TRANSCAN
Sustained collaboration of national and regional programmes in cancer research

TRANSCAN-3

Funded projects on:

Novel translational approaches to tackle the challenges of hard-to-treat cancers from early diagnosis to therapy

October 8th - 9th

2024

Catania - Sicily

JTC-2022 Kick-off SYMPOSIUM

This event is co-organized by:

ALLEANZA CONTRO IL CANCRO

MINISTRY OF HEALTH
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Ministero della Salute

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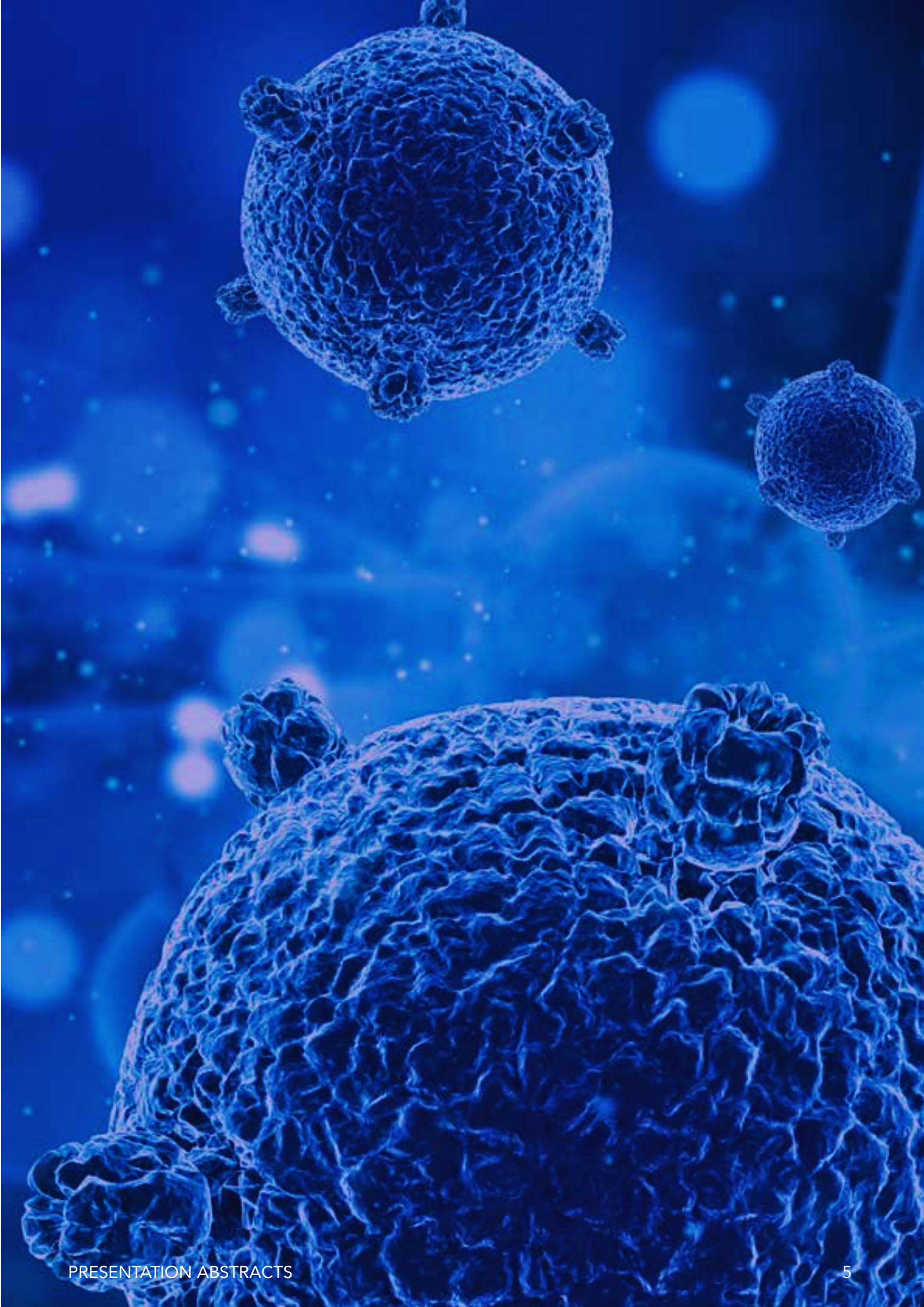
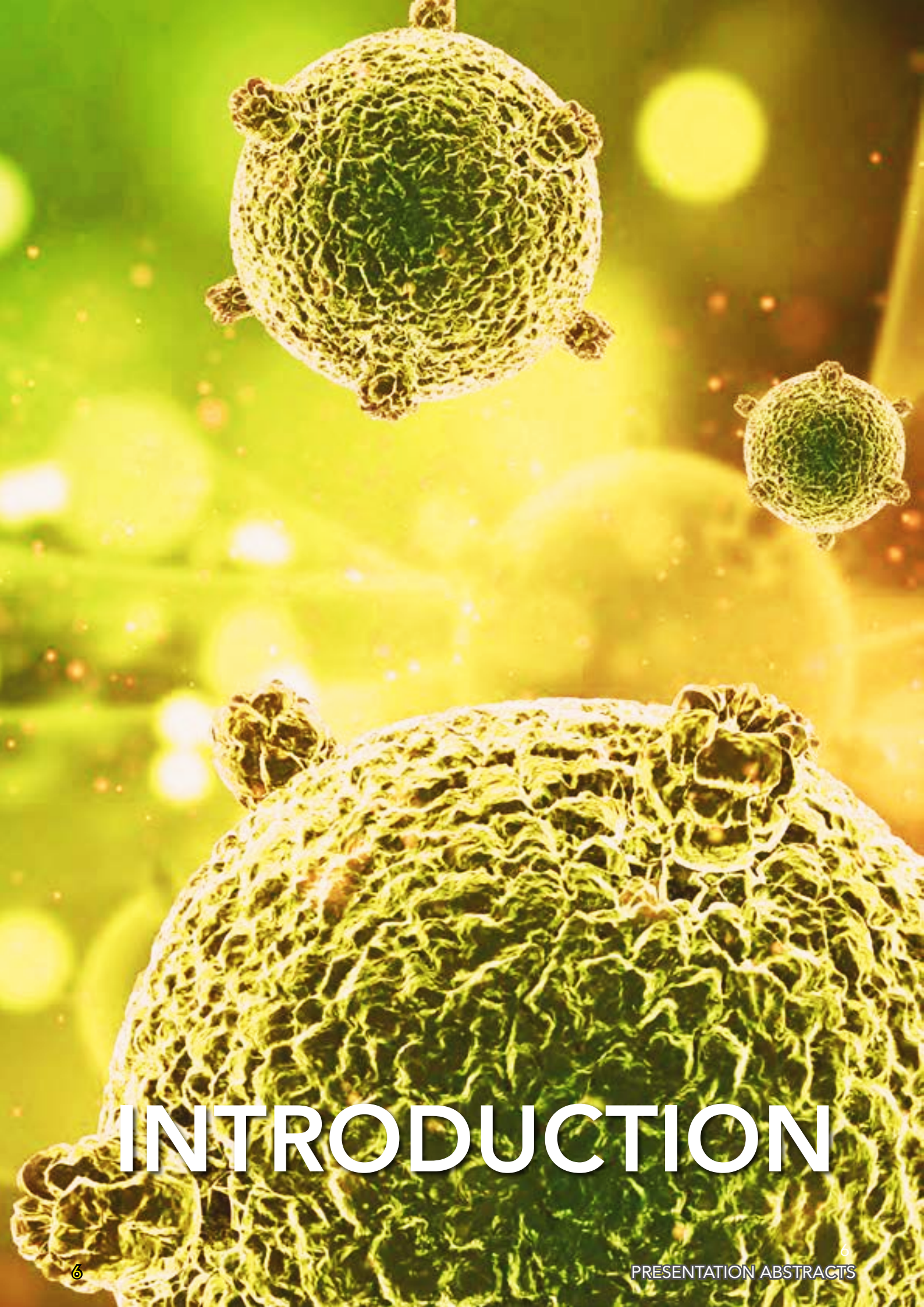
CONTENT





