**A UK underpinning platform to study immunology and immunopathology of COVID-19: The UK Coronavirus Immunology Consortium**


**Executive summary**

The immune response to SARS-CoV-2 is the critical determinant of outcome after infection but although this can suppress virus replication ('immunity') it can also contribute to symptoms such as lung inflammation ('immunopathology').

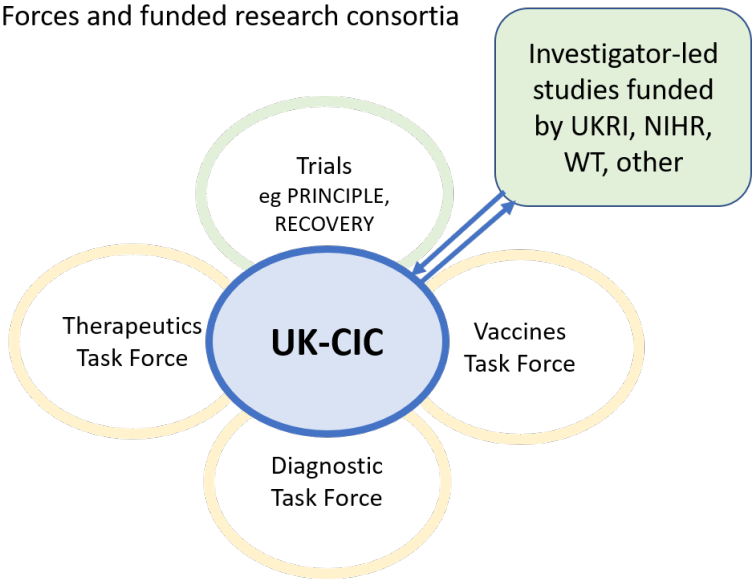
The mechanisms by which protective immunity is achieved, and immunopathology is mediated, are largely unknown. This is a major limitation in the management of the SARS-CoV-2 pandemic, as such knowledge underpins development of diagnostics, treatments and vaccination, as well as social distancing policies.

Here we propose to establish an integrated UK consortium to deliver, at pace, a co-ordinated and agile research programme to study the immunity and immunopathology of COVID-19. This will focus around 10 regional centres of excellence to address key research challenges at the current time. ***These have also been encapsulated in the 5 questions recently formulated by SAGE and which are addressed directly in this proposal.***

Studies will be performed across the life course and powered to address the importance of factors such as, ethnicity and co-morbidity.

- This proposal was formulated in response to questions arising from SAGE and the report (submitted to SAGE) from the British Society for Immunology and the Academy of Medical Sciences.
- In developing this we have received detailed information on current activity from UK academic centres and NIHR Biomedical Research Centres (BRC). We have also considered, and integrated where possible, all COVID-19 immunology grant awards and cohorts.
- The proposed team comprises leading UK academic groups and findings will be translated rapidly to policy makers, academic & industrial collaborators and the public.


**A national integrated research approach:**
UK-CIC at the core, connecting strategic Task Forces and funded research consortia



**Background**

A recent report[1] for SAGE produced by the AMS/BSI Immunology Expert Advisory group highlighted the knowledge base regarding understanding of the immunology and immunopathology of COVID-19. In a very fast-moving area, the key point to emerge is ***that a fragmented approach is limiting depth of understanding and impacting on how successfully we can manage, prevent and treat this pandemic disease***.

***Specific issues*** include:

- *ad hoc* sample collection
- lack of transparency regarding available resource
- limited standardisation in samples, assays, data processing and visualisation pipelines
- little or no integration with longer term strategic goals
- unclear path to translation, policy and impact.

Unlike in other areas there is ***not a pre-existing platform to evaluate immunity and immunopathology of this disease***. However, these insights are critical to treatment selection for clinical trials, clinical management of patients and for the development of diagnostics and vaccines and social distancing policies.

