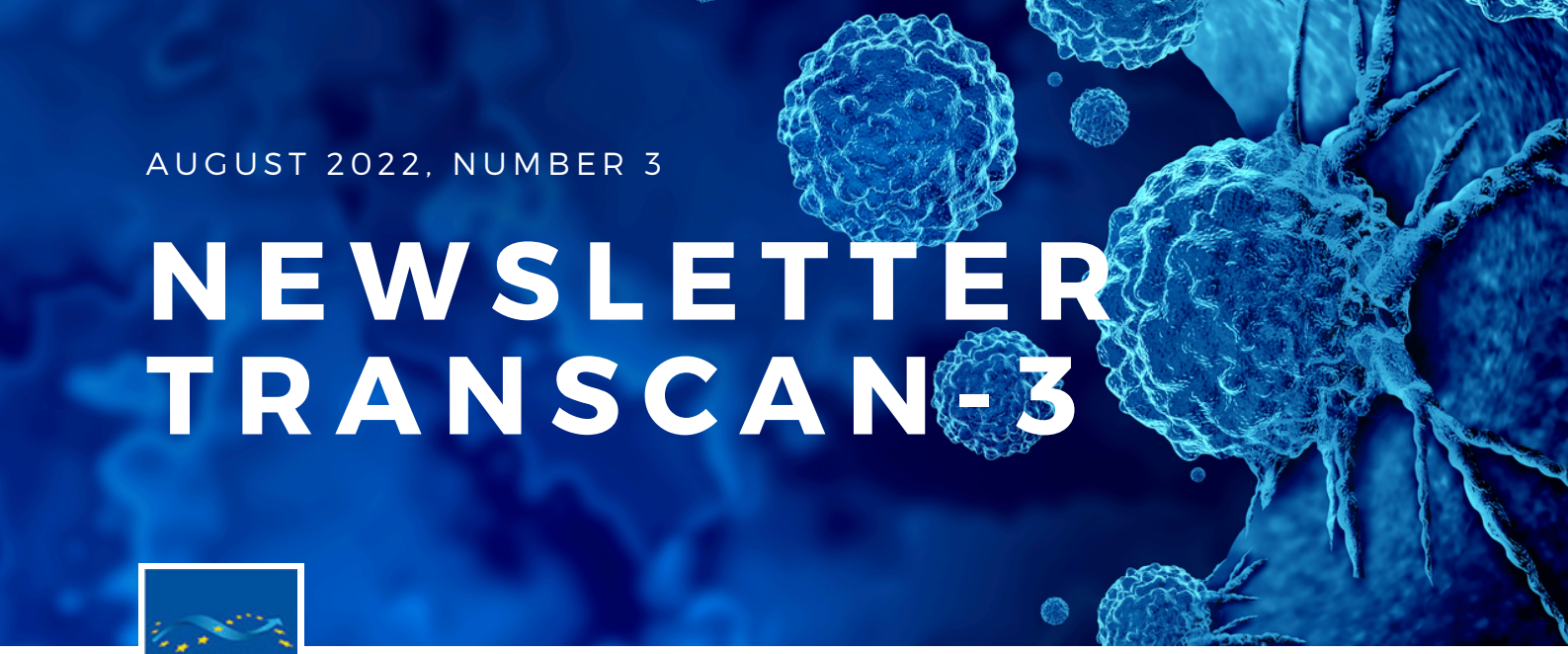

AUGUST 2022, NUMBER 3

NEWSLETTER TRANSCAN-3

On behalf of the TRANSCAN-3 consortium, we are happy to send you the 3rd newsletter. This newsletter issue opens with an interview with **Dr. Stephanie Houwaart**, TRANSCAN-3 Scientific Advisory Board (SAB) member and coordinator of patient interests of the German Cancer Aid, who provides a general vision of patient involvement in cancer research and the potential impact of engaging patients in programmes such as TRANSCAN-3. Read the interview **here**.

This issue also includes the **call statistics** and details of the **20 projects** chosen to be funded under the Joint Transnational Call co-funded by the European Commission (JTC 2021) on the topic: "**Next generation cancer immunotherapy: targeting the tumour microenvironment**".

