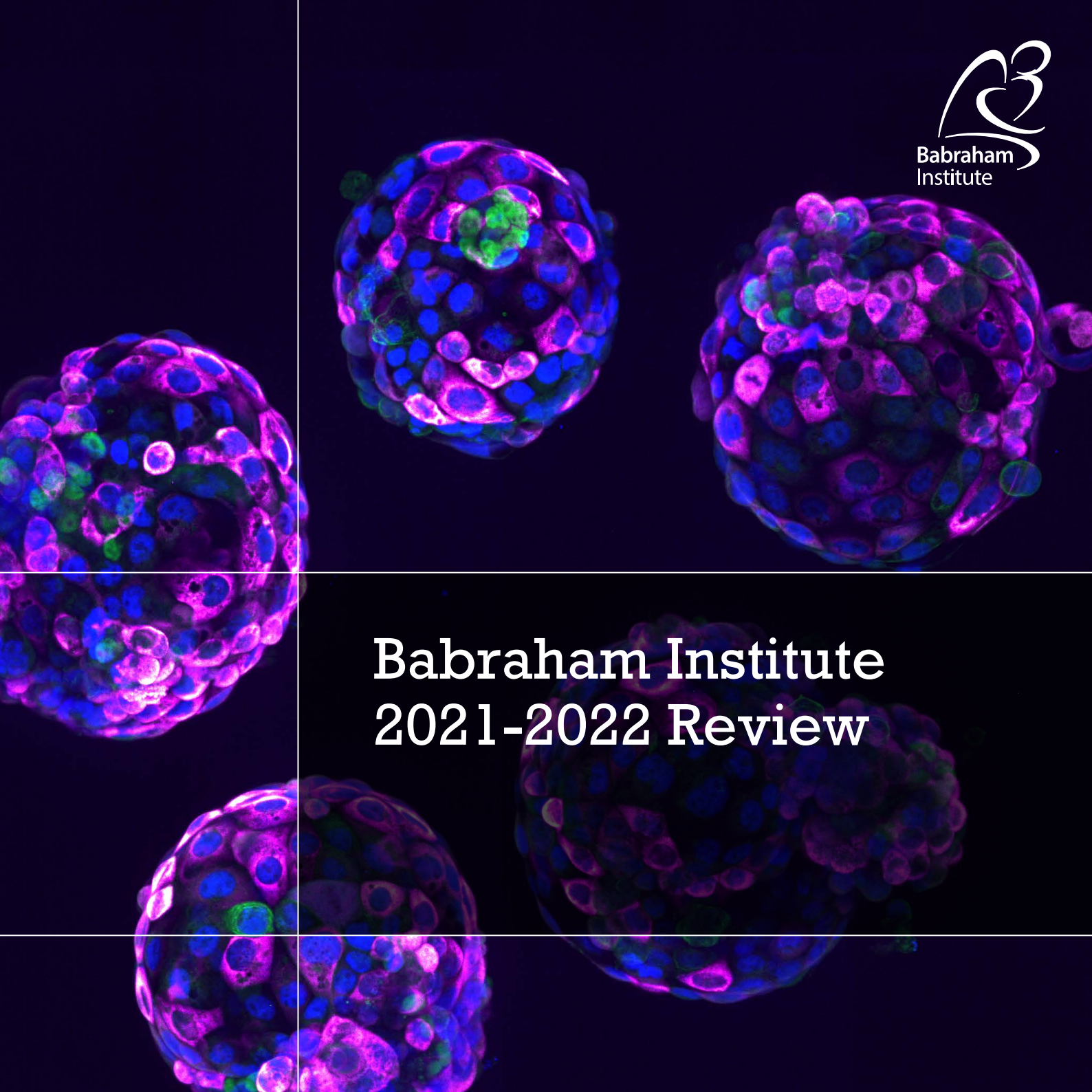


Babraham Institute

Babraham Institute 2021-2022 Review

We make discoveries that help us understand human biology and improve lifelong health

Contents

Director's welcome

Dr Simon Cook
Institute Director

I'm pleased to welcome you to this combined overview of the Institute's achievements and activities in 2021 and 2022. Rather than a directory of our individual research groups and science facilities we focus on the achievements of individuals, our 'teams' and the Institute as a whole, as well as illustrating the wider life of the Institute. Anyone wanting further information on our talented research groups and innovative facilities can enjoy our recently refreshed website.

I hope you particularly enjoy the feature articles, which introduce three of our newest group leaders, and delve into development, putting a spotlight on the work of Peter Rugg-Gunn and his group, part of the Institute's Epigenetics research programme but also part of the ambitious Human Developmental Biology Initiative.

As in previous years, the summary infographics on on pages 7-10 provide an at-a-glance overview of performance across several core metrics.

A new section celebrating the achievements of our researchers, technical specialists and wider support staff allows us to see how the drive and skills of our entire community are advancing knowledge and science. We have continued with the award of our annual prizes to recognise outstanding contributions in research, facility support, knowledge exchange and commercialisation and public engagement, as well as achievements in promoting equality, diversity and inclusivity. We have also introduced a new award for contributions to research integrity. Along these lines, the Institute published its organisational values for the first time: Benefit, Innovation and Integrity. You can read more about these in the following section but, in essence, they capture the commitment of the Institute to excellence and impact across its activities. The key elements of everything we do can be split into our People, Science, Culture and Impact so the following sections share highlights from each of these areas and give snapshots of how we put our values into action.

Our People

In 2022 I was delighted to welcome Professor Dame Linda Partridge DBE, FRS, FRSE, FMedSci as a new member of the Board of Trustees. As a world-renowned scientific leader in ageing research, Linda brings an expert understanding of the Institute's burgeoning research focus and valuable leadership experience.

During 2021 and 2022 we welcomed six new group leaders. Ian McGough (2021) and Della David (2022) joined our Signalling programme (see the features on page 33 & 39); Ian is studying Wnt signalling in tissue maintenance and both Ian and Della will build on existing strengths in proteostasis. Three new group leaders joined our Epigenetics programme; Philipp Voigt (2021), Sophie Trefely (2022) and Teresa Rayon (2022). Sophie is studying how diet-derived metabolites act as signals in the nucleus to control gene expression whilst Philipp is studying how histone modifications promote or repress gene transcription. Learn more about Philipp in the feature on page 35. Teresa is studying the biological and biochemical basis of timing; why, given the high conservation of genetic programmes throughout the animal kingdom, is the duration of embryogenesis and lifespan species-specific? In Immunology we welcomed Arianne Richard (2022) who is studying how T cells sense and integrate information from both infection and the physiological environment to generate appropriate immune responses (more about Arianne and her research in the feature on page 37). Our group leaders have also celebrated some remarkable success in the award of personal fellowships (see pages 15-18).

We also welcomed two new honorary group leaders to the Institute. Kathy Niakan (University of Cambridge & The Crick Institute) is affiliated with our Epigenetics programme, whilst Valerie O'Donnell (University of Cardiff) is affiliated with Signalling.

We have seen some significant leadership changes during this period. Jon Houseley took over the role of Head of Knowledge Exchange and Commercialisation. Following the death of Michael Wakelam, Wolf Reik took on the role of Director in 2021 but subsequently moved on to head up the Altos Cambridge Institute. I stepped into the role of Interim Director in 2021 and then Director in 2022 and was pleased to host the memorial symposium for Michael and oversee the naming of The Michael Wakelam Building, which houses our science facilities.

Our Science

The last two years have seen so many remarkable scientific advances by the Institute it is difficult to pick out just a few highlights.

- Researchers in the Reik lab (Epigenetics programme) rejuvenated human fibroblasts by approximately 30 years (measured by various ageing clocks) using transient cellular reprogramming by inducible expression of Yamanaka factors (1). This discovery received international media attention.

- The Linterman lab (Immunology programme) used studies in aged mice together with human vaccination studies and in vitro systems to define how ageing influences vaccine responses, providing mechanistic insight that can be applied to boost the immune response in older people (2). Dr Michelle Linterman was awarded a European Research Council Consolidator Grant in

Links: More Institute news at www.babraham.ac.uk/news

1 A jump through time – new technique rewinds the age of skin cells by 30 years
2 Babraham Institute scientists find clues to explain reduced vaccine response with age
3 Developing our understanding of the fundamentals of autophagy
4 Institute's animal facility receives international accreditation for animal care
5 Green Labs gets the gold
6 Institute's first Animal Technicians Conference puts the spotlight on skills, support and career development

March 2022 to support a project to build a comprehensive picture of how germinal centre biology changes with age.

- The Florey lab (Signalling programme) discovered a new pathway of non-canonical autophagy (called CASM) and defined the genetic and biochemical features that distinguish it from autophagy (3).

- Our research utilises a range of methods from cell and yeast cultures to model organisms, including *Drosophila, C. elegans* and mice, to donated human samples and is underpinned by eight science facilities. In 2022 our animal facility was recognised as a beacon of good practice by the award of Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) accreditation, recognising the high standards of care and commitment to animal welfare at the Institute (4).

Our Culture

We believe that excellent, trusted research and resulting social and economic impacts can only flourish in a positive and inclusive research culture that values everyone's contributions towards research integrity, openness, equity and diversity.

- The Institute's Research Integrity Steering Group brings roles together from across the Institute to embed and strengthen research integrity (founded on rigour and excellence) and ensure that we conduct research in a way that allows others to have confidence in our results.

- In October 2022 Green Labs, a staff-led initiative to reduce the environmental footprint of our research (and associated activities), received a Gold Award from SOS-UK Green Impact recognising leadership and sustained efforts to reduce the environmental impact of the Institute and the wider Babraham Research Campus (5).

- Since becoming a signatory to the Technician Commitment in 2019 we have established a steering group, raised the profile of technical specialists in roles across the Institute, improved recognition (through external and internal award participation) and supported technician-led events such as the Institute's first Animal Technician Conference in November 2022. This event was the brainchild of two Institute animal technicians who saw the benefits of bringing like-minded people together in an event tailored for animal technicians (6).

- After being one of the first organisations to receive 'Leader in Openness' status in 2019 under the Concordat on Openness on Animal Research, the Institute was delighted to maintain its Leader status in May 2022 in recognition of its continued commitment to transparency and engagement about the use of animals in research (7).

- The Institute's parents and carers are very grateful to have such incredible on-site childcare provision from the Institute's Nursery. The exceptional level of care and early years education was reflected by the Nursery achieving its fourth consecutive Outstanding OFSTED rating in March 2022 (8).

- Our successful Roving Researcher initiative, launched in 2020, continues to mitigate the impact of long-term leave on career development and research outputs (9).

- Our multi-faceted wellbeing programme encompasses mentoring, employee assistance, mental health first aiders, lifestyle advice and wellbeing training opportunities.

Our Impact

- Commercialisation of Institute science continues apace. 2022 saw Aila Biotech spun out from the Institute's Immunology programme and the continued success of our spin-out Enhanc3D Genomics, which raised £10 million in Series A financing. We also have active collaborations with major pharmaceutical companies and licensing agreements, including of the intellectual property associated with the rejuvenation reprogramming technique published by the Reik lab in 2022.

- The Institute's Research Access Programme (10) continues to provide opportunities for undergraduate students to get hands-on research experience (run virtually in 2021 and in person in 2022).

- Working with a Europe-wide consortium of institutes (ORION OS), the Institute's Public Engagement team designed and carried out a dialogue event to understand public hopes and concerns around genome editing. This informed the development of an Open Science Action Plan to better embed transparent practices in research institutions and foster public understanding of science.

The Institute remains integral to the success of the Babraham Research Campus, supporting early-stage companies through: consultancy; collaborations; provision of cutting-edge science facilities; company staff training and, most recently, through a Campus-BBSRC Collaborative Training Partnership PhD programme. The programme will support 15 CASE PhD studentships (2022-2025) co-supervised by Institute group leaders and campus companies. In addition, UKRI-BBSRC Flexible Talent Mobility Award (FTMA) support and Campus Impact Acceleration Accounts (CIAA) awarded in 2022 have enhanced academic-industry collaborative R&D, industry-facing facility activities, translational and entrepreneurial training and networking opportunities. In these ways we support innovation, translation, enterprise and entrepreneurship as part of the long term vision of the Babraham Research Campus (11).

7 Institute maintains Leadership in Openness status

8 Outstanding, Outstanding, Outstanding, Outstanding

9 Blog articles on the Roving Researcher initiative

10 Blog series sharing RAP student perspectives

11 Institute welcomes future vision for the Babraham Research Campus

Life sciences research for lifelong health

As a pioneering fundamental life science research institute, our overarching aims are to understand the human biology that underpins health, share this knowledge onwards by working closely with those who can develop and apply it and by doing this, ultimately progress interventions that promote health. As an institute strategically supported by the Biotechnology and Biological Sciences Research Council (BBSRC), part of UKRI, the Institute is a vital component of the national and international ecosystems for bioscience research and innovation.

We are a vibrant and passionate community of scientists and specialists with diverse skills, experiences and roles. We recognise that only by starting with the best ideas, in an environment that supports innovative discovery science and allows people to perform to the best of their abilities, will we successfully feed this discovery pipeline and achieve our aim of applying excellence to make discoveries that benefit people's lives.

Our vision:

For the Institute:
Our vision for the Institute is to create a supportive and dynamic organisation where people, ideas and research thrive. The work of the Institute reflects a shared commitment to excellence, making valuable contributions to our knowledge of fundamental human biology and working with translational partners to make sure that our discoveries are developed to benefit lives.

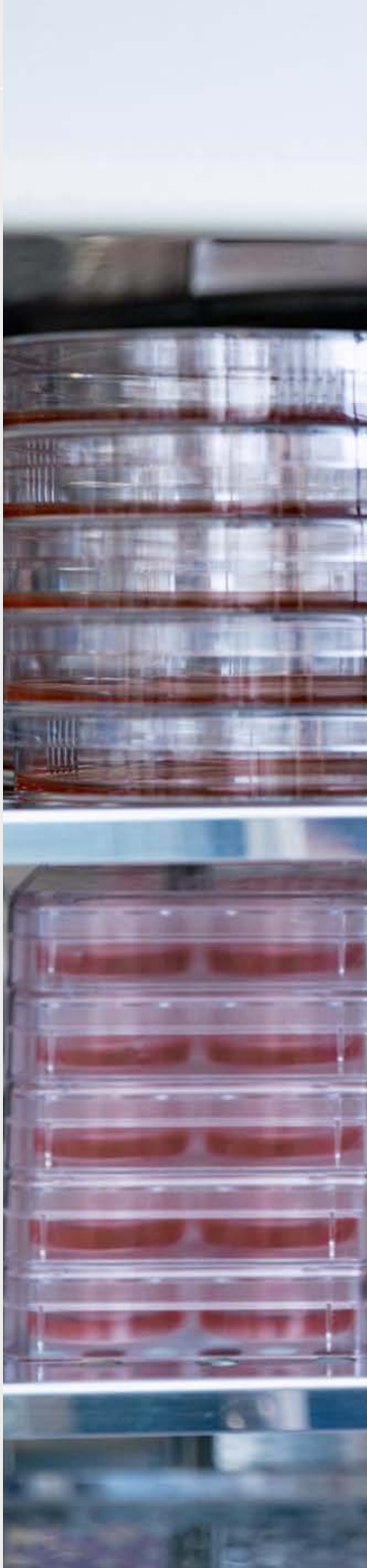
We undertake world-leading research that is robust, innovative and cohesive to make ground-breaking advances. Our science facilities underpin our research activities and are maintained at the cutting edge by talented staff to enable the application of the latest technologies. We encourage exciting, cross-disciplinary research to advance knowledge and are deeply rooted within the wider research and innovation ecosystem.

