Nigel Clarke Memorial Education Bursary Report
2017 Recipient – Annabelle Enriquez

I would like to thank the Australasian Association of Clinical Geneticists for choosing me to be a co-recipient of the Nigel Clarke Memorial Education Bursary in 2017.

I was fortunate enough to meet Nigel in my first year in Clinical Genetics, during which he supervised me in a Neurogenetics Clinic. In that single afternoon, Nigel impressed me with his clinical acumen and sincere compassion. More remarkable to a clueless, overwhelmed trainee, Nigel treated me as an equal and seemed to take genuine interest in what I had to contribute. It was only after this brief meeting that I heard about Nigel's outstanding achievements as a clinician and scientist.

I was therefore very honoured and humbled to receive this bursary in Nigel's memory during my last year of training as a clinical geneticist. A critical part of my training has been my research into the genetic causes of birth defects, and the support provided by the bursary has enabled me to share my research findings with a wide range of audiences.

Birth defects affect 3-6% of babies, leading to significant morbidity and mortality, yet the underlying cause is unknown in most cases. I am part of a multidisciplinary research team led by Professor Sally Dunwoodie at the Victor Chang Cardiac Research Institute in Sydney and we recently discovered a novel cause of severe multiorgan birth defects. We found that that disruption of genes involved in nicotine adenosine dinucleotide (NAD) synthesis causes NAD deficiency, leading to malformations in the heart, vertebrae and other organs in humans and mice. NAD is an essential molecule in biological organisms and is required in hundreds of cellular reactions underpinning energy metabolism, DNA repair, and effective gene transcription. NAD is so important that there are at least two pathways leading to its synthesis: the *de novo* pathway that is affected by the genetic variants in our patients, and a salvage pathway using vitamin B_3 as substrate. Furthermore, in our mouse models, we found that giving vitamin B_3 to the pregnant mice prevented the pups from developing congenital anomalies. Thus, not only have we identified an important cause of congenital anomalies, we may have potentially also found an easily accessible way to prevent these defects in humans. We are continuing with further laboratory and clinical research to enable clinical translation of these findings.

I had the opportunity to describe these findings in an oral presentation at the HGSA conference in Brisbane last year. The following week, our discovery was published in the *New England Journal of Medicine*, with extensive media coverage worldwide. Since then, I have given 12 talks on our research in different scientific, clinical and community settings, enabling me to promote awareness about birth defects. Each presentation has generated substantial interest and various questions from the audience have challenged me to keep searching for answers. I have been able to forge collaborations to accelerate further understanding of congenital malformations and their management. Being selected to give oral presentations at the Sydney Cardiovascular Symposium in December 2017 and at the International Clinical Cardiovascular Genetics Conference in May 2018 has also allowed me to hear about cutting edge research from leaders in different fields of cardiovascular genomics and to draw upon the most current evidence in my patient care.

I am deeply grateful to Nigel's family and to the Australasian Association of Clinical Geneticists for awarding me the Nigel Clarke Memorial Education Bursary. This investment in my training has afforded immeasurable opportunities in my career as clinician researcher.