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Homegrown COVID-19 booster vaccine:

Building New Zealand's biomedical capability

Professor Graham Le Gros at the VAANZ launch of the mRNA nanomedicine platform.

A homegrown COVID-19 booster vaccine could protect our population against future waves and variants of COVID-19. But more than that, developing the capability to make our own vaccines is establishing an independent pipeline for Aotearoa New Zealand's future biomedical endeavours.

"We've got some of the greatest scientists in the world. We've some really advanced technology and insight. I believe we have some cutting-edge vaccine candidates that could be of major benefit in minimising COVID-19 and all its variants to come," says Professor Graham Le Gros, who oversees Vaccine Alliance Aotearoa New Zealand – Ohu Kaupare Huakete (VAANZ) as Programme Director.

Established in 2020 as part of the Government's vaccine strategy, at a time when COVID vaccines were yet to be developed, VAANZ has pivoted to address two key concerns in the evolving pandemic – a booster vaccine for variants of concern such as Delta and Omicron and vaccines to protect broadly against future coronaviruses.

VAANZ Science Director Associate Professor James Ussher says VAANZ's most promising candidate is a protein-based vaccine which works in a similar way to many traditional vaccines.

"Dr Davide Comoletti at Victoria University of Wellington has used genetic information from the virus's distinct spikes to replicate and manufacture a spike protein in the lab. He has focused on the part of the spike that's most exposed – the part that physically attaches to the human host cell and that has been shown to be recognised by the immune system.

"By focusing the immune response on the critical part of the spike protein, this vaccine induces a highly effective immune response, including against variants."

> **"...we have some cutting-edge vaccine candidates that could be of major benefit in minimising COVID-19 and all its variants to come."**

The candidate has undergone a range of preclinical trials both here in New Zealand and at the National Institutes of Health in Washington DC. The next stage will involve establishing the safety and appropriate

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From the Director

Like many of you, I look forward to the easing of restrictions and a return to a semblance of normality, but I want to caution that we're not out of the woods quite yet.

We have a long road ahead. Like any virus, the COVID-19 virus evolves as it adapts in response to our eradication efforts. The next stage of this pandemic is anticipating what's next, and making sure we're prepared for whatever this virus – or any other – might throw our way five, ten years from now.

The Malaghan Institute has an important role to play in this future preparedness. Thanks to cutting-edge technologies like mRNA, made possible thanks to our generous supporters, we are well on our way to front-footing this virus and ensuring New Zealand enjoys the best and most effective long-term protection.

Thank you.

Prof Graham Le Gros
CNZM FRSNZ FRCPA (Hon)
Director

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dosage of the vaccine in humans in a small clinical trial, planned for early 2023. If this initial study has positive results, the efficacy of the vaccine in humans would need to be established in a much larger study to investigate if the vaccine helps to invigorate the immune response in those who have previously been vaccinated or infected.

A major technical and scientific challenge to bring this candidate into fruition as a viable vaccine is how we could potentially scale up and manufacture enough doses to cater to New Zealand and the Pacific.

"You can make a medicine in small amounts and it'll work really well. Making large quantities and ensuring the same quality in terms of safety and effectiveness is a totally different ball game. We must implement safety procedures and quality checks at every part of the pipeline," says Prof Le Gros. "Scaling up will take money and time, and we're very grateful for the support we've had from the Government to date and for the donors who are with us every step of the way."

As well as aiming to develop a more effective and durable COVID-19 booster vaccine, VAANZ's focus throughout has been on building New Zealand's capability and platforms for vaccine development to meet the current and future demands of infectious disease threats. This has included building capability for local manufacturing.

"The whole process of researching vaccines, implementing the capacity to conduct human clinical trials and then scaling up for manufacturing is paving the way to establishing a complete biomedical pipeline right here in Aotearoa."

In parallel, VAANZ is in the process of establishing New Zealand's very own mRNA nanomedicine platform – the technology the Pfizer vaccine was built on – paving the way for homegrown vaccines and therapeutics.

