AECC Excellence- BITRECS call

RESEARCH LINES

RL 1. Pioneering Strategies to Maximize Immunotherapy Efficacy in lymphoid malignancies

RL 2. Pioneering Strategies to Maximize Immunotherapy Efficacy in breast cancer

RL 3. Precision oncology to maximize benefits from immunotherapies in liver cancer

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AECC Excellence- BITRECS call

Group: Lymphoid Neoplasms Program

Principal investigator: Iñaki Martín-Subero (IMARTINS@recerca.clinic.cat) and Armando López-Guillermo (alopezg@clinic.cat) with the collaboration of Sonia Guedan (sguedan@recerca.clinic.cat) and Cristina Fillat (cfillat@recerca.clinic.cat)

Title: Pioneering Strategies to Maximize Immunotherapy Efficacy in lymphoid malignancies

Key words: microenvironment, immunotherapy, cellular therapy, lymphoproliferative disorder, refractoriness

Description of the research line:

The AECC-IDIBAPS Excellence Program focuses on one of the major clinical challenges in cancer research to decipher the determinants driving susceptibility to immunotherapy. The project is organized in several packages:

- *Investigate the mechanisms of response and resistance in molecular and cellular immunotherapy.* The intention is understanding mechanisms eliciting immunotherapy-refractory lymphoid neoplasms. The work will be focused on the refractoriness of different diffuse large B cell lymphoma (DLBCL), mantle-cell lymphoma (MCL), and DLBCL transformed from chronic lymphocytic leukemia (Richter Transformation, RT), from patients included in the institutional academic CAR-T cell program in the trials using ARI-0001 and ARI-0003 in refractory LBCL and RT, and two different trials in MCL, IMCL2015 and IMCL2023. In addition to these studies, patients´ T-cells pre- and post-infusion at different time points are also expected to be examined.

- *Discover new biomarkers to predict immunotherapy outcomes.* Biomarker identification for immunotherapy in lymphoid malignancies will be the main focus. The investigation of the expanded cohort of DLBCL, MCL and RT in which IDIBAPS will have bulk whole genome/exome sequences and transcriptome will be done. In a large proportion of all these samples IDIBAPS has cryopreserved viable cells to further functional studies and ctDNA at diagnosis and different time points of the follow-up. Clinical and serum parameters prospectively assessed at the clinical trials will be integrated, including volumetric PET/CT parameters, and the characteristics of the cellular therapy products.

- *Explore and address vulnerabilities to improve resistance management in preclinical models.* Tackling vulnerabilities and exploring strategies to overcome resistance in lymphoid neoplasia preclinical models will be the priority. In this package it will be included mechanistic studies modulating specific proteins and pathways using gene editing, antibodies, and drugs to overcome resistance using in vitro patient-derived preclinical models containing tumour and microenvironmental cells. In addition, recent developments on synthetic biology and genome editing to develop next-generation CAR-T cells able to overcome tumour resistance will be considered as well.

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Principal investigators involved: Iñaki Martín-Subero (IMARTINS@recerca.clinic.cat) and Armando López-Guillermo (alopezg@clinic.cat) with the collaboration of Sonia Guedan (sguedan@recerca.clinic.cat) and Cristina Fillat (cfillat@recerca.clinic.cat)

Research groups leading the action: The Lymphoid Neoplasms Program is one of the IDIBAPS programmes made up of eight groups interested in different aspects of lymphoid tumours, and aims to broaden the knowledge of these diseases in order to improve patient care in three areas: improving diagnostic tools, better defining patient prognosis, and developing new therapeutic approaches such as the identification of new target molecules and the development of immunotherapies and cell therapies. Therefore, the candidate will be working with these groups (plus that of Dr. Sonia Guedán, devoted to cellular therapy) in a patient-oriented research.

Additional information of the research group:

- **Importance of the clinician-scientists within the group:** The physician-scientist figure will represent the link between the different most translational groups and the clinical reality of patients to whom research is ultimately directed. It is of particular interest that the candidate knows all the clinical aspects (diagnosis, prognosis, treatment) and the basics of translational research. Among the former, it is important that he/she understands the development of clinical trials in the early phases, in which a large number of patients will be enrolled.

- **Interest of the group to recruit a clinician-scientist:** For the entire group of lymphoid neoplasms, it is essential to have a clinician-scientist with a specific interest in translational research. Therefore, such a person should be trained in two aspects: 1) clinical training, i.e. understanding the diagnostic and therapeutic difficulties of treatment resistance in patients with lymphoma, and 2) translational training, i.e. understanding the pathophysiological mechanisms involved in treatment resistance and how to overcome them.

