TRANSCAN
Sustained collaboration of national and regional programmes in cancer research

TRANSCAN-3

Funded projects on:

"Next generation cancer immunotherapy: targeting the tumour microenvironment (JTC 2021)"

and

"Combination therapies against cancer: new opportunities for translational research (JTC 2024)"

FINAL SYMPOSIUM

October 20th-22nd

2026

Palazzo De' Toschi
Piazza Minghetti 4D, 40121
Bologna, Italy

This event is co-organized by:

Ministero della Salute

MINISTRY OF HEALTH
For a healthier life

ALLEANZA CONTRO IL CANCRO

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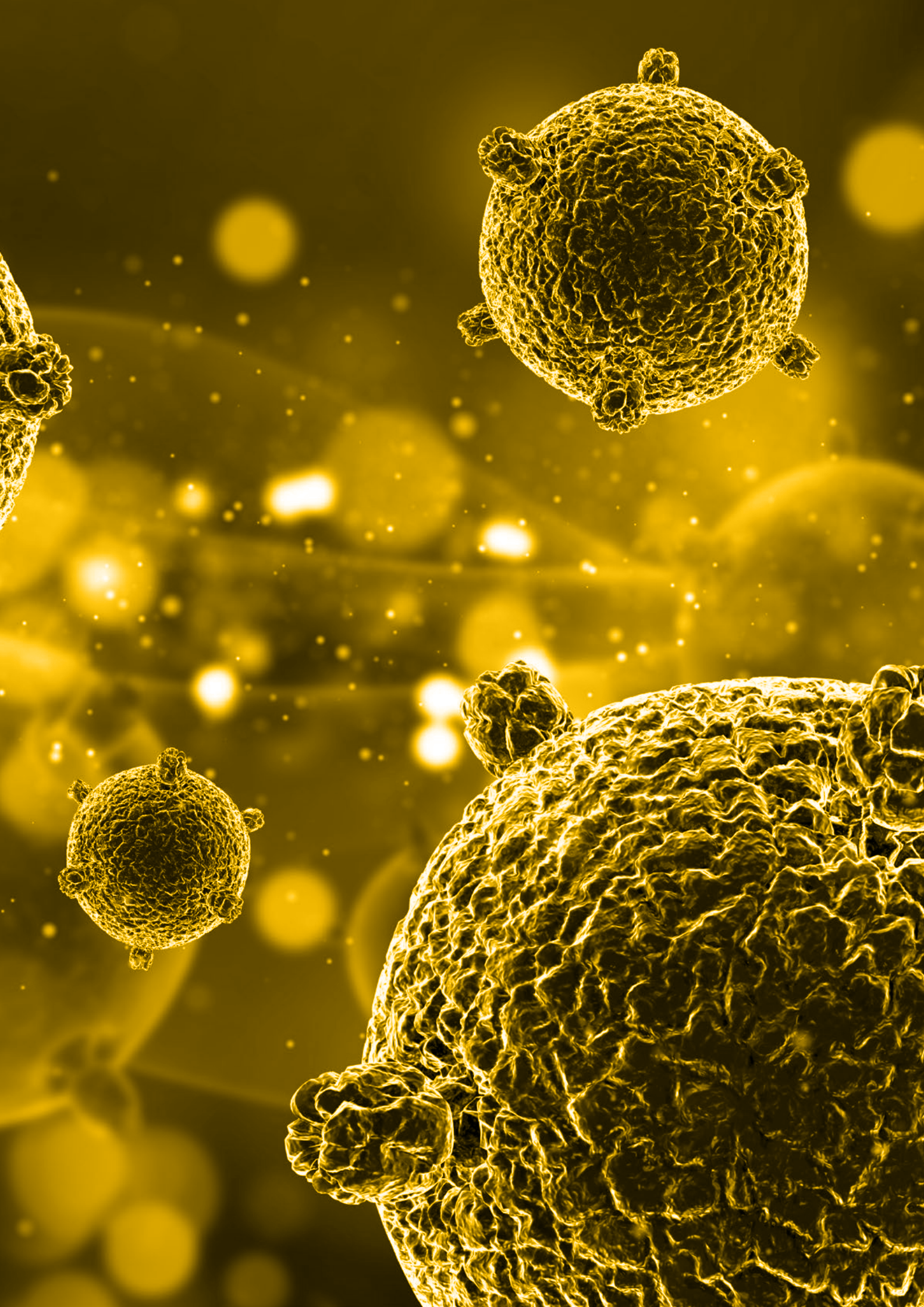

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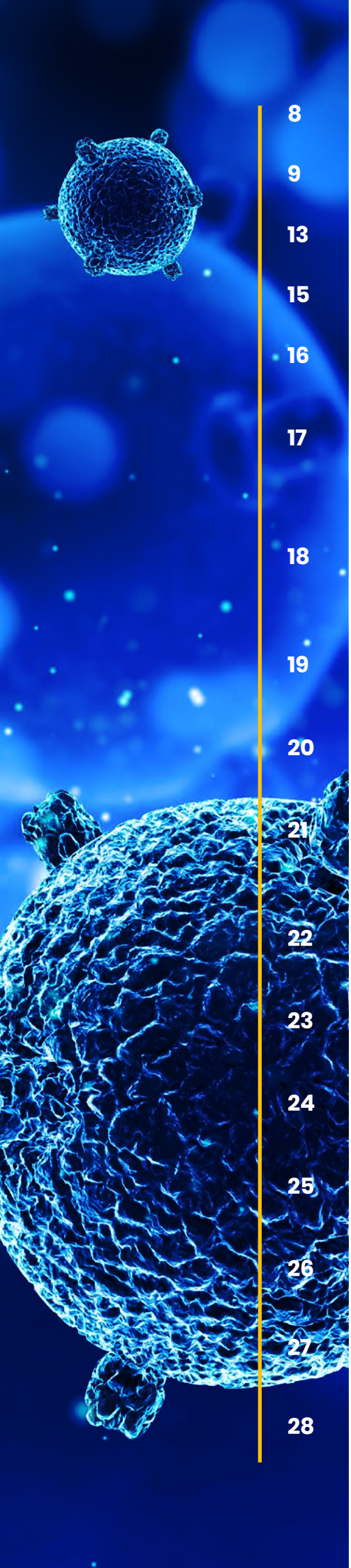

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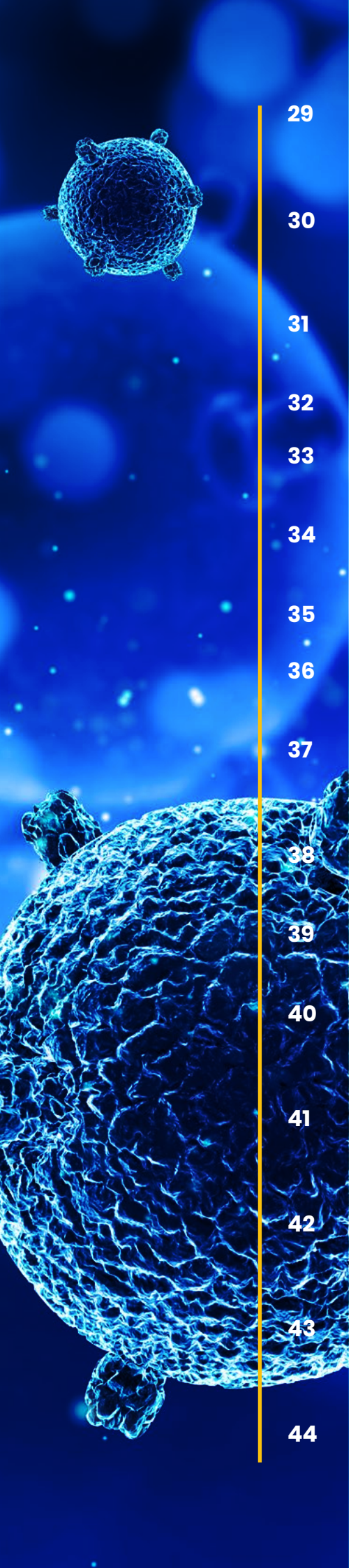

Reprogramming of the tumor microenvironment with modular engineered CAR-T cells to augment the efficacy of immunotherapy (SmartCAR-T)

Targeting acute myeloid Leukemia immunosuppressive microenvironment by combined IDO1 inhibition and PD-1 blockade (TALETE)

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Targeting ROBOs and SLIT guidance cues in the immunosuppressive stromal context of pancreatic cancer (TRanSLIT)

Circulating tumour microenvironment components as Urothelial Cancer Immunotherapy Response Predictors (UCIPredict)

JTC2024 PROJECTS

FunctionAl preCision mediCinE pLatform for the trEatment of pancReATic cancEr (ACCELERATE)

Building an ex vivo complex tumour microenvironment platform for development of combination therapies and drug resistance studies in head neck cancer (BePrepared)

Development Of Patient-derived organoid PLatforms for Evading Resistances in Lung Cancer (DOPPLER-LC)

Targeting tumor heterogeneity in pediatric high-grade gliomas (GLIO-COMBO)

Human avatar on chip for advancing personalized cancer therapies by integrating vascular and immune components in a Tumor-on-Chip model (HAVOC)

Immune oncology Drug Discovery & Decision - Advanced ex Vivo Approach To Accelerate Response prediction for combined therapies in ovarian cancer (ioAVATAR)

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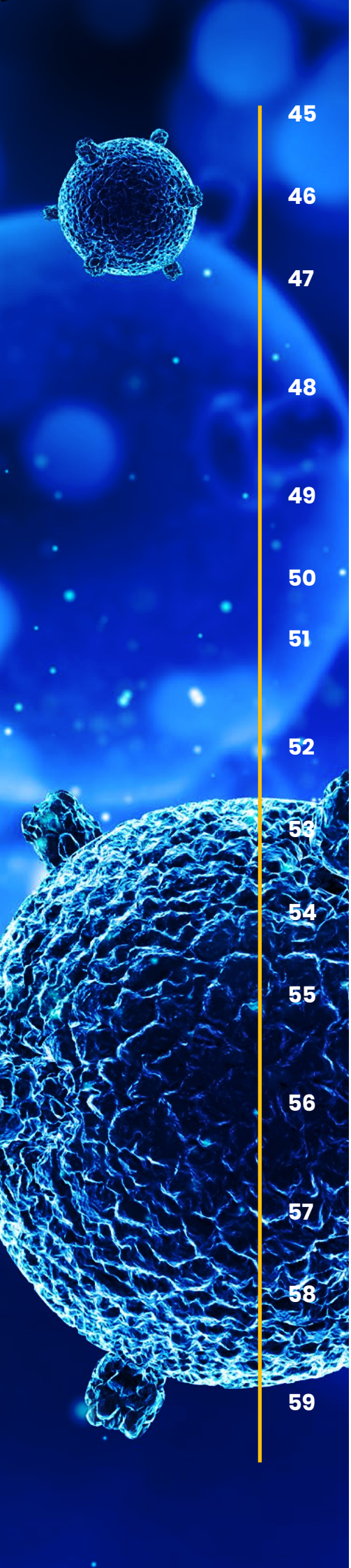

45 Search for combinational therapy to target clonal haematopoiesis in solid malignancies (SARAH)

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48 TAD disruption and aberrant expression as leukaemia metabolic vulnerabilities for novel combination therapy tests in a drug screening platform (TOSCANINI)

49 Radiothermal-Driven Immune Activation to Tackle Pancreatic Hypoxic Tumours (XPANTHER)

POSTERS

50 POSTER #1: JTC2021 Project ANEMONE Human and AI assessment of the tumour immune microenvironment in pleural mesothelioma: concordance and prognostic relevance in ANEMONE

51 POSTER #2: JTC2021 Project CHRYSALIS NK cells Impair Lung TIL Proliferation by Targeting CD127⁺ CD4 T⁺ Cells

52 POSTER #3: JTC2021 Project PIXEL From Geneticsto the Niche: Deciphering Bone Marrow and Extramedullary Acute Myeloid Leukemia

53 POSTER #4: JTC2021 Project TALETE Exploring Immunosuppressive Mechanisms in the Acute Myeloid Leukemia Microenvironment

54 POSTER #5: JTC2021 Project TALETE Extracellular Vesicles in Acute Myeloid Leukemia Uncover Immunometabolic Functions and Reveal Prognostic Biomarkers of Early Therapy Response

55 POSTER #6: JTC2021 Project TALETE Mesenchymal Stromal Cells Protect Acute Myeloid Leukaemia Cells from Venetoclax-Induced Apoptosis Through a Cd90-Mediated Adhesion Pathway

56 POSTER #7: JTC2021 Project TENACITY Development of Nectin-2 Specific Nano-CARs for the Treatment of Melanoma

57 POSTER #8: JTC2021 Project TENACITY Targeting the Immune Checkpoint CD155 (PVR) with Single-Domain Antibodies for the Treatment of Melanoma

58 POSTER #9: JTC2021 Project TRanSLIT ROBO1 Links Aggressive Tumor Cells to Endothelial Proximity and Chemotherapy Tolerance in Pancreatic Cancer

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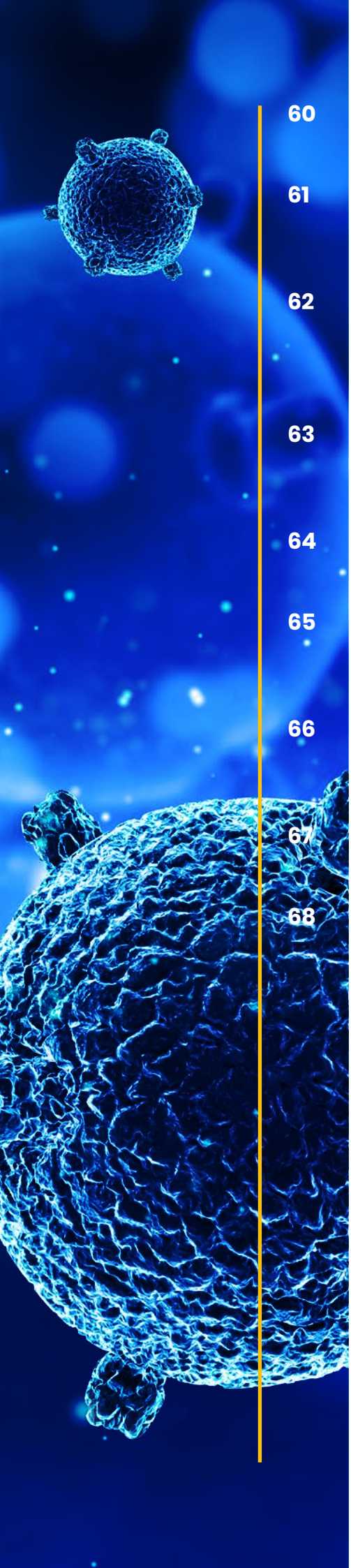


POSTER #10: JTC2021 Project TRanSLIT Targeting ROBOs and SLIT Guidance Cues in Pancreatic Cancer Microenvironment

POSTER #11: JTC2024 Project ACCELERATE Integrated Genomic and Pharmacogenomic Profiling to Identify Therapeutic Subgroups in Pancreatic Ductal Adenocarcinoma

POSTER #12: JTC2024 Project ACCELERATE Establishment of Patient-Derived Organoids from Resected Pancreatic Ductal Adenocarcinoma: Feasibility, Morphology and Genomic Concordance After Upfront Surgery or Neoadjuvant Therapy

POSTER #13: JTC2024 Project ioAVATAR Establishing Ovarian Cancer Patient AVATAR Models from Malignant Ascites and Debulking Solid Tumor Tissue to Study Immunotherapy Approaches

POSTER #14: JTC2024 Project SARAH TET2-mutated Clonal Hematopoiesis Leads to an Inferior Survival in Patients with Advanced-Stage Cancer

POSTER #15: JTC2024 Project TITAN Patient-Derived Organ-on-Chip to Evaluate Chemo-Immunotherapy Response and Tumor–Immune Dynamics in Cholangiocarcinoma

POSTER #16: JTC2024 Project TITAN Novel Cancer Therapy: Inducing Double-strand DNA Breaks to Foster Tumour Cell Death, Antigenicity and Immunotherapy Response in New Personalized Models

POSTER #17: JTC2024 Project XPANTHER Multifunctional Photothermal Nanoparticles for Pancreatic Cancer within XPANTHER Project

Additional Speakers

Introduction

Cancer is one of the leading causes of death and represents a significant global burden of disease. In Europe it ranks as the primary cause of morbidity after cardiovascular diseases, accounting for over 4.33 million new cases each year (GLOBOCAN 2024; https://gco.iarc.who.int). Cancer remains a major public health challenge, contributing substantially to healthcare expenditure and posing a considerable socio-economic burden in Europe and globally. Addressing the need to reduce cancer incidence and mortality and improve patients' quality of life requires coordinated efforts and the rapid and effective bidirectional transfer of relevant research findings between bench and bedside. Translational cancer research plays a pivotal role in addressing these needs, requiring coordinated research priorities and resources across countries to maximise its impact.

The ERA-NET TRANSCAN-3 (Aligning national/regional translational cancer research programmes and activities) is a collaborative network of ministries, funding agencies and research councils with programmes in translational cancer research, funded by the European Commission under the EU framework programme Horizon 2020. The network comprises 31 partners from 20 Countries and continues the previous ERA-NET TRANSCAN and TRANSCAN-2 programmes. Altogether since 2011, 12 annual Joint Transnational Calls (JTCs) have been launched and 143 transnational projects have been funded.

Under TRANSCAN-3, successive Joint Transnational Calls have supported collaborative research addressing key challenges in translational cancer research. Under the 2021 call, "*Next generation cancer immunotherapy: targeting the tumour microenvironment*", co-funded by the European Union, 20 transnational consortia comprising 107 research groups from 15 countries were funded. The projects aimed to advance personalised cancer treatment through new tools and targeted immunotherapy strategies based on a better understanding of the tumour microenvironment. The 2024 call, "*Combination therapies against cancer: new opportunities for translational research*", funded 15 transnational consortia involving 73 research groups from 13 countries. The projects aim to improve personalised cancer treatment by developing new combination therapy strategies and approaches to overcome treatment resistance.

