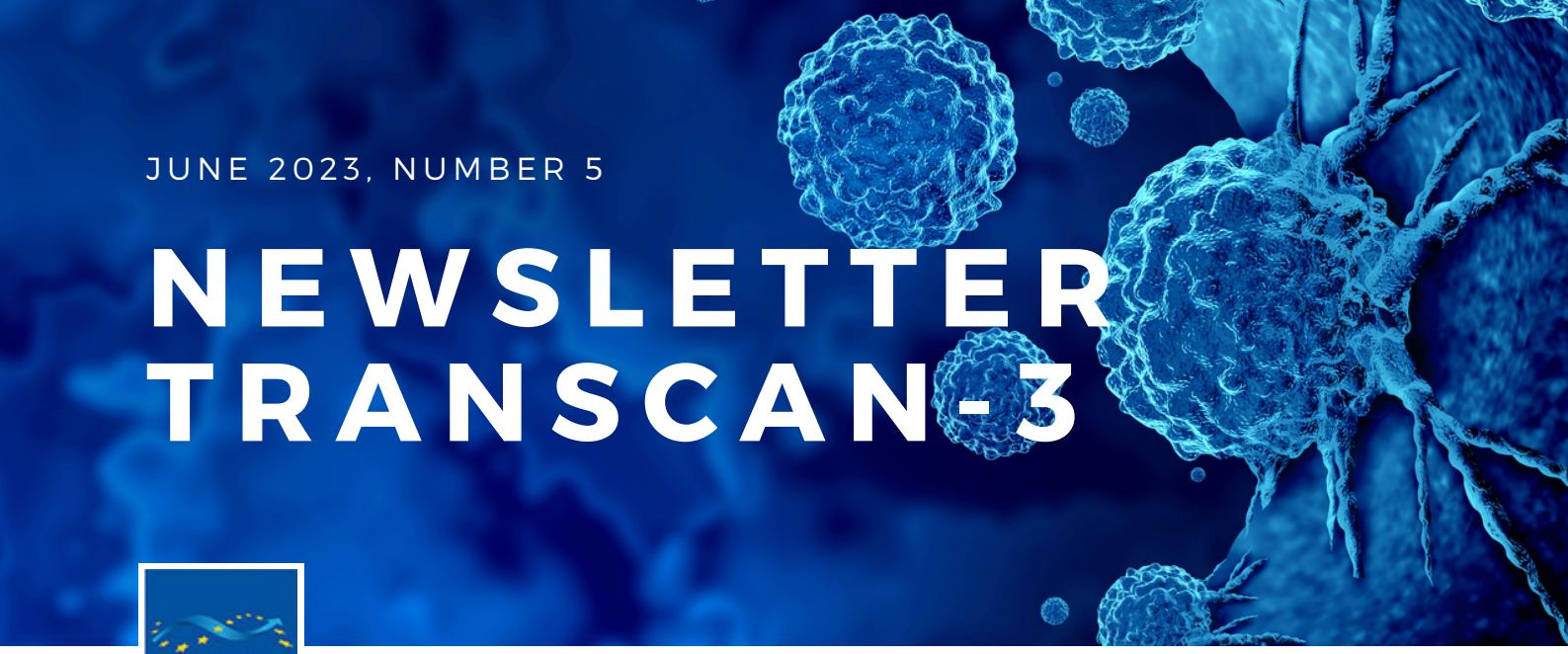

JUNE 2023, NUMBER 5

NEWSLETTER TRANSCAN-3

On behalf of the TRANSCAN-3 consortium, we are happy to present the 5th newsletter of the project with updates on calls for proposals, funded projects, events and more!

This issue includes:

- Updates on TRANSCAN-3 activities and events
- Statistics JTC 2022
- Summary of funded Projects JTC 2022
- Updates about JTC 2023
- Cancer-related initiatives from TRANSCAN-3 partners

Enjoy reading!

Do not miss any TRANSCAN-3 news and the project results visiting the project website.
Follow our social media pages for periodical updates!

- LinkedIn
- Twitter

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1. Update on TRANSCAN–3 activities and events

Two and a half years in and **TRANSCAN-3 is advancing successfully thanks to the cross-national cooperation** of 31 funding organisations, from 20 countries, with the common goal of supporting high-impact translational cancer research!

After the successful completion of **the co-funded** Joint Transnational Call 2021 (**JTC 2021**) on the topic of **"Next generation cancer immunotherapy: targeting the tumour microenvironment"**, the 20 projects that were awarded are now up and running boosting international cancer research.

Earlier this year the TRANSCAN-3 team gathered in Florence, Italy with the Scientific Advisory Board to review the progress of the TRANSCAN-3 project and to integrate their advice.

Moreover, the **evaluation of the full proposals of JTC 2022 on "Novel translational approaches to tackle the challenges of hard-to-treat cancers from early diagnosis to therapy"** by the Scientific Evaluation Committee took place during this meeting.

After this fruitful meeting the final list of the 14 successful consortia was established and communicated to the researchers. Check out the call statistics (2) and the awarded projects (3) in the upcoming sections!

Moreover, the team also worked on getting everything ready for the third call **JTC 2023 on the topic of "Translational research on cancer epigenetics"** (4) and started preparing for the first **Scientific Symposium that will take place in Riga, Latvia this fall on October 17th and 18th.**

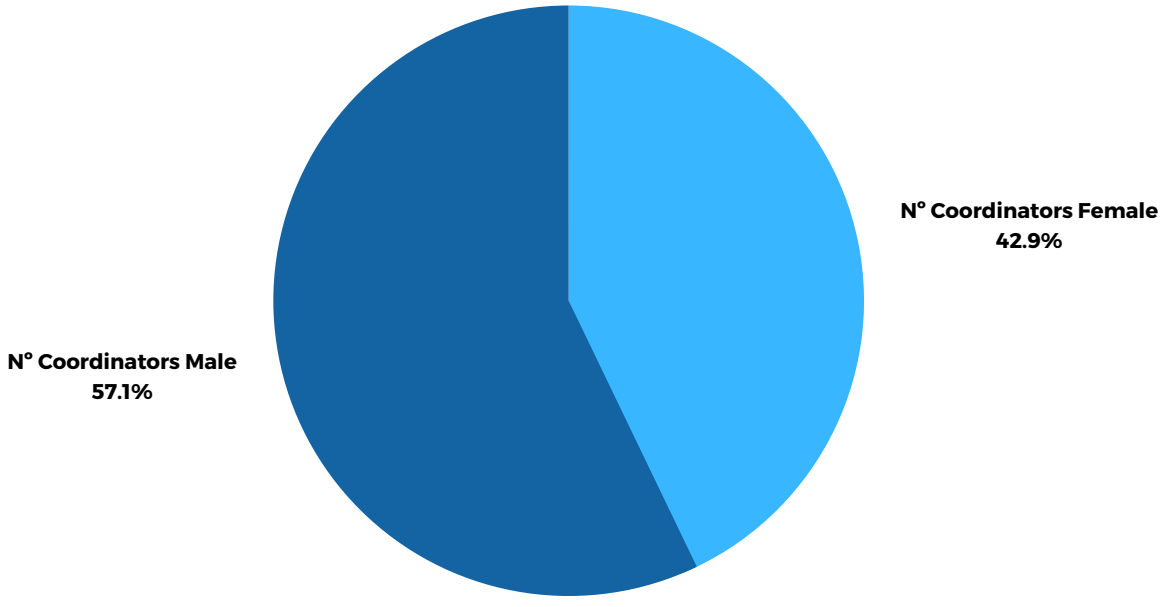
2. Statistics from JTC 2022

JTC 2022 Call statistics

JTC 2022	# Proposals	# Countries involved	# Research groups
Eligible pre-proposals	70	17	307
Eligible full proposals	40	17	191
Funded projects	14	15	64

