MOTHERS AND BABIES RESEARCH CENTRE

GRAND CHALLENGES PROGRAM

2020-2024

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

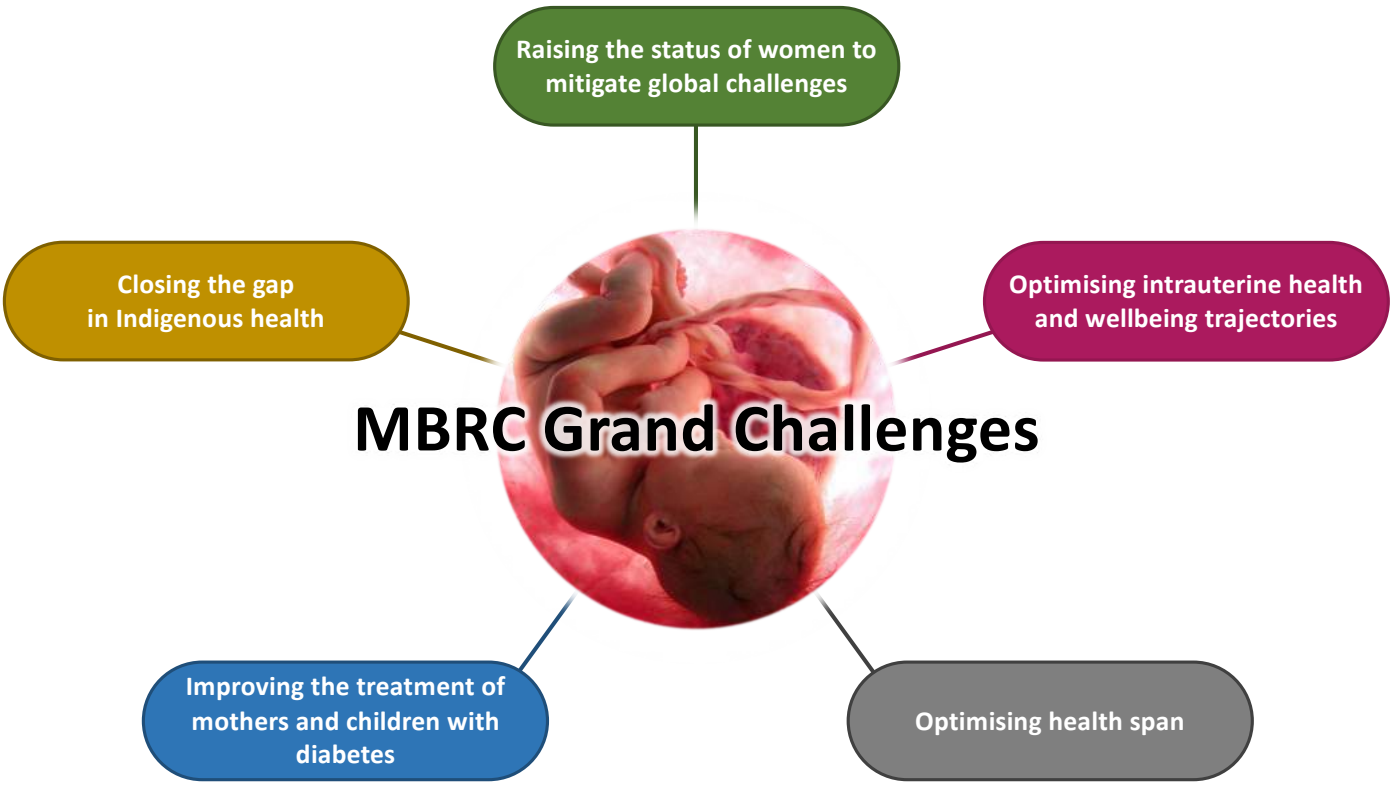
Image by Lee Dedman: a MBRC PhD candidate from the School of Creative Design

HMRI Hunter Medical Research Institute

The **Mothers and Babies Research Centre** is a multidisciplinary group of scientists with special expertise in solving complex problems that impact on pregnant women and their children. This document sets out the Grand Challenges that the Centre staff discussed and unanimously agreed to support at a meeting in December 2019. The Grand Challenges identify the strategic goals of the Centre for the next 5 years. The Centre staff will assess progress towards these goals each 12 months and re-assess their appropriateness, identify obstacles to their attainment and establish priorities to facilitate progress.