The TRANSCAN-3 Final Symposium marks both the culmination of the JTC2021 projects and the beginning of a new generation of TRANSCAN-3 research under JTC2024. It brings together JTC2021 consortia, now completing their projects and presenting their findings, with the newly funded JTC2024 consortia as they embark on their research. By connecting researchers at these different stages, the symposium provides an opportunity to share knowledge and experience, foster scientific exchange and networking, and promote new collaborations across the translational cancer research community. Young scientists are particularly encouraged to participate, present and discuss their work, and engage with colleagues in related fields.

We hope you enjoy and benefit from the symposium!

TRANSCAN-3 Final Symposium

Agenda

Venue: Palazzo De' Toschi, Piazza Minghetti, 4D, Bologna, 40121

Day 1: Tuesday, October 20th, 2026

12:30 – 13:30	**Welcome Light Lunch**
13:30 – 14:00	**Welcome and Introduction**
Session 1	**Chairs: Aideen Ryan and Atanasio Pandiella**
14:00	**PIXEL,** Luca Aldo Edoardo Vago - JTC2021
14:25	**UCIPredict,** Marta Dueñas - JTC2021
14:50	**SmartCAR-T,** Maik Luu - JTC2021
15:15	**HAVOC,** Peter Loskill - JTC2024
15:30	**ioAVATAR,** Leticia Oliveira-Ferrer - JTC2024
15:50 – 16:45	**Coffee Break & Poster Session (Even-numbered posters)**
Session 2	**Chairs: Theodora Katsila and Violaine Goidts**
16:45	**PREDICO,** Giuseppina Arbore - JTC2021
17:10	**BIALYMP,** Jana Tegethoff - JTC2021
17:35	**BePrepared,** Ingeborg Tinhofer-Keilholz - JTC2024
17:50	**DOPPLER-LC,** Antonio Maraver - JTC2024
18:05	**LUNGOIDS,** Judith Guasch - JTC2024
18:20	**METRICs,** Mohamed Elgendy - JTC2024
20:00	**Networking Dinner**

Day 2: Wednesday, October 21st, 2026

08:55	**Arrival & Welcome (please be seated for a 09:00 start)**
Session 3	**Chairs: Violaine Goidts and Pedro Berraondo**
09:00	**ImmuMet,** Martina Seiffert - JTC2021
09:25	**RISEBrain,** Medyouf Hind - JTC2021
09:50	**SeqPerGlio,** Mario Chiariello - JTC2024
10:10 – 11:00	**Coffee Break & Poster Session (Odd-numbered posters)**
11:00 – 11:45	**Patient Engagement in Cancer Research | Mila Ogalla Toledo**
Session 4	**Chairs: Atanasio Pandiella and Theodora Katsila**
11:45	**PERIMMUNE,** Jesse Demuytere - JTC2021
12:10	**ANEMONE,** Fiorella Calabrese - JTC2021
12:35	**GLIO-COMBO,** Eddy Pasquier - JTC2024
12:50	**MELANOLOCK,** Luigi Fattore - JTC2024
13:05 – 14:05	**Lunch**
Session 5	**Chairs: Aideen Ryan and Pedro Berraondo**
14:05	**CHRYSALIS,** Jules Sotty - JTC2021
14:30	**LipidMac,** Diletta Di Mitri - JTC2021
14:55	**MAGNOLIA,** John Stagg - JTC2021
15:20	**iParaCyts,** Joan Seoane - JTC2021
15:50 – 16:35	**Coffee Break & Poster Session (All posters)**

16:35 – 18:35	**Workshop:** Impact Assessment of TRANSCAN: from Research to Translational Benefits | Ulf Tölch, BIH QUEST Centre, Charité, Berlin, Germany
20:00	**Networking Dinner**

Day 3: Thursday, October 22nd, 2026

08:55	**Arrival & Welcome (please be seated for a 09:00 start)**
Session 6	**Chairs: Atanasio Pandiella and Theodora Katsila**
09:00	**IMMOSCAN,** Hanna Taipaleenmäki - JTC2021
09:25	**TENACITY,** Tobias Bald - JTC2021
09:50	**TALETE,** Antonio Curti - JTC2021
10:15	**TITAN,** Jesús María Bañales - JTC2024
10:30	**TOSCANINI,** Martina Ghetti - JTC2024
10:45	**ACCELERATE,** Michela Cortesi - JTC2024
11:00 – 11:40	**Coffee Break & Voting for Best Poster**
Session 7	**Chairs: Violaine Goidts and Atanasio Pandiella**
11:40	**Pur-Ther,** Elena Adinolfi - JTC2021
12:05	**TRanSLIT,** Ilse Rooman - JTC2021
12:30	**TANGERINE,** Victor Raul Moreno Aguado - JTC2021
12:55	**SARAH,** Cyrus Khandanpour - JTC2024
13:10	**XPANTHER,** Ana Espinosa - JTC2024
13:25 – 13:45	**Poster Prize Ceremony & Closing Remarks**

13:45 – 14:30	**Farewell Lunch**
14:20 – 17:00	**Workshop for Early Career Researchers: Use of AI tools in research**

Session Chairs

We are pleased to introduce the distinguished chairs for our symposium sessions. Their leadership and dedication to advancing cancer research will guide the discussions and ensure a productive exchange of ideas. As we explore the latest developments in the field, their expertise will be invaluable in fostering collaboration and innovation among participants. Below, we present brief biographies and photographs of our session chairs, whose contributions will enhance the experience for all attendees.

Pedro Berraondo

Pedro Berraondo is Principal Investigator and leader of the Cytokine-Based Therapies Research Group at Cima Universidad de Navarra, Spain. He obtained his degree in Pharmacy in 1999 and his PhD in Pharmacy in 2004 from the University of Navarra. His research focuses on the development of innovative immunotherapeutic strategies, particularly cytokine-based therapies, engineered bifunctional molecules and immunocytokines, and the use of mRNA for the development of new anticancer drugs. His work spans basic and translational cancer immunology, with the aim of enhancing anti-tumour immune responses and developing safer and more effective therapies. He has co-authored more than 190 scientific publications and is co-inventor on 11 patents, several developed in collaboration with the pharmaceutical industry and licensed or transferred to biotechnology companies.

Violaine Goidts

Violaine Goidts is a molecular biologist with over ten years of leadership experience, dedicated to understanding glioblastoma and developing innovative therapies. She studied biology at the University of Namur and Uppsala University, carried out her Master's thesis at the Dana-Farber Cancer Institute/Harvard Medical School, and earned her PhD in Human Genetics from the University of Ulm (Germany). After postdoctoral training at the German Cancer Research Center (DKFZ), she established her own independent research group, where she continues to explore how glioblastoma stem-like cells drive tumor growth and therapy resistance.

Her team combines functional screens with -OMICS approaches to identify vulnerabilities and design targeted treatments. Current projects range from nanoparticle-based drug delivery and PROTAC strategies to innovative DNA barcoding technologies that track drug penetration at the single-cell level. With a strong interest in entrepreneurship, she is passionate about bridging academic discovery and clinical application, and is actively pursuing the translation of her research into a biotech startup to accelerate innovation in precision oncology.

Theodora Katsila

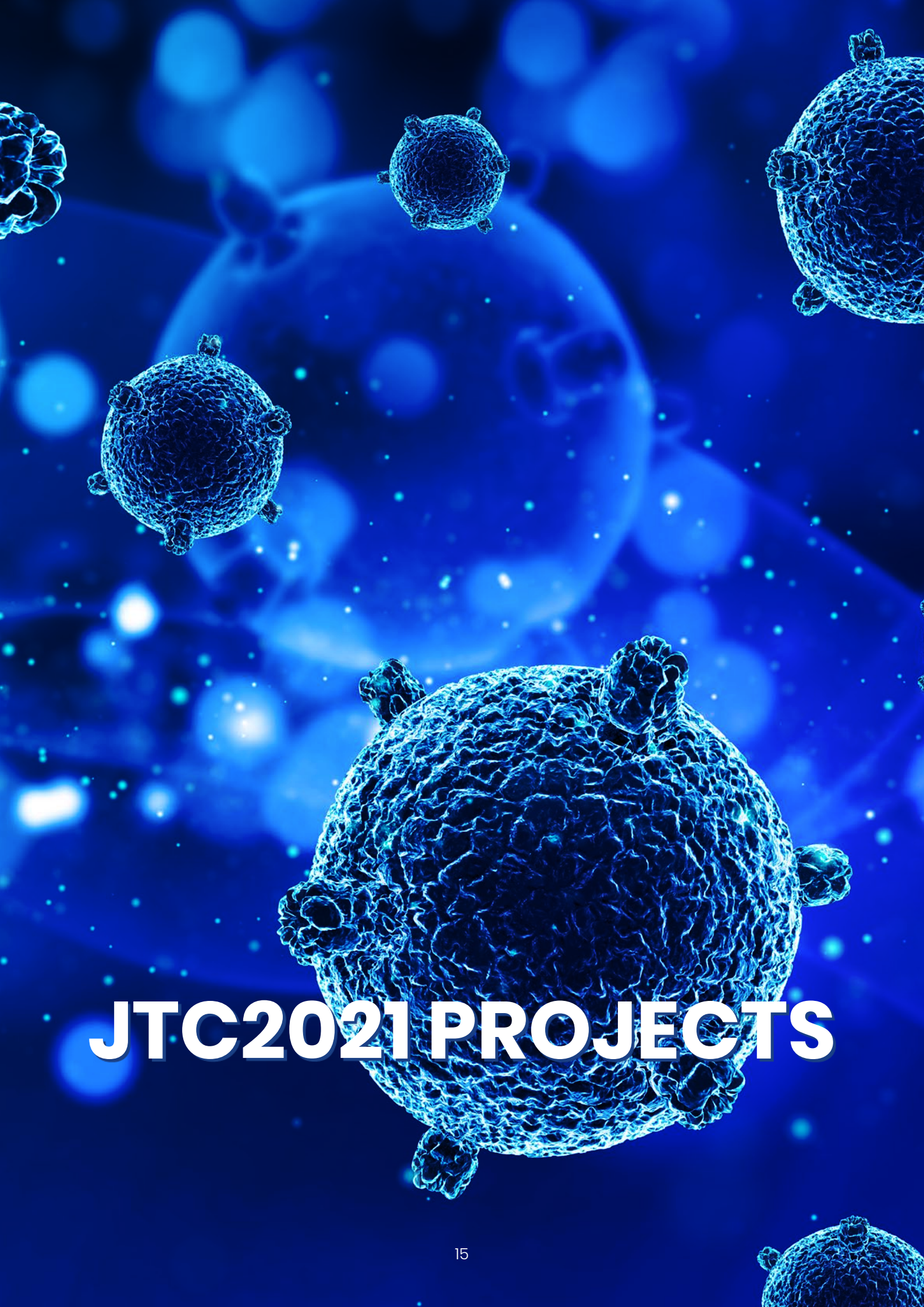
Theodora Katsila is Head of the PLEION Lab | Biomarker Discovery: Translational Research at the National Hellenic Research Foundation, Greece. A leader in biomarker discovery and translational research, her work focuses on Safe-By-Design repurposing of drugs, advanced materials and smart systems. For this, her team leverages proteoforms, AI and digital/ molecular biomarkers. Dr. Katsila's lab launched IN3, a tri-modal innovation engine that fuses in silico, in vitro and in/ex vivo approaches into a single framework, designed to fast-track safe, effective advanced materials, smart systems and therapeutics from concept to society. Many forms, one insight.

Atanasio Pandiella

Atanasio Pandiella, MD, obtained his PhD in Medicine and Surgery from the University of Santiago de Compostela in 1987. He completed pre- and postdoctoral training at the CNR Center of Cytopharmacology and the Ospedale San Raffaele in Milan and subsequently spent three years at the Memorial Sloan Kettering Cancer Center in New York. After returning to Spain, he worked at the University of Las Palmas and later joined the University of Salamanca. He is currently a full professor at the Cancer Research Center (CIC) and the Biomedical Research Institute of Salamanca (IBSAL). His research focuses on the molecular mechanisms underlying cancer development and progression and on the identification and preclinical evaluation of novel therapeutic strategies, with particular expertise in breast and ovarian cancer, oncogenic signalling and targeted therapies.

Aideen Ryan

Aideen Ryan is Professor in Tumour Immunology at the University of Galway, Ireland. She obtained her BSc in Biochemistry from the University of Galway and her PhD in Medicine from University College Cork, where she studied mechanisms of tumour immune evasion. Following postdoctoral training in cancer and regenerative medicine at the University of Galway and research experience at Barts Cancer Institute in London, she established her independent research group in 2017. Her research focuses on understanding how tumour stromal cells shape anti-tumour immune responses, particularly in colorectal cancer, and on identifying new approaches to overcome immune suppression and improve the effectiveness of cancer immunotherapy. She has published extensively in leading journals in the area of stromal cells in anti-tumour immunity and serves on the executive council of the Irish Society of Immunology. Aideen has secured over €20M in national and international research funding as PI and co-PI. Aideen's research discoveries on immunity in cancer, are recognised by keynote invitations and international research excellence awards and she is a named inventor on patents arising from her translational research.



JTC2021 PROJECTS

The ANswer within the microEnvironment: Malignant pleural mesothelioma resistance to Old and NEw drugs (ANEMONE)

Presented by Fiorella Calabrese
University of Padova
Italy

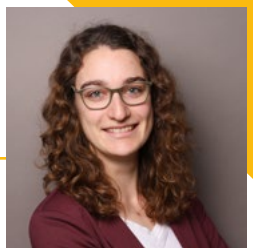
Background and Rationale: Pleural mesothelioma (PM) is an intrathoracic neoplasia with an unfavourable prognosis. Although rare, a high peak incidence is expected in 2020-2025. The most important risk factor is asbestos exposure that leads to a protracted immune response, making PM a candidate for immunotherapeutic approaches. However, to date the overall response rates to treatment with immune checkpoint inhibitors (ICI) are only 10-20%.
Hypothesis: The hypothesis is that the tumour microenvironment (TME), particularly tumour immune microenvironment (TIM), plays a crucial role in the development/progression of PM, affecting survival of mesothelial cells and escape from immunosurveillance.
Aim: The main goal of the project is the identification of predictive biomarkers of ICI response.
Methods: The research will be done on 360 chemo naïve pleural biopsies from PM patients that will undergo neoadjuvant chemotherapy followed by surgery or palliative systemic treatment (platinum-based chemotherapy or ICI). A subset of PM tissues from patients undergoing surgery will be investigated before and after treatment. The research will be based on a multidisciplinary and interdisciplinary approach. Through advanced statistical methods (machine learning algorithms), clinical data, and findings from immunofluorescence, high-throughput molecular assays, radiomics, and magnetic resonance will be integrated to identify the most discriminative predictive features for the ICI treatment response. Experimental models (in vitro and in vivo) for functional studies will also be considered.
Expected Results and Potential Impact: ANEMONE is built upon the strong belief that there are specific key pathways and TME/TIM markers capable of predicting the prognosis and the response to ICI in PM patients. The identification of these pathways could have a strong impact on PM patient management allowing a better treatment response and outcome.

Project Coordinator:
Fiorella Calabrese, University of Padova, Italy

Project Partners:
Luka Brcic, Medical University of Graz, Austria
Lina Carvalho, University of Coimbra, Portugal
Chiara Romei, Azienda Ospedaliero-Universitaria Pisana, Italy
Ilze Strumfa, Riga Stradiņš University, Latvia

Bispecific antibodies in Lymphoma: Microenvironmental profiling to predict treatment response and uncover immunogenic resistance mechanisms (BIALYMP)

Presented by Jana Tegethoff
University Hospital Düsseldorf,
Germany



Redirection of autologous T-cells through bispecific antibodies (BsAb) is an important therapeutic principle to treat B cell lymphomas. Treatment response, however, is heterogeneous, highlighting the need for a better understanding of resistance mechanisms and biomarkers for response prediction.
Both tumour intrinsic, e.g. genetic and epigenetic alterations, and extrinsic factors, e.g. composition and functional state of the lymph node (LN) microenvironment, determine the response to BsAb. We aim to identify, understand and exploit them to improve treatment strategies.
Aim 1: Improve our understanding of the LN microenvironment of relapsed and refractory B cell lymphomas. Composition and biological state of LN derived microenvironmental cells will be characterised at multiple levels by single-cell transcriptomics (CITE-Seq), DNA mutation analysis and proteomics. To characterise the spatial organisation, including T-cell engagement, we will analyse matched FFPE tissues using multiplexed immunofluorescence.
Aim 2: To understand how lymphoma cell characteristics and LN microenvironment influence the activity of BsAb, we will perform functional ex-vivo response profiling of drug BsAb combinations in increasingly complex tumour models.
Aim 3: We will characterise the most relevant microenvironmental features from Aims 1&2 in patients treated with BsAb. With support of the German, French and Italian Lymphoma societies we will assemble patient cohorts to identify biomarker signatures for response or resistance to BsAb in vivo. To improve patient stratification we will transfer these biomarkers to a clinically applicable assay.
All generated data will be centrally managed with shared computational data analysis workflows jointly usable by all partners, enabling rapid, multi-approach, transparent analyses.
Altogether, we aim to expand the understanding of the lymphoma microenvironment, uncover treatment response markers and enable improved T-cell based immunotherapies.