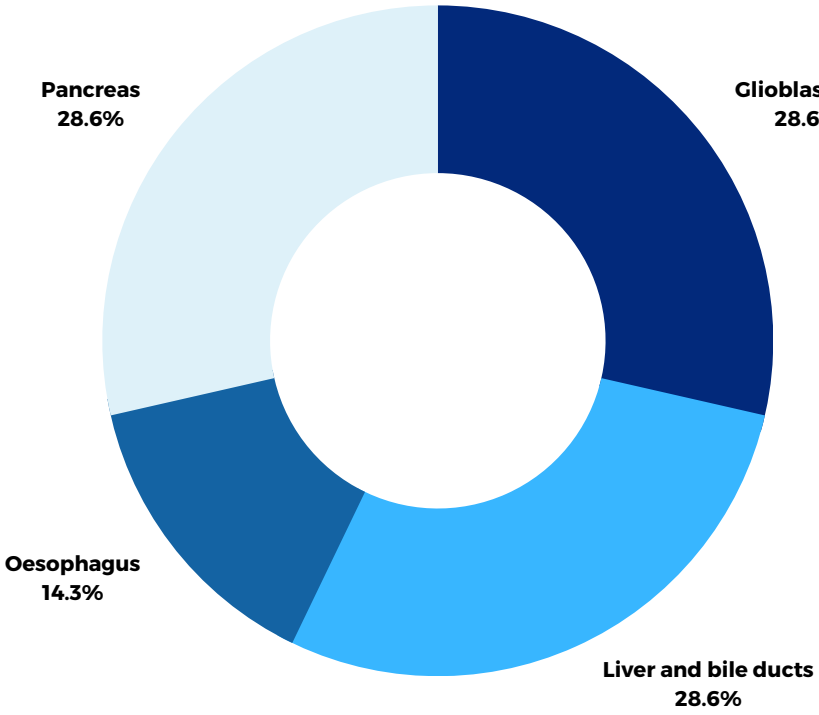
The table shows the number of countries and research groups for submitted pre-proposals, full proposals and funded projects. The overall success rate between the pre-proposals and the funded projects is 20% and the success rate referred to the full proposals is 35%.

Gender distribution of coordinators – Funded projects

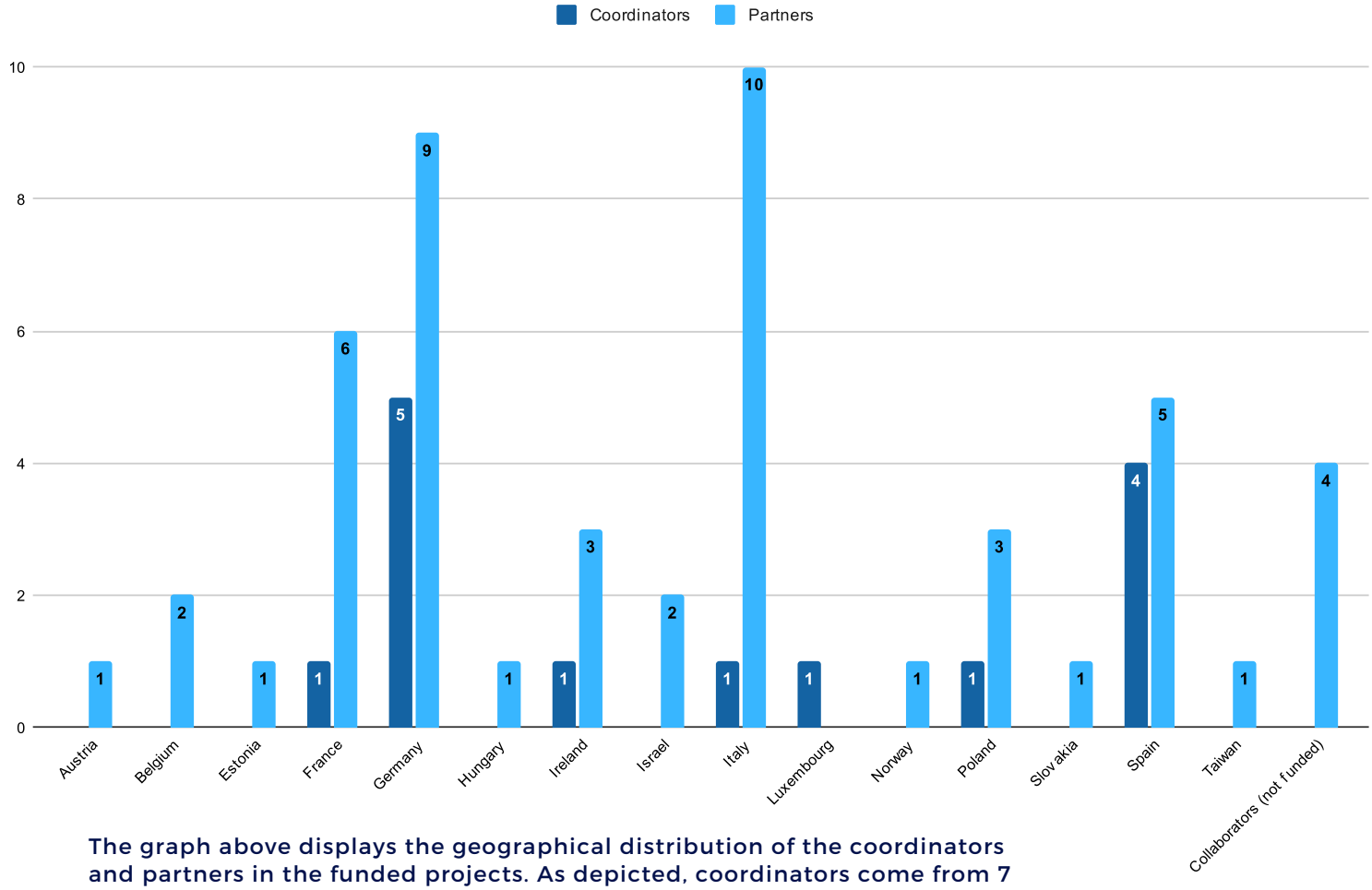


The graph shows the gender distribution of coordinators for the funded projects which reflects a low difference between male and female coordinators distribution.

