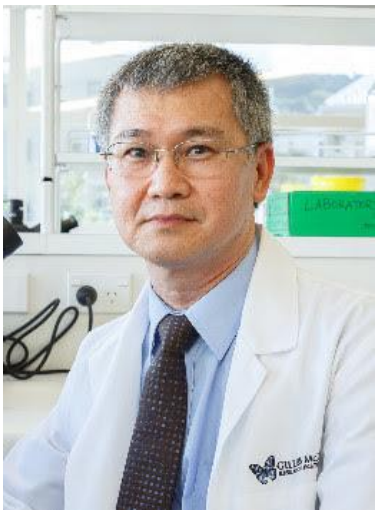
Newsletter Issue#24, May 2021

GILLIES McINDOE
RESEARCH INSTITUTE
Pioneering future treatment of cancer

Cause for celebration



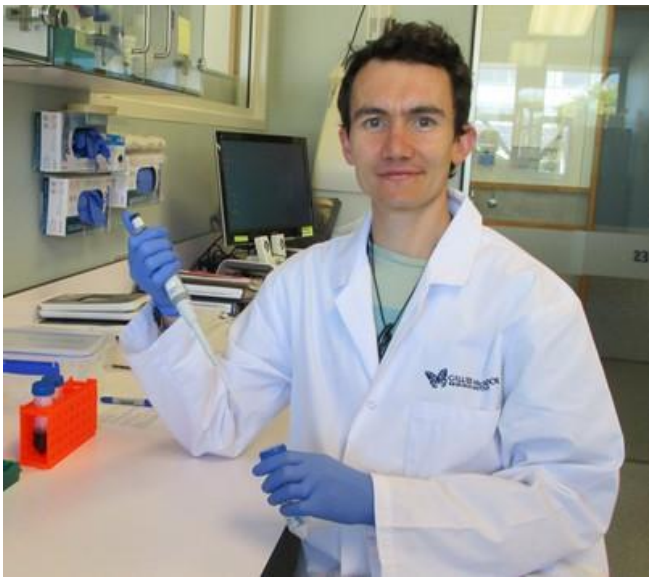
This newsletter marks some of our team's key milestones. We're pleased to share with you the encouraging results of our glioblastoma Phase I clinical trial. We congratulate Matt Munro on receiving his PhD, and we look forward to Dr Sam Siljee embarking on his PhD study. Thanks to our valued supporters and helpers, we've been able to share more of our research with the wider community. We hope to see many more of you at future events this year.

As pleased as we are to share these developments with you, a shadow hangs over our work. We can't start Phase II of our glioblastoma clinical trial, which will treat more patients, without significantly more funding. As always, we thank everyone who has helped us on our journey so far. We've covered more distance in a short time than we thought was possible. We look forward to what the future brings!

Dr Swee Tan ONZM, MBBS FRACS PhD

Executive Director

Congratulations Matt Munro on finishing your PhD!



GMRI PhD student Matt Munro has recently completed his PhD at Victoria University of Wellington, and we welcome him back to the team as a post-doctoral research fellow.

We warmly congratulate team member Matt Munro on completing his PhD study. Matt began with the GMRI as a research assistant in 2016. In 2017, he began his PhD study working alongside our research team. Matt will continue with us as a post-doctoral research fellow. His next project investigates a possible cause of colon cancer, under the supervision of our Chief Scientist Dr Sean Hall.

Pushing the boundaries of PhD research

Matt's PhD thesis investigated the role of cancer stem cells and the renin-angiotensin system in colon cancer. His thesis is titled *Characterisation of Cancer Stem Cells and the Renin-angiotensin System in Colon Adenocarcinoma.*

The examiners of Matt's thesis commented that 'the scope of the thesis pushed the boundaries of a PhD thesis', and that his work 'represents a substantial, original and outstanding contribution to the field.'

Matt's findings suggest colon cancer may respond to our treatment

Matt found that components of the renin-angiotensin system are present on colon cancer stem cells. He tested medications that block the renin-angiotensin system on cells grown from colon cancers. His results showed that these medications caused a reduction in both cancer stem cell markers and cancer cell metabolism.

These oral medications included beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. All of these off-patent, low-cost medications are commonly used for treating high blood pressure.

