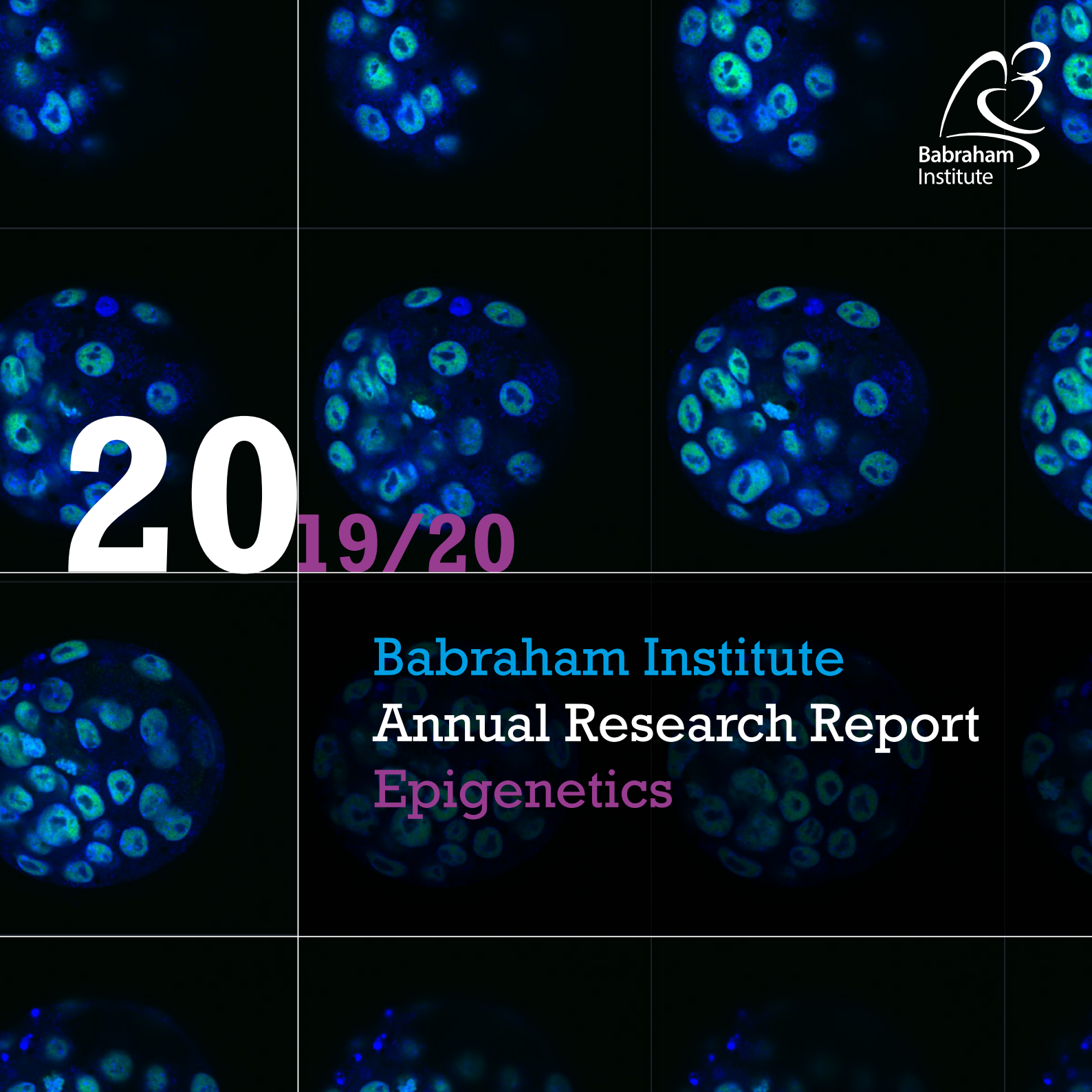
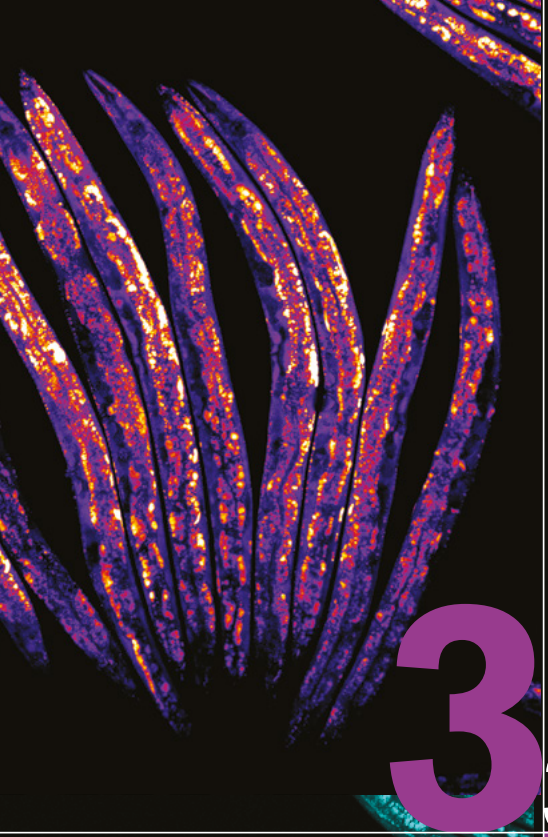
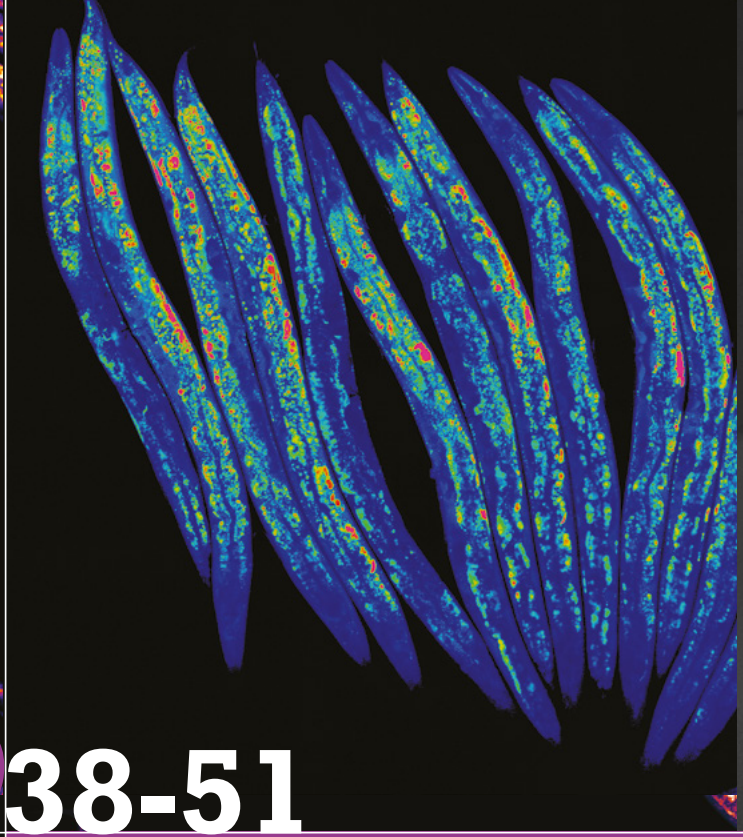


