Wolvetang Group

Professor Ernst Wolvetang

Induced pluripotent stem cells, in vitro disease models, novel regenerative medicine approaches

The Stem Cell Engineering Group (SCEG), led by Senior Group Leader Professor Ernst Wolvetang, aims to understand the molecular and cellular processes that underlie childhood neurological diseases as well as ageing-related neurodegenerative diseases. The Wolvetang group establishes induced pluripotent stem cells from skin or blood cells donated by patients with various brain diseases, creating an inexhaustible supply of cells that can generate each cell type of the human body. By manipulating the genome make-up and expression of genes in brain cell types derived from these human stem cells, they can not only understand the relationships between gene function and human disease, but also use these cells to discover and test novel therapeutics.

To better model the 3D architecture and connectivity of the brain the group employs brain organoids, and optogenetic tools for stimulating and visualizing neuronal activity, and single cell transcriptome analysis to interrogate the gene regulatory networks that govern the behaviour of brain cells.

"These human mini-brains resemble small sections of the human cortex, and this allows us to examine how this biological computer is built and to understand how things go awry in neurological diseases and ageing" Professor Wolvetang said.

Currently these brain organoids are used to investigate the progression of neurological diseases such as Alzheimer's disease, childhood myelination diseases and schizophrenia.

As Co-Director of the UQ Centre in Stem Cell Ageing and Regenerative Engineering (UQ-StemCARE), Prof Wolvetang has embarked on a number of new collaborations focused in the area of aging and regenerative medicine. Of note is a project in collaboration with the European Research Institute for the Biology of Aging (ERIBA), which involves looking at a new class of proteins that may be involved in the development of plaques in the brains of Alzheimer's patients.

In a joint project with Professor Martin Pera from the University of Melbourne, the group published work in *Elife*, reporting the discovery of new inhibitors of the kinase DYRK1A that resides on chromosome 21, and likely plays a role in early onset Alzheimers disease and craniofacial abnormalities in Down Syndrome. In work published in *Frontiers in Cellular Neuroscience*, the group reported on gene regulatory pathways involved in Ataxia-Telangiectasia (A-T). A-T is characterised by degeneration of the cerebellum, cancer and a weakened immune system because children lack the ability to repair broken DNA.

"Most sufferers of Ataxia-Telangiectasia die before they are 20, because their hind brain degenerates, and we still don't exactly know why this happens, but using our stem cell models we are now not only getting closer to solving this riddle but also to screening drugs that can help these patients." said Professor Wolvetang.

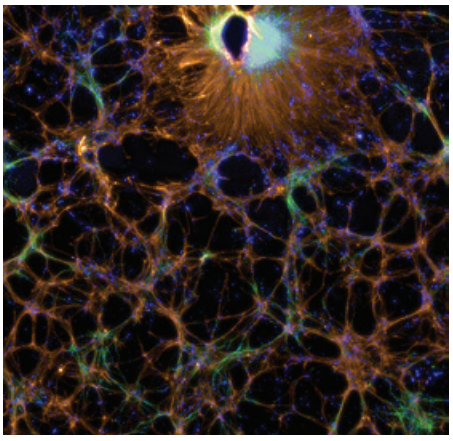
Supported by philanthropic funding from patient and parent support group BrAshA-T, the Wolvetang group used patient samples to develop IPSCs, generate hindbrain organoids and performed the first gene expression study on human A-T brain cells. Using CRISPR genome editing they have now corrected the defective gene in A-T iPSC.

Professor Wolvetang is also heavily involved in outreach activities for A-T and childhood leukodystrophies, including engaging with school students and encouraging them to participate in fundraising.

"It's important to engage younger people in medical research — to convey how exciting science is and explain its real world impacts."

In 2017, Prof Wolvetang was awarded two NHMRC grants (CIA and CIB) related to work on A-T and Schizophrenia. The group further received an ARC Linkage Infrastructure, Equipment, and Facilities grant together with UQ-StemCARE Co-Director Professor Justin Cooper-White, to support the establishment of an automated stem cell bioengineering ("AutoStem") facility that will enable critical insights into the molecular mechanisms that underlie the loss in stem cell function and tissue homeostasis as we age.

The functional genomics strategies and discovery platforms developed in the Wolvetang group will enable the development of patient-specific personalised medicine approaches for rare diseases affecting children as well as ageing related diseases that touch us all.



www.aibn.uq.edu.au/wolvetang