The DHSC/UKRI COVID-19 Rapid Response Rolling Call provides potential support to the academic community but for maximum impact within 12 months it is essential that we coordinate at a national level to identify knowledge gaps, drive research and share data/insights. This will act to:

- develop coordinated infrastructure and oversight across the UK immunology and life sciences community
- reap the benefits of prior investments in life sciences with flexibility to accommodate new research questions as they emerge
- identify and prioritize knowledge gaps
- use this new knowledge to inform diagnostic, vaccine and drug development, as well as other critical policy areas, via engagement with appropriate COVID-19 Task Forces, charity and industry.

**Our proposal: A coordinated solution**

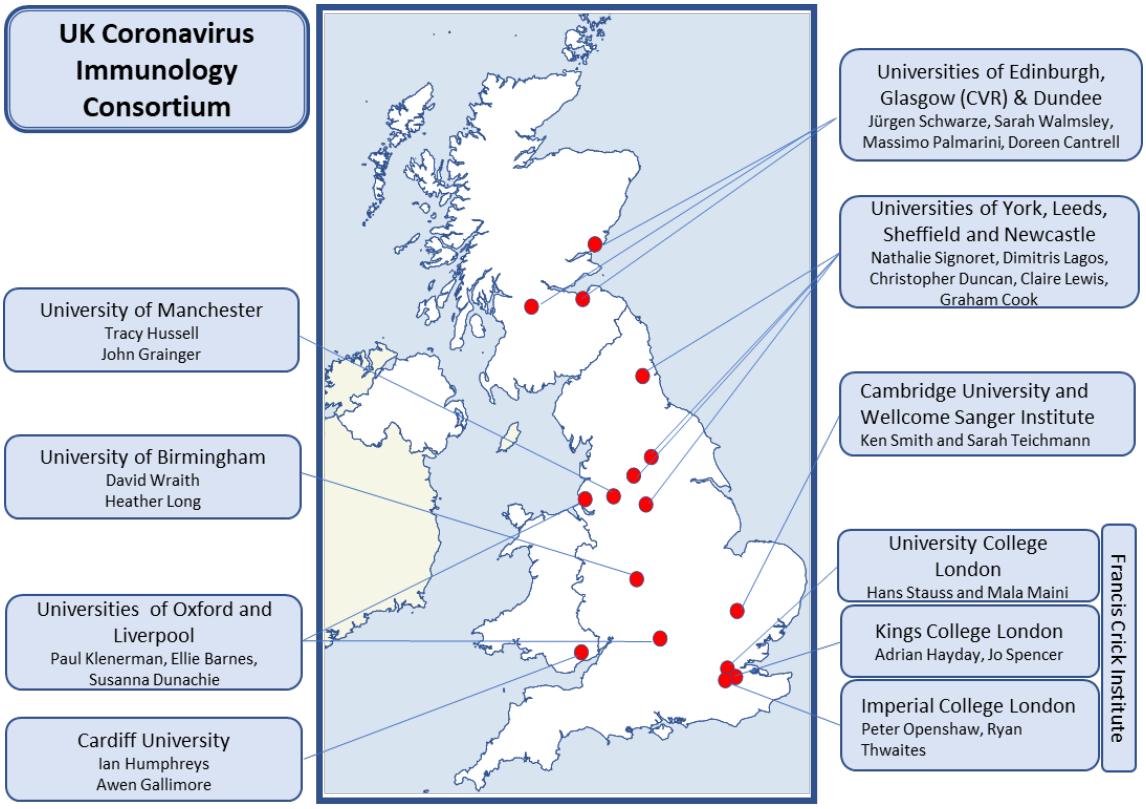
Our model will coalesce and coordinate the UK immunology community to address priority questions with an initial focus on delivering public health benefit within 12 months.

The consortium will interact closely with ongoing investments and core facilities such as ISARIC, Covid GenOMICC, COG-UK, Covid19CellAtlas and the COVID-19 Protein Portal.

**Virology expertise** will be provided from an advisory group, guiding on issues such as viral mutation status and immune response, animal models and environmental transmission.

