# Martin Turner
[Immunology]

We study molecular mechanisms that regulate changes in gene expression needed to produce, maintain and activate cells, called lymphocytes, in the immune system. Our work focuses on the role of proteins that bind to messenger RNA – molecules that provide the essential intermediate step in information transfer from DNA to proteins. We aim to characterise fundamental mechanisms controlling lymphocyte development and function throughout the life-course.
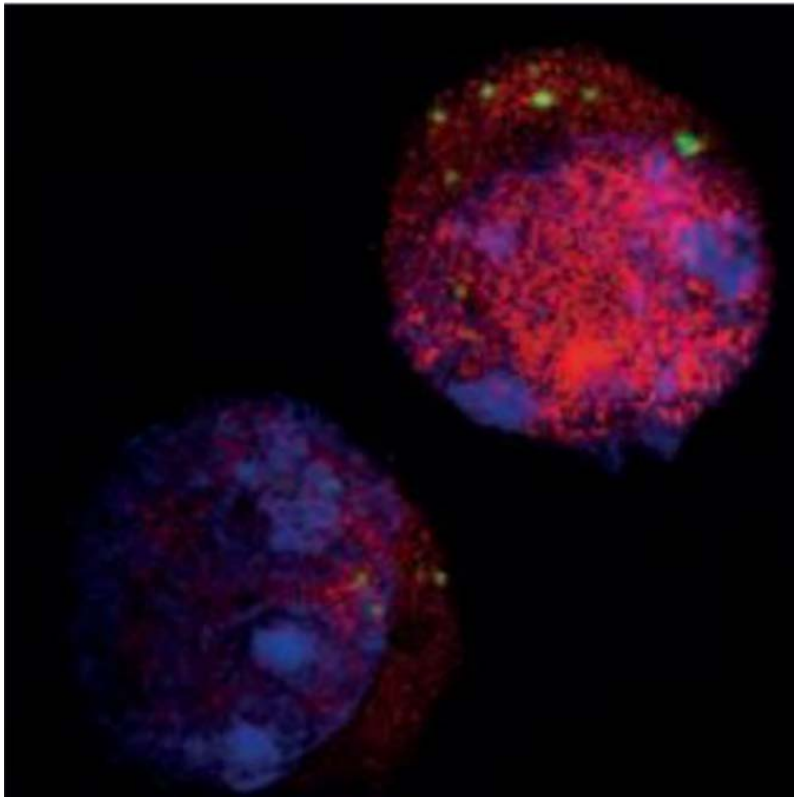
Structured Illumination Microscopy (SIM) images for the RNA binding proteins ELAVI1 (red) and DCP1 (green) with DNA stained in blue in activated B lymphocyte cells.

Geoff Butcher
[Immunology]

Defending the body from disease requires an effective immune system with stable populations of mature T and B lymphocytes – types of white blood cells. A group of proteins, called GIMAPs, play an important role in ensuring there are always enough of these cells. By studying this we can improve our understanding of lymphocyte survival and discover new opportunities to treat certain diseases.
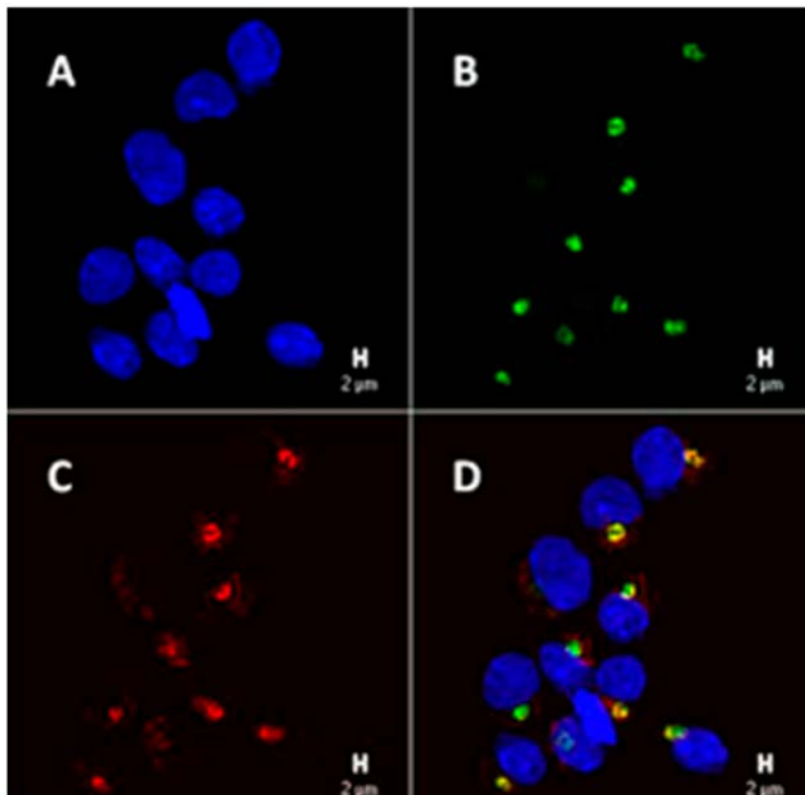

GIMAP1 expressed in a mouse NKT cell line [C1498] is located in the Golgi apparatus.
A.   DAPI stain for DNA
B.   Detection of giantin, a standard marker for the Golgi
C.   Detection of endogenous GIMAP1 using a specific monoclonal antibody
D.   Overlay of A-C demonstrating co-localisation of GIMAP1 and giantin

Michelle Lintermann
[Immunology]

With age, the function of the immune system declines, rendering older people more susceptible to infections and less able to benefit from vaccination. Our research aims to understand how the immune system changes with age, to determine if we can improve vaccination efficacy in older people.
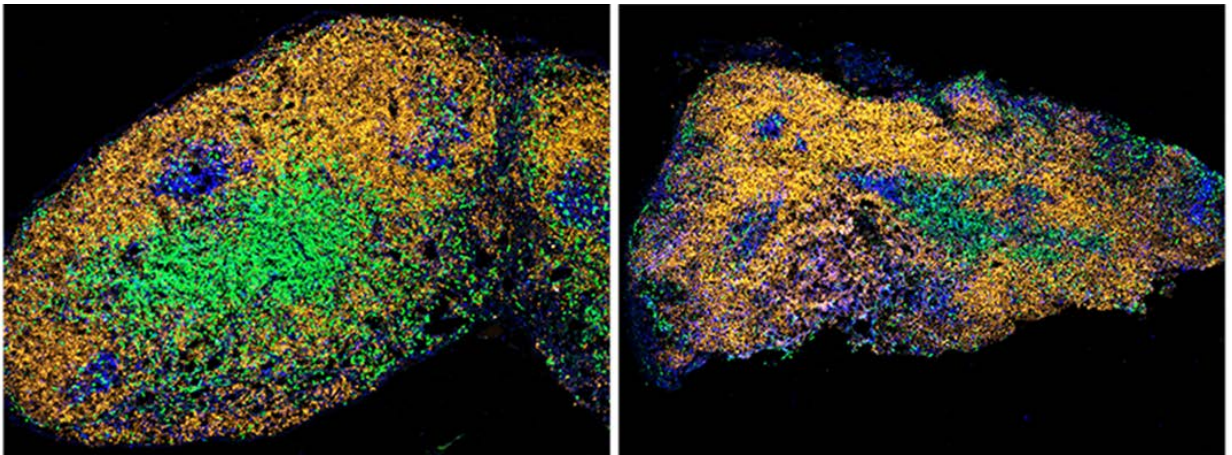

Poor germinal centre responses in aged mice after immunisation. This image shows a section of inguinal lymph nodes taken 14 days after immunisation. In a 2 month old mouse (left) there are large germinal centres (Blue Ki67 staining surrounded by yellow IgD staining) that contain T follicular helper T cells (green CD3 staining), these structures are smaller in 22 month old mice (right).