Type of cancer – Funded Projects

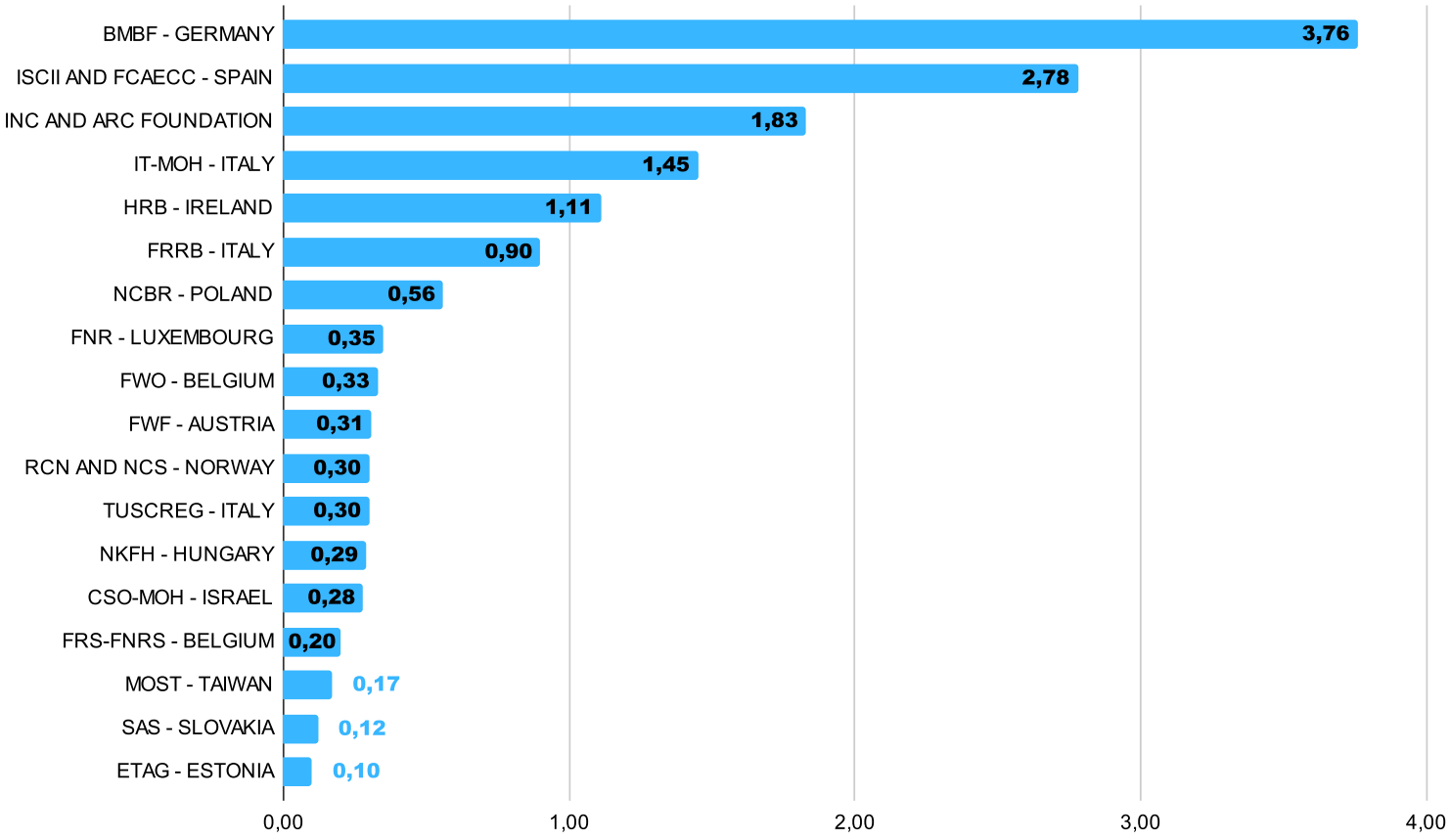


Geographical distribution of coordinators and partners – Funded projects



The graph above displays the geographical distribution of the coordinators and partners in the funded projects. As depicted, coordinators come from 7 different countries, the partners come from 14 different countries, and there are 4 research groups that will participate in funded projects that will not receive funding from the consortium.

Funded Projects budget by Funding Organisation



The graph presents the budget dedicated (M€) for the funded projects by funding organisations. The total budget invested in this call is 15.1 M€.

3. JTC 2022: list of funded projects

1

ANGELA: Early detection of esophageal squamous cell carcinoma with the Cytosponge coupled with molecular biomarkers and machine learning

Coordinator:
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Partners:
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Miloslav Karhánek, Slovak Academy of Sciences, Bratislava, Slovakia
Marcel Gehrung, Cyted Ltd., Cambridge, England

Background: Esophageal squamous cell carcinoma (ESCC) carries significant mortality and remains the predominant type of esophageal cancer worldwide. Since a potential screening regime for ESCC would have to rely on endoscopy, this creates substantial challenges regarding its cost-effectiveness and applicability. Therefore, we hypothesize that a non-endoscopic Cytosponge cell collection device could provide a novel approach to ESCC screening.

Aims: The primary aim is to evaluate the diagnostic yield of Cytosponge combined with tissue biomarkers (p53-immunohistochemistry[p53-IHC]) and molecular biomarkers for detecting ESCC and its precursor lesions. As secondary aims, we plan to assess the utility of machine learning-based approaches to assist pathological assessment of the Cytosponge samples. Lastly, we aim to investigate the use of Cytosponge in sampling the esophageal microbiota and its potential role in identifying at-risk individuals for ESCC utilizing microbial biomarkers.

Methods: In this multicentre study, we plan to recruit patients within three risk groups for ESCC: 1. healthy controls, 2. high-risk individuals (previous head-and neck cancer/ ESCC), and 3. patients with known early ESCC. Each patient will undergo high-definition endoscopy and a Cytosponge examination. The biomarker assay, including p53-IHC and shallow whole genome sequencing, will be tested within the Cytosponge samples and compared with the final endoscopic diagnosis. Machine learning algorithms will be applied to digitalized cytology to detect atypical cells and regions of p53-IHC overexpression. Lastly, we will extract microbial DNA from Cytosponge samples to assess any taxonomic diversity within three risk groups for ESCC.
Potential impact: We hope to develop a novel, effective, and affordable diagnostic assay that, coupled with a minimally-invasive Cytosponge device, could be implemented in a clinical setting, improving the early detection of ESCC and, eventually, patient outcomes.

