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New approaches to drug development

UNIVERSITY OF CAMBRIDGE
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New approaches

As I write, the Michaelmas Term is nearing its end and I can confidently say that things are indeed back to normal, at long last. The place is buzzing with undergrads coming and going to lectures and practicals, and the familiar sight of supervision groups huddled around every spare table has returned. Research group meetings and seminars are now pretty much all face to face, much to everybody's relief – we have all spent more than enough time on Zoom and Teams over the past couple of years.

If you visit the Department you will see that our main entrance has been refurbished to create a more welcoming and functional space. We've retained some of the original features, such as the beautiful parquet floor, and have complemented these with new lighting and wall treatments. I think that what we have looks fresh and inviting, but still fits in with the distinctive 1950s aesthetic of the building.

The theme for this issue is how we are developing new approaches to combatting disease. Of course there is a long history of chemists making significant contributions to the development of drugs, but as you will read in this issue our involvement goes way beyond the traditions of medicinal chemistry. The fundamental research in Shankar Balasubramanian's group has implications on the early detection of cancers, while Gonçalo Bernardes writes about the importance of effective interaction with clinicians and pharma companies. You can also read about how Melinda Duer and her group are developing a new understanding of the role the extracellular matrix plays in disease, and how this opens up new avenues for therapies – such as those being explored with her commercial collaborator James Harrison.

We have some fascinating contributions from former members of the Department about how their careers have developed – some continuing in chemistry, and some taking quite different paths. And finally to remind us that Covid is still with us, there is an excellent account of the work which led to Pfizer's anti-viral Paxlovid.

James Keeler
Head of Department

Cover photo depicts microscopic tendon cells taken in Professor Melinda Duer's lab.

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New gift for Alzheimer's disease research

Mr R. Derek Finlay (Emmanuel 1952) has given another £2 million to promote further innovation in the Department's Centre for Misfolding Diseases (CMD), located in our Chemistry of Health building.

Derek's association with the CMD began in 2015, when he was inspired by hearing Professor Sir Chris Dobson talk about its work to discover the molecular origins of protein misfolding and aggregation disorders such as Alzheimer's and Parkinson's diseases. Derek then gave £5 million to found the Una Finlay laboratory in memory of his wife, who died of Alzheimer's disease in 2016.

The Una Finlay laboratory and the Chemistry of Health building were officially opened in 2018. These facilities have brought together a range of formerly disparate research groups to collaborate on research programmes into these still incurable diseases.

The building also has an integrated incubator, which currently hosts Wren Therapeutics, a company founded on CMD research. Wren Therapeutics has key researchers with an industrial background who know how to lead drug discovery programmes and scale production up to industrial size, while at the same time researchers often move from the CMD to Wren (and back), enhancing the exchange of ideas and techniques.

This rare two-way flow between research and industry has proved to be one of the CMD's strengths. And with his new gift, Derek hopes to enhance this successful recipe even further.

The official opening of the Chemistry of Health building in 2018 from left: Vice-Chancellor Stephen J. Toope, R. Derek Finlay and his daughter Fiona Finlay, Dame Fiona Reynolds, then Master of Emmanuel College, Lord Wilson of Dinton, former Master of Emmanuel College, and the late Professor Sir Christopher Dobson.

Centre for Misfolding Diseases co-directors Professors Tuomas Knowles and Michele Vendruscolo will use Derek's new gift to further research into Alzheimer's disease and other protein misfolding disorders.

"I hope this further gift will bring us even closer to the development of new treatments for these diseases."

Derek Finlay

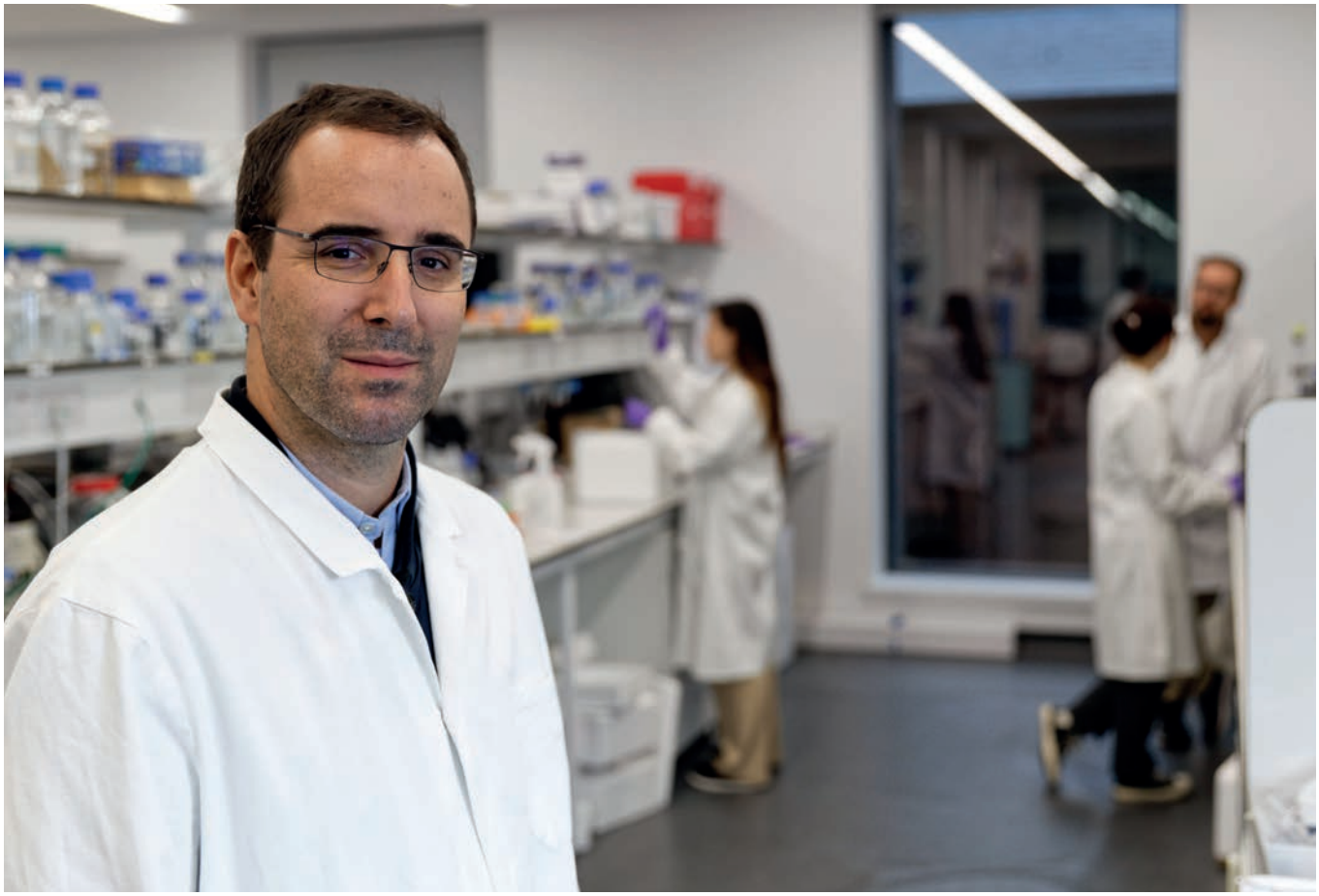
Derek's gift creates a partnership between Emmanuel College, St John's College and this department, who will each bring their own strengths and resources to the group. The gift will fund postdoctoral researcher positions and a number of postgraduate 'Una Finlay scholars,' who will be hosted by Emmanuel College. The gift will also provide further research funds and support for outreach.

"I first supported the Chemistry of Health building in memory of my dear late wife, Una, who suffered from Alzheimer's," says Derek. "The researchers in the CMD have already made so much progress, and I hope this further gift will bring us even closer to the development of new treatments for these diseases."

Students in the Chemistry of Health building.

A new approach to drug development

Professor of Chemical Biology Gonçalo Bernardes has been rethinking his approach to researching and developing targeted cancer therapeutics.



Nathan Pitt, University of Cambridge.

Professor Gonçalo Bernardes.

Gonçalo Bernardes is a busy man. He regularly commutes between his labs in Cambridge and the Instituto de Medicina Molecular in Lisbon. Then there are regular trips to the East coast of the United States, where he is a Senior Fellow at Flagship Pioneering in Boston, and to the West coast for his work as a member of the Scientific Advisory Board for Neoleukin Therapeutics in Seattle, as well as countless academic meetings all over the world.

What is driving him? "What motivates me is this dream about helping patients," Gonçalo says. For this reason, Gonçalo thrives on his different roles, despite the toll on his time. In fact, he says the combination of different roles has caused him to completely rethink his approach to research.

Thinking outside the box

As a Senior Fellow at Flagship Pioneering, Gonçalo is involved in company creation. And in his visits to Neoleukin he learns what they are working on while advising them on how to conjugate small molecules and antibodies to their therapeutic proteins in order to achieve localisation and maximum concentration in tumour tissues.

"The traditional way in drug discovery research was to perform a screening campaign against a specific target, find a molecule and develop it," he explains. "During the pandemic, it became clear that that is not sufficient."

Gonçalo has grown to understand that the best way to help patients is to work together with clinicians, patients and the pharma industry to understand their needs.