Where you can read the results of Matt's research

Matt has published his research papers arising from his PhD work in international journals, two of them in PLoS ONE. He is currently preparing two other papers for publication. The published papers are:

- Cancer stem cell subpopulations in primary colon adenocarcinoma

- Colon adenocarcinoma-derived cells that express induced-pluripotent stem cell markers possess stem cell function
- Cancer stem cells in colorectal cancer: a review

Come and hear Matt's PhD findings

Matt will present his findings at The Wellington Club in June (details below). Our 2020/2021 summer students will also present the results from their research.

When: 4.30pm 21 June
Where: The Wellington Club

Please contact Cindy Naresh (details below) if you would like to join us.

Email: ea@gmri.org.nz
Phone: 04 282 0366

Matt's next research project investigates the cause of colon cancer

Matt's next project will investigate the role of gut bacteria and the ATF6 gene in the development of colon cancer. Through this research, he hopes to find out more about whether *bacteroides fragilis* (a common gut bacteria) causes cancer-related DNA mutations in normal colon cells. He'll also investigate whether the ATF6 gene is involved in this process. To test this, Matt will replicate part of a human colon using a human organoid system — a microscopic human colon that he'll develop in the GMRI laboratory.

Certain bacteria may play a part in causing colon cancer, such as *bacteroides fragilis*. These bacteria produce toxins that are thought to be carcinogenic and can degrade the protective mucus layer in the gut. They can outcompete good bacteria, and this change is thought to be partly due to diet.

The ATF6 gene helps cells respond to stress caused by improperly formed (misfolded) proteins. However, this gene also increases inflammation. Overactive ATF6 and inflammation have both been associated with colon cancer, although AFT6-associated cancer seems to depend on harmful bacteria being present.

Many thanks to everyone who supported Matt in his projects!

All of us at the GMRI, including Matt, are very grateful for the generous support we've had for his projects. Matt received a three-year scholarship from New Zealand Community Trust and generous support from The Lloyd Morrison Trust.

Matt acknowledges and thanks his supervisors for their support: Dr Lifeng Peng from Victoria University of Wellington, Dr Swee Tan from the GMRI, and Dr Susrutha Wickremesekera from the Wellington Regional Hospital. Matt also thanks the patients who donated their tissue samples to the GMRI tissue bank.

Fundraising for the future

Our Chief Scientist Dr Sean Hall talked about his work developing human organoids at a recent morning tea at Seatoun Bowling Club in Wellington.

While our researchers busily work behind closed doors, we're fortunate to have dedicated helpers organising events where we share our research with the wider community. One such occasion was a morning tea at the Seatoun Bowling Club in February.

The event helped us raise $18,800, thanks to generous donations from local businesses and a number of people. The money will go towards our research programme and clinical trial. We'll hold similar events in May and June.

At the event, our Chief Scientist Dr Sean Hall talked about his work developing human organoids, to better understand and treat cancer, vascular birthmarks, and fibrotic conditions. Human organoids are microscopic organs grown from human cells.

The second presentation was given by our Executive Director Dr Swee Tan. Swee gave an update on the encouraging results from our Phase I clinical trial on glioblastoma, a severe type of brain cancer.

We have many people to thank for this event: Carol Law and her enthusiastic team for their organisational and catering skills, the Seatoun Bowling Club for hosting us, our MC John Ashby for his usual charm, Kevin Newson for his ongoing support, and of course the donors who were present. We also sincerely thank those who donated the prizes for our auction.

We'd love to see you at our event in June

In June, our 2020/21 summer students will present findings from their projects. This summer's students were Min Xin Lee, Lachlan Parlane, and Jason Su. Once again, we thank the Deane Endowment Trust for supporting our summer student programme. Matt Munro will also present findings of his PhD study at the event.

