TRANSCAN
Sustained collaboration of national and regional programmes in cancer research

TRANSCAN-3

Co-funded projects by the EC on:

Next generation cancer immunotherapy: targeting the tumour microenvironment

October 17th-18th
2023
University of Latvia
Riga

JTC-2021 Kick-off SYMPOSIUM

Latvijas Zinātnes padome

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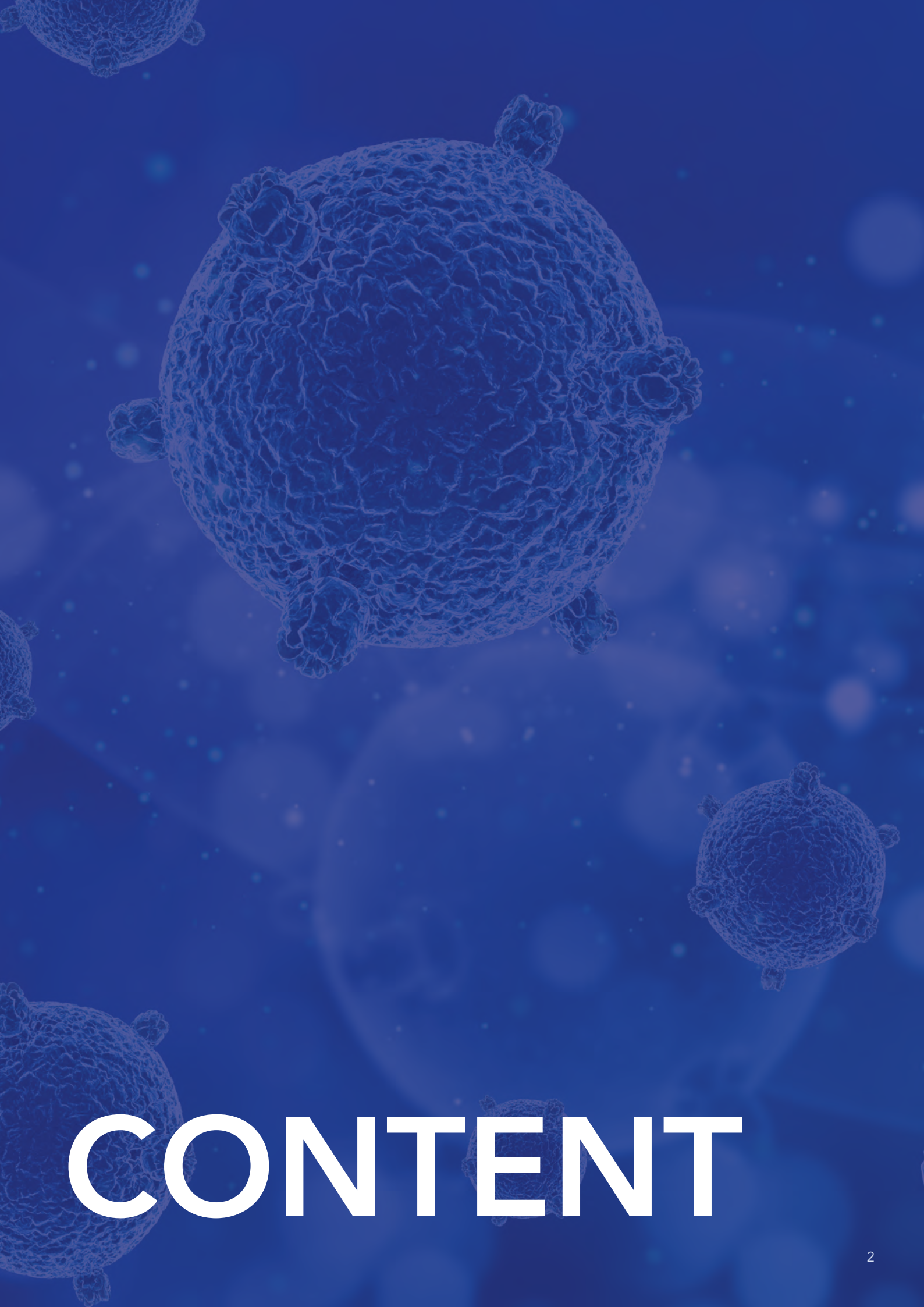
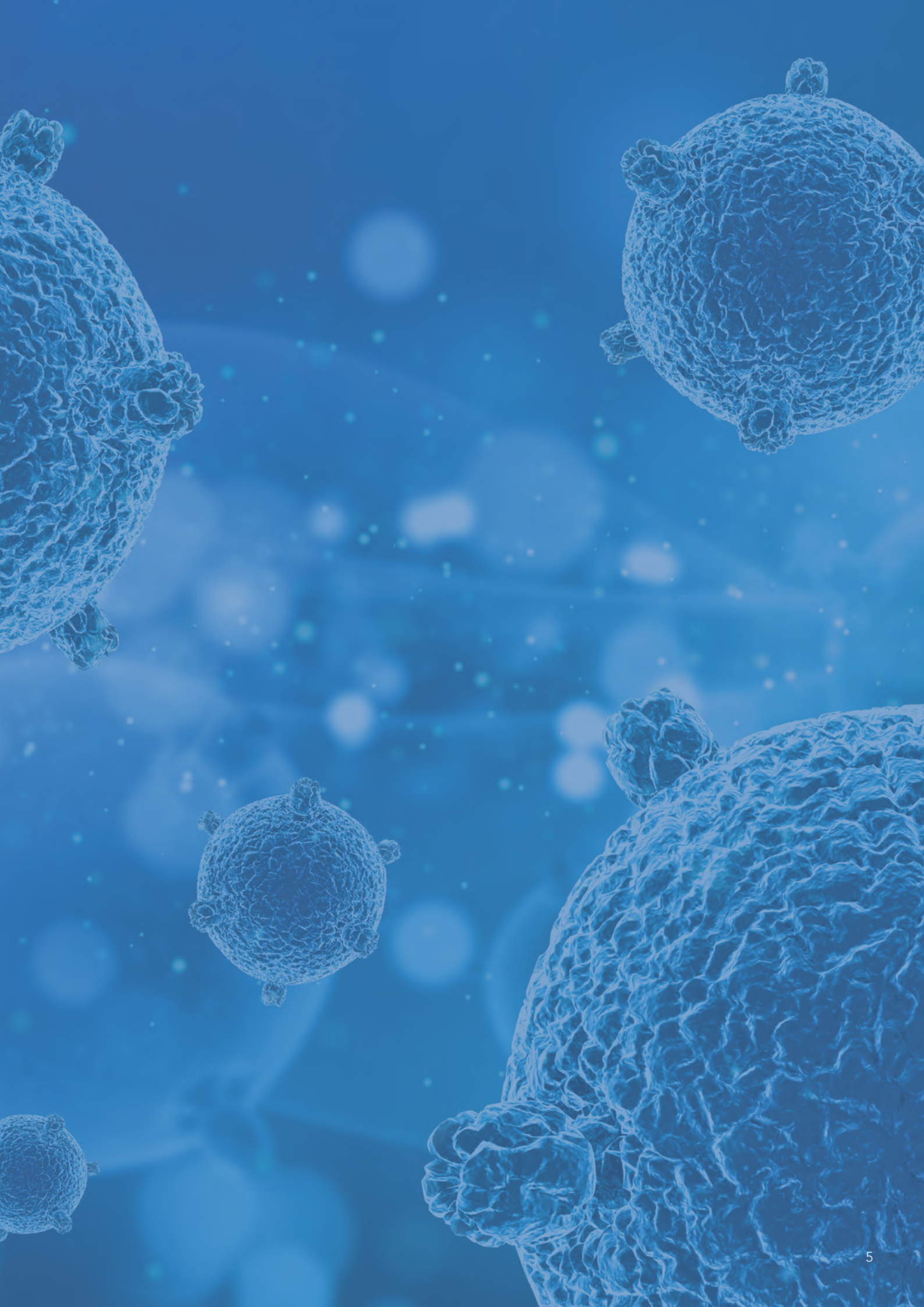
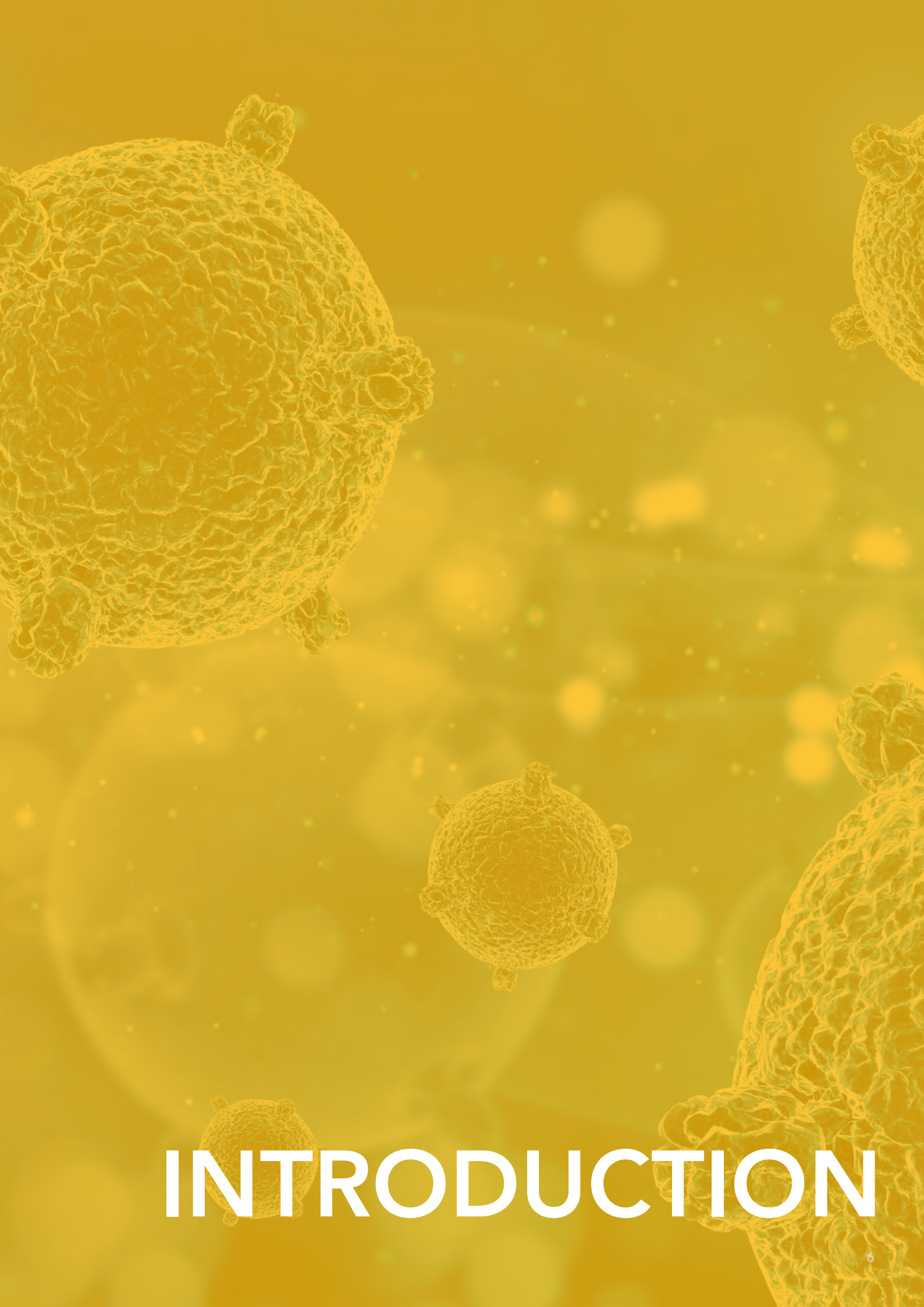


