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

JTC 2016 - PRE-PROPOSAL SUBMISSION PHASE CLOSED

"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)

Results from the pre-proposal phase by April 2017

Submission deadline for invited full proposals: 7th June 2017

JTC 2015 - CLOSED CALL - OVERVIEW OF 7 FUNDED PROJECTS

The JTC 2015 on "**Immunology and immunotherapy of cancer: strengthening the translational aspects"** aimed at developing transnational innovative projects in translational cancer research, clearly oriented towards a rapid application of new, more selective and effective tools and strategies for the immunotherapy of neoplastic diseases.

The call was motivated by the notion that, despite cancer diagnosis and treatment have improved significantly over the last decade, and many therapeutic strategies have been explored and developed, in many cases these modalities, along with surgery, are not efficacious in eradicating the disease and are often characterized by an elevated toxicity. Furthermore long-term survival rates for most patients with advanced cancer remain low, thus there is a need for cancer treatments with favourable benefit and toxicity profiles that may lead to an improvement of the outcome. Nowadays large efforts are placed in identifying potential novel therapeutic targets and developing more selective, effective and less toxic therapeutic agents and interventions.

The recent increased understanding of the human immune system, of the basic mechanisms involved in the recognition of cancer cells by innate and acquired immune cells and of escape pathways put in place by cancer and its microenvironment, have paved the way for the development of innovative immunotherapeutic strategies. In addition, many studies have reported that chemotherapy drugs and irradiation can be helpful in breaking immune tolerance and inducing microenvironment for adoptive cell therapy. It is now widely recognized that cancer immunotherapy, mainly due to the use of checkpoint inhibitors, is one of the major breakthroughs of the last years in medicine with profound impact on the quality of life and long-term survival in a good proportion of cancer patients affected by a variety of solid and liquid cancers. Most importantly, the intersection of cancer immunology with cancer genomics through the diffused use of next generation sequencing has provided increasing evidence that efficacy of checkpoint inhibitors is intertwined with the individual mutational burden of cancer cells. In such a context, the necessity to develop personalized approaches to cancer immunotherapy aiming at improved patient care (efficacy and safety), and cost-effectiveness, currently represent a major challenge. Taking this into account, translational research directed to enhance the development of personalized immunotherapy against cancer is now considered a research topic boding a previously unexpected potential high impact on the management of cancer patients, thus deserving special attention in the promotion of the international cooperation in this field.

Three main aims of the call were identified:

- Aim 1: Identification and validation of shared or personalized mutated human tumour antigenic targets.
- Aim 2: Development of new and combined immunotherapeutic strategies for cancer patients.
- Aim 3: Translational research for clinical application of cancer immunotherapy.

At the completion of the call, 7 transnational projects were selected for funding, with a total allocated budget of 6,3 M€.

Graph 1: Number of proposals (pre/full/funded)

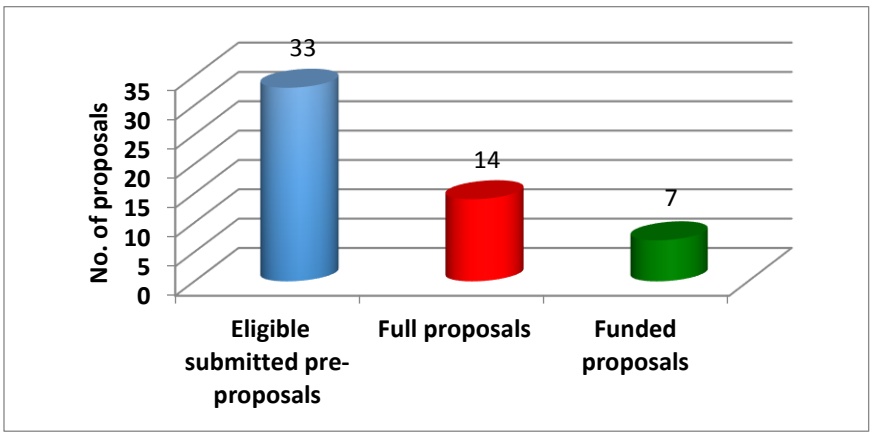

Table 1: Number of involved Principal Investigators in (pre/full/funded) proposals JTC 2015 and gender distribution