Project Coordinator:
Wolfgang Huber, European Molecular Biology Laboratory (EMBL), Germany

Project Partners:
Sascha Dietrich, Heidelberg University Hospital, Germany
Karin Tarte, Université de Rennes 1, France
Camille Laurent, INSERM, France.
Peter Horvath, Eotvos Lorand Research Network, Biological Research Centre, Hungary
Claudio Tripodo, University of Palermo, Italy

Characterization of stromal and innate lymphoid cell populations involved in immunotherapy resistance in High-Grade Serous Ovarian Cancer through multiOMICS analysis (CHRYSALIS)

Presented by Jules Sotty
Princess Margaret Hospital
Canada

High-grade serous ovarian cancer (HGSOC) is an aggressive pathology, which requires new therapeutic strategies to improve patient outcome. Cancer treatment has taken a step forward with the advent of immunotherapy but has failed to be efficient in HGSOC. To overcome this, it is important to understand tumour biology and take into account the whole tumour ecosystem, composed of tumour cells and surrounding microenvironment. The tumour microenvironment (TME) includes different cell types. Cancer associated fibroblasts (CAF) and innate lymphoid cells (ILC) are abundant components of the TME. Interestingly, partners identified distinct CAF and ILC subpopulations in HGSOC and demonstrated that specific CAF and ILC subpopulations (CAF-S1 and ILCreg) display immunosuppressive activities by reducing T lymphocyte anti-tumour activity.
Based on solid preliminary data, we consider that CAF and ILC are able to inhibit, putatively in a synergic way, anti-tumour functions of several immune components. The immunosuppressive TME induced by these cells could explain the immunotherapy resistance observed in HGSOC patients.
To further characterize CAF and ILC in HGSOC leading to immunotherapy resistance, our research proposal will:
- Define how their diversity is generated
- Study all their interactions within the TME, especially with the immune component
- Develop a new diagnostic tool based on artificial intelligence (AI) to predict patient response to immunotherapy

We will use innovative technologies to study each cell individually and perform a fine tumours characterisation in time and space. The strengths of our consortium reside in our complementary expertise and access to HGSOC patient cohorts. We aim to move toward translational clinic and provide to clinicians a new diagnostic tool to guide patient therapeutic strategy.

Project Coordinator:
Fatima Mechta-Grigoriou, Institut Curie, Centre de recherche, France

Project Partners:
Fabian Theis, Helmholtz Zentrum München GmbH, Germany
Pamela Ohashi, University Health Network (UHN), Canada

The role of IMMune OSteoclasts in CANcer – Implications for therapy (IMMOSCAN)

Presented by Hanna Taipaleenmäki
Ludwig-Maximilians-University Munich
Germany

Primary bone tumors and bone metastases affect patients across all age groups and remain largely incurable. Tumor progression in bone is critically shaped by the bone microenvironment, a specialized immunological and metabolic compartment in which osteoclasts have conventionally been regarded as terminally differentiated, bone-resorbing cells. Accumulating evidence indicates that osteoclasts also possess innate immune competence, processing antigens, secreting cytokines, expressing immune checkpoint molecules and modulating T-cell responses. In murine models and in patient biopsies of osteosarcoma and breast cancer bone metastasis, we identified osteoclast-like cells within tumor lesions at sites anatomically separated from active resorption, suggesting a non-canonical function at the tumor–bone interface. IMMOSCAN was designed to test the hypothesis that these cells represent a distinct subset, immunosuppressive osteoclasts, that sustains a cancer-permissive niche through immune modulation and bidirectional signaling with tumor cells.

Five partners addressed this across harmonized bone metastasis and osteosarcoma models in immunocompetent and immunodeficient hosts, patient biopsies and human osteoclast cultures, integrating spatial transcriptomics, bulk and single-cell transcriptomics, cross-species analysis, myeloid lineage fate-mapping, extracellular vesicle biology and functional immunoassays. These cells recurred across tumor entities, skeletal sites and host immune backgrounds, developed independently of adaptive immunity and correlated with disease burden. They carried a conserved transcriptional program spanning immune regulation, cytokine signaling, metabolic adaptation and migration, preserved between tumor types and between species. Pharmacological osteoclast depletion restored immune infiltration in tumor-bearing bone, tumor-educated osteoclasts constrained effector T-cell activation and favored regulatory populations, and extracellular vesicles were established as a bidirectional mediator of this crosstalk.

These findings define three complementary intervention axes, metabolic, checkpoint and vesicle-directed, several addressable with clinically available compounds, and identify the osteoclast as a targetable immune regulator supporting the combination of bone-directed intervention with immunotherapy.

Project Coordinator:
Hanna Taipaleenmäki, Ludwig-Maximilians-University Munich (LMU), Germany

Project Partners:
Anna Maria Teti, University of L'Aquila, Italy
Dominique Heymann, University of Nantes, France
Claudine Blin, Université Côte d'Azur, France
Thomas Levin Andersen, University of Southern Denmark, Denmark

Invigorating immunity against brain metastases in lung and breast cancer patients (ImmuMet)

Presented by Martina Seiffert
German Cancer Research Center
Germany

Brain metastases (BrMet) are a devastating complication in breast and lung cancer and a main cause of death. Novel immunotherapies have revolutionized treatment of cancer, but response rates are hard to predict, especially for BrMet patients. We have quantified immune cells in BrMet tissue of patients with lung or breast cancer and observed a higher number of T cells compared to primary brain tumours, but also a high heterogeneity in T-cell numbers. Interestingly, high infiltration of T cells in BrMet was associated with longer survival of patients. We hypothesize that immune cell infiltration and function in BrMet is regulated by the tumour microenvironment (TME), and an improved understanding of niche-specific factors, cell types, and mechanisms will help to improve immunotherapy in BrMet patients.
In ImmuMet, we will characterize the BrMet niche in patient-derived tissues and blood, PDX and immunocompetent mouse models to define TME subclasses and unravel clinical associations. We will acquire single-cell and spatial tissue data, multiplexed flow cytometry, and serum analyses, combined with integrative bioinformatics and modelling approaches, including own and publicly available data, to build a knowledge base that guides the selection of candidate genes, pathways, cellular interactions, and molecular mechanisms, which we will validate and modulate in established patient-derived organoid and mouse models. The ImmuMet consortium benefits from the complementary expertise of wet lab scientists with a strong research focus on tumour immunology and BrMet biology, clinicians who are at the forefront of treatment decisions, collaboration partners heading clinical trials and registries for BrMet patients, and informaticians who are experts in integrating omics data and developing prediction models. We expect to unravel molecular mechanisms of immune cell infiltration and function in the BrMet TME and to increase the success rate of immunotherapy for BrMet patients.

Project Coordinator:
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Project Partners:
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Bozena Kaminska, Nencki Institute of Experimental Biology PAS, Poland
Neta Erez, Tel Aviv University, Israel
Manuela Zucknick, University of Oslo, Norway

Understanding and therapeutically exploiting the immunosuppressive paracrine signalling in the tumour microenvironment of metastatic lesions (iParaCyts)

Presented by Joan Seoane
Fundación Hospital Universitario Vall d'Hebron
Spain

Our consortium proposes the integrated study of immunosuppressive cytokines expressed in liver metastatic lesions. While most of the studies in immune-oncology are focused on primary tumors, the majority of patients treated with immunotherapies suffer from disseminated metastatic disease and, in many instances, liver metastasis. Liver metastases are common, confer dismal prognosis, constitute a clear unmet medical need, and are strongly associated with resistance to immunotherapy. We will study five highly relevant cytokines (TGFß, TNFa, IL8, LIF and GDF15) in liver metastasis. The reasons for this choice include evidence for integrated regulation of this cytokine network, the existence of inhibitory compounds against these targets, which are undergoing early clinical development in our institutions, and the availability of serial biopsies from liver metastases. We hypothesize based on preliminary data that these 5 paracrine cytokines are crucial to promote tumor escape from the immune system in liver metastases, with potential redundancies when considering them as therapeutic targets.
Our aims are: 1- Epidemiology of the cytokines in human liver metastases. 2- Effect of the inhibition of the cytokines on tumor growth and the cancer immune response. 3- Study of the tumor immune landscape in patients treated with inhibitors of these cytokines in the context of clinical trials.
Our studies will focus on patient-derived samples as well as syngeneic animal models of liver metastasis. Importantly, pre- and on-treatment biopsies from liver lesions in early phase clinical trials testing inhibitory compounds will be studied.
Our project will evaluate the five immunosuppressive cytokines as therapeutic targets in isolation or in potential synergistic treatment combinations, identify predictive biomarkers of response to the blockade of the cytokines, and discover novel therapeutic targets for the treatment of liver metastasis.

Project Coordinator:
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Bruno Segui, Cancer Research Center of Toulouse, INSERM, France
Jörg Wischhusen, University Hospital Wuerzburg, Germany
Gianluigi Giannelli, Ente Ospedaliero Specializzato in Gastroenterologia "Saverio de Bellis" – IRCCS, Italy
Pinar Pir, Gebze Technical University, Türkiye

Exploiting lipid-laden macrophages to overcome resistance to cancer immunotherapy (LipidMac)

Presented by Diletta Di Mitri
IRCCS Istituto Clinico Humanitas – Humantas Mirasole SPA
Italy

Immune checkpoint blockade (ICB) has revolutionized cancer care yet is ineffective in most patients. Predicting which patients will respond to ICB and how to enhance efficacy are major challenges. ICB efficacy is dependent on the presence of functional T cells in tumors, which are impacted by macrophages. We have discovered that lipid-laden macrophages (LLM) infiltrate tumors to promote cancer progression in association with immune evasion and poor ICB response. Moreover, intra-tumoral LLMs are elevated in response to over nutrition via dietary fat. How LLMs accumulate lipids to impact ICB and whether they are predictive of ICB efficacy remain unexplored. Our objective is to determine how LLMs limit ICB and how this can be controlled via diet. We hypothesize that LLM predict poor ICB response and that targeting LLM will enhance ICB efficacy. Our goals are to determine (1) the utility of LLM in predicting ICB efficacy and T cell dysfunction in patients; (2) the origin and functional role of LLM in immunosuppression, haematopoiesis and ICB resistance; & (3) how LLM and ICB are impacted by diet and obesity. To establish causality, we will focus on tumors in close proximity to lipid-rich adipose tissue, such as ovarian (OC), prostate (PCa) and breast cancer (BC), which have high LLM and respond poorly to ICB. We will explore the link between LLM and ICB efficacy in patients using samples from a prospective Phase II clinical trial (OC) and human tumor biobank (OC, PCa, BC). In preclinical models, we will use state-of-the-art fate-mapping tools, imaging techniques and spatially resolved single cell technologies to dissect the interplay between LLM & T cells following ICB and over nutrition. Our work will provide insight into the rewiring of tumor-supportive and immunosuppressive programs in LLM and how diet influences these processes. Weight is an intersectional determinant of health inequities and leveraging diet to improve ICB efficacy may reduce cancer health disparities.

Project Coordinator:
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Project Partners:
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MAppinG adaptatioN Of tripLe negative breast cancer microenvironments to ImmunotherApy (MAGNOLIA)

Presented by John Stagg
Centre Hospitalier de l'Université de Montréal
Canada

Triple negative breast cancer (TNBC) accounts for 15-20% of all breast cancers with over 200,000 cases each year. TNBC has the worst outcome with few treatments available. Despite important progress and recent approval of immunotherapy for TNBC, clinical benefits remain modest and restricted to a subset of patients. Notably, there is currently no reliable means to tell if a patient with TNBC will benefit or not from immunotherapy.

To address this, we will perform multi-omics analysis of primary and metastatic TNBC lesions obtained from 2 randomized phase II clinical trials headed by our consortium: i) the GeparNuevo trial, investigating the addition of anti-PD-L1 to neoadjuvant chemotherapy in early TNBC; and ii) the SYNERGY trial, evaluating the combination of chemotherapy with anti-PD-L1 with or without an anti-CD73 mAb in previously untreated locally recurrent inoperable or metastatic TNBC.

Our objective is to define the adaptation of TNBC to immunotherapy with specific aims:

1) Identify features of TNBC tumors associated with response and resistance to immunotherapy by state-of-the-art profiling technologies (bulk tumor and single cell sequencing, spatial transcriptomics and proteomics)

2) Determine the impact of immunotherapy on the evolution of TNBC tumors through the profiling biopsies before and after treatment

3) Evaluate the predictive value of the discovered biomarkers by testing their association with clinical response

4) Develop preclinical TNBC models to functionally validate that targeting specific pathways discovered in aims 1) to 3), as well as identified putative targets by our consortium (i.e. CHI3L1, PAR-2, B7H4), synergize with anti-PD-1/L1.

Our project will allow clinicians to better identify TNBC patients with predicted benefit from immunotherapy, will validate therapeutic targets to enhance response to immunotherapy and will provide new strategies for next generation immunotherapies of TNBC.

Project Coordinator:
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Project Partners:
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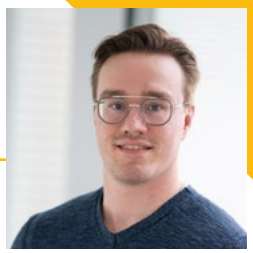
Morag Park, Goodman Cancer Institute, McGill University, Canada
Evelyne Meyer, University of Ghent, Belgium

INTRAPERITONEAL IMMUNE MODULATION FOR COLORECTAL PERITONEAL METASTASES (PERIMMUNE)

Presented by Jesse Demuytere
Ghent University
Belgium



Background and rationale: More effective therapies for peritoneal metastases (PM) from colorectal cancer (CRC) are urgently needed. Only a minority of patients respond to immune checkpoint inhibitors (ICIs). Modulation of the tumor immune microenvironment by intraperitoneal (IP) administration of immune modulators such as agonists of the toll like receptors (TLRs) may elicit responsiveness to ICIs.
Hypothesis and Aims: We hypothesize that in situ immune modulation using IP administration of TLR agonists using nanoparticle (NP) formulations may be an effective treatment of colorectal PM, either as a single agent or in combination with ICIs. We aim to characterize the immune contexture of PM, to develop NPs for TLR agonists, and to analyse toxicity, biodistribution, and anticancer efficacy of the selected NPs.
Methods: WP1. Immunogenomic characterization of human colorectal PM: we will interrogate the immune TME in clinical samples using advanced platforms including single cell RNAseq and spatial transcriptomics. WP2. Establishment of relevant mouse models WP3. Design of polymeric and oily core NPs: we will synthesize and completely characterize NPs of selected TLR 7/8 agonists and OX. WP4. Pharmacokinetics, toxicity, and biodistribution of NPs: using IFN-ß reporter mice, we will analyse downstream signaling after IP delivery of TLR agonists. Toxicity and biodistribution will be tested in syngeneic mouse models. WP5. Immunogenicity and anticancer efficacy of NPs after IP delivery: the immunogenicity and anticancer efficacy of different combinations of OX based NPs, TLR agonist based NPs, and systemic ICIs will be tested along with the modulating role of the gut microbiome. WP6. Toxicity and PK/PD in a large animal model: the selected formulation(s) will be tested in a mini pig model. WP7. Project Coordination
Expected results and potential impact: This project will pave the way for IP immune modulation in patients with colorectal PM.

Project Coordinator:
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Kjersti Flatmark, Oslo University Hospital, Norway
Giovanna Lollo, Université Claude Bernard Lyon 1, France
Tugba Suzek, Mugla University, Türkiye

Profiling and functional analysis of the Immune environment of eXtramedullary leukemia rELapses (PIXEL)

Presented by Luca Aldo Edoardo Vago
IRCCS Ospedale San Raffaele
Italy

Disease recurrence after allogeneic hematopoietic cell transplantation (allo-HCT) is frequently driven by failure of the donor immune system at controlling the outgrowth of residual cancer cells. Intriguingly, acute myeloid leukemia (AML) relapses after allo-HCT often occur in extramedullary (EM) sites, suggesting a causative link between altered tissue homing and immune escape, and exemplifying how the microenvironment can impact on the efficacy of adoptive immunotherapy. In the present project, a transnational consortium will investigate the mechanisms driving EM AML relapses, leveraging on the key positioning of the six partners in national networks to accrue a sizable cohort of cases, and taking advantage of their consolidated and complementary expertise in the use of cutting-edge methodologies to study primary patient samples.
In particular, we will combine the latest omic technologies to "pixelize" EM relapses into their finest details, and then reconstruct and validate their driver processes through advanced ex vivo functional assays and in vivo animal modeling. We will investigate whether the escape mechanisms described in the bone marrow have a role also in EM sites, if the pathological kinase signaling that is characteristic of EM AML affects the immune microenvironment, and how oxidative stress and lactic acid metabolism come into play in this relapse modality. Availability of samples collected longitudinally in time will provide the unique controls represented by the same tumor in its microenvironment of origin and before exposure to the immune selective pressure of allo-HCT, allowing to identify features that are unique to EM post-transplantation relapses, and to functionally validate their causative role.
The Ultimate goal of the project will be to understand which of the distinctive features of EM relapses is necessary for their emergence and maintenance, and could thus represent a vulnerability to be exploited for targeted therapeutic approaches.

Project Coordinator:
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Defining Predictive Immunedeterminants of response to neoadjuvant Chemoradiation in Oesophageal adenocarcinoma (PREDICO)

Presented by Giuseppina Arbore
Vita-Salute San Raffaele University
Italy

Background and rationale: Esophageal adenocarcinoma (EAC) has aggressive locoregional spread with median overall survival =1 year. EAC patients undergo neoadjuvant chemotherapy or chemo-radiotherapy (NAC/R) and surgery. Only about 20% of treated patients achieve a pathological complete response (pCR) with down staging of tumor and/or lymph nodes (LNs), and significantly increased 5-year survival compared to non-responders. However, there are no predictors of response to NAC/R directing the appropriate treatment selection for each patient. This prompts the definition of the mechanisms of response to NAC/R, to improve the stratification of patients and inform the design of more precise therapies that can increase the response rate.
Hypothesis: We hypothesize that pCR achieved in EAC patients upon NAC/R may result from pre-existing immunoreactive tumor microenvironment (TME) leading to stimulation of tumor-specific T cell responses, contributing to cancer elimination and long-term response, implying that NAC/R is an indirect immunotherapy approach.
Aims: Our preliminary results, obtained on treatment-naïve EAC biopsies, identified multidimensional signatures strongly supporting a pre-existing immunoreactive TME in the responders. We will confirm and extend the signatures predicting the response to NAC/R, by profiling new cohorts of treatment-naïve EAC biopsies.
Methods: We will integrate: 1. Genomic signatures derived by WES and RNA-seq with 2. Spatially resolved definition of their immune landscape and metabolic pathways by tissue transcriptomics, proteomics and metabolomics, and 3. Correlate those with the regression of the tumor and LNs obtained after NAC/R.
Expected results and potential impact: We expect to define 1. Immunological mechanisms of EAC response to NAC/R; 2. Potential multivariable immune markers of response to NAC/R that better stratify patients; 3. New molecular pathways that may be harnessed to improve the therapeutic responses of EAC patients.