In addition, on May 23, 2022, TRANSCAN-3 launched the second Joint Transnational Call for proposals (JTC 2022) focused on "**Novel translational approaches to tackle the challenges of hard-to-treat cancers from early diagnosis to therapy**". More information can be found **here**.

Most relevant **upcoming events and initiatives** promoted by TRANSCAN-3 partners can be found at the end of the newsletter.

Do not miss any TRANSCAN-3 news and the project results: visit the **new website**.

Follow our social media pages for periodical updates!

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An interview with the patient representative Dr. Stefanie Houwaart, TRANSCAN-3 SAB member and coordinator of patient interests of the German Cancer Aid

1 How would you define the concept of patient engagement in research? Which strategies can be followed for improving patient participation?

The concept of patient engagement can be illustrated as a "ladder of participation". The steps of this ladder stand for different degrees of intensity of engagement. From bottom to top those steps are: co-option, compliance, consultation, co-operation, co-learning and collective action. It is important to notice that **proper patient engagement starts with the step of consultation, since compliance refers to the involvement of patients as patients in clinical studies or as partners in interviews**. Especially qualitative research with patients is sometimes regarded as patient engagement which is not the case unless patients are a part of the team as collaborative partners, e.g. as peer interviewers. However, the ladder of participation does not rate the different degrees of participation. All of them are valuable and their useful implementation depends on the context.
In my opinion, the most important "strategy" is a genuine interest in the patient perspective, respect and empathy. I specifically name empathy, because this also encompasses **to accept and not to judge the experiences and needs of patients**. Which may not be easy at first as evaluation and criticism are vital aspects of science. That is why proper patient engagement may lead to an overall cultural change of science.

2 What is the expected contribution and impact of engaging patients in programs such as TRANSCAN-3?

Patient representatives contribute their specific perspective and expertise from the broad setting of living with certain health conditions. This is complementary to the scientific perspective and expertise of diseases and health problems. Thus, **the patient perspective brings more knowledge and data to the table enabling the investigation of problems from different angles and also to develop a more patient oriented research**. So, the expectation is to contribute knowledge and aspects that are specifically not a repetition of the scientific facts from a research perspective.
The impact of patient engagement can be very broad and diverse. It often leads to a more patient oriented research, e.g. a very practical impact would be the adaption of a study protocol to be more suitable for patients to take part in the study and thus improving patient recruitment and lowering drop out quotes. As equally important, patient engagement leads to relationships between scientists and patient representatives, to a mutual deeper understanding and often to further research ideas and collaborations.

3

What are the main hurdles hindering patient engagement in cancer research and how can we improve patient engagement in future cancer research?

There are different hurdles depending on what we are looking at. On the side of the patient representatives, we simply need more people to act as patient representatives. This people require resources: time, energy, financial support. They also need encouragement, which brings us to the other side – the scientific one. There we need a welcoming culture – the aforementioned genuine interest, but we also need to **enable patient representatives to co-research**. This can be done via qualification and the development of instruments, e.g. adapted evaluation forms, so that patient representatives are able to work scientifically.
Having listed some of the hurdles, it is evident that funding organizations play a crucial role in improving patient engagement in research. Via funding patient representatives as co-researchers in scientific projects and involving patient representatives in the implementation of funding calls and in review boards, funding organizations can significantly improve overall patient engagement. As a patient representative in the scientific advisory board of TRANSCAN-3 I am very thankful for the opportunity to bring in the patient perspective and discuss research calls with different stakeholders.

4

What do you expect most from cancer research in the next 5 years?

I expect a more holistic approach regarding cancer. Cancer research is mostly thought of research for new therapies or clinical trials. This is without a doubt of very high importance. But cancer affects the whole life of a person in their immediate setting – their family, friends, the workplace and also their financial situation. Since cancer is more and more a chronic than a deadly disease – thanks to all the therapies! – I expect **more research investigating and improving the life with cancer with all its various aspects.**

5

In your opinion, what is the biggest shortcoming in cancer research today that needs to be solved as soon as possible?