2

BileCanMet: Precision medicine in cholangiocarcinoma: accurate tools for early detection and identification of PRMT5 as a novel pharmacological target

Coordinator:
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Partners:
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Christian Trautwein, RWTH Aachen University Clinic, Aachen, Germany
Meritxell Huch, Max Planck Institute of Molecular Cell Biology and Genetic, Dresden, Germany

Background: Cholangiocarcinoma (CCA) patients´ survival 5 years post diagnosis is <10%. This is mainly due to late diagnosis and few effective drugs, including some targeted agents. Better tools for early accurate diagnosis and effective therapies are needed.

Hypothesis: 1. NGS-based mutagenic analysis of bile cell free DNA (cfDNA) has very high sensitivity for early CCA diagnosis, far superior to current procedures. Thus, bile may be a liquid biopsy matrix to detect CCA. 2. CCA treatment can be improved by targeting epigenetic pathways.

Aims: 1. Demonstration of bile as a liquid biopsy matrix for CCA diagnosis. Primary: Prospective validation of bile cfDNA NGS analysis as a diagnostic tool in patients with suspicion of CCA. Secondary: Characterize the bile bacterial microbiome and bile acid (BA) profile in CCA patients. 2. Identification of protein arginine methyltransferase 5 (PRMT5) as a novel target in CCA. Primary: Validate PRMT5 overexpression in CCAs and the antitumoral effects of its inhibition. Secondary: Identify PRMT5's mechanisms in CCA development and drug resistance.

Methods: Aim 1. We will collect bile from patients with newly diagnosed undetermined biliary stenoses and test bile cfDNA with a commercial NGS panel. Diagnostic sensitivity and specificity will be compared with current clinical tools. We will analyse bile microbiome and BA profile, establishing clinical correlations. Aim 2. We will confirm PRMT5 expression in large cohorts of CCA tissues. Clinical correlations will be established. We will test antitumoral effects of PRMT5 inhibition in CCA cells, organoids and relevant mouse models. Molecular mechanisms will be studied.

Expected results and impact: Bile cfDNA NGS analysis will revolutionize CCA diagnostic speed and accuracy. Candidates for targeted therapy will be identified. Analysis of bile microbiome and BAs will provide pathogenic insights. PRMT5 validation as therapeutic target will accelerate the performance of clinical trials.

3

CAR4PDAC: Hijacking stroma antigens for CAR–T cell immunotherapy of PDAC

Coordinator:
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Partners:
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Anna Mondino, IRCCS Ospedale San Raffaele, Milan, Italy
Hana Agül, Comprehensive Cancer Center Munich TUM, Munich, Germany

Pancreatic adenocarcinoma (PDAC) represents one of the most lethal Hard-To-Treat Cancers, accounting for more than 90% of pancreatic malignancies and being predicted to become the second leading cause of cancer-related death by 2030. To address such a cogent unmet medical need, CAR4PDAC project plans the delivery of a novel and alternative therapeutic approach based on the targeting of the fibronectin/integrin axis by Chimeric Antigen Receptor (CAR)-T cells. Such strategy is expected to overrule the contribution of fibronectin, its extradomain A (EDA) spliced version, and of integrins to tumour growth, migration, invasion and to the reorganization of the tumour extracellular matrix and intratumor immunosuppression. Our preliminary data indicate that CAR-T cells targeting EDA show antitumor effect in several tumour models expressing EDA in the tumour extracellular matrix, and that EDA is highly expressed in PDAC tumour stroma. Moreover, an anti-avb6/avb8 dual targeting CAR-T can recognize mouse and human PDAC in vitro and in vivo. Thus, evidence produced by the CAR4PDAC consortium indicates that EDA and avb6/avb8 integrins represent potential novel CAR-T cell targets for PDAC treatment. Combining relevant mouse models, patient-derived organoids and state-of-the-art genomic technologies, the specific objectives foresee: 1) the preclinical validation of EDA and avb6/avb8 integrins as antigens in PDAC samples of available biobanks and human organoids. 2) their targeting by CAR-T cells against PDAC in mouse models, patient-derived xenografts and human organoids. 3) understanding the molecular mechanism behind CAR-T function. 4) the delivery of CAR-T manufacturing under GMP conditions and the accrual of data for the compilation of an IMPD. Expected results should impact the management of PDAC patients lacking therapeutic options, by the delivery of proprietary tools suitable for clinical and commercial development by existing European enterprises and medical centres.

4

iCC-Strat: Risk stratification and subtyping of intrahepatic cholangiocarcinoma for early detection of recurrence and response to immuno-therapy

Coordinator:
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Partners:
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Sandrine Katsahian, Institut national de la santé et de la recherche médicale, Paris, France
Andras Kiss, Semmelweis University, Budapest, Hungary

Background: Intrahepatic cholangiocarcinoma (ICC) is the second most prevalent hepatic cancer with 5-year survival rates below 10%. Tumours are often detected in advanced stages. Surgical resection is limited to non-advanced cases. Cytotoxic chemotherapy has only a moderate benefit. Most patients present recurrent ICC. Repeat treatment is life-prolonging but requires early diagnosis. Our preliminary data demonstrate that the proteome of primary ICC enables stratification of recurrence risk. Immune checkpoint blockade is an option but only for a subset of ICC patients.

Hypotheses: (a) after initial treatment blood profiling using genomics or proteomics will enable early diagnosis of recurrent ICC; (b) histomorphological, genomic, and (phospho-)proteomic profiling of primary ICC will yield markers for stratification of (early) recurrence risk; (c) single-cell profiling ICC undergoing immune therapy will uncover molecular markers for response and delayed recurrence.

Methods: We will assemble a multi-centre ICC cohort (n > 550). Genomic, (phospho-)proteomic, and histo-morphological profiling will be performed. For ICC cases undergoing immuno-therapy (n > 50) we will perform single-cell RNA-seq and single-cell GET-seq to assess copy number variation, epigenetic landscapes, and chromatin dynamics. Liquid biopsies (blood) obtained from 60 ICC patients will be obtained at 3-, 6-, and 12-months posttreatment to probe cell-free DNA, circulating tumor cells, and serum proteome for markers of recurrent ICC. Data will be analysed in an integrated manner by an expert in the field using statistical methods that are adequate for omics-type data.

Results and impact: Proteomic or genomic determinants in primary ICC that are prognostic for recurrence enable tailored follow-up schemes. Circulating markers that signal recurrent ICC enable timely intervention. Cellular profiles indicative of response to immuno-therapy enable tailored therapies even for advanced ICC to delay recurrence.

5

IdeaTMEHCC: Identification of therapeutic targets using HCC DErived organoid Augmented with TME components.

