fusion

THE MAGAZINE OF THE SIR WILLIAM DUNN SCHOOL OF PATHOLOGY

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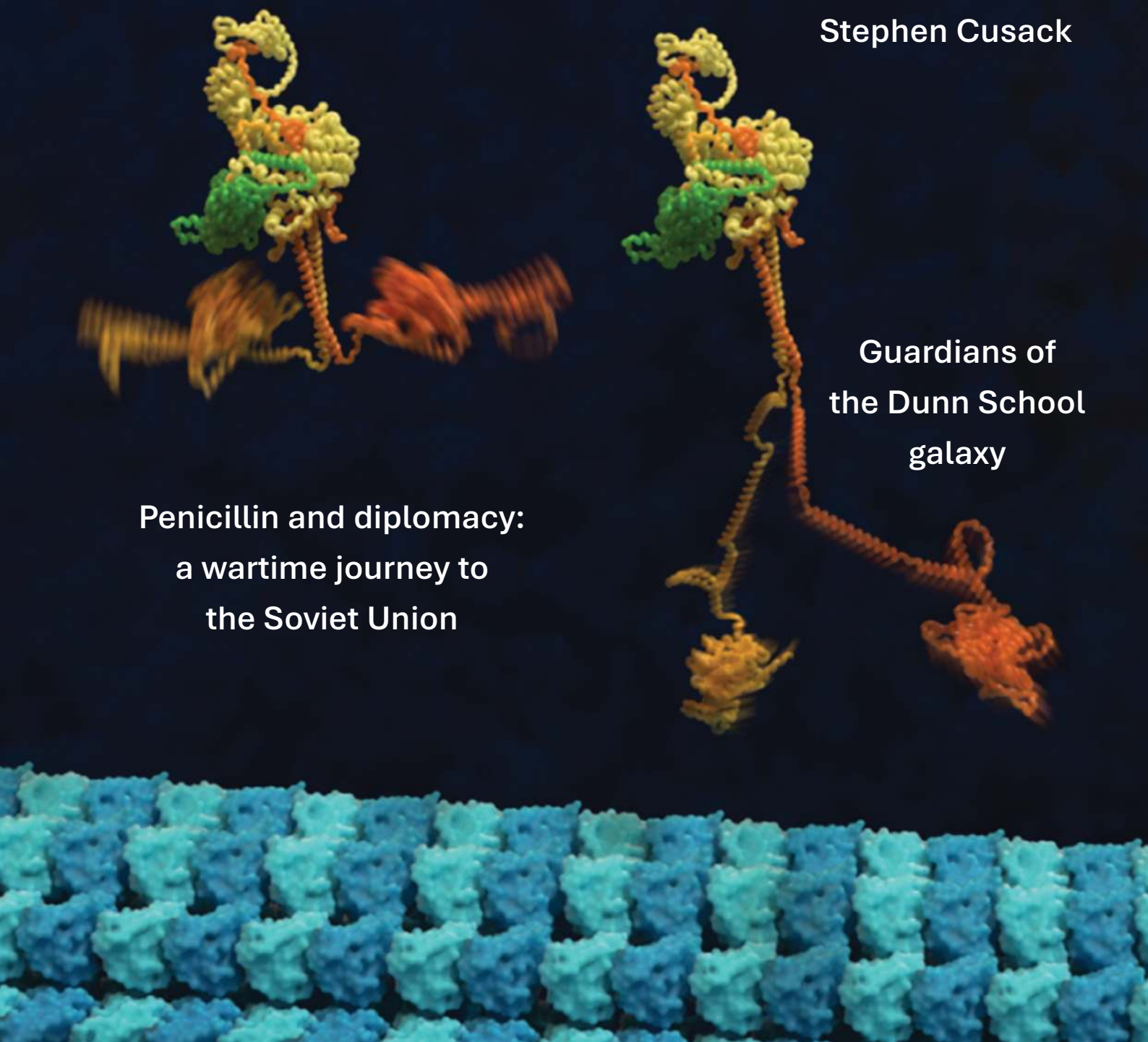
Motors, messages, and motion: inside the world of cilia

An interview with Stephen Cusack

Guardians of the Dunn School galaxy

Penicillin and diplomacy: a wartime journey to the Soviet Union



SIR WILLIAM DUNN SCHOOL OF PATHOLOGY

Welcome...

Writing the introduction to Fusion always provides an opportunity for me to reflect on the Dunn School year – both our achievements and the engagement we enjoy with our alumni and friends. Planning the 2027 centenary has revealed how much interest and warmth former members of the department retain, years and even decades after they leave.

I am happy to report that the Dunn School continues to thrive scientifically. Mathew Stracy, who until now has been one of our Wellcome funded early career fellows, has recently been appointed as an Associate Professor (Oxford's main academic position), with a tutorial fellowship at Lady Margaret Hall. Mathew's exciting work on bacterial persistence and antimicrobial resistance was featured in Fusion two years ago, and we are thrilled that he will now be a permanent group leader. I am also pleased to let you know that Sally Cowley has become a full group leader in the department with an Associate Professor title. The Head of the James and Lillian Martin Centre for Stem Cell Research, Sally is a leader in microglial biology and pluripotent stem cell models, and her promotion was overdue.

I can also announce two newcomers. Teresa Thurston joined us last Autumn as an Associate Professor with a tutorial fellowship at Magdalen College. Teresa moved from Imperial College in London, and her focus is on understanding the cell biology and infection strategies of two intracellular pathogens, Salmonella, which is responsible for ~ 1 million death per year world-wide; and *Burkholderia*, which is a particular problem in lower-middle income countries. Our most recent appointment is Alex Borodavka, who will join us in January as an Associate Professor with a tutorial fellowship at Brasenose College. Alex, who will move his group here from Cambridge, studies RNA viruses and how their genomes are segmented to ensure successful replication, with a particular focus on rotaviruses that infect children – killing upwards of 200,000 a year. All four of these appointments epitomise our mission to support fundamental discovery research that has the potential to transform human health.

Beyond recruiting great new people, another indicator of departmental success is the external recognition and awards that our scientists win. There are too many to mention all, though you will often see them posted in the news section of our website and on our social media accounts (we are active on Bluesky and LinkedIn). Nevertheless, I would like to highlight the election of Kevin Foster as a Fellow of the Royal Society, and Teresa Thurston's appointment to the EMBO Young Investigator Programme. At their respective career stages, both of these represent major success. Congratulations to Kevin and Teresa, as well as to everyone else who has received accolades in the last year.

Importantly, external recognition is not limited to group leaders: for example, in the last 12 months Carolin Kobras, Laura de Nies and Emma Roberts – all senior postdocs – have been awarded personal fellowships to initiate their own independent research careers within their host lab. José Cabezas-Caballero, a student in Omer Dushek's group, was awarded the Physiological Society Award at a STEM for Britain event in Parliament. And I'd like to congratulate Natalie Davis and Lucy Bryant, Dunn School apprentices, for both being recognised in the Oxford Apprentice Awards.

Reflecting on the last year is also inevitably associated with farewells. Most prominently, David Vaux is retiring, 50 years after arriving as a student in Oxford and almost 35 years after becoming a Dunn School group leader. David has been a leading figure in the Department and the University, and a wise counsellor to me on many occasions. We will all miss him, though, of course, we hope and expect to stay in close touch. We also said goodbye to Jo Peel, who had been my Executive Assistant for 11 years and whose commitment, hard work, and thoughtfulness I hugely appreciated. I am very pleased to report that her successor, Helly Worsdell, is proving to be a great new addition to the team. Sadly, and as written about elsewhere in this issue, Eric Sidebottom died in June 2025. Eric was associated with the Department for around 60 years, as a medical student, a University Lecturer in Experimental Pathology and, after his retirement, in a role he developed for himself, as the Dunn School's historian. He is missed by many who knew him as a warm and endlessly enthusiastic promoter of the Department.

We are of course now busy planning the centenary. There are updates in this edition and by the time of the next Fusion, all details should be finalised. An ambitious challenge we have set ourselves is to use the centenary as a catalyst to endow more graduate scholarships, ensuring that we can maintain our amazing record of supporting the very best young scientists – even at a time when University and Departmental finances are bleak. More about this vision in the future but I am thrilled now to announce the generous endowment by my predecessor Herman Waldmann of the Stephen Cobbold

Studentship. It is hard to think of a philanthropic gift with more impact than supporting future generations of Dunn School research students.

I hope you enjoy this edition of Fusion, which has been brilliantly edited by Catarina Vicente and Hannah Calkin.

Unusually, this issue also showcases the literary talents of our staff and students, including original science poetry and a short story set in a research institute uncannily like the Dunn School. Let me finish by reminding you that we will be hosting a major celebration on 7th July 2027, to which we would love to welcome back as many alumni and friends as possible. Hold the date! Please also stay in touch: we love to hear from you, including visits in person; you can always make contact via alumni@path.ox.ac.uk.

Matthew Freeman

Contents

Some arrivals and departures

Arrivals

The last year has seen the arrival of two new research groups to the Dunn School:

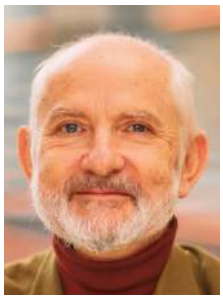
Teresa Thurston joined us last Autumn as an Associate Professor with a tutorial fellowship at Magdalen College. Teresa moved from Imperial College in London, and her focus is on understanding the cell biology and infection strategies of two intracellular pathogens, *Salmonella*, which is responsible for ~ 1 million death per year world-wide; and *Burkholderia*, which is a particular problem in lower-middle income countries.

Our most recent appointment is **Alex Borodavka**, joining us as an Associate Professor with a tutorial fellowship at Brasenose College. Alex, who is relocating from the Department of Chemical Engineering and Biotechnology in Cambridge, studies RNA viruses and how their genomes are segmented to ensure successful replication, with a particular focus on rotaviruses that infect children – killing upwards of 200,000 a year.

In the support teams, James Sturgess has joined as Head of Finance and Helly Worsdell is the new Executive Assistant to the Head of Department. Hannah Calkin joined us as our new Centenary Communications and Events Officer (more later in the issue) and Chris James is the new electronics engineer in the workshop team. Jessica Rushton joined as a new apprentice in Philip Cobden's team.

Departures

In the last year, we saw the retirement of four of our group leaders.



William James retired after 40 years as a PI in the department. Over this period he lead a research group studying HIV-macrophage biology using stem cell technology. He also held various senior roles within and outside the Dunn School, including as Pro Vice-Chancellor (Planning and Resources) and establishing the James & Lilian Martin Centre. At the time of his retirement he was a Fellow of Brasenose College.

Shona Murphy joined the Dunn School in 1991, held an MRC Senior Research Fellowship from 1993-2003 and was awarded the title of Professor of Molecular Genetics in 2014. She is also a Senior Research Fellow at Lady Margaret Hall, where she continues to teach. Shona's group worked on transcription and RNA processing in human cells, specialising most recently in the role of cyclin-dependent kinases in these processes.

Meanwhile **Quentin Sattentau** relocated his group to the Max Delbruch Centre for Molecular Medicine in Berlin. Quentin was originally a sabbatical visitor in Geoff Smith's lab from 1998-1999, returning as a group leader from Imperial College in 2003, initially as a lecturer and then as Associate Professor at Magdalen College. Alongside his research on HIV, Quentin contributed to many aspects of Dunn School life, including co-chairing our EDI committee and leading our successful Athena Swan Silver Accreditation renewal.

David Vaux is also retiring, 50 years after arriving as a student at Oxford and almost 35 years as a Dunn School group leader. His group has over the years studied many aspects of how post-translational modifications impact on human disease. He was a Fellow at Lincoln College, and held several senior positions within the university, with a special focus on undergraduate teaching, including Deputy Director of Pre-Clinical Studies and Deputy Head of the Medical Sciences Division.

We also said goodbye to Jo Peel, who was the Executive Assistant to our Head of Department for 11 years, and who contributed so much to the life and culture of the department.

News

A round-up of news from the last year. You can read these and other stories on our website www.path.ox.ac.uk

Honours for Dunn School researchers: some of the highlights

Kevin Foster was elected Fellow of the Royal Society, recognising his contribution to integrate ecological and evolutionary principles into microbiology to understand the human microbiome and other microbial communities.

Georgia Isom and **Mathew Stracy** have both been awarded ERC starting grants to work on antibiotic resistance. The Isom lab studies how bacteria build the cell envelope, a major determinant of antibiotic resistance in bacteria as it provides a physical barrier to protect against antibiotics. The Stracy lab is working to better understand the effect that antibiotics have on the gut microbiome and the spread of antibiotic resistance within it. We also congratulate Mathew Stracy for his recent appointment as Associate Professor of Cell and Molecular Biology in association with Lady Margaret Hall. Mathew joined the Dunn School in 2022 as a new group leader, supported by a Wellcome Trust Henry Dale Fellowship.

Teresa Thurston joined the prestigious EMBO Young Investigator Programme, which supports and recognises group leaders in the early stages of their independent career, and supports them through a variety of ways, including networking opportunities, training in leadership skills, and more.

Jose Cabezas-Caballero, a graduate student in the Dushek group, was awarded the prestigious Physiological Society Prize. The award recognises Jose's research on T cell engineering, as well as his ability to engage a wide audience on the therapeutic potentials of this work. As a result of the award, Jose has been invited to become a member of the Parliamentary and Scientific Committee.

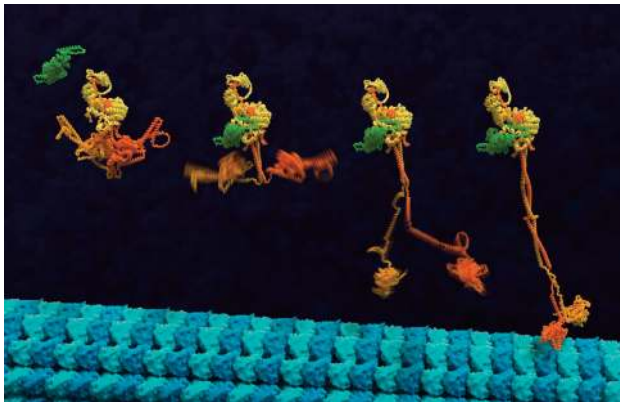
Finally, many congratulations to all Dunn School postdocs recently awarded fellowships! These fellowships include **Carolin Kobras** who was awarded a 2024 BBSRC Fellowship and **Laura de Nies** and **Emma Roberts** who were both awarded a Wellcome Trust Early Career Fellowship.

In other news...

The key to start kinesin-2 motor proteins

Published in Nature Structural & Molecular Biology, a new study by the Roberts and Toropova groups uncovers how kinesin-2 motor proteins are switched on and off.

Kinesin-2 motors are known for their role in carrying cargo along microtubules and building cellular structures called cilia, but until now, the molecular mechanism that governs when and how they become active has remained unclear. The new study reveals how a small structural feature – the β-hairpin motif – in the tail of kinesin-2 plays a central role in keeping the motor in an inactive conformation. Using a combination of structural biology, single-molecule imaging, and live-cell assays, the collaborative work shows how this motif binds the motor domains and prevents them from engaging their microtubule track.



Activation occurs when kinesin-2 binds to a cargo adaptor such as APC, which interacts with the β-hairpin motif and occludes it – releasing the motor domains for movement along their track. This tightly regulated mechanism ensures that kinesin-2 activity is precisely coordinated with cargo binding and spatial requirements inside the cell.

"This discovery gives us a detailed structural framework for how kinesin-2 motors are turned on only when needed" said Dr Katerina Toropova. "It provides insight into how transport is controlled in processes ranging from cilia formation to neuronal cargo delivery" said Dr Anthony Roberts.

The study also highlights the importance of this regulatory system *in vivo*. Mutations that prevent autoinhibition lead to motor accumulation at the ciliary tip, impairing recycling and disrupting normal function – a finding with implications for understanding human ciliopathies.

With the β-hairpin motif conserved across eukaryotes, the work sheds light on an ancient and widespread mechanism for regulating motor proteins at the molecular level.

Y RNA fragments help cells repair DNA damage

Published in Nucleic Acids Research, a new study by the Gullerova group reveals how cells can work together to survive DNA damage.

The DNA inside cells is susceptible to damage from endogenous and exogenous sources. This damage can potentially lead to disastrous consequences for cells and whole organisms. To prevent the buildup of mutations and the development of diseases like cancer, cells rely on the DNA damage response (DDR) – a network of pathways that detects and repairs DNA damage. Importantly, this response is not limited to individual cells. Through the release of exosomes – small, membrane-bound compartments – cells can communicate and coordinate DDR across their environment. These exosomes carry proteins and RNA, and their contents change when cells are exposed to damaging conditions such as irradiation. This allows healthy, unexposed 'bystander' cells to prepare for and resist potential DNA damage.

The Gullerova lab has been investigating the lesser-known role of non-coding RNAs in the DNA damage response. In their latest study, they show that following DNA damage, the RNA-binding protein YBX1 selectively packages a specific class of non-coding RNAs – Y RNA fragments – into exosomes. These exosomes are then taken up by neighbouring cells. Once inside, the Y RNA fragments interact with YBX1 and the DNA repair protein PARP1 at the sites of DNA damage. This interaction enhances DNA repair processes and improves cell survival, demonstrating a cooperative response to DNA damage at the population level.

This exciting study demonstrates the important and underappreciated role RNA plays in coordinating DNA repair between cells, providing new insight into how organisms protect themselves from genetic instability.

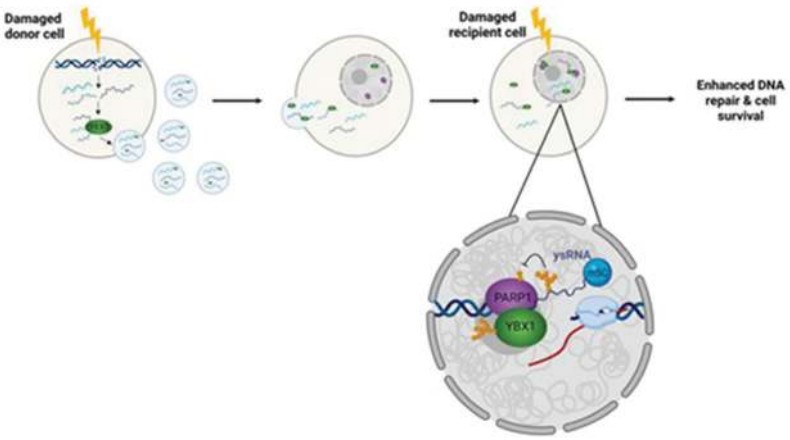
Professor Gullerova explains: "This study reveals that RNA can play a critical role in sustaining DNA repair process across populations of cells. It's a powerful example of how cells support one another in the face of damage".

Written by Isabella Maudlin (Hinch lab)

Boosting vaccines with harmless bacteria to fight intestinal pathogens

Published in Science, a ground-breaking study by the Slack group reveals how combining vaccines with friendly bacteria can boost vaccination efficacy and potentially reduce reliance on antibiotics.

The international collaboration between Professor Emma Slack, from the Dunn School and the ETH Zurich, and Professor Médéric Diard from the Biozentrum at the University of Basel, has developed a game-changing approach to combat harmful intestinal bacteria. Their research, conducted in mice, shows that combining oral vaccines with harmless bacteria is a highly effective approach to improving vaccine efficacy. The harmless bacteria outcompete the pathogenic bacteria for nutrients in the intestine, working in synergy with the vaccine to eliminate pathogenic bacteria more effectively than vaccination or treatment with harmless bacteria alone.



This combined approach not only prevented *Salmonella* infection in mice but also eliminated established pathogenic *E.coli* infections. For this approach to work, the harmless bacteria must be able to thrive in the same environment as the pathogenic bacteria, with similar nutrient, oxygen and acidity requirements. The researchers used genetic engineering to develop a competitive harmless bacteria strain, though naturally selected *E. coli* strains were also effective.

"Although we can decimate pathogenic bacteria with a vaccine, we need harmless

microorganisms to fill the resulting niche in the intestinal ecosystem in order to achieve long-term success," explained Professor Slack. "It's like gardening. If you want to avoid weeds in an area of the garden, you must plant other plants there after weeding. If you leave the soil empty, the weeds will just grow back."

In the fight against antimicrobial resistance, this method offers a promising alternative to antibiotics, targeting pathogens without contributing to resistance. It opens the door for future research aimed at applying this approach in humans, offering the potential to eliminate antibiotic-resistant strains and improve public health.

Written by Isabella Maudlin (Hinch lab)

Developing an AI Powered Platform for RNA-drug discovery

Monika Gullerova, has secured seed funding to develop an AI powered platform for RNA-drug discovery.

A team of four will work on the Raiden project, the aim of which is to achieve >95% predictive ability and to spin out a company that will lead in the field of RNA targeting by small compounds for new generation of therapies.

The Raiden project addresses a significant unmet need in drug discovery by focusing on small non-coding RNAs (ncRNAs), which play a crucial role in gene regulation and are frequently implicated in diseases like cancer and drug resistance. Despite their importance, targeted therapeutics for ncRNAs remain underdeveloped, relying on oligonucleotide therapies, which face challenges such as delivery, stability, off target effects and heavy modifications, creating a gap in RNA-focused drug discovery, especially for small molecules.

The Gullerova Lab's solution, Raiden, is an AI-Enabled RNA-Drug Interaction Discovery Platform that leverages machine learning and deep learning techniques to identify small molecules that bind to specific RNAs. Raiden uniquely combines two innovative approaches: (1) integration of 3D RNA structural features to identify "druggable" regions and (2) experimental validation of its predictions, generating real-world data that continuously refines the platform's accuracy.

Unlike competitors that focus predominantly on proteins or messenger RNA, Raiden is specifically designed to target small non-coding RNA. The Gullerova Lab's dual-modality approach differentiates them by integrating advanced 3D RNA structure analysis with a robust library of small compounds, setting a new standard for precision and scalability in RNA-targeted drug discovery.

Originally published by Wadham College

New advances towards optimising the antigen sensitivity of CAR-T cells

A new paper by the group of Omer Dushek makes important advances towards improving CAR-T technology.

White blood cells such as T cells continuously patrol the body in search of abnormal cells, such as infected or cancerous cells. T cells detect molecules called 'antigens' on the surface of abnormal cells using their T cell antigen receptors (TCRs). T cells are remarkably sensitive: they can become activated by the presence of a single antigen on a cell. This sensitivity is important because infectious organisms and cancer cells are very good at hiding from T cells by lowering the amount of antigen on the cell surface.

An exciting new treatment for cancer is to redirect T cells to target a patient's cancer cells. This is done by using genetic engineering to express chimeric antigen receptors (CARs) on T cells. CARs have an extracellular part that binds a target antigen on the cancer cell and an intracellular part derived from the TCR that sends an activating signal into the T cell. The antigens that CARs target on cancer cells cannot normally be recognised by TCRs, which is why CARs effectively re-direct and boost a patient's T cells to kill cancer cells. This therapy is very effective for targeting antigens expressed at high levels on leukaemias and lymphomas. However, many patients relapse when cancer cells emerge that have lower levels of antigen on their surface. One reason why this escape is possible is that CARs are not very sensitive and so are unable to 'see' these new cancer cells. There is an urgent need to increase the sensitivity of CARs to prevent these relapses. More sensitive CARs would also allow CAR T cells to be used in treating a wider variety of cancer antigens that are expressed at low levels.

In new work, Burton et al (2025) have now engineered CAR-T cells to display ultra-high antigen sensitivity that can match the sensitivity of the TCR. This was achieved by engineering elongated variants of the adhesion receptor CD2 or by reducing the physical size of standard CARs.

To exploit these technologies for optimising CAR-T cell sensitivity, Prof Dushek and Prof Anton van der Merwe have founded a spinout company, MatchBio Ltd. While improved CARs will transform the treatment of cancer, they may also prove useful for treating intractable infections and autoimmune disease.

Foster group contributes to popular children's science programme

The Dunn School group brought the science of the microbiome to 'Operation Ouch!', a popular BBC programme presented by Doctors Chris and Xand Van Tulleken.