CONTENT

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 4.3 million new cases each year (GLOBOCAN 2020 http://gco.iarc.fr). Cancer is a challenge for public health, as it can become a chronic disease contributing substantially to the growth of medical expenditures and constituting a major socio-economic issue for Europe as well as globally. To address the increasing need to reduce incidence and mortality of malignancies and to improve the quality of life of cancer patients, a coordinated effort is necessary. A rapid and effective bidirectional transfer of relevant cancer research findings between bench and bedside would play a pivotal role. The key area of translational cancer research addresses these needs, however, the research efforts in the field should be harmonized and integrated so as to profit from coordination at the transnational level.

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 is composed of 31 partners from **20 Countries**. It is the continuation of the previous programmes ERA-NET TRANSCAN-2 and TRANSCAN. Altogether since 2011, 10 annual Joint Transnational Calls (JTCs) have been launched and 113 transnational projects have been funded.

Under the call launched in 2021 on the topic "Next generation cancer immunotherapy: targeting the tumour microenvironment", which was co-funded by the European Union, **twenty** transnational consortia including 107 research groups from 15 countries were funded. The Call ultimately aims at funding research that will improve the efficacy of personalised treatment of cancer patients through the development of new tools and targeted immunotherapy strategies, based on a better understanding of tumour microenvironment functions and of their impact on the disease course.

This 1st Symposium of TRANSCAN-3 brings together all 20 of the funded consortia from JTC2021 in order to present the research that will be carried out in these projects. It also aims to foster networking and scientific discussion amongst researchers from related research fields, as well as to increase the opportunities for new collaborations. Young scientists are encouraged to join and discuss their work with scientists from their field of research.

We hope you enjoy and benefit from the symposium!

