DECEMBER 2023, NUMBER 6

NEWSLETTER TRANSCAN-3

On behalf of the TRANSCAN-3 Consortium we are glad to present our 6th newsletter with the latest updates about the project, the joint calls for proposals and the funded projects. This issue includes:

Enjoy reading!

Do not miss any TRANSCAN-3 news and the project results visiting the project website.
Follow our social media pages on LinkedIn and Twitter

1. TRANSCAN–3 Activities: JTC 2021 Symposium in Riga

On October 17th and 18th we had the pleasure to celebrate our first TRANSCAN-3 Symposium to gather and present all the research projects awarded in the co-funded call JTC 2021: "Next generation cancer immunotherapy: targeting the tumour microenvironment"

With close to 100 participants joining both on site and remotely, we enjoyed a two-day event full of great research and networking. Among the attendees, we were honored with the presence of the EC project officer Laura García Ibañez, as well as researchers and representatives from the funding agencies from 19 countries, including participants coming from outside of Europe and overseas.

> The Transcan symposium exceeded my expectations. The quality of the research being funded is phenomenal with the potential to really make a difference for patients. The in-person symposium was a great opportunity for me to develop new collaborations, notable with colleagues from Spain and Germany

John Stagg - MAGNOLIA project coordinator
Centr Hospitalier de l'Université de Montréal, Canada

In addition to all the great project presentations and scientific discussions, the programme included other interesting talks on intellectual property, active patient engagement in the research process, and success stories from TRANSCAN-2.

1

Michele Dubbini – EC IP Helpdesk Service

Michele walked the attendees through the roadmap that an idea undergoes from inception until having a real impact, reviewing the key definitions and milestones of the process as well as useful documents and considerations to be kept in mind when establishing a research consortium.

For more information about the European IP Helpdesk services and resources visit www.ec.europa.eu/ip-helpdesk.

2

Bettina Ryll– Patient engagement in Cancer Research

With both her experience in research and patient advocacy and engagement, Bettina shared very interesting insights about the patient involvement in research. She highlighted how patient engagement can be "more serious and more fun" and reviewed different types of engagement strategies and levels presenting useful resources and tools to enhance patient participation.

Some resources from the Melanoma Patient Network Europe:

- V2A2: A tool to promote patient agency through effective patient information
- MPNE patient engagement 1-0-1
- Understanding the difference between patients- patient advocates and patient advocacy experts
- Different types of patient engagement in research

3

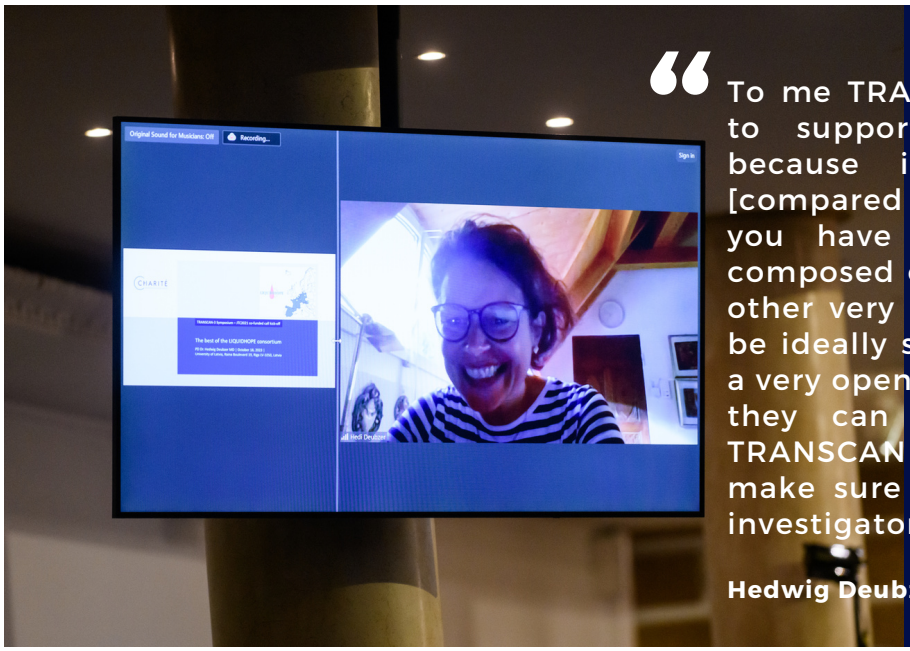
Hedwig Deubzer – Peer Learning TRANSCAN-2

LIQUIDHOPE coordinator Dr. Hedwig Deubzer started by sharing some exciting scientific results of her project which focused on advancing liquid biopsies for monitoring and personalized treatment of children with neuroblastomas with a consortium composed of six teams from six different countries. The team has published a total of 22 publications, a patent has been granted to Prof. Vandesompele and, as a result of their collaboration, they secured further funding and prepared further additional applications.