Back in the summer of 2024 the Foster Lab was approached with an unusual request. Could we help to answer the question 'Why do my feet smell bad after wearing trainers all day?'. We gladly accepted the challenge and put our experience culturing the human microbiome to a new use!

The question was asked by a child contributing to a popular science programme made by CBBC, 'Operation Ouch!'. After sourcing tubs and trays to use as giant petri dishes and some willing volunteers, we experimented in the lab, culturing the microbiome of washed and unwashed feet. After a several attempts, we were ready. In September we travelled to the 'Operation Ouch!' studio and the CBBC presenters, Doctors Chris and Xand Van Tulleken, carefully placed their feet on the giant petri dishes we had prepared. After a few days' incubation, the microbial footprints were grown and looking great for filming.

The Foster Lab team, Xuedan Wang, Ryan Teo, Louise Pankhurst and Frances Spragge attended a day's filming at the studio to look after the cultures – with Frances making an on-camera appearance! The stars of the show were the magnificent microbial footprints, used by Chris and Xand to explain how the diverse set of microbes living on your feet produce organic acids that cause that distinctive used shoe smell.

Despite the smell, Chris and Xand explained in a child-friendly way how your skin microbiome is normal and healthy and can help protect you from more dangerous pathogenic microbes. They advised viewers that washing your feet and changing your socks regularly prevents build-up of dead skin which can cause extra growth of the microbes and abundant organic acid production.

The Foster Lab team had a great outreach experience seeing how this popular CBBC science programme is put together and making our own contribution to the programme. We can't wait to see our microbial footprints on air and will also then discover whether Frances' guest appearance made the final cut! Episode 7 of the 13th series of 'Operation Ouch!' titled 'What a Stinker!' is now available on iPlayer.

Written by Dr Louise Pankhurst (Foster group)

Dunn School Celebrates Renewal of Silver Athena Swan Accreditation

The Dunn School is delighted to announce the renewal of its Silver Athena Swan accreditation by AdvanceHE in November 2024. This prestigious award reflects the department's ongoing commitment to advancing gender equality, inclusivity, and excellence.

Since its last award in 2018, the Dunn School has made significant progress in its equality, diversity, and inclusion (EDI) agenda. Key achievements include:

- Enhanced Gender Balance: The proportion of female academic staff has risen from 15% to 36%, supported by targeted recruitment and mentoring initiatives.
- Professional Development: Programmes such as leadership training, skills workshops, and grant application support have been instrumental in advancing career progression, particularly for women.
- Support for Carers: Internal funding schemes for career development and childcare costs have helped staff and students balance professional and personal responsibilities.
- Positive Workplace Culture: Anti-bullying initiatives, including bystander training and dedicated Harassment Advisors, have fostered a respectful and supportive environment.

Athena Swan Award committee

Looking ahead, the Dunn School's 2024-2029 action plan focuses on addressing the "leaky pipeline" in senior roles, expanding mentorship programmes, improving workload distribution, and raising awareness of carers' grants and family-friendly policies.

The department extends its gratitude to application leads Quentin Sattentau and Louise Cotterell and colleagues from the Athena Swan Self-Assessment Team and EDI Committee for their contributions, as well as to all members of the Dunn School community who help make it a place where everyone feels valued and supported.

In memoriam

We are deeply saddened to announce the passing of former Dunners

Dr Eric Sidebottom, 1938 – 2025
Eric was part of the Dunn School community for over 60 years—as a medical student, researcher, lecturer, and later as the department's historian. He was known for his warmth, enthusiasm, and deep commitment to the Dunn School and its people.

He came to Oxford to study medicine at a time when Howard Florey and Hans Krebs were still lecturing undergraduates. After completing his clinical training in London, he returned to Oxford in 1966 as one of Henry Harris's first DPhil students. His early research focused on the function of the nucleolus, and he later worked on cancer, using Harris's pioneering cell fusion techniques to investigate metastasis.

Eric later played a major role in overseeing undergraduate teaching within the department, a role that expanded into significant responsibilities, including chairing the Faculty of Medicine board. Throughout the 1970s and 1980s he played a central role in coordinating medical teaching across Oxford's pre-clinical departments. In the late 1980s, he worked at the Imperial Cancer Research Fund before returning to Oxford five years later.

After his retirement he developed a role for himself in the department as our historian and became a leading expert on the history of medicine at Oxford. He wrote two books- 'Oxford Medicine: A Walk Through Nine Centuries' and 'Penicillin and the Legacy of Norman Heatley'—and gave talks on the subject extensively (including on cruise ships!). He was a tireless campaigner for the recognition of Oxford's contribution to the penicillin story, and in particular that of Norman Heatley. He was also a Fellow of Lincoln College.

Eric's contributions to science, education, and the history of medicine will be remembered by many. He will be greatly missed.

A fuller article commemorating Eric and his career will be included in next issue of Fusion.

Dr Jane Stinchcombe, 1966 – 2024
Jane was a skilled electron microscopist, who worked with Gillian Griffins in the Dunn School in the early 2000s, where she contributed to paradigm shifting discoveries that changed the way we think about how immune cells work. Kind and generous with her time, she will be dearly missed.

Valerie Boasten, 1937 - 2024
Valerie joined the Sir William Dunn School of Pathology in 1983 as the personal assistant to the then Head of Department, Professor Sir Henry Harris, after previously serving as PA to the Director of Social Services for Oxfordshire County Council. Following the formidable Mrs Finch-Mason, renowned for rigorously controlling access to the head of department, Valerie adopted a different approach, characterised by quiet indispensability and calm efficiency. After Sir Henry's retirement in 1994, she continued her role as PA to Herman Waldmann, Professor of Pathology and new head of the Dunn School at the time.

After stepping down from her PA duties, Valerie transitioned into the role of part-time administrator for the EPA Cephalosporin Fund, the EPA Research Fund, and the Guy Newton Research Fund—trusts established by Sir Edward Abraham to manage royalties from the antibiotic cephalosporin. Valerie remained dedicated to these roles until her retirement from the Dunn School in 2013.

In addition to her contributions to the department, Valerie had a deep interest in the broader affairs of the University. In 1998, she was appointed as Oxford's first-ever female Bedel and was later promoted to Senior Bedel, Bedel of Divinity, in 2003. She served in this prestigious role until 2015. Her ceremonial duties were vast, including bearing the mace at University events in the Sheldonian Theatre. She was also frequently seen volunteering as an usher at local performances, including at the Oxford Playhouse Theatre. Her remarkable service was recognised in 2015 when the University awarded her an Honorary Master of Arts degree, joining the ranks of earlier Dunn School stalwarts such as Peggy Turner and Jim Kent.

Valerie will be remembered for her warmth, dedication, and many years of invaluable service to the Dunn School and the University of Oxford. Her presence, both in the department and in the broader life of the University, will be greatly missed.

If you are aware of any Dunn School alumni who have passed away recently and would like to celebrate their life in the next issue of Fusion, please contact us at alumni@path.ox.ac.uk.

All in favour say "AI": insights into AI use in the Dunn School

Clare De'Ath

Artificial intelligence has taken the world by storm and is now part of many aspects of our daily life. Research is no exception. In this article, Clare De'Ath (Isom lab) examines how AI is being used across the Dunn School, including its potential and caveats.

Artificial Intelligence or 'AI' has become something of a buzzword in recent years, especially since the advent of large language models such as OpenAI's ChatGPT. In the scientific community, tools in the AI landscape have been used pretty extensively over the past decade but this has continued to rise in recent years. The Life Sciences are no exception, with the proportion of papers specifically mentioning AI- or machine learning-related terms rising to 5% in 2023 (1). So, looking closer to home, how is AI being used in the Dunn School?

To answer this question, I collected responses from members of the department spanning different positions and research areas. From this feedback (and a huge thank you to all who reached out to help!), I was able to understand how we are (or are not) using AI at several levels. This ranged from tools used by research groups in their respective fields to personal day-to-day use. I also considered tools under active development by researchers in the Dunn school. This article covers the current applications of AI in the Dunn school in addition to its future potential.

The AI Landscape

There are several terms encompassed under the umbrella term AI which are often used interchangeably (though not always correctly). By understanding where these concepts fit in the AI landscape, a tool's purpose or function becomes much clearer (**Figure 1**). **AI** broadly refers to a field of computer science dedicated to producing machines or algorithms capable of performing tasks typically requiring human intelligence. This can be subdivided into machine learning (**ML**) - which uses algorithms to learn from existing datasets - and natural language processing (**NLP**) - which uses algorithms to understand and interpret human-like language. Deep learning (**DL**), a subset of ML, uses neural networks to learn from data and make subsequent predictions; crucially, its hierarchical structure of interconnected nodes organised by layers can tackle large datasets and complex problems. These neural networks play a fundamental role when producing generative AI technology - which has garnered significant attention over the last couple of years since the release of OpenAI's ChatGPT in 2022. Large language models (**LLMs**) provided by tech companies (including OpenAI, Anthropic, Meta and DeepSeek), form a subset of generative AI utilising DL and NLP to understand and generate human-like text for a wide range of prompts.

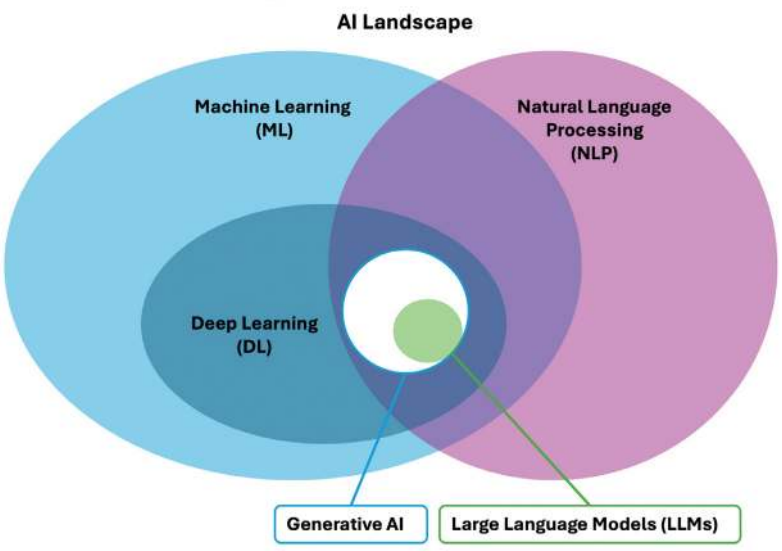


Figure 1: The AI Landscape. AI can be split by two fields of machine learning (**ML**) and natural language processing (**NLP**), which also intersect. Deep learning (**DL**) is a subset of ML using neural networks to learn from datasets. This can be combined with NLP which analyses and learns from natural speech for generative AI approaches - including large language models (**LLMs**) which can understand and generate new text.
Figure adapted from Inwedo blog posts(2,3).

AI in Research

Structural Biology

As a structural biologist, I couldn't resist first highlighting the huge impact AI has had on my field. AlphaFold2 - a DL protein structure prediction algorithm developed by Google DeepMind - was first released in 2021(4). Since its conception, it has quickly shaped structural biology projects by its ability to generate predictions of three-dimensional protein structures with much greater accuracy than previously possible, even in the absence of experimental data. In the Dunn School, I spoke to Dr Georgia Isom and Dr Katerina Toropova on how AlphaFold and other AI tools have contributed to research within their groups. Both labs (the Toropova lab with their Dunn School collaborators, Dr Anthony Roberts' lab) have recently published papers utilising AlphaFold structural models in combination with their experimental data (5,6). These are just two examples of an increasing movement towards integrating AlphaFold models with experimental assays as a robust means to understand protein function(s) and molecular mechanisms.

In the Isom lab, most projects would not exist in their current form without AlphaFold and related tools. The ability to predict novel folds and simulate proteins together offers a streamlined approach for targeting complexes, designing structural-functional mutagenesis studies and evaluating structural homology. In their most recent paper on the protein YhdP (6) , AlphaFold was fundamental in ascertaining novel insights into a system that is challenging to work with *in vitro*. This structural prediction revealed a bridge-like architecture favourable for YhdP's putative lipid transport role and subsequently guided functional mutagenesis experiments to probe the relative importance of bridge segments. This culminated in a model for how YhdP may build the inner leaflet of the outer membrane in Gram negative bacteria - a crucial barrier in conferring intrinsic levels of resistance to antibiotics (7).

By nature of their diverse roles, proteins often operate within a vast conformational and complex landscape to fulfill their function. Although AlphaFold is a powerful tool, it remains limited in its ability to predict multiple conformational states, complexes of unknown stoichiometries and protein-ligand interactions. The work in the Toropova and Roberts labs focuses on the kinesin and dynein motors that drive bidirectional transport of cargoes in cilia and flagella via ATP hydrolysis. They are prime examples of multi-component systems that cycle through multiple conformational states. To better understand these complex mechanisms of action, both labs use another tool called cryoDRGN (8). This employs a neural network to target both conformational and compositional heterogeneity in single particle cryo electron microscopy (**cryoEM**) datasets. This is proving to be hugely insightful for their work on the dynein-2 motor, which undergoes rapid-ATP-hydrolysis-induced conformational rearrangements to transport its cargoes, the molecular mechanisms of which have not yet been structurally characterised (9–11).

The Toropova and Roberts labs also study these dynamic processes *in situ* via cryo electron tomography (**cryoET**) - an electron microscopy technique which visualises systems in their native subcellular context. By collecting 2D projection images from rapidly frozen samples in a series of tilt angles, 3D reconstructions, or 'tomograms', can be built. This technique also has huge potential for studying disease-related structural defects in cilia from patients with impaired cilia transport. However, manual annotations to ascertain features of interest are currently a significant rate-limiting step during processing. Recently, AI has helped make significant progress in this direction with the availability of new software such as Dragonfly, which uses neural networks to automate segmentation (12). Moreover, the launch of the CryoET Data Portal by the CZII, which provides open access to annotated cryoET tomograms, can accrue increasing amounts of training data. Dr Toropova is excited by the future potential of this to enable the identification of ever smaller and/or complex features. Work towards training neural networks to tackle specific problems with ever-increasing accuracy will be hugely exciting for many groups in the Dunn School that adopt a structural approach.

Genomics

To consider genomics research streams in the Dunn School, I was fortunate to chat with Prof Sam Sheppard from the Ineos Oxford Institute, temporarily based in our department while waiting to relocate the lab to their permanent home in the Life and Mind Building across the road. His lab focuses on microbial genomics and evolution, aiming to understand selection-driven genome variation that define ecological niches and epidemiological patterns of pathogens. Whilst classic genomics approaches relied on statistical inference to understand underlying relationships between datasets, we discussed how increased computational processing power paved the way for the supplementation of more advanced ML approaches. ML applies past experience to predict future patterns that may be non-linear with datasets of increasing size and complexity. Therefore, ML approaches have become fundamental in genomics research over the past decade, with many significantly more computationally efficient than traditional statistical methods.

A compelling example of ML in microbial genomics comes from the Sheppard lab's research project to understand the population genomics of pathogenic *Staphylococci* species. Notably, *S. epidermidis* - a common skin commensal - can cause under-recognised infections associated with implanted medical devices (13). These often originate from strains present on the skin or in the hospital environment. To understand why certain pathogenic strains survive and proliferate in clinical settings, they employed a pangenome-wide association study (**pGWAS**). GWAS work by using generalised linear models (**GLMs**) to ascertain which variables are best predicted by the other. In this case, genes associated with pathogenicity were identified from human disease-causing isolates. These disease-causing genes were subsequently validated by statistical correlation to *in vitro* phenotypic assays. The use of random forest (an ensemble ML method combining outputs from multiple decision trees to enhance predictive accuracy and robustness) on these isolated genes also found the best-ranked genetic elements for causing disease. Following this work, Sam noted that the lab is integrating elastic net regression into GWAS workflows. Elastic nets combine Lasso and Ridge methods to reduce model overfitting and address multicollinearity whilst mitigating their individual limitations (14).

This combination is thus opening new avenues to more accurately identify true positives and group correlated mutations together.

Although ML is well indoctrinated into many genomics approaches, caution is taken with DL approaches due to implicit bias risk. It can be difficult to deconvolute (by nature of the many layers of a neural network) how models have distinguished patterns in the data. If a model begins to use unexpected or incorrect signals in the data to predict relationships, this may lead to biased conclusions that are untrue (15,16). Additionally, conversations with Laura and Michelle from the Stracy lab about their metagenomics research into microbial communities also led to some interesting discussions on how incomplete genomes and westernised datasets may not offer the best training models for future tools. This leans into the concept of building more bespoke tools to tackle specific questions that could be obscured by generalising experimental datasets. By incorporating good validation practices, this can be mitigated and accounted for (17).

Pioneering new AI tools

RAIDEN

Aside from pre-existing tools used across research groups in the Dunn School, there are also novel AI tools being designed to address unmet needs in research. Prof Monika Gullerova secured seed funding in 2025 to develop RAIDEN: RNA AI-driven Drug-discovery Expandable Node which has also been launched as a spin-out company RAIDEN THERAPEUTICS (18). RAIDEN is a specialised DL tool being developed for RNA ligands, addressing the missing infrastructure for large-scale screening of RNA-small molecule drug interactions to uncover novel therapeutics. Central to this platform is the linearity with current research in the Gullerova lab, with focus on small non-coding RNAs and the ability to experimentally validate predictions from in silico experiments ultimately enhancing RAIDEN's future accuracy. This seamless duality between lab research and building AI tools that address requirements in the field represents an exciting application of cutting-edge research in the Dunn School. For original coverage of RAIDEN, check out the following articles from Wadham college (19) and the Dunn School (20).

Personal use

Having discussed much of the departmental science being enhanced by AI tools, there is also the impact that they have had on a personal scale. Several members of the department highlighted their use of generative AI as a supportive tool for phrasing emails, prompting writing tasks and troubleshooting coding. There is also an increasing use of LLMs to curate and summarise relevant literature, especially as a springboard for users to branch into new, unfamiliar fields. The supplementation of LLMs with retrieval-augmented generation systems (RAGs) can enhance this process by gathering relevant and up-to-date information from external sources. These are then implemented into the generation process and cited for improved traceability. However, there have been hard limits to generative AI use, especially in administrative roles that must handle personal and confidential data.

What does the University of Oxford recommend?

As highlighted in a previous departmental newsletter (May 2025), free versions of platforms should not be used for personal data or confidential results. Microsoft Copilot is already available as an extension to our Microsoft 365 apps (including outlook and teams). A more powerful version of Copilot is available with an educational license in addition to educational licenses for ChatGPT, which are now freely available to all members of the University.
Both are recommended to be used following the University guidelines set out here:

https://communications.admin.ox.ac.uk/communications-resources/ai-guidance (21).

In summary, data processed by Copilot Edu or ChatGPT Edu under these licenses will not be used to train future iterations of the model making it amenable to confidential data (with prior approval from the Information Compliance team).

Note that the guidance for the use of AI is ever-changing to match the dynamic growth of this field. It is important to keep track of updates offered by the University and only use approved platforms for work.

Conclusions and Future Perspectives

Overall, AI used in the Dunn School has mostly revolved around ML or DL algorithms embedded in our respective fields. More recently, the Gullerova lab has actively developed AI tools *in situ* with their research. Finally, we are beginning to make more use of generative AI to support our day-to-day work. Whilst this is being encouraged in the University there are still outstanding considerations to be made such as:

- The environmental impact of using AI for scientific research
- The impact of implicit bias in AI systems in the context of Equality, Diversity and Inclusion (EDI)
- Avoiding hallucinations (inaccurate or misleading information) from generative AI by rigorous prompting and validation strategies
- Ensuring that governing and funding bodies regard AI as a supportive tool and not a replacement for scientific expertise

As it stands, AI has led to exciting breakthroughs in our contributions to scientific fields in addition to enhancing many of our day-to-day productivities and project bandwidth. With increasing guidance from the University and the availability of educational licenses, this should be set to continue in a positive trajectory as we expand the use of AI in the Dunn School (**Figure 2**)!

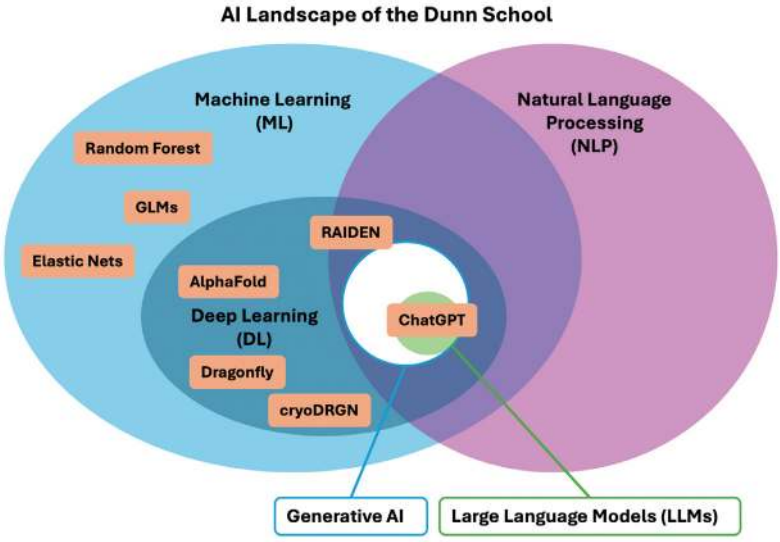


Figure 2: The AI landscape of the Dunn School? AI approaches or tools mentioned in this article placed into their respective fields for comparison.

Acknowledgements

Firstly, a huge thank you to the Fusion team for featuring my article in this issue with special thanks to Cat Vicente for her guidance, editing and support. Additionally, I would like to thank the members of the Dunn School who responded and engaged with me on the article including Dr Georgia Isom, Dr Kat Toropova, Prof Sam Sheppard, Dr Laura de Nies, Yiyun Michelle Fan, Dr Ben Cooper, Louise Cotterell and Dr Saroj Saurya. An additional thanks to Dr Georgia Isom and Dr Kat Toropova for their insights on drafts.

Abbreviations: AI - Artificial Intelligence, **ML** - Machine Learning, **NLP** - Natural Language Processing, **DL** - Deep Learning, **LLM** - Large Language Model, **CryoEM** - Cryo Electron Microscopy, **CryoET** - Cryo Electron Tomography, **pGWAS** - PanGenome Wide Association Study, **GLM** - Generalised Linear Model, **RAG** - Retrieval Augmented Generation system, **EDI** - Equality, Diversity and Inclusion

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21. Guidelines on the use of generative AI

Teaching Pathology in the Dunn School – 2004 to 2024

David R Greaves

Undergraduate teaching, both lectures and practical classes, are an important part of life in the Dunn School. Many Dunn School graduate students and postdocs have contributed to undergraduate teaching in the department over the years, gaining valuable teaching experience. Medical and biomedical students have benefitted enormously from their scientific curiosity, knowledge and enthusiasm. In this issue of Fusion, David shares personal reflections on his 20 years contributing to undergraduate teaching in the Dunn School.

I arrived in the Dunn School as a postdoctoral research fellow in November 1993 and I regularly volunteered to be a classroom demonstrator for practical classes led by Simon Hunt, Stephen Goss and David Vaux. The practical classes back then took place on the second floor of the Dunn School in a dedicated space that was later converted into what is currently the laboratories of Geoff Smith and myself. The upkeep of the classroom and preparation for the practical classes was led by a dedicated technician Judy Couglin and she was ably assisted by Liz Darley who occupied the adjacent histology lab.

In 1999, I gave my first lecture to second year medical students in the old Dunn School lecture theatre on cardiovascular pathology. This seemed fitting as I had just been awarded a fellowship from the British Heart Foundation. Giving my lectures in the original Dunn School lecture theatre, built in 1926, I was aware that I was continuing a tradition of teaching the basis of human disease in a long line of succession that included Howard Florey and many others. Still working in the Dunn School at that time were support staff who had been instructed to lock the door of the lecture theatre at two minutes past 9 o'clock to prevent students turning up late to Lord Florey's lectures (!)