TRANSCAN-3 JTC-2021 Kick-off Symposium

Agenda

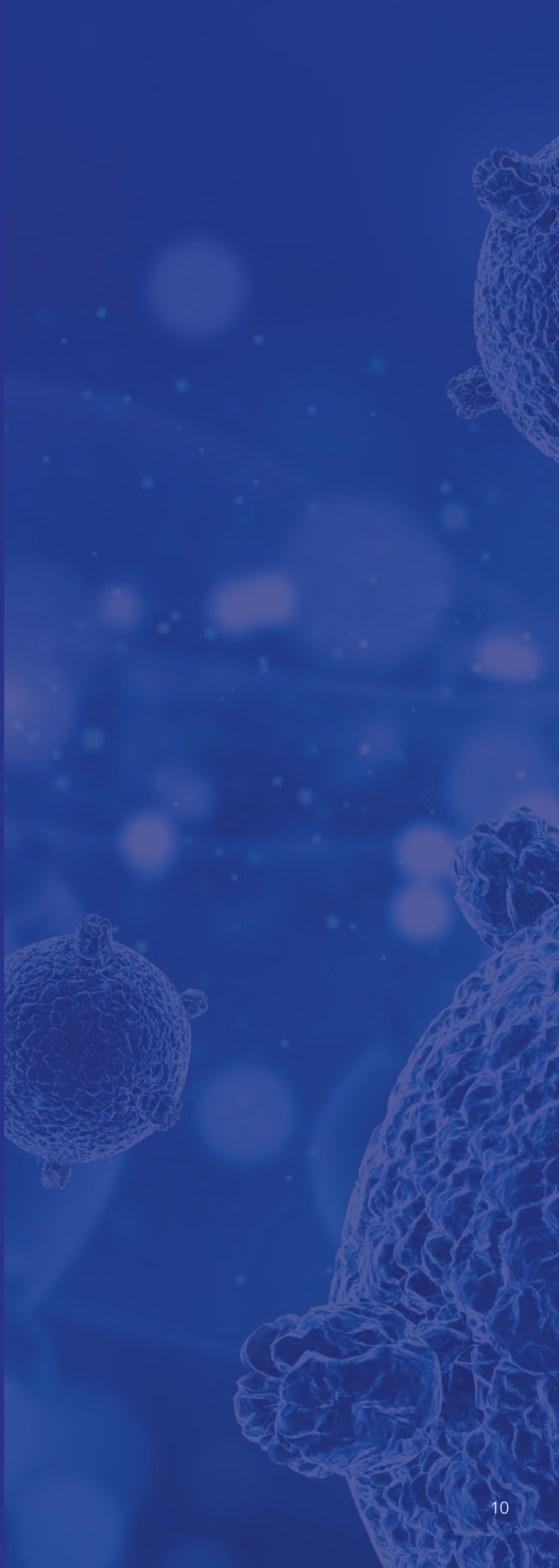
University of Latvia, Raina Boulevard 19, Riga LV-1050, Latvia

Day 1: Tuesday, October 17th, 2023

9:00-9:30	Registration
9:30-10:00	Welcome and introduction TRANSCAN-3 coordination, JTC2021 Joint Call Secretariat and local host
Session 1	**Chair: Atanasio Pandiella**
10:00	**PIXEL**, Luca Aldo Edoardo Vago
10:20	**BIALYMP**, Peter-Martin Bruch
10:40	**iParaCyts**, Joan Seoane
11:00	**SmartCAR-T**, Maik Luu
11:20-11:50	*COFFEE BREAK*
Session 2	**Chair: Atanasio Pandiella**
11:50	**MAGNOLIA**, John Stagg
12:10	**CHRYSALIS**, Douglas Chung
12:30	**UCIPredict**, Marta Dueñas
12:50	**TANGERINE**, Victor Raul Moreno Aguado
13:10-14:10	*LUNCH*
14:10-16:10	WORKSHOP ON PROTECTION AND EXPLOITATION OF RESULTS FROM RESEARCH PROJECTS I Michele Dubbini, EC IPR Helpdesk Service
16:10-16:40	*COFFEE BREAK*
Session 3	**Chair: Aideen Ryan**
16:40	**RISEBrain**, Manuel Valiente
17:00	**TumorOUT**, Cristina Fornaguera
17:20	**IMMOSCAN**, Claudine Blin
17:40	**ImmuMet**, Martina Seiffert
18:00-18:30	"MAKING CONNECTIONS" - gathering for early career researchers
18.45	*TOUR and NETWORKING DINNER*

Day 2: Wednesday, October 18th, 2023

9:00	SHORT WELCOME
9:10-10:00	PEER LEARNING - TRANSCAN-2 COORDINATORS SHARE THEIR INSIGHTS Yvonne Kohl, NExT consortium (JTC 2017) Hedwig Deubzer, LIQUIDHOPE consortium (JTC 2017)
Session 4	**Chair: Aideen Ryan**
10:00	**Pur-Ther**, Elena Adinolfi
10:20	**PREDICO**, Giuseppina Arbore
10:40	**TALETE**, Antonio Curti
11:00	**TRanSLIT**, Ilse Rooman
11:20-11:50	*COFFEE BREAK*
11:50-12:30	PATIENT ENGAGEMENT IN CANCER RESEARCH Dr. Bettina Ryll, Melanoma Patient Network Europe
Session 5	**Chairs: Atanasio Pandiella & Aideen Ryan**
12:30	**ANEMONE**, Fiorella Calabrese
12:50	**TENACITY**, Tobias Bald
13:10	**LipidMac**, Diletta Di Mitri
13:30	**PERIMMUNE**, Sarah Cosyns
13:50-14:10	FEEDBACK SESSION AND SUMMARY
14:10-15:10	*FAREWELL LUNCH*



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 Stradinš University, Latvia

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

Presented by Peter-Martin Bruch
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 Douglas Chung
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 Claudine Blin
Université Côte d'Azur, France

Bone tumors and bone metastasis affect patients from children to elderly. Despite advances in diagnosis and treatment, they are incurable and thus, new therapies are needed. In the bone microenvironment, cancer cells disrupt the physiological balance between bone-forming osteoblasts, bone-resorbing osteoclasts and immune cells, leading to excessive bone destruction and promoting cancer development. Standard treatments include chemotherapy, radiation, antiresorptive therapies and immunotherapies. However, the bone environment is largely immunosuppressive, which renders patients with bone tumors less responsive to such treatments.