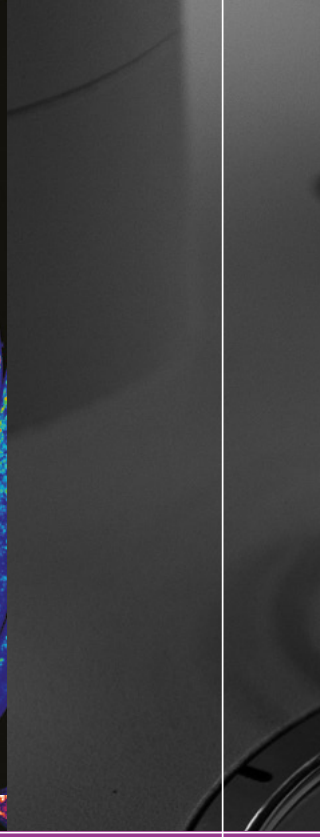
Babraham Institute

2019/20

Babraham Institute
Annual Research Report
Epigenetics







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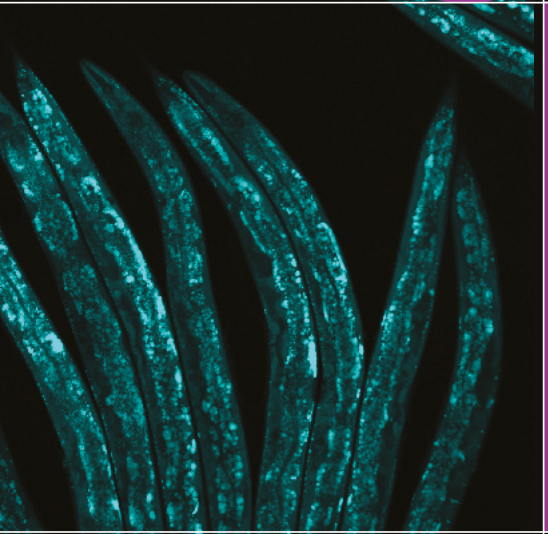
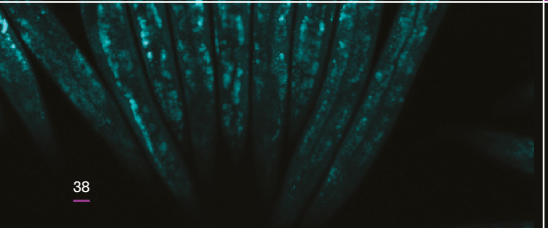


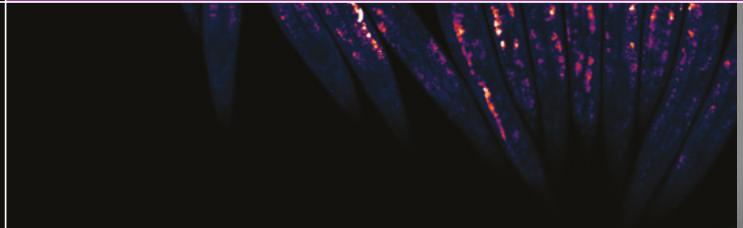
Epigenetics

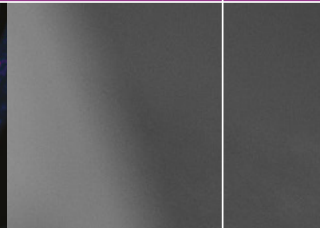
Inside cells, genetic information stored in DNA is packaged by proteins into a structure called chromatin. Epigenetics is the study of chemical modifications to DNA and to chromatin and the effects that these modifications have on genome function. Epigenetic marks are involved in the creation of different types of cells from stem cells and epigenetic changes over time are associated with ageing. Epigenetic marks also provide a form of cellular memory, recording certain information about past events and potentially carrying it between parent and child.

Our work in this area aims to enhance our understanding of how epigenetics shapes human development and affects healthy ageing by examining:

- How stem cells develop into different types of cells
- How epigenetic differences influence cell diversity
- The impacts of diet on epigenetics, health and ageing
- The inheritance of epigenetic memory between generations
- How life events affect biological ageing through an epigenetic clock
- New approaches and technologies to drive further progress



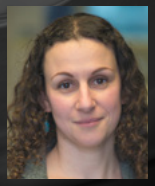




Group leaders

Gavin Kelsey

Olivia Casanueva



Maria Christophorou

Jon Houseley

Wolf Reik

Peter Rugg-Gunn

Stefan Schoenfelder

Martin Howard

Honorary group leader

Gavin Kelsey
Programme leader

Group members

Honorary fellows:
Courtney Hanna
Vicente Perez Garcia

Postdoctoral researchers:
Chris Belton
Juan Castillo Fernandez
Hannah Demond
Antonio Galvao
Elena Ivanova
Anastasios Mastrokolias

Research assistant:
Bess Chau

PhD students:
Gintare Sendzikaite
Leach McHugh

Visiting scientists:
Jordana Sena Lopes
Laura Saucedo-Cuevas (Left in 2019)
Claire Senner (Left in 2019)
Shinichi Tomizawa (Left in 2019)

Visiting student:
Caroline Faessler (Left in 2020)
Rebecca Koeck (Left in 2019)
Maribel Montufar-Martinez (Left in 2019)
Benjamin Planells (Left in 2019)
Edyta Walewska (Left in 2019)
Karolina Wolodko (Left in 2020)

Epigenetic legacies from eggs

As well as genetic information, the egg and sperm contribute epigenetic annotations that can influence how genes act after fertilisation. We examine how epigenetic patterns are set up 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 for the health of a child.

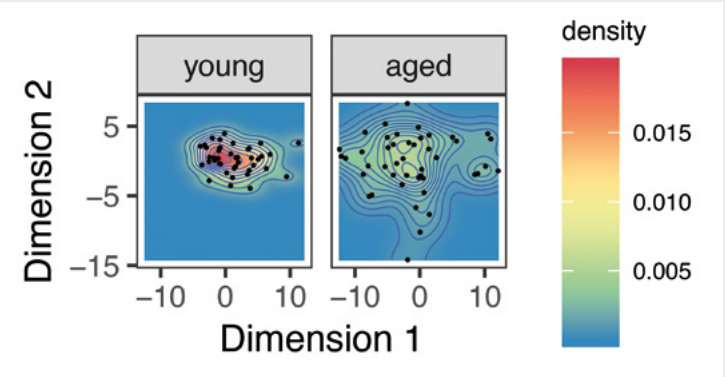
Current Aims

A major aim is to understand how repressive chromatin marks in oocytes lead to long-term silencing – imprinting – of genes from the mother, particularly in cells that form the placenta. We are seeking to understand the genetic elements that carry this epigenetic memory between generations, how they control these 'imprinted' genes, and how important the genes are for development and function of the placenta and consequently growth of the fetus. To investigate these questions, we develop methods to profile epigenetic information in small numbers of cells or even single cells, as well as using gene-editing methods.

Progress in 2019 and 2020

A highlight has been the discovery that a newly-described form of imprinting is controlled by genomic parasites – endogenous retroviral elements. Such elements can be co-opted during evolution as novel gene control modules. They can act in a highly tissue-specific way, and are controlled by the epigenetic machinery, suggesting they could be influenced by environmental or nutritional factors (ref. 2). This discovery also provides clues about the conservation of this form of imprinting.

We also provided the first genome-wide assessment of DNA methylation and gene expression in eggs from aged female mice (ref. 3). Eggs from older females had less active and less consistency in gene expression. Methylation in general correlated well between eggs from younger and older mice, providing reassurance that age does not affect key sites of DNA methylation in the genome, but there were gene-specific changes coupled to gene transcription differences.



Oocytes (egg cells) from reproductively old female mice have more variable gene expression than those from younger females. This is depicted as a 2D distribution of the distances between single oocytes as based on their similarity in gene expression. From Castillo-Fernandez, J. et al. (2020).

Selected Impact Activities

- Group representation for the 'Race Against the Ageing Clock' exhibit at the Cambridge Science Festival, March 2019.
- Plenary speaker at the 18th International Conference on Pre-implantation Genetic Diagnosis Geneva, April 2019.
- Speaker at Royal Society of Medicine continuing professional development workshop on 'Epigenetics', June 2019.

