



Advancing a Precision Medicine Paradigm in Metastatic Colorectal Cancer:
Systems based patient stratification solutions

Welcome to the Winter 2021/22 Newsletter for the COLOSSUS Project

What is COLOSSUS?

The fundamental objective of COLOSSUS is to provide new, more effective stratification tools and therapeutic interventions, specifically tailored for people with poor prognosis, difficult to treat Microsatellite Stable RAS mutated metastatic colorectal cancer (MSS RAS mt mCRC). There are currently limited therapeutic options once people with this type of colorectal cancer develop resistance to their treatment. Thus, there exists an urgent clinical need for a more personalised treatment paradigm.

The COLOSSUS consortium is delivering impact and progress beyond the state of the art across six key areas:

- Establishing new subtypes for MSS RAS mt CRC patient stratification and treatment.
- Implementing an integrative Systems Modelling framework for the discovery of new methods for MSS RAS mt CRC patient stratification and treatment.
- Establishing clinically feasible computational tools to predict MSS RAS mt patient response.
- Developing new clinically applicable diagnostic test prototypes to stratify MSS RAS mt CRC patients.
- Identifying and testing new combinatorial treatment options for MSS RAS mt CRC patients.
- Developing new algorithms to identify pathway-based biomarkers for stratifying CRC subtypes.

Message from COLOSSUS Coordinator Prof. Annette Byrne, RCSI



Prof. Annette Byrne
COLOSSUS
Coordinator

“Much of our work in the initial phase of the project was focused on securing access to retrospective tissue samples from biobanks and initiating the COLOSSUS translational trial across sites in Spain, Germany and Ireland.

More recently, COLOSSUS partners have been working on the analysis of samples towards the identification of novel COLOSSUS subtypes for MSS RAS mt CRC, which has now been achieved. This is a major milestone for the project, and now allows downstream analyses and workstreams to progress.

We welcome the addition of a new radiomics workstream to the project, which will provide in-depth information about phenotypic tumour changes over time.

Approximately 30% of all human cancers possess activating RAS mutations. Data emerging from COLOSSUS on new biomarkers, stratification models, novel drug combinations and therapeutic strategies in the RAS mt setting may also have significant additional impact within the broader oncology space.”



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Spotlight on The Institute for Cancer Research (ICR)



In the Systems and Precision Cancer Medicine team at the ICR, our research focuses on translational cancer research and patient benefit and leverages national and international clinical trial and tissue resources. Our interdisciplinary work effectively integrates experimental, computational and clinical biology.



*Dr Anguraj
Sadanandam*

Cancers are highly heterogeneous at molecular and phenotypic levels, so it is essential to stratify cancer patients to deliver more personalised cancer diagnosis and therapy. To this end, the Systems and Precision Cancer Medicine team's efforts build on our pioneering molecular stratification in different cancers, including colorectal and pancreatic cancers, among others.

The team systematically studies tumour and immune/stromal heterogeneity by developing innovative artificial intelligence and machine-learning models to concurrently integrate multi-omics with phenome data. Multi-omics data include, but are not limited to, image, transcriptome, genome and methylome. Phenome data include clinical outcomes and in vitro/in vivo data such as proliferation and migration, for example. This careful, systematic approach of data integration generates biomarkers and highly probable hypotheses for personalised cancer therapies.

Once identified, biomarkers can be translated into potential molecular assays and tested in the clinic or in trial/study samples. Hypotheses about suitable treatments can also be validated using mechanism-based pre-clinical models and experiments.

Our approach streamlines solutions to evolving areas in the field of multidisciplinary science including inter/intra-tumoral heterogeneity, companion diagnostic assay development, deconvolution statistical approaches, cell-of-origin/phenotypes-based evolution of tumour, and pre-clinical trials for modelling precision cancer therapy.

COLOSSUS Translational Study Update

Recruitment to the COLOSSUS translational study closed at the end of September 2021. The study is providing the COLOSSUS team with essential samples from MSS RAS mt mCRC patients, which are then analysed in the project. The collection of samples from these patients is a fundamental resource for our work, which we hope will ultimately benefit other patients with this disease.

We acknowledge and thank the patients and the ten clinical sites involved: in Ireland: University Hospital Limerick; Bon Secours Hospital Cork; Tallaght University Hospital, Dublin; Vincent's University Hospital, Dublin and Beaumont Hospital, Dublin, in Germany: University Hospital Mannheim; Onkologische Schwerpunktpraxis Speyer and Onkologische Schwerpunktpraxis Heidelberg, and in Spain, the Barcelona hospitals: Hospital Universitari Vall d'Hebron and the Institut Catala d'Oncologia; L'Hospitalet de Llobregat.



Translational Models of Colorectal Cancer: Università degli Studi di Torino

Recent technological advances have provided powerful insights into the molecular determinants of human tumours. In many cases tumour regression has been the result of blocking a single mutant protein responsible for both the initiation and maintenance of the cancer, called an oncogenic driver mutation. Often oncogenic driver mutations are found in the very genes responsible for the production of the proteins that maintain normal cell growth, division and survival.

