PHENOTYPE

Issue 37 | 2022
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LETTER FROM THE EDITORS

Dear readers,

You are holding in your hands a very special issue of Phenotype. If you are joining us for the first time – a very warm welcome! *Phenotype* started out in 2008 both in print and online as a journal of the biochemical society at the University of Oxford, and now in 2022 our editors span the globe. They are graduate students, clinician scientists, and postdocs who join us from Charité Universitätsmedizin and Max Delbrück Center for Molecular Medicine in Berlin, from Research Center for Molecular Medicine (CeMM) in Vienna, from the Scripps Research Institute in San Diego, from Harvard University, and of course from Oxford University.

The mission of the journal is to inform scientists and those who like science about exciting developments from the perspective of those who drive research – postdocs, graduate students, and medical students. As such we publish short scientific reviews, research articles, news &views, and Op-eds.

Issue 37 begins with an exclusive address by the Vice Chancellor of Oxford, Dame Louise Richardson on p. 4.

In this issue we would like to acknowledge the tireless work of our editors from across the globe with a collage called "Faces of *Phenotype*" overleaf.

We are grateful to entrepreneur, scientist and a visionary Christian Tidona who tells us about bridging industry and academia in his institute BioMed X, p. 6-7. The interview is followed by a narrative of a postdoc who experienced and survived the BioMedX bootcamp (p. 10-11).

In June 2022 the first Oxford Berlin Summer School on Molecular Mechanisms of Inflammatory Diseases took place and brought together renowned scientists from Oxford University, Charité Universitätsmedizin, and DRFZ. See our report and photos from the event on p. 13-15.

For our behind the scenes look at Cell Press we sat down with the Senior Publisher Dr Jessica Miles. Jessica manages the Trends series of reviews journals spanning life sciences and chemistry and leads a team of 16 PhD-trained, expert Editors to drive editorial direction and strategy across the portfolio and support innovation across Cell Press (p. 16-17).

In the past we have covered stories of academics transitioning to industry, however the opposite also happens. On p. 18-19 Grace Pixton shares her story of going from academia to industry and back to academia.

A story of courage, perseverance, and hope: a Ukrainian scientist Alina Frolova tells us about doing research and supporting other scientists amidst war in Ukraine, p.20-22.

We stay committed to addressing the issues of mental health. Our anonymous contribution in this issue focuses on doing science with bipolar disorder, p.23.

On p. 24-25 group leader Georg Busslinger (CeMM) tells us about his exciting journey to become a group leader.

Professor Ana Pombo has done her research both in Oxford and in Berlin. In "Aspire to Inspire" she reflects on life and research in both cities p. 26-27.

On p.28-29 find out about membrane integrity during protein transport in a mini review by Rebecca Harry.

Bakhrom Muinjonov discusses the intriguing hypothesis of association of Epstein Barr Virus and multiple sclerosis (p.303-1),

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Enjoy!

Marina Kolesnichenko & Stefania Monterisi
Co-Editor-in-Chiefs of Phenotype

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Cover contributor

Confocal image of the CA3 area of the hippocampus showing parvalbumin-expressing interneurons (cyan) in SNAP25 cO brains where layer 5 pyramidal neurons are silenced.

Cover design by **Florina Szabo**, DPhil student at Prof. Zoltan Molnar's group at the Department of Physiology, Anatomy & Genetics, University of Oxford.

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VICE CHANCELLOR'S ADDRESS

Oxford University Vice Chancellor Dame Louise Richardson addresses *Phenotype* readers across the world.

The academic community across the world, like so many others, has been appalled by the humanitarian catastrophe that is unfolding in Ukraine. While we have been overwhelmed with admiration for the bravery that is being shown, our hearts go out to those whose lives have been disrupted, homes destroyed, and family members killed in the unprovoked invasion of the country. We extend our sympathies too to those brave Russians who have sought to distance themselves from the actions of their government.

At Oxford, we have a long tradition of assisting refugees and, as in other universities, we are united in a shared commitment to do what we can to help. We are offering up to 20 scholarships for undergraduate students from Ukraine, and another 26 scholarships for graduate students to obtain masters degrees. We are also working with CARA, with the Royal Society, and with personal connections to provide support and a safe place to work for Ukrainian academics. In addition we have established a fund to help support initiatives to assist those affected by the crisis.

When the war is over there will be a major job of reconstruction to be done. We look forward to working with our Ukrainian colleagues to rebuild their universities and their country.

Professor Dame Louise Richardson AAAS AcSS FRSE RIIA
Vice-Chancellor, University of Oxford


Photo by John Cairns

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. . . a challenging and rewarding option for Oxford Biochemists

Training as a Patent Attorney is a career path that will enable you to combine your understanding of biochemistry and related disciplines with legal expertise. You will leave the lab environment yet remain at the cutting edge of science and technology, applying your knowledge and skill in a commercial context. Your role will be to help to protect intellectual property assets and grow businesses.