Importantly, recent findings including from our consortium identified specific bone cells that can link bone destruction and immune suppression and therefore may represent key players in the development of bone cancer and metastasis. The goal of the IMMOSCAN consortium is to uncover the role and mechanisms of action of these bone cells in bone cancer and metastasis. The IMMOSCAN consortium combines complementary and interdisciplinary strengths of five partners that bring together pre-clinical models and patient samples as well as state-of-the art technologies allowing to characterize bone cell specificity, function and location in the bone environment, and how they interact with each other to induce or maintain immunosuppression and cancer development. During the course of the project, we aim to identify and characterize these cells in the bone-cancer microenvironment and explore mechanisms to target them as a novel therapeutic strategy to improve the efficacy of immunotherapy and control tumor progression in bone. The findings of the project are expected to increase our understanding of the complex bone-cancer microenvironment and identify novel targetable pathways for innovative immune therapy in bone cancers.

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.

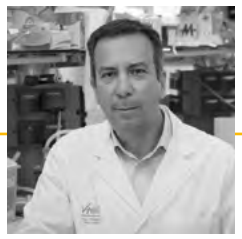
In ImmuMet, we will characterize the BrMet niche in patient-derived tissues and blood, PDX and immunocompetent mouse models to define TME subclasses and unravel clinical associations. We will acquire single-cell and spatial tissue data, multiplexed flow cytometry, and serum analyses, combined with integrative 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:
Martina Seiffert, German Cancer Research Center (DKFZ), Germany

Project Partners:
Christel Herold-Mende, University of Heidelberg, Germany
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:

Joan Seoane, Fundación Hospital Universitario Vall d'Hebron – Fundación Privada Institut d'Investigació Oncològica de Vall d'Hebron (VHIO), Spain

Project Partners:

Ignacio Melero Bermejo, Fundación Instituto de Investigación Sanitaria de Navarra, Spain
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:
Diletta Di Mitri, IRCCS Istituto Clinico Humanitas – Humanitas Mirasole SPA, Italy

Project Partners:
Giovanni Scambia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Italy
Daniela Quail, Goodman Cancer Research institute/McGill University, Canada
María Casanova-Acebes, Centro Nacional de Investigaciones Oncológicas, CNIO, Spain

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:
John Stagg, Centre Hospitalier de l'Université de Montréal, Canada

Project Partners:
Thomas Karn, Goethe University Frankfurt, Germany
Christos Sotiriou, Université Libre de Bruxelles, Belgium
Fatima Mechta-Grigoriou, Institut Curie, Centre de recherche, France
Morag Park, Goodman Cancer Institute, McGill University, Canada
Evelyne Meyer, University of Ghent, Belgium

INTRAPERITONEAL IMMUNE MODULATION FOR COLORECTAL PERITONEAL METASTASES (PERIMMUNE)

Presented by Sarah Cosyns
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:
Wim Ceelen, Ghent University, Belgium

Project Partners:
Laurence Zitvogel, Institut Gustave Roussy, France
Andreas Bosio, Miltenyi Biotec B.V. & Co. KG, Germany
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:
Luca Aldo Edoardo Vago, IRCCS Ospedale San Raffaele, Italy

Project Partners:
Robert Zeiser, Universitätsklinikum Freiburg, Germany
Friedrich Stölzel, Universitätsklinikum Carl Gustav Carus Dresden, Germany
Enrico Derenzini, IRCCS Istituto Europeo di Oncologia (IEO), Italy
Armin Zebisch, Medical University of Graz, Austria
Maria Carolina Florian, Fundació Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Spain

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:
Paolo Dellabona, IRCCS San Raffaele Hospital, Italy

Project Partners:
Giorgia Marisi, IRCCS Istituto Romagnolo per lo Studio dei Tumori 'Dino Amadori' (IRST), Italy
Oliver Schilling, University Medical Center Freiburg (UKL-FR), Germany
Guillaume Piessen, CHU de Lille, France

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:
Elena Adinolfi, University of Ferrara, Italy

Project Partners:
Katja Christina Weisel, University Medical Center Hamburg-Eppendorf, Germany
Valérie Vouret-Craviari, CNRS, IRCAN, France
Antonino Romeo, Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST s.r.l., Italy
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 Manuel Valiente
Centro Nacional de Investigaciones Oncológicas Carlos III, Spain

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:

Manuel Valiente, Fundación del Sector Público Estatal Centro Nacional de Investigaciones Oncológicas Carlos III, Spain

Co-Coordinator:

Hind Medyouf, Institute for Tumor Biology and Experimental Therapy, Germany

Project Partners:

Itay Tirosh, Weizmann Institute of Science, Israel
Luca Bertero, University of Turin, Italy
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:
Michael Hudecek, Universitätsklinikum Würzburg, Germany

Project Partners:
Sanaz Taromi, Universitätsklinikum Freiburg, Germany
Emmanuel Donnadieu, INSERM, France
Jo Caers, CHU de Liège, Belgium
E. Paola Neri, University of Calgary, Canada
Cem Mirili, Private Ortadogu Hospital Adana, Türkiye

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:
Antonio Curti, IRCCS Azienda Ospedaliero - Universitaria di Bologna, Italy

Project Partners:
Christiane Opitz, Deutsches Krebsforschungszentrum (DKFZ), Germany
Rafael Argüello, Centre National de la Recherche Scientifique (CNRS), France
Bjørn-Tore Gjertsen, University of Bergen, Norway
Una Riekstina, The University of Latvia, Latvia
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:
Jakob Nicolas Kather, University Hospital Aachen, Germany
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:
Michael Hölzel, University Hospital Bonn, Germany
Daniela Massi, University of Florence, Italy Mario Mandala, University of Perugia, Italy
Josep Malvehy, Fundació Clinic per la Recerca Biomédica (FCRB), Spain
Piotr Rutkowski, Maria Sklodowska-Curie National Research Institute of Oncology, Poland

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:
Corinne Bousquet, INSERM, France
Rémy Nicolle, INSERM, France
Luca Cardone, National Research Council (CNR), Italy
Jean-Luc Van Laethem, Université Libre de Bruxelles - Erasme University Hospital, Belgium
Elisa Espinet, Bellvitge Biomedical Research Institute (IDIBELL), Spain

Innovative mRNA vaccine against NSCLC: Designing a platform of targeted polymeric nanoparticles for efficient personalized therapy (TumorOUT)

Presented by Cristina Fornaguera
Universitat Ramon Llull (URL), Spain

Non-small cell lung cancer (NSCLC), is among the top six leading causes of death worldwide. Current treatments only enable low survival rates, highlighting the need for more efficient therapies. The cancer treatment paradigm has shifted to immunotherapies, which can double patient survival. They are based on the activation of the immune system against cancer cells, involving the whole tumour microenvironment (TME). However, the effect of this novel therapy is still limited to subsets of patients In this context, we aim to design a personalized nano-immunotherapeutic approach, based on the use of polymeric nanoparticles encapsulating nucleic acids. These will act as antigens to immunize patients against tumor antigens and achieve the self-killing of tumour cells; and immune-modulate the TME by silencing immunosuppressor genes.

To achieve this goal, we built a consortium comprising six experienced and recognized European groups. Specifically, we have clinical oncologists, experts on lung tumors, who will determine key antigens against which to vaccinate. We have molecular biologists and polymer chemistry experts on the synthesis of antigen mRNAs. In addition, we have experts on fine characterization at nanoscale, who will characterize the nanosystems and their interaction with biologicals. We also have experts on the in vitro characterization of efficacy, who will determine which formulation will be selected for the final in vivo therapeutic efficacy test, performed by the expert partner on orthotropic lung cancer models. Last, we will complete the project by transferring the technology to facilitate its arrival to the market.

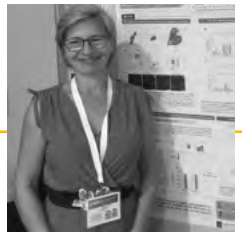
At the end, TumorOUT aims at having a validated, combined, personalized nanoimmunotherapy against NSCLC, ready to start regulatory preclinical and clinical trials.

Project Coordinator:
Cristina Fornaguera, Universitat Ramon Llull, Spain

Project Partners:
Rafael Rosell, Hospital Germans Trias i Pujol, Spain
Jan Dörrie, Universitätsklinikum Erlangen, Germany
Karsten Niehaus, Bielefeld University (UniBi), Germany
Nathalie Bonnefoy, Institut de Recherche en Cancérologie de Montpellier, INSERM, France
Dganit Danino, Technion, Israel Institute of Technology, Israel

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.