Rahul Roychoudhuri [Immunology]

Effector T cells of the immune system can prevent infections and cancer but they can also cause autoimmune and allergic inflammation. These harmful responses are restrained by tolerance mechanisms. While they are beneficial, a similar process – called immunosuppression – restricts the immune system's ability to tackle chronic infections and cancer. We study these mechanisms, their effects as we age and their roles in disease.
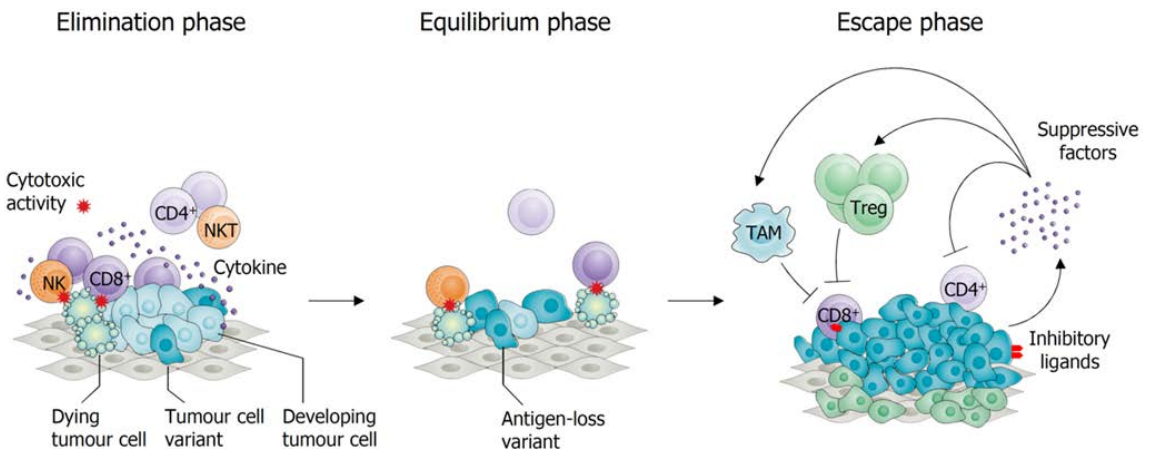

Tumour development is characterized by an initial 'elimination' phase, during which a majority of cancer cells are destroyed by components of the immune systems, including CD8+ T cells and NK cells. After this, tumours enter the 'escape' phase, where immunosuppression through recruitment of anti-inflammatory cells results in evasion from immune control and unrestrained tumour growth.

Anne Corcoran

[Immunology]

The immune system creates antibodies to help fight diseases, which are made by white blood cells called B lymphocytes. By mixing and matching genetic information, these cells can produce billions of different antibodies to combat different diseases. We are interested in the mechanisms involved because the reduced ability to produce effective antibodies is one of the reasons the immune system weakens as we age.
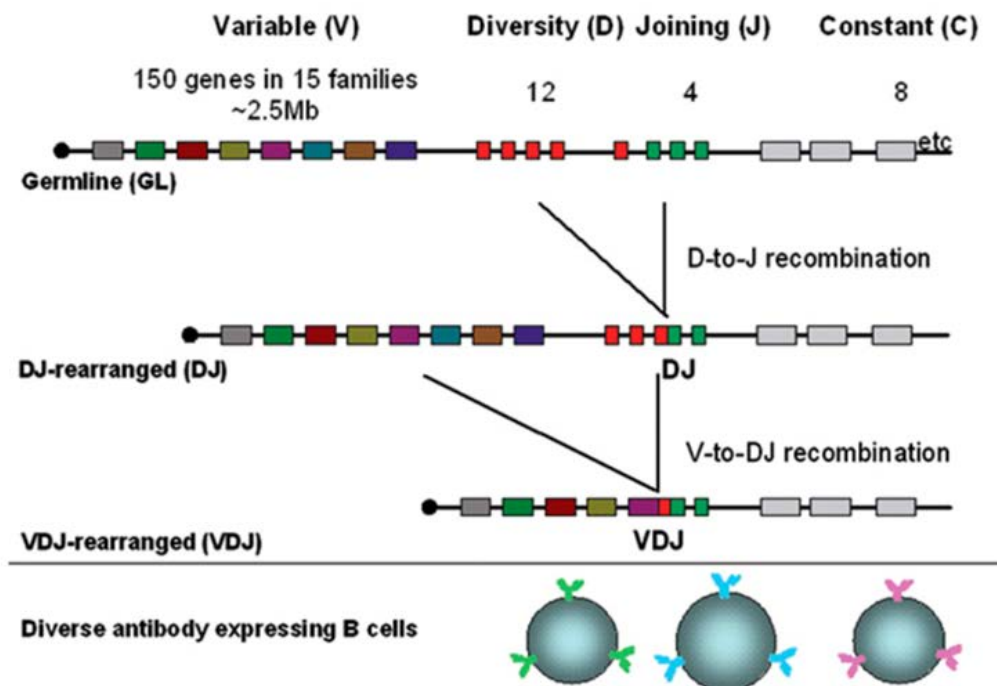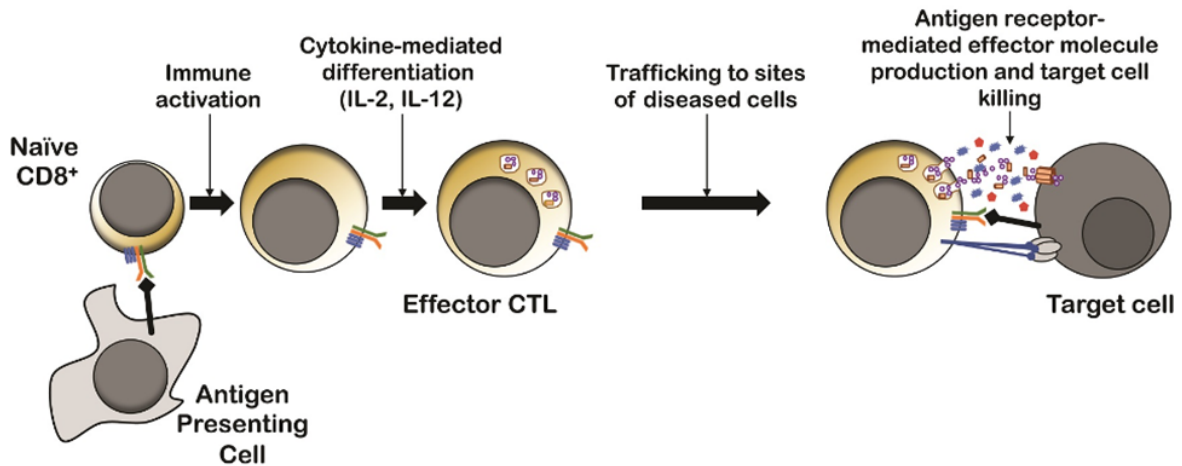

Recombination or 'shuffling' of genes in the immunoglobulin heavy chain (IgH) locus is the first step in generating the huge repertoire of antibodies to combat disease. Ageing can result in a reduced repertoire, which contributes to impaired response to infections in elderly people. Conversely if it's opened up excessively, or not closed down after recombination, inappropriate DNA breaks may occur, which may be repaired incorrectly causing B cell lymphomas.