INTRODUCTION

Cancer is one of the leading causes of death and represents a significant global burden of disease. In Europe it ranks as the primary cause of morbidity after cardiovascular diseases, accounting for over 4.5 million new cases each year (GLOBOCAN 2022 http://gco.iarc.fr). Cancer is a challenge for public health, as it can become a chronic disease contributing substantially to the growth of medical expenditures and constituting a major socio-economic issue for Europe as well as globally. To address the increasing need to reduce incidence and mortality of malignancies and to improve the quality of life of cancer patients, a coordinated effort is necessary. A rapid and effective bidirectional transfer of relevant cancer research findings between bench and bedside would play a pivotal role. The key area of translational cancer research addresses these needs, however, the research efforts in the field should be harmonized and integrated so as to profit from coordination at the transnational level.

The ERA-NET TRANSCAN-3 (Sustained collaboration of national and regional programmes in cancer research) is a collaborative network of ministries, funding agencies and research councils with programmes in translational cancer research, funded by the European Commission under the EU framework programme **Horizon 2020**. The network is composed of 31 partners from **20 Countries**. It is the continuation of the previous programmes ERA-NET TRANSCAN-2 and TRANSCAN. Altogether since 2011, eleven annual Joint Transnational Calls (JTCs) have been launched and 126 transnational projects have been funded to date.

Under the call launched in 2022 on the topic "Novel translational approaches to tackle the challenges of hard-to-treat cancers from early diagnosis to therapy", **fourteen** transnational consortia including 64 research groups from 15 countries were funded. The motivation for this call was driven by the urgent need to address hard-to-treat cancers (HTTC), which continue to have low survival rates despite overall advances in cancer care. These cancers often face multiple therapeutic challenges, including late detection, tumor heterogeneity, and resistance to existing treatments. This call aims to fund innovative translational research to develop new diagnostic, therapeutic, and drug delivery strategies to significantly improve patient outcomes by overcoming the obstacles these types of cancers present.

This 2nd Symposium of TRANSCAN-3 brings together all 14 of the funded consortia from JTC 2022 in order to present the research that will be carried out in these projects.
It also aims to foster networking and scientific discussion amongst researchers from related research fields, as well as to increase the opportunities for new collaborations. Young scientists are encouraged to join and discuss their work with scientists from their field of research.

We hope you enjoy and benefit from the symposium!

TRANSCAN-3 JTC-2022 Kick-off Symposium

Agenda

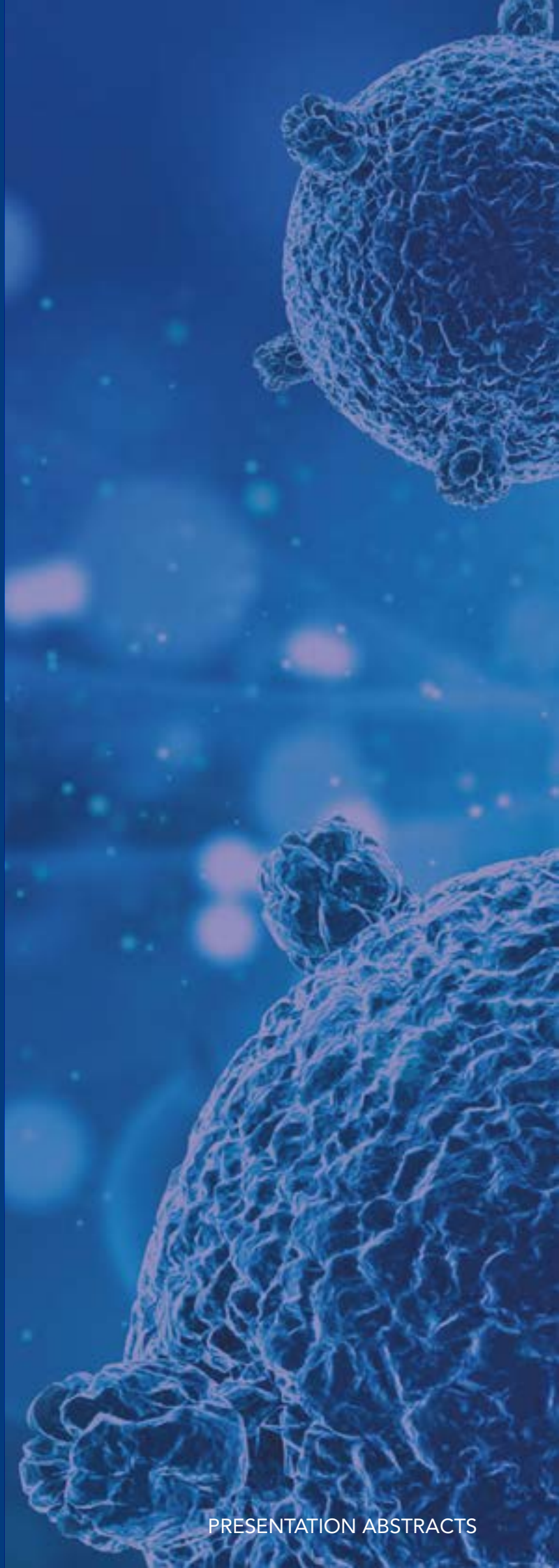
Venue: Hotel NH Catania Centro
Piazza Trento 13, 95129 Catania, Sicily, Italy

