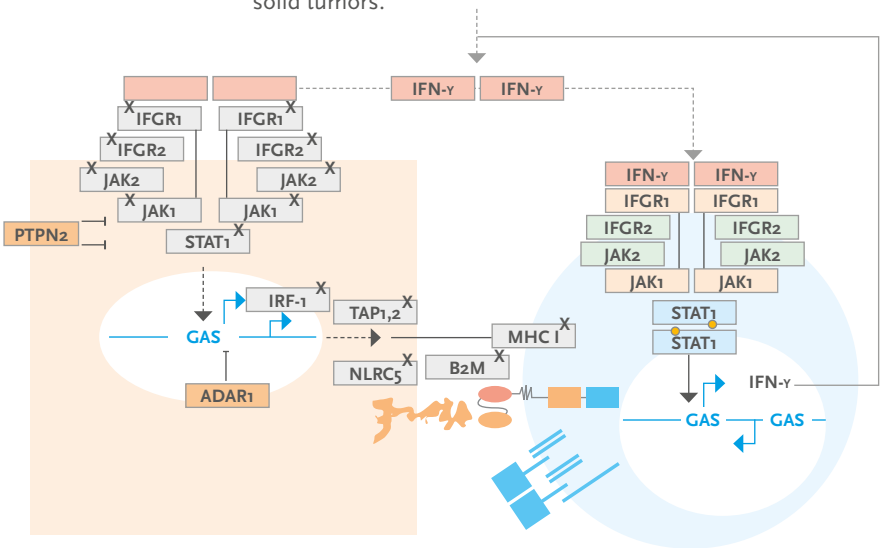

Figure: Mechanisms of resistance to immunotherapy driven by IFNγ signaling disruption. The different components inactivated (in shades of gray and with an x) or upregulated (in yellow) in the different models of resistance to immune therapies described in Martinez-Sabadell et al. 2021.

PI PAPER PICK 2021

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PRECLINICAL & TRANSLATIONAL RESEARCH

MODELS OF CANCER THERAPIES GROUP

Principal Investigator Laura Soucek **Senior Investigator** Jonathan Whitfield **Research Associate** Mariano F. Zacarías-Fluck **Post-Doctoral Fellow** Jastrinjan Kaur **Technicians** Génesis Martín Fernandez, Erika Serrano del Pozo **PhD Students** Fabio Giuntini, Íñigo González-Larreategui

STRATEGIC GOALS

- Preclinically validate novel therapeutic strategies against MYC in breast, brain, lung, neuroblastoma, melanoma, colorectal cancer, and multiple myeloma.
- Validate anti-MYC Omomyc-based cell penetrating mini-proteins for cancer therapy.
- Define the role of MYC in promoting cancer immune evasion and test the efficacy of MYC inhibitors and IO combination treatments in cancer treatment.
- Investigate how the MYC network functions in Max-defective gastrointestinal stromal tumors (GISTs) and Small-Cell Lung Cancer (SCLC) to define actionable targets to tackle these unmet clinical needs.

HIGHLIGHTS

- In 2021, Laura's laboratory has continued to publish science of excellence. Amongst other manuscripts, they published an article in *Life Science Alliance*, pointing to the Wnt signaling receptor Fzd9 as an essential molecule for MYC-driven tumorigenesis in pancreatic islets, first authored by Mariano Zacarías-Fluck and Toni Jauset, a former PhD student from her lab.
- Alongside Sandra Martínez-Martín (a former postdoc in the lab now working at Peptomyc), Laura Soucek authored a review in *Cancer Drug Resistance* on MYC inhibitory strategies for the treatment of multiple myeloma.
- Jonathan Whitfield and Laura Soucek published a review in the *Journal of Cell Biology* summarizing the different strategies adopted thus far against MYC as well as drug development efforts aimed at targeting MYC. They also highlight the initiation of the clinical trial with OMO-103, the compound developed by Laura's group and the VHIO and ICREA spin-off Peptomyc.
- Jonathan and Laura also co-edited the second edition of *The Myc Gene: Methods and Protocols* (Springer Protocols, Humana Press) and authored the introductory chapter entitled: *An "-omycs" Toolbox to Work with MYC*.
- Laura Soucek's group has also co-authored papers in *EMBO Journal* and *Blood Advances*, thanks to collaborations with the groups of Bruno Amati and Roberto Chiarle, on non-specific and sequence-specific DNA binding in MYC-driven transcription, and BCL6 as a therapeutic target in Burkitt lymphoma, respectively.
- The lab received funding through the *I+D+I en Líneas Estratégicas en colaboración público-privada* program, from the Spanish Ministry of Science and Innovation. This project involves VHIO, Peptomyc (VHIO and ICREA spin-off), the Hospital 12 de Octubre (Madrid, Spain), and CIMA, and aims at using MYC inhibition to overcome immunotherapy resistance in KRAS-driven NSCLC with diverse mutational profiles.

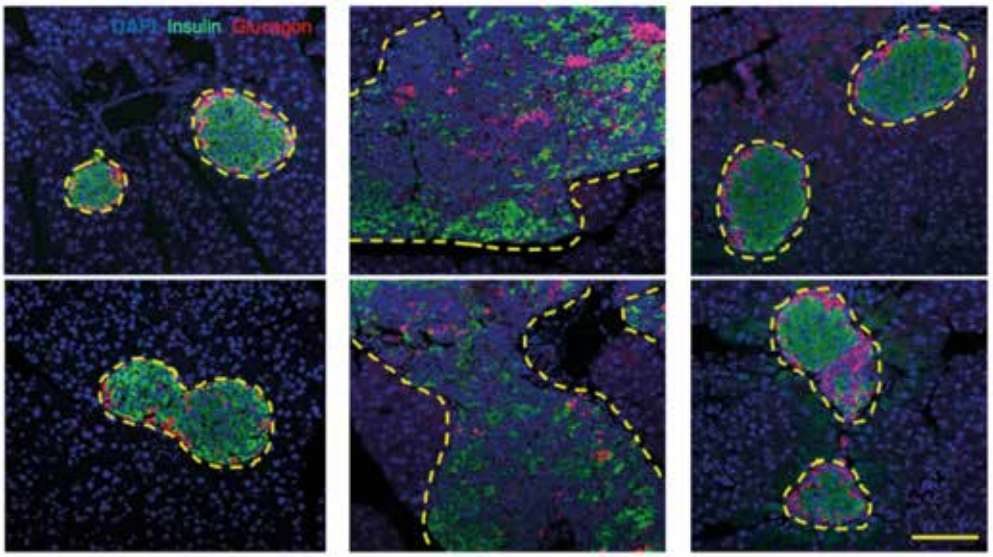
SUMMARY

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 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). Notably, the first Omomyc-derived compound, OMO-103, entered clinical trials Phase I/IIa in May 2021.

Our group has continued to contribute to cancer research in general and, more specifically, as a leader in the MYC field, by (co) authoring articles and reviews, exploring new aspects of MYC biology in different pathologies and summarizing efforts to develop a clinically viable MYC inhibitor.



Fzd9$^{KO/KO}$BclXL **Fzd9$^{WT/WT}$;MycER;BclXL** **Fzd9$^{KO/KO}$;MycER;BclXL**

Figure: Adapted from Zacarías-Fluck et al.: Wnt signaling receptor Fzd9 is essential for MYC-driven tumorigenesis in pancreatic islets. Left panel: control islets. Middle panel: MYC-induced insulinomas. Right panel: expansion of insulinomas is prevented by the absence of Fzd9.

PI PAPER PICK 2021

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PRECLINICAL & TRANSLATIONAL RESEARCH

PROSTATE CANCER TRANSLATIONAL RESEARCH GROUP

Principal Investigator Joaquin Mateo **Senior Investigator** Nicolas Herranz **Post-Doctoral Fellows** Irene Casanova, Luisa Delgado **PhD Students** Sara Arce, Julian Brandariz **Technicians** Olaia Baylo, Teresa Casals, Natalia Castro, Sarai Cordoba, Lucila González **Clinical Data Curator** Magdalena Guardiola **Bioinformatician** Daniel Aguilar **Masters Student** Arnau Solé

STRATEGIC GOALS

- To investigate correlations between patient molecular profiling and clinical outcome that can guide more precise prostate cancer treatment strategies.
- Study how prostate cancers adapt to therapy, with a focus on targeting emerging vulnerabilities to delay disease recurrence.
- Investigate tumor heterogeneity in response to therapy in preclinical and patient-derived xenograft models (PDX), as well as by interrogating patient biopsies.
- Develop new liquid biopsy tools that can be used to monitor tumor evolution.
- Apply computational pipelines towards investigating genomic signatures in prostate cancer.
- Development of academic clinical trials to validate in the clinic our laboratory results, and leveraging patient biopsies for correlative studies.

HIGHLIGHTS

- We serve as central sample repository for 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. VHIO acts as the national lead for this project that has already enrolled >250 men with advanced prostate cancer in Spain and >2500 worldwide.
- We received the CRIS Cancer Foundation Clinical Talent Award, allowing us to expand our group with bioinformatics expertise to study genomic signatures in prostate cancer.
- Regarding our interest in tumor adaptation and therapy-induced senescence, our group participates in a consortium that was awarded with a Coordinated Groups grant by the *Asociación Española Contra el Cáncer* - AECC (Spanish Association Against Cancer).
- In collaboration with the Urology, Oncology and Radiology teams at the Vall d'Hebron University Hospital (HUVH), we have generated PDX models from prostate cancer biopsies.
- We are conducting our first investigator-initiated clinical trial, a phase II study co-targeting AR and PARP in metastatic hormone-naïve prostate cancer, which is actively recruiting in 9 hospitals across Spain.

SUMMARY

Our research model follows a bench-to-bedside-and-back approach. We have set up a platform for acquiring longitudinal samples from advanced prostate cancer patients, both tumor tissue as well as liquid biopsies, that can be used to investigate the evolving features of the disease, but also to generate patient-derived laboratory models of advanced prostate cancer that we can leverage to investigate new therapeutic strategies at the bench.

Moreover, the launch of investigator-initiated clinical trials is central to our research strategy, as a platform for correlative studies that can optimize the drug development pathway for prostate cancer patients. At present, we are the central laboratory for two academic multi-center clinical trials, as well as serve as the national repository for the IRONMAN registry; an important international effort to build a large bank of clinical data and biospecimens from metastatic prostate cancer (mPC) patients.

We aim to integrate insights in molecular biology, genomics, transcriptomics, computational sciences and clinical data towards developing precision medicine strategies for prostate cancer patients. To this end, our team comprises biomedical scientists with expertise in cancer biology, genomics and transcriptomics, bioinformatics and liquid biopsy, as well as medical oncologists and clinical data managers.

One of our main lines of research is to decipher how prostate cancers adapt to exposure to systemic therapies, particularly androgen-targeting agents, with a particular focus on the cell cycle and DNA damage response regulation and the emergence of quiescent and senescent phenotypes that can drive drug resistance. By studying in-vitro and in-vivo models, including patient-derived xenografts (PDX) from the patients participating in our clinical studies, we aim to understand how to target emergent phenotypes through drug combinations. These studies are currently funded by grants from the Spanish Ministry of Health, *Fundación FERO* (FERO Foundation - see page 29), *Asociación Española Contra el Cáncer* - AECC (Spanish Association Against Cancer), as well as through collaborations with biopharmaceutical companies.

Our group also aims to pursue the molecular characterization of advanced prostate cancer, focusing on how tumors evolve in a heterogeneous manner as they become resistant to different treatments. We have therefore set up a genomics and transcriptomics platform in the lab to perform DNA and RNA profiling from patient biopsies. We are developing novel liquid biopsies assays that will enable us to study the disease though longitudinal samples. By exploiting publicly available genomics datasets from patients at different stages of disease, our computational scientists investigate how the genomic profile of disease changes over time. These studies are currently funded by grants from the US Department of Defense's (DoD) Congressionally Directed Medical Research Programs (CDMRP), the Spanish Ministry of Health, CRIS Cancer Foundation, AECC, *Fundación FERO*, and the "la Caixa" Foundation.

Lastly, given that well-annotated correlative clinical data is crucial to establish the potential relevance of molecular data, our team maintains databases collecting outcome data for all patients who donate samples for our studies to perform subsequent correlative analysis.

To more rapidly advance the field, we believe in team science. We therefore participate in several different collaborations that pool resources and combine cross border expertise across several different research teams and groups.

In summary, our research integrates different modalities of data generated in the lab that can lead to the design of therapeutic interventions aimed at improving outcomes for prostate cancer patients.

PI PAPER PICK 2021

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PRECLINICAL & TRANSLATIONAL RESEARCH

SARCOMA TRANSLATIONAL RESEARCH GROUP

Principal Investigator César Serrano **Pre-Doctoral Fellows** Alfonso García Valverde, David Gómez Peregrina, Gemma Mur Bonet, Iván Olivares Rivas, Daniel Pilco Janeta **Senior Technician** Jordi Rosell Aluja **Graduate Student** Morris Schöffski

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.
- Clinical drug development in sarcomas across phase I to phase III clinical trials.

HIGHLIGHTS

- Our group leads high-level studies towards the clinical implementation of liquid biopsy in GIST patients.
- We have been awarded by the *Asociación Española Contra el Cáncer* - AECC (Spanish Association Against Cancer) Senior Clinician Program to study the evolutionary landscape of resistance in GIST.
- César Serrano has been part of the international research teams whose work has led to the approval of ripretinib and avapritinib for the treatment of GIST patients.
- Our group is fully committed to generating laboratory models from most sarcoma subtypes thanks to the support received from patients through the #SarcModel initiative.

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: sarcomas driven by simple genetic alterations, such as translocations or specific activating mutations; and tumors with complex and unbalanced genomic aberrations. Both include diverse sarcoma subtypes often with profound differences in their molecular makeup, course of disease and therapeutic approach.

We focus on the study of sarcomas with oncogenic dependency on specific drivers of disease. Among these, gastrointestinal stromal tumor (GIST) is the most common malignant mesenchymal neoplasm and constitutes a paradigmatic model for studying oncogene addiction and identifying structural and functional mechanisms for drug response and resistance.

Ongoing efforts aim at achieving a deeper biological understanding of GIST and other sarcomas in order to advance drug development. The heterogeneity of mechanisms of resistance represents one of the major challenges in improving outcomes for these patients. We therefore seek to identify crucial molecules and signaling mechanisms in GIST biology that can serve as therapeutic vulnerabilities.

Our group also continues to validate a core set of molecules that are co-regulated by KIT downstream pathways and identified through extensive whole transcriptome studies across several clinically representative human GIST models.

We also perform high-throughput genomic and transcriptomic studies to decipher the evolving patterns of resistance in GIST throughout the course of disease, as well as investigate liquid biopsy in sarcoma to provide robust evidence that will help to more precisely guide treatment decisions by plasma sequencing. In addition, the GISTomics project, a European initiative driven by our group, aims to advance insights into the landscape of GIST evolution.

Beyond GIST, our group has initiated new lines of research focused on other sarcoma subtypes, including muscle-derived sarcomas (leiomyosarcoma and rhabdomyosarcoma), angiosarcoma, and liposarcoma. Functional precision medicine is a major focus of research in these neoplasms.

Our aim is to have a true clinical impact by improving the daily treatment and care of our patients. We are proud to report that our Sarcoma Multidisciplinary Unit has been designated as an Expert Sarcoma Center of the European Reference Network ERN-EURACAN, and thus constitutes an optimal setting for translating cancer discovery into clinical benefits.

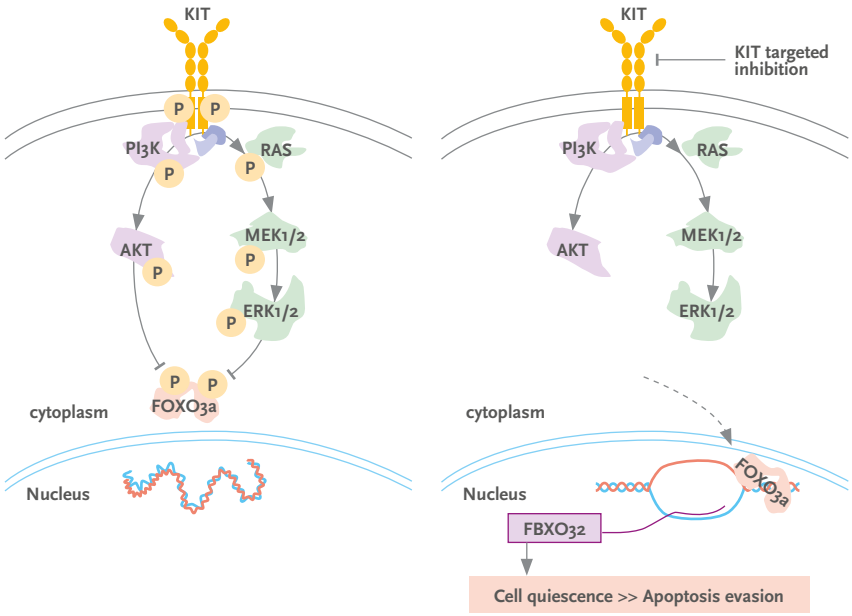

Figure: KIT/PDGFRA oncogenic tyrosine kinase signaling is the central oncogenic event in most gastrointestinal stromal tumors (GIST), which are human malignant mesenchymal neoplasms that often feature myogenic differentiation. Although targeted inhibition of KIT/PDGFRA provides substantial clinical benefit, GIST cells adapt to KIT/PDGFRA driver suppression and eventually develop resistance. We uncovered E3 ubiquitin ligase Atrogin-1 -the main effector of muscular atrophy in cachexia- as the most critical and GIST-cell-specific pro-survival mechanism that enabled the adaptation to KIT-targeted inhibition by apoptosis evasion through cell quiescence. Buttressed on these findings, we established in vitro and in vivo the preclinical proof-of-concept for co-targeting KIT and the ubiquitin pathway to maximize the therapeutic response to first-line imatinib treatment. Adapted from García-Valverde et al. *Oncogene*, 2021.

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PRECLINICAL & TRANSLATIONAL RESEARCH

STEM CELLS & CANCER GROUP

Principal Investigator Héctor G. Palmer **Post-Doctoral Fellows** Oriol Arqués, Jordi Martínez-Quintanilla, Isabel Puig **PhD Students** Alex Mur, Lorena Ramirez, Candida Salvans Gorjón **Technicians** Laia Cabellos, Debora Cabot, Irene Chicote, Jordi Vergés Sanjaime

STRATEGIC GOALS

- Advance insights into tumor dormancy.
- Study the role of epigenetic factors governing dormancy in chemoresistance, minimal residual disease, relapse, dissemination and metastasis.
- ONIRIA Therapeutics - modulating cell dormancy to combat cancer.
- Develop small drug modulators of cancer cell dormancy to block cancer progression.
- Molecularly-matched targeted therapies.
- Unveil the mechanisms of response to drugs targeting EGFR, BRAF, MEK, ERK, LGR5, Wnt, or PARP.
- Refinement of advanced cancer models.
- Expand our PDX collection and develop new orthotopic models as well as live imaging techniques.

HIGHLIGHTS

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

SUMMARY

VHIO's Stem Cells & Cancer Group studies the mechanisms that enable tumors to evade effective treatments and progress to advanced stages of disease.

We use multi-omics approaches to reveal unexpected alterations related to tumor and single cell phenotypes. Combining gene editing (CRISPR/Cas) with classical signaling biochemistry in cancer cell lines as well as genetically modified mice, patient-derived organoids (PDO) and xenografts (PDX), our group investigates the functional relevance of these newly identified alterations in patients' response to therapies.

We participate in a global multidisciplinary task force incorporating medical oncologists, surgeons, radiologists, and nurses. This strong collaboration aims to rapidly translate laboratory results to the clinic.

Main research lines include:

Tumor cell dormancy

The study of the intriguing biology of cancer cell dormancy as a driver of chemoresistance, formation of minimal residual disease, and disease relapse in patients.

We previously discovered a core epigenetic network that governs dormancy of tumor cells (Puig et al. 2018)*, and are now investigating the function of TET2, DPPA3 and other epigenetic and transcription factors governing dormancy in greater depth. Importantly, our group is 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

We work 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 (Tenbaum et al. 2012; Puig et al. 2013; Capdevila et al. 2020)**.

Based on our discoveries, we are designing new prescreening tests for the genetic-guided enrolment of patients in clinical trials. Importantly, findings are helping to define new rational drug combinations to treat cancer patients with progressive disease.

Preclinical cancer models

Our group is also expanding and characterizing its PDX collections (CRC, neuroendocrine and peritoneal pseudomyxoma), and optimizing their use in evaluating drug efficacy and metastasis by orthotopic injection and live imaging (TC, PET and Echography).

Lastly, we are developing ambitious projects through the EurOPDX, PERSIST-SEQ, CRCelerate Consortia, co-founded by VHIO. These partnerships comprise all the main reference groups working with PDX, single cell sequencing and cancer models in Europe.

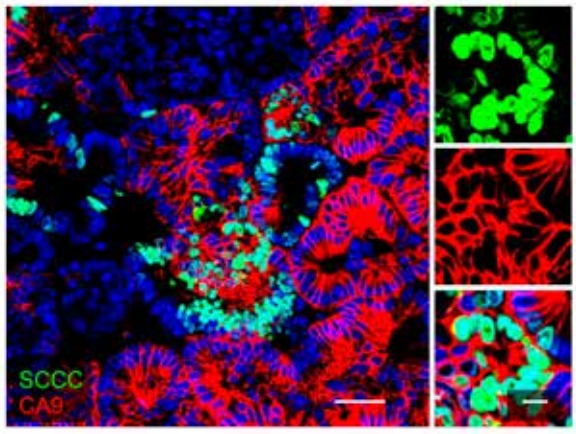

Figure: Slow Cycling Cancer Cells (SCCC) reside in hypoxic areas (CA9 marker). A set of epigenetic regulators sustain the survival of a reservoir of SCCC in low oxygen tumor niches.

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PRECLINICAL & TRANSLATIONAL RESEARCH

TUMOR BIOMARKERS GROUP

Principal Investigator Josep Villanueva **Post-Doctoral Fellow** Chiara Bellio **Graduate Student** Mireia Pujals **Technicians** Marta Emperador, José Ángel Robles, Ferran Soler

STRATEGIC GOALS

- Characterize the role of RAGE in breast cancer invasion and metastasis.
- The characterization of mechanisms adopted by tumor cells to communicate with their microenvironment during treatment to identify secreted response/resistance biomarkers to cancer drug therapies.
- The identification of mechanisms of acquired resistance to current therapies in breast cancer.

HIGHLIGHTS

- We have uncovered a role of RAGE in the cellular plasticity of triple-negative breast cancer (TNBC) invasive cells. We have also shown that cellular plasticity of TNBC cells can be modulated by specific RAGE antagonists. We envisage that these reagents will ultimately serve as new therapeutic tools against this tumor type.
- We have continued to focus on the development of response and resistance biomarkers to cancer drugs used in the clinic to treat TNBC patients. Furthermore, we have been working towards the identification of mechanisms of acquired resistance to current anti-cancer medicines.

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.

We aim to characterize the mechanisms adopted by these cells to communicate amongst themselves as well as with their microenvironment during tumorigenesis, and exploit these data to advance biomarker and drug target discovery.

Our group'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 disease progression, thus representing potential therapeutic targets.

Our methodological focus 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. Strikingly, when secretome profiles are carefully produced and analyzed, 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 be implicated in tumorigenesis.

In line with this notion, our recent efforts in 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.

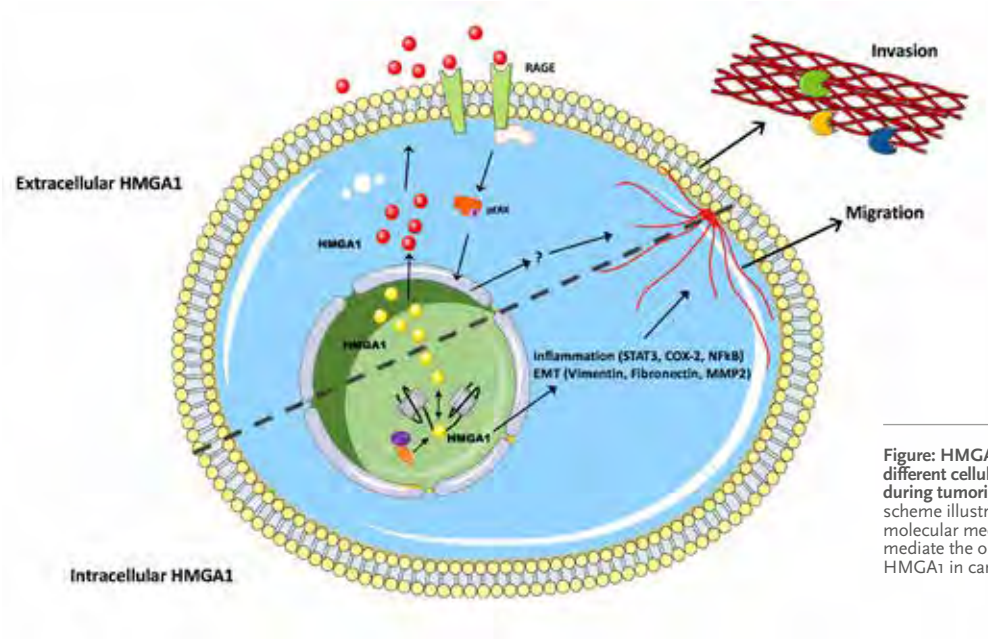

Figure: HMGA1 works in different cellular compartments during tumorigenesis. The scheme illustrates the known molecular mechanisms that mediate the oncogenic role of HMGA1 in cancer.