A principle of UK-CIC is that it will exploit UK science infrastructure but ***ensure that it builds on the international knowledge base***. Regular updates of publications and pre-prints within coronavirus immunology will be sourced and shared by the management team.

[1] 1/BSI Expert summary – Covid-19 Immunology Research: What do we know and what are the research priorities? https://www.immunology.org/sites/default/files/Final_COVID-19_Immunology_report.pdf

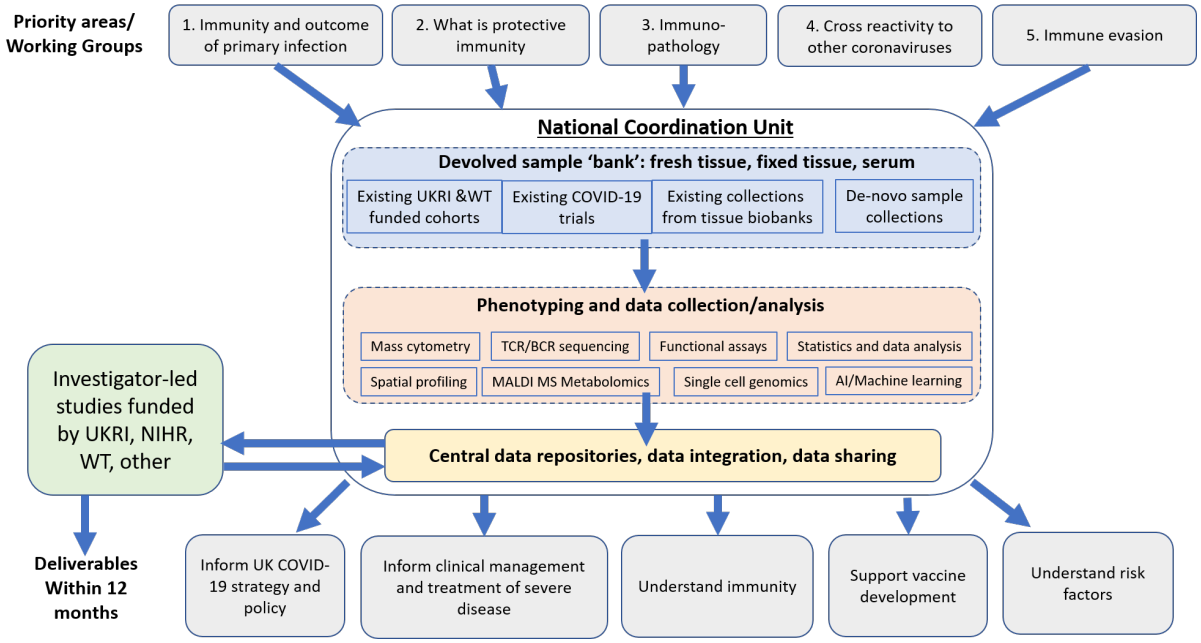



**Principles of Operation**

The consortium will address the five major questions arising from SAGE (see Appendix 1 for how UK-CIC will address each question).