When: 4.30pm 21 June
Where: The Wellington Club

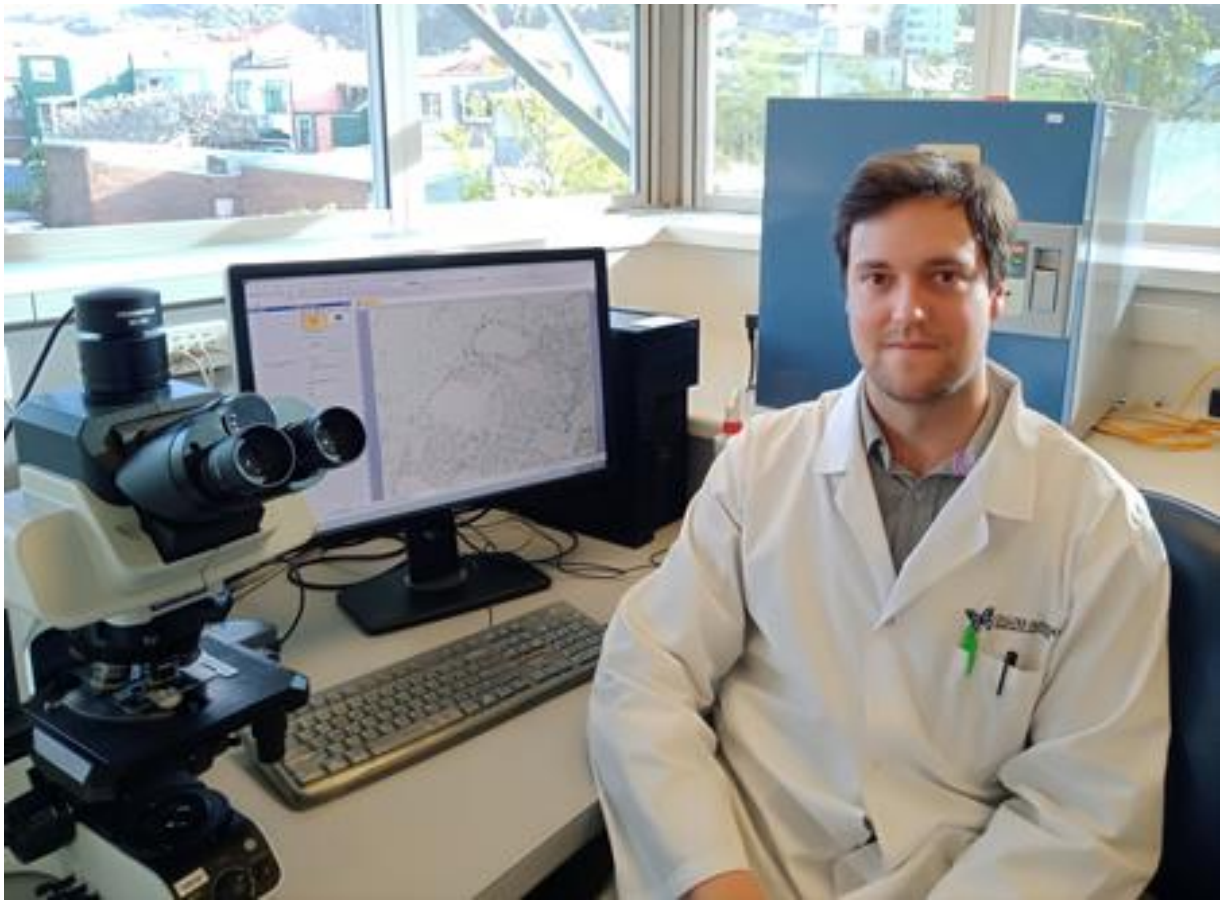
To register for this event please contact Cindy Naresh.

Email: ea@gmri.org.nz
Phone: 04 282 0366

Our thanks to everyone who makes these events a success

From our team of organisers to our other supporters and donors — thank you for your ongoing involvement and support. Our achievements are only possible with your help!

PhD research at two world-class facilities



Dr Sam Siljee first came to the GMRI as a summer student. He'll now start his PhD study investigating early changes in lung cancer.

In October last year, we ran an article about former summer student Dr Sam Siljee investigating a new low-cost treatment for keloid disorder. Sam was recently awarded a PhD scholarship by Victoria University of Wellington (VUW) for his PhD research, which will be carried out at the GMRI and VUW.

Sam will investigate early changes in lung cancer using an emerging research method known as human organoids. Organoids are three-dimensional structures made from human cells that mimic the organs from which they originate. Research with organoids is becoming an increasingly important part of medical enquiry, and is now recognised as the gold-standard research method.

