International team cracks mammalian gene control code

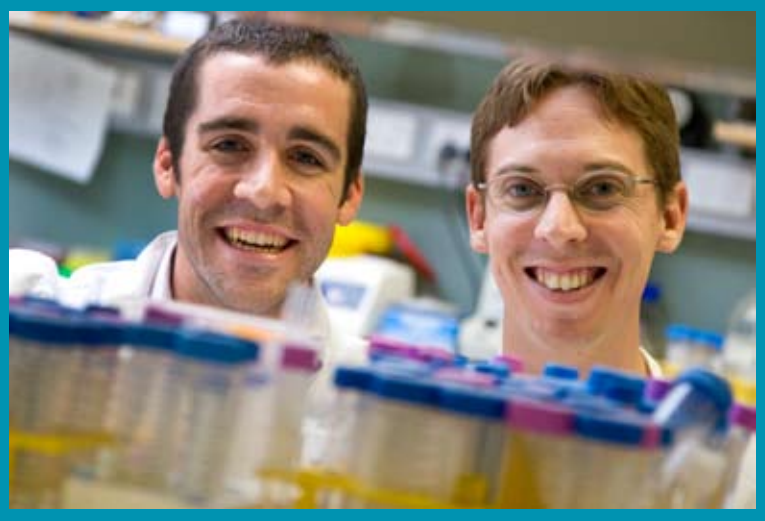
An international consortium of scientists, including researchers from the IMB, have probed further into the human genome than ever before.

They have discovered how genes are controlled in mammals, as well as the tiniest genetic element ever found.

Their discoveries were published in three milestone papers in leading journal *Nature Genetics*.

The research was coordinated by the RIKEN Yokohama Omics Science Center in Japan as part of the FANTOM4 consortium, with researchers from the IMB playing major roles in two of the papers.

PhD student Ryan Taft led one paper, on which Professor John Mattick was the senior author, while Associate Professor Sean Grimmond was a senior author on another paper led by Dr Geoff Faulkner.



(L-R) Dr Geoff Faulkner and Ryan Taft.

"FANTOM4 has shown that instead of having one or a few 'master regulator' genes that control growth and development, there is a sophisticated network of regulatory elements that subtly influence the ways in which genes are expressed in different cells in the body," Professor John Mattick said.

This information will be very useful to medical and biological researchers, according to Associate Professor Sean Grimmond.

"We can use it to discover how cells transform from rapidly-growing 'blank slate' cells to mature cells with a specific function. This knowledge will help us determine, for example, why some cells turn cancerous, or how to control stem cells for use in regenerative medicine."

One of the papers describes the discovery of tiny RNAs, the smallest genetic elements yet known, which are linked to the expression of individual genes. Tiny RNAs are 18 nucleotides long, 100 times smaller than an average gene.

"Researchers had previously noticed small lengths of RNA in the genome, but thought that they were degraded segments of larger genetic elements," Mr Taft said.

"We found that they were too common and too specifically distributed to be rubbish. They are widely associated with promoters that switch on genes, and we believe they may have a role in gene activation. Once we understand their role more explicitly, we hope to use tiny RNAs to artificially control gene expression."

RNA is a molecule similar to DNA that translates the genetic information in DNA into proteins, or as in the case of tiny RNAs, can regulate longer RNA molecules before they are translated to proteins.

Another paper investigated retrotransposons, genetic elements that move around the genome and leave copies of themselves behind.

"The dogma in the field is that retrotransposons are only active in cancer cells and cells that turn into eggs and sperm," Dr Faulkner said. "Our results showed that retrotransposons that can no longer move around the genome may still be expressed in a broad range of cells, and thereby regulate the expression of nearby genes."

This is the fourth incarnation of the FANTOM consortium, which seeks to discover more about the workings of mammalian genomes through large-scale "systems biology" approaches.

Professor Mattick said that it had been a "privilege to be part of this consortium".

"It is another example of the wonderful and productive collaboration we have enjoyed with Japan over recent years," he said.

National honour for IMB scientist

A University of Queensland scientist has become the only newly-elected Queensland-based researcher to be selected to become a Fellow of the Australian Academy of Science, one of the highest scientific honours in Australia.

Professor Rob Parton from the IMB was elected for his work on the cell surface, which has a range of applications including the potential to improve drug delivery and better understand prostate cancer.

Professor Parton received a $4 million Australia Fellowship in January, which will fund research into tiny cellular vehicles that bud off from the cell surface and could deliver drugs directly to specific sites in the body, meaning healthy cells won't be targeted.

The focus of Professor Parton's work is on caveolae, small pits in the cell surface that have a role in some diseases, as well as in regulating the growth and fat balance of cells.

"We have shown that caveolins, the major proteins of caveolae, are needed for the liver to regenerate" Professor Parton said.

"We are also studying the interaction between caveolae and lipid droplets, which store fats and thus can play a role in obesity. We are also looking at the link between caveolins and prostate cancer."

Professor Rob Parton.

Professor Parton is one of sixteen newly-elected Fellows, chosen for their significant contributions to science both in Australia and internationally. He is the third IMB researcher to become a Fellow, after Professor Peter Koopman and Professor John Mattick were elected last year.

Finding a pathway to new virus drugs

IMB researchers have taken an important step in the characterisation of a viral infection pathway, which may potentially lead to the development of new drugs targeting a broad range of viruses including human immunodeficiency virus (HIV) and Ebola virus.

Dr Michael Landsberg, in conjunction with a team of four other scientists, recently solved the 3D structure of a key controlling enzyme in the pathway of enveloped virus infection.

Vps4 is an enzyme which controls the budding of small, lipid-enclosed vesicles from cell membranes. Cells use this process to transport proteins and other important molecules to different destinations.

Importantly, a number of viruses including HIV, Ebola, hepatitis and herpes simplex viruses appear to hijack this pathway to facilitate their own spread from infected cells to healthy cells within a host organism.

"There is growing evidence that therapeutic strategies which target Vps4 are able to elicit a protective response against infection by at least some of these viruses," Dr Landsberg said.

"This has recently been demonstrated by a team of US scientists who observed that 70% of laboratory mice deficient in Vps4 were able to survive injection with an otherwise lethal dose of Ebola virus. Conversely, a survival rate of less than 20% was observed in normal mice, comparable to human survival rates following outbreaks of the most lethal forms of the virus."

In research published in the March 11th issue of the international journal Structure, Dr Landsberg and fellow UQ scientists Associate Professor Ben Hankamer, Rosalba Rothnagel, Dr Parimala Vajjhala and Griffith University's Dr Alan Munn (formerly of the IMB) were able to determine the 3D structure of what they and a number of other scientists worldwide believe is the biologically active form of Vps4.

"In order to develop new therapeutics which target Vps4, it is critical that we first know the 3D structure of the biologically active form of the enzyme," Dr Landsberg said.

"Our study gives some insights into this structure and, in so doing, has identified important regions of the enzyme which are required for it to assemble into its fully functional, biologically active form."

The team used a technique known as Single Particle Analysis to determine the 3D structure of Vps4, which involves using a transmission electron microscope to record tens of thousands of images of individual protein molecules in different molecular orientations at high magnification. The images are then combined by computational techniques to obtain a structure of the protein in 3D.

"The next step now is to build on this research and identify parts of Vps4 which can potentially be targeted by drugs, and in so doing block its role in virus infection.

"This would be a crucial step in preventing the spread of viruses throughout the body and lessening the effect of diseases such as ebola and HIV."