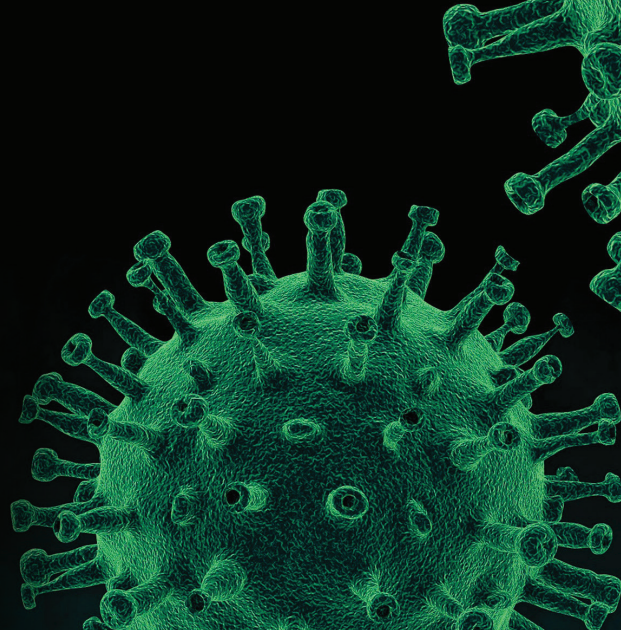
COVID-19
Projects at Centenary



COVID-19 lab establishment, ex vivo human and in vivo mouse infections, and testing a range of potential effective treatments – Professor Phil Hansbro, Head, Centenary UTS Centre for Inflammation

We are setting up a COVID-19 laboratory exploring SARS-CoV-2 infections of primary human airway epithelial and blood cells. Additionally, we are establishing a humanised ACE2 expressing mouse colony, and then mouse models of infections. This work will be combined with unique severe asthma, COPD and high fat diet/obesity models to assess mechanisms of increased COVID-19 susceptibility. Age (young, adult, old) and sex differences will also be assessed. We will also be testing new treatments that we have investigated in other inflammatory diseases targeting; inflammasomes, microbiomes, epigenetics, oxidative stress and immunometabolism, monoclonal antibodies, azithromycin, MAIT cells and others. Furthermore, we will perform discovery bulk and single cell RNA-sequencing, proteomics and many other 'Omics to provide detailed insights of the disease.

Defining immune parameters of clinical outcomes and interactions with TB – Professor Warwick Britton AO, Head, Centenary Institute Tuberculosis Research Program and Research Director, Sydney Local Health District

In collaboration with clinicians caring for COVID-19 patients we will assess innate and anti-viral immune responses (immune cell populations, serum antibodies, serum cytokines and whole blood transcriptomic responses) in the blood of COVID-19 patients with different symptoms to understand the links. We will also assess SARS-CoV-2 infection in health workers in clinical settings using serology and investigate household transmission. Will also investigate the effect of SARS-CoV-2 infection on susceptibility to tuberculosis infection.

Understanding aged susceptibility to COVID-19 – Professor Jennifer Gamble, Head, Centenary Institute Vascular Biology Program and Professor Mathew Vadas AO, Executive Director, Centenary Institute

One of the most striking features of COVID-19 is its high morbidity and mortality in the aged. The underlying biology of this susceptibility is unknown. We aim to dissect the link between COVID-19 and the aged and understand the inflammatory response of young versus aged individuals, with a particular focus on the endothelium.

