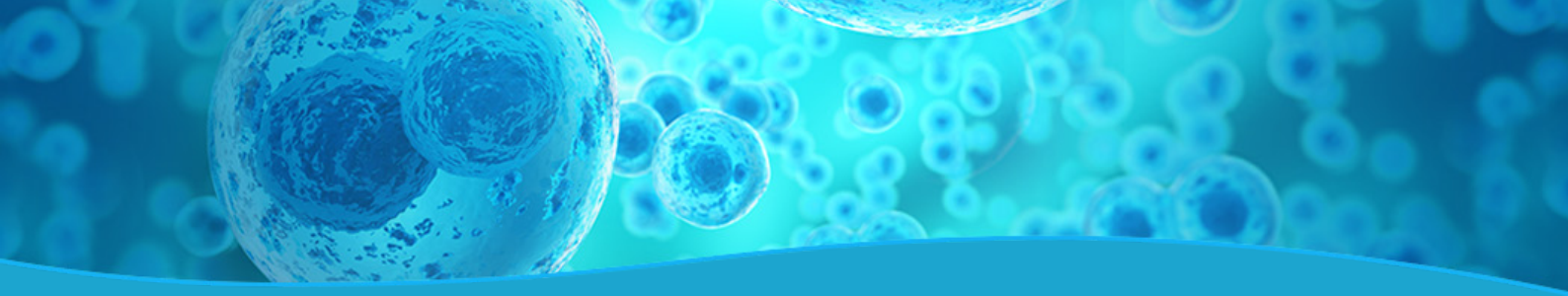

ERA-NET TRANSCAN-2

NEWSLETTER 8

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TRANSCAN-2

Outcome of Joint Transnational Call 2017 (closed call)

"Translational research on Rare Cancers"

Overview of the 12 funded projects

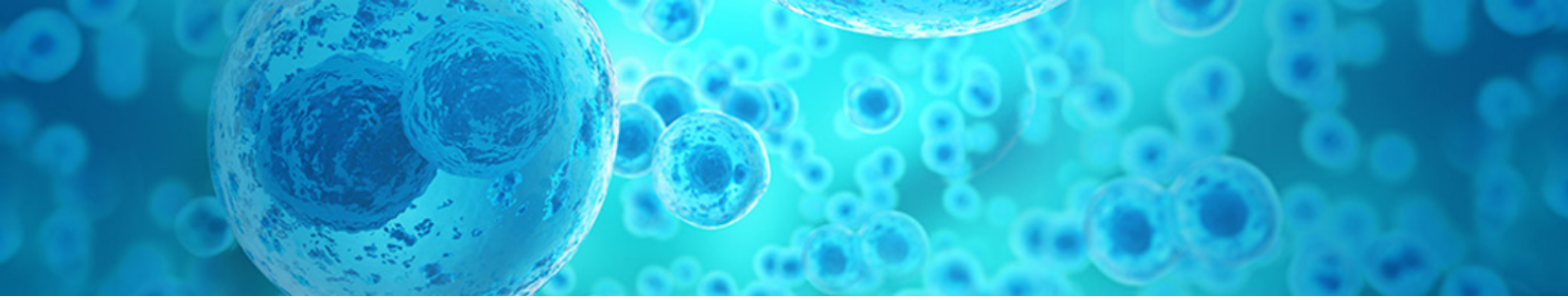
INTRODUCTION TO JTC-2017

The call on rare cancers was motivated by the consideration that diagnostic and therapeutic management of affected patients may pose particularly difficult challenges, mainly related to the small numbers of patients' cohorts and difficulties in referring patients to large centers with multidisciplinary expertise. The low incidence of these diseases tends to significantly constrain the ability of performing studies with adequate statistical power. Additionally, low numbers inevitably translate into a limited availability of high quality, clinically annotated, bio-specimen samples necessary to explore the underlying molecular mechanisms of the diseases. The abovementioned limitations have a negative impact on the number of treatments, thus affecting patients' outcomes. Based on the RARECAREnet (http://www.rarecarenet.eu/) definition, rare cancers are those with an incidence rate of <6 per 100,000 per year in the European population.

More information can be found on
http://www.transcanfp7.eu/

This project has received funding from the European Union›s Horizon 2020 Research and Innovation Programme under grant agreement no 643638.