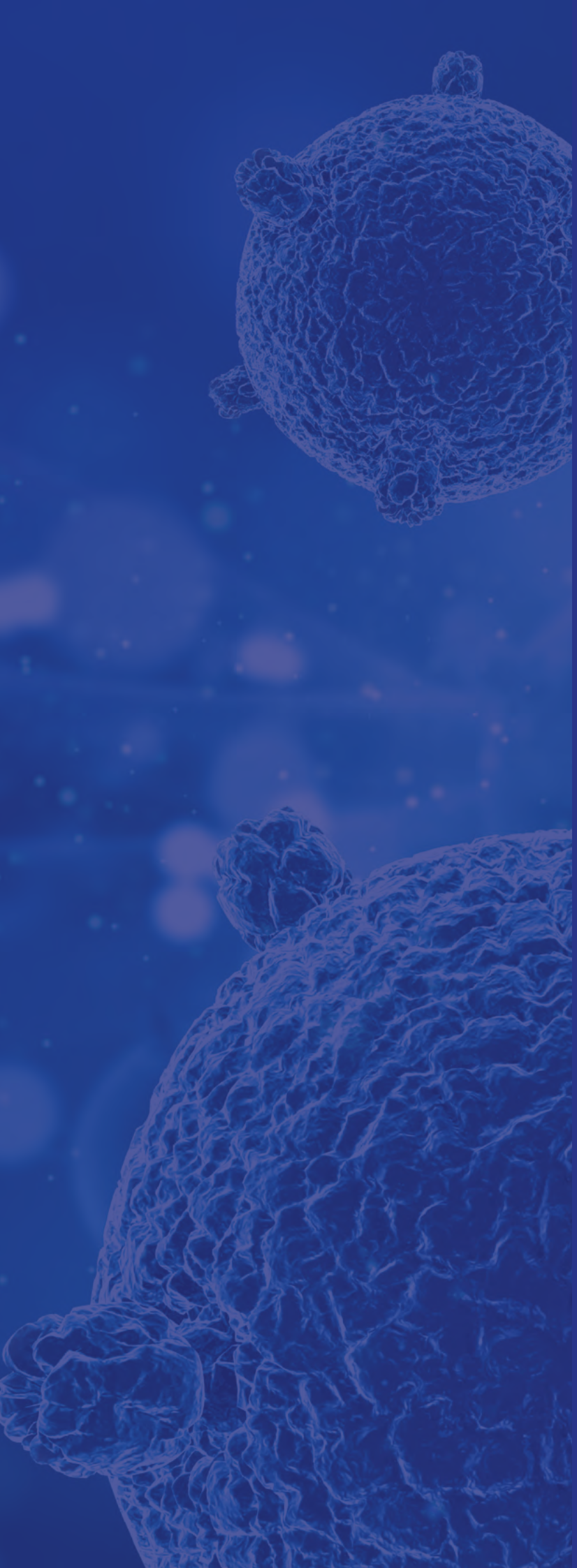
Hypothesis and aims: Implementation of liquid biopsy biomarkers will improve diagnosis, prognosis and prediction of IT response in UC patients. The main objective of this project is to identify molecular and cellular signatures from urine and blood samples to develop a robust and reproducible laboratory 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:
Marta Dueñas, Consorcio Centro de Investigación Biomédica en RED M.P. (CIBER), Spain

Project Partners:
Gökce Güllü Amuran, Marmara University, Türkiye
Carmen Jerónimo, Portuguese Oncology Institute of Porto Research Center, Portugal



Additional Speakers

With a B.A. in international law from the Catholic University of Milan, Italy and an M.A. in intellectual property (IP) law from the University of Alicante, Spain. **Michele Dubbini** is a Senior IP & Innovation Advisor and legal expert with more than nine years of experience in the field. Since 2014, he has supported the European IP Helpdesk as a speaker for webinars and on-site training events on IP Rights throughout Europe. Thanks to his international legal background and IP expert knowledge, he contributes to the creation and revision of consortium agreements and grant contracts for multinational research consortia and speaks at training events and workshops EURICE (European Research and Project Office GmbH) is involved in in the framework of H2020 and Horizon EU projects.

Yvonne Kohl is Senior Scientist in Toxicology and Deputy Head of the "Cell Models & Toxicology" Group at the Fraunhofer Institute for Biomedical Engineering IBMT (Germany). She holds a PhD in nanotoxicology and is PI of several national and international research projects. Currently, she is coordinator of the EU project ActiTOX (Active organotypic models for nanoparticle toxicological screening) and was coordinator of the TRANSCAN-2 project NExT. Her main research topics are focused on nanosafety assessment, biological in vitro barriers, advanced chip-based assays and miniaturized in vitro models. She is author of >35 peer-reviewed papers and Member of the German Society for Experimental and Clinical Pharmacology and Toxicology.

Project NExT: Due to their rarity, pancreatic neuroendocrine tumors (PanNETs) present significant challenges in their management. These challenges include difficulties in determining which patients would benefit from additional therapy, and assessing the response to treatment in a timely manner. By identifying specific novel biomarkers and developing methods for the early detection of PanNETs, the NExT project aimed to address these challenges. Thanks to the collaborative effort of 6 partners in Greece, Latvia, Slovakia, Spain and Germany, a biobank of tissue and blood samples from PanNET patients was established, and these samples were analyzed to study the molecular characteristics of the tumors. Several genes were identified that showed potential as diagnostic and prognostic markers for PanNETs. Protocols were also developed for growing PanNET cells in the laboratory using tissue samples obtained during surgery, enabling testing potential treatments.