Publications

www.babraham.ac.uk/our-research/epigenetics/gavin-kelsey

@LabGavin

- Sendžikaitė, G. *et al.* (2019) A DNMT3A PWWP mutation leads to methylation of bivalent chromatin and growth retardation in mice. ***Nat. Commun.*** 10:1884
- Hanna, C. W. *et al.* (2019) Non-canonical imprinting in extra-embryonic tissues is driven by endogenous retroviral insertions. ***Genome Biol.*** 20:225
- Castillo-Fernandez, J. *et al.* (2020) Increased transcriptome variation and localised DNA methylation changes in oocytes from aged mice revealed by parallel single-cell analysis. ***Aging Cell*** 19: e13278

Olivia Casanueva

Group members

Senior research assistant:
Sharlene Murdoch
(Left in 2019)

Postdoctoral research scientists:
Laetitia Chauve
Celia Raimondi (Left in 2020)
Pun Suriyalaksh (Left in 2020)
Boo Virk (Left in 2019)

PhD students:
Janna Hastings (Left in 2019)
Abraham Mains (Left in 2019)

Research assistants:
Aina Bellver Sanchis
(Left in 2020)
Andriana Botan (Left in 2019)
Francesca Hodge
(Left in 2020)
Sheikh Mukhtar (Left in 2020

Visiting students:
Fatemeh Masoudzadeh
(Left in 2020)

Using systems biology tools in C. elegans to extend life

It is estimated that more than 20% of the global population will be over 60 by 2050, the highest percentage of older persons in recorded history (World Health Organization factsheet on Ageing and Health, 2018). Over the last two decades studies have drawn a remarkable link between metabolism, stress and longevity and this links needs exploration in the face of current societal challenges. We use the nematode C. elegans to study this important question.

Current Aims

The specific problem that we look at in my lab is the interplay between stress and metabolism during early ageing. To tackle this question, we have optimised new cutting-edge computational tools that bring new perspectives and insights into the problem. We have also used more traditional methods to uncover a novel longevity pathway. This is a neuronal thermostat that senses and help animals adapt to warming temperatures by modulating fat desaturation across tissues.

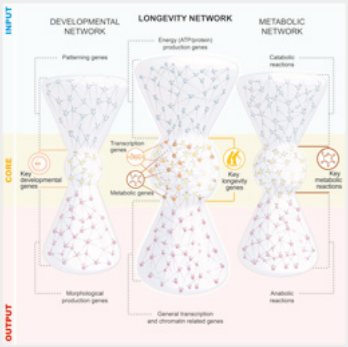
Progress in 2019 and 2020

My group used two very different and complementary approaches to explore key concepts that characterise longevity pathways. In one approach, we used classic genetics and lipidomics to discover that neurons can sense environmental temperature and send neurohormonal signals to help the body cope with a warming environment. We find that the neuronal thermostat regulates the membrane lipid composition and in doing so, extend lifespan. A similar neuro-hormonal axis may be key to healthy ageing in humans.

In a second approach, we took a highly systemic view of the germline longevity pathway and applied computational tools to understand how information flows within a network of gene interactions. This 'bird's-eye view' of a longevity pathway has a high predictive value for identifying the key genes that contribute to long life.

Selected Impact Activities

- The lab showcased the power of genetics using C. elegans as a model organism at the Cambridge Science Festival in 2019 as part of the 'Race Against the Ageing Clock' exhibit.
- The lab hosted students as part of the Institute's Schools' Day events in 2019 and 2020.
- We also presented our work at the 17th Animal Science Meeting (2019), co-organised by the Royal Society of Biology and the Animals in Science Regulation Unit.



Network inference methods allowed us to obtain a 'bird's-eye view' of long-lived sterile worms. The hour-glass shape of information flow in the longevity network (at the centre) is similar to other well-described networks (developmental and metabolic networks). In the longevity network, the information from the input module—enriched in genes required for the production of energy—feeds information to a core module. The core module, in turn, feeds back information to an output module that is enriched in genes that modulate basal transcription and chromatin remodelling. What is very striking is that the hour-glass shape is predictive of functionality: the core module is enriched in genes that are key to long life. This finding fast-tracks ageing research in model organisms and can potentially be applied to humans.

Publications

www.babraham.ac.uk/our-research/epigenetics/olivia-casanueva

- Özbey, N. *et al.* (2020). Tyramine acts downstream of neuronal XBP-1s to coordinate inter-tissue UPRER activation and behavior in C. elegans. ***Dev. Cell*** 55(6):754-770.e6
- Okkenhaug, H. *et al.* (2020) Worm-align and Worm_CP, two open-source pipelines for straightening and quantification of fluorescence image data obtained from Caenorhabditis elegans ***J. Vis. Exp.*** (159):10.3791/61136
- Chauve, L. & Le Pen, J. *et al.* (2020) High-throughput quantitative RT-PCR in single and bulk C. elegans samples using nanofluidic technology. ***J. Vis. Exp.*** (159):10.3791/61132

Maria Christophorou

Group members

Postdoctoral researcher:
Johanna Grinat

PhD students:
Daniel Moore
Robert Walmsley

Signalling to stem cell chromatin

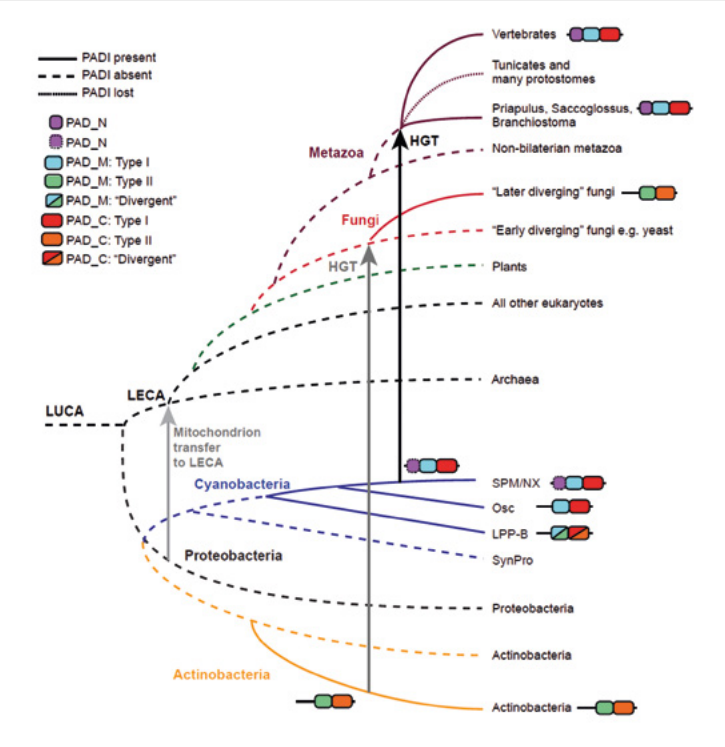
Changes in the cellular environment, such as stresses and developmental cues, affect the epigenetic and transcriptional state of cells, thereby influencing cell identity. We aim to understand how environmental signals are translated into epigenetic changes through studying the biochemical regulation of epigenetic factors. We focus on one particular type of biochemical mechanism, the conversion of arginine residues to non-coded citrullines, or protein citrullination.

Current Aims

The citrullinating enzyme PADI4 modulates transcription and chromatin compaction and has well-established roles in innate immunity and the development of autoimmunity. We discovered that PADI4 also has a role in stem cells, regulating the establishment of pluripotency during cell reprogramming and early embryo development. Our current research aims to identify the mechanism through which PADI4 influences cell fate during embryo development, in adult tissues, and during the generation of induced pluripotent stem (iPS) cells. In parallel, we study the biochemical mechanisms that determine PADI4 activation and how citrullination, in turn, modulates the function of epigenetic regulators.

Progress in 2020

Our work towards understanding PADI4 activation led us to the unexpected discovery that the PADI enzymes, which were widely thought to be vertebrate-specific, are also present in some bacteria and fungi and have a highly unusual phylogenetic distribution. Through studies of phylogeny, protein structure, sequence evolution and protein biochemistry, we demonstrated that animal PADIs were introduced into animals through horizontal gene transfer from cyanobacteria. This work has implications for how we think about the organismal roles of PADIs, why they were retained and multiplied during animal evolution and how aberrant citrullination may promote the development of autoimmune diseases.