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BEST OF BOTH WORLDS

Interview with Christian Tidona, founder of BioMedX

We sat down with Christian Tidona, who is a scientist, biotech entrepreneur, business angel, and a founder of numerous successful companies. Christian studied molecular biology and received his doctoral degree from the University of Heidelberg. As a scientist, Christian authored numerous seminal scientific papers, and his book *The Springer Index of Viruses*, is a key encyclopedic reference for virology.

Throughout his entire professional life, Christian's focus was to seed innovation at the interface between academia and industry. In 2013 Christian founded BioMed X – an independent research institute that tackles most pressing and challenging questions in biomedical research. BioMed X offers scientists recruited to the institute a unique opportunity to answer such questions with the support and collaborations from both industry and academia. The institute started 17 research groups since its creation.

***Phenotype:** Christian, it's very nice to see you again and*

thank you for doing this interview. So first of all, what inspired you to found BioMed X?

Christian Tidona: Very good question. I started studying biology, and at that time your goal would have been to become a professor as there was no real alternative. I always found that I don't fit this.

One of the reasons why I started BioMed X was to allow young people to explore alternative paths: to allow people to learn about a potential industry career or about a potential career in a startup. Academic research is good for publishing papers, but not much of this research will end up helping people. For the young researchers who are looking for purpose in their life and for creating impact for the benefit of patients, there are not many places.

And in our case [BioMed X] is about you, about new drugs, new diagnostics, and extending healthy lifespan. And most of that is accomplished via basic research. I tried to create an ecosystem where young biomedical researchers can have additional career perspectives and a general purpose and impact for the benefit of patients.

***Phenotype:** What does BioMed X stand for?*

CT: We have this slogan – two worlds, one Institute, and that is what it is all about. It is combining the best of these two worlds, academia and industry, which are usually quite separate. It is about allowing young, creative academic researchers to come up with ideas, but at the same time get the guidance on how to translate that into something that someday will help the patient. This combination of these two worlds is at the basis of BioMed X because we are all focused on biomedical research and the X originally stood for the unknown, for what we wanted to discover.

***Phenotype:** Who are you recruiting to BioMed X? Are you recruiting mostly scientists or entrepreneurs?*

CT: It is all about research at BioMed X. We are recruiting young talents from around the world: PhD students, Post-docs, master students. When they join BioMed X they will be exposed to the pharma industry and in some of our programs also to entrepreneurs, and then they will learn everything else they need. It is not a prerequisite to have experience in pharma.

What you need to bring to BioMed X is deep scientific knowledge, passion for science, willingness to share your ideas, and communication to co-create with other teams. Everything else you will learn at BioMed X.

***Phenotype:** How is BioMed X different from a usual research Institute?*

CT: One aspect that we have already touched upon is the interface between academia and industry. We combine

this typical academic research environment with advice, guidance by mentors, and know-how to generate data sets, which then from an industry side would be regarded as validated datasets. This is something which you usually do not learn at the university. Usually your work ends as a publication. There is this discussion at the moment about reproducibility of published research. And this of course is a big hurdle. I call this the new disease - biology validation gap. This is the reason why big pharma is not moving into a new disease biology, because what they read in papers is not validated according to their standards. Most of that, in other words, is not reproducible. And that's what we're helping our teams to focus on - experiments that have the right controls and that have the right number of parallel experiments to be statistically significant.

That is one of the main features. And another feature is also that we put a lot of effort into our culture, you will find our core values in every room: in our labs and offices in the campus of the university of Heidelberg. These [core values] are - cross leverage, cross-pollinate, and aim high. Cross leverage means growing by helping others. We have a family style environment where we expect the neuroscientist to help the electrical engineer that is building sensors and the immunologist to help the bioinformatician.

Second is cross pollination. We embrace diversity because this is the basis of innovation. The more different perspectives from which you look upon the same problem, the higher the probability that a truly innovative solution will happen. Our fellows come from all parts of the world from all religions, all genders, all ethnic backgrounds and cultures. And that's very important for this type of environment. And then - Aim high: We want people who want to grow as talents, as leaders, as people, and make the best use of that time in such an environment.

***Phenotype:** So who should apply?*

CT: Ideally it would be scientists in the early part of their career. They have already maybe their first publication or even several publications, they have worked in one or two labs and are now at the point in their lives where they have to make a tough decision. So first decision- will I be a professor or someone in an industry, or someone in a startup?

This is the first decision. And usually there is no easy way back because for example, to become a professor, you need to have a continuous publication record. So if you spent a couple of years doing something else, getting back [into academia] will be very tough.