Day 1: Tuesday, October 8th, 2024

12:00-12:30	**Registration** (light lunch)
	Welcome address
12:30-13:00	Introduction: TRANSCAN-3 coordinator
	JTC2022 – "Hard to treat cancers" I JTC2022 Joint Call Secretariat
Session 1	**Chairs: Theodora Katsila and Lakis Liloglou**
13:00	**ReachGLIO**, Pilar Sánchez-Gómez
13:25	**MATTO-GBM**, Ilinca Popp and Montserrat Carles Fariña
13:50	**NK-4-GBM**, Clair Gardiner
14:15	**PLASTIG**, Anna Golebiewska
14:40 - 15:10	*COFFEE BREAK*
Session 2	**Chairs: Theodora Katsila and Lakis Liloglou**
15:10	**IdeaTMEHCC**, Luca Di Tommaso
15:35	**T-Plex EAC**, Ebru Aydin Kurtulmus
16:00	**ANGELA**, Wladyslaw Januszewicz
	PANEL ON PATIENT ENGAGEMENT IN CANCER RESEARCH:
16:25-17:25	Vanesa Abón Escalona, Manoj Lalu, Juan-José Ventura
	Moderated by Sebastian Hückesfeld
17:30-18:30	"MAKING CONNECTIONS" - gathering for early career researchers
	NETWORKING DINNER
20:00	Piazza Scammacca Piazza Scammacca, 9. Catania Centro

Day 2: Wednesday, October 9th, 2024

8:40	SHORT WELCOME
8:45-11:00	RRI WORKSHOP by QUEST Centre, Berlin
11:00 – 11:30	COFFEE BREAK
Session 3	**Chairs: Theodora Katsila and Lakis Liloglou**
11:30	**iCC-Strat**, Oliver Schilling
11:55	**PANC-P53**, Giovanni Blandino
12:20	**PaCaNano**, Frauke Alves
12:45	**CAR4PDAC**, Juan José Lasarte
13:10-14:10	*LUNCH*
Session 4	**Chairs: Theodora Katsila and Lakis Liloglou**
14:10	**SIMMBAP**, Teresa Macarulla
14:35	**PRECEDENCE**, Oreste Segatto
15:00	**BileCanMet**, Carmen Berasain
15:25-15:45	FEEDBACK SESSION AND SUMMARY
15:45-16:30	*FAREWELL COFFEE*



Session Chairs

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

Theodora Katsila

Dr. Katsila is the Head of the Biomarker Discovery & Translational Research Laboratory at the National Hellenic Research Foundation, Greece. A leader in biomarker discovery and translational research, her work focuses on advancing translational precision medicine through digital and molecular biomarkers. Her expertise includes state-of-the-art repurposing of drugs, advanced materials, and smart systems. For this, a rich toolbox has been set that consists of computational and experimental pipelines: multi-omics, EVs, cheminformatics, and 3D cell models. Dr. Katsila's lab drives innovation by transitioning from serendipity-driven to data-driven medicine, with an emphasis on biomarker-guided trial design and patient-centric healthcare solutions.

Triantafillos (Lakis) Liloglou

Dr. Liloglou is the Director of the CardioRespiratory Research Centre and the Programme Lead for the Master of Surgery (MCh) at Edge Hill University. An expert in molecular oncology, his research focuses on genetic and epigenetic instability in respiratory cancers, particularly in the discovery and validation of biomarkers for early detection, therapeutic stratification and disease monitoring. Dr. Liloglou remains actively involved in the Liverpool Lung Project and Liverpool Head and Neck Centre, contributing to advancements in the field.

Early detection of esophageal squamous cell carcinoma with the capsule sponge device coupled with molecular biomarkers and machine learning (the ANGELA study)

Presented by Wladyslaw Januszewicz
National Institute of Oncology, Poland

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 capsule-sponge cell collection device could provide a novel approach to ESCC screening.

Aims: The primary aim is to evaluate the diagnostic yield of the capsule-sponge device 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 samples.

Methods: In this multicenter 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 a high-definition endoscopy followed by a capsule-sponge examination. The biomarker assay, including p53-IHC and shallow whole genome sequencing, will be tested within the capsule-sponge 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.