In my opinion as a patient representative, the biggest shortcoming is the insufficient patient orientation and the pressure to investigate “safe problems and harvest low hanging fruit”. The first one may seem to be strange since cancer research aims to help cancer patients. But it is tightly connected to the second one which is an overall systematic problem of how research is financed and as a result conducted. As far as I can see, at the moment cancer research is mostly results oriented and aims to be successful in the scope of projects. Additionally, research projects must also fulfil other scientific needs: publications, qualifications, career advancements and of course to receive further funding. As a former researcher myself I understand that. But this leads to investigating “safe problems”, while **we also need risky, creative and highly explorative research to tackle the still enormous challenges cancer patients and their clinicians are confronted with**. That for, all of us stakeholders need to talk about the research system and whether it works in a way to allow for the research that we need. And here, I think, lays the hope, expectation and contribution of patient engagement: **to lead towards a more patient oriented and more explorative research.**

Results of the EC co-funded Joint Transnational Call 2021

TRANSCAN-3 launched its first Joint Transnational Call (JTC) for research proposals, co-funded by the European Commission (EC), in April 2021 (JTC2021). In the framework of this call, 28 funding organizations from 19 countries, together with the EC, joint forces to fund the best collaborative transnational research projects under the topic of "Next generation cancer immunotherapy: targeting the tumour microenvironment". Ultimately, 20 transnational consortia were selected for funding with a total budget of 25.9 million Euros.

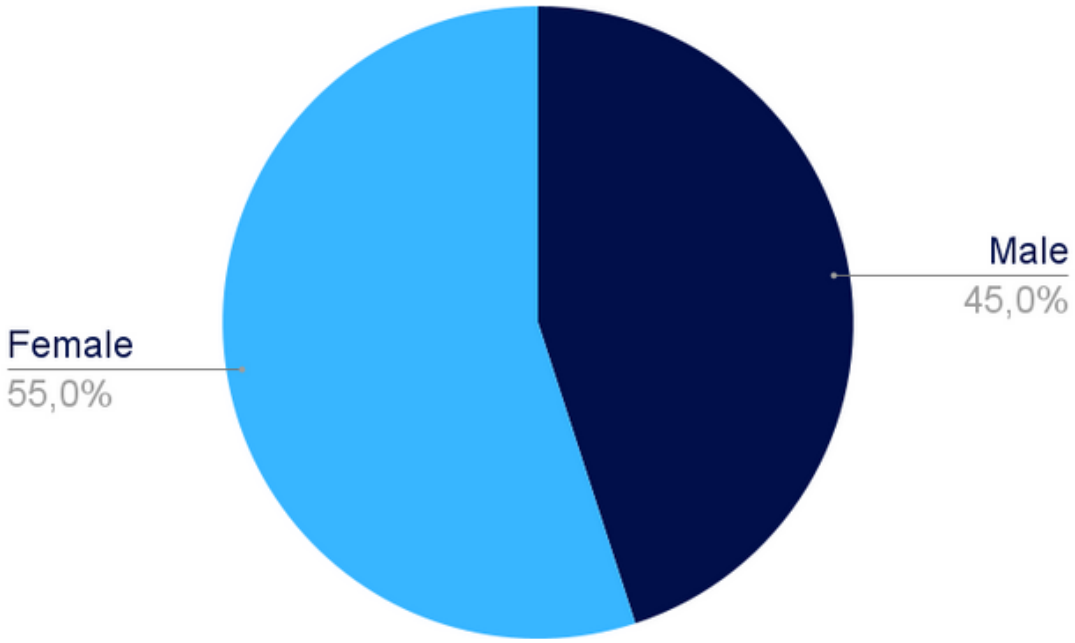
JTC 2021 Call statistics

The table below shows the number of countries and research groups for submitted pre-proposals, full proposals and funded projects. The overall success rate between the pre-proposals and the funded projects is 12%.

JTC 2021	#Proposals	# Countries involved	# Research groups
Eligible pre-proposals	161	19	737
Eligible full proposals	56	19	279
Funded projects	20	15	107