Produced by MIZS, SI and CSO-MOH, IL



Main translational research goals in rare cancers are achieved through studies of cohorts of patients with available biospecimens linked to cancer registry data. The aims of the call were related to:

1) Design and conduct of translational research studies exploiting/combining resources from current clinical trials, bio-repositories and epidemiology-type resources;

2) Development and exploitation of translational research platforms (e.g., patient derived xenograft models/organoids/tissue collections) to study drug responses/resistance and toxicity, and perform drug screens or repurpose approved anticancer drugs;

3) Implementation of precision biomarkers for better stratification of the clinical cohorts.

The JTC 2017 has raised interest among the scientific community: 92 research proposals, involving 429 multidisciplinary teams from 17 countries, were received.

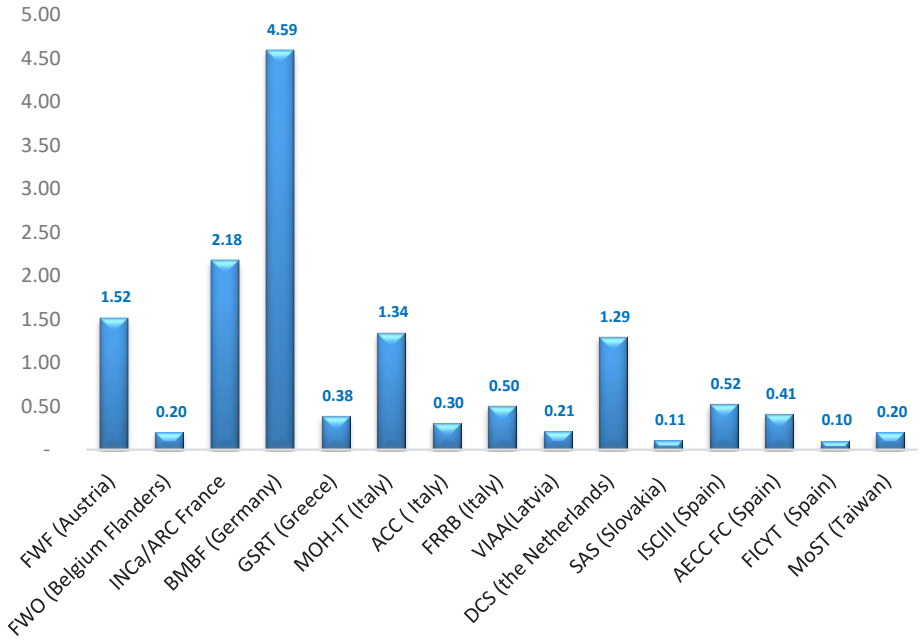
At its completion, 12 transnational projects were selected for funding, with a total allocated budget of € 14.87 million.

CALL STATISTICS

Table 1: Number of submitted (pre/full/funded) proposals under JTC-2017

JTC 2017	Proposals	Countries involved	Principal investigators
Eligible pre-proposal	92	17	429
Eligible full proposal	38	15	179
Funded proposals	12	11	57

Figure 1: Budget spent (M€) for the funded projects by funding organisation



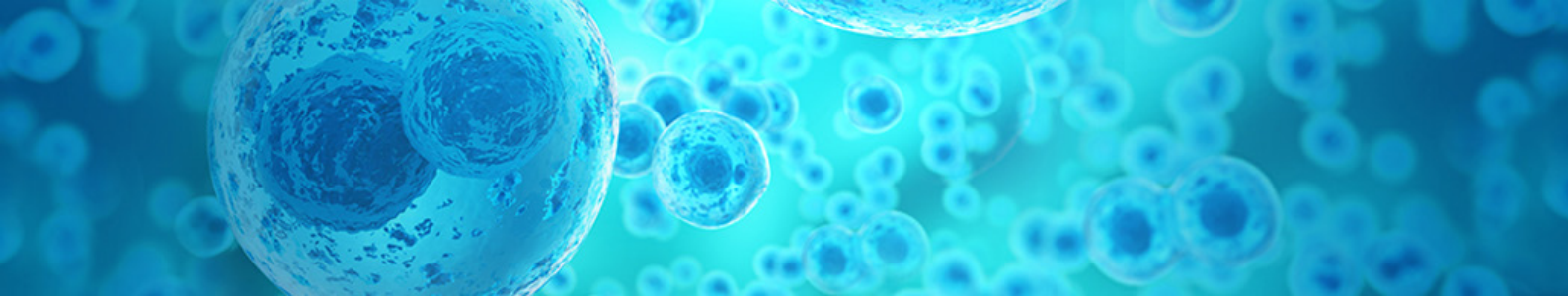
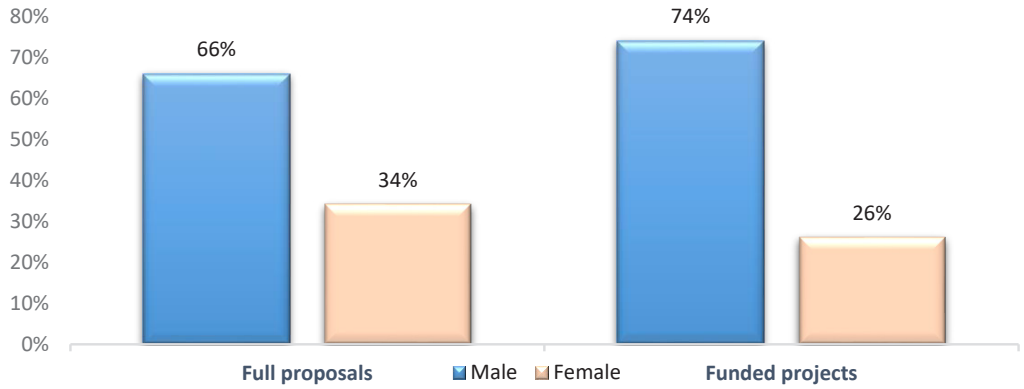