PI PAPER PICK 2021

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PRECLINICAL & TRANSLATIONAL RESEARCH

TUMOR IMMUNOLOGY & IMMUNOTHERAPY GROUP

Principal Investigator Alena Gros **Post-Doctoral Fellows** Pierre Levy, Jara Palomero **Graduate Students** Judit Díaz, Andrea Garcia, Maria Lozano, Anna Yuste **Technicians** Immaculada Creus, Albert Marín **Student** Maria Fidel **Lab Manager** Noelia Alcazar **Computational Technician** Jonatan González

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 rapidly identify tumor-reactive lymphocytes as well as the specific target antigens recognized.
- 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 finalized the clinical grade validations of TIL expansion for the treatment of patients at Vall d'Hebron in collaboration with the Blood and Tissue Bank (BST), a public agency of the Catalan Government's Department of Health. This work was supported by funding received from the BBVA Foundation and its Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI) at VHIO.
- Together with Elena Garralda, Principal Investigator of VHIO's Early Clinical Drug Development and Director of our Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch, we received authorization from the *Agencia Española de Medicamentos y Productos Sanitarios* (AEMPS - Spanish Regulatory Agency), and initiated patient recruitment for a phase I clinical study to test the safety and tolerability of neoantigen-selected TIL for patients with solid tumors refractory to standard therapies.
- 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 and eliminate cancer. However, tumors evade the immune response through multiple mechanisms. Immunotherapies exploit the immune system to attack cancer. Clinical studies have shown that immune checkpoint inhibitors and T-cell-based therapies can mediate tumor regression in patients with metastatic disease. Thus, in addition to surgery, radiation therapy and chemotherapy, immunotherapy has become the fourth pillar of anti-cancer therapy.

Our group's work has demonstrated that tumor-reactive T cells can frequently be detected circulating in the blood of cancer patients, regardless of the specific tumor type. Tumor-reactive lymphocytes can recognize cancer neoantigens, derived from mutated gene products, and these appear to play an important role in the clinical efficacy of cancer immunotherapies. Furthermore, we have reported biomarkers expressed preferentially on tumor and neoantigen-reactive lymphocytes residing in tumors and in circulation.

Thanks to the support received from the BBVA Foundation's Comprehensive Program of Cancer Immunotherapy & Immunology - CAIMI (page 140), as well as other funding agencies, we aim to leverage these biomarkers to reveal T-cell characteristics associated with the clinical efficacy of immune checkpoint blockade in patients treated at the Vall d'Hebron University Hospital (HUVH). In addition, we are currently developing tailored and minimally-invasive T-cell therapies targeting neoantigens derived from peripheral blood.

Through our group's long-standing collaboration with Elena Garralda, Principal Investigator of VHIO's Early Clinical Drug Development Group (page 106), and Director of our Research Unit for Molecular Therapy of Cancer (UTIM) – CaixaResearch (page 149), we recently received authorization from the *Agencia Española de Medicamentos y Productos Sanitarios* (AEMPS - Spanish Regulatory Agency) in May 2021 to initiate a phase I clinical trial to test the safety and tolerability of neoantigen-selected TILs.

In this clinical trial we use a highly personalized approach (see Figure) to screen for T-cell mediated recognition of mutated antigens using autologous antigen presenting cells that can process and present in all the potential human leukocyte antigen (HLA) restriction elements. In this pilot clinical study funded by the *Instituto de Salud Carlos III* – ISCIII (Carlos III Health Institute), we aim to treat up to 10 patients with epithelial cancers and melanoma refractory to standard therapies. By enriching for neoantigen-reactive lymphocytes, we hope to extend the efficacy of TIL therapy beyond melanoma.

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 personalized immunotherapies against cancer.

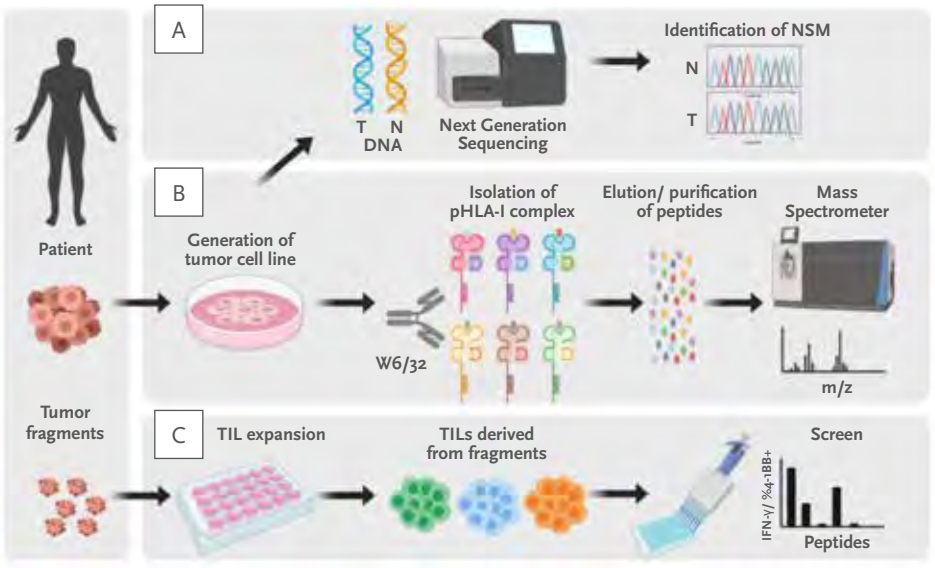

Figure: Personalized approach to identify tumor and neoantigen- specific TILs. A) We sequence normal and tumor DNA to identify all the non-synonymous mutations. B) In parallel we attempt to generate a tumor cell line. When generated, we isolate the peptide-MHCI complexes and we identify the peptides presented by MHCI by the tumor cell line by Mass spectrometry. C) Finally, we screen the TILs expanded from the tumor for recognition of the candidate neoantigen peptides identified in A) or elluted from MHCI in B).

PI PAPER PICK 2021

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CLINICAL RESEARCH

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CLINICAL RESEARCH

For another year, due to the safety issues brought about by COVID-19, we had to adjust our approach to this report's photography. With the exception of some of our larger groups*, we have ensured that as many group members as possible have been included, and without masks. Each individual picture was taken at a distance in locations away from areas dedicated to the care of our cancer patients. For faculty working remotely, we invited them to submit their photos from home.

*** Considering certain logistical and spatial issues, we have unfortunately had to repeat pictures of some of our larger groups and units from VHIO's Scientific Report 2019 - as indicated in the corresponding pages.**

CLINICAL RESEARCH

BREAST CANCER & MELANOMA GROUP

Principal Investigator Cristina Saura **Medical Oncologists and Clinical Fellows** Miriam Arumi, Judith Balmaña, Meritxell Bellet, Maria Borrell, Marta Capelan, Mara Cruellas, Santiago Escrivá, Patricia Gómez, Eva Muñoz, Mafalda Oliveira, Carolina Ortiz, Isabel Pimentel, Lucia Sanz, Esther Zamora **Clinical Nurses** Anna Suñol, Anna Vázquez **ESMO Translational Research Fellow** Andri Papakonstantinou

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 early and advanced disease.

Melanoma:

- Our Melanoma Unit leads one of the largest networks in Spain and across Europe, and is also one of the most active groups in early stage and metastatic disease clinical trials in melanoma and other skin tumors. Each study is tightly connected with the corresponding translational research lines led by VHIO scientists in collaboration with our clinical investigators.

HIGHLIGHTS

- Relevant contributions in drug approval. Thanks to the leadership position of our investigators, we have contributed to the approval of therapies including trastuzumab deruxtecan, tucatinb, sacituzumab govitecan or margetuximab for patients with advanced breast cancer, pembrolizumab for stages IIB/IIC in the adjuvant melanoma setting, new combinations such as nivolumab plus relatlimab for the treatment of metastatic melanoma, and pembrolizumab for patients with advanced squamous cell carcinoma.
  We are currently involved in the development of some of the most promising therapies for breast cancer or several IO combinations, targeted therapies and anti-PD1 for SCC and BSC treatment that will lead to new approvals in the near future.
- Precision medicine. Thanks to VHIO's Molecular Prescreening Program Program (page 156), driven by one of our Institutional Programs, the Advanced Molecular Diagnostics Program – DIAMAV (page 138), supported by the FERO Foundation, we continue to identify potential patients with molecular alterations as an enrichment strategy for clinical trials in breast cancer with *PI3KCA*, *ESR1* or *HER2* mutations and *BRAF*, *NRAS*, *LAG3*, *TYRP1* and other mutations for patients with melanoma and other cutaneous tumors.
- Our Institute's proteomics and cfDNA platforms have also helped us to advance insights into tumor biology. In skin tumors we are developing a personalized platform to identify high risk tumors in the early setting and new mutational alterations in the metastatic in collaboration with VHIO's Molecular Prescreening Program and our Phase I Clinical Trial Unit (page 149).

SUMMARY

The main area of expertise of our Breast Cancer Group, led by Cristina Saura, is clinical research focused on drug development and associated translational research. In addition to maintaining high patient recruitment in our studies, even during the challenging scenario of the COVID-19 pandemic, we also play a leading role in many of the clinical trials that we run. This enables us to apply 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 the field including trastuzumab deruxtecan, tucatinib, neratinib, margetuximab and SYD985. In collaboration with VHIO's Growth Factors Group led by Joaquín Arribas (page 88), we explore cancer drug resistance to these agents through VHIO's in-house established PDX models. Alongside Paolo Nuciforo's Molecular Oncology Group (page 132), 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 84), we have developed several PDX models to advance insights into 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 addition to our participation in clinical trials testing combinations of immunotherapies and promising antibody drug conjugates, we are investigating the dynamics of ctDNA in early TNBC and collaborating in pioneering projects focused on cell-based therapies directed by Alena Gros, PI of VHIO's Tumor Immunology and Immunotherapy Group (page 100), to develop novel personalized T-cell therapies against cancer.
- cfDNA: In collaboration with VHIO's Cancer Genomics Group led by Ana Vivancos (page 130), 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 Group, also focused on other malignant skin tumors, is led by Eva Muñoz. She has actively participated in the development of -and active recruiting for- several phase I, II and III trials to study various emerging therapies for the treatment of these diseases. This group leads its own research program incorporating clinical investigators, dermatologists, and VHIO investigators, in collaboration with other national and international institutions.

Their studies focus on new targeted therapies and resistance to immunotherapy by conducing purely translational research centered on cutaneous, mucosa, acral and uveal melanoma, and other skin tumors. Eva's group mainly investigates squamous and basal cell carcinoma acquired resistance and disease progression, and assesses new combinations for the treatment of melanoma. Her team also maps therapeutic avenues, follow up standards, and seeks to identify biomarkers for a more precise treatment selection matched to the specificities of our patients.

PI PAPER PICK 2021

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CLINICAL RESEARCH

EARLY CLINICAL DRUG DEVELOPMENT GROUP

Director of Clinical Research at VHIO Josep Tabernero **Principal Investigator, Early Clinical Drug Development Group, Director, UITM – CaixaResearch** Elena Garralda **Associate Investigators, Senior Consultants** Judith Balmaña, Joan Carles, Enriqueta Felip, Elena Garralda, Teresa Macarulla, Ana Oaknin, Cristina Saura, Josep Tabernero **CORE Phase I Investigators** Guzmán Alonso, Irene Braña, Vladimir Galvao, Julia Lostes, Honey K. Oberoi, Katerin Rojas, Omar Saavedra, Maria Vieito **Phase I Investigators** Daniel Acosta, Juan David Assaf, Iosune Baraibar, Maria Borrell, Ana Callejo, Jaume Capdevila, Susana Cedrés, Marc Diez, Elena Élez, Santiago Escrivá, Alejandro García, Carmen García, Macarena González, Francisco Grau, Jorge Hernando, Patricia Iranzo, Alexandre Martínez, Rafael Morales, Eva Muñoz, Alejandro Navarro, Mafalda Oliveira, Carolina Ortiz, Nuria Pardo, Francisco Javier Ros, Francesc Salvá, Nadia Saoudi, Cristina Suárez, Helena Verdaguer **Data Manager** Roger Berché **Clinical Nurse Specialist** Marta Sanz

HIGHLIGHTS

- Despite the COVID-19 pandemic, we have successfully continued with our activities and programs to test the best-in-class drugs. We have carried out many clinical trials with new targeted agents, novel-novel combinations, immuno-oncology, ADC, and epigenetic drugs.
- Within the scope of our CaixaResearch Advanced Oncology Research Program (page 139), we have performed several clinical trials with patients selected based on molecular alterations: mutations in AKT1, EGFR, IDH1, ALK, ROS1, BRAF, NRAS, KRAS, FGFR1 and 2, MET, HER2, HER3, RET; ATM; BRCA, amplifications in HER2, AKT 1, 2, and 3, FGFR1, MET, NOTCH1-4, rearrangements of NTRK1-3 ROS1, ALK, BRAF, RSPO2/3, RET, NRG and FGFR1-3.
- As part of our BBVA Foundation Comprehensive Program of Cancer Immunotherapy & Immunology - CAIMI (page 140), we have continued our line of research to characterize hyperprogressive disease with immunotherapy. We have secured further funding to evaluate the biological mechanisms of hyperprogressive disease in collaboration with Paolo Nuciforo, PI of VHIO's Molecular Oncology Group (page 132), Rodrigo Toledo, one of VHIO's translational investigators, along with other international collaborators including Sergio Quezada, University College London - UCL (UK).
- We have continued our collaboration with VHIO's Rodrigo Toledo to monitor the cfDNA of patients receiving immunotherapy and characterize the clonal evolution of these patients.
- Also, within the context of our BBVA Foundation's CAIMI program, in collaboration with Raquel Perez-Lopez, PI of our Radiomics Group (page 122), we have established a radiomic signature to predict response to immunotherapy. We have secured further funding to see how this correlates with the genomic evolution observed in patients.
- We have continued working on our program for advanced therapies in solid tumors, as well as implemented our own academic TILs program in collaboration with Alena Gros' Tumor Immunology & Immunotherapy Group at VHIO; our CAR-T cell project funded through a grant received from the *Asociación Española Contra el Cáncer* – AECC (Spanish Association against Cancer) in 2019. We also continue to pursue our research into NK cells in collaboration with colleagues at the *Clínica Universidad de Navarra* (Spain), in addition to other cell-based therapies.
- Our group has launched a project to accelerate the digitalization of phase I units: SMART Experimental Cancer Medicine Trials eNABLED, in collaboration with Rodrigo Dienstmann, PI of VHIO's Oncology Data Science (ODysSey) Group (page 118), supported by a Cancer Research UK (CRUK) Accelerator Award.
- Supported by EU's Horizon 2020 Framework Programme, we are coordinating the Cancer Core Europe Consortium-Building Data Rich Clinical Trials (CCE-DART) project (page 37). This pioneering project will develop interconnected tools to reduce the current complexity of investigator-initiated trials and better guide clinical decision-making by incorporating cutting-edge digital technologies and platforms.

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 – CaixaResearch with 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, and pharmaceutical companies).

SUMMARY

Our group focuses on proof-of-concept and proof-of-mechanism clinical 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 our Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch (page 149), 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 studies (biomarker development, profound understanding of mechanisms of action and resistance).

We participate in VHIO's Molecular Prescreening Program (page 156), 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 204), and the Cancer Core Europe - CCE (page 197), 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 – CaixaResearch, have continued to lead the Basket of Baskets (BoB) trial. This academic study, endorsed by CCE, 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. During 2021, we have also continued to search for funding to add new modules.

In addition, we coordinate the EU-funded Cancer Core Europe Consortium-Building Data Rich Clinical Trials (CCE-DART) project (page 37). By harnessing and incorporating powerful cutting-edge technologies, methods and platforms, CCE-DART investigators will spur the design, development, and ringing in of a new generation of data rich, dynamic studies in oncology over the next years to come.

Our Early Drug Development Group and Phase I Unit UITM – CaixaResearch continue to establish VHIO as a leading reference in driving drug development and targeted therapies in oncology. Testament to this are the number of patients who entrust us with their care (551 patients enrolled in phase I and basket studies in 2021), the portfolio of different trials available (207 phase I trials including 27 basket studies in 2021), and the novelty of our programs in precision medicine and immunotherapy drug development. This is also evidenced by our leading role in CCE's Clinical Trials Task Force.

Our BBVA Comprehensive Program of Cancer Immunotherapy & Immunology – CAIMI (page 140), continues to expand. This year we have collaborated with Alena Gros, PI of VHIO's Tumor Immunology & Immunotherapy Group (page 100), to initiate our NEXTGEN- TIL trial, evaluating neoantigen selected TILS in epithelial tumors and melanoma, and we have secured funding to start another cellular therapy trial based on NK cells in collaboration with colleagues at the Cancer Center of the *Universidad de Navarra* (CIMA), in 2022.

We have also fostered important alliances with the pharmaceutical industry 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.

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CLINICAL RESEARCH

EXPERIMENTAL HEMATOLOGY GROUP

Principal Investigator Francesc Bosch **Translational Research Coordinator** Marta Crespo **Clinical Research Coordinator** Pau Abrisqueta **Experimental Lab Manager** Gemma Pujadas **Hematologists/Lead Investigators** Pere Barba, David Beneitez, David Valcárcel **Post-Doctoral Scientists** Laura Palomo, Panagiota Spantidea **PhD Students** Cristina Hernandez, Daniel Medina, Carlota Pages, Soraya Peralta **Technician** Ana María Garrido **Hematologists/Lab Specialists** Olga Benitez, Adoracion Blanco, Sabela Bobillo, Cecilia Carpio, Maria Laura Fox, Laura Gallur, Mercedes Gironella, Gloria Hidalgo, Gloria Iacoboni, Moraima Jiménez, Marta Julia, Ana Marin, Lucía Martín, Maria Martinez, Antonieta Molero, Julia Montoro, Mayda Navarrete, Margarita Ortega, Guillem Orti, Ana Ortuño, Carles Palacio, Ana Pérez, Elisa Roldán, Olga Salamero, Silvia Saumell, Ángel Serna, Barbara Tazon

* For logistical issues brought about by the current COVID-19 pandemic, we are repeating pictures of some of our larger groups, services and units from our 2019 Scientific Report.

STRATEGIC GOALS

- We translate preclinical findings into clinical benefits 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.
- Understanding the tumor immune microenvironment for the development of immunotherapeutic strategies that target each individual's immune biology.

HIGHLIGHTS

- Our group is committed to studying the effectiveness and safety of Sars-Cov-2 vaccination in our hematological patients.
- In 2021 we co-authored 75 scientific papers, and were main authors (first, last and/or corresponding) of 19 among these. 52% of these articles are published in journals in the first quartile, with an accumulative Impact Factor of 129.
- This year we have initiated six new projects as PIs/Coordinators, four of which are supported through grants received from competitive calls, including *La Fundació La Marató de TV3* and the *Instituto de Salud Carlos III* - ISCIII (Institute of Health Carlos III).

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 comprises hematologists and biological scientists who work closely together to design, conduct and lead our research programs.

We aim to address unmet clinical 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 treatment outcomes.

We seek to provide new therapeutic options for our patients by deciphering the mechanisms implicated in the pathogenesis and progression of hematological malignancies. Our investigators conduct preclinical studies of new therapeutic approaches for patients diagnosed with hematological malignancies. We identify novel biomarkers in hematology that will lead to a more rational and precise diagnosis, prognosis and treatment of patients.

The Hematology Clinical Trials Unit is currently participating in more than 140 recruiting clinical studies, including phase I clinical trials (n=49) and first-in-human studies of targeted therapies, both in lymphoid and myeloid malignancies. Last year 182 patients were included in our clinical studies, with 83 patients enrolled in phase I trials.

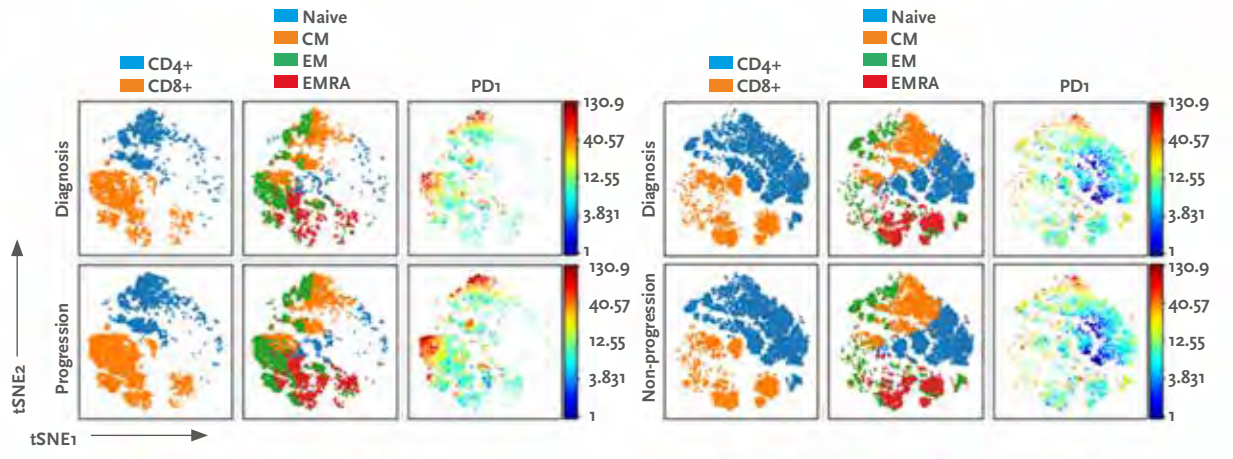

Figure I: Jiménez et al. 2021. Immunological and genetic kinetics from diagnosis to clinical progression in chronic lymphocytic leukemia.

Cellular and humoral immunogenicity of the mRNA-1273 vaccine against SARS-CoV-2 in patients with hematologic malignancies

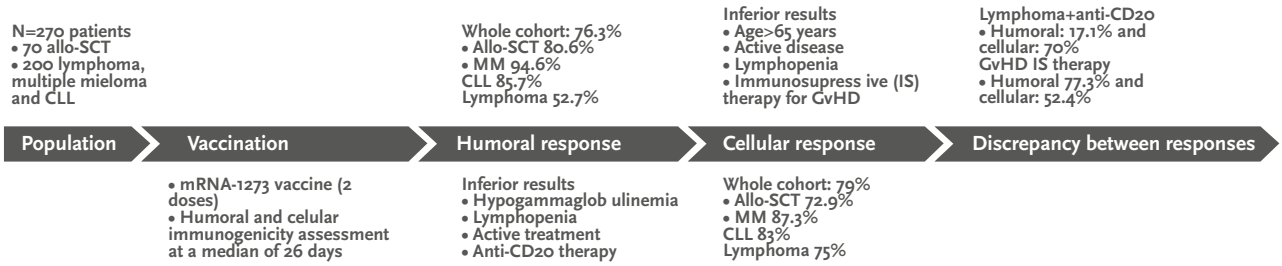

Figure II: Jiménez et al. 2021. Cellular and humoral immunogenicity of the mRNA-1273 SARS-CoV-2 vaccine in patients with hematologic malignancies.

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CLINICAL RESEARCH

GASTROINTESTINAL & ENDOCRINE TUMORS GROUP

Principal Investigator Teresa Macarulla **Medical Oncologists and Clinical Fellows** Daniel Alejandro Acosta, María Alsina, Iosune Baraibar, Jaume Capdevila, Florian Castet, Marc Diez, Elena Élez, Carles Fabregat, Alejandro Garcia, Jorge Hernando, Javier Ros, Francesc Salvà, Nadia Saoudi, Josep Tabernero, Helena Verdaguer **Translational Investigator** Rodrigo A. Toledo **Clinical Nurse Specialists** Ariadna García, Alexandre Sierra **Sample Managers** Gemma Pruna, Ines Suarez

SUMMARY

VHIO's Gastrointestinal & Endocrine Tumors Group continues to play an essential role in developing molecular therapies against GI malignancies. We pioneer transformative research of excellence and lead the development of new anti-cancer agents in early-phase clinical trials to generate novel biomarkers and targets that accelerate the delivery of precision oncology to our patients.

In 2021, our group played a central role in several clinical trials evaluating the efficacy of immunotherapy and targeted agents in GI tumors. Among these, we co-authored a manuscript describing the interim results of the phase III KEYNOTE-811 showing the benefit of standard-of-care trastuzumab and chemotherapy plus anti-PD-1 in patients with advanced-stage HER2+ gastric cancer. Importantly, amidst the COVID-19 pandemic, we have led and participated in several studies evaluating the impact of SARS-CoV2 infection in therapy response, outcomes and long-term effects of the disease in cancer patients, and contributed to generating guidelines to minimize the impact of the pandemic in patient care.

