



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

# Welcome to the Winter 2020/21 Newsletter for the COLOSSUS Project

## ***The COLOSSUS Project***

Approximately 50-55% of all colorectal cancer cases involve mutations (mt) in the RAS genes. A large cohort of these cases are classified as microsatellite stable or MSS. Current treatment for metastatic MSS RAS mt colorectal cancer includes chemotherapy +/- the medicine bevacizumab. Unfortunately, there are limited treatment options for people with this type of cancer once they develop resistance to standard treatment. Thus, treating people with MSS RAS mt cancer effectively can be challenging.

COLOSSUS is a Horizon 2020 funded project that aims to provide new, more effective ways to classify people with MSS RAS mt metastatic colorectal cancer and to develop better treatments for them. The COLOSSUS consortium is studying blood and tissue samples and applying advanced multi-omic computational modelling approaches to identify new MSS RAS mt subtypes. Our approach is designed to help us predict patient outcomes under standard treatment and to enable the design of more targeted, personalised regimens.

### ***Message from COLOSSUS Coordinator Prof. Annette Byrne, RCSI***



*“Much of our work in the first half of COLOSSUS focused on the preparations for, and launch of, the COLOSSUS multi-centre translational study in Ireland, Germany and Spain, securing access to samples from biobanks and performing -omics analyses on the samples obtained. More recently (November 2020), the consortium has identified novel disease subtypes. This major achievement for the project paves the way for further analysis and new workstreams to progress.*

*The COLOSSUS consortium has worked closely together to overcome a number of challenges (including the introduction of GDPR and the advent of COVID-19). Additional samples have been obtained, alternative translational trial sites have opened, and amendments to the trial protocol have been made to help increase recruitment. We have worked diligently and as a close-knit team. We recently published our fifteenth paper and in February 2020 organised our second public-patient event involving MoTriColor (a related colorectal cancer Horizon 2020 funded project) and several patient advocacy organisations.*

*In the months ahead, we look forward to building on our findings in relation to the identification of novel MSS RAS mutant subtypes.”*



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## Computational Modelling in Systems Biology

*Dr Dirk Fey of UCD explains some of the techniques being used in COLOSSUS*



In biology, things seldom work in isolation. Individual molecular structures, like genes and proteins work together to function. In turn, cells work as part of a wider tissue, organ or system in the body. Likewise, organisms interact with each other in ecosystems and societies. Systems Biology Ireland (SBI, <https://www.ucd.ie/sbi/>) uses mathematical and computer modelling to help make sense of this complexity. Founded in 2009, SBI is situated on the University College Dublin campus.



In collaboration with COLOSSUS partners, our 'dry-lab' research uses a series of observations or measurements from biological samples and builds the data into a computer model to predict how the biological molecules interact. We use machine learning or artificial intelligence (AI) to show how molecular interactions might change in a MSS RAS mt colorectal cancer setting, and integrate data from the cells into larger systems such as tissues, organs or the body as a whole. This effective, iterative scientific process helps inform which laboratory experiments should be performed next.

In cancer, tumour cells in the body 'go rogue'. Cancer cells stop responding to the body's communication signals in the way that healthy cells do. This is a result of a 'rewiring' of the cells internal signaling networks and an alteration in how cells communicate and grow within their network. At SBI, we seek to better understand these changes in order to identify more effective combinations of existing anti-cancer drugs that are more efficacious and with less toxic side effects for patients. We also help design new anti-cancer drugs by identifying nodes in cancer signaling to predict what could happen if they become disrupted.

In addition to myself working on the COLOSSUS project at SBI, there are PI Prof. Walter Kolch, Dr David Gomez-Matallanas, and PhD candidates Aoife Nolan and Annabelle Nwaokorie. Prof. Kolch oversees the overall project, and we work very closely with Dr Gomez and Aoife Nolan who drive SBI's experimental work on the project, providing invaluable data for building the models. Annabelle Nwaokorie and I then take these data to build computational models of key colorectal cancer signalling networks. Annabelle's approach is to combine data-driven (machine learning) modelling approaches with knowledge-driven mathematical modelling, and in this way build better, more detailed models. We hope that one day these models can be used to predict the therapy responses of patients and guide their treatments.

## The COLOSSUS Translational Trial

Our multi-centre trial for people with advanced microsatellite stable RAS-mutated metastatic colorectal cancer (MSS RAS mt mCRC) receiving chemotherapy +/- bevacizumab is ongoing in Spain, Germany and Ireland. We have recently updated the COLOSSUS study protocol and have broadened our eligibility criteria to help increase recruitment.

Study sites are located at: **Ireland:** Tallaght University Hospital, Dublin; St Vincent's University Hospital, Dublin; Bon Secours Hospital, Cork; Beaumont Hospital, Dublin and University Hospital Limerick.

**Spain:** Hospital Universitari Vall d'Hebron, Barcelona

and Institut Catala d'Oncologia at L'Hospitalet de Llobregat, Barcelona. **Germany:** University Hospital Heidelberg, Mannheim; Onkologische Schwerpunktpraxis, Speyer and Onkologische Schwerpunktpraxis, Heidelberg.

Further information about the study and the sites can be found at [cancertrials.ie](https://www.cancertrials.ie), [clinicaltrials.gov](https://clinicaltrials.gov) and [https://www.colossusproject.eu/the\\_project/colossus-translational-study/](https://www.colossusproject.eu/the_project/colossus-translational-study/).



*VHIO COLOSSUS study team*

## News and Dissemination Round-up

### COLOSSUS plenary meeting, October 20, 2020

Working to the 'new normal', COLOSSUS researchers from all corners of Europe came together using Zoom for the annual plenary meeting on October 20, 2020. All work package leaders presented to showcase the work undertaken over the last 12-months and lay out their future plans. The team has made good progress towards achieving its key milestones - in particular, novel COLOSSUS subtypes were discussed in detail at the meeting and finalized shortly afterwards.