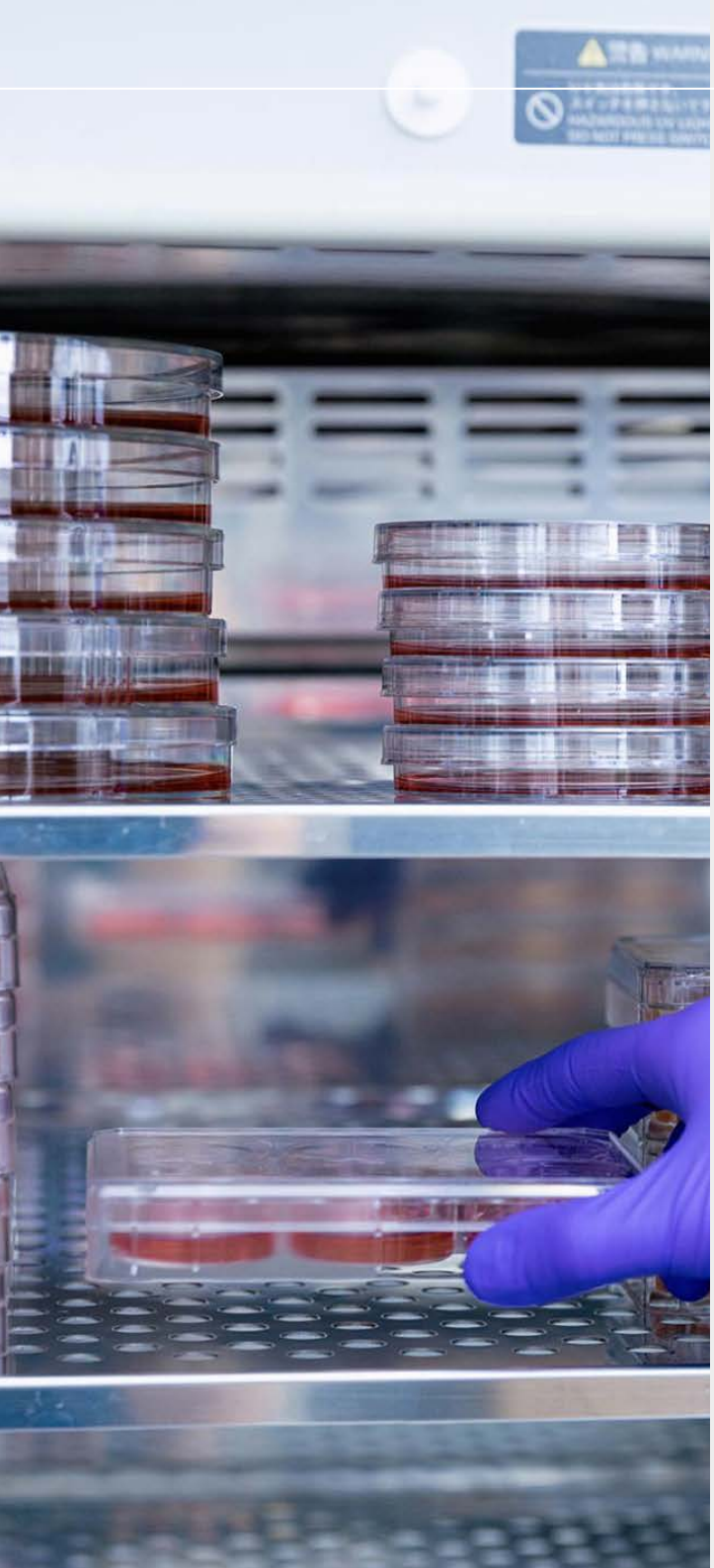
Our partnerships with academic and commercial bioscientists allow better science to happen more efficiently on both sides.

For our research culture:
The Institute is proud to have made positive progress in embedding an equality, diversity and inclusivity action plan that aims to overcome identified barriers to people achieving their best. We are proud of the innovative projects put in place, from social meet-ups that introduce and connect individuals from different parts of the organisation, to the Institute's Roving Researcher initiative that allows the momentum of research projects to be maintained while researchers take longer periods of leave.

Our passion for scientific discovery is applied across all our activities, working with others to respond to and inspire innovation in our research, in our knowledge exchange, public outreach and also internally in maintaining a positive and inclusive community and developing the researchers and entrepreneurs of tomorrow.

We are committed to reducing the barriers to accessing research, supporting open science and also widening the opportunities for people to experience research through targeting traditionally under-served audiences through our schools engagement activities and Research Access Programme.





For the impact of our science:
One in six adults will be aged 60 years or over by 2030, and our research sparks the innovative advances that will improve lifelong health.
Our research creates new knowledge about the biology of the earliest moments of development and explores how age and age-related disease affect the functioning of our bodies.

We share our science widely, working across the academic and commercial sectors to catalyse and advance knowledge together. We contribute to shaping and informing policy on areas of relevance to our work, including new and developing areas of science, we engage with public audiences, and we work with individuals and education providers to inform people's understanding of science and scientific career opportunities.

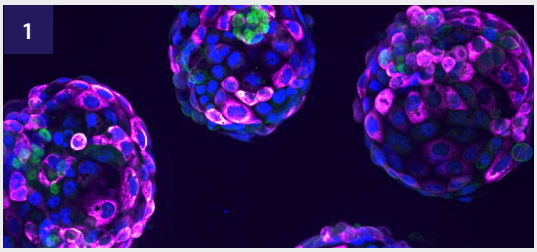
Successful training of researchers and commercialisation of our research contributes to the UK bioeconomy. With support from the Institute's Knowledge Exchange and Commercialisation team and entrepreneurial mentorship, research innovations with commercial potential benefit from a well-established system of opportunities to develop from concept to successful spin-out.

The Institute sits at the heart of the Babraham Research Campus and plays a vital role in supporting the success of the early-stage commercial companies on site through direct research collaborations and through access to our research expertise and science facilities.

Ultimately, our research will change people's lives through the medical interventions and treatments that are developed based on the improved understanding of human biology that we help create, and by influencing lifestyle choices and healthcare advice. Innovations in research technologies are an important by-product of our research and our expertise and contributions to advancing the scientific community's capabilities have a global impact in research and for the bioeconomy.

The Babraham Institute at a glance

1



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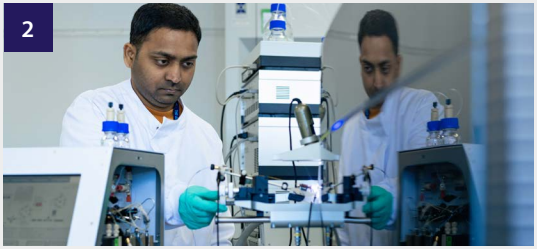
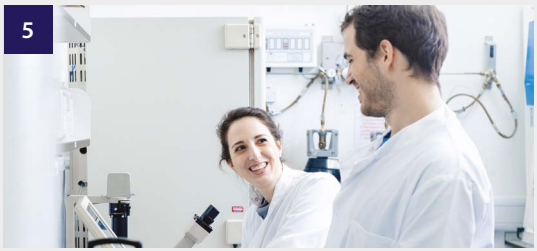


3

Biotechnology and Biological Sciences Research Council

4

5



1. Life science research for lifelong health: We are a centre of excellence in fundamental human biology, discovering and studying how our bodies work and what changes with disease and also as we age.

2. Our research spans three interconnected programmes: Epigenetics, Immunology and Signalling, and is underpinned by eight pioneering facilities.

3. We are strategically funded by BBSRC, part of UKRI, and also secure competitive research grants to support our work.

4. The Institute community is made up of around 350 people, working together to achieve our aims. Our staff and students come from over 30 countries.

5. By creating the environment for science, people and ideas to thrive we make discoveries in human biology that provide the foundation for innovative advances in improving and protecting health.

6. We are committed to providing excellent training and opportunities for our PhD students to produce tomorrow's research leaders and also share our expertise with visiting researchers from around the world.

7. We are co-located with around 60 bioscience companies on the Babraham Research Campus and have active research and development collaborations with 12% of the companies on site. Many companies on the Campus benefit from access to the equipment and expertise in our science facilities.

8. We gained our first Silver Athena SWAN award in 2015 and were awarded a renewed Silver award in 2018 under the expanded Athena SWAN charter. Our equality4success strategic initiative shapes our action plan and our priorities are set by Institute-wide consultation.

9. Our Research Access Programme, which launched in 2020, provides summer placements to undergraduate students from under-represented or disadvantaged backgrounds.

10. The Institute's values are: Benefit, Innovation, Integrity. They frame our 'code of conduct', articulate our beliefs and principles, and outline how we aspire to function and be recognised. They illustrate how we work as an organisation and with others to achieve our mission and speak to our vision of an internal Institute culture.

6

7

8

EQUALITY CHARTER

Athena SWAN
Silver Award

9

10

Learn more at www.babraham.ac.uk

Performance in 2021

OUR COLLABORATIVE ACADEMIC PROJECTS

UK AND WORLDWIDE

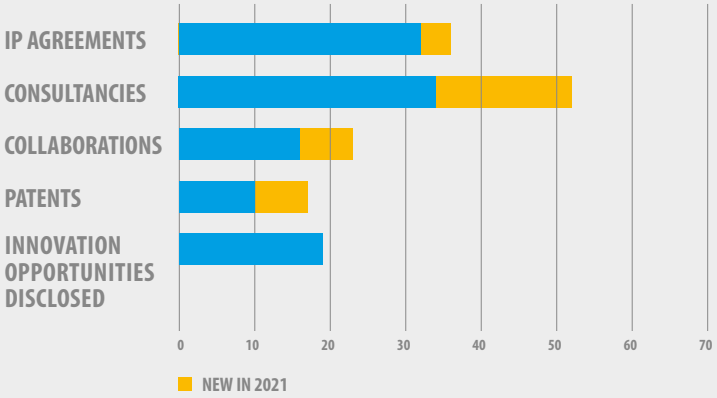
Working with others in 2021

65 ACTIVE PROJECTS

21 COUNTRIES

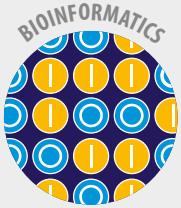
94 ORGANISATIONS

Working with commercial partners

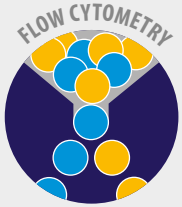


People we've trained in our scientific facilities this year

>1,276



818

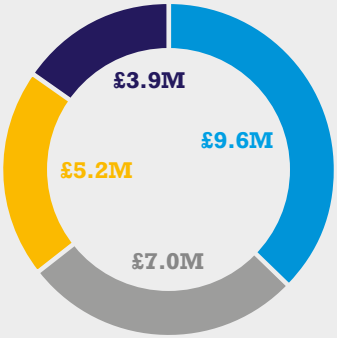


349

>89

20

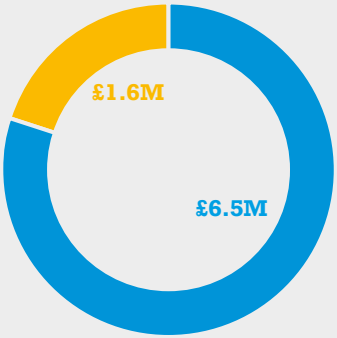
2021 income



£25.8M

- Core ISP grants & BBSRC non-grant income
- Income from services provided by the Institute
- Competitively awarded grant income in 2021
- BBSRC additional income (including business cases, equipment etc.)

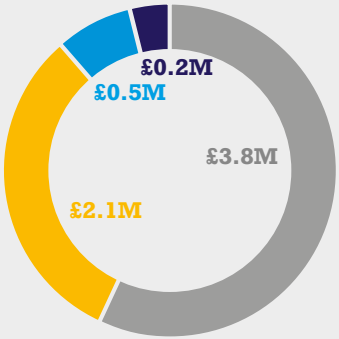
Value of all grants awarded in 2021



£8.1M

- UK funders
- International grants*

Value of UK grants awarded in 2021



£6.5M

- Wellcome Trust
- MRC
- BBSRC
- Milner Therapeutics Institute

*International grant sources:
Euopean Commission (EC) £0.7M

2021 successes

29
ONLINE PUBLIC ENGAGEMENT EVENTS

INVOLVING

70
STAFF AND STUDENTS

3,608
PEOPLE ENGAGED

114
PUBLICATIONS

97
RESEARCH PUBLICATIONS

17
REVIEWS

PROUD SUPPORTER OF THE
Technician Commitment

8
PhDs COMPLETED

Performance in 2022

OUR COLLABORATIVE ACADEMIC PROJECTS

UK AND WORLDWIDE

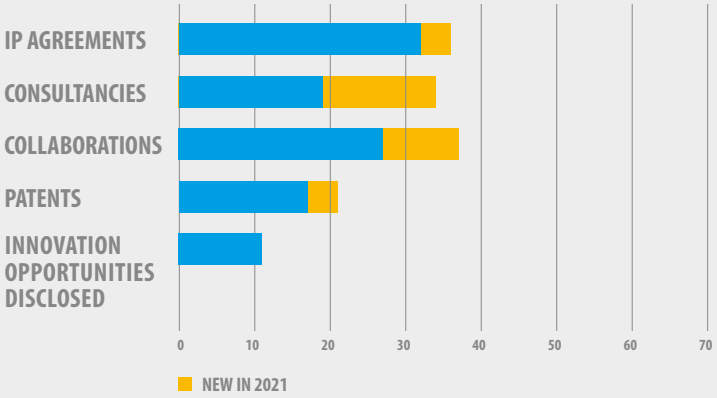
Working with others in 2022

65 ACTIVE PROJECTS

16 COUNTRIES

63 ORGANISATIONS

Working with commercial partners



People we've trained in our scientific facilities this year

>1,416

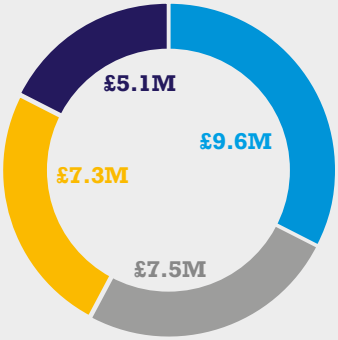
BIOINFORMATICS **990**

FLOW CYTOMETRY **305**

IMAGING **>89**

ANIMAL FACILITY **32**

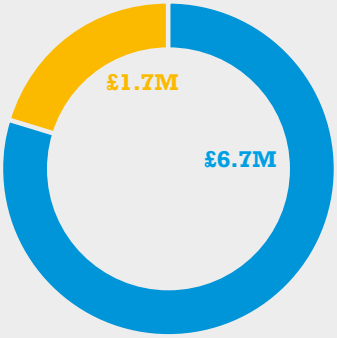
2022 income



£29.6M

- Core ISP grants & BBSRC non-grant income
- Income from services provided by the Institute
- Competitively awarded grant income in 2022
- BBSRC additional income (including business cases, equipment etc.)

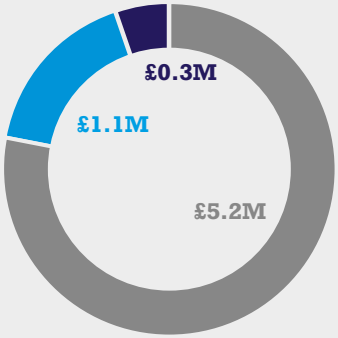
Value of all grants awarded in 2022



£8.4M

- UK funders
- International grants*

Value of UK grants awarded in 2022



£6.7M

- Wellcome Trust
- BBSRC
- Milner Therapeutics Institute

*International grant sources:
UKRI Horizon Europe £1.7M

2022 successes

25
ONLINE PUBLIC ENGAGEMENT EVENTS

21
IN PERSON PUBLIC ENGAGEMENT EVENTS

INVOLVING

67
STAFF AND STUDENTS

3,198
PEOPLE ENGAGED

76
PUBLICATIONS

66
RESEARCH PUBLICATIONS

10
REVIEWS

PROUD SUPPORTER OF THE
Technician Commitment

10
PhDs COMPLETED

Highlights

Through scientific and operational excellence, leading change, creating aspirations and opportunities, our people are shaping the Institute's culture, delivering impact through our research and wider work, and opening up access to research careers. This collection of highlights captures some of the achievements made in 2021 and 2022 across different areas of the Institute. A deeper level of detail can be accessed using the hyperlinks.