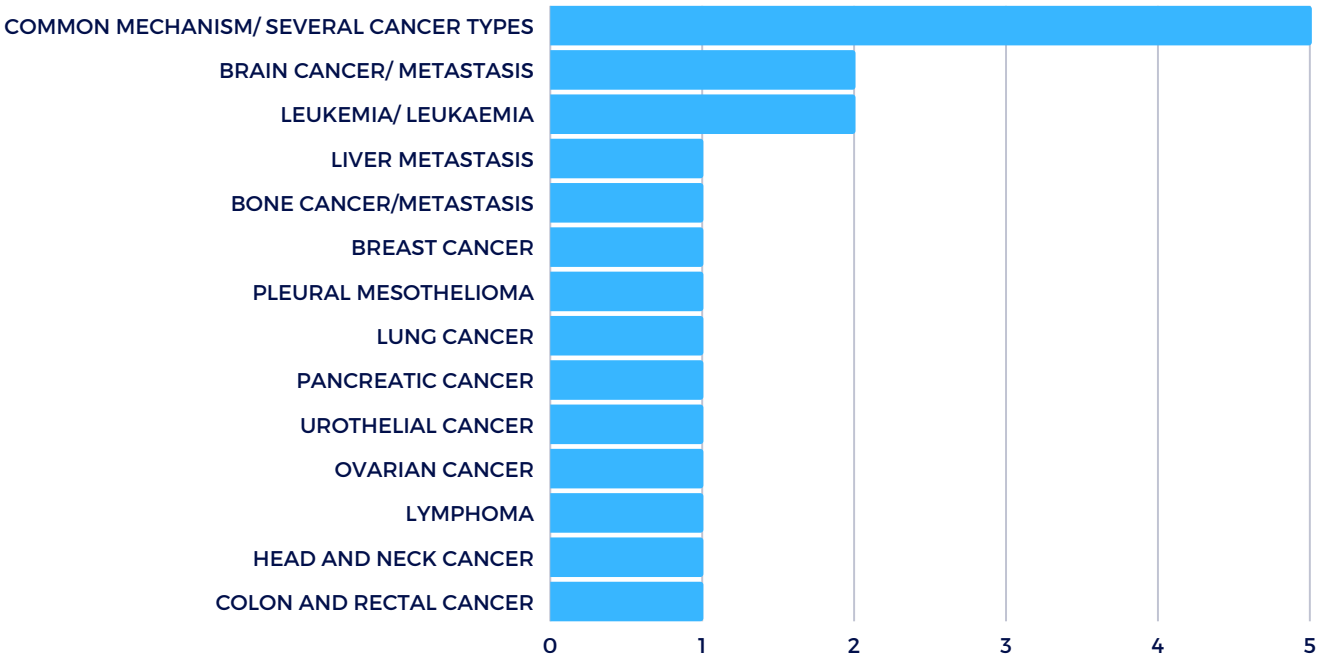
The graph below shows the gender distribution of coordinators for the funded projects. The gender distribution considering all research groups participating in the consortia shows instead a slightly different result, with 47% females and 53% males.

