PI profile

## Julian Knight

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|  | **Professor Julian Knight**  **Titles**: Professor of Genomic Medicine, Deputy Director of WHG, Director of GMS DPhil programme, Honorary Consultant Physician, Fellow of Merton College  **Location**: Wellcome Centre for Human Genetics  **Department**: Nuffield Department of Medicine  **Group**: Knight group  **Webpage**: https://www.well.ox.ac.uk/people/julian-knight  **Email**: julian@well.ox.ac.uk  **PA**: Sarah Butler <sbutler@well.ox.ac.uk> |

### GMS themes:

* Genomic and –omic technologies
* Functional genomics
* Genome biology (genomes and genetic variation)
* 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

My current research uses a genetics and -omics led approach to understand why some individuals develop an inappropriate or dysregulated immune response to infection, how this may contribute to disease, and opportunities to advance precision medicine approaches. Complementing this, we aim to characterise the nature and functional significance of disease associated genetic variants in disease relevant contexts and innovate ways to use such knowledge to validate drug targets.

Understanding the nature and basis of individual variation in the response to infection

(a) Genetic and epigenetic modulators of the induced innate immune response

(b) Functional genomics of sepsis response and development of a precision medicine approach

(c) Understanding heterogeneity in COVID-19 infection using a multi-omic approach

Genetics-led drug target identification and prioritisation

We are developing computational approaches to enhance the utility of human genetics for understanding disease pathogenesis and novel therapeutic targets. This involves use of functional genomic profiling and integrative analysis to understand genes and pathways responsible for GWAS together with knowledge of network connectivity (for example using Priority Index http://pi.well.ox.ac.uk). We are also applying an integrated -omic approach to determine the regulatory epigenomic landscape of ankylosing spondylitis and the impact of disease-associated genetic variation in a disease context together with ongoing work focusing on drug targets involving IL12/23 pathways.

Project areas: human disease genetics, functional genomics, epigenetics, infection, immunity, drug targets, multi-omics

### Specific project proposals:

* Validating a genetics-led approach to drug target prioritisation in immune traits
* Resolving heterogeneity in the response to infection using -omics

Please contact me directly for further information.

*These pages were reviewed/updated:* ***28th September 2021***

Project proposal

# **Title**: Validating a genetics-led approach to drug target prioritisation in immune traits

Supervisors: Prof Julian Knight

Wet/dry lab mix (approx): 50% wet lab, 50% dry lab

### Description:

The high attrition rate in late-stage drug development requires new approaches to establish evidence for target validation, the therapeutic hypothesis that perturbing a target will benefit patients with minimal toxicity. Human genetic evidence predicts successful progress along the drug development pipeline but systematic use in drug target validation has not yet been achieved.

This project would be an opportunity to join an established research effort within the Knight group to develop approaches to maximise the informativeness of genetics for drug target identification and validation as well as related questions such as prediction of adverse effects, predicting mechanisms of therapeutic modulation and identifying repurposing opportunities.

The relative balance of computational and wet lab work in the project will depend on the individual student’s interests. We aim to build and validate computational tools and pipelines, and to generate experimental evidence to support this. You would apply cutting-edge functional genomic approaches and gain significant expertise in bioinformatics. The project would provide relevant training for a laboratory rotation or form the basis for a 3-year doctoral research project.

### Training Opportunities:

You would have the opportunity to gain valuable bioinformatic skills in the analysis of genetic and -omic datasets and more broadly within the drug target prioritisation approaches we are establishing that integrates and leverages information involving common and rare disease alleles, functional genomic and epigenomic annotations, population genetic diversity, systems immunology, connectivity, interactions, model organism phenotypes and ontologies. Examples of experimental approaches that you would use include high throughput CRISPR screens and siRNA knock down together with use of highly selective chemical probes (small molecule inhibitors generated by Structural Genomics Consortium) to determine the consequences of modulating specific targets. You would apply these to patho-physiologically relevant phenotypic readouts for the trait of interest, including using iPSC, primary human cells and where possible patient-derived cellular assays. You would also leverage publically accessible data, for example from compound screens within the Library of Integrated Network-based Cellular Signatures together with existing genome-wide mutagenesis and CRISPR screens. This work is made tractable by our established collaborations with academia and industry. You will benefit from working within a supportive research group with a strong track record in graduate student training and mentoring. You will have the opportunity to regularly present your work within the group, to your peers within the Centre as well as at international conferences. Students are encouraged and supported to undertake further relevant training courses in Oxford and elsewhere depending on need.