We have also made significant progress in validating and developing non-invasive liquid biopsy technologies and biomarkers to enable a more precise monitoring of cancer patients. Moreover, our research keeps providing evidence that molecular profiling of patients is an effective approach to guide the selection of GI cancer patients for targeted treatments that result in improved outcomes.

Our multidisciplinary team integrates medical oncologists and clinical investigators, a translational researcher with expertise in biomarker discovery, a research nurse dedicated to monitoring patients in research programs, laboratory technicians specialized in molecular biology and patient-derived xenografts (PDX), data curators, as well as other professionals involved in the study of precision medicine against GI malignancies. We also work in close collaboration with other VHIO researchers and groups through our highly interactive and functional Taskforces in colorectal and pancreatic cancers.

STRATEGIC GOALS

- Discovery and validation of novel biomarkers in GI tumors.
- Development of relevant preclinical models (in vitro, in vivo with PDXs and organoids) with emphasis on the identification of predictive markers and mechanisms of primary and secondary resistance.
- Molecular characterization of GI diseases, in particular colorectal, gastric, pancreatic, hepatobiliary tract, cancers and NETs. Study of targetable subtypes and tumor heterogeneity.
- Clonal evolution studies, with special emphasis in BRAF mutant tumors.
- Use of liquid biopsy (ctDNA, Mutant Allele Fraction) to study disease evolution (GI tumors).
- Development of early clinical research with innovative targets.
- Clinical research in late stage with more translational 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 and microenvironment.

HIGHLIGHTS

- Development of over 40 different projects (translational research) for GI cancer malignancies.
- We lead some investigator-initiated-trials (IITs) for difficult-to-treat conditions (NoCanTher study, GETNE1509, BRAVE trial).
- We are also leading a multicenter academic clinical phase 1b/2 trial to evaluate a new combination of drugs: encorafenib, cetuximab and bevacizumab-bvzr, in patients with BRAFV600E mCRC. This study is funded by the *Instituto de Salud Carlos III* – ISCIII (Carlos III Health Institute), granted in 2021.
- Prospective studies in CRC homogeneous populations in 1st line treatment to study prognostic and predictive value of ctDNA and its correlation with tumor vascularization. Non-invasive methods (liquid biopsy and MRI) - AECC, TV3 Marató.
- New studies on MAF (Mutant Allele Fraction) of BRAFV600E in plasma as a tool for the therapeutic monitoring of patients with a poor prognosis, supported by TTD, Mutual Mèdica, Fundación CRIS contra el Cáncer.
- Understanding the colorectal cancer microbiome: implications in therapy (OPTIMISTICC).
- Participation in EU Horizon 2020-funded projects and consortia including MoTriColor, IntraColor, COLOSSUS, LEGACY, NoCanTher, and THRUST.
- Our group is a partner of many national and international consortia and networks including Cancer Core Europe (CCE), WIN, and CIBERONC
- Single cell profiling persistence to immunotherapy (Partner of Choice, AstraZeneca).
- ACRCelerate: Colorectal Cancer Stratified (ACCELERATOR CRUK).
- BioPrinted hydROgel MicrofluIdicS to mimic patient-specific tumor metastatic microenvironment (PROMISE, CaixaHealth).
- TuMICC: Understanding which mechanisms are utilized by tumor cells to resist therapy and identify patient specific resistance before initiating treatment (Grupos Coordinados, AECC).
- Our group leads efforts in understanding the efficacy of PARP inhibitors in pancreatic cancer (Partner of Choice, ISCIII).
- We collaborate (and lead) large efforts in defining the molecular landscape of gastric cancer (LEGACY project, ISCIII).
- We lead the FIH application of a novel nanoparticle-based therapy for pancreatic cancer (NoCanTher study)
- Biomarker validation in biliary tract cancer.
- We lead the phase II TALENT trial, providing novel evidence for the efficacy of lenvatinib and pointing to the potential value of agent in the treatment of advanced GEP-NETs.

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CLINICAL RESEARCH

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

Principal Investigator Joan Carles **Medical Oncologists and Clinical Fellows** Nely Díaz, Macarena Gonzalez, Joaquin Mateo, Rafael Morales, César 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 novel and optimal treatments including immune-based therapeutics, targeted therapies, radioligands, and new chemotherapies.
- Conduct clinical trials at different stages of disease with emphasis on a histology-tailored design and multidisciplinary approach.
- 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).
- Microbiota studies to identify biomarkers for immunotherapies to treat bladder and kidney cancers.
- Expand our translational research platform for glioblastoma in collaboration with VHIO's Gene Expression & Cancer Group led by Joan Seoane (page 86).
- 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) for sarcoma tumors and other rare diseases.
- Develop novel tools and techniques including liquid biopsy to more precisely tailor treatments against mCRPC, GIST and kidney cancer.

HIGHLIGHTS

- In prostate cancer, we have consolidated our Task Force and Serum Bank, and have performed more than 2000 blood extractions in 2021. These efforts enable us to participate in different translational studies including our lead of the IRONMAN project in Spain.
- We have expanded our phase I program across all tumor types studied by our group.
- We continue to foster and develop new collaborations with different VHIO groups and external partners.

SUMMARY

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

In 2021 we continued to consolidate our expert Prostate Cancer Task Force. By closely connecting clinical and translational researchers at VHIO and the Vall d'Hebron Research Institute (VHIR), we have initiated various translational prostate cancer projects. We are also pursuing translational studies in kidney cancer, working with other partners including the Biomedical Research Institute of Bellvitge (IDIBELL, Barcelona).

Over recent years, several advances have led to 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, are considered the new standard of care in first-line therapy. We are studying new combinations including HIF-2 alpha inhibitors and immunomodulators

In bladder cancer, immunotherapy has shown activity in metastatic disease and is now being tested in the neoadjuvant setting and in non-muscle-invasive bladder cancer. It has recently been shown that immunotherapy as maintenance therapy after 4/6 cycles of chemotherapy in first-line treatment improves progression-free survival (PFS) and overall survival (OS). Molecular alterations have been identified in bladder cancer such as FGFR mutations. The unmasking of molecular alterations enables us to develop new targeted drugs. Also under development are antibody-drug conjugates (ADCs) for the treatment of patients with metastatic disease.

Our group, and others, have observed that immunotherapy could also be effective in 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. Another innovative treatment for prostate cancer is theragnosis by administering radioligands using beta emitters. This type of therapy requires close collaboration with nuclear medicine teams to coordinate the administration and follow-up of patients.

We have participated in recent studies that have shown the utility of immune checkpoint inhibitors (ICIs) in the adjuvant treatment of bladder and kidney cancers with a high risk of disease recurrence. These studies can only be performed by working closely with our Vall d'Hebron University Hospital's (HUVH) Urology Department.

We also collaborate with various other renowned research centers including the Cleveland Clinic (Ohio, USA), University of California, San Francisco (California, USA), and 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 continued to expand our translational research program in prostate cancer working alongside VHIO's Prostate Cancer Translational Research Group, led by Principal Investigator Joaquin Mateo (page 92), as well as other hospitals in Catalonia.

Our main focus is metastatic castration-resistant prostate cancer (mCRPC), and we are working on a project led by Joaquin Mateo, 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 U.S. Department of Defense (DoD) Congressionally Directed Medical Research Program. Additionally, we are participating in the IRONMAN project directed by the Memorial Sloan Kettering Cancer Center (MSKCC – New York, USA), as the Spanish national repository for the IRONMAN registry. This international program aims at building a comprehensive bank of clinical data and biospecimens from metastatic prostate cancer patients. Our involvement in this project is supported by the Movember Foundation and *Fundación FERO* (FERO Foundation - page 29).

We are collaborating with VHIO's Radiomics Group (page 122), headed by Raquel Perez-Lopez, 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 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, radiation oncologist, radiologist, and a medical oncologist to establish a circuit for the systematic metastatic tissue acquisition from prostate cancer patients at Vall d'Hebron.

We have expanded our avatar program for kidney cancer tumors in collaboration with IDIBELL and implanted 35 tissue samples, 15 of which have grown. We were able to obtain data about treatment resistance in 8 cases. In organoids, we have sent 4 cases and 3 are growing. 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. This research is 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, alongside VHIO's Gene Expression & Cancer Group led by Joan Seoane (page 86), we continue to develop our translational research platform for glioblastoma. We analyze cfDNA in blood and cephaloraquidic liquid to assess primary CNS tumors and metastases.

Our group also participates 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: *Screening Platform 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). In GIST tumors, we are working with Jonathan Fletcher's lab at the Brigham and Women's Hospital (Boston, USA).

We are now recognized as a Reference Unit of the Spanish National Health System (*Centros, Servicios y Unidades de Referencia del Sistema Nacional de Salud* - CSUR) for the treatment of sarcoma patients. This accreditation enables us to participate in the European Reference Network (ERN) for sarcoma tumors and other rare diseases.

Since César Serrano set up his own research team, VHIO's Sarcoma Translational Research Group (page 94) in 2019, we have consolidated different clinical trials with new drugs in GIST by leading and participating in phase I-II-III studies. 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 2021 we welcomed three fellows from Spain for 3-month short stays.

PI PAPER PICK 2021

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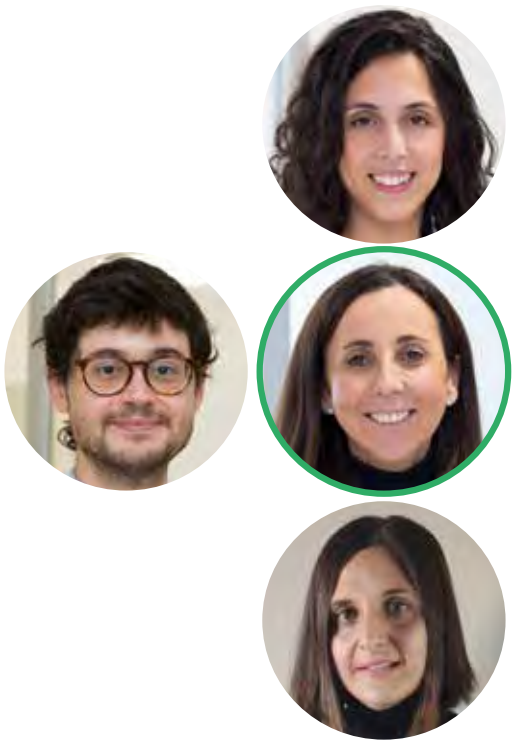
CLINICAL RESEARCH

GYNECOLOGICAL MALIGNANCIES GROUP

Principal Investigator Ana Oaknin **Medical Oncologists** Lorena Fariñas, Carmen García Durán, 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:
  - Develop and advance 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 lead other clinical trials toward defining next generation treatment regimens:

- Ana Oaknin signed the FDA filing of dostarlimab (PD-1 inhibitor) in MSI-H recurrent endometrial cancer after presenting the results of the clinical trial, included in the file, at the Society of Gynecologic Oncology's (SGO) 2019 Annual Meeting, 16 -19 March (Honolulu, Hawaii).
- Ana is the global lead of a phase III Investigator-Initiated Trial for first line metastatic cervical cancer (the BEATcc trial) running in the 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 Principal Investigator of the ATOMICC clinical 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 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 and groups in gynecological oncology including the Gynecologic Cancer InterGroup (GCIG) as the Spanish representative for its Cervical Cancer and Phase II Trial Committees, and the Spanish clinical lead of the Gynecologic Oncology Group (GOG). We also belong to the European Network of Gynecological Oncology Trial groups (ENGOT).

Contributing to the advancement of the treatment of gynecological malignancies, we have participated in the development of a number of therapies that are now the current standard of care for different malignancies.

In 2021 we participated in several important clinical trials that have generated new and compelling data. As an example, we led the GARNET study. This trial includes the largest series of patients with endometrial cancer (EC) treated with immunotherapy; the anti-PD-1 agent, dostarlimab.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion in February 2021, recommending dostarlimab for the treatment of patients with EC who have progressed on platinum therapy.

While metastatic cervical cancer is a devastating disease, over recent years we have succeeded in expanding therapeutic approaches which have mainly been driven by immunotherapy. Moreover, we are working on other targeted agents such as neratinib that is showing promising results (Oaknin et al. 2020)*.

Our Principal Investigator, Ana Oaknin, 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); is Co-Chair of GCIG's Cervical Cancer Committee; and a Faculty Member of the European Society for Medical Oncology's (ESMO) Annual Meeting's Gynecological Tumors Track (2019-2023) for which she was appointed as Chair at the ESMO 2019 Congress, 27 September – 01 October (Barcelona, Spain). She was also Discussant of the results of two phase III trials that were presented during the Track's Presidential Symposium.

In 2021, Ana Oaknin was appointed as Subject Editor of ESMO's Guidelines Committee, and was Co-Chair of the virtual International Gynecologic Cancer Society's (IGCS) Annual Global Meeting, 30 August – 02 September, 2021.

PI PAPER PICK 2021

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CLINICAL RESEARCH

HEREDITARY CANCER GENETICS GROUP

Principal Investigator Judith Balmaña **Senior Scientist** Sara Gutiérrez-Enríquez **Associate Investigator** Orland Díez **Post-Doctoral Fellow** Renan Gabriel Gomes **Medical Oncologist** Mara Cruellas **Genetic Counselors** Estela Carrasco, Adrià López, Sara Torres **Project Manager** Mònica Pardo **Pre-Doctoral Students** Ester Aguado, Joanna Domènech, Alejandro Moles **Graduate Students** Sara Hermosa, Cristina Zamarreño **Clinical Nurse Specialist** Eduard Pérez Ballestero **Data Curator** Maite Torres **Auxiliary Clinician** Carmen Aguilar

STRATEGIC GOALS

- The 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.
- Implementation of the RAD51 assay as a clinical biomarker for PARPi therapy, and a biomarker of homologous recombination repair deficiency (HRR-D) among non-BRCA mutation carriers and those with variants of uncertain significance (VUS).
- Evaluate the preventive effect of denosumab on breast cancer prevention in *BRCA1* mutation carriers (BRCA-P trial).
- Optimize the genetic diagnosis of HBOC.
- Identify cellular and genomic biomarkers as predictors of late toxicity after radiotherapy.

HIGHLIGHTS

- Prior to the COVID-19 pandemic and lockdown we initiated a project to explore predictors of patients' acceptance of telegenetics in hereditary cancer. In 2020 we investigated the impact of COVID-19 on telegenetics versus in-person visits. Our research included the predictive analysis of personality traits and the opinion of health care providers to identify challenges in implementing e-health.
- We continue our longitudinal registry of mutation carriers in hereditary cancer, and we are investigating personality traits as predictors of the psychological impact of multigene testing, mainly focused on genetic uncertainty.
- Recruitment of women with familial breast cancer to perform individualized breast cancer risk assessment with PRS analysis and non-genetic risk factors.
- We are clinically validating the RAD51predict assay as a functional biomarker of homologous recombination repair deficiency and a predictor of PARPi resistance.
- In collaboration with other expert Spanish groups, we have compiled the first guide to standardizing and improving the classification of *ATM* gene variants that increase the risk of breast or prostate cancer.
- We are leading research into the value of RAD51 foci in the interpretation of variants of unknown clinical significance in *BRCA1*, *BRCA2* and *PALB2* genes as part of one of the ERAPerMed project's work packages. This project is coordinated by Violeta Serra, PI of VHIO's Experimental Therapeutics Group (page 84).
- In spite of the COVID-19 pandemic, we have continued to enroll patients in the RADprecise project and achieved 60% of the total expected inclusion in the breast cancer cohort. This collaborative project funded by ERAPerMed aims to personalize radiotherapy by incorporating cellular response to irradiation in the treatment planning in order to minimize radiation toxicity.

SUMMARY

Our group focuses on the clinical development of PARP inhibitors (PARPi) in early *gBRCA1/2* breast cancer, and novel combinations in the advanced disease setting. We have consolidated our collaboration with VHIO's Experimental Therapeutics Group led by Violeta Serra (page 84), which 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 disease progression. Our group has identified a functional biomarker for PARPi sensitivity that has been tested preclinically. We are now validating this biomarker in samples from clinical trials and in standard clinical practice.

We also focus on addressing the challenges associated with the implementation of advances in the diagnosis of hereditary cancer susceptibility and applying these insights in 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 and studying 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 received funding to assess genetic cancer risk estimation and cancer-risk adapted approaches including polygenic risk score (PRS) analysis. A longitudinal national-based registry of mutation carriers incorporates prospective data to explore health outcomes.

Led by our Senior Scientist, Sara Gutiérrez-Enríquez, we pursue our interest in 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. We also aim to decipher the role of intronic, splicing, and missense variants in major HBOC genes and investigate the yield of long-read RNA-seq. In collaboration with VHIO's Radiation Oncology Group led by Jordi Giralt (page 120), Sara Gutiérrez-Enríquez is independently leading research on predictive genetic and cellular markers of susceptibility to radiotherapy-induced clinical toxicity.

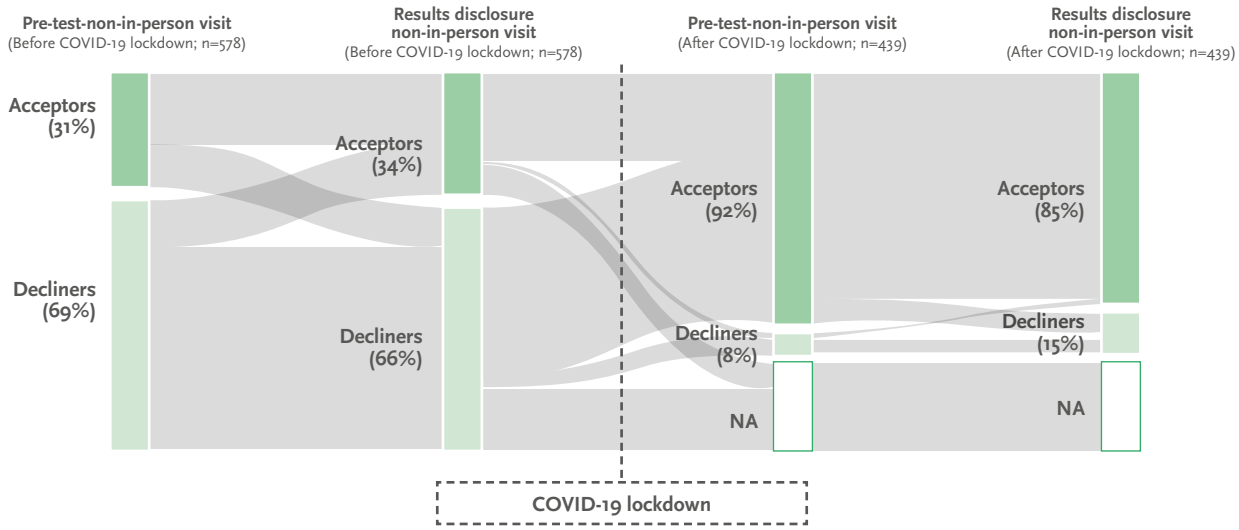

Figure: Evolution of patients' reported acceptance of non-in-person visits in hereditary cancer before and after the lockdown by COVID-19.

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CLINICAL RESEARCH

ONCOLOGY DATA SCIENCE (ODysSey) GROUP

Principal Investigator Rodrigo Dienstmann **Biostatisticians** Víctor Navarro, Guillermo Villacampa **Biomedical Engineer** Anna Pedrola
Data Curators Gloria Castillo, Raquel Comas, Magdalena Guardiola, Fiorella Ruiz, Sara Torres, Cristina Viaplana

STRATEGIC GOALS

Facilitate clinical-molecular correlative studies at VHIO:

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

Promote evidence-based medicine and clinical trial recruitment:

- Promote the clinical implementation of the Molecular Tumor Board Portal (MTBP), a decision support system for the selection of the most appropriate treatment for cancer patients based on genomics data, including clinical trial opportunities. This 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 by the Cancer Core Europe (CCE) Consortium's Basket of Basket (BoB) trial and the open access version is available at: http://mtbp.org.

Collaborative research on Big Data 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 investigators working on clinical and preclinical research. This has resulted in several impactful publications within our field, oral presentations at some of the most prestigious oncology conferences, as well as statistical leadership in multiple phase II-III trials.
- Our group is an active member of AACR's Genomics Evidence Neoplasia Information Exchange (GENIE) project, and other international data sharing initiatives such as EUCANCan that catalyze precision oncology through the development of regulatory-grade registries aggregating and linking cancer genomics data with clinical outcomes from tens of thousands of cancer patients treated at the participating institutions.
- Since clinical trials represent a great opportunity for cancer patients to access innovative molecularly-guided therapies, as part of the EUCANCan project we have developed the OncoTrialsTrack portal. This open web platform (https://oncotrialstrack.vhio.net) empowers healthcare providers in the difficult and time-consuming task of finding the most suitable clinical trial for cancer patients and also contacting investigators from recruiting sites for case discussion and referral. Unlike other databases, OncoTrialsTrack offers a user-friendly interface with an up-to-date catalogue of molecularly and semantically tagged clinical trials.

SUMMARY

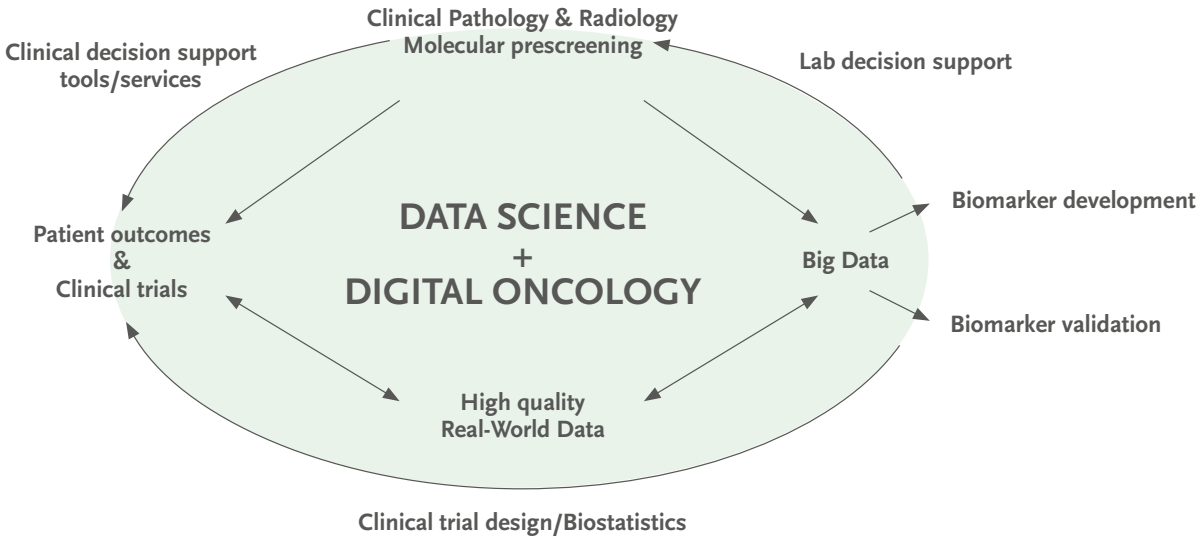
VHIO's ODysSey Group promotes translational research in precision oncology by integrating cancer molecular profiling data with clinical outcomes of oncology patients treated at the Vall d'Hebron University Hospital (HUVH).

To analyze big and real-world data, our group designs and maintains comprehensive clinical-molecular databases and develops customized decision-support systems for researchers who have an interest in correlative analyses for hypothesis-generation and biomarker validation. We also provide assistance to investigators for the calculation of sample size, clinical trial design, electronic case reporting and statistical analyses.

We also participate in international multi-omic data analyses projects, foster collaborative research in computational oncology, and 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.

Together with VHIO's Cancer Genomics Group, Molecular Oncology Group and Early Clinical Drug Development Group, we co-lead VHIO's in-house Molecular Prescreening Program (page 156), and create informatics tools to explore and visualize multi-omics data for research purposes.

We provide support in the interpretation of next-generation sequencing tests and educate clinicians on emerging biomarkers. During Molecular Tumor Board meetings, we promote precision oncology by providing guidance regarding inclusion in early clinical trials with biomarker-guided targeted agents or immunotherapies, and genetic counseling alerts in the instance of pathogenic germline variants.



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CLINICAL RESEARCH

RADIATION ONCOLOGY GROUP

Principal Investigator Jordi Giralt **Radiation Oncologists** Manel Altabas, Sergio Benavente, Alexandra Giraldo, Raquel Granado, Xavier Maldonado, Soraya Mico, Begoña Navalpotro, Monica Ramos, Victoria Reyes, Ramona Verges

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 ISO 9001/2008 recertification in the field of radiation oncology.
- Clinical research: accelerate and advance clinical research in radioimmunotherapy (RIT).