Potential impact: We hope to develop a novel, effective, and affordable diagnostic assay that, coupled with a minimally invasive capsule-sponge device, could be implemented in a clinical setting, improving the early detection of ESCC and, eventually, patient outcomes.

Project Coordinator:
Wladyslaw Januszewicz, National Institute of Oncology, Poland

Project Partners:
Michal F. Kaminski, National Institute of Oncology, Poland
Mathieu Pioche, Hospices Civils de Lyon, France
Miloslav Karhánek, Slovak Academy of Sciences, Slovakia
Marcel Gehrung, Cyted Ltd., UK

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

Presented by Carmen Berasain
Centro de investigaciones biomédicas en red (CIBER), Spain

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 analyze bile microbiome and BA profile, establishing clinical correlations. Aim 2. We will confirm PRMT5 expression in large cohorts of CCA tissues and establish clinical correlations. Additionally, we will investigate the anti-tumoral effects of PRMT5 inhibition in CCA cells, organoids, and relevant mouse models, while also studying the underlying molecular mechanisms involved.

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.

Project Coordinator:
Matias Ávila, Centro de investigaciones biomédicas en red (CIBER), Spain

Project Partners:
Luca Aldrighetti, Università Vita-Salute San Raffaele, Italy
Marcin Krawczyk, Warsaw Medical University, Poland
Pavel Strnad, Aachen University Clinic, Germany
Meritxell Huch, Max-Planck-Gesellschaft zur Förderung der Wissenschaften e.V., Germany

Hijacking stroma antigens for CAR-T cell immunotherapy of PDAC (CAR4PDAC)

Presented by Juan José Lasarte
Fundacion Instituto de Investigacion Saniatria de Navarra, Spain

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 tumor growth, migration, invasion and to the reorganization of the tumor extracellular matrix and intratumor immunosuppression. Our preliminary data indicate that CAR-T cells targeting EDA show antitumor effect in several tumor models expressing EDA in the tumor extracellular matrix, and that EDA is highly expressed in PDAC tumor 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 indicate 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 centers.

Project Coordinator:
Felipe Prosper, Fundacion Instituto de Investigacion Sanitaria de Navarra, Spain

Project Partners:
Antonio Pineda, Fundacion para la Investigacion Medica Aplicada, Spain
Anna Mondino, IRCCS Ospedale San Raffaele, Italy
Hana Algül, Comprehensive Cancer Center Munich TUM, Germany

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

Presented by Oliver Schilling
University Medical Center Freiburg, Germany

Background: Intrahepatic cholangiocarcinoma (ICC) is the 2nd most prevalent hepatic cancer with 5-year survival rates <10%. Tumors 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-center 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 post-treatment to probe cell-free DNA, circulating tumor cells, and serum proteome for markers of recurrent ICC. Data will be analyzed 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.

Project Coordinator:
Oliver Schilling, University Medical Center Freiburg, Germany

Project Partners:
Andrea Casadei Gardini, Vita-salute San Raffaele University, Italy
Sandrine Katsahian, INSERM UMRS, France
Andras Kiss, Semmelweis University, Hungary

Identification of therapeutic targets using HCC DErived organoid Augmented with TME components (IdeaTMEHCC)

Presented by Luca Di Tommaso
Humanitas Mirasole SPA, Italy

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-organoid (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 HCC-PDO, however, lacks Tumor Micro Environment (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 TMEenriched-HCC-PDO; 2: To explore connections between TMEs and HCC drug efficacy using TMEenriched-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 TMEenriched PDO. Evaluate the effect of drugs for HCC on TMEenriched 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.

Project Coordinator:
Luca Di Tommaso, Humanitas Mirasole SPA, Italy

Project Partners:
Julien Calderaro, Henri Mondor Hospital, University Paris Est Creteil and INSERM Paris, France
Diego Calvisi, Universitätsklinikum Regensburg, Germany
Yu-Yun Shao, National Taiwan University Hospital, Taiwan

Multimodality Artificial intelligence open-source Tools for radiation Treatment Optimization in patients with Glioblastoma (MATTO-GBM)

Presented by Ilinca Popp[1] and Montserrat Carles Fariña[2]

[1] Medical Center - University of Freiburg (UKL), Germany
[2] Fundación para la investigación del Hospital Universitario La Fe de la Comunidad Valenciana (HULaFE), Spain

Background, rationale: 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: 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/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.