The distribution of PADI genes across the tree of life and proposed model of PADI evolution

Publications

www.babraham.ac.uk/our-research/epigenetics/maria-christophorou

@MAChristoLab

- Christophorou, M.A. *et al.* (2014). Citrullination regulates pluripotency and histone H1 binding to chromatin. ***Nature*** 507(7490):104-8
- Casanova, V. *et al.* (2020). Citrullination alters the antiviral and immunomodulatory activities of the human cathelicidin LL-37 during rhinovirus infection. ***Front. Immunol.*** 11:85
- Wiese, M. *et al.* (2019). Citrullination of HP1γ chromodomain affects association with chromatin. ***Epigenetics Chromatin.*** 12(1):21

Jon Houseley

Group members

Senior research associate:
Cristina Cruz

Postdoctoral researchers:
Anna Channathodiyil
Ryan Hull (Left in 2019)
Alex Whale

PhD students:
Dorottya Horkai
Neesha Kara
Andre Zylstra (Left in 2020)

Research assistant:
Michelle King (Left in 2020)

Visiting students:
Ania Daniels Uribarri
Sumaera Rathore
(Left in 2019)
Fabiola Vacca (Left in 2019)

How cells interact with their environment

We study how cells adapt to their environment at the genetic and epigenetic level, particularly how they adjust to challenging and toxic environments. This contributes to our understanding of how our cells change in response to environmental pressures and as a consequence of ageing. Our work aims to discover ways of improving health throughout life and to find better approaches to chemotherapy.

Current Aims

1. To determine how conflicts between replication and transcription cause mutations in patterns specific for the current environment, leading to both chromosomal changes and formation of extrachromosomal DNA.

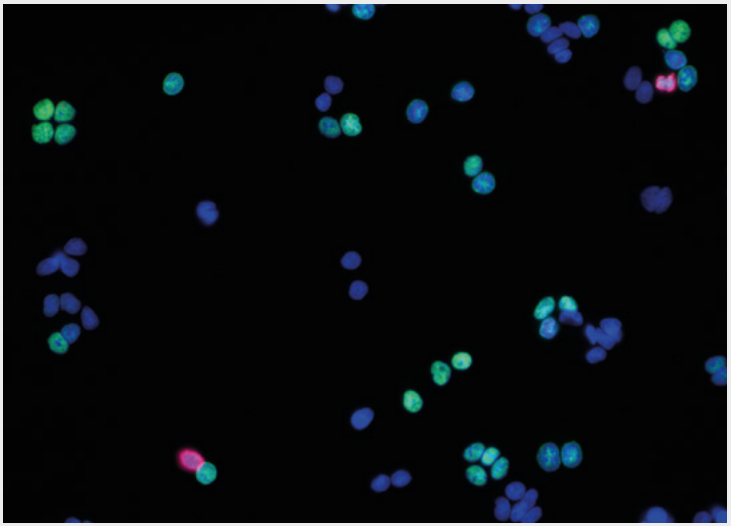
2. To elucidate the contribution of DNA replication errors to the acquisition of novel mutations in cancer cells that underlie acquisition of drug resistance.

3. To understand how epigenetic marks contribute to gene expression changes during ageing, and the extent to which these age-linked changes are controlled by signalling of nutrient availability.

Progress in 2019 and 2020

We have continued our work on extrachromosomal circular DNA – unstable DNA species that often host oncogenes and drug resistance genes in cancer cells. Circular DNA is implicated in cellular ageing, and we are investigating the accumulation of circular DNA during ageing and the impact of circular DNA on ageing phenotypes. This work is revealing how circular DNA can accelerate adaptation to challenging environments, promote drug resistance and mediate progressive changes in cell physiology.

In 2020 we saw major advances in our work on mechanisms of adaptive genome change, as we learn more about how replication defects caused by environmental change can form new adaptive mutations. The resulting publications will emerge next year, but some of the underlying methods, for example to improve genome-wide analysis of small, defined cell populations, have been released.



HT-29 cells (a colorectal cancer cell line), stained for DNA replication (green, EdU incorporation) and mitosis marker phopho-H3S10 (red). Image acquired in the Institute's Imaging facility by Prasanna Channathodiyil.

Selected Impact Activities

- We contributed a research spotlight article on epigenetics in ageing for The Physiological Society policy document 'Growing older, better'.
- We have a new collaboration in place with AstraZeneca to recruit a PhD student who will study the acquisition of drug resistance during chemotherapy.
- Our work was featured in an article on extrachromosomal circular DNA in Chemical and Engineering News: The curious DNA circles that make treating cancer so hard.

Publications

www.babraham.ac.uk/our-research/epigenetics/jon-houseley

@HouseleyLab

- Hull, R.M. *et al.* (2019). Transcription-induced formation of extrachromosomal DNA during yeast ageing. ***PLoS Biol.*** 17:e3000471
- Hull, R. M. & Houseley, J. (2020). The adaptive potential of circular DNA accumulation in ageing cells. ***Curr. Genet.*** 66:889-94
- Prada-Luengo, I. *et al.* (2020). Replicative aging is associated with loss of genetic heterogeneity from extrachromosomal circular DNA in Saccharomyces cerevisiae. ***Nucleic Acids Res.*** 48:7883-98

Wolf Reik

Group members

Laboratory manager:
Annalisa Mupo

Senior research scientists:
Stephen Clark
Wendy Dean (Left in 2019)
Debbie Drage
Mariya Rostovskaya
Fatima Santos

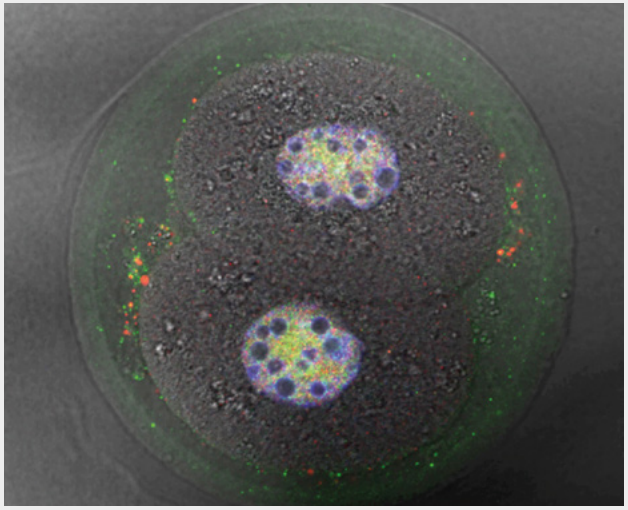
Research fellow:
Irina Abnizova
Melanie Eckersley-Maslin (Left in 2020)
Irene Hernando Herraez
Aled Parry
Carine Stapel
Jasmin Stowers

Postdoctoral researchers:
Abdulkadir Abakir
Ricard Argelaguet
Julia Spindel
Chris Todd

PhD students:
Diljeet Gill
Oana Kubinyecz
Georgia Lea
Juliette Pearce (Left in 2020)
Brendan Terry

Research assistant:
Laura Benson

Single-cell multi-omics landscape of development and ageing



Mouse two-cell embryo stained for DNA-blue, Dppa2-green and Smarca5-red. Credit: Oana Kubinyecz, Reik lab.

We are interested in epigenetic gene regulation in mammalian development and ageing. Epigenetic marks (such as DNA or histone modifications) act in concert with cell signalling and transcription factors to regulate cell fate. We are particularly interested in the epigenetic rules that govern cell fate decisions in early development, and how cell fate degrades during ageing. Our research uses single-cell sequencing methods to investigate cell fate decision at the level of individual cells.

Current Aims

A primary interest of the group is the regulation of zygotic genome activation, the sudden springing to life of transcription of the embryonic genome shortly after fertilisation. Our work also looks to identify DNA binding proteins which 'prime' enhancers or promoters for gene activation at later stages in development. In terms of our expertise in epigenetic clocks, we are working on a protocol by which human fibroblasts are reprogrammed towards induced pluripotent stem cells (iPSCs) but then released from reprogramming to adopt their original cell identity again whilst becoming more youthful in the process.