"Engaging with companies like Flagship and Neoleukin helps me think about ways to translate my research so that it can be used to help patients," he says. "I get a better feeling of what is being developed in drug development and clinical trials and what is needed for the next generation of therapeutics. It really expands my knowledge and prompts a lot of thinking about what is needed.

"We also need a more multidisciplinary approach. There is a big move in the US towards bringing disciplines together like engineering, chemistry, biology and physics. And we need to work more closely with the clinical side."

As an example, Gonçalo cites TargTex, a Portuguese biotech company based on research from the Bernardes Lab which he founded. TargTex is developing a new therapy for glioblastoma multiforme (GBM), an aggressive and difficult to treat brain cancer.

The therapy involves a hydrogel which can be implanted in the brain after surgery, which slowly releases a selective cancer-destroying molecule identified by the Bernardes team.

TargTex is hoping to start Phase 1 clinical trials (the first step in testing a new treatment in humans) in Spain and the USA next year.

Gonçalo regularly meets clinicians at the Hospital de Santa Maria in Lisbon. "I spend time with the oncology clinical team every other week, where I can sit in on the discussion about each of the patients. This is very important, and helps me to devise the next strategies and to think outside the box," says Gonçalo.

Key research

Delivering cytotoxic drugs (drugs that kill cells) to specific tumour sites without damaging healthy molecules is a key research area for Bernardes and his research group. "Helping patients means developing approaches that have less systemic toxicity and are more effective," says Gonçalo. "In doing this there are tremendous molecular challenges, and chemistry can be central in providing a solution for those."

The goal is to improve cancer treatments while reducing their side effects, and the researchers are developing a number of different techniques to do this. One technique involves 'masking' the active drug by using a molecular carrier such as an antibody that releases the payload only when it reaches a specific tissue, which means it won't damage healthy cells along the way.

The group recently successfully demonstrated this technique on ortho-quinones, which are known to kill cancer cells but typically fail clinical trials because they also kill too many healthy cells. This could open a whole new area of more effective targeted cancer treatments.

Last year Gonçalo was recognised with a Blavatnik prize for the development of RNA degraders. "We design small molecules that are able to degrade RNAs, but the small molecule degraders will only work when brought into close proximity to a specific RNA modification or structure, so in principle we can develop molecules that are benign to healthy cells but kill the ones that are dependent on those RNAs."

Gonçalo is also very keen to develop tools which can be used by other researchers. "It's very important that what we do can be widely applied, and find uses beyond our lab and our own questions. I think this is really key."

A new perspective

"My perspective has evolved – my interactions with pre-clinical projects to move molecules toward the clinic have helped me redefine the tools that I want to develop chemistry for," explains Gonçalo. "We hope our methods may be used in labs around the world to help develop new drugs with improved effectiveness and reduced side-effects for some of the most common diseases, such as cancer."

First things first

Professor Sir Shankar Balasubramanian is perhaps best known for inventing Solexa Next Generation DNA Sequencing with Professor Sir David Klenerman, which enabled fast, accurate, low-cost and large-scale genome sequencing. Here, Shankar notes that fundamental research is at the heart of everything we do in chemistry.

It is not surprising that Professor Sir Shankar Balasubramanian is focused on research into the very basis of what makes up life – DNA. "To frame the discussion," he says, "we don't directly work on anything therapeutic. We work on fundamental discoveries, which of course will ultimately have implications on diagnostics and healthcare. But the fundamental research must come first."

Shankar's large, multi-disciplinary research group has two laboratories – one within the department and the other at The Cancer Research UK, Cambridge Institute, on the Cambridge Biomedical campus.

"Each lab has a different emphasis in terms of expertise. We have the equipment, infrastructure and knowledge in chemistry to design and make molecules and to make biophysical measurements. Our lab at CRUK is essentially a cell biology lab, which is a good environment to do complex cell biology experiments. We also do a lot of sequencing-based experiments there," he says.

Not always a double helix

Most recently, Shankar's interest has centred on particular types of four-stranded DNA structures known as G-quadruplexes (G4s). "DNA is a relatively static part of the genome, we tend to think of it as the hardware an organism has to work with," he explains. "But DNA can also change structures – it is not always the double helix we have all heard about."

Shankar's research team have discovered that the four-stranded G4s are highly abundant in human embryonic stem cells[1]. "They seem to be especially relevant to pluripotent stem cells, which have the potential to be converted into any type of cell," he explains.

The group's research indicates that the G4s are tightly linked to the genes that transcribe the DNA instructions, which tell the cell what specific functions to develop. This means that where the transcription process goes wrong – such as in cancer tumours – G4s could be implicated.

A new hypothesis

The traditional view is that the transcription factors recognise a sequence and bind to the double helix. However, Shankar has published a hypothesis which challenges this perceived wisdom[2]. He believes the transcription factors are acting as 'binding hubs', which recruit and bind proteins that then go on and activate the gene. "It's a non-classical model of how genes are controlled. The implications are that fundamentally it's a mechanism for controlling genes that is new and different. If this view gains acceptance, that would be a fairly big change in thinking."

The research does have implications in cancer. The group has shown that the characteristics of different breast cancers are embedded in different patterns of G4s[3]. "So there's almost a signature that can be traced through these structures, that tells you about the characteristics of the cell or tumour," says Shankar.

The group is studying tumours, pre-cancerous and healthy tissue, to understand the progression of the precancerous state to the tumour. "At the Biomedical campus I'm surrounded by cancer biology colleagues, several of whom run clinics and have access to clinical samples. So we can go from the biology to clinically relevant systems, which means we're always moving forward to understanding how our basic science can be applied in a clinical context."

"We and others in the field have shown that you can design synthetic drug-like molecules and get them into cells so they bind to the quadruplexes when they form. This means you can actually change the transcription, which fits with the view that G4s are intrinsically involved. If you can compete with a transcription factor, you can prevent the mechanistic consequence of it, and that means you have the potential to disrupt the expression of the tumour."

Earlier disease detection

The changes in transcriptional states might even provide useful information about a disease condition that hasn't happened yet. This could have implications for disease

Nathan Pitt, University of Cambridge.

Professor Sir Shankar Balasubramanian in the lab.

detection, diagnosis and understanding of the different sub-types of tumour, known as stratification.

"Our ultimate vision is to prevent the disease before it actually happens. If you can do this, not only is the outcome better but the quality of life for the person and the economic cost to them and the healthcare system is lower."

"New things are being learned day by day as more human genomes are being sequenced. Babies are tested for many things right from day one and even pre-natally. I see an extension from that to whole genome sequence analysis.

"The economics have transformed. There's talk of a £100 or £200 genome, so it would be no more expensive than other tests. It's technically possible, but we need to build more understanding of the genome, and a framework for handling the information."

"Our ultimate vision is to prevent the disease before it actually happens."

Shankar Balasubramanian

[1]Zyner et al, *G-quadruplex DNA structures in human stem cells and differentiation, Nature Communications* (2022), 13, 142.

[2]Spiegel et al, *G-quadruplexes are transcription factor binding hubs in human chromatin, Genome Biology* (2021) 22, 117.

[3]Hänsel-Hertsch et al, *Landscape of G-quadruplex DNA structural regions in breast cancer, Nature Genetics* (2020) 52, 878-883.

Rethinking cancer therapy

On breaking the mould, locking the matrix and making waves.

Cambridge Oncology, a new company co-founded by Professor Melinda Duer and James Harrison, CEO of Cycle Pharmaceuticals, is pioneering a new drug that combats cancer tumours by targeting their environment.

Let's start from the beginning

Melinda's research focuses on the molecular structures of biological tissues, such as bone, tendon and the extracellular matrix (ECM). These interests led her to found Cambridge Oncology with her former student, James Harrison, who studied at Robinson College where Melinda is a Fellow.

"So I still have her red pen on my Part I coursework somewhere in my attic," jokes James.

After a successful career in the city, James founded Cycle Pharmaceuticals ten years ago, improving existing drugs that, in particular, treat children with lifelong and life-threatening genetic diseases. Their combined expertise makes a formidable combination in drug discovery and promises some exciting projects that are making their way to patient trials.

Cycle Pharmaceuticals

Cycle Pharmaceuticals has developed pharmaceutical products for rare metabolic diseases such as tyrosinemia, and recently launched a drug for phenylketonuria. Hundreds of children depend on Cycle medicines every day, including 30 children from developing countries that receive free-of-charge drugs. In 2023, Cycle will start treating multiple sclerosis patients.

Several years ago, Melinda and James began research into new uses of existing drugs. Their collaboration started when Melinda found a way to treat vascular calcification, or hardening of the arteries, but needed an expert on how to transform research into a product for patients.

"James not only understood the science but also understood the processes that could take our research and turn it into a real treatment that helps people," comments Melinda.