Coordinator:
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Partners:
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Diego Calvisi, Institute of Pathology University of Regensburg, Regensburg, Germany
Yu-Yun Shao, National Taiwan University Hospital, Taipei, Taiwan

Background: More than 70% of Hepatocellular carcinoma (HCC) are diagnosed in advanced stage, with a 5-year survival rate of ˜20%, consistent with the definition of Hard-To-Treat Cancer. Despite encouraging results, all in all the treatment for HCC is far from adequate and new therapies are imperative to improve patients' outcome. Patient-derived-organoids (PDO) , represented a breakthrough in the field of drugs screening and personalized therapeutics. In keeping with this, HCC-PDO were successfully used as a proof-of-concept to screen new drugs for HCC. Current HCCPDO, however, lacks Tumour Microenvironment (TME) component, a major limitation taking into consideration that several HCC treatments are TME-(vascular; immune)-modulators.

Rationale: Preliminary data show that HCC vascular TME influences response to anti-angiogenic but not to immune modulators drugs. IDEA-TMEHCC is therefore based on the IDEA to explore on an adequate preclinical model, how TME components influence HCC response to drugs. The research hypothesis is to create HCC-PDO enriched with different types of TME and test on these models available and experimental drugs for HCC.

Aims: 1) To create TME enriched-HCC-PDO; 2) To explore connections between TMEs and HCC drug efficacy using TME enriched-HCC-PDO; 3) To understand the determinants of drug response using spatial and molecular approaches
Methods: Prospectively collect biological specimen from 250 HCC and generate TME enriched PDO. Evaluate the effect of drugs for HCC on TME enriched PDO. Understand the determinants of response by molecular characterization and spatial transcriptomic analysis.

Expected results and potential impact: We expect to establish 70 PDO with different typologies of TME; to identify TME-specific drug sensitivities and predictors of treatment benefit. The impact will be to better stratify HCC patients and improve patients' outcome.

6

MATTO-GBM: Multimodality Artificial intelligence open-source Tools for Radiation Treatment Optimization in patients with Glioblastoma

Coordinator:
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Partners:
Luis Martí-Bonmatí, Fundación para la investigación del Hospital Universitario La Fe de la Comunidad Valenciana ,Valencia, Spain
Radu Grosu, Vienna University of Technology, Vienna, Austria
Segundo Francisco García Argüello, Fundación General Universidad de Málaga - Unidad de Imagen Molecular, Málaga, Spain

Background: Diagnosis, staging/treatment of Glioblastomas (GBM) has been commonly based on Magnetic Resonance (MR). The standard treatment includes the macroscopically complete tumour resection followed by radiotherapy treatment (RT) with concurrent temozolomide chemotherapy. Unfortunately, 90% of GBM progress within 2 years.

Hypothesis: Positron Emission Tomography (PET) based on the amino-acid radiotracer O-(2)-18F-Fluoroethyl-LTyrosine (FET) has been proposed to overcome MR limitations when differentiating local recurrence (LR) from radiogenic alterations. A personalized RT strategy based on tumour heterogeneity, defined by multimodality imaging, could allow escalating RT treatment doses to high-risk tumour subareas while sparing doses in organs at risk.

Aims primary/secondary: We aim to identify biologically active tumour tissue associated with LR in GBM by the best imaging modality (or combination), in order to replace the homogeneous dose distribution conventionally delivered in RT, by a dose distribution scaled based on the patient's specific risk profile of LR.

Methods: Our project involves 410 patients 2 prospective/ 2 retrospective cohorts. 120 patients have MRs and PET before RT and 230 additionally for the follow-up. From them, 30 will be imaged by an hybrid PET/MR. Artificial intelligence will be applied for GBM segmentation, for prediction of LR time and location, for generating CT from MR and for identification of patient groups (clustering), who could benefit from a given dose escalation in RT, based on radiobiological modelling.

Expected results and potential impact: All resulted models will be joined in an open-source tool making possible the integration of results by different health institutions worldwide, in order to adapt GBM treatment based on the individual risk pattern. Our proposal represents therefore an important step in personalized medicine for GBM. An improvement in patient care and quality of life is therefore expected.

7

NK-4-GBM: Metabolically optimised NK cell therapies for Glioblastoma

Coordinator:
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Partners:
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Sophie Lucas, Université catholique de Louvain, Bruxelles, Belgium
Karl-Johan Malmberg, Universitetet i Oslo, Oslo, Norway

Background: Glioblastoma Multiforme (GBM) is an incurable form of brain cancer. However, there is now an opportunity to apply the advances in cellular immunotherapy to treat GBM. Natural Killer (NK) cells are cytotoxic lymphocytes that kill tumour cells. However, GBM tumours create an environment rich in metabolites (eg. fatty acids) and proteins (eg. TGFβ) that potently suppress NK cell metabolism and cytotoxicity.

Hypothesis: The metabolic microenvironment of GBM is a key driver of NK cell dysfunction and a limiting factor for NK cell immunotherapies.

Aims: Our primary aim is to establish the nature the suppressive metabolic tumour microenvironment (TME) and to understand how this interferes with infiltrating NK cells. This will guide our secondary aim of developing novel approaches to bolster NK cell metabolism for enhanced cytotoxic activities against GBM tumours.

Methods: Spatial distribution of the metabo-lipidome and TGFβ actions within GBM tumours will be performed by DESI-/MALDI-mass spec imaging (Germany) and multiplex immunofluorescence imaging (Belgium). Modelling will estimate the relationship between metabolites, lipids, TGFβ Pathway components and the immunological landscape with respect to NK cells abundance and functionality (Ireland/Germany). Flow cytometry, confocal and electron microscopy (Ireland/Norway), will define the metabolic phenotype of GBM infiltrating NK cells. Identified strategies such as genetic engineering of NK cells and/or antibody blockade of TGFβ axis for metabolic resilience will be tested in a murine GBM model and applied to human NK cell therapeutic platforms (Norway) towards generating cellular products for clinical trials.

Expected results and potential impact: This research will determine the metabolic restraints experienced by GBM infiltrating NK cells that impair cytotoxicity and develop new strategies to bolster therapeutic NK cells to open a new horizon for effective NK cell-based immunotherapies for GBM.

8

PaCaNano: Development of a pancreatic cancer drug–nanocarrier system selectively targeting tumour cells and tumour stroma to overcome treatment failure

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Partners:
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Pieter Van der Veken, Universiteit Antwerpen, Wilrijk, Belgium
Annarosa Arcangeli, University of Florence, Florence, Italy
Lapo Bencini, Azienda Ospedaliero-universitaria Careggi, Florence, Italy

PaCaNano hypothesizes that therapeutic failure in pancreatic cancer (PC) can be overcome via a novel nanoparticle (NP) technology that allows targeting both cancer and stroma cells. To deliver proof-of-concept, we have selected gemcitabine phosphate (GemP) nanoparticles, recently developed by project partners KIT and UMG. These NPs have a very high gemcitabine load (80% by mass) and have already shown preclinical promise in PC. PaCaNano aims to further optimise these NPs by adding 'tumour homing' units: 1) a 'diabody', patented by partner UNIFI, that will guide GemP-NPs to PC cancer cells. 2) Alternatively, a UAMC1110 derivative will be used that offers specificity for FAP+ cancer-associated fibroblasts (CAFs). UAMC1110 was discovered by partner UANTWERP. It is the CAF-targeting unit of all 'FAPI' theranostics.