Progress in 2019 and 2020

We have carried out a screen for regulators of zygotic genome activation in the mouse. The screen was undertaken in embryonic stem cells by CRISPR activation with a single cell transcriptional read-out. We identified several proteins such as Dppa2, Smarca5, and Patz1 as putative ZGA regulators. We are now testing the roles of these proteins in mouse embryos in vivo. We also found that the two DNA binding proteins Dppa2 and Dppa4 are important for priming of promoters of bivalent developmental genes. Bivalent genes are marked by both active and repressive histone modifications which keeps them poised for future activation. Dppa2 and Dppa4 were found to be important for targeting bivalency to promoters of developmental genes and thus for the later activation of these genes.

Selected Impact Activities

- We were awarded a Wellcome Collaborative Award and an ERC Advanced Grant.
- Melanie Eckersley-Maslin won the 2020 Metcalf prize and was appointed group leader at Peter MaCallum Cancer Centre Melbourne.
- Wolf Reik was named Highly Cited Researcher in 2020 (Clarivate Analytics).

Group members

Visiting scientists:
Romina Durigon (Left in 2019)
Daniel Ives (Left in 2019)
Ferdinand von Meyenn
Nelly Olova

Visiting students:
Daniel Elias Martin Herranz
Adriana Fonseca (Left in 2019)
Lori Kregar (Left in 2020)
Tim Lohoff
Hendrik Vogt

Publications

www.babraham.ac.uk/our-research/epigenetics/wolf-reik

@ReikLab

- Lohoff, T. *et al.* (2021) Highly multiplexed spatially resolved gene expression profiling of mouse organogenesis. ***Nat. Biotechnol.*** in press
- Alda-Catalinas, C. *et al.* (2020) A single-cell transcriptomics CRISPR-activation screen identifies new epigenetic regulators of zygotic genome activation. ***Cell Syst.*** 11:25-41
- Eckersley-Maslin, M. *et al.* (2020) Epigenetic priming by Dppa2 and 4 in pluripotency facilitates multi-lineage commitment. ***Nat. Struct. Mol. Biol.*** 27:696-705

Epigenetic regulation of human development

Peter Rugg-Gunn

Group members

Senior researcher:
Clara Novo (Left in 2019)

Postdoctoral researchers:
Stephen Bevan
Claudia Semprich
Yang Wang

PhD students:
Adam Bendall
Mandy Collier (Left in 2019)
Charlene Fabian
Andrew Malcolm
Kate Maskalenka

Visiting scientist:
Jazmine Murray (Left in 2020)

Visiting student:
Monica Della Rosa
(Left in 2019)

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 biology.

Current Aims

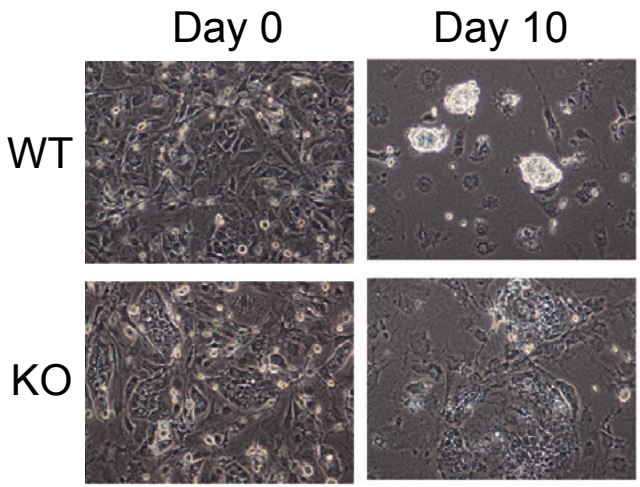
We aim to understand the epigenetic and gene regulatory mechanisms that operate in unspecialised pluripotent stem cells and in cells transitioning towards more specialist cell types. We examine how these mechanisms are established in development, how they control cell state changes more generally, and how their alteration can be helpful to reprogramme mature cell types back into an unspecialised form. Our work also investigates how certain epigenetic marks can anticipate future decisions made by stem cells as they specialise. Applying this information will allow us to more precisely control cell fate decisions and to better understand the processes that shape human development.

Progress in 2019 and 2020

It is increasingly important to understand how pluripotency, the ability to specialise into all other cell types, is established during human development and in stem cell lines. Towards this goal, we have completed a genome-wide genetic screen that has newly identified many genes and pathways that are involved in establishing pluripotency in human cells. We found that the identified factors have important roles in controlling gene activity and epigenetic modifications to DNA. Investigating these processes will help to define the molecular mechanisms that control early development and will provide new insights into stem cell properties such as cell identity, differentiation and reprogramming.

Selected Impact Activities

- Working with the ORION Open Science consortium, we participated in a series of events to better understand public attitudes in different European countries towards genome editing technologies.
- We co-authored a strategy report by the Regenerative Biology and Stem Cell Working Group commissioned by the BBSRC.
- We collaborated with Lonza and Pfizer to leverage our understanding of gene regulatory control to improve manufacturing processes.



Microscopy images showing human stem cells before (Day 0) and after (Day 10) reprogramming into a 'naïve' pluripotent state. The image shows the dramatic effect observed when a key epigenetic protein that we have identified is removed from the cells. The normal, wild-type cells (WT) are shown in the upper row, where 'naïve' pluripotent cells can be seen at Day 10 as a tightly compacted ball of cells. In contrast, cells lacking the protein (KO) shown in the lower row are unable to generate naïve pluripotent cells, revealing that the identified epigenetic protein has a critical function in establishing naïve pluripotency in humans.

Publications

www.babraham.ac.uk/our-research/epigenetics/peter-rugg-gunn

@RuggGunnLab

- Wojdyla, K. *et al.* (2020) Cell-surface proteomics identifies differences in signaling and adhesion protein expression between naive and primed human pluripotent stem cells. ***Stem Cell Rep.*** 14:972-988
- Ortmann, D *et al.* (2020) Naive pluripotent stem cells exhibit phenotypic variability that Is driven by genetic variation. ***Cell Stem Cell*** 27:470-481
- Rugg-Gunn, P. (2019) Transcription factors make the right contacts. ***Nat. Cell Biol.*** 21:1173-1174

Stefan Schoenfelder

Group members

Postdoctoral researcher:
Yang Cao

3D genome organisation and effect on genome function

The three-dimensional organisation of our genome is tightly linked to its function. Gene regulatory elements such as enhancers control spatiotemporal gene expression programmes in development by engaging in contacts with their target genes, sometimes over large genomic distances. Our research investigates how the three-dimensional organisation of the genome enables specific enhancers to control gene expression during stem cell renewal and differentiation.

Current Aims

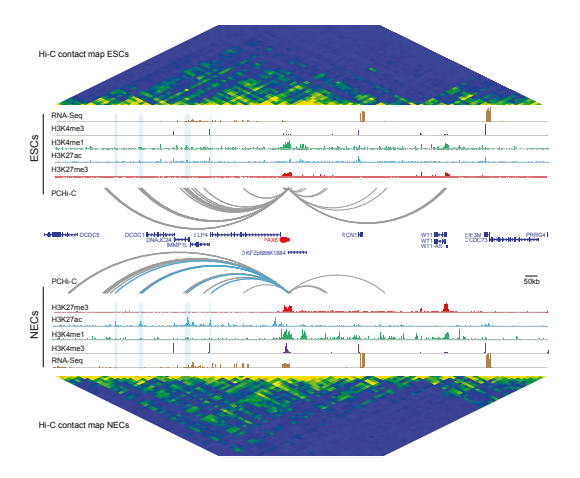
Human induced pluripotent stem cells (iPSCs) hold great potential for cell-based applications in regenerative medicine and disease modelling. However, individual iPS cell lines differ markedly in their ability to differentiate into bespoke cell types for applications in biomedicine. Non-coding genetic variants are emerging as key contributors to this functional heterogeneity between iPSCs, but their role is poorly understood. We combine functional genomics approaches with human genetics to understand how regulatory variants in the non-coding genome affect cell fate decisions during stem cell differentiation.

