Australian Institute for Bioengineering and
Nanotechnology, and Queensland Brain Institute
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# Scott Sullivan Fellowship Final Report
# Dr Shyuan Ngo

# Overview

*The Scott Sullivan Research Fellowship in motor neuron disease (MND) will accelerate research output and co-ordinate preclinical trials for promising new therapies. The Fellow will act as a bridge collaborating between the clinic at the Royal Brisbane and Women's Hospital (RBWH) and the Queensland Brain Institute researchers. The Fellow will help with banking and databasing of blood/cells/tissue/RNA and conduct research directed at finding a treatment for MND.*

Scott Sullivan

# A personal word from the Scott Sullivan MND Research Fellow

As I look back over the past five years and prepare my final report as the Scott Sullivan MND Research Fellow (2015-2020), I can honestly say that I am filled with so many emotions. It has been a very challenging but equally memorable time; I think it will come as no surprise to you when I say that there have been many ups and equally a number of downs throughout this time.

I am humbled to have been given the opportunity to serve the MND community in this role for the last five years. I have the greatest pride in what I, and the larger team, have achieved. I feel very fortunate to have been able to establish strong and lasting relationships with people impacted by MND, the MND Foundations and Organisations, and the clinicians and researchers who are all in this fight together. I am overcome with sadness, knowing that there are many incredibly amazing people who have gone before us. Yet with this sadness, comes a feeling of humility and hope, because I know that the altruism and commitment of people impacted by MND to help each other, and to contribute to the greater good and a better future is what will lead to the cure.

When I took up this role in 2015, I knew that the Scott Sullivan MND Research Fellowship, born in memory of "Sully", was created to bring to fruition, a vision that he, and many others who live with the impact of MND have – a world free from MND. As I take you through the last five years of our research, I hope you will see that, collectively, we are heading in the right direction.

In March, my role as the Scott Sullivan MND Research Fellow will come to an end. I wouldn't be telling the truth if I said that it will be easy to step down. But with the turn of the Fellow, there will be new ideas. Exciting research. More breakthroughs. I pass on this honour of being the Scott Sullivan Fellow, and am very much looking forward to seeing what the new Fellow will establish and achieve.

Before I go, I want to give my thanks to everyone who has contributed to where I am today. My family, friends, colleagues, and mentors. I want to thank the MND community, near and far, for believing in, contributing to, and for supporting our research. I am so thankful to all past and present members of the Ngo laboratory for their hard work, long hours and perseverance – I hope you know that everything you have done is making a difference. Thanks must go to the MND and Me Foundation, the Royal Brisbane & Women's Hospital Foundation and the University of Queensland's Queensland Brain Institute (QBI), Australian Institute for Bioengineering and Nanotechnology (AIBN), and School of Biomedical Sciences (SBMS) who have, throughout the years of transition, pulled out all stops to make this Fellowship the success it is. I want to thank Scott for who he was (is!) and everything he stood for. To Sarah Sullivan, I thank you for believing in me to carry out this research in Scott's memory. My thanks to Paul Olds for always being a cool cucumber and for being supportive of all that we have done. A heartfelt thanks to Dr Robert Henderson and Prof Pamela McCombe for always being big fans of the work that has been developed through this Fellowship, and for sharing their knowledge of the clinical aspects of MND. A special thanks to Prof Naomi Wray who is undoubtedly the best mentor! And of course, the biggest thanks to Derik, my partner, who many of you know, for just being downright awesome.

While this is a goodbye from me with respect to the Scott Sullivan MND Research Fellowship, it is not the last that you will see of me. At the beginning of April, I will transition into my next role as a FightMND Mid-Career Research Fellow, and I will continue my commitment to MND research and the MND community.

Dr Shyuan Ngo

# Research Update

## There is no I in team.

The Scott Sullivan MND Research Fellowship, though awarded to one individual, supports something that is much bigger than the singular. It has supported me in driving the continuation, expansion, and the growing success of a unique research program in MND that is core to the Ngo laboratory. The research program, which focuses broadly on energy balance in MND, initially started in the laboratory in 2012 where we used mouse models to study the disease, before expanding in 2015 to include natural history studies in people living with MND. In 2017, the program was expanded yet again, to incorporate the use of human-derived cells to model disease in a dish. The marrying of the use of mouse and human-derived models of disease with research involving people living with MND is integral to our goal of translating research findings into clinical trials for MND. This multi-faceted approach has also been the foundation upon which we have now established ourselves, and Australia, as world-leaders in this area of MND research.

The research that we have undertaken over the last five years has seen the emergence of strong collaborations that span Australia, France, Netherlands, United Kingdom, United States of America, Colombia, and China. These collaborations have also been key to a research program that is supported through the value-adding of knowledge that can only be achieved through trans-disciplinary research; research that combines the fields of neuroscience, neurology, physiology, biochemistry, metabolism and endocrinology, cell and molecular biology, stem cell biology, genomics, statistics, and proteomics.

Our research has been supported by state-of-the-art infrastructure at The University of Queensland and The Royal Brisbane & Women's Hospital, and unmatched personnel support from these two Institutions, as well as The Wesley Hospital, the MND and Me Foundation, and MND Australia.

Funding-wise, we have been fortunate enough to have had successes with funding applications that were sent to the National Health and Medical Research Council, FightMND, the MND Research Institute of Australia, Wesley Medical Research, the Royal Brisbane & Women's Hospital Foundation, and The University of Queensland.