"Scaling up will take money and time, and we're very grateful for the support we've had from the Government to date and for the donors who are with us every step of the way."

The mRNA platform is first being put to use on a pilot mRNA COVID-19 vaccine, based on VAANZ's spike protein vaccine candidate, providing a real opportunity to build the know-how and infrastructure for future mRNA vaccine development and GMP production capacity in New Zealand.

"This independence from international pharmaceutical companies will set the stage for national research initiatives that can be driven to address specific health outcomes that are relevant to Aotearoa's unique population," says Prof Le Gros.

"I see setting up these research avenues and biomedical pipelines as part of our responsibility on the VAANZ platform and the contract the Malaghan Institute has undertaken for the New Zealand people."

Clinical study shows strong immune response to Pfizer vaccine across New Zealanders

A clinical study Ka Mātau, Ka Ora (from knowledge comes wellbeing) – the largest evaluation of COVID-19 vaccine immune responses in Māori and Pasifika – has shown near universal strong immune responses in New Zealand vaccine recipients, after two doses.

The study assessed immune responses to the Pfizer-BioNTech vaccine in people with no prior exposure to COVID-19 28 days after second vaccination, evaluating the ability of vaccine-induced immune responses to neutralise viral variants in the New Zealand population.

"Antibody responses overall were robust and consistent with international data, and reassuringly were not related to ethnicity, gender or obesity," says Dr Fran Priddy, the Executive Director of Vaccine Alliance Aotearoa New Zealand – Ohu Kaupare Huaketo (VAANZ).

"These results can give confidence to everyone who has received the Pfizer vaccine and those still undecided about getting vaccinated or boosted that this is an effective vaccine."

Malaghan Institute Clinical Immunologist Dr Maia Brewerton says that while the study showed no difference in the antibody immune response in Māori when compared to non-Māori, the rates of infection and hospitalisation from COVID-19 remain higher amongst Māori and Pasifika.

"This study highlights the importance of driving up vaccination rates and correcting health and social inequities to reduce the burden of disease amongst these groups."

Making friends with enemies: Unexpected solutions to our allergy epidemic

As a postdoctoral researcher, Dr Francesco Vacca is at the forefront of the Malaghan Institute's hookworm programme.

Dr Vacca is trying to identify inflammation-suppressing molecules that human hookworms release and better understand the effect they have on immune cells in the body. His goal is to find new and innovative ways to manage chronic and severe inflammation for those suffering allergic and inflammatory disease.

"Many people have allergic and autoimmune conditions that there is currently no cure for," says Dr Vacca. "I want to provide reliable answers and solutions for these people."

Dr Vacca conducted his PhD at Edinburgh Napier University on mechanisms used by mouse parasites to modulate the immune system. He found an opportunity to translate his findings to help people when he heard about the Malaghan Institute's hookworm clinical programme.

Growing up in a small town on the island of Sardinia, Italy, Dr Vacca had a constant fascination with science, spurred on by his father who was a science teacher at his school.

"My father played a huge role in my decision to be a scientist. We had a large collection of books in the house. Books about astronomy, geology, the human body. Whatever interested me, we'd always have a book on it."

Dr Vacca brings that same curiosity and enthusiasm to this clinical trial as he helps to underpin exactly how hookworms, that for generations we have tried to eliminate from our lives, might just be able to provide the solutions to our modern-day afflictions.

Improving CAR T-cell therapy to target solid tumours

CAR T-cells are changing the game in how we fight previously untreatable blood cancers. However, much still stands in the way of CAR T-cell therapy becoming an effective treatment option for all cancer types, particularly in solid tumours like lung or breast cancer. Researchers at the Malaghan Institute are working hard to improve CAR T-cell therapy, finding innovative solutions to apply CAR T-cell technology to abroader range of cancers.

Dual CAR T-cells

Dr Rachel Perret leads the Malaghan Institute's Freemasons CAR T-cell Research Programme and works alongside Clinical Director Dr Rob Weinkove to improve the CAR T-cells' ability to find and target cancer.