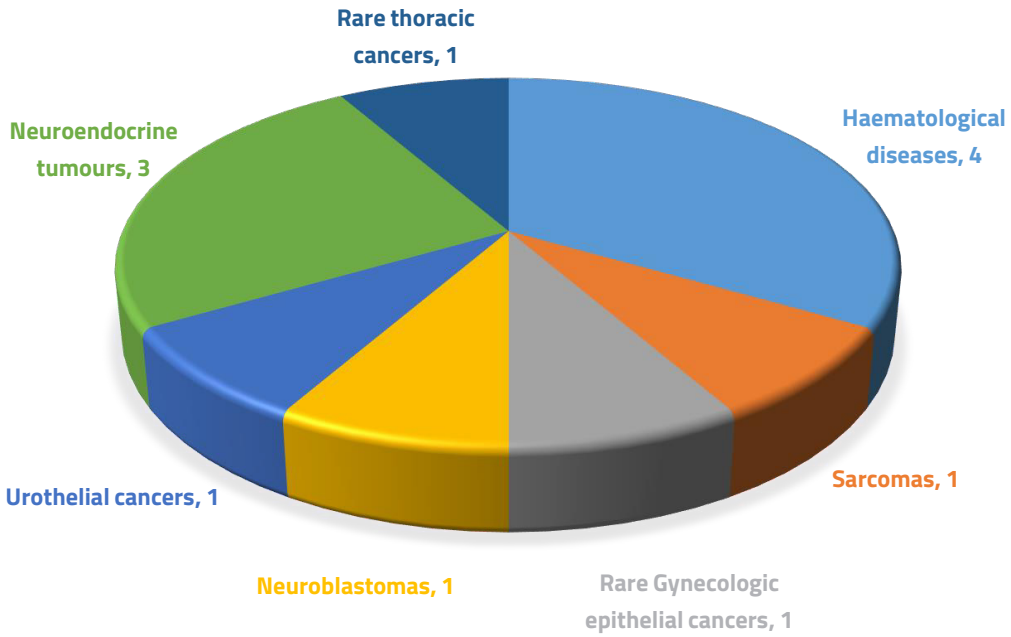
Figure 2 Gender ratio of the Principal investigators involved in the 38 full proposals and 12 funded projects