Grand Challenges

1) Raising the status of women to mitigate global challenges, including climate change and economic migration
2) Optimising intrauterine health to achieve optimal health and wellbeing trajectories for life through the application of precision medicine
3) Learning from placental aging to optimise health span
4) Closing the gap in Indigenous health by improving the health and wellbeing of Indigenous mothers and their children
5) Improving the treatment of mothers and children with diabetes



Raising the Status of Women to Mitigate Climate Change and Economic Migration

Arguably, Climate Change and Economic Migration are the two greatest global challenges to the wellbeing of humanity in the 21st century. Climate change threatens to create massive disruption by flooding low lying islands and vast sections of highly populated countries, such as Bangladesh, while creating deserts in previously fertile lands. Concurrently with climate change, the world is seeing massive human migration from areas with low incomes to areas of relatively high incomes; from South America to North America, from Africa and the Middle East to Europe, and from South Asia to Australia. This human migration is creating political instability, xenophobia and untold human suffering. Both Climate Change and Economic Migration are consequences of the low status of women in the past and currently in many parts of the world.

The status of women impacts on their educational and economic opportunities. There is a strong correlation between the level of a woman's education and their chosen fertility rate. High levels of human fertility are closely linked to the growth in the global human population, which is a major driver to global warming (https://www.brookings.edu/blog/future-development/2016/02/16/climate-change-fertility-and-girls-education/). Any rational plan to mitigate future global warming should reduce global population growth by improving the status of women and their educational attainments.

Economic migration from areas of low income to areas of higher income and the status of women are also linked. The low-income areas are largely regions where subsistence farming dominates the economies. In subsistence farming communities, women usually have low status and men own the farmland. As perinatal mortality and the toll of infectious diseases has declined, due to antibiotics and vaccination, the effective fertility of the women has increased so that the farms are unable to support the increased numbers of children. As the children turn into unemployed men and women, violence increases and both war and economic migration follow.

It is evident that raising the status of women in low income countries is an important mechanism to ameliorate both climate change and economic migration. The Mothers and Babies Research Centre has experience and expertise in this arena.

We have focused our activities in Nepal. In collaboration with the Nepalese government, we have created two programs that raise the status of Nepalese rural women. The first focuses on reducing maternal mortality and the second on improving access to education through the provision of sanitary napkins.

Reducing Maternal Mortality

Maternal mortality is an important indicator of both maternal health and the status of women. In many low-income countries, such as Nepal and Indonesia, maternal deaths are not reliably recorded, a further reflection of the status of women. The estimates of maternal mortality in Nepal are one in 338 pregnancies, while in Finland the rate is one in 33,333; as women in Nepal have more pregnancies, the lifetime risk of dying during pregnancy may be as high as one in 50. The low maternal death rate in Finland,

Australia and other developed countries indicates that the majority of maternal deaths are avoidable.

Maternal deaths occur because of three delays in the provision of effective care: a delay in the family realising that a woman is in difficulty and taking action, a delay in transport to a health facility, and a delay in the provision of care on arrival at the health facility. To reduce maternal mortality, the solution must address all three delays concurrently as any alone is able to lead to the death of the woman. In Nepal, singing is a popular folk medium. To capitalise on this, we have created a singing program to raise the awareness of rural villagers of the needs of pregnant women. This carefully evaluated program was especially effective for illiterate villagers. The songs address the first delay-decision making at the village level. To address the second and third delays we have introduced a helicopter retrieval program for women with obstetric emergencies. The program, funded by the Nepalese government, repurposes military helicopters for the retrievals and inks villagers in remote and inaccessible regions to hospitals able to supply emergency care, such as blood transfusion and Caesarean section. So far in 2019, the program has successfully evacuated close to 100 women, with only one death after dispatch of the helicopter. This program is a highly visible commitment of the Nepalese government to the wellbeing of pregnant women. The arrival of a helicopter to rescue a pregnant woman in a remote village has enormous symbolic significance to all the villagers, making a clear statement that the lives of women matter.

What funding did we use to achieve these outcomes?

Binod Bindu Sharma received a University of Newcastle International PhD Scholarship and a private donation and used these to develop the program.