Who we are

New groups welcomed to the Institute

In 2021 and 2022 the Institute appointed a number of new group leaders to strengthen collaboration between research programmes and develop new themes of research. In 2021 the Institute appointed Dr Ian McGough, and Dr Philipp Voigt, Dr Teresa Rayon, and Dr Sophie Trefely. Dr Rayon and Dr Trefely work across the Signalling and Epigenetics research programmes. In 2022 we welcomed Dr Della David and Dr Arianne Richard.

Who we are

NUS Green Impact

GOLD AWARD

Delivered by Students Organising for Sustainability - UK

Green Labs makes progress on sustainability

Babraham Institute was awarded a Gold Award from the SOS-UK Green Impact programme for environmental and social responsibility, enacting a wide range of sustainability actions. The Green Labs team, and nine companies across the Babraham Research Campus, took over 500 actions collectively to become a more sustainable workplace. New activities included tackling ultralow freezer efficiency through racking and 'chilling up' (shifting temperature from -80 to -70) and addressing single use plastic in the lab by implementing recycling for the ~45,000 media bottles used each year.

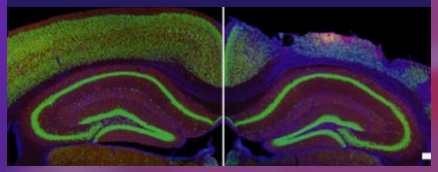
Impact

ENHANC3D GENOMICS

Enhanc3D Genomics continues to gain ground

The spin out company Enhanc3D Genomics, co-founded by Stefan Schoenfelder, secured further seed funding in March 2021 and raised an additional £10m in series A funding in October 2022. The company's proprietary technology platform, GenLink3D™, integrates molecular biology technologies with machine learning to map the 3D structure of the genome at high resolution.

Impact



New horizons for drug delivery technology

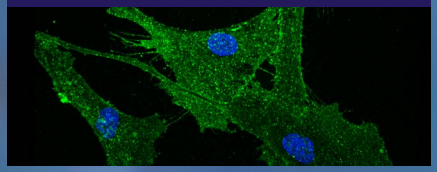
Aila Biotech, spun out from the Institute in 2022, is engaged in the development of an innovative biologic therapy demonstrating promising pre-clinical efficacy in the treatment of neuroinflammation. Aila's approach builds on research undertaken at the Institute by the Liston lab with collaborators at VIB and KU Leuven in Belgium.

Culture & Impact

Embedding responsible research practices

The Institute developed an Open Science action plan as a result of a collaborative four-year Horizon 2020 project ending in September 2021, which involved the Institute and eight other life sciences research performing and funding organisations from across Europe. The ORION Open Science project aimed to embed open science and responsible research and innovation principles in the policies, practices and processes of participating organisations and to inspire others. The Institute's participation in the project also generated a public engagement resource called Virus Fighter which was co-created between researchers, school students and a games development company and participation in a public dialogue project to explore public attitudes towards the use of genome editing technology in life science research.

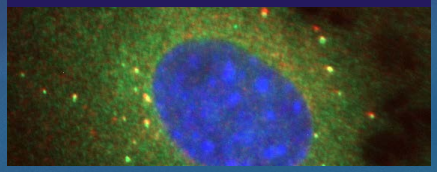
Discovery



New technique rewinds the age of skin cells by 30 years

Diljeet Gill and Wolf Reik published details of their new technique for rejuvenating skin cells. Their method rewinds the cellular biological clock by around 30 years according to molecular measures, significantly longer than previous reprogramming methods. The partially rejuvenated cells showed signs of behaving more like youthful cells in experiments simulating a skin wound.

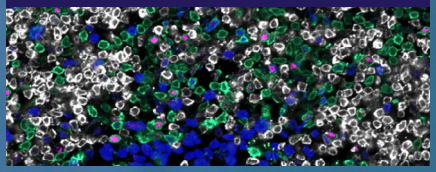
Discovery



At the cutting edge of autophagy

In 2021, autophagy took centre stage for the Signalling research programme. Nicholas Ktistakis joined an ambitious Milner Consortium collaboration to target autophagy with the view to treating neurodegeneration. This news was followed by a landmark publication from the Florey lab, who published their discovery of a molecular marker unique to the 'non-canonical' autophagy pathway. Their results will allow researchers to distinguish between different branches of the autophagy pathway, which could be particularly useful in translational research.

Discovery



Gaining important immunological insights

Michelle Linterman and her team assessed multiple aspects of the vaccination response following a 'flu vaccine and identified age-related differences where the vaccine stimulated pro-inflammatory signalling which affects cells key to developing a strong immune response. This study suggests that interventions to dampen inflammation at the time of vaccination may boost immune responses in older people.

Highlights

Culture

Roving Researcher maintains research momentum

The Roving Researcher position continues to support staff during long-term leave and providing additional support during times of high demand in the Institute's scientific facilities. During 2021 and 2022, the Roving Researcher position supported 12 teams.

Tomorrow's researchers

Research Access Programme success continues

Life sciences undergraduate students entering their final year of study from under-represented groups joined the Institute for a virtual five-week placement. The students completed projects relating to the work of their host group, experienced life as a PhD student, and learnt about a variety of Institute based careers. In 2021 the Institute hosted eight students through virtual placements and in 2022 five students joined groups for an in-person placement.

Culture

Technicians leading the way

The second Research Institute Technician Symposium took place in 2021. Mike Hinton, Web Development Manager, was invited to talk about his career and Matt Fairbairn, IT Support Specialist, received the Technical Skills Specialist Award for his outstanding contribution to the Institute. The Institute also launched our Technician Commitment plan, setting out the steps to further recognise and support technical and support staff. In 2022, the Institute's first Animal Technician Conference, organised by animal technicians saw over 170 delegates from across the UK gather to hear talks on scientific progress, best practice careers and communication.

Tomorrow's researchers

Collaborative Training Partnership funding secured for future PhD projects

Babraham Research Campus Ltd, and the Babraham Institute secured funding for fifteen PhD studentships from BBSRC as part of a Collaborative Training Partnership (CTP). Through a tailored programme of skills training and scientific and industry supervision the partnership will produce a cohort of bioscience researchers equipped with excellent research skills and commercial know-how. The first six students joined the programme in October 2022.

Sharing our science

Researchers in classrooms for Meet a Bioscientist

Our 'Meet a Bioscientist' schools engagement event ran in 2022, linking with British Science Week and National Careers Week, to engage over 900 young people across 15 schools and sixth forms. The hybrid event was run as a stand-in for the Institute's usual Schools' Day event and was supported by 35 researchers and technicians speaking about the Institute's research, careers in science, and what being a scientist is really like.

Sharing our science

Sixth Form Conference makes a triumphant return

In December 2022, the Institute opened its doors to local students and their parents, carers and teachers, for the Babraham Institute Sixth Form Conference, which saw around 100 people attend from around the south-east. The theme of the conference was healthy ageing, to reflect a key focus of the Institute's research. Students entered posters into the design competition, heard about careers and listened to research talks. This was the first large scale in-person event hosted after the Covid-19 pandemic.

Excellence

First of its kind flow cytometry event showcases spectral cytometry

The Institute's Flow Cytometry team hosted a showcase event discussing spectral flow cytometry, a technique with unique capabilities and advantages for research. The event was made up of talks from internationally-recognised speakers working at the forefront of spectral cytometry in addition to tours of the Institute's facility, which has one of largest number of spectral flow cytometers in the world. A second symposium is planned for 2023.

Excellence

Institute's animal facility receives international accreditation for animal care

The Institute's Biological Support Unit received full accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) in 2022. The AAALAC assessment recognised the high standards of care and commitment to animal welfare at the Institute. The accreditation comes in addition to the Institute's renewal of our Leader in Openness status.

Excellence

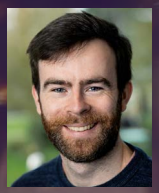
Outstanding Ofsted nursery

In 2022, the Institute's Nursery received a fourth Outstanding rating after its Ofsted inspection. The report praised the Nursery's approach to engaging children with learning and supporting their wider development, and the strength of its relationships. The Institute's Nursery provides excellent childcare for over 100 children aged from six months to four years old, supported by a team of 40 staff members (across childcare, administration and catering).

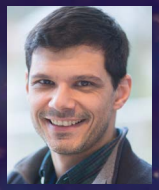
Awards, fellowships and achievements

Dr Melanie Eckersley-Maslin, a BBSRC Discovery fellow in the Reik lab until December 2020, received the 2020 Metcalf Prize from the National Stem Cell Fundation of Australia in recognition of her early-career leadership in stem cell research. Melanie moved from the Institute to start her independent research career at the Peter MacCallum Cancer Centre in Melbourne, Australia.

Dr Martin Turner, Head of the Immunology programme, was elected to The Academy of Europe (Academia Europaea).



Dr Claudia Ribeiro de Almeida, tenure-track group leader in the Immunology programme, and Dr Ian McGough, tenure-track group leader who joined the Signalling research programme in 2021, both received Sir Henry Dale Fellowships. In Claudia's case this allowed her to pursue an exciting avenue of research and in Ian's case, he established his independent research group at the Institute.



Dr António Galvão, a member of the Kelsey lab, received the New Investigator Award in 2021 from the Society for Reproduction and Fertility and showcased his work on the epigenetic inheritance of predisposition to obesity at the society's Fertility Meeting and the SRF annual conference in 2022.

Dr Alena Moudra, a postdoctoral researcher in the Liston lab, became a Research Associate at Lucy Cavendish College in November 2021, which provides post-doctoral membership of the college to increase networking and interdisciplinary exchange.

Ntombizodwa Makuyana, a PhD student in the Liston lab, won The LucEnt 2021 Challenge (a partnership between Lucy Cavendish College, the Judge Business School and Cambridge Precision Ltd.) for her project the '100 Young Women Initiative' which aims to break down barriers to career progression for young women in Africa.

2021

Matt Fairburn, Desktop User Support in the Institute's Computing team, received the Technical Skills Specialist award in the 2021 Research Institute Technician Awards after being nominated by Institute colleagues.

Professor Adrian Liston, a senior group leader in the Institute's Immunology programme (2019-2023), was elected Fellow of the Academy of Medical Sciences for his pioneering research in immunology and neuroimmunology.

Dr Arianne Richard, tenure-track group leader in the Immunology programme, received an MRC Career Development Award in December 2021 to start her lab at the Institute. This fellowship grant funds Arianne and a postdoctoral research scientist for five years to work on a project to investigate the regulation of T cell differentiation by stimulation strength.

2021 annual prize winners with Institute Director Dr Simon Cook (fifth from left)

In the Institute's 2021 annual prizes the following teams and individuals were recognised for their achievements in research excellence, facility operation, knowledge exchange and commercialisation, public engagement, supporting equality and diversity, and creating an engaging scientific image.

- Dr Jo Durgan received the 2021 Sir Michael Berridge Award for her research published in April 2021 which allows researchers to distinguish between branches of the autophagy pathway.
- The Biological Support Unit (BSU) received the facility award in recognition of their efforts to adapt to new ways of working and for their support of essential experiments during the pandemic.
- The Knowledge Exchange and Commercialisation Prize was awarded to senior research scientist Dr Maria Rostovskaya for her leadership on a cell therapy translational research project originating from her research.
- Two teams shared the Public Engagement Prize for their work on developing the Virus Fighter interactive outbreak simulator and the online Epigenetics Escape Room.
- Roving Researcher, Dr Melanie Stammers, received the equality4success Prize for her support of researchers on long-term leave.
- The Image Prize was awarded to Dr Laetitia Chauve, a postdoctoral researcher in the Epigenetics programme, for her scanning electron micrograph of the head of an adult *C. elegans* worm.

Awards, fellowships and achievements

Dr Teresa Rayon, tenure-track group leader in the Epigenetic and Signalling research programmes, was awarded an ERC Starting Grant (now a UKRI frontier Research Grant) in January 2022. The funding supports work to understand the molecular and metabolic mechanisms that control developmental timing.

Institute staff associated with the application of flow cytometry were recognised by the International Society for Advancement of Cytometry (ISAC). Dr Rachael Walker, the Head of the Institute's Flow Cytometry facility, was elected an ISAC Council Member and Dr Oliver Burton from the Liston lab was awarded an ISAC scholarship to support future leaders in cytometry.

Dr Michelle Linterman, a group leader in the Immunology research programme, was awarded funding from the European Research Council (ERC) to expand our understanding of vaccine response with age. Dr Linterman's ERC Consolidator Grant will fund a five-year project building a comprehensive picture of how germinal centre biology changes with age.

Dr Danielle Hoyle, Head of Research Operations and Deputy Director of Operations, completed an MBA with the Open University and is applying business practices in her role to support the efficiency and effectiveness of the Institute's research.

Christopher Hall, Deputy Manager of the Institute's Flow Cytometry facility, was awarded the Royal Microscopical Society Cytometry Medal in 2022. The award recognises outstanding scientific achievements by scientists applying flow cytometry in the field of immunology or cell biology.

Dr Johanna Grinat, a postdoctoral researcher in the Christophorou lab, was awarded a Marie Skłodowska Curie Fellowship.

2022

Dr David, (group leader in the Signalling research programme) and Dr Peter Rugg-Gunn (group leader in the Epigenetic research programme) received Wellcome Discovery Awards which recognise bold and creative research that is expected to deliver significant shifts in understanding in areas with potential to improve human life, health and wellbeing. Dr David's research will advance our knowledge of protein quality control outside of cells and the role regulatory molecules play in ageing of the brain while

Dr Peter Rugg-Gunn's project will advance our understanding of the epigenetic environment of human early embryo development and reproductive health.

2022 annual prize winners and PhD student poster and presentation prize winners with Institute Director Dr Simon Cook (second row, fourth from left)

The Institute's annual prizes for 2022:

- Dr Maria Rostovskaya, a senior research scientist in the Epigenetics research programme, received the 2022 Sir Michael Berridge Prize for her research which addressed key evolutionary questions about the changes in the early embryo that give rise to the amnion.

- Dr James Dooley, senior staff scientist, received the Knowledge Exchange and Commercialisation Prize for his work commercialising research from the Liston lab.

- Dr Simon Rudge, senior research associate in the Signalling research programme, received the Public Engagement Prize for his involvement in the Protein Challenge, a practical project for secondary school students, since its launch in 2015.

- PhD students Yasmeen Al-Mufti and Jake Cross received the equality4success award for their campaign to increase PhD stipends at the Institute to parity with other research institutes in Cambridge.

- The Image Prize was awarded to Dr Irene Zorzan and Dr Teresa Rayon. Named 'Blackberry field' the image shows human embryo-like structures derived from human embryonic stem cells (blastoids).

The 2022 annual prizes included a new award to recognise contributions to research integrity. The inaugural award was made to Dr Anne Segonds-Pichon, Biological Statistician from the Institute's Bioinformatics team, for her role in developing staff training and shaping an environment where scientists are free to pursue scientific questions in an ethical manner.

Research and facilities

Immunology

By working on mouse and human immunology and developing new tools, technologies and conceptual frameworks in which to understand immunity, we hope to contribute to improved health for all.