Gender distribution: Coordinators

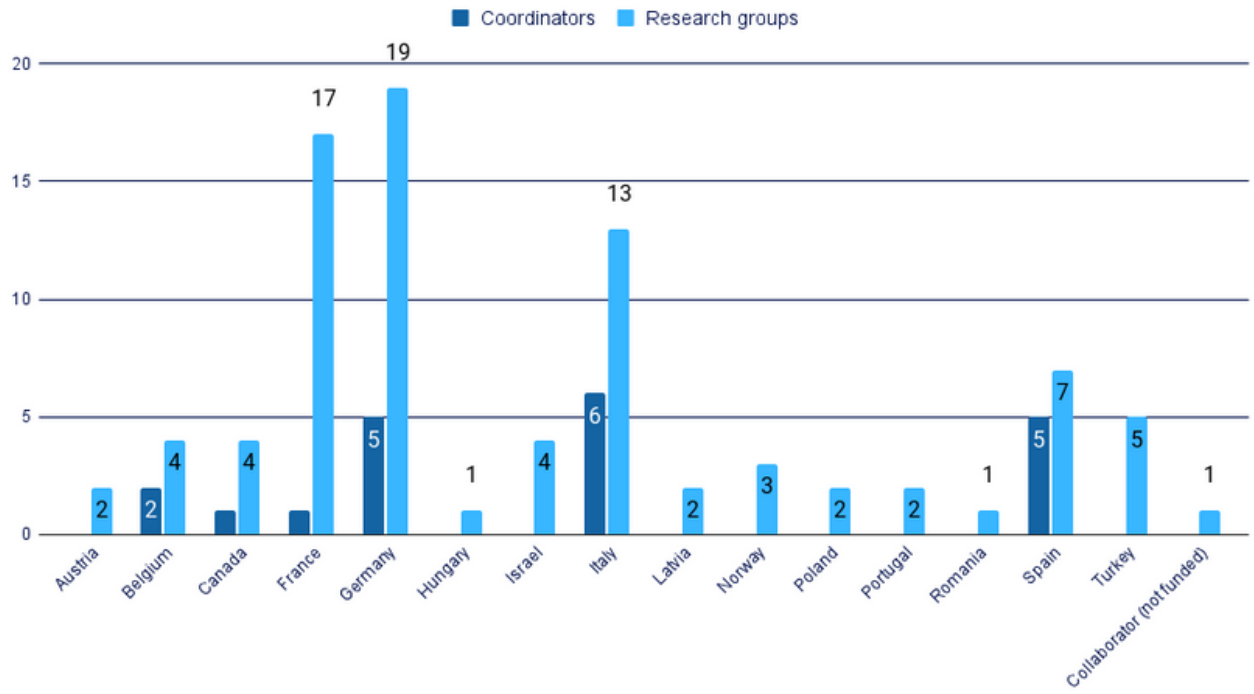


The following graph shows the cancer types that are studied in the framework of the funded projects. As illustrated, there is a wide variety of cancer types covered in awarded projects of this call, and a group of 5 projects focused on common cancer mechanisms and several cancer types.

Type of pathology – Funded Projects

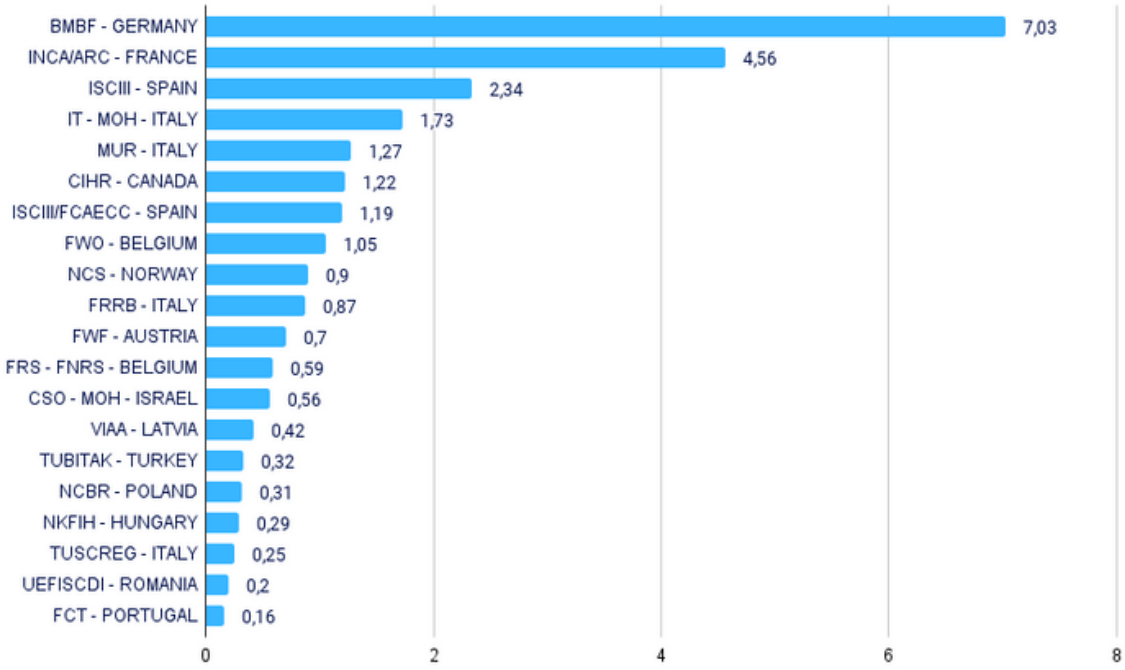


The graph below displays the geographical distribution of the coordinators and partners in the funded projects. As depicted, coordinators come from 6 different countries, the partners come from 15 different countries, and there is a research group that will participate in a funded project that will not receive funding from the consortium.



The following graph presents the budget dedicated (M€) for the funded projects by funding organisations, including EU Co-funding. The total budget requested for this call is 25.9 M€.