What are the future goals for this program?

Our goal over the next 5 years is to extend the helicopter and social awareness program to other low-income countries in Sub-Saharan Africa, South Asia and the Pacific. This will be achieved by performing a cost-benefit analysis of the Nepalese intervention to document the impact of the program and provide data for the Nepalese government and the governments of other low-income countries with high maternal mortality rates.

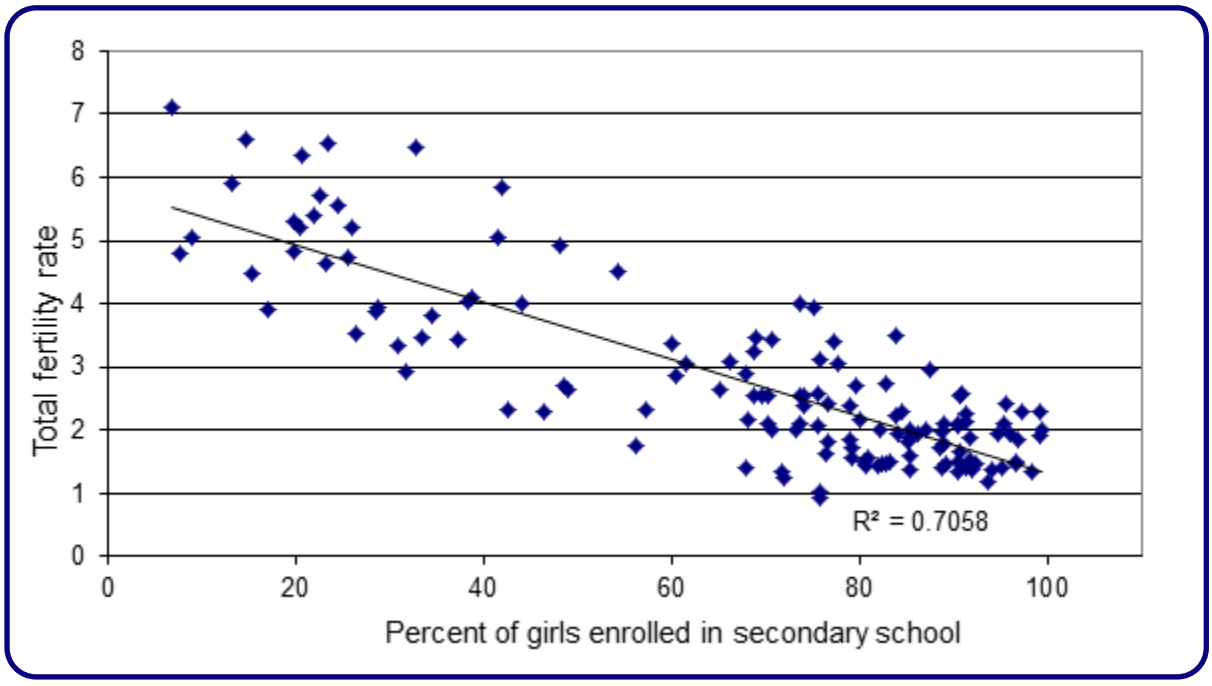
What resources are available to achieve this goal?

The University of Newcastle has provided an international PhD scholarship for a Nepalese student to perform a cost-benefit analysis with the supervision and support of UoN academics. The UoN has been developing strong links with the Governments of Ethiopia and Kenya and pilot projects and we envision pilot projects in these countries. Support for these initiatives will be sought from international aid agencies, such as the Gates Foundation and through DFAT.

Staff from the Centre include Laureate Professor Roger Smith AM, Professor Craig Pennell, Dr Binod Bindu Sharma. Professors Andrew Searles from the HMRI and Francesco Paolucci from the Newcastle Business School will guide the Cost-Benefit Analysis

Improving the Access of Girls to Education through the Provision of Sanitary Pads

In Nepal, there are extensive taboos surrounding menstruation that severely impact on the ability of girls to gain secondary education. Chhaupadi is a form of menstrual taboo that prohibits Hindu women and girls from participating in normal family activities while menstruating, as they are considered "impure". During chhaupadi, women are banned from the house and are required to live in a cattle shed, or a makeshift dwelling known as a menstruation hut, for the duration of their period. This is a life-threatening practice, especially in a Himalayan winter. The community attitude to menstruation makes it exceedingly difficult for girls to continue to attend school after they begin menstruation. This curtails their educational achievements, reduces their employment and economic opportunities, increases the likelihood of marriage at a young age and birth of children as teenagers.