Project Coordinator:
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Project Partners:
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New immunotherapies targeting the key purinergic checkpoints in the tumor microenvironment (Pur-Ther)

Presented by Elena Adinolfi
University of Ferrara
Italy

Immunotherapy is based on the concept that we should re-activate the physiological anti-tumor immune response rather than kill tumour cells with chemotherapy. This efficient therapeutical strategy is based on the blockade of molecules called Immune checkpoints and has revolutionized current oncological treatments. However, immunotherapy has drawbacks since it often activates immune-mediated aggression of healthy tissues or tumors become refractory. Therefore, novel pathways modulating the anti-tumor immune response without side effects needs to be identified. Tumors are rich in ATP, a molecule playing several roles, including stimulation of immune cells, promotion of tumor proliferation and generation of an immunosuppressant named adenosine. We have developed original techniques to measure ATP in tumors and verify how its concentration changes in response to therapy. We also developed highly innovative small antibodies named nanobodies raised against molecules interacting with ATP inside tumors called “purinergic checkpoints”. We plan to verify whether this weaponry of highly innovative reagents will improve the therapy of three tumors selected for their resistance to immunotherapy: lung adenocarcinoma, glioblastoma multiforme, and multiple myeloma. We will test the effect on the growth of experimental tumors of nanobodies highly selective for the purinergic checkpoints. In addition, we will explore the impact of the combined administration of purinergic checkpoints and immune checkpoints. Finally, with this project, we plan to set the basis for first-in-man experimentation to verify the efficacy of the combined administration of immune checkpoint blockers together with selected purinergic checkpoint inhibitors.
We are confident that our efforts will pave the way to the definition of novel and effective anti-cancer therapeutic protocols.

Project Coordinator:
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Project Partners:
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Sahil Adriouch, University of Rouen Normandy, France
Peter Bannas, University Medical Center Hamburg-Eppendorf, Germany

Reverting immune suppression to elicit brain metastasis control (RISEBrain)

Presented by Medyouf Hind
RWTH Aachen University Hospital
Germany

Treatment strategies against brain metastases (BrM) do not alter disease course leading to 2-year overall survival below 10%. Emerging protocols that are effective against disseminated cancer are leading to a paradoxical increase in brain relapse. Thus, BrM represents a growing societal challenge as it often becomes the most relevant clinical entity in patients with an otherwise controlled systemic disease. In the brain, immune checkpoint blockade (ICB) may not be sufficient to overcome the hurdles associated with an established immune suppressive tumor microenvironment (TME), as reflected by the limited benefits on symptomatic metastases, likely due to reduced abundance of T cells and penetration of therapeutic antibodies compared to other organs. We hypothesize that lifting immune suppression locally is a pre-requisite to achieve full benefit of immunotherapies in BrM.
Aim 1: Define, in a holistic approach, TME candidates that govern local immunosuppression and/or resistance to ICB in BrM by applying RNAseq (single cell and bulk) and spatially resolved multispectral imaging to clinical cohorts of human BrM, including patients treated with ICB.
Aim 2: Take advantage of a Phase II trial using a STAT3 inhibitor in patients with BrM, as well as preclinical models and patient-derived organotypic cultures (METPlatform), to explore the functional and molecular consequences of targeting STAT3 and/or other recently identified candidates on (1) BrM progression and (2) resistance to ICB. This will be complemented by longitudinal biomarkers tracking in liquid biopsies using next generation biosensors, with the objective to integrate them in a portable point-of-care tool kit.
Aim 3: Delineate the broader impact of immunotherapies in human BrM, predict new determinants of local immunosuppression and anticipate resistance mechanisms that will be explored in rationally designed pre-clinical studies, by leveraging the data sets generated in Aim1 and 2.

Project Coordinator:
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Co-Coordinator:
Hind Medyouf, Institute for Tumor Biology and Experimental Therapy, Germany

Project Partners:
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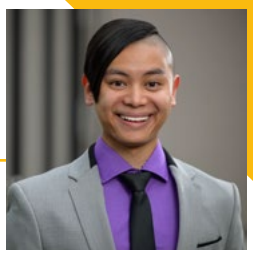
Serap Aksu, Koç University, Türkiye
Marc Schmitz, National Center for Tumor Diseases, Germany

Reprogramming of the tumor microenvironment with modular engineered CAR-T cells to augment the efficacy of immunotherapy (SmartCAR-T)

Presented by Maik Luu
Universitätsklinikum Würzburg
Germany



Background & Hypothesis: We are pursuing the development of cancer immunotherapy with T cells expressing synthetic Chimeric Antigen Receptors (CARs). CAR-T cells are poorly prepared to withstand the physical and immunological barriers in the hostile tumor microenvironment (TME). Principal TME components that diminish CAR-T cell function include stromal fibroblasts and regulatory immune cells. We hypothesize that CAR- T cells can be instructed by advanced gene-engineering to remove (seek & destroy) or modify (seek & modulate) negative TME influences, thereby 'paving their own way' for delivering antitumor efficacy.
Specific Aims: Aim 1. To determine key components in the TME of multiple myeloma (MM) and small cell lung cancer (SCLC) as exemplary hematologic and solid tumors. Aim 2. To develop SmartCAR-Ts which destroy or modulate the TME in MM and SCLC. Aim 3. To determine the gain in antitumor function of SmartCAR-T cells and extrapolate insights to other tumor entities.
Methods: We will perform systematic multi-omics analyses on MM aspirates and SCLC biopsies to describe TME state and dynamics, high-content imaging to comprehend TME composition, spatial organization and super-resolution microscopy to quantify TME biomarkers. We have established a CAR pipeline for MM and SCLC, as well as engineering approaches to destroy negative components in the TME and to modulate them beneficially.
Expected Results & Impact: We anticipate that SmartCAR-T cells will confer more potent and durable antitumor reactivity. We will deliver a platform that can be rapidly adjusted to other tumor types. The TME-response functions are integrated into SmartCAR-T cells as a 'stand alone, single shot treatment' without the need for expensive combination therapy. This allows scalable economic production and broad patient access in a sustainable way for health care systems.

Project Coordinator:
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TArgeting acute myeloid Leukemia immunosuppressive microEnvironment by combined IDO1 inhibiTion and PD-1 blockadE (TALETE)

Presented by Antonio Curti
IRCCS Azienda Ospedaliero - Universitaria di Bologna
Italy

Background, rationale: Survival of Acute Myeloid Leukemia (AML) patients is poor. Immunotherapies have the potential to circumvent some of the mechanisms leading to treatment failure, but their exploitation against AML has been unsatisfactory due mainly to the incomplete understanding of the interactions between leukemia and immune cells in AML microenvironment. In that, the causative role of immunosuppressive bone marrow (BM) pathways, including overexpression of immune checkpoint (IC) receptors, such as PD-1 and tryptophan degradation via indoleamine 2,3-dioxygenase (IDO)1 is not fully elucidated.
Hypothesis: IDO-1-based microenvironment mechanisms of resistance hamper AML immunotherapy
Aims: 1. Decipher the composition of the BM microenvironment; 2. Unravel the contribution of the immune microenvironment in response to azacitidine and venetoclax; 3. Functionally validate ex-vivo data by in vitro modeling
Methods: BM samples will be collected from a cohort of AML patients receiving the combination of azactidine and venetoclax, which represents the backbone for innovative therapeutic strategies in AML through the addition of novel compounds, such as immunomodulatory drugs.
The project activities will be structured in 4 interconnected and integrated work packages:
WP1: Project management, ethics, dissemination, and training, capacity building activity.
WP2: Characterization of BM microenvironment: mass cytometry, single-cell RNA-seq, immunometabolism, and epigenetics (multi-omics).
WP3: Experimental in-vitro modeling to validate mechanisms of resistance
WP4: Methodology, Biostatistics, and Bioinformatics: integrated analysis of clinical and multi-omics data.
Expected results and potential impact: The expected discovery of microenvironment-based mechanisms of susceptibility to immunotherapies will affect clinical practice by improving patients' election. The expected development of a novel platform for BM microenvironment investigation will impact technology transfer by providing advanced diagnostic tools.

Project Coordinator:
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Giovanni, Martinelli, IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" (IRST), Italy

Artificial-intelligence-based end-to-end prediction of cancer immunotherapy response (TANGERINE)

Presented by Victor Raul Moreno Aguado
Bellvitge Biomedical Research Institute (IDIBELL)
Spain

Background: Cancer immunotherapy with immune checkpoint inhibitors (ICIs) is widely used in multiple cancer types, with proven benefits. However, response is not guaranteed, difficult to predict, and serious toxicity may occur. Predictive biomarkers for ICIs response exist, but only few of them are clinically used because they require tissue samples, are costly and increase turnaround time. Thus, there is an urgent clinical need to predict response to ICIs at patient's level.
Aims: TANGERINE partners have developed artificial intelligence (AI)-based histology image analysis and computed tomography (CT)-based radiomics for predicting immune features related to ICIs response. We propose to a) expand and combine them to develop and validate an end-to-end open AI tool to predict response and toxicity to ICIs; and b) identify cellular structures and image patterns associated with ICIs response that explain model predictions.
Methods: Digital images of tumour histopathology slides and CT scans will be retrieved, linked to clinical outcomes data and anonymized for analysis. An initial retrospective (2017-21) data retrieval from 1800 patients at 6 centres will continue with a prospective recruitment of 600 more to validate models. Patients that received ICIs as first line for any tumour will be included and response recorded according to iRECIST. Radiomics and deep convolutional neural networks will be used. Model explainability will use spatial transcriptomics data on a subset of 30 patients. At analysis, homogenous subgroups will be considered, as gender and ethnicity.
Expected results and potential impact: TANGERINE will provide a public-available, non-invasive, low-cost tool based on routinely available images and clinical data to accurately predict ICI response and toxicity. The explanatory module might identify new patients on which ICI may be beneficial. The transnational collaboration will provide patients with enough variability to build generalizable models.

Project Coordinator:
Victor Raul Moreno Aguado, Bellvitge Biomedical Research Institute (IDIBELL), Spain

Project Partners:
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Julien Calderaro, Henri-Mondor University Hospital, France
Gad Rennert, Technion & Carmel Medical Center, Israel
Raquel Perez-Lopez, Fundación Hospital Universitario Vall d'Hebron, Spain
Nicoleta Zenovia Antone, The Oncology Institute "Prof Dr. Ion Chiricuta", Romania

TargEting the Nectin fAmily to boost Cancer ImmuniTY (TENACITY)

Presented by Tobias Bald
University Hospital Bonn
Germany

Immune checkpoint Inhibitors (ICI) have demonstrated therapeutic efficacy in many cancer types, but only subgroups of patients have durable responses. One reason is the enormous complexity of interactions within the tumour microenvironment (TME). Identifying the underlying networks to develop complementary treatment strategies beyond existing ICIs is a central challenge for basic and clinical research. With this end in view, the nectin / nectin-like molecules are an emerging class of immune regulators within the TME. They interact with both T-cell-inhibitory (TIGIT/CD96/CD112R) and activating receptors (CD226). However, our understanding on the expression, spatial context, function and potential redundancy of nectin family members in the TME is in its infancy.
The TENACITY team seeks to (a) systematically map the expression landscape of nectin family members in the TME across different cancer types (b) assess their impact for the efficacy of ICIs and (c) develop single-variable domain nanobodies to target multiple nectin family members. In a concerted effort, we will determine the spatial context of nectin family members in tumor samples from fully annotated cohorts of patients with melanoma, head and neck squamous cell carcinoma, renal and lung cancer using cutting edge ultra-highplex immunofluorescence analyses (CODEX®). In addition, we will integrate transcriptomic and driver mutation landscapes to further elucidate the importance of nectin/nectin-like molecules for the efficacy of ICIs. Finally, we will generate novel diagnostic probes and potential biologicals using our nanobody platform. To enable the clinical development of potential lead candidates, we will determine the therapeutic efficacy of our nanobodies using patient-derived tumour organoids from aforementioned cancer types.
In TENACITY, we will shed light and untangle the complexity of nectin family members in cancer to enable evidenced-based combination immunotherapies and to develop innovative treatment approaches.

Project Coordinator:
Tobias Bald, University Hospital Bonn, Germany

Project Partners:
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Daniela Massi, University of Florence, Italy Mario Mandala, University of Perugia, Italy
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Targeting ROBOs and SLIT guidance cues in the immunosuppressive stromal context of pancreatic cancer (TRanSLIT)

Presented by Ilse Rooman
Vrije Universiteit Brussel
Belgium

Pancreatic ductal adenocarcinoma (PDAC) is a cancer of high unmet need with rising incidence and bleak overall 5-year survival rates below 10%. The tumour has a barrier of scar-like tissue that shields it from being attacked by the immune system. Therapies to target the shield as well as immunotherapy have so far been unsuccessful. Up to 30% of patients seem to have mutations in genes from the SLIT-ROBO pathway. This pathway operates in the nervous system but is also used by the vascular system to form new blood vessel for crosstalk with tumour cells, allowing them to metastasize. Recent studies also show that SLIT-ROBO impacts on the immune system. Hence, and building on substantial preliminary data, we hypothesize that SLIT-ROBO determines the spatial positioning of pancreatic tumour cells and their immunosuppressive environment, specifically in the most aggressive subtype of PDAC. This hypothesis will be pursued by a consortium of cancer biologists, computational biologists, a gastroenterologist, a pathologist and chemists. Underpinned by novel methods, we will define the landscape of different cell types that express different SLITs and ROBOs, and derive a 'spatial score' to be used as a biomarker that can predict response to a novel therapy. Smart experimental models with cells derived from patient tumours will provide insights into escape of immune-control and metastasis, and will be test platforms for compounds to therapeutically target the SLIT-ROBO system. For the latter, we envision a two-pronged drug development strategy to add-on to commonly used immunotherapeutic drugs effective in other cancers; We test existing drugs, approved for other conditions, and we generate a novel compound. We anticipate disruption of the tumour's internal organization that allows efficacious drug combinations with immunotherapy. Given the prevalent alterations in SLIT-ROBO, TRanSLIT can 'TRanSLaTE' into an innovative therapy for a substantial proportion of PDAC patients.

Project Coordinator:
Ilse Rooman, Vrije Universiteit Brussel, Belgium

Project Partners:
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Rémy Nicolle, INSERM, France
Luca Cardone, National Research Council (CNR), Italy
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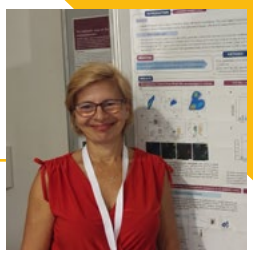
Circulating tumour microenvironment components as Urothelial Cancer Immunotherapy Response Predictors (UCIPredict)

Presented by Marta Dueñas
Consorcio Centro de Investigación Biomédica en RED M.P. (CIBER)
Spain



Background and rationale: Urothelial carcinoma (UC) is the 9th most common cancer worldwide. There are not reliable biomarkers to predict prognosis, therapy response or metastasis. Although liquid biopsy has emerged as a reliable tool for tumour surveillance, nothing has been done with the circulating components of the tumour microenvironment (TME). In this context, UCIPredict will develop an innovative and reliable urine and blood-based biomarker test for response prediction to immunotherapy (IT) and tumour recurrence, using non-invasive techniques measuring circulating biomarkers from tumour and TME.
Hypothesis and aims: Implementation of liquid biopsy biomarkers will improve diagnosis, prognosis and prediction of IT response in UC patients. The main objective of this project is to identify molecular and cellular signatures from urine and blood samples to develop a robust and reproducible laboratory tool for personalized therapy and IT response prediction in UC patients. We will 1) Identify potential molecular targets to guide IT treatments in UC, 2) Detect circulating tumour cells (CTCs) and tumour hybrid cells (THCs) in IT treated and metastatic patients and 3) Evaluate immunomodulation for IT outcome.
Methods: We will develop a multinational platform with a transversal study design using urine and blood samples from UC patients. We will employ high standing, high throughput technology, guided by standard operational procedures (SOPs) that will be validated by multinational laboratories.
Expected results and potential impact: UCIPredict will provide a non-invasive innovative tool for patient prognosis and IT response in UC. Its implementation on the clinical practice for IT response prediction would increase the rate of patient receiving the best clinical benefit. UCIPredict use will prevent treating nonresponding patients, which would not only avoid unnecessary suffering for many patients, but also a significant saving for healthcare systems.

