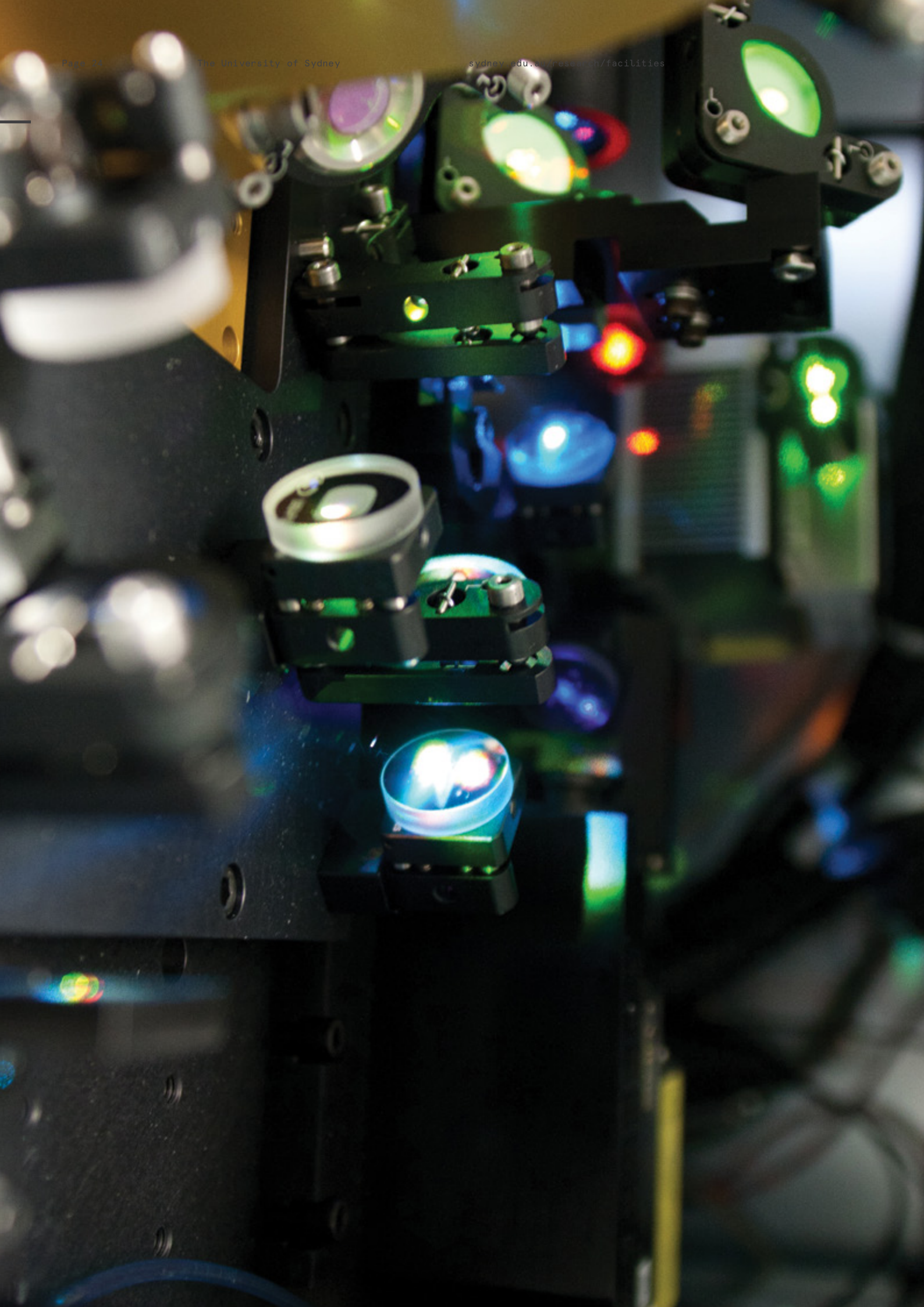
Core Research Facilities
Sydney Cytometry Case Studies

THE UNIVERSITY OF SYDNEY



SYDNEY CYTOMETRY

Sydney Cytometry provides access to cytometry and cell-sorting techniques in quantitative cell science to address questions in cell biology and biomedical research, applied clinical research and trials, and the diagnosis of cancer and other diseases.

Centenary Institute
life saving research
Cancer. Inflammation. Cardiovascular.