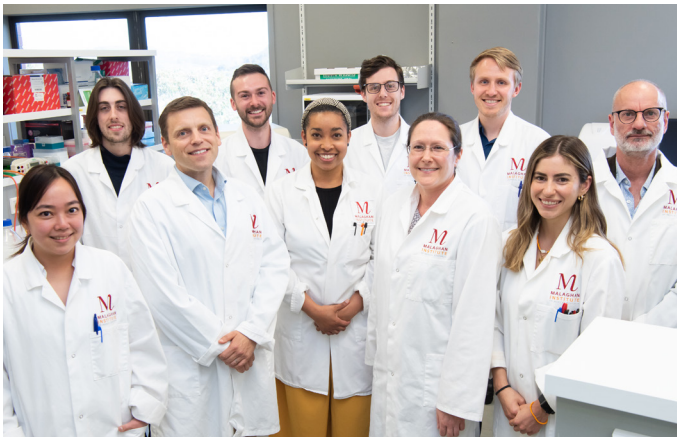
"We're trying to design a dual CAR system where we'll make T-cells that can target two different cancer proteins instead of one," says Dr Perret. "That way, we can guard against cancers losing a single protein and becoming 'invisible' to the immune response."

Current CAR T-cells can only recognise a limited range of proteins – one CAR can only target one cancer protein. Using dual CARs, the resulting CAR T-cells are more likely to respond to morecancer cells within a tumour. The team are currently investigating whether dual CAR T-cells are effective in patients with different forms of blood cancer, with the hope to broaden their work to target solid cancers.

"Solid tumours typically express their proteins 'heterogeneously' – as in not every cell expresses the same target," says Dr Perret. "By applying dual CARs to our CAR T-cells, we increase the chances that the therapy will recognise all the cells in a tumour and so more effectively remove it from the body."

Combination therapies

Unfortunately, even with dual CAR T-cells recognising up to two different proteins on a cancer cell, when it comes to solid tumours, it's unlikely that current CAR T-cells will correctly identify every cell in a tumour as cancerous. This is simply because of how cancer cells in a solid tumour vary in their expression.



The CAR T-cell research team

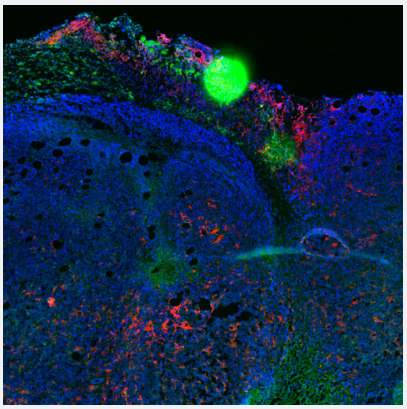
However, rather than relying on CAR T-cells to correctly identify every single variation of a cancer cell in a solid tumour, Professor Ian Hermans' lab is investigating ways to get around this limitation by creating CAR T-cells that work in combination with chemotherapy.

The research involves arming the CAR T-cells with an enzyme that activates a chemotherapeutic drug once it binds to a cancer cell. Once this chemotherapy drug is activated, it destroys the surrounding cells, which hopefully includes the parts of the tumour the CAR T-cells could not target.

The added benefit of this method is that it allows very direct and targeted chemotherapy application without the negative side-effects that chemotherapy injected into the bloodstream can bring.

> **"That way, we can guard against cancers losing a single protein and becoming 'invisible'..."**

Both these research projects represent the wide range of approaches under investigation that may lead to the development of CAR T-cells that are more durable and effective at targeting different types of tumours for destruction.



Interactions between solid tumours and our immune system

Solid tumours are dense clusters of cancer cells dividing uncontrollably. Their density is part of what makes them so difficult to treat, as the tightly-packed cells form a physical barrier that prevents immune cells or chemotherapies from penetrating their depths, leaving tumours weakened, but not eradicated.

Here we can see pink immune cells trying their best to infiltrate the thick fortress of blue tumour cells. The bits the immune cells can't reach will likely survive treatment and grow back.