Project Coordinator:
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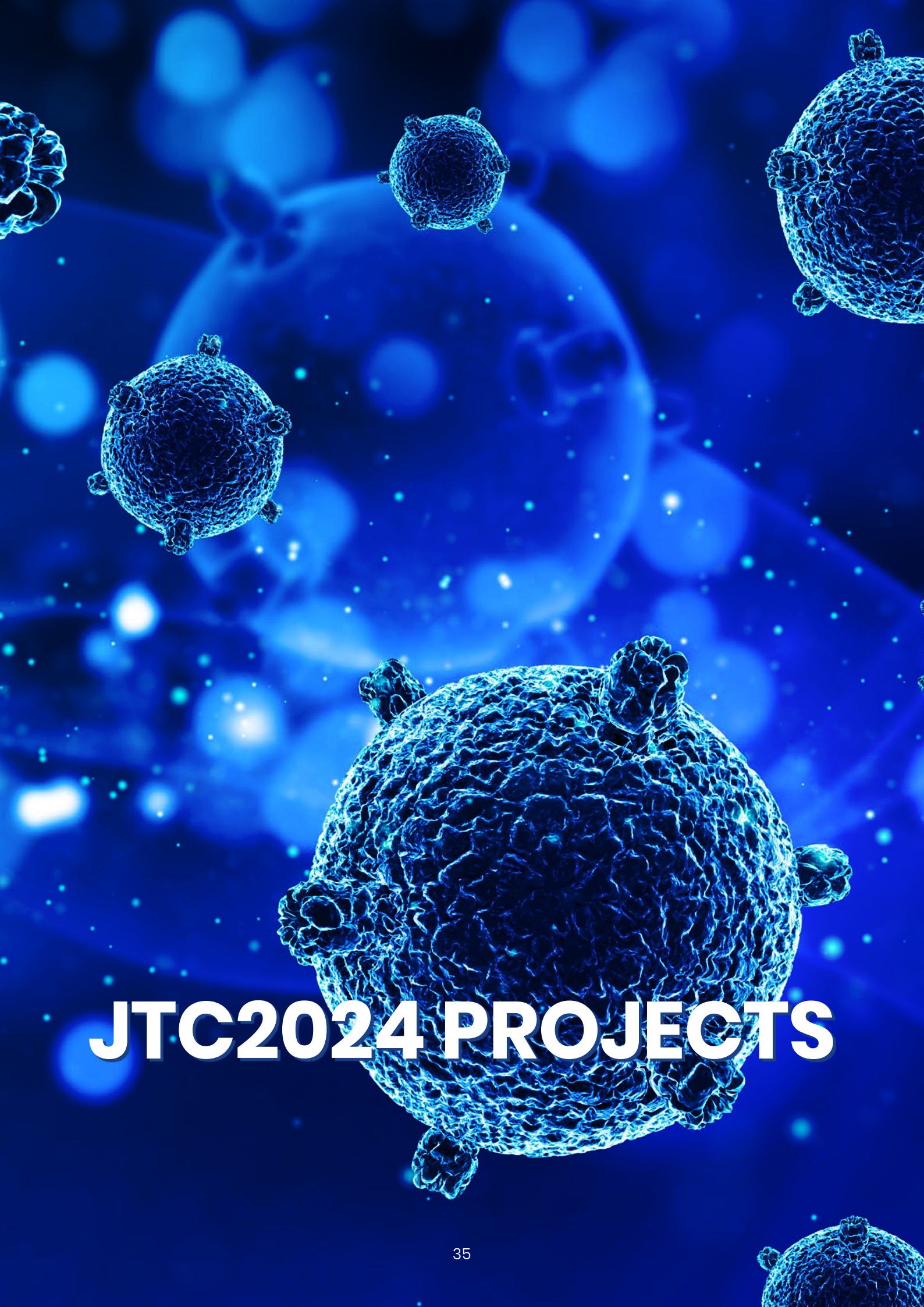

JTC2024 PROJECTS

FunctionAl preCision mediCinE pLatform for the trEatment of pancReATic cancEr (ACCELERATE)

Presented by Michela Cortesi
IRCCS, Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori"
Italy

BACKGROUND: Despite advances in understanding pancreatic cancer (PC), many patients do not benefit from standard therapies and experience significant toxicity. While combination therapies can improve outcomes, the large number of possible combinations and high testing costs make experimental screening impractical. Computational methods offer a strategy to accelerate the identification of effective drug combinations.
HYPOTHESIS: We hypothesise that deep learning approaches fine-tuned with patient-specific data can identify optimal drug combinations tailored to individual patients. Multiple precision medicine trials have highlighted challenges for patients lacking treatments designed for their specific mutations. Functional precision medicine (FPM) directly exposes patient-derived tumour cells to drugs, revealing tumour vulnerabilities not necessarily driven by genomic aberrations. We hypothesise that integrating FPM, including molecular tumour profiling, clinical data, and high-throughput drug sensitivity testing on patient-derived organoids (PDOs), will uncover new treatment options for PC and other tumours with limited therapeutic choices.
AIMS: 1. Develop an FPM platform for PC integrating in vitro drug testing, omics, and clinical data to match patients with effective therapies and provide real-time treatment recommendations. 2. Identify therapy response/resistance biomarkers. 3. Identify resistance mechanisms.
METHODS: Using a panel of FDA-approved drugs, single-drug responses will be assessed in each PDO. A deep learning model, pre-trained on large-scale drug synergy datasets, will then be fine-tuned using patient-specific molecular data to predict personalised drug combination synergies. Prioritized combinations will be tested in matched PDOs, and the top-scoring combinations will be validated in patient-derived xenograft (PDX) models. Finally, FPM and molecular characterization data will be integrated with patient-specific clinical data to generate a therapy decision-support report.
EXPECTED RESULTS AND IMPACT: We expect to build a platform for PC combinatorial drug testing, integrating patient specific clinical, genomic and transcriptomic data with FPM results. Potential clinical impact: i) to return treatment recommendations in real time to the physician in a clinically exploitable timeframe ii) to identify more effective treatment options for PC patients iii) to provide a proof-of-concept platform for clinical study design.

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Building an ex vivo complex tumour microenvironment platform for development of combination therapies and drug resistance studies in head neck cancer (BePrepared)

Presented by Ingeborg Tinhofer-Keilholz
Charité – Universitätsmedizin Berlin
Germany

Head and neck squamous cell carcinoma (HNSCC) is among the ten most common cancers worldwide. Despite aggressive multimodal treatment, survival has improved little over recent decades, and recurrence rates remain high (40-60%). Approved molecular therapies are limited, particularly for recurrent disease, and are often used without biomarker guidance. Improved preclinical models are therefore needed to support the development of more effective combination therapies. Current models, including tumour cell lines, xenografts, and patient-derived organoids (PDOs), lack key components of the human tumour microenvironment (TME), such as immune and stromal cells, which can influence treatment response. We hypothesise that incorporating human TME components into PDOs will improve their utility for developing novel combination therapies and identifying biomarkers to guide treatment selection.

Our objectives are: (1) Complexify PDOs with TME components; (2) Screen standard treatments, novel drug combinations, and radiotherapy-drug combinations in clinical development to identify the impact of the TME on tumour cell killing; (3) Elucidate resistance mechanisms and identify novel targets for combination therapies and biomarkers for patient selection.

This project leverages the consortium's expertise in patient-derived xenograft (PDX) and PDO models, multi-omics tumour profiling, biomarker development, and drug/radiosensitivity screening. We will use PDOs derived from fresh patient specimens and established PDO/PDX models. PDOs will be complexed with HLA-matched allogeneic or autologous TME components using standard approaches or innovative bioprinting. Models will be refined to mimic treatment-resistant conditions, including hypoxia and altered glucose metabolism. Multiparametric fluorescence imaging will assess treatment efficacy and TME effects on tumour cell killing. Single-cell RNA sequencing, spatial transcriptomics, and proteomics will be used to elucidate resistance mechanisms and identify biomarkers.

Through our collaborative partnership and expertise in HNSCC clinical trials, promising findings can be translated into future studies of candidate combination therapies, with significant medical and socioeconomic benefits for recurrent HNSCC.

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Development Of Patient-derived organoid PLatforms for Evading Resistances in Lung Cancer (DOPPLER-LC)

Presented by Antonio Maraver
Institut national de la santé et de la recherche médicale (INSERM), Montpellier
France

Background: Lung cancer remains the leading cause of cancer-related death globally. Despite advancements in targeted therapies for oncogene drivers like EGFR and KRAS mutations, both intrinsic and acquired resistance ultimately limit their effectiveness. While in vitro studies using 2D cultures have identified resistance mechanisms, they do not adequately reflect the complexity of the tumour microenvironment (TME) and 3D tumour structure seen in vivo.
Hypothesis and Aims: A collection of patient-derived xenografts (PDX) from lung cancer allowed our consortium to publish seminal studies on FGFR, Notch and Farnesyltransferase pathways in EGFR-driven lung cancer resistance. Two breakthroughs enable us to further mimic the human disease: 1. Development of PDX models resistant to targeted therapy; 2. Development of patient-derived organoids (PDXDO), allowing us to study intrinsic and acquired resistance at high scale. DOPPLER-LC aims to standardize PDXDO protocols across the consortium, improve reproducibility and establish platforms for testing therapies targeting resistance. mRNA switching technology provides a novel approach to overcome resistance by controlling mRNA translation in resistant cancer cells.
Methods: 1. Development of PDX models representing clinically significant MET, RET, ALK, ROS, and BRAF alterations; 2. Generation of PDXDO from these PDX models; 3. Comparative OMICs analysis of resistant and parental PDXs to identify resistance biomarkers and therapy-evasion pathways; 4. Testing available drugs to target resistant signatures identified through OMICs in PDXDOs and confirmation of our best strategies in PDXs; 5. Evaluation of mRNA switching technology in PDXDOs as a potential approach to overcome treatment resistance.
Expected Results and Impact: This project will improve our understanding of intrinsic and acquired resistance, enabling the identification of predictive biomarkers and novel therapeutic strategies. By improving therapeutic targeting, it has the potential to enhance progression-free and overall survival and support the development of innovative clinical trials within our network. DOPPLER-LC consortium aims to push the boundaries of precision oncology, offering new opportunities to address resistance and improve survival of lung cancer patients.

Project Coordinator:
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Targeting tumor heterogeneity in pediatric high-grade gliomas (GLIO-COMBO)

Presented by Eddy Pasquier
Centre National de la Recherche Scientifique (CNRS)
France

Background: Pediatric high-grade gliomas (pHGGs) account for 10% of childhood brain tumours but over 40% of brain cancer-related deaths in children. Although molecular profiling has identified distinct genetic drivers and enabled patient stratification, first-line treatment remains intensive cranial irradiation, which is largely palliative, with fewer than 10% of patients surviving two years post-diagnosis. There is an urgent need to address therapeutic resistance and develop models that support the rational design of novel combination therapies.
Hypothesis: Tumour heterogeneity directly contributes to therapeutic resistance of pHGGs and its targeting via biology-guided combinatory treatments may enable long-term disease control.
Aims: (i) Defining how tumour heterogeneity contributes to treatment resistance using innovative in vitro models of pHGG; (ii) Developing optimal treatment associations using combination screening; (iii) Evaluating the therapeutic potential of these novel combinatorial treatments using multiple clinically-relevant and complementary models of pHGG.
Methods: Robust patient-derived pHGGs models established by members of our consortium will be used to characterize inter- and intra-tumour heterogeneity of pHGGs by single-cell RNA sequencing before and after treatment. Two therapy types will be studied: standard of care (radiotherapy and chemotherapy) and small molecules in clinical development for the treatment of pHGG (e.g. ONC201). Large-scale analysis will be used to identify key pathways activated in treatment persistent cells and guide the design of a drug library targeting these pathways. This library will be screened alone and in combination with standard of care or small molecules in pHGG patient-derived neurospheres to reveal potent combinatorial treatments, which will then be evaluated in models incorporating the microenvironment at different scales.
Expected results & impact: Our project will reveal the extent of inter- and intra-tumoral heterogeneity in pHGGs and its contribution to treatment resistance. It will also molecularly dissect escape mechanisms, thus unveiling targetable vulnerabilities that can be therapeutically leveraged. Our biology-guided drug combination screen may identify potent combinatory treatments for specific molecular subtypes of pHGGs, thus ethically and effectively contributing to the improvement of precision medicine algorithms for paediatric brain tumours.

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Project Partners:
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Human avatar on chip for advancing personalized cancer therapies by integrating vascular and immune components in a Tumor-on-Chip model (HAVOC)

Presented by Peter Loskill
Eberhard Karls University Tübingen
Germany

Background: Despite advances in breast cancer therapies, certain tumours remain lethal due to their evasion of immune system attacks. This immune evasion is strongly influenced by the tumour microenvironment (TME), which includes tumour endothelial cells (TECs), immune cells, cancer-associated fibroblasts (CAFs), and the extracellular matrix (ECM). TECs exhibit abnormal phenotypes that promote tumour progression and metastasis by increasing angiogenesis, remodelling the ECM, and modulating immune responses. This altered TEC environment impairs effective immune cell infiltration and challenges current therapeutic strategies.
Hypothesis: A microfluidic tumour-on-chip platform modeling the TME, particularly TEC interactions and immune cell dynamics, will allow pretesting and tailoring of immunotherapies.
Primary aim: Establish a human-relevant in vitro model of breast cancer, incorporating the TME and TECs, on a robust and scalable microfluidic tumour organ-on-chip (TrOoC) platform.
Secondary aims: Optimize a microfluidic platform for modelling the tumour-specific TME with patient-specific material, enabling high-throughput and -resolution interrogation of tumour-TME-immune cell interactions. We will conduct personalized testing of standard therapies and test the effects of therapeutic bispecifics in combination with existing therapies on-chip.
Methods: Adaptation of a tubeless microfluidic platform to host patient-derived tumour organoids, TECs, CAFs, and peripheral blood mononuclear cells. Optimization will use commercial and in-house derived cell lines, followed by integration of patient-derived cells. The TrOoC platform will support long-term culture and be characterized via immunofluorescence, multicolour flow cytometry, cytokine assays, and single-cell RNA sequencing. Personalized therapeutic testing will be conducted with bispecific antibodies, alone or combined with TME-modulating therapeutics.
Expected results and impact: We expect the TrOoC platform to recapitulate central aspects of the breast cancer TME, enabling detailed studies of tumour-immune interactions and TEC behaviour, and to provide a robust tool for preclinical testing of anti-cancer strategies focusing on perturbation of the TME. By enabling personalized testing, this technology could improve therapeutic strategies and patient outcomes in breast cancers. In the long run, the platform may be adapted to other tumour types, extending its value for personalized treatment selection.

Project Coordinator:
Laura de Rooij, CeMM Research Center for Molecular Medicine, Austria

Project Partners:
Stefan Krauss, Oslo University Hospital, Norway
Peter Loskill, University of Tübingen, Germany

Immune oncology Drug Discovery & Decision - Advanced ex Vivo Approach To Accelerate Response prediction for combined therapies in ovarian cancer (ioAVATAR)

Presented by Leticia Oliveira-Ferrer
University Medical Centre Hamburg-Eppendorf
Germany

Immune checkpoint inhibitors (ICI) have revolutionized the treatment of cancer, but their efficacy in ovarian cancer (OC) remains limited. However, the innate immune system, particularly tumour-associated macrophages (TAMs) and dendritic cells (DCs), represents a promising therapeutic target in the context of OC. TAMs build up the majority of cells in the tumour microenvironment (TME) and have the advantage over T cells of being quickly recruited into the tissue, not requiring antigen presentation for activation and having high plasticity.

Our preliminary data show that immunosuppressive (M2-like) macrophages and DCs are abundant in the OC tissue and ascites of patients, and that targeting different myeloid checkpoints significantly affects anti-OC phagocytosis, cytotoxicity and T cell activation. However, models recapitulating the complex cellular interactions in the TME of OC and enabling validation of combination immunotherapies are currently lacking. Therefore, our primary aim is to develop patient AVATARs, complex ex-vivo models that twins the pathophysiological escape mechanisms in OC patients using two approaches: fluidic organ-on-chip models and tissue slice cultures. We will test novel immune oncology (IO) drug combinations on TAMs and DCs in this model based on existing and own preliminary data, and also in combination with established T cell immunotherapies (IT). Additionally, assessment of baseline and post-treatment immune profiles based on flow cytometry, single cell/bulk RNAseq, in situ multi-immunofluorescence and spatial transcriptomics will be performed on selected samples and IO drug combinations. Using these OMICs data and bioinformatics, we will comprehensively investigate the effects of combined myeloid T cell IO drug strategies on the tumour-immune cell interactions in our ioAVATARs.

The overall goal of ioAVATAR is to establish a reliable ex-vivo model to identify and validate combination therapies that generate effective and sustained anti-OC immunity, with a particular focus on TAMs and DCs. Long term goals are to translate the most promising IO drug combinations into the clinic and develop a patient avatar model that can be used in the clinic for personalized response prediction. By using antibodies that are already implemented in clinical trials, we expect that translation into the clinic is feasible.

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Subtype-specific Lung Cancer Organoids based on artificial ECM for Precision Oncology: Closing the Gap Between Preclinical Models and Patient Care (LUNGOIDS)

Presented by Judith Guasch
Institute of Materials Science of Barcelona (ICMAB-CSIC)
Spain

Background: Lung cancer, with a 5-year survival rate below 20%, is the leading cause of cancer-related mortality globally. Non-small cell lung cancers (NSCLCs) account for most cases, with adenocarcinoma (ADC) and squamous cell carcinoma (SCC) being the two main histological phenotypes. Current therapies are limited by poor clinical responses and drug resistance. A thorough understanding of its tumour microenvironment (TME), which plays a pivotal role in disease progression and treatment efficacy, is considered key to addressing these challenges.
Hypothesis: Patient-derived preclinical models reflecting key characteristics of NSCLC ADC and SCC subtypes will better replicate patient tumour behaviour and responses than existing models.
Aims: Develop an advanced human-based NSCLC patient-derived tumour organoids (PDTO) platform reflecting the unique tumour biology of ADC and SCC subtypes. Specifically: 1) design and synthesize biohybrid hydrogels-based artificial extracellular matrix (ECMs) capable of mimicking the physicochemical properties of human NSCLC tissues, assisted by computational tools; 2) develop and characterise ADC and SCC subtype-specific PDTOs within the tailored ECMs, incorporating immune and stromal elements, to study how the TME influences cancer progression; 3) assess functionality of PDTOs as a testing platform using a novel radio- and immunotherapy combination.
Methods: We will integrate synthetic chemistry techniques with cell biology methods, assisted by computational tools (digital pathology and molecular modelling) to develop subtype-specific human-based NSCLC PDTOs. These models will be characterised and compared to parental tumours and gold-standard alternatives, through a multi-technique approach with last generation omics. Functionality of the PDTOs as a platform to test combination therapies, consisting of radio-enhancing nanoparticles and immune checkpoint inhibitors, will also be validated.
Expected results and impact: The project aims to deliver a cutting-edge NSCLC PDTO platform that captures the tumour complexity of the ADC and SCC subtypes. By integrating subtype-specific human-based ECMs, together with specific immune and stromal components, we aim at offering a robust model to assess novel combination therapies and improve personalised treatments for NSCLC patients, ultimately improving patients' outcomes.