Sarah Ross
[Immunology]

T lymphocytes are a critical component of the immune system and are vital for fighting infection and preventing the growth of diseased or damaged cells. Our aim is to understand both healthy and impaired immune responses and identify factors that can lead to autoimmunity, declined immune function with ageing and immunosuppression associated with the growth of tumours within the body.


Immune activation

Cytokine-mediated differentiation (IL-2, IL-12)

Trafficking to sites of diseased cells

Antigen receptor-mediated effector molecule production and target cell killing

Naïve CD8+

Effector CTL

Antigen Presenting Cell

Target cell

Naïve CD8+ cells patrol the body and are maintained in a quiescent state until they are alerted to signs of infection. Once alerted, they can be activated and differentiated into a CD8+ Effector T lymphocyte, which can go to sites of diseased cells and kill target cells. This needs to be functioning effectively for our immune system to keep us healthy.

Claudia Ribeiro de Almeida
[Immunology]

We study the molecular mechanisms underlying diversification of antibody genes by B cells, which are a key part of the immune system. These antibodies are encoded by immunoglobulin loci. Our aim is to understand the basic principles of immunoglobulin gene diversification to gain insight into how B cells can effectively fight infections, how these responses change through our lives and the role this plays in age-related immune dysfunction.
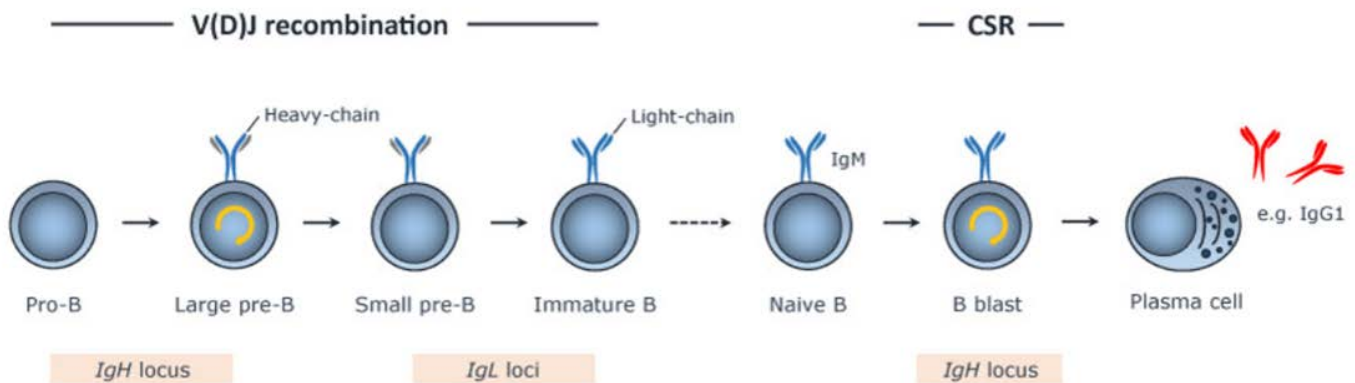

Development of B lymphocyte antibodies by V(D)J recombination and Class Switch Recombination (CSR) at immunoglobulin loci needs to occur for B cells to effectively fight infections. With age, these recombination mechanisms don't function as well, and so the older immune system is not as able to fight infections, making an individual more likely to become unwell.

Adrian Liston [Immunology]

We work on regulatory T cells, which are a type of white blood cell that suppresses the immune response. They prevent autoimmune disease and control how active our immune system is. The number of these cells in our blood goes up as we get old, which may contribute to the immune-supressed state of older persons. We seek to understand these cells so that we can harness their power to fine-tune the immune system for healthy ageing.

WT   Het   KO
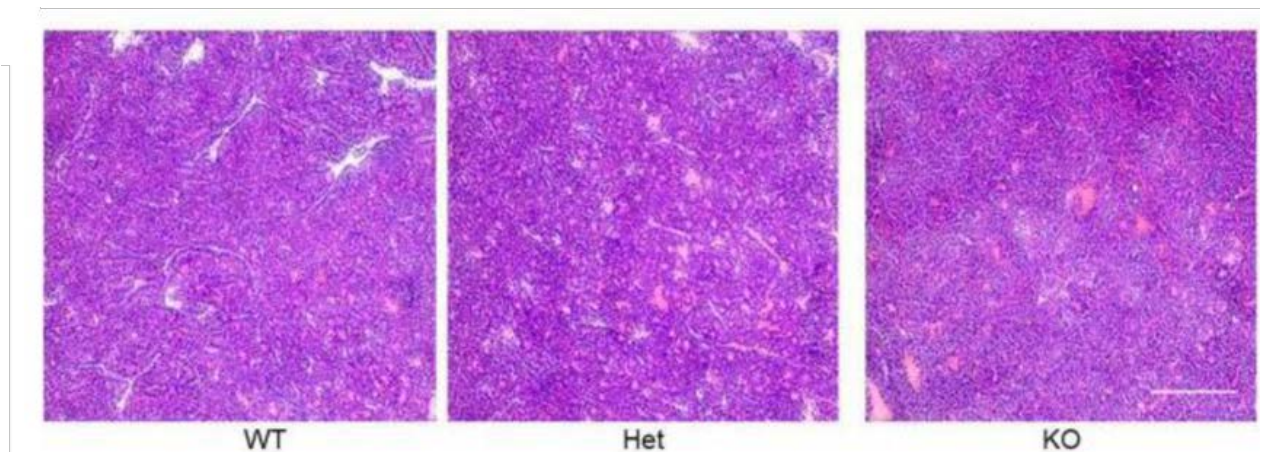
Knockout Mice see reduced expression of miR-342 in tumours. This gene is thought to be have a tumour suppressive role, and this model provides evidence as to whether this is the case in different tumour models.