To improve the access of Nepalese girls to secondary education we have lobbied the Nepalese government to provide free sanitary napkins to all schoolgirls. In the 2019 Nepalese budget, $6.4M annually was allocated for the provision of napkins to each schoolgirl. The sanitary napkins are being made in Nepal using washable cotton material with a Gortex inner layer to provide a barrier against leakage.

How was this outcome achieved?

The sanitary napkin project was conceived by Roger Smith AM and implemented by Dr Binod Bindu Sharma by advocating at the national and provincial levels in Nepal.

What are our future goals for improving the status of girls and women?

Nepal is not the only country in which menstruating girls are regarded as “unclean”. The Greek Orthodox Church expects menstruating girls to not attend church services;

this is but one example. These attitudes to a fundamental part of female biology lead to direct and subtle discrimination against girls and women in society. We seek to challenge these attitudes by normalising menstruation and the commodities required to minimise the inconvenience associated with menstruation for girls and women. To achieve this goal, we will develop an international exhibition of sanitary items and seek to make sanitary pads a fashion item.

What resources are available or required to achieve these goals?

The UoN has provided a Vice-Chancellor's PhD scholarship to Fine Arts Honours graduate Michelle Jenkins. Michelle will develop the International Exhibition of Sanitary Items and suitable sanitary fashion items as part of her PhD project. The project will require international travel and a budget for materials and exhibitions. It is anticipated that the funding for this project will be achieved by "Crowd Funding" given the wide community ramifications of the project and its impact on 50% of the global population directly and the remaining 50% indirectly.

Optimising intrauterine health to achieve optimal health and wellbeing trajectories for life through the application of precision medicine