We will also add FAP-activatable, non-toxic chemotherapy prodrugs to the stroma-targeting NPs. For this, SN38, vedotin and daunorubicin have been selected. SN38 is the toxic, active metabolite of irinotecan which is also part of the FOLFIRINOX therapy in PC. Vedotin and daunorubicin are highly toxic chemotherapeutics, of which the potential could be exploited in PC via direct delivery to the tumour. PaCaNano will investigate all NPs first in vitro: in cells (cancer cells/CAFs), in PC-tissue and in patient-derived organoids. In vivo research will include biodistribution and efficacy studies in KPC and PC-PDX mice. In this framework, we will also investigate a 2-step strategy: FAP-targeting NPs are first used to ablate the dense tumour stroma. This will expose cancer cells, which will be targeted with the corresponding GemP-NPs in a second step. The ability to deliver highly cytotoxic drugs in high concentrations specifically to tumour/metastases is expected to minimise adverse effects and maximise therapeutic benefit, with a higher chance of curing PC patients. The NP platform is also very flexible and can be applied to other chemotherapeutics and cancer types.

9

PANC-P53: Innovative peptide- and RNA-based strategies to modulate p53 for pancreatic cancer therapy

Coordinator:
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Partners:
Moshe Oren, The Weizmann Institute, Rehovot, Israel
Giovanni Blandino, Regina Elena National Cancer Institute, Rome, Italy

Background: Pancreatic Ductal Adenocarcinoma (PDAC) often presents with mutations in KRAS (>80%) and inactivating and/or potentially gain-of-function mutations in the tumour suppressor.

TP53 (60-70%). The latter contributes to reprogramming PDAC towards more malignant phenotypes. However, so far p53-targeted therapies have met limited clinical success, mainly due to off-target effects and difficulties in delivering them at pharmacologically relevant doses within tumour cells.

Hypothesis: Current obstacles to p53 targeted therapy in PDAC could be overcome by delivering structure-specific p53 modulators using controllable nanovectors, including small MUTp53 reactivating peptides and WTp53-enhancing long non-coding (lnc)RNAs.

Aims: Primary aim is proof-of-concept (PoC) of preclinical efficacy for delivery of lead compounds using controllable liposomal carriers to PDAC organoids and mouse xenografts. Secondary aims are (1) understanding mechanisms including effects on tumour microenvironment; (2): identifying biomarkers of response.

Methods: Novel peptides and human lncRNAs that target either MUTp53 or WTp53 will be delivered to PDAC in a microfluidic system that mimics a pancreatic environment through X-ray lipid nanoparticles. PoC will be established in human PDAC xenografts in mice.

Expected results and impact: This multidisciplinary project involves chemists, structural, molecular and cell biologists as well as clinicians. Innovation resides in the novelty and originality of the compounds tested and in their delivery into PDAC using nanovectors controllable through X-rays. Combining these technologies will break the deadlock for reactivating p53 and thus provide a blueprint for early phase trials aimed at sensitizing PDAC to combined therapeutic modalities, fulfilling the objectives of Aim2 of TRANSCAN-3: identification and validation of novel therapeutical targets for hard-to-treat cancers.

10

PLASTIG: Tackling tumour heterogeneity and PLASTIcity as resistance mechanisms in Glioblastoma

Coordinator:
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Partners:
Marc Sanson, Paris Brain Institute, Paris, France
Dieter Henrik Heiland, Medical Center University of Freiburg, Freiburg, Germany
Jochen Prehn, Royal College of Surgeons in Ireland, Dublin, Ireland

Background: We will investigate treatment resistance mechanisms in glioblastoma (GBM), the most aggressive brain tumour. It is still unclear which mechanisms allow GBMs to escape therapeutics, including targeted therapies.

Hypothesis: GBM display strong intrinsic plasticity and adapt reversibly to microenvironments, forming a dynamic ecosystem. The role of plasticity in creating resistant states upon treatment is elusive. We hypothesize that high plasticity allows GBM persistent cells to adapt dynamically to resistant states upon treatment. Treatment may simultaneously modulate microenvironment, leading to an overall resistant ecosystem. Such alterations may lead to a long-term evolution upon recurrence.

Aims: We will investigate molecular mechanisms allowing GBM to adapt to treatment in time and space. We aim (i) to reveal the dynamic adaptation of the GBM ecosystem during treatment and the long-term consequences at recurrence; (ii) to identify molecular regulators of plasticity as therapeutic targets; (iii) to validate novel biomarkers and combinatory treatment strategies in patient avatars.

Methods: We will investigate resistance to standard-of-care chemotherapy and targeted therapies (EGFR, CDK4/6). Spatial transcriptomics will reveal longitudinal changes in patients after treatment. Dynamic adaptation to treatment in time and space will be assessed in patient-derived organoids and xenografts. Molecular mechanisms will be examined genetics and epigenetic levels. Machine learning approaches will reveal biomarkers of resistance and regulators of plasticity, which will be validated by spatial multiplexing and in co-treatment efficacy study.

Expected results and impact: PLASTIG will bring better understanding of the role of plasticity in GBM resistance. We will elucidate therapeutic targets for next-generation combinatorial treatments and predictive biomarkers of treatment response to improve stratification of patients for personalised therapies.

11

PRECEDENCE: Genotype matched therapies in intrahepatic cholangiocarcinoma: a multipronged strategy for improving efficacy and combating resistance

Coordinator:
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Partners:
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Maeve Lowery; Trinity St. James Cancer Institute, Dublin, Ireland
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Cholangiocarcinomas (CCA) are rare tumours with a dismal prognosis and limited treatment options. Recent advances in high-throughput genomic sequencing revealed that 40% of intrahepatic CCA (iCCA) harbour genomic alterations (namely FGFR2 fusions, ERBB2 amplification, IDH1 and BRAF gain of function mutations) that predict patients' assignment to therapies based on oncogene-targeted drugs (OTDs). While results from precision oncology trials were encouraging, enthusiasm was mitigated by the observation that rate and duration of responses are limited by resistance.

Our leading hypothesis is that exploitation of OTDs to their full potential in CCA requires that resistance mechanisms are understood and counteracted pharmacologically. Because the inhibition of oncogenic drivers in other tumour types has been shown to cause also changes in the cellular composition of the tumour microenvironment (TME), consequently affecting tumour-host interactions, we further hypothesize that understanding OTD-induced changes in the immune CCA TME will be key to design rationale-based combinations of immune checkpoint inhibitors (ICIs) with OTDs.