In 2004, I was appointed as a University Lecturer and the head of the department Herman Waldmann asked me to take on responsibility from Simon Hunt for organising and delivering the second year Pathology Course, then called General Pathology and Microbiology. That year all our lectures, seminars and practical classes moved from the Dunn School to the newly opened Medical Sciences Teaching Centre (MSTC) building. Current "dunners" will

have spent time in the 204-seat lecture theatre for departmental seminars, the annual students' day and postdoc symposium but may not have visited the dedicated undergraduate laboratory teaching labs on the first, second and third floors.

During the twenty years that I was responsible for the teaching of pathology I initiated several changes in the way our teaching is delivered. Very early on I changed the name of the course to BM Principles of Pathology to stress that we wanted to teach key principles of pathology before the medical students revisited the subject in the 4th year as part of the course in Laboratory and Clinical Medicine.

When I started teaching in Oxford there was a three-year Physiological Sciences course that took ~20 students a year and ran alongside the A100 Medicine course. For several years there was much debate about how best to update this course. Finally, this led to the launch of the Biomedical Sciences (BMS) course in the academic year 2011-2012. Currently there are ~40 students enrolled on this course which is now a 4-year course that allows students to study all the topics that are taught to medical students with additional courses delivered by other departments including biochemistry, experimental psychology and physics.

Members of the Dunn School provide bespoke teaching for BMS students through a brand-new first year Immunology course delivered by Emma Slack and Sumana Sanyal and second year BMS Infection and Immunity classes, until recently delivered by Rachel Exley and Christoph Tang, soon to be taken on by Teresa Thurston.

Practical classes have always played a central role in teaching pathology in the Dunn School and if we learned one thing from teaching pathology during the COVID pandemic it was that the student learning experience was greatly diminished without face-to-face teaching, hands-on access to teaching materials and facilitated small group discussions in person.

Even before we were forced to deliver all our teaching online it was clear that we could not illustrate all aspects of our pathology syllabus with practical classes, so we started using Computer Aided Learning as part of the BM Principles of Pathology course. Our first foray into online learning in 2010 was led by William James and Damion Young and we tried to illustrate some of the principles of infectious disease transmission and public health by modelling an outbreak of a new variant of the Influenza virus. Student written work was marked and moderated by online assessors.

I feel that one of the most significant changes I made to pathology practical classes was introducing demonstrator training and making all classroom demonstrators who successfully completed the training course wear blue lab coats. This innovation meant that there was nowhere for demonstrators to hide from answering student questions and more importantly it made our classroom demonstrators feel more confident about delivering small group teaching within a supervised learning environment. For me there is no more enjoyable sight than seeing a well-run pathology practical class with a mix of young people wearing blue and white lab coats talking about bacteriology, immunology or pathology.

Another innovation aimed at delivering a more interactive teaching experience came with the introduction of the 'studentscope' into our practical classes. With help from a long-term supporter of undergraduate teaching and microscopy within the university, Alan Todd, we started using a CCD camera that could fit into the eyepiece of any undergraduate classroom microscope. This allowed demonstrators and classroom leaders to share images that students had obtained themselves with Gram staining, blood smears or histology slides.

I started running the Immunology poetry competition in 2018 when I took over giving the Hilary term lectures on Immunodeficiency. To engender more audience engagement with a notoriously 'dry' topic I challenged the BM and BMS students to capture the essence of some aspect of immunopathology by writing a haiku of 17 syllables rather than writing an essay of 3 sides of A4, some of which can be read throughout this issue of Fusion. I also started awarding spot prizes for student histology drawings of white blood cells or granulomata.

As I pass over responsibility for the organisation of the second-year pathology course to Ulrike Gruneberg I am proud of the diversity, enthusiasm and commitment of Dunn School staff currently delivering lectures and classroom teaching to undergraduate students.

Taking part in the undergraduate teaching at the Dunn School has been one of the most enriching experiences of my time at Oxford. Demonstrating has not only allowed me to connect with both students and faculty in a different perspective, but also to get to know aspects of people, their curiosity, humour, or ways of thinking, that are often hidden in the lab.

For me, good teaching starts with genuine enthusiasm for the subject, because if you don't enjoy what you're explaining, your students will notice. Each class is a carefully framed slice of reality, and it's impossible to communicate it well if it doesn't resonate with you. I always try to put myself in the students' shoes: How would I like this topic to be explained to me? Demonstrating gives us a chance not only to break away from uninspiring teaching models we may have experienced, but also to create the kind of learning environment we once needed ourselves. I believe that teaching and science go hand in hand. University education shouldn't just repeat what is in textbooks, it should foster debate, critical thinking, and the kind of reflective practice that fuels scientific discovery. I truly believe that every researcher should be involved in some form of teaching, including the mentorship of younger scientists. This not only helps us as scientists to learn how to communicate our ideas more effectively, but it also challenges the outdated notion of the scientist as an isolated figure detached from society.

I strongly suggest those who lack experience in teaching to take part in it, you never know when you'll find a new passion!

Luciano Marasco Gutierrez (Proudfoot group)

A haiku writing competition is just one of the innovative methodologies used as part of undergraduate teaching in the Dunn School, as explained by David Greaves in his article above. You will find several examples of student haikus throughout this issue of Fusion, as well as a few original poems from David himself.

Aaron Johnson - Wadham College

Old drugs, new purpose-
Signals reawakening,
fibrosis at bay.

"I liked this haiku written by graduate student Aaron about his British Heart Foundation-funded work on drug repurposing, which he presented at an international meeting in Japan." DG

New look, same legacy: our Centenary logo reveal

With 2027 approaching soon, we are excited to reveal our new Centenary logo!

The logo was inspired by two entries to the Centenary logo competition we launched in May this year; we then worked with Toponym Design to create the final design.

Anna Caballé

The two winning submissions were the creations of an alumna - Anna Caballé, and a current staff member - Lindsay Stimson.

Anna spent three productive years in the Dunn School as a postdoc, where she combined her research in mitotic centrosome assembly in the Raff Lab with her passion for science communication, as a writer and editor for the Dunn School NewsDesk (also see the article on page 42). She was also an active member and president of the (then) Dunn School Postdoc Association and a JRF at Wolfson College. In 2019, Anna joined Oxford Nanoimaging (ONI) to pursue a career in science writing and marketing. While at ONI, Anna held roles as a Grant Writer, Product Manager, and Content Strategy Manager, working across Marketing, Product, and Business Development. During her time at ONI, she secured over £1.5 million in grant funding for various super-resolution imaging applications, delivered award-winning campaigns that boosted brand awareness and sales, and launched new products to make ONI's technology more accessible worldwide. In 2024, Anna relocated to Southern Switzerland, where she established her own marketing consulting business. Specializing in marketing strategy, content development, and communications, she now works with life science and biotech companies based in the UK, the US, and Switzerland.

Lindsay has worked at the Dunn School for 13 years taking on multiple roles across the department. As the lab manager in Chris Tang's group, Lindsay oversees the day-to-day operations of the lab to ensure it runs smoothly, safely, and efficiently. In addition to her primary role, Lindsay assists Chris Tang, Martin Maiden (Dept. of Biology) and Syma Khalid (Dept. of Biochemistry) to organise termly meetings for OxBacNet — a university-wide network connecting microbiologists across departments and disciplines. Lindsay is also a member of the professional services staff team with responsibility for managing the department's website. More recently, Lindsay has helped set up a new outreach working group with colleagues and has joined the Centenary team as an Event and Communications Officer, helping with organising events and preparing for 2027.

Keep an eye out for the logo in our Centenary communications, events and even on merchandise! We would like to thank all the current and past members of the department who participated in the competition.

Meet the Centenary Team!

The team working behind the scenes on our Centenary celebrations are Hannah Calkin, Cat Vicente and Lindsay Stimson.

You can contact the team by emailing alumni@path.ox.ac.uk.

Better coating, better clarity: upgrading SEM capabilities at the Dunn School

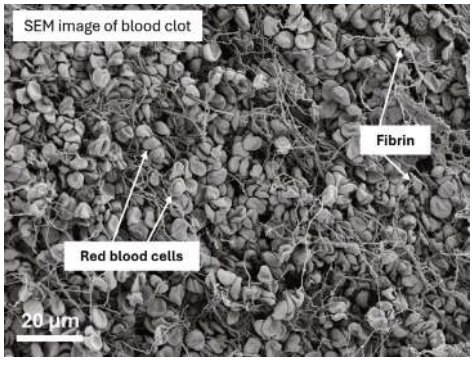
Charlotte Melia

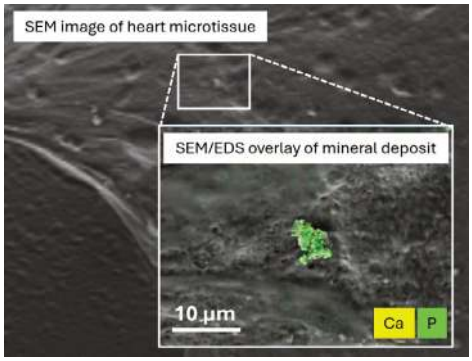
Our new Electron Microscope Facility manager reflects on the impact of the upgrade of the new SEM sample coating unit, thanks to a generous gift from Sarah and Nigel McLean.

Researchers capture images of the organisms they study to gain meaningful insights into their development, form and function. We can measure the distribution of starch granules in a slice of leaf or identify the cargo in a vesicle one thousand times smaller than the width of a human hair. We can observe both the catastrophic effect of mutations on key structures, and their reversal after treatments. These investigations are made possible by electron microscopes, which provide high-resolution structural information about biological samples ranging from isolated proteins or organelles through to whole cells and tissues. These images can be incredibly rich, providing information not only about features of interest but the context in which they operate.

At the Dunn School Electron Microscope Facility, we work with researchers across Oxford to produce high quality image data using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Electron microscopy requires careful sample preparation to ensure fine features are preserved and resolvable. For SEM, which is used to assess the surface features of samples, a key step is adding a protective and conductive coating to the sample. This coating is very thin – typically less than 10 nanometres – to avoid obscuring features of interest. However, the coating must be of sufficient thickness and evenness to ensure electrons from the SEM can conduct away from the region of interest, which can otherwise cause imaging artefacts.

Thanks to the incredible generosity of Sarah and Nigel McLean the Dunn School Electron Microscopy Facility was able to upgrade its SEM sample coating unit this year to a high vacuum Leica ACE600 model, which can produce particles with a very small diameter or ‘grain size’. Combined with an advanced stage that improves the coating uniformity, this enables high-resolution imaging of even highly topographic or bulky samples, which are normally very challenging targets; we are now able to analyse strands of fibrin that are tens of nanometres wide on the surface of a whole blood clot several millimetres in diameter (image data courtesy of Rebecca Burton). This new unit has also improved the quality of data acquired by Electron Dispersive Spectroscopy (EDS), a technique that measures the energy of X-rays generated by the interaction of the SEM beam with the sample. The energies of these X-rays indicate the sample composition in the area they were generated, allowing elemental maps to be collected that are overlaid with the SEM images of the sample surface (image data courtesy of Qiao You Lau). This technique has a surprising utility in biological investigations, for instance in understanding the accumulation and distribution of the harmful mineral deposits that underly arterial calcification. The new unit deposits homogenous films of carbon onto these samples, avoiding detrimental contamination issues that undermine EDS data collection.





It was wonderful to welcome Nigel and Sarah back into the department at the end of April to show them the new unit and the difference it’s already making to our projects. We are tremendously appreciative of their support, as these upgrades keep the Facility at the forefront of imaging in research and ensure a bright future for biological electron microscopy across Oxford.

Penicillin and diplomacy: a wartime journey to the Soviet Union

Isaac Wong

We recently had the pleasure of hosting a visit to the Dunn School by Rosalind Barnes and her family. Rosalind is the niece of Dr Gordon Sanders, a former University Lecturer at the Dunn School and close colleague of Howard Florey. Rosalind gave the Dunn School the original typescript of Dr Sanders' report and diary of a unique visit conducted with Florey to Moscow during the Second World War. Here, Isaac Wong shares a few highlights and his reflections on a unique trip and a fascinatingly personal historical record.

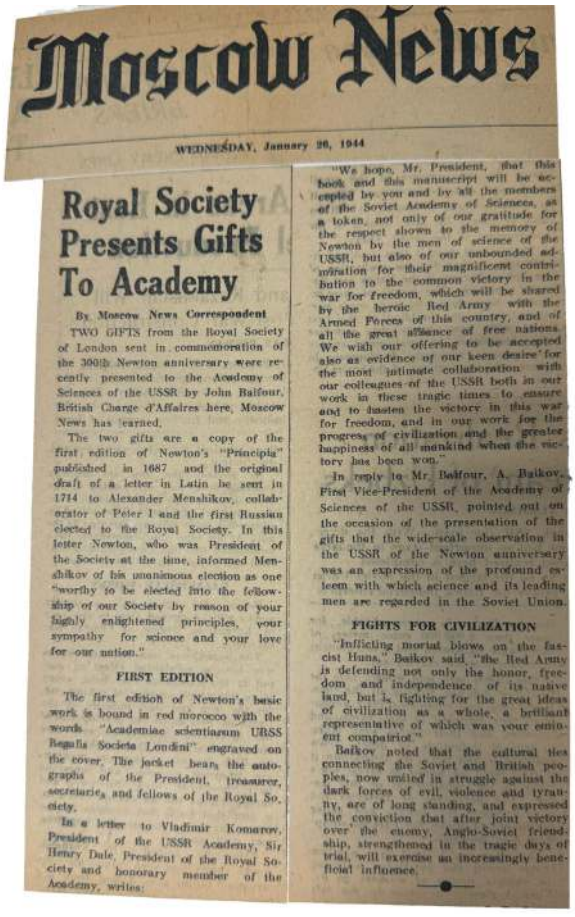
Prof. Howard Florey (left) during the trip

The timing of the development of penicillin gave it huge strategic importance in the second World War. Before its widespread use, infected wounds were often life-threatening; even minor injuries could prove fatal. On the battlefield, penicillin slashed mortality rates dramatically. By 1944, the United States and Britain had begun mass-producing the antibiotic, but the production methods were closely guarded war secrets.

Against this historical backdrop, and with the war balanced on a knife edge, a scientific delegation left England for Moscow in January 1944; the Soviet Union was of course an ally. The UK and the U.S.A had been invited by the Russian Government to nominate a scientist each to "visit Moscow to discuss advances in the field of medicine which, for security reasons, could not then be published". Prof Howard Florey was asked by the Medical Research Council to represent the UK and nominated his colleague, Dr Gordon Sanders, a University Lecturer at the Dunn School, to accompany him. Prof Albert Baird Hastings, a biochemist from Harvard University, represented the U.S.A., accompanied by cancer researcher Dr. Michael Shimkin.
The document kindly donated to the Dunn School by Rosalind Barnes provides Sanders' personal account of the journey. As well as describing high-level scientific diplomacy, Sanders paints a vivid picture of the personal and social angles of the two men undertaking an extraordinary journey at the height of the war. From car crashes in north London to sight-seeing in Tehran, and plenty of details about food that must have felt especially exotic to people based in war-rationed Oxford, Sanders' report provides a fascinating insight into the trip. The full document has been digitized and, like all our important archival material, it will be given to the Bodleian Library so that it is properly kept and available to scholars.

Navigating a World at War

Despite the 1943 Soviet victory in the Battle of Stalingrad, traveling to Moscow remained perilous. Following advice to route through North Africa and the Middle East, the team reached Cairo only to find the British Embassy unprepared to assist. In contrast, the American Embassy immediately offered support. Later, in the Persian Gulf, a Warrant Officer named Denke noted that the Americans built permanent facilities and volunteered manpower and materials, but an uncooperative RAF officer chose to keep personnel in makeshift tents. The RAF's problem, Denke grumbled, stemmed not from a shortage of planes or resources but from poor organization.



Moscow News

WEDNESDAY, January 26, 1944

Royal Society Presents Gifts To Academy

By Moscow News Correspondent

TWO GIFTS from the Royal Society of London sent in commemoration of the 300th Newton anniversary were recently presented to the Academy of Sciences of the USSR by John Balfour, British Charge d'Affaires here, Moscow News has learned.

The two gifts are a copy of the first edition of Newton's "Principia" published in 1687 and the original draft of a letter in Latin he sent in 1714 to Alexander Menshikov, collaborator of Peter I and the first Russian elected to the Royal Society. In this letter Newton, who was President of the Society at the time, informed Menshikov of his unanimous election as one "worthy to be elected into the fellowship of our Society by reason of your highly enlightened principles, your sympathy for science and your love for our nation."

FIRST EDITION

The first edition of Newton's basic work is bound in red morocco with the words "Academiae scientiarum URSS Regalis Societa Londini" engraved on the cover. The jacket bears the autographs of the President, treasurer, secretaries, and fellows of the Royal Society.

In a letter to Vladimir Komarov, President of the USSR Academy, Sir Henry Dale, President of the Royal Society and honorary member of the Academy, writes:

"We hope, Mr. President, that this book and this manuscript will be accepted by you and by all the members of the Soviet Academy of Sciences, as a token, not only of our gratitude for the respect shown to the memory of Newton by the men of science of the USSR, but also of our unbounded admiration for their magnificent contribution to the common victory in the war for freedom, which will be shared by the heroic Red Army with the Armed Forces of this country, and of all the great alliance of free nations. We wish our offering to be accepted also as evidence of our keen desire for the most intimate collaboration with our colleagues of the USSR both in our work in these tragic times to ensure and to hasten the victory in this war for freedom, and in our work for the progress of civilization and the greater happiness of all mankind when the victory has been won."

In reply to Mr. Balfour, A. Baikov, First Vice-President of the Academy of Sciences of the USSR, pointed out on the occasion of the presentation of the gifts that the wide-scale observation in the USSR of the Newton anniversary was an expression of the profound esteem with which science and its leading men are regarded in the Soviet Union.

FIGHTS FOR CIVILIZATION

"Inflicting mortal blows on the fascist Huns," Baikov said, "the Red Army is defending not only the honor, freedom and independence of its native land, but is fighting for the great ideas of civilization as a whole, a brilliant representative of which was your eminent compatriot."

Baikov noted that the cultural ties connecting the Soviet and British peoples, now united in struggle against the dark forces of evil, violence and tyranny, are of long standing, and expressed the conviction that after joint victory over the enemy, Anglo-Soviet friendship, strengthened in the tragic days of trial, will exercise an increasingly beneficial influence.

Newspaper clip on 26 January 1944

One entry describes a particularly tense flight from Abadan to Tehran, both in what was then Persia. Sanders was wedged among six rugged oil workers and two British officers who alone had proper seats. The rest of the passengers balanced on metal stools known as “frying pans”. At one point, a crew member warned, “You might just as well give your soul to God as your arse belongs to the devil.” This dark humor reflected the genuine threats they faced. They paused at Habbaniya near Baghdad to refuel before continuing under brilliant sunshine, while Sanders kept a constant watchful eye on the “blue bag” - a suitcase containing a white canvas sack sealed at the Foreign Office, and filled with penicillin samples and confidential documents.

Arriving in Tehran, the team encountered an unforeseen challenge: Florey fell seriously ill with influenza, forcing an unexpected 26-day stay in the city. Tehran had recently hosted the conference in November 1943, where Allied leaders Winston Churchill, Franklin Roosevelt, and Joseph Stalin had discussed post-war geopolitics. During this involuntary pause, Sanders took the opportunity to deliver a lecture on blood transfusion (an area that was of particular research interest to him for his entire career) at the Anglo-Iranian Institute (although I could not identify the exact institute to which the diary referred). Indeed, a recurring theme of the trip was that both Florey and Sanders took every opportunity to lecture and interact with other researchers along the journey.
Tehran itself reflected the activity and challenges of a strategic crossroads, teeming with Allied personnel and local entrepreneurs looking to profit from the war effort. During the lengthy stopover, Sir Reader Bullard, the British Minister in Iran, shared a modern Persian saying that captured the Allied dynamic: “The British do all the talking, the Persians do all the work, and the Americans just build, build, build.” Sanders recorded it in his diary with wry amusement, noting how the city was brimming with foreign soldiers, diplomats, and engineers. Once Florey’s health improved, the group travelled to Baku and finally onto Moscow.

The journey home was equally adventurous, travelling via Tehran, Cairo, Beirut, Jerusalem, Luxor and Casablanca; again, with Florey and Sanders utilising their time to lecture and meet with local researchers.

Visiting Russia

Eventually, the delegation reached Moscow, where their visit fell under the strict management of VOKS, the Soviet agency overseeing cultural relations. Despite this official oversight, the report describes constructive and friendly scientific interchange when Florey presented on penicillin production and usage. Leading Soviet researchers, notably Prof Zinaida Yermolyeva, expressed keen interest.

Under the Soviet model, the central government planned and funded research on a massive scale, directing scientists to meet crucial public health objectives. During their tour, Florey and his colleagues visited the Central Institute of Microbiology and Immunology, which Sanders described in his diary as

Left to Right: Dr. Sanders, Profs. Florey and Yermolyeva

“more of a factory than a research lab” owing to its emphasis on high-volume vaccine production, especially for typhus, a threat to both military and civilian populations. They also observed investigations into gramicidin at V.I.E.M. (the All-Union A.M. Gorki Institute for Experimental Medicine), reflecting Soviet ambitions to expand antibiotic applications, with even an apparent ambition to treat nerve lesions (not something that even a miracle drug like penicillin can do).

Despite the drive for scientific advancement, ideological controls remained pervasive. All official exchanges had to pass through VOKS, and personal contact with foreign researchers was effectively prohibited. Sanders’s diary vividly illustrates this state-controlled atmosphere. During an opening session at the Soviet Academy of Science, a speaker took the rostrum and read a list of about twenty names (beginning with Stalin, Molotov, and Voroshilov). After each name, the audience rose and applauded “almost by numbers.” One scheduled speaker was swapped out for another, and Sanders noted “Stalin” was the only word he could recognize, repeated in every sentence. This meticulously staged display struck him as illustrating how patriotism and ideology were woven into everyday scholarly lives under Stalin’s regime.

There were also opportunities to experience the cultural offerings of Moscow. Sanders refers to several visits to see the

A photo taken in the Laboratory of the Biochemistry of Microbes. Top left to right: Drs. Severin, Livitov, Sanders, Prof. Dorfman, an unknown researcher and Dr. Kaplun. Front left to right: Profs. Yermolyeva and Florey

ballet and the opera, and at times his diary is more a rather idiosyncratic art critique than scientific account. His reviews range from "skirt tight which made her potter like a mouse. If only she had walked!" to "In the evening we went to see Swan Lake. Red ink needed to indicate its superb quality. No words are adequate".

Legacy of a Remarkable Journey

It would require the research and expertise of an historian to assess the true legacy of this journey. After returning from the mission, Sanders writes that Florey submitted a detailed report on the Moscow expedition to the Medical Research Council. The MRC no longer keeps a copy of this document, nor knows whether it still exists. If it does, it is probably in the UK National Archives, where the historic files of the MRC are kept. https://discovery.nationalarchives.gov.uk/details/r/C813609].

Furthermore, it is unclear how this trip was publicized and interpreted by researchers and the public in Russia, especially considering the subsequent cold war. Nevertheless, the expedition undertaken by Florey, Sanders, Hastings, and Shimkin illustrates the extraordinary hurdles that wartime scientists faced to share key medical discoveries. Sanders' diary reminds us that even in the darkest moments of war, researchers pressed on with disseminating their research. And of course, the global context provided a remarkable backdrop to a personal account of the journey.

Sanders would continue to travel. His obituary in The Times refers to a subsequent scientific exchange visit to China, where he spent a year with the Sino-British Science Co-operation Office of the British Council. Indeed, Rosalind Barnes has recently added to her gift to the Dunn School by presenting us with two beautiful scrolls of calligraphy marking the visit. In 1949, 1951 and 1953 he also spent several months at Canberra, helping with the design of the John Curtin School of Medical Research in the Australian National University, to which Florey was an adviser. Sanders also took several long trips to the United States, to discuss his own research on microcirculation.

