PI profile

## Alexander Mentzer

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| C:\Users\ischmidt\AppData\Local\Microsoft\Windows\INetCache\Content.Outlook\7IDJAGTS\Wellcome_Trust_by_John_Cairns_Mentzer_cropped.jpg | **Dr Alexander Mentzer****Titles**: Group Leader and Academic Clinical Lecturer in Infectious Diseases and General Medicine**Location**: Wellcome Centre for Human Genetics and John Radcliffe Hospital**Department**: Nuffield Department of Medicine **Group**: Human genetic susceptibility to infection**Webpage**: <https://www.well.ox.ac.uk/research/research-groups/mentzer-hill-group> **Email**: alexander.mentzer@ndm.ox.ac.uk  |

### GMS themes:

* Genomic and –omic technologies
* Genomics of disease
* Application of genomics in the clinic (diagnostics and therapeutics)

### Research Overview

Human genetic diversity has both been shaped by, and influences how we respond to infectious disease which continues to pose an enormous global burden of morbidity and mortality as highlighted recently by the COVID-19 pandemic. It remains unclear the extent to which this genetic diversity influences immune responses in the context of vaccination and how we can use this information to target or tailor international vaccination efforts against a variety of infectious pathogens or use this information at the clinical front-line for patients unwell with infectious diseases. Our research group uses antibody responses as a model of conserved antigen-specific immune response against infectious agents and then correlates these responses with human genetic diversity to understand these relationships both following natural infection exposure and vaccination. We have developed bespoke multi-antigen antibody assays (Brenner, Mentzer et al PLOS One 2018, 2019) to facilitate such measurements in very large cohorts around the world including UK Biobank (Mentzer et al, Nat. Comms. 2022), the China Kadoorie Biobank (Yao et al, BMJ Open, 2022) and various vaccinated infant cohorts across Africa (Muriuki\*, Mentzer\* et al Sci Adv 2019) and Asia. Using these approaches we have found that diversity in complex regions of the genome such as the major histocompatibility complex and immunoglobulin loci strongly affect responses to natural infectious challenge from agents such as the human herpesvirus family members and vaccination responses against agents such as *B. pertussis*, the cause of whooping cough. Our current objectives are to expand and combine these datasets to understand how much human genetic diversity affects responses against multiple infections simultaneously or whether such variation effect is pathogen-specific, and understand the scope of these effects to other emerging infections such as COVID-19. We also aim to use these population insights in unique samples collected in the acute hospital setting. Ultimately it is hoped that this work will inform both future vaccination efforts to help develop more tailored yet universally effective vaccines against multiple infectious agents, and also novel diagnostic and prognostic approaches for patients presenting to hospital with infectious diagnoses.

Project areas: Genome-wide association studies, analysis of immune and complex traits, stratified and personalised medicine

### Specific project proposals:

* ‘The functional consequences of human genetic variation on response to infectious disease’

Please contact directly for further information.

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Project proposal

# **Title**: The functional consequences of human genetic variation on response to infectious disease

Supervisors: Dr Alexander Mentzer, Professor Adrian Hill

Wet/dry lab mix: can be varied but may be 20-50% wet lab, 50-80% dry lab

### Description:

In close collaboration with Professor Adrian Hill at the Jenner Institute and other collaborators in the Wellcome Centre, UK Biobank and other institutes around the world we have generated multiple independent datasets looking at how human genetic diversity affects response to natural infection and vaccination. We have found that variation at multiple loci across the human genome contribute to immune responses against infectious antigens and, in some cases, protection against disease. An overall goal of this project is to combine these datasets to understand how much of this variation is infection- or population-specific, and then to use downstream approaches to understand the impacts of these changes to a molecular level but there are multiple complex regions and diseases that can be studied allowing for a programme tailored to any interested student. The genomic regions of particular interest include the major histocompatibility complex and immunoglobulin loci with diseases including viral infections (such as herpes, hepatitis, HIV and coronavirus) and bacterial diseases that may cause sepsis.

Any sub-project under this proposal would be designed in 2 stages; the first being a meta-analysis of relevant datasets central to the core objectives of the Mentzer group, and the second phase being an opportunity to follow up these findings using a combination of approaches dependent on the earlier findings. The first stage would be well suited to a laboratory rotation giving an excellent introduction to computational or dry lab skills whereas both could form the basis of a 3-year doctoral project giving the opportunity for a combined dry and wet-lab experience. At the time of writing, specific sub-projects include fine-mapping and molecular characterisation of MHC association signals with multiple infections, long-range sequencing characterisation and mapping of RNA-Seq reads for Immunoglobulin loci, and metagenomic approaches for pathogen detection in whole blood RNA. There may also be increasing opportunities to look at the effects of human genetics on responses to novel agents of interest such as SARS-CoV-2, the cause of COVID-19. Our group has a strong emphasis on tailoring the project to the individual and supporting the individual to achieve outstanding scientific output.

### Training Opportunities:

This project is designed to give an excellent introduction to computer science with rapid availability of datasets and tailored pipelines for data integration and analysis under close supervision that would provide necessary skills for interpretation and hypothesis testing. There is flexibility in the project and connections with multiple labs within the University to enable a diverse and complete follow-up of findings tailored to the interests of the candidate that can provide exposure and comprehensive training in molecular biology, immunology and functional genomics using experimental analysis or direct wet-lab exposure to methods such as flow cytometry, antigen peptide processing, binding and presentation, gene expression analysis, ELISA and other immunoassays. There will be regular opportunities to present work to laboratory colleagues and internationally at conferences and meetings.

### Background reading / references:

* Mentzer AJ\*, Brenner N\* et al **2022**; A scalable 20-agent Multiplex Serology platform applied to UK Biobank to define host-pathogen-environment relationships and disease susceptibility; Nature Communications; <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8983701/>
* COMBAT Consortium **2022**; A blood atlas of COVID-19 defines hallmarks of disease severity and specificity; Cell <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8776501/>
* Antibody evasion by the P. 1 strain of SARS-CoV-2; Dejnirattisai W\*, Zhou D\*, Supasa P\*, Liu C\*, Mentzer AJ\* et al **2021**; Cell. 184 (11) 2939
* Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent COVID-19 patients **2020**; Peng Y\*, Mentzer AJ\*, Liu G\*, Yao Z\*, Dejnirattisai W\* et al; Nat. Imm 21, 1336 (2020)
* Mentzer AJ\*, Muruiki JJ\*, Band G, et al. **2019**; The ferroportin Q248H mutation protects from anemia, but not malaria or bacteremia; Science Advances; 4;5(9):eaaw010
* Dilthey AT, Mentzer AJ, Carapito R et al. **2018**; HLA\*PRG:LA - HLA typing from linearly projected graph alignments; Bioinformatics; pii: btz235
* Brenner N, Mentzer AJ, Butt J, Braband KL, Michel A, Jeffery K, Klenerman P, Gärtner B, Schnitzler P, Hill A, Taylor G, Demontis MA, Guy E, Hadfield SJ, Almond R, Allen N, Pawlita M, Waterboer T **2019**; Validation of Multiplex Serology for human hepatitis viruses B and C, human T-lymphotropic virus 1 and Toxoplasma gondii; PLoS One:14(1):e0210407
* Brenner N, Mentzer AJ, Butt J, Michel A, Prager K, Brozy J, Weißbrich B, Aiello AE, Meier HCS, Breuer J, Almond R, Allen N, Pawlita M, Waterboer T **2018**; Validation of Multiplex Serology detecting human herpesviruses 1-5; PLoS One: 13(12):e0209379