ARMI EXTERNAL SEMINAR SERIES 2024

MONASH University | ARMI AUSTRALIAN REGENERATIVE MEDICINE INSTITUTE

"Immune disease and genetics: starting to fill the gaps"

Prof Ken Smith – Director WEHI

Abstract

Genetics can be used to reveal and delineate important immunological pathways. Understanding the impact of genetic variation on human disease is central to this, but is hampered by knowledge and data gaps – for example our focus on common (via GWAS) or extremely rare (monogenic disease) variants ignores those of intermediate frequency, and most studies ignore much of the 98% of the genome that is non-coding. Recent attempts to bridge these gaps in studies in immune-mediated disease will be discussed.

Primary Immunodeficiency (PID) is characterised by recurrent infection, autoimmunity and malignancy. It can have a devastating impact on the lives of patients and their families, and management is aided by genetic diagnosis. 80% of PID patients have no overt family history, and thus have been intractable to gene discovery. We explored whole genome sequencing (WGS) to enhance diagnosis in a UK-wide study in adult PID and found a genetic diagnosis in <25%. By applying Bayesian analytical techniques, we identified multiple new PID-associated genes; causative deletions in regulatory regions; and interplay between novel high- penetrance monogenic and common variants, beginning to explain the variable penetrance of PID. The discovery of a TRAF3 haploinsufficiency syndrome will be discussed as an exemplar. Ongoing work to integrate new functional approaches with deep clinical, immunophenotyping and repertoire data to enhance discovery will then be outlined.

Bio

Ken is the 7th Director of the Walter and Eliza Hall Institute of Medical Research, Professor and Head, Department of Medical Biology, Faculty of MDHS, University of Melbourne and the current Galli Chair. Ken was until recently the Head of the Department of Medicine at Cambridge, and directed the Cambridge Institute for Therapeutic Immunology and Infectious Disease. He trained in nephrology and clinical immunology in Melbourne, and completed his PhD at the WEHI. He was a Wellcome Trust Investigator and ran a MRC Programme, was elected as a Fellow of the Academy of Medical Sciences in 2006, to the American Association of Physicians in 2020, and was awarded the Lister Institute Research Prize in 2007.

Ken Smith's research studied immunological mechanisms underlying immune-mediated disease and immunodeficiency in humans. His lab ran a translational program in autoimmune disease that has led to the discovery of a prognosis-predicting biomarker entering the clinic, and to the identification of new pathways driving disease outcomes in autoimmunity and infection. They lead the "INTREPID" primary immune deficiency study. By integrating genetics with human and animal studies, the laboratory seeks to reveal fundamental immunological mechanisms relevant to disease, and to translate them for the benefit of patients.

EVENT DETAILS

DATE:

22 October 2024

TIME:

2:00pm

VENUE:

Room G19
15 Innovation Walk
Monash University
Clayton Campus

HOST:

Dr William Roman &

Prof Graham Lieschke

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