Using organoids to advance our research

Although not the most common cancer, lung cancer is the biggest cause of cancer deaths in New Zealand, with Māori and Pasifika having the worst outcomes. Although the sustained anti-smoking campaigns and other policies have reduced lung cancer caused by smoking, a large proportion of lung cancers are not smoking-related, especially in women.

Sam says organoids will allow him to observe early changes in lung cancer over time. This observation reveals stronger results than previous research techniques — static snapshots from formalin-fixed pieces of tissue and two-dimensional cell culture systems.

Organoids research places the GMRI at the forefront of scientific inquiry along with the international science community. We can get closer to observing disease processes happening in real time, and make findings that more accurately translate into improvements in health.

Traditionally in research, basic biology and early discovery of new treatments cannot use humans as testing systems.

'Various other research models, such as testing on animals, have their advantages and disadvantages, but animals are fundamentally different to humans,' Sam says.

'The beauty of organoids is that they're relatively complex structures consisting of different cell types. They're three-dimensional, much more like the organs they represent, and mimic pathologies that researchers are studying.

'Organoids are also very interesting in how they form themselves from a mix of cell types, or stem cells, when provided with the right environmental cues. This is just like in the developing human body.'

Sam will create organoids at the GMRI for his research

Sam will create two different types of organoids at the GMRI for his research — one that is submerged in cell culture media, the other on a membrane surface. Both organoids will have different types of functioning cells to mimic the system that keeps human lungs clean. These cells include those that secrete mucus and those that have beating hairs to sweep mucus along.

'Strictly speaking, these are organoids of the airways (breathing tubes), rather than of the lungs themselves,' Sam says.

Collaboration between two world-class research facilities

Sam will divide his research time between the GMRI and VUW's world-class proteomics facilities at the School of Biological Sciences. This capability will allow Sam to study individual proteins and subtle changes to the structure of proteins, which is very important in the context of diseases. Sam's supervisor at VUW, Dr Lifeng Peng, is a world expert in this area.

Sam says he feels incredibly fortunate to be working at both research facilities.

'This opportunity gives me unrivalled access to dedicated cell culture facilities, state-of-the art automated immunohistochemical staining systems, and fluorescent microscopy using the sophisticated confocal microscope at the GMRI. It also gives me access to state-of-the art mass spectrometry and many other facilities at VUW,' he says.

'I'm lucky to have as my supervisors both Chief Scientist Dr Sean Hall and Dr Swee Tan at the GMRI, and Dr Lifeng Peng at VUW. I see this project very much as a collaboration between the GMRI and VUW.'

Explaining a few complex terms

To help understand some of the more complex terms related to Sam's research, he's provided some explanations.

Cell culture: The process in which we keep cells and organoids alive in highly controlled environments. Most of us take for granted what our bodies normally do to control the environment for our cells. With cell cultures, we monitor and control variables like temperature, humidity, carbon dioxide, acidity and nutrients as the cells are growing. We manipulate cells in special cabinets where we ensure the cells do not escape the lab and prevent inadvertent introduction of infections or foreign cells. We grow them in specialised incubators that have controlled temperature, moisture, and gases such as oxygen and carbon dioxide.

Staining: Most cells and tissues are naturally transparent, so we need to stain them with certain markers so that we can see them under the microscope. At the GMRI, we use specialised stains with antibodies that identify particular proteins of interest. The antibodies we use work like the molecules used by the immune system to target specific bacteria and other invading organisms. The state-of-the art automated staining system at the GMRI gives more reliable and consistent results and is more efficient, especially with higher sample volumes.

Fluorescent microscopy: The GMRI's sophisticated confocal microscope is a specialised form of microscopy using lasers rather than a conventional light source. This process gives higher resolution (and therefore detail). Even more importantly, it allows us to investigate multiple markers simultaneously on the same slide — we're able to label each marker with a different fluorescent colour, and separate out the colours for analysis.

Mass spectrometry: A complex and advanced technique where molecules are sorted by precise weight and charge. The world-class mass spectrometry system at VUW allows individual proteins to be detected and identified in a mixed sample. The real strength of this approach is that it allows researchers to take an unbiased observation of a complex biological sample — they can look at all the proteins present, rather than focusing only on a few markers that a scientist may choose to investigate.