In addition to the great progress, Dr. Deubzer shared some insights with JTC 2021 awardees for the success of their consortia:

- Ensure open access to all biomaterials.
- Involve and encourage everyone, including researchers at all levels of their careers.
- "No touch" agreement for novel ideas – indispensable for open exchange
- Secure high visibility of consortium through project presentations at international conferences

To conclude, Dr. Deubzer stressed the importance of TRANSCAN projects in the support of early career researchers.



> "To me TRANSCAN is a unique platform to support young investigators, (…) because it is a smaller platform [compared to than EU consortia]. When you have well balanced consortium composed of a few labs that know each other very well young investigators can be ideally supported because they have a very open-minded environment where they can also support each other. TRANSCAN is very crucial as platform to make sure that we can support young investigators"
>
> **Hedwig Deubzer** – LIQUIDHOPE Coordinator

Additionally, a gathering for early career researchers was organized to foster the networks and listen to the needs of the younger researchers as they are the future of cancer research.

"The TRANSCAN Symposium is a very good initiative to establish new collaborations at European (and indeed international) level, in the very specific field of cancer immunotherapy. Personally, it was very useful for me to see where research trends are going, and, given that our project was the most different from the others (most of them seek to understand patient responses to treatments through molecular and cellular analysis of tumour cells, while ours seeks a new therapy), it allowed me to establish several collaborations in fields where no interest would have arisen had it not been for the meeting at the event."

Cristina Fornaguera – TumorOUT Coordinator

"The TRANSCAN-3 symposium in Riga was great not only because of the beautiful city, great organisation, tasty food and well-planned programme. It was a perfect opportunity to discuss scientific approaches across various diseases and biological questions as well as general aspects of collaborative research projects across both national and disciplinary borders. The discussions between clinicians, biological and bioinformatical researchers, funding partners and patient representatives have shown me new perspectives important for my future scientific work."

Peter-Martin Bruch – BIALYMP

VISIT THE IMAGE GALLERY

2. Updates about TRANSCAN-3 JTC 2023

After the successful launch, evaluation and award of the first two calls of TRANSCAN-3, the consortium is currently working on its third call JTC 2023 "Translational research on cancer epigenetics".

TIMELINE OF THE CALL

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

Following the call's timeline, JTC 2023 was launched in May and the call for submissions of pre-proposals closed this summer and a total of 83 proposals were received. On October 19th and 20th the Scientific Evaluation Committee gathered in Riga to discuss the proposals and selected a total of 41 proposals to be invited for full proposal stage, with a deadline for submission on December 15th.

Both SEC members and funders are very pleased about the great level of ideas and projects presented and look forward for the next evaluation phase in early 2024. Also, on behalf of both the SEC and the Network Steering Committee we take the chance to thank and congratulate all candidate teams for their efforts.

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

French National Cancer Institute, France

Charlotte Gudewicz

transcan-jtc2023@institutcancer.fr

3. TRANSCAN–2 Success stories

1

INTRACOLOR: tackling colorectal cancer heterogeneity to halt disease recurrence and combat targeted drug resistance.

Project Coordinator:
Josep Tabernero, Vall d'Hebron Institute of Oncology – Vall d'Hebron University Hospital, Barcelona, Spain.

Partner 2: Sabine Tejpar, Katholieke Universiteit Leuven, Leuven, Belgium.
Partner 3: René Bernards, The Netherlands Cancer Institute, Amsterdam, Netherlands.
Partner 4: Teresa Troiani, Second University of Naples, Naples, Italy.
Partner 5: Andrés Cervantes, Biomedical Research Institute INCLIVA. Hospital Clínico Universitario de Valencia, Valencia, Spain.
Partner 6: Sabrina Arena, Fondazione del Piemonte per l'Oncologia (FPO) IRCCS – Candiolo Cancer Center, Candiolo, Italy.