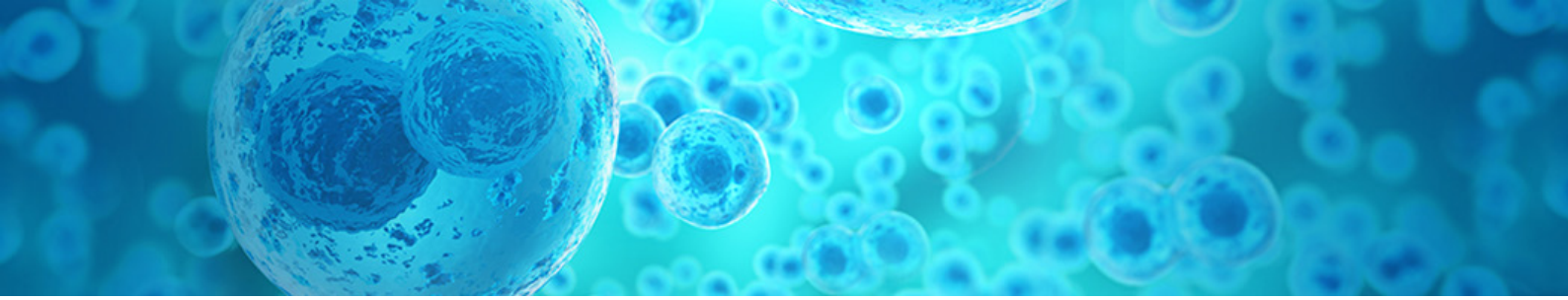


TOPICS OF THE JTC-2017 FUNDED PROJECTS

According to the RARECAREnet classification by site, the 12 funded projects can be grouped as follows:

Figure 3: Distribution of research pathologies in the proposals selected for funding





Haematological diseases

ERANET-PLL: Implementation of (epi)genetic and metabolic networks in the targeting of T-cell prolymphocytic leukemia

Coordinator:

Marco Herling

Project Partners:

Richard Moriggl

Philipp Staber

Emmanuel Bachy

Ingo Roeder

T-PLL is the most frequent mature T-cell leukemia, yet it occurs at an incidence of 0.6/Mio in the EU. Its chemotherapy resistance translates into a very poor patient survival. There are no approved drugs for T-PLL. The study will capitalize on unique prerequisites, e.g. a large repository of well-annotated material, an open clinical registry, or T-PLL animal models to analyze to which degree genomic and epigenetic alterations as well as basal and inhibitor-induced metabolic signatures dictate differential substance activities. Bio-computational modelling will integrate the data towards prediction tools of in-vitro drug sensitivities and synergies. Drug candidates will be validated in various preclinical systems. The extracted set of molecular strata will finally be interrogated in a prospective interventional trial. The study will also identify biomarkers that discern T-PLL patient towards targeted compounds for treatment decisions and trial designs.

EuroTCLym: Translational research in peripheral T-Cell lymphomas: From characterization to novel targets

Coordinator:

Lorenz Truemper

Project Partners:

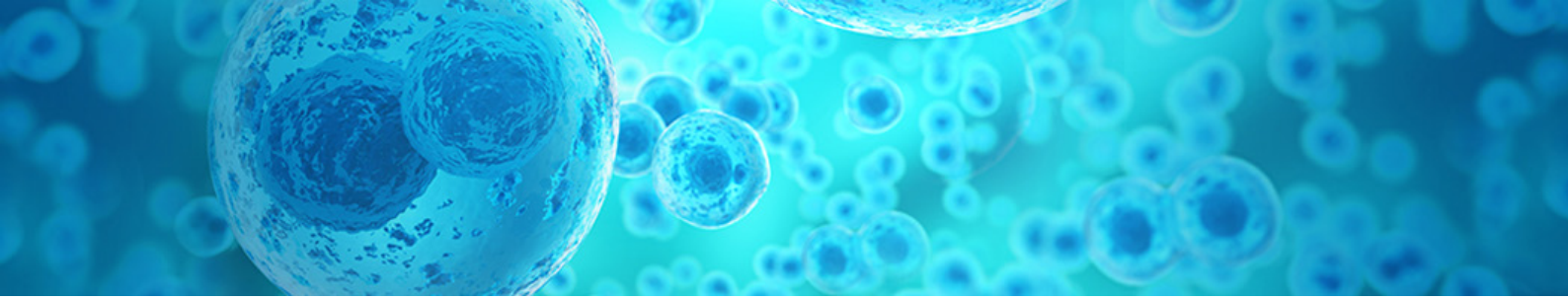
Reiner Siebert

Philipp Staber

Daphne de Jong

Olivier Tournilhac

Peripheral T-cell lymphomas (PTCL) are a heterogeneous group of rare lymphoid malignancies with poor prognosis. The biology and the underlying genetic and epigenetic alterations of these diseases is still poorly understood and mechanisms of progression and relapse remain elusive, precluding clinical progress. A unique collection of clinically annotated PTCL samples from multiple prospective European trials and from population-based cohorts will be utilized to establish a biobank of these samples, accompanied with centrally reviewed detailed pathologic assessment. Whole exome sequencing and genome-wide DNA methylation profiling will be performed to unravel pivotal mechanisms determining the unique biology and clinical behavior of PTCL. Correlating these data with clinical endpoints will allow to identify prognostic genetic and epigenetic biomarkers. The study will elucidate molecular targets and perform ex vivo drug screening assays on (epi-)genetically characterized PTCL samples to develop novel therapeutic strategies.