Read about Sam's first time as a summer student in 2015

Read about Sam's investigations into a novel low-cost treatment for keloid disorder

The Phase I results are in for our glioblastoma clinical trial

It all stacks up — results from our Phase I clinical trial suggest our treatment could improve outcomes for patients with glioblastoma.

Results of our Phase I clinical trial on glioblastoma, a severe brain cancer, show that the our treatment is safe with minimal side effects, preserves patients' quality of life, and could extend life expectancy. We're seeking more funding to start our glioblastoma Phase II clinical trial, where we plan to treat more patients at an earlier stage in their illness.

Our treatment is safe and preserves patients' quality of life

Glioblastoma is a deadly form of brain cancer. The cancer and its conventional treatment can severely impact patients' quality of life. Our Phase I clinical trial shows that our treatment is safe with minimal side effects, and preserves patients' quality of life during treatment. Our treatment consisted of a combination of low-cost common medications that can be taken orally at home.

Read more about how our proposed method of treatment works

Our Phase I clinical trial enrolled patients with recurrent glioblastoma who had exhausted conventional treatment options. In our proposed Phase II clinical trial we'll recruit 75 patients, and start treatment at an earlier stage of the cancer.

Our treatment may increase life expectancy of patients with glioblastoma

Analysis of results of our glioblastoma Phase I clinical trial shows that it may improve life expectancy of the patients.

The overall median survival of patients with glioblastoma is 14.6 months following conventional treatment. Our Phase I clinical trial shows a median survival time of 20 months. These results are encouraging and the Independent Data Monitoring Board has recommended a Phase II clinical trial, to allow further assessment of outcomes.

Who will be recruited for our Phase II clinical trial

We'll recruit 75 patients including Māori, Pasifika, and other disadvantaged minority communities, for the study.

We need more funding before we can start

We're actively seeking funding from existing and prospective new supporters and funding bodies so we can begin our Phase II clinical trial. The funding we need is beyond our present resources and the support we've had from our generous donors over the years.

We're very thankful for the wonderful support we've received along the way. We're excited to see the results the Phase II glioblastoma clinical trial brings!

How to donate

We're always looking for philanthropic, business, and other donations so we can continue our important work. You can make one-off or regular donations, or you could consider making us a beneficiary of your estate or family trust.

Transforming lives with your generous support

We're seeking to start our glioblastoma Phase II clinical trial. But we need more support than ever to get there.

As we prepare to commence our Phase II clinical trial for glioblastoma, a severe brain cancer, we need more support than ever. We've made it this far because of the generous support of many people. We're grateful to every one of you, whether you've helped us as a donor, a patient, an attendee at one of our public events, or as a helpful hand behind the scenes.

Our donors are a vital part of our team

A significant amount of funding for our research comes through donations from people like you. We're also supported by businesses (our corporate champions), a range of philanthropic trusts and organisations, and through grants from charities and other bodies. While the funds we've received so far have made a huge difference to our progress, we'll need even more support for our glioblastoma Phase II clinical trial.

The individuals, families, and others who donate to our research are a very special part of the GMRI. We value our relationships with our donors immensely.

Reaching above and beyond for significant support

The funding we need for our glioblastoma Phase II clinical trial is beyond our current resources and the capacity of our regular support base. But between us and with support from other people and funding bodies, we are hopeful we can achieve a significant lift in support. And once we do, we'll start the Phase II clinical trial, subject to necessary approvals.

Where we'll spend the funding we receive

Subject to funding being available, we have big plans for our glioblastoma Phase II clinical trial and associated research. In our glioblastoma Phase I trial we treated patients at the end-stage of their illness, when all conventional treatment options had been exhausted. For the Phase II clinical trial, we plan to test our treatment on a larger number of patients with glioblastoma.

In Phase I of our trial we recruited 18 patients who had exhausted conventional treatment options. For Phase II, we'll need to recruit 75 patients to achieve statistical significance.

How you make a difference

By donating, you're making a difference that's potentially transformational to the lives of people suffering from cancer now and into the future. Through our research, we're aiming to create a treatment that's effective, less intrusive, more affordable, and can be delivered closer to home.

We are deeply grateful for all donations in support of our research and cancer treatment, whether they're small or large, regular or one-off, anonymous or recognised. All are vital and valuable to our mission.