### Background reading / references:

* Fang H, Consortium U-D, De Wolf H, Knezevic B, Burnham KL, Osgood J, Sanniti A, Lledo Lara A, Kasela S, De Cesco S, Wegner JK, Handunnetthi L, McCann FE, Chen L, Sekine T, Brennan PE, Marsden BD, Damerell D, O'Callaghan CA, Bountra C, Bowness P, Sundstrom Y, Milani L, Berg L, Gohlmann HW, Peeters PJ, Fairfax BP, Sundstrom M & Knight JC. A genetics-led approach defines the drug target landscape of 30 immune-related traits. *Nat Genet* 2019; 51:1082-1091.
* Fang H, Chen L & Knight JC. 2019 From genome-wide association studies to rational drug target prioritisation in inflammatory arthritis. The Lancet Rheumatology 2, 50-62

Project proposal

# **Title**: Resolving heterogeneity in the response to infection using -omics

Supervisors: Prof Julian Knight, Dr Alex Mentzer

Wet/dry lab mix (approx): 50% wet lab, 50% dry lab

### Description:

The dysregulated host response to infection results in organ dysfunction and death, accounting for substantial morbidity and mortality in intensive care but the basis for why this develops in only specific individuals with an infection remains unclear. We are taking novel integrative multi-omics approaches to understand this in sepsis and COVID-19, with a view to developing personalised therapy that is appropriate to the individual patient at a particular stage in their illness.

This project would form the basis of a laboratory rotation or a 3-year doctoral research project. In sepsis, we have established one of the largest cohorts of patients for genomic studies worldwide, the UK Genomic Advances in Sepsis (GAinS) Study. With our collaborators we performed the first substantive genome-wide association study for outcome in sepsis and complemented this with functional genomic analysis showing that transcriptomic signatures predict underlying response state, outcome and response to therapy. Moreover, we found that a patient's genetic background influenced this with specific genetic variants associated with differences in gene expression dependent on their immune response state. This was further emphasised by our findings in healthy volunteers of expression quantitative trait loci for the response to bacterial endotoxin.

The COVID-19 Multi-omic Blood ATlas (COMBAT) Consortium has performed deep phenotyping of COVID-19 patients in Oxford using multi-omic profiling in blood, combined with knowledge of host genetics, pathogen diversity and immunological response, to allow an integrated systems biology approach to understanding the nature and basis of observed disease heterogeneity and drivers of severe illness. This includes bulk and single-cell transcriptomics, proteomics, repertoire sequencing and epigenomics, plasma profiling using timsTOF mass spectrometry and multiplexed immunoassays, serology, host genetics and viral sequencing.

This project will aim to follow up on this work to understand individual variation in the response to infection leveraging ongoing work in sepsis and COVID-19 through the UK GAinS and COMBAT studies, and how this could be used to develop and apply therapy. The work provides the opportunity to define the individual response to infection, the specific modulated genes and pathways that may be important in pathogenesis and potential drug targets, and how to use this knowledge effectively to develop personalised therapy. The project will benefit from access to large genomic and clinical datasets, both publicly available and those generated in house. Depending on the structure and duration of the project this could involve using statistical genetics and epidemiology to fine map genetic associations and establish their functional basis; bioinformatics to leverage genomic and epigenomic data, functionally annotate and integrate with diverse related data types to identify and prioritise potential novel drug targets; systems biology and integrative analysis approaches to maximise the informativeness of complex multidimensional datasets; genome editing to knockdown expression of specific genes or investigate the impact of particular genetic variants to establish mechanism; and application of single cell -omic and immune profiling approaches to further define pathogenesis.

### Training Opportunities:

This project will offer a comprehensive training programme in genomic science together with molecular biology and immunology. As described above, this can include both dry (bioinformatics/statistics/computational science) and wet lab (molecular biology/functional genomics/immunology) work, making it an ideal DPhil project for students wishing to gain skills in both areas. There are established sample and data collections for the proposed work, together with a very strong collaborative research network with other researchers on the GMS programme in this area (including within COMBAT Rachael Bashford-Rogers, Calli Dendrou, John Todd, Jim Hughes, Tatjana Sauka-Spengler, Ben Fairfax, Steve Sansom and Irina Udalova). The required wet lab and bioinformatic approaches are well established with expertise in complex trait genetics, gene expression profiling, next generation sequencing technologies including RNA-seq and ChIP-seq, expression quantitative trait mapping, epigenomic profiling, genome editing, immunological assays and other approaches. Students will benefit from working within a supportive research group with a strong track record in graduate student training and mentoring. You will have the opportunity to regularly present your work within the group, to your peers within the Centre as well as at international conferences. Students are encouraged and supported to undertake further relevant training courses in Oxford and elsewhere depending on need.

### Background reading / references:

* Burnham KL, Davenport EE, Radhakrishnan J, Humburg P, Gordon AC, Hutton P, Svoren-Jabalera E, Garrard C, Hill AVS, Hinds CJ*,* Knight JC. Shared and Distinct Aspects of the Sepsis Transcriptomic Response to Fecal Peritonitis and Pneumonia. *Am J Respir Crit Care Med 196*, 328-339 (2017).
* Davenport EE, Burnham KL, Radhakrishnan J, Humburg P, Hutton P, Mills TC, Rautanen A, Gordon AC, Garrard C, Hill AVS, Hinds CJ & Knight JC. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. *Lancet Respir Med* 4, 259-271 (2016).
* Fairfax BP, Humburg P, Makino S, Naranbhai V, Wong D, Lau E, Jostins L, Plant K, Andrews R, McGee C & Knight JC. Innate immune activity conditions the effect of regulatory variants upon monocyte gene expression. *Science* 343, 1246949 (2014).
* COMBAT Consortium 2021 A blood atlas of COVID-19 defines hallmarks of disease severity and specificity. medRxiv, 2021.05.11.21256877.