Our experimental approach entails the multi-omics interrogation of molecular determinants of OTD resistance in CCA clinical samples and genetically defined pre-clinical models carrying the above cited BRAF, ERBB2, FGFR2 and IDH1 genetic alterations. The multidimensional data will be analysed at increasing depth, i.e. from single-level approach (e.g. transcriptome analysis of a patient cohort selected for a specific driver mutation) to AI-driven network-level analyses that integrate multi-omics data from several models (e.g. patients' data, patient-derived xenografts (PDX) and mouse models).

These analyses are expected to discover determinants of resistance/sensitivity to OTDs, guide the clinical translation of biomarker-driven approaches and combination therapies capable of increasing OTD efficacy, alone or in combination with ICIs, in CCA

12

ReachGLIO: Reaching the heterogeneous vascular landscape of glioblastoma with multifunctional nanomedicines.

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Caroline Mysiorek, Artois University, Lens, France
Bruno Sarmento, Institute for Investigation and Innovation in Health University of Porto, Porto, Portugal
Juergen Popp, Leibniz Institute for Photonic Technology, Jena, Germany
Tambet Teesalu, University of Tartu, Tartu, Estonia

Background: Glioblastoma (GBM) - the most frequent and aggressive brain tumour - treatment has not changed in the last 25 years. All clinical trials have failed, mostly because of the limited penetration of the drugs through the blood-brain barrier (BBB) and their poor distribution in the heterogeneous GBM tissue. Strategies to selectively open the BBB and the use of nanoparticles (NPs) improving the drug penetration into tumours and malignant cells, have been proposed, although they have not arrived in clinical trials yet.

Hypothesis and aims: We hypothesize that the combination of BBB opening approaches with drug loaded and tumour-targeted NPs can improve the treatment of GBM patients. To prove this thesis, two leads will be followed: 1) SNGR-TNF, a potent and stable derivative of NGR-TNF molecule with the ability to permeate the BBB and already validated in brain lymphomas, will be tested in combination with temozolomide. 2) We will design, synthesize and characterise NPs loaded with highly active anti-GBM drugs and functionalised with specific peptides to improve tumour penetration and access to cancer stem cells. Finally, the most promising NPs will be then tested in combination with SNGR-TNF.

Methods: Candidate nanomedicines will be screened in state-of-the-art in vitro GBM models developed by our experts in GBM biology. In vivo experimental therapy studies using SNGR-TNF and nanomedicines will be carried out on clinically relevant GBM mouse models and spontaneous canine gliomas. Our experts in photonics will analyse the distribution of nanocarriers and drugs in cells and tumours.

Potential impact: ReachGLIO will provide the pre-clinical framework needed to develop a novel and effective therapy for GBM based on NP loaded with potent anti-GBM drugs, alone or in combination with SNGR-TNF. This work will attract future investments needed to conduct Investigational New Drug-enabling studies and, eventually, GBM clinical trials.

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SIMMBAP: Systemic immunological determinants of tumour evolution and therapy response in BRCA–mutated pancreatic cancer

Coordinator:
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Partners:
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Patients with pancreatic ductal adenocarcinoma (PDAC) are in dire need of early detection biomarkers and effective treatments. While advanced tumours have been well-described, the changes occurring in tumour initiation remain ill-defined. Moreover, the organismal-level effects of cancer-predisposing factors on the systemic immune environment and their impact on disease progression and therapy response remain unexplored. We hypothesize that an in-depth study of the reciprocal interactions between local mechanisms of tumorigenesis and the host's systemic immunity will uncover mechanisms, non-invasive biomarkers and actionable targets to improve early detection and treatment of PDAC in patients at high risk.
SIMMBAP integrates clinical investigators, cancer biologists and computational scientists seeking to expose actionable changes in circulating immune cells and circulating tumour DNA (ctDNA), focusing on well-defined high-risk populations or PDAC patients harbouring germline pathogenic variants in BRCA1/2. We will integrate ctDNA analyses, single-cell multiomics and clinical datasets using state-of-the-art computational tools to chart the systemic pre-cancer landscape in individuals at risk of PDAC (Aim 1). Expanding these analyses to baseline and post-treatment blood and tissue samples from patients with advanced PDAC, the project will nominate tumour-intrinsic and systemic immune/inflammatory traits associated with tumour evolution and therapy response (Aim 2). These candidates will be functionally probed using mouse models and organoid systems that mimic the pathogenesis of gBRCA-PDAC (Aim 3). Through this multidisciplinary approach, SIMMBAP will produce an atlas of systemic molecular and immunological patterns associated with cancer predisposition, expose actionable mechanisms licensing PDAC initiation and therapy resistance, and uncover new immune biomarkers and therapeutic targets that pave the way to novel early diagnosis and interception strategies.

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T-Plex EAC: T-Plex-Capture: Isolation of neoantigen-specific CD8+ T cell receptors for patient-specific immunotherapy in esophageal adenocarcinoma (EAC)

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Background: Adenocarcinoma of the esophagus or esophagus/gastric junction (EAC) is an aggressive disease with median overall survival of less than a year. EAC patients undergo neoadjuvant chemo/chemoradiotherapy (NAC/R) followed by surgery, but only 20-30% of them respond. However, a fraction of patients failing NAC/R respond to adjuvant immunotherapy by immune checkpoint blockade with anti-PD-1 mAb, suggesting the ability of EAC to generate tumour antigens stimulating autologous T cell responses.

Hypothesis: We posit that adjuvant immunotherapy response of EAC patients can be further improved by enhancing anti-tumour T cell responses by approaches, entailing vaccination with tumour-specific antigens and/or adoptive transfer of ex vivo expanded tumour-specific T cells.

Aims: Our main objective is to provide proof of concept for the feasibility of integrating bioinformatics, biotechnology, artificial intelligence and immunology to T-Plex-Capture, an innovative multiplex platform enabling the identification of HLA-I-presented neoantigens for cancer vaccines, and the isolation of respective autologous CD8+ T cells and T cell receptors (TCRs) for adoptive cell therapy.

Methods: WES and RNA-seq data from EAC samples of patients not responding to NAC/R will be utilized to in silico predict HLA-I presented mutated or frameshift tumour peptides by advanced artificial intelligence platforms. Predicted epitopes will be incorporated into recombinant HLA-I proteins and coated onto color-coded T-Plex-Capture magnetic beads, which will be applied to isolate autologous tumour-specific CD8+ T cells, followed by single-cell TCR sequencing and functional validation of cloned TCRs.

Expected results and potential impact: With this innovative strategy, we intend to accelerate the presently cumbersome workflow of identification of tumour neoantigens and of specific T cells/TCRs, for their clinical application to improve the response of EAC patients to adjuvant immunotherapy.

4. Third TRANSCAN–3 call JTC 2023 open for submission

On May 9th, 2023, ERA-NET TRANSCAN-3 launched its third call for proposals **(JTC 2023)** with the support of 24 organizations from 19 countries on the following topic: **"Translational research on cancer epigenetics".**

The expected outcome of the call is to fund research projects that will ultimately **improve the efficacy of current detection, diagnosis, prognosis, and treatment of cancers, through the development of novel approaches based on a better understanding of cancer epigenetics.** The specific objectives of this funding opportunity are to stimulate new partnerships between researchers and clinicians and support original, high-quality projects, with significant clinical impact.