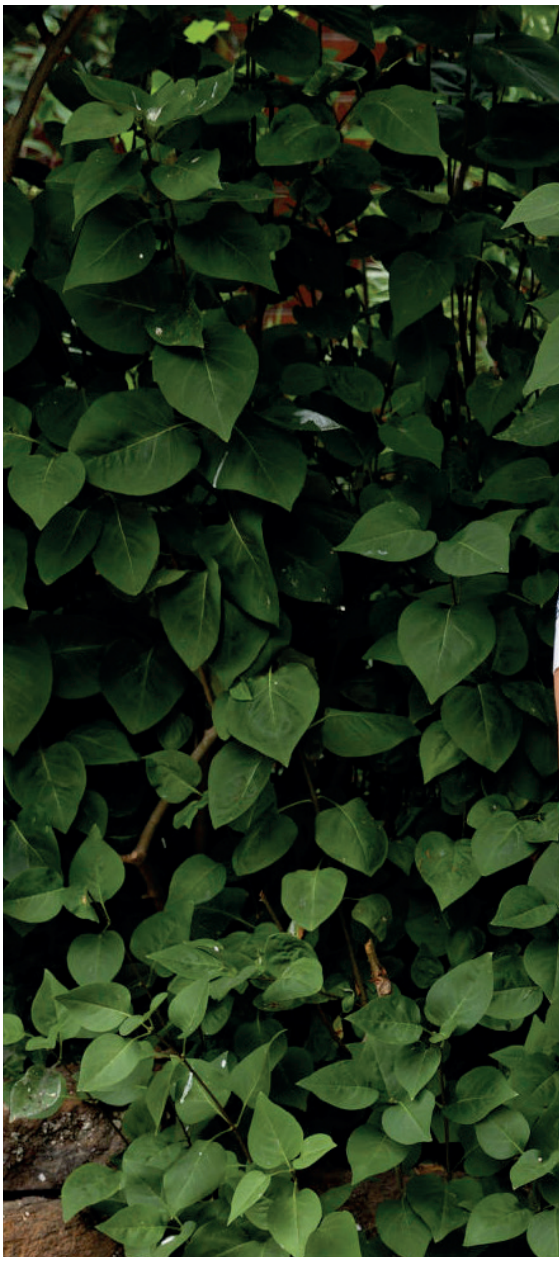
This treatment for hardened arteries has entered clinical trials and was only the beginning of their collaboration. With Cambridge Oncology, they are looking at different problems and pioneering a new type of drug that combats cancer tumours by targeting their environment.

The Extracellular Matrix

The human body is made up of cells and they are held together in a scaffold called the extracellular matrix. This matrix is implicated in degenerative diseases, ageing, and the spread of cancer.

"It all started when we first chemically cross-linked a matrix," comments Melinda, "and we were looking through the microscopes at these stationary cells, and I kind of glibly said 'I wonder if we could do that for cancer cells.'"

"The ECM is the environment our cells exist in," says Melinda. "Imagine the weather; certain plants thrive in different climates and wither in others. Instead of targeting the cancer cells directly, we are changing their



Professor Melinda Duer and James Harrison

"We want to take our research and turn it into a real treatment that helps people."

Melinda Duer

Nathan Pitt, University of Cambridge

environment so that they cannot survive."

Cancer cells contain mutations that make them different from healthy cells, and the same is true for the ECM surrounding the tumour. Instead of targeting the tumour directly, Cambridge Oncology is aiming for the ECM.

James adds: "Our drug is making a cage around the tumour cells by cross-linking the ECM and making the environment more viscous. It makes it harder for the cancer cells to move and grow. They can't draw energy from their environment so they go dormant or die."

A drug for neurosurgeons

Cancer Oncology's initial target is glioblastoma, a deadly and common form of brain cancer. Melinda and James realised this was a disease that they could meaningfully contribute towards since treatment for patients is so limited and life expectancy after diagnosis is not promising.

Animal testing is often a necessary first step in determining drug efficacy, and here, ethically conducted mouse trials were very successful. The new drug trapped cancer cells so they could not grow or migrate. The mice lived longer, maintained their body weight and generally showed healthy mouse behaviour. The next challenge was adapting the technology so that it could be used in humans.

The answer was a liquid that is applied to the brain directly by a neurosurgeon during surgery after a tumour has just been removed. The drug only interacts with the ECM around cancerous cells that remain in the brain tissue after surgery, so healthy brain cells are not at risk.

"A topical drug has the freedom to be designed solely to target the tumour without worrying about delivery through the bloodstream," adds James. "It is a huge challenge to design drugs that can pass through the blood-brain barrier. It exists specifically to keep large molecules out!"

Successful models

The field of ECM manipulation is rich and largely uncharted. The potential of this emerging technology is untapped, and it is teams like Cambridge Oncology that can make headway into this unknown.

"With hard work and some luck, we hope to bring this treatment to clinical trials within the next 18 months," adds James.

Thomas Kress

Dr Uliana Bashtanova, Professor Melinda Duer and PhD student Rakesh Rajan in the Cambridge Botanical Gardens.

A bone to pick

Science is sometimes detective work that leads to unexpected revelations, such as a mysterious signal that redefined how we think about hardening of the arteries.

No strangers to medical innovation, the Duer lab discovered the world's first drug that has the potential to manage hardening arteries.

Normally, when cells are damaged they activate an enzyme called PARP (poly ADP ribose polymerase). Curiously, the Duer lab, in collaboration with Professor Cathy Shanahan at King's College London, identified the product of PARP enzymes (poly(ADP ribose)) when analysing hardened artery samples.

"We'd been working for years on hardening of the arteries and stumbled over the trigger for calcification in bones," explains Professor Melinda Duer. "And that trigger was produced by the PARP enzymes. And then we found it in arteries too."

Currently, PARP inhibitors play a role when treating diseases such as cancer but the Duer lab is taking promising steps to use PARP inhibitors to regulate atherosclerosis.

This dangerous disease causes fat build up inside the arteries. The fatty deposits then calcify, turning the flexible artery tissue rigid. Before PARP was discovered to play a role in hardening of arteries, the main treatment was surgery to remove the hardened tissue which was an option that posed a lot of risk – and just isn't applicable in some cases. The Duer lab suggested an alternative which has entered proof of principle clinical trials, sponsored by Cycle Pharmaceuticals.

A strange discovery

Rakesh Rajan, a final year PhD student, was preparing tissue samples in the lab for analysis with nuclear magnetic resonance (NMR) spectroscopy.

"When I joined the lab," explains Rakesh, "I was researching collagen. That meant working with osteoblasts, which are cells that can make a lot of collagen, amongst other things, like bone. As our research reached the next degree of sophistication we looked into these

materials more deeply and this led to looking at calcification, or fatty deposits, in the muscular tissues of arteries.

"Generally, osteoblasts belong on the skeleton not in the arteries, so finding cells in our models of vascular tissue behaving like bone cells was quite a surprising discovery."

He adds: "We found some signals in the NMR analysis that looked unusual. They looked a bit like signals we'd expect from DNA, except not quite, so we investigated the mystery and they turned out to be from poly ADP ribose."

Finding poly ADP ribose in the samples led to the question of whether it was involved in the process of mineralisation. It turned out that when PAR combined with collagen molecules it led to mineralisation. The implications of discovering this and the role it plays in hardening arteries opened up new possible treatments.

New discoveries, new treatments

"PARP inhibitors currently play a role in treating certain cancers like breast cancer," comments Dr Uliana Bashtanova, who led some of this research. "We thought: can PARP inhibitors also be used to inhibit accidental calcification in arteries? So, we started to look for inhibitors that only block the particular type of PARP we measured most of in arteries, and we found we could with an antibiotic called minocycline."

Whilst an antibiotic might not be an ideal solution, it is preferable to invasive surgery. Clinical trials for minocycline have started and the team hopes that this is only the beginning of research into novel atherosclerosis treatments.

A long tale

The latest research in the Duer lab looks at how tendons respond to trauma.

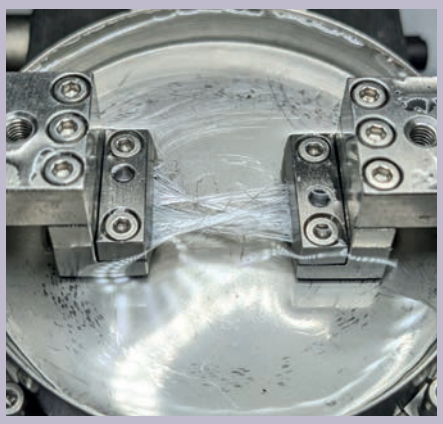
Tendons are like pulleys that let us move our hands, shoulders, knees and toes without a second thought. So what happens when this cord of strong, flexible tissue is damaged? Thomas Kress, a final year PhD student in Prof Melinda Duer's lab, is studying the molecular effects of stress on tendons.

"How do the cells repairing these tendons know whether to repair them or make them stronger?" asks Professor Melinda Duer. "Logically, a tendon that has been damaged before needs a way to communicate that it needs more than a regular repair, but what is this signal? This is the question that launched this research."

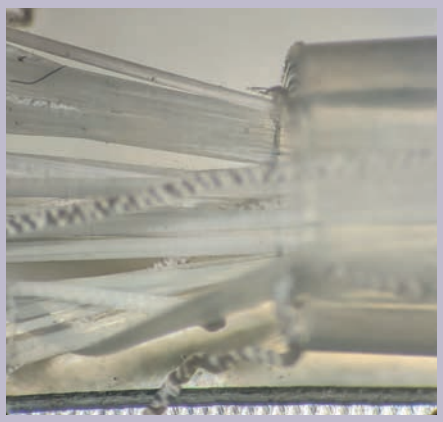
Thomas's latest experiment examines a mysterious new spectroscopic signal that appeared when he was investigating torn tendons. This unknown signal could be a sign that some bonds were broken and transformed into new chemicals when the tendons were structurally damaged, and so the investigation began.