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– www.sydneycytometry.org.au

Immune modifying particles to treat malaria

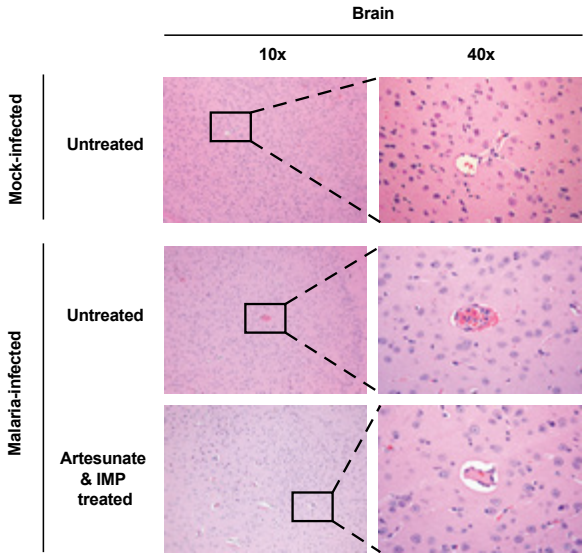
The World Health Organisation estimates that more than 400,000 people around the world die from malaria each year. Severe malaria occurs when infection of the red blood cells by the malaria parasite makes them stick to blood vessel walls in the brain and lungs. White blood cells then accumulate around these sticky red cells, gradually blocking the flow of blood, causing illness and death.

In 2018, Professor Georges Grau, Professor Nicholas King and PhD candidate Paula Niewold (all School of Medical Sciences, Faculty of Medicine and Health) utilised state-of-the-art analysis capabilities at **Sydney Cytometry**. They examined the body's immune response to malaria parasites in an effort to reduce the amount of white blood cells available that 'stick' to infected red blood cells. The researchers identified the Ly6Clow monocyte as a potential for targeted therapy to alleviate the disease.

In this specific study, severe malaria was treated with both the conventional treatment and new immune modifying particles that targeted the Ly6Clow monocytes in mouse models.

As a result, the survival rate increased dramatically – to around 90% (the current conventional treatment yields only a 50% survival rate, while the untreated survival rate is 0%).

The findings of the study were published in the *Nature Communications Biology*. The research was supported by a National Health and Medical Research Council Project grant and a grant from the Merridew Foundation.

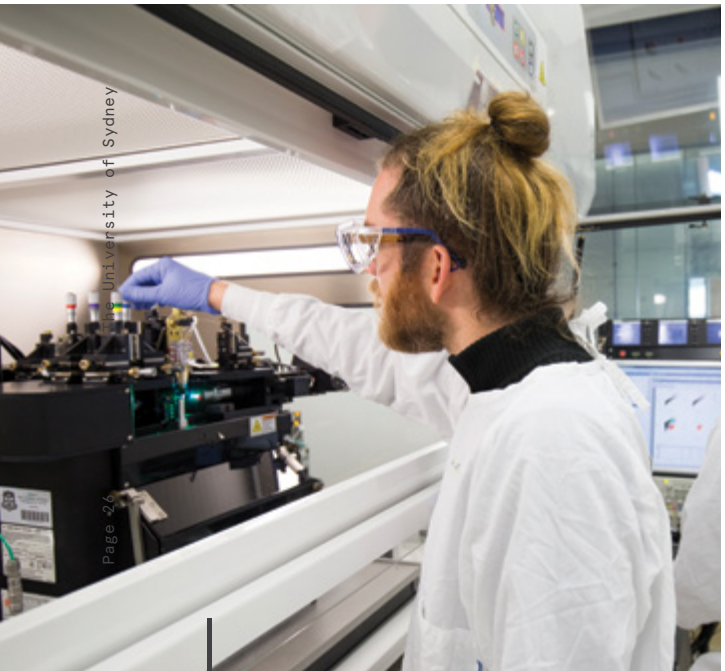


Right: Stained brain sections from mock-infected mice, malaria-infected mice with no treatment, or malaria-infected mice treated with a combination of artesunate and immune-modifying nanoparticles (IMP). In untreated infected mice, the blood vessels are blocked with accumulations of white blood cells, compared to uninfected mice, and reduced in the immune-modifying nanoparticle (IMP) -treated animals.

Reducing inflammation in COVID-19 patients

Acute Respiratory Distress Syndrome (ARDS) is associated with widespread inflammation of the lungs, causing severe shortness of breath, with laboured, rapid breathing, and can be fatal. ARDS has been observed in patients with severe COVID-19, requiring the use of oxygen – and in the worst cases can require a ventilator.

A newly awarded, one million dollar Medical Research Future Fund grant –*'IMPACT-ICO: Trials of Immune-Modulatory Particles and Colchicine To Improve COVID-19 Outcomes'* – hopes to reduce the effects of ARDS in patients by reducing the massive inflammatory response that causes the syndrome.