Project Coordinator:
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Project Partners:
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Tackling resistance to immunotherapy in advanced melanomas through the inhibition of oncomiRs by Locked Nucleic Acids (MELANOLOCK)

Presented by Luigi Fattore
IRCCS Regina Elena National Cancer Institute
Italy

Immunotherapy with Immune Checkpoint Inhibitors (ICIs) has become the frontline therapy for patients with metastatic melanoma, independent of BRAF-mutational status. Despite its clinical efficacy, 40–60% of patients do not achieve significant therapeutic response, and a substantial proportion of responders relapse within 2 years. Reprogramming of the tumour immune microenvironment (TIME) towards an immunosuppressive phenotype has emerged as a major determinant of resistance to ICIs. Strategies aimed at reprogramming TIME may help tackle both innate and acquired immune resistance. Over the last few years, microRNAs (miRNAs) have emerged as orchestrators of therapy resistance in melanoma. In this project, we plan to apply a Locked Nucleic Acid (LNA)-based strategy targeting specific miRNAs involved in shaping TIME towards an immune-evasive phenotype and demonstrate their therapeutic efficacy in innovative pre-clinical models. This approach aims to tackle resistance to ICI immunotherapy in advanced melanoma. The miRNAs targeted in this project were recently identified by miRNA-seq profiling of serum samples from melanoma patients before starting ICI therapy, revealing a subset of 19 oncogenic miRNAs (oncomiRs) highly up-regulated in non-responders.
Starting from these data, 4 oncomiRs were selected based on i) higher levels of deregulation and ii) association with melanoma patients' prognosis based on TCGA data. Moreover, digital PCR (dPCR) performed on RNAs extracted from extracellular vesicles (EVs) from melanoma cells confirmed the presence of these oncomiRs, suggesting their role in TIME shaping. Our hypothesis is that these circulating miRNAs are released by melanoma cells and regulate post-transcriptional mechanisms responsible for shaping an immune-evasive TIME. Preliminary results revealed that these miRNAs govern pathways including i) the CXCR3-CXCL9/CXCL10 axis, which regulates the recruitment and positioning of effector T cells within the TIME, and ii) GZMB and PRF1 expression, crucial for the cytotoxic activity of CD8 T lymphocytes (CTLs). More recently, we demonstrated that inhibition of one of these four miRNAs by LNAs increases CXCL9 release from human macrophages. In turn, conditioned media (CM) from LNA-treated macrophages better attract T lymphocytes than CM from macrophages treated with control LNAs. Based on these preliminary results, this project aims to target these oncomiRs using LNAs to potentiate immunotherapy in advanced melanoma, using different immunocompetent preclinical models, namely 3D organotypic and humanized PDX models.

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Metabolism/Metagenomics-based strategies for sensitization to Radio- and Immuno- therapy Combinations (METRICs)

Presented by Mohamed Elgendy
University Hospital Dresden
Germany

Despite the expanding interest in immunotherapy (IMT), only a minority of patients experience substantial benefits, highlighting the need for predictive biomarkers and combinatorial strategies. Radiotherapy (RT) may exert synergistic effects by priming the tumour microenvironment (TME), but may trigger both immunostimulatory and immunosuppressive pathways. Thus, optimal integration of RT and IMT requires understanding RT-induced immunological changes in the TME, identifying synergistic and predictive strategies, and establishing effective RT schedules.

METRICs aims to unravel determinants of response to IMT and IMT/RT combinations related to the host (gut microbiome and systemic metabolic landscape) and tumour metabolic profile, and test metabolism/microbiome-based strategies to enhance RT-IMT combinations. We hypothesize that these factors may serve as predictive biomarkers and targets for interventions. Supporting this, our preliminary data implicate the host metabolome and cancer cell-specific metabolic programs in determining the response to T cell-based immunotherapies.

Gut microbiota metagenomic and plasma metabolic analyses of samples from patients at different time points after CAR T cell infusion, as well as tumour and bone marrow biopsies, revealed abundance of Akkermansia muciniphila in the gut micorobiome and decreased indole metabolic pathway in responding patients. In a mouse model of high-grade B cell lymphoma, combined CAR T cell treatment and Akkermansia spp. supplementation improved tumour control and survival.

We will collect tumour and sequential blood and stool samples from 400 cancer patients across 3 centres (161 already biobanked), treated with IMT-RT combinations or, as comparators, other IMT combinations +/- chemotherapy and single-agent IMT or RT. Metabolomics and metagenomics will identify perturbations associated with response. Strategies to sensitize to the combination will be validated in various models, while different RT regimens will be tested to optimize the combination. Finally, we will dissect the impact of cancer cell metabolic profiles on response. Thus, METRICs progresses from clinical observations and multi-omics analyses to preclinical validation and strategies ready for clinical testing.

Project Coordinator:
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Search for combinational therapy to target clonal haematopoiesis in solid malignancies (SARAH)

Presented by Cyrus Khandanpour
University Hospital of Schleswig-Holstein
and University of Lübeck
Germany

Background: Clonal haematopoiesis of indeterminate potential (CHIP) is frequently observed in older individuals, where hematopoietic stem cells acquire mutations in genes like TET2 or JAK2, leading to epigenetic dysregulation or persistent JAK/STAT signalling, respectively. These mutations drive clonal expansion of lymphoid and myeloid cells without overt hematologic malignancy. Preliminary data suggest that, likely through deregulated inflammatory signalling, CHIP promotes the development and progression of solid tumours, including NSCLC and pancreatic carcinoma. However, the underlying mechanisms remain unknown. This proposal aims to elucidate CHIP's role in tumorigenesis and develop CHIP-targeted therapies.
Hypothesis: CHIP mutations, particularly TET2 and JAK2, create a pro-inflammatory environment by increasing cytokines like IL-6, IL-1β, and TNF-α. This chronic inflammation promotes tumorigenesis, enhancing cancer cell proliferation, survival, angiogenesis, and metastasis. CHIP also alters immune surveillance, leading to immune exhaustion and reduced checkpoint inhibitors efficacy. We hypothesize that targeting CHIP-associated inflammation and immune dysregulation can directly affect cancer cells and improve therapy outcomes by interfering with JAK2, LSD1 and its associated transcription factor GFI1, key regulators of pro-inflammatory processes.
Aims: 1. Demonstrate targeting CHIP-related immune alterations improves therapy outcomes; 2. Investigate how CHIP-associated immune cells alter cancer cell physiology using animal models and patient samples; 3. Identify drugs targeting CHIP-induced inflammation that synergize with anti-cancer treatments, focusing on LSD1 and JAK2 inhibitors.
Methods: We will study macrophages, T cells, and neutrophils, using murine models, ex vivo systems, and primary patient samples. Complementary screening approaches will test the efficacy of LSD1 and JAK2 inhibitors, alone or combined with other drugs, to enhance established therapies by targeting CHIP-driven inflammation.
Expected Results and Impact: We will model CHIP in mice and human cell systems to clarify its role in cancer progression and therapy response. We anticipate that LSD1 or JAK2 inhibitors combined with anti-tumor treatments can improve outcomes in NSCLC and pancreatic carcinoma patients, who currently have poor prognosis.

Project Coordinator:
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Intraoperative tumour sequencing for personalized loco-regional drug combination therapy against glioblastoma recurrences (SeqPerGlio)

Presented by Mario Chiariello
Istituto per lo Studio, la Prevenzione
e la Rete Oncologica (ISPRO)
Italy

Background: Glioblastoma (GB) is the most common malignant primary brain tumour and remains largely incurable, with a median survival of 14 months and 5-year survival of 6.9%. Standard-of-care combines surgical resection, radiation and temozolomide (TMZ) chemotherapy. However, diffuse invasiveness precludes complete resection, genetic heterogeneity drives chemo- and radio-resistance and the blood brain barrier (BBB) limits drug penetration. Thus, novel approaches are needed to eliminate infiltrating cells remaining after primary tumour resection.
Hypothesis: We hypothesize that "personalised" drug combinations can counteract intratumor heterogeneity through local delivery at the tumour site using biocompatible drug-loaded gels.
Aims: Assess feasibility of overcoming intratumor heterogeneity and BBB-imposed limitations on intracranial drug accumulation, using patient-derived in vitro and in vivo models recapitulating GB genetic and anatomic complexity. Preoperative biopsy limitations will be overcome by ultrafast nanopore sequencing-based tumour profiling during surgery, enabling identification of patient-specific targets and targeted drug combinations for local delivery by biocompatible thermogels.
Methods: We will develop ultrafast tumour profiling by nanopore sequencing and assess tumour-tailored drug combinations in patient-derived organoids and explants, evaluating proliferation, apoptosis and invasion. Therapeutic gels carrying these drug combinations will then be assessed in vivo by resecting patient-derived orthotopic GB and filling the resulting cavity with the gel. Recurrences will be followed-up by in vivo imaging and Kaplan-Meier survival analysis. Based on preclinical results, we will evaluate a dose escalation, phase 1a clinical trial of safety, tolerability and clinical activity of biocompatible gels containing selected targeted drugs.
Expected results and impact: Our approach addresses two major causes of GB recurrence: tumour heterogeneity-driven drug resistance and limited drug delivery across the BBB. Local delivery of tumour-tailored drug combinations during surgery may enable personalised control of GB recurrence with low systemic toxicity. This 3-year project will establish preclinical efficacy and evaluate the approach in a proof-of-concept phase 1a trial for recurrent GB.

Project Coordinator:
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Novel Cancer Therapy: Inducing Double-strand DNA Breaks to Foster Tumour Cell Death, Antigenicity and Immunotherapy Response in New Personalized Models (TITAN)

Presented by Jesús María Bañales
Biogipuzkoa Health Research Institute (BHRI)
Spain

Background: Cancer remains leading cause of mortality worldwide, with 10 million deaths in 2022 and projected 77% increase in new cases by 2050. Platinum (Pt)-based chemotherapeutics are fundamental for treating solid cancers, but resistance develops in up to 70% of patients, limiting their effectiveness. Current Pt-based drugs, like Cisplatin (CisPt), primarily cause single-strand DNA breaks, enabling cancer cells to activate DNA repair mechanisms and develop resistance.
Hypothesis: We hypothesize that novel chemotherapeutic agents inducing high-frequency double-strand DNA breaks can overcome DNA repair-mediated resistance, enhancing cancer cell death and tumour immunogenicity and potentially improving immunotherapy efficacy. Recent collaboration between BHRI and UPV/EHU groups led to the design, synthesis, and patenting (PCT/EP2023/083500) of "Aurkine", a novel family of chemotherapeutic agents with unique polyelectrophilic activity against DNA in cancer cells.
Aims: We aim to assess the therapeutic potential of Aurkine, alone and combined with immune checkpoint inhibitors (ICIs), using mouse and patient-derived models developed by our consortium. We will test various cancer types as a proof of concept, focusing on biliary cancer (cholangiocarcinoma). Specific aims: 1) Develop translational, personalized cancer models, including 2D and 3D in vitro and ex vivo, and in vivo models; 2) Evaluate the anti-tumour effects and molecular mechanisms of Aurkines, alone and combined with ICIs; 3) Profile tumour mutational burden, molecular characteristics, and neoantigens with or without Aurkine (+/- ICIs).
Methods: We will employ 2D and 3D human in vitro and ex vivo cancer models, including Patient-Derived Organoids (PDOs), human Precision-Cut Tissue Slices (PCTS), and a human Cancer-on-CHIP platform, alongside cancer animal models with different etiological backgrounds.
Expected Results and Impact: Our goal is to develop next-generation targeted therapies for both treatment-naïve and CisPt-resistant cancers, leveraging innovative personalized models. The consortium's outcomes have the potential to transform drug design, personalized cancer modelling, and clinical practices, ultimately advancing research and improving treatment management and outcomes for patients with cancer.

Project Coordinator:
Jesús María Bañales, Biogipuzkoa Health Research Institute (BHRI), Spain

Project Partners:
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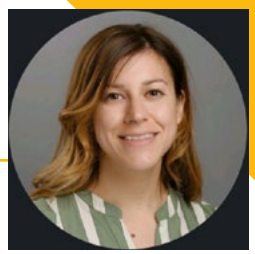
TAD disruption and aberrant expression as leukaemia metabolic vulnerabilities for novel combination therapy tests in a drug screening platform (TOSCANINI)

Presented by Martina Ghetti
IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori", (IRST)
Italy



Background: Despite therapeutic advances, relapse/refractoriness in acute myeloid (AML), B-cell acute lymphoblastic (B-ALL) leukaemia and chronic myeloid leukaemia in blast phase (CML-BP) remain unmet medical needs. Our ERA PerMed MEET-AML project data show that, beyond genomic changes, 3D genome organization contributes to oncogene activation in leukemic cells. Disrupted chromatin interactions, particularly Topologically Associated Domain (TAD) boundary loss resulting in gene deregulation, represent a new leukemogenic mechanism.
Hypothesis: TAD disruption could be a major mechanism of leukemogenesis, involving leukaemia stem-cell metabolic reprogramming and targetable vulnerabilities. Pathologic expression of novel leukemic transcripts could generate unexpected drug sensitivities and combination strategies.
Aims: We aim to elucidate how TAD boundaries disruption, potentially driven by chromosome rearrangements, deletions or mutations, alters metabolism-related gene expression and identifies targetable metabolic vulnerabilities in AML, B-ALL, and CML-BP. We will also set up a drug sensitivity screening platform for identifying combination therapies targeting these vulnerabilities.
Methods: Using multi-omics analysis, including Hi-C and long-read sequencing, associated with an individual drug sensitivity screening platform, we will investigate TAD hijacking events and their impact on the regulation of oncogenes and genes involved in leukemic cell metabolism in adult AML, B-ALL, and CML-BP patients. Computational methods will integrate omics with the high throughput ex vivo drug sensitivity test of combinations of FDA-approved or metabolism-related drugs, with most promising vulnerabilities validated by functional studies.
Expected results and impact: Focusing on patients resistant to standard therapies, and based on in vitro drug sensitivity assay and by “in silico” identification of potential metabolic leukemic targets, associated with TAD disruption and deregulated transcripts, TOSCANINI is expected to provide a novel approach to combination therapies and identify new therapeutic approaches in difficult-to-cure leukemic patients.

Project Coordinator:
Felipe Prosper, IdiSNA - CLINICA UNIVERSIDAD DE NAVARRA (IdiSNA-CUN), Spain

Project Partners:
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Radiothermal-Driven Immune Activation to Tackle Pancreatic Hypoxic Tumours (XPANTHER)

Presented by Ana Espinosa
Institute of Materials Science of Madrid (ICMM-CSIC)
Spain

Pancreatic ductal adenocarcinoma (PDAC) is an immunologically cold tumour with characteristics that hinder effective antitumor immune responses. Unlike "hot" tumours, which exhibit high levels of immune cell infiltration and response, PDAC creates a hostile environment that evades immune surveillance and therapy. The tumour microenvironment (TME) is hypoxic and immunosuppressive, further impairing immune cell function. PDAC also has a low mutational burden and few neoantigens, reducing susceptibility to immune checkpoint blockade therapies.

Hyperthermic radiotherapy (HRT) is an advanced cancer treatment approach that combines hyperthermia (therapeutic heating of tumour) with radiotherapy, enhancing its effectiveness and promoting neoantigen generation and antitumor immune responses. Cancer treatment based on nanoparticles (NPs), while promising for heat delivery and tumour targeting due to their small size, faces challenges. Inadequate release of therapeutic agents limits efficacy, while TME complexity impedes precise targeting and selective delivery. Lack of standardized protocols combining NP-based treatments with existing therapies hinders clinical integration.

The XPANTHER project aims to integrate HRT with innovative NP-based treatments in in vitro models recapitulating the human TME. It will examine oxidative ion release and cascades from efficient heaters (molybdenum oxide and iron oxide NPs) and radiosensitizers (hafnium oxide NPs) in tumoroid and tumour-on-a-chip (ToC) models adhering to 3R (Replace, Reduce, Refine) rules. The project will also enable advanced in operando physical characterization using techniques such as synchrotron radiation-based X-ray absorption spectroscopy.

The project comprises three modules: 1) turn immunologically cold pancreatic tumours into hot tumours through combined HRT; 2) use novel NPs as efficient releasers of metal ions triggering ROS for efficient radio and thermal therapies; 3) target hypoxic tumours on tumoroid and ToC models based on PDAC that could benefit from multimodal nano therapies, associated with hypoxia-related radiation resistance. The goal is to advance NP-based treatments, improving therapeutic advantages over conventional methods for precise, personalized cancer treatment. Expected outcomes include enhanced quality of life, reduced healthcare costs, and advancement of nanotherapies towards clinical application.