Funded Projects budget by Funding Organisation



Joint Transnational Call 2021, EC co-funded: list of funded projects (in alphabetical order according to their acronym)

1

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

Coordinator:
Fiorella Calabrese, University of Padova, Italy

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

Lay summary:
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.

2

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

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

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

Lay summary:
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.

3

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

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

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

Lay summary:
High grade serous ovarian cancer (HGSOC) is a highly 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 of importance to understand the tumor biology and take into account the whole tumor ecosystem, composed of tumor cells and their surrounding microenvironment. The tumor 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-tumor activity. Based on solid preliminary data, we consider that CAF and ILC are able to inhibit, putatively in a synergic way, anti-tumor functions of several immune components. The immunosuppressive TME induced by these cells could explain the immunotherapy resistance observed in HGSOC patients.
To go further in CAF and ILC characterization 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

To carry out our ambitious proposal, we'll use innovative technologies to study each cell individually and perform a fine tumors characterization 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.

4

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

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

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

Lay summary:
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, anti-resorptive 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.

5

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

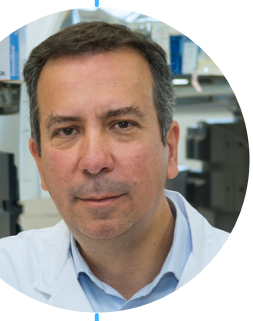
Coordinator:
Martina Seiffert, Deutsches Krebsforschungszentrum, Germany

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

Lay summary:
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.

6

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



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

Partners:
Ignacio Melero Bermejo, Fundación Instituto de Investigación Sanitaria de Navarra, Spain
Bruno Segui, INSERM, France
Jörg Wischhusen, University Hospital Wuerzburg, Germany
Gianluigi Giannelli, Ente Ospedaliero Specializzato in Gastroenterologia "Saverio de Bellis" – IRCCS, Italy
Pnar Pir, Gebze Technical University, Turkey

Lay summary:
Our consortium proposes the integrated study of immunosuppressive cytokines expressed in liver metastatic lesions. While most of the studies in immunooncology 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 5 highly relevant cytokines (TGFß, TNFa, IL8, LIF and GDF15) in liver metastasis. The reasons for this choice are: (i) Evidence for integrated regulation of this cytokine network; (ii) the expertise of the members of the consortium; (iii) inhibitory compounds against these targets are undergoing early clinical development in our institutions and serial biopsies from liver metastases are and will become available.

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 5 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.

7

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

Coordinator:
Diletta Di Mitri, IRCCS Istituto Clinico Humanitas – Humantas Mirasole SPA, Italy

Partners:
Giovanni Scambia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Italy
Daniela Quail, The royal institution for the advancement for learning/McGill university, Canada
María Casanova-Acebes, Centro Nacional de Investigaciones Oncológicas, CNIO, Spain

Lay summary:
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, intratumoral LLMs are elevated in response to overnutrition 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 overnutrition. 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.

8

MAppinG adaptatioN Of triple negative breast cancer microenvironments to ImmunotherApy (MAGNOLIA)

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

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, McGill University, Canada
Evelyne Meyer, University of Ghent, Belgium

Lay summary:
Triple negative breast cancer (TNBC) accounts for 15 to 20 percent 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 multiomics 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.

9

INTRAPERITONEAL IMMUNE MODULATION FOR COLORECTAL PERITONEAL METASTASES (PERIMMUNE)

Coordinator:
Wim Ceelen, Ghent University, Belgium

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, Turkey

Lay summary:
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 RNA seq 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 minipig model.
WP7. Project Coordination
Expected results and potential impact
This project will pave the way for IP immune modulation in patients with colorectal PM.

10

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

Coordinator:
Luca Aldo Edoardo Vago, IRCCS Ospedale San Raffaele, Italy

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

Lay summary:
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.
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.

11

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

Coordinator:
Paolo Dellabona, IRCCS San Raffaele Hospital, Italy

Partners:
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Oliver Schilling, University Medical Center Freiburg (UKL-FR), Germany
Guillaume Piessen, CHU de Lille, France

Lay summary:
Background, rationale. Esophageal adenocarcinoma (EAC) has aggressive loco-regional spread with median overall survival =1 year. EAC patients undergo neoadjuvant chemotherapy or chemoradiotherapy (NAC/R) and surgery. Only about 20% of treated patients achieve a pathological complete response (pCR) with downstaging of tumor and/or lymph nodes (LNs), and significantly increased 5-year survival compared to nonresponders. 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 hypothesise 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 them 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.