Len Stephens , Phil Hawkins

[Signalling]

Signalling pathways are biological systems that allow cells to communicate and respond to changes in their surroundings. We study a pathway that involves the production of chemical signals by proteins called PI3Ks. This pathway plays a major role in the regulation of growth, metabolism, and immunity, and changes to this pathway are seen during ageing and in various human cancers.
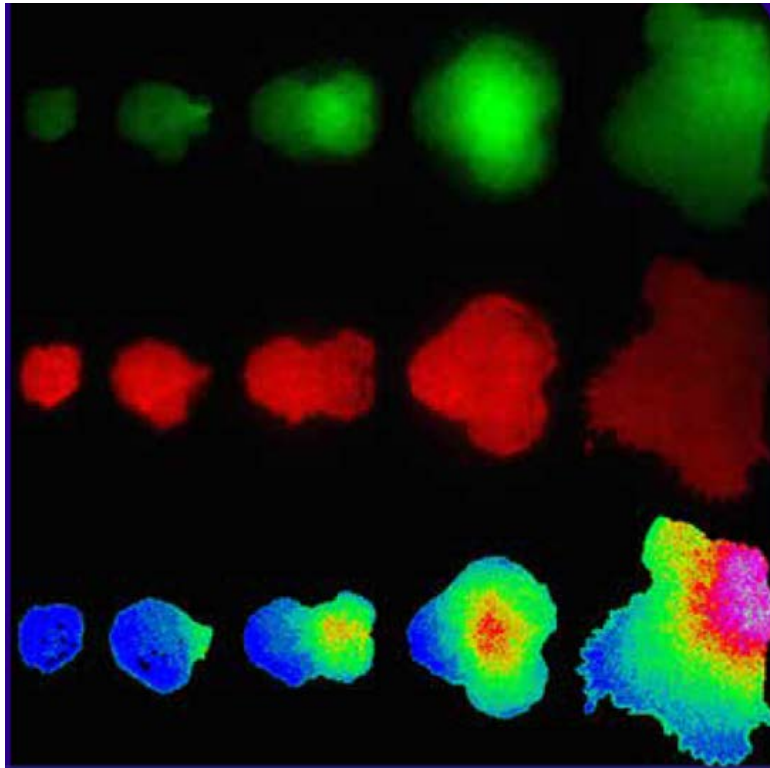

Image shows a type of white blood cell called a neutrophil moving in response to a chemical stimulus. The green images show the distribution of the signaling lipid PIP_3, a chemical signal produced by PI3K. The red images show a marker labelling the outside of the cell (used as a reference). A ratio image created from both is shown in rainbow colours. Neutrophils migrate to sites of infection and are a key component of the body's deference mechanisms.

Simon Cook

[Signalling]

Information from a cell's surroundings contribute to how it behaves and how it will change in the future – called cell fate decisions. Protein kinases influence cell fate decisions – whether to divide, change cell type or die – by transmitting information from the outside into the cell. We study how protein kinase pathways function, how they are controlled and how they determine cell fates because this affects processes such as wound repair in old age.
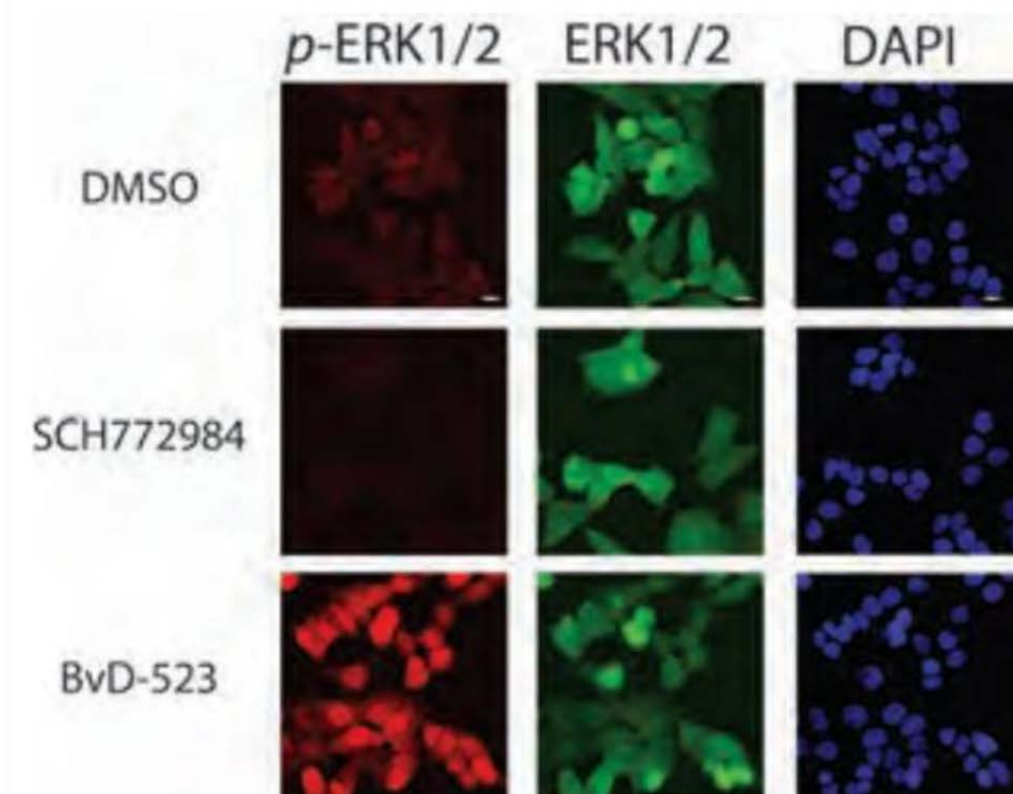
Representative high-content microscopy (HCM) images showing the rapid nuclear accumulation of p-ERK1/2 (red) following 2h treatment of cells with the catalytic ERK1/2 inhibitor (ERKi) BvD-523. In contrast, the dual-mechanism ERKi SCH772984 effectively inhibits ERK1/2 phosphorylation. The nucleus is stained with DAPI (blue) and a total ERK1/2 (green) control is shown

Oliver Florey
[Signalling]

Cells need to be able to break down and recycle parts of themselves, a process called autophagy, so they can stay healthy. Disruption of this process is associated with many age-related effects, including cancer and neurodegeneration. Our research involves phagosomes, which are cellular structures that contain things that have been brought in from outside the cell. We explore the molecular mechanisms underlying autophagy and several similar pathways to understand their roles in health and disease.
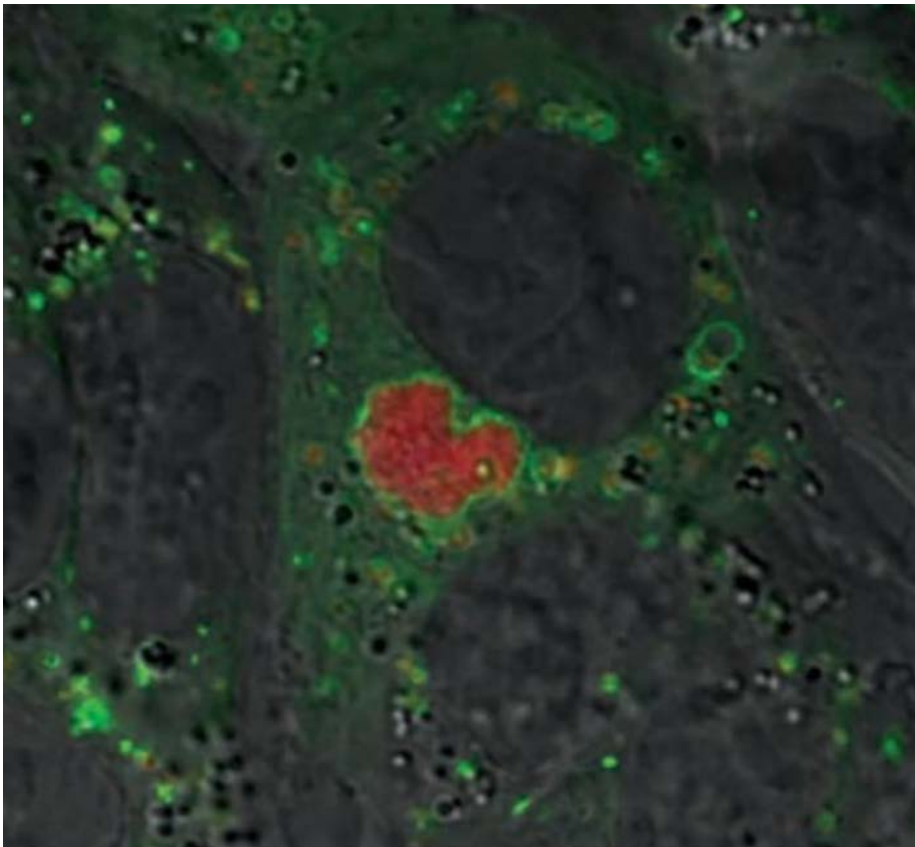