Acknowledgements

Special thanks go to Gordon Sanders' family for generously donating his wartime diary, thereby preserving a vital piece of history. Their contribution not only enriches our understanding of the Dunn School's legacy but also serves as a valuable reminder of the power of personal accounts to pivotal moments in science and world affairs.

Also, thanks to Catarina Vicente, Andrii Gorelik, Sarosh Habib and Chatrin for critically reviewing this article and offering invaluable feedback, greatly improving its clarity and depth.

Cecile Durkin - St Anne's college

"I really enjoyed the poetry competition - it was a fun and engaging way to reflect on the material we were learning from a more creative perspective. Your use of poetry in lectures, alongside the competition, brought a light-hearted and enjoyable tone to what was otherwise a content-heavy (but undoubtedly very interesting) module."

Autoimmunity:
Waves of white cells rise,
mistaking self for the foe,
silent war unfolds.

"In Cecile's haiku I liked the way that waves of white cells arise, they make one dumb mistake (mistaking self for foe), then nothing is the same again - I love the idea of autoimmunity as a silent war initiated by misguided Samurai knights." DG

Launching the Memories Collection Project

As we look ahead to celebrating our Centenary, we are excited to launch our **Memories Collection Project** – an initiative to gather and share the stories, people, and moments that have shaped the Dunn School over the past 100 years.

This project is open to all our alumni, friends and family of alumni, as well as our current staff. Any stories of time spent in (or outside) the lab, memorable discoveries, or simply the day-to-day experiences that made the Dunn School feel like more than just a place of work or study.

As part of this project, we're also creating a feature called Forgotten Faces. Our aim is to create a tribute to those colleagues who may not have received wide recognition at the time, but whose contributions, character, or quiet support left a lasting impression on those around them (and were often not included in our portrait collection). If someone made a real difference during your time here, we'd love for you to share their story with us.

If you have any photographs, documents, or other artefacts that help tell your story, we would be very interested to know about them.

These memories and materials will play an important part in how we mark 100 years of the Dunn School - preserving its legacy and celebrating our community. Please get in touch with us at alumni@path.ox.ac.uk - we look forward to hearing from you!

Inflammation

Acute versus chronic
What is the difference?

Obviously, duration -
Weeks, months, years...

Failure to return to homeostasis
Will bring pain and tears

But for this persistent, chronic
Inflammation what is the basis?

This term we will meet many examples
Granulomas, atheromas, even tumours

Like Leo Tolstoy's unhappy families
Each tissue is unhappy in its own way*

But do keep an eye out for macrophages
And their helper T lymphocytes

I hope my slides will inspire you to
draw diagrams, write poetry..

And maybe one day inspire you
To develop new treatments

One thing is certain as
the population grows older
Inflammaging!

David R Greaves 11 02 2025

*After the opening words of Anna Karenina by Leo Tolstoy, "All happy families are alike; each unhappy family is unhappy in its own way"

Motors, messages, and motion: inside the world of cilia

Girish Mali, Anthony Roberts and Katerina Toropova

Over the last two years, the Dunn School has welcomed three new groups researching the molecular mechanisms underlying the function of the cilia. Here, Girish, Anthony and Kat explain why we should care about this organelle, and the various approaches they are using to probe at its role in health and disease.

The ~30 trillion cells that make up the human body fall into more than 200 major types. Virtually all of these cell types grow an antenna-like structure called a cilium, which projects from the cell surface into the environment (Figure 1). Over the years, it has emerged that cilia (also known as eukaryotic flagella) serve a variety of vital physiological roles in the body.

One broad class of ciliary function is sensing environmental stimuli, such as light, olfactants, morphogens and fluid flow, and converting them into processed information for the rest of the cell. Another is motility: a subset of cilia actively beat with a wave-like motion to generate cell propulsion, for example in sperm cells, or to move fluid over the epithelia lining the airways and oviduct.

Defects in the architecture and composition of cilia cause a diverse group of human disorders collectively known as ciliopathies (Figure 1). Deciphering the mechanisms by which cilia are assembled, function and move is thus fundamental to understanding a wide array of biological processes and the molecular basis of human disease states.

Work within the Dunn School focuses on understanding the mechanisms underpinning cilia formation and function (Roberts and Toropova groups) and the machinery that powers cilia beating (Mali group). A connecting theme in these studies is the dynein family of motor proteins. These are enormous protein complexes which use the energy generated from ATP hydrolysis to move along microtubule tracks. In this article, we highlight our recent insights into cilia and dyneins and frame some of the key outstanding questions in the field.

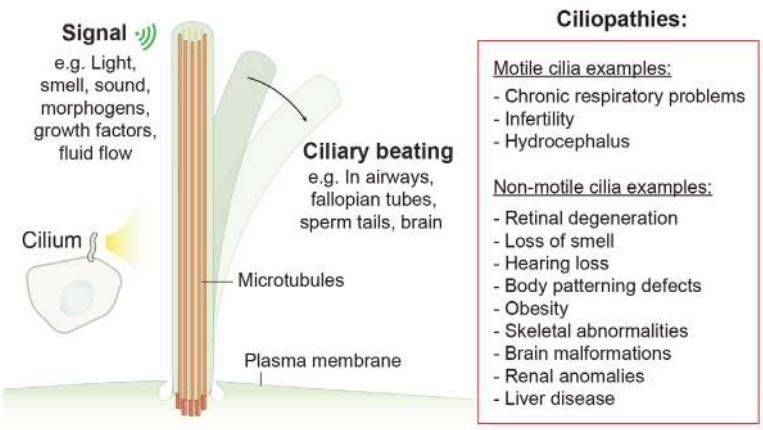


Figure 1. Motile and non-motile cilia are essential for human health.

Molecular "trains" that carry cargoes into and out of cilia

Katerina Toropova and Anthony Roberts

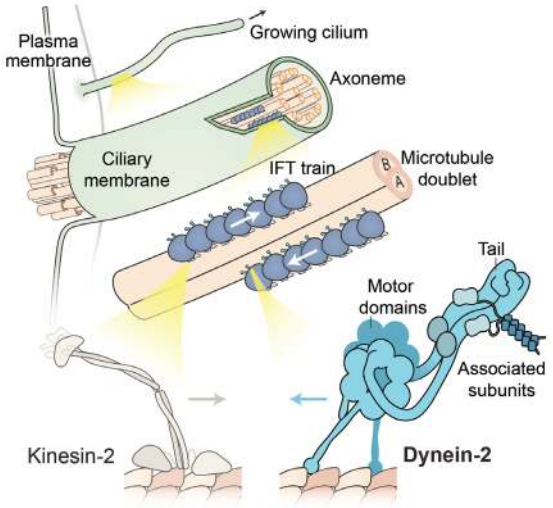


Figure 2. Kinesin-2 transports IFT trains containing components such as tubulin needed for cilia assembly at the tip. Dynein-2 carries out reciprocal transport moving trains containing cargo such as GPCRs, from the ciliary tip to the base, and out of cilia for downstream signaling.

All cilia are built around a cylinder of microtubule doublets, which extend from a base at the plasma membrane. Cilia grow by addition of material to their distal tips. The central mechanism underpinning the formation and function of cilia is a motor protein-driven process called intraflagellar transport (IFT). IFT is a bidirectional transport system that moves ciliary components from the cytoplasm to the tip of the cilium and returns products to the cell body. Cargoes of IFT include both structural components (e.g. tubulin), needed for cilia assembly, and functional components (e.g. G-protein coupled receptors (GPCRs)), needed for signalling.

IFT is powered by ATP-fueled motor proteins that move along the outer surface of the microtubule doublets (Figure 2). The motor driving anterograde IFT towards the ciliary tip is a kinesin-2 motor. Retrograde IFT is driven by dynein-2, a large molecular machine comprising a dimer of two force-generating motor domains and 14 associated subunits.

To carry out cargo transport, dynein-2 and kinesin-2 are integrated into long (~200 nm) linear arrays termed “IFT trains" (Figure 2) containing dozens of copies of each motor protein. However, even though the motors move in opposite directions, IFT trains do not undergo tug-of-war motions along the ciliary length. Instead IFT trains travel to the tip of the cilium (kinesin-2 direction) then return to the base (dynein-2 direction) in an apparently deterministic fashion. The activity of the motors must therefore be tightly coordinated.

A “cross-legged” conformation enables dynein-2 motor regulation

One collaborative focus of the Toropova and Roberts labs is to understand the precise coordination between the opposite-directionality motor proteins in IFT. For dynein-2, this involves addressing: 1) How is dynein-2 switched off on anterograde kinesin-driven trains? and 2) How is dynein-2 activated at the tip to power retrograde transport?

To answer these and other mechanistic questions, the Toropova and Roberts labs combine expertise in structural, biochemical, cell biological, and single molecule imaging methods. Previously, the labs uncovered how dynein-2 is switched off – by assuming an autoinhibited state where the two motor domains of dynein-2 stack against each other in a “cross-legged” conformation that inhibits ATPase activity and motility. This structural work, using cryo electron microscopy, also unveiled the “tail” domain of dynein-2 and how it is sculpted into an asymmetric arrangement that matches the shape of the IFT train. This work revealed, in molecular detail, how dynein-2 binds the IFT train and is transported to the ciliary tip without interfering with kinesin-2.

Continued collaborative work in the laboratories focuses on the mechanism of dynein-2 activation at the ciliary tip, as well as key questions about ciliary cargo dynamics: specifically, how cargoes needed for cilia assembly and function enter and leave cilia, and how cilia maintain a selectivity barrier that excludes non-ciliary proteins.

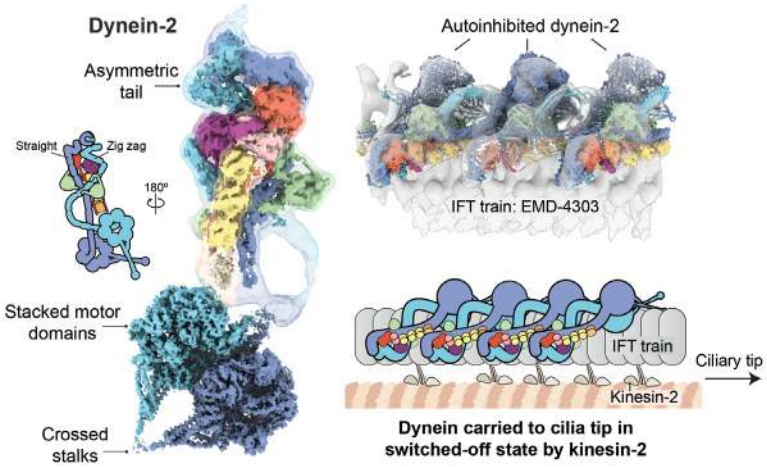


Figure 3. Cryo-EM structure of human dynein-2 reveals its autoinhibited state with stacked motor domains and crossed stalks (regions of dynein-2 that lead to microtubule binding domains – “feet” of dynein). Fitting into cryo-ET map of in situ anterograde train (EMD-4303) reveals how asymmetric tail binds the IFT train and the molecular contacts between adjacent dynein-2 molecules in the train-loaded arrangement. In this way, dynein-2 is carried as passive cargo to ciliary tip where they are activated.

Defects in ciliary transport cause severe disorders

The importance of transport within cilia in human health is underscored by the severe disorders that arise from its dysfunction. Mutations in genes encoding IFT trains components cause cranioectodermal dysplasia, nephronophthisis, and Jeune syndrome, among other conditions. Mutations in dynein-2 cause short rib thoracic dysplasia, characterized by severe shortening of long bones (e.g. ribs) and insufficient lung capacity at birth. These conditions can be devastatingly life-limiting, with limited targeted therapy beyond surgical intervention and palliative care. By improving our understanding cilia assembly and function at the molecular level, this research in the Dunn School has the potential to provide avenues for treatment for these severe syndromes.

Dyneins that generate the ciliary beat

Girish Mali

Biological motion is a key attribute of life. An entire branch of the eukaryotic tree of life, the ciliates, use motile cilia on cell surfaces to power the motion of single-celled organisms in fluid. In humans, motile cilia drive fundamental processes ranging from the swimming of sperm cells to the clearance of mucus out of lungs.

The human lungs are constantly exposed to airborne viruses and bacteria. The first line of defence against deadly respiratory pathogens is achieved by the coordinated beating motion of hundreds of motile cilia on the surfaces of lung cells, with the whip-like beating motion of cilia clearing out pathogens trapped in mucus. Loss of mucus clearance due to faulty cilia is a hallmark of a debilitating lung condition called Primary Ciliary Dyskinesia (PCD) in humans. Static or poorly beating cilia that are unable to clear out pathogen-infused mucus result in recurrent infections which can cause lung failure if not properly managed. PCD is incurable and affects ~1 in 7,500 newborns. Given its severity and with cases on the rise globally, health complications associated with PCD pose a significant challenge for affected individuals and healthcare services.

Why do cilia stop moving? We know from studies spanning many years that a specific class of dyneins found solely in cilia, called axonemal dyneins, power cilia movement. Axonemal dyneins come in two flavours, the outward facing outer dynein arms (ODAs) and the more inward facing inner dynein arms (IDAs). ODAs are the major force generators in cilia whereas the IDAs determine the waveform of beating cilia. Axonemal dyneins are related to cytoplasmic dyneins (such as dynein-2) and work in a similar manner. Their key function is to breakdown ATP and transmit the mechanochemical forces that accompany this reaction onto the microtubules inside cilia. Exquisite coordination of the mechanochemical cycles of teams of dyneins ultimately leads to the generation of a ciliary beat.

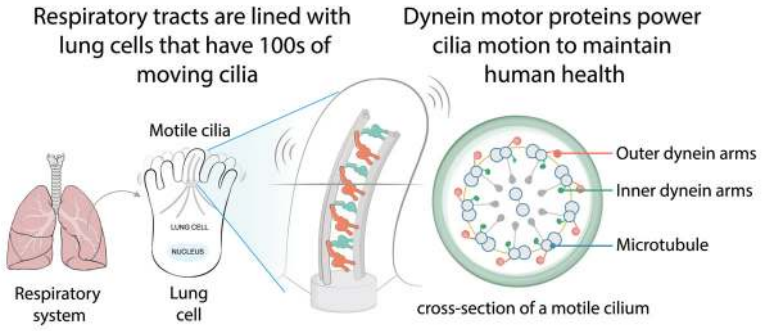


Figure 4. The large and small airways of the lungs are lined with several millions of cells that bear beating cilia. Zooming into one such cilium reveals the distribution and intricate organisation of axonemal inner and outer dynein arm motors, which are docked radially onto ciliary microtubule doublets. As opposed to the "feet" of dynein-2, which walk on ciliary microtubule filaments, the "arms" of axonemal dyneins grab onto the ciliary microtubule filaments closest to them, which they then pull and release in a highly coordinated manner to bring about sliding and bending of motile cilia.

So, is PCD caused by a power failure inside cilia? Yes, to a large extent. The leading cause of PCD is the critical loss of the power generating ODA motors in cilia. Loss of ODAs can occur due to their mis-assembly or mis-delivery. To understand why, we need a clear understanding of how ODAs (and IDAs) are assembled and delivered correctly in the first place. Addressing this challenging question is one of the key focus areas of the Mali group. Building dyneins is a sizeable task for a cell as they are very large multi-component machines. For instance, a single ODA motor is comprised of 15 individual protein components. Delivering the thousands of assembled ODAs and IDAs that are needed to power cilia is also a complex logistical challenge as the motors must be kept switched off before reaching cilia and then turned on in a coordinated manner inside cilia to generate the beating motion.

We know from biochemical and genetic studies that a newly discovered set of proteins called dynein axonemal assembly factors (DNAAFs) is dedicated to building and delivering

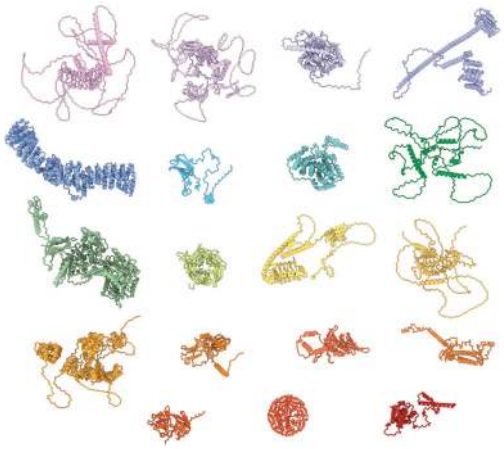


Figure 5. A family portrait of the DNAAF protein family generated using AlphaFold shows that each of the 19 DNAAFs has a unique 3D structure. Some DNAAFs share common structural domains. Several DNAAFs contain stretches of intrinsic disorder which can be seen as loops interspersed between structured domains. The unique structure with disorder feature of the DNAAFs make them a particularly challenging yet exciting set of proteins to study.

axonemal dyneins to their final sites of action. While we currently don't know how most of the 19 known DNAAFs work precisely, we think that DNAAFs work like teams on an assembly line to build several thousands of axonemal dyneins in a finely-tuned, multi-step assembly process. To fully understand the assembly and regulation of axonemal dyneins, the Mali lab focuses on addressing three broad questions.

How do DNAAFs bring different axonemal dynein components together?

The Mali lab is using a proteomics approach to address this question. This allows homing in on possible interactors of each DNAAF, which could inform on their molecular function. It also allows mapping of potential protein-protein interactions between DNAAFs and specific dynein components. The group then performs biochemical reconstitutions to directly test the proteomic interactions. For example, making recombinant DNAAFs and dynein components and mixing them in a test-tube in different combinations to see if they bind to each other. This enables screening for strong and stable biochemical partnerships between various DNAAFs and dynein components, from which the lab deduces how they might bring dynein components together for assembly. Lastly the Mali lab uses bioimaging methods to ascertain where within the cells do DNAAFs form these molecular partnerships. Overall, these studies provide a wealth of information on how DNAAFs form functional molecular complexes that build axonemal dyneins.

What do teams of DNAAFs look like?

Directly looking at the three-dimensional (3D) structures of the DNAAF complexes is the most straightforward way of understanding how they work at a molecular level. The Mali group combines many snapshots of EM pictures and models generated by a computational protein structure prediction algorithm called AlphaFold (AF) to construct 3D models of DNAAF complexes. These models are validated using the biochemical tools described above. 3D reconstructions provide the Mali lab sufficient detail to develop testable hypotheses on how DNAAFs might work together to assemble the various components of dynein motors. Importantly, structural models allow mapping of the locations of PCD-causing mutations. Studying their impact on the formation or stability of DNAAF complexes will ultimately help us elucidate the molecular causes underlying PCD.

How are axonemal dyneins switched off and on?

Another key focus area in the lab is the regulation of axonemal dynein motor activity. ODAs are powerful motors that consume a lot of cellular ATP, especially when made in large quantities. Motor activity must therefore be precisely controlled by the cell for the efficient use of cellular resources. Previously, researchers in the Mali lab showed how the motor activity of ODAs is dampened in the cell by a specific DNAAF protein

called Shulin (aka DNAAF9), which acts as a packaging factor during ODA transport to cilia. More recent data has identified a new player called ARL3 and we propose that it is involved in relieving Shulin's inhibition to promote switching on of ODA motor activity specifically inside cilia. The Mali lab's studies on the inhibition and activation of ODA motors are providing new insights into the complex ways in which cells regulate ciliary molecular motors.

Shedding light on cilia and dyneins

The Dunn School provides the ideal environment to address questions at the forefront of cilia and dynein research, with its interdisciplinary ethos, state-of-the-art equipment, and collaborative culture. Together with exciting intersections with the centriole research of Jordan Raff's group, the synergistic work of the Mali, Roberts, and Toropova groups aims to illuminate the inner workings of cilia as self-organising sensory and motile organelles.

Guardians of the Dunn School galaxy

Helly Worsdell

The following article is the first in what we hope will be an interesting series for Fusion readers – an insight into the professional service staff who support the scientific work of the Dunn School. Our first look is at the workshop department. This article has been written by Helly, who has recently joined the Dunn School as EA to our Head of Department.

I'm very new to the Dunn School and I was literally two days in when the penny dropped that we have an outstanding workshop department: two fantastic induction sessions with Wayne Swan and Samantha Knight and a response time of mere minutes when I logged a workshop request. When it was suggested *Fusion* run an article about the department, I leapt at the chance to write it and have spent several hours following them all around, finding out about the complexities of the department, the equipment, and the building and how those are managed. I've worked in many different industries / sectors (I'm really old!) and this is, hands down, the best workshop department I've ever come across. I hope you all know this but if not, let me tell you, the Dunn School is incredibly fortunate to have them.

Broadly speaking the department is split into two teams. The first team is facilities and workshop e.g. the bricks, mortar, and machinery, run by Wayne and Peter Stroud. The second team looks after services and health and safety, run by Philip Cobden and his deputy Samantha. Both teams have different supply responsibilities (oh, and we have Philip, assisted by Wayne and colleagues to thank for making the annual Summer Party happen – no mean feat!). It's a wonderfully diverse group of people – ranging in age from early 20s to 70s – who clearly like and respect each other. I witnessed this first-hand when I tagged along for a recent fire drill.

Back in 1972 Peter was going to start a career as a car designer at Cowley but at the last minute decided to join his dad, who ran the workshop here at the time, instead and the Dunn School has benefitted ever since. The wider scientific world has benefitted too, the Stroud children, Matthew and Jacqueline, are both on course for Professorships in their chosen fields – heart disease and soil science respectively – what an impressive legacy, not only for Peter and Janet, but also the Dunn School.

Peter is a "complete engineer", a wide-ranging skill set that is less common nowadays. He can make anything and does so on his ancient, trusty machines – converting from metric to imperial to metric again with precision. In the kindest, humblest way, Peter knows everything about everything and he's the first point of call for anyone on the team who has a question, problem or issue. Peter will know how to sort it. And, as with most things in life, there's often nuance to making a troublesome centrifuge work again, or a fiddle that will reset the fridge and get it back to the right temperature as quickly as possible without the delay of a call out. This knowledge isn't available in a manual or watchable on YouTube – it's learned from experience.

Being able to fix stuff on site also saves the Dunn School tens of thousands of pounds each year, as well as many research hours. It's simply not economical to replace a whole piece of machinery because a pin has snapped or lose hours of research because you've got to wait for an engineer to get on site in a couple of days' time. Wayne and Peter's teammates – Tony Chaudhry, Martin Smith, Bruce Coppen, Chris James and Franco Fuoco – are all highly skilled and able to turn their hand to anything. Tony you'll have seen working his way around the building, testing electrical equipment; Martin looks after all the cooling equipment and Bruce, all the equipment amongst others, that supplies gas, water and steam. Chris has responsibility for the incubators and CO_2 supplies, and Franco is an electrical technician. Wayne, Peter, Bruce, Martin, and Chris all do emergency cover too – that's a week on, then four off, of 24/7 support – coming in at any time of the night or weekend when the Building Management System alarm goes off.

(SIDEBAR: ALWAYS make sure you've secured a fridge or freezer door properly, so that an emergency call out isn't triggered and someone has to come in at 2am to fix an entirely preventable issue. And P.S. when the zombie apocalypse starts and you're holed up in the Dunn School, fighting off the walking dead, do not drink the demined water – if the zombies don't get you, the water will most definitely finish you off.)

Wayne's team has a wealth of knowledge and hundreds of years' experience between them but it's difficult, nigh impossible, to persuade younger people into these roles. The same old challenge that the wider university and many businesses throughout Oxford face – salaries that don't match local living expenses, let alone property prices. And there's no apprenticeship that fits the type of all-encompassing role / skillset that Wayne needs, so it's a double whammy of challenges. I can see that succession planning might be a worry, but I think the Dunn School more than benefits from the wisdom that such a diverse group brings to the table.

Given the nature of the work done here, the services and health and safety team hold a heavy responsibility. Thankfully, Philip has been with the university for nearing three decades and Samantha has been with the Dunn School for 25 years. And thank goodness because there's a lot more to Services and Health and Safety than just wearing lab coats and safety glasses (all the same, I've observed that everyone needs reminding to wear them). Of course, there's a lot of hazardous material – how it's handled, stored, and used needs careful consideration and constant monitoring – then there's all the hazardous equipment to dispose of too, and apart from anything else we need protecting from ourselves.