Project Coordinator:
Anca-Ligia Grosu, Medical Center - University of Freiburg (UKL), Germany

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

Metabolically optimised NK cell therapies for glioblastoma (NK-4-GBM)

Presented by Clair Gardiner
Trinity College Dublin, Ireland

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 (e.g. fatty acids) and proteins (e.g. 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.

Project Coordinator:
David Finlay, The Provost, Fellows, Foundation Scholars & the other Members of Board of the College of the Holy & Undivided Trinity of Queen Elizabeth near Dublin, Ireland

Co-Coordinator:
Clair Gardiner, Trinity College Dublin, Ireland

Project Partners:
Peter Oefner, Universität Regensburg, Germany
Karl-Johan Malmberg, University of Oslo, Norway
Stephen MacNally, Beaumont Hospital, Ireland
Sophie Lucas, Université catholique de Louvain, Belgium

Development of a Pancreatic Cancer drug-Nanocarrier system selectively targeting tumour cells and tumour stroma to overcome treatment failure (PaCaNano)

Presented by Frauke Alves
University Medical Center Göttingen, Germany

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 optimize these NPs by adding 'tumor 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 tumor. 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 tumor 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 tumor/metastases is expected to minimize adverse effects and maximize 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.

Project Coordinator:
Frauke Alves, University Medical Center Göttingen, Germany

Project Partners:
Claus Feldmann, Karlsruhe Institute of Technology, Germany
Pieter Van der Veken, Universiteit Antwerpen, Belgium
Annarosa Arcangeli, University of Florence, Italy
Lapo Bencini, Azienda Ospedaliero-universitaria Careggi, Italy

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

Presented by Giovanni Blandino
IRCSS Regina Elena National Cancer Institute, Italy

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

Project Coordinator:
Pierre Hainaut, University Grenoble Alpes, Inserm U1209, CNRS 5309, France

Project Partners:
Moshe Oren, Weizmann Institute of Science, Israel
Giovanni Blandino, Regina Elena National Cancer Institute, Italy

Tackling tumor heterogeneity and PLASTIcity as resistance mechanisms in Glioblastoma (PLASTIG)

Presented by Anna Golebiewska
Luxembourg Institute of Health, Luxembourg

Background: We will investigate treatment resistance mechanisms in glioblastoma (GBM), the most aggressive brain tumor. 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 persister 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 personalized therapies.

Project Coordinator:
Anna Golebiewska, Luxembourg Institute of Health, Luxembourg

Project Partners:
Marc Sanson, Sorbonne Université & Assistance publique-Hôpitaux de Paris, France
Dieter Henrik Heiland, University of Freiburg, Germany
Jochen Prehn, Royal College of Surgeons in Ireland University of Medicine and Health Sciences (RCSI), Ireland

Genotype matched therapies in intrahepatic cholangiocarcinoma: a multi-pronged strategy for improving efficacy and combating resistance (PRECEDENCE)

Presented by Oreste Segatto
Regina Elena National Cancer Institute, Italy

Cholangiocarcinomas (CCA) are rare tumors with a dismal prognosis and limited treatment options. Recent advances in high-throughput genomic sequencing revealed that 40% of intrahepatic CCA (iCCA) harbor 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 tumor types has been shown to cause also changes in the cellular composition of the tumor microenvironment (TME) - consequently affecting tumor-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 analyzed 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.

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REACHing the heterogeneous vascular landscape of GLIOblastoma with multifunctional nanomedicines (ReachGLIO)

Presented by Pilar Sánchez-Gómez
Instituto De Salud Carlos III, Spain

Background: Glioblastoma (GBM) - the most frequent and aggressive brain tumor - 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 tumors and malignant cells, have been proposed, although they have not arrived to clinical trials yet.

Hypothesis and aims: We hypothesize that the combination of BBB opening approaches with drug loaded and tumor-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 characterize NPs loaded with highly active anti-GBM drugs and functionalized with specific peptides to improve tumor 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 analyze the distribution of nanocarriers and drugs in cells and tumors.

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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Systemic IMMunological determinants of tumor evolution and therapy response in BRCA-mutated pancreatic cancer (SIMMBAP)

Presented by Teresa Macarulla
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Patients with pancreatic ductal adenocarcinoma (PDAC) are in dire need of early detection biomarkers and effective treatments. While advanced tumors have been well-described, the changes occurring in tumor 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, noninvasive 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 tumor DNA (ctDNA), focusing on well-defined high-risk populations or PDAC patients harboring 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 tumor-intrinsic and systemic immune/inflammatory traits associated with tumor 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-Capture: isolation of neoantigen-specific CD8+ T cell receptors for patient-specific immunotherapy in Esophageal AdenoCarcinoma (T-Plex EAC)

Presented by Ebru Aydin Kurtulmus
PEPperPRINT GmbH, Germany

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 tumor antigens stimulating autologous T cell responses.