According to recently reported statistics (1), over 1.9 million new colorectal cancer (CRC) cases and 935,000 deaths were estimated to occur in 2020, representing around one in 10 cancer cases and deaths. Overall, CRC ranks third in terms of incidence, but second in terms of mortality. The global burden of this tumor type is expected to increase by 60%, to over 2.2 million new cases and 1.1 million annual deaths, by the year 2030 (2).

Added to these alarming trends and forecasts, CRC is a highly complex and heterogeneous disease with many molecular mechanisms and biological processes implicated in its development and progression. Further, the frequent occurrence of several of these alterations confer resistance to current treatments including standard chemotherapy and targeted agents.

Over the past decade, there have been several genomic-based successes in advancing critical insights into the molecular make-up of CRC including the relatively recently defined four consensus molecular subtypes (CMS) of this disease (3), While these developments continue to spur important progress towards developing, matching and measuring novel therapies according to the specificities of each identified molecular subtype, each individual patient, putting the brakes on the molecular culprits that drive tumor initiation, development, and growth still represents a colossal therapeutic challenge and an unmet clinical need.

In response, the four-year TRANSCAN-2 funded translational project INTRACOLOR, aimed at advancing insights into the evolution of resistance to novel target-directed therapies in CRC tumors based on the genetic and epigenetic analysis of intratumoral heterogeneity dynamics.

Running in parallel with the EU Horizon 2020 funded MoTriColor's early phase clinical trials, coordinated by VHIO's Director Josep Tabernero, assessed three novel targeted therapies for metastatic CRC (mCRC), each matched to distinctive gene expression signatures.

Representing a comprehensive framework for translational research, the investigators from six leading European cancer centers, prospectively integrated emerging molecular data in preclinical models and MoTriColor's proof-of-concept studies.

Incorporating six MoTriColor partners, the pioneering INTRACOLOR project was designed to enable the evaluation of paired samples to identify molecular alterations in primary versus metastatic samples as well as the acquisition of resistant clones. Tumor samples were collected and evaluated prior and post treatment of patients included in MoTriColor's clinical trials. The close connectivity and collaboration between both projects allowed the generation of sophisticated preclinical clinical trial associated xenograft models (CTAX) that reproduce the patients' disease in mice to test the efficacy of novel therapies as well as identify and measure potential primary or acquired resistance. A total of 55 paired samples were analyzed and 13 CTAX models were generated from tumor tissue obtained directly from MoTriColor patients.

The main impact of the INTRACOLOR project has been the discovery of new potentially targetable alterations for a molecular subpopulation of mCRC patients. An illustrative example was a CTAX model generated from a patient enrolled in MoTriColor. Exhaustive molecular analysis revealed that in addition to tumor microsatellite instability (MSI) and hypermutation status, an NTRK gene fusion was also present. The CTAX model showed a high response to NTRK inhibitors, with the mice presenting complete responses.

This discovery is relevant since it could lead to a paradigm shift in clinical practice for the treatment of mCRC patients whose tumors present the MSI phenotype. Molecular tumor profiling should be performed to identify oncogenic fusion genes that confer high addiction and sensitivity to existing targeted-drugs, which should be advanced in the lines of treatments and potentially prioritized versus immunotherapies. While fusions are found at a low frequency in CRC, this particular case has opened up ongoing research aimed at optimizing molecular prescreening for the detection of oncogenic fusions.

Importantly, the INTRACOLOR CTAX models will now be used in future prospective research projects to identify new mechanisms of resistance and sensitivity to the proposed therapies. As an example, preliminary analysis is already underway to confirm whether CTAX models can be used to identify peptides presented on HLA-I / HLA-II and recognized by T cells. Moving forward, this may lead to the unmasking of novel mechanisms of response and resistance to immune-based treatments.

The INTRACOLOR project required a close collaboration between clinicians and basic researchers. To build a network in an international consortium has been a challenge that has led us to learn that these efforts are possible and successful.

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249.

2. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Prz Gastroenterol. 2019;14(2):89-103. doi:10.5114/pg.2018.81072.