Philip and his team are there to enable – they will rise to whatever the challenge is, come up with a work around and make it safe and doable.

I spent some time with one of the youngest members of the health and safety team, Natalie Davis, who started here as an apprentice and stayed on – so 7 years in total. Natalie, Lucy Bryant (also originally an apprentice) and Gonzalo Ramirez Roman, who are all lab techs, start their days getting any waste items (like pipettes) into the autoclave where they're all cleaned and made safe to be collected by waste companies. It can be hot, messy work but they all get stuck in. Endless bottles and vials need steam cleaning. Replenishing supplies of these, and culture and bacteriological media, is a constant churn (Natalie has making plates down to a fine art).

Philip is a proactive enabler of his team, ensuring that his colleagues are motivated and their ambitions fulfilled. For instance, it turns out that Gonzalo is an expert at computer-aided design, and really enjoys it, and Wayne needed someone to update floorplans. Problem solved, the cost stays in-house, and Gonzalo gets to broaden his role.

Ross Griffiths-Walford is often seen at his shifts on reception or working round the building testing electrical devices but he's also an integral part of both teams within the workshop department – helping whenever he's needed as he knows most of the processes and roles in the department. He also deals with a large volume of invoice paperwork – a chap of many hats.

Aaron Masih is our Stores Manager, and he works alongside Samantha to keep things running smoothly - some 50 to 60 packages arrive each day. As well as having to be delivered around the site, often as quickly as possible, there's a raft of paperwork to complete too – boxes to tick, forms to fill – sometimes running into the 100s per day. Aaron's been here for 12 years – starting as a lab tech and progressing to Stores Manager when the role became vacant. His dad who also worked as a lab tech, got him the job here, when Aaron was straight out of school. How lovely is that?! (Martin suggested Tony when a vacancy came up, Chris was known to the team from his previous job. You get the picture – you don't get your mates or family onboard unless you love where you work.)

Peter said something that made a very strong impression on me – he said that "science suffers" when things go wrong, machinery breaks down etc. and you can absolutely sense that that's what motivates every member of the workshop department – their passion for what they do is contagious and every one of them has an amazing work ethic. I've simplified each of their complex and demanding roles massively for the sake of brevity, to produce an article not a thesis, and as well as reacting to issues day to day, as a department they proactively strive to get ahead of problems. An impressive group of people, and as I said at the start – we're very fortunate to have them contributing so much to the day to day running, and important work, of this department.

The Oxford Stephen Cobbold Graduate Scholarship

Stephen Cobbold

Ensuring the future of graduate study at the Dunn School is one of our fundraising objectives for the department's Centenary in 2027. We were delighted that our former Head of Department, Professor Herman Waldmann, decided to contribute to this effort by supporting the establishment of a new endowed graduate studentship in honour of his former colleague, Professor Stephen Cobbold (jointly with the EPA Research Fund). Here, Stephen himself (now Emeritus Professor of Cellular Immunology) reflects on the importance that funding had in his career, and his advice for those starting in science now.

I am honoured and pleased to have a graduate scholarship endowed in my name, particularly as my early career depended on such funding. I was the first member of my working-class family to go to university, by winning a scholarship to read biochemistry at Christ Church, where I discovered an interest in the (then) relatively new field of immunology. This led to an MRC funded graduate studentship with Herman Waldmann's group, then in the Department of Pathology outpost at Addenbrookes Hospital, Cambridge.

Rather than bore you with the details of my academic career which you can easily Google, I would like to try and give some insight to my motivation and approach to science. I have always been a problem solver and developed a love of technology at an early age. I also taught myself to play the piano until my parents could afford to send me to lessons. My father was an electrician and encouraged me to learn about electronics at a time when that involved valves (vacuum tubes) and high voltages. I built my first very basic music synthesiser in a cardboard box at the age of 11. Over the next 10 years I built my own electronic piano, a MOOG-style synth and my first computer, a Sinclair ZX81 from a kit. This had 1kb (!!) of memory and stored data on a tape recorder. I used this to write my first database program in BASIC to catalogue my science fiction paperback collection.

Despite the financial help of a scholarship at Christ Church, money was tight, so I tried to earn extra money playing in a band (using my self-built electronic instruments and second-hand, self-repaired, amplifiers and lighting systems). This wasn't profitable, so I switched to running a discotheque, initially lugging our equipment around different colleges at weekends on a porter's trolley. This was much more successful and allowed me to buy and run a Mini van.

When I started my PhD studies in Cambridge I was excited by the new technology of monoclonal antibodies (mAbs) and their potential to solve the particular issue of graft versus host disease (GVHD) after allogeneic bone marrow transplantation. This project generated huge libraries of mAbs and their sub-clones, each one of which needed to be individually frozen in vials within liquid nitrogen vessels. An exponentially increasing number of vessels would rapidly become unsustainable unless we could throw away those clones that after screening were of no use. My solution was to write our own database program on the "latest" Acorn computer with 32k of RAM and 2x100k of disc storage. With around 15,000 vials to catalogue and so little computer memory, this required some ingenious coding. This database became the mainstay of our storage system during our time in Cambridge. When we moved to the Dunn School in 1994 I was asked if I could do something similar to catalogue the frozen vials left in storage by the retiring Prof. Henry Harris. This led to the CellBank program that still underlies the system used in the Dunn School today.

My interest in computer coding and statistics also played a major role in how we still define leukocyte cell surface antigens. Back in 1986 I wrote a database and rapid analysis and visualisation application using novel Bayesian statistical clustering (with David Spiegelhalter) of antibody binding data. This was used in real-time at the conference workshop to assign mAbs according to their cluster of differentiation (CD number) and allowed, for example, the first discovery of CD45 isoforms. This application was such a success that I was asked to set up similar systems to analyse mAbs against dog (Canine Leukocyte Antigen Workshop, CLAW), sheep, cow and horse leukocytes. With funding from the Wellcome Trust, I was, for a while, considered a leader in the field of veterinary immunology.

By the late eighties the Waldmann Group were running clinical studies to test whether the mAb CAMPATH1 could control GVHD by removing contaminating T cells from donor bone marrow. This involved different transplant centres all around the world. The problem was that each centre insisted on designing their own protocols, which is a nightmare from a statistical viewpoint. At that time there was no standard method of survival analysis nor any software available, so I had to write my own from scratch, using the recently published (1984) "Cox" proportional hazards model. The program could interpolate for missing data and allowed us to model "What if" outcomes by generating computed actuarial survival curves and confidence limits on the screen. Through this we discovered the "best" protocol was one that added CAMPATH1 to the marrow and then infusing the combination into the patient. This protocol depleted GVHD-causing T cells from the marrow as well as T cells in the patient that could cause graft rejection. A simplified version of the program was also used by other groups using animal models at a time when power calculations and statistical analysis were rarely considered.

By the time the group moved to Oxford our work on *in vivo* use of mAbs to modulate both human and mouse immune responses meant that we were under constant pressure to scale up their production to multi-gram quantities. The Therapeutic Antibody Centre was set up by Geoff Hale and Herman Waldmann to provide clinical-grade antibodies in a specialised building with expensive equipment, but for our murine studies we needed something simpler. We built a bioreactor system for each antibody made from a kidney dialysis cartridge, a silicon tubing gas exchanger, a peristaltic pump and a large bag of air balanced Iscoves culture medium that ran on a trolley in the top floor warm room. I happened to be working at that time in the lab that had a brass plaque on the door to honour the contribution of Norman Heatley to the mass production of penicillin, and I like to think our bioreactors followed in his tradition. These bioreactors provided enough mAbs for all our *in vivo* murine tolerance studies, as well as for numerous collaborators around the world. We also provided mAbs to emerging biotech companies who could conjugate them to fluorescent markers, market them, and provide a royalty income stream back to the Dunn School. It is this income stream that enabled, in part, the endowment for the Stephen Cobbold Graduate Scholarship.

Through my career I have been a PI on a Wellcome Trust veterinary grant and co-PI (individually with Herman Waldmann and Sir Roy Calne) on MRC program grants. I co-founded two startup companies (TolerRx, Boston, USA and BioAnaLab, UK). I was also awarded a grant from the EPA Research Fund to provide a Flow Imaging facility capable of robust statistical analysis across millions of multi-coloured fluorescent-labelled cell images. I used this to show that most of the published information on the role of asymmetric cell division in the generation of T cell memory was artefactual and that T cell commitment was stochastically determined.

Although I had many opportunities during my career to take up more senior positions in other universities, I decided to stay in Oxford. This was partly for health reasons, but mainly to try and see through the development of CAMPATH (Alemtuzumab) as a drug for clinical use in transplantation and autoimmune diseases. As detailed in Fusion 15, page 16 (2016) I even received treatment with CAMPATH for my own successful kidney transplant in 2015.

What I enjoyed most during my career was being at the bench, teaching and solving problems with our DPhil students and post-docs. I believe that the most important part of scientific research is passing on your expertise to others. Therefore, I participated fully in the teaching and examination of both graduates and undergraduates and would encourage others to do the same. I have presented all this work from my own point of view, but I must acknowledge and thank all the other members of our group through the years, and especially the outstanding leadership of Herman Waldmann.

Call for cricketers!

The Dunn School's earliest cricket club records date from 1953 and throughout the years there have been several revivals of the team. In 2027, we are hoping for another one!

We would like to organise a mixed gender cricket game between our alumni and current staff as part of our Centenary celebrations. Whether you were once a Dunn School cricket club member yourself, or just interested in the sport, do get in touch with us (alumni@path.ox.ac.uk).

If you'd like to read more about the history of the cricket club, Eric Sidebottom wrote a piece for issue 8 of Fusion, published in 2009, called 'Champions: A History of the Dunn School Cricket Club'. All previous issues of Fusions can be found on our website – www.path.ox.ac.uk/centenary/fusion-magazine/

The 1980 Dunn School cricket team. *If you recognise yourself or a former colleague in this photo, please let us know!*

An interview with Stephen Cusack

In this edition of *Fusion*, we talk to world-renowned structural biologist Prof. Stephen Cusack. He is best known for his structural studies of protein-RNA complexes in viral replication, gene expression and innate immunity. In particular, he performed ground-breaking work on influenza virus polymerase, elucidating its structure and unique mechanisms of RNA synthesis. He was the Head of the European Molecular Biology Laboratory (EMBL) laboratory in Grenoble from 1989 and 2022, and the recipient of a wide range of honours, including Fellowship of the Royal Society and membership of EMBO. In 2024, Prof. Cusack joined the Dunn School as a Visiting Professor of Structural Biology.

You started your career as a theoretical physicist, but switched to biology during your postdoctoral work. What was the impetus for this change, and do you think it was beneficial for your career?

Following my undergraduate studies in mathematics and theoretical physics at Cambridge University, I pursued a PhD in theoretical solid-state physics at Imperial College, London (1973-1976). During my PhD, out of curiosity, I attended lectures in molecular biology, including some on protein structure and this drew me to the idea of trying to understand the molecular basis of life. This also chimed with my childhood upbringing, where my mother's enthusiasm for biology (she was a school biology teacher) and the family's long-standing interest in wildlife (we used to spend holidays close to Minsmere, a famous bird reserve on the Suffolk coast) inspired in me a lifelong love of nature and living things. I had no formal advanced training in chemistry or biology, so this meant that I did not know things in basic biology that I should have known, but on the other hand my physics background allowed me to rapidly pick up structural biology techniques such as small-angle scattering and X-ray crystallography.

Embracing new technologies and fostering technical collaborations have been an important driver for your research. Can you tell us more about this?

Until 10 years ago, X-ray crystallography was the most powerful method to determine the detailed atomic structure of biological macromolecules such as proteins and nucleic acids. I learnt the intricacies of this method during a sabbatical stay in Harvard in 1985 in the group of Don Wiley, where I worked on the influenza virus receptor binding protein, the haemagglutinin. When the European Synchrotron Radiation Facility (ESRF) was built in Grenoble in the early 1990s, X-ray crystallography became the central technique I used for my research. I worked in various areas and determined the first structures of several aminoacyl-tRNA synthetases, the adenovirus fibre and penton base proteins, parts of the signal recognition particle, the nuclear cap-binding complex and the innate immune RNA sensor Rig-I. In 2014, my group determined the first complete influenza virus polymerase structure. This breakthrough depended not just on the quality of the ESRF X-ray facilities but also on mastering how to purify and crystallise the intact and functional polymerase. Over the last ten years we have continued to work on influenza polymerase, taking advantage of technical advances such as high resolution structure-determination by electron cryo-microscopy. Even more recently, structure prediction using AlphaFold, developed by machine learning from experimentally determined structures deposited in the Protein Data Bank, has emerged. As all structural biologists have found, far from making them redundant, AlphaFold is an additional tool that enhances their ability to give insight into biological mechanisms. Keeping up with new technologies is a must in science, however this can depend on the resources available to a laboratory. Hence it is very important to fund state-of-the-art infrastructures for structural biology that are openly accessible to external users.

You mention your work on influenza. Could you tell us more about this research, and also its broader impact?

A major focus of my lab has been to determine the structure and mechanism of action of the heterotrimeric RNA-dependent RNA polymerase of influenza virus, the key virally-encoded enzyme involved in viral replication. This remarkable molecular machine is responsible for two distinct processes: transcription, that is copying the viral genomic RNA template into viral messenger RNA (mRNA, used to make viral proteins), and replication, whereby genome replicates are synthesised for packaging into progeny virions. We first identified small, independently folded domains within the polymerase subunits, the X-ray crystal structures of which turned out to be very useful for structure-based antiviral drug development. Indeed, in 2009 I co-founded a company called Savira pharmaceuticals to exploit this knowledge to develop inhibitors targeting the cap-binding and endonuclease activities of the polymerase. However, despite partnering with Roche, we were not able to develop clinical candidate antivirals and Savira was disbanded in 2016. However soon after, we collaborated with Shionogi, a competing Japanese pharmaceutical company, to characterise their endonuclease inhibitor, called baloxavir. In 2018 this compound, marketed as Xofluza, became the first new anti-influenza drug to be approved for clinical use for over 20 years.

Over the last ten years we have been refining our understanding of how the influenza polymerase works. We are now mainly using the new, powerful technique of single-particle electron cryo-microscopy (cryo-EM), which can yield structures of equal detail to X-ray crystallography. However, it has the advantage that the sample can be heterogeneous and would therefore not generally yield crystals suitable for X-ray analysis. Influenza polymerase is a complicated molecular machine, with moving parts, and we have specialised in using cryo-EM to determine the structure of the polymerase trapped at different points during the mRNA synthesis (transcription) cycle, that is the initiation, elongation and termination steps. This has revealed the remarkable dynamical changes in polymerase structure as it synthesises viral mRNA. We have also studied how the influenza polymerase interacts with the host transcription machinery, notably cellular polymerase II, which is the essential first step in viral mRNA synthesis.

Currently we are studying the distinct process of viral genome replication, an even more complicated mechanism that involves two viral polymerases (one which actually replicates the genome and another which helps package it) and a host cellular protein called ANP32. Interestingly and crucially, avian and human ANP32 proteins differ in a significant way and this provides a barrier to avian influenza strains infecting humans. Avian strains (like the H5N1 bird flu circulating worldwide now, which has recently started infecting cows) can only replicate in humans if they mutate their polymerase to adapt to human ANP32. Understanding the mechanism of adaption of avian influenza to humans is critical to recognise early warning signs about a potential new influenza pandemic. Since such a future influenza pandemic is virtually inevitable, development of new vaccines and anti-viral drugs and a pandemic strategy is an urgent, ongoing need.

Influenza polymerase in chocolate 2015

Taking on the directorship of EMBL Grenoble was another important milestone of your career. What are you most proud of achieving in this leadership position?

Given EMBL Grenoble's central position on the European Photon and Neutron (EPN) Science Campus in Grenoble, I was always very keen to develop mutually beneficial collaborations with our neighbouring institutes. Since the beginning of the 1990s, we have had a very close working relationship with the European Synchrotron Radiation Facility (ESRF), developing much of the advanced instrumentation that is needed to take full advantage of the finely focussed and intense ESRF X-ray beams for macromolecular crystallography and small angle scattering. Much of the world-leading instrumentation we developed has been commercialised and sold worldwide. I also worked to make sure that EMBL Grenoble was a key player in many of the EU-funded, Europe-wide initiatives in structural biology, most of them co-ordinated by Professor Dave Stuart at Oxford, including Instruct, the European structural biology infrastructure. But we also had to be very strong in structural biology research ourselves, and recruiting of excellent young group leaders was always a critically important task. At another level, I am proud to have initiated in the early 1990s the laboratory annual ski day to help foster a sense of community within EMBL Grenoble. This event has continued to this day (except during the Covid-19 pandemic) and is as popular as ever!

What excites you about the research landscape now and into the next decade?

I have devoted my career to exploiting *in vitro* structural biology mostly using recombinant proteins and reconstituted complexes, as this approach gives the highest resolution structures. However 'cellular structural biology' technologies are now developing, notably electron cryo-tomography, which permit determination of structures in their cellular complex, albeit at generally lower resolution. This is a very exciting prospect, particularly in the field of molecular virology, since the interaction of viral proteins with cellular proteins and organelles is crucial to better understanding of virus-host molecular warfare.

You have recently retired, and also joined the Dunn School as a Visiting Professor. What are you hopes for your association with us?

I retired at the end of 2022, but thanks to my EMBL Emeritus status and the generosity of the new Head of EMBL Grenoble, Kristina Djinovic Carugo, I am able to freely come into EMBL when I wish to work on my ongoing projects on viral polymerases from influenza and related viruses and on co-transcriptional RNA processing. My last postdoc, Benoit Arragain, left at the end of 2024, and he did a remarkable job, together with other collaborators, to keep new cryo-EM data coming in so that we stay state-of-the-art in our field. We have published several papers (including the work on the influenza replication complex and on the snRNA nuclear export complex) and several more are submitted or in preparation (e.g. on the cap-snatching complex between influenza polymerase and cellular Pol II). So, although I am retired, I am still very much immersed in research and will give invited talks at two virology meetings later in the year. Whereas former postdocs have taken over several of my projects, to ensure the future of my influenza work I have taken a different and more unusual strategy, which is to work closely with former competitors in the field, namely Prof. Ervin Fodor (Dunn School) and Prof. John Grimes (STRUBI, Henry Wellcome Building of Genomic Medicine)! This was a

major part of the motivation to join the Dunn School as a Visiting Professor and I thank Ervin, in particular, for hosting me on my visits. The other motivation was to get away from the routines of Grenoble and imbibe the sparkling intellectual atmosphere of Oxford, where I have many other scientific collaborators and friends.

This interview was adapted and expanded from an article by Maryvonne Hasle in La Gazette du Laboratoire', which can be accessed here:

https://www.gazettelabo.fr/archives/315/page%2030.pdf

Laiba Malik - Hertford College
"Sir, I just want you to know that knowing you're going to read something I wrote is really embarrassing - I'd feel better sending this if it was anonymous. Also, this took me forever to write so I hope you like it..."

Antibodies strike
Synovium under siege
Inflamed joints break down

What we *really* know about the gut microbiome: the Gut Florists at Glastonbury

Erik Bakkeren, India Brough and Rebecca Jeffery

'Science outreach' may bring to mind images of school activities or science fairs. But there are many creative ways in which to engage the public, and in the most unexpected places. Here, Erik Bakkeren from the Foster group and India Brough and Rebecca Jeffery from the Powrie group (Kennedy Institute) discuss bringing gut research to music lovers.

When you take probiotics, you are improving your gut health, right? Well, the answer is not as simple as you might think. Decades of research have taught us that in, and on, our bodies we host trillions of microbes, collectively called the human microbiome. The microbiome within our digestive tract— the gut microbiome, or sometimes colloquially 'the gut flora'—is the most studied and has the highest density of microbes. It is known to provide many health benefits including helping us digest our food and provide nutrients, prime and mature our immune system, and protect against disease-causing pathogens. But *how* does our gut microbiome provide its benefits?

It is a frequent misconception amongst the public that products focusing on gut health promoted by social media influencers or companies, or even those found in supermarkets, can provide a quick, generic fix to our health by focussing on the gut microbiome. Unfortunately, the research community lacks a full understanding of how these supplements, probiotics or foods affect us. This means that many products may do nothing at all, or may even cause harm. The apparent disconnect between public perception and the current state of research needs attention. Originally founded in 2022 by microbiome researchers based at the Kennedy Institute of Rheumatology (Group of Prof. Fiona Powrie, a former Dunner!), *The Gut Florists* is an outreach project that aims to make this communication disconnect a priority. Over its nearly 3 years of operation, the project has evolved in both ideas and personnel to include microbiome researchers at the Dunn School (Group of Prof. Kevin Foster) and the Oxford Centre for Microbiome Studies (Figure 1). Initially conceptualised after seeing how popular the topic of microbiome research was during volunteering for another University of Oxford-based outreach project at Glastonbury, countless efforts have been spent developing stall activities, artwork and funding applications to make the Gut Florists outreach project a reality. In addition to attending several school science festivals, the Gut Florists has successfully operated at Glastonbury Festival in 2023 and 2024, gauging public perception on the gut microbiome, interest in microbiome research and current understanding of strategies targeting gut health.

Figure 1: The Gut Florists at Glastonbury Festival in 2024 with Prof. Fiona Powrie. Left to right: Rebecca Jeffery, India Brough, Fiona Powrie (KIR), Frances Spragge (Dunn School), Ffion Hammond (KIR), Erik Bakkeren (Dunn School), Avery Robinson (KIR).

Figure 2: Temporary tattoos of the Glastonbury 2024 headliners reimagined as bacteria, created by Dr. Nicholas Ilott (KIR). SZA as Methicillin-resistant *Staphylococcus aureus* (MRSZA), Coldplay as the causative agent of the bubonic plague (Coldplague), Shania Twain as *Salmonella Typhimurium*), and Dua Lipa as LipA, a virulence factor of *Listeria monocytogenes* (Dua LipA).

Glastonbury is the largest greenfield music and performing arts festival in the world and, therefore, a unique opportunity to communicate with a crowd of approximately 200,000 members of the public that we would otherwise not reach through our traditional science-based festival and school outreach event efforts. Glastonbury festival is a particularly productive space in which to discuss the microbiome, as those in attendance are typically interested in gut health conceptually and other stall vendors incorporate "gut-friendly" aspects in their marketing and products. For example, there is frequent emphasis on fermented and plant-based items amongst food vendors. In the style of Glastonbury Festival, we gave away temporary tattoos of the Glastonbury headliners reimagined as bacterial species (Figure 2) as well as bacterial pom-pom keychains, which also doubled as a way of evaluating the success of our activity.

During the course of the 2024 festival we gave away 656 tattoos, 97 pom-pom keychains and had an estimated 2,000 visitors to the stall. Given the number of festival-goers we interacted with, our days were long and very full on. However, in the evenings we were able to relax and even got to catch a few performances! On the stall, we encouraged festival goers to take part in a survey on their thoughts and knowledge of the microbiome (Figure 3). As we expected, and in line with the frequency with which gut health is found in media streams, most festival-goers thought that gut health was important and had heard of the gut microbiome. When asked about taking probiotics, which are live microorganisms with claims to improve gut health, answers were more mixed. In general, regardless of whether an individual was taking probiotics or not, there were questions about their effectiveness. This led to productive discussions about the effect of diet on the gut microbiome, why interventions like probiotics or nutrient supplements may or may not be successful, and the pros and cons of alternative therapies like faecal microbial transplants. We referred festival-goers to a list of resources about the gut microbiome that we had compiled, through which they could learn more (https://hero.page/gutflorists/glastonbury-2024). Finally, we asked them to leave their thoughts about the gut microbiome, the stall, or any remaining questions.