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Group: Translational Genomics and Targeted Therapies in Solid Tumors

Principal investigator: Aleix Prat (alprat@clinic.cat)

Title: Pioneering Strategies to Maximize Immunotherapy Efficacy in breast cancer

Key words: breast cancer, immunotherapy, tumor microenvironment, biomarkers, targeted therapies

Description of the research line:

The AECC-IDIBAPS Excellence Program focuses on one of the major clinical challenges in cancer research to decipher the determinants driving susceptibility to immunotherapy. The project is organized in several packages:

- *Investigate the mechanisms of response and resistance in molecular and cellular immunotherapy.* The objective is understanding mechanisms of immunotherapy response in breast cancer. Selected tumor samples from patients included in different breast cancer immunotherapy trials at Hospital Clínic Barcelona will be investigated.

- *Discover new biomarkers to predict immunotherapy outcomes*. The main purpose is achieving biomarker identification for immunotherapy in breast cancer through the study of expanded cohorts of the patients from the trials mentioned above. The project aims to extend the utility of the HER2DX and TNBCDX tests, groundbreaking tool developed by the spin-off Reveal Genomics, measuring the tumour immune cell response in early-stage HER2-positive and triple-negative breast cancer respectively; as well as the novel toolkit, DNADX, a DNA-seq platform that harnesses AI to predict RNA and protein changes, furthering the ability to identify clinically relevant subtypes and guide therapy decisions. This comprehensive approach will expand the armamentatium of biomarkers for breast cancer, furher empowering diagnostic tools like HER2DX, TNBCDX and DNADX and improving the precision of immunotherapy treatment predictions for various subtypes of breast cancer.

- *Explore and address vulnerabilities to improve resistance management in preclinical models*. To actively test innovative antibody-based therapies, including ADCs (antibody-drug conjugates) and CAR-T (chimeric antigen receptor T-cells), against a spectrum of specific targets is foreseen. Central to the strategy to be followed is the use of patient derived xenografts (PDXs) from individuals with advanced best cancer treated at the Breast Unit of the Hospital Clínic Barcelona, complemented by classical cell lines that have been genetically modified to express these targeted antigens. This dual approach ensures a comprehensive evaluation of potential therapies.

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Principal investigators involved: Aleix Prat

Research groups leading the action:

The Translational Genomics and Targeted Therapies in Solid Tumors Lab focus on the diagnostics and treatment of cancer. The main objectives of the group are (1) to identify genomic biomarkers predictive of response to targeted therapies; (2) to understand the mechanisms of drug resistance and tumor progression; (3) to identify and validate new therapeutic targets; and (4) to characterize the interaction between tumor cells and the tumor microenvironment and their impact on response to treatments. The goal of the team is to use genomic and molecular data to guide clinical trial design and biomarker development and to understand molecular mechanisms of drug sensitivity in order to identify optimal treatment regimens for patients with solid tumors. The team has significantly contributed to the assessment of the prognostic value of intrinsic molecular subtypes in early-stage and metastatic breast cancer. The group has developed HER2DX and TNBCDX, two diagnostic tests to guide systemic treatment in early-stage HER2-positive breast cancer and triple-negative breast cancer, respectively, as well as DNADX, a DNA-based predictive test, which aids in treatment decisions for metastatic breast cancer. Within the field of immunotherapy, the team is conducting novel cell therapy trials. The team is proficient in translating research into successful clinical trials and tools. The Translational Genomics and Targeted Therapies in Solid Tumors team, which is led by Prof. Aleix Prat, consists of medical oncologists, pathologists and biologists, has the expertise, leadership, training and motivation necessary to successfully carry out the proposed project.

Additional information of the research group:

- **Importance of the clinician-scientists within the group**

Clinician-scientists play a pivotal role by bridging the gap between clinical practice and laboratory research. The unique perspective of clinician-scientists enhances the team's ability to translate genomic and molecular data into actionable clinical trials and therapeutic strategies, particularly in the rapidly evolving fields of targeted therapies and immunotherapy.

- **Interest of the group to recruit a clinician-scientist**

The group is actively interested in recruiting a clinician-scientist. This addition will further strengthen the team, currently comprised of medical oncologists, pathologists, and biologists, by ensuring that clinical insights are directly integrated into research projects. Ultimately, this strategic recruitment aims to optimize treatment regimens for patients with solid tumors and advance the field of translational genomics and targeted therapies.