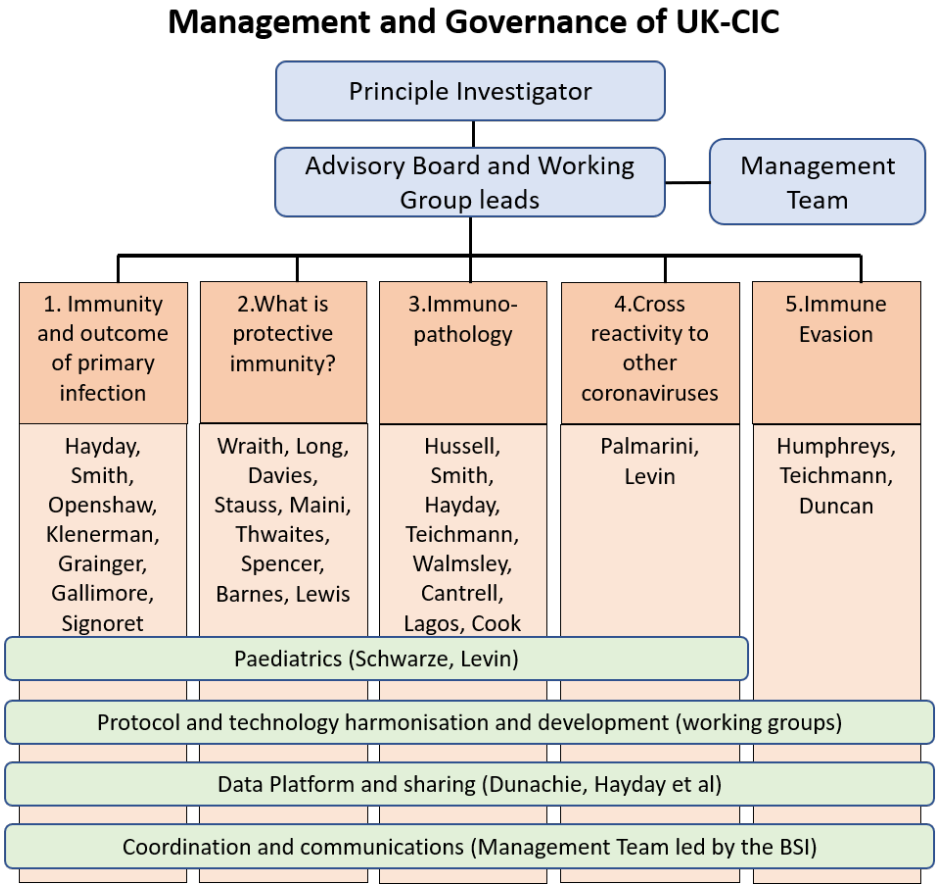
- A working group will be established in each of these five areas to develop, coordinate and lead the research, sharing activity across centres with appropriate expertise and facilities.
- Funding will be assigned according to scientific need rather than 'per-centre'.
- Harmonised data integration and communication platforms will be established.

**Flow chart of Consortium operation**



**Management and Governance**
**Principal Investigator:** Professor Paul Moss (University of Birmingham)
**Advisory Board**: Arne Akbar (Chair), Deborah Dunn-Walters, Janet Lord, Paul Kaye
**Management team** to support coordination, communication and administration and enabled by the **British Society for Immunology**. Note:

- A virtual conference on SARS-CoV-2 immunology will be delivered late 2020/early 2021.
- Partnerships will be established with **professional bodies and charities** in areas such as respiratory, renal and cardiac disease, in addition to those focused on paediatrics.



### 4.3 Deliverables

**Within 1 month**

- Establish a publicised UK platform which can be built on by further research groups, ensuring UK coordination (and thus avoidance of fragmentation and duplication of research efforts)
- Set up data sharing platform with integrated analysis of current data
- Core analytical platforms defined for use in therapy and vaccine studies
- Initiate interactions with international consortia
- Engagement with UK (Oxford and Imperial) COVID-19 vaccine and convalescent plasma transfer trials

**Within 3 months**

- Collaborative data available from all Priority areas
    - Novel insights into cellular basis of immunopathology
    - Assessment of cellular and humoral correlates of immunity
    - Sample collection ongoing from targeted cohorts (e.g. Children and BAME), coordinating with projects funded under DHSC/UKRI highlight notices.
- Data and insights available to inform UK strategy and policy on:
    - Clinical management and treatment of severe disease, seeking to intervene in milder disease and prevent clinical progression.
    - Features of protective immune response
    - Immune analysis to guide social distancing and epidemiology
    - Open data website and publication

