PI profile

## [David] [Church]

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|  | **Dr. David Church****Titles**: Associate Professor, Cancer Research UK Advanced Clinician Scientist and Group Leader **Location**: Wellcome Centre for Human Genetics**Department**: Nuffield Department of Medicine **Group**: Tumour Genomics and Immunology Group**Webpage**: https://www.well.ox.ac.uk/research/research-groups/church-group**Email**: david.church@well.ac.uk |

### GMS themes:

* Functional genomics
* Genomics of disease
* Genomic analysis (bioinformatics and statistical genetics)
* From genes to clinic (target discovery, structural biology, medicinal chemistry)
* Application of genomics in the clinic (diagnostics and therapeutics)

### Research Overview

We study colorectal and endometrial cancer to understand their biology and to improve patient care. Our main focus is the interaction between genomic instability and the antitumour immune response in these tumours, but we have several projects outside this area.

Project areas:

Colorectal cancer; endometrial cancer; cancer genomics; digital pathology, biomarker, immune escape .

### Specific project proposals:

* Novel immune escape mutations in mismatch repair deficient cancer
* Characterisation of driver mutations in endometrial cancer

etc.

Please contact directly for further information.

*These pages were reviewed/updated:* ***[insert date]***

Project proposal

# **Title**: Novel immune escape mutations in mismatch repair deficient cancer

Supervisors: David Church, Tim Elliott, Nicola Ternette

Wet/dry lab mix (approx): 75% wet lab, 25% dry lab

### Description:

DNA mismatch repair deficiency (MMRd) occurs in many cancer types where it causes hypermutation and instability at DNA microsatellites (MSI). MMRd/MSI tumours have been shown to be especially immunogenic, owing to the enrichment of mutated peptides they present as a conseequence of their mutation burden. Accordingly, these tumours frequently demonstrate loss of function alterations in components of the antigen presentation pathway machinery, the consequence of which is to enable escape from immune surveillance. However, current understanding of these is limited. Our unpublished analysis of >10,000 cancer whole genome sequences (WGS) from the Genomics England 100,000 Genomes Project (GEL 100KGP) has identified two novel genes which commonly subject to loss of function mutations in MMRd/MSI cancer. Both function in class I antigen processing and presentation and thus represent candidate immune escape mutations. This project seeks to perform detailed characterisation of both. Briefly, it will entail:

* Definition of genomic, transcriptomic and immunologic correlates of novel immune escape mutations in GEL 100KGP cases and additional clinical trial cohorts
* Functional analysis of novel immune escape mutations in model systems including cutting edge methods of immunopeptidomics and protein trafficking

Supervision will be available for all aspects of the project by postdoctoral scientists. There will be opportunity to travel to collaborators institutes for a period if desired.

### Training Opportunities:

Analysis of whole genome sequence data; analysis of AI based image analysis; general molecular biology techniques; exposure to specialist methods including protein trafficking and immunopeptidomics.

**Project proposal**

# **Title**: Characterisation of driver mutations in endometrial cancer

Supervisors: David Church

Wet/dry lab mix (approx): 75% wet lab, 25% dry lab

### Description:

Endometrial cancer is the most common gynaecological malignancy in the developed world, yet has been understudied until the publication of the TCGA molecular analysis in 2013. More recently, our unpublished analysis of the unique cohort of endometrial cancers with whole genome sequencing (WGS) from the Genomics England 100,000 Genomes Project has revealed identified more than 50 driver genes, which vary across molecular subgroups and in combinations. While the function of some is well characterised, for many current understanding is minimal or lacking. This project will address this by genomic and functional analyses. Specifically it will:

* Perform detailed analysis of driver mutations in the GEL 100KGP endometrial cancers under the umbrella of the GeCIP
* Develop functional models of novel alterations to test their effect on cellular phenotype and therapeutic sensitivity
* Examine the basis of mutation cooperativity and antagonism using in selected cases using these systems

Supervision will be available for all aspects of the project by postdoctoral scientists. There will be opportunity to travel to collaborators institutes for a period if desired.

### Training Opportunities:

Analysis of whole genome sequence data; ; general molecular biology techniques; experience in the development of and analysis of functional model systems.