What did we learn from this experience? Generally, the public was excited to have conversations about the gut microbiome, reflecting on our stall as "important", "informative", and "interesting". In addition, visitors commented that "given the benefit [of the gut microbiome] it is comparatively underfunded." To us, this highlighted the timely nature of our outreach activity. However, many festival-goers also asked us questions about what we could specifically recommend to improve gut health, given the state of the field.

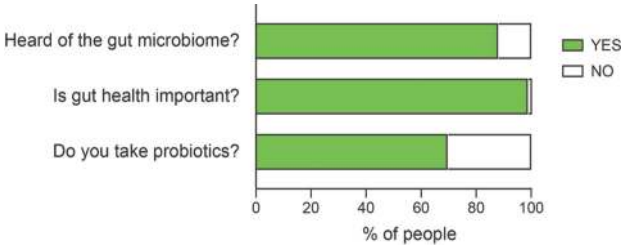


Figure 3: Survey results (n=166).

So, can we recommend anything to generically improve gut health based on the current state of the field, as the public seems to want? Microbiome research has evolved dramatically, and we now know that some microbes tend to cause more problems than others, and some have associations with beneficial health outcomes. The problem is that what a healthy microbiome looks like is not completely clear. Each of us has a unique composition of microbes that are affected by our unique genetics, environmental factors, and diet. It seems like the only generic pattern at the moment is that diverse microbiomes are associated with better health outcomes. As the field continues to evolve, we may be more ready to make clear predictions about when certain microbes will be useful and when others are detrimental. Who knows when the next break-through will be! But until then, we plan—and encourage others—to have open discussions with the public about what research can and cannot tell us. The Gut Florists will continue with outreach events in 2025 such as Pint of Science, and aim to be at Green Man 2025 in Wales.

David R Greaves

"I wrote this poem when I realised how much time we spend in the BM Principles of Pathology class book explaining plural nouns of either Latin or Greek origin."

On plural nouns in pathology

A bacterium is singular
Bacteria however is plural
In empyema - they're pleural (!)

A granuloma is just one
Of granulomata there are many
And they are not always found in the lung (!)

Making a gift to the Dunn School

The Dunn School owes its existence to a philanthropic gift, and over the years has been the beneficiary of many acts of philanthropy, not least from those who have worked and studied here.

Any gift made to the Dunn School helps to further research here, whether it is made to support a specific initiative, such as our centenary goal to endow graduate studentships, or at the discretion of the Head of Department. If you would like to make a gift to the Department this year, please get in touch with us at alumni@path.ox.ac.uk.

You will have the option to select gift aid so that we can reclaim tax on your gift, and if you are a higher rate tax-payer, you can also set your gift against your tax liability for the year. All gifts made to the Dunn School from the USA are also fully tax-deductible, when made through the University's 'giving vehicle' there, the Americans for Oxford, Inc organization.

Leaving a legacy

If you are considering leaving a gift to the Dunn School in your will, we will be pleased to have an informal chat with you, providing any guidance you may need and the wording to share with your solicitor or family members. A will is very personal, and we quite understand if you prefer to keep your intentions private. However, if you do wish to let us know about a gift in your will to the Dunn School, we will be delighted to be able to thank you personally.

Personal reflections on Howard Florey

Gordon Sanders

In this issue [page 18], we feature a personal report by Dr. Gordon Sanders about a scientific trip to Moscow with Howard Florey during the Second World War. The report was kindly donated by Dr. Sanders' niece, Rosalind Barnes, and her family. The family also shared another valuable document: Dr. Sanders' reflections on his long working relationship with Professor Florey. Likely written for Florey's funeral or memorial, it offers a unique personal insight. We present it here in full, as originally written.

Dr A.G. Sanders, A Senior Research Fellow in the Sir William Dunn School of Pathology, Oxford University, and at present a Visiting Fellow in the John Curtin School of Medical Research, writes:

I have known the late Lord Florey for 32 years since I first went to work with him as a DPhil student and for most of that time I have been closely associated with his work in the Sir William Dunn School of Pathology in Oxford. It is of Florey in Oxford and on some of his wartime and postwar travels that I shall write. He was a most stimulating person to work with and had the highest standards. He was always kind, thoughtful for others and considerate of the welfare of all members of the department. When the time came for anyone to leave, Florey would take a lot of trouble personally in finding a suitable post for him.

During the War most of the laboratory work was on penicillin and he gathered around him a team of people for this purpose, all of whom were infected with his own enthusiasm. In the summer of 1943 he was in North Africa as adviser on the first large-scale trial of penicillin on the wounded from the invasion of Sicily. Here he also took the opportunity of exercising his skill with a cine camera and made a very fine documentary film of this unique occasion.

Later that year he was asked by the Medical Research Council to visit Moscow at Stalin's invitation to exchange information with medical and scientific workers there. He was joined by Professor Baird Hastings of Harvard University, who represented the United States. Each took one personal assistant and I was fortunate enough to be asked by Florey to accompany him. We left Oxford on 23 December 1943 and had a most tedious journey to Tehran via Cairo. In Tehran, Florey was seriously ill with viral pneumonia and was treated in the American hospital there. Further delayed by bad

weather we eventually reached Moscow on 1 February 1944 and stayed for one month. Florey had a strenuous program there imparting information not only on penicillin but on nine other topics of major importance such as D.D.T., B.A.L., anti-malarials and others, all of which were on the secret list. On the social side there was also a heavy program of official receptions. In this too he excelled as he was a good conversationalist, well informed on a wide variety of topics. Relaxation was provided by several visits to the Bolshoi theatre to see opera and ballet which he thoroughly enjoyed.

Back in Cairo he decided to write the official report to the Medical Research Council before returning to England where he knew that much paper work would be waiting for him. Throughout the entire trip, which was very exhausting, and often irritating, Florey was always even-tempered and able to see the funny side of things. On one particularly tiresome occasion, he made the dry comment "I think this trip is going to look better in retrospect".

The British Council took advantage of his visit to Egypt by asking him to lecture in Beirut and Jerusalem. While still in Egypt we took three days holiday and visited Luxor and the Valley of the Kings, where, as in Jerusalem, he made a travel film. This was the first of a series which he called the "Penicillin Perigrinations". These were shown to the laboratory staff in Oxford at the annual Christmas parties. Other films were made when he travelled to receive honorary degrees in South America and New Zealand, but one of the most popular was the one he made in Australia in 1953 when he was in Canberra for discussions about the John Curtin School of Medical Research. One sequence in this film "brought the house down". It showed him sunbathing at a picnic lunch by Lake George and it was so composed that it looked as if he was in the nude. Sunbathing he called "exposing the torso" and later coined the delightful words "to torsify" and "torsification". These and many of his other amusing neologisms will continue to be used by his friends.

In 1948 the late Lord Nuffield wanted Florey to accept quite a large sum of money personally in recognition of his work on penicillin. Characteristically, Florey declined the personal gift, but asked Lord Nuffield to give the money to Lincoln College, of which Florey was a Professorial Fellow, to endow three research fellowships. The original three fellows were all members of the penicillin team.

Another of Florey's projects was the introduction of "Middle Common Rooms" into the Oxford scene. Many D.Phil. students passed through his hands and he was most unfavourably impressed by the entire lack of special facilities for these people in the colleges which they were obliged to join. A start was made in his own college, aided by a benefaction from the Albert and Mary Lasker Foundation in New York which Florey was able to obtain. It has been a great success and is being copied by other colleges. Many Australian postgraduate students have benefited from Florey's forethought in this matter.

When the lease of his house near the laboratory fell in he built a new one at Marston, a village just outside Oxford, from which he later took part of his title as Baron Florey of Adelaide and Marston. Here he started to take an interest in gardening, being particularly fond of roses.

Another of Florey's little-known accomplishments was painting in oils at which he had quite unusual talent. Every year he used to disappear on vacation and be completely incommunicado. Later some new pictures from his brush would appear on the wall of his study at the laboratory or in his home. These pictures would reveal that he had made a trip to the south of France or Spain. He loved travelling and spoke many languages so fluently that he could not only give lectures but also make witty and impromptu after-dinner speeches.

His death will be deeply regretted by many all over the world, but felt most keenly by those who knew him well.

David R Greaves

“Dedicated to my brother Duncan who died of a massive and unexpected heart attack on 31 12 2024”

You can’t see me!

I am one metre ninety-three,
That much you can see.

I am sixty-four if I’m a day
But my hair has not (yet) turned grey (yay!)

I could definitely be slimmer
I’m no runner; I’m no swimmer.

But it’s the things you cannot see
That are going to kill me

My total cholesterol
My HDL:LDL ratio
My hypertension
My (genetic) inheritance

Judging me by my appearance
Tells you only half the story

My most important risk factors are invisible!

David R. Greaves 13 02 2025

From bench to vaccine: towards the development of a vaccine for meningococcal disease

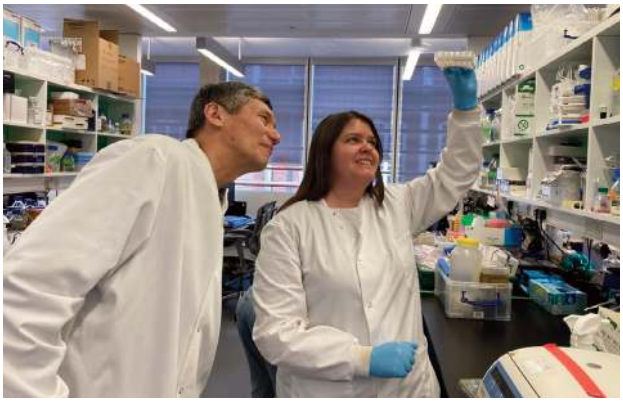
Christoph Tang

The Tang lab seeks to understand how pathogens colonise specific niches in the body, evade elimination by the immune system, and cause disease, with a particular focus on *Neisseria* spp., which are leading causes of bacterial meningitis and gonorrhoea, and enteric pathogens, such as *Shigella* spp. Here, Chris describes several years of work in the lab towards the development of a MenB vaccine, a collaborative endeavour across several generations of Tang lab members, collaborators in Oxford and further afield, and key industry partners, The Serum Institute of India.

The initial focus of my lab was to understand how the bacterial pathogen, *Neisseria meningitidis* causes disease. Infection with this bacterium usually leads to asymptomatic colonisation of the upper airway; the human nasopharynx is the only reservoir for the meningococcus, which is a human-adapted pathogen. Invasive meningococcal disease (IMD) is much rarer than colonisation and results from invasion of the pathogen into the bloodstream (leading to sepsis) or layers around the brain (causing meningitis). At the time, IMD was the second most common cause of death in children aged 1-5 in the UK, and I had witnessed first-hand the devastating nature of this condition as a junior doctor at the John Radcliffe Hospital.

Therefore, the longer-term aim for the group was to prevent IMD by developing vaccines based on a better understanding of how the meningococcus colonises the upper airway and causes IMD. In the UK, there was a vaccine to protect against one strain of *N. meningitidis,* MenC. The vaccine was based on the polysaccharide capsule that surrounds the bacterium. Introduction of the MenC vaccine was a success; within a few years, the vaccine virtually eliminated MenC disease. However, MenC accounted for less than a third of IMD cases, with the rest caused by MenB. Similar approaches could not be employed against MenB as its capsule is made of a polysaccharide found in the human body. MenB had evolved to cover itself in a human sugar, which is not detected by the human immune system: an example of molecular mimicry. Thus, non-capsule based vaccine targets were needed to solve the problem of MenB.

The complement system contributes to the human innate and adaptive immune system. Complement factors are abundant in serum and promote antibody-mediated uptake of pathogens by phagocytic cells and lysis of bacteria. The major complications of IMD stem from its ability to survive and replicate within the systemic circulation where it avoids killing by complement. Work on how the MenB evades the human complement system began in the lab following a genetic screen we performed to identify factors that the bacterium requires to survive in the bloodstream. The screen identified several genes in the meningococcus that influence its interactions with complement. Rachel Exley, a post-doc in the lab, found that a mutant lacking a gene required for



lactate uptake had reduced survival in the bloodstream and in human serum. She showed that lactate was an important energy source for the meningococcus and was used to synthesise its capsule, which protects the bacterium from complement-mediated killing. This highlighted an intimate link between the nutritional status of the bacterium and its virulence. For this human adapted pathogen, metabolism and virulence go hand in hand. Pioneering work by Harry Smith had shown similar effects in the related pathogen, *Neisseria gonorrhoeae*, albeit through a distinct mechanism as the gonococcus does not have a capsule.

The importance of complement in protection against *N. meningitidis* infection is evident from the susceptibility to IMD of individuals with inherited or acquired defects in complement. People who cannot lyse bacteria because of a complement deficiency are at a > 10,000 fold increased lifetime risk of developing IMD. Therefore, the lab further investigated how the bacterium escapes killing by complement, and we soon discovered that it scavenges a human complement protein, factor H, which is abundant in human serum. Factor H acts like a switch, turning off the complement system. The main role of factor H is to protect the endothelial cells lining the circulatory system from inappropriate attack by complement. We found that by recruiting human factor H, the meningococcus can better withstand elimination by the complement system. This work was a collaboration with Bob Sim at the MRC Immunochemistry Unit in Oxford. Bob was remarkably generous and provided us with the expertise, patient advice, and reagents needed for these studies.

Although we had shown that factor H is bound by a protein expressed by the meningococcus on its surface, another group found that the molecule responsible and named it factor H binding protein (fHbp). Subsequent work by us and others highlighted the importance of human factor H and bacterial fHbp in meningococcal biology. For example, a human genome wide association study (GWAS) found that polymorphisms in the factor H locus influence susceptibility to IMD in the general population (i.e. among people not in families with rare genetic defects). Furthermore, a bacterial GWAS we performed with Danny Wilson and Martin Maiden in Oxford showed that single nucleotide polymorphisms (SNPs) in the meningococcal genome in and around the fHbp gene determine whether infection with a strain is likely to lead to harmless colonisation or IMD. We found that these SNPs affect the regulation of fHbp, and prevent its increased expression at higher temperatures, such as when the bacterium transits from the cooler temperatures in the upper airways into the bloodstream.

fHbp turned out to be a lead vaccine antigen against MenB, being developed by Pfizer and GSK. For the Pfizer vaccine, fHbp was the only antigen in their vaccine, while fHbp is part of a cocktail of antigens in the GSK vaccine.

So, what were the challenges in further developing fHbp-based vaccines? First, the versions of fHbp in the Pfizer and GSK vaccines were unmodified so still expected to be functional and bind factor H, which could affect the immunogenicity of fHbp. Could vaccines be developed with non-functional fHbps? Second, could data from whole genome sequences (WGS) of disease-causing isolates be exploited for vaccine design? As chair of the scientific advisory board of the Meningitis Research Foundation (MRF), I was involved in instituting the MRF genome library with Martin Maiden, Ray Borrow (National Meningococcal Reference Laboratory), and Julian Parkhill (Sanger Centre). The library contains the WGS of isolates from all cases of IMD in England and Wales since 2008. This revealed that the sequence of fHbp is highly diverse, so several versions of the fHbp are needed to provide broad coverage. And finally, could we devise fHbp-based vaccines that also provide protection against another antigen, as we had also found that a small proportion of strains in the UK do not express fHbp.

Addressing these challenges required further investigation of the nature of fHbp itself and how it binds human factor H. We collaborated with Susan Lea (previously at the Dunn School) to define the structure of fHbp bound to human factor H. We found that fHbp consists of two barrels and defined the sites on the protein that mediate its tight binding to factor H. This paved the way for generating a series of non-functional fHbps which had much diminished, and in some cases undetectable, binding to factor H. fHbps can be divided into three families based on differences in their sequence, and we were able to generate non-functional fHbps belonging to each of the three families of fHbp.

We also identified the region of human factor H that is recognised by fHbp. Factor H is divided into 20 distinct segments, with segments 6 and 7 necessary for binding to bacterial fHbp. This enabled us to employ transgenic mice to assess our vaccine candidates; the mice expressed factor H which mostly consists of the murine version of the protein, but with the key segments humanised to allow binding to fHbp. Immunisation studies with non-functional fHbps showed that they were as, and in some cases more, effective vaccines compared with wild-type fHbp. Therefore, future MenB vaccines will likely include non-functional fHbps. During the purification of fHbp it became clear that proteins belonging to one of the families were relatively fragile; the first of the two fHbp barrels begins to unfold at 37°C. This is not ideal for a vaccine, and might explain why only fHbps from two of the families had been included in the Pfizer vaccine. Therefore, Stijn van der Veen in the lab stabilised this version of fHbp by comparing the sequence and structures of stable and unstable fHbps. Both the generation of non-functional fHbps and its stabilisation are examples of structural vaccinology. In this approach, antigens are modified, based on knowledge of their structure, to enhance immunogenicity and suitability as vaccines.

Scrutiny of sequences in the MRF genome library revealed that around 1% of strains that cause IMD in the UK do not produce fHbp, so would not be covered by a vaccine that only contained this protein. Therefore, adding another antigen would increase coverage of a fHbp-based MenB vaccine. PorA is another surface molecule which had proven successful in protecting individuals against IMD. Outer membrane vesicles (OMVs), composed of blebs of the outer membrane of bacteria, include surface proteins such as PorA and have been used to stop epidemics of MenB caused by a single strain. However, OMVs do not provide broad protection against circulating strains. Protection from OMVs is mediated by PorA, with individuals protected from infection with strains expressing the same PorA as in the OMV vaccine, but not against strains with different PorAs. As we had a catalogue of sequences of both fHbp and PorA and their structure, we decided to use fHbp as a scaffold to present the immunogenic, surface-exposed part of PorA. Within a single chimeric molecule, mostly made of fHbp but also in part PorA, we aimed to generate immune responses against two important surface targets on MenB. Introducing the PorA epitope at certain points in fHbp could at the same time render fHbp non-functional. The task of constructing and evaluating these fHbp:PorA chimera was initiated by Rachel Exley, then continued by Ilse Jongerius, Sarah Hollingshead and Hayley Lavender, who all contributed to generating and testing these chimeric antigens.

While these studies in the lab provided proof-of-principle for vaccine design, the key question is how they perform in clinical studies. The journey from bench to first in person is usually long and expensive, and we have been fortunate to have the Serum Institute of India (SII), in particular the team led by Dr Pisal, as partners as we head to clinical trials with

these MenB vaccines. The SII are the largest vaccine manufacturers in the world, and have themselves made significant breakthroughs in the prevention of IMD. As part of the Meningitis Vaccine Project, which was headed by Marc la Force (who was a visiting Professor at the Dunn School in 2019), the SII manufactured a vaccine against MenA strains, which has eliminated IMD caused by this strain in sub-Saharan Africa, saving hundreds of thousands of lives. Furthermore, the SII have made a combined vaccine (MenFive) which is highly effective against all the strains of *N. meningitidis* that cause IMD except for MenB. Our shared vision is that the MenB vaccine, originally developed at the Dunn School, will be the final piece in the jigsaw and help bring about a world free of invasive meningococcal disease IMD.

The lab's strategy for MenB vaccines focused on refining key antigens through detailed knowledge of their function and structure. Antigen engineering to enhance immunogenicity and broaden strain coverage relies on a deep understanding of the mechanisms pathogens use to evade immune detection. In this context, the recruitment of human factor H by meningococcal fHbp represents not only a sophisticated immune evasion strategy, but also a critical vulnerability, an Achilles heel that can be exploited for vaccine development. However, such advances are only possible through a multidisciplinary approach, integrating microbiology, genetics, establishing and interrogating genome databases, immunology, protein engineering, and structural studies. The lab has been fortunate to work with many outstanding collaborators whose expertise and commitment have been instrumental throughout this effort. Progress in this area is not achieved in isolation, and relies on sustained teamwork across disciplines and institutions. It has been a privilege to work with a dedicated and highly skilled team in the lab, whose contributions have been essential to advancing the work from discovery science through to vaccine design and evaluation. The complexity of vaccine development demands patience and persistence, and underscores the critical importance of teamwork in science, where concerted collective action surpasses what can be achieved by any one individual. Saying this, two long-standing members of the lab have been central to this success. Rachel has provided outstanding mentorship and scientific leadership across multiple projects, guiding the direction of research and training new lab members, while contributing to teaching at the Dunn School and Somerville College. Lindsay Stimson played a central role in laboratory organisation and operations, ensuring the smooth running of our work and supporting the broader team. Their expertise and dedication have been fundamental to the lab's achievements.

As our work on MenB at the Dunn School winds down, our sights are now set firmly on the gonococcus, an even more elusive target. Like the meningococcus, *N. gonorrhoeae* is a human-specific pathogen, and it too has evolved sophisticated strategies to avoid elimination by the immune system. These strategies are so effective that natural infection with the gonococcus does not protect individuals against future episodes. There is now an urgent need for a gonococcal vaccine, as global rates of disease and antimicrobial resistance are increasing. We have made encouraging initial steps in the development of a gonococcal vaccine, again by targeting its capacity to subvert the human immune system. However much remains to be done to outwit this highly challenging pathogen.

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Seraj Ali – Jesus College and **Shreyas Adhikari** – Trinity College

"Shreyas and I were completely swept away by your poetry and have spent a long and toiling evening preparing for you an anthology. We have poured our souls into this, and we hope sincerely that you enjoy.

My student accomm
Covered by a mouldy balm
Tis aspergillus!

I kissed a medic
I then got tired and sick
Glandular fever!

My life is ending
My nucleus is bending
Time for NETosis!

"Dear Seraj, Dear Shreyas
Wow that is a lot of haikus - from Aspergillus to Zoonosis, you have identified a good percentage of the 5 and 7 syllable works in the BM Principles of Pathology syllabus. I particularly enjoyed your verse on freshers' 'flu - EBV and the shades of I kissed a girl by Katy Perry." DG

Opening the doors to the local community

Hannah Calkin

Oxford Open Doors in an annual event run by the Oxford Preservation Trust. It grants members of the public access into historic buildings and community spaces that are not usually accessible, and is a great opportunity for the local community to explore the beautiful architecture and hidden stories of our town.

On Saturday 13 September, the Dunn School opened its doors to members of the public. Though not the first time we have hosted an Oxford Open Doors Tours, thanks to the past efforts and enthusiasm of Eric Sidebottom and Colin Cook, this was our first participation for many years. Unlike many other venues participating in Oxford Open Doors, where the public explore by themselves, we offered two guided tours, accommodating 36 people per tour.

Each tour started in the library where visitors were given an overview of the Dunn School, our history and current research. We of course did not forget to include the always surprising fact that, despite our name, we do not actually research Pathology here! Visitors were then split into two groups who, in turn, had a chance to both learn about our history and our current research.

The highlight of the history tour was a visit to the Head of Department's office, almost unchanged since Florey's time. Here, visitors learnt about the world changing research on penicillin and cephalosporins, and a chance to see (but alas, not touch!) our penicillin bedpan (the only one that survives in the Dunn School). Along the way, 100 years of inspiring scientists and transforming research were highlighted through stops at various of our black and white portraits, as well as fascinating connections between past Dunners and Hollywood stars, Inspector Morse, Roger Bannister and even a UK Prime Minister!

The second part of the tour highlighted the Dunn School's current microbiology research. In the morning session, researchers from Georgia Isom, Chris Tang and Teresa Thurston's groups presented their work on bacterial-host interactions and antimicrobial research. Visitors were introduced to the techniques these teams use to investigate how bacteria engage with human cells and how their work aims to assist combating AMR. In the afternoon, volunteers from Kevin Foster, Emma Slack and Mathew Stracy's groups used their session to offer insights into the microbiome and the dynamics of bacterial communities. Their presentations underscored how these microscopic ecosystems influence health and disease, and how understanding them will help shape the future of biomedical science.

This event was both a fantastic outreach opportunity, but also great experience for our centenary. It allowed us to plan, and test in action, a safe, accessible and hopefully interesting tour of the Dunn School. Throughout 2027, our centenary year, we plan to welcome alumni, family and guests to the Dunn School and provide guided tours.

Sign-up to our Alumni and Friends Network!

We, at the Dunn School, are very proud of the achievements of our alumni. We established the Dunn School Alumni and Friends Network to keep in touch with former staff, students, and their family and friends.