Progress in 2019 and 2020

We have mapped the gene regulatory landscape across a panel of iPSC lines by profiling chromatin accessibility, 3D genome organisation and long-range enhancer-promoter contacts genome wide. This lays the foundation for our ongoing functional dissection of the gene regulatory networks in human pluripotent stem cells, using a combination of massively parallel reporter gene assays and CRISPR (epi)genome editing. Our aim is to identify non-coding genetic variants that contribute to functional heterogeneity between human pluripotent stem cell lines, and to understand how they exert their function in the context of the three-dimensional organisation of the pluripotent genome.

Selected Impact Activities

- Incorporation of a start-up company 'Enhanc3D Genomics' (as co-founder) commercialising Institute research.
- Talk at Masters' student course 'Genomic Medicine: Epigenetics and Epigenomics'.
- Participation in the Institute's Schools' Day 2020.



Developmental control of enhancer-promoter contacts during early human cell lineage specification: Transcriptional upregulation of PAX6 during the conversion of human embryonic stem cells (ESCs) into neuroectodermal cells (NECs) is accompanied by the formation of enhancer-promoter contacts in NECs (mapped by Promoter Capture Hi-C; PCHi-C), which involves both novel enhancer-promoter contacts and the emergence of the enhancer associated mark acetylation at lysine 27 of histone H3 (H3K27ac) at genomic regions that already interacted with PAX6 in ESCs (modified from Freire-Pritchett et al., eLife 2017).

Publications

www.babraham.ac.uk/our-research/epigenetics/stefan-schoenfelder

@stefanschoenfe1

- Schoenfelder, S.& Fraser, P. (2019) Long-range enhancer-promoter contacts in gene expression control. ***Nat. Rev. Genet.*** 20:437-455
- Olan, I. *et al.* (2020) Transcription-dependent cohesin repositioning rewires chromatin loops in cellular senescence. ***Nat. Commun.*** 11:6049
- Thiecke, M.J. *et al.* (2020) Cohesin-dependent and -independent mechanisms mediate chromosomal contacts between promoters and enhancers. ***Cell Rep. 32***:107929

Martin Howard
Honorary group leader

Group members

Visiting postdoctoral researcher:
Govind Menon

Probing epigenetics through mathematics

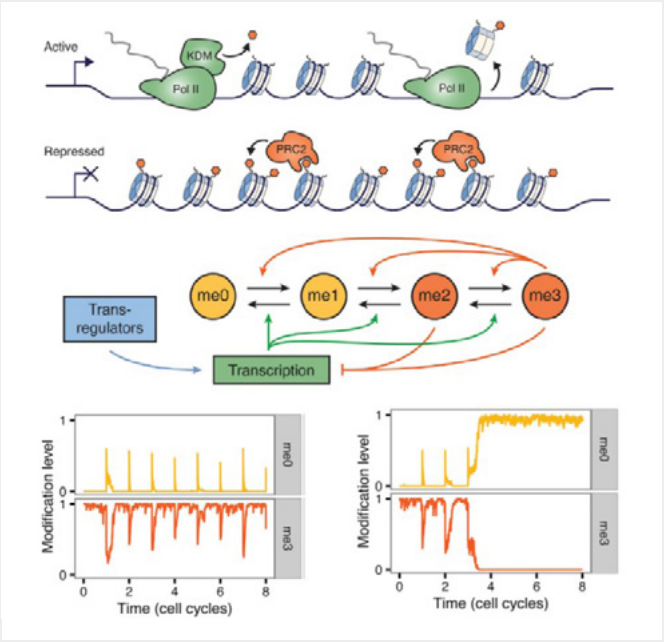
Our research explores how epigenetic memory is stably stored and propagated through the cell cycle. We take a theoretical approach using mathematical modelling in combination with experiments from collaborators, in an iterative cycle. This interdisciplinary approach helps to speedily unlock underlying mechanisms in systems which are otherwise too complex to dissect with experiments alone.

Current Aims

My lab at the John Innes Centre is currently investigating epigenetics in the context of the stable gene silencing provided by the Polycomb system, vital to developmental transitions and environmental response. In particular, we are trying to understand how memory of the Polycomb silenced state is propagated despite the perturbation of DNA replication. We are also investigating the dynamics of DNA methylation and how it is stably propagated. The group also has a long-standing interest in spatiotemporal protein dynamics and patterning processes, which we are currently studying through the phenomenon of crossover interference in meiotic crossover positioning.

Progress in 2019 and 2020

We uncovered a new state of Polycomb silencing (ref. 3) present after the apparatus that initialises the silenced state has disassembled, and whose epigenetic stability is modulated through Single Nucleotide Polymorphisms (SNPs). The system we studied is epigenetically silenced by prolonged cold: we therefore investigated how the cold is perceived, which led us to a novel mechanism [ref. 2] where cold slows growth and thereby allows the concentration of a stable protein to rise. Finally, we investigated the consequences of rapid cell cycles in the early Drosophila embryo [ref. 1], finding that rapid cycling may play a crucial role in keeping chromatin naïve. Collaborations with group leaders at the Babraham Institute are also now being developed, focusing particularly around the concept of bivalency (with the Reik lab).



Modelling Polycomb epigenetic dynamics. Top: schematic of chromatin state in active (upper) and silenced (lower) state. Middle: key ingredients of a mathematical model for Polycomb dynamics. Bottom: simulation of silenced state (high H3K27me3) periodically perturbed by DNA replication (left) and of silenced state switching to an active state (right).

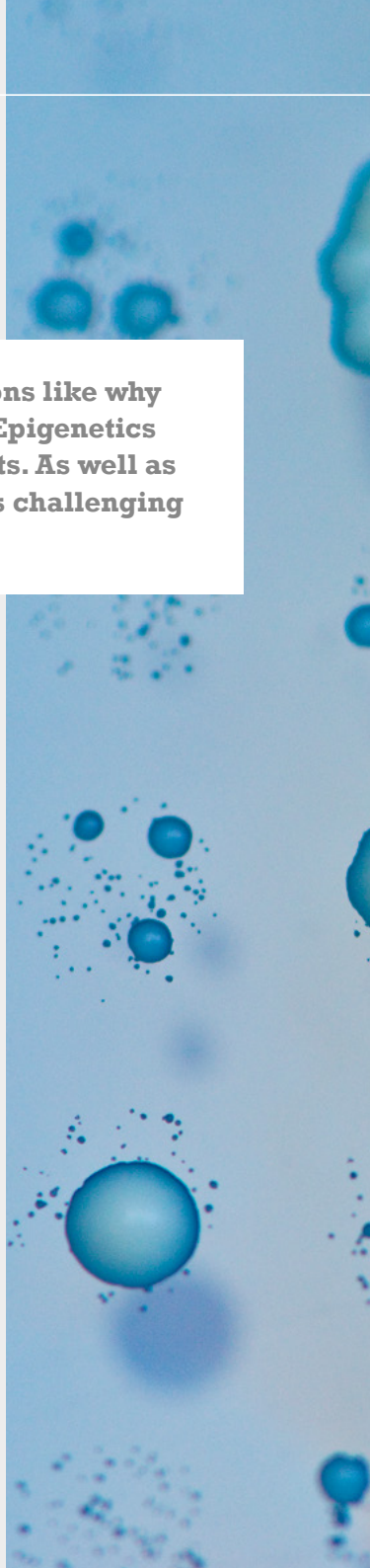
Professor Howard is a senior group leader at the John Innes Centre and joined the Institute in 2020 as an honorary group leader as part of an affiliate programme that develops exciting research collaborations in areas of complementary expertise.

Publications

www.babraham.ac.uk/our-research/epigenetics/martin-howard

- Reinig, J. *et al.* (2020) A theoretical model of Polycomb/Trithorax action unites stable epigenetic memory and dynamic regulation. ***Nat. Commun.*** 11:1-16
- Zhao, Y., Antoniou-Kourounioti, R.L. *et al.* (2020) Temperature-dependent growth contributes to long-term cold sensing. ***Nature*** 583:825-829
- Qüesta, J.I., Antoniou-Kourounioti, R.L. *et al.* (2020) Noncoding SNPs influence a distinct phase of Polycomb silencing to destabilize long-term epigenetic memory at Arabidopsis FLC. ***Genes Dev***. 34:446-461

How yeast is reshaping ideas on ageing



Healthy ageing is one of society's most pressing concerns, but basic questions like why we age remain a mystery. Dr Jon Houseley, a group leader in the Institute's Epigenetics programme, studies the ways in which yeast cells adapt to new environments. As well as uncovering new connections between adaptation and ageing, his research is challenging our ideas about ageing itself.