Prediction and validation of SARS-CoV-2 variants of concern – Dr Dan Hesselson, Head, Centenary Institute Directed Evolution Laboratory

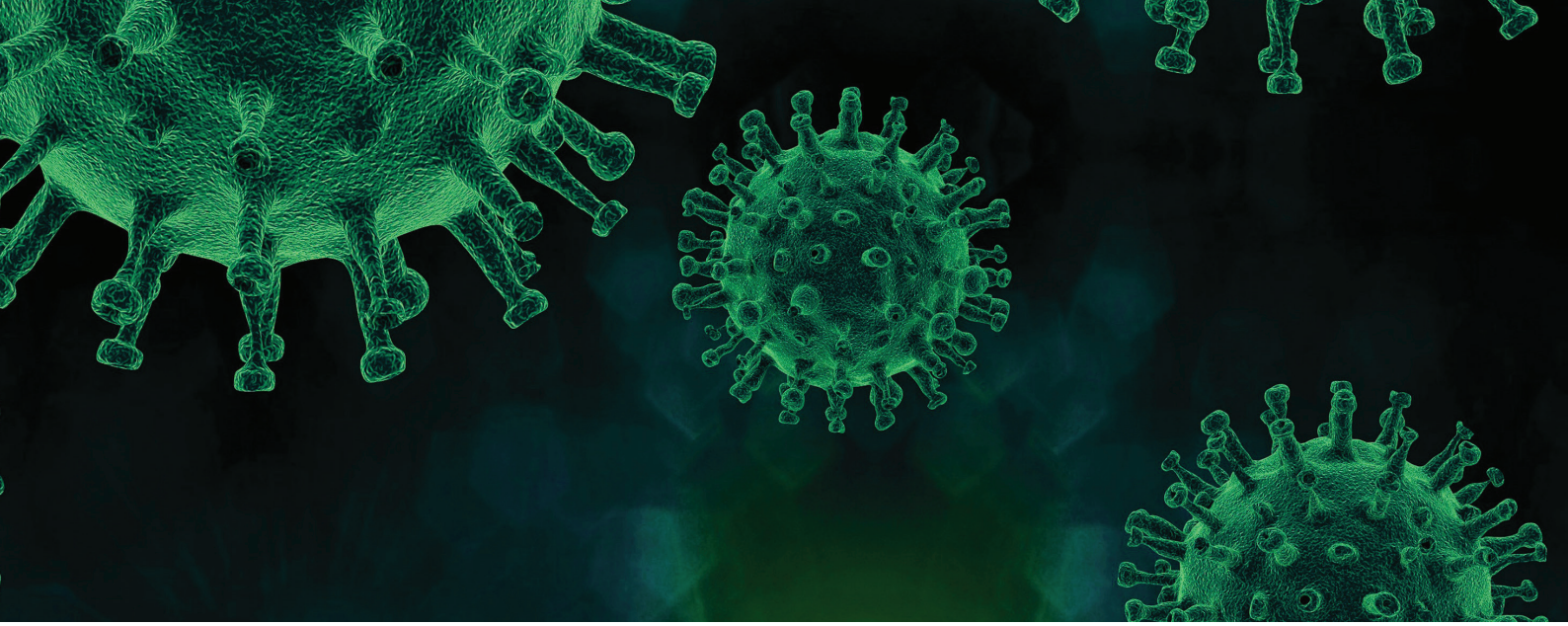
In our study we will determine how the SARS-CoV-2 virus could evolve to enter cells more efficiently (increasing infectivity), which will help identify and possibly contain emerging strains. We'll do this by first mapping human genes and pathways that could be hijacked by an evolving SARS-CoV-2 virus to facilitate cellular entry. We will then apply a new directed evolution system to identify all SARS-CoV-2 variants that modify entry through known (e.g. ACE2) or newly identified SARS-CoV-2 receptors. Overall, we will provide the first comprehensive assessment of virtually all potential evolutionary strategies SARS-CoV-2 could use to further enhance its infectivity.

Identifying inhibitors of the infection of the eyes and lungs by SARS-CoV-2 – Clinical Associate Professor Guy Lyons, Centenary Institute Immune Imaging Program

Proteoglycans are essential facilitators of coronavirus binding to cells. We will identify what are the proteoglycan protein cores in both eye and lung tissues that mediate this binding, and what are the glycan sugar structures that enable it. We will then develop agents that have sufficient specificity to be clinically useful in both the eyes and lungs.