Second decision: you could be at the point in your life when you want to start a family and you want to be in a place where your spouse also has career opportunities and where you can raise children. Our scientists get a lot of support in relocating with their entire families. We organize visas and jobs for their spouses, and if they have children, we organize kindergarten or school spots, and new homes because it is very important.

So it is not just work – it is also life, which is important. Talent is distributed evenly across the globe, but the opportunity to use the talent is not. And this means we need to make sure that we build these local innovation ecosystems that are in the top 10 lists of the top talents of the world, where they want to start a family and where they want to be creative.

***Phenotype:** When you invite people for an interview they go through a bootcamp. So what inspired you to create the bootcamp?*

CT: Actually, it came out of another initiative in which I was involved with the company Merck, the world's oldest pharma company, which is more than 350 years old. There I developed something which is called the Merck innovation cup, which we are running this year for the

12th year. The idea was to have a worldwide call for applications, to have top talents, and then to invite the best ones to a local bootcamp in order to develop new ideas for the big questions of Merck.

There was an additional aspect, which was bringing them together with the retirees from the research department who would then provide mentorship to these young people. This bootcamp ends with a cash prize for the winner. And then once I sat over lunch with the former head of the discovery research of Merck, and I said that we are putting so much effort in identifying talent. We bring them here, we run the bootcamp, and then we give them a cash prize and send them back home.

So why don't we keep them for a while? Merck agreed to sponsor the first three research groups and that's how BioMed X started.

***Phenotype:** Now you have 17 groups that completed these projects, and some people got positions in academia and some went to industry. Could you tell us about your alumni – where are they now?*

CT: One example is Balca Mardin. It is an interesting story! When she came to the bootcamp, everybody thought she was very junior (in her early thirties).

Every team has a different starting budget, and this was a very high budget. At the end of the bootcamp, everyone agreed on Balca, but since she was very junior, [we said] let's start with a lower budget, and if she performs well after one year, she gets the rest of the budget. Of course she met all the milestones, got the rest of the budget, and then in the following years, got even further budget increases. At the end of the year she was running the biggest group at BioMed X. After five years she got an offer from Merck and she and one of her postdocs now runs the group for another three years after she left. They had top publications and [I am] so very proud of that! And this is not a single case. About 50% of our fellows go to industry and 50% to academia.

We have a joint interest with our pharma partners, that we want to publish well.

We have around 200 alumni and they stay connected with the ecosystem. Whenever we post a call it is shared with the friends and it's getting bigger that way. It is really nice to see how people grow and then they become heads of departments and heads of institutes. The family just becomes bigger.

***Phenotype:** For postdocs and PhD students in academia it is very difficult getting foot in the door with big pharma. All of your collaborations are with these top-notch companies. What kind of companies have you collaborated with so far?*

CT: Our first partner was Merck. [We also partnered with] Boehringer-Ingelheim, Abbvie, Johnson & Johnson. Now we have started a new site in Israel that is focusing on startups – it is called AION labs. And partners there include Merck, Pfizer, AstraZeneca, and Tennova. We are focusing on artificial intelligence for drug discovery and development, and we also have Amazon as a partner.

Within these pharma companies we are working with different therapeutic areas - neuroscience, oncology, immunology, respiratory sensor development.

***Phenotype:** Where can people find out about upcoming calls and how, who do they contact?*

CT: We publish all our calls, publications, and also job offers on our website. The attractive part for young talent is that you put in your CV and your data once into the system and then whenever you see something you like, you come back, you update and you press apply.

***Phenotype:** What kind of advice irrespective of whether people are applying to BioMed X or not, would you give to early career researchers?*

CT: First of all, it's very important that you use every single minute of your professional life to build a network, which means whenever you meet someone, you come across, someone you think you can learn from, or someone who could be a collaboration partner, or just someone whose ideas you like, connect on LinkedIn, stay connected, and work with those connections.

Second is to find yourself a mentor - someone who is at least one business generation older than you and who you can ask for advice.

During my startups period, I always had 2, 3, 4, seniors, who I was lucky enough to call my mentors. And whenever I was not quite sure whether I was going in the right direction, I just called them up and had a cup of coffee and then discussed new ideas. This is very important. You can find them everywhere. You go to a conference and you see someone you admire, then you shake his or her hand and you sit and you introduce yourself and say that you would like to share some ideas. I've never seen a senior person say no, I'm not going to talk with you.

So you just need the guts to go there and shake hands.

