Name	FRANCESCA CICCARELLI
Position	Seconded Group Leader (King's)
Year joined *(Crick or founder institute)*	2017

Career History

2003 – 2005: Postdoctoral Fellow, Peer Bork Group, EMBL-Heidelberg
2005 – 2013: Principal Investigator, European Institute of Oncology Milan
2014 – 2018: Reader in Bioinformatics and Genomics, King's College London
2017: Group Leader, Francis Crick Institute
2018: Professor of Cancer Genomics, King's College London

Major Awards, Honours and Prizes

Promoted to Professor at King's College London in 2018
Co-theme lead of the Cancer Research UK KHP Centre (since 2017)
Co-theme lead of the Cancer Research UK City of London Centre (since 2017)

Membership of external committees, editorial boards, review panels, SABs etc

GENOMIC PROJECTS AND CONSORTIA

Since 2017: member of the Steering Committee of OCCAMS
Since 2017: affiliated member of oesophageal cancer ICGC
Since 2015: Executive Committee of the Pan cancer GeCIP (Genomics England)

ADVISORY BOARDS AND COMMITTEES

2020: Chair of the Review Panel of the GSTT BRC Genomics Platform
Expert Committee Translational Research Grant Call Oncopole of Toulouse
Faculty recruitment panel, Luxembourg Centre for Systems Biomedicine (LCSB)
Cancer Research UK Expert Review Panel - Children and Young People's Cancer Innovation Award
2019: Ad hoc member of the Cancer Research UK Pioneer Award Committee
Faculty recruitment panel, Institute of Cancer Research (ICR) London
Review panel for the national genomics infrastructure, Swedish Research Council
2018: Review panel of the Research Training Group, German Research Foundation (DFG)
Tenure-track review panel for the Institute of Cancer Research (ICR) London
2017: Science Advisory Board of the Oncopole of Toulouse (France)
Advisory board of the Next Generation Sequencing Congress (Oxford Global)

Lab Name	*Cancer Systems Biology Laboratory*

Research programme and achievements

PAST AND PRESENT

We apply computational and wet-lab approaches to study gastrointestinal cancer genetics, focusing on translational applications.

Representative research lines of my lab include:

(1) identifying cancer driver genes in oesophageal cancer to enhance early detection. We have developed a new approach to identify cancer driver genes based on machine learning to overcome the widespread intra- and inter-patient cancer heterogeneity of oesophageal cancer. This approach builds on our distinctive expertise to characterise the systems-level properties of cancer genes and use them to predict new cancer driver events in individual patients.

(2) targeting cancer vulnerabilities to develop novel intervention. We have optimised a computational and experimental method that led to the successful identification of dependencies involving known tumour suppressors such as SMARCA4, CDH1, DNMT3A, and STAG2. We aim to refine this method to prioritise vulnerabilities with high potential of being therapeutically relevant and test them in patient-derived organoids (PDOs, which we have established in our lab).

(3) profiling immune and genetic heterogeneity in cancer onset and response to therapy. We recently discovered that patients with multiple primary bowel cancers inherit damaging mutations in a variety of immune genes, including cytokines and Toll-like receptors. These patients also present with aberrant immune profiles and high levels of tumour immune infiltrates. The hypothesis is that the altered immune genes modify gut immunity by inducing perturbations in the homeostatic immune network. We therefore set up a high-dimensional, multi-regional and multi-omic platform based on genomic, transcriptomic and single cell immune-phenotyping (solid CyTOF) screening. We are currently applying this platform to unravel the interactions between aberrant immunological functions and cancer presentation and map the dynamic interplay in space and time between immune and genetic intra-tumour heterogeneity in response to immunotherapy.

FUTURE PLANS

I see our future work increasingly intertwined with translational cancer research to exploit the full potential of patient profiling and data integration in directing clinical intervention. In the next years, we will focus mostly on two areas:

(1) apply personalised cancer driver predictions in the clinical setting. We have started to explore the utility of our machine learning approach in the clinic by evaluating our predictions of driver events during the cancer genomic medicine multi-disciplinary team meetings in the oncology department of King’s College Hospital. In parallel, together with the CRUK Commercial Partnerships team responsible for the commercialisation of AI and Big Data assets, we are exploring the possibility of patenting and commercialising our software.