Hypothesis: We posit that adjuvant immunotherapy response of EAC patients can be further improved by enhancing anti-tumor T cell responses by approaches, entailing vaccination with tumor-specific antigens and/or adoptive transfer of ex vivo expanded tumor-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 tumor 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 tumor-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 tumor neoantigens and of specific T cells/TCRs, for their clinical application to improve the response of EAC patients to adjuvant immunotherapy.

Project Coordinator:
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Project Partners:
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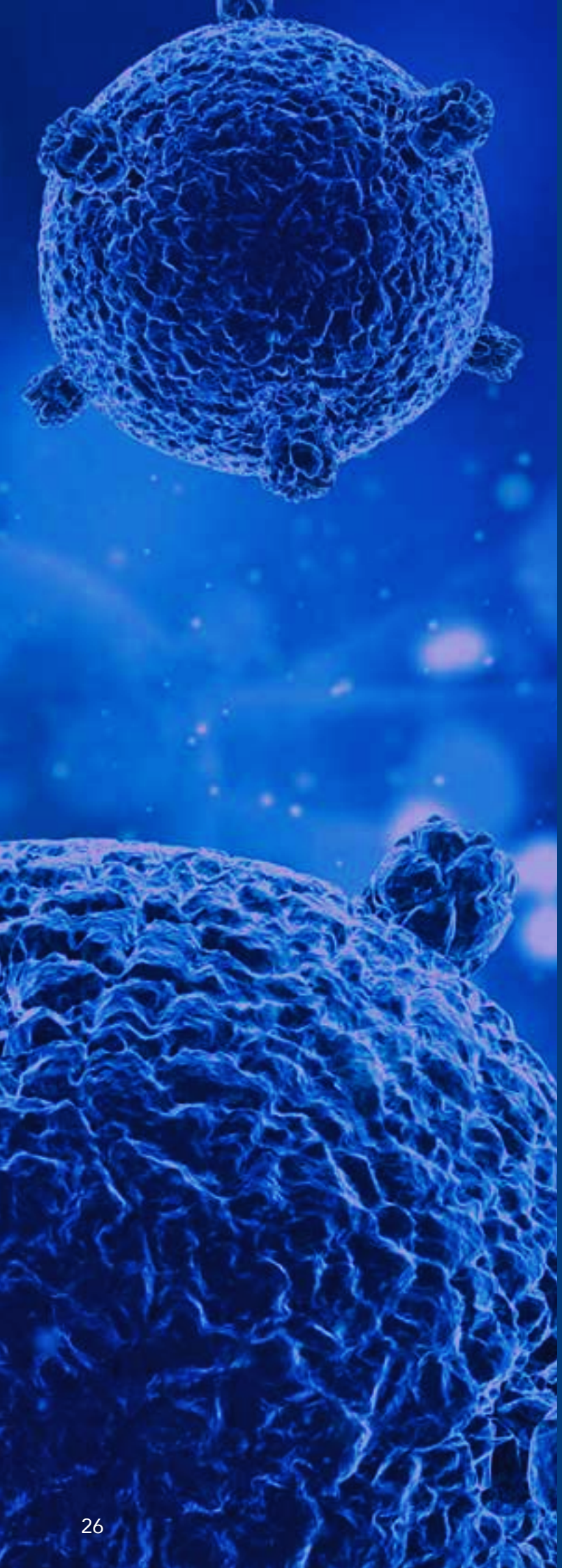


Additional Speakers

Patient Panel

Vanesa Abón Escalona studied biology in the Complutense University of Madrid and obtained her PhD in Biomedical Sciences at the KU Leuven University in Belgium. In 2019 she joined the Scientific Foundation of the Spanish Association Against Cancer (FC AECC), the biggest cancer association in Spain. Among other duties, Vanesa is the leader of the Patient Advocacy programme, through which she is working to engage patients in cancer research, by establishing the novel patient advocate figure in the organisation.