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Group: Translational Research in Hepatic oncology

Principal investigator: Josep M. Llovet (jmllovet@clinic.cat)

Title: Precision oncology to maximize benefits from immunotherapies in liver cancer

Key words: **Hepatocellular carcinoma – Immunotherapies - Precision oncology**

Description of the research line:

The AECC-IDIBAPS Excellence Program focuses on one of the major clinical challenges in cancer research to decipher the determinants driving susceptibility to immunotherapy. The project is organized in several packages:

- *WP1- Investigate the mechanisms of response and resistance in molecular and cellular immunotherapy.* The main purpose is understanding mechanisms of immunotherapy response in hepatocellular carcinoma (HCC) by using ***scRNA-seq and spatial transcriptomics*** in patients with tumors treated with atezo+bev

- *WP2- Discover new biomarkers to predict immunotherapy outcomes.* Biomarker identification for tumour response in HCC will be the main focus. A cohort of 350 FFPE tumour biopsies of atezo+bev-treated patients by ***bulk RNASeq and large-scale targeted DNA sequencing*** will be investigated. Transcriptomic and genomic data will be used to assess the predictive value of response to this immune therapy.

- *WP3- Explore and address vulnerabilities to overcome primary resistance in preclinical models.* The main objective is ***exploring the efficacy and tolerability of new drugs in syngeneic HCC tumour-mouse models***. Orthotopic murine models will be scanned by magnetic resonance imaging (MRI) and HCC bearing mice will undergo different therapeutic treatments, in selected arms – similar to a clinical trial. To determine treatment efficacy, tumour growth will be monitored by MRI, and overall survival will be analysed and compared to the current standard of care treatment. To identify mechanism of action related to the tested treatments, tumours will be excised and analysed by RNAseq, flow cytometry, immunohistochemistry, and spatial transcriptomics and scRNAseq, if required.

Research group leading the action:

The Translational Research in Liver Cancer Group, led by Prof. Llovet, is at the forefront of both translational and clinical research on liver cancer globally. Prof. Llovet, MD, PhD is Professor of Medicine – Hepatic Oncology at the University of Barcelona, Group Leader and Professor of Research-ICREA in the Liver Unit, IDIBAPS-Hospital Clínic, and Director of the Liver Cancer Program and Professor of Medicine at the Icahn School of Medicine at Mount Sinai, NY. He has devoted his career to the pathogenesis and treatment of liver cancer, publishing ~375 articles (~152,491 citations, h-index: 154) and leading ~127 projects. These publications have been published in NEJM, Nature, Lancet, Lancet Oncology, Cancer Cell, Nature

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Nature Rev Clin Oncol, J Clin Oncol and Gastroenterology. He has been nominated as a global Top 1% cited researcher (2014 to 2024) and is Editor-in-Chief of *JHEP Reports* (2024–29). In terms of projects, the group coordinates the European Project THRIVE (EU Horizon Europe Program, the ASPIRE Consortium (AECC Foundation) and lead the International HCC Consortium with around 40 acdemic partners. In the US and Europe.

The group primarily focuses on (1) understanding the molecular and immunogenomic mechanisms underlying hepatocellular carcinoma (HCC), (2) identifying prognostic biomarkers and predictors of treatment response, and (3) discovering novel therapies to improve survival rates for patients diagnosed with HCC.

Importance of the clinician-scientists within the group

Clinician-scientists play a central role in our group, ensuring that translational research remains tightly aligned with clinical needs. We lead international Consortiums of Liver Cancer groups (up to 40) and have a tissue back of 3000 samples. In addition, we work in close collaboration with the Liver Unit at Hospital Clinic. In our team of 15 members, we count with 3 MD (2 hepatologist and 1 pathologist) offering continuous, practice-based input that shapes research priorities and interpretation. Additionally, Professor Llovet's clinical and academic role at Mount Sinai Hospital-New York (Director of the Liver Cancer Program with 24 faculty) further expands our global clinician-scientist network, facilitating access to diverse patient cohorts and enhancing the clinical relevance and applicability of our research.

Interest of the group to recruit a clinician-scientist

Recruiting a clinician-scientist is essential to bridge research and clinical practice, ensuring the relevance, consistency, and applicability of results, and facilitating the rapid translation of findings into innovative strategies that improve HCC management. Our team benefits from a combination of clinical and translational genomics-based and lab-based expertise. A Clinician-scientist will provide the knowledge to bring the questions from the clinical side and explore them with a translational perspective. Our research integrates patient-derived samples from HCC patients treated with stage-specific strategies, including immunotherapy, and advanced preclinical models, with a strong focus on biomarker discovery and mechanisms of resistance to current treatments.

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