**Within 6 months**

- Research progress:
    - Detailed understanding of cellular mechanisms underlying immunopathology of COVID-19.
    - Comparative immunological analysis from UK therapy trials.
    - Determination of major immunogenic proteins within SARS-CoV-2
    - Analysis of immune architecture of immunity and immunopathology using immunohistochemistry and NanoString technology
    - Correlation of immunopathology with sites of viral replication
- Data and insights available to inform UK strategy and policy on:
    - New therapeutic targets for management of severe disease
    - Guidance on optimal vaccine design
    - Immune analysis guiding personalized ‘individual risk’ epidemiology
- British Society for Immunology Conference on emerging research and insights
- Intensification of publications and public communications

**Within 12 months**

- Comprehensive outputs from all Priority areas
  - Deep understanding of mechanisms of immunopathology and analysis of samples from intervention studies initiated from the Consortium
- Detailed understanding of the differential impact of immune response on SARS-CoV-2 outcome in relation to age, ethnicity, exposure, co-morbidities in the UK population
- Further data and insights available to inform UK strategy and policy on all areas stated above as well as developing optimal vaccination policy and potential differential requirements for individuals and population subgroups
- Prioritisation of future immune research directions
- Legacy of co-ordinated UK research consortium within immunology and banks of resources that will enable continued detailed research into this disease

**<u>Indicative budget of £10M</u>**

**Immunity and Primary infection (£2M)**

Flow cytometry, CyTOF, Transcriptomics and TCR/BCR sequencing
Tissue collection

**Protective Immunity (£2.5M)**

Targeted cohort collection. Optimize antibody and cellular assays; T cell recognition of virus. Molecular histology with spatial transcriptomics and NanoString

**Immunopathology (£2.5M)**

Deep phenotyping and functional analysis of immune subsets
scRNA-Seq and cellular proteomics

**Cross reactivity of Coronaviruses (£0.5M)**

Analysis of unique or shared antibody and T cell epitopes
Epidemiological analysis of banked samples

**Immune evasion (£1.5M)**

Cytokine assays, evasion of cellular recognition, ISG screens and CrispR screens.

**Data sharing and coordination (£0.5)**

**Management (£0.5M)**

| | Birmingham | Cambridge & Wellcome Sanger | Cardiff | Edinburgh, Glasgow (CVR) & Dundee | Imperial College London | Kings College London | University College London | Manchester | Oxford & Liverpool | York, Newcastle, Leeds and Sheffield |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Francis Crick Institute | | | | | |
| Immunity and outcome of primary infection | | | | | | | | | | |
| What is protective immunity ? | | | | | | | | | | |
| Immuno-pathology | | | | | | | | | | |
| Cross-reactivity to other coronavirus | | | | | | | | | | |
| Immune evasion strategies of SARS-CoV-2 | | | | | | | | | | |

**Assessment of Centre capabilities to address SAGE questions**

## Appendix 1 – Key question arising from SAGE and how these will be addressed

**Question 1 - What role does the immune system play in determining variation in susceptibility to primary infection, how does this vary across the life course and what are the key biomarkers ?**

**Synopsis**: The clinical outcome after primary infection is very heterogeneous and strongly influenced by factors such as age, gender, ethnicity and co-morbidity. The relative importance of differential immune response in these settings is unknown. This information will help to guide clinical management, epidemiology and discovery science.

**Work to date:**

- Large numbers of blood samples after acute infection analysed, determining phenotype and function of immune subsets: great majority from hospitalised adult patients; some prospective sampling
- Significant number of scRNAseq datasets of PBMCs from adult patients from the UK and other countries
- Serology analysis underway using a variety of platforms
- Excellent database of serum proteome.