Image shows a Mouse Embryonic Fibroblast (MEF) cell – a type of cell that is easy to grow and study in the lab – an autophagy protein called LC3 (labelled in green) is targeted to a phagosome housing a dead cell (red), showing its subcellular localisation.

Nicholas Ktistakis

[Signalling]

Through a process called autophagy, cells are able to digest parts of themselves as a way to repair damage or to provide a source of nutrients to help survive starvation. My group aims to understand how this pathway is triggered and what the molecular details of the autophagic response are. Autophagy is critical for the extension of lifespan, and is therefore a significant factor that affects healthy ageing.

The PI3P paradox: the same lipid signal for two opposite cell decisions
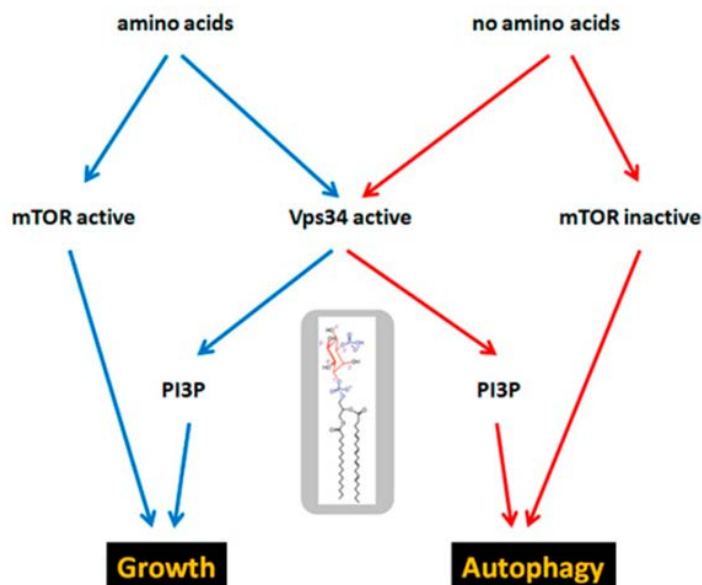
Under plentiful nutrients, PI3P appears to regulate in part the activity of the protein kinase target of rapamycin (TOR), a master regulator of cell growth. Upon nutrient depletion, TOR becomes inactivated and another pool of PI3P regulates the induction of autophagy, a conserved cellular response for the generation of nutrients from self digestion.

Michael Wakelam

[Signalling]

Fat molecules, also called lipids, play many roles inside and outside of cells. For example, they act as barriers, carry signals and are energy sources. Amongst other things, lipids are signals that help cells to respond to changing diet, infections and ageing. By using a range of methods to examine different lipids inside and outside of cells we aim to enhance our understanding of the varied roles they perform.

ACSS2
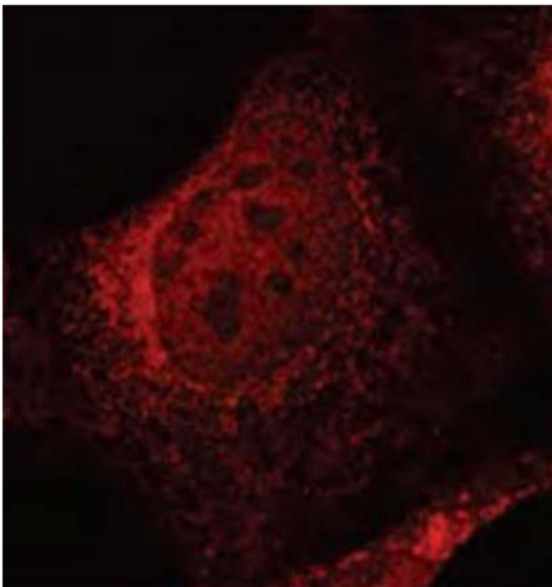
ACSS2 + DAPI
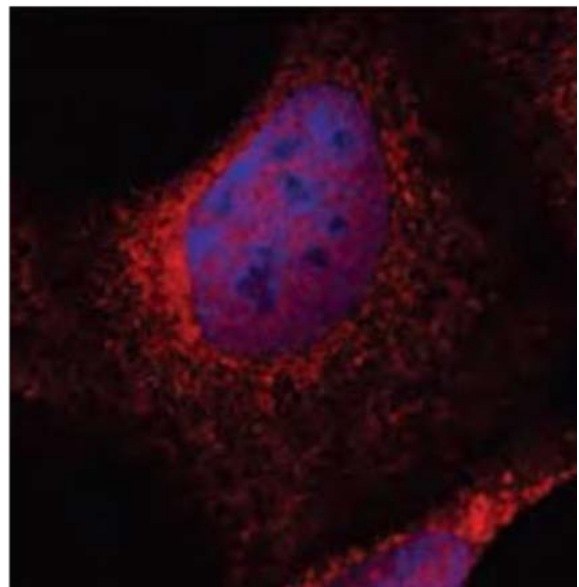
Microscopy imaging of the ACSS2 protein (red) in HEK-293 cells, a type of human cells often studied in the lab. ACSS2 is a key enzyme that acts at an early step in the synthesis of lipids and is found throughout cells. Images were taken using the Nikon A1R confocal microscope at 60x magnification. DAPI was used to show DNA in the cell nucleus (blue).