Signalling

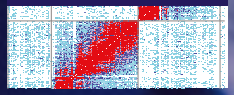
By working in model cell systems and organisms (worms, flies and mice) we hope to understand how signalling controls cellular and organismal resilience and how this can be applied to improve human health.

Epigenetics

Our research explores how epigenetic tags are set up during development and how they are modified by what we eat and as we age, with a view to understanding how defining and maintaining the epigenome promotes health across the lifespan.

Facilities

Bioinformatics

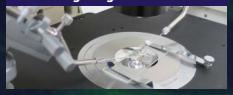


Biological Chemistry

Biological Support Unit

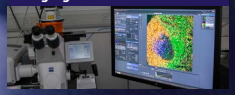
Flow Cytometry

Gene Targeting



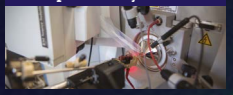
Genomics

Imaging



Lipidomics

Mass Spectrometry



Group Leaders and Facility Heads

Immunology

Martin Turner
Programme leader

Anne Corcoran

Michalle Linterman

Adrian Liston

Claudia Ribeiro de Almeida

Arianne Richard

Sarah Ross

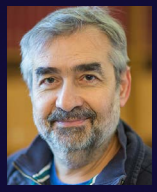
Signalling

Simon Cook
Programme leader

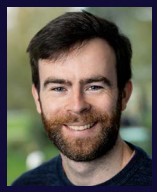
Della David

Oliver Florey

Phill Hawkins



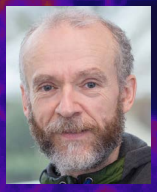
Nicholas Ktistakis



Ian McGough

Rahul Samant

Hayley Sharpe



Len Stephens

Heidi Welch

Valerie O'Donnell
Honorary Group Leader

Epigenetics

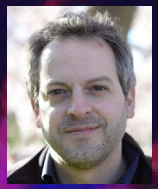
Gavin Kelsey
Programme leader

Olivia Casanueva
(left in 2021)

Maria Christophorou

Jon Houseley

Peter Rugg-Gunn



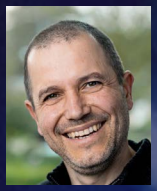
Stefan Schoenfelder

Martin Howard
Honorary Group Leader

Kathy Niakan
Honorary Group Leader

Wolf Reik
Honorary Group Leader since 2022

Facilities



Simon Andrews
Head of Bioinformatics

Jonathan Clark
Head of Biological Chemistry

Paula Kokko-Gonzales
Head of Genomics
(left in 2022)

Andrea Lopez
Head of Lipidomics

Asif Nakhuda
Head of Gene Targeting

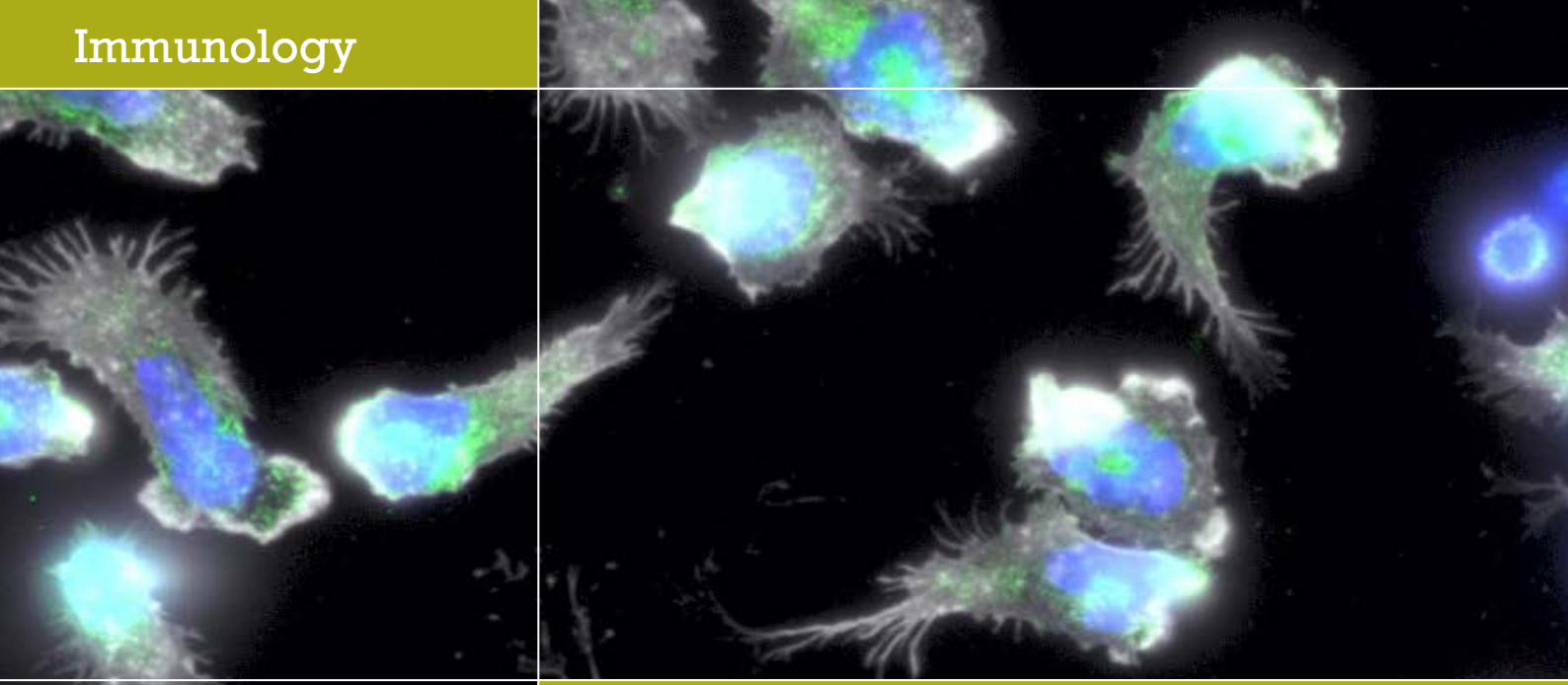
David Oxley
Head of Mass Spectrometry

Rachael Walker
Head of Flow

Simon Walker
Head of Imaging

Marc Wiltshire
Co-facility Head, Biological Support Unit

Paul Symonds
Co-facility Head, Biological Support Unit



Overview and broad aims

We all know what it means to be ill and that immunity generated through vaccination or infection is a good thing. But how is immunity produced in the body, by cells and molecules? How can we harness the power of the immune system, while maintaining tissue homeostasis?

These are fundamental questions that Institute immunologists are seeking to understand in more depth. By working on mouse and human immunology and developing new tools, technologies and conceptual frameworks in which to understand immunity, we hope to contribute to improved health for all.

Progress and research highlights in 2021 and 2022

A decline in adaptive immunity is one of the most widely recognised consequences of ageing. As we age our immune cells respond less robustly and our susceptibility to age-related inflammatory damage increases. The work of the Immunology research programme aims to understand the molecular and cellular basis of immunity with a view to informing the development of protective interventions to improve vaccine design and immunisation strategies and maintain health in older age.

One of the programme's most important activities in 2021 was Institute immunologists contributing their know-how to the pandemic. Martin Turner assessed funding applications as a member of the UKRI-BBSRC Covid-19 Cohort of Experts. The Linterman lab, in collaboration with the Jenner Institute, Oxford, published a pre-clinical study of the Oxford/AstraZeneca Covid-19 vaccine in aged mice (Silva-Cayetano *et al.* 2021). They also reported on how ageing influences influenza specific helper T cells in humans. The Liston lab ran immune phenotyping studies in patients to predict which individuals are prone to develop severe Covid-19 symptoms, requiring hospitalisation, and what the immune correlates are for poor response to Covid-19 vaccines.

2021 and 2022 saw notable contributions to the global research effort through the development of enabling research tools which allow us and others to analyse, visualise and think about data in new ways. The Liston Lab described Autospill, an algorithm for the compensation or spectral unmixing of flow cytometry data and removal of autofluorescence that is suitable for high-dimensional data analysis. Peter Chovanec, a PhD student in the Corcoran lab, published a paper introducing Canvas (Chromosome architecture network visualisation at scales) to generate high-resolution maps of gene regulatory interactions, chromatin profiles and transcription factor occupancy, and a comprehensive data resource produced by Sarah Ross detailed how killer T cells remodel their proteome in response to oxygen deprivation (hypoxia).

Work from the Turner lab on RNA-binding proteins ZFP36 and ZPF36L1 illustrated their importance in mediating T cell activation signalling and regulating the potency of cytotoxic lymphocytes. This work has relevance both to vaccine design and T-cell therapies.

We were delighted to welcome Arianne Richard in 2022 as a new tenure-track group leader and MRC Career Development fellow who joined us to study the molecular and cellular biology of CD8 T cells. Arianne's expertise in immunology and the molecular analysis of single cells will allow new questions to be addressed on how pathogens and the immunological environment shape T cell responses.

Impact highlights

Anne Corcoran, working with Elizabeth Wynn, the Institute's EDI manager, was awarded a grant from the British Society for Immunology (BSI) to host a series of talks 'Black in Academia' highlighting the experiences and challenges of Black immunologists, with the aim of increasing awareness of our individual and institutional responsibility to remove barriers to progression of Black academics. Anne also featured in a Q&A on Instagram on 'Covid-19, infection and immunity', aiming to provide informed answers by immunologists to questions from the public in a rapidly changing pandemic landscape.

Aila Biotech was spun out of the Institute in 2022 to commercialise work from the Liston lab on the development of a targeted therapeutic treatment to prevent brain inflammation following injury.

Michelle Linterman received an ERC Consolidator Grant in March 2022. The team will work with the Cambridge Biorepository for Translational Medicine to create the most comprehensive dataset to date on how the human germinal centre reaction is altered by ageing.

Martin Turner was awarded funding through the Milner Therapeutics Consortium to build on novel findings in T cell biology.

Looking ahead

Across the programme we will work together to deliver outputs that will advance the frontiers of biology, developing a foundation of knowledge that will enable efforts to maintain and protect health. By uniting the expertise of researchers within the programme, across the Institute and with collaborators, we will continue to develop new knowledge that is cross-disciplinary. Building on recent discoveries, we will explore new avenues in uncovering how RNA binding proteins affect immune memory, exhaustion, and antigen-independent activation.

With the appointment of Arianne Richard and in collaboration with our colleagues in the Epigenetics research programme we will initiate an exciting programme of work looking at the molecular and cellular physiology of CD8 biology relevant to T cell memory.

Publications

Silva-Cayetano, A. *et al.* (2021). A booster dose enhances immunogenicity of the COVID-19 vaccine candidate ChAdOx1 nCoV-19 in aged mice. *Med* 2(3):243-262.e8

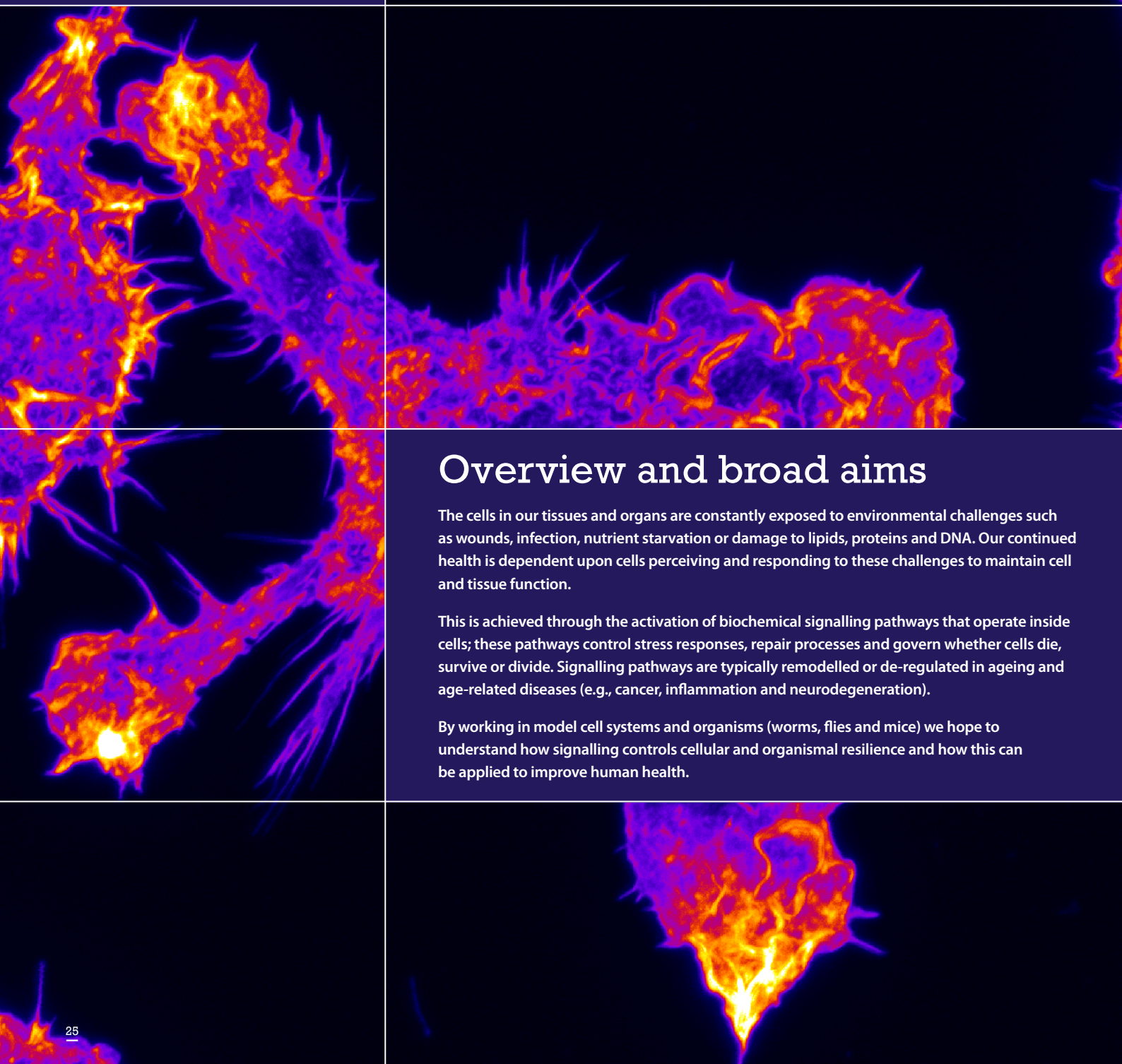
Burton, A.R. *et al.* (2022). The memory B cell response to influenza vaccination is impaired in older persons. *Cell Rep* 41:111613

Petkau, G., Mitchell, T.J., Chakraborty, K. *et al.* (2022). The timing of differentiation and potency of CD8 effector function is set by RNA binding proteins. *Nat Commun* 13:2274

Turner, D.J. *et al.* (2022). A functional screen of RNA binding proteins identifies genes that promote or limit the accumulation of CD138+ plasma cells. *eLife* 11:e72313

Whyte C.E. & Singh, K. *et al.* (2022). Context-dependent effects of IL-2 rewire immunity into distinct cellular circuits. *J Exp Med* 219(7):e20212391

Richard, A.C. (2022). Divide and conquer: Phenotypic and temporal heterogeneity within CD8+ T cell responses. *Front Immunol* 13:949423



Overview and broad aims

The cells in our tissues and organs are constantly exposed to environmental challenges such as wounds, infection, nutrient starvation or damage to lipids, proteins and DNA. Our continued health is dependent upon cells perceiving and responding to these challenges to maintain cell and tissue function.