HIGHLIGHTS

- Over 90% of our patients treated with radical radiotherapy have been treated using highly complex techniques.
- Treating patients using our Halcyon LINAC - the very first to be installed in Spain.
- We continue to participate in a project combining radiotherapy with nanoparticles against head and neck cancer.
- We have implemented the `breath hold' technique and are treating some of our patients using this approach.
- Our continued participation as national representatives of radiotherapy in the International Society of Paediatric Oncology (SIOP) clinical studies for the treatment of medulloblastoma (PNET5), ependymoma (EP2), and Wilms (umbrella).

SUMMARY

Our group is integrated within the Radiation Oncology Department of the Vall d'Hebron University Hospital (HUVH), and focuses on 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.

We recently 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 as well as specialized trainings for indications, administration procedures, quality control methods, as well as the incorporation of novel tools and approaches 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 a very small volume (5-10 mm in diameter), requiring extremely precise techniques.

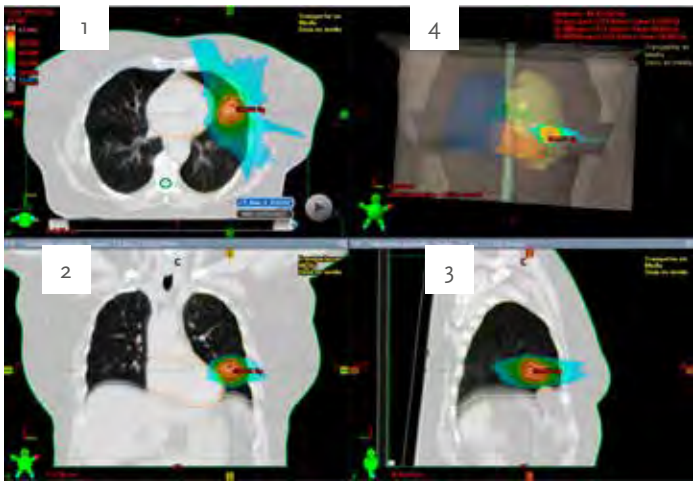

Figure: Dosimetry of a 4D lung SBRT. Image 1 shows a cross-sectional view, image 2 a coronal view, image 3 a sagittal view, and image 4 a three-dimensional reconstruction. The prescribed total dose is 60 Gy, given in 3 fractions of 20 Gy.

PI PAPER PICK 2021

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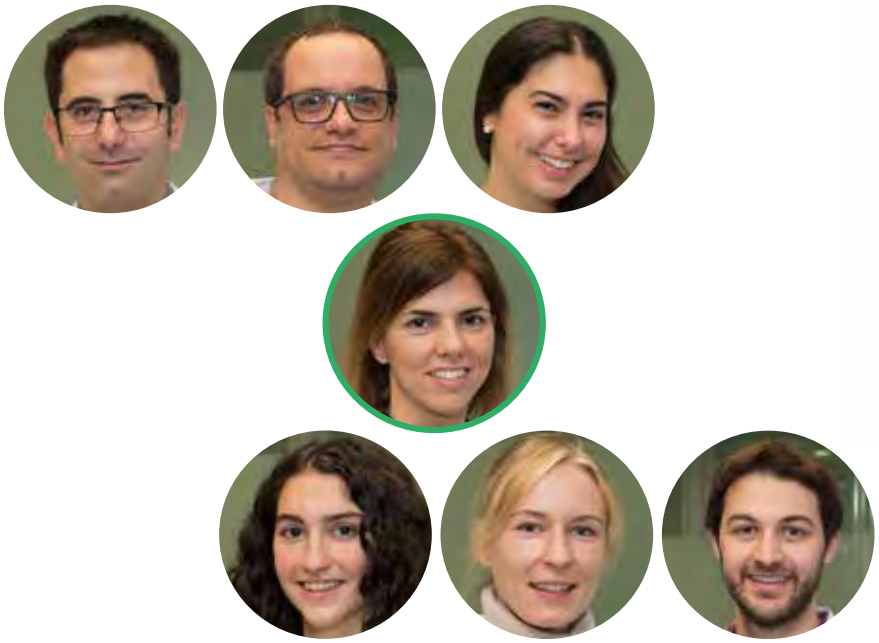
CLINICAL RESEARCH

RADIOMICS GROUP

Principal Investigator Raquel Perez-Lopez **Post-Doctoral Fellows** Kinga Bernatowicz-Goma, Francesco Grussu **PhD Students** Alonso García, Marta Ligero, Olivia Prior **Student** Maria Balaguer **Computer Scientist** Camilo Monreal



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 in clinical trials.
- Integrate radiomics and genomics in translational studies to achieve 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

- We now participate in the EU-funded Cancer Core Europe Consortium's DART project – Building Data Rich Clinical Trials. Aimed at optimizing clinical trial design, we provide support to achieve image protocol standardization and integration of novel imaging biomarkers.
- Our group has recently joined the COLOSSUS Consortium – Advancing a Precision Medicine Paradigm in metastatic Colorectal Cancer: Systems based patient stratification solutions. This European Commission Horizon 2020-supported project aims to unravel new subtypes of RAS mutant colorectal cancer. We lead and coordinate the project's medical imaging area and apply radiomics & machine learning models to explore imaging phenotypes characteristic of these new sub-types, and predictive models of response to standard of care therapy.
- In 2021, Raquel Perez-Lopez was awarded with a *Proyecto Coordinado* grant from the *Asociación Española Contra el Cáncer* - AECC (Spanish Association Against Cancer), and a grant from the *Instituto de Salud Carlos III* – ISCIII (Institute of Health Carlos III).
- We have developed and validated a combined CT-radiomics and clinical signature with predictive value of response to immunotherapy. This study has been published in *Radiology* (Ligero et al. 2021).
- We have also collaborated in a study of perfusion MRI as a diagnostic support system to distinguish the two most common malignancies in the brain (glioblastomas and metastases), recently published in *European Radiology* (Pons-Escoda et al. 2022)*.
- We have designed a method for 3-D CT-radiomics standardization and computation of imaging habitats for evaluation of tumor heterogeneity, published in *Scientific Reports* (Bernatowicz et al. 2021).
- The continued expansion of existing partnerships with other groups as well as new collaborative projects to increase the inclusion of imaging studies in translational research projects.

SUMMARY

Our Radiomics Group continues to expand. In 2021, Camilio Monreal joined our team to set up and run our own computational server to provide new opportunities for the study of deep-learning and integrative multi-comics models. We are also pleased to announce that Olivia Prior, granted with a "la Caixa" Foundation Doctoral INphINIT Fellowship, joined our group to explore non-invasive imaging biomarkers for better characterizing colorectal cancer (CRC). In collaboration with the Nuclear Medicine and Hematology Departments at the Vall Hebron University Hospital (HUVH), Maria Balaguer pursued her end-of-degree research project focused on PET/CT-radiomics for optimizing patient selection and monitoring response in patients with lymphoma treated with CAR-T cells.

Over the past year, we have fostered new collaborations with leading imaging research groups at Cardiff University (Wales, UK), the Champalimaud Foundation (Lisbon, Portugal), and the New York University School of Medicine (NY, USA). We have also forged new partnerships with other cutting-edge research institutes including the German Cancer Research Center - Deutsches Krebsforschungszentrum, DKFZ (Heidelberg, Germany), and the Uniklinikum Aachen University Hospital, RWTH Aachen (Aachen, Germany). Together, 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) – CaixaResearch led by Elena Garralda (page 149), and thanks to the support received through an AstraZeneca Partners of Choice Award, we are working on the PREDICT study to develop predictive biomarkers of response to immune checkpoint inhibitors by combining radiomics, genomics and the molecular characterization of the tumor microenvironment by multiplexed assays.

In 2021 we have also been awarded by the *Asociación Española Contra el Cáncer* - AECC (Spanish Association Against Cancer), to participate in a comprehensive project coordinated by Manuel Serrano, IRB Barcelona – Institute for Research in Biomedicine (Barcelona, Spain), to explore the role of senescence in cancer. By applying advanced magnetic resonance imaging (MRI), our group will develop novel, non-invasive biomarkers of this phenomenon to be tested in pre-clinical models as well as in patients.

We also participate in the EU-funded Cancer Core Europe Consortium's DART project – Building Data Rich Clinical Trials, which is led by VHIO's Elena Garralda. Aimed at optimizing clinical trial design, we are providing support to achieve image protocol standardization and integration of novel imaging biomarkers.

Our Group has recently joined the COLOSSUS Consortium – Advancing a Precision Medicine Paradigm in metastatic Colorectal Cancer: Systems based patient stratification solutions. This multi-center European Commission Horizon 2020-supported project aims to unravel new subtypes of RAS mutant colorectal cancer. Raquel Perez-Lopez leads and coordinates the medical imaging area of this project where she applies radiomics and machine learning models for exploring imaging phenotypes characteristic of these new sub-types, and predictive models of response to standard of care therapy.

We are also exploring new diffusion-weighted MRI protocols to evaluate biological-specific metrics regarding tissue cellularity and cell size in the liver. We envision that the metrics derived from this new assay will have important applications as non-invasive biomarkers in cancer. Francesco Grussu, a Post-Doctoral Fellow of our group, has been granted a *Beatriu de Pinós* post-doctoral fellowship this year to pursue this research.

Thanks to the support received from the *Instituto de Salud Carlos III* – ISCIII (Institute of Health Carlos III), and the Prostate Cancer Foundation's (PCF) Young Investigator Award, our group coordinates a multi-center prospective study of whole-body diffusion-weighted MRI as a response biomarker of bone metastasis in prostate cancer patients. This study has now expanded to include breast cancer patients thanks to funding from *La Marató de TV3* (PreciMet study).

We have established several interdisciplinary partnerships with various VHIO groups to work together on translational research projects. Our ethos of team science is key to 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 to ultimately improve outcomes for cancer patients.

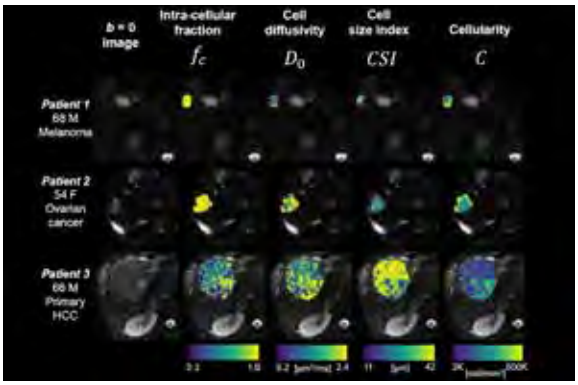


Figure: Tracking microstructural tumor changes upon immunotherapy with multi parametric Magnetic Resonance Imaging (MRI).

PI PAPER PICK 2021

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CLINICAL RESEARCH

THORACIC TUMORS & HEAD AND NECK CANCER GROUP

Principal Investigator Enriqueta Felip **Medical Oncologists and Clinical Fellows** Juan David Assaf, Irene Braña, Ana Callejo, Susana Cedres, Patricia Iranzo, Alexandre Martinez, Alejandro Navarro, Nuria Pardo **Associate Researcher** Ramon Amat **Post-Doctoral Fellows** Caterina Carbonell (wet-lab), Joan Frigola (bioinformatician) **Clinical Nurse Specialist** Mireia Soleda

STRATEGIC GOALS

- Expansion of our translational thoracic cancer program in non-small cell lung cancer, small cell lung cancer and mesothelioma.
- 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 new approaches.
- Potentiate novel therapies including immunotherapeutic and targeted agents for the management of patients with thoracic and head and neck malignancies.
- Achieve a deeper understanding of intratumoral heterogeneity and its clinical implications.
- Further strengthen multidisciplinarity for optimal patient care.

HIGHLIGHTS

- We have further strengthened collaboration between our translational thoracic cancer genomics Unit and our clinical team. By integrating genomics, molecular biology and clinical data, we aim to advance insights into 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 team strives to match currently available targeted therapies with specific molecular alterations identified in patients, unmask 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 our efforts also focus on ameliorating clinical outcomes by working in close connectivity with professionals across other disciplines.

Precision medicine for the treatment of advanced lung cancer is no longer an ambition. It is a guiding principle. We establish molecular determinants of disease in individual tumors and circulating cell-free DNA (cfDNA) by liquid biopsy, to more effectively tailor therapies to the specificities of each patient's individual 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) – CaixaResearch, led by Elena Garralda (page 149). Additionally, we contribute to VHIO's early clinical drug development efforts (page 106). We also manage other less common thoracic malignancies including head and neck cancer, small cell lung cancer, mesothelioma, thymoma and neuroendocrine tumors.

PI PAPER PICK 2021

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CORE TECHNOLOGIES

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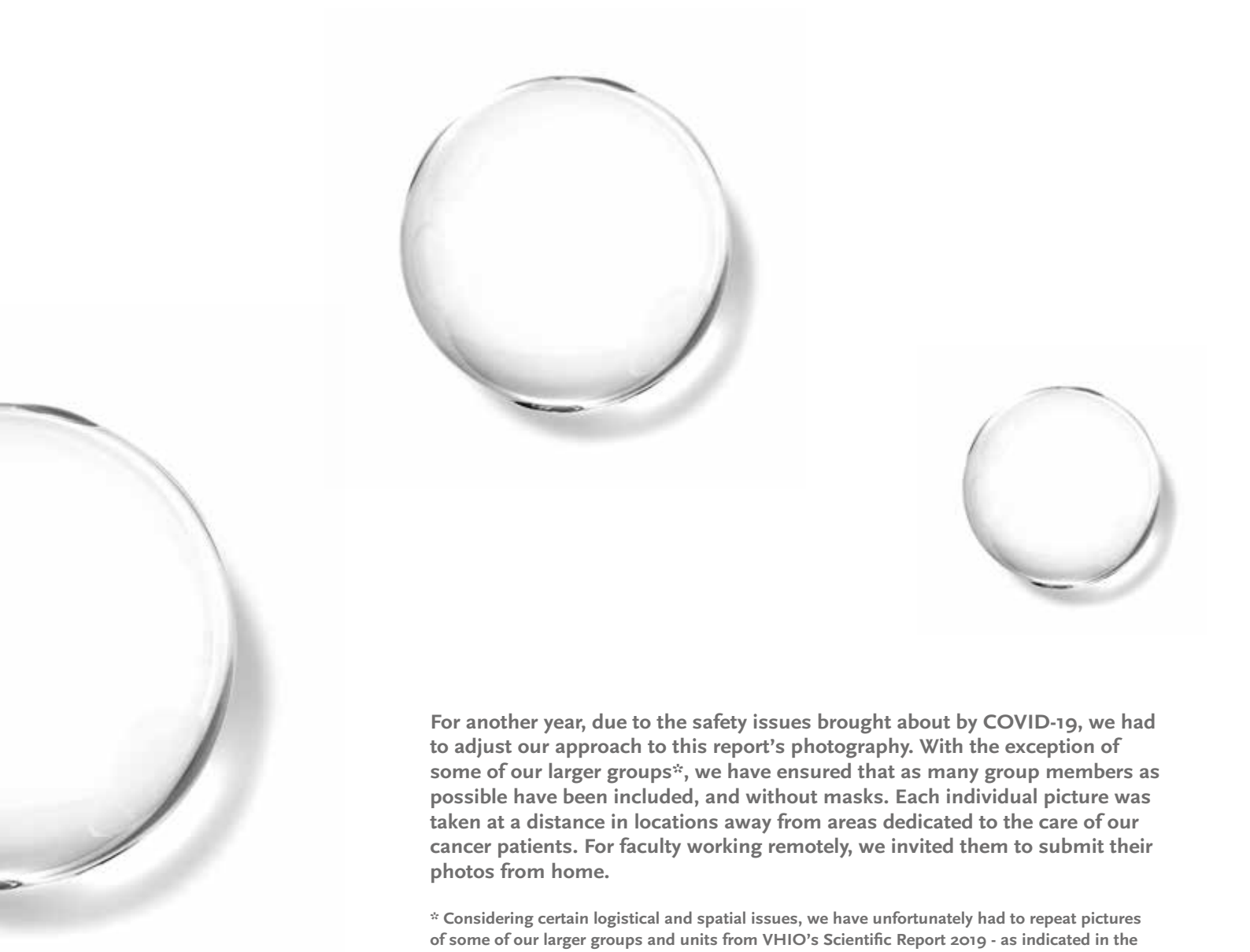
CORE TECHNOLOGIES



For another year, due to the safety issues brought about by COVID-19, we had to adjust our approach to this report's photography. With the exception of some of our larger groups*, we have ensured that as many group members as possible have been included, and without masks. Each individual picture was taken at a distance in locations away from areas dedicated to the care of our cancer patients. For faculty working remotely, we invited them to submit their photos from home.

*** Considering certain logistical and spatial issues, we have unfortunately had to repeat pictures of some of our larger groups and units from VHIO's Scientific Report 2019 - as indicated in the corresponding pages.**

CORE TECHNOLOGIES

BIOINFORMATICS UNIT

Unit Head Lara Nonell **Bioinformaticians** Mercè Alemany, Pau Marc Muñoz-Torres

STRATEGIC GOALS

- The implementation of state-of-the-art pipelines and tools for the analysis and visualization of different omics datasets, including publicly available datasets.
- Application of advanced bioinformatics techniques for the identification and validation of biomarkers for cancer diagnostics.
- Generation of computational models to integrate different types of omics data that foster personalized medicine using classical or cutting-edge machine learning techniques.
- Establish collaborative research with VHIO groups to promote the use of advanced computational methods for data analysis, visualization and interpretation.
- Set up an appropriate and scalable computational infrastructure for bioinformatics analyses.
- Coordinate an internal bioinformatics network aimed at sharing knowledge and optimizing resources.

HIGHLIGHTS

- The setting up of VHIO's computational cluster which operates with Slurm and Docker for task management. In addition, Nextflow facilitates the automation of bioinformatic pipelines.
- Recruitment of expert bioinformaticians to support VHIO's pioneering cancer research.
- Establishment of standard pipelines for the processing and analysis of genomic, transcriptomics, epigenomics and metagenomics datasets.
- Collaboration with several groups for the analysis of omics data sets, ranging from raw sequencing data alignment to the development of functions for the appropriate visualization of assessment results.
- Our group provides guidance to several investigators for their computational processes.
- We participate in various consortia and task forces.
- Representation of VHIO in projects such as IMPaCT and VEIS.

SUMMARY

Our Bioinformatics Unit provides research groups with cutting-edge computational resources for the analysis of cancer-related omics data. We support VHIO investigators through the implementation of state-of-the-art bioinformatic pipelines to process multi-omics datasets.

Collaborating with researchers across multiple projects, we participate in several phases of investigation from conception or experimental design through to bioinformatic data analysis and final publication, with particular focus on visualization and functional interpretation. Our computational procedures are based on open-source software developed in a safe and reproducible environment. We also provide advice and mentorship to other bioinformaticians at VHIO.

This Unit is a member of the Spanish translational bioinformatics network, TransBioNet, which is coordinated by the Spanish National Bioinformatics Institute (INB) and works in conjunction with the European Life Science Infrastructure for Biological Information (ELIXIR). We also represent VHIO in various consortia and taskforces.

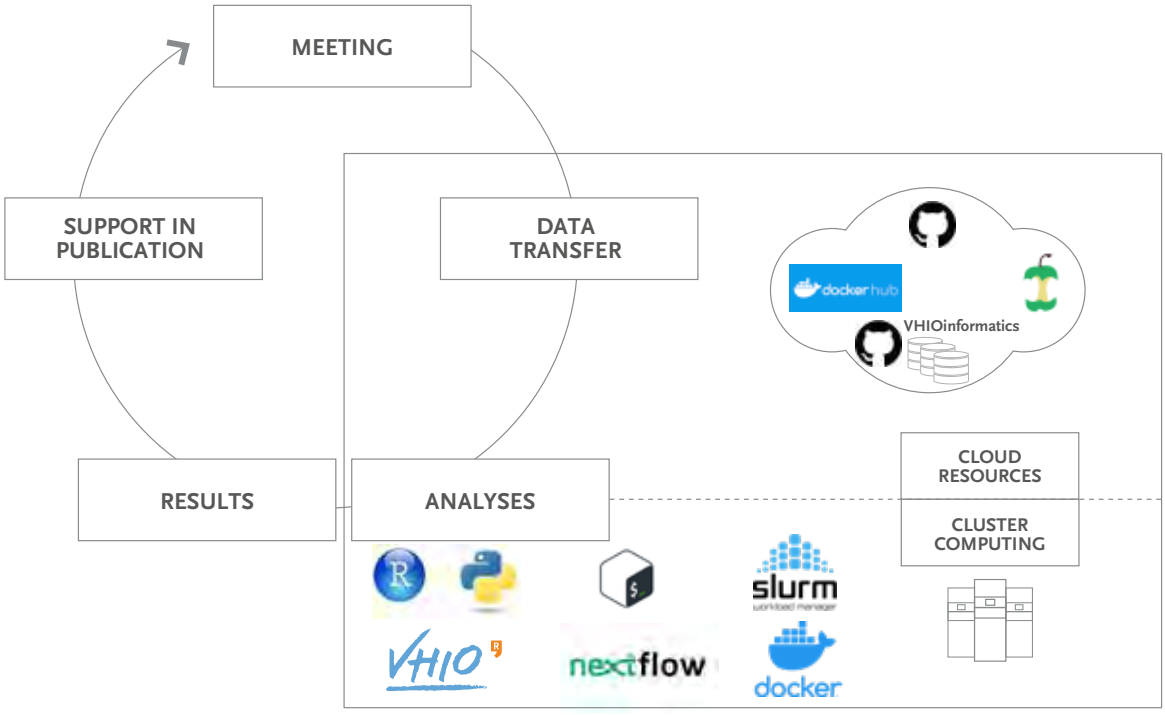


Figure: Cycle of our bioinformatics service at VHIO, which typically starts with a meeting with the investigator followed by data transfer to our core computational resources for analysis. These resources include VHIO's computational cluster and other web-based tools. Once data have been analyzed, results are discussed with the investigator, who also receives support to publish and make the data available.

CORE TECHNOLOGIES

CANCER GENOMICS GROUP

Principal Investigator Ana Vivancos **Post-Doctoral Fellows** Ester Castillo, Alberto González **Specialized Technicians** Cecilia García, Deborah G. Lo Giacco, Eva Hernández, Judit Matito, Zighereda Ogbah **Bioinformaticians** Gustavo Rodriguez, Marina Gómez, Maria Vila **Technicians** Giuseppe Buono, Raquel Casquero, Agatha Martín **Research Support Technician** Jenifer Gonzalez

STRATEGIC GOALS

- Develop and implement improved strategies for routine patient prescreening with a large pan-cancer panel in a setting of excellence.
- Provide cutting-edge applications in cancer genomics through the use of novel technologies and protocol development.
- Prioritize translational projects and partnerships that further strengthen VHIO's renowned excellence in oncology.
- Implement the Guardant360® CDx liquid biopsy test as the first laboratory in Europe to apply this assay from Guardant Health.

HIGHLIGHTS

- VHIO is a founding partner of the Cancer Core Europe Consortium – CCE (page 37), 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), National Center for Tumor Diseases–DKFZ- NCT (Heidelberg, Germany), and the National Cancer Institute of Milan (INT). Our group serves as co-leader of CCE's Genomics Task Force and is responsible for the alignment of genomic testing across all member institutions.
- We have validated our 450 gene capture panel for mutations, Tumor Mutational Burden and for Copy Number Alterations, to be used in VHIO's Molecular Prescreening Program.
- In liquid biopsy, we have developed our custom NGS test with Unique Molecular Identifiers (UMIs) combined with the Copy Number Alteration analysis using Shallow Whole Genome Sequencing (sWGS). This will be our first disease tracking test in the clinical setting.
- It is thanks to our institutional Advanced Molecular Diagnostics Program – DIAMAV (our molecular prescreening efforts, page 138), supported by the FERO Foundation, that VHIO is one of the few centers in Europe to run such a comprehensive program. Molecular profiling, performed in over 1100 patients each year as candidates for enrollment in our Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch early phase clinical trials (page 149), enables us to more precisely match an increasing number of individual patients to our studies.

SUMMARY

VHIO's Cancer Genomics Group serves as a Core Technology laboratory. We are also dedicated to translational research as well as the development of novel genomic tests.

Our group provides cutting-edge applications in cancer genomics through state-of-the-art technologies and the development of new, fully validated tests that are used in the clinical research setting. Our lab is equipped with an n-Counter (Nanostring) platform, two digital PCR platforms (BEAMing Sysmex and ddPCR, BIO-RAD) and four NextGen Sequencers; MiSeq, NextSeq and HiSeq2500 from Illumina, and a MinION from Oxford Nanopore Technologies.

We are also initiating the technical transfer of the Food and Drug Administration (FDA)-approved Guardant360® CDx liquid biopsy test for comprehensive genomic profiling. Incorporating this liquid biopsy technology at the beginning of 2021, VHIO is the first cancer research center in Europe to have a laboratory equipped with this cutting-edge platform. Helping to overcome the limitations and certain challenges of tissue biopsies, this technology provides complete genomic results in all solid tumors from a simple blood draw in seven days.

