THE ERA-NET: ALIGNING NATIONAL/REGIONAL TRANSLATIONAL CANCER RESEARCH PROGRAMMES AND ACTIVITIES:

TRANSCAN-2 is funded by the European Commission **under the EU framework programme Horizon 2020**, in continuity with the preceding ERA-NET on translational cancer research - TRANSCAN.

It is a collaborative network of ministries, funding agencies and research councils with programmes in translational cancer research, with the main objective to coordinate activities of partners in the translational cancer research funding, avoiding the duplication of efforts and with a more efficient use of available resources. **The network is composed of 28 partners from 19 countries.**

The project aims at deepening and extending the transnational cooperation among partners through exchange of information, harmonisation of funding mechanisms and assessment of results of the funded research projects, facilitating the transnational cancer funding in Europe and thus contributing to the building of the European Research Area.

To reach its aims, TRANSCAN-2 launches **Joint Transnational Calls** (JTCs) for research proposals. The launch of four calls has been planned in the project lifetime.This model enables an efficient use of the dedicated national resources and the coordination of the financial management of multinational research projects.

NEW CALL FOR PROPOSALS 2016 (Third call)

"Minimally and non-invasive methods for early detection and/or progression of cancer" (launched on 2nd December 2016)

Submission deadline for pre-proposals: 13th February 2017

CLOSED JOINT TRANSNATIONAL CALLS

So far two calls for proposals were successfully completed by TRANSCAN-2 with a total 23 joint projects supported and an overall budget of 23,5 M€.

In the first, JTC 2014 co-funded by the European Commission, launched in January 2015 on: "Translational research on human tumour heterogeneity to overcome recurrence and resistance to therapy," 16 projects were funded, with a spent budget of 17,2 M€ (including 3,4 M€ from the European Commission).

The second call, JTC 2015, was launched in December 2015 on: "Immunology and immunotherapy of cancer: strengthening the translational aspects". 7 projects were selected for funding, with a total budget of 6,3 M€.

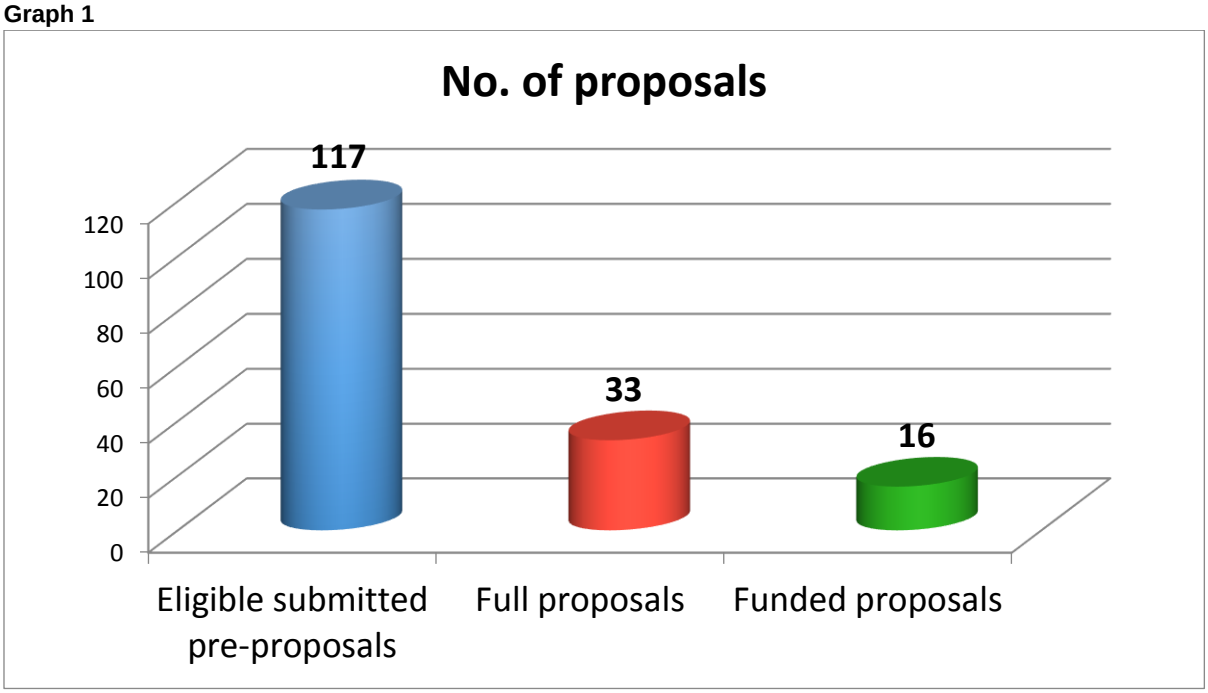
OVERVIEW OF 16 FUNDED PROJECTS FROM JTC 2014 (co-funded by the European Commission)