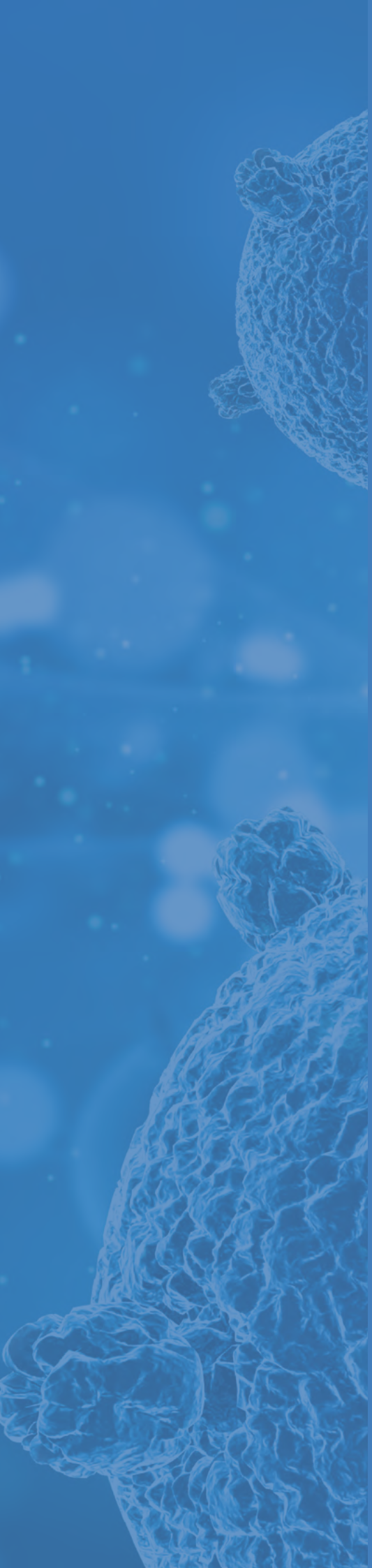
Hedwig Deubzer is the deputy medical director and research group leader at the Department of Pediatric Oncology & Hematology of Charité – Universitätsmedizin Berlin. Her lab strives to advance liquid biopsies for disease monitoring and personalized treatment of infants and children with neuroblastoma. Her research has a central focus on defining and combining the best biomarkers and analysis methods to optimally monitor evolving disease in the patient.

PD Dr. Med. Deubzer has coordinated the multinational collaborative project, LIQUIDHOPE, funded in the framework of TRANSCAN-2 Joint Transnational Call 2017 on "Translational research on rare cancers". The LIQUIDHOPE consortium combined internationally recognized experts in neuroblastoma pan-omics and computational discovery with leading pediatric oncologists to advance this emerging clinical paradigm change, which includes the use of liquid biopsies to monitor disease status in children with high-risk neuroblastoma. LIQUIDHOPE aimed to accelerate transfer of liquid biopsy approaches into the clinic within three parallel research arms designed to overcome current hurdles in (1) therapy response assessment, (2) minimal residual disease (MRD) monitoring and (3) actionable target identification, and define the best marker/analysis method or combination thereof for patient monitoring as its secondary aim. LIQUIDHOPE applied targeted metabolomics; cfDNA whole-exome sequencing; cfDNA transcriptional start site and methylation profiling; unbiased total RNA profiling to monitor long noncoding and circular RNA disease markers; droplet digital PCR of DNA/RNA disease markers; automated multiple marker imaging and sophisticated bioinformatics. LIQUIDHOPE identified potential predictive markers for treatment response, MRD, relapse and treatment choice in blood/bone marrow surrogates to advance unique liquid biopsy-based innovations for patient monitoring and personalized treatment of children battling neuroblastoma.

Bettina Ryll is the founder of the Melanoma Patient Network Europe and was member of the first EU Cancer Mission Board. A physician by training and with a PhD in Biomedical Sciences from University College London, she became a patient advocate after losing her husband to cancer.

Her work focuses on patient-centric innovation, covering the full spectrum from basic research over successful translation and clinical trials to timely and equitable implementation. Most recently and trigged by her work on the EU Cancer Mission Board, her particular interest has been how to best leverage the potential of personalized medicine for patients and society through novel forms of collaboration and the support of health policy and governance.

Bettina Ryll currently works as strategist for Vision Zero Cancer, a mission-driven innovation ecosystem in health financed by Sweden's Innovation Agency Vinnova.



Organizing Committee:

Liron Even-Faitelson, Chief Scientist Office, Ministry of Health, Israel
Maija Bundule, Latvian Council of Science, Latvia
Uldis Berkis, Latvian Council of Science, Latvia
Laura Kunga-Jēgere, Latvian Council of Science, Latvia
Maria Romero, Ministry of Health, Italy

Other contributors:

Foundation for the Promotion of Applied Scientific Research and Technology in Asturias, Spain
Regional Foundation for Biomedical Research, Lombardy Region, Italy
National Institute of Health, Italy
Tuscany Region, Italy
Alliance Against Cancer, Italy
Slovak Academy of Sciences, Slovakia

NOTES

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