12

New immunotherapies targeting the key purinergic checkpoints in the tumor microenvironment (Pur-Ther)

Coordinator:
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Partners:
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ValérieVouret-Craviari, CNRS, 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

Lay summary:
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.

13

Reverting immune suppression to elicit brain metastasis control (RISEBrain)

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

Partners:
Itay Tirosh, Weizmann Institute of Science, Israel
Luca Bertero, University of Turin, Italy
Serap Aksu, Koç University, Turkey
Marc Schmitz, Institute of Immunology, Germany

Lay summary:
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. Thus, we hypothesize that lifting immune suppression locally is a pre-requisite to achieve full benefit of immunotherapies in BrM. Aim 1: we will apply RNAseq (single cell and bulk) and spatially resolved multispectral imaging to clinical cohorts of human BrM, including patients treated with ICB, to define, in a holistic approach, TME candidates that govern local immunosuppression and/or resistance to ICB in BrM. Aim 2: we will 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: we will leverage the data sets generated in Aim1 and 2 to 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.

14

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

Coordinator:
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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, Turkey

Lay summary:
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 (SLAMF7, BCMA), SCLC (ROR1, CD133) and ROR2 (cross-entity); and expression cassettes with co-receptors to destroy negative components in the TME and with inducible soluble factors cytokines and immune fusion proteins to modulate the TME.
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.

15

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

Coordinator:
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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

Lay summary:
Background, rationale
Survival of Acute Myeloid Leukemia (AML) is poor. To improve patients' outcomes, immunotherapy is a promising strategy. The causative role of immunosuppressive bone marrow (BM) microenvironment, where overexpression of immune checkpoint (IC) receptors, such as PD-1 and tryptophan degradation via indoleamine 2,3-dioxygenase (IDO)1 mediate immune-tolerance, is emerging. However, an early translation of IDO1 and IC inhibitors in AML has provided modest clinical results.
Hypothesis
IDO-1-based microenvironment mechanisms of resistance hamper AML immunotherapy
Aims
To explore TRANSCAN-3 AIM1, the following objectives will be addressed:
1. To decipher the composition of the BM microenvironment
2. To unravel the contribution of the microenvironment to resistance mechanisms
3. To functionally validate ex-vivo data by in vitro modeling
Methods BM samples will be collected from a cohort of AML patients prospectively enrolled in Phase 1-2 immunotherapy clinical trial with Azacitidine, anti-IDO1 (Epacadostat), and anti-PD1 (INCMGA00012). 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 (co-cultures, cell interactions).
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 resistance and the identification of biomarkers associated with response will affect clinical practice by improving patients' selection. The expected development of a novel platform for BM microenvironment investigation will impact technology transfer by providing advanced diagnostic tools.

16

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

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

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

Lay summary:
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.

17

TargEting the Nectin fAmily to boost Cancer ImmuniTY (TENACITY)

Coordinator:
Tobias Bald, University Hospital Bonn, Germany

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

Lay summary:
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 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 tumor 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.

18

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

Coordinator:
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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

Lay summary:
Pancreatic ductal adenocarcinoma (PDAC) is a cancer of high unmet need with rising incidence and bleak overall 5-year survival rates below 10%. The tumor 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 tumor 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 tumor 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 tumors 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 tumor'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.

19

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

Coordinator:
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Partners:
Rafael Rosell, Hospital Germans Trias i Pujol, Spain
Jan Dörrie, Erlangen-Nürnberg, Germany
Karsten Niehaus, Bielefeld University (UniBi), Germany
Nathalie Bonnefoy, INSERM, France
Dganit Danino, Technion, Israel Institute of Technology, Israel

Lay summary:
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 tumor 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 tumor cells; and immunomodulate 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, we will have a validated, combined, personalized nano-immunotherapy against NSCLC, ready to start regulatory preclinical and clinical trials.

20

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

Coordinator:
Marta Dueñas, Consorcio Centro de Investigación Biomédica en RED M.P. (CIBER), Spain

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

Lay summary:
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. 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 tumour microenvironment.
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 non-responding patients, which would not only avoid unnecessary suffering for many patients, but also a significant saving for healthcare systems.