Figuring out the source of this new signal was a challenge, partly because stretching tendons without custom equipment is an imprecise art. The testing that produced this new signal involved stretching a tendon, then placing a section inside a capsule that was spun inside an NMR machine. The next rounds of testing have used a new specialist clamp that can stretch and hold the tendons with a greater precision.

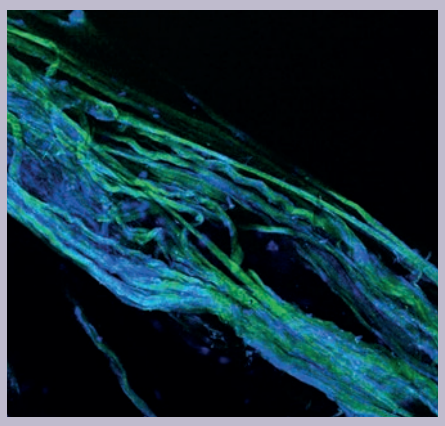
HOW IT WORKS



Tendons placed in custom clamp.



Tendons stretched until transparent.



Tendons can then be examined under a microscope.

Don't stop me now

Elizabeth 'Lizzie' English wanted to connect with other women in neuroscience but couldn't find quite the right organisation. So she started the Women in Neuroscience Network in the UK.

Women in neuroscience network

"Statistically, there is a decrease in the percentage of women in neuroscience as you go up the career ladder," comments Lizzie, who is a second-year PhD student studying Alzheimer's disease in Professor Sir David Klenerman's group. "I want to build an environment that is welcoming for women who are in neuroscience at all career stages, to make them feel like they have a place there."

The Women in Neuroscience UK network is part of Lizzie's solution. With the network, she aims to connect everyone dotted across the UK who studies neuroscience and is interested in gender disparities in research culture. Lizzie has chaired two panels in the network's debut year, inspiring discussion and speculation around the interplay between gender and dementia, concussions and autism diagnoses.

Klenerman lab

Much of the research in the Klenerman lab involves degenerative disorders caused by misfolding proteins. Alzheimer's disease is a brain disorder that can cause dementia and is thought to be caused by protein clumping in the brain. These clumps build up into aggregates and these are the subject of Lizzie's research.

"I'm investigating a region of the brain called the middle temporal gyrus, and that is believed to be impacted by Alzheimer's disease," comments Lizzie. "It's an honour to be able to use these samples. They were once part of someone's mind."

She compares healthy and diseased human brain samples using custom microscopes that are built by the group. Protein aggregates are even smaller than cells and difficult to see even under a microscope, so to investigate these aggregates Lizzie adds different antibodies to the samples, that bind to specific proteins and fluoresce. For the first year of her PhD, she worked on refining these methods, and will soon scale up the sample size with hopes to define different candidate mechanisms responsible for Alzheimer's disease.

ISTAART ambassador

If completing a PhD and starting a nationwide network wasn't enough, Lizzie was also selected as one of 25 global ambassadors for The Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment. ISTAART is a global initiative supporting dementia researchers. Recently, she volunteered with the society at the Alzheimer's Association International Conference, the largest dementia research conference in the world.

The Alzheimer's Association funded her travel to the conference, which was based in San Diego this year. "I met so many inspiring scientists I would never otherwise have seen, and made friends with ambassadors from Australia to Brazil."

Elizabeth English representing ISTAART at the the Alzheimer's Association International Conference.

"I wanted to make a space for women in neuroscience at all career stages to talk about their experiences."

Elizabeth English

If you are interested in joining the Women in Neuroscience network you can find more information on their website, https://womeninneuroscience.wixsite.com/winuk

Paterson Group alumni: Where are they now?

A symposium to celebrate the work of Professor Ian Paterson and his recent retirement was held at Jesus College in May. We caught up with three former Paterson group members who returned to speak at the symposium, including his first and last group members.

Dr Victoria Steadman Vice President of Business Development and Integrated Partnerships, Sai Life Science Paterson Group member 1996-2000

Vicky Steadman has always enjoyed the exploratory nature of organic chemistry. "You come up with a hypothesis based on the literature and then you test it. If it doesn't work you go back to the drawing board and try something else. It encourages problem solving, which is useful in everything, not just chemistry," she says.

Vicky recalls the Paterson group as being very collaborative and supportive. "Ian was a great supervisor – he was friendly and encouraging, and always helpful with suggestions when things were not working as planned – which happens a lot in chemistry," she says. "We also had a bit of a tradition of going to the Panton Arms, which was a lot of fun."

After her PhD and a postdoc in the US, Vicky worked at Merck and then at GSK, but then decided to try a smaller company, so she joined Selcia, which worked with global pharma, biotechs and academics to carry out research on their behalf. "That was my first experience of a contract research organisation," she says.

During her 12 years at Selcia, Vicky gradually became more involved in business development, which suited her. "It's one of those roles that not everyone could do as a chemist," she explains. "You need to have a certain type of outgoing nature to get out of the lab – which is technically focused – into more of a relationship-building type of role."

Two years ago these skills propelled Vicky to join Sai Life Science, an international contract research organisation which works with companies globally to provide research and development services. Vicky's role is in business development, supporting the discovery side of Sai, with a particular focus on winning integrated partnerships.

Vicky was thrilled to be invited to speak at Ian's retirement symposium in May. "So many people who I haven't seen for years flew in from around the world, and it was interesting seeing all the different types of things they were doing– some are academics, some are high in industry, some in biotech, some patent attorneys. It was a wonderful reunion and fantastic to reconnect with people who I hadn't seen for a very long time."

Vicky was particularly pleased to speak at the symposium about how she had used Paterson's own boron-mediated anti-Aldol reactions and retrosynthetic approach to synthesise a set of molecules used in the treatment of hepatitis C and other diseases.

"What a pleasure it was both being a PhD student in Ian's group, and to be invited to speak at the Symposium. Many thanks to Ian for everything."

Dr David Laffan
Former Senior Director of Chemical Development, AZ
Paterson Group member 1985-88

David Laffan with Professor Ian Fleming at the symposium.

David came up to King's in 1981 to read Natural Sciences, and was surprised to find himself drawn to organic chemistry, which appealed to him because of its visual nature. "It's also an endless source of puzzles that you get to solve," he says.

On the recommendation of his friend Varinder Aggarwal (now Professor of Synthetic Chemistry at the University of Bristol), David applied to complete a PhD with Ian Paterson.

David enjoyed his time in the Paterson group, where he and Ian Mason were Ian's first postgrads. David's research project was on the total synthesis of erythromycin. "It was tough going," he recalls. "You never get as far as you hope to get – that's just life in research."

After completing his PhD, David spent six productive years at Lonza, a contract development and manufacturing company in Switzerland, before joining Zeneca in 1995 (which became AstraZeneca after the merger in 1999), where he has been involved at all stages of the drug development process, until his retirement in October.

At the symposium David spoke about the difficulties of achieving AstraZeneca's net carbon zero target for 2030.

"We've got a very good handle on what we can do for traditional small molecules, about how to make them more sustainable and improve the carbon footprint. But some new medicines such as oligo-nucleotides are much bigger and create more waste. We do have a plan for improving this, but we can't just optimise what we have – we have to re-imagine the whole process."

The company is working with the regulatory authorities and other pharma companies to meet their goals. "We recognise that it isn't simply our problem, and we're working with regulators, other companies and the UK government. It's important to acknowledge that this doesn't have to be an area that we compete with other pharma – we can collaborate."

"It's hard, but we know we can meet it. We know the direction we are going and that we will get better."

Dr Tegan Stockdale
Trainee Patent Attorney
Paterson Group member 2017-2022

From Ian Paterson's first student we come to his final group member, Tegan Stockdale, who passed her viva days before Paterson's retirement symposium in May, earning the title "Dr" just in time for the programme.

Tegan might never have come to Cambridge at all but for Professor Mary Garson, Tegan's friend and mentor at the University of Queensland, who was a contemporary of Ian here in the 1970s. Tegan recalls: "Mary said to me – you should spread your wings and apply to my old stomping grounds – and so I did."

And what a final student to have – Tegan had completed a Bachelor of Science in Chemistry and Biochemistry while also obtaining a Bachelor of Laws at the University of Queensland. She graduated the top of her honours year (roughly equivalent to a Master's integrated research year).

Tegan is now a trainee patent attorney at D Young & Co in London. "I basically had to choose between passions," she says. "But one of the things that truly inspires me now is seeing that scientific research come to fruition and becoming implemented in the real world."

Tegan is also completing a postgraduate certificate in intellectual property law at Queen Mary University of Law. "I'm enjoying everything about my job and course – I don't think there's a day that's gone by that I haven't learned something new," she says.

"There's this term in patent law and biotechnology called synergy. You add different things together but the combination of the parts is more than what you would have expected. I feel that putting together my science knowledge and legal knowledge in this profession is a good example of that. The sum of its parts is much, much more."

Women in Chemistry

Charlotte Allerton is Chief Scientific Officer, Anti-Infectives, and Head of Medicine Design at Pfizer, where the oral therapeutic for COVID-19, Paxlovid, was discovered.