No. of involved principal investigator	Pre-proposals	Full proposals	Funded proposals
Female	38	21	11
Male	106	42	24
Total	**144**	**63**	**35**

Graph 2: Country of provenience of Principal Investigators

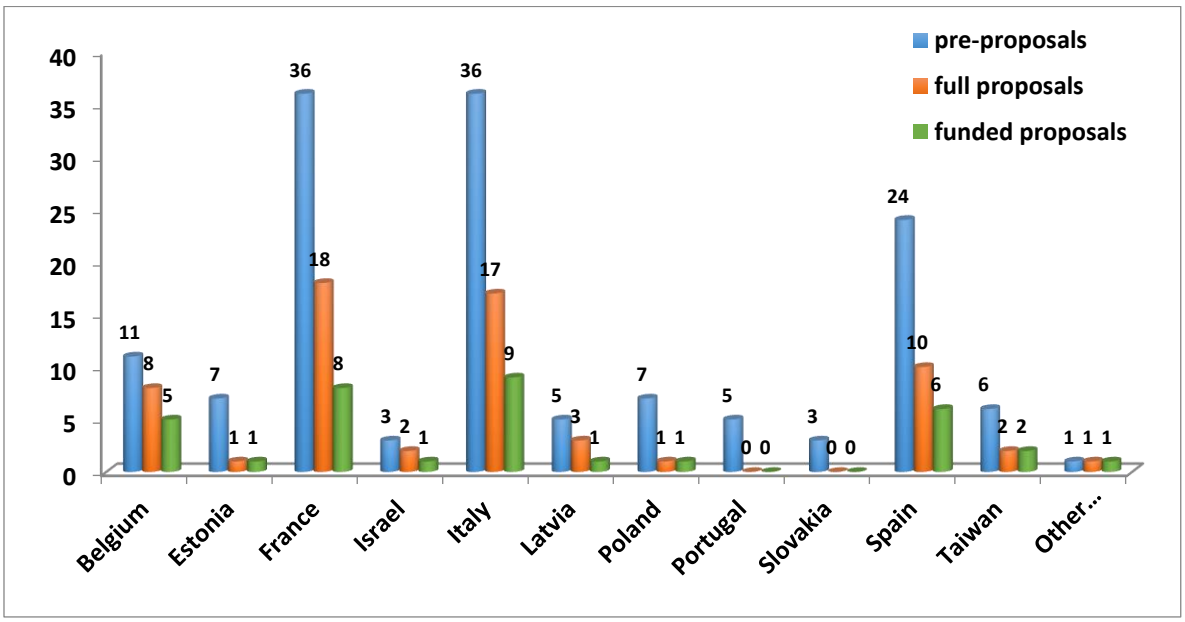

Table 2: Funded projects

Organ site*	Acronym and title of the project	Aims of the project
Breast cancer **Skin cancer**	**DIgesT** - Impact of dietary intervention on tumor immunity	Breast cancer and melanoma - To determine if fasting-mimicking diet (FMD) modulates immune cell profiles in cancer patients and tilts the balance from immunosuppressive to antitumor immune responses. - To evaluate in mouse models if FMD improves antitumor immune response, alone or combined with ICIs. - To clarify the molecular mechanisms underlying FMD-induced immune modifications. - To analyze the effect of FMD on gut microbiota, as a possible link to systemic immune modulation.
Skin cancer	**EPICA** - Dual epigenetic targeting and immunotherapy to fight against cancer	Melanoma - To study the molecular events underlying the anti-tumor and immunomodulatory activities of the newly defined G9a/DNMT1 dual inhibitor (CM272) in vitro and in vivo in comparison with approved hypomethylating agents. - To develop a novel combinatorial strategy with state-of-the art immunotherapies leading to a first-in-man clinical study.
Liver cancer	**HEPAMUT** - Mutated neo-antigens in hepatocellular carcinoma	Hepatocellular carcinoma - To evaluate the mutational rate in hepatocellular carcinoma (HCC) samples and predict the presentation of neo-epitopes by HLA-A2*01 allele. - To assess the frequency of specific T cell response to such mutant epitopes in HCC patients, before and after treatment with checkpoint inhibitors (CI). - To validate the immunogenicity of neo-epitopes in an HLA-transgenic mice and their therapeutic effect in a patient-derived xenograft (PDX) animal model. - To identify mutated full-length proteins presented on the surface of HCC cancer cells. - To develop MAbs to such mutated proteins and validate their specificity in vivo in a PDX animal model.
Tumours of the nervous system	**IMMUNOGLIO** - Deciphering immune response against glioblastoma to find new targets	Glioblastoma - To study of the antitumor immune response against glioblastoma (GBM) to unravel new effectors and immunosuppressive pathways important for the regulation of anticancer immunity and to discover new immune activating strategies with the objective to isolate subgroups of GBMs that could benefit from an immunotherapy approach.