If you haven't yet joined, please sign up to -

- Receive regular updates on what is happening in the Dunn School.
- Keep up to date with our centenary celebration plans in 2027.
- Have access to exclusive events and opportunities.

And please spread the word! If you are still in touch with anyone from the department who you think would also be interested in signing-up, please send them the link.

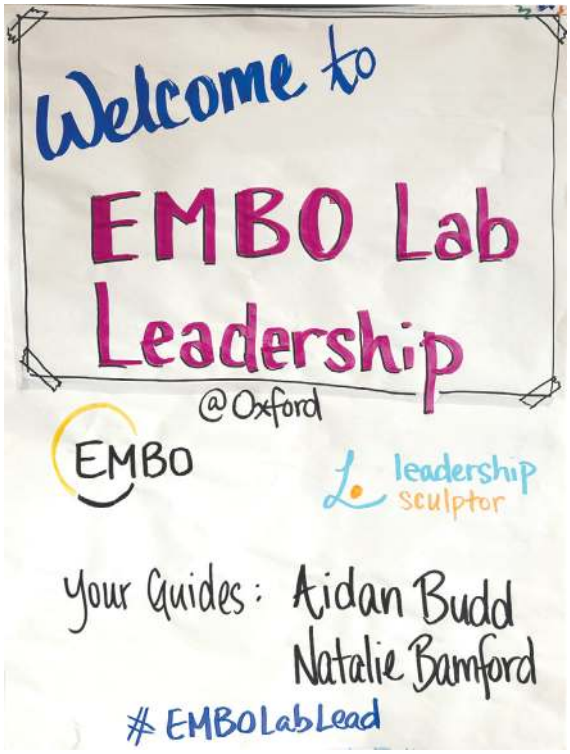
Leading the way: the EMBO postdoc leadership course

Thomas Williams

In the previous issue of *Fusion* we announced the launch of the Dunn School Postdoc Programme, a structured programme of career development opportunities open to our postdocs. One significant progress since then has been improving access to leadership training. In this issue, Thomas reflects on his experience attending the prestigious EMBO postdoc leadership course, which the Dunn School hosted for the first time early this year.

The EMBO lab leadership course. Like a lot of people, I'd heard it was very useful for those leading or planning to lead their own group, and I was actively encouraged to attend it. When the Dunn School, in conjunction with the Weatherall Institute of Molecular Medicine, decided to host the course, I jumped at the chance to attend. However, I still had no real idea what to expect: tips about how to balance extra responsibilities, insights into a whole new layer of administration and budget management, and how to be inspirational? I was ready to take vast amounts of notes and discover things I hadn't even thought about.

What I was not expecting on that first day was a circle of chairs and an agreement that the room would be a safe space for sharing. This launched three days of personal discovery through targeted introspection, covering aspects of the personality traits which drive me, what's important to me in a lab environment, and which parts of my job are most important, and which I (and others) value the most. Through this process I've achieved a much greater understanding of what's important to me in the workplace, and what I can do to help promote these aspects, both now and in the future: whether that's in academia, industry, or elsewhere.



On the first day we covered what we think leadership and management is: inspiring and motivating others, and helping a team work effectively. Important and complementary aspects for effectively running a group! We went on to delve into the roles we undertake and the relative importance each one has to different people within an organisational structure, from ourselves to supervisees and supervisors. We explored the characteristics of effective teams and how

these can be disrupted through a lack of clear goals, a negative atmosphere, and internal competition. We finished off the day exploring our own personal and professional values, and how, when shared, these feed into the effective functioning of a team. Clarifying, discussing, and acting out shared values will be important aspects when I'm either recruiting or being recruited in the future.

On the second day we started by discussing emotional intelligence in small groups, about how we had handled situations without letting heightened emotions negatively impact our behaviour and strategies we found useful. This peer-to-peer discussion format, used extensively in the course, was supremely effective at allowing us to reflect upon what we'd done well, and what we could do better and was an extremely valuable learning tool. We then moved on to the related topic of our (self-judged) personalities, and how that affects which situations we might find more challenging, letting us be more prepared for them. We then discussed patterns of communication and how the way we speak, and the type of questions we ask, sets up a particular response style: this certainly helped me identify areas where I could do better in my personal life, notwithstanding the benefits at work! Finally, we talked about when and where to provide feedback in the most effective, supportive, manner and ways of motivating, which will vary in effectiveness depending on the person.

If that seems like a lot to pack into two days, it was! But we still had one more day to go, and four more topics: conflict management, coaching, the working environment, delegating, and empowering others. These topics each complemented several of those from the days before, allowing us to re-engage with, and reinforce the learning from, e.g. effective teams. By again discussing with peers situations we'd been in when these applied we were able to personalise our learning and reflect on how we could do better as well as gaining a better understanding of challenges faced by others.

Through attending the EMBO lab leadership course, and taking the time to step back from hectic research schedules and look inwards, I have gained a far greater understanding of who I'd like to be as a leader, and the traits I want those leading me to have. I've gained greater understanding about how a research group is like a garden: it needs to be constantly tended or risk becoming full of nettles and brambles. Most importantly, I know how to stop those spiny shoots appearing, and how to deal with them if they do. I have no hesitation in joining the gaggle of people recommending attendance to anyone thinking of going into a management position. Before you attend think about challenging and successful interactions you've had, keep an open mind, and be ready to share.

An update on our neighbours

Hannah Calkin

Issue 20 of *Fusion*, published in 2023, included an article about the building of the Life and Mind Building (LaMB) directly opposite the Dunn School; and whilst the initial planned opening was 2024, the LaMB building is officially opening this Autumn.

The LaMB building is the new home of the University's Department of Experimental Psychology and Department of Biology (merging the department of Zoology and Plant Sciences), with the aim of promoting collaboration and openness between the fields of research and education in this new space.

The Dunn School will therefore be saying goodbye to the Ineos Oxford Institute for Anti-Microbial Research (IOI) who have been in the Dunn School since 2021 while waiting for their new facilities at the LaMB. The Institute is a collaboration between the Department of Biology and the Department of Chemistry, led by Professor Tim Walsh.

When speaking to Tim about IOI's time at the Dunn School, he said:

"After five years in Oxford, a highlight of mine has been experiencing the friendliness of the Dunn School - it stands out as a department with strong moral fabric. Matthew has been outstandingly accommodating and the facilities, finance, and all the professional service staff involved in the running of the Dunn School have been kind, efficient, and communicative. My team and I are very appreciative of our time here."

We also say goodbye to the groups of Professors Martin Maiden and Sam Sheppard, who have also called the Dunn School their home since 2022.

The LaMB boasts impressive views, with the dreaming spires of Oxford visible from their café (figure 1) and the Dunn School from every north-facing window (figure 2). We look forward to the opening of the LaMB and the new buzz it will bring to the University Science Area!

The science-policy interface: reflections from the Royal Society's pairing scheme

Isaac Wong

Isaac Wong (Raff lab) shares his participation in the 2025 edition of the Royal Society's prestigious pairing scheme, that took him from the Dunn School to Westminster.

I have often viewed politics as irrelevant to the pursuit of science, believing that scientists should be driven solely by curiosity and objective inquiry. As a result, I spend most of my time immersed in laboratory work, rarely paying attention to broader societal issues. However, conversations with colleagues who have directly experienced significant shifts in global political climates have made me increasingly aware of how profoundly political contexts shape our quality of life and influence the course of scientific discovery.

The Royal Society's pairing scheme "aims to help to build relationships between scientists and politicians, ensuring that policymakers can make decisions based on the best scientific evidence." Running since 2011 in partnership with the Government Office for Science, it has featured a number of prominent politicians, including the current Prime Minister Sir Keir Starmer, Greg Clark, former Chair of the Commons Science and Technology Committee, Nick Clegg, former Deputy Prime Minister, and Caroline Lucas MP, former leader of the Green Party. I was one of the 30 UK scientists who this year spent 4 days in Westminster engaging with politicians and civil servants.

I was paired with Dr. Adam Thompson, the newly elected MP for Erewash, Derbyshire, who has a scientific background in metrology. Our discussions primarily focused on research funding challenges, notably the issue known as the "valley of death"—a critical phase where promising research often stalls due to insufficient bridge funding. We identified recurring trends where limited UK funding pushes talented researchers abroad. Adam highlighted concerns regarding funding structures favouring short-term grants, resulting in significant job instability within academia. Coupled with inadequate salaries and increasing childcare expenses, these issues considerably strain researchers, negatively impacting their productivity and overall quality of life.

Adam also mentioned the long-term supply of STEAM (Science, Technology, Engineering, Arts, and Mathematics) professionals essential for supporting a robust knowledge-based economy. Addressing this issue requires both long-term educational strategies and immediate policies to attract skilled professionals to the UK. However, he acknowledged that such short-term policies are often hindered by the complexities and high costs associated with UK visa application processes.

Another interesting exercise was the "Policy Maker for a Day". Assigned to a diverse group of scientific experts and senior civil servants, we acted as the Department for Environment, Food, and Rural Affairs (Defra). Facing an imaginary ministerial request about using magnets to rescue stranded whales—quickly recognized as scientifically impractical, the exercise highlighted significant cognitive differences between scientists and civil servants. For example, scientists instinctively explored underlying causes and alternative solutions, whereas civil servants prioritized immediate and politically acceptable responses under significant time pressure and public scrutiny. One civil servant notably remarked, "I have approximately 15 minutes to brief my Minister on complex scientific issues before major decisions. A 30-page literature review isn't feasible. I need the evidence, implications, and alternatives on one page." This clearly demonstrated policymakers' bandwidth constraints, highlighting the necessity of concise, evidence-based scientific communication.

Moreover, the series of talks delivered by professionals from the Royal Society, Institute for Government, the Science and Technology Committee of the House of Lords and the Parliamentary Office of Science and Technology (POST) were an important component of the "Pairing Scheme". These talks provided valuable insights into the structure and functioning of the UK government and parliament. I learned how parliament engages with academia to inform policy decisions and address key issues effectively, for example parliament regularly engages academia to inform policy

decisions by actively seeking expert evidence on emerging issues. Scientists also have opportunities to participate informally through All-Party Parliamentary Groups (APPGs) which encourage mutual dialogue and influence between scientists and policymakers.

Importantly, participating in the Royal Society's Pairing Scheme profoundly improved my understanding of how politics shape science and vice versa. Recognizing and effectively navigating these political realities is challenging but essential for fostering an innovative and prosperous scientific community which ultimately leads to a sustainable knowledge-based economy and benefits the UK society as a whole.

(edited by Catarina Vicente and Sarosh Habib)

Dunn roll, please... our name announcement!

In issue 20 of *Fusion*, we asked readers for suggestions of names to describe someone who currently works or studies in the Dunn School, or who did so in the past.

Thank you to all of you who sent a suggestion! We are excited to announce that the winning name is '***Dunner***', a term that most of us already instinctively use.

So, all of you reading today are officially Dunners - or fond enough of a Dunner that you choose to keep up-to-date with the Dunn School!

Reflections from the Dunn School NewsDesk

Bella Maudlin

In this article, Bella Maudlin (Hinch lab), the current editor of the Dunn School News Desk, spotlights three former members of the team, and how they benefitted from this writing and editing experience.

It is vital for any researcher to be able to explain their complex research to a variety of audiences, including peers, funding bodies, and the taxpaying public who help to fund us. The Dunn School NewsDesk plays a key role in showcasing the department's diverse fundamental and translational research, as well as the fantastic achievements of its members. Run by volunteers, it is a great opportunity to practice your science communication skills - not only to benefit your own research, but also to develop invaluable translational skills that you can take into any career. Here, former NewsDesk members share their experiences and how this has helped them in their careers.

Dr Shaked Ashkenazi, former writer and editor, now Content Marketing Manager
www.linkedin.com/in/shaked-ashkenazi-sa5

"Looking back at my time as a writer and an editor in the Dunn School NewsDesk, I can see the impact on my professional growth in three different aspects:

1. Knowing your audience (or to put it in an "industry term", your "user's journey"): starting from what the reader already knows and what information they are after. To me, this is the starting point of any writing task, and I remember thinking about this often in my roles at the NewsDesk. As an example, what language should I use? What should my article focus on? etc.

2. Connecting with the researchers and hearing about their work from them. Science is often very collaborative, and in my experience, even more so in the non-academic sector. Proactively approaching researchers and working together with them to make sure that they are happy with what we were doing was a skill to learn and to perfect. Once this is successful, a good relationship is established and that leads to future collaborations, whether in future articles or in other aspects of the work.

3. Leading a small team of volunteers was another important aspect of this work, in my opinion. I felt that I had to balance between motivating the team members to write content in a timely manner (it is essential when writing news, after all) and being sensitive and considerate regarding their other commitments, which naturally, often took priority. I also remember trying to come up with new creative ways to raise awareness and recruit new members.

Apart from that, there is no denying that any contemporary scientist will benefit from learning how to translate complex scientific discoveries into short, clear, intriguing messages."

Dr Anna Caballe, former writer and editor, now Founder & CEO – ACBio
www.linkedin.com/in/anna-caballe-ch

"Back in 2017, a team of keen writers was needed for the Dunn School NewsDesk, and I quickly felt extremely committed to it. I wrote Research Highlights and Dunn School news, and later, I became an editor. We strived to run like a professional unit, even seeking support from experts like Visiting Professor Roger Highfield, OBE. I'd write one piece every month or two and edit several others. I'd use incubation times, work on weekends, or stay up late to fit that work into my long lab days, but I absolutely loved it. Something inside me kept wanting to do this and keep learning more about creative writing, copywriting, and editing. I enrolled in a Writing in the Sciences online course and attended workshops about professional science communication and journal editing. Even though my postdoc was plain sailing, I knew an academic career wasn't for me. Scientific writing and communication seemed to be my calling.

Could I get a job that would somewhat fit my years of research expertise and postdoc salary? After attending career seminars, talking to professionals outside academia, and continuing to volunteer as a science writer, I was ready to apply to my first non-academic job. I prepared a portfolio with my best articles and assessed what I had learned. While at the NewsDesk, I learned to work in a different team, developed editing and copywriting skills, and inspired other writers. I brought my learnings as a postdoc, my portfolio, and my endless motivation to the job interview. The rest is history. I've now worked in Science Writing and Marketing for over 6 years. Seeing my work valued by peers and customers, and published across channels fills me with joy and pride. If someone had told me in 2017 that in 2025 I'd be running my own Marketing Consulting, Content Strategy & Comms business and having fun, I probably wouldn't have believed them! I feel particularly grateful to Matthew Freeman, Jordan Raff, Sonia Muliyil, and everyone at the Dunn School for supporting the News Desk and those doing their best to skillfully put words down on paper."

Dr Laura Hankins, former writer and editor, now Communications and Engagement Manager

"I worked on the Dunn School Newsdesk during my PhD, and it was a great experience that supported my transition into a career in science communication. The NewsDesk gave me the chance to meet others in the department, learn more about the research going on outside my own lab, and hone my science writing skills. One of the things I enjoyed most was writing Research Highlights for the department website. This proved to be useful training; after my PhD, I went on to work at The Company of Biologists, a publishing company where my job involved writing Research Highlights on a regular basis! My career is still evolving (I now work in university communications), and I value my time on the Newsdesk as an important first step in my training."

We are always looking for new members to join the NewsDesk writing team! As part of the NewsDesk team, you will have a chance to hone your non-academic writing skills, covering newsworthy events related to the Dunn School, and practice your science communication by highlighting recent research from the department.

If you are interested or need more information, please email:

isabella.maudlin@path.ox.ac.uk (current Editor) or catarina.vicente@path.ox.ac.uk (Head of Scientific Strategy and Projects)

David R Greaves
A short poem for World Haemophilia Day

Oh, Factor Ten
You are my favourite zymogen!

Antimicrobial resistance research at the Dunn School receives 3-year funding boost

Catarina Vicente

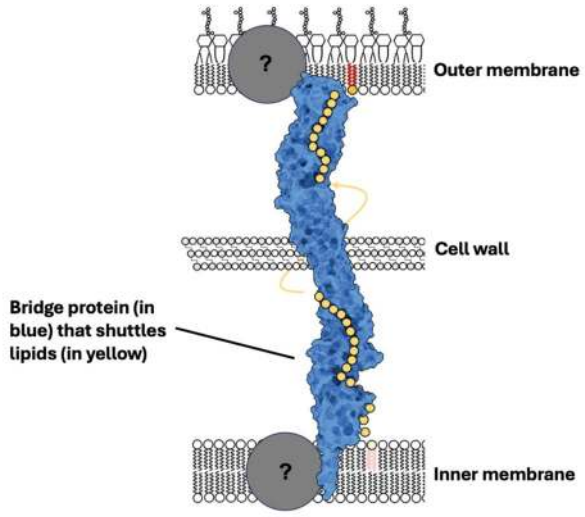
The generous gift by Juliet and Andrew Wilkinson will allow the group of Georgia Isom to pilot an exciting new approach in the study of Gram-negative bacteria

Antimicrobial resistance (AMR) is one of the biggest health challenges of our time. It puts at risk many of the gains of modern medicine, not least those catalysed by the development of penicillin and cephalosporins here in the Dunn School.

Certain bacteria (known as Gram-negative bacteria) are particularly resistant to antimicrobials. This is in part due to the double layer of protection around them: two lipid membranes that can prevent the entry of antibiotics into bacterial cells.

To maintain these barriers, bacteria use transporter bridges that directly connect the two membranes. The group of Dr Georgia Isom uses a combination of structural, biochemical and microbial approaches to study these transporters and their role in resistance.

One of the technical challenges of resolving the structure of these transporters is that they lose their structural integrity when they are not stretched between the two cell membranes. The generous gift of the Wilkinson family will allow Dr Suzi Letham, a postdoc in the Isom group, to pilot the use of DNA origami to create scaffolds to maintain tension on transporters outside cells. This should facilitate cryo-EM structural analysis of these proteins and may also provide a roadmap for other researchers studying other medically important molecules that are also currently difficult to image.

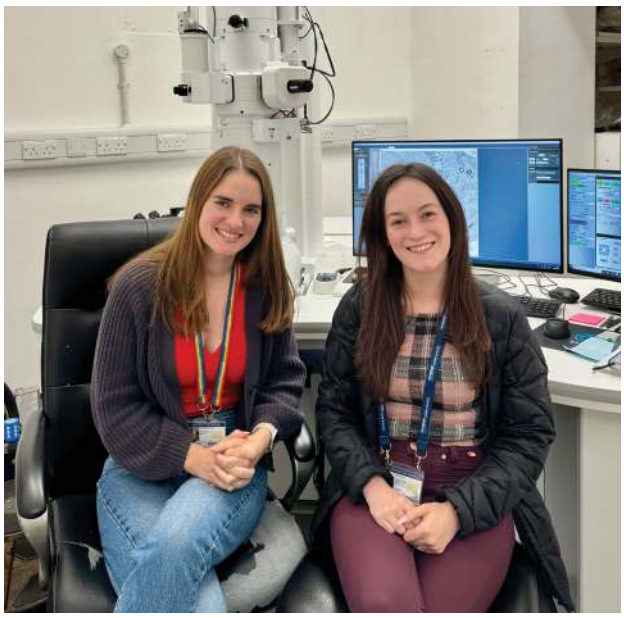


Proteins form bridges between the inner and outer membranes, to shuttle lipids that make up the membranes. When these proteins are removed from the cell, they are no longer under tension and become difficult to image.

"We are incredibly grateful for the generous donation from the Wilkinson family." said Georgia and Suzi "The methodology we want to develop is not something easily funded from other sources, making this donation really impactful. It gives us the chance to develop cutting-edge methods to answer important biological questions, with huge benefit to the research field as well as our professional careers."

The generous gift of the Wilkinson family will support the development of this project over the next three years. We were delighted to welcome Andrew, Juliet and their daughter to the Dunn School earlier this year, where they had the opportunity to meet Georgia and see how this research is conducted in our labs.

"We were keen to support an up and coming lab doing highly experimental research that might otherwise be difficult to fund." said the Wilkinson family "We saw a very specific connection between the funding and the project, which made it very interesting and rewarding for us, something that doesn't always happen with much larger scale projects. After meeting Georgia, we felt like we'd be supporting both ground-breaking research and dynamic young scientists"



Dr Georgia Isom (L) and Dr Suzi Letham (R)

Blood Groups

A, B and O – here's
what you need to know

Two sugary (glyco-) proteins
On the red cell surface

Called A and B, determine
What blood type you will be

i.e. Blood types A or B, AB or O
Where the 'O" stands for Ohne (that's German for without either)

There are some other blood groups
Including Duffy, Kell and Kidd

But Haemolytic disease of the foetus
Is caused by the blood group Rhesus

Your blood type information
Is essential for blood donation!

So many patients are dependent on
Getting blood donated by strangers

Your name we don't need to know;
Just whether you are A, B, AB or O.

David R Greaves 10 06 2025

Inspired by reading about Mina Holland's baby Vida who was born with Diamond-Blackfan anaemia
https://dauntbookspublishing.co.uk/book/lifeblood/

The Sign of Seven

Andrew Souter

The Sign of Seven is a Fusion first - a short story inspired by the Dunn School; written by Andrew Souter, our Head of HR.

The 6am sun was cherry red as Amber arrived at work. She'd decided to come in early to ring her father, who she predicted, would be waking up from his post-lunch-beer snooze. The time difference from Oxford to Adelaide made phone calls hard work. That is to say, hard work for Amber. There was a tacit understanding in her family that, given she was the one that abandoned them for a job on the other side of the planet, she'd also be the one that had to get up at the crack of dawn to phone home. The unfairness stung, but with a family like hers she was adept at supressing emotions. Besides, Oxford was at its most beautiful in the morning.

Amber loved Oxford. She loved cycling home through the biting cold of winter peering through her scarf. She loved watching rugby and drinking ale in a timber framed pub older than America. She loved plunging into the river on her lunch break during the few short weeks the locals called summer. But most of all she loved the buildings. From the ramshackle frost tinted shop fronts with higgledy-piggledy windows to the grand imposing colleges with their crenulated turrets and elegant spires.

Amber's affinity for historic architecture meant she was delighted to be greeted by the handsome edifice of the Fanny Hesse of Pathology some three years before. At a hundred years old the red bricked building corbelled with muscular sandstone was a mere teenager compared to some of the others that surrounded it. But to Amber the School had a quiet dignity that others lacked. Many of the original features remained, including the dual perron staircase that transported you from street level to the warm and inviting marble clad reception foyer. Amber revelled in the history of the place. A place, in which the best part of a century earlier, one of her countrymen, Dr Howard Florey, had used the mould from his pocket to develop penicillin as a chemotherapeutic agent. Changing the course of mankind's history forever.

"FLOREY?!? Is that you clacking down the corridor?" rang a smooth melodious voice.

Amber smiled and stopped at the doorway from where the voice came. The aroma of freshly brewed coffee wafted around the room.

"You haven't stayed here all night again Professor?" Amber said.

"Time and tide wait for no man, er, or woman Florey, and nor do the frontiers of science! Now, I'm glad you're here..." Professor Scott a slight, immaculacy dressed man with an aquiline nose and keen eyes which gave him hawkish impression, paused midsentence looking skyward. They both heard footsteps from the floor above. "Can't you tell your little friend to keep it down up there. Traipsing around like he's on a catwalk," said the Professor.

"Siri? I'm afraid that's the nature of his facility. On his feet the whole time. The Cuban heels don't help though," said Amber and they shared a smile.

"Tell him I'll buy him some carpet slippers for Christmas. Anyway where was I, that's right. Take a look at this," said the Professor.

"Penicillinase production and intrinsic resistance to pencillins and methicillin-resistant cultures of *Staphylococcus aureus*? This is your first ever publication?"

"That's right, almost 60 years ago. It might help with that resistance issue we discussed last week. Took me all night to find it." He gestured vaguely to the room behind him. Amber believed him. His wood panelled room was covered, floor to ceiling, with heaving shelves filled with hundreds of volumes of leather bounds books. Some slim pamphlets, some thick tomes, but all arranged neatly not one sitting a millimetre proud of the others.