This is achieved through the activation of biochemical signalling pathways that operate inside cells; these pathways control stress responses, repair processes and govern whether cells die, survive or divide. Signalling pathways are typically remodelled or de-regulated in ageing and age-related diseases (e.g., cancer, inflammation and neurodegeneration).

By working in model cell systems and organisms (worms, flies and mice) we hope to understand how signalling controls cellular and organismal resilience and how this can be applied to improve human health.

Progress and research highlights in 2021 and 2022

We study both receptor-mediated signalling pathways (PI3K, MAP Kinase, PTPases, GTPases, Wnt) and stress-induced signalling pathways that converge on autophagy and proteostasis processes. In the last two years we have welcomed Ian McGough and Della David as new group leaders in Signalling. Della's research on protein aggregation and ageing has clear overlaps with the work of Rahul Samant (proteostasis) and Nick Ktistakis and Oliver Florey (autophagy), consolidating critical strength in these areas.

In receptor-mediated signalling Len Stephens, Phill Hawkins and collaborators have identified distinct PI3Kδ signalling complexes that function in populations of cells in the immune system. In a landmark study they have also demonstrated that the acyl chain composition of inositol lipids serves as a code facilitating 'metabolic channelling' from PIP_2 to PI thereby ensuring the efficient and resilient functioning of the PIP_2 -PLC signalling pathway (Barneda *et al.* 2022). Heidi Welch's lab have shown that a receptor adaptor protein called norbin suppresses innate immunity to pneumococcal infection. Simon Cook's lab have demonstrated an unexpected dominant role for IKKα in inflammatory activation of NF-κB activation in colorectal epithelial cells. Finally, Hayley Sharpe's lab has uncovered the mechanism by which Afadin is recruited to the receptor phosphatase PTPRK, with implications for cell-cell adhesion and gut health (Hay *et al.* 2022).

Autophagy, a process activated by nutrient starvation, drives degradation of cellular proteins to create building blocks for synthesis of proteins required for cell survival.

Autophagy promotes healthy ageing, in part by degrading damaged and otherwise toxic proteins, but can also degrade pathogens including viruses. Nick Ktistakis has been involved in a major international project to show how invading viruses are identified and targeted for autophagic destruction (Dong *et al.* 2021); the significance of this is self-evident in light of the Covid-19 pandemic.

Oliver Florey's lab have made great progress in understanding a specialised form of non-canonical autophagy called CASM for short that is activated in response to cellular stress associated with infection, damage and ageing. The Florey lab have now defined a new molecular signature that defines CASM (Durgan *et al.* 2021), identifying components that are critical for CASM activation (Ulferts *et al.* 2021) and for maintenance of lysosomes (Goodwin *et al.* 2021). This finding has major implications for maintaining cell and organismal health.

Signalling colleagues have also published a series of authoritative reviews on the role of signalling in the maintenance of health, in disease and key research methods. These have included reviews on the control of NFκB signalling and strategies to inhibit RAF (Simon Cook), the molecular details of autophagy initiation (Nick Ktistakis), the role of Rho GTPases (Heidi Welch), the role of protein tyrosine phosphatases in cell adhesion (Hayley Sharpe) and systems for clearance of misfolded proteins (Rahul Samant).

All colleagues have given seminars on the international stage at prestigious conferences, ensuring our work is shared widely.

Impact highlights

During 2021-22 the Signalling programme continued its close work with the biotech and pharmaceutical sector including collaborative projects with AstraZeneca (Hayley Sharpe, Simon Cook, Len Stephens & Phill Hawkins), PhoreMost (Simon Cook), Mission Therapeutics and Casma Therapeutics (Oliver Florey).

Nick Ktistakis started a research collaboration coordinated by the Milner Therapeutics Consortium which aims to discover novel, actionable autophagy targets in neurodegeneration. This multi-centre collaboration involves Nick's lab, ALBORADA Drug Discovery Institute, MRC Mitochondrial Biology Unit and is funded by Astex, Eisai and Eli Lilly.

In 2021 Hayley Sharpe was awarded a three-year extension to her Sir Henry Dale Fellowship and also delivered the Lister Prize lecture. We were also delighted to see Ian McGough awarded a Sir Henry Dale Fellowship (2021) and Della David receive a Wellcome Discovery Award (2022).

Looking ahead

In 2023 we will focus on future plans for renewal of our strategic funding from BBSRC, including a major focus on ageing and proteostasis, reflecting our evolving research programme and new recruits.

In October 2022 we welcomed four new PhD students. Two joined the McGough lab (funded by the MRC and the Cambridge Trusts) whilst two joined the Cook and Samant labs funded by the new BBSRC CTP PhD Programme, with Babraham Research Campus companies Mission Therapeutics and PhoreMost. In 2023, we will welcome another CTP PhD student to the Cook lab working with Cancer Research Horizons.

Finally, we will create research training opportunities for young people from disadvantaged backgrounds through our Research Access Programme, run in partnership with In2Science.

Publications

Durgan, J. *et al.* (2021) Non-canonical autophagy drives alternative ATG8 conjugation to phosphatidylserine ***Mol Cell*** 81(9):2031-2040

Ulferts, R. *et al.* (2021) Subtractive CRISPR screen identifies the ATG16L1/vacuolar ATPase axis as required for non-canonical LC3 lipidation, ***Cell Rep*** 37(4):109899

Goodwin, J.M. *et al.* (2021) GABARAP sequesters the FLCN-FNIP tumor suppressor complex to couple autophagy with lysosomal biogenesis. ***Sci Adv*** 7(40):eabj2485

Dong, X. *et al.* (2021) Sorting Nexin 5 mediates virus-induced autophagy and immunity. ***Nature*** 589(7842):456-461

Hay, I.M. *et al.* (2022) Molecular mechanism of Afadin substrate recruitment to the receptor phosphatase PTPRK via its pseudophosphatase domain. ***eLife*** 11:e79855

Barneda, D. *et al.* (2022) Acyl chain selection couples the consumption and synthesis of phosphoinositides. ***EMBO J*** 41(18):e110038

Overview and broad aims

Our development depends on more than just our genes, the genetic instructions we inherit from our parents. Genes are governed by an extra layer of information that instructs them when and where to be active.

We refer to this information, which is made up of reversible chemical tags on our DNA and chromosomes, as 'epigenetic'. But as well as being essential for healthy development, some epigenetic information can be altered more easily than the DNA sequence by factors in our environment.

Our research explores how epigenetic tags are set up during development and how they are modified by what we eat and as we age, with a view to understanding how defining and maintaining the epigenome promotes health across the life course.

Progress and research highlights in 2021 and 2022

Cell models are indispensable in our work to understand developmental processes, in particular to recapitulate events in early human embryos. They enable us to test the roles of individual genes or conduct genome-wide screens, helping to illuminate the molecular and signalling mechanisms controlling the earliest cell-fate decisions. Using human embryonic stem cells, Wolf Reik's lab identified cells that resemble cells from human embryos at a time when embryonic genes are first activated, which will help identify the processes by which genes are first switched on in development. Peter Rugg-Gunn's lab has identified how changes in the epigenetic machinery help reconfigure cell identity during the cell-state transitions that occur in the early embryo.

At particular times in development, there are major changes in the epigenetic tags that normally silence genes, such as in the cells that give rise to the egg and sperm, raising questions about how genes can be properly regulated. Working with Petra Hajkova's lab at the MRC London Institute of Medical Sciences, we found that these precursor cells solve this using alternative epigenetic tags but, unexpectedly, male and female cells rely on different marks.

To understand how our genome responds to environment challenges across the life course, we need to be able to map sites of DNA damage, but existing methods have been cumbersome or lack precision. Neesha Kara, a PhD student in Jon Houseley's lab, has developed a highly versatile new method to simultaneously map DNA damage and replication, which can be applied equally well to the small genome of yeast cells and to complex mammalian genomes. Jon's lab is now using this exciting new method in a number of research questions in his own lab and with collaborators, from how yeast cells maintain their genomes during ageing, to understanding the impact of anti-cancer drugs on DNA replication in tumour cells.

Building on the ability to 'reprogramme' differentiated cells in stem cells, Diljeet Gill, a PhD student in Wolf Reik's lab, developed a way to partially reprogramme aged cells, allowing cells to be rejuvenated without being converted to a stem cell state. This method may help benchmark strategies for rejuvenation using pharmacological or nutritional interventions rather than genetic modifications.

We are delighted to have welcomed three new tenure-track group leaders to the programme, Philipp Voigt, Sophie Trefely and Teresa Rayon – Sophie and Teresa both jointly appointed with the Signalling programme. Sophie brings unique expertise to explore metabolism in the nucleus, which will help elucidate links between nutrients and epigenetic mechanisms. Teresa seeks to understand how the speed at which we develop is controlled, and what this tells us about ageing. Philipp studies how epigenetic marks (chromatin states) are set up during development, which will help us understand how epigenetic information is eroded as we age. In 2021, we also welcomed Professor Kathy Niakan as an honorary group leader, who undertakes pioneering research into the molecular events of early human embryogenesis and is starting to work with Peter Rugg-Gunn's lab on epigenetic regulation in human embryos.

Impact highlights

Members of the Epigenetics programme created an online 'Epigenetics Escape Room', which premiered at the Cambridge Festival (March-April 2021) and attracted more than 500 participants over the two weeks of the festival. The activity featured six puzzles that introduce players to epigenetics and several of our scientific facilities, and which a player must solve to finish a research project and publish their paper. A grant from the Institute's Public Engagement Seed Fund allowed us to adapt the escape room to a schools' version, which was piloted with the whole of Year 10 at Swavesey Village College in October 2021 in a joint event with Cambridge LaunchPad.

Enhanc3D Genomics, a spin-out company based on the Promoter Capture Hi-C technology developed at the Institute by Stefan Schoenfelder and colleagues followed a successful seed funding round (£1.75m) by securing Series A funding (£10m). The company now employs over fifteen full-time research staff and bioinformaticians.

Maria Rostovskaya was awarded the Knowledge Exchange and Commercialisation prize in 2021 for her work with Peter Rugg-Gunn and Wolf Reik on the generation of amnion epithelial cells from human embryonic stem cells. Amnion cells derived in the dish may have important clinical applications such as in wound healing.

Looking ahead

We are particularly interested in exploring the connections between metabolites in our cells and the stability of the epigenetic information that safeguards how genes are controlled over our life-course. This recognises the fact that the machinery that adds epigenetic tags to our DNA and chromosomes uses molecules naturally produced by metabolic pathways in our cells. We hope to investigate these connections using new ability to quantify metabolite levels in different parts of the cell, and to test whether modulating metabolic flux provides robustness to epigenetic information and improves ageing health.

Publications

Chovanec, P. *et al*. (2021) Widespread reorganisation of pluripotent factor binding and gene regulatory interactions between human pluripotent states. ***Nat Comms*** 12:2098

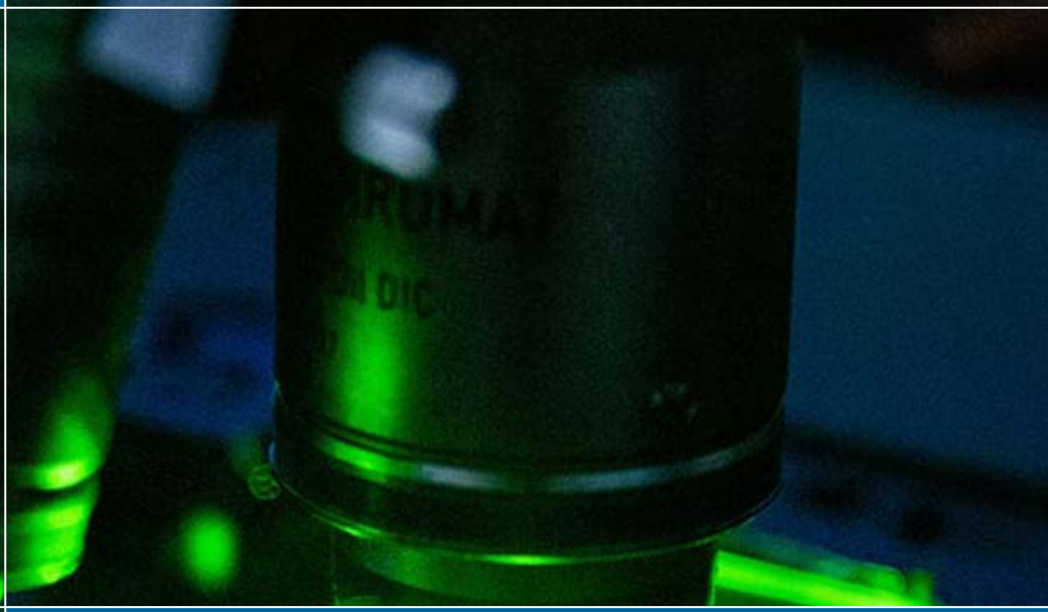
Collier, A.J. *et al*. (2022) Genome-wide screening identifies Polycomb repressive complex 1.3 as an essential regulator of human naïve pluripotent cell reprogramming. ***Sci Adv*** 8:eabk0013

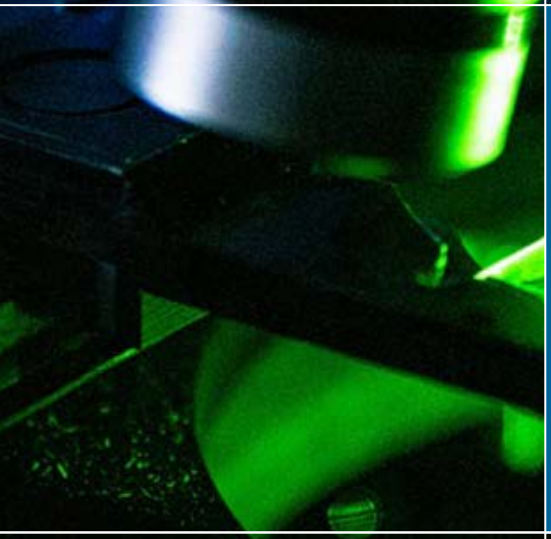
Kara, N. *et al*. (2021) Genome-wide analysis of DNA replication and DNA double-strand breaks using TrAEL-seq. ***PLoS Biol*** 19:e3000886

Huang, T.C. *et al*. (2021) Sex-specific chromatin remodelling safeguards transcription in germ cells. ***Nature*** 600:737-742

Taubenschmid-Stowers, J. *et al*. (2022) 8C-like cells capture the human zygotic genome activation program in vitro. ***Cell Stem Cell*** 29:449-49

Gill, D. *et al*. (2022). Multi-omic rejuvenation of human cells by maturation phase transient reprogramming. *eLife* 11:e71624



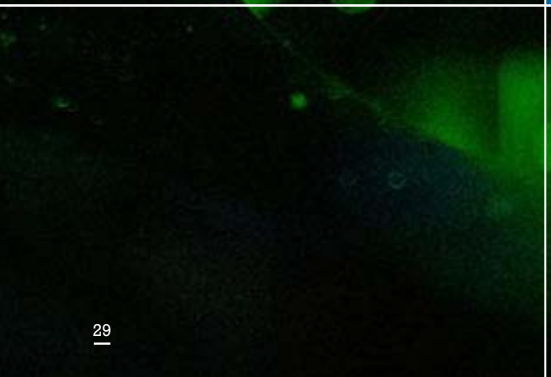


Pushing the boundaries with new capabilities

Underpinning our world-leading research are eight cutting-edge research facilities that support our science at the Institute. Thanks to their extensive expertise, our facilities also offer their services and training to external companies and individuals.