**Outstanding research questions**

Combining cellular analyses at scale with demographics and clinical data
Comparison of immune response in blood and tissue
Immune response in children and asymptomatic or mildly symptomatic patients
Correlation of innate immunity with adaptive antibody and cellular response

**Investment:**

- Combine current immune phenotyping datasets to maximise statistical power utilising machine learning (*www.jimmunol.org/content/early/2019/06/13/jimmunol.1900033*)
- Define optimal immunophenotype panels to be used consistently across centres in future studies.
- Invest in completing phenotyping of rare immune cell subsets
- Support analysis of *fresh* immune subsets – e.g. neutrophils and myeloid subsets
- Enhance analysis of *functional* capacity of cells
- Target collection of underrepresented cohorts such as children, asymptomatic and mildly symptomatic cases
- Utilize combined databases to correlate immune response with:
    - Host genetics, notably ethnicity.
    - Viral genome, linking with Sanger database
    - Environmental factors : diabetes; cardiovascular and renal disease

**This will deliver** the largest global meta-analysis of immune phenotype during acute disease according to clinical outcome, in relation to demographics such as age and ethnicity. This will guide prognostic and mechanistic studies. The work will also define core immunophenotype panels for future studies, including analysis of therapy and vaccine trials

**Question 2 - How is protective immunity generated, what are its characteristics and duration, and how effectively is protective immunity boosted upon re-exposure to infection?**

**Synopsis**: The efficacy and duration of immunity after infection is uncertain. The characteristics of antibody and cellular immunity, how they develop and their relative importance in different populations are unknown. This information will guide population screening and vaccination policy.

**Work to date:**

- Large number of serological assays now developed.
- Initial studies to define T cell recognition of viral proteins
- Availability of biobanks of convalescent samples, including many in health care workers that enable serial sampling.

**Outstanding research questions**

- Fine details of antibody response including specificity, titre, isotype and relation to neutralising function in all demographic groups
- Relative importance of antibody production in different tissues e.g. airways
- The magnitude and specificity of antibody response across the lifecourse
- Features of T cell recognition of viral proteins
- Stability of humoral and cellular responses over time in prospective studies

**Investment:**

- Comprehensive assessment of features of humoral immunity in serum, saliva and nasal secretion and correlation with neutralisation assays
- Define T cell recognition profile of CD4+ and CD8+ T cells: including development of clinical assays that can rapidly determine cellular immune status
- Utilize and target prospective sample collections to determine longevity of immune memory
- Incorporate analyses that include intermittent assessment of viral carriage in order to assess potential for boost from asymptomatic re-infection
- Compare immune profiles throughout convalescence of patients enrolled in clinical trials (including immunomodulatory drugs) with other patients

**This will deliver** a comprehensive understanding of features of protective immunity in the UK population.

| | paediatric | | | | | | Adult | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Asymptomatic/ mild | | severe | | convalescent | | Asymptomatic/ mild | | severe | | convalescent | |
| | serum | cells | serum | cells | serum | cells | serum | cells | serum | cells | serum | cells |
| ISARIC | | | ✓ | (✓) | | | | | ✓ | (✓) | | |
| Virus Watch | | | | | | | | | | | ✓ | ✓ |
| Birmingham | | | | | | | | | | | ✓ | ✓ |
| NHSBT | | | | | | | | | | | ✓ | ✓ |
| UK Biobank | | | | | | | | | | | ✓ | ✓ |
| NIHR Bioresource | | | | | | | | | ✓ | (✓) | | |
| story | | | | | ✓ | ✓ | | | | | | |
| Born in Bradford | | | | | ✓ | ✓ | | | | | | |
| Belfast cohort | | | | | ✓ | ✓ | | | | | | |
| Dimond Consortium | | | | | | | | | ✓ | ✓ | | |

**Summary of major UK SARS-CoV-2 sample collections for potential collaboration**

**Question 3 - Does the host immune response contribute to pathology and thus what is the role of immunomodulatory therapies in COVID-19 ?**

**Synopsis**: Widespread tissue inflammation is often seen during COVID-19 and it is not known to what extent this results from viral replication or immune-mediated damage. Immunopathology may be mediated by antibodies and/or immune cells. Access to tissue is challenging and requires biopsy or post-mortem. Many current therapy trials are based on immunomodulatory drugs, but mechanisms are unknown.