Quant-ALL: Automated, absolute quantification of MRD in ALL patients by droplet microfluidics, single DNA copy barcoding and IG/TR amplicon NGS

Coordinator:

Tobias Hutzenlaub

Project Partners:

Alessandro Rambaldi

Giovanni Cazzaniga

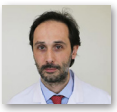
Anastasia Hadzidimitriou

Michaela Kotrova

The assessment of minimal residual disease (MRD) during first-line therapy is regarded as the most important prognostic factor in acute lymphoblastic leukemia (ALL). Multiparameter flow cytometry is not fully standardized and requires expert skills. Allele specific PCR of clonal immunoglobulin (IG) and T-cell receptor (TR) gene rearrangements is time consuming and needs patient-specific reagents. In this context amplicon based IG/TR NGS was introduced, which allows for the characterization of millions of IG/TR rearrangements in parallel without the need for patient specific reagents, thus allowing IVD-guided analytical validation. Goals of the project are to establish an amplicon based IG/TR NGS approach using single DNA copy barcoding and droplet microfluidics; to optimize existing bioinformatics tools; to transfer this technology to a pre-existing centrifugal microfluidic platform for automation and standardization; to validate the technology for ALL using biobanked follow-up samples. Expected results are the full automation of a high throughput technology for MRD quantification in ALL.

EuroMDS: An integrated European platform to conduct translational studies in myelodysplastic syndromes based on the EuroBloodNet infrastructure

Coordinator:



Matteo Giovanni Della Porta

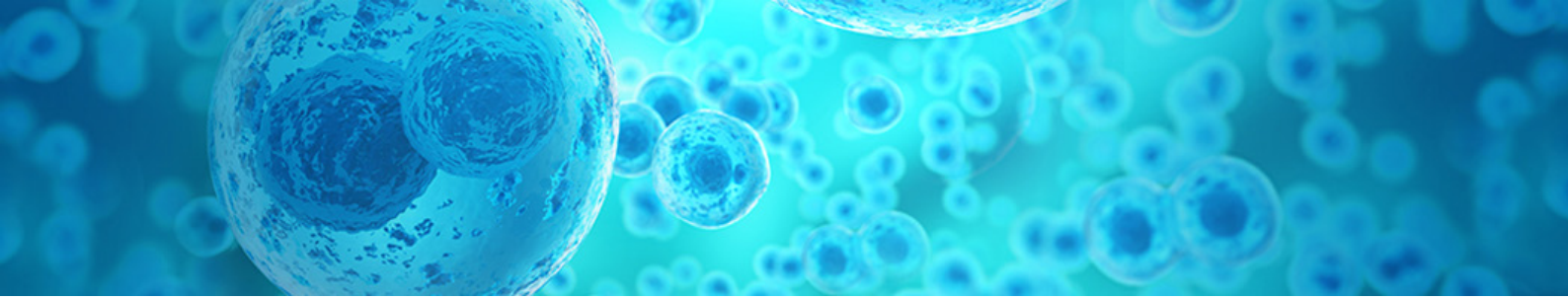
Project Partners:

Pierre Fenaux

Uwe Platzbecher

Francesc Sole

Myelodysplastic syndromes (MDS) are rare cancers with unmet medical needs. The hypothesis is that comprehensive analyses of large patient population will allow to correctly estimate the effect of each mutation on clinical outcomes, and that niche factors and immune dysfunctions may influence the development of MDS, clonal evolution and response to treatments. The aims are to investigate gene mutations, niche factors and immune dysfunctions influencing the development of MDS, and define biomarkers for early identification of individuals at risk; to develop prognostic models for MDS patients through integration of comprehensive genomic/clinical information; to define biomarkers to better stratify the individual probability of response to specific treatments. The study will characterize how clonal hematopoiesis relates to the induction of MDS clinical phenotype, test the utility of gene sequencing, define effective prognostic systems and biomarkers and stratify the individual probability of response to treatment.