Like so many, Charlotte Allerton was inspired to pursue her chemistry degree by a particularly dynamic teacher at school. At the University of Nottingham, Charlotte developed a deep love of both organic chemistry and mathematics, but, upon graduation these two loves meant Charlotte was torn between pursuing a career as an actuary (maths) or in the pharmaceutical industry (chemistry).

A visit to Pfizer in Kent clinched her decision: "I was attracted to the practical nature of the work and its link between the chemistry I'd learned and the potential to benefit human health," she says.

Starting with Sandwich

Charlotte's career with Pfizer started at the Sandwich site in Kent where she worked in synthesis technologies. She then worked on medicinal chemistry programmes at sites in the UK and Japan ("an incredible experience"), before moving to Connecticut in 2012 to become Head of Pharmacokinetics, Dynamics & Metabolism (PDM). "PDM is really about how our body deals with drug molecules," she explains.

Since 2016, Charlotte has been based at Pfizer's Cambridge, Massachusetts site as Head of Medicine Design, which she describes as a combination of medicinal chemistry, PDM, and Discovery Sciences, and where Charlotte's experience, in-depth knowledge, and leadership have contributed to the successful design of many of Pfizer's oral therapeutics.

EPNAC.com

Accepting the Heroes of Chemistry award on behalf of Pfizer's Medicine Design team.

Paterson group

Early in her career, Charlotte attended Jesus College where she earned a Master of Philosophy (MPhil). "I was becoming increasingly interested in the broader aspects of drug design and development, and I could see the advantages of having a deeper discipline knowledge," she says. Charlotte spent a happy and productive year in Professor Ian Paterson's organic synthesis group. "I had the advantage of being in industry and having the context of the application of organic chemistry in drug discovery, which made me hungry to learn as much as I could during my time there," she says.

Charlotte found the Department very welcoming. "Professor Steven Ley encouraged me to attend his problem sessions, and other academics allowed me to attend undergrad and grad lectures," she recalls, "So I made the most of my time there, made friends for life, like I did at Nottingham, and remain grateful to the University of Cambridge."

Charlotte returned to Cambridge earlier this year to speak at Prof. Paterson's retirement symposium. "I am indebted to Ian to this day for everything he invested in me, the mentorship he gave me, and the great things I learned from him and the other students in his group," she says. In return, Paterson recalls Charlotte as being one of the best students he ever had.

Designing a COVID-19 treatment

Charlotte explains that Pfizer's Medicine Design team are focused on designing and selecting the molecules that will ultimately be taken into clinical development to treat disease. She points out: "The properties of a molecule are determined at the moment of conception – whether a molecule will get to the right place in the body, stay there long enough, be administered safely and and have the therapeutic potential we want – all that rests in the molecule we select."

This challenge was clear when the team was asked to develop a treatment for the SARS-CoV-2 virus, which causes COVID-19.

Charlotte explains: "Inside the cell, the SARS-CoV-2 virus releases viral RNA, which is translated into two large polyproteins. The main protease breaks them up into smaller proteins so they can go on to form some of the viral replication machinery."

Nucleoside inhibitors block viral replication, but Charlotte's team, guided by research project leader and fellow Cambridge alum Dafydd Owen, decided to target the main protease (see page 20). "We decided to design a molecule that would block or inhibit the protease which, in turn, would prevent the breakup of the large polyproteins and essentially stop viral replication."

The team started with a molecule that had been designed at the Pfizer La Jolla site for the 2003 SARS coronavirus outbreak. "Unfortunately, it had been designed to be taken intravenously, and we wanted an oral therapeutic so we could treat early in disease and prevent people from progressing to very severe COVID-19 and hospitalisation," she says.

"Ultimately, in a four-month drug discovery programme, enabled by some very committed colleagues as well as many of our investments in artificial intelligence and structure-based drug design, we identified the molecule nirmatrelvir. It's a very potent binder to the SARS-CoV-2 main protease, and in doing that it has great antiviral activity in cells."

Nirmatrelvir is co-administered with ritonavir, which boosts its level in the blood by blocking an enzyme in the liver that breaks it down, to maximise clinical efficacy. Together nirmatrelvir and ritonavir make Pfizer's oral therapeutic, Paxlovid.

Paxlovid has gone on to achieve emergency authorisation in various countries around the world, including the UK. Pfizer's Medicine Design team received an American Chemical Society 2022 Heroes of Chemistry award for this achievement. Charlotte says: "To us it's another great example of the power of chemistry: a unique molecular structure potently inhibits the target in patients to have a positive impact on healthcare."

Women and diversity in chemistry

"Creating and working in an inclusive culture is so important to ensuring we can all do our best at work every day," says Charlotte. "During my career, I have been greatly enabled by strong networks, coaches and mentors – both men and women – who have helped me progress and learn.

"There is plenty of data available that shows diverse teams are the highest performing teams. Over the last couple of years, we have seen impressive work across industry and academia to develop therapeutics and vaccines for COVID-19, building on a foundation from years of scientific innovation, and I have reflected on the diversity of the teams that have enabled that work."

"Creating and working in an inclusive culture is so important to ensuring we can all do our best at work every day."

Putting the plan into action

Dr Dafydd Owen completed his PhD with Professor Steven Ley in 1998. He is now Senior Scientific Director, Medicinal Chemistry at Pfizer and was lead author of the 2021 Science paper which describes Pfizer's oral COVID-19 treatment, Paxlovid.[1]

"In the Ley group, I learned all about how to make molecules from scratch, which was valuable training. In industrial medicinal chemistry, you must combine all that knowledge to make a molecule with a purpose in mind, with a function and a potential use," says Dafydd. "But you can't test them unless you can make them, which is what I learned at Cambridge."

After his PhD and a year of postdoctoral research, Dafydd joined Pfizer's Sandwich site in 1999, where Charlotte Allerton, whom he had overlapped briefly with at Cambridge, had started a few years earlier (page 18). "The Pfizer Sandwich site had a particular reputation for medicinal chemistry excellence, and I wanted to work for the best," he says. "I wasn't wrong: Pfizer was leading a lot of the thinking in how industrial medicinal chemistry should be done at the time."

In 2011, Dafydd was given the opportunity to move to Cambridge, Massachusetts, where he started to focus on external collaborative work with universities and industrial consortia.

COVID-19 research

Then came 2020 and a pandemic which shook the world. In early 2020, Pfizer announced it was working on a vaccine.

Dafydd recalls: "On a Friday in March, Charlotte asked me, if we were to do this, how would you do it and what would you need? I started mapping it out and by the following Monday morning we had a plan to put into action."

The research team Dafydd and Charlotte assembled faced a number of obstacles, not least of which was lockdown. "We were adjusting to the shock of being at home and running a programme in a completely unconventional way, with the lofty goal of discovering a drug in time to make a difference to the pandemic, a process which would normally take 13 years. I take my hat off to the people who were given special permission by the authorities to go into the labs in early 2020, when there was no vaccine."

The research team started with a viral main protease inhibitor first identified by Pfizer in the SARS outbreak of 2003. That research had progressed as an intravenously delivered molecule, which is significantly different from the practicality of an oral drug. "My job was to lead and build the team from this starting point to a safe, effective oral therapy for SARS-CoV-2. Scientifically, the challenge was to transform an intravenous agent into an oral agent – to do this, we ended up having to change 75 percent of the structure. By September 2020, we knew we were on to something."

The team was able to harness Pfizer's research and development strengths, and Dafydd 's team worked with Charlotte and others to guide the molecule through all the standard safety tests. "We started in March, made the molecule by July, and by September it was ready for scale up."

"We started in March, made the molecule by July, and by September it was ready for scale up."

Dafydd Owen

The new treatment started Phase 1 clinical trials in March 2021. "To get to this point in less than a year by any stretch is amazing," says Dafydd. The pivotal Phase 2/3 clinical trial started in July 2021.

Dafydd recalls the moment he heard the results of the clinical trials: "In November 2021, we learned that the external Data Monitoring Committee recommended we cease further enrollment into the trial due to the overwhelming efficacy observed. It was a very, very proud moment as you can imagine. I'm not ashamed to say that I cried.

"It is a powerful situation for a chemist to have played a part in the invention of a molecule that can help the world in its fight against COVID-19."

Dafydd was lead author on the paper that shared the research story through the end of the Phase 1 studies, which was featured on the cover of Science magazine in December 2021. "It was an utterly unforgettable week."

Dafydd says: "I'd like to reiterate Charlotte's role in this. She is a modest individual, a great frontline scientist and a great research leader. It's amazing to me that our paths crossed early in life at Cambridge when we were both just learning to be organic chemists."

"It's an understatement to say it is special when your training has played a large part in saving lives."

[1]Dafydd R. Owen, Charlotte M.N. Allerton, et al, *An oral SARS-CoV-2 M^{pro} inhibitor clinical candidate for the treatment of COVID-19,* Science (2021) 374, Issue 6575, 1586-1593.

Legacy augments Todd-Raphael scholarship fund

The Todd-Raphael fund has been used over the years to support students in the Abell, Ley and Paterson groups. Now the fund has received a £5000 legacy from the estate of Professor Ralph Raphael's widow Prudence, who died last year.

Louise Birch, the first-ever Raphael Scholar, with her supervisor Chris Abell in 2011.

Ralph's daughter Sonia writes: "Tony and I both knew that Mum wanted to support the Todd-Raphael fund. We are pleased that we have been able to do this from her estate. It is good that there will be continuing support for students, something that was dear to both Ralph and Prudence's hearts."