Project Coordinator:
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Project Partners:
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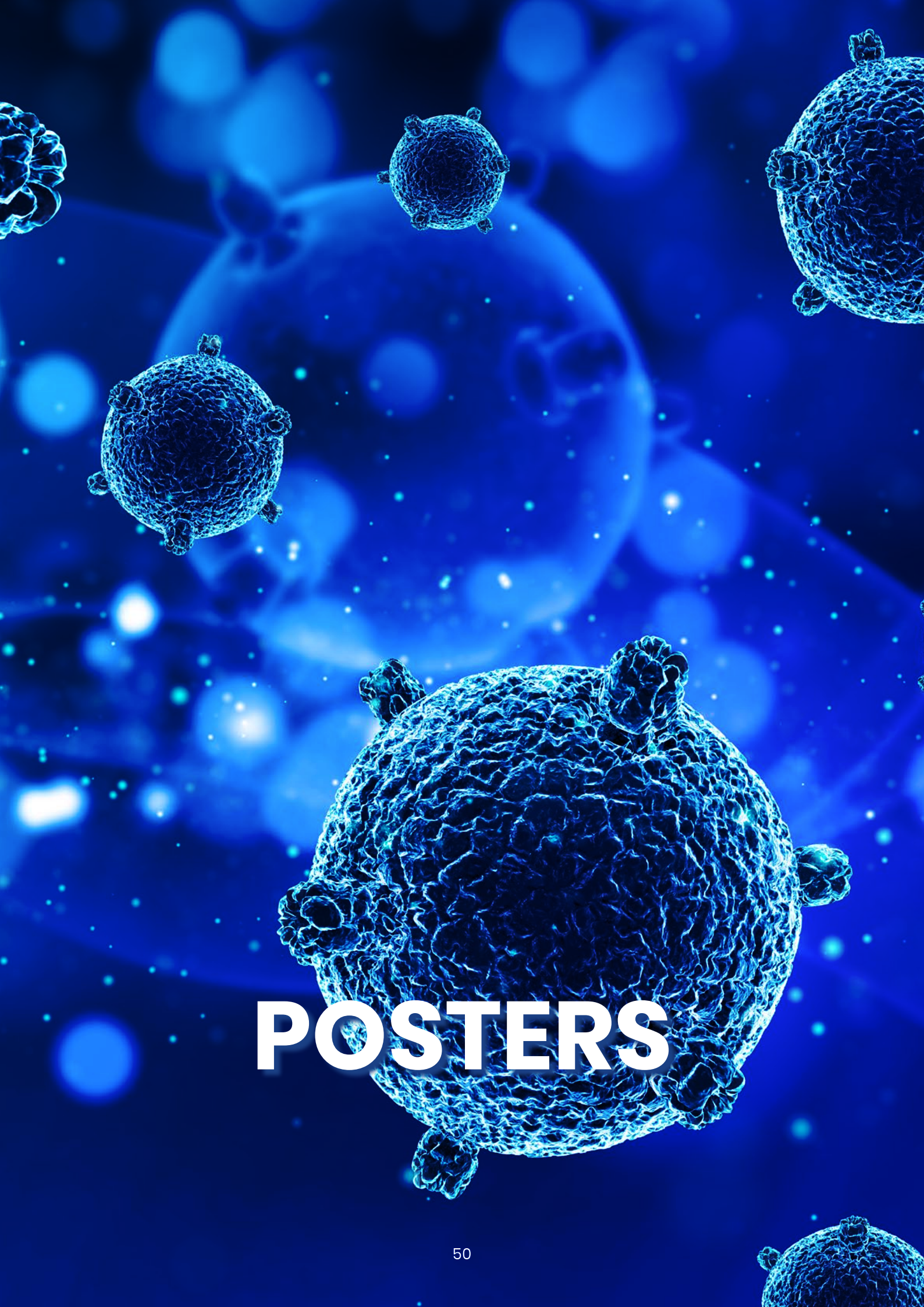
Yoann Lalatonne, Inserm U1148 Sorbonne Paris Nord University and Avicenne Hospital , France
Adriana Annušová, Slovak Academy of Sciences (CEMEA SAS), Slovakia



POSTERS

POSTER #1: JTC2021 Project ANEMONE
Human and AI assessment of the tumour immune microenvironment in pleural mesothelioma: concordance and prognostic relevance in ANEMONE

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Giulia Pasello[1], Federica Pezzuto[1], Luca Vedovelli[1], Cecilia de Chellis[1], Matteo Daverio[1], Andrea Dell'Amore[1], Eleonora Faccioli[1], Chiara Giraudo[1], Lina Carvalho[2], Ana Filipa Ladeirinha[2], Fatima Ramalhosa[3], Ilze Strumfa[4], Luka Brcic[5], Lipika Kalson[6], Leigh Marsh[6], Andrea Quaranta[7], Gabriella Serio[7], Anna Maria Catino[8], Greta Alì[9], Chiara Romei[9], Dario Gregori[1], Fiorella Calabrese[1]

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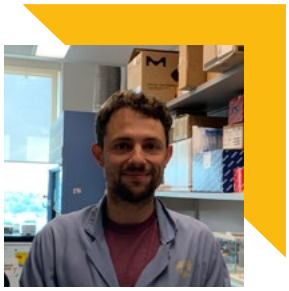
Abstract:

Background: We investigated whether artificial intelligence (AI) assessment of the tumour immune microenvironment reproduces pathologist readings and their prognostic information in pleural mesothelioma.
Methods: The multicentre ANEMONE cohort included 367 patients. Two pathologists and a AI-backed Visiopharm® pipeline assessed seven immune markers (CD3, CD4, CD8 CD20, CD68, CD163), with FOXP3 available in a subset. Agreement was evaluated using intraclass correlation coefficients (ICC) and weighted kappa. Human and AI measurements were compared using Cox models adjusted for age, histology, ECOG performance status and first-line therapy, with matched analysis populations, multiplicity correction and sensitivity analyses.
Results: Human–AI ICCs were 0.79–0.87 for CD3, CD8, CD68 and CD163, but 0.58 for CD20. Human-read CD20 showed an inverse association with mortality (hazard ratio per standard deviation, 0.80; nominal p=0.006), whereas AI-read CD20 did not (HR, 1.00). The human CD20 association did not reach significance after Benjamini–Hochberg correction (adjusted p=0.084). Adding human CD20 to the clinical-plus-AI model improved fit (p<0.001) and survived correction across nested-model comparisons. No robust association with treatment response was established.
Conclusions: AI may support immune-marker quantification, but should not replace pathologist assessment. Human-read CD20 remains a candidate prognostic marker requiring external validation before clinical use.

POSTER #2: JTC2021 Project CHRYSALIS
NK cells Impair Lung TIL Proliferation by Targeting CD127+ CD4+ T Cells



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Abstract:

A substantial proportion of non-small cell lung cancer (NSCLC) patients remain unresponsive to immune checkpoint inhibitors. Recent studies have shown that natural killer (NK) cells can impair the efficacy of immunotherapies by suppressing T cell response. This study aims to characterize the potential immunoregulatory functions of NK cells within lung tumor-infiltrating lymphocytes (TIL).

TIL from resected NSCLC samples (n=45) were profiled by flow cytometry at baseline and expanded in culture with high dose IL-2. Our analysis identified that CD127+ CD4 T cells were enriched in TIL from early-stage tumors and were associated with TIL proliferation. Conversely, cytotoxic NK cells (CD56+ CD16+) were associated with impaired TIL expansion. Coculture experiments further demonstrated that intratumoral NK cells were suppressing CD127+ CD4 T cells ex vivo. Further investigations will focus on assessing the therapeutic potential of modulating NK–T cell interactions to improve antitumor T cell responses.

POSTER #3: JTC2021 Project PIXEL
From Genetics to the Niche: Deciphering Bone Marrow and Extramedullary Acute Myeloid Leukemia

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Julia Frimmel[1, 2, 3], Sophie Steinhäuser[1, 2], Karin Huber[1, 2, 3, 4], Miriam Denker[1, 2], Jan Hahn[5, 6], Manuela Moritz[5], Ayham Moustafa[5, 6, 7], Florian Tran[8, 9], Katharina Fleischhauer[10, 11], Andreas Heinold[12], Thuja Arrieta-Balanos[10, 11], Esteban Arrieta-Balanos[10, 11], Heidi Altmann[13], Monika Brüggemann[1], Leo Ruhnke[13], Armin Zebisch[14], Annette I Garbe[1, 2], Friedrich Stölzel[1, 2, 4]

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[3] Detlef Zillikens Clinician Scientist Academy of Precision Health in Schleswig-Holstein (PHSH), Kiel, Germany
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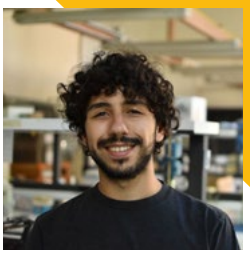
Abstract:

Acute myeloid leukemia (AML) is a highly heterogeneous malignancy shaped by genetic alterations and the tissue microenvironment. In extramedullary (EM) AML, characterized by leukemic tissue infiltration and poor clinical outcomes, the interplay between these factors remains poorly understood. Here, we compared bone marrow (BM) and EM AML to characterize EM-specific genetic and microenvironmental features, delineate niche-dependent disease programs, and identify therapeutic vulnerabilities.

Targeted sequencing of 72 EM AML samples identified somatic mutations in 70 cases, with a striking enrichment of RAS pathway alterations (55.6%). NPM1, ASXL1, TET2, and NRAS were among the most frequently mutated genes. Paired BM and EM samples showed high mutational concordance, while RAS-mutated EM AML was associated with inferior overall survival and remained an independent adverse prognostic factor. Spatial transcriptomics of EM AML revealed distinct myeloid, stromal, and endothelial niches. Spatial proteomic profiling of vascular-proximal versus distal AML blasts identified 159 differentially expressed proteins and enrichment of pro-leukemic signatures, with MYC Targets V1 showing the strongest enrichment. Consistently, the co-culture of THP-1 AML cells with HUVECs demonstrated a clear deregulation of MYC target genes. In summary, our study identifies unique genetic and microenvironmental characteristics of EM AML, providing new insights into the mechanisms driving disease biology.

POSTER #4: JTC2021 Project TALETE
Exploring Immunosuppressive Mechanisms in the Acute Myeloid Leukemia Microenvironment



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Ismael Sanchez Polanco[1], Marilena Ciciarello[2-4], Dorian Forte[2], Jiayin Liu[2], Valentina Salvestrini[1], Darina Ocadlikova[1], Federico Pasini[2], Antonio Curti[1].

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Abstract:

Survival of Acute Myeloid Leukaemia (AML) is poor. To improve patient outcomes, immunotherapies have the potential to circumvent some of the mechanisms leading to treatment failure, but their exploitation against AML has been unsatisfactory. The major reason for this lies in the largely incomplete understanding of the interactions between leukaemia and immune cells in the AML microenvironment. In particular, the causative role of immunosuppressive bone marrow (BM) pathways remains poorly understood.
We collected BM samples from a cohort of AML patients receiving azacitidine and venetoclax, a backbone combination for innovative therapeutic strategies in AML through the addition of novel compounds, such as immunomodulatory drugs. We set up experimental in vitro models to validate putative resistance mechanisms, particularly Treg induction and AHR pathway activation.
The expected discovery of microenvironment-based mechanisms of susceptibility to AZA VEN therapy will affect clinical practice by improving patient selection. The expected development of a novel platform for BM microenvironment investigation will impact technology transfer by providing advanced diagnostic tools.

POSTER #5: JTC2021 Project TALETE
Extracellular Vesicles in Acute Myeloid Leukemia Uncover Immunometabolic Functions and Reveal Prognostic Biomarkers of Early Therapy Response

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[3] University of Bologna, Department of Statistical Sciences, Bologna, Italy;
[4] Aix Marseille Univ, CNRS, INSERM, CIML, Centre d'Immunologie de Marseille-Luminy, Marseille, France

Abstract:

Background: Acute myeloid leukemia (AML) is an aggressive clonal hematological disease, characterized by metabolic reprogramming and by a high relapse rate. Extracellular vesicles (EVs) have emerged as promising tools for monitoring disease evolution.
Methods: Peripheral blood (PB) samples were collected from AML patients at diagnosis, early after treatment (azacitidine/venetoclax), and from healthy donors. EVs were purified from platelet-poor plasma by size exclusion chromatography and were analyzed for surface markers.
Results: We explored the signature of EV surface markers before and after therapy. At diagnosis, we found that EVs from low-risk patients showed 9 differently expressed surface markers (e.g., CD44, CD29, CD25) compared to high-risk patients, suggesting their putative prognostic role. Remarkably, cell adhesion and immune interaction markers were already significantly reduced after early post-therapy timepoints, including CD44, CD119, CD59, CD31, HLA-ABC, and CD133/1. Notably, partial responder AML patients exhibited an increased expression of CD133/1 before therapy, compared to complete responders. Interestingly, we found that both at diagnosis and after therapy, the enzymatic moieties CD73 and CD39 were highly co-expressed on CD90+ EVs, whereas they were significantly less present on CD90- EVs.
Conclusions: EVs represent an important tool for liquid-biopsy in AML and might be functionally involved in disease progression.

POSTER #6: JTC2021 Project TALETE
Mesenchymal Stromal Cells Protect Acute Myeloid Leukaemia Cells from Venetoclax-Induced Apoptosis Through a Cd90-Mediated Adhesion Pathway

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Giulia Corradi[2], Samatha Bruno[1], Manuela Piazzi[3,4], Vittoria Cenni[3,4], Jéssica Albuquerque[6], Célia Chobti[6], Diana Passaro[6], Antonio Curti[5] and Marilena Ciciarello[1,3,4].

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[6] Leukemia and Niche Dynamics Laboratory, Université de Paris, Institut Cochin, Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifiqu e, Paris, France

Abstract:

Among new treatment options for acute myeloid leukemia (AML), venetoclax and azacitidine (VEN/AZA) leads to higher complete remission rates and prolonged overall survival, although relapse remains an issue. Leukemic cells can hijack physiological pathways via physical interactions with bone marrow niche cells to favor survival and therapy resistance.
To investigate AZA/VEN resistance, we optimized an in vitro MSC/leukemic cell co-culture model to separate VEN-sensitive (floating) from VEN-resistant (adherent to MSCs) leukemic cells and compared Gene Expression Profiling (GEP). We found 663 differentially expressed genes in adherent vs. floating MV4-11 cells mainly belonging to cell migration, adhesion, and proliferation pathways.
Among these, we focused on Thy-1/CD90, whose overexpression correlates with tumor aggressiveness and poor prognosis in AML. To better mimic the complex bone marrow microenvironment that hosting leukemic cells, we implemented a 3D microfluidic niche-on-a-chip model, where endothelial cells and MSCs form vascular networks within a hydrogel matrix. Using immunofluorescence analysis in this 3D system, we validated that CD90 expression is specifically induced on leukemic cells upon interaction with the niche components.
Our study demonstrates that MSCs protect AML cells from AZA/VEN-induced apoptosis through tight adhesion/CD90-mediated pathways. We are now characterising Thy-1/CD90 interactors and downstream pathways underlying MSC-mediated resistance.

POSTER #7: JTC2021 Project TENACITY
Development of Nectin-2 Specific Nano-CARs for the Treatment of Melanoma

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Gonzalo Saavedra[1], Franziska Schneppenheim[1], Melanie Rauen[1], Benjamin McEnroe[1], Johannes Siewert[1], Florian Schmidt[2,3], Stephan Menzel[3], Michael Hoelzel[1], Nicole Glodde[1]*, Tobias Bald[1]*.

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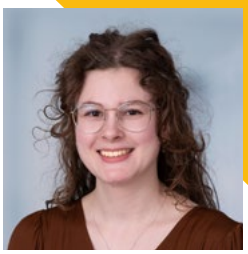
[3] Core Facility Nanobodies, University of Bonn, Germany
*Senior authors contribute equally

Abstract:

Recently, the first adoptive T cell therapy for melanoma received regulatory approval, paving the way for the development of next-generation cellular immunotherapies. Here we set out to develop a CAR T cell therapy for the treatment of melanoma using Nectin-2 specific single domain antibodies (sdAb) as antigen recognition domain.
First, we conducted an immunisation campaign, producing and selecting a diverse pool of 14 sdAbs. Flow cytometric characterisation revealed 10 sdAbs specific for human Nectin-2 and three with cross-reactivity to murine Nectin-2. Importantly, none of the sdAbs bound to other Nectin family members, confirming high target specificity. A variety of Nectin-2 sdAbs were cloned into our second-generation CAR construct, enabling efficient transduction of human and mouse T cells. Upon co-culture of Nectin-2 Nano-CARs with human or mouse melanoma cell lines, we observed robust IFN-γ and TNF-α production. Real-time killing assays showed efficient and dose-depended melanoma cell killing by our Nano-CARs, while Nectin-2 knockout cells were largely resistant. Building on these results, we established an in vivo CAR-transfer model in immunocompetent C57Bl/6 mice, demonstrating disease control without adverse effects in the syngeneic B16 melanoma model. Next, we will investigate the long-term efficacy in vivo and explore sdAb-engineering to further refine our therapy.

POSTER #8: JTC2021 Project TENACITY
Targeting the Immune Checkpoint CD155 (PVR) with Single-Domain Antibodies for the Treatment of Melanoma



Franziska Schneppenheim[1],
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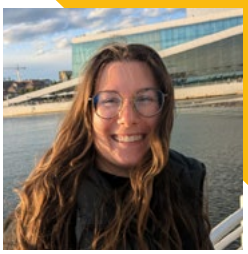
Abstract:

Melanoma is the deadliest form of skin cancer, and its incidence and mortality are rising. A promising target for melanoma is the immune checkpoint CD155 (PVR), which is highly expressed on several cancer entities and contributes to immunosuppression and immune escape.
After an immunization campaign, we were able to identify 10 single domain antibodies (sdAbs), which specifically bind to human CD155 and show no cross-reactivity with other Nectin and Nectin-like family members, or the mouse ortholog. With the AlphaFold2 algorithm, we performed in silico epitope predictions which we experimentally validated. Using a co-culture assay with primary human T cells, we identified several sdAbs that bind to the IgV-type domain of CD155 and thus prevent the interaction and internalization of the T cell activating receptor CD226. The internalization and degradation of CD226 has shown to render tumor infiltrating lymphocytes (TILs) dysfunctional, benefiting immune evasion.
Subsequently, several sdAbs were cloned into second-generation CAR constructs. Co-culture assays with CD155 expressing and deficient melanoma cell lines revealed specific production of TNF-α and IFN-γ by our CD155-Nano-CAR T cells. In the future, we will investigate the potential of CD155-nano-CAR T cells to kill melanoma cells in vitro and in vivo using Xenograft and syngeneic models.

POSTER #9: JTC2021 Project TRanSLIT
ROBO1 Links Aggressive Tumor Cells to Endothelial Proximity and Chemotherapy Tolerance in Pancreatic Cancer



Selina Mader[1],
Eva Rodriguez Aznar[1], Jack Brons[1], Ellis Michiels[1], Ken Matsumoto[1], Oier Azurmendi Senar[2], Kosta Stošić[2], Sophie Monique Irene De Cock[1], Zeynep Madran[3], Hippolyte Audureau[3], Philippe Soubeyran[4], Rebekah Crake[5], Akeila Bellahcène[5], Tatjana Arsenijevic[2,6], Elisa Espinet[7], Jean-Luc Van Laethem[2,6], Corinne Bousquet[3], Sandra Tuyaerts[1], Ilse Rooman[1]

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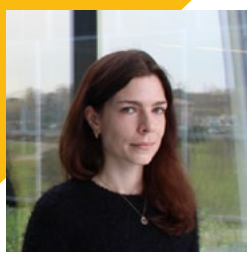
Abstract:

Tumor cell plasticity and environmental interactions drive pancreatic cancer aggressiveness and therapy response. The SLIT-ROBO pathway, known for regulating axon guidance positioning, is implicated in pancreatic cancer, but its role in tumor organization and drug response remains poorly understood.

We integrated (spatial) transcriptomics, multiplex immunofluorescence, and RNAscope analyses on human pancreatic ductal adenocarcinoma (PDAC), PDAC patient-derived xenografts and samples of adenosquamous cancer of the pancreas (ASCP). ROBO1 function was assessed in pancreatic tumor cell lines using siRNA-mediated knock-down, migration, invasion and network formation assays, endothelial co-culture experiments and gemcitabine response assays.