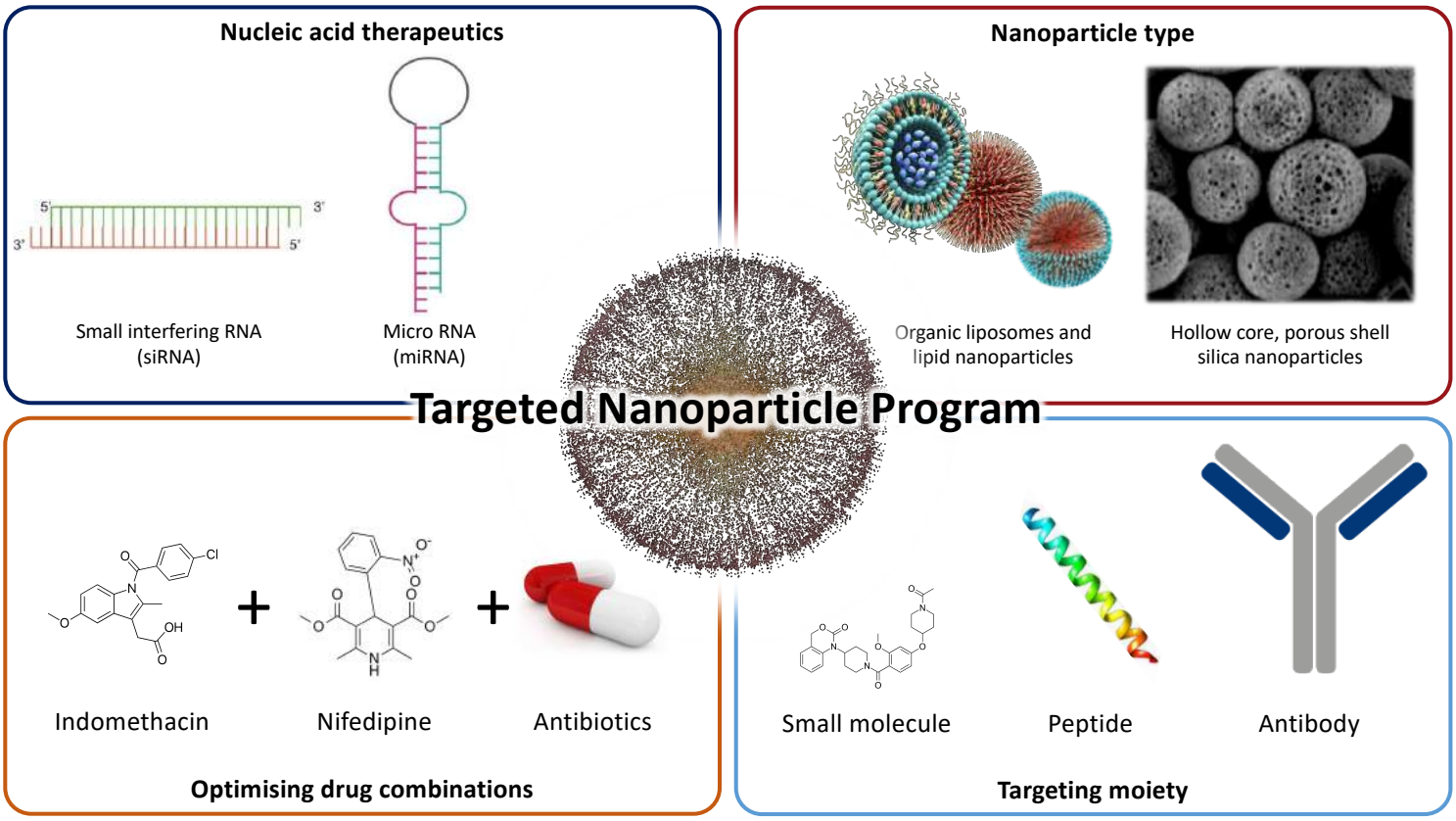
The gestational age of the baby at the time of birth is an important predictor of future school performance and likely adult earnings. Similarly, birth weight predicts the future development of hypertension, diabetes and renal function. The development of maternal hypertension and proteinuria during pregnancy, called pre-eclampsia, is a threat to the immediate health of mother and baby but also to the mother's future cardiovascular health and risk of diabetes. The most extreme event for the unborn child is unexpected intrauterine death, which occurs in approximately one in every one hundred and fifty pregnancies. All these pieces of scientific evidence indicate that the intrauterine environment is a critical determinant of the future health and wellbeing of the individual. Yet, each individual is unique in the sense that they have a unique genome, thus pregnancy is an event that must be optimised for the individual mother and the individual fetus. Such individual management is the goal of Precision Medicine. Precision Medicine seeks to ensure the best possible treatment is tailored to the specific needs of the individual, and in the case of pregnancy, to both the mother and fetus.

How will we optimise intrauterine health?

To optimise intrauterine health, we will establish the Newcastle 1000 prospective cohort and link clinical data from this cohort with that of other national and international cohorts. We will relate fetal and maternal genome data to key outcomes, including the gestational age at delivery, the birth weight, development of pre-eclampsia and maternal gestational diabetes, the occurrence of stillbirth and subsequent educational, growth and wellbeing, including mental health for mother and child.

In association with the Newcastle 1000 Birth Cohort, the Mothers and Babies Research Centre will conduct a program of research to specifically explore the mechanisms of stillbirth, diagnostics to predict stillbirth and treatments to prevent stillbirth. This work will build on our international lead in linking stillbirth to aging of the placenta supported by the Haggarty Family Foundation (HMRI donor). We will develop therapeutics in collaboration with Professor Lei Fu from the School of Pharmacy, Shanghai Jiao Tong University, China. Our work on placental aging is expected to provide insights into human aging in general as the mechanisms are expected to be conserved. Frailty in old age is an increasing problem in the 21st Century as the global population ages, especially in developed countries. Therapeutics are required to ameliorate frailty and optimise human health span or effective life span. This work will be conducted in collaboration with Associate Professor Doug Smith of the School of Biomedical Sciences and Pharmacy.

The Mothers and Babies Research Centre also has an active program to elucidate the mechanisms of premature labour, to develop diagnostic tests to predict preterm labour and therapeutics to delay birth in the setting of preterm labour. It is unlikely that we will be able to prevent all cases of preterm birth, and for those that deliver preterm, we need approaches to ameliorate the consequences of preterm birth. We therefore have an animal research program to trial new approaches to minimising the effects of preterm birth on brain development and future mental health. Work on premature birth is conducted in collaboration with the BORNE Foundation in the UK. Our program will include the development of nanoparticles targeted to the muscle cells of the uterus using the oxytocin receptor as the target. The nanoparticles have been successful in delaying delivery in a mouse model of preterm birth. Our Centre will also seek to improve human health by the application of novel technologies developed as part of the Mothers and Babies Research Centre program, including use of nanotechnology for the diagnosis and treatment of cancer and other diseases.