Who are you going to become? An academic, an industry leader, or a start-up entrepreneur? You cannot do everything at once. And in order to make this informed decision, gather as much information as possible, and find a place that allows you to grow and to gain additional skills outside of your immediate box. ■

BOOTCAMP

The BioMed X Bootcamp Experience

This is Swathi Lingam, now a postdoctoral researcher at BioMed X. She now develops 3D in vitro models to investigate protective tissue factors in autoimmune diseases. Prior to joining BioMedX, Swathi Lingam was a research fellow at the National University of Singapore, developing novel cellular therapeutics against degenerative retinal diseases and studying the correlation between retinal ageing and degeneration. Before that, she was a postdoctoral scientist at DPAG, Oxford, where she studied the function of an ABC transporter in diabetes. She completed her PhD in Biochemistry and MSc in Cancer Research from the University of Manchester, where she studied two ABC transporters involved in multidrug resistance. In her free time, she enjoys reading, blogging about science, and staying fit by swimming and kickboxing. Swathi was selected as one of the postdoc candidates for the bootcamp at BioMed X. Unlike other candidates who were on site, Swathi participated from Singapore virtually via MS Teams.

Swathi's team was slected as one of the two finalists, but did not win. Due to Swathi's exceptional performance on the team, BioMed X decided to hire her. This excerpt is from Swathi's notes from the bootcamp. In summer 2021, Swathi joined BioMed X as a postdoc in the group of Mojca Frank Bertoncelj (winner of the bootcamp).

Day 2: Tuesday, 9th March 2021

14:00 Heidelberg (21:00 Singapore)

Another day of hard work and brainstorming and researching, but at least we have a brilliant idea for the project!

So strange to interact with Monica and Toni (not real names) through a giant screen, but we make an excellent team with complementary scientific expertise! Seems like M and T have an endless supply of cookies and coffee. I sadly have to make my own coffee and wash up after.

16:00 Heidelberg (23:00 Singapore)

We are now polishing our presentation for Christian's visit. The presentation is awesome. T has a talent with BioRender so it looks like something from a posh brochure.

18:00 Heidelberg (01:00 Singapore)

Christian and Thomas (Head of Research BioMed X) just left. The project is rubbish! Apparently, it is too academia and would not work in pharma... We are skipping our dinner/ breakfast. More cookies and coffee for M and T. The box of snacks next to my chair is looking worryingly depleted. Back to the drawing board!

22:00 Heidelberg (05:00 Singapore)

M and T have an argument about the project. And I feel myself losing the will to keep going. Coffee is not working anymore! Christian should be here any moment again.

23:00 Heidelberg (06:00 Singapore)

The project is still too academia...

00:00 Heidelberg (07:00 Singapore)

Thomas and Christian went to bed. Now it is (just) the mentors from J&J joining us via MS Teams every couple of hours. They just take us apart!

01:00 Heidelberg (08:00 Singapore)

I call it a night. T and M carry on. I will continue tomorrow (today in a few hours!).

Day 4: Wednesday 11th March 2021

03:00 Heidelberg (10:00 Singapore)

My circadian rhythm is conspiring against me and refuses to let me sleep. Must focus on the benefits of being in a different time zone! I wish I could deliver caffeine intravenously.

This is "dry-run" presentation day. While I was passed

out, M & T put together rough slides. It takes a few hours and I do take a nap in the middle, but they're looking presentation worthy!

10:00 Heidelberg (17:00 Singapore)

I am on my millionth cup of coffee.

16:00 Heidelberg (23:00 Singapore)

