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Lung cancer collaboration tackling health inequities

A collaboration between the University of Auckland's Auckland Cancer Society Research Centre (ACSRC) and the Malaghan Institute aims to address Aotearoa's leading cause of cancer death by improving immunotherapies that target lung cancer.

More than 1000 Kiwis die from lung cancer each year according to Lung Foundation NZ Tupapa Pūkahukahu, with survival rates well below international norms. Māori are 3.5 times more likely to die from the disease than non-Māori.

Funded by the Health Research Council of New Zealand and the Maurice Wilkins Centre for Molecular Biodiscovery, the collaboration aims to create new immunotherapeutic tools or stimulants that boost the effectiveness of existing anti-cancer immunotherapies, improving overall patient response rates to this disease.

"Lung cancer has a large inequity in health outcomes for Māori," says ACSRC Associate Professor Adam Patterson, who is leading the research. "Although immunotherapies like immune checkpoint inhibitors are on their way, experience from overseas indicates only about 10-30% of patients respond, so there is significant room for improvement."

"We're developing novel adjuvants or immune stimulating agents that would potentially make lung tumours more responsive to immunotherapies like checkpoint inhibitors," says ACSRC lead medicinal chemist Associate Professor Jeff Smaill. "Studies to confirm this are being undertaken at the Malaghan Institute, with the aim of identifying a lead candidate to move forward into clinical trials in the near future."

▲ Dr Regan Fu, left, with Professor Ian Hermans. Dr Fu will be screening different hypoxia-activated immunostimulants to determine potential candidates for clinical trial.

From the Director

As winter illnesses continue to bite, I'm aware that for many we are simply exhausted from hearing about the pandemic and its rise and fall as it sweeps across the country.

While I agree that we have had enough COVID-19 news to last a lifetime, it is important to acknowledge, not just for our own sakes, but for the health of our loved ones, that we still have a way to go to truly 'move on' from this disease. And the only way we can achieve this is through better vaccines.

It will take years before we as a society build up enough immunity to where Sars-CoV-2 is no longer a global threat, and the quickest and most effective way to do this is to develop vaccines that not only target the latest variant, but offer wide and long-term protection, something the original vaccines don't.

I want to assure you that we are continuing to do all we can to make New Zealand's own pan-COVID vaccine that will cover the different variants and provide long-lasting protection. This will take some time yet, but I am confident that with your support it is something we can absolutely achieve together.

Regards,

Professor Graham Le Gros | Director
CNZM FRSNZ FRCPA (Hon)

The Malaghan Institute's Professor Ian Hermans says the aim is to make the site of the tumour more immune-responsive. "There are immune cells in and around tumours, but their activity is suppressed which makes them unable to effectively respond to therapy, or to recruit other immune cells to the site.

However, because of their physical structure, solid tumours share properties that can be exploited by researchers to develop ways to help a patient's immune cells overcome this therapeutic barrier. Hypoxia, or a lack of oxygen, is one such property – a condition brought about partly as a result of the tumour's dense, rapid growth.

For decades, researchers at the ACSRC have been perfecting the design of 'hypoxia-activated' drugs that are selectively activated in tumours where oxygen levels are low. This concept is now being applied to an immune-stimulating drug which, when activated in the tumour, will act like an adrenaline shot to nearby immune cells, significantly boosting their activity.

Through this targeting mechanism, the stimulant is only biologically-active in the tumour, and is inactive in healthy tissues which are typically well-oxygenated – ensuring the immunotherapy gets to where it's most needed. This has the added benefit of lowering any potential related toxicities to healthy tissues making the treatment safer for patients, with fewer side-effects.

"Through our collaborative efforts we have designed a number of promising candidates that target hypoxic regions," says Prof Hermans. "This grant will help evaluate these different candidates so that we can optimise the design to get the best targeting in combination with checkpoint inhibitors. We'll also be studying the exact mechanisms behind this hypoxia-activated immunostimulant, to make sure it's targeting the immune cells in the ways we anticipate and that we more fully understand any potential side-effects or toxicities that may arise."

Assoc Prof Patterson says any New Zealand clinical trial of the lead candidate would focus on strategies to achieve active recruitment and support of Māori participants. But he cautions that it will still be some time before any clinical trials start.

"By the end of the grant we expect to have identified, validated and patent-protected a lead candidate for clinical evaluation," he says. "If that's successful, we'd be looking to move forward into human studies, but this can be influenced by many factors along the way and could take several years yet."

Breast cancer research shows promise for future vaccine development

A unique vaccine targeting specific breast cancer antigens has been shown to delay tumour growth and prevent breast cancer metastasis in preclinical models.