The JTC 2014, co-funded by the EC, on **"Translational research on human tumour heterogeneity to overcome recurrence and resistance to therapy"** aimed to fund studies on human tumour heterogeneity in order to direct therapeutic intervention and identify new targets for the development of efficacious precision therapeutic strategies, which are able to prevent tumour recurrence or resistance.

The call was motivated by the notion that human tumour heterogeneity can be considered as one of the most important causes contributing to treatment failure. Due to tumour heterogeneity issues, the prognosis evaluation may be confounded, thus leading to inadequate therapeutic strategies and ultimately to recurrence. Tumour complexity is a result of a continuous crosstalk between the tumour cells and the environment. Evaluating tumours as complex bodies and not simply as a mass of tumour cells is crucial, exposing the need of developing integrated approaches. Multi-omics/system biology approaches provide unique opportunities for elucidating intra-tumour heterogeneity by strategies combining technologies (genomic, epigenomic, cellular, microbiotic, exposome, metabolomic, nanotechnology, imaging, etc.), resources and data. Therefore, tumour heterogeneity is considered a major challenge to address in the next decade with the need to focus efforts on improving sampling and analysis methods, which are able to record these phenomena, deciphering the mechanisms underlying intra-tumour heterogeneity and its dynamic process as well as assessing its impact on the efficiency of therapeutic strategies.

At the completion of the call, 16 projects were selected for funding.

Graph 1

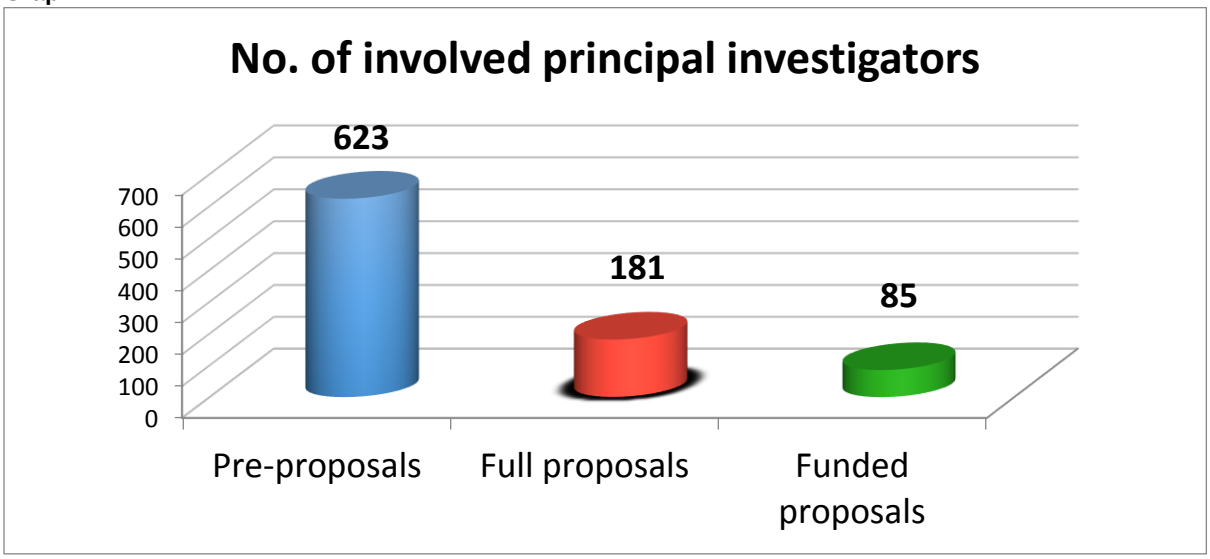


According to the tumour classification by organ site (World Cancer Report 2014, International Agency for Research on Cancer, WHO), the funded projects can be grouped as follows:

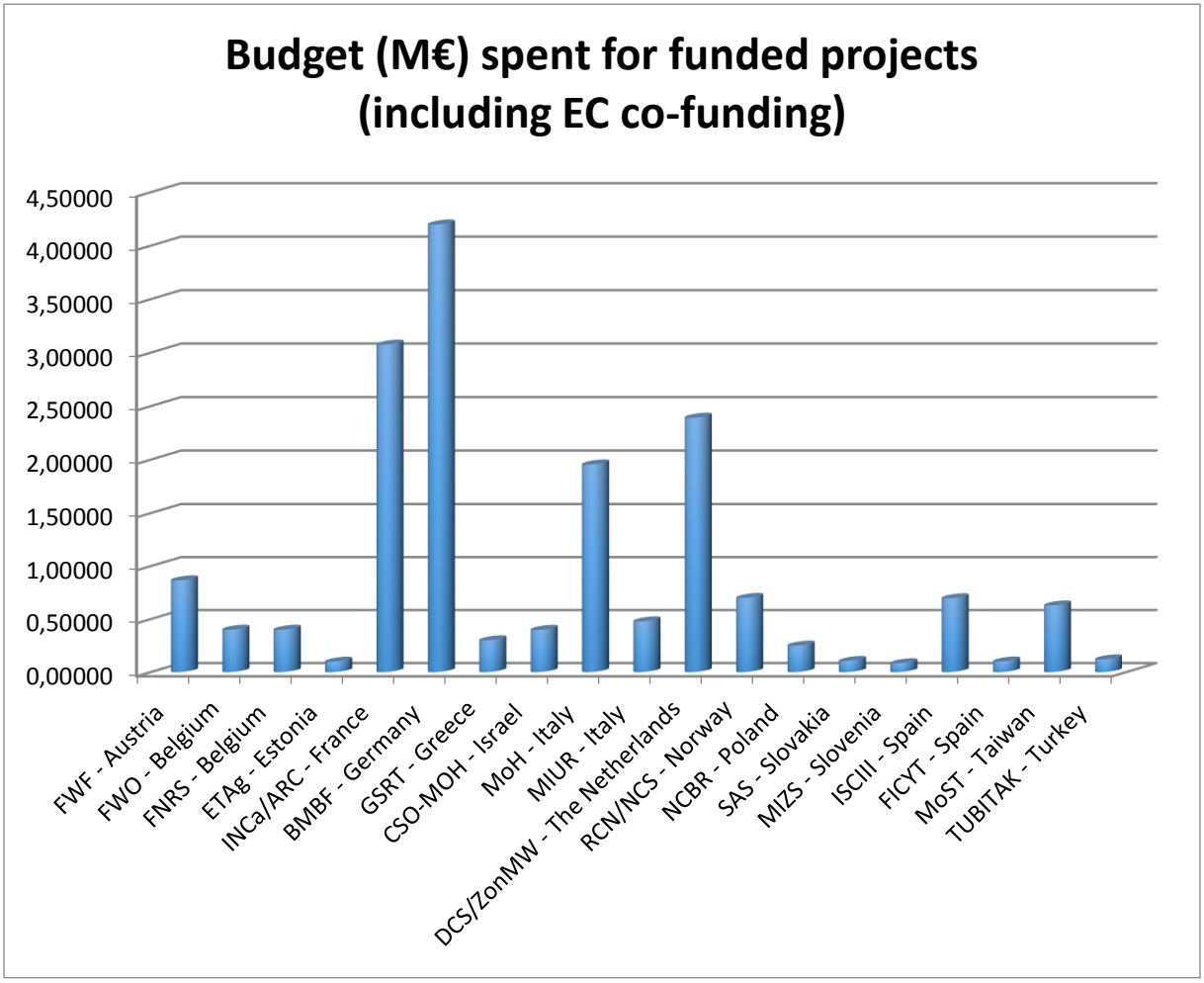
Organ site	Acronym and title of the project	AIMS of the project
Lung cancer	BeFiT – Patient-derived models for intratumour functional heterogeneity and its implications for personalized medicine	Lung adenocarcinoma. Study of the genetic heterogeneity among malignant cells, cancer stem cells and tumor microenvironment plasticity within a tumor. Potential therapeutic intervention (personalized medicine). First-in-human phase I clinical trial using a netrin-1 mAb.
	CEVIR - Cancer evolution and identification of relapse-initiating cells	Non-small lung cancer. Identification of relapse-initiating cells (RICs), study of their origin (from dividing clones of the primary tumour or rarely-dividing stem-like cells) and developing of blood-borne monitoring assays.
Breast cancer	CCE Breast - Clinical impact of intratumor heterogeneity in metastatic breast cancer	Metastatic breast cancer (mBC). Identification of predictor for early death in mBC to define a subset of patients for an appropriate drug approval based on phase II data. Study of the mechanism of resistance to PI3K or Her2 inhibitors to develop early strategies to overcome resistance. Identification of new targets located in subcellular fractions.
	Het Met - Intratumour heterogeneity, clonal selection and metastatic propensity in breast cancer	Breast cancer. Characterization of the genetic alteration and heterogeneity of axillary limph node as compared to the matched primary tumour. Analysis of the profile of circulating tumour cells. Identification of potentially "druggable" genomic aberrations responsible for lymphatic and hematogeneous dissemination.
	TH4RESPONS - Clinical utility of tumour heterogeneity in triple negative breast cancer and high-grade serous ovarian carcinoma for prediction of therapy response	Triple negative breast cancer - Ovarian high grade serous carcinoma. Definition of tumour heterogeneity in clinical samples from primary, recurrent, and metastatic cancers using multi-omics techniques. Use of patient derived xenograft to investigate biomarkers of resistance to be validated for clinical utility.
Oesophageal cancer	ARREST - Approaching recurrence and resistance mechanisms in esophagogastric adenocarcinomas from the prospective MEMORI trial	Esophagogastric junction adenocarcinomas (EAC). Identification of metabolic and proteomic intratumor molecular heterogeneity in tumor material from the MEMORI trial and consequent isolation of therapy-resistant subpopulation. Deliver of potential alternative therapeutic targets for EAC and robust classifiers for therapy decision-making.