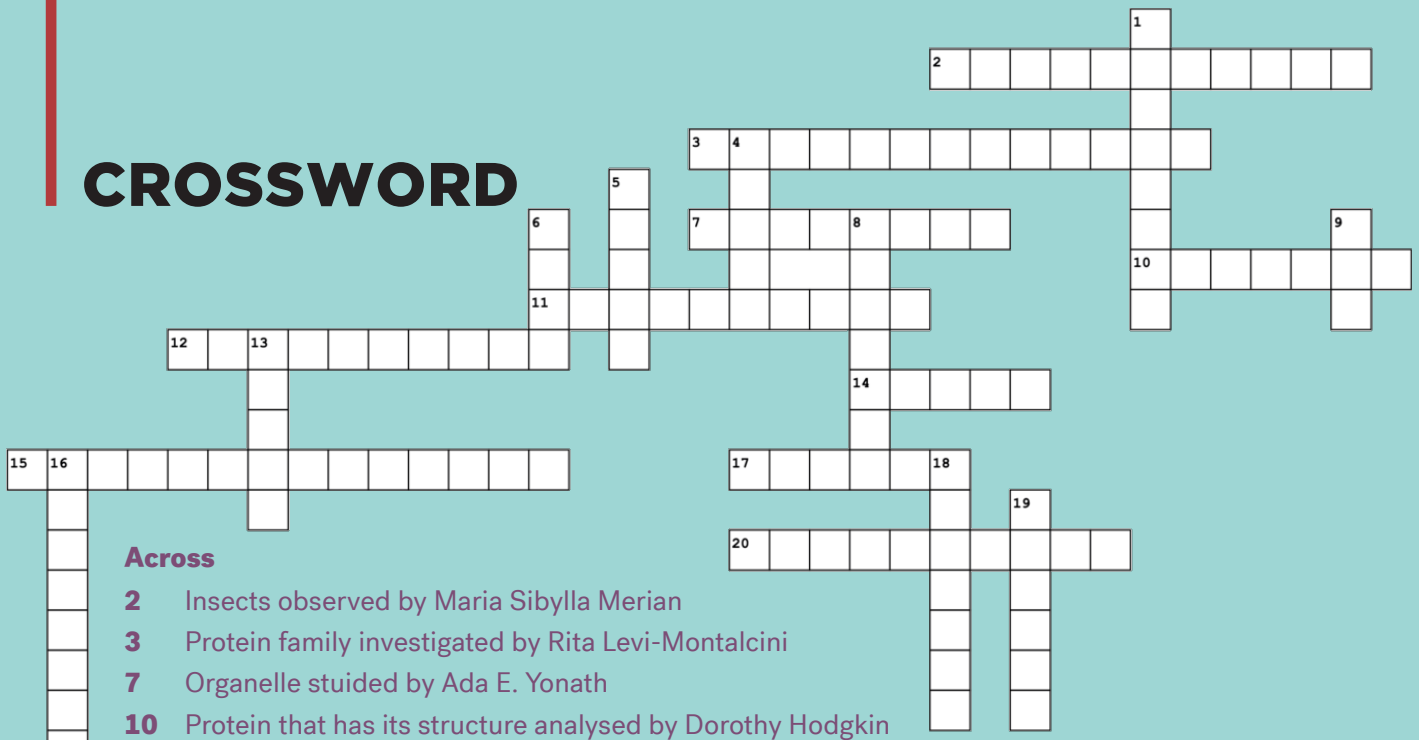
M decided we will all present the project. It feels like I spent years working with the two of them already. I think we are all on autopilot.

20:00 Heidelberg (03:00 Singapore)

So the presentation was 85% successful, according to Christian. I think we did well and - what's more important – we are still intact as a team. One of the biggest surprises was the interaction between members among some other teams. Lack of sleep obviously makes the inner jerk come out in some people.

I am hopeful we will do well on the big day. Go team ST&M!! ■

CROSSWORD



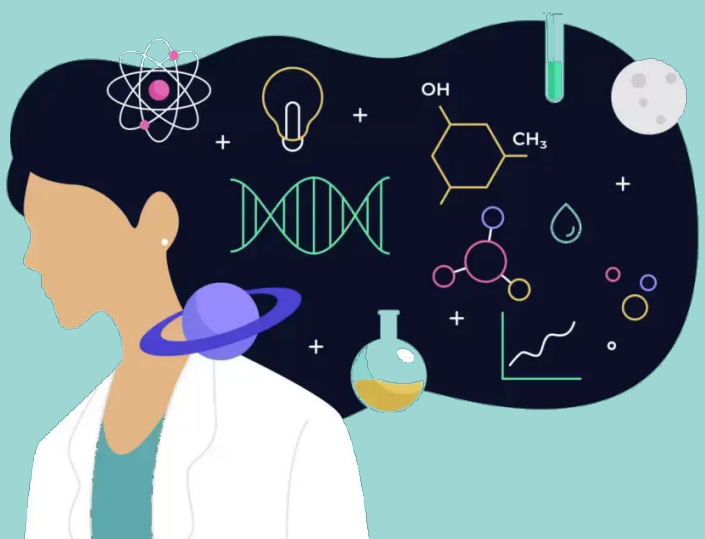
Across

2 Insects observed by Maria Sibylla Merian
3 Protein family investigated by Rita Levi-Montalcini
7 Organelle stuided by Ada E. Yonath
10 Protein that has its structure analysed by Dorothy Hodgkin
11 Animals studied by Jane Goodall
12 Stuided jumping genes
14 Received the Nobel Prize for her work in rational drug design
15 To what invention led the research of Alice Evans?
17 Technique discovered by Doudna & Charpentier
20 Enzyme co-discovered by Elizabeth Blackburn

Enjoying the crossword?

The first few persons to send over a completed crossword with the correct solution will receive a small cash prize from *Phenotype*! Our email is oxphenotype@gmail.com.