In the context of translational research, this topic will comprise two general aims, each with several specific aims, which concur to the possible clinical applications. Proposals should cover one or several of the specific aims listed below and should be built from a sound hypothesis. Particular attention should be given to gender balance inclusion in order to intercept sex/gender differences and to consider the role of these differences in the addressed questions.

Aim 1) The role of epigenetics in cancer initiation and progression

- Specific aim 1.1: To understand cancer initiation and progression by characterisation of the epigenetic landscape.
- Specific aim 1.2: To define epigenetic features of cells in the tumour microenvironment that may promote tumour progression (e.g., immune cells, vascular cells, microbiota).
- Specific aim 1.3: To study the role of epigenetic modifications as predictors of cell persistence or treatment resistance.
- Specific aim 1.4: To validate epigenetic markers useful to improve early detection and diagnosis by exploring the correlation between epigenetics and clinical cancer manifestation.

Aim 2) Validation of new epigenetics-based therapeutic strategies to limit cancer progression, prevent relapse/recurrence or increase the efficiency or reduce toxicity of existing anti-cancer therapies.

- Specific aim 2.1: To validate novel therapeutic targets (novel targets should be evaluated in translational studies with regard to their impact on treatment efficacy, safety and patient reported outcomes).
- Specific aim 2.2: To study the potential use of epigenetic modulators to overcome resistance to anti-cancer therapies.
- Specific aim 2.3: To develop novel epidrugs/therapeutic approaches, through phase I and II clinical trials (investigating combinations of available treatments, new therapeutics, new administration schemes, etc.) to improve safety and efficacy of treatments (objective responses; patient reported outcomes regarding morbidity and quality of life; …).
- Specific aim 2.4: To develop novel theranostic approaches involving epigenetics of cancer. Approaches combining diagnostic (imaging technics) and targeted treatment to detect cancer cells and assess treatment efficacy (radionuclide, radiopharmaceuticals, nanoparticles, nanomaterial, …).

TIMELINE OF THE CALL

9 May 2023	Publication of the call
29 May 2023 at 16:00 (CEST)	Opening of the online submission system for pre-proposals
21 July 2023 at 12:00 (CEST)	Deadline for pre-proposal submission
27 October 2023	Communication of results of pre-proposal assessment and invitation to full-proposal stage
13 November 2023 at 16:00 (CET)	Opening of the online submission system for full proposals
15 December 2023 at 12:00 (CET)	Deadline for full-proposal submission
Expected for May 2024	Communication of the funding decisions to the applicants
September 2024	Expected project start (also subject to regional/national procedures)

Pre-proposals must be submitted online via the electronic proposal submission system PT-Outline: https://ptoutline.eu/app/transcan2023

For further information, please visit https:/transcan.eu or contact the Joint Call Secretariat (JCS):

French National Cancer Institute, France
Charlotte Gudewicz
transcan-jtc2023@institutcancer.fr

5. Other initiatives from partners

The Scientific Foundation of the Spanish Association Against Cancer (FCAECC)

AECC TALENT MSCA COFUND POSTDOCTORAL FELLOWSHIPS

This September FCAECC will launch the first call for **its MSCA COFUND postdoctoral fellowship programme AECC Talent**, a unique opportunity for talented postdoctoral cancer researchers across the globe to carry out their **research projects in one of the selected host cancer research centres in Spain**.
Host research centres participating in the programme are accredited by FCAECC as excellent in cancer research by means of a rigorous assessment process that guarantees their quality, impact, and leadership in cancer research at national and international level. Fellows will have a wide choice of entities and multidisciplinary teams in which to carry out the project of their interest, following a bottom-up approach. In addition, fellows will be able to carry **out international, intersectoral and interdisciplinary secondments**, that may range from one month to one year, through which they will boost their networking opportunities and expand their interdisciplinarity. Moreover, AECC TALENT will provide a **comprehensive training programme** to its fellows with yearly sessions that will range from specific courses and seminars on research skills to non-research oriented transferable skills, innovation and leadership courses provided by experts in the corresponding fields. The call will open on September 28th. Stay tuned and visit FCAECCs website for more information!

WORLD CANCER RESEARCH DAY

The **World Cancer Research Day** (WCRD), launched in 2016, is an annual international event taking place **on September 24th** that aims to promote global collaboration for cancer research and to increase survival, facilitate access to scientific advances worldwide, and reduce the global burden of cancer.
This initiative creates and consolidates a yearly momentum to raise awareness and commitment for research on cancer and highlights the goals of the World Declaration for Research on Cancer to be achieved by 2025.
More than 600,000 people and 100 entities from over 20 countries around the world have endorsed the WCRD and actively contribute to spread the campaign key messages and reach people from every corner of the globe. You can also support WCRD by signing the declaration here.
For further information on the WCRD global campaign and to join this global movement, please visit the website www.worldcancerresearchday.com or contact the WCRD technical secretariat worldcancerresearchday@gmail.com.

ARC FOUNDATION

CALL FOR PROJECTS

Postdoctoral fellows in France
The aim of this call for is to support young researchers in carrying out their cancer research project as part of a postdoctoral fellowship in a laboratory located in France. The funding covers the salary of the laureates during the duration of the project:

- Postdoctoral grants directly at the end of the thesis (PhD) for a period of 24 or 36 months maximum
- Postdoctoral grants to relocate to France for experienced postdoctoral fellows who have spent at least 24 months abroad as part of a previous postdoctoral internship.

For more details please visit Post-doctorants en France.

Recruiting international leaders in Oncology
This annual call for proposal aims to bring a high-level researcher from abroad to set-up a research team in a French structure, and to develop the most innovative and comprehensive research projects in oncology.
Every year, Fondation ARC allocate up to 1.5 million euros over 5 years to support the installation of a researcher and his/her team, as well as the implementation of their research program. For more details please visit Recruiting international leaders in oncology 2023.

RESEARCH PRIZES – LÉOPOLD GRIFFUEL AWARDS

Through two prestigious awards of **€150,000 each**, Fondation ARC rewards researchers whose careers and work have led to **major breakthroughs** in cancer research in the following categories:

- **Basic research**
- **Clinical and translational research**

Closing on October 2nd, all details about these prizes and the application can be found on the site 52nd Fondation ARC Léopold Griffuel Awards

ONCOLOGY CONFERENCE

The Young Cancer Researchers Days (Journées Jeunes Chercheurs) are among the flagship events of the ARC Foundation. A real moment of meeting and sharing, they are divided into two days animated by different highlights.

These days are open to any cancer researcher, registration is free but compulsory. JJC 2023 will take place next October 12th and 13th Visit the website for more information.

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