Our goals over the next 5 years will be to:

1) Establish Newcastle 1000 and recruit 1000 mothers and their babies annually for 5 years
2) Elucidate the cause of stillbirth, develop clinically predictive diagnostics for stillbirth, develop therapeutics to reduce the likelihood of intrauterine death in at risk fetuses
3) Apply the lessons from placental aging to optimise human health span
4) Elucidate the cause of preterm labour; develop clinically predictive diagnostics for preterm labour; develop clinically useful therapeutics to prevent and arrest preterm labour; and meet the regulatory requirements for a human trial. Develop methods to minimise the impact of preterm labour on the infant brain
5) Elucidate the specific role of the renin-angiotensin system in pre-eclampsia and growth restriction

What resources do we require to meet these goals?

This program of activities to optimise birth outcomes is ambitious and will require substantial funding. We will derive our funding from our philanthropic supporters, state medical research funding, federal government support and international support. We will seek to obtain partnerships with diagnostic and therapeutic companies.

What resources will we commit to this program?

The Mothers and Babies Research Centre has substantial expertise in these areas amongst its senior staff including: Scientia Professor Emeritus Eugenie Lumbers, Laureate Professor Roger Smith AM, Professor Craig Pennell, Professor Tamas Zakar, Professor Jon Hirst, Associate Professor Kirsty Pringle, Dr Yogavijayan Kandasamy, Dr Jonathan Paul, Dr Kaushik Maiti, Dr Jorge Tolosa, Dr Hannah Palliser, Dr Julia Shaw, Dr Zakia Sultana and Carol Wang. General infrastructure will be provided by Dr John Fitter, Laboratory Manager and Safety Officer, Financial Officer Joanne Davies, Ethics Officer and grant application expertise Dr Giavanna Angeli, Research Assistant Maria Bowman, Recruitment Personnel Anne Wright, Sharron Hall and Pam Howell.

The program will also benefit from our local, national and international collaborators. Collaborators on our stillbirth research include: Dr Carlos Riveros, from the Hunter Medical Research Institute, Laureate Professor John Aitken, from the UoN Priority Research Centre for Reproductive Science, Professors Stephen Tong and Sue Walker, from The Mercy Hospital, Melbourne, Professor Lisa Martin, from Monash University, Melbourne, Dr David Paterson, from ANSTO, Dr Michael Jones, from the Queensland University of Technology, Professor Jon Hyett, from the University of Sydney, and Professor Vicki Clifton, from the Stillbirth CRE at the Mater Hospital Brisbane. International collaborators include Professor Lei Fu, from the SJTU in Shanghai, Professor Terry Morgan, from Oregon Health and Science University, Portland, USA, Professor Andrew Blanks of Warwick University and Professor Mark Johnson and colleagues from the BORNE Foundation at Imperial College, London, England.

Closing the Gap in Indigenous Health by Improving the Health and Wellbeing of Indigenous Mothers and their Children

A major challenge for Australian society is to close the gap in life span and wellbeing between Indigenous Australians and the rest of the community. Successive governments have committed to achieving this goal, but it remains elusive with most markers indicating minimal improvements in outcomes, particularly for rural and remote Aboriginal people. The Mothers and Babies Research Centre has taken the view that Indigenous health will not match that of non-Indigenous Australians until the health of Indigenous mothers matches that of their non-Indigenous sisters. Life is a trajectory beginning in the uterus and poor intrauterine growth and premature birth lead to numerous adverse outcomes, from poorer school performance to early onset diabetes, kidney failure and heart disease. Indigenous mothers are more likely to have a premature baby and more likely to have a growth restricted baby. To identify the causal pathways leading to the excess in premature births, growth restricted babies and early onset kidney failure the Centre has established programs in Tamworth, Walgett and Townsville and conducted collaborative research in the Northern Territory.