Theme: Women in Science

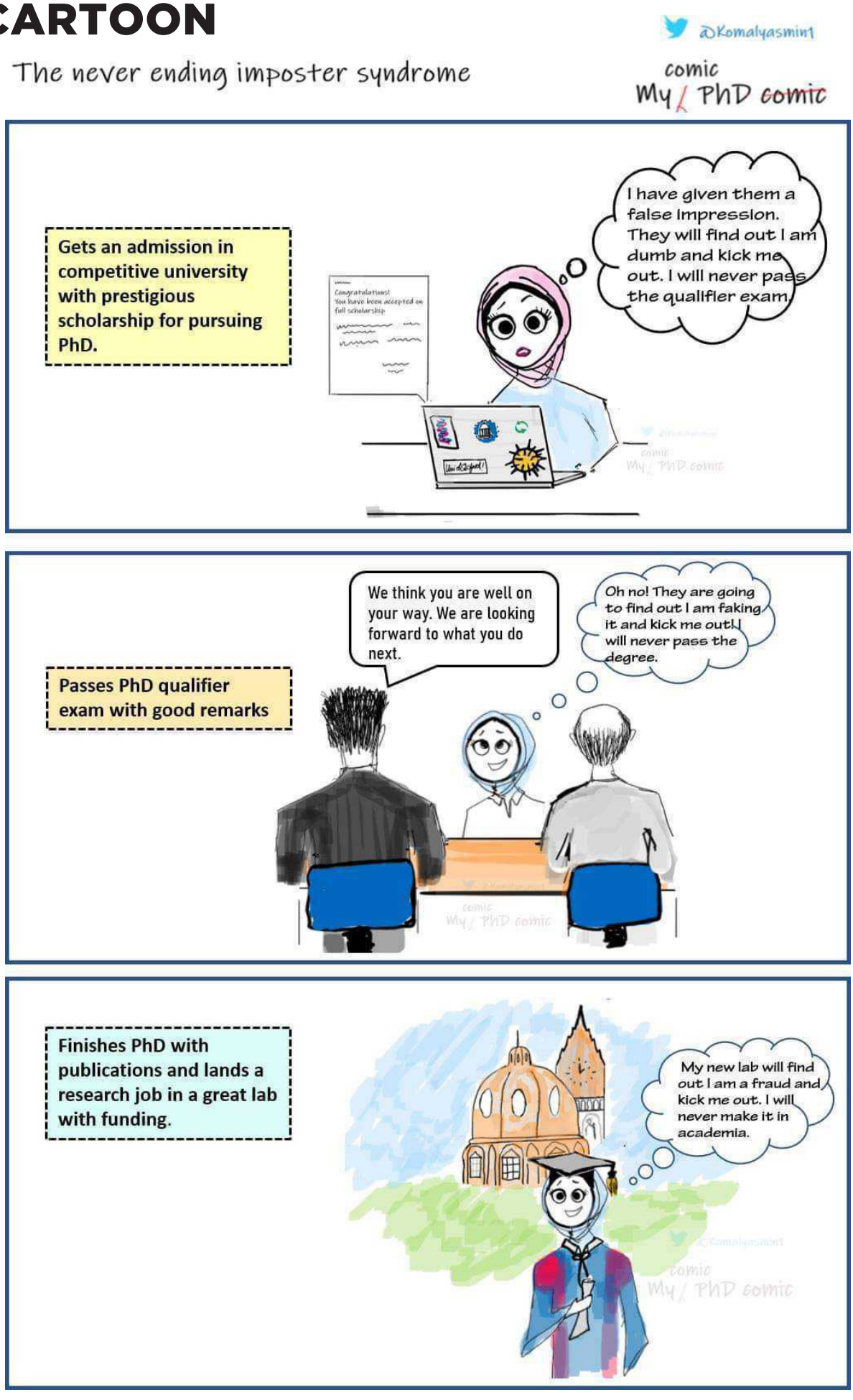


Down

1 Took the first photo of DNA
4 Immunological method co-invented by Eva Engvall
5 First person to receive two Nobel Prizes
6 Discovered hundreds of genes for odorant sensors
8 Discovered sex chromosomes
9 Virus co-discovered by Françoise Barré-Sinoussi
13 The Shark Lady
16 Substance discovered by Tu Youyou to treat malaria
18 Element discovered by Ida Eva Noddack
19 Phages discovered by Esther Lederberg

CARTOON

The never ending imposter syndrome



5 years into the OxBer Partnership

On June 7–8th Oxford-Berlin Partnership hosted a symposium in Berlin. Speakers and panelists included Oxford Vice Chancellor Dame Louise Richardson, Chancellor Lord Christopher Francis Patten, and other prominent Oxford academics. The Partnership was established almost five years ago, to maintain and promote Oxford's vital research collaborations with Europe, partly in response to the UK referendum and Brexit. See also our previous issue 34 (interview with Professor Alastair Buchan, founding director of Oxford in Berlin). The Partnership is headed by Professor Andy Hurrell, who was appointed as the Academic Director on the Oxford side of the partnership, and Professor Çiğdem İşsever as the Academic Director in Berlin.