"Thanks Professor this is great. You do know you can print this off PubMed anytime you want it, right?"

"Ah Florey, have I not taught you anything? There needs to be some effort to our endeavour. Where's the poetry in dragging things out of a computer? You've got to feel something to understand it. We are discoverers. Intrepid explorers unravelling the mysteries of the base industry of life. LIFE, dear girl. The invisible forces that animate the Universe. It's a privilege to do what we do. The others; the police officers, the lawyers, the clowns and the chimney sweeps, they'll never see it. The world is more beautiful than they'll ever know," said the Professor without a hint of self-consciousness.

Amber liked Professor Scott. She enjoyed the endearing nickname he'd given her: a reference to her antipodean heritage and the great scientific pioneer, Dr Florey himself. She sympathised with some of his sentiments but she couldn't help feel that he didn't grasp the pressure of being a modern day postdoc in the cut throat world of academic science. They chatted for a few minutes in which Amber indulged more of the Professor's sermons about the nature of science. Amber eventually made her excuses and left.

As she travelled through the bowels of the building the wood panelled walls gave way to maintenance corridors, adorned with cables, wires and piping. After a while she came across yet another early riser; Jonas Visser a fabric engineer responsible for the smooth operation of the School's buildings. Jonas was a stout florid faced man with flaming red hair.

"Mornin' Amber. 'ere what you make of this?" said Jonas. The wall was lined with hundreds of black and white photographs. A Hesse School tradition: every time a student obtained their PhD their photo was placed on the wall. Jonas indicated to a gap in the portraits. There, in place of a photograph was instead a large letter "A" written in black ink.

"What is it?" said Amber perplexed.

"You tell me kid. You're the one with the PhD. Someone has stolen a picture and drawn this," said Jonas giving Amber a quizzical look with beady fat encircled eyes. "Some student joke no doubt. Not sure I get it mind. Its bleedin' epoxy paint. No way that's coming off."

"How weird. Do you know who's photo it was?" said Amber. "E.M. Parker – 1962," said Jonas immediately.

"Wow, that's quite a memory."

"Huh? Well when you've walked down this corridor as many times as I have you remember stuff. I've got the whole layout of this building seared into the backs of my eyelids."

"Listen Jonas, I've got to go and ring my folks. Good luck with the photo thief."

*

Amber didn't manage to speak to her father that morning. By the time she reached her desk, the video screen just hung as a black empty void. A knot of guilt constricted in her stomach which only loosened as the day came to an end, lubricated by the first gulp of warm foamy beer in the King's Arms.

"So what's all that about?" said Siri Shankarmurthy, a lithe young man with a mop of curls and brown grinning eyes after Amber had told him about the missing picture. "Bit creepy isn't it? I find that Jonas bloke a bit weird as well. He's only been here three months but he seems to be everywhere, all the time. Over the last month alone, he's been cleaning my windows, checking the air con, he even tried to inspect our security doors for issues but that's handled by a specialist estates team."

"Three months? I thought it was way longer than that."

"Yeah I was chatting to Maria in HR. Apparently, he was the only candidate willing to accept half the advertised salary. You know everything is about penny pinching round here."

"You haven't heard anything about the picture have you? No students mentioning anything?" said Amber.

"You must be joking right? They don't talk to me. I may look like a Sri Lankan Timothee Chalamet, but don't let that fool you. They're all scared to death of me," said Siri, with a hint of pride.

He wasn't wrong. Siri, had a fierce reputation amongst staff. He was in charge of the containment level 5 facility, which was the most secure biocontainment laboratory at the University, housing samples of numerous potentially fatal pathogens. Siri took his job seriously and had been known to dress down even the Head of Department on occasion. Although Amber had always found him to be kind and generous, a touch acerbic perhaps, but infinitely loyal.

"Oh am I glad to be out in the fresh air!" said Siri as he sank back into his seat, exhaling.

Amber looked round at the stuffy bar packed with a throng of students, university staff and tourists.

"Well, you know what I mean? Just being out of the facility," continued Siri, noticing the look on Amber's face. "It can just be a bit oppressive you know? Everything is multifactorial authentication, the windows are bonded, reinforced with steel bars, even the walls are hulk proof. Some of this stuff is extremely dangerous and in the wrong hands could be weaponised, so it needs to be like Fort Knox, I get it. But you try being desperate for the loo and being trapped in the vaults of a bank. It's not pretty!"

They'd brought a deck of cards, as was their custom, and spent a pleasant evening gossiping and laughing surrounded by the comfortable background drone of the bar. After, they walked back to the Fanny Hesse School to collect their bicycles. Siri, who had been quizzing Amber about the missing picture all night insisted they take a look. Infected with the mellow confidence of the pub, Amber agreed. The building took on an altogether different feeling at night. Amber couldn't help but occasionally glance over her shoulder down the long corridors that descended into nothingness. When they rounded the corner to the corridor with the missing photo of E.M. Parker, they both froze. At the end of the corridor a figure, shrouded in darkness, was reaching for the wall. Suddenly it turned to face them, dropping something that smashed on the floor, then it bolted away from them clattering through the fire exit at the end of the corridor.

Amber and Siri stood in silence for a moment their hearts racing then Siri said, "Soooo that'll get the adrenaline pumping. What was all that about?"

"I'm not sure," said Amber as she walked down the corridor to where the figure had been standing.

"I'm gonna need another pint after this," said Siri who reluctantly followed her.

Amber bent down and picked up the smashed object. It was a photograph of a young man; J.W. Love - 1962. She looked at the wall and, and sure enough, in the void where the picture had been was another letter, this time the letter "T".

"Er...Amber? I think we're going to have to speak to someone," said Siri. A slight tremor in his voice. He was gesturing to a broad section of the wall where several other gaps were showing, all filled with different letters. "Did we just see the person defacing these portraits?"

Amber hoped not, because she was absolutely convinced she recognised the figure that had just fled the scene, and she didn't want Professor Scott to get into trouble.

*

"A. I. M. H. U. R. T.? that's all the letters right? Seven of them. What does it mean? Aim hurt? Some kind of threat maybe? You know, 'I'm aiming to hurt someone,' that type of thing?" said Siri as they had lunch the next day. They had reported the missing photos but no one had any explanation and the appearance of the letters had become something of a curio, with many members of the department filing down to the basement to take a peek.

"Threatening who? This isn't CSI Miami, Siri. What I don't understand is why there was only one photograph on the floor," said Amber.

"Well we disturbed them in the act didn't we. They got spooked and dropped the picture when they ran away."

"Maybe. But I don't buy it. Where were the other pictures? They weren't carrying a stack of framed photos when they ran away. And what about the letters? That paint was dry last night and they certainly didn't have any pots or brushes with them? It was dark but not that dark. I'm not so sure we saw the person that did it. I think all that was done hours before."

"Come on Amber. They ran from us like their life depended on it. If that doesn't smell of guilt I don't know what does," said Siri.

Amber didn't tell Siri she thought she saw the Professor. He'd always been a paragon of dignity and respect, it didn't sit right with her that he'd be involved in some silly childish prank. But she agreed with Siri about one thing; if it was Professor Scott she saw, he certainly did look like he was running for his life.

Amber needed to speak to the Professor, preferably alone. She was sure there would be a rational explanation. When she dropped by his office later that afternoon, she found, to her surprise, his door closed. The Professor never closed his door, and was almost always at his desk. Which was positioned directly, almost comically, in front of the doorway so he could harangue students that walked past into discussing their projects. Amber knocked carefully on the door before opening it. It was empty. She had one foot in the corridor when she noticed something peculiar. The Professor's desk had moved. Not far, but one side had been pushed back about a foot and it was covered in crumbs.

Amber closed the door, turned down the corridor and nearly bumped into straight into Jonas who was wrestling with a ladder.

"Wocha Amber, I could have killed you with this thing," he gestured to the ladder, "you after the Professor? I've not seen him since yesterday. I think he's ill."

"You saw him yesterday?"

"Yeah he looked white as a ghost. We were chatting about those weird vanishing pictures. I was just telling the Professor about the new ones after E.M Parker's was discovered missing. That was at about 6am right? The others must have been done sometime between then and 11am. That's the time I came down here to work on that minus 80 freezer and spotted the five other missing pictures."

"So there were 6 missing pictures and 6 new letters in total by 11am yesterday? Then the one we found behind J.W Love's photo last night, making seven letters in total. That's very interesting. Jonas, I don't suppose you remember the names of the other five do you?"

"Erm, let me see. It was Koontz, Salaman, Migliacci, Cruickshank & Medawar I think. All from 1962."

"And you told the professor these names?"

"Yeh, he seemed very interested."

There was something about those names that registered with Amber. She couldn't quite put her finger on it. She'd read them somewhere recently. She was sure of it. Then it struck her and she plunged her hand into her rucksack to bring out the Professor's first publication. There at the bottom of the page was a list of authors; T.W. Scott, E.M. Parker, F.P Koontz, M.R. Salaman, A. Migliacci, A.H. Cruickshank, D. Medawar, J.W. Love & R.G. Stein.

*

"Aaah, 'at's be'er," said Siri thickly through a mouthful of biscuit. "I was starving," he said after swallowing. "So remind me again why are we here?"

“I need to see the Professor, and you are the only person I know with a car,” said Amber.

“Taxi driver? Right. Gotcha. And this is all because you think the professor is in danger? Who thinks they’re in CSI Miami now?”

“I don’t think he’s in danger. I think he thinks he’s in danger. There’s a difference.”

The Professor lived in a delightful chocolate box cottage and bees bumbled round towers of teetering foxgloves as they walked to the front door. When they knocked the Professor emerged slowly, peering from behind the door which he was almost using as a shield.

“Florey?” he said in a desperate whisper.

“Hello Professor. Can we come in?”

The front room was comfortable if cramped. Amber and Siri squeezed together into a squashy sofa.

“What’s going on Professor? Someone has left you a message: ‘Aim Hurt’? Behind the photos of all your old student friends.” Amber didn’t use the word “threat”. She could see the Professor was visibly nervous and she didn’t want to say anything that could unsettle him further. The Professor sighed, leaning his head back into his armchair. For the first time since she’d known him he looked tired, almost frail.

“I don’t suppose you’d accept ‘coincidence’ as an adequate response?” said the Professor, peering down his nose at Amber.

“Occam’s razor isn’t that sharp,” said Amber. The Professor grinned despite himself.

Then the Professor, speaking with the measured delivery of a practised storyteller, began. He spoke about how he’d arrived in Oxford as a scared boy; about how he’d found, for the first time, companionship in his fellow students; about how they’d lived, and studied and ate and slept together; about how they’d discovered a shared calling in the pursuit of scientific enquiry; about how, at the end of one term, they’d all gone on a sailing trip to celebrate the publication of their first manuscript; and about, how everything changed forever, with the slip of a knot.

“You see I’d tied the rigging. My best friend Ruth Stein, wanted to check the knots to be sure. But I got angry and told her I knew what I was doing. I was young and brash and full of testosterone. When the rigging came loose the boom swung out of control. It all happened so fast, Ruth was still smiling as she slipped into the white surf. It’s a smile I see every night now.” His eyes were glassy with tears. Amber could see the Professor was hurting, but she couldn’t think of anything that could comfort him.

“Ruth Stein? That’s R.G. Stein right? She’s listed as an author on your first publication isn’t she?” Amber pulled out the paper and handed it to the Professor, pointing to the last name on the list of authors. “But she’s different from the rest of the authors. I looked for her photo on the wall but I couldn’t find one. And it’s not one of the stolen ones. They’re all accounted for. Seven missing photos replaced by seven letters.”

“You won’t find Ruth’s photo because there isn’t one. The accident happened before we obtained our PhDs. She was given a posthumous authorial credit but she never obtained a PhD, so she never got a photo on the wall.”

“But what is all this about Professor? I still don’t understand what the missing photos and what does “Aim Hurt” mean?” said Siri, who until now had been quiet.

”Nothing,“ said the Professor.

“Come on professor. We’re here to help you,” said Siri.

“No, he’s being literal. Aren’t you professor? Aim Hurt, is literally meaningless,” said Amber.

“You are sharp Florey,” said the professor with admiration. “The missing photos and the letters, they’re a direct message to me. But it’s an anagram – look. It’s not ‘Aim Hurt’. Take a look and rearrange those letters.”

“Aim Hurt, I. AM. RUTH?” said Amber slowly.

“She’s alive!” spurted the Professor miserably. “And she’s coming for me because I killed her. Don’t ask me how, I went to her funeral for Christ’s sake. But she is. I can feel it in my bones. When you two saw me last night. Not all the letters had been revealed. Jonas had told me earlier in the day about the others but the message wasn’t complete. I went down to the basement to confirm my suspicions. When I discovered the final letter behind John Love’s picture it brought back all those painful memories. I was terrified. So I ran. Look at me Amber, I’ve been at my desk from dawn till dusk for the best part of 60 years, and now I’m barricading myself in my own home. Too frightened to move for fear of a spectre I know can’t exist. But believe me. She does.” That was the first time he’d ever used Amber’s real name. She’d never seen the Professor like this before. Usually he was so calm and in command. But now he seemed childlike and vulnerable.

“No I’m sorry I just don’t believe it,” said Amber. The words came out harsher than she intended.

“I’m telling you that’s what the message means. ‘I AM RUTH’, you must believe me,” said the Professor. His voice sounding pathetic.

"Oh I am quite sure that's what the message says, and that it was meant for you. But it will take more than that to convince me Ruth Stein's ghost is floating through the place hiding pictures and slopping paint on the walls. There a vast gulf between evidence and proof Professor. You taught me that." Looking at the Professor's forlorn face, Amber felt like she was wounding an already lame animal but her patience was wearing thin and her father had shown her directness could sometimes be a kindness, if a cruel one. Amber continued; "come on. How many degrees have we got between us? We must be able to work this out. What is it you brits say in a crisis? 'put the kettle on'. I think this is going to be a two-brew solution."

"You're quite right Florey," said the Professor slapping his knee as he rose out of the chair, his face mustering some grit. "I'm afraid I can't offer you any biscuits. Can't stand the crumbs you see. You may have noticed but I have a thing about being tidy. I'll see if I have a little fruit cake tucked away somewhere."

Siri shot Amber a conspiratorial smile, they both knew the Professor's reputation as an obsessive.

"Hold on, did you just say crumbs?" said Amber. Something half-satisfying had slotted into place in Amber's mind. "That's it. Professor! I think I've found your ghost. Come on Siri. We need to get back to the School, we might already be too late. I have a horrible feeling a crime is about to be committed."

"Aww can we at least take the fruit cake with us," said Siri.

"No time to waste, something tells me the Professor is not at the heart of this mystery. You are!" Siri stared back in astonishment.

*

Amber's mind was fizzing, piecing together little snippets of information she'd seen or heard over that last 24 hours, as they raced back to the office, but now it was still and relaxed, as she stood with Siri in the complete darkness of his category 5 facility.

"At some point you're going to have to actually start explaining what on earth we're doing here," Siri whispered.

"Shh. If I'm right, you'll understand everything in a few minutes. But for now shut up and get ready with that torch," replied Amber.

Siri and Amber stood there for what seemed like hours, the darkness swirled and danced, playing tricks on their eyes. Then suddenly Siri said, "what's that?" Sure enough, a dull drone could be heard growing steadily louder and louder. Then they could feel a slight tremble at their feet, before a shard of light cut through the darkness like a knife. Slowly a skeletal hand flexed through the floor followed by a slowly emerging head. Amber could feel Siri draw back in shock, letting out a high pitched wail.

"NOW" she cried. And Siri, fumbling with the torch, shone a light on Jonas' head poking through the floor like a grotesque puppet.

"ARGH" he cried, half blinded. He looked like someone that had been stung by a jellyfish under the surface. They heard a scuffle of muffled voices as he was dragged down into the floor below.

"We've got him Amber", called a security guard up through the hole.

"Cheers Jon. I'll be down in a second," said Amber as she peered down into Professor Scott's office to see Jonas being pinned to the floor by several large men in security guard uniforms.

*

The next day, Amber, Siri and Professor Scott met in the Professor's office. Which had again been imbued with the welcoming smell of strong coffee.

"I feel a bit sheepish about the whole thing Florey," said the Professor as he looked up at the ruined ceiling. "Here's me, a man that has dedicated his whole life to science, jumping at shadows and ghosts. When all along it was some thug trying to steal some pathogenic material to sell on the black market? My god, could you imagine the devastation if you two hadn't have stopped him."

"That's alright professor. We had it under control," said Siri. Amber smiled at the bravado, remembering the shrill shrieks of the night before.

"There are a few things I don't understand though. For one: how did you know it was Jonas that was planning to break into the lab," said the Professor.

"Well, it's simple really," said Siri. "Well basically... what is was.... Yeah Amber, how did you know?"

"I didn't. Not really. It wasn't until we shined the light on him last night that it was confirmed. But he was, in many ways, the only candidate. Siri, you said he has only been here for 3 months. Yet he told me he'd managed to memorise the whole corridor of photos. I've walked that corridor for 3 years and not remembered one name. Then there was the fact he took half a salary, that smacked of someone that was desperate to get the position. What sort of person would work here for half the money? Unless there was something valuable to be gained. And finally, you mentioned he was constantly examining access to the facility. He'd got access

to the entire layout of the building through his job. Clearly, he had worked out that it was impossible to enter the facility by any normal means, given the heightened security measures. Impenetrable from all sides you said, except it seems, no one thought about the floor. Perhaps the architects thought it was too far-fetched to conceive of someone burrowing up through the ceiling below."

"Yes I can see how that would be the preserve of detective fiction," said the Professor.

"It was your comment about crumbs that sewed everything together for me. When I came to see you yesterday, your office was empty, I noticed your desk was pulled askew and there were crumbs on your desk. You're a fastidious man Professor, who hates biscuits because of how messy they are, it didn't add up that you'd let your office in such disarray. Those weren't crumbs on your desk. It was sawdust from the floor joists Jonas had been trying to saw through. I even bumped into him carrying the ladder he needed to get up there."

"And the missing photos and the cryptic message?" said the Professor.

"Once he'd decided to get to the facility through the floor he needed unfettered access to the room below; your office. He had to remove you. Which, as you spend most of your waking hours, working erratically often late into the night, wasn't easy. So he came up with the elaborate plan of the message behind the photos. He must have been researching your past for weeks."

"Sheesh. Remind me never to try and pull the wool over your eyes Florey. You antipodeans are fierce creatures. It's horrifying Ruth's memory was brought into it. Although, knowing Ruth, she'd have loved the drama," said the professor. Amber couldn't decide if it was sentiment or melancholy reflected in his eyes.

*

Back at her desk Amber's phone tone rhythmically pulsed.

"Gud aye?" grunted a male voice.

"Hi Dad," said Amber.

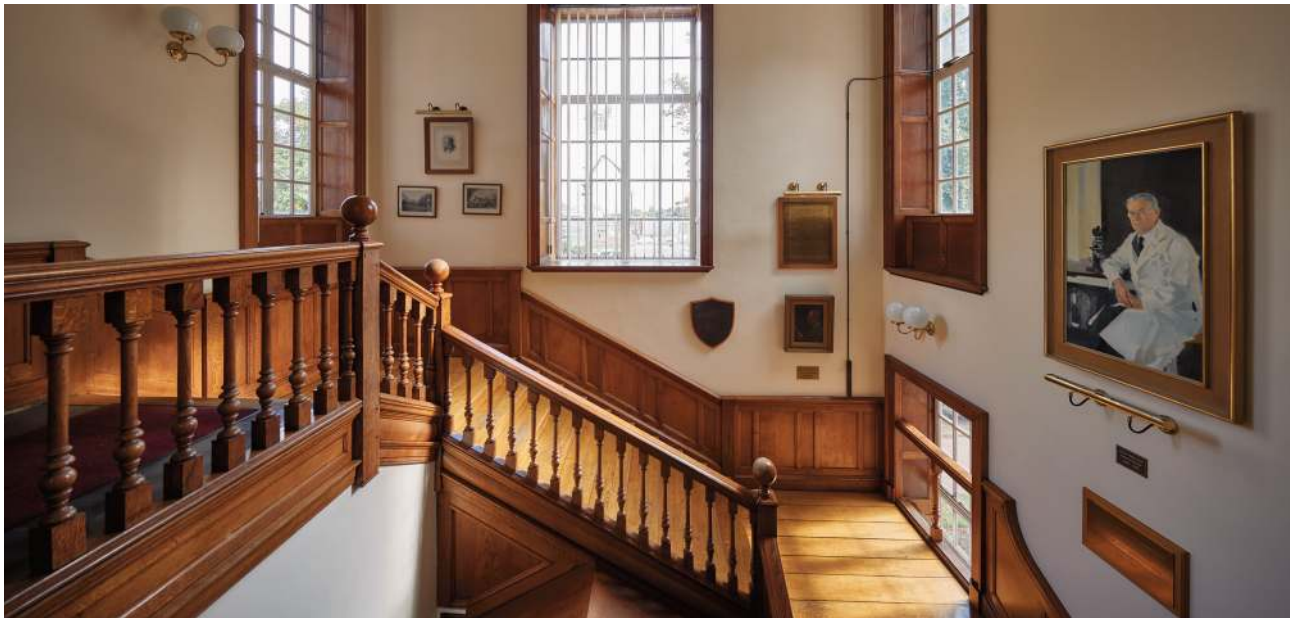
"Who's this," came the response after a short delay.

"It's me Dad. You'll never guess what's just happened."

"Oh hey Amber love," interrupted Amber's father. "Listen, can I call you back? The footy's about to kick off."

"Sure Dad. It wasn't very exciting anyway," said Amber into the drone of a line gone dead.

"Clowns and chimney sweeps Florey!" came the soft voice of the Professor. Amber didn't know how long he'd been there but she was glad he was. "Don't worry dear girl. Come with me, I've just discovered an old manuscript I'm sure you'll find most interesting."



Zoe de Zeeuw - Hertford College

What is tolerance?
Treg, AIRE and some selection
No autoimmune

UNIVERSITY OF OXFORD

From the *Fusion* Archives...

The following is a selection of excerpts, chosen by the Editor from past editions of *Fusion*, that give a flavour of events and topical issues within the Dunn School during years gone by...

THE SIR WILLIAM DUNN SCHOOL OF PATHOLOGY
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Ten years ago...

In 2015, *Fusion* gave readers a brief history on 'Cancer Research in the Dunn School' written by the late Dr Eric Sidebottom.

"My second important advance comes from the work of Henry Harris and colleagues in Stockholm and Oxford. That work was first published in Nature in 1969 under the title "The suppression of malignancy by cell fusion". The paper provoked a wide range of responses from frank disbelief via amazement and excitement to admiration. It ultimately led to the identification of anti-oncogenes – or tumour suppressor genes as they are now known - and a new understanding of the genetic changes in malignant cells. Harris continued with this line of work for the rest of his life. His conclusions were often controversial but he continued to do experiments long after his official retirement and, even after he gave up his laboratory in the Dunn School, his daughter, Ann, working in America, continued the search for factors influencing the suppression of malignancy. Their last joint paper was published in 2013. It is also notable that in 2008, Harris published a re-translation of Theodor Boveri's seminal work "Concerning the origin of malignant tumours" published in German in 1914."

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Twenty years ago...

The fourth issue of *Fusion* (2005) included Professor Siamon Gordon's work on 'You, Me and HIV', a children's book written to help combat the spread of HIV/AIDS through educating children across sub-Saharan Africa about how the virus is contracted. Over 70,000 free copies of the children's book were distributed to NGOs, schools and at camps across South Africa.

Professor Gordon, who at the time was the GlaxoSmithKline Professor of Cellular Pathology at the Dunn School, said "HIV now affects ten per cent of the population in South Africa, and while anti-retroviral treatments are slowly becoming available in some areas, much more needs to be done to inform and educate the population about the spread of the virus. I hope that You, Me, & HIV will play an important part in educating children about the facts of infection".

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