Dr Jon Houseley is a heretic. Along with others in the field of ageing research, he is questioning long-established orthodoxies of ageing. For decades, ageing has been seen as inevitable, a paradigm that has so far failed to help us answer the most basic questions about the nature of ageing.

If you rewind to the 1920s, however, alternative theories of ageing existed. Rather than simply a slow, inexorable process akin to a once pristine car rusting and breaking down, some argued that ageing had evolved for some purpose. In the absence of evidence, they lost the argument. Today, Houseley and others think they may have been right.

"I've been in the field long enough to say that you should be wary of any theories about ageing – including mine," says Houseley. "The problem is that 60 years on, it's really hard to know what this conserved underlying mechanism that's breaking down in ageing actually is. We need fresh ideas, even if they are heretical."

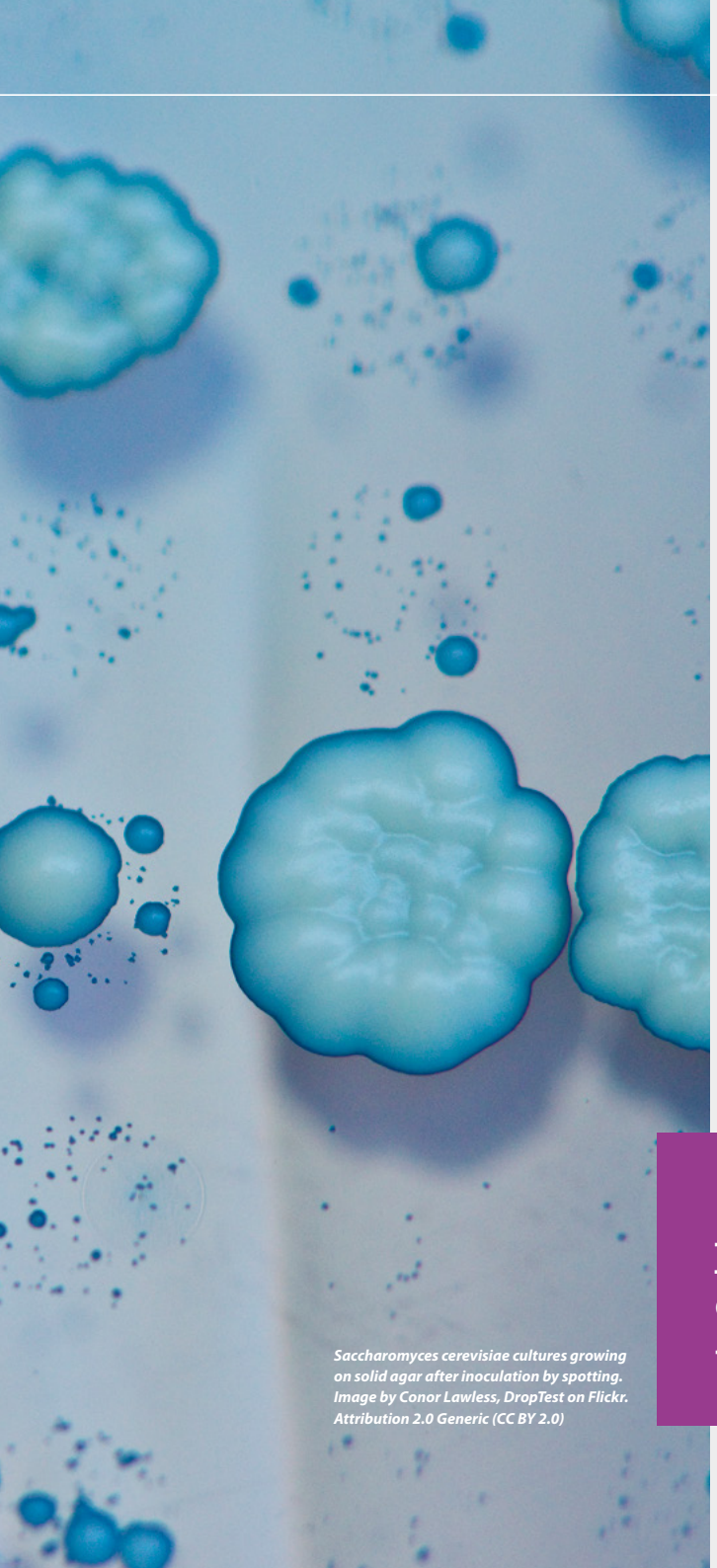
Ageing is hard to study. So much happens in a slow and concerted way in myriad systems that coming up with cause and effect is mind-bogglingly hard. Many genes and processes are involved, all of which are interconnected, so identifying the underlying 'thing' has so far proved impossible. It's even possible that ageing is not, in fact, one single thing.

"Ageing is really difficult to get your hands on, which is why we've started to revisit these old debates. But rather than argue about it intellectually, we have rolled up our sleeves and done experiments with yeast," Houseley explains. "Using yeast, we are asking whether there are situations in which being old is an advantage – and it turns out that there are."

One of Houseley's central aims is understanding how organisms adapt to challenging – and changing – environments. "It sounds like a weird fit with our focus on ageing," he admits. "But a major angle we have on ageing is that it could be a process that exists in basic eukaryotes like yeast to help them cope with stress."

His studies provide persuasive evidence to support this idea. One focused on CUP1, a gene in yeast that allows cells to survive in high-copper environments. Some yeast cells make extra copies of the CUP1 gene, allowing them to survive and outcompete cells with fewer copies of the gene.

Surprisingly, the study revealed that extra copies of CUP1 result from an active process rather than random mutations. "We think of genomes as long-term, stable repositories of information but they change – and not only over evolutionary timescales," says Houseley. "We know genome changes are hallmarks of cancer, but we're discovering them in healthy cells too. Some parts of the genome are very prone to change, suggesting that organisms



Saccharomyces cerevisiae cultures growing on solid agar after inoculation by spotting. Image by Conor Lawless, DropTest on Flickr. Attribution 2.0 Generic (CC BY 2.0)

have more control over their genomes than once thought."

But this raises a problem: cancer aside, organisms care about the genomes they pass on to future generations and are careful to minimise mutation rates in their genes. This is where ageing can be useful, because genome changes can be restricted to old cells that only reproduce rarely, and to the strange non-chromosomal DNA elements that accumulate in old cells.

The Houseley lab examined how yeast forms circular non-chromosomal DNA elements in response to copper and how this differs between young and old yeast cells. The results revealed that older yeast cells hoard circular DNA containing extra copies of genes like CUP1. "It's like a selfish insurance policy," he says. "But while these extra genes might provide an evolutionary advantage, they might also come at the cost of ageing because these extra bits of DNA could hamper normal essential cell pathways."

Understanding more about DNA circles, and how cells can change particular parts of their genomes in response to particular environments has important implications for both cancer and ageing. Cancers use DNA circles to carry cancer-causing oncogenes and to adapt in the face of chemotherapy, enabling them to develop resistance to anti-cancer drugs.

Houseley is at pains to stress that evidence for ageing being adaptive in yeast does not mean it's also adaptive in higher eukaryotes. It does, however, explain how it evolved and may explain why ageing still occur in higher organisms despite bringing no benefit.

As well as setting us on a new path to better understanding ageing, his research is also relevant to efforts to stop cancers from becoming drug resistant and could pave the way to healthier ageing. "Ageing is the biggest risk factor in a vast number of human disorders, but to come up with ways of dealing with ageing, we first need to understand it," he concludes. "At the moment, we don't understand how ageing works in any organism, so knowing how it works in one – even yeast – would be a major advance."

> 'Some parts of the genome are very prone to change, suggesting that organisms have more control over their genomes than once thought.'