Over the last five years, the Partnership has supported over 80 research projects and numerous workshops (including the Oxford Berlin Summer School on Molecular Basis of Inflammatory Diseases (p. 14 of this issue), in which over a thousand faculty, researchers and students have been involved. Over one million euros have been provided directly to the activities by Oxford and the four institutions within the Berlin University Alliance (Humboldt, Charité, Free University, Technical University), as well as over another million euros in Grand Challenge awards, funded by the Berlin University Alliance, in Global Health and Social Cohesion. All this activity has generated some 12 million euros in additional funding from third party sources.

The symposium held on the 7–8th of July was the first of its kind and it brought together diverse researchers, artists and faculty spanning disciplines from politics, medicine, to literature, and to performing arts. The panels comprising experts from both cities and beyond discussed topics including responses of universities to the pandemic, impact of Artificial Intelligence on our lives, and how academia connects with public through production of knowledge.

The event was organised by Alasdair MacDonald (Oxford Coordinator of the Oxford Berlin Research Partnership), Emilia Boehm, Anna Craemer, Helen Paul, and Maike Bonn and the Directors Çiğdem İşsever and Andy Hurrell.

For more information about the Oxford-Berlin Partnership and future events, see https://oxfordinberlin.eu.

Phenotype: After two years of virtual meetings, this event was everything one could wish for! It was truly the best of both worlds of Oxford and of Berlin. The symposium was held in the beautiful Berlin Brandenburg Academy of Sciences in the center of Berlin, and brought together top academics across diverse fields. Indeed, you could not have wished for more illustrious panel members. For example, the discussion on how Berlin and Oxford Universities responded to the pandemic was led by Vice Chancellor Dame Louise Richardson, Professor Axel Pries (Dean of Charité Universitätsmedizin Berlin), Professor Heyo Kroemer (CEO of Charité Universitätsmedizin Berlin), and Professor Chris Conlon (Head of Experimental Medicine Division, Oxford University). Do you risk allocating 1 million pounds to development of a vaccine that may fail? Louise Richardson talked about the historical decision to fully support Covid research at Oxford. Heyo Kroemer discussed the impact of the pandemic on the medical staff at Charité that was (is) on the frontline during the pandemic.

The structure and organisation of the symposium was one of its main strengths: it provided for numerous opportunities for participants to interact with the experts and the speakers during the panel discussions and also during coffee breaks and lunches. In the evening, the speakers and panelists joined the audience for an informal drink (and more discussions!)

We are looking forward to more such events both here in Berlin and of course also back in Oxford! ■

Oxford Event at the Embassy: Marina Kolesnichenko, Vice Chancellor Dame Louise Richardson, Prof. Alastair Buchan

Impression of the OxBer MBID Summer School 2022

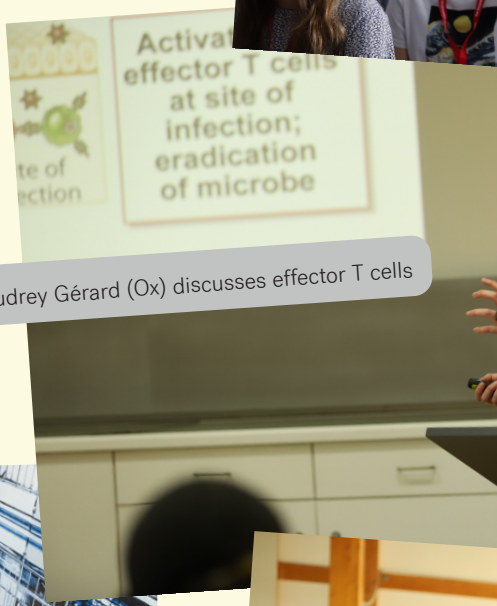
By Julia Hecker. Julia is a PhD Candidate in the groups of Britta Siegmund and Carl Weidinger at the Charité – Universitätsmedizin Berlin.

On June 9–10th I attended the Oxford-Berlin School on Molecular Basis of Inflammatory Diseases. I decided to apply because I wanted to learn more about inflammatory diseases and their mechanisms and meet and discuss with other PhD students and PIs about their latest research.

During the first day of the school I was impressed by the excellent and engaging talks and the exciting data presented by the speakers and also by the PhD students during the poster sessions. I really enjoyed the breaks and the poster sessions where I could easily interact with other students from Oxford. I think that Oxford and Berlin have both excellent scientist and great techniques at their sites and we should interact more to get the best out of it!

I am looking forward to repeat this summer school and hope next year we can visit Oxford! ■

Participants from Charité: Julia Hecker, Sonja Walling, Adrian Huck



Prof. Audrey Gérard (Ox) discusses effector T cells

Over 100 participants at the Summer School

Second day of fun!

Organiser Prof. Ahmed Hegazy

Prof. Andreas Diefenbach (Ber) gives another brilliant talk..

Plenty of opportunities to ask questions.

Prof. Max Löhning (Ber) shares his exciting research.