Colorectal cancer	INTRACOLOR - Evolution of resistant clones to novel target-directed drugs in colorectal tumors. A genetic and epigenetic study of intratumoral heterogeneity dynamics	Metastatic colorectal cancer (mCRC). Study of the genetic and epigenetic nature of acquired resistance in advance CRC treated with target-directed drugs. Description of the evolution of resistant clones with distinctive genetic alterations and gene expression profiles. Testing the use of new single or combined treatments with drugs targeting those alterations present in arising resistant clones, in PDX models derived from patients that progressed to anti-PDL1, anti-BRAF or anti-TGFbeta drugs.
	TACTIC - TArgeting Colon Tumor Initiating Cell heterogeneity	Colorectal cancer. Identification of unique markers, pathways and resistance mechanisms defining tumor initiating cells (TICs). Identification of genetic heterogeneity within TICs and validation of markers and therapies to target quiescent TICs. Linking of quiescent TICs to patient outcome and analyzing novel therapeutic approaches.
Cancers of the female reproductive organs	PROMETOV - Proteogenomic and targeted metabolomic analysis of ovarian cancer heterogeneity and its contribution to recurrence and therapy resistance	Ovarian cancer . Study of the contribution of tumor heterogeneity (TH) to resistance and recurrence in ovarian cancer by multi-omics measurements of matched PTs, metastases and plasma. Development of assays for markers of clinically relevant ovarian TH and evaluation of treatments targeting the heterogeneous factors identified to contribute to resistance and recurrence.
Haematopoietic and lymphoid malignancies	DRAMA - Defeating Recurrence and resistance in AML:Multigenomic Approaches to analyse heterogeneity	Acute Myeloid Leukemia (AML). Identification of rare mutations and epimutations in primary AMLs. Validation pipelines for the assessment of their functional significance/predictive value. Generation of (epi)genomic data, planning of a clinical diagnostic study for the validation of the findings in AML patients, set-up of a clinical grade panel of markers for patient stratification.
	FIRE-CLL - Fighting Resistance in CLL	Chronic Lymphocytic Leukemia (CLL). Study of patient-specific genetic and microenvironmental heterogeneity to bring a curative perspective by combination treatment. Genetic characterization of individual and spatial clonal heterogeneity. Measuring impact of microenvironment and immune surveillance in relation to clonal heterogeneity. Breaking treatment resistance by tailored combination strategies.
	GCH-CLL - Genetic and cellular intratumor heterogeneity as predictor of chronic lymphocytic leukemia outcome and treatment resistance	Chronic Lymphocytic Leukemia (CLL). Investigation of intratumor heterogeneity, from different topographic location and time points. Analysis of impact of in vitro treatment and extracellular stimuli on tumor heterogeneity and cellular behavior. Integration of experimental and clinical data using mathematical tools to build up a model allowing prognosticating disease evolution, treatment outcome and resistance.
	IntraMMclo - Multiple myeloma intra-clonal heterogeneity: evolution and implications of targeted therapy	Multiple myeloma (MM). Study of the process of clonal evolution during the development of MM from premalignant precursor conditions to active disease stages. Definition of the impact of chemotherapy and/or immunotherapy on intra-clonal selection, and of the role the tumour microenvironment on clonal dynamics in MM patients.
Skin cancer	ITEM - Dissecting phenotypic heterogeneity of human melanoma: building a rationale for active immunotherapies overcoming immunologically-induced dedifferentiation	Melanoma. Identification of non-overlapping sets of genes expressed by distinct melanoma cell subpopulations and their changes during immunotherapy. Validation as antigenic targets the proteins encoded by the genes overespressed by the distinct melanoma cell subpopulation identified in the first step.
Tumours of the nervous system - Childhood malignancies	ONTHETRRAC - Overcoming Neuroblastoma Tumour HETerogeneity, Resistance and RecurrAnCe	Neuroblastoma (NB).Definition of a systematic combined analysis of genomic/RNA/epigenetic changes in primary/metastatic patient samples. Establishment of a robust technique for disease monitoring and detection of druggable mutations. Validation of biomarkers. Recommendations for the best strategies to molecularly diagnose/monitor disease for implementation into the next high-risk/relapse NB trial protocol.
	TORPEDO - Targeting Of Resistance in PEDiatric Oncology	Childhood malignancies. Development of rational combination therapies for different childhood solid malignancies to be tested as a next wave of clinical trials within the ITCC early phase clinical trial consortium (http://www.itcc-consortium.org). Identification of common resistance mechanisms to targeted drugs. Establishment of a joint European repertoire of molecularly well-characterized PDX models. Study the role of tumor subclone heterogeneity in determining the response to targeted drugs.