Sarcomas

BRCAddict: Harnessing BRCAness as a therapeutic target in high-risk pediatric solid tumors

Coordinator:

Stefan Michael Pfister

Project Partners:

Didier Surdez
Birgit Geoerger
Jan Molenaar
Johannes Gojo
Johannes Schulte

Despite major efforts to apply next-generation molecular diagnostics, cure rates for pediatric solid tumors at relapse remain dismal. Approximately 50% do not have an obvious genetic drug target. Recent pediatric pan-cancer study suggests that a large proportion of different solid tumor types show a mutational signature compatible with BRCAness, implicating sensitivity to PARP inhibition. The aim is to assess the sensitivity of BRCAness positive tumors to combinations of PARP inhibitors and DNA-damaging chemotherapy in vivo, and tune a BCRAness calling algorithm by using preclinical in vivo response data for its first clinical application. Also the project will strive to understand the "degree of BRCAness" necessary to sensitize for PARP inhibition. Results and biomarker evaluation will lay the groundwork for a molecularly stratified study across pediatric solid tumors within the ITCC network.

Urothelial Cancers

MOLCARUTUC: Comprehensive genomic characterization of upper urinary tract urothelial carcinoma and paired bladder recurrences

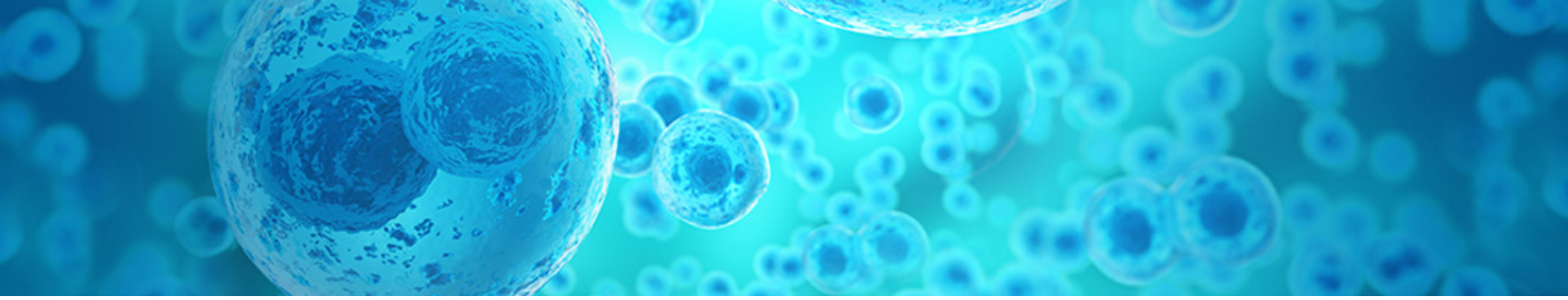
Coordinator:

Joost L. Boormans

Project Partners:

Yves Allory
Bernardo Herrera
Arndt Hartmann

Upper urinary tract urothelial carcinoma (UTUC) patients have poor outcomes and a high risk of intravesical recurrences (IVR) after radical surgery, but tools that predict an IVR are lacking and more effective therapies are needed. This project identifies novel genetic leads for improved diagnostics and therapy by genomic characterization of UTUC and IVR as the solution to address these clinical needs. The study aims to clarify the clonal origin of UTUC and IVR, and to identify genomic alterations of UTUC as novel druggable targets and predictors of treatment response. Whole exome sequencing, microsatellite instability analysis, and immunohistochemistry will be done to assess tumor mutational burden (TMB), mismatch repair deficiency, and immune infiltration. New actionable targets, such as UTUC with high TMB, will be identified as targets for precision-guided immunotherapy leading to durable therapy responses.



Rare Gynecologic Epithelial Cancers

ROCSANbio: Anti-PD1 and Niraparib (PARPi) combination therapy in gynae carcinosarcoma: Identification of response-predictive biomarkers and resistance mechanisms

Coordinator:

Isabelle Ray Coquard

Project Partners:

Marc-Henri Stern

Sandro Pignata

Elena Ioana Braicu

Carcinosarcomas (CS) are rare and aggressive tumors. Gynecologic CS have a 5-year overall survival <10% and most patients relapsed after standard treatments. The ROCSANbio translational program, merge with a phase III trial that evaluate PARPi/anti-PD1 combination in relapsed CS. The aim will be to define biomarkers within tumors and blood predicting anti-PD1/PARPi response in CS, and to investigate the effect on quality of life (QOL) and patient-reported outcome (PRO). The secondary aim will be to identify resistance mechanisms. The unique access to materials at diagnosis, inclusion and progression will allow to compare responding and non-responding patients for tumor immune infiltrate and immune checkpoint expression, EMT signature, HRD signature, TMB, tumor neo-epitopes and T-cell response. The plan is to identify biomarkers predicting response, impact on QOL for patients and to discover novel resistance targets representing better candidates for combination therapy.