Molecular Prescreening at VHIO (page 156), is co-led by our group's Principal Investigator, Ana Vivancos, alongside Paolo Nuciforo, Elena Garralda, and Rodrigo Dienstmann, Principal Investigators of our Molecular Oncology (page 132), Early Clinical Drug Development (page 106), and Oncology Data Science – OdysSey (page 118) Groups, respectively.

Supported through our institutional Advanced Molecular Diagnostics Program (DIAMAV), powered by the FERO Foundation (page 138), 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) – CaixaResearch (page 149), directed by Elena Garralda. Patients' suitability for inclusion in any given clinical trial is assessed based on their respective genomic profile and pathologic features.

We have 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). 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 that we provide, we have attained ISO 15189 flexible accreditation for both our Amplicon-seq testing and 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 immunotherapies. Based on nanostring and RNA-seq technologies for the detection of an immune signature, we use the VIGex tool. Our group is particularly interested in liquid biopsy and RNA-based analysis of tumors for microenvironment profiling.

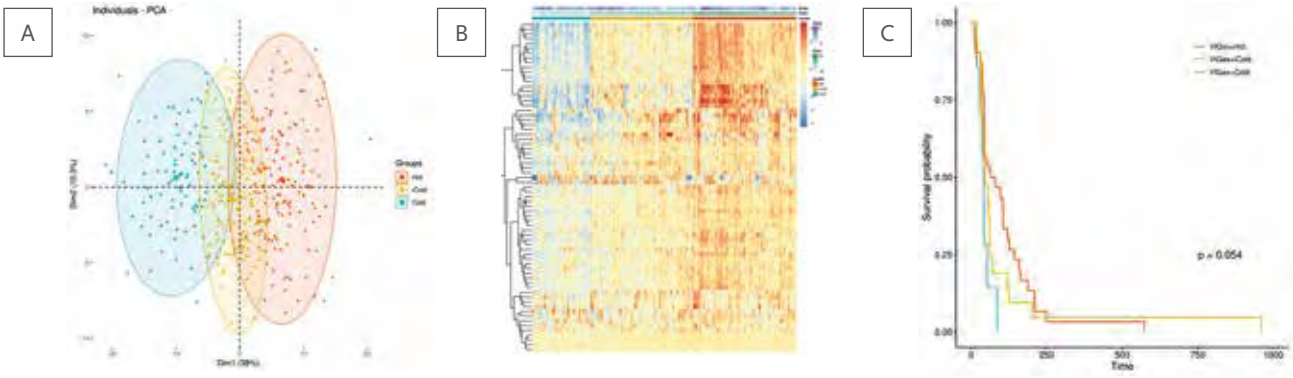


Figure: VIGex classification of 398 cancer metastatic Sample according to nCounter (NanoString) gene expression(69 immuno-related genes). Gene expression values were normalized to the geometric mean expression of 19 housekeeping genes, then log2-transformed and centered around mean. A) PCA showing the 3 clusters identified with PAM (partioning around medoids) method (Hot, iCold, Cold). B) Heatmap showing relative gene expression and PCA values of the 69 immuno-related genes with Hot, iCold and Cold groups. C) Kaplan-Meier plot showing time to progressionofthe Hot, iCold and Cold groups of an independent cohort of 58 samples.

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CORE TECHNOLOGIES

MOLECULAR ONCOLOGY GROUP

Principal Investigator Paolo Nuciforo **Attending Physicians** Roberta Fasani, Siarhei Mauchanski, Sara Simonetti **Laboratory Supervisor** Jose Antonio Jiménez **Laboratory Assistant** Mª Ángeles Diaz **Post-Doctoral Fellow** Francisca Gallego **PhD Students** Stefania Napoli, Garazi Serna **Technicians** Lidia Alonso, Eloy Garcia, Margarita Gonzalez, Xavier Guardia, Paola Martinez, Gertrudis Sánchez, Lidia Sánchez, César Javier Sevillano **Student** Inés Terrones

STRATEGIC GOALS

- Discovery and validation of novel biomarkers using tissue-based technologies.
- Identification of targetable alterations as part of VHIO's Molecular Prescreening Program (page 156).
- Application of molecular and digital 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's research programs.

HIGHLIGHTS

- Immune microenvironment characterization and dynamics in HER2-positive breast cancer.
- Identification of SARS-CoV-2 placenta infection and its impact on neonatal outcome.
- We have received funding from *La Marató TV3* to study the role of microbiome in COVID-19 susceptibility and prognosis in patients with cancer.
- Pathology Task Force leader for the Cancer Core Europe Consortium – CCE (page 37).

SUMMARY

VHIO's Molecular Oncology Group applies 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 130), Oncology Data Science - ODysSey Group (PI Rodrigo Dienstmann, page 118), and our Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch (directed by Elena Garralda, page 149), we participate in our in-house Molecular Prescreening Program (page 156). We molecularly profile over 1,100 patients each year as candidates for enrolment in early phase clinical trials at the UITM – CaixaResearch.

Our group also serves as one of VHIO's Core Technology Platforms and our laboratory is therefore key to VHIO's translational research lines and programs. We actively participate in all projects involving the use of human tissue collected from patients. These include 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 contributions are reflected by several high-impact factor collaborative papers published throughout 2021.

Additionally, we continue to work independently and in partnership to decipher the impact of the microbiome in colorectal cancer development and progression. In particular, we developed a *Fusobacterium nucleatum* diagnostic assay that permits the simultaneous visualization and quantification of bacteria within tumors. Using this assay we identified, for the very first time, *Fusobacterium nucleatum* as a biomarker of relapse in rectal cancer (Serna G. et al. 2020) *.

We are also leading the FUSOMAP, a 3-year project funded by the Mutua Madrileña Foundation and Instituto de Salud Carlos III - ISCIII (Institute of Health Carlos III), to develop microbiota-based diagnostic and prognostic models by mapping intratumoral Fusobacterium and associated gut microbiota in early-stage colorectal cancer. Lastly, in 2021 we were awarded by La Marató TV3 to investigate the relationship between Sars-CoV-2 and the microbiome in cancer patients.

As a Core Facility, we have provided support for 363 clinical studies conducted at Vall d'Hebron, representing approximately 70% of all currently open trials at our institution. Our involvement in these 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 2021, we performed approximately 3000 molecular determinations on samples for patient inclusion in clinical trials, and over 40,000 tests to support basic and translation research. We have also served as the central laboratory of choice for several international studies, and successfully maintained the prestigious ISO15189 accreditation that endorses quality and competence.

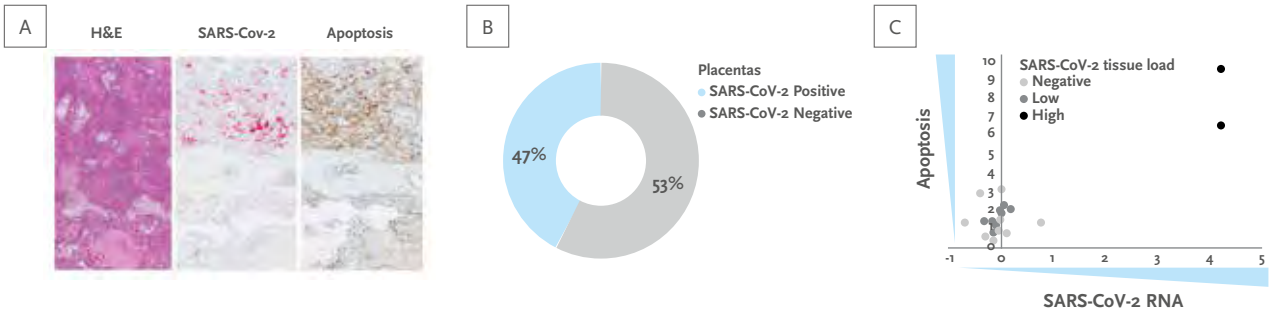

Figure: Severe SARS-CoV-2 placenta infection can impact neonatal outcome in the absence of vertical transmission. A) Histopathological and molecular features of the placenta with severe injury. B) Frequencies of SARS-CoV-2 placenta positivity in COVID-19 positive women. C) Correlation between SARS-CoV-2 load and apoptosis by immunohistochemistry in placental tissues.

PI PAPER PICK 2021

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CORE TECHNOLOGIES

PROTEOMICS GROUP

Principal Investigator Francesc Canals **Technician** Luna Martín

STRATEGIC GOALS

- As a Core Facility, we provide services in proteomic techniques to other research groups.
- We perform proteomic screening for novel biomarkers to help develop cancer therapeutics.
- Development of mass spectrometry-based assays for the analysis of biomarkers in clinical samples.

HIGHLIGHTS

- The provision of proteomic services to VHIO groups, oncology professionals at the Vall d'Hebron University Hospital (HUVH), and members belonging to the ProteoRed-ISCIII Carlos III Networking Proteomics Platform.
- Application of proteomic and phosphoproteomic screening to the characterization of CRC PDX models.
- The setting up of mass spectrometry based analytical methods for the monitoring of specific drugs in plasma and tumor tissue, to assess preliminary pharmacokinetics in preclinical mouse models.
- Characterization of specific protein interactomes,
- Proteome-wide thermal shift analysis to characterize protein-drug interactions.

SUMMARY

Our group serves as a Core Technology Platform We provide state-of-the-art proteomic methodologies to investigators at VHIO, and incorporate 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 developed immune-MS based assays with improved selectivity and accuracy in the analysis of low abundance biomarker proteins in plasma or CSF samples.

We have applied proteomic analysis methods to the proteomic and phosphoproteomic characterization of patient-derived xenograft (PDX) models of colorectal cancer (CRC). PDXs constitute an ideal platform for the molecular characterization of CRC at the proteomic level. Complementing genomic classification, we are exploring the suitability of this characterization as a tool for tumor subtype classification.

We have set up methodologies for the mass spectrometry analysis of drugs in biological samples to study their pharmacokinetics and bioavailability in mouse models. In addition, we have applied proteomic analysis to the characterization of protein-protein interactors, and protein-drug interactions

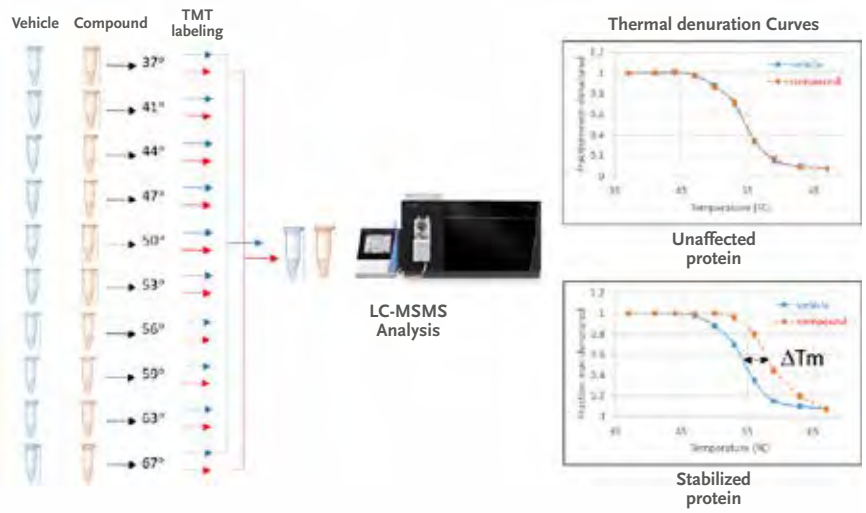

Figure: Target binding analysis by Proteome-Wide Cellular Thermal Shift Assay (CETSA): Cells or cellular protein extracts, treated or untreated with the compound of interest, are heated to different temperatures, inducing protein denaturation. The supernatants following centrifugation, containing the soluble non-denatured fraction of each protein, are analyzed by LCMSMS using the multiplexing TMT methodology. Proteins not affected by the compound display similar denaturation curves. (top). Proteins able to bind the compound get stabilized, displaying a thermal shift in their melting curves (bottom).

PI PAPER PICK 2021

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INSTITUTIONAL PROGRAMS & TASK FORCES

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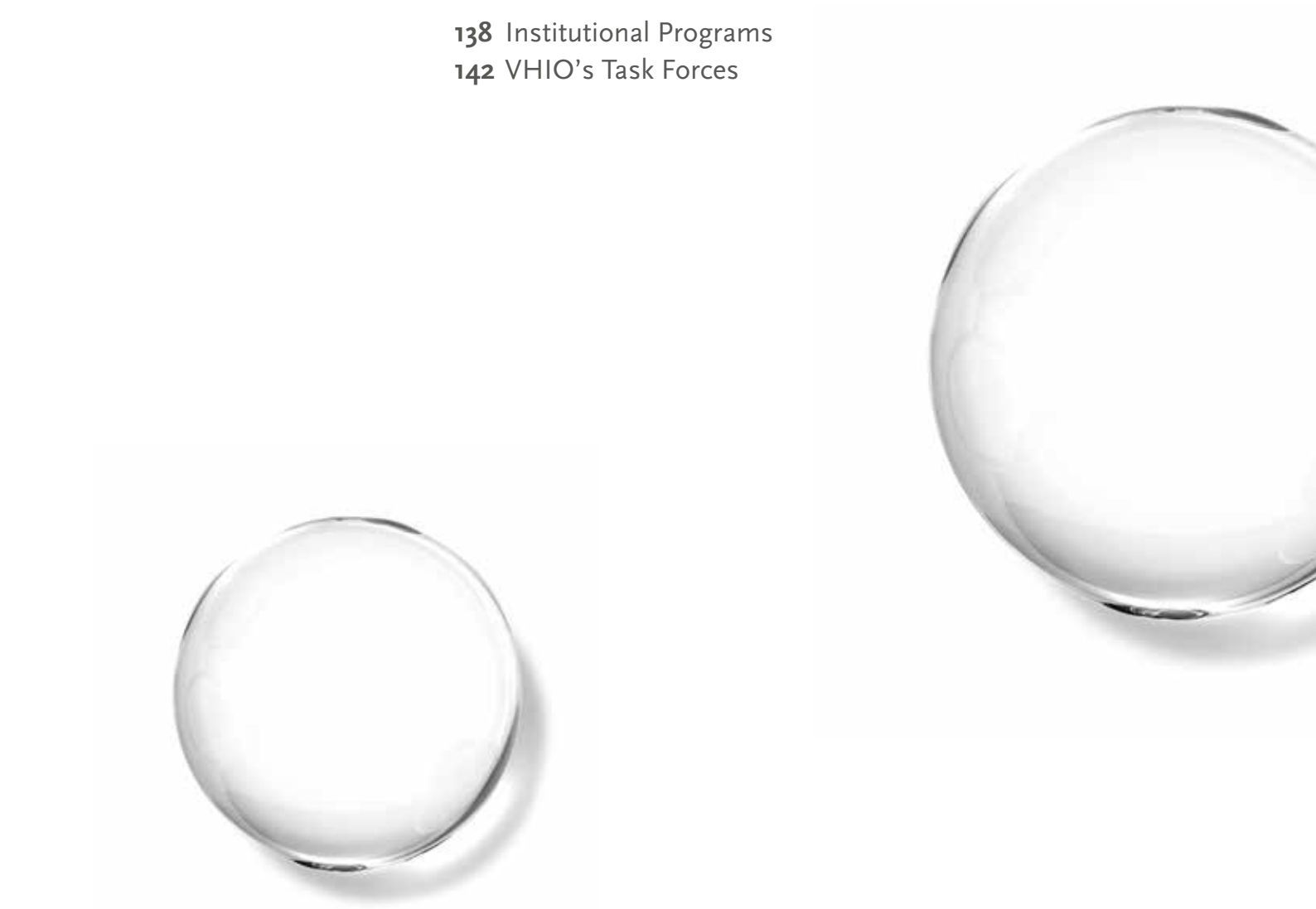
INSTITUTIONAL PROGRAMS & TASK FORCES



INSTITUTIONAL PROGRAMS

FERO Foundation: driving advanced molecular diagnostics against cancer

Our Molecular Prescreening Program (page 156) is powered by one of our Institutional Supporters and Patrons, the *Fundación FERO* (page 29). FERO's Institutional Advanced Molecular Diagnostics Program (DIAMAV) catalyzes precision medicine at VHIO. Over the last decade, this program has provided access to advanced molecular diagnostics to more than 8,000 cancer patients, and is critical in matching targeted therapeutic approaches with hundreds of clinical trial opportunities.

This pioneering program, also counting on the support and expertise provided through our Research Unit for Molecular Therapy of Cancer (UITM) - CaixaResearch, is co-led by VHIO's Ana Vivancos, Paolo Nuciforo, Elena Garralda, and Rodrigo Dienstmann, Principal Investigators of our Cancer Genomics, Molecular Oncology, Early Clinical Drug Development, and Oncology Data Science (ODysSey) Groups, respectively.

Serving as a Transversal Clinical Trials Core Service, our expert team focuses on the clinical implementation of advanced molecular diagnostics to optimize the selection of therapies for patients being considered for enrollment in clinical trials, as well as continued medical education on emerging cancer biomarkers for precision cancer therapy. By advancing molecular profiling in patients, personalized treatment strategies based on the genomic or pathologic profile of each individual patient can be more effectively matched to the molecular makeup of their respective disease.

Our researchers and clinical investigators identify specific molecular risk factors and better predict the potential efficacy of specific agents tailored to each particular tumor. These insights better guide our multidisciplinary teams to assess and establish patients' suitability for inclusion in early phase clinical trials conducted at VHIO's UTIM – CaixaResearch.

It is thanks to the backing received from FERO that our Molecular Prescreening Program continues to establish itself as a reference in prescreening and oncogenomics in Europe. Thanks to our cutting-edge technologies and platforms, we continue to extend the promise of precision medicine in oncology to an increasing number of individuals. In 2021, we performed tumor molecular profiling in 1,138 cancer patients as candidates for enrolment in clinical trials.

In short, FERO's Institutional Program enables us to lead and run such a comprehensive program. In so doing, we continue to 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, and develop cancer diagnostics for the early detection of disease.

"la Caixa" Foundation

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

Cancer is a leading cause of death worldwide, with an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020. While survival rates continue to improve, there are still many tumor types with no effective treatments. Clinical trials are crucial to identifying and developing novel therapies against cancer and are only possible at VHIO thanks to the continued support received from one of our Institutional Supporters and Patrons, the "la Caixa" Foundation (page 30).

Building on the successes of the two previous VHIO -"la Caixa" Institutional 3-year Programs, the CaixaResearch Advanced Oncology Research Program (2020-2023), continues to spur our development of more potent and precise anti-cancer medicines. It also enables us to fortify existing research lines, initiate new projects, and lead frontier research in some of the most relevant and rising focus fields in precision oncology; those that show particular promise in solving the multiple questions that stand in the way of more effectively combating this disease.

Our Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch (page 149), also supported by the "la Caixa" Foundation, allows us to pursue our transformative research lines aimed at unpicking the complex role that the microbiome plays in cancer development, drive 'big data'-derived insights, develop 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.

Clinical trials performed at this Unit have led and/or contributed to the approval of more than 30 anti-cancer agents by either the U.S. Food and Drug Administration (FDA), or the European Medicines Agency (EMA), or both. It is thanks to the support received that we can continue to 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, Cancer Genomics, Molecular Oncology, Oncology Data Science (ODysSey) Groups, led by Elena Garralda, Ana Vivancos, Paolo Nuciforo, and Rodrigo Dienstmann, respectively.

Within the scope of our CaixaResearch Advanced Oncology Research Program, Elena Garralda's team has performed several clinical trials with patients selected on molecular alterations: mutations in AKT1, EGFR, IDH1, ALK, ROS1, BRAF, NRAS, KRAS, FGFR1 and 2, MET, HER2, HER3, RET; ATM; BRCA, amplifications in HER2, AKT 1, 2, and 3, FGFR1, MET, NOTCH1-4, rearrangements of NTRK1-3 ROS1, ALK, BRAF, RSPO2/3, RET, NRG and FGFR1-3.

The matched dedication of our clinical and translational investigators across all VHIO programs and groups, as well as our transversal clinical trials core services enables us to expand our portfolio of clinical studies and include an increasing number of patients, year-on-year.

Importantly, all of our teams have continued to rapidly overcome the many challenges posed by the COVID-19 pandemic. They have successfully maintained our clinical research activities and continued to include patients in clinical studies – even reporting increased activity in some areas compared to previous years. In 2021, our Unit participated in 207 ongoing phase I studies, 27 of which are Basket trials (a 6% increase compared with 2020). This year, 66 new trials opened; 5 as Baskets, with 551 patients enrolled.

Among the many highlights in 2021 was the expansion of the Basket of Baskets (BoB). This academic study, endorsed by CCE, 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. During 2021 we opened a new module targeting FGFR pathway alterations as well as searched for funding for new modules.

Fundación BBVA

BBVA Foundation: generating new insights into the mechanisms of resistance and response to immune-based therapies

Considering the successes of the very first VHIO-BBVA Foundation Program on Tumor Biomarkers Research that launched back in 2011, VHIO and the *Fundación BBVA* - one of our Institutional Supporters and Patrons (page 31), - renewed their agreement in in 2018. Building on the achievements of the first program, our 4-year Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI), centers on advancing research into the natural mechanisms governing how T lymphocytes react to cancer and how to use these anti-tumor responses to develop more personalized and potent immune-based therapies and treatment strategies.

Representing an important forward step in advancing agents that inhibit checkpoint regulation of the immune system, this VHIO Institutional Program aims at achieving a deeper understanding of mechanisms of resistance and response to these therapies, and prioritizes the early clinical drug development of those therapies and combinations that show most promise.

Under the leadership of our Director, Josep Tabernero, CAIMI counts on the expertise of Elena Garralda, Director of our Research Unit for Molecular Therapy of Cancer (UITM) - CaixaResearch, who heads up the program's clinical research, and Alena Gros, Principal Investigator of our Tumor Immunology & Immunotherapy Group, who leads its translational research. It also relies on our Molecular Prescreening Program, co-led by Ana Vivancos, Paolo Nuciforo, Elena Garralda, and Rodrigo Dienstmann, Principal Investigators of VHIO's Cancer Genomics, Molecular Oncology, Early Clinical Drug Development, and Oncology Data Science (ODysSey) Groups, respectively.

Over the past three years, CAIMI has enabled the development of various translational projects linked to the early clinical development phases of immunotherapy. Just some focus areas include the development of cell-based therapies such as killer T cells for non-responders to current immunotherapies, and characterizing hyperprogressive disease with immunotherapy to advance insights into this phenomenon. In 2021, we established a radiomic signature to predict response to immunotherapy, led by Raquel Perez-Lopez, Principal Investigator of our Radiomics Group, and are now exploring how this correlates with the evolution of disease in patients.

Importantly this year, Alena Gros' and Elena Garralda's teams finalized the clinical grade validations of tumor-infiltrating lymphocytes expansion for the treatment of certain cancer patients at the Vall d'Hebron University Hospital (HUVH), in collaboration with the *Banc de Sang i Teixits* - BST (Blood and Tissue Bank), a public agency of the Catalan Department of Health.

Most recently, they received authorization from the AEMPS to initiate a phase I clinical trial, NEXTGENTIL-ACT, to study the safety and tolerability of neoantigen-selected tumor-infiltrating lymphocytes (TILs) for patients with solid tumors refractory to standard therapies. By enriching for neoantigen-reactive lymphocytes, the aim is to fortify the efficacy of TIL therapy in epithelial cancers. Patient recruitment is now underway.

VHIO's TASK FORCES

STRATEGIC GOALS

- Foster research collaborations in-house and externally by providing a multidisciplinary platform that promotes interaction between researchers and other healthcare professionals in oncology.
- Identify and disseminate new funding opportunities (competitive and non-competitive), for the development, coordination, compilation, writing, and logistical management of new research proposals.
- Create, maintain and standardize the necessary resources (CRF, informed consents, and databases), required to optimize the development of ongoing research.
- Improve circuits in sampling and procedures as well as data collection to accelerate research.
- Identify the needs of the research groups and professionals in oncology who are participating in our Task Forces (TF), including logistics, resources, mediation, and provide solutions to meet these requirements.
- Propose milestones and contingency plans.
- Identify the needs of patients and clinical challenges and translate these areas into targeted research opportunities.
- The central management of patient data according to project pipelines and cohorts.

HIGHLIGHTS

- We have consolidated our task forcing model by increasing the number of participants and projects.
- We have created a new TF devoted to the involvement of patients, their families, and caregivers in our research. This team initiated a new project this year, with other potential activities currently under review.
- Through the digitalization of our activities, we have succeeded in maintaining and growing our TFs throughout the COVID-19 pandemic.

SUMMARY

Aimed at accelerating cancer discovery through team science, VHIO's multidisciplinary teams, coordinated by our Scientific Area (page 164), also work together as dedicated Task Forces (TFs) that have been established in line with VHIO's strategic plan and core research priorities.

Our TFs comprise preclinical and translational researchers, clinical investigators and medical oncologists, pathologists, other medical disciplines, clinical research nurses, data curators and study coordinators, as well as project managers, among others.

Covering breast, colon, gastroesophageal, kidney, melanoma, neuroendocrine, rectal, pancreatic, prostate, and gynecological cancers, onco-imaging, as well as patients' involvement in research, VHIO's TFs regularly convene to synergize efforts, boost collaborations among groups and between specialists, and continuously revise patient circuits, sampling and ethics toward advancing cancer science and precision medicine.