Skin cancer	**IMMUSPHINX** - Targeting sphingolipid metabolism to improve anti-melanoma immunotherapy	Melanoma - To study the efficacy of novel approaches combining sphingolipid blocking agents (SBA) with immune checkpoint inhibitors (ICI). - To determine how sphingolipids (SLs) affect tumor microenvironment and facilitate anti-melanoma immune responses by analyzing the sphingolipidome of tumors and plasma, and by identifying immune signatures. - To study whether intratumoral SL metabolizing-enzymes and/or peripheral blood SLs could serve as biomarkers predictive of ICI efficacy. These parameters as well as treatment efficacy in melanoma patients will be analyzed using (Ir) RECIST both in a retrospective and prospective manner.
Breast cancer **Colorectal cancer** **Head and neck cancer** **Skin cancer**	**Microther** - Improving immunotherapy of solid tumors by targeting the immunosuppressive tumor microenvironment: from pre-clinical "proof-of-concept" to the development of phase Ib study	Triple negative breast cancer, colorectal cancer, head and neck cancer and melanoma - To perform a retrospective bio-molecular characterization of immunosuppressive cells and matricellular proteins in TM of 4 tumors (triple negative breast cancer, TNBC; head and neck, HNSCC; melanoma and colorectal cancer, CRC). The immunosuppressive TM will be evaluated even in pre e post-chemotherapy (CT) lesions from patients receiving neoadjuvant therapy. - To exploit mouse models for testing synergistic anti-tumor activity of ICB combined with drugs targeting the immunosuppressive TM. Combinations will be based on results from Aim 1 as well as on available off-the-shelf drugs known to target the TM. - To design phase Ib clinical study in TNBC, HNSCC, melanoma and CRC assessing activity of ICB associated with microenvironment modulators chosen according to results of Aim 1 and 2.

Kidney cancer	**REVOLUTION** - Prediction of nivolumab action in metastatic renal cancer patients:Treg function, tumoral access and NK interactions as predictive biomarkers of immunotherapy	Renal cancer - To evaluate Tregs function on peripheral blood/neoplastic tissue from metastatic renal carcinoma (mRCC) patients undergoing nivolumab treatment. Ex vivo effect of CXCR4 antagonists (PCT/IB2011/000120/ EP2528936B1/ US2013/0079292A1) and other Tregs targets antagonists (ICOS,CD39/CD73) or agonists (TLR7L) as putative anti-PD1 resistance mechanisms. - To evaluate NK function on peripheral blood/neoplastic tissue from mRCC patients undergoing nivolumab treatment. Ex vivo effect of CXCR4 antagonists. - To explore the biological rationale for coupling CXCR4 antagonist with anti PD-1 in in vivo models of renal cancer.

Organ site*: According to the tumour classification by WHO in World Cancer Report 2014, International Agency for Research on Cancer.

THE SECOND TRANSCAN-2 SYMPOSIUM IN PREPARATION

Second Symposium is planned for 13th September 2017.

More information will be available in the following TRANSCAN-2 newsletters.

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