With the evolving landscape of the biosciences field, our facilities adapt to new technology and to meet the needs of the research projects in progress. In 2022, the capabilities of the Lipidomics facility were transferred into our Mass Spectrometry facility.

In 2021-22 three of our facilities, Imaging, Flow Cytometry, and Mass Spectrometry, have undergone transformations to update and advance their capabilities for the benefit of scientists on site, in Cambridgeshire, and across the UK.



Imaging in new dimensions

Following strategic investment from BBSRC, 2021 and 2022 have seen a major overhaul of the Institute's Imaging facility. A critical objective of this process has been updating and replacing the facility's heavily-used workhorse instruments to ensure that our core capabilities remain cutting-edge. New imaging platforms include a Leica Stellaris point-scanning confocal microscope for multi-colour high resolution imaging and an Olympus SpinSR confocal microscope for rapid 3D live cell imaging.

Further enhancements have been made with major upgrades to an existing Nikon confocal microscope and a Nikon super resolution microscope. Additional investment has expanded our range of technologies to include a Miltenyi MACSima deep phenotyping platform with the capability to image an unlimited number of fluorescence labels in one sample.

Together, these new and enhanced imaging systems offer numerous benefits including new capabilities, improved sensitivity, higher resolution, greater automation, improved ease of use, better stability and the ability for remote access.

All of the facility's most heavily-used systems are now configured to offer maximum flexibility and are optimised to accommodate the wide range of applications demanded by the Institute's science. Moreover, these new systems will help the facility support its increasing base of commercial users, strengthening the Institute's important role in supporting innovation.

Expanding the spectrum of flow cytometry services

Following our reinvention of the Flow Cytometry facility in 2021, with the investment in spectral flow cytometers, these instruments have proved to be essential tools for Institute scientists.

Spectral flow cytometry allows scientists to build large multi-colour panels (over 40) with ease, giving more insight into cell populations, rare events and ultimately gaining more information about each cell. The facility now houses two Aurora full spectral analysers to increase capacity within the facility for full spectral analysis. This allows our world-class science to be carried out on identical instruments with no compromise on booking time.

Following their installation in January 2022, the facility also utilises two Thermo Fisher Invitrogen Bigfoot full spectral high-speed cell sorters. Having beta tested this instrument for Propel labs since August 2020, we were aware that the Bigfoot sorter is the world's most advanced sorter. The three Bigfoot sorters within the facility give us a unique opportunity to be able to sort large numbers of cells on all three instruments simultaneously.
The Bigfoot combines flexibility, precision, speed, usability and accuracy allowing the facility to keep up to date and be at the forefront of spectral flow cytometry whilst efficiently delivering our world-class sorting service for Institute scientists as well as external companies and academics.

The facility continued to support external scientists with 27 companies using the facility in 2022; 20 based on the Babraham Research Campus and seven external. Our popular flow cytometry training courses held with the Francis Crick Institute saw 184 delegates attend at least one module of our virtual or in-person courses.

Exploring the metabolome

In 2021, a new theme emerged across the Institute's research programmes; the metabolome. This encompasses the small molecules that power the basic functions of the cell such as energy production and synthesis of biomolecules, and act as critical signalling molecules linking nutrient environment to cellular behaviour. With increased focus on the links between nutrient signalling, metabolism and epigenetic gene control, the Institute received funding for equipment to expand the capabilities within the Mass Spectrometry facility to perform direct metabolite analysis.

Mass spectrometry is the most important technique for the study of metabolism due to its high sensitivity and specificity allowing simultaneous detection and differentiate of multiple metabolites. Specifically designed for metabolite analysis, the Thermo Scientific Orbitrap IQ-X Tribrid mass spectrometer coupled to a Vanquish Duo ultra-high-performance liquid chromatography system will meet the growing demand for high-end metabolomics capabilities at the Institute.

In addition to providing opportunities for current Institute scientists to explore new avenues, the new equipment will be crucial for the research of of recently appointed group leaders Dr Teresa Rayon and Dr Sophie Trefely.

Sophie Trefely has marked herself out as a future leader in metabolomics, as evidenced by her development of mass spectrometry-based methods to analyse metabolism at sub-cellular resolution. Her results have revealed distinct regulation of metabolism in the nucleus which would otherwise go unnoticed. Sophie's research seeks to understand the signalling function of dietary metabolites, especially acetyl CoA, and how they impact epigenetic regulation in ageing, obesity and type 2 diabetes.

Teresa Rayon's lab studies the regulatory and dynamic processes that control biological timing across and within species. Teresa's recent findings show that differences in the pace between mouse and human during motor neuron differentiation corresponds to differences in protein turnover. Little is known about the rates of energy consumption within equivalent cell types in mouse and human. Following on from some preliminary measurements, Teresa will look to measure the metabolic flux in mouse and human neural progenitors and perform non-targeted stable isotope labelling metabolomics using the Orbitrap IQ-X Tribrid MS. These results will allow the design of perturbation experiments to determine the effect of metabolic pathways on tempo control and protein turnover.

Looking beyond the immediate benefits to researchers on the Babraham Research Campus, strengthening the metabolomics provision in the Cambridge area, and the UK as a whole, will ensure that metabolomics research groups have the resources they need to flourish in the UK and take advantage of the extensive fundamental science ecosystem around them.

Our contribution to the Babraham Research Campus

The Babraham Research Campus is a thriving and dynamic ecosystem where the benefits and strengths created by combining world-leading academic research with commercial life science companies are demonstrated on a daily basis.

The Babraham Research Campus is regularly highlighted as one of the leading places for research and innovation, providing outstanding support to early-stage bioscience enterprise. A major strength of the Campus is the co-location of the world-leading academic research and capability of the Babraham Institute with over 60 companies, comprising 2,000 employees and 200 academic researchers, where collaboration between academic and commercial research has long been a key component for the Campus's success.

In 2021, the Campus partners (the Babraham Institute, the Biotechnology and Biological Sciences Research Council, and Babraham Research Campus Ltd) published a refreshed joint strategy (1) to set the course for the continued development of the Campus. These strategic objectives aim to ensure that excellent research (both academic and commercial) continues to flourish, and that the capabilities and facilities on site support both the start-up and scale-up phases of a bioscience company's journey to deliver a highly connected, sustainable and dynamic ecosystem that creates new discoveries, therapeutics, jobs and growth to support the UK economy.

The formalisation of this joint strategy has refreshed the commitment the Institute has long had in providing key scientific skills, equipment and capabilities to companies through provision of cutting-edge scientific services and by encouraging a range of Campus company-Institute collaborations. The Institute's facilities are used by 83% of the Campus's bioscience research companies, with scientific method training provided to 56% of these. Over the last three years there have been an average of five Institute-Campus research collaborations each year and four jointly-supervised PhD studentships.

Specific collaborative initiatives spearheaded by the Institute in 2021 have included the Institute and Campus successfully securing funding for fifteen PhD studentships from UKRI-BBSRC as part of a Collaborative Training Partnership (CTP). Rolling out over a period of three years, eleven different Institute research groups will host students as they undertake their PhDs in partnership with thirteen Campus companies. Each CTP student will conduct their research within one of the Institute's three research programmes and spend time working with one of the Campus-based companies. The close location of companies to the Institute will allow students to benefit from a high degree of interaction with their industrial partner throughout the period of their studentship. Through a tailored programme of skills training and scientific and industry supervision the partnership will produce a cohort of bioscience researchers equipped with excellent research skills and commercial know-how. Students will also shadow early-stage life science ventures as they participate in the Campus' five-month bioentrepreneurial programme, Accelerate@Babraham, which will provide insight to the spin out/start-up process and an awareness of key commercial knowledge areas.

Accompanying these studentships, a range of Institute-initiated Campus networks have developed, improving the visibility and range of seminars and events offered by the Institute on diverse translational, professional career and academic themes, as well as the development of focused networking opportunities to co-create collaborative Campus researc projects. One significant network established in 2021 was the creation of an industry mentorship scheme that enables one-to-one connections between Campus scientific staff and early-stage

“ The Institute’s facilities are used by 83% of the Campus’s bioscience research companies.”

Institute researchers. This is proving a highly valued initiative, allowing Institute researchers to explore industry scientific career opportunities in the pharma, biotech and biomed sectors and providing training and professional development skills to the scientific mentors. The high level of interest in this scheme highlights the value Campus researchers place on being able to transition between academia and commercial science, in encouraging the movement of scientific and entrepreneurial talent and skills between Campus organisations.

1. Babraham Research Campus Strategy & Vision sets out its vision and ambition for its future, 12/05/2021. https://babraham.com/babraham-ecosystem/campus-strategy-vision/

Time flies

Joining a new organisation and building your research team during a pandemic isn't ideal but new group leader Dr Ian McGough is pleased he's found his niche, and gorgeous trail running routes, alongside a very warm welcome. Here he explains his passion about flies as he works to answers unexplored questions about morphogens in ageing.

When Dr Ian McGough joined the Institute in July 2021, Covid-19 restrictions were still in place. The campus was quiet, and the rest of his team didn't join him until six months later. "It was a little lonely at first, but everyone's been super helpful and accommodating," he recalls.

And he had his flies – thousands of them – for company. A passionate drosophilist, Ian's arrival signals the return of flies to the Institute after an absence of some years. Many signalling pathways were first discovered in *Drosophila* and, despite being eclipsed by mouse models in many fields, flies remain powerful research tools – provided you ask them the right questions.

Ian's research questions concern morphogens – signalling proteins that play a critical role in development and act as the blueprint for tissue formation. When morphogens are secreted, the signalling molecules form a gradient, meaning that some cells receive a lot of the signal while others get only a little. "This is the way that morphogens can pattern whole tissues," he explains.

" It's one of the things that happens with ageing, this failure of tissues to rejuvenate."

Although there are many morphogens, Ian's lab focuses on two: Wnt (pronounced wint) and Hedgehog. As well as directing development, morphogens maintain healthy tissue structure and function in adulthood by regulating how stem cells repair, replace and regenerate lost or damaged cells. And while their role in development is well studied, much less is known about how morphogens like Wnt and Hedgehog work in adulthood and their involvement in the decline in tissue renewal that happens during ageing.

"I'm interested in the gradients of the morphogens in adulthood, and in particular how they're affected in ageing. Because as we age, these tissues stop renewing. It's one of the things that happens with ageing, this failure of tissues to rejuvenate."

Carving out your own scientific niche requires the combination of curiosity, assessing the lie of the land, and carefully selecting the tools of your trade. Recognising an opportunity, Ian is set to explore this less-charted ground of what happens to morphogens with age. Are they driving this decline in tissue renewal as we age? A couple of recent papers suggest the answer is yes, and that decreased morphogen signalling in the intestine is responsible for the loss of the vital stem cell pool needed for tissue maintenance.

Before arriving at the Institute, Ian worked at the University of Bristol and the Francis Crick Institute in London, where he solved a question that had puzzled Wnt researchers for decades, namely how a signalling protein with fatty, water-hating parts could diffuse well enough to act via a concentration gradient.

An image of the Drosophila gut, the structure that is equivalent to the human small intestine. Blue fluorescence marks cell nuclei and white fluorescence shows the location of a phosphorylated protein involved in the signalling pathway that establishes a molecular gradient to maintain tissue patterning and homeostasis.

Image by Xinshu Xu (Babraham Institute)

" Flies are amazing for studying ageing because they reach the human equivalent of 70 years-old in just 45 days."

Now, his lab wants to answer two new and important questions: how do Wnt and Hedgehog work at a mechanistic level, and how do the components of these pathways change with age? "We want to know how they work because morphogens are critical in development and ageing, but we can't answer the second question without knowing the answer to the first," he says.

While his colleagues at the Institute know him as a successful scientist and former UK Young Cell Biologist of the Year, they may be unaware that some of his grit comes from Gaelic football. "It's a weird mix of football and basketball, but what I love about the sport is how physical it is; you man mark your opponent, meaning there are 15 individual – often quite aggressive – battles in each game. It also means you need to be mentally strong," says Ian.

Running his new lab and experiments should offer a more straightforward challenge. He'll be using *Drosophila* – housed in a new temperature-, humidity- and light-controlled fly room – to study Wnt and Hedgehog's role in ageing. "*Drosophila* is my model for the ageing work because the fly intestine declines with age – stem cells over proliferate, the gut gets leaky," he says.

As a signaller and an outdoor type, Ian and the Institute play to each other's strengths. "It's a great place for signalling, I can just walk down the corridor and talk to leading experts in related areas and perhaps together we can tease things apart. It's also a match for the direction I want to take my lab – into developmental signalling pathways but in an adult and an ageing context. And with Wnt and Hedgehog, I bring something new to the place," he says. "I'm not a museum or theatre-goer so London was wasted on me. The grounds here are amazing, there's 5km of trail running just over the bridge, so for me, the Institute is just perfect."

From Latin to the lab

Dr Philipp Voigt joined the Institute in December 2021 to set up a new group in the Epigenetics programme. But on leaving school he wanted to teach maths and Latin. Here, he explains the biological conundrums he aims to answer – and why Latin grammar could yet come in handy.

Despite being a biochemist Dr Philipp Voigt has always had a problem with biology. "In school I never liked biology; there were too many facts to memorise that were seemingly unconnected. But I did like physics and chemistry. There, you have a set of rules or principles that you apply to everything in order to explain the facts," he says.

The same penchant for principles accounts for his early love of Latin. "It was the first foreign language I had in school, and so the first time I really got to understand grammar. When you acquire your native tongue, you don't really think about its rules too much," says Philipp.

Today, what once frustrated him about biology now fascinates him. A system of rules must exist, it's just that biological systems are so mind-bogglingly complex that the rules are very hard to discover, he argues.

"People often say that biology doesn't work like this but it does. Biology doesn't exist outside the laws of physics and chemistry. It just uses so many things to make these amazing and complex systems."

" Biology doesn't exist outside the laws of physics and chemistry. It just uses so many things to make these amazing and complex systems."

The area he wants to help bring order and understanding to is epigenetics, although he began his research in signalling. Both are fields where the Institute is a world leader, so Philipp is delighted to have the Institute as the team's new home. "With my PhD I went into signalling, so I've known about the Institute's work since then," he says. "I moved into epigenetics as a postdoc and as I want to make connections between the two, there can be no better place than here."

An overarching focus for epigenetics is the fact that the same genome in every cell in our body gives rise to many different cell types. The key question, therefore, is how does one set of instructions produce such dizzying diversity?

There are many ways we think this happens, including transcription factors and histone proteins, which work together to orchestrate the process.

"These histone-based systems work by bookmarking genes as 'on' or 'off', supporting the whole process of controlling the gene expression pattern that's active in the cell," says Philipp. "This supporting function is very important because like bookmarks, they make it much easier to find the page – or gene – you're looking for in a long book or strand of DNA."

Not surprisingly, there is much we don't yet understand. A key area for Philipp's new group is the epigenetic regulation controlling gene expression during development, where he's focusing on modifications to histone proteins. As well as being responsible for keeping DNA tightly packed into cells, these proteins also have a regulatory job to do.

"If we can find some first principles that describe all these systems, then we have a fighting chance of emerging back into the light."

"We want to understand how the presence of one bookmark influences the presence and function of another. We are working on one particular set of combinations of two bookmarks, each of which has a different modification, one of which is thought to be active and the other repressive," he explains.

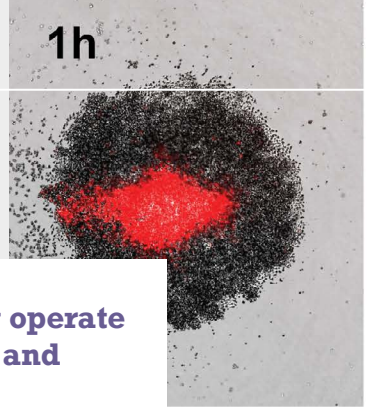
The question of why a gene is bookmarked both 'on' and 'off' has puzzled researchers for years and theories that this serves to keep genes primed or poised for action are still controversial. "We know both these bookmarks are there, and that these genes are then activated or repressed during development. What we don't know is whether the same things would still happen if those bookmarks weren't there," says Philipp.

