COLOSSUS

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

Welcome to the Spring 2023 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 to poor prognosis, difficult-to-treat microsatellite stable (MSS) RAS mutated (mt) metastatic colorectal cancer (mCRC) patients. There are currently limited treatment options once people with this type of colorectal cancer (MSS RAS mt mCRC) develop resistance to their treatment. Thus, an urgent clinical need exists for effective alternatives for this group.

The COLOSSUS Project is delivering impact and progress beyond the state of the art by:

- Implementing an integrative systems modelling framework for the discovery of new methods for MSS RAS mt CRC patient stratification.
- Using network and pathway modelling of multi-omic MSS RAS mt mCRC datasets to identify new therapeutic targets for MSS RAS mt mCRC.
- Establishing clinically feasible computational tools to predict MSS RAS mt mCRC patient response.
- Identifying and testing new combinatorial treatment options for MSS RAS mt mCRC patients.

Message from COLOSSUS Coordinator Prof. Annette Byrne, RCSI

The COLOSSUS Team

The main goal of the COLOSSUS project is to find new potential therapies for patients with a form of colorectal cancer that can be difficult to treat (MSS RAS mt mCRC). The project started in January 2018. Since then, we have collected multiple patient samples from different cohorts, completed the COLOSSUS translational trial, generated and analysed multi-omics data, applied novel computational modelling approaches and identified possible novel targets of vulnerability. We have also achieved several key publications and presented at numerous conferences and events. The project ends on June 30th 2023. As we enter the last phase, we are completing the final stage analysis of samples, and laboratory testing of possible new drug combinations for future application in patients. We are looking forward to analysing our final results in detail, publishing our findings and identifying exploitation pathways for COLOSSUS innovations, so that we can ultimately deliver concrete benefits to patients. It has been a pleasure to lead such a dedicated team of researchers and I want to record my thanks to them all, as the project nears the finish line!

RCSI

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PI in the Spotlight
Professor Diether Lambrechts

Danielle Nicholson at Pintail Limited posed a set of questions to Professor Diether Lambrechts, Head of the Laboratory of Translational Genetics, VIB about his work in cancer research and his career.

What are some of the ways your research changed from 1999 to 2023?

My research group is focused on tackling important questions in oncology by translating genome-scale data sets into clinically applicable knowledge, by applying cutting-edge genome sequencing technologies and applied bioinformatics. In the first years of my research career, I mainly studied single-nucleotide polymorphisms (DNA mutations) and their role in cancer susceptibility. The volume of the datasets that we generated in these years was much, much smaller. Nowadays, we use single-cell multi-omics profiling technologies to study similar research questions. The complexity of the data sets has grown enormously. We now use big servers with lots of computing power, and we perform complex network analyses or use artificial intelligence methods to investigate our datasets. So over time, data analysis methods have become increasingly important. Nowadays, the majority of my lab members are actually dry-lab computational biologists.

In your opinion, what is most exciting about cancer research today? What has enabled this progress? What is necessary to progress this further?

Over the past decade, we have made tremendous progress in understanding cancer mechanisms and cancer therapies, thanks in part to state-of-the-art high-resolution technologies such as single-cell technologies, and doing translational research in a phase 2-3 cancer clinical trial by applying these new technologies to the samples obtained during the trial. I think it is important to include translational research in the study protocol from the beginning when starting a clinical trial. The technologies/methods are becoming increasingly sophisticated and the application of these technologies to large groups of multicentre clinical trial cancer samples will provide many more insights into cancer biology and identify reliable biomarkers to stratify patients for appropriate therapy, preventing serious side effects and saving costs. This can be a success story if we collaborate with different teams, each with their own expertise and access to clinical samples, such as in the COLOSSUS collaboration.

How is COLOSSUS important to the Center for Cancer Biology at the VIB?

Collaborative projects such as COLOSSUS are important for cutting-edge research. An international multidisciplinary collaborative project brings together several world-renowned groups with expertise and samples to apply advanced technologies and complex analyses to samples from clinical cancer trials. COLOSSUS is a follow-up study to an earlier European project (Angiopredict) that provided important insights into colorectal cancer. Angiopredict proved that when groups work together in a complementary effort, they make the most of each group's expertise. And of course, one can also use the relationships and friendships that you build during such projects later on within other research collaborations.

Prof. Diether Lambrechts

Read the full interview at https://www.colossusproject.eu/news/interview-with-professor-diether-lambrechts-vib.

COLOSSUS and the next generation of researchers

COLOSSUS is dedicated to educating and training the next generation of research leaders. Meet PhD candidate Aoife Nolan, based at the University College Dublin. Aoife's thesis is titled "Profiling Mutant KRAS Protein Expression in Colorectal Cancer" and her supervisor is Dr David Gomez Matallanas.