Information about the ongoing call: JTC 2022

On May 23rd, 2022, ERA-NET TRANSCAN-3 launched its second call for proposals (**JTC 2022**) with the support of 23 organizations from 17 countries on the following topic: "**Novel translational approaches to tackle the challenges of hard-to-treat cancers from early diagnosis to therapy**"

In this second call, research projects must be centred on one or more of the **hard- to-treat-cancers (HTTC) subtypes** characterized by very poor prognosis (5-year survival rate<25%) and for which survival has not improved significantly over the last decades, namely glioblastoma, oesophageal, pancreatic, gallbladder, liver, and lung/pleural cancers.

Current difficulties include the inadequacy of standard diagnostic tools or established early detection methods in the general population, but also the inefficacy of available treatment options, due to intrinsic resistance and/or ineffective drug delivery. In this JTC 2022 proposals will have to cover at least one of the following aims:

Aim 1: Identification/validation of novel early diagnostic approaches
Aim 2: Identification/validation of novel therapeutic approaches
Aim 3: Development of novel drug delivery strategies

The call is closed for submission.

Next steps:

17 November 2022	Opening of the submission system for full proposals
15 December 2022 at 12:00 (CET)	Deadline for full-proposal submission
April 2023	Expected communication of the funding decisions to the applicants
September 2023	Expected project start (also subject to regional/national procedures)

International initiatives supported by TRANSCAN-3 partners

Fondation ARC Léopold Griffuel Award (France)

Created in 1970 in accordance with the late Mrs Griffuel's last will and testament, the **Fondation ARC Léopold Griffuel Award** from the Fondation ARC is one of the most important prizes in the field of cancer research in Europe. The award is divided into two distinct categories: **Basic Research Award & Translational and Clinical Award**.

Through two prizes of €150,000 each, the Fondation ARC rewards researchers whose work has led to a major breakthrough in basic research or in translational and clinical research in oncology. The **51th Fondation ARC Léopold Griffuel Award** will be awarded at an official ceremony on April 27, 2023 in Paris.

The application file must be submitted before October 3rd, 2022, 3:00 PM (GMT + 1).

For further information about the application, visit the following website or contact PrixARCLeopoldGriffuel@fondation-arc.org.

The VISION project (Slovakia)

The Biomedical Research Center of the Slovak Academy of Sciences (BMC SAS) is coordinating the EU-funded VISION project, together with researchers of the TRANSCAN-2 NeXT project (JTC2017), to promote strategies and initiatives to strengthen scientific excellence and innovation capacity for early diagnosis of gastrointestinal cancers. The list of invited lectures and courses organized by the VISION project foreseen between October 2022 and February 2023 are the following:

- **October 5, 2022, invited lecture**
  Tumor-associated Macrophages: re-education with Lipid Nanoparticles to avoid Liver Metastasis in PDAC (**Adrián Palencia Campos**, Ph.D. student, Cancer Stem Cells and Fibroinflamatory Tumor Microenvironment Group, Ramon y Cajal University Hospital (IRYCIS), Madrid, Spain)

- **October 19, 2022, course**
  Gastrointestinal Stromal Tumours (GIST).
  A series of 3 lectures prepared by the team of (Prof. **Nikolaos Memos, Hippokration General Hospital, Athens, Greece**):
  1. The pathology and molecular mapping of GIST (**George Agrogiannis, MD, Ph.D**)
  2. Surgical challenges of GIST tumors (**Nikolaos Memos, MD, Ph.D**)
  3. Targeted therapy for GIST (**Jose Duran Moreno, MD, MSc**)

- **November 30, 2022, invited lecture**
  Next-generation sequencing in cancer research and diagnosis (**Pantelis Hatzis**, Ph.D. Institute for Fundamental Biomedical Research and Head of Fleming Genomics Facility in the Biomedical Sciences Research Center 'Alexander Fleming' in Athens, Greece)

- **February 8, 2023, invited lecture**
  Radiomics and radiogenomics in cancer (**Dr. Carolina de la Pinta**, Radiation Oncologist, Ramon y Cajal University Hospital (IRYCIS), Madrid, Spain).

Information about the events and the registration form can be found here.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 964264.