The internal organization of these expert teams varies depending on their size, workflow, participants, and activities. They each have an appointed Chair and are coordinated by an allocated project manager to set respective agendas, compile meeting minutes, follow up on action points/ tasks, and work together to establish alignments, interactions and synergies across all TFs.

Illustrative of VHIO's commitment to teamwork, clinical researchers from other medical specialties across Vall d'Hebron and/or other local hospitals in Catalonia, as well as investigators from the Vall d'Hebron Barcelona Hospital Campus and other research institutions, actively contribute to the activities of our TFs.

We seek to identify additional areas that require task force teams. As an example, in 2021 we launched a new TF dedicated to patients that aims to involve and engage patients, their families and caregivers in our research. Also in the planning are potential transversal TFs focused on additional areas including cancer prevention and early detection in alignment with ongoing policies and activities such as the European Code Against Cancer and the Cancer Mission.

VHIO's TRANSVERSAL CLINICAL TRIALS CORE SERVICES

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VHIO's TRANSVERSAL CLINICAL TRIALS CORE SERVICES

For another year, due to the safety issues brought about by COVID-19, we had to adjust our approach to this report's photography. With the exception of some of our larger groups*, we have ensured that as many group members as possible have been included, and without masks. Each individual picture was taken at a distance in locations away from areas dedicated to the care of our cancer patients. For faculty working remotely, we invited them to submit their photos from home.

*** Considering certain logistical and spatial issues, we have unfortunately had to repeat pictures of some of our larger groups and units from VHIO's Scientific Report 2019 - as indicated in the corresponding pages.**

VHIO's TRANSVERSAL CLINICAL TRIALS CORE SERVICES

CLINICAL TRIALS OFFICE

Director, Clinical Trials Office Marta Beltran **Head, Start-Up Unit and Clinical Trials Liaison** Silvia Perez **Head, Data Entries** Ignacio Carcela **Head, Hematology** Laura Segura **Lead Study Coordinators** Eulalia Aliende, Guillem Cunill, Montse Moreno, Gemma Mur, Olga Padrós, Cristina Perez, Júlia Sedó, Ester Serra **Leads, Data Entries** David Alvarez, Gloria García, Eva Lázaro, Alberto Rojo **Study Coordinators** Aitana Almodóvar, Enric Alvarez, Eva Banus, Marina Barbero, Anna Cabrera, Júlia Caparrós, Laia Catalán, Paula Chiquillo, Nuria Clotet, Constancio Collado, Natàlia Écija, Núria Farras, Carlos Fernández, Danis Fernánez, Queralt Ferrer, Anna Giralt, Laia Gispert, Sara Gutiérrez, Montse Hernandez, Josu Iraola, Alejandro Lahire, María López, Raquel Madrenas, Alba Martínez, Elena Martinez, Sònia Martínez, Magda Masana, Ana Matres, Thais Miquel, Mireia Mira, Alejandro Pardines, Jordi Perera, Cristian Rosales, Marta Rotxes, Álvaro Rueda, Elena Sánchez, Laura Sancho, Laura Saucedo, Júlia Sedó, Samira Sehir, Jana Simón, Maria Del Mar Suanes, Albert Texidor **Data Entries** Cristina Aguilar, Sara Álvaro, Nestor Babon, Samanta Bascuas, Carlota Bellot, Laia Benitez, Elisabet Beseran, Helena Carbonero, Clara Escala, Adrià Jaime Fernández, Neus Iserte, Joan Izquierdo, Bàrbara Juanmiquel, Eva Marín, Sílvia Marín, Carla Martinez, Raquel Masip, Miriam Meseguer, Carina Monclús, Paula Nuñez, Adriana Oños, Victor Ortega, Ana Pedraza, Sergio Perez, Xavier Perez, Joana Pinyol, Eva Puerma, Olga Reyes, Isabel Rico, Alberto Rojo, Jordi Romero, Rosa Romero, Blanca Ruiz de la Torre, Judith Serrano, Inés Tejero, Júlia Toledo, Marta Vidigal **Clinical Trials Assistants** Gisela Andrés, Cristian Campderros, Nuria Carballo, Marc Palomar

* For logistical issues brought about by the current COVID-19 pandemic, we are repeating pictures of some of our larger groups, services and units from our 2019 Scientific Report.

STRATEGIC GOALS

- Contribute to the development of novel therapies against cancer.
- Consolidation as an international reference for clinical trials in oncology and hematology.
- Guide patients enrolled in clinical trials to comply with the protocol requirements and help them with daily life throughout the duration of their participation.
- Standardize clinical trial processes to ensure optimal quality and the compliance of Good Clinical Practice (GCP).

HIGHLIGHTS

- We continue to report important numbers of clinical trials performed and respective patient recruitment.
- Optimal management of complex protocols which are increasingly demanding.
- Implementation of new tools and procedures to increase the quality and efficiency of research.
- Reorganization of our Clinical Trials Office to implement transversal projects.

SUMMARY

Established 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 and administrators who coordinate phase I–IV clinical studies and also participate in several translational research projects at VHIO.

Organized into 4 groups (start-up unit, oncology study coordinators, oncology data entries, hematology study coordinators and data entries) covering all tumor types and studies, this team is managed by our Clinical Trials Office Director, Marta Beltran.

Clinical Trials in Oncology

In 2021 we managed 4 phase 0, 180 phase I, 27 basket, 153 phase II, and 147 phase III clinical studies with active recruitment throughout the year (Figure I), with patient enrolment totaling at 1,326 (Figure II). 183 new trials were initiated, including 12 post-authorization trials, and rollover studies. In addition, we continue to follow up patients who were recruited prior to 2021 and are still enrolled and receiving study treatment (890 patients in total, and 2016 in follow-up).

Figure I: **Annual distribution of oncology clinical trials (Phase 0, I + Baskets, II–III) and post authorization trials with active recruitment.**

	2013	2014	2015	2016	2017	2018	2019	2020	2021
Phase 0							1	2	4
Phase I & basket trials	75	83	106	129	137	161	162	195	207
Phase I Specific Tumor Type (STT)	29	36	32	44	45	53	59	79	75
Phase I Non Specific Tumor Type (NSTT)	46	47	68	71	75	86	80	90	105
Basket			6	14	17	22	23	26	27
Phase II STT trials	96	99	94	117	107	131	141	148	153
Phase III trials	61	64	89	108	111	107	121	129	147
N° clinical trials	232	246	289	354	355	399	425	474	511
Post authorization & rollover trials		5	14	16	19	33	34	34	36

Figure II: **Annual recruitment of patients enrolled in oncology clinical trials (Phase 0, I + Baskets, II–III) and post authorization trials.**

	2013	2014	2015	2016	2017	2018	2019	2020	2021
Included in Phase 0							1	1	15
Included in Phase I & basket trials	345	303	370	453	445	508	499	521	551
Phase I Specific Tumor Type (STT)	107	79	79	84	80	110	124	178	138
Phase I Non Specific Tumor Type (NSTT)	238	224	262	301	289	334	303	307	342
Basket			29	68	76	64	72	36	71
Included in Phase II STT trials	257	302	327	333	323	361	337	230	341
Included in Phase III trials	241	166	282	343	328	329	285	332	419
Total of patients included	843	771	979	1129	1096	1198	1122	1084	1326
Included in post authorization & rollover trials		20	56	50	80	184	164	156	280

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 a leading reference in early clinical studies. Reflective of our recognized excellence, VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch, directed by Elena Garralda (page 149), has been re-accredited by the *Generalitat de Catalunya* (Government of Catalonia).

As we continue to render personalized medicine more precise by matching therapies to the specificities of each individual patient, each individual tumor, the requirements and selection criteria for inclusion in certain studies are becoming more complex.

We are dedicated to expanding our portfolio of trials in to ultimately establish new treatment models with highly selective drugs. Our Unit continues to fine-tune patient selection criteria in order to identify those patients who are most likely to benefit from novel therapies, including emerging immune-based treatments, tailored to individual patients' molecular 'measurements'.

Clinical Studies in Hematology

In 2021 we managed 49 phase I, 2 basket, 35 phase II, and 60 phase III clinical trials with active recruitment throughout the year (Figure III) with patient enrolment totaling at 182 patients (Figure IV). 67 new trials were initiated, including 6 post-authorization trials, and rollover studies. In addition, we continue to follow up patients who were recruited prior to 2021 and are still enrolled and receiving study treatment (140 patients in total, and 105 in follow-up).

Clinical research is hematology is spearhead by Francesc Bosch, Principal Investigator of VHIO's Experimental Hematology Group (page 108).

Figure III: **Annual distribution of hematology clinical trials (Phase I + Basket, II and III) and post authorization trials with active recruitment**

	2018	2019	2020	2021
Phase I	25	31	39	51
Phase I Specific Disease	24	30	37	47
Phase I Non Specific Disease	1	1	2	2
Basket				2
Phase II trials	28	24	36	35
Phase II Specific Disease	28	23	35	34
Phase II Non Specific Disease		1	1	1
Phase III trials	50	51	45	60
Phase III Specific Disease	50	51	42	59
Phase III Non Specific Disease			3	1
N° clinical trials	103	106	120	146
Post authorization & rollover trials	15	22	25	28

Figure IV: **Annual distribution of hematology clinical trials (Phase I + Basket, II and III) and post authorization trials with active recruitment**

	2018	2019	2020	2021
Included in Phase I	38	55	59	84
Specific Disease (SD)	37	55	56	84
Non Specific Disease (NSD)	1		3	
Basket				
Included in Phase II trials	20	38	39	42
Specific Disease (SD)	20	38	39	42
Non Specific Disease (NSD)				
Included in Phase III trials	52	56	55	56
Specific Disease (SD)	52	56	51	56
Non Specific Disease (NSD)			4	
Total of patients included	110	149	153	182
Included in post authorization & rollovers trials	1	6	38	51

The prestige of HUVH's Medical Oncology Department, led by VHIO's Director, Josep Tabernero, is recognized by pharmaceutical and biotechnology companies. It has also become a reference program and selected by the industry to carry out complex clinical trials. The number of participating centers in these studies is highly restricted.

Clinical sites are selected based on the highest quality standards 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. In 2021, we also conducted more than 16 investigator-Initiated trials (IITs) in oncology.

VHIO's TRANSVERSAL CLINICAL TRIALS CORE SERVICES

RESEARCH UNIT FOR MOLECULAR THERAPY OF CANCER (UITM) – CAIXARESEARCH

Director Elena Garralda **Co-Director** Josep Tabernero **Executive Team** Marta Beltran, Elena Garralda, Ángeles Peñuelas, Gemma Sala **Clinical Head** Elena Garralda **Associated Investigators, Senior Consultants** Judith Balmaña, Joan Carles, Enriqueta Felip, Elena Garralda, Teresa Macarulla, Ana Oaknin, Cristina Saura, Josep Tabernero **CORE Phase I Investigators** Guzmán Alonso, Irene Braña, Vladimir Galvao, Julia Lostes, Honey K. Oberoi, Katerin Rojas, Omar Saavedra, María Vieito **Phase I Investigators** Daniel Acosta, Juan David Assaf, Iosune Baraibar, Maria Borrell, Ana Callejo, Jaume Capdevila, Susana Cedrés, Marc Diez, Elena Élez, Santiago Escrivá, Alejandro García, Carmen García, Macarena González, Francisco Grau, Jorge Hernando, Patricia Iranzo, Alexandre Martínez, Rafael Morales, Eva Muñoz, Alejandro Navarro, Mafalda Oliveira, Carolina Ortiz, Nuria Pardo, Francisco Javier Ros, Francesc Salvá, Nadia Saoudi, Cristina Suárez, Helena Verdaguer **Clinical Trials Office Director** Marta Beltran **Start Up Unit Head** Sílvia Pérez **Data Entries Head** Ignacio Carcela **Lead Study Coordinators** Eulàlia Aliende, Montserrat Moreno **Coordinators** Aitana Almodóvar (Sponsor dedicated), Eva Banús, Constancio Collado, Guillem Cunill, Núria Farràs, María López, Ana Matres (Sponsor dedicated), Elena Martínez, Sonia Martinez (Sponsor dedicated), Gemma Mur, Alejandro Pardines, Joel Puig, Laura Saucedo, Albert Teixidor (Sponsor dedicated) **Lead Data Entries** Gloria García **Data Entries** Eva del Castillo (external staff), Andrea Gómez (Sponsor dedicated), Lidia Martinez, Gerard Orriols, Sergio Pérez, Montserrat Pujadas, Isabel Rico, Jordi Romero, Inés Tejero (Sponsor dedicated), Gaudí Vall, Marta Vidigal **Clinical Trials Office Administrative Support** Nuria Carballo, Marc Palomar **Nursing Head** Ángeles Peñuelas **Nurse Coordinator** Sonia Valverde **Operational Research Nurses** Inés Depares, Andrea Martínez, Alba Silverio **Nurses** Elena de Cabo, María Luisa Fargas, Marta Mate, Isabel Muñoz, Teresa Navarro, Gianmarco Russi **Nurses Assistants** Mª Ascensión Clop, Mireia Hernández, Cristina Resina **Inventory Managers** Susana Flores, Araceli García-Platas **UITM – CaixaResearch Administrative Support (Schedulers)** Laura Abellán, Mª Teresa Mendoza, Noelia Moles, Marc Palomar **Head, Clinical Research Oncology Pharmacy Unit** Isabel Cidoncha **Clinical Director, Pharmacy Service** Maria Queralt Gorgas **Senior Pharmacists** María Josep Carreras, Laura Maños **Pharmacists** Montserrat Carreres, Carla Esteban, Celia Fernández, Lorena García, Patricia García, Pablo Latorre, Rocío Paucar, Pilar Rovira, Eugenia Serramontmany, Javier Varela **Technicians** Romina Bellini, Esther Carabantes, Bryan Cárdenas, Angelica Cely, Ismael Delgado, Rafael Diaz, Ariadna Jabalera, Roser Klimt, Susana Mulet, Isabel Pérez, Marta Pozo, Alan Thompson, Silvia Torralba, Alexandre Valle, Noemi Visus **Data Entry** Carmen Torres **Secretary** Isabel Mª Alerany

*For logistical issues brought about by the current COVID-19 pandemic, we are repeating pictures of some of our larger groups, services and units from our 2019 Scientific Report.

STRATEGIC GOALS

- Early clinical drug development and translational research led by our UITM – CaixaResearch clinical investigators and VHIO researchers: 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 this Unit to VHIO's preclinical and translational projects. We also collaborate with various other 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 Task Force 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.

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 130) we benefit from applications that enable us to generate faster results. These include 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 Molecular Prescreening Program (page 156), namely, disease-oriented mutation panels for our NGS platforms.
- We have established alliances with several pharma companies as the preferred site for testing their novel and most relevant therapies, including GlaxoSmithKline OCTC, Roche ImCORE, and Astra Zeneca/MedImmune Partner of Choice Network (page 206).
- Our investigators 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 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. We are engaged in ongoing and advanced negotiations with pharmaceutical companies to increase the number of modules.
- We have introduced Molecular Tumor Board meetings to discuss the most relevant genomic features of complicated cases and evaluate possible treatment options.
- We have launched an advanced cell-based therapy program, and are participating in several pharma sponsored trials to evaluate the role of TIL therapy. We are also exploring an academic TIL product in collaboration with Alena Gros (PI: VHIO's Tumor Immunology & Immunotherapy Group, page 100).
- In collaboration with several other VHIO groups, we head our CaixaResearch Advanced Oncology Research Program (2020-2023), also supported by the "la Caixa" Foundation (page 139).

"la Caixa" Foundation

SUMMARY

Inaugurated in June 2010, thanks to the support received from the "la Caixa" Foundation (page 30), VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch 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 m^2, our Unit is located within the General Area of the Vall d'Hebron University Hospital (HUVH), 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. Our UITM – CaixaResearch incorporates a multidisciplinary team comprised of medical oncologists, clinical trial coordinators and data managers, nurses and nurse technicians, pharmacists, as well as administrative personnel.

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 types and how to treat them in an individualized way – getting the right therapy to the right patient, at the right time. As the statistics show (page 147, Figure I), we continue to do so for an increasing number of patients.

For another year, we have had to rapidly adjust to overcome the many challenges posed by the COVID-19 pandemic. All our efforts have focused on successfully maintaining our clinical research activities and continuing to include patients in our clinical trials. During 2021, our Unit participated in 207 ongoing phase I clinical trials, 27 of which are Basket trials (a 6% increase compared with 2020).

Our facilities, coupled with our multidisciplinary clinical teams, enable us to continue to expand our portfolio of phase I studies with 551 patients enrolled (a 6% increase compared with 2020). This year we opened 66 new trials; 5 as Baskets.

Research carried out at our Unit by VHIO's Early Clinical Drug Development Group (page 106), directed by Elena Garralda, 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 collaborate 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.

We also participate in VHIO's Molecular Prescreening Program (page 156), that performs molecular analyses of patients' tumors to select the best possible treatment with the experimental therapeutics available. Thanks to our Cancer Genomics Group (PI: Ana Vivancos, page 130) and their development of existing applications 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 are equipped to perform faster and more precise mutational analyses of tumor suppressor genes as well as translocations and gene amplifications.

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 Ángeles Peñuelas (page 152), pathologists from the Vall d'Hebron University Hospital's Molecular Pathology Department, radiologists and interventional radiologists, our Clinical Trials Office directed by Marta Beltran (page 146), Database Managers, VHIO's Clinical Research Oncology Pharmacy Unit headed by Isabel Cidoncha (page 154), our Quality & Processes Unit headed by Gemma Sala (page 160), as well as many other healthcare specialists including dermatologists, cardiologists, and ophthalmologists.

VHIO's TRANSVERSAL CLINICAL TRIALS CORE SERVICES

CLINICAL RESEARCH ONCOLOGY NURSES

Nurse Supervisor Mª Angeles Peñuelas **Nurse Supervisor's Assistant** Juan Manuel Garcia **Nurse Coordinators** Cristina Casal, Tania Sánchez, Sonia Valverde **Nurses** Andrea Caballero, Anna Maria Carro, Mª Elena de Cabo, Mª Luisa Fargas, Margarida Marcos, Marta Mate, Carmen Moína, Mireia Moral, Isabel Muñoz, Teresa Navarro, Lydia Velez **Operational Research Nurses** Inés Depares, Andrea Martinez, Alba Silverio **Nursing Assistants** Xenia Ángeles, Katherine Espinoza, Susana Flores, Mireia Hernández, Mª Ascension Martin, Ana Belen Ortiz, Cristina Resina

* For logistical issues brought about by the current COVID-19 pandemic, we are repeating pictures of some of our larger groups, services and units from our 2019 Scientific Report.

SUMMARY

Clinical trials in oncology are essential for developing novel, more effective targeted therapies against cancer as well as improving survival, side effect profiles and the quality of life of our patients. Advances in oncology care and the delivery 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 tasks including identifying trends in side effects, and closely collaborating with multidisciplinary teams to develop and evaluate patient management. They contribute to clinical studies by collating samples and quality data, as well as provide excellence in nursing care and optimal symptom management for all patients enrolled in our clinical trials.

The COVID-19 pandemic continued to pose challenges in 2021, which naturally demanded adaptive procedures, circuits and structures. Where possible, our clinical groups and oncology nurses had, in many cases, to continue to re-think conventional patient care. With the safety of our patients as the highest priority, Angeles Peñuelas led her team to work together with VHIO's medical oncologists and clinical investigators to swiftly establish adaptive approaches to ensure the optimal running of clinical studies, while delivering the highest levels of quality patient care.

Newly introduced measures throughout the COVID-19 waves –whenever/wherever possible- included remote monitoring as well as dispensation of medication for certain patients receiving orally administered therapies, and telematic clinical consultations.

VHIO's clinical research oncology nurses are specialized in molecular therapies and represent an essential element of the multidisciplinary teams involved in the studies performed and coordinated at VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch and Clinical Trials Office, directed by Elena Garralda and Marta Beltran, respectively.

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 our patients who receive the full range of expertise, guidance, and the necessary follow-up throughout the course of their participation in clinical studies. As importantly is the psychological support that 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 required to make fully informed decisions concerning their treatment options. In 2021, across the 511 actively recruiting trials in oncology, patient enrollment totaled at 1,326. Regarding clinical studies in hematology, across the 146 active trials, a total of 182 patients were enrolled. Our clinical teams also continue to follow up patients that were recruited prior to 2021 who are still enrolled and receiving treatment.

VHIO continues to expand its portfolio of clinical trials to establish novel treatments with highly selective drugs, as well as 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

CLINICAL RESEARCH ONCOLOGY PHARMACY UNIT

Head of the Clinical Research Oncology Pharmacy Unit Isabel Cidoncha **Head of the Pharmacy Service** Maria Queralt Gorgas **Pharmacists** Montserrat Carreres, Carla Esteban, Celia Fernández, Lorena García, Patricia García, Pablo Latorre, Rocío Paucar, Pilar Rovira, Eugenia Serramontmany, Javier Varela **Technicians** Romina Bellini, Esther Carabantes, Bryan Cárdenas, Angelica Cely, Rafael Diaz, Elisabeth Gabilan, Ariadna Jabalera, Roser Klimt, Susana Mulet, Isabel Pérez, Sergio Pizarro, Marta Pozo, Madiha Shaheen, Alan Thompson, Silvia Torralba, Noemi Visus **Data Entry** Carmen Torres **Secretary** Isabel Mª Alerany

* For logistical issues brought about by the current COVID-19 pandemic, we are repeating pictures of some of our larger groups, services and units from our 2019 Scientific Report.

STRATEGIC GOALS

- Excellence in the services that 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, II and III studies treated with orally administered medicines to improve safety, compliance and the efficacy of these therapies.
- Successful sponsor audits as well as inspections carried out by regulatory authorities.

HIGHLIGHTS

- 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 provides clinical and technical support for the prescription, preparation, and administration of cytostatics in clinical trials, as well as 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.

"la Caixa" Foundation

SUMMARY

Our Unit is ISO 9001:2015 certified and is part of the Medical Oncology Department of the Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus. It is thanks to the funding received from the "la Caixa" Foundation, that our new Facility, the Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch- Clinical Research Onco-Hematology Unit opened last year, 2020. Equipped with all the very latest technologies, it enables us to provide even higher quality in 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 expert pharmacists are specialized in hospital and oncology pharmacy. The Unit's laboratory technicians prepare cytostatics and other parenteral therapies used in clinical trials, as well as closely monitor and follow-up our patients.

Pharmacological Research in Oncology Support Program

This program is directed by our team of pharmacists and laboratory technicians specialized in clinical trials. They are responsible for the management of study supplies including storage, dispensation, and traceability control.

In 2021 they managed drugs used in 609 active clinical trials in oncology & hematology, and 11,719 resupply deliveries/clinical trial supplies receptions. Our cutting-edge system for controlling storage temperature -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 for monitoring and reporting temperature deviations.

Regarding the design and validation of our Unit's drug preparation process traceability system, we ensure qualitative and quantitative quality control of our computerized system.

In 2021 our dispensing staff actively participated in 280 pre-study visits, 280 initial visits, 2014 monitoring visits, 160 close-out visits, and also successfully passed 8audits, and 2 ISO inspection.

Additionally, 44,261 clinical trial drugs have been dispensed and validated by our pharmacists, 12,969 of which were for oral administration, 1,230 for IM/ subcutaneous administration, and 29,974 for IV administration. A total of 234 Standardized Dispensing Procedures for clinical trials have been drawn up and we have performed 985updates of these procedures due to subsequent amendments to protocols or pharmacy manuals. 103 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 29,974. We also included 363 antineoplastic therapeutic schedules in our prescription software.

Our Pharmaceutical Care Program for patients enrolled in phase I clinical trials: we performed 967 visits, 447 screenings, 967 C1D1s, and 1,050 follow-ups, also compiling patient diaries and/or instructions for patients (in the absence of documentation provided by the respective sponsor).

VHIO's TRANSVERSAL CLINICAL TRIALS CORE SERVICES

MOLECULAR PRESCREENING PROGRAM

FERO Foundation Advanced Molecular Diagnostics Program (DIAMAV)

Co-leadership Ana Vivancos, Principal Investigator, VHIO's Cancer Genomics Group, Elena Garralda, Director, VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch, Principal Investigator, VHIO's Early Clinical Drug Development, Paolo Nuciforo, Principal Investigator, VHIO's Molecular Oncology Group, Rodrigo Dienstmann, Principal Investigator, VHIO's Oncology Data Science (ODysSey) Group **Program Coordination** Susana Aguilar **Research Support Technician** Jenifer González

STRATEGIC GOALS

- Clinical implementation of advanced molecular diagnostics to optimize the selection of therapies for patients being considered for enrolment in clinical trials.
- Continued medical education with standardized reports of genomic alterations and weekly Molecular Tumor Boards.
- Constant revision and update of molecular diagnostic tests to cover emerging cancer biomarkers for precision cancer therapy.

HIGHLIGHTS

- VHIO is an 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.

