The COLOSSUS Project

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

Professor Annette Byrne, Professor of Physiology and Head of the RCSI Precision Cancer Medicine (PCM) Group

Colorectal cancer (CRC) is any cancer of the large bowel including colon and rectal cancer. Cancers that have spread to other parts of the body (metastatic cancers) are most challenging to treat. CRC is the third most common cancer in Europe with 530,611 new cases and 260,000 related deaths in 2018. It is thought that approximately 50 to 55% of metastatic CRC cases harbour disruptions to specific parts of the cells called the RAS genes. RAS genes control cell growth and division, so mutations or disruptions of these genes leads to uncontrolled cell growth (the cell becomes cancerous). This is because these cells no longer respond to the body's own natural defence response to kill and eliminate damaged cells.

When RAS mutant metastatic CRC cells possess a repair mechanism to help correct gene mutations, they are classified as microsatellite stable or MSS. Current treatment for MSS RAS mutated metastatic CRC (MSS RAS mt mCRC) is primarily based on 5- fluorouracil based chemotherapy +/- bevacizumab. However, when patients develop resistance to this treatment there are limited treatment options. New and more effective stratification tools and therapeutic interventions are therefore urgently needed.

COLOSSUS is an EU-funded Horizon 2020 project that brings together a multidisciplinary team of 13 partners from 7 countries to break new ground in the treatment of MSS RAS mt mCRC. The project is coordinated by Prof Annette Byrne at the RCSI University of Medicine and Health Sciences. Other partners are:

- Ireland: University College Dublin, Cancer Trials Ireland and Pintail Limited;

- Spain: Vall d'Hebron Institute of Oncology;

- France: INSERM and HalioDx;

- The U.K.: The Institute of Cancer Research;

- Belgium: VIB;

- Germany: Epigenomics, Heidelberg University and GeneXplain, and

- Italy: University of Torino.

COLOSSUS - Main Aims

In COLOSSUS, researchers are collecting and studying tissue samples and blood from people with MSS RAS mt mCRC. Based on these analyses, researchers will assign patients to smaller subgroups and will develop more tailored treatments for them. The research programme is designed to help predict patient outcomes under standard treatment and to enable the design of more targeted, personalised regimens (an approach called precision medicine). The aim here is to develop better, more effective treatments for people with this condition so that the right patients can be given the right treatments at the right time.

The Research Programme Explained

The consortium is analysing colorectal tissue and blood samples from MSS RAS mt mCRC patients in existing biobanks. In addition, COLOSSUS is conducting a translational trial in Spain, Germany and Ireland. With consent, samples of blood and tumour tissue are collected from people with MSS RAS mt mCRC. The consortium applies a unique approach to study the samples collected. This involves transcriptomic, genomic, metabolomic, epigenomic and proteomic analyses and the application of an immune-based diagnostic test (Immunoscore®). Using advanced mathematical and computer modelling, the resulting datasets will be used to establish new MSS RAS mt mCRC subtypes with unique signalling dependences. The team will also identify new actionable pathways, biomarkers and targets across subtypes to help predict patient outcomes.

The subtypes identified in COLOSSUS will be interrogated in state of the art pre-clinical, patient-derived xenograft studies where we aim to identify new combinatorial treatment options. The newly described subtypes will
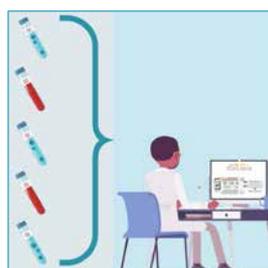
Harnessing the power of systems biomedicine, network analysis and computational modelling to identify new actionable pathways
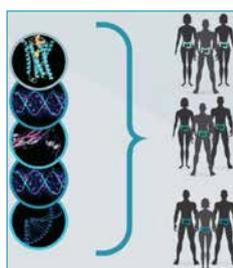
RESOURCES: BIOREPOSITORY & TRIAL SAMPLES

DATA PRODUCTION: MULTI-OMICS PROFILING

DISCOVERY: SUB-TYPING & ACTIONABLE PATHWAYS

VALIDATION: CLINICAL PORTABILITY & THERAPIES

COLOSSUS Clinical Trial in Ireland, Spain, Germany

Precision Medicine

RAS-mutated microsatellite stable (MSS) mCRC

Prof Annette Byrne, COLOSSUS Coordinator at the Royal College of Surgeons in Ireland remarks "The COLOSSUS strategy is based on our ability to integrate systems biomedicine, network analyses and computational modelling approaches to identify new actionable pathways, biomarkers and targets across RAS mutant colorectal cancer. We aim to identify new treatments and develop diagnostic assays for this intractable disease. Metastatic colorectal cancer is a highly prevalent, and complex pathology with a significant patient health and economic impact both within a European and global context." Prof Byrne continued: "A centralized data repository and data exchange platform has been established for genomic, proteomic, metabolomics and clinical data; all samples for the retrospective cohort have been identified and the translational study has enrolled its first patients in Germany, Ireland and Spain and is progressing."

also be validated as novel patient stratification tools within the COLOSSUS translational study. Industry partners will develop clinically relevant and commercially viable assays for stratification of MSS RAS mutated patients based on the COLOSSUS subtypes. The potential impact of these assays on CRC associated healthcare costs will further be assessed.

The COLOSSUS project began in January 2018 and will run until December 2022. We hope our work will ultimately enable the design of more targeted and personalized treatment programmes for people with MSS RAS mt mCRC. We aim to benefit CRC patients and their families, clinicians and health care systems and to deliver wider economic benefits in the longer term.

The COLOSSUS Translational Trial

The Chief Investigator for the COLOSSUS trial in Ireland is Professor Ray McDermott. The Irish hospital sites due to participate in the trial include:

- Tallaght University Hospital;
- St Vincent's University Hospital;
- University Hospital Limerick;
- Bon Secours Hospital, Cork; and
- Beaumont Hospital Dublin.

To learn more about COLOSSUS (including recruitment to the COLOSSUS translational trial), visit our website (www.colossusproject.eu), watch our explainer video and join our conversation on Twitter @COLOSSUSEU and Facebook (COLOSSUSEU).