### Communicating COLOSSUS to the public

With MoTriColor (Horizon 2020, grant no. 635342) Drs Rodrigo Dienstmann, (PI of the Oncology Data Science Group at the Vall d'Hebron Institute of Oncology (VHIO) and Joint Scientific Lead of COLOSSUS) and Ramón Salazar, (Head of the Medical Oncology Department at the Hospital Duran i Reynals) hosted an interactive public meeting for people with colorectal cancer, their carers, and relatives on February 27, 2020 at the VHIO in Barcelona. In the round table discussion, associations Europa Colon España, Spanish Association Against Cancer (AECC), El Grupo Español de Pacientes con Cáncer (GEPAC) and Dones en Actiu participated and an individual who had participated in a clinical trial spoke.

### Training

*Pay It Forward Machine Learning Training Association* is the brainchild of COLOSSUS PI Dr Anguraj Sadanandam, Institute of Cancer Research (ICR) to further develop tomorrow's leaders in top-notch cancer research and data science. The training may be of interest to students who want to work on real-time projects in bioinformatics. Interested students can make contact via the Pay It Forward LinkedIn group: link [here](#).

### Conference highlight

PhD candidate Aoife Nolan presented COLOSSUS research in a poster entitled: "*The KRAS proteins KRAS WT, KRAS G13D and KRAS G12V bind to specific interactors and have different affinities for proteins in their common interactome in Colorectal Cancer cells*" at the February 26-28, 2020 Irish Association of Cancer Research (IACR) meeting.

### COLOSSUS in Hospital Professional News

The COLOSSUS Project featured in the December 2020 issue of the Irish journal *Hospital Professional News* digital edition. The issue was dedicated to cancer clinical trials ongoing in Ireland.

### Recent academic publications

COLOSSUS researchers have published 15 articles in peer review journals to date and more publications are in progress. Recent publications include:

*Conservation of copy number profiles during engraftment and passaging of patient-derived cancer xenografts* with Woo, X.Y., Giordano, J., Srivastava, A. et al., *Nat Genet* 53, 86–99 (2021). <https://doi.org/10.1038/s41588-020-00750-6>.

*Implementing Systems Modelling and Molecular Imaging to Predict the Efficacy of BCL-2 Inhibition in Colorectal Cancer Patient-Derived Xenograft Models*, Alice C. O'Farrell and Monika A. Jarzabek et al, *Cancers* 2020, 12(10), 2978; <https://doi.org/10.3390/cancers12102978>.

*Colorectal cancer residual disease at maximal response to EGFR blockade displays a druggable Paneth cell-like phenotype* Barbara Lupo et al, *Science Translational Medicine* 05 Aug 2020: Vol. 12, Issue 555, eaax8313 <https://stm.sciencemag.org/content/12/555/eaax8313.editor-summary>.

*The murine Microenvironment Cell Population counter method to estimate abundance of tissue-infiltrating immune and stromal cell populations in murine samples using gene expression*, Florent Petitprez, Sacha Levy, et al, *Genome Med* 12, 86 (2020). <https://doi.org/10.1186/s13073-020-00783-w>.

*EGFR Blockade Reverts Resistance to KRASG12C Inhibition in Colorectal Cancer*, V Amodio, et al, *Cancer Discov* 10:1129-1139, 2020. <https://doi.org/10.1158/2159-8290.CD-20-0187>.

You can view details of all our COLOSSUS publications on our website: <https://www.colossusproject.eu/project-publications/>

## COLOSSUS Partner in the Spotlight: Pintail Limited



Pintail Ltd is an Irish SME specialising in the creation and delivery of multi-national, multi-partner research projects. Working with leading scientific coordinators and teams from across Europe, Pintail helps to turn great science into excellent funded projects, securing highly-competitive support from Horizon 2020, ERC, Marie Curie and other EU programmes, as well as national bodies such as the UK's MRC, USA's NIH and Ireland's



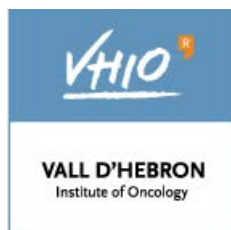
SFI. After securing the funding, Pintail then supports the coordinators of their projects throughout the project life-time, dealing with administration, reporting and liaison with the funding body, as well as Communications and Future Planning. Pintail has worked closely with COLOSSUS coordinators RCSI on several projects, including AngioPredict, ApoDecide and IMI's PD-MitoQUANT.

Pintail was founded in 2001 by its current Director, Ciaran Clissmann. It currently supports coordinators from universities, research institutions and companies from Ireland, Germany, Denmark, Italy, and the UK, in fields including cancer research, regenerative medicine, photonics, obesity, behavioural science, auto-immune diseases, medical imaging and more. Pintail Limited's Nora Ward and Danielle Nicholson support COLOSSUS and its partners with a range of management, communication and dissemination tasks.

To learn more about Pintail, visit their website <https://pintail.eu/> or follow them on Twitter <https://twitter.com/PintailLimited> or Facebook <https://www.facebook.com/pintail.eu>.

## The COLOSSUS partners

COLOSSUS involves 13 partners from 7 different countries and brings together a multidisciplinary team with expertise including: cancer immunology, systems biology, computational modelling, bioinformatics, omics analysis, clinical oncology/pathology, preclinical research/imaging, clinical trials, health economics and patient engagement.



For more information visit the project website:

[www.colossusproject.eu](http://www.colossusproject.eu)

Connect with COLOSSUS on  Twitter,  Facebook,  ResearchGate