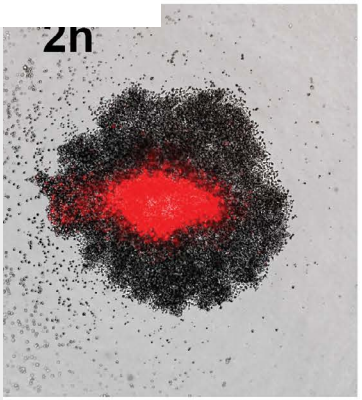
Knowing more about these systems is important, because as well as turning genes on and off correctly during development, when these systems begin to fail during ageing they cause disease. Based on epigenetics, researchers in allied disciplines are already using epigenetic targets to develop new ways of treating cancer, and understanding how genes are regulated in early development might also provide important insights that enable us to make specific tissues for regenerative medicine.

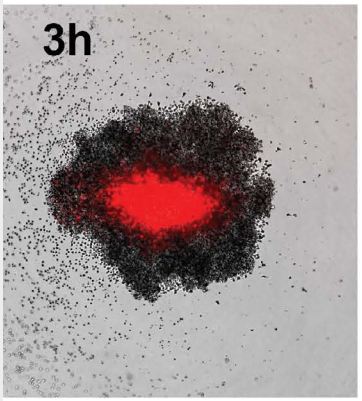
Despite the huge challenges ahead, Philipp often draws on the history of science for inspiration. "My dad turned 87 this year, and when he went to school, DNA wasn't even a thing! The same with the asteroid impact that wiped out the dinosaurs – that was a mystery until the 1980s. Knowledge has developed so fast over the past 50 years – but we're still discovering new things."

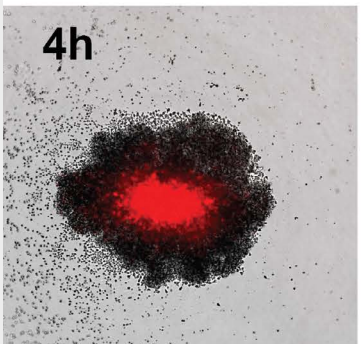
As science delves ever deeper, each new discovery seemingly throws up additional questions, and this ever expanding body of knowledge brings him back to Latin and the grammar of language. "We are reaching a point where you can't know everything you need to know in order to do what you're trying to do," he concludes. "If we can find some first principles that describe all these systems, then we have a fighting chance of emerging back into the light."

Natural born killers









Dr Arianne Richard talks about T cells, how knowing more about how they operate could open up new vaccines against viruses and new therapies for cancer, and why the Institute is the best place for her to tackle these questions.

While she's relatively new to the Institute, Dr Arianne Richard, a tenure-track group leader in the Immunology programme since April 2022, feels at home in Cambridge. Born and brought up near Boston, she "migrated" down the east coast of the United States throughout her education, doing her undergraduate degree in Biochemistry at Columbia University, New York and spending the second half of her PhD at the National Institutes of Health (NIH) in Washington, DC.

The first part of her PhD – through the NIH Oxford-Cambridge Scholars Program – involved two years in Cambridge. "That was my first introduction to Cambridge," says Richard. "I loved the research culture and the atmosphere, so after my PhD I sought out a postdoc position at the University and was there for six years before starting my own group at the Institute."

With a background in immunology and genomics, she selected the Institute for its strength in the field.

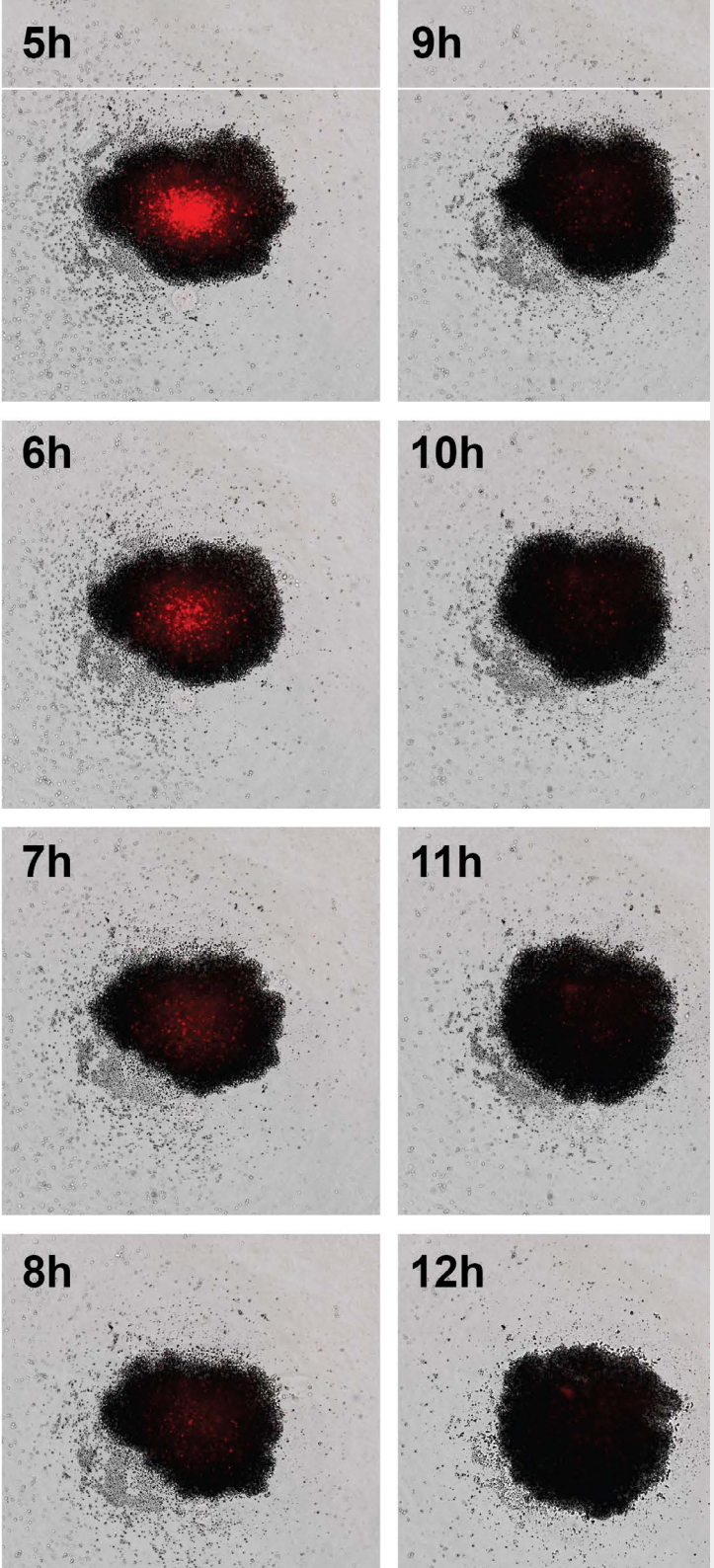
" To develop universal vaccines, we need to know more about T cells"

"The Institute has a such an incredible and cohesive immunology programme. I was particularly excited to join the programme here because they're doing fascinating, cutting-edge fundamental work on how immune cells function, particularly lymphocytes, which include the cells I'm interested in – T cells."

A type of white blood cell, CD8 T cells are critical for how our immune system responds to infections as well as cancer. When these cells encounter virus or cancer cells, a cascade of events follows; the T cell divides many times but not all its offspring are the same. Some specialise as killer cells while others become the system's memory. Killer T cells mediate this protective effect through their remarkable ability to recognise infected or cancerous cells. These they attach to via an 'immunological synapse' before firing tiny packets of toxic molecules into their target to kill it.

Richard studies T cells because as well as being killers, they are clever and complex. "They are part of the adaptive immune system, so as well as fighting current infection, they can create what we call immunological memory, which means they're better at fighting the same infection when they meet it again in the future," she says. How T cells decide whether to give rise to killer or memory progeny – and the factors that influence that decision – is what Richard wants to understand.

T cells do not exist in a vacuum, nor do they operate alone. Many factors will influence a T cell's decision about its progeny, including where it is and whether any inflammation is present. And as well as making the right decisions for themselves, the T cells must also work together so the population as a whole responds appropriately. "That means T cells are integrating all these signals from many different components, acting collectively and interactively as they influence each other's behaviour," explains Richard.



A series of time-lapse images showing T cells killing tumour cells (shown in red).

" The Institute's facilities are phenomenal and collaborating across programmes is just so valuable"

The overarching question her lab is addressing is how do antigens – molecules on infectious or cancerous cells which trigger an immune response – and environmental factors influence T cell response? Because it's such an intricate and important question, Richard is focusing on three key aspects: the influence of T cells' location within the lymph node; how T cells respond to different strengths of antigen signalling; and how T cells signal to each other to regulate the immune response.

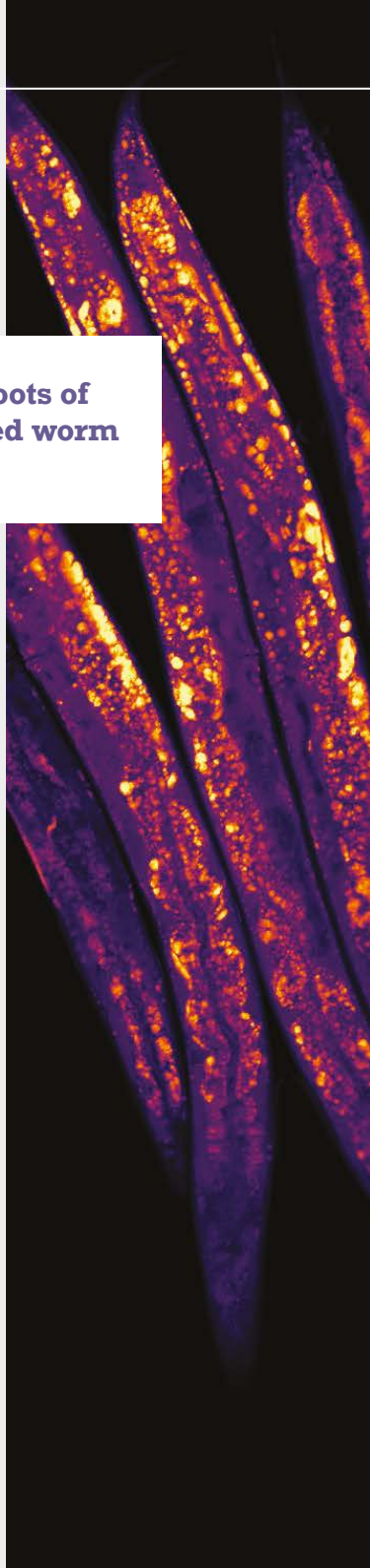
To do so, she's using a raft of techniques, from powerful single cell technology – an area pioneered at the Institute – to protein changes and epigenetics. It's challenging work, but understanding more about T cells' decisions could open up new ways to influence those decisions, with important therapeutic or translational impact.

One potential benefit is development of T cell-targeting vaccines. These hit the headlines during the Covid-19 pandemic, because as the virus mutated, the neutralising antibodies produced by vaccines became less effective against the virus, but the same issue has also been a problem for influenza vaccines for decades. "One potential route to a universal vaccine is to engage T cell responses in a greater way. These are often directed against parts of the virus under the surface, so although they don't completely prevent infection, they can dramatically reduce the severity of an infection," says Richard.

Other potential therapeutic benefits include manipulating T cell responses via immunotherapies – an area of huge interest in cancer treatment – and so-called checkpoint inhibitors, which effectively take the brakes off and reinvigorate T cell responses in the face of cancer.

Because the answers Richard is seeking cut across immunology, signalling and epigenetics – the Institute's trio of programmes – she's upbeat about what she can achieve. "The specialised science facilities here are phenomenal, which makes it possible to use techniques that I wouldn't otherwise have dreamed of using," she concludes. "And being able to collaborate across programmes with researchers in the same building is just so valuable. It's a great place to be situated in order to think about these different angles to how these cells respond."

From tiny worms to big discoveries



Dr Della David reflects on her first 12 months at the Institute, reveals the roots of her own scientific curiosity, and explains how a tiny, transparent, short-lived worm is enabling her to discover new ways of promoting healthy ageing.

Since arriving at the Institute in spring 2022, Dr Della David has been busy setting up her new group in the Signalling programme. Her work – on protein aggregation and healthy ageing – sits squarely within the Institute's core mission of healthy ageing research. Attracted by its outstanding research facilities, her research complements and expands cutting-edge work at the Institute.

"Getting to know everyone – all these new personalities – has been really nice, and I've been discovering how differently things work here compared with Germany – the communication styles, the hierarchies, the organisation," she says. "But mainly I've really appreciated how welcoming and friendly people are. There are several groups in the Institute's Signalling programme working on protein quality control and ageing and it's so stimulating to be able to discuss subjects we're all really interested in."

Her interest in ageing began when, as a young undergraduate, she read a pair of papers by two women scientists – Maria Grazia Spillantini, Professor of Molecular Neurology at the University of Cambridge and Cynthia Kenyon, Professor of Biochemistry at the University of California, San Francisco (UCSF).

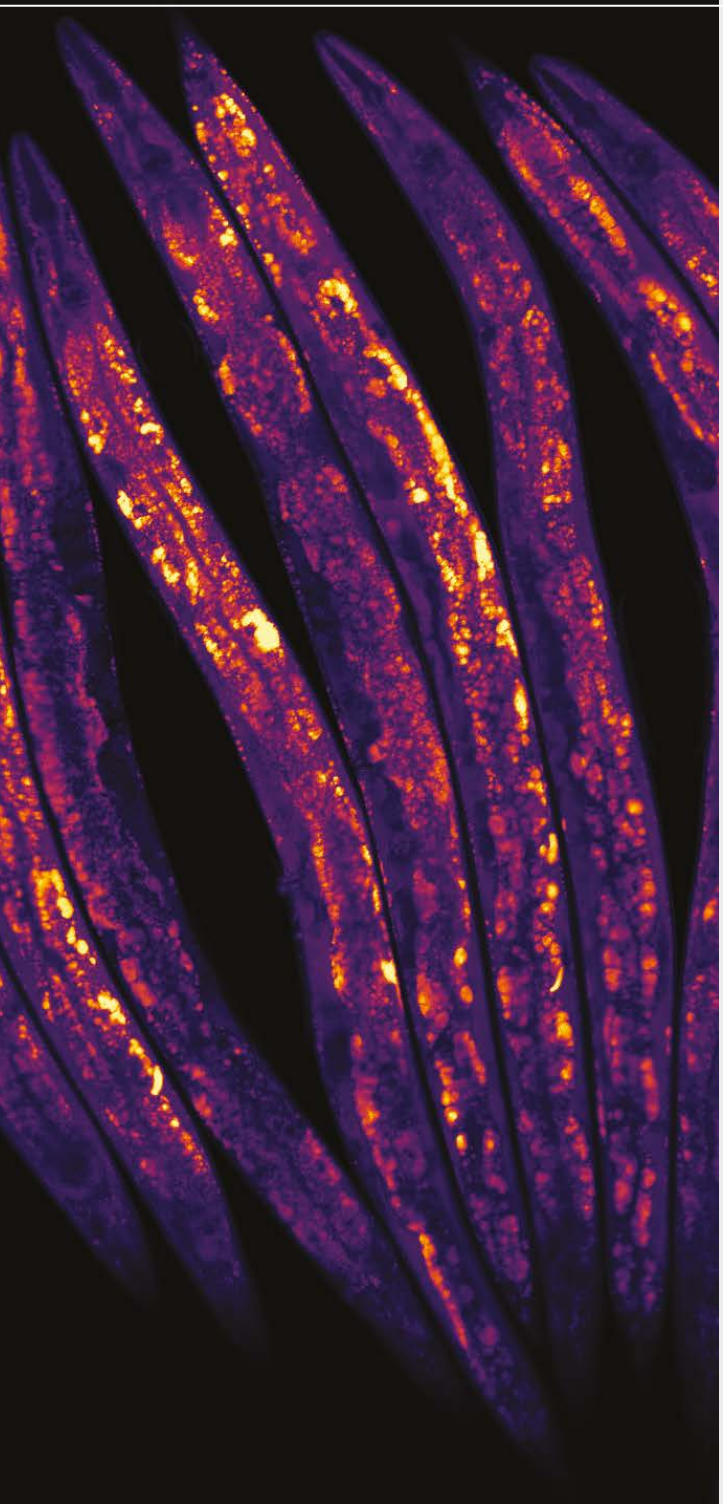
> **" *C. elegans* is an amazing model for doing ageing research"**

"The first was on protein aggregation, and that was so cool. The second challenged the prevailing view that ageing was an intractable process of decline, and I thought that was really fascinating," she recalls. "So I decided to do a PhD on protein aggregation and then a postdoc on ageing in Cynthia's lab."