"Like many other families out there, cancer has been a part of mine. Both sides of my family have been affected by cancer, be it grandparents, aunties, and uncles. Therefore, I've always had an interest in trying to understand cancer and how it works. So, when I was presented with the opportunity to do a PhD in colorectal cancer, I grabbed it with both hands.

My project involves the investigation of different KRAS mutant proteins in a colorectal cancer context. Particularly, to establish if there are any differences that are specific to each KRAS mutation. Until very recently KRAS mutations were all thought to be equal. However, based on previous findings in our group and the work carried out during my PhD, we believe KRAS mutants are not equal and should not be treated as such.

Aoife Nolan

The significant findings from my project were that: 1) Different KRAS mutant proteins cause different effects within cells and tumour tissues, which potentially lead to different outcomes among CRC patients. 2) Different KRAS mutants have different interactions with other proteins in the cell. 3) Importantly, we also observed certain KRAS mutants were associated with different outcomes in CRC patients."

Read more about Aoife's work here https://www.colossusproject.eu/news/aoife-nolan-colossus-phd-candidate-at-ucd-provides-an-update

The COLOSSUS consortium

Presentations & Popular Press

- Dr Ian Miller of the RCSI presented COLOSSUS research findings at the recent World Molecular Imaging Congress 2022, September 28th–October 1st, 2022 in Miami Beach, FL, USA. Ian's poster was titled: "*Establishing a novel double contrast-enhanced CT imaging protocol to Monitor Metastatic Colorectal Tumours in Pre-clinical models.*"

- The RCSI's Dr Jonathan Briody contributed an editor-invited piece on COLOSSUS research for the 'oncology focus' issue of Hospital Professional News this September (2022): "*Understanding the Health Economics of Colorectal Cancer: A COLOSSAL undertaking*."

- On May 23rd and July 12th, Dr Jonathan Briody, Health Economist at the RCSI, organized a webinar titled "*Policies to reduce drug expenditure without harming patients*". It featured his COLOSSUS health economics work conducted with Professor Kathleen Bennet (RCSI).

- KRAS Kickers (www.kraskickers.org/) featured a short piece about COLOSSUS in their May 2022 newsletter.

- In April 2022, UCD early-stage researcher Aoife Nolan wrote a blog titled "Bowel Cancer: Go with your gut!" for Systems Biology Ireland describing her research within COLOSSUS.

- At the Irish Association for Cancer Research meeting, March 30th – April 1st in Cork, Ireland, University College Dublin PhD candidate Aoife Nolan presented a poster and gave an oral presentation titled "*Investigation of KRAS mutant Effect on Cell Signalling and Protein Expression Profiles in Microsatellite Stable Colorectal Cancer.*"

- An interview with COLOSSUS Coordinator Prof. Annette Byrne, RCSI entitled: "*International collaboration: A precision medicine approach to treating metastatic colorectal cancer*" was published online on February 10th 2022 as an RCSI Impact Case Study.

Recent Publication news

- Myer PA, Kim H, Blümel AM, Finnegan E, Kel A, Thompson TV, Greally JM, Prehn JH, O'Connor DP, Friedman RA, Floratos A, Das S. *Master Transcription Regulators and Transcription Factors Regulate Immune-Associated Differences Between Patients of African and European Ancestry with Colorectal Cancer. Gastro Hep Adv.* 2022;1(3):328-341. doi: https://doi.org/10.1016/j.gastha.2022.01.004.

- Tedesco M, Giannese F, Lazarević D, Giansanti V, Rosano D, Monzani S, Catalano I, Grassi E, Zanella ER, Botrugno OA, Morelli L, Panina Bordignon P, Caravagna G, Bertotti A, Martino G, Aldrighetti L, Pasqualato S, Trusolino L, Cittaro D, Tonon G. *Chromatin Velocity Reveals Epigenetic Dynamics by Single-Cell Profiling of Heterochromatin and Euchromatin. Nat Biotechnol.* 2022; 40:235-244. doi: https://doi.org/10.1038/s41587-021-01031-1

- Patricia Jaaks, Elizabeth A. Coker, Daniel J. Vis, Olivia Edwards, Emma F. Carpenter, Simonetta M. Leto, Lisa Dwane, Francesco Sassi, Howard Lightfoot, Syd Barthorpe, Dieudonne van der Meer, Wanjuan Yang, Alexandra Beck, Tatiana Mironenko, Caitlin Hall, James Hall, Iman Mali, Laura Richardson, Charlotte Tolley, James Morris, Frances Thomas, Ermira Lleshi, Nanne Aben, Cyril H. Benes, Andrea Bertotti, Livio Trusolino, Lodewyk Wessels and Mathew J. Garnett, *Effective drug combinations in breast, colon and pancreatic cancer cells, Nature* 603, 166–173 (2022). doi: https://doi.org/10.1038/s41586-022-04437-2

For more information visit the project website:
www.colossusproject.eu

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