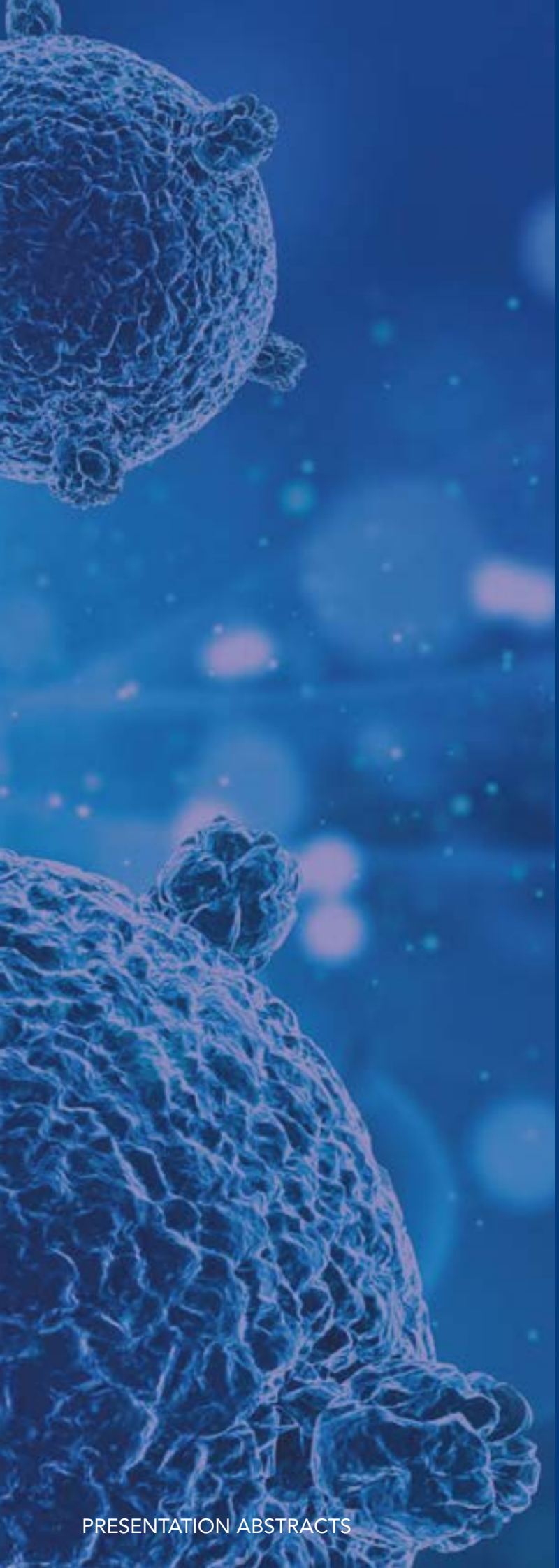
Manoj Lalu is an Scientist at the Ottawa Hospital Research Institute, affiliated with the Acute Care Research and Regenerative Medicine Programs. He is also an Anesthesiologist at The Ottawa Hospital and an Associate Professor in the Department of Anesthesiology and Pain Medicine at the University of Ottawa. He co-leads the Blueprint Translational Research Group, which focuses on improving the speed and success of bench-to-bedside translation. Dr. Lalu is highly regarded for his pioneering work in patient engagement, ensuring that patients are actively involved in the research process and contributing to the improvement of the translational pathway.

Juan-José Ventura of Cancer Patients Europe studied Pharmacy and obtained his PhD at the University Complutense of Madrid. He has conducted basic research in international institutions such as EMBL, HHMI, CNIO, University of Cambridge and KU Leuven. He has aimed to find target cells and molecular biomarkers that could be used for diagnosis and therapy of several cancers (Liver, Colon, Lung). After switching his career path, he moved to work as patient advocate. He has participated in more than 20 EU research projects and helped to bring the voice of patients to the latest research trends.

RRI Workshop

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

René Bernard is the Coordinator for Value and Open Science at Charité Universitätsmedizin, Berlin, within the NeuroCure Cluster of Excellence. He earned his PhD in Pharmacology from the University of Michigan and completed postdoctoral training at both the University of Michigan and Charité Universitätsmedizin. His research experience spans multiple domains within neuropharmacology, where he combines a strong foundation in both scientific inquiry and pedagogy. He is dedicated to advancing the rigor, transparency, and reproducibility of research across the field. In his current role, he works closely with many laboratories, providing essential guidance on implementing the core principles of rigorous and transparent biomedical research. By bridging translational neuroscience with practical implementation of Open Science and transparency, he empowers researchers to enhance the quality and impact of their work, ensuring that their findings are both reliable and meaningful.



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