Professor Ralph Raphael became Head of the then Department of Organic and Inorganic Chemistry in the early 70s. He was greatly respected for his outstanding synthetic work, but also for his inspiring undergraduate lectures and his warm sense of humour. When Raphael died in 1998, Professor Steve Ley launched an appeal for a Ralph Raphael Memorial studentship, which later became the Todd-Raphael Scholarship.

Former students

Louise Birch, who completed a PhD in the Abell group in 2004, was the first student to benefit from the studentship. At the time Louise said: "I am very happy to have this opportunity and I hope that I can do justice to Professor Raphael's memory." Louise is now a Principal Science (Computational Chemistry) at Sygnature Discovery, a drug discovery company based in Nottingham.

Another studentship holder was Simon Williams, who completed a PhD on the synthesis of marine natural products in the Paterson group in 2015. Simon recalls: "It was a good group to work in – Ian put together small teams to work on his total synthesis projects, which meant you always had someone to bounce ideas off of, and there was always a lot of camaraderie."

Simon, who is now a Team Leader at Syngenta in Zurich, says what he learned in the Paterson group has served him well. "The Paterson group gave me an excellent training in practical chemistry. The type of total synthesis we did there is often called the best sort of training for organic chemistry, and I agree with that. I still apply a lot of the techniques and actions I learned as a student in my job today. I also learned a lot about project planning and trouble-shooting for large total synthesis projects, which has been incredibly useful."

Other students to benefit from the studentship included Marcus Baumann in the Ley group (2010) and Daniel Holt in the Abell group (2007), and the fund can now continue to support deserving postgraduates who demonstrate potential in the field of organic chemistry.

Todd-Raphael studentship holder Simon Williams.

Our Twitter page is a unique place to hear from early career scientists in our department. Over 2022, three researchers have taken over our Twitter account to show you a day in the life of a chemist at Cambridge. Here are the highlights:

Trending now...

Your fast guide to the whos, whats and whys of the chemistry department.

Sandile Mtetwa
Group: Professor Andrew Wheatley

Sandile has an eye on increasing global access to clean energy. She is studying metal-organic frameworks to increase the lifetime that electric charge can be stored in a structure.

Diversity is a core driving force for Sandile and she is a co-chair that founded the organisation Africans in STEM. The mission is to highlight scientific contributions by Africans in STEM and create a network for collaboration and connection.

Sonja Osbild
Group: Professor Silvia Vignolini

With experience in dyes, Sonja wanted to approach colours from a sustainable angle. She is working on structural colours which rely on their molecular arrangement to determine their colours as opposed to pigments or dyes.

Sonja is developing coloured materials using plant fibres such as cellulose as the building blocks. Her focus is on testing and refining new methods to make structurally coloured films.

Oluwatomi Akingbade
Group: Sir David Klenerman

Tomi's work in an NHS COVID-19 testing laboratory was essential for realising her interest in early interventions and therapeutics. Her research involves the study of proteins called amyloids, which are the first proteins that have been linked with Alzheimer's disease.

During her scientific career, Tomi felt the need for a network of other black women scientists to share experiences and advice, so she started the Black Women in Science Network.

Save the date

For the chance to chat to a scientist on Twitter, join Srijit Seal who will be curating @ChemCambridge on the 7 December. Srijit is part of Professor Andreas Bender's group creating computer models that interpret data on human cells and how they respond to different toxins.

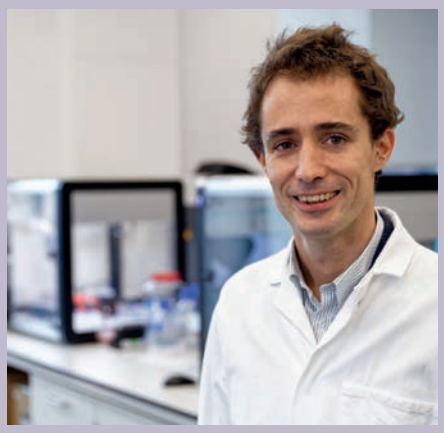
Noticeboard

Athena Swan Silver Award renewed

We are delighted to have been awarded a renewal to our Athena Swan silver award. Professor Melinda Duer states: "This is wonderful recognition of the huge amount of work by many people to make our Department a more diverse and inclusive place to live and work."

Department naming ceremony

A special ceremony was held in July to celebrate the naming of the Department, and to thank Dr Yusuf Hamied and his wife Farida for their generous support. The Yusuf Hamied fund makes it possible to attract the brightest students, early career academics and professors.



ERC Starting Grant Award

Dr Pietro Sormanni was awarded a highly competitive Starting Grant for €1.5 million from the European Research Council. This will enable the Sormanni group to develop a platform for antibody design, which aims at providing powerful tools to address biomedical questions, and for novel diagnostic and therapeutic applications.

Early Excellence in Science Award

Dr Yanira Méndez Gómez, a postdoctoral researcher and MSCA fellow in Professor Gonçalo Bernardes' research group, was awarded the Bayer Foundation Early Excellence in Science Award 2022 in the area of medicine, for her research involving antibodies.

Mental health plant sale

Dr Alexander Forse hosted a plant sale, selling over 70 plants, the proceeds of which went to Mind charity for mental health. The event raised over £700. Scientists looking for a green desk buddy had a veritable jungle of plants to choose from, all grown by Alex.

Frenkel awarded IOP prize

Emeritus Professor Daan Frenkel has been awarded the 2022 Institute of Physics Sam Edwards Medal and Prize. The award cites Frenkel's seminal contributions to the understanding of the kinetics, self-assembly and phase behaviour of soft matter systems.

Careers in medical science

Catch up with these alumni who are now early career researchers in medicinal chemistry, and find out how their PhDs at Cambridge have prepared them for drug discovery.

Dr Andrew Phillips at Sygnature Discovery.

SYGNATURE DISCOVERY

Dr Andrew Phillips

Group: Professor Ian Paterson
Thesis: Studies Towards the Total Synthesis of Patellazole B

After his PhD in synthetic chemistry, Andrew Phillips wanted to transfer into a medical chemistry role and Sygnature Discovery, a drug discovery service, was a great option. At Sygnature, Andrew has worked on Non-Hodgkin's Lymphoma and Cushing's syndrome drugs.

These drugs are still being tested in later stages of drug development and Phillips says it is rewarding to be part of the drug discovery process.

Whilst the pace and practice of Sygnature is different from academia, Andrew says his time at Cambridge put him in a good position to enter the role. He has also returned to Cambridge to host workshop days and practise interviews for careers in medicinal chemistry for current PhD students.

"My PhD was very synthetic chemistry oriented, and total synthesis gave me a broad education which was the perfect training for going into medical chemistry. Really, medical chemistry is best learnt on the job, and synthesising molecules can be as much of an art as a science," he says.

Aside from punting along the river, Andrew spent his time at Cambridge working towards elucidating the structures of patellazoles; a family of natural marine molecules that are toxic to human colon tumour cells. As a member of the Paterson group, he developed a route towards Patellazole B which has particularly high potency. He believes this gave him the experience and interest in pursuing medicinal chemistry further.

Carolina Orozco at AstraZeneca.

ASTRAZENECA

Dr Carolina Orozco

Group: Professor Sophie Jackson
Thesis: From antibody-drug conjugates to masked antibodies: biophysical insight for the rational design of future therapies

Carolina Orozco had the great fortune to study a PhD that fed into her first job. She describes her transition from academia in Sophie Jackson's group to industry at the labs in Granta Park with AstraZeneca.

During her time in the Jackson group, Carolina compared different antibody masks to define some of the different features of successful masks. Antibody therapy is often used in treating cancers, where a drug is attached to an antibody that will tightly bind to a cancer cell expressing a specific antigen.

Antibodies are designed to fight one specific antigen, such as a receptor on a virus, but they are not tissue-selective. This means that the antibody will always bind to this antigen even if it is found in healthy tissue, even at low levels. Drug designers want to prevent the antibodies they make from affecting healthy tissue and reduce unpleasant side effects.

One method to make the antibody drug delivery more specific is to place a mask over specific chain of proteins in the antibody. This is a small protein that covers up the antibody binding site that can only be removed by enzymes present within the tumour which cleave the linker between the mask and the antibody. Healthy cells can't remove the mask and stay safe.

"Designing a mask is not a trivial question," comments Carolina, "It needs to combine two antagonistic concepts; it must stay bound on the protein to inactivate whilst the linker is intact, but also come off the protein at the right point. The mask has to cover the binding site and come off when it finds a tumour."

To find the perfect balance, Carolina tested three different masking candidates with different masking properties and found that a medium affinity had the most success as a mask because it can be removed quickly. A high affinity mask would adhere to the drug successfully but then never come off.

Carolina is now applying the skills she's learnt around protein production and biophysics at AZ.

From the archives...

Shankar Balasubramanian and David Klenerman have received many accolades, including knighthoods, for their co-invention of Solexa Next Generation DNA Sequencing, which revolutionised biology and genomic medicine. But when did we first report on their ideas?

Shankar Balasubramanian's group in 1998 from Chem@Cam (Issue 3).