Graph 2



Graph 3



NEWS FROM THE FIRST TRANSCAN-2 SYMPOSIUM

One of the tasks of TRANSCAN-2 is dedicated to the organisation of a series of symposia that include the presentation of the results of projects funded by TRANSCAN and TRANSCAN-2. The aim is to increase awareness of the outcome and the impact of the funded projects in the field of translational cancer research and to disseminate the information to the public. **The first symposium, which was held on 14th September 2016 in Rome, Italy, at Istituto dell'Enciclopedia Italiana, brought together:**

- The coordinators of projects funded under the first joint transnational call for proposals launched in December 2011 on: "Validation of biomarkers for personalised cancer medicine" (JTC 2011).
- Outstanding experts in the field of cancer biomarkers, some of whom are also members of the TRANSCAN and TRANSCAN-2 Scientific Advisory Boards, whilst others were involved in the review and selection process of these funded projects.
- The interested programme owners/managers: Representatives of the funding organizations, who participated in the call preparation, implementation and in the project funding.

PROJECT COORDINATORS:
1) Arango Diego (VALPRAXIN*) Fundació Institut de Recerca Hospital Universitari Vall d'Hebron, Centre d'Investigacions en Bioquímica i Biología Molecular (CIBBIM), Barcelona, Spain;* ***2) Bondanza Attilio (HAPLO-IMMUNE)*** *IRCCS Ospedale San Raffaele Experimental Hematology and Bone Marrow Transplantation Unit, Milan, Italy;* ***3) Criscitiello Carmen (UGI1)*** *The European Institute of Oncology (Istituto Europeo di Oncologia – IEO), Milan, Italy;* ***4) Dirksen Uta (PROVABES)*** *University Hospital Muenster, Paediatric Haematology and Oncology, Münster, Germany;* ***5) Garassino Marina Chiara (Bio RaRE)*** *Fondazione IRCCS Istituto Nazionale dei Tumori (INT) Medical Oncology, Milano, italy;* ***6) Gennari Alessandra (ET-FES)*** *Regione Liguria – E.O. Ospedali Galliera Medical Oncology - E.O. Ospedali Galliera, Genoa, Italy;* ***7) Lianidou Evi (CTC-SCAN)*** *Analysis of Circulating Tumor Cells Lab, Department of Chemistry, University of Athens, Greece;* ***8) Mikołajczak Renata (GRAN-T-MTC)*** *National Centre For Nuclear Research, Radioisotope Centre POLATOM, Otwock, Poland;* ***9) Stanulla Martin (TRANSCALL)*** *University Hospital Schleswig-Holstein, Department of Pediatrics, Kiel, Germany.*

INVITED EXPERTS:
1) Barak Vivian*, Immunology Laboratory for Tumor Diagnosis, Dept. of Oncology, Hadassah Medical Center, Israel;* ***2) Carneiro Fatima****, IPATIMUP, Medical Faculty of Porto Department of Anatomic Pathology, Hospital S. João, Porto, Portugal,* ***3) Giavazzi Raffaella****, Istituto di Ricerche Farmacologiche "Mario Negri", Milano, Italy;* ***4) Gratwohl Alois****, University Hospital Basel, Basel, Switzerland;* ***5) Guinn Barbara****, Department of Life Sciences, University of Bedfordshire, Luton, United Kingdom;* ***6) Muschel Ruth****, Gray Institute for Radiation Oncology and Biology, Department of Oncology, Oxford, United Kingdom;* ***7) Pandiella Atanasio****, Centro de Investigacion del Cancer, IBMCC, Salamanca, Spain;* ***8) Pauwels Patrick****, Center for Oncological Research, University of Antwerp, Wilrijk, Belgium;* ***9) Ringborg Ulrik****, Cancer Center Karolinska, Karolinska University Hospital, Solna, Sweden;* ***10) Schulz-Knappe Peter****, Protagen AG, Dortmund, Germany.*

The symposium focused both on the scientific achievements reached so far by each funded consortium, on the exchange of information, feedback and pinpoint the encountered bottlenecks, in particular those related to the TRANSCAN procedures, and suggestions of possible solutions for the implementation and enhancement of future activities in TRANSCAN-2.

The day program included the following:

1. An overview of TRANSCAN and TRANSCAN-2.
2. An overview of the 2011 call motivation, aims, procedures, implementation and results.
3. A keynote lecture on the processes of development, validation and clinical use of biomarkers.
4. Scientific presentations of 9 (out of 10) funded projects including scientific achievements of each consortium as well as encountered issues and suggested solutions.
5. An open discussion, following each presentation, between projects coordinators, attending experts and members of the funding organizations.
6. Two roundtable discussions to evaluate the impact of the funded projects and to discuss the issues that the coordinators of funded consortia faced.

This event was the first time that coordinators met the representatives of funding organizations. During this meeting, the coordinators were able to express themselves in a non-scrutinizing environment on the process of implementing their project and working in a consortium funded by TRANSCAN. This face-to-face meeting allowed both sides to better understand the processes that might hinder the excellent science conducted.

In addition to some constructive criticism on the approval process, two very positive aspects were raised during the roundtable discussions: (i) TRANSCAN is really favouring cohesion and networking within the EU and associated countries, and this falls within EU transnational collaboration aims. (ii) Scientifically speaking, such networking is expected to increase the quality of conducted research and resulting publications of the participating groups. The outcome of the excellent scientific work conducted in the funded consortia may augment competitiveness and visibility of the EU and associated countries.

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