Rare Thoracic Cancers

TOPMESO: A translational platform for de-orphaning malignant pleural mesothelioma

Coordinator:

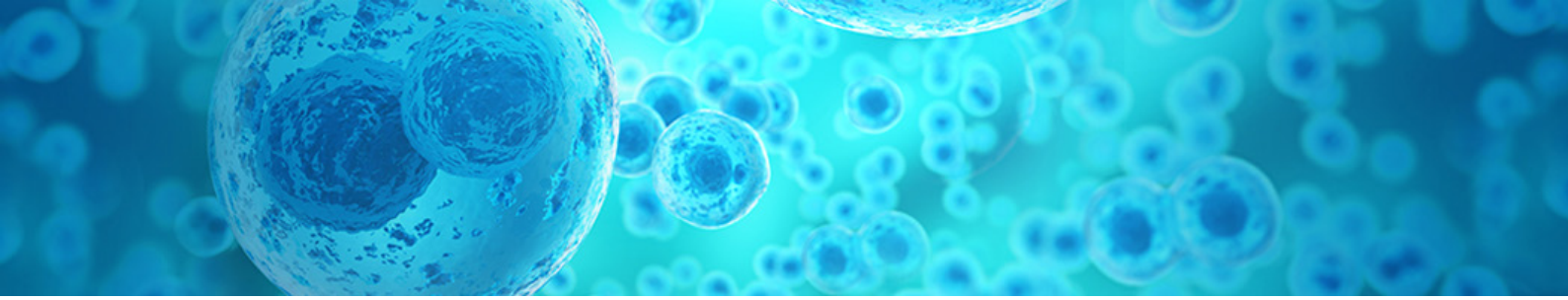
Federico Bussolino

Project Partners:

Luis Paz-Ares

Paul Baas

Pleural malignant mesothelioma (MPM) is a rare (incidence 3 case/100,000 people) and fatal malignancy, associated with occupational and environmental exposure to asbestos. Relatively few genetic lesions largely oncosuppressor combined with autocrine and paracrine inflammatory loops and an immunosuppressive state represent the current knowledge on MPM pathogenesis. This study aims to identify actionable pathways, new therapeutic strategies and predictive biomarkers. This goal will be reached by exploiting a prospective observational clinical trial to fuel a robust and clinically annotated living biobank, constituted by primary cell cultures, patient-derived xenografts (PDXs) and innovative 3D-immune-organoids. This strategy will enable performing a comprehensive molecular annotation of patient samples and living MPM preclinical models, functional and pharmacogenomics screens in MPM preclinical models in order to prioritize novel combination therapies for clinical testing as well as identifying candidate predictive and prognostic biomarkers in MPM patients treated with chemotherapy alone or combined with treatment targeting vascular and immune systems, metabolism and DNA epigenetic regulation.



Neuroendocrine Tumours

PMTR-pNET: Predictive models of therapy response in pancreatic neuroendocrine tumors

Coordinator:

Thomas M. Gress/
Malte Buchholz

Project Partners:

Hans Kestler

Massimo Milione

Emmanuel Barillot

Pancreatic neuroendocrine tumors (PanNETs) are rare neoplasms of the pancreas with a mortality rate of 60%. The PMTR-pNET consortium comprises clinical partners with access to well-defined cohorts of PanNET patients, as well as computational biology groups contributing expertise in integration of heterogeneous biological data and biological network modeling. The PMTR-pNET project will perform systems biology-based analyses of large PanNET data sets to identify novel marker signatures in PanNET samples predicting individual patient response to approved therapies. This project is expected to implement precision biomarker models for a better therapeutic stratification of PanNET patients, thereby improving clinical decision making and medical treatment options.