Our program in Tamworth and Walgett was established with a generous donation from the Thyne Reid Foundation (HMRI donor). It was identified by the local community that Aboriginal mothers were not attending Antenatal care facilities in Tamworth because of the perception that they would be discriminated against. As antenatal care is important for the detection of maternal diabetes and hypertension, as well as monitoring the growth of the fetus, we sought approaches to improve access to this important service for Indigenous women. A building was rented within walking distance from the Aboriginal community in the Tamworth suburb of Coledale and renovated to provide an antenatal service with ultrasounds and an art studio and gallery. An Indigenous artist was employed to teach Aboriginal art to attending mothers. The team invited health professionals, such as midwives, dieticians, lactation consultants and physiotherapists to attend the art workshops and pass on knowledge while creating art works. Tribal elders were welcomed to the centre to pass on traditional knowledge. The program has been running successfully for 10 years and over 300 Indigenous mothers have attended for care. The program has mapped kidney development in the Aboriginal babies as well as the mental health of the mothers. We also extended the

program to the remote town of Walgett. A sign of the success of the program is its recurrent support from the Office of the Prime Minister.

In Townsville, neonatologist Dr Yoga Kandasamy has established a program to detect early signs of kidney disease in Indigenous babies. Dr Kandasamy's program has been funded by successive NHMRC grants and has identified that Indigenous babies are more likely to be born with small kidneys, predisposing them to early onset kidney failure. Townsville Hospital receives high risk mothers from throughout northern Queensland and Dr Kandasamy has successfully developed methods to follow up the babies over this vast geographic area. The program seeks to detect babies at high risk of kidney failure and to put in place methods to ameliorate kidney damage.

In the Northern Territory, members of the Mothers and Babies Research Centre have collaborated with Steve Gutheridge, Professor of Child Development/Population Health and Policy at the Menzies School of Health Research, Darwin. Using linked data analysis, Ellie McEwan, Roger Smith and Steve examined the associations between birth weight and school outcomes, as measured by the NAPLAN assessments. Their data showed that birthweight directly correlates with school performance for Indigenous children. That is, the heavier the baby, the more likely it was to do better at the NAPLAN assessment.

The Mothers and Babies Research Centre has also undertaken research into the origins of low birthweight in Aboriginal children using the ObstetriX pregnancy and perinatal database of the Hunter and New England Health Service. This analysis examined whether low birth weight was due to genetic differences between Indigenous and non-Indigenous babies. The results have international significance as they revealed that healthy Indigenous and non-Indigenous babies were the same weight and that cigarette smoking was the dominant cause of low birth weight.

These results will guide government and health policy to improve outcomes for Indigenous mothers and their children and help to close the gap.

Our Goals in Indigenous Health

To help Close the Gap we will:

1) In collaboration with the local community, continue the Gomeroi Gaaynggal program in Tamworth and Walgett to build a bigger database that will guide the community on the pathways to better health for Indigenous mothers and their children. The work will focus on issues seen as important by the local steering committee. Topics raised so far include mental health, diabetes, kidney disease and smoking.
2) Maintain recruitment in Townsville to increase the power of the research to identify the causal pathways leading to kidney failure and diabetes, and potential opportunities for early intervention and prevention.
3) Develop Indigenous research capability by recruitment of Indigenous research staff and providing opportunities for training and leadership.
4) Extend data linkage projects in collaboration with the Menzies School of Health Research in Darwin to characterise the impact of pregnancy and perinatal health on long-term child development, including future earning capacity and interactions with the criminal justice system. A full understanding of the pathways to good outcomes will offer role models for Indigenous families.
5) Work with collaborators to develop effective interventions to lower the rate of smoking in Indigenous communities, particularly among women of reproductive age.

How will we achieve these goals?

We will achieve these goals with funding from philanthropic donors, from continued support by the Department of the Prime Minister and by competitive grants through the NHMRC and the Medical Research Future Fund.

What will the Mothers and Babies Research Centre commit to achieve these goals?

The Mothers and Babies Research Centre will commit substantial time from Associate Professor Kirsty Pringle, who will lead the research component of the Tamworth and Walgett program, and Dr Yoga Kandasamy, who has led the Townsville project since its inception. Professor Roger Smith will continue to be active in the Tamworth, Walgett and Townsville programs and promote the collaboration with Professor Gutheridge in Darwin.

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In partnership with the

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