Promoter Capture Hi-C: from academic tool to £1.5M startup

Fundamental research is vital for science and society. Many medical and technological revolutions are rooted in basic research, yet those roots can be hard to trace. Today, spinouts are key to turning academic bioscience into healthcare treatments. Dr Stefan Schoenfelder, a group leader in the Institute's Epigenetics programme and co-founder of Enhanc3D Genomics, discusses taking a tool developed for fundamental research and building a business around it.

Setting up a new biotech spinout is a demanding business, full of funding rounds, legal structures and recruitment decisions. Doing so at the start of a global pandemic, however, adds a new set of challenges. Founded in January 2020, Enhanc3D Genomics secured its first round of funding the following month and by March 2021 had closed a second round of funding worth £1.5 million.

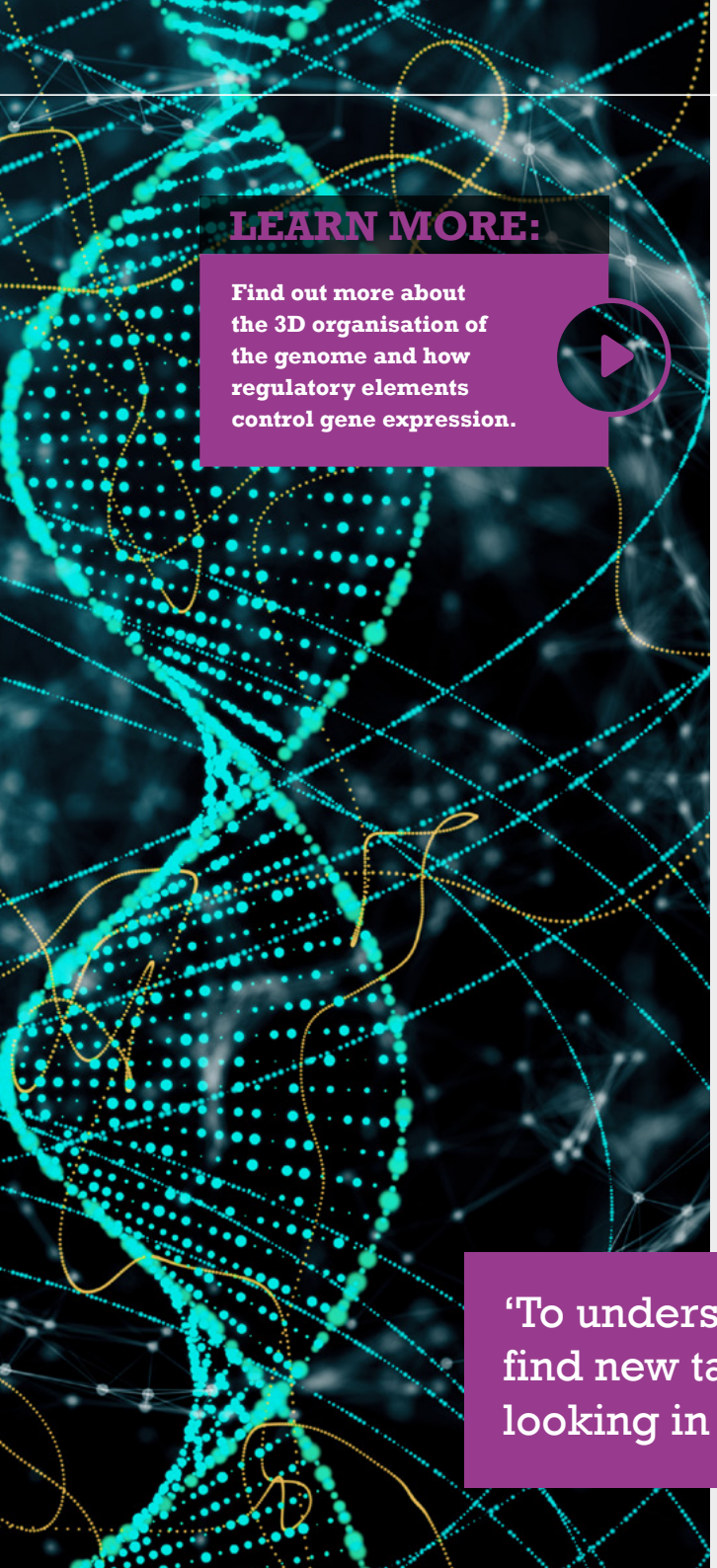
Being involved in a biotech spinout is somewhat surprising for Schoenfelder, who has worked at the Institute for 15 years, because it was never part of his career plan. "If you'd asked me five years ago, I'd have said that I wanted to focus solely on academic research," he explains. "I've always hoped my research would help patients, but never saw myself as part of the commercial world. Now, I believe that I can play a more active role in making that transition from basic science to clinical application."

The first fully sequenced human genome was published in 2003, with hope that this 'operator's manual' for the human body would revolutionise our ability to treat, prevent and cure disease.

During the past two decades, however, research has revealed that our DNA contains intricacy and complexity unimagined in 2003. Together with our genes, the non-coding sequences of DNA between the genes – once dismissed as 'junk DNA' – are just as important. And as well as its linear sequence, the 3D structure of DNA as it is folded within the nuclei of our cells is crucial, because it brings genes into close proximity to their regulatory elements – a key step in gene expression control.

According to Schoenfelder: "These regulatory elements function like molecular switches to control which genes are active, and thus produce proteins, in which cells. This process of gene expression control is vital to allow cells – which all contain the same genes – to specialise to carry out different tasks, and to help them respond to changes." Identifying which regulatory elements act on which genes has been an epic challenge in genome biology, but thanks to an ingenious modification to the Hi-C technique called Promoter Capture Hi-C, developed by Schoenfelder and his colleagues at the Institute, this can now be done for all human genes in a single experiment.

Crucially, studies deciphering the 3D folding of the genome at high resolution also reveal how small mistakes in regulatory elements interfere with normal control of



LEARN MORE:

Find out more about the 3D organisation of the genome and how regulatory elements control gene expression.

genes, leading to a greater chance of developing specific diseases.

The best example of how Promoter Capture Hi-C is helping researchers understand the genetic basis of important human diseases comes from so-called Genome Wide Association Studies (GWAS): hugely powerful studies sequencing the whole genome of people with and without particular diseases to spot the differences involved in causing the disease. By applying Promoter Capture Hi-C, research by the Institute linked the tiny changes in non-coding DNA to target candidate genes implicated in rheumatoid arthritis, type 1 diabetes and Crohn's disease.

"The vast majority of genetic variants associated with disease are located in non-coding parts of our genome," says Schoenfelder. "That means if we want to understand how most diseases arise – and find new targets for therapy – we need to be looking in the non-coding genome."

Having pioneered Promoter Capture Hi-C as a tool for doing fundamental research into gene regulation, Stefan and his colleagues soon realised it could be invaluable in understanding diseases and finding new ways to treat them, and that the best way to translate their fundamental research into clinical applications was through a spinout.

The company's vision is ambitious. "Our vision is to create 3D genome maps of all the cell types in the human body. If we succeed, it will be a unique database that will allow us to establish causal links between disease-associated regions and disease genes in almost every disease. Then, we will partner with experts in different disease areas to find new therapeutic targets," Schoenfelder says.

Reflecting on a momentous year, he is enthusiastic about the spinout process and Enhanc3D Genomic's potential: "The prospect of creating a legacy that uses fundamental research to create a business and help patients is hugely exciting."

"Covid-19 has shown the world what small, agile biotech firms can achieve. The most amazing research stories have come out of companies like Moderna and BioNTech," he concludes. "I hope more people now see there's lots of interesting research going on in biotech. The Institute and the many companies on the Campus create the ideal environment to foster these interactions. We need to get out of our ivory towers a bit more!"

'To understand how most diseases arise – and find new targets for therapy – we need to be looking in the non-coding genome'

Babraham Institute
Babraham Research Campus
Cambridge
CB22 3AT
UK

www.babraham.ac.uk
Tel: +44 (0)1223 496000
babraham.contact@babraham.ac.uk
@BabrahamInst

The Babraham Institute

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