PREDICt: Profiling radioresistant differentiated thyroid cancer: Genes, immunity, cancer stem cells and epithelial-mesenchymal transition

Coordinator:

Martina Sollini

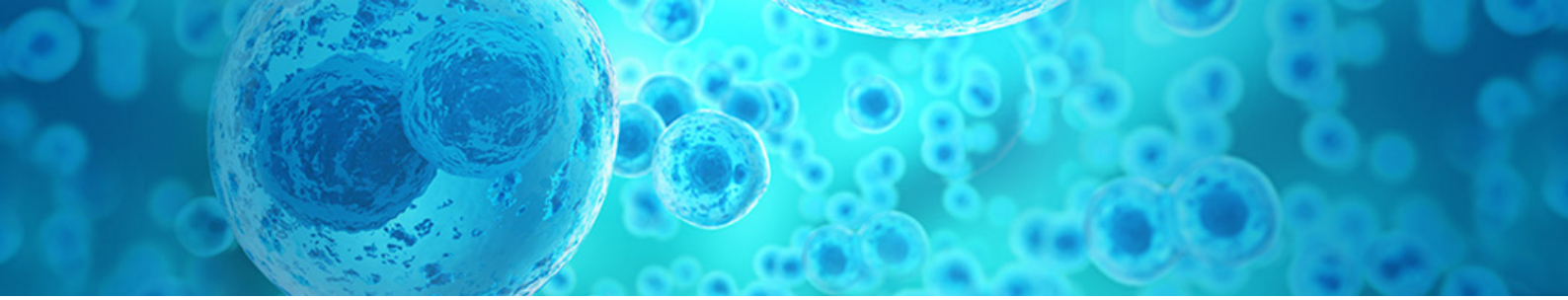
Project Partners:

Markus Luster

Oscar K. Lee

Ciarrocchi Alessia

Radioiodine-refractory (RAI-R) differentiated thyroid cancer (DTC) is a challenging tumor. The study aims to evaluate the genetic, transcriptomic profiles and the role of cancer stem cells (CSC), epithelial- mesenchymal transition (EMT) and immunity in RAI-R DTC; to identify RAI-R DTC biomarkers and to develop RAI-R DTC organoids. Exome sequencing will be performed and gene expression profile will be investigated. Focus on genes involved in EMT or in CSC biology will be posed to explore their role in RAI-R. The miRNA and proteins will be tested as serum biomarkers. Images will be analyzed (radiomics and/or machine learning) to test their prognostic role. Tissue samples will be used to develop RAI-R organoids. Diverse molecular and genetic profiles as well as different biomarkers between RAI-R and RAI-S are expected to possibly impact high-risk DTC patients management and treatment, their quality of life and healthcare costs.



NExT: Establishing an algorithm for the early diagnosis and follow-up of patients with pancreatic neuroendocrine tumors

Coordinator:

Yvonne Kohl

Project Partners:

Alfredo Carrato
David Hevia
Vita Rovite
Bozena Smolkova
Manousos Konstadoulakis

Standardized clinical management of pancreatic neuroendocrine tumours (PNETs) is restricted by different aspects of the disease: rarity, heterogeneous presentation, limited understanding of PNET-biology, lack of risk stratification systems. Circulating tumour cells (CTCs) are considered attractive biomarkers for liquid biopsies. By building up a tissue bank of genetically characterized tumours and the development of patient-derived xenografts (PDXs), the aim is to identify PNET-specific biomarkers to design a NExT generation nanotechnology based microfluidic device and to integrate the technology of minimally invasive liquid biopsy in the early detection of PNETs. Better understanding of the etiopathogenetic determinants involved in PNETs formation will deliver a nanotechnology based microfluidic device that by means of CTCs detection will present a powerful tool for early detection of PNETs and patients' follow-up, contributing to better medical treatment.

Neuroblastomas

LIQUIDHOPE: Advancing liquid biopsies for monitoring and personalized treatment of children with neuroblastomas

Coordinator:

Hedi Deubzer

Project Partners:

Lieve Tytgat
Jo Vandesompele
Jaime Font de Mora
Gudrun Schleiermacher
Sabine Taschner-Mandl

The embryonal tumor, neuroblastoma, accounts for 11% of all cancer-related deaths in children. Liquid biopsies have the power to revolutionize clinical care for children with high-risk neuroblastoma by reflecting precise disease status at any time during treatment and care. The LIQUIDHOPE consortium combines internationally recognized experts in neuroblastoma pan-omics and computational discovery with leading pediatric oncologists to advance this emerging clinical paradigm change. The study aims to accelerate transfer of liquid biopsy approaches. It will apply targeted metabolomics, cfDNA WES, cfDNA TSS and methylation profiling, unbiased total RNA profiling to monitor lncRNA and circRNAs disease markers, ddPCR of DNA/RNA disease markers, automated multiple marker imaging and sophisticated bioinformatics. The project can identify and validate predictive markers for treatment response, relapse and treatment choice in blood/bone marrow surrogates to advance unique liquid biopsy-based innovations for patient monitoring and personalized treatment of children battling neuroblastoma.