**Work to date:**

- Analysis of immune cells within blood during disease
- Studies of complement, antibody and cell-mediated immunopathology initiated
- Limited studies of tissue biopsies (e.g. lung; kidney)
- Post-mortem specimens available
- Development of assays to assess viral replication (CVR, Glasgow) and features of immune infiltration in tissue sections

**Outstanding research questions**

- Detailed cellular analysis of fresh biopsies
- Intensive transcriptomic and proteomic analysis of key immune subsets for potential therapeutic targets
- Differential effects on target tissues such as lung, kidney, bowel, heart.
- Analysis of post-mortem tissue to assess viral replication and immunopathology
- Utilizing this information to select new therapies for COVID-19

**Investment**

- Collection of fresh tissue during tissue inflammation and intensive analysis of immune infiltration
- Extend detailed assessment of immune cells to include cellular proteomics and single cell RNA sequencing
- Interrogate the basis of inflammatory disorders in children after Covid infection
- Develop consortium to study histology sections, using in situ hybridisation, multiplex immunostaining and multiplex smFISH/in situ sequencing, spatial transcriptomics and NanoString GeoMX to define viral replication and mechanism of immunopathology.
- Correlation of serum inflammatory profile with disease for therapeutic insight
- Initiate studies of the mechanism and potential management of immunopathology in relation to antibody-directed enhancement, complement and cellular immunopathology

**This will guide** effective treatment of COVID-19 and inform vaccine policy.

**Question 4 - Is there immunological cross-reactivity to other coronaviruses and, if so, is it protective or does it contribute to pathology ?**

**Synopsis**: There are four seasonal coronaviruses that circulate in the community. These are clinically mild but do not generate sustained immunity. Potential immune cross-reactivity between these viruses and SARS-CoV-2 may provide relative protection *or* enhance immunopathology of COVID-19. The latter is one potential explanation for severe disease in older people. This information will inform vaccine policy across the lifecourse.

**Work to date:**

- Epidemiology of seasonal CoV infection now defined
- Serum collections available to study epidemiology of infection history prior to SARS-CoV-2 pandemic

**Outstanding research questions**

- Serology and T cell assays that define specific immune response to each CoV subtype
- Epidemiological information that defines the importance of CoV status prior to SARS-CoV-2 infection and during long term memory

**Investment:**

- Develop serological and T cell assays against each seasonal CoV
- Study co-infection profiles with other respiratory viruses and bacterial lung microbiome during and after SARS-CoV-2 infection
- Define regions of potential immunological cross reactivity between CoV and SARS-CoV-2 viruses

**This will deliver** a comprehensive understanding of cross reactivity between coronaviruses, address lessons that may be learnt from seasonal infection and define the importance of seasonal infection in relation to clinical outcome at age of infection.

**Question 5 - What, if any, are the immune evasion strategies of SARS-CoV-2?**

**Synopsis**: Viruses evolve mechanisms to evade and limit host immune responses. There is currently very little knowledge regarding how important these are for SARS-CoV-2. This information will guide new treatment approaches for treatment of COVID-19.

**Work to date:**

- Established expertise in IFN-signalling at CVR, including assays to test the activity of ~1400 ISGs against SARS-CoV-2
- Early studies of NK cell and T cell recognition of infected cells.
- Cloning of SARS-CoV-2 genes into expression systems for analysis of individual SARS-CoV2 proteins in immunoevasion assays.

**Outstanding research questions**

- Detailed understanding the basis for potential evasion of innate signalling pathways
- Potential mechanisms of evasion from cellular recognition of virus-infected cells

**Investment:**

- Biochemical basis for SARS-CoV-2 suppression of IFN signalling
- Development of models of viral infection of primary cells and organoids *in vitro*, including CrispR screens
- Studies of mechanism of evasion from cellular recognition (e.g. down regulation of HLA and 'stress' proteins)

**This will deliver** mechanistic understanding of how the virus has evolved to evade immune recognition. This may partially explain individual outcome of infection and will provide insight into novel therapeutic opportunities.