SUMMARY

VHIO's Molecular Prescreening Program, driven by FERO's Institutional Advanced Molecular Diagnostics Program – DIAMAV (page 138), catalyzes precision medicine at VHIO. Over the last decade, this program has provided access to advanced molecular diagnostics to more than 8,000 cancer patients, and is critical in matching targeted therapeutic approaches with hundreds of clinical trial opportunities.

This program, also counting on the support and expertise provided through our Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch (page 149), is co-led by VHIO's Ana Vivancos, Paolo Nuciforo, Elena Garralda (also Director of the UITM), and Rodrigo Dienstmann, Principal Investigators of our Cancer Genomics, Molecular Oncology, Early Clinical Drug Development, and Oncology Data Science (ODysSey) Groups, respectively. Activities are coordinated by Susana Aguilar, Head of our recently created VHIOTECA Unit (page 158), in collaboration with Jenifer González, Research Support Technician (VHIO's Cancer Genomics Group).

The main objective of molecular prescreening at VHIO is to facilitate the clinical implementation of emerging cancer biomarkers that help to optimize the selection of therapies for patients being considered for enrollment in clinical trials. Our program guides clinicians in selecting both standard-of-care and investigational anti-cancer treatments and spurs clinical-molecular correlative research at VHIO. Diagnostic tests are developed and validated in-house for the cost-effective and streamlined identification of tumor molecular alterations of major interest in drug development.

Tumor profiling includes a variety of genomic techniques including next-generation sequencing panels (NGS) for the detection of mutations, copy number variations, gene fusions and RNA expression signatures, as well as histopathological techniques such as immunohistochemistry (IHC) and in situ hybridization (ISH) for protein and gene expression profiling.

In 2021, we have performed tumor molecular profiling in 1,138 cancer patients that are candidates for enrollment in clinical trials.

Interpretation of next-generation sequencing tests and educating clinicians on emerging biomarkers is another of our priority areas. During Molecular Tumor Board and Genetic Tumor Board meetings, we facilitate data exchange among a broad range of experts for the review of patients' medical histories and cancer molecular profiles in order to more precisely guide treatment decisions and preventive measures.

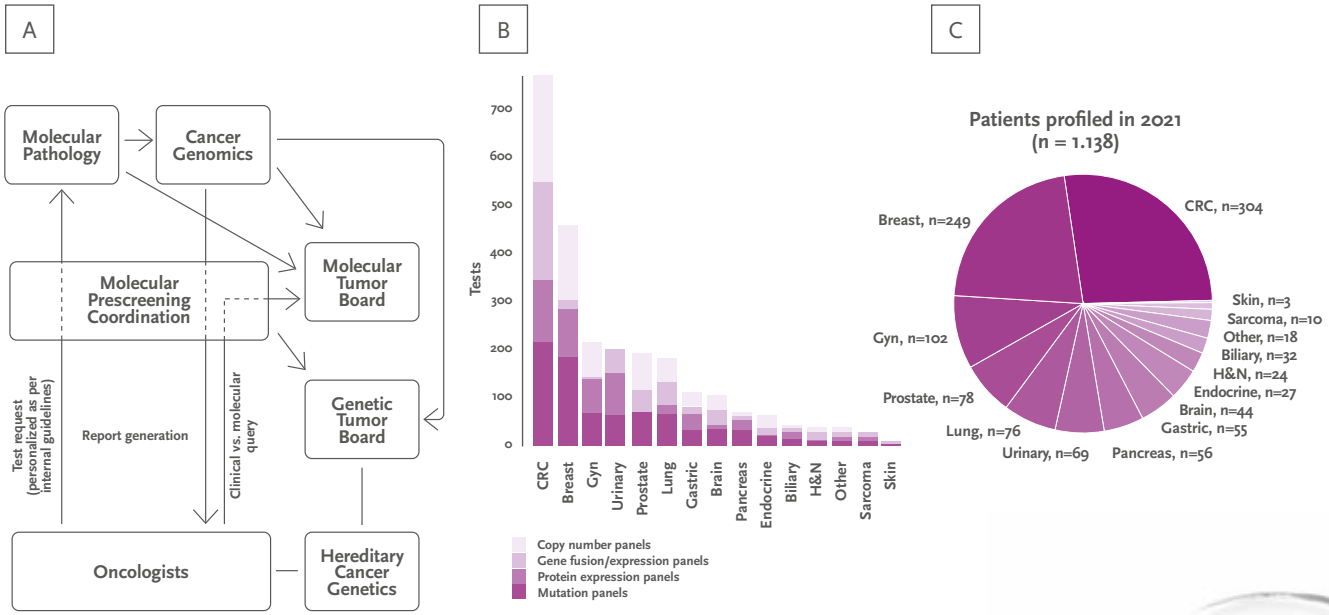


Figure: Molecular Prescreening Program at VHIO. (A) Interrelationship between Genomic and Molecular Pathology laboratories with clinical oncologists, and the functionality of the Prescreening Program. (B) Number of genomic and proteomic tests per tumor type. (C) Distribution of tumor types profiled in 2021.

VHIO's TRANSVERSAL CLINICAL TRIALS CORE SERVICES

VHIOTECA UNIT

Unit Head Susana Alguilar **Clinical Research Oncology Nurses** Ariadna García, Marta Sanz, Alex Sierra, Mireia Soleda, Anna Suñol, Anna Vázquez **Sample Managers** Inés Castro, Gemma Pruna **Research Support Technician** Ana Hernández

STRATEGIC GOALS

Consolidation of existing circuits:

- Provide support to researchers in the extraction, registration and storage of samples (mostly plasma) and database maintenance.
- Standardize protocols and establish Standard Operating Procedures (SOPs).
- Maintain optimal registration and archiving of the informed consent of the patients.
- Creation and consolidation of new circuits: establish new circuits for the collection of different plasma and tumor samples (e.g. feces, saliva, breast milk, etc.), sample and patients' data, and tailor them accordingly to meet the requirements and specificities of research projects.
- Research support: collaborate with different teams of clinical and preclinical researchers to help set up new projects and collaborations using existing or new samples.

HIGHLIGHTS

Active participation in the following international projects:

- EUCANCan: a federated network of aligned and interoperable infrastructures for the analysis, management and homogeneous sharing of genomic oncology data for Personalized Medicine.
- Molecular Tumor Board (MTB) of the Cancer Core Europe (CCE) Consortium's Baskets of Baskets (BoB).
- Genomics Evidence Neoplasia Information Exchange (GENIE) Project of the American Association for Cancer Research (AACR).

SUMMARY

Our VHIOTECA Unit was created in 2021 to support researchers for the obtention, registration and preservation of biological samples other than tumoral tissue (plasma, feces, saliva, etc.) from cancer patients, and facilitate the use of these samples in research projects.

The use of liquid biopsy testing in cancer patients for the identification of new biomarkers of response and resistance to therapy, coupled with its incorporation in clinical research projects requiring plasma, have led to a significant increase in the extraction of blood samples from cancer patients.

This activity requires a suitable structure, dynamization of circuits and the optimization of resources. For this reason, our first objectives are to consolidate existing circuits and processes so that they are consistent and reliable, and to ensure the optimal use of samples in the best possible conditions. We are also committed to supporting VHIO researchers in setting up new projects and collaborations that require the use of these types of samples.

Another area of growing interest of research in clinical oncology is the study of the microbiome during tumor development and progression, especially in colorectal cancer. These studies require the collection and genomic and molecular analysis of stool samples as well as the completion of questionnaires for subsequent epidemiological studies. To support our researchers, we aim to create a new sample and data collection circuit that facilitates the development and execution of projects.

Our team comprises clinical research oncology nurses specialized in specific tumor types, technical staff for sample processing and registration (sample managers), and technical support staff for sample logistics and management, database creation and maintenance.

VHIO's Molecular Prescreening Program

Since 2017 our Head of Unit, Susana Aguilar, has coordinated molecular prescreening at VHIO (page 156), and now collaborates closely with the program's Research Support Technician, Jenifer González. This program is co-led by Ana Vivancos, Elena Garralda, Paolo Nuciforo, and Rodrigo Dienstmann, PIs of our Cancer Genomics (page 130), Early Clinical Drug Development (page 106), Molecular Oncology (page 132), and Oncology Data Science (ODysSey - page 118) Groups, respectively.

VHIO's TRANSVERSAL CLINICAL TRIALS CORE SERVICES

QUALITY & PROCESSES UNIT

Director Gemma Sala **Quality Managers** Javier Fonts, Isabel González **Quality Technician** Miriam Artigas **Sample Managers** Alma Calahorro, Gerard Perez, David Vendrell **Schedulers** Laura Abellan, Laura Castejon, Maria Teresa Mendoza, Noelia Moles, Marc Palomar

STRATEGIC GOALS

- Cross-support and common clinical trial tasks including scheduling, sample management, and the direction of quality and processes.
- Collaborate with all teams participating in our clinical trials, detecting non-conformities and making improvements from the very outset.
- Promote prevention versus correction to ensure that the methodologies and improvements implemented.
- Successfully pass all audits and site inspections.
- Standardize processes and generate a good flow of communication between teams, as a key operating element.
- Carry out periodic and predefined quality controls relating to documentation, circuits and procedures.
- Conduct regular training sessions to review and further enhance quality.
- Renew and improve the implementation and development of the Government of Catalonia's Certification of VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch (page 149).
- Develop and update Standard Operating Procedures (SOPs) to standardize circuits, and provide all necessary trainings.
- The organization of in-house courses: Good Clinical Practice (GCP), revision of electrocardiogram (ECG), cardiopulmonary resuscitation (CPR).

HIGHLIGHTS

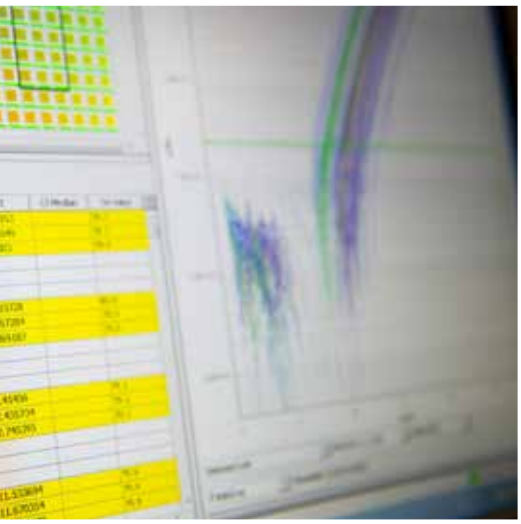
- Clinical trials in oncology and hematology.
- Our Unit has collaborated in more than 600 active trials and we have successfully passed 17 audits and 3 inspections in 2021 (the Government of Catalonia's inspection of VHIO's Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch, and inspections conducted by the European Medicines Agency – EMA, and the Food and Drug Administration – FDA).
- We have actively participated in the revision and improvement of circuits, detecting incidents and proposing corrective actions, and in the homogenization and optimization of processes.
- We have also collaborated in the internal training of staff involved in clinical trials.

SUMMARY

Headed by Gemma Sala, VHIO’s Quality & Processes Unit was established in 2020 to further improve quality and unify processes in clinical trials carried out at VHIO.

Our Unit is made up of quality, and transversal support teams including sample managers and schedulers. We perform numerous tasks related to clinical trials and all of our activities are carried out by assuring excellent quality, ensuring that the processes governing them are both optimal and homogeneous.

Quality is of parmount importance in performing clinical trials. Guaranteeing that all the current regulations of these studies are complied with is therefore essential. These homogeneous efforts follow Good Clinical Practice (GCP) guidelines, with the safety of patients as the top priority throughout.



VHIO's SCIENTIFIC MANAGEMENT AREA

mobile version

scan to visit

VHIO's SCIENTIFIC MANAGEMENT AREA

For another year, due to the safety issues brought about by COVID-19, we had to adjust our approach to this report's photography. With the exception of some of our larger groups*, we have ensured that as many group members as possible have been included, and without masks. Each individual picture was taken at a distance in locations away from areas dedicated to the care of our cancer patients. For faculty working remotely, we invited them to submit their photos from home.

*** Considering certain logistical and spatial issues, we have unfortunately had to repeat pictures of some of our larger groups and units from VHIO's Scientific Report 2019 - as indicated in the corresponding pages.**

VHIO's SCIENTIFIC MANAGEMENT AREA

SCIENTIFIC MANAGEMENT AREA

Head of Area Alejandro Piris Giménez **Senior Managers** Neus Bayó, Elena Chavarria, Javier Gonzalo, Josep Maria Miquel, Sandra Porta, Xenia Villalobos **Clinical Senior Manager (Advanced Therapies)** Silvia Martin-Lluesma **Task Force Officers** Cristina Molero (Gastroesophageal Cancer and GI non-CRC), Mireia Sanchís (Colorectal Cancer) **Project Manager Technicians** Senior: Isabel Vallvé, Junior: Sara Belon Ubeda, Berta Colldeforns **Masters Students** Marta Fonseca, Marc López, Anna Sánchez

STRATEGIC GOALS

- Identify and promote new research opportunities involving academic and industry partners.
- Write, coordinate and manage scientific proposals.
- Launch and monitor institutional research programs.
- Promote intramural research through education, networking, and communication programs.

HIGHLIGHTS

- In 2021, we maintained a good track record with a success rate of 29%, out of 189 grant (competitive) applications.
- Our Area has managed more than 9.5 million EUR granted through the proposals submitted in 2021 by VHIO groups.
- Reflective of the research support that we provide to VHIO is our co-authorship of several publications (see Paper Pick).
- We co-lead major EU consortia. Just some of these include the Cancer Core Europe (CCE) consortium's CCE-DART project – the first H2020 grant awarded to the Cancer Core Europe Consortium, COLOSSUS (H2020), and CCE's *Basket of Baskets*. We are also collaborate with numerous project boards and are in involved in several other work packages.
- We have provided support to our Scientific Direction through the management of scientific data and all the necessary documentation and actions required to develop research proposals. Additionally, we have secured funding from the Spanish Ministry of Economic Affairs and Digital Transformation (MINECO), and obtained a European Networks and Management grant to support the internationalization of our research and dissemination activities and personnel.

SUMMARY

VHIO's Scientific Management Area is a well-established Unit that supports our leadership and promotes the scientific activity of our research groups by facilitating the development and execution of scientific proposals and programs. In addition, we coordinate the activities of VHIO's Task Forces to foster synergies between our multidisciplinary teams and spur joint research programs in oncology at the Vall d'Hebron University Hospital – HUVH (Vall d'Hebron Barcelona Hospital Campus).

Our responsibilities include financial and scientific management, strategic scientific support, and the implementation of institutional actions across transversal areas such as education, ethics and regulatory issues, scientific dissemination, and the coordination of research activities related to VHIO's participation in several consortia and partnerships globally. Additional activities include the assessment and preparation of grant application proposals, dissemination of national and international funding opportunities for research groups, and the continued monitoring and coordination of awarded research projects, among others.

Our group further optimizes opportunities for the internationalization of researchers by devising personalized plans for VHIO's scientific groups, centralizes and conceptualizes research proposals from our Task Forces, and proactively matches selected research priorities with competitive calls. We also spearhead highly innovative technological project proposals to increase VHIO's success rate in calls, such as the *Innovative Medicines Initiative* (IMI) within the *Horizon Europe* framework, and oversee VHIO's involvement in European projects as project coordinators or partners. Lastly, our Area is continuously working to enhance its organizational structure and project management processes with the goal of expanding VHIO's capacity to conduct research of excellence in oncology.

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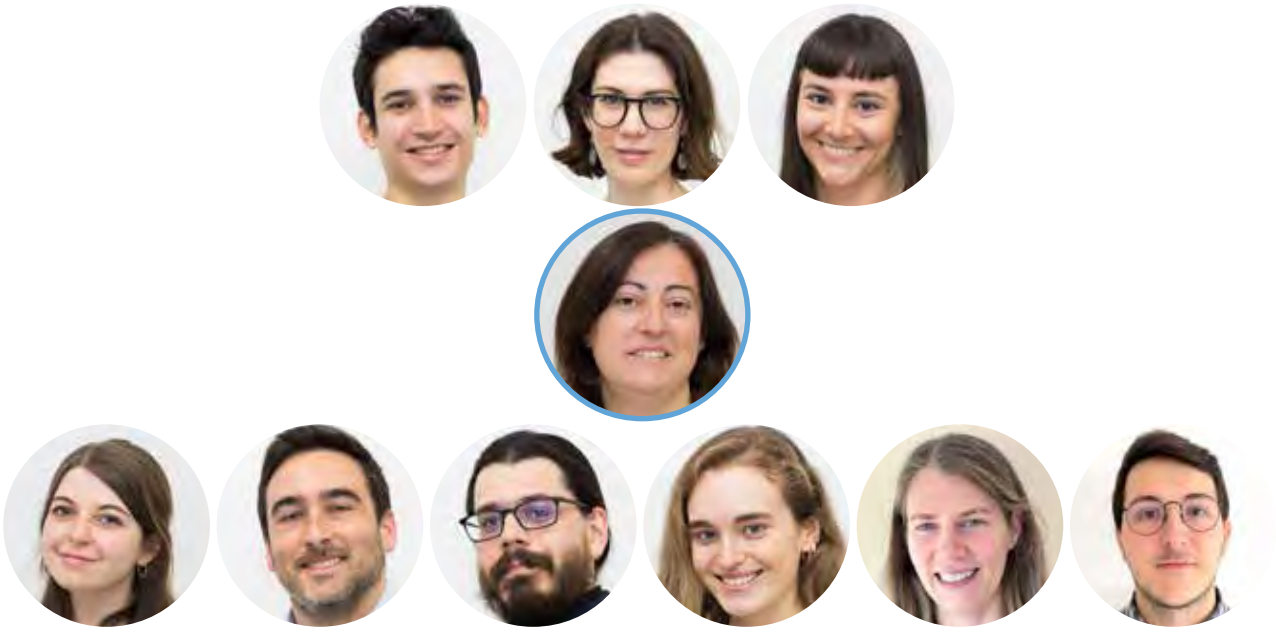
VHIO's SCIENTIFIC MANAGEMENT AREA

ACADEMIC CRO (VHIO – aCRO)

Unit Head Susana Muñoz **Lead Clinical Research Associates (Lead CRAs)** Marta González, Darío López, Anna Palazón **Clinical Research Associates (CRAs)** Soraya Alonso de Caso, Pol Barbarroja, Carlos Márquez, Pablo Martínez **Medical Writer** Marta Carboneras **Clinical Research Associate Trainee (CRA Trainee)** Judith Bautista



AREA SUMMARY

VHIO's Academic Contract Research Organization (VHIO - aCRO), has extensive experience in conducting sponsored trials and investigator-initiated trials (IITs). We offer a complete package of start-to-end management services required to perform clinical trials and studies. Our multidisciplinary team enables us to operate as a full service CRO in clinical studies from phase I to IV.

We also provide guidance to all researchers and sponsors on how to achieve the best experimental design, and offer logistical advice in order to maximize their resources. With a team of 10 professionals, our Unit 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 our Unit by incorporating a clinical project manager and a clinical trials assistant. This will allow us to even more effectively manage current and future clinical trials, optimize CRO digital tools for working remotely, as well as continue to bring out the best in each team member to enhance VHIO's aCRO.

STRATEGIC GOALS

- Clinical project management support to awarded R&D projects (European/Pharma funded), academic oncology clinical trials led by our Medical Oncologists and Clinical Investigators at VHIO and the Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Barcelona Hospital Campus.
- Academic CRO for IITs.
- Academic CRO for pharmacy sponsored trials where VHIO is involved in the development of the studies.

HIGHLIGHTS

- In 2021, our academic CRO successfully managed a number of major projects including AGI-134.FIM.101, TOPIC, IRONMAN, MONEO, DUREC, BRCA-P, CA209-7J3, MoTriColor, BoB, among others. Most of these are led by by our Medical Oncologists and Clinical Investigators at Vall d'Hebron's Medical Onology Department, headed by Josep Tabernero, VHIO's Director.
- Of particular note, two clinical trials in cell therapy with TILs and NKs initiated this year. These studies are logistically managed by our Unit.
- During 2021, we successfully met the regulatory requirements for all our trials (first submissions and amendments).
- Our CRA team monitored more than 150 patients in different hospitals across Spain.
- We managed clinical trial drug requirements in more than 25 national hospitals.
- We have also demonstrated sufficient benefits that support CRO activities for non-funded academic trials.

FULL LISTING OF ARTICLES PUBLISHED BY VHIO INVESTIGATORS IN 2021

Articles published by VHIO Investigators in 2021 with allocated Impact Factor (IF):

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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.

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:

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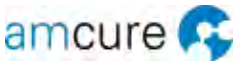

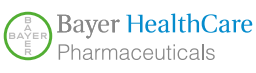


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Cancer Core Europe (CCE) is a unique partnership aimed at addressing the cancer care - cancer research continuum challenge. Launched in 2014, this working consortium represents a critical mass of activity for the successful integration of all cancer care information, clinical research and outcome research, led by its 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.

www.cancercoreeurope.eu

Supported by EU's Horizon 2020 Framework Programme, last year celebrated the launch of the Cancer Core Europe Consortium's Building Data Rich Clinical Trials (CCE-DART). Coordinated by VHIO, this innovative project (see below), aims at harnessing and incorporating powerful cutting-edge technologies, methods and platforms, to spur the design, development, and ringing in of a new generation of data-rich, dynamic studies in oncology.

The Basket of Baskets (BoB) trial is a modular, open-label, phase II, multicenter study to evaluate targeted agents in molecularly selected populations with advanced solid tumors. This study is carried out under the Cancer Core Europe (CCE) umbrella, with VHIO as trial sponsor.

This modular basket clinical trial consists of two parts: part A (iPROFILER), which includes the common procedures for tumor molecular profiling and treatment recommendation, and part B (iBASKET), which corresponds to the therapeutic portion. The purpose of part A is to assess participants' tumor tissue in order to identify whether their respective tumors have certain mutations in cancer-related genes. This analysis provides information about potential targeted therapies that specifically attack those gene mutations. The purpose of part B is to offer participants a personalized anti-cancer treatment based on the detected gene mutations in tumors.

www.basketofbaskets.eu

The EU-funded Cancer Core Europe Consortium's Building Data Rich Clinical Trials (CCE-DART), coordinated by VHIO, is carried out in collaboration with other leading experts from within the Cancer Core Europe Consortium (CCE). By harnessing and incorporating powerful cutting-edge technologies, methods and platforms, CCE-DART investigators will design and develop a new generation of data-rich, dynamic studies in oncology.

Building on the CCE-developed Basket of Baskets (BoB) investigator-initiated and adaptive trial which launched in 2018, CCE-DART further enhances BoB's harmonized, molecular multi-tier profiling platform to more precisely match patients to novel anti-cancer medicines based on the genetic specificities of their individual tumors. In parallel, the researchers will continue to develop multiple treatments in genomically-selected populations.

www.cce-dart.com

This project has received funding from the European Union's Horizon 2020 framework programme research under grant agreement No. 965397.

Launched in 2019, the OPTIMISTICC Cancer 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.

www.optimisticc.org

COLOSSUS–*Advancing a Precision Medicine Paradigm in metastatic Colorectal Cancer: Systems based patient stratification solutions*, 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 seeks to 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.

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.

www.eucancan.com

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

The main objective of the EU-supported EURAMED *ROCC-N-ROLL: EURopeAn MEDical application and Radiation prOteCtion Concept: strategic research agenda aNd ROadmap interLinking to heaLth and digitization aspects*, is to generate a European consensus on research needs and priorities in medical radiation applications and corresponding radiation protection to optimize the use of ionizing radiation in medicine.

Led by coordinating partner, the European Institute for Biomedical Imaging Research, Vienna (Austria), this pan-European consortium connects a total of 29 research centers, including VHIO. Taking the lead on radiation application in oncological diseases, VHIO will work with other experts in other settings including neurovascular as well as cardiovascular diseases, and explore relevant clinical scenarios, as well as provide patients' perspectives.

Specifically, VHIO researchers will analyze the needs of research in radiation application and corresponding radiation protection in oncology by identifying gaps and opportunities. Compile an overview of clinical situations that require the application of ionizing radiation in diagnosis and treatment, provide an outlook on envisaged future applications and trends in the oncology field.

www.cordis.europa.eu/project/id/899995

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No: 899995.

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.

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.

www.immune-image.eu

Coordinated by the Josep Carreras Leukemia Research Institute, Barcelona (Spain), the EU-funded Interreg POCTEFA PROTEOblood Consortium is co-funded by the European Regional Development Fund/European Social Fund, and aims to optimize, share and exploit latest technologies for the study of protein homeostasis in two prevalent subtypes of leukaemia and lymphoma: acute myeloid leukemia (AML) and diffuse large b-cell lymphoma (CLBCL) in the POCTEFA region (Spain-France-Andorra).

