Functional evaluation of candidate genes and mutations that cause failure of bone marrow neutrophil production

Professor Graham Lieschke

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White blood cells come in many shapes and types. A failure to make white blood cells leads to the recurrent infections that are problematic for Bone Marrow Failure Syndrome patients. Professor Graham Lieschke, from Monash University's Australian Medicine Regenerative Institute, is particularly interested in phagocytes, the white cells that repair tissue damage and fight infection. Professor Lieschke elaborates, "Phagocytes perform the process of phagocytosis – cleaning up debris and foreign invaders by engulfing them - gobbling them up. We study how the two types of phagocytes, neutrophils and macrophages, form during embryonic development, function to do their job, and how their supply is maintained through life."

Fascinatingly, the animal model system Professor Lieschke's laboratory uses is the zebrafish. Zebrafish are small tropical fish native to South East Asia, approximately 2.5 – 4 cm long. Zebrafish have similar white blood cells to humans, possess conserved genetic

and molecular regulatory pathways, and as they are transparent, are exceptionally good at providing high resolution imaging in living tissues. Zebrafish genetics provides a tool for studying the regulation of white blood production.

Professor Lieschke's project has enabled the exploration of the consequence of mutations in genes identified in patients with white blood cell development problems. For a selected number of gene changes, he is trying to answer the question: are these just incidental findings, or are these genetic mutations actually the cause of the patient's problems with white blood cell development? With advances in sequencing whole genomes, that is all the DNA encoded in an individual's genes, clinicians and scientists are now aware of the enormous genetic variation in humans. Understanding functional consequences of each particular variant is one of the great challenges. Professor Lieschke is chipping away at this, one variant at a time, for a selection that are strong candidates to be important in particular patients and their families. "It would be great if there wasn't such a bottle neck," he laments. "Current methods including ours are research-intensive and very focussed on individual variants. Ultimately, a functional proof of disease-causation is needed to supplant a presumption of involvement. As the database of genetic mutations that are causative of disease accumulates, predictions based on prior information will become more and more accurate."

Professor Lieschke's work is vitally important, "Knowing that a genetic change is the cause of the problem provides diagnostic precision for patients and their families, and opens the path to rational design of curative genetic and/or pharmacological approaches."

Professor Lieschke's career spans an amazing period in clinical haematology, from first knowing about blood cell growth factors as just an activity in a laboratory dish (his Bachelor of Medical Science BMedSci project) through to standing at the bedside of some of the first patients to receive them as drugs (as a Clinical Research Fellow), and then seeing their use become routine for supporting white blood cell counts as treatment of some forms of bone marrow failure and during cancer chemotherapy delivery. He is a Melbourne University BMedSci and Medicine graduate, and undertook his specialist clinical training in Parkville. His post-doctoral training took him to Boston and New York, but otherwise he has devoted his professional life to working in Melbourne hospitals and institutes. His free time interest is rather quirky though – he possesses a mad passion for the organ and choral music of J.S. Bach and is an outstanding pipe organist and conductor.

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Central to the work being undertaken in the Lieschke laboratory is the brilliant mind of Dr Vahid Pazhakh, who performs the genetic work that is at the core of the Maddie's Vision funded project. Dr Pazhakh obtained his PhD from Monash in the Lieschke laboratory as an international student, and is now here to stay in Australia. In 2020, a Master of Biotechnology student, Lingge Tu, is also working on the zebrafish genetics and helping to score the blood cell numbers in the experiments that disrupt the genes of interest. It is rather remarkable to conceive that the humble zebrafish, a small and robust creature, is assisting in unlocking the answers of Bone Marrow Failure Syndromes!