Shankar received his first mention in Chem@Cam Summer 1998 (Issue 2) when he was appointed as the Department's new organic lecturer at age 31. The article notes: "Shankar used to be a DJ specialising in R & B and early Hip Hop."

The next mention soon followed in the Autumn 1998 (Issue 3) edition, which reported on Shankar's early research into telomeres and combinatorial chemistry, again covering Shankar's work as a DJ when he was a student!

The first mention of Solexa sequencing came in Chem@Cam Autumn 2001 (Issue 12), in a report about media interest in Solexa, the new company formed by Shankar and David to commercialise their invention. The article (which unfortunately misspells Shankar's name) says: "Solexa will transform the identification of genes and will eventually have the capacity to map an individual human genome in a day."

How right they were!

The opening of the new company, Solexa, which hopes to exploit the researches of the dept's **Shankar Balusubramanina** and **David Klenerman** was the lead feature in the 'Business News' section of *The Cambridge Evening News* on 22 May. The article reported Sir Alex Broers' comments that the new company was 'brilliant'. Solexa will transform the identification of genes and will eventually have the capacity to map an individual human genome in a day. The article said that £2 million has been put into the company by venture capital investors Abingworth, but Solexa is now seeking a further £10 million to enable it to expand.

Scan from Chem@Cam (Issue 12) 2001.

Black Women in Science Network marks Black History Month

PhD student Oluwatomi Akingbade founded the Black Women in Science Network when she was an undergraduate at the University of Nottingham in 2018. "I wanted to connect with other black women in science, and sometimes it was hard to find them," explains Tomi. "I wanted to give them a platform – there are many excellent black women scientists, and we have quite a unique voice that people don't often hear."

Now almost five years old, the Network is still growing, with about 175 active members, and a total of 370 subscribers. Tomi has recently expanded the core team: "I have six more volunteers to help us with the various activities we're promoting," she says. This is a change from the days when Tomi was the sole organiser working from her bedroom.

The Network celebrated Black History month with a bit of a twist this year. Tomi explains: "Black History month is normally a month when we talk about historical figures in science, but for obvious reasons there really aren't that many historical black women scientists."

"Yes, there have been some amazing black women scientists. But why not celebrate how many black women scientists there are now and amplify their voices– it's the whole ethos of 'let's give them their flowers while they are here – not wait until they pass.'"

So the Network's event in October, held in the historic venue of the Academy of Medical Sciences in London, was an opportunity for black women in science and science-related careers to meet, network and celebrate their work. "It was a safe space to congregate and have a good time, which left everyone feeling energised. We wanted to acknowledge the past, but also to celebrate the fact that we are the present and the future."

With the new team of volunteers, the Network is going 'full steam ahead' for next year. "Up to now we have had monthly on-line brunch talks, but I'd like to organise a couple of brunch talks across different areas of the UK in person," says Tomi.

The Network will also be starting season two of its regular podcasts. Season 1 focused on black women and health in a series of 10 podcasts. "Our original plan was for six podcasts, but the response was so good, we expanded it to 10," says Tomi. The plan for Season 2 is also for 10 podcasts, focusing on the topic of race in research.

Tomi Akingbade is researching Alzheimer's disease.

"We'll also be turning five in April – last year we marked our anniversary by hosting talks on-line, but next year we'd like to organise an in-person event. I'd also like to launch another mentorship scheme," she enthuses. "Really now is a call for funding – we've done pretty much everything we can do for free."

The first Black Women in Science Network live brunch will be held here in the Department early in 2023. For further details, contact admin@bwisnetwork.com.

Upcoming events

11 January 2023

Cambridge Chemistry Energy Transition Lecture

Hanadi Sleiman, Professor of Chemistry and Canada Research Chair in DNA Nanoscience at McGill University, will speak at the annual Cambridge Chemistry Energy Transition Lecture. She will describe how her research group has taken DNA out of its biological context to build nanostructures for applications in biology and materials science. The lecture will be held in the BMS Lecture Theatre starting at 2pm.

Please email lks27@cam.ac.uk if you would like to attend.

Professor Hanadi Sleiman.

18 March 2023

Chemistry Open Day

Budding scientists from 5 to 105 are welcome at the Chemistry Open day, which will be held in the department on Saturday the 18th of March 2023, from 10am to 4pm. We will be returning to our pre-Covid format, with lots of hands-on activities like elephant toothpaste and lemon batteries to stimulate the curiosity of young chemists.

Organiser Emma Powney tells us the slime pond will once again feature in the fun – she says she has accumulated 150 kg of cornflour over lockdown and needs to put it to good use! No need to book - just show up and be ready for an adventure!

We gratefully acknowledge The Walters Kundert Charitable Trust whose support makes it possible for us to put on this event.

For more alumni events, see back of issue.

Professor Mary McPartlin 1932 -2022

It is with great sadness that we announce the death of Prof. Mary McPartlin, aged 89.

Mary McPartlin was Professor of Structural Chemistry at London Metropolitan University (formally University of North London), who had long-standing scientific links with our department.

She worked closely with Jack Lewis and Brian Johnson on cluster chemistry in the golden-years of metal-metal cluster bonding and theory in the mid-1970s. At that stage she had established herself as a specialist for the crystallography of particularly demanding polynuclear metal complexes.

Born in Glasgow in 1932, Mary studied chemistry at Battersea Polytechnic before accepting a position in industry. After four years dedicated to the development of water softeners for the company Permutit, she took the opportunity to re-enter academia, first at the University of Strasbourg to work there for a year and, subsequently, a teaching position at Hatfield College (now the University of Hertfordshire) in 1960.

Less than two years later she was asked by a colleague at the University of New South Wales to recommend a gifted student as a doctoral candidate there. Mary indicated she would be interested, and it was during her PhD under G.A. Barkley in Sydney that she was trained as a crystallographer.

As a structural chemist at the University of North London, she not only solved the structures of most of the key clusters of the heavier group 8 metals but also made many

Mary McPartlin and Lutz Gade discuss osmium cluster structures in the department, 1990.

significant contributions to the conceptual theoretical framework of cluster chemistry, resulting in her promotion to a personal chair around 1990. The collaboration with Cambridge led to frequent regular visits to the department, and coach trips of Cambridge PhD students to her lab on Holloway Road. She was the recipient of the 1987 RSC Structural Chemistry Award and invited as a key speaker at many conferences throughout the 1980s and early 90s, including the Platinum Metals Conference in 1990 held at Cambridge.

After her retirement Mary became a visiting professor here and continued to work in collaboration with Dominic Wright for close to ten years. She took the greatest pleasure in solving the most challenging crystallographic problems she could find in the building and elsewhere (in addition to solving the *Times* cryptic crossword puzzle almost every day). Mary was an inspiration to so many students both internationally and here at Lensfield Road and throughout her career – an exceptionally cultured, class-act in every sense and very much 'your highly intellectual great aunt' to so many young researchers who had the fortune of working with her.

Dominic S. Wright
(University of Cambridge)
Lutz H. Gade
(Heidelberg University)

Designer antibodies

Bespoke antibodies designed and tested in the lab are a promising tool to speed up drug design.

As research becomes more specialised and niche, we need groups to actively take disparate streams of knowledge and weave them together. Take antibodies and computer models. The Sormanni lab is developing a computational pipeline to simplify antibody discovery.

Antibodies are key tools to address questions and enable discoveries in biomedical research, are the workhorses of most diagnostic assays, and are increasingly used to treat a wide range of diseases as therapeutics, including cancer and neurodegeneration.

The current main method to discover new antibodies for a given target is to immunise animals, which has moral, time, and expense drawbacks. This new pipeline draws from a huge database of interacting fragments and it is much faster than conventional laboratory-based approaches.

Dr Mauricio Aguilar Rangel, first author of this research[1], said "We are excited about the results of our approach, as it opens the door for studying new targets of biological relevance. But most important, we see this as an important stepping-stone for developing a more comprehensive way of designing antibodies in silico".

A perfect antibody

The computer initially scans the target that scientists want to address, for example, a cancer cell receptor or a viral protein. Then, the computer finds candidates that could bind to the chosen target and ranks them based on their compatibility with the target and on other properties. For example, their solubility. The scientists then take the top candidates and test their binding to the target in the lab.

A perfect antibody will attach itself only to its target and not to other proteins or surfaces. For example, in antibody-based anti-cancer therapy, the antibody latches onto the cancerous cell and either stifles its growth or destroys it whilst leaving healthy cells alone.

"We are aiming to make this pipeline time and cost-efficient so that it is simple to use in routine laboratory settings," comments Dr Xing Xu, a research associate in the Sormanni lab, who is working on the next phases of this research.

When the computer software suggests an antibody, the antibody should be a potential lock to the target site. However, so far the locking is relatively weak. It is thus scientists like Xing's job to refine it further so that the antibody strongly binds to the pre-determined surface. If this can be achieved, one can easily acquire an antibody with a high binding affinity to the pre-selected surface, which in most cases is a functional area related to the development of diseases.