In collaboration with the Ferrier Research Institute, the Malaghan Institute has been working on developing stimulatory molecules that act as 'vaccine adjuvants'. An adjuvant works alongside a vaccine targeting specific breast cancer markers (antigens) to boost the immune system's natural response to the cancer, helping it kill all affected cells, not just at the main tumour site, but elsewhere in the body too.

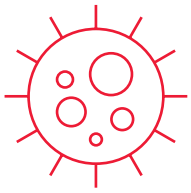
"We investigated our vaccines in models of both HER2-positive breast cancer and triple negative breast cancer," says Postdoctoral Fellow Dr Olivia Burn. "We're particularly interested in triple negative breast cancer because it can present as a more aggressive kind of breast cancer and currently has very limited treatment options.

"First-we combined segments of the HER2 protein with our immuno-stimulatory compound – a glycolipid which activates a particular immune cell population – to enhance the immune response against HER2. A single dose of this treatment delayed tumour growth and prevented its growth in the lung. Then, in a model of triple-negative breast cancer we used a different vaccine that targeted parts of the protein NY-ESO-1, which is often over expressed in these cancers, particularly when it has spread to other organs and found similarly encouraging anti-tumour results."

Dr Burn says that while breast cancer is very treatable, the principal cause of breast cancer mortality is not the initial tumour itself, but its spread to other parts of the body. "Preventing this spread, or metastasis, is key to reducing the number of people who die from this disease.

"Future steps could include progressing this vaccine design,possibly using RNA technology, where the whole protein for HER2 and NY-ESO-1 could be used as a vaccine target, which would provide greater population coverage," says Dr Burn. "RNA technology could also make it easier to investigate other relevant breast cancer markers and help us assess if metastasis to other organs, such as the liver, can be prevented."

▼ Dr Olivia Burn



Breast cancer is one of the most common forms of cancer. Around 1 in 9 Kiwi women are affected by breast cancer in their lifetime, according to the Breast Cancer Foundation, and while the survival rate is high thanks to early detection measures such as screening, more than 650 women in New Zealand die from breast cancer every year.

PRENATAL ANTIBIOTIC USE LINKED TO CHILDHOOD ALLERGIC DISEASE

A review of data from various clinical studies has found that children born to mothers who take antibiotics during pregnancy are at higher risk of developing asthma and other inflammatory or allergic diseases.

The findings, published in *Allergy*, highlight the need to better understand what's behind this relationship, and the importance of responsible antibiotic stewardship throughout the prenatal period.

"A meta-analysis is an analysis of analyses," says Postdoctoral Fellow Dr Alissa Cait, who led the study. "We synthesised results from 11 prospective and 16 retrospective studies to determine a statistically significant increased likelihood of children developing wheeze, asthma, dermatitis, allergic rhinitis and food allergy if antibiotics were used during pregnancy.

"Importantly, the findings were consistent if antibiotics were prescribed during any trimester, and true of all antibiotic classes except cephalosporins."

While significant, Dr Cait cautions the findings are limited in their scope and warrant deeper investigation.

"We found that the studies looking at this topic weren't necessarily representative of the wider population, so were difficult to estimate the true effect of these antibiotics. So far all we can see is an interesting correlation – not necessarily causation. They also don't give us any information on the biological mechanisms behind this relationship. What it does emphasise is the need for in-depth studies in this space."

"A big part of this is really getting to the bottom of questions like what part of antibiotic use is leading to increased risk of allergic disease? Maybe by understanding the mechanisms behind it we can find interventions and ways to mitigate the increased risk not just during pregnancy, but in other instances, too."

▲ Dr Alissa Cait

"A big part of this is really getting to the bottom of questions like what part of antibiotic use is leading to increased risk of allergic disease?"

Emerging Researcher Grant to understand how infections shape a developing immune system