Heidi Welch

[Signalling]

Certain proteins can enable cells to move through their surroundings, a process that can be important for immune cells to be able to find infectious bacteria for example. We study these proteins, such as Rac, examining how they are controlled and activated. By monitoring protein activity inside cells, we are learning more about their roles in the immune response and in cancer.
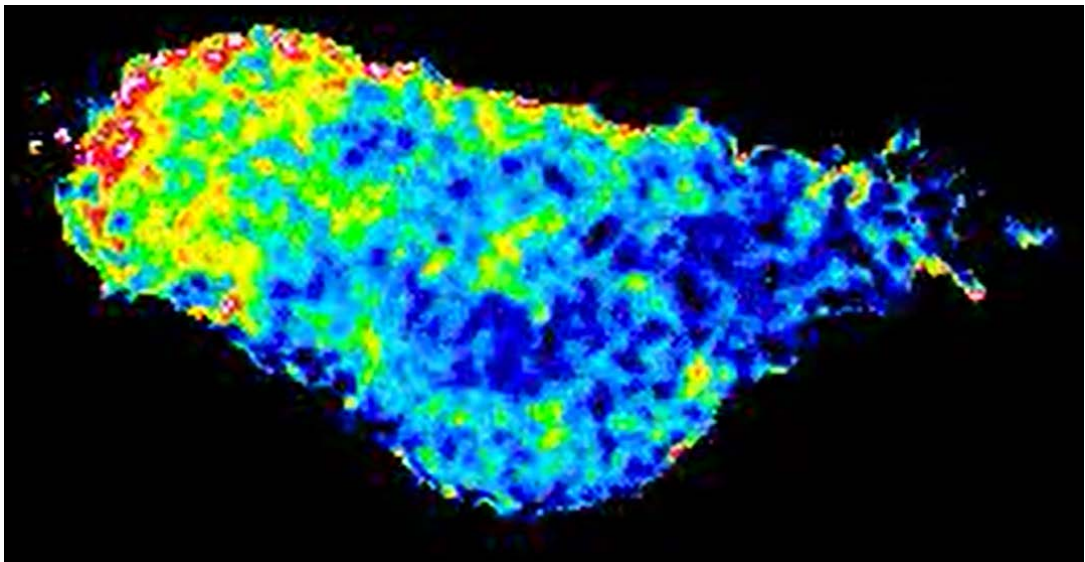
During neutrophil chemotaxis, active Rac is mostly found at the leading edge of the migrating cell. This shows Rac activity in a neutrophil from the Rac-FRET reporter mouse. This was made by FLIM-FRET time-lapse imaging of a Rac-FRET neutrophil as it migrates towards the chemoattractant fMLP (on the left). Rac activity is pseudo-coloured; red = high, blue = low.

Wolf Reik

[Epigenetics]

Epigenetics is the study of how reversible modifications to DNA can control access to genetic information. Epigenetic mechanisms are able to regulate gene expression and can behave as a form of memory that records the history of a cell. We are studying epigenetic memory during early embryonic development, and how it decays during ageing.
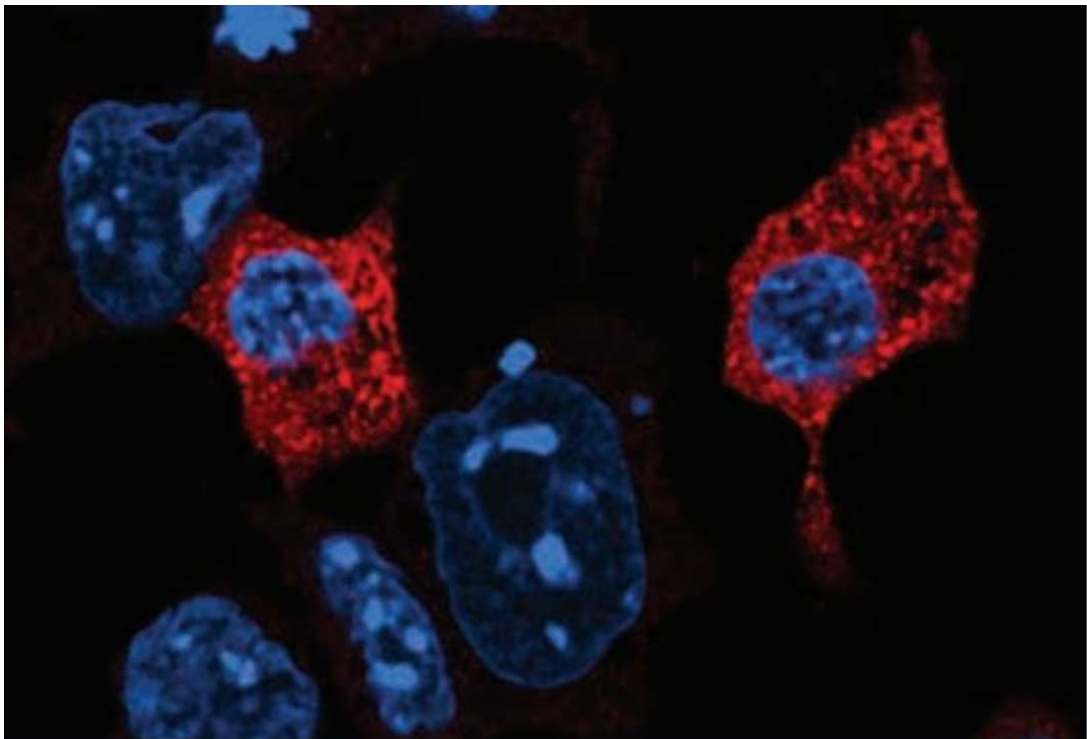

Image of fluorescently labelled embryonic stem cells. These cells have been modified to mimic the effects of epigenetic reprogramming changes that happen in developing embryos. DNA in the cells is marked in blue. Red indicates cells that contain active transposons – mobile pieces of DNA that can become active during reprogramming.

Olivia Casanueva

[Epigenetics]

Of the thousands of genes that have been linked to ageing, many affect how living things deal with external challenges linked to stress and nutrition. Such findings underscore the balance between genes and environment that govern our lifespans. Our lab aims to understand the non-genetic influences on lifespan and responses to stress by using the nematode worm, *C.elegans,* as a model organism.
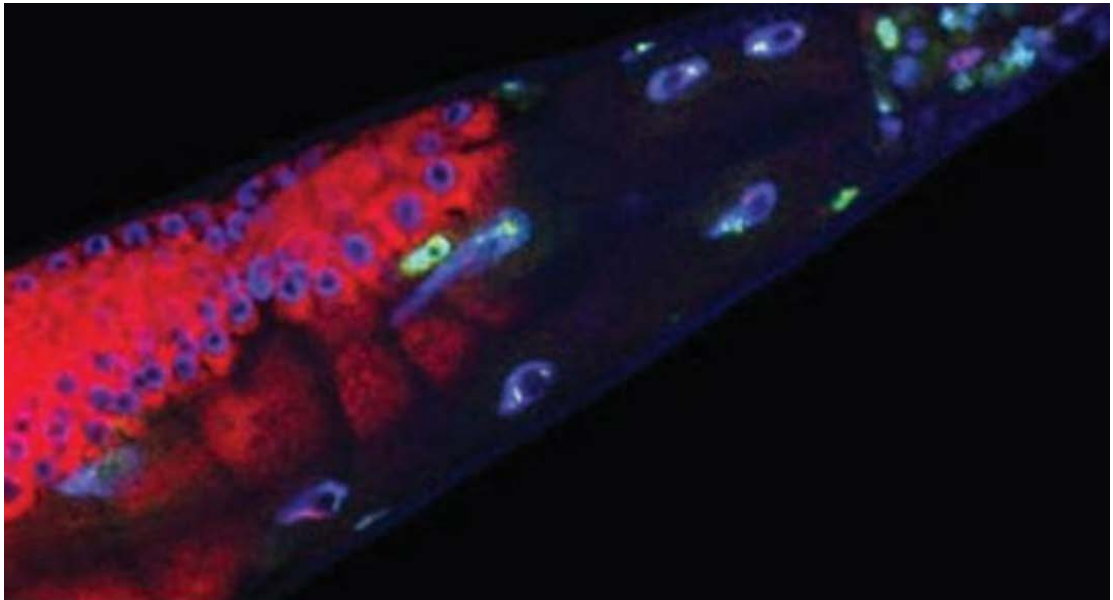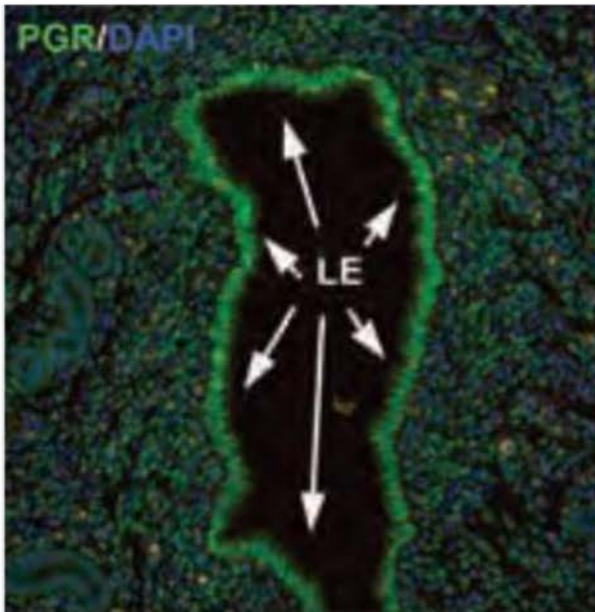