Understanding why the elderly are more susceptible to COVID-19 – Associate Professor Patrick Bertolino and Dr David Bowen, Joint Heads, Centenary Institute Liver Immunology Program

Interstitial lung macrophages (large white blood cells) are critical in organising the immune response in the lung. Located in the interstitium where the exacerbated immune response that kills COVID-19 patients occurs, these cells might play a critical role in the disease's development. We will determine whether this is the case in mouse models. We will particularly investigate whether the number of these interstitial macrophages increases with age as this might explain why the coronavirus is more severe in older infected patients.



COVID-19 research targets human enzymes – Professor Mark Gorrell, Head, Centenary Institute Liver Enzymes in Metabolism and Inflammation Program

An enzyme called TMPRSS is widespread in the human body and is essential for SARS-CoV-2 (COVID-19) and similar viruses to infect us. This enzyme modifies a molecule on the coronavirus so that the virus is then able to enter our cells at the start of infection in the human body. We want to develop a drug that stops the TMPRSS enzyme from helping the virus and is both effective and safe. We can do this using our expertise and a unique drug screening approach. The successful development of such a drug could be a novel therapy for past, current, and possibly future, SARS-CoV coronaviruses.

Vascular-targeted therapies for COVID-19 treatment – Associate Professor Mathias Francois, Head, Centenary Institute David Richmond Laboratory for Cardiovascular Development: Gene Regulation and Editing Program and Dr Stefan Oehlers, Head, Centenary Institute Immune-Vascular Interactions Laboratory

We are developing a novel treatment that has a dual mode of action: 1) anti-viral combined with 2) anti-vascular. The aim is to prevent outgrowth of blood and lymphatics vessels during the inflammatory response induced by viral infection. This molecular strategy is to avoid the acute respiratory distress syndrome (ARDS) secondary to SARS-Cov2 infection in most severe cases. This study involves a collaboration with a Melbourne based biotech to develop the first in class inhibitors for a novel molecular target. (Francois research group)

Lung immunopathology during the acute respiratory distress syndrome (ARDS) phase of severe COVID-19 appears to follow a similar pattern to other severe pulmonary infections that we have expertise in. Specifically, we have shown benefit to inhibiting the growth of blood vessels, infection-induced blood vessel leakiness, and infection-associated haemostasis. We will determine if these treatments are of benefit in severe SARS-CoV-2 infections. (Dr Stefan Oehlers)

Repurposing existing vaccine platforms to develop new COVID-19 candidates – Professor Jamie Triccas, School of Medical Sciences, University of Sydney and Affiliate Faculty, Centenary Institute

Building on our extensive expertise in the development of vaccine candidates against lung pathogens, we are combining SARS-CoV-2 antigens with existing licensed vaccines to develop novel products for human delivery. Lead candidates are currently being evaluated in animal trials at the Centenary Institute.

Investigation of non-tuberculous mycobacteria co-infections – Dr Stefan Oehlers, Head, Centenary Institute Immune-Vascular Interactions Laboratory

Non-tuberculous mycobacteria are prevalent in at-risk groups such as COPD patients, co-infections are a common feature of COVID-19 mortalities. Projects are: 1) Vaccination against Mycobacterium abscessus, 2) Better in vivo model of antibiotic treatments against chronic M. abscessus infection to reduce the impact of COVID-19 in our high risk patient populations.

Identification of mechanisms of infection and replication of SARS-CoV-2 – Professor Greg Neely, Head, Dr. John and Anne Chong Lab for Functional Genomics, The Charles Perkins Centre School of Life & Environmental Sciences and Centenary Institute Directed Evolution Laboratory

We will use CRISPR genome editing of human cells to identify factors that can modulate SARS-CoV-2 infection. This has the potential to help us develop new COVID medicines that are rapidly translatable.