## Motor Neuron Disease (MND) – one diagnosis, many faces.

MND is a progressive neurodegenerative disease that, unfortunately, causes death usually within 3-5 years from diagnosis. Although it is characterised by the death of neurons in brain and spinal cord that control voluntary movement, it is a highly variable disease in terms of age of onset, site of symptom onset, and rate and pattern of disease progression. Superimposed on the clinical variability of MND is the underlying complexity of genetic contribution, environmental influence, and the pathogenic pathways that lead to motor neuron degeneration. It is internationally recognised that the complex nature of MND has impacted drug development efforts. Over the last 25 years, >50 randomised controlled trials of proposed effective drugs have failed to show positive results. It is therefore, mission critical, that we make inroads into developing more tailored, and more effective treatments for MND.

## Metabolism and MND – not just an innocent bystander?

In normal physiology, metabolic homoeostasis (energy balance) results from the balance of energy intake and energy expenditure. In healthy people, food intake and the absorption of nutrients are theoretically balanced with energy that is expended during rest, during activity, and in response to food intake (thermogenic effect of food).

Since the 1980's there have been many studies that have shown that energy imbalance occurs in MND. While this energy imbalance has been proposed to impact prognosis, in 2015, the cause for energy imbalance, and the impact and relevance of energy imbalance on clinical features of disease, and disease progression and outcome in MND patients was still largely undefined.

## Clinical research outcomes

*Clinical research is important to us. We cannot treat MND if we do not understand MND and how it impacts each individual.*

In 2015, we initiated our natural history studies in patients living with MND as well as people not affected by MND. The primary aim of these studies was to create a better understanding of how each person responds to MND from an energy balance perspective, and how we could use this knowledge to develop better treatments. In studying the complex energy balance equation, we have looked at the relationship between energy supply and use, dietary intake, the gut microbiome, physical activity and disease progression. When we designed this arm of our research program, there was one ultimate goal; to take what we learned in these natural history studies into the laboratory, with the view to find therapeutic candidates and to initiate a clinical trial by 2020.

Through our clinical research, we have observed a number of things that speak to the complexity of MND. Some of our findings have been published, others are currently under consideration for publication, and the remaining discoveries will be published in future. Some research outcomes include discoveries showing that:

- Hypermetabolism (when energy use at rest is higher than what is expected) in MND patients is linked to a more rapidly progressing disease and increased risk of earlier death.
- The gut microbiome is just as complex as MND, and while it might be linked to MND outcomes, studies in larger numbers of people are needed to establish if this is really the case.
- Dietary intake is different in people with MND when compared to people without MND, and the dietary constituents are also different. We are currently completing the analysis of this data.
- Activity is generally reduced in people with MND, and might be linked to fatigue. We are completing the analysis of this data and have transitioned what we have learnt about the impact of fatigue into the laboratory for therapeutic testing.
- Activity trackers could be useful for helping us to conduct remote monitoring of the progression of disease in MND patients.

## Laboratory-based research outcomes

*Lab-based research is critical. Can we decipher the nuances of MND so that we can target them to slow or halt disease?*

In the laboratory, we use a number of pre-clinical models of disease to identify what causes MND and the molecular changes that occur as a consequence of MND, so that we can identify targets for therapeutic development. The use of mice allows us to study the cause and impact of disease, and to identify the effects of drug treatments in a whole organism. Using muscle and skin biopsies from our MND patients and control volunteers, we can generate muscle fibres and stem-cell derived neurons in a dish to study why they might be susceptible to death and to screen potential drug candidates. With the blood samples that we collect from MND patients and control volunteers, we run assays to determine if there is a difference in the expression of molecules or proteins that might be linked to the control of energy balance.

Through our laboratory-based research, we have made some discoveries that have improved our knowledge of the disease. Much like our clinical work, some of these findings have been published, others are currently under consideration for publication, and the remaining discoveries will be published in future. Some of our laboratory-based research highlights include the observations that:

- Hypermetabolism also occurs in the SOD1 mouse model of MND and this happens at a time when the muscles increase their dependence on use of fat for generating energy.
- Treatment of SOD1 mice with drugs that modify how cells use fat and sugar for energy can reverse hypermetabolism and/or improve function.
- Treatment of SOD1 mice with a drug that changes how the body responds to sugar seems to improve function. We are currently testing if this might be due to improvements in fatigue.
- There is altered expression of molecules that control energy balance in the blood of people living with MND when compared to people without MND.
- Energy use in muscle fibres generated from MND patient muscle biopsies appears to align with what we see in mouse models. The results are also in line with the variability of MND and we are currently determining how closely our measures of muscle fibre metabolism is related to whole-body energy use and clinical features in respective donors.
- Energy use in stem-cell derived neurons generated from MND patient skin biopsies is variable from patient to patient, and we are currently linking this data back to measures of whole-body energy use and clinical features in respective donors.
- We are the first laboratory to generate directly reprogrammed neurons (skin that has been turned directly into a neuron by bypassing the stage of conversion back to a stem cell) from MND patients in Australia. These cells are absolutely critical for us as we can use them to study neurons that are considered to be more “adult-like”.

## Looking into the future – new things are on the horizon.

Moving forward, we will keep developing our work into studying the various aspects of energy balance in MND. We will continue to integrate our clinical and laboratory-based research to generate the best possible research outcomes to inform clinical practice. In the coming year, and moving into the future we will focus on:

- Completing our pre-clinical testing of therapeutic compounds that modify energy use in mouse and human-cell derived models of MND.
- Expanding our pre-clinical testing of promising therapeutic compounds via collaboration with biotech companies.
- Establishing new research to determine how the toxic protein aggregates found in neurons in MND might interact with mitochondria, the powerhouses of the cell, to affect how energy is generated to sustain the function and survival of cells.
- Running our first clinical trial for MND (we hit our 2015 five-year goal!).

All in all, many things have come together for us to conduct our research. The future looks promising. I hope that we have done you proud.

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