Young adult worms after heat shock (a sudden increase in temperature; 34°C for 30 mins). DNA inside cells is stained in blue. Messenger RNA (mRNA) from the hsp-90 gene are in red and mRNA from the hsp-70 gene are in green.

Myriam Hemberger

[Epigenetics]

A functional placenta is critical for normal embryonic development and lifelong health. The placenta develops from cells derived both from the embryo and from the mother. Trophoblast stem cells originate from the fertilised embryo and come together with cells from the mother's uterus to form a highly unique integrated unit. We focus on how genes are regulated during placenta formation and the effects of maternal age on this process.

E3.5 uterus **young** female   E3.5 uterus **aged** female
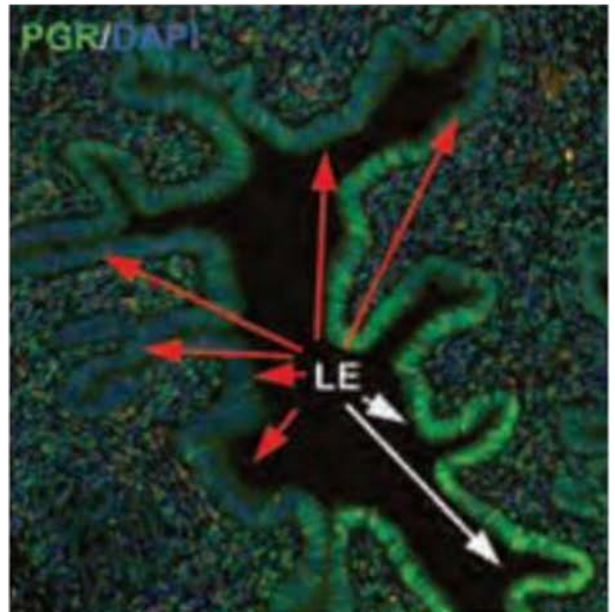
Uteri from young and aged female mice 3.5 days into pregnancy. The progesterone receptor protein (PGR) is shown in green and DNA labelled in blue using a stain called DAPI. White arrows point to the luminal epithelium (LE) – cells that line the uterus – with strong PGR expression. In young females the PGR signal is evenly distributed throughout the entire LE. Red arrows in aged uteri point to regions of the LE with reduced PGR levels.

Jon Houseley

[Epigenetics]

Cells can react and change in response to environmental pressures. These pressures and the way in which cells can react to them change with age. We study how cells adapt to their environment at the genetic and epigenetic level, particularly how they adjust to challenging and toxic environments. Our work aims to discover ways of improving health throughout life and to find better approaches to chemotherapy.
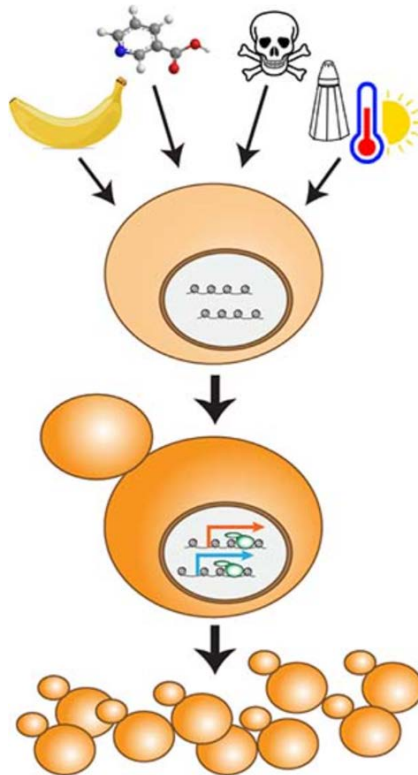

External cues, such as nutrient availability, the presence of a drug, cell death signals, salt concentrations and temperature all have an effect on a cell. Cells must react to these environmental cues and express the correct genes to the correct level to thrive. This may or may not be possible given their existing genetic information and how it is regulated.

Stefan Schoenfelder
[Epigenetics]

98% of our DNA does not code for proteins. Within these non-coding regions, are regulatory elements that function as molecular switches to control which genes are active in which cells. Our aim is to identify these regulatory elements to understand which genes they control and how altering their function can lead to developmental malformations and disease.
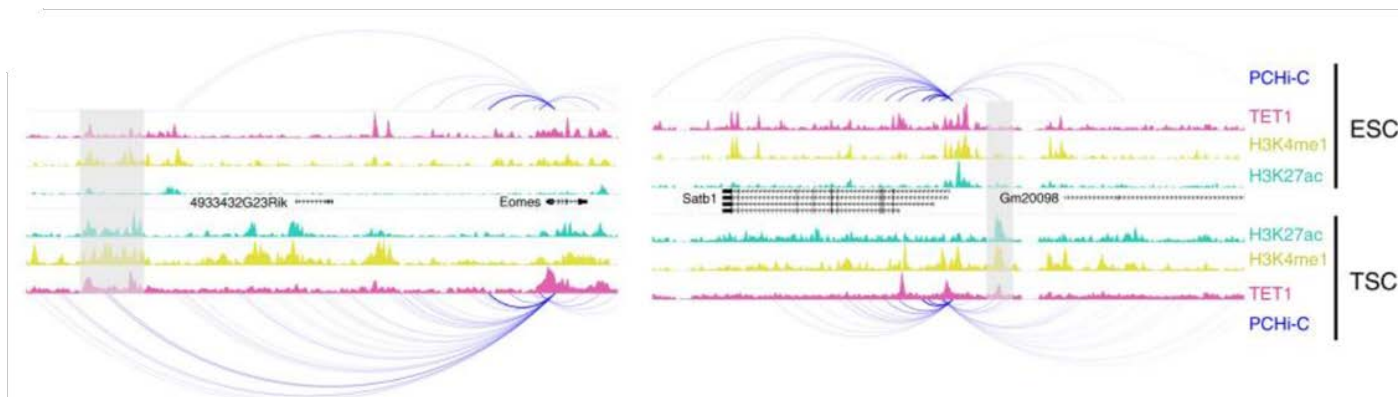

Promoter capture Hi-C experiments in mouse trophoblast (TSC) and embryonic (ESC) stem cells was carried out understand how the organisation of DNA in chromatin causes cells to be of certain types. Key TSC genes are kept repressed in ESCs, and seem to exhibit interactions between H3K27me3-marked regions (H3K27ac). Key TSC genes are enriched for enhancer-gene contacts in TSCs specifically, which helps to maintain the expression of TSC-relevant genes in this cell type.