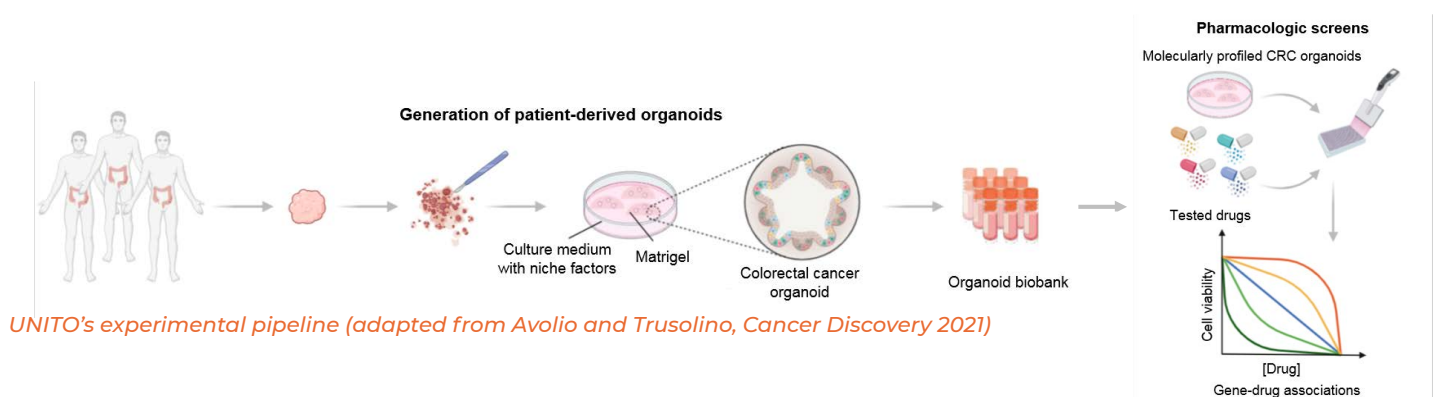
However, many new, important technological advances have not been translated into effective treatments very quickly. This is due to the difficulty in predicting how the complex mutational background and the adaptive resilience of cancer cells influence the activity of the main oncogene and modify the response to therapies. Sophisticated models of the disease and specialist research teams can quicken this process.



The team at UNITO

The Translational Cancer Medicine unit of the Istituto di Candiolo (University of Turin School of Medicine) explores the mechanisms of tumour dependency on oncogenic drivers and how this dependency is affected by genomic or functional modifiers, with an emphasis on colorectal cancer (CRC).

UNITO's experimental pipeline interrogates multi-dimensional data for discovery and hypothesis validation, then follows on with cell-based mechanistic investigations and preclinical validation in patient-derived organoids, or tumouroids. Tumouroids are models of cancer created from fragments of human tumour tissue or suspensions of disassociated tumour cells cultured in a gel-like three-dimensional environment. These models are used to test the efficacy of anti-tumour molecules and therapies in a living organism. Through this approach, the Translational Cancer Medicine unit have made significant contributions to the finding that the hyperactivation of many treatment-responding oncogenic products correlates with resistance to cetuximab and panitumumab (two anti-EGFR cancer treatments). Pharmacologic inhibition of such resistance mechanisms re-sensitises cancer cells to anti-EGFR therapy, thus broadening therapeutic options for people with colorectal cancer.



Livio Trusolino, M.D. Ph.D., Professor at the University of Torino Medical School: “Our studies provide a systematic functional approach to evaluate response to targeted therapies in human cancers, highlight new mechanisms of responsiveness to anti-EGFR therapies, and provide a new vocabulary for the molecular management of colorectal cancer with immediate clinical implications.”

In COLOSSUS the team at UNITO are bringing their expertise to bear testing novel combinatorial treatment strategies for MSS RAS mt mCRC COLOSSUS subtypes.

Dissemination Round-up

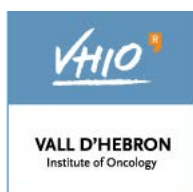
- Dr Jonathan Briody gave a virtual presentation to the Royal College of Surgeons in Ireland Postdoc Society on September 22nd, 2021 as part of National Postdoc Appreciation Week.
- Aoife Nolan, PhD candidate at the University College Dublin presented a poster at the European Association for Cancer Research (EACR) 2021 online meeting that took place June 9th – 12th, 2021. Aoife's poster is titled 'Investigation of KRAS mutant Effect on Cell Signalling and Protein Expression Profiles in Microsatellite Stable Colorectal Cancer.'
- On May 21st, 2021, Cancer Trials Ireland hosted an online 'Cancer Retreat' for the clinical trials community of oncologists (medical, radiation and surgical), haematologists, researchers, research nurses, clinical site managers, teams, and patients. The event provided an opportunity to discuss how the cancer trials community, national and international, works together, how that could be improved, and the challenges and opportunities that may emerge in the next five years.
- Dr Ian Miller, Honorary Lecturer and Imaging Specialist at the RCSI spoke with the students at Harold's Cross National School, in Dublin on 19th April 2021, as part of Science Week 2021. Fifty students in 2nd Class (7-8 years old) enjoyed Ian's short talk entitled "Life, Cells and DNA" which was followed by a demonstration of how to extract DNA from cheek cells.

Publication news

Congratulations to Aoife A. Nolan, N.K. Aboud, Walter Kolch and David Matallanas. Their open-access paper *Hidden Targets in RAF Signalling Pathways to Block Oncogenic RAS Signalling* (*Genes* 2021, 12, 553), <https://doi.org/10.3390/genes12040553> was published on April 10th, 2021.

Partner news: Veracyte acquires HaliuDx

On August 3rd, 2021, Veracyte, Inc. completed its acquisition of COLOSSUS partner HaliuDx to solidify its reach into global markets while expanding its scientific capabilities and diagnostics scope into 8 of the 10 top cancers as defined by U.S. incidence. *"This important acquisition is the culminating piece in a series of strategic initiatives and acquisitions that we believe will enable Veracyte to achieve our vision of improving outcomes for patients worldwide at every step of their journey,"* said Marc Stapley, Veracyte's chief executive officer. *"HaliuDx's European manufacturing infrastructure and operations, along with the company's immunology capabilities and best-in-class diagnostic products, have the potential to fuel our growth in cancer diagnostics. We look forward to welcoming the talented HaliuDx team to the Veracyte family and working together to build a leading global diagnostics company."*



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