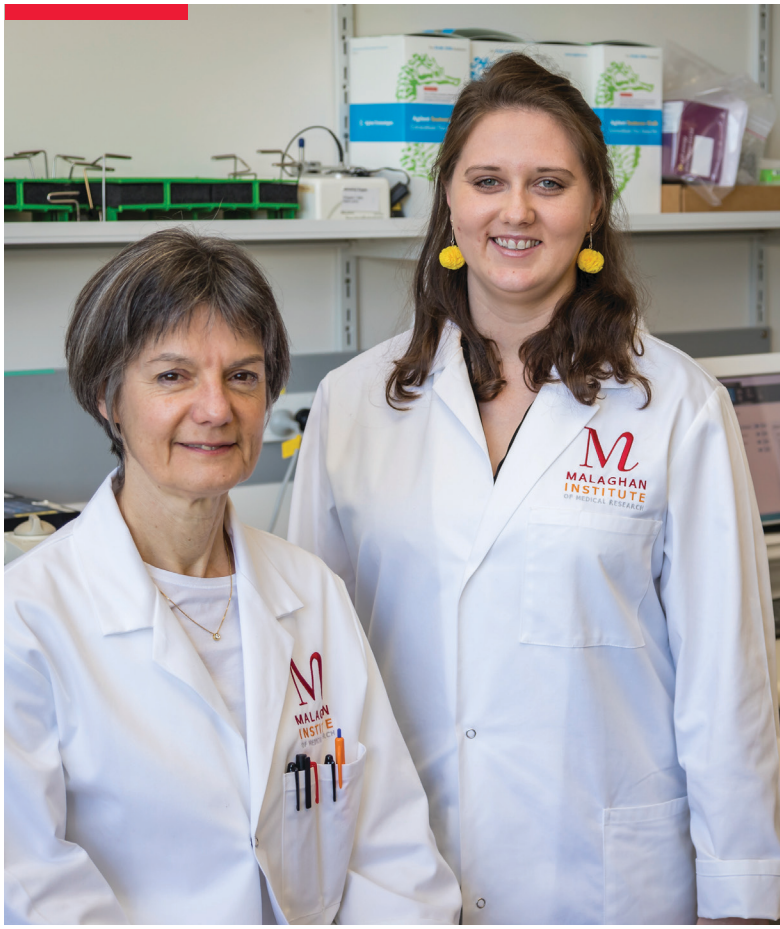
Dr Kerry Hilligan has been awarded a prestigious Health Research Council Emerging Researcher Grant worth $250,000 over three year, to establish a research platform understanding how early infections or challenges to a developing immune system shape and influence it later in life.

"I hope that my research will assist in identifying processes that are associated with protective immune responses," says Dr Hilligan. "The aim is to then incorporate targeting of these pathways in the development of vaccines and other preventative measures."

"With the immune system – like pretty much everything – practice and learning is key."

How our immune system faces new infectious challenges is shaped by the threats it has faced before. This relatively new area of research aims to shed light not just on how the immune system fights infections, but also how it learns or distinguishes between 'good' and 'bad' immune responses. Distinguishing between these responses becomes important, as 'bad' or unwanted immune responses can give rise to conditions such as allergic or autoimmune diseases.

"With the immune system – like pretty much everything – practice and learning is key," says Dr Hilligan. "An immune system that develops in the absence of all germs does not work well at all, so we know that exposure to different types of bugs is important to teach the immune system how to function effectively. Exactly what lessons all these different bugs teach the immune system is not clear – this is what I am investigating."



▲ Dr Kerry Hilligan (right) with Professor Franca Ronchese

"Exposure to different types of bugs is important to teach the immune system how to function effectively."

WITH A LITTLE HELP FROM OUR FRIENDS

From running charity fundraisers in their local communities to advocating for the Malaghan Institute across their own professional and personal networks, our Friends are a vital part of the Malaghan team. Jane Paterson is Chair of the Wellington Friends and has a connection with the Institute that goes back many years.

"My mother introduced me to the Malaghan Institute and when she died in 1988 she asked for donations to go to the Institute instead of flowers. So I have known about their work for a long time. When my late husband, Ian Paterson, became a member of the Trust Board, I wanted to have more involvement myself so joined the Friends in about 2017," says Jane.

While COVID-19 has impacted their ability to get out in the local community, over the years the Wellington Friends have raised funds for the Institute through events such as fashion parades, cocktails parties and charity golf days.

"Each member contributes different skills but together we have the shared desire to ensure the scientists at the Institute are able to continue their fabulous research without distraction."

Jane says she is in awe of the work of the scientists at the Malaghan who together with the talented support team, do amazing work to fight disease throughout the world.

"The fact that it is a completely independent research organisation is also important."

Alongside volunteering for the Malaghan Institute, Jane has a long history of community service.

"I am a member of the Port Nicholson Rotary Club and the Rotary motto of Service above Self resonates strongly with me. I have always been involved supporting organisations such as school committees, coaching sports teams, or raising funds for charities like Mary Potter Hospice. Giving back to the community is part of my DNA and something I have instilled in my own family."

JANE PATERSON
Chair of the Wellington Friends

Friends of the Malaghan Institute are currently active in Hawke's Bay, Taupō, Bay of Plenty and Wellington. If you would like to get involved contact our fundraising team on 04 499 6914 or fundraise@malaghan.org.nz

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