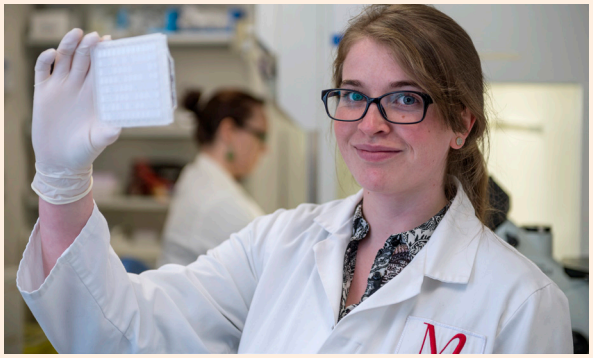
Designing ways to deliver cancer therapies directly to the heart of a tumour is a key area of research for the Hermans Lab at the Malaghan Institute.

New study opens doors for immunotherapies for prostate cancer

Recent research from the Malaghan Institute has uncovered a new way prostate cancer could be targeted by immunotherapies.

The study, funded by the Prostate Cancer Foundation and published in *Frontiers in Immunology*, found that immune cells that can reside in prostate tissue, called MAIT cells, function abnormally and have an abundance of a molecule called PD-1 on their surface. When these MAIT cells were activated using a vitamin B variant and the PD-1 molecule was blocked, it resulted in anti-tumour activity that destroyed the cancer cells. This research was conducted by Dr Ellie-May Jarvis as part of her PhD with the Malaghan Institute.

"Immunotherapies that effectively treat prostate cancer are not yet a standard of care. This dual strategy of activating MAIT cells and blocking PD-1 could offer a potential way of treating malignancies including prostate cancer," says Dr Robert Weinkove, Clinical Director at the Malaghan Institute, who supervised the research.



Prostate cancer is one of the most prevalent cancers that affect men. Current treatments for prostate cancer can have a severe effect on the patient's quality of life.

"MAIT cells could be a good target for immunotherapies because, unlike other types of T-cells, they can all be activated by the same molecule, a specific vitamin B variant. This is significant as we don't have to engineer very specific T-cells for each patient," says Dr Weinkove.

"More work needs to be done to understand if it can be applied in clinical trials, but it's a promising starting point."

Inaugural Te Urungi fellowship awarded to Dr Theresa Pankhurst

A new fellowship to strengthen relationships between the Malaghan Institute and Māori communities and ultimately improve health outcomes for Māori has been awarded to postdoctoral researcher Dr Theresa Pankhurst (Ngāi Tahu, Ngāti Kahungunu, Ngāti Porou) who says it blends two of her biggest passions: immunology and Te Ao Māori.

Te Urungi Fellowship has been established by the Malaghan Institute's Māori advisory group, Te Urungi. The fellowship is a three-year programme which Dr Pankhurst will spend at the Malaghan and on secondment to the Babraham Institute at the University of Cambridge.

"Ultimately I want to learn skills and build a research portfolio that I can bring back to Aotearoa and use in the future to conduct research that aims to address Māori health inequities."

A huge thank you!

From all of us at the Malaghan Institute, thank you for your support during our recent annual appeal. Together, we raised more than $240,000 to support better, gentler, more accessible treatments for diseases that affect all our lives.

As a charity, our life changing research can't happen without our supporters. THANK YOU!

Fundraise for the Malaghan Institute

Are you interested in fundraising for the Malaghan? We all want to find better treatments and cures for disease, and you can help! Jump online to donate.malaghan.org.nz/raise-for-research and you will find everything you need to set up and run a fundraiser to support life-changing research. From fitness challenges to bake sales – you can help us get that much closer to breakthrough treatments for disease. Happy fundraising!

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We are committed to taking our research into the community to provide treatment options for all.

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People we love are suffering and dying from diseases we don't know enough about. But we do know the immune system holds the key to prevention, treatment and cures. With your support we can gain a deeper understanding of how our immune system works to help us create better, lower cost treatments for New Zealanders in need.

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