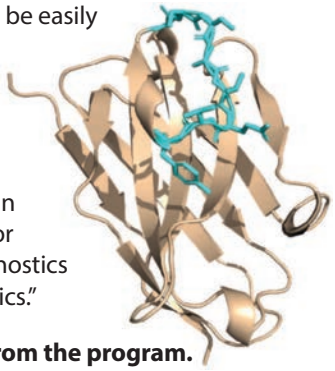
From screen to bench

Starting from a computer-designed antibody, Xing deploys methods of in vitro directed evolution to optimise it further. This approach mimics evolution in a test tube, and starts with the construction of a library of variants of the original antibody, by introducing mutations on its binding surface. Then, subsequent rounds of screening are used to isolate from the library those variants that bind most tightly to the target. The result is a new antibody with improved binding characteristics over the one designed by the computer, but still binding to the same region selected with the software.

"Instead of the conventional antibody, we work with a specialised format, called a nanobody, which is around ten times smaller of the size of a full-length antibody. These small bullets have more versatile uses and are potentially useful for developing into a drug to target these hard-to-reach proteins," Xing adds.

"When it comes to the blood-brain barrier, the antibodies inside our bodies cannot penetrate it effectively, which means that it is complicated to treat conditions in the brain. So, that is one reason why we are working with nanobodies," comments Xing.

"Plus, nanobodies are naturally more stable and can be easily produced in single-celled organisms, facilitating the downstream development in a large-scale for research, diagnostics and therapeutics."



A 3D model from the program.

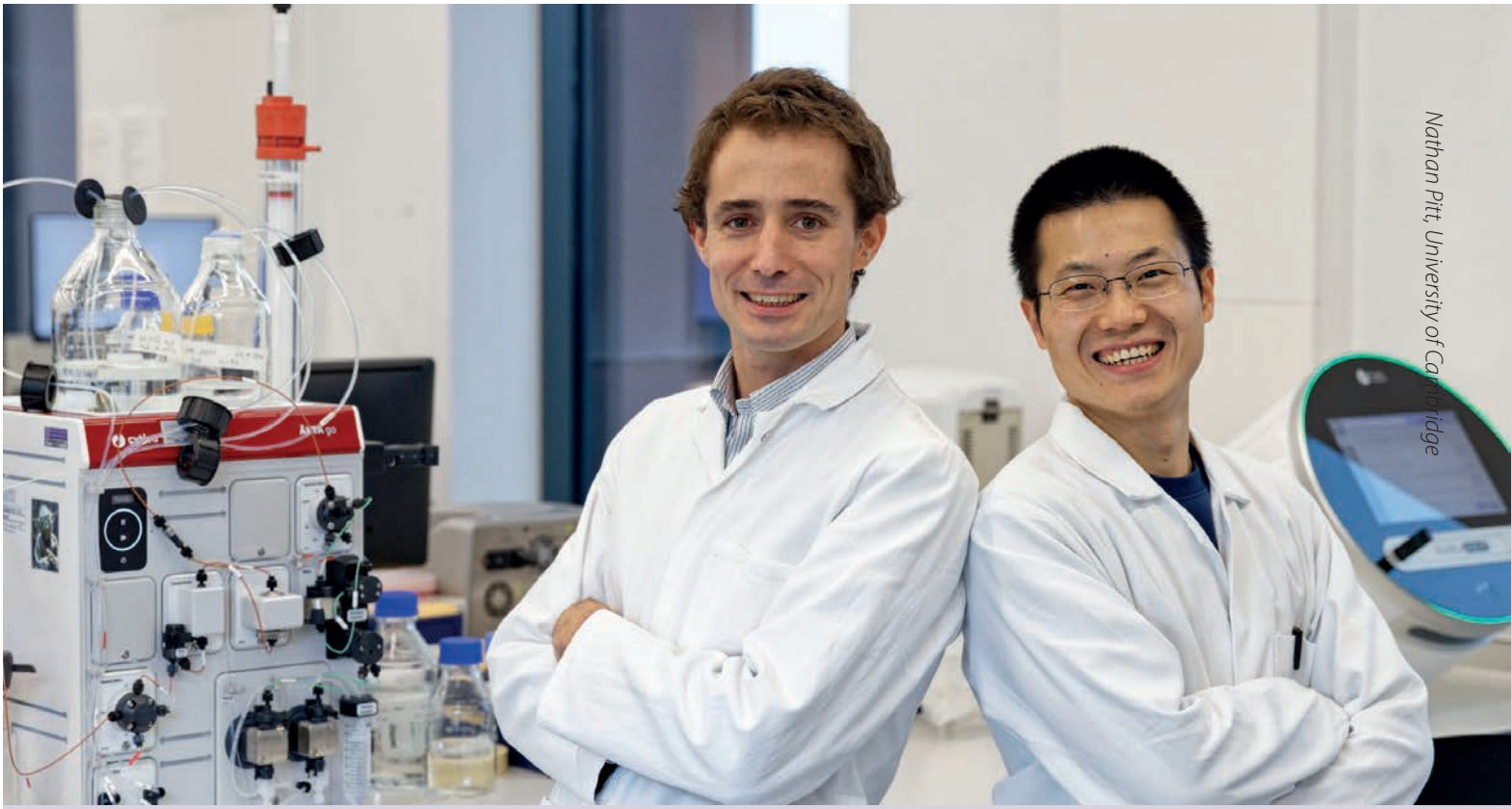
Make it simpler

An antibody is made from roughly 1500 amino acids. A nanobody is a smaller section of an antibody, around 120 amino acids long.

Covert infiltration

The blood-brain barrier is a membrane that protects the brain from toxins. It is also notorious for preventing large molecules, like antibody drugs, from reaching the brain. Antibodies are too large to pass through the blood-brain barrier but nanobodies may be small enough to slip through. This opens up a new avenue for drug discovery for brain conditions.

[1]Rangel et al., *Fragment-based computational design of antibodies targeting structured epitopes, Science Advances* (2022), 8, 45.



Nathan Pitt, University of Cambridge

Dr Pietro Sormanni and Dr Xing Xu.

El-Eff-Tee

A lateral flow test that uses a single drop of blood.

In the past three years, lateral flow tests like the rapid at-home Covid tests, have cemented themselves in the public vocabulary. With the same momentum as liquid diffusing up a strip of paper, a newly established partnership between the Sormanni Lab and 52 North Health, a Cambridge Cancer Research UK spinout, is redefining how we think of lateral flow tests (LFTs) to test for life-threatening conditions. Dr Pietro Sormanni and his research group are designing and testing new antibodies to power LFTs that use a drop of blood from a finger prick to test for infections in immunocompromised people.

The LFT the researchers are working on checks for certain white blood cells in the blood called neutrophils, which are a good indicator that a healthy body is fighting an infection. Immunocompromised people, such as patients on chemotherapy, have low neutrophils and are at risk of a condition called neutropenic sepsis, as infections that could normally be fought off easily can quickly become life-threatening.

Three dimensional modelling

The lab uses 3D computer modelling to design the antibody molecules on the strip, which change colour when they sense infection. The computer examines the structure of the protein that they are testing for, for example a receptor on the surface of neutrophil cells, and the software predicts the sequences of antibody molecules that will react to that protein. For example, the COVID-19 virus has a unique spike protein that is bound by antibodies on the strip, which causes LFT tests to react and produce the dreaded red line.

The computer algorithms developed in the Sormanni group trim down the time and expense of antibody discovery. They also target specific surfaces of proteins which is crucial when designing antibodies for specific human cells, like neutrophils. Because many cells in the human body share similarities, the researchers must design antibodies that target the small differences.

Results in 10 minutes

The LFT being produced by 52 North Health, called NeutroCheck, will show a result in around ten minutes. Sormanni hopes it will help patients and doctors make quick decisions about the need for antibiotics and hospitalisation.

"We have tested our device performance in over 200 blood samples from Addenbrooke's Hospital, Cambridge and we have performed user testing with patients interacting with the device in around 40 individuals," states Dr Saif Ahmad, an academic consultant oncologist at Addenbrooke's Hospital and co-founder of 52 North Health.

"Where do I see this technology going?" speculates Sormanni, "Well, potentially more sophisticated LFTs where there are multiple bands on a single test that can test for multiple things. Or potentially bands that are printed with different densities so that you end up with data about the quantity of the target protein and not just its presence or absence."

This partnership is supported by a UKRI KTP grant, and 52 North Health will commence the NeutroCheck clinical validation study in 2023.

Upcoming alumni events

Dr Hamied 'Frontiers in Chemistry' alumni webinar

A rainbow of colours from your fruit bowl

Wednesday 14 December 2022 6pm to 7pm GMT

Register at www.alumni.cam.ac.uk/events/dr-hamied-frontiers-in-chemistry-alumni-webinar-a-rainbow-of-colours-from-your-fruit-bowl

Find out how Professor Silvia Vignolini and her Bio-inspired Photonics group are making everything from biodegradable glitter to edible, iridescent hydrogels using one of the world's most abundant and sustainable materials.

Professor Silvia Vignolini "Making colours with your 5-a-day".

PhD student Thomas Parton "Self-assembly with a twist".

Dr Peter Wothers alumni lecture and reception

Jane Marcet's remarkable *Conversations on Chemistry*

McGrath Theatre, St Catharine's College, Cambridge and online Saturday 11 February 2023 5pm to 8pm GMT

More information at https://chemistryalumnilecture.eventbrite.co.uk

In a lecture marking the UN International Day of Women and Girls in Science, Dr Peter Wothers will reveal how in 1806 a pioneering woman demonstrated that chemistry was not just for men. Followed by drinks reception.

Dr Peter Wothers "Jane Marcet's remarkable *Conversations on Chemistry*".