3. Guinney J, Dienstmann R, Wang X, de Reyniès A, Schlicker A, Soneson C, Marisa L, Roepman P, Nyamundanda G, Angelino P, Bot BM, Morris JS, Simon IM, Gerster S, Fessler E, De Sousa E Melo F, Missiaglia E, Ramay H, Barras D, Homicsko K, Maru D, Manyam GC, Broom B, Boige V, Perez-Villamil B, Laderas T, Salazar R, Gray JW, Hanahan D, Tabernero J, Bernards R, Friend SH, Laurent-Puig P, Medema JP, Sadanandam A, Wessels L, Delorenzi M, Kopetz S, Vermeulen L, Tejpar S. The consensus molecular subtypes of colorectal cancer. Nat Med. 2015 Nov;21(11):1350-6. doi: 10.1038/nm.3967. Epub 2015 Oct 12. PMID: 26457759; PMCID: PMC4636487.

2

Interview with early career researcher Giovanni Crisafulli – INTRACOLOR project

Giovanni Crisafulli carried out his PhD thesis in Mathematical logic, Computer Science and Bioniformatics at Università degli Studi di Siena, and successfully completed his PhD in 2012. He is experienced bioinformatician with a demonstrated history of working in the research industry (private and public), skilled in Cancer, Bioinformatics, Systems Biology, Oncology, Molecular Genetics and NGS.

How do you think this project has advanced our knowledge about the disease?

Precision medicine is based on the personalized care of each patient, taking into account the individual characteristics of each tumor. Despite this, we know that personalized therapies, although they might allow immediate clinical benefit, do not usually lead to a complete and long lasting response. Due to evolutionary forces and heterogeneity, the tumor evolves to resist therapy. In the JTC2014 project, we addressed the issue of heterogeneity and resistance, which is one of the most relevant challenges to defeat cancer. In fact, we traced the emergence of resistant clones through blood and generated preclinical models that allowed us to study novel therapeutic combinations to overcome resistance to commonly used therapies. These studies have improved and increased our knowledge on both technical and genetic sides for the role of tumor heterogeneity in mediating the emergence of drug resistance.

What has TRANSCAN-2 funding meant to you to carry out and be part of this project?

These funds were helpful for both the establishment of patient-derived models (PDXs) from patients enrolled in the CT3 Motricolor trial and for the development of an assay to identify low-frequency mutations in patients' blood.

PDXs and other preclinical models have been derived from patients with different microsatellite status and different response to the immuno-checkpoint blockade. These models have been completely annotated at the genomic level and have been used to test novel combinatorial strategies to overcome resistance to currently available therapies. Regarding the second point, patients' tissues are usually analyzed to determine the genetic characteristics of a tumor that will guide the choice of therapy in the field of precision medicine. In detail, only a small part of the tissue was analyzed and this does not allow us to capture tumor heterogeneity due to the sampling, especially in the metastatic setting. The liquid biopsy approach, on the contrary, allows for the identification of DNA molecules that have been released from all parts of the tumor, thereby better representing the clonal dissection of the tumor. However, liquid biopsy has some limitations: since the DNA released by the tumor is diluted in the patient's normal/germline DNA, the identification of tumor clones is challenging and the assay optimization for the identification of low frequency mutations becomes very relevant.

Thanks to the TRANSCAN-2 funding, we were able to generate novel clinically-relevant models and to carry out the set-up and optimization of a genetic assay to track the evolution of the tumor using the liquid biopsy approach.

How has the transnational collaborative aspect of the project contributed to project success?

This project has allowed us to get in close contact with colleagues from different fields and countries. These interactions have increased our scientific and cultural exposure, allowing us to broaden our horizons and leading researchers to focus on ambitious goals that are shared by multiple research fields. Specifically, the close contact between the preclinical and clinical sides has provided the oncologists with new weapons and more therapeutic options for improving patient care.

Anything else you would like to highlight about your experience?

I have been involved in research, working in both public and private sectors, initially dealing with the development of vaccines in a private company and then focusing on cancer research. I am happy and proud to have participated in this project because I think that projects like this allow different research groups with different expertise to meet and discuss, sharing their knowledge and skills in order to achieve a common goal and to train the hard core of future European researchers.

4. Other initiatives from partners

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

The largest national call from FCAECC to date "AECC 70% Survivorship Challenges" moves to its second phase. This action, which counts with a budget of 10M€ aims at supporting a nationwide, multidisciplinary project that responds to a clinical unmet need with impact in cancer patient survival.

Moreover, the results generated must be able to generate equity in the whole Spanish territory, in cancer patients as in increasing building capacities of the clinicians. Four preproposals have been selected for the second phase and are now in the process of building the consortia.

Visit the call website (in Spanish) to read more about the pre-selected projects and for further information about this call. Deadline for submission of full proposals: January 23rd 2024

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 964264.