ROBO1 was the predominant ROBO receptor in pancreatic tumor epithelial cells, highly expressed in ASCP and a distinct GATA6+/KRT17+ co-expressor PDAC, associated with high cellular plasticity and chemoresistance. ROBO1 promoted tumorigenic phenotypes related to migration and enabled tumor cells to localize near and interact directly with endothelial cells, forming hybrid vascular-like structures. The ligand SLIT2, highly expressed by ASCP tumor endothelial cells, acted as a chemoattractant for ROBO1+ tumor cells. ROBO1 also promoted gemcitabine tolerance and marked GATA6+/KRT17+ cells consistent with drug-tolerant persisters enriched after chemotherapy. These findings position ROBO1 as a mediator of tumor-endothelial proximity linked with chemotherapy tolerance, revealing previously unrecognized roles for an axon guidance receptor in pancreatic cancer organization and drug tolerance.

POSTER #10: JTC2021 Project TRanSLIT
Targeting ROBOs and SLIT Guidance Cues in Pancreatic Cancer Microenvironment



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Abstract:

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal cancer characterized by a dense desmoplastic stroma dominated by heterogeneous cancer-associated fibroblasts (CAFs), which contribute to tumour progression and therapeutic resistance. The SLIT/ROBO pathway, implicated in cell migration, angiogenesis, and tumour progression, is genetically altered in a substantial proportion of PDACs and may contribute to tumour–stroma interactions.
Using bulk and single-cell RNA sequencing, and spatial transcriptomics, we identified CAFs as the primary source of SLIT2 and SLIT3 in PDAC. Distinct CAF populations expressed SLIT2, SLIT3, both, or neither, occupying different spatial niches. SLIT2-expressing CAFs were enriched near tumour, whereas SLIT3-expressing CAFs were associated with pancreatic stellate cells and more distant to tumour. Transcriptomically, SLIT2^{high} CAFs displayed inflammatory, WNT-associated and profibrotic transcriptional programmes, while SLIT3^{high} CAFs exhibited features of normal pancreatic fibroblasts and vascular/neurogenic programmes. We confirmed these features using in vitro SLIT2^{high} and SLIT3^{high} CAFs.
Together our findings suggest SLIT2/ROBO1 as a possible target for TME normalization.

POSTER #11: JTC2024 Project ACCELERATE
Integrated Genomic and Pharmacogenomic Profiling to Identify Therapeutic Subgroups in Pancreatic Ductal Adenocarcinoma

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Abstract:

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy with significant molecular heterogeneity despite its relatively uniform histological appearance. Molecular profiling is becoming vital for determining prognosis and selecting treatment strategies.

Tumor-enriched FFPE tissue from 44 PDAC cases were analyzed using the TruSight™ Oncology 500 v2 panel. FASTQ files were processed using the DRAGEN engine v3.11.2 and variants were filtered and annotated using **VarSome Clinical**, retaining PASS variants with depth >100, VAF >1%, coding impact, and AMP Tier I–II classification, while excluding benign and likely benign variants. Therapeutic candidates were identified and prioritized using **PanDrugs**, and drug response profiles were clustered using Jaccard distance.

Eighty-two functional variants were identified in 12 genes, with **KRAS** and **TP53** being the most frequently mutated. PanDrugs identified therapeutic candidates in 83% of patients and revealed three subgroups with low, intermediate, and high predicted drug sensitivity. The high-sensitivity subgroup comprised more than half of the samples and exhibited shared therapeutic vulnerabilities despite genomic differences. In addition, PDX models were included and clustered with a specific patient subgroup.

These results highlight the heterogeneity of PDAC and suggest that molecular profiling and PDAC tumor models represent relevant preclinical tools for evaluating subgroup-specific therapeutic strategies.

POSTER #12: JTC2024 Project ACCELERATE Establishment of Patient-Derived Organoids from Resected Pancreatic Ductal Adenocarcinoma: Feasibility, Morphology and Genomic Concordance After Upfront Surgery or Neoadjuvant Therapy

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Abstract:

Background and aims: Pancreatic ductal adenocarcinoma (PDAC) is aggressive, with poor prognosis and treatment resistance. As neoadjuvant therapy (NAT) may reduce tumor cellularity and tissue quality, this study evaluated PDO establishment after upfront surgery or NAT.
Methods: Patients undergoing pancreatic surgery were prospectively enrolled. Fresh tumor specimens were collected and processed using a standardized PDO protocol. PDO morphology was assessed by bright-field microscopy and compared with histopathology. WES libraries were prepared using Illumina DNA Prep with Exome 2.5 Enrichment and sequenced on a NovaSeq 6000.
Results: 104 patients were enrolled and tissue was available from 71. 8 non-PDAC samples were excluded, leaving 63 patients: 40 upfront surgery and 23 NAT. PDOs were established in 42 (66.7%), including 28/40 (70.0%) and 14/23 (61.0%), respectively. PDOs retained key tumor morphology, including glandular organization, epithelial polarity, and cellular/nuclear atypia, and NAT-derived PDOs expanded despite fibrosis and reduced cellularity. KRAS and TP53 were the most frequent somatic alterations in fresh tumors and matched PDOs. Genomic concordance varied individually, with no evident reduction after NAT versus upfront surgery.
Conclusions: PDO establishment from resected PDAC is feasible after upfront surgery and NAT. PDOs preserve tumor morphology, may also model residual disease and chemoresistance.

POSTER #13: JTC2024 Project ioAVATAR
Establishing Ovarian Cancer Patient AVATAR Models from Malignant Ascites and Debulking Solid Tumor Tissue to Study Immunotherapy Approaches

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Abstract:

Introduction: Ovarian cancer is characterized by intraperitoneal dissemination and an immunosuppressive tumor microenvironment (TME), limiting the efficacy of immune checkpoint inhibitors (ICIs). We therefore aim to establish patient-derived 3D "Ovarian Cancer Avatar" models from malignant ascites and solid tumor tissue collected at UKE that preserve patient-specific tumor–immune interactions, enabling reliable assessment of responses to ICIs.
Methods: The workflow comprises multiparametric flow cytometric characterization of initial cell populations and ICM expression, ex vivo cultivation and ICI treatment of patient-derived samples, followed by functional response analyses, including macrophage phagocytosis assays.
Results: Ascites and solid tumor tissue showed marked interpatient heterogeneity and distinct immune profiles. T cells predominated in ascites, whereas solid tumor tissue was enriched in myeloid cells. Supplemented autologous ascites enabled preservation of cellular composition and ICM expression during ex vivo culture. A Matrigel-based culture system is being established for solid tumor-derived tumoroids to maintain tumor–immune interactions. Furthermore, macrophages expressed immune checkpoint molecules including MARCO, TIM-3, and CD39, as well as components of the "don't eat me" CD47-SIRPα axis, highlighting potential targets for macrophage-directed immunotherapy approaches.
Conclusion: These patient-derived AVATAR models capture key features of the ovarian cancer TME and provide a platform for individualized evaluation of immunotherapeutic responses.

POSTER #14: JTC2024 Project SARAH
TET2-mutated Clonal Hematopoiesis Leads to an Inferior Survival in Patients with Advanced-Stage Cancer

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Abstract:

Introduction: Clonal hematopoiesis of indeterminate potential (CHIP) is age-related, more prevalent among cancer patients and has been associated with adverse clinical outcomes. Tumor-infiltrating clonal hematopoiesis (TI-CH) may confer an additional survival disadvantage, with a poorly understood pathophysiology.
Methods: We retrospectively analyzed 1,617 tumor-normal paired samples with whole exome sequencing and 104 samples with RNA-seq of 1,530 patients with advanced-stage cancer in the setting of a molecular tumor board at the University Hospital Schleswig-Holstein. CHIP variants were identified in blood and in matched tumors. CHIP prevalence was assessed together with clinical and molecular tumor information and considering confounding factors.
Results: CHIP was detected in 354/1,530 patients (23.1%) and was associated with older age (median 63.9 vs. 56.5 years; OR 1.04/year, 95% CI 1.03–1.05; p<0.001), without significant variation across tumor entities. Frequent mutations involved DNMT3A (19%), PPM1D (18%), TET2 (17%), CHEK2 (16%), and TP53 (11%). Median overall survival did not differ by CHIP status; however, TET2-mutated CHIP independently predicted inferior survival (HR 2.09, 95% CI 1.02–4.28; p=0.04). CHIP-positive tumors showed altered gene expression, including reduced fatty-acid and lipoprotein metabolic pathways.
Conclusion: CHIP is common and age-dependent in advanced cancer. TET2-mutated CHIP may independently predict poor survival.

POSTER #15: JTC2024 Project TITAN
Patient-Derived Organ-on-Chip to Evaluate Chemo-Immunotherapy Response and Tumor–Immune Dynamics in Cholangiocarcinoma

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Abstract:

Introduction: Intrahepatic cholangiocarcinoma (iCCA) is characterized by an immunosuppressive tumor microenvironment (TME), poor T-cell infiltration, and therapy resistance, with mechanisms driving heterogeneous patient responses remaining unclear. We used a patient-derived CCA-on-chip model to evaluate PD-L1's role in tumor-immune interactions and chemo-immunotherapy responses in a physiologically relevant human platform.
Methods: Primary iCCA cells were isolated from surgical specimens and cultured in 2D or within the CCA-on-chip. IHC for CK7/CD3 was performed on patient-matched tumor tissue. Transcriptomic data from a public iCCA dataset (OEP001105; n=167) were analyzed via xCell and R software. Tumor-immune interactions on-chip were assessed through confocal imaging of T-cell migration, tumor viability, apoptosis, cytotoxicity, and RT-qPCR.
Results: The CCA-on-chip faithfully mirrored the tumor architecture and immune infiltration of patient specimens. Transcriptomic analysis showed PD-L1-high tumors were enriched in immunosuppressive cytokines and protumoral immune cells; consistently, high- and low-PD-L1 patient-derived chips showed reduced T-cell infiltration and impaired antitumor activity.
On-chip chemo-immunotherapy responses mirrored patient clinical outcomes, confirming the model's predictive potential.
Conclusion: High PD-L1 expression was associated with a higher immunosuppressive TME and an exhausted T-cell phenotype in iCCA. The patient-derived CCA-on-chip offers a physiologically relevant model to study tumor-immune interactions and predict patient-specific chemo-immunotherapy responses, supporting translational immuno-oncology applications.

POSTER #16: JTC2024 Project TITAN
Novel Cancer Therapy: Inducing Double-strand DNA Breaks to Foster Tumour Cell Death, Antigenicity and Immunotherapy Response in New Personalized Models

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Abstract:

Background: Cancer caused approximately 10 million deaths worldwide in 2022, and incidence is projected to rise by 77% by 2050. Platinum-based chemotherapy remains fundamental to treating solid tumours, but resistance develops in up to 70% of patients. Unlike cisplatin, which mainly induces single-strand DNA lesions, Aurkines are novel polyelectrophilic agents designed to generate double-strand DNA breaks selectively in cancer cells, potentially enhancing tumour cell death and immunogenicity.
Aims: TITAN aims to evaluate the therapeutic potential of Aurkines, both alone and in combination with immune checkpoint inhibitors (ICIs) across multiple tumour types, with particular focus on cholangiocarcinoma.
Methods: Therapeutic efficacy will be assessed using translational 2D and 3D models, including patient-derived organoids, precision-cut tissue slices, Cancer-on-CHIP platforms, and complementary in vivo models. Tumour mutational burden, molecular profiles, and neoantigen generation will be characterised following Aurkine exposure, with or without ICIs. Regulatory-compliant preclinical studies will be conducted with a CRO.
Expected Impact: TITAN aims to develop next-generation therapies for treatment-naïve and cisplatin-resistant cancers, accelerating clinical translation and improving treatment management and outcomes for patients with cancer.

POSTER #17: JTC2024 Project XPANTHER Multifunctional Photothermal Nanoparticles for Pancreatic Cancer within XPANTHER Project

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Abstract:

Pancreatic ductal adenocarcinoma is characterized by a highly hypoxic and treatment-resistant microenvironment, motivating the development of multifunctional nanomaterials for localized therapeutic approaches. Within the TRANSCAN-3 project XPANTHER, we are investigating photothermal nanomaterials based on both metal oxides, including iron oxide nanoparticles (IONPs), and metals, including platinum nanoparticles (PtNPs). Previous studies have highlighted the importance of the biological environment and 3D tumour organization in determining nanoparticle-mediated photothermal response[1], as well as the complex intracellular transformation of iron oxide nanoparticles[2].

Both nanoparticle systems are being characterized by transmission electron microscopy (TEM) in solution and after internalization in PANC-1 cells. Cellular viability and nanoparticle uptake are evaluated by viability assays and ICP-OES, complemented by TEM analysis of intracellular localization and aggregation. For PtNPs, preliminary photothermal experiments in PANC-1 cells using live/dead confocal imaging indicate a cellular response following photothermal activation. Particular attention is being paid to the influence of intracellular aggregation on photothermal behaviour, building on the photothermal potential of Pt-based nanostructures[3].

In parallel, biological models are being extended towards PANC-1 spheroids and multicellular systems incorporating THP-1 monocytes, providing a first step towards more complex tumour-microenvironment models. These studies establish a framework for the subsequent evaluation of multifunctional nanoagents in advanced radiothermal strategies within XPANTHER.

Acknowledgements
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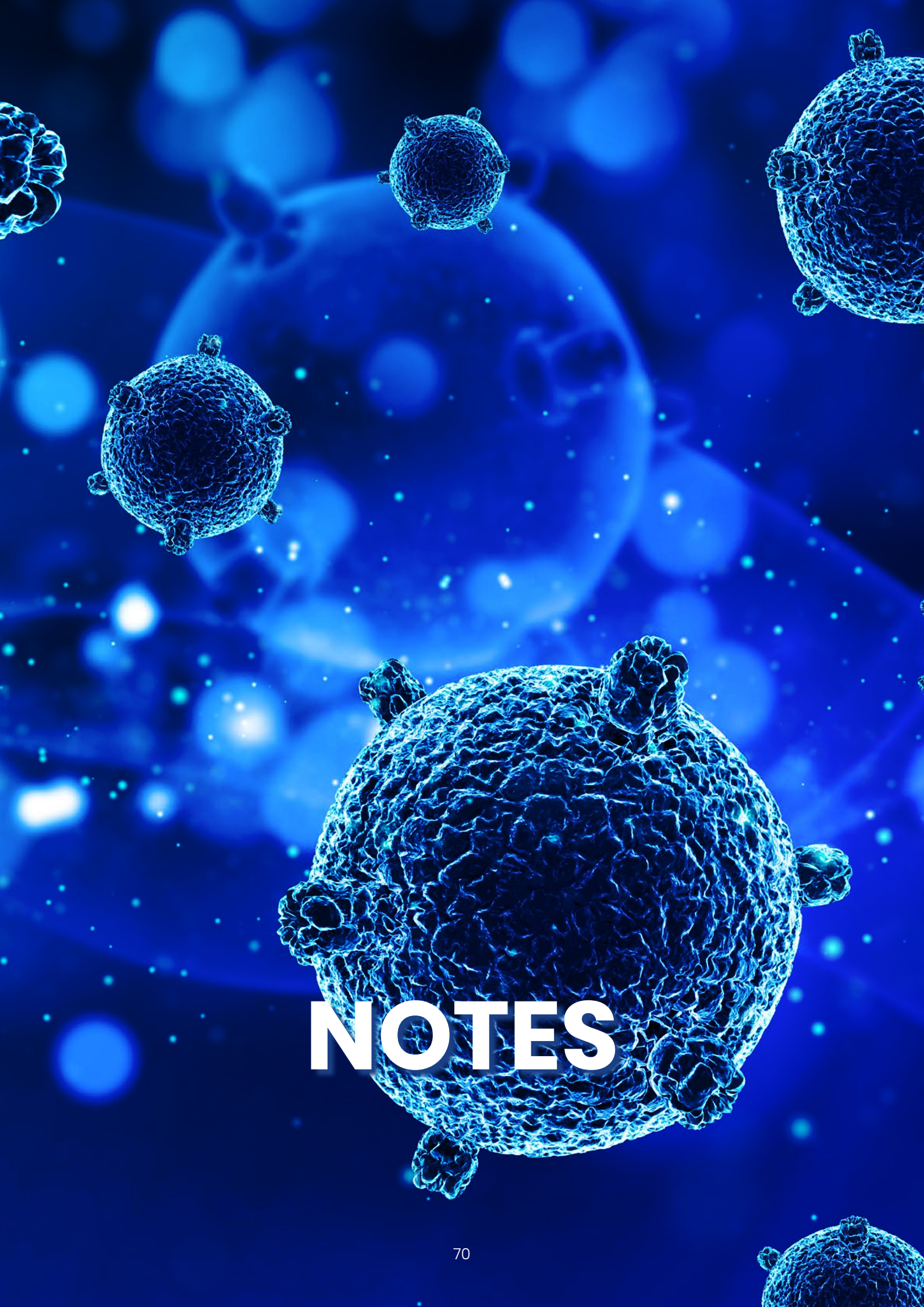
ADDITIONAL SPEAKERS

Mila Ogalla Toledo

Mila Ogalla Toledo is the Advocacy and Community Engagement Manager at Patvocates. She is a patient advocate, public speaker and communication specialist whose work is driven by her lived experience with colorectal cancer and a strong commitment to equity, diversity, and inclusion. She actively collaborates with international patient organisations and has contributed to global discussions on early-onset cancers, including the first Global Early-Onset Colorectal Cancer (EOCRC) Think Tank. Spoken at international conferences and policy events, including the European Parliament and Commission, and ESMO GI, bringing the patient voice into rooms where research and policy decisions are shaped. Passionate about bridging the gap between patients and healthcare systems so that lived experience meaningfully shapes research, policy, and care.

Ulf Tölch

Ulf Tölch obtained his PhD in biology at Ludwig Maximilans University in Munich. His research includes cognitive neuroscience, quantitative methods and statistical modelling of decision making. After his habilitation in psychology, he joined the BIH QUEST Center for responsible Research. He is currently elected center head and spokesperson. He also serves as a research group leader where his group explores robust methodological approaches in preclinical settings to inform and improve research decisions. Beyond this he is also responsible for educational formats and training at the QUEST.



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