It was during Della's postdoc at UCSF that she first worked with *Caenorhabditis elegans,* a tiny nematode, which Sydney Brenner pioneered as a model organism at the Medical Research Council Laboratory of Molecular Biology in Cambridge during the 1960s. Commonly found on compost heaps eating bacteria and fungi, *C. elegans* attracted Brenner because it was a comparatively simple organism, had a nervous system, and was easy to grow in bulk and to study with a light microscope.

Sixty years on, it's helping scientists untangle the role of protein aggregation in ageing. "*C. elegans* is an amazing model for doing ageing research," says David. "It's short-lived, with a life span of two to three weeks, and experiences a number of the declines we see in humans – from wrinkled skin and digestive problems to muscle weakness and memory troubles. It's a hermaphrodite, so you can produce approximately 300 babies per parent, and it's transparent. That's really important because we can tag proteins with fluorescent markers, follow them during the worms' lives, and watch the proteins clump together into these intractable aggregates."

Using the worm, David has already achieved groundbreaking results. To date, much research has focused on protein quality control inside cells, where researchers have discovered



“ We want to discover ways to promote healthy ageing and alleviate age-related diseases”

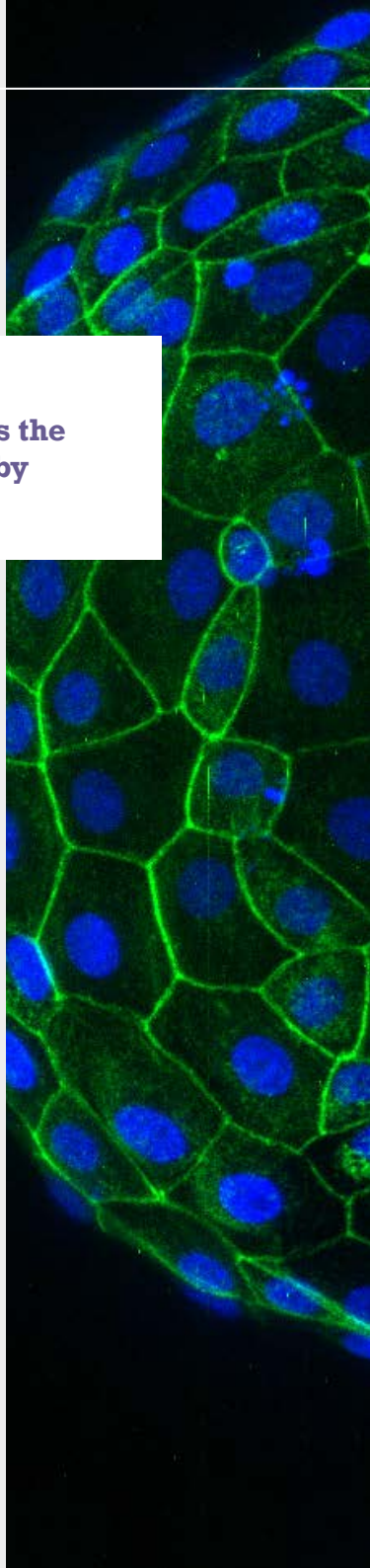
some 2,000 components that help keep proteins healthy and functional. Much less was known, however, about what happens outside cells, and before arriving at the Institute, David and her team discovered dozens of elements that control protein quality in the so-called extracellular space.

“We and others found that protein aggregation happens both inside and outside cells during normal ageing, as well as part of disease, and that it actively promotes ageing – triggering and accelerating the functional decline of tissues. We also discovered completely new ways of preventing proteins from aggregating to build tissue resilience,” she explains.

At the Institute, her new group’s aims are to understand at the molecular level what’s going on during ageing. Continuing their focus on protein aggregation, the team are investigating the mechanisms that protect against excessive extracellular protein accumulation in worms and then mouse models, and exploring new ways of maintaining the quality of proteins outside the cell. And because ageing is not a linear process, with certain parts of our bodies ageing more rapidly than others, Della is also keen to know what drives this heterogeneity in tissue-specific ageing. “The ultimate goal of our lab is to discover mechanisms to promote healthy ageing and alleviate age-related diseases,” she says. It’s knowledge David hopes will open up new therapies to delay age-related disabilities in humans: “If you can keep your proteins functional for longer, and avoid them accumulating in these toxic aggregates, your cells and tissues are going to be better off. It’s possible, for example, that we might be able to use gene therapies to express protective proteins in specific areas of the body to promote healthy ageing.”

And to answer these questions, she believes the Institute is the best place to be. “I feel very privileged to be doing science here,” she concludes. “There’s such great expertise here at the Institute and Cambridge area on the mechanisms of protein quality control. Being part of this community and sharing ideas and expertise helps all our research flourish and move forward as fast as possible.”

Delving deeply into development



Dr Peter Rugg-Gunn talks about the challenges of studying early human development, his group's groundbreaking discoveries, and why he believes the Human Development Biology Initiative – a five year, £10m project funded by Wellcome – will lead to a step change in the field.

As far as biological questions go, the origins of human life are as fundamental as they get. How – from one fertilised egg – do our bodies pattern into a mosaic of hundreds of different cell types that enable us to think, feel and do? It's a question Dr Peter Rugg-Gunn, a senior group leader in the Institute's Epigenetics programme and chief investigator of the Human Developmental Biology Initiative (HDBI), finds fascinating.

His work focuses on the first 14 days of our existence when the embryo undergoes extraordinary change, transforming from a uniform ball of cells into something poised to establish the embryonic body plan. During this early period, the embryo forms the progenitor cells of the placenta, which enable it to implant into the uterus and without which development cannot happen. At the same time, it must conserve special pluripotent cells at its core that will diverge at a later stage in development into the dozens of different cell lineages which become our diverse tissues with myriad functions.

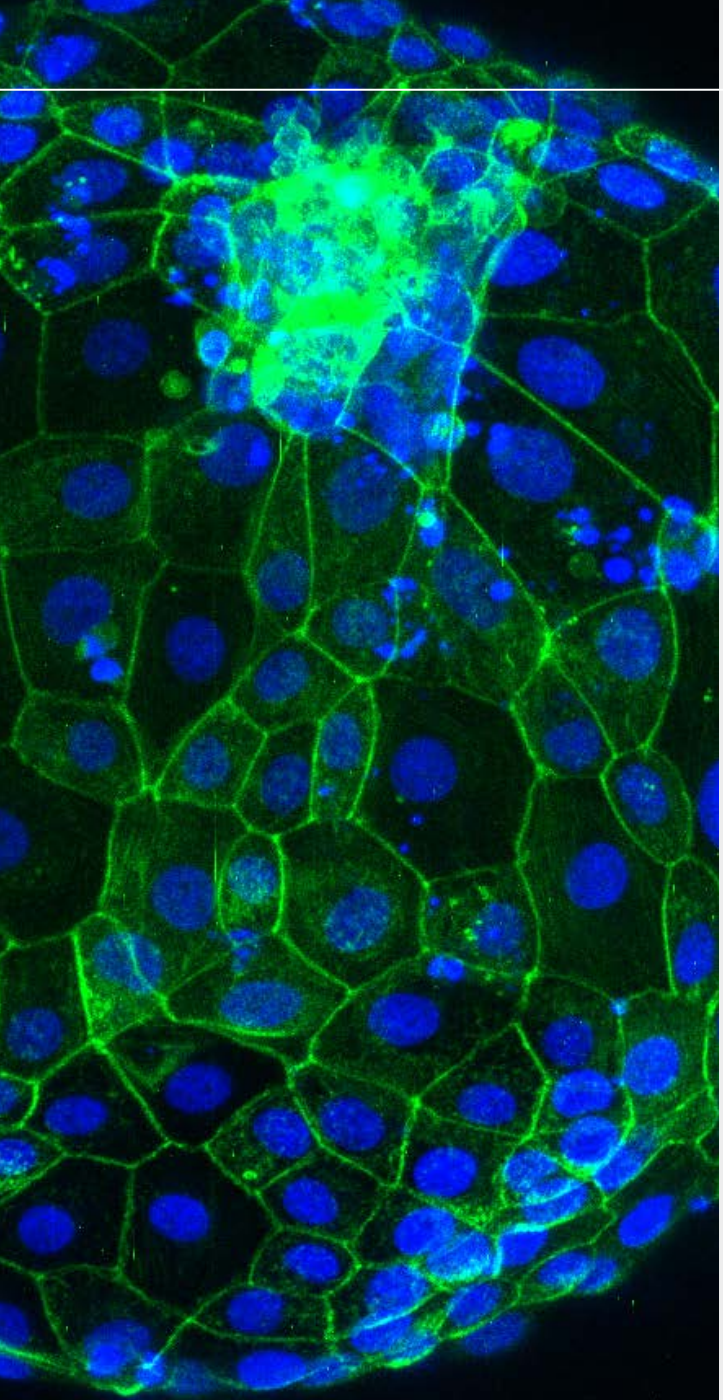
"It's an absolutely fascinating period in our lives, especially when you consider the challenges the early embryo must overcome. As well as being an extremely busy period of development, when so many things are going on, it's also a time of great epigenetic change, which is why it's such an interesting system for us to study," he explains.

> **" Once an embryo implants in the uterus, we don't know what happens next. You can't see them, you can't study them, and this is a real gap in our understanding"**

Epigenetics describes the additional layer on our genetic code that ensures the correct genes are switched on and off at the correct times and in the correct cells. Precisely how the embryo orchestrates such complex changes are at the heart of Rugg-Gunn's research, as it's a part of human development that science knows relatively little about.

"We know a reasonable amount about the first seven days of development, because of all the work that has been carried out on in-vitro fertilisation (IVF). We also have some understanding about embryos from about eight weeks post-conception from studying embryos donated for research purposes by women who have had abortions," he explains. "But, in between these stages, once an embryo implants in the uterus at the end of the first week, we don't know what happens next. You can't see them, you can't study them, and this is a real gap in our understanding."

There are many reasons why addressing this gap matters. Around 50% of embryos fail to develop past the first three weeks of development, and this figure is even higher following IVF. So understanding more about how embryos develop after implantation could increase the success rate of IVF, alleviating the heartache caused by infertility and recurrent miscarriage. This developmental period is also when several serious congenital disorders first arise; the origins of which we know very little about. More widely, investigating these early stages would also expand our knowledge of embryonic stem cells, which are pluripotent cells with similar properties to those in early embryos.



Microscopy image of a human embryo 7 days after fertilisation. Nuclei are shown in blue, and the shape of each cell is outlined in green. The image kindly provided by Dr Matteo Molè (Babraham Institute).

" HDBI will move the field on further and faster"

Embryonic stem cells are widely used in research and are part of the development of stem cell therapies with potential applications in a wide range of diseases.

A good example is work from Rugg-Gunn's group, which in 2022 published new discoveries about the amnion lineage, cells that form the membrane envelope which cushions the developing embryo. "It's a critical tissue during development, the origins of which were largely unknown in humans," he says. "As well as protecting the embryo, amnion cells have special properties that can promote wound healing. For this reason, amnion tissue donated after childbirth has been used to treat wounds for over 100 years. Our discovery on the origins of amnion cells means we can now convert embryonic stem cells into amnion cells and culture these cells in the lab, instead of having to rely on donated tissues. This allows us to work with much more standardised cells and scale them up to the numbers that might one day be compatible with helping to treat chronic wounds."

His group has also developed a groundbreaking new in vitro culture system that mimics the implantation of early human embryos into the uterus. The system means that for the first time ever, researchers can study the crosstalk between the embryo and endometrium until day 14 – the legal limit for culturing human embryos for research.

Most exciting of all for Rugg-Gunn and his group is being part of the Wellcome-funded HDBI. The initiative involves dozens of research teams across the UK who work together to try to understand how cell lineages are established at different stages of development.

Embedded into the science is an exciting public engagement programme which aims to explore society's views on human embryo research and to find out whether hopes and concerns might have changed since the UK's Human Fertilisation and Embryology Act came into force more than 30 years ago. During 2023, the Institute is leading a public dialogue focused on early embryo research, and in particular the 14-day limit on culturing embryos.

For both science and society, HDBI will have far-reaching impacts on the field of human development, Rugg-Gunn believes: "It's a really exciting initiative: it's ambitious in its questions and its scale; it's timely because we now have powerful imaging and single-cell molecular technologies, several of which were developed at the Institute; and because HDBI will set up new experimental platforms that will enable more researchers to do high quality human developmental biology research, it will move the field on further and faster."

Looking ahead for the group's wider research, progress also looks promising with the award of a Wellcome Discovery Award to Rugg-Gunn in 2022. "With all the tools at our disposal, I feel that we're on the cusp of filling these critical knowledge gaps and really unlocking a new level of understanding that will support healthy development, healthy pregnancies and stem cell technologies that will mean healthier lives for everyone."

Future plans

2023 sees the Institute focusing on its next quinquennial application for long-term strategic funding from BBSRC. This is an opportunity to build on our strengths and set ambitious new targets where we can deliver innovative contributions towards bioscience for improved health and new strategies to promote healthy ageing. Our fundamental research is more important than ever to secure health for the global ageing population and reduce the disease burden faced by health systems across the globe.

We will continue to work to uncover the fundamental knowledge of how our bodies work from the early stages of development through to maximising health in later years, investigating both the processes that maintain health and those that drive age-related functional decline. The Institute's cutting-edge immunology research and our growing expertise in the molecular mechanisms that maintain the healthy 'steady state' balance in our cells, tissues and organs position the Institute at the leading edge of this field. I look forward to our research and partnerships generating exciting new insights in this area.

We will continue to feed forward these discoveries through collaborations with other scientists, clinicians and policymakers and will build on our strong track record of biotech and pharma collaborations to deliver impact. This will include our burgeoning collaborations with commercial bioscience companies on the Babraham Research Campus and with our partner, Babraham Research Campus Ltd, in delivering a dynamic programme of entrepreneurial skills training for students and staff to train the next generation of bioinnovators.

It is notable that 2023 marks the 25th anniversary of the Institute's launch of Babraham Research Campus (then simply the Babraham Bioincubator). It is exciting and gratifying to see our vision for a vibrant cross-sector research campus, with the Institute at its heart, going from strength to strength and serving as a model for other Research and Innovation Campuses.

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