Doctors in Training Grant

PRELIMINARY REPORT

Taking blood pressure from mice in our preeclampsia model

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Pregnancy and childbirth is a time of great joy and excitement for most women. Unfortunately, not every woman gets to experience the delight of taking home a healthy baby. I am completing a PhD through the University of Melbourne with the Translational Obstetrics Group, under the supervision of Dr Natalie Hannon and Professor Stephen Tong, focussing on novel approaches to treat pregnancy complications, particularly preeclampsia.

Preeclampsia is one of the most serious conditions of pregnancy, leading to significant maternal mortality worldwide, with even greater fetal losses. It is a multi-system disorder affecting maternal vessels (causing hypertension and endothelial dysfunction), kidneys, liver, the haematological system, the brain and the fetoplacental unit, causing fetal growth restriction. At this stage, only delivery of the placenta stops disease. Unfortunately, if delivery is required at very preterm gestations, the dilemma remains that by treating preeclampsia, we can iatrogenically inflict prematurity on the infant, with its own significant complications. For that reason, any drug that could stop, or even slow the progression of preeclampsia, has the potential for tremendous impact in the field of obstetrics.

One of the major arms of my PhD involves looking at improving treatments in an obese population. Obesity is the greatest public health challenge of our time, with two-thirds of Australians now overweight or obese. Obesity complicates almost all aspects of obstetrics, but of great relevance, dramatically increases the prevalence of preeclampsia. Although often associated with late onset preeclampsia, it also doubles the risk of developing the disease early. We can no longer ignore obesity as a significant factor when searching for therapies. The laboratory that I'm working with has developed a novel preeclamptic mouse model, and we are now in the process of replicating the mouse model, with the added insult of obesity. The obese mice group eat a high fat "Western style" diet, which has already led to them gaining over 20 percent excess weight compared to their lean counterparts, in a matter of weeks.

Our project involves testing two separate drugs, metformin and esomeprazole, both with excellent proof of concept data from *in vitro* and *ex vivo* models importantly performed in human placental cells and tissues. If we can demonstrate, in an obese preeclamptic mouse model, that either drug works, it may provide a safe therapy to halt or slow the progression of preeclampsia.

Obesity is an often-neglected area in clinical experiments, yet is becoming more and more prevalent. If we can demonstrate effective treatment of preeclampsia in our obese mouse model, we may also pave the way for future preeclampsia prevention strategies in morbidly obese pregnant women. This project is exciting and ongoing, with expected completion near the end of this year. Importantly, these drugs already have proven safety in pregnancy, creating serious potential in humans as a preeclampsia treatment.

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1. Dr Natalie Binder (left) and I with our mice in the obese preeclampsia mouse model experiment
2. Recording data for our obese mice model in the animal facility
3. With the Translational Obstetrics Group, University of Melbourne

The second main focus of my PhD involves the development of targeted treatments to the placenta, using nanoparticles. Over the past decade there have been major advances in targeted drug delivery systems, led by the field of oncology. Biocompatible nanoparticles can be coated with peptides or antibodies that specifically bind to epitopes found only on tumour cells, or in our case, the placenta. This means that when injected, the nanoparticles will predominantly go to the placenta, thus minimising the amount of drug that reaches other organs. In other words, nanoparticles are able to maximise efficacy in the target organ, while minimising side effects. In pregnancy, the added benefit of targeted treatment is that the exposure of the developing fetus to any drugs is minimised, which is of particular importance during the time of early embryonic development.

One of the first steps to developing the nanoparticles has been for us to strip the plasma membrane from trophoblast (placental) cells, to work out what specific proteins are present only in the placenta, and nowhere else in the body. By doing this, we will be able to come up with potential targets for our nanoparticles. This process is exciting as it could lead to novel targeting mechanisms within the placenta.

Secondly, we hope to design our own liposomal nanoparticles. Liposomes have been examined by other research groups because of their ability to stably encapsulate drugs or moleculesß, while also being non-toxic. Using methods taken from the oncology field, we hope to design our own liposomal nanoparticles. In preeclampsia, the placenta releases toxins that cause damage to the maternal vasculature. One of the major toxins released is soluble Flt1 (sFlt1). The group I am working with has siRNA that can silence sFlt1. We aim to try to package the siRNA to silence sFlt1 in our liposomal nanoparticles, which will form the basis of the later stages of my PhD.

One of the greatest aspects of doing a PhD with a group like the Translational Obstetrics Group is the travel opportunities. Attending conferences and learning from worldwide experts is an essential part of research. This year I have already travelled to San Diego for the Society of Reproductive Investigation conference, where I was able to listen to and meet internationally renowned speakers.

Later this year I will be attending the International Federation of Placenta Associations conference in Japan, where we present and learn a lot of top placental science. These opportunities not only help you learn science, but also to see the wider world of what is out there with regard to research opportunities, and what other lab groups around the world are discovering.

My PhD so far has been a steep learning curve. While previously I spent all of my time working clinically in obstetrics, seeing patients, operating and delivering babies, now I spend my time weighing and injecting mice and learning a variety of lab skills. Working closely with some incredible scientists, including my supervisor Dr Natalie Hannan, has opened my eyes to the whole world of basic science. At the end of my PhD I hope to have enough of an understanding of the process behind developing novel therapeutics to have an ongoing collaboration with scientists in the future. As a clinician, I can help identify gaps in treatment, and with scientific training hope to be able to think of ways to feasibly come up with solutions. I thank MIGA for helping make this opportunity possible through their Doctors in Training Grants Program.