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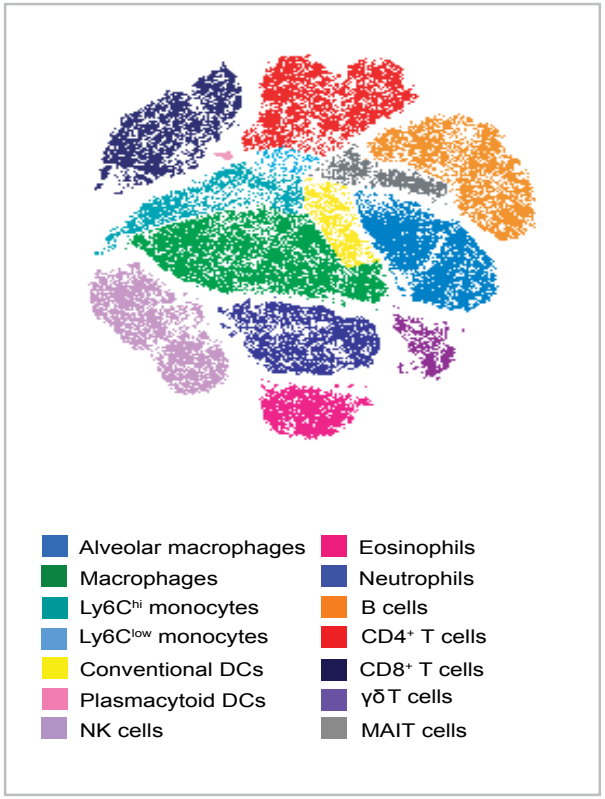
A clinical trial supported by **Sydney Cytometry** will be key to understanding the cellular response to COVID-19, specifically how inflammatory monocytes (normally protective blood cells), can induce ARDS in some patients. In some cases, very large numbers of these cells, equipped with a range of powerful chemical weaponry to control infection, migrate to the lungs to fight the virus infection. However, when inflammatory monocytes accumulate in large numbers, many normal uninfected cells lining the lung passages are inadvertently killed in the massive inflammation triggered, causing significant collateral damage to the lungs. This phenomenon is known as a "cytokine storm".

Immune-modifying nanoparticles

This clinical trial is designed to develop a treatment for cytokine storms and aims to reduce inflammation in two ways: by reducing the number of inflammatory monocytes going to the lungs, and by directly reducing the intensity of the inflammation that causes the collateral damage. Reducing the number of inflammatory monocytes going to the lungs will be achieved by injecting immune-modifying nanoparticles intravenously into COVID-19 patients.

The trial is being led by Professor Tony Keech, Deputy Director of the National Health and Medical Research Council Clinical Trials Centre, Professor Nicholas King, key user of **Sydney Cytometry** and Associate Professor Sanjay Patel, Director of the Cardiac Catheterisation Laboratories at Royal Prince Alfred Hospital and Group Leader at the Heart Research Institute. These investigators are working together with clinicians from the Royal Prince Alfred Hospital, Royal North Shore Hospital, The George Institute and UNSW to treat 240 patients with ARDS related to COVID-19. **Sydney Cytometry** will enable the measurement and analysis of the complex blood cell profiles in the trial patients' blood samples and allow researchers to monitor changes before and after treatment. This novel treatment has the potential to work not only on ARDS patients but as a complementary therapy on a wide range of illnesses including viral infections, autoimmune diseases and heart disease.

> "The cutting-edge instrumentation and world-class analytical data pipeline at Sydney Cytometry will allow us to monitor changes in the blood profiles of patients in this trial in unprecedented detail and are absolutely crucial to its success."
>
> **Professor Nicholas King**



Representation of the different innate cell types that were activated in the lungs when the Advax vaccine was administered.

Understanding the immune response in the lungs of tuberculosis patients

Tuberculosis is an infectious disease that mainly affects the lungs but can attack any part of the body. Despite existing with humans for thousands of years, tuberculosis remains the number one killer by a single infectious agent in the world today. It has been estimated that approximately a third of the world's population is latently infected with tuberculosis, meaning they are infected but are not yet experiencing disease.

While there is a vaccine currently in use for tuberculosis, the protection afforded by this vaccine varies and is least effective in the countries with the highest tuberculosis infection rates. While tuberculosis is treatable via administering a cocktail of antibiotics for months on end, the side-effects of this regime often make patients ill.

Exploring treatment pathways

To combat these issues, researchers from the Microbial Pathogenesis and Immunity lab; Kia Farrell, Erica Stewart and Dr Claudio Counoupas (all School of Medical Science, Faculty of Medicine and Health) have been investigating multiple tuberculosis vaccine candidates. Of particular interest is the subunit-vaccine candidate CysVac2 (Advax), which has been shown to be more effective when administered as an inhaled aerosol.

The research team which was led by Professor James Triccas (School of Medical Sciences, Faculty of Medicine and Health) utilised the capabilities at **Sydney Cytometry** to better understand the immune response to this vaccine as it occurs in the lung, and what leads to its enhanced protective effect when inhaled.

> Using the imaging, flow cytometry and mass cytometry facilities of Sydney Cytometry, they were able to study in detail the kinetics of specific cellular uptake by using a fluorescent form of Advax, to determine which cells were creating a stronger immune response in the lungs and lung-draining lymph nodes.

The findings of this study were published in *Mucosal Immunology*. The study was supported by the National Health and Medical Research Council Centre of Research Excellence in Tuberculosis Control and an NHMRC Project Grant.

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