(2) optimise our platform for high-dimensional tumour profiling for patient stratification. We are mapping the dynamic interplay between immune and genetic intra-tumour heterogeneity in tumours from patients showing complete response, primary and acquired resistance to immunotherapy in the context clinical trials. From one side, this will allow us to unravel the roles of innate and adaptive immunity in response to immunotherapy. From the other side, this approach will help patient stratification and inclusion in clinical trials based on biomarkers of response.

Research outputs

Nulsen J, Misetic H, Yau C, Ciccarelli FD. (2021) *Pan-cancer detection of driver genes at the single-patient resolution*. Genome Medicine 13(1):12. DOI: 10.1186/s13073-021-00830-0
Paper describing our machine learning approach that integrates somatic alteration data with systems-level gene properties to predict drivers in individual patients. We demonstrate robust performance and benchmark its performance against other driver detection methods showing a lower false positive rate and superior patient driver coverage.

Bortolomeazzi M, Keddar R, Montorsi L, Benedetti L, Temelkovski D, Choi S, Petrov N, Todd K, Ward S, Wilson G, Al Bakir M, Swanton C, John S, Miles J, Banafshe B, Parker PJ, Rodriguez-Justo M, Shiu KK, Spencer J, Ciccarelli FD. (2021) *Immunogenomics of colorectal cancer response to immune checkpoint blockade.* bioRxiv. DOI: 10.1101/2020.12.15.422831
Multi-omic and high dimensional profile of 543 tumour regions and associated tumourmicroenvironment colorectal cancers (CRCs) subsequently treated with Pembrolizumab or Nivolumab. We were able to show that anti-PD1 inhibitors are most effective in highly infiltrated CRCs where they may release the interactions between macrophages and CD8 T cells thus promoting their priming and expansion in intra-tumour niches.

Mourikis, T, Benedetti L, Foxall E, Perner J, Cereda M, Lagergren J, Howell, M, Yau, C, Fitzgerald R, Scaffid P, Ciccarelli FD. (2019) *Patient-specific cancer genes contribute to recurrently perturbed pathways and establish therapeutic vulnerabilities in esophageal adenocarcinoma*. Nature Comms 10:3101. DOI: 10.1038/s41467-019-10898-3
Application of our machine learning method to complete the annotation of driver events in 261 oesophageal cancer patients. We also experimentally validate the potential of predicted drivers to enhance oesophageal cancer cell proliferation capabilities.

Repana D, Nulsen J, Dressler L, Bortolomeazzi M, Kuppili Venkata S, Tourna A, Yakovleva A, Palmieri T and Ciccarelli FD. (2019) *The Network of Cancer Genes (NCG): a comprehensive catalogue of known and candidate cancer genes from cancer sequencing screens*. Genome Biology 20:1. DOI: 10.1186/s13059-018-1612-0
https://genomebiology.biomedcentral.com/articles/10.1186/s13059-018-1612-0
Latest release of our manually curated repository of 2372 genes whose somatic modifications have known or predicted cancer driver roles. These genes were collected from 275 publications, including two sources of known cancer genes and 273 cancer sequencing screens of more than 100 cancer types from 34,905 cancer donors and multiple primary sites. This represents a more than 1.5-fold content increase compared to the previous version. The resource is widely used as a source of cancer genes.

Cereda M, Gambardella G, Benedetti L, Iannelli F, Guerra R, Mourikis TP, Puccio I, Patel D, Basso G, Sinha S, Laghi L, Spencer J, Rodriguez-Justo M, Ciccarelli FD. (2016) *Patients with genetically heterogeneous synchronous colorectal cancer carry rare damaging germline mutations in immune-related genes.* Nature Communications 7:12072. DOI: 10.1038/ncomms12072
We show that multiple colorectal cancers affecting the same patient have independent genetic origins, acquire dissimilar somatic alterations, and have different clone composition. These patients show a higher occurrence of inherited damaging mutations in immune-related genes and have a different composition of immune cell populations in tumour and

normal mucosa. This suggests an environmental field effect that promotes multiple tumours likely in the background of inflammation.