Comprising six other partners - CIC bioGUNE, IQS, CNRS, INSERM, Anaxomics Biotech, and VHIO, the investigators will use modelling collections from patient-derived studies to recreate the tumor microenvironment ex vivo, and apply innovative proteomic approaches associated with system biology analysis and small molecule design, to facilitate the complete characterization of proteopathies and development of more effective therapies that will then be validated through xenoinjerts.

www.poctefa.eu/ayudas-de-estado-y-minimis

The project has been co-financed by:

The European Regional Development Fund (ERDF) through the Interreg V-A Spain-France-Andorra Programme (POCTEFA 2014-2020) – Ref: EFA360/19.

European Regional Development Fund/European Social Fund.

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.

Seeking to improve patient outcomes by applying personalized medicine at the three levels of prevention, this consortium implements a personalized medicine strategy at the first level of prevention, improves early gastric cancer detection at the second level of prevention, and improves treatment through the identification of high-risk populations.

www.legacy-h2020.eu

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

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 identifies 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.

This project 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, provides preliminary data on its efficacy in humans, and aims 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.

ONCNGS PCP

The EU-funded ONCNGS project aims to tackle the common, unmet need in oncology to profile multiple tumor types at the molecular level in the broadest possible way, promoting an economically sustainable and de-centralized model that allows a secure and transparent access to sensitive data.

ONCNGS challenges the market to research and develop novel affordable solutions to provide the best NGS tests for all solid tumor and lymphoma patients. The challenge consists of providing efficient molecular DNA/RNA profiling of tumor-derived material in liquid biopsies by means of a pan-cancer tumor marker analysis kit including NGS analysis integrated with an ICT decision support system, and an analytical test for interpretation and reporting.

www.oncngs.eu

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 874467.

ONCODISTINCT is a research network bringing together academic lead investigators sharing the same vision for innovative clinical research.

Established by several cancer centres in and outside of Europe, this network comprises a multidisciplinary group of investigators with expertise in early drug development and clinical research.

Together, they aim to address the current challenges in oncology and improve patients' outcomes by designing and conducting innovative clinical studies, and accelerating the development of anti-cancer medicines in solid tumors, particularly in settings with unmet medical needs.

This network currently connects 25 cancer centers and university hospitals and fosters collaborations between oncologists, organ specialists, radiotherapists and scientists across the ONCODISTINCT sites, as well as pharmaceutical companies. Established seven years ago, the network is dynamically evolving as it continues to incorporate new clinical centers and think tank institutes as members.

www.oncodistinct.net

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 program 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

PROMISE - BioPrinted hydrogel MicrofluidicS to mimic patient-specific tumor mEtastatic microenvironment is a project coordinated by IBEC (*Institut de Bioenginyeria de Catalunya*) that wants to put 3D bioprinting at the service of improving the survival of cancer patients.

3D bioprinting enables the generation of three-dimensional cell models that imitate the human physiology to test new therapeutic strategies in the laboratory. These models can accurately mimic the patient's specific tumor and its surrounding environment.

This project, which combines 3D bioprinting and advanced liquid biopsy techniques in an organ-on-a-chip device, seeks to provide physicians with new tools to understand and monitor disease evolution in patients with metastatic colorectal cancer aimed at improving survival rates.

VHIO participates in the clinical validation of this microfluidic platform based on hydrogels that mimic the tumor microenvironment on cells derived from patients with metastatic colorectal cancer. We will validate this technology in specific patient cohorts.

www.fundacionlacaixa.org/en/caixaresearch-health-call-2020-project-bioprinting

"la Caixa" Foundation

This project has received funding from the "la Caixa" Foundation's CaixaResearch Health Call 2020 under the grant agreement No. HR20-00637.

RAD51predict – Patient stratification based on DNA repair functionality for cancer precision medicine is an ERAPerMed funded project led by VHIO. It aims to establish the prevalence of functional HRR deficiency (HRD) and its predictive value for personalized treatment with platinum salts and PARPi in breast cancer, ovarian cancer, prostate cancer, and endometrial cancer using the RAD51 immuno-assay and genomic assays.

This project seeks to perform an economic evaluation of selecting patients for PARPi treatment based on the RAD51 assay, genomic assays, or the current selection criteria to provide functional validation of germline/somatic genetic variants of unknown significance (VUS) using patients' data, cell lines and assessment of HRR markers in the tumor; integrate functional HRD data into existing public genomic databases; transfer the RAD51 assay as a predictive test in the clinic, and develop multiplexed protocols, automatization of image analysis, and real-time monitoring in circulating tumor cells.

This project is supported by the ERAPERMED2019-215 award, granted by *Fundación Científica de la Asociación Española Contra el Cáncer* (AECC FC) and by the *Instituto de Salud Carlos III* (ISCIII) through the *Acción Estrategica en Salud* (AES) 2019, both within the ERA PerMed framework.

SPECTAcolor - The EORTC Biobank Project. 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 the genetic profiling of patients suffering from advanced colorectal cancer.

https://www.eortc.org/blog/category/spectacolor

RADprecise - *Personalized radiotherapy: Incorporating cellular response to irradiation in personalized treatment planning to minimize radiation toxicity*, is supported by funding received through ERAPerMed's co-funded Joint Translational Call 2018 and was founded in 2019 by 7 leading organizations from Spain, Italy, Germany and France.

This 3-year project seeks 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 colleagues at the German Cancer Research Center (DKFZ), Germany, project partners 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, apply new biological data as well as readily available genomic data to develop models that can more precisely predict adverse effects from radiotherapy, to be validated in independent samples.

www.erapermed.eu

This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No. 779282

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 establishes 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 characterizing blood-based tumor-educate platelets (TEPs) for the evaluation of patients treated with immune checkpoint inhibitors using novel sequencing technologies.

The second project focuses 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 primarily seeks 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.

UpSMART Accelerator seeks to improve experimental cancer development across the UK, Italy, and Spain, by providing early-phase clinical teams with digital healthcare products (DHP) for the real-time access to a wealth of patient data, and thus enable faster decision making. The UpSMART Consortium consists of 23 participating institutes across Experimental Cancer Medicine Centres (ECMCs) in the UK, and Early Drug Development Units (EDDUs) in Spain and Italy. The program will test existing digital tools at these 23 phase I Units.

UpSMART will develop and provide all clinical sites with free to use access to new digital healthcare technology tools and improved approaches in trials that enable patients' access to tomorrow's medicines today. This project promotes the wider scale sharing and implementation of digital healthcare products as well as training in digital healthcare product approaches.

www.upsmart.digitalecmt.com

The program was awarded a CRUK Accelerator Award.

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 counts on the multidisciplinary expertise of investigators at VHIO, the Spanish National Cancer Research Center – CNIO (Madrid, Spain), and the University of Washington (USA).

Aimed at more precisely gauging response in patients to standard therapies, the team is developing new, more effective and tailored treatment strategies, as well as designing 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

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.

www.winconsortium.org

NEW CONSORTIA – officially launched in 2021

IMPaCT – *Infraestructura de medicina de precision asociada a la ciencia y tecnología*, is a collaborative structure for the genomic medicine implementation in the Spanish National Health System, coordinated by CIBER.

VHIO participates in Work Package 4, focused on cancer, and leads the unknown primary tumors part. WP4 aims to establish genomic methods to analyze the tumors, create a portfolio of diagnostic services, standardize laboratory protocols and sample processing methods in order to establish variant interpretation guidelines and agree on a clinical report model.

A network of high-capacity genomic analysis centers based on existing centers will be established. This infrastructure will focus on rare diseases, cancers of unknown origin, and pharmacogenetics. This is a national program aimed at establishing standardized procedures to guarantee equitable access to genomic analysis. The Centre for Genomic Regulation (CRG), Barcelona, will be responsible for the centralization of samples.

Convocatoria Infraestructura de Medicina de Precisión Asociada a la Ciencia y Tecnología - IMPaCT. Ref: IMP/00009, Coordinator: the CIBER network. This Project is funded by the Subdirección General de Evaluación y Fomento de la investigación dentro del Fondo Europeo de Desarrollo

PERSIST-SEQ is a public-private partnership funded by the Innovative Medicines Initiative (IMI), with representation from academic institutions, small- and medium-sized enterprises, public organizations and pharmaceutical companies.

The PERSIST-SEQ five-year international collaboration, led by the Oncode Institute (Utrecht, The Netherlands) and AstraZeneca, comprises 18 partners including VHIO and aims to provide the cancer research community with a new gold standard workflow for single-cell sequencing by developing and validating best practices as well as generating and analyzing high-quality FAIR data.

Empowering the scientific community to unravel therapeutic resistance and develop smarter therapeutic strategies to better treat cancer and prevent drug resistance, PERSIST-SEQ will employ an open access model to build and sustain its benchmarking procedures and centralized European data infrastructure. This model reduces duplication of efforts, thereby promoting collaboration across disciplines and ensuring efficient adoption of state-of-the-art single cell technologies.

www.persist-seq.org

PERSIST-SEQ is funded by the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No. 101007937. This Joint Undertaking receives support from the European Union's Horizon 2020 research an innovation programme and EFPIA.

Other collaborations:

The AstraZeneca/MedImmune – VHIO Alliance drives advancements at the preclinical, clinical and translational research levels across 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.

In 2020, AstraZeneca/Medimmune announced its Partner of Choice Network, comprising nine of the world's most renowned research centers and institutes in oncology to accelerate research against some of the most difficult-to-treat cancers. Selected partners of choice are the Cambridge Cancer Center (UK), Institut Gustave Roussy (France), Johns Hopkins University (USA), Memorial Sloan Kettering Cancer Center (USA), Oregon Health and Science University/Knight Cancer Institute (USA), Peter MacCallum Cancer Center (Australia) Princess Margaret Cancer Center (Canada), University of Navarra (Spain), and VHIO.

This network serves a forum for data sharing and cancer discovery in real-time. Scientific insights and findings generated through clinical studies are exchanged among partner institutions for the development and implementation as best practices in oncology. AstraZeneca will support selected clinical and non-clinical research proposals from the partners' investigators to expedite novel scientific research and innovative clinical trial design aimed at developing new strategies in precision medicine against cancer.

www.astrazeneca.com

The SCITRON *Consorcio público-privado de Investigación Científica y Translacional en Oncología* (Consortium for Scientific Translational Research in Oncology) is a scientific program which was established in collaboration with Novartis in 2017.

As a new model of R&D collaboration, this initiative connects experts 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 is a 27 partner-strong collaboration that aims to advance discovery in cancer immunotherapy. It connects internationally renowned scientific and clinical experts in immune-based therapeutic strategies in oncology who work together to assess and advance 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 insights 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

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 *Institució CERCA–Centres de Recerca de Catalunya* (CERCA Institute of Research Centres of 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.

www.cerca.cat/en/

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/about-vhio/hrs4r/

Also reflective of our dedication to excellence and the quality of our services and procedures, VHIO's Cancer Genomics and Molecular Oncology Groups are both ISO-accredited for their testing methods and technologies.

VHIO continues to meet the high standards in quality and procedures in the audit of our clinical trials Units, carried out by the *Generalitat de Catalunya* (Government of Catalonia). Our Research Management is also endorsed by ISO 9001 Certification.

NEW FUNDING AND PROJECTS IN 2021

For a complete listing of all our current supporters and funding sources see section Funding & Consortia (pages 194-207).

INSTITUTIONAL SUPPORTERS

VHIO patrons (more information see pages 27-31)

Departament de Salut: Budgetary support
Departament d'Empresa i Coneixement: Budgetary support

VHIO's CELLEX Building & Infrastructures

Advanced Molecular Diagnostics Program (DIAMAV), and other VHIO investigators, groups and projects

Research Unit for Molecular Therapy of Cancer (UITM) – CaixaResearch, and CaixaResearch Advanced Oncology Research Program

Comprehensive Program of Cancer Immunotherapy & Immunology (CAIMI)

Center of Excellence Severo Ochoa

INTERNATIONAL SUPPORT

H2020-JTI-IMI2-2020-20-two-stage– International Consortium
Building a reproducible single-cell experimental workflow to capture tumour drug persistence– PERSIST-SEQ
Ref: 101007937
PI VHIO: Héctor G. Palmer
Stem Cells & Cancer Group

National Cancer Institute
Overcoming Drug Resistance in HER2-Positive Breast Cancer
Ref: 5R01CA244601-02
PI: Joaquín Arribas
Growth Factors Group

Translational/Clinical Research Fellowship
Integration of genomic testing and patient expectations into prostate cancer treatment decision-making
Granted to Pablo Cresta
Mentor: Joaquin Mateo
Prostate Cancer Translational Research Group

European Moleular Biology Organization (EMBO) Postdoctoral Long Fellowship
Ref: ALTF 293-2021
Granted to Gonçalo Rodrigues
Mentor: Joan Seoane
Gene Expression & Cancer Group

Breast Cancer Research Foundation Grant
Immune Senolysis Against Breast Cancer
Ref: BCRF-21-008
PI: Joaquín Arribas
Growth Factors Group

NATIONAL FUNDING

Ajuts per a la incorporació de personal investigador postdoctoral al sistema català de ciència i tecnologia dins del programa Beatriu de Pinós
Advancing magnetic resonance imaging against liver cancer
Ref: 2020 BP 00117
Granted to Francesco Grussu
Project Director: Raquel Perez-López
Radiomics Group
Co-funded by the H2020 Programme - Marie Skłodowska-Curie Actions COFUND (BP3, Ref: 801370)

Ajuts per a la contractació de personal investigador novell – FI Predoctoral
Non-invasive, personalized, T-cell therapies targeting recurrent hot spot driver mutations in cancer
Ref: 2021 FI B 00365
Granted to Anna Yuste
Project Co-Directors: Josep Tabernero & Alena Gros
Gastrointestinal & Endocrine Tumors Group
Tumor Immunology & Immunotherapy Group

DEPARTAMENT DE SALUT
Ajuts per Investigadors en Formació (PIF-Salut)
Desenvolupament de teràpies cel·lulars personalitzades no invasives focalitzades en atacar el mutanoma tumoral en pacients amb càncers d'endometri metastàtic
Ref: SLT017/20/000131
PI: Alena Gros
Tumor Immunology & Immunotherapy Group

Ajuts per Investigadors en Formació (PIF-Salut)
Imatge de precisió i intel.ligència artificial per una millor caracterització de la resposta del càncer a immunoteràpia
Ref: SLT017/20/000080
PI: Raquel Perez-Lopez
Radiomics Group

Ajuts per Investigadors en Formació (PIF-Salut)
Búsqueda de biomarcadores predictivos de respuesta a inhibidores de PARP y quimioterapias basadas en platinos en cáncer de mama y ovario hereditario
Ref: SLT017/20/000081
PI: Violeta Serra
Experimental Therapeutics Group

Proyectos I+D+i Retos de Investigación.
Mining the molecular determinants of the personalized antitumor T-cell response in cancer patients to develop more effective immunotherapies (PersImmune)
Ref: PID2020-118529RB-I00
PI: Alena Gros
Tumor Immunology & Immunotherapy Group
Grant funded by the European Commission European Development Fund: A way of making Europe

Proyectos I+D+i Retos de Investigación.
Targeting synthetic lethality in Chromatin Regulatory Genes for gastrointestinal cancer treatment (ChromSynthLeth)
Ref: PID2020-115097RA-I00
PI: Jose Antonio Seoane
Cancer Computational Biology Group
Grant funded by the European Commission European Development Fund: A way of making Europe

Proyectos de I+D+i en líneas estratégicas, en colaboración público-privada
Using MYC inhibition to overcome immunotherapy resistance in KRAS-driven NSCLC with diverse mutational profiles (MYCOMBIO)
Ref: PLEC2021-007959
PI: Laura Soucek
Models of Cancer Therapies Group
Grant funded by the European Union NextGenerationEU/Planes Nacionales de Recuperación, Transformación y Resilencia (PRTR)

Proyectos de I+D+i en líneas estratégicas, en colaboración público-privada
Early molecular nanoDIAGnostics of Brain tumors using Immune-PET (DIAGBI)
Ref: PLEC2021-008034
PI: Joan Seoane
Gene Expression & Cancer Group
Grant funded by the European Union NextGenerationEU/Planes Nacionales de Recuperación, Transformación y Resilencia (PRTR)

Ayudas para Contratos Ramon y Cajal
Ref: RYC2020-029098-I
Granted to Tian Tian
Chromatin Dynamics in Cancer Group
Grant funded by the European Union NextGenerationEU/Planes Nacionales de Recuperación, Transformación y Resilencia (PRTR)

Ayudas Contratos Juan de la Cierva Formación
Ref: FJC2020-046226-I
Granted to Joan Frigola
Project Director: Enriqueta Felip
Thoracic Tumors & Head and Neck Cancer Group
Grant funded by the European Union NextGenerationEU/Planes Nacionales de Recuperación, Transformación y Resilencia (PRTR)

Ayudas contratos Predoctorales para la formación de Profesores Universitarios
Ref: FPU20/04812
Granted to Iñigo González
Project Director: Laura Soucek
Models of Cancer Therapies Group

VHIO projects managed through the *Instituto de Investigación Sanitaria Acreditdo Institut de Recerca* (Accredited Research Institute - Vall d'Hebron)

Proyectos de Investigación Clínica Independiente
Multi-target approach including anti-angiogenic agent to overcome treatment resistance in BRAF mutant metastatic colorectal setting (BRAVE)
Ref: ICI21/00097
PI: Elena Élez
Gastrointestinal & Endocrine Tumors Group
Grant funded by the European Union NextGenerationEU/Planes Nacionales de Recuperación, Transformación y Resilencia (PRTR)

Proyectos de Investigación en Salud
Genomic evolution of advanced prostate cancer under selective pressure from novel therapeutic strategies
Ref: PI21/00430
PI: Joaquin Mateo
Prostate Cancer Translational Research Group
Grant funded by the European Commission European Development Fund: A way of making Europe

Proyectos de Investigación en Salud
CtDNA in breast milk for early detection of pregnancy associated breast cancer
Ref: PI21/01020
PI: Cristina Saura
Breast Cancer & Melanoma Group
Grant funded by the European Commission European Development Fund: A way of making Europe

Proyectos de Investigación en Salud
PRECISION: Deciphering colon cancer heterogeneity with machine learning and precision imaging
Ref: PI21/01019
PI: Raquel Perez-Lopez
Radiomics Group
Grant funded by the European Commission European Development Fund: A way of making Europe

Proyectos de Investigación en Salud
Transcriptomic and (epi)genetic hallmarks of CNS-tropism in diffuse large B cell lymphoma
Ref: PI21/01190
PI: Marta Crespo
Experimental Hematology Group
Grant funded by the European Commission European Development Fund: A way of making Europe

Proyectos de Cooperación Conjunta Internacional
A Machine learning approach to Identify patients with Resected non-small-cell lung cAnCer with high risk of reLapsE (MIRACLE)
Ref: AC21_2/00052
PI: Enriqueta Felip
Thoracic Tumors & Head and Neck Cancer Group
Grant funded by the European Union NextGenerationEU/Planes Nacionales de Recuperación, Transformación y Resilencia (PRTR)

Proyectos de Desarrollo Tecnológico en Salud
First-in-class small drug activtors of TET2 for the treatment of cancer
Ref: DTS21/00169
PI: Héctor G. Palmer
Stem Cells & Cancer Group
Grant funded by the European Commission European Development Fund: A way of making Europe

RICORS
RICORS Terápias Avanzadas
Ref: RD21/0017/0035
PI: Francesc Bosch
Experimental Hematology Group
Grant funded by the European Union NextGenerationEU/Planes Nacionales de Recuperación, Transformación y Resilencia (PRTR)

Proyectos de Investigación de Medicina Personalizada de Precisión
Integrative genomic, digital imaging and clinical information towards Precision Oncology Optimization – INGENIO
Ref: PMP21/00107
Grant funded by the European Union NextGenerationEU/Planes Nacionales de Recuperación, Transformación y Resilencia (PRTR)

Ayudas para la Intensificación de la Actividad Investigadora
Ref: INT21/00076
Granted to Jaume Capdevila
Gastrointestinal & Endocrine Tumors Group

Ayudas para Contratos Rio Hortega
Ref: CM21/00099
Granted to Mara Cruellas
Project Director: Judith Balmaña
Hereditary Cancer Genetics Group

Ayudas para Contratos Predoctorales de Formación en Investigación en Salud
Ref: FI21/00279
Granted to Paula Romero
Project Director: Ana Vivancos
Cancer Genomics Group

PRIVATE FUNDING

"la Caixa" Foundation

Health Research "la Caixa" Project
BioPrinted hydROgel MicrofluIdicS to mimic patient-specific tumor mEtastatic (PROMISE)
PI: Elena Élez
Gastrointestinal & Endocrine Tumors Group

Ayudas Predoctorales InPhinit Retaining
Deciphering spatial and temporal cancer heterogeneity with machine learning and precision imaging
Granted to Olivia Prior
Mentor: Raquel Perez-Lopez
Radiomics Group

Ayudas Predoctorales InPhinit Retaining
OncoPeptides: mining the secreted microproteome for novel regulators of PDAC biology
Granted to Marion Martínez
Mentor: Maria Abad
Cellular Plasticity & Cancer Group

Ayudas Predoctorales InPhinit InComing
Armouring a p95HER2 CAR T for the controlled secretion of antitumor agents upon T-cell activation
Granted to Ariadna Grinyó
Mentor: Joaquín Arribas
Growth Factors Group

Beca FERO en Investigación Oncológica Traslacional
Exploitng therapy-induced senescence in a synthetic lethal approach to treat advanced Prostate Cancer
PI: Nicolás Herranz
Prostate Cancer Translational Research Group

Biopsia líquida en cáncer cerebral pediátrico: Análisis de ADN circulante en el líquido cefalorraquídeo de pacientes pediátricos con meduloblastoma para ayudar a la detección caracterización y tratmiento del tumor cerebral en la recaída
PI: Joan Seoane
Gene Expression & Cancer Group

Uso de nuevas tecnologías para la identificación de marcadores de sensibilidad y resistencia a terapias dirigidas en Cáncer Colorrectal Metastásico
PI: Josep Tabernero
Gastrointestinal & Endocrine Tumors Group

Grupos Coordinados AECC- NATIONAL CONSORTIUM
Tumoral senescence induced by anti-cancer therapies constitutes a novel prognostic biomarker and a therapeutic target
PI VHIO: Maria Abad/ Joaquin Mateo/Raquel Perez-Lopez
Cellular Plasticity & Cancer Group
Prostate Cancer Translational Research Group
Radiomics Group

Clínico Junior AECC
CtDNA in breast milk for early detection of pregnancy associated breast cancer
Granted to Carolina Ortiz
Project Director: Cristina Saura
Breast Cancer & Melanoma Group

Investigador AECC
Deciphering the molecular mechanisms of tumour cell resistance to cancer therapies
Granted to Isabel Puig Borreil
Project Director Héctor G. Palmer
Stem Cells & Cancer Group

Postdoc AECC
Overcoming cancer immunotherapy resistance: new combinatorial strategies to improve immunotherapies
Granted to Enrique Javier Arenas
Project Director: Joaquín Arribas
Growth Factors Group

Projectes de Recerca Sobre la COVID
Microbiota composition as risk predictor in cancer patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
PI: Paolo Nuciforo
Molecular Oncology Group

Programa Joves i Ciència. Premio Pedrera Talents
Granted to Iosune Baraibar
Co-Mentors: Elena Élez & Joan Seoane
Gene Expression & Cancer Group
Gastrointestinal & Endocrine Tumors Group

Becas SEOM para Proyectos de Investigación en Cáncer de Mama
ADNtc en leche materna para la detección precoz de cáncer de mama asociado al embarazo
PI: Cristina Saura
Breast Cancer & Melanoma Group

Becas SEOM para Proyectos de Investigación en Cáncer de Mama
Impacto de la microbiota mamaria e intestinal en el pronóstico y en la respuesta al tratamiento con inhibidores de checkpoint inmunitario en cáncer de mama
PI: Mafalda Oliveira
Breast Cancer & Melanoma Group

Programa CRIS Talento Clínico
Prostate cancer genomic evolution and signatures of DNA damage repair deficiencies.
PI: Joaquin Mateo
Prostate Cancer Translational Research Group

Becas Junior GETNE Proyecto de Investigación 2021
Estudio de la expresión de antígenos como posibles dianas de conjugados anticuerpo-fármaco en tumores neuroendocrinos
PI: Alejandro García
Project Director: Jaume Capdevila
Gastrointestinal & Endocrine Tumors Group

Premios a la Investigación en Cancer de Mama Metastásico
Identification of response biomarkers of a novel HER3-topoisomerase I inhibitor antibody drug conjugate (U3-1402) using breast cancer patient-derived xenoimplant models
PI: Violeta Serra
Experimental Therapeutics Group

Premio Mutual Médica
Beca identificación y validación de mecanismos de resistencia y respuesta a terapias dirigidas para pacientes con cáncer colorrectal metastásico BRAFV600E mutado
PI: Javier Ros
Project Director: Elena Élez
Gastrointestinal & Endocrine Tumors Group

Ayudas TTD a Proyectos de Investigación en Tumores Digestivos
New biomarkers for monitoring the acquisition of resistance to BRAFV600E inhibitors in metastatic colorectal cancer
PI: Elena Élez
Gastrointestinal & Endocrine Tumors Group

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