Gavin Kelsey

[Epigenetics]

20

As well as genetic information, the egg and sperm also contribute epigenetic marks that may influence gene activity both during and after fertilisation. We examine epigenetics during egg development and the effects of epigenetic marks on gene activity in the embryo. Our goal is to understand whether, through epigenetics, factors such as a mother's age or diet have consequences on the health of a child.
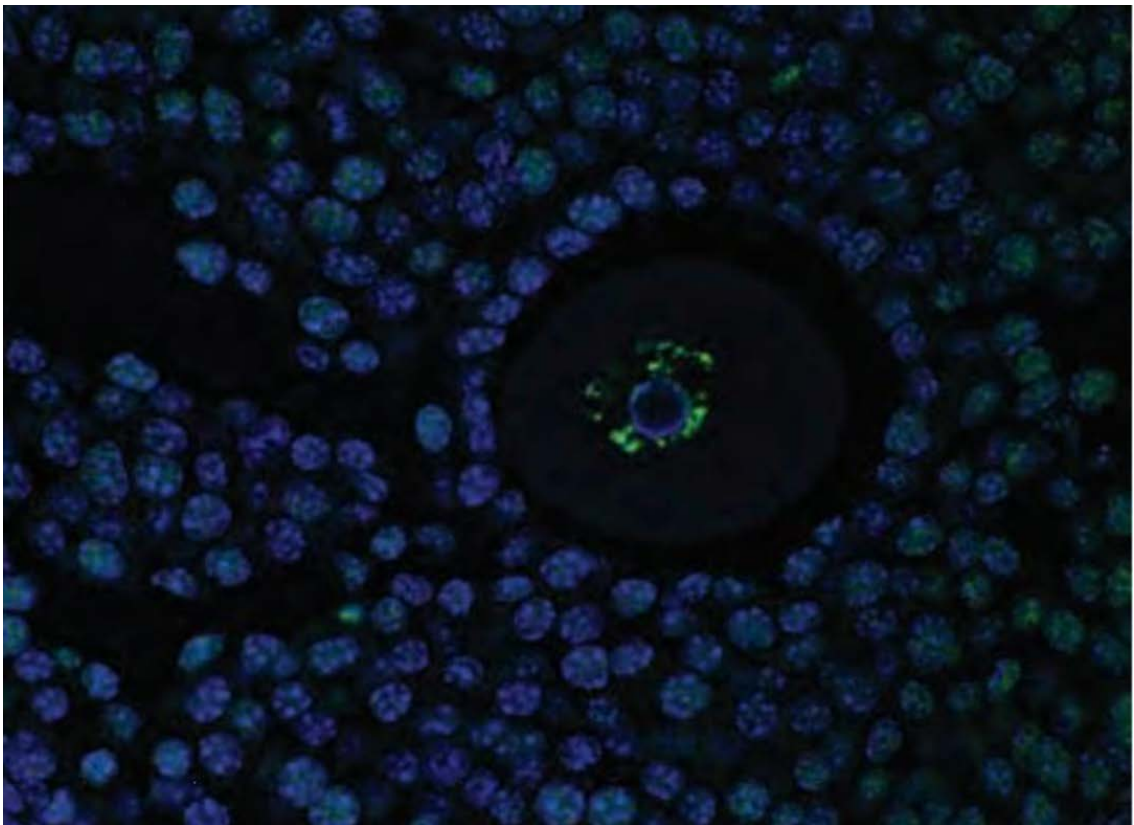

A mouse cell inside an ovary. DNA in each cell is shown in blue, epigenetic methylation marks are shown in green.

Peter Rugg-Gunn
[Epigenetics]

How DNA is packaged in cells and the use of biochemical switches in the genome are key aspects of the epigenetic control of gene activity. We are interested in understanding how epigenetic processes are established during human development and during the differentiation of stem cells to form various cell types. This is important for understanding health and for finding ways to use stem cells in regenerative medicine.
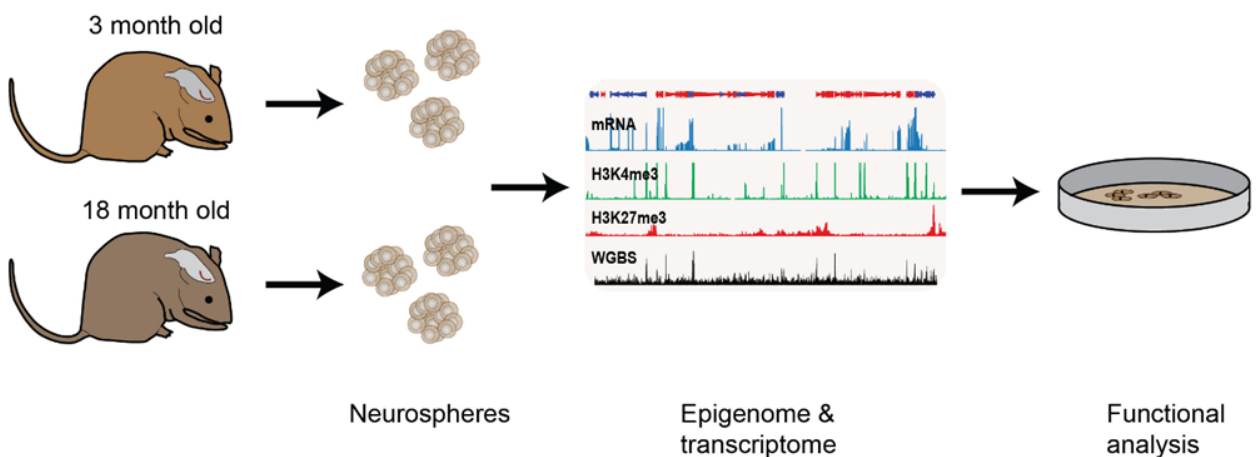
This diagram shows how we are trying to understand how epigenetic information changes over the life course of an individual. Though examining changes that occur upon neural stem cell (NSPCs) during ageing at a transcriptional and epigenetic level in adult (3 months old) and aged (18 months old) mice. We identified hundreds differences, and are now following up on these results to see if we can uncover new regulators of age-associated decline in neural stem cell function.