Keynote Speaker: Prof. Fiona Powrie from Oxford. *Phenotype* interviewed Prof. Powrie in Issue 35.

OxBer poster session: bringing two worlds together!

"We believe that one of the best ways to strengthen the relationship between Oxford and Berlin is to teach and learn together, sharing our ideas, knowledge, and expertise. The OxBer Summer School unquestionably achieved this, setting the scene for future collaborations and team working."
– Co-organiser of the event, Alexander Clarke, University of Oxford.

INSIDE CELL

Behind the Scenes with Jessica Miles, Publisher at Cell Press

Jessica Miles, PhD, is the Trends Publisher at Cell Press. She manages the Trends series of reviews journals spanning life sciences and chemistry and leads a team of 16 PhD-trained, expert Editors to drive editorial direction and strategy across the portfolio and support innovation across Cell Press. She is co-chair of the journal editorial policies on sex and gender reporting in research workstream of Elsevier's Gender Working Group. Previously, Dr Miles directed the high-profile Cell Symposia conference series and worked in the legal sector prior to joining Cell Press. She holds a doctorate in Microbiology from Yale University.

Phenotype: **Were you always interested in the world of publishing? Could you also talk about your journey into your current role of Senior Publisher for Trends and Society journals?**

Jessica Miles: I think it's a bit of a running joke in scholarly publishing that few people grow up dreaming of entering this line of work. Although I've been interested in science communication from an early age, after learning about the life and work of Michael Faraday, I had never envisioned becoming a publisher. In retrospect, it's an absolute perfect fit with my interests! I think part of the reason I hadn't considered publishing was that I didn't really know of anyone in this industry until after I applied to work at Cell Press.

Phenotype: **You've spent some time working for a patent law firm. How was that experience?**

JM: It was absolutely fascinating being at the nexus between research, law and policy, and industry and commercialization. In a lot of ways, it is not dissimilar to being in publishing because you are constantly getting to learn about really exciting science before it's published, and you are often working with scientists directly to help them translate their work beyond the bench. I was also fortunate to work with clients who were pursuing patents in many different countries, and there was a lot of opportunity to collaborate with international teams of patent practitioners.

Phenotype: **How hard was it to move from academia into a role in Patent law and then Cell Press?**

JM: I would say it was more "effortful" than "hard," because the process was enjoyable, but also time-consuming! For me, I did quite a lot of informational interviews with patent practitioners (attorneys, patent agents, and PhD-trained scientists working in patent law) to learn more about the career path, day-to-day work, and how best to prepare myself for this type of career. I tried as much as possible to keep in touch with the people I interviewed and found, eventually, that one of them was hiring. I applied for that opening and was (happily!) selected. If you are an attorney in a firm, building new relationships and identifying new practice areas for your group are very important skills for long-term success, so I tried to view these early activities as an opportunity to practice skills that would be helpful later on in my career.

Also, with any job search, the only jobs that are truly available to you are the ones that are hiring when you're open to new job opportunities. That is to say – you can spend a significant amount of time preparing to move into a particular industry, but it's important to keep in mind that the end goal is identifying attractive roles that are open when you are ready to make a change. Sometimes, there can be a gap between what you think you'd like to do, in theory, and, in reality, what roles are available in the timeframe you're searching. Oddly enough, I had not planned to join Cell Press in the role that I wound up taking: there was an opening for a Scientific Product Manager at the time I was looking to

make a transition from patent law, and I looked at the job description and thought, "I've never seen anything like this before, but it looks fantastic, and I think I could do this."

Phenotype: **You currently manage around 16 editors working on different journals. How has that experience been?**

JM: It's been a delight and an honour. I liken my role to that of a conductor of an orchestra: all of the players are immensely talented and very capable of performing individually, and my role is really to help create and translate a unified vision to our diverse group. Our journals span life and social sciences, as well as chemistry, so I'm constantly exposed to interesting ideas and different research communities.

Phenotype: **In your opinion, what's the future of publishing when it comes to transparency and reproducibility?**

JM: Being at Cell Press, we have a long tradition of innovation in transparency and reproducibility and we're very proud to have led and contributed to pioneering initiatives in this area, such as STAR Methods, STAR Protocols, transparent peer review, Figure 360, and the CRediT taxonomy. I know we'll always be thinking creatively about how publishing should continue to evolve in these areas.

Phenotype: **What's the aim/scope of Trends journals and how are they different from other review journals?**

JM: Since the first Trends journal was founded in 1976, we've brought the world provocative, cutting-edge reviews written by inspiring and authoritative voices in science. Over the years, we've cultivated a platform to empower our authors to pave the way for future research and push the boundaries of conventional thinking.

Our articles do more than simply summarise the literature; they synthesise the data, put forward new ideas and challenge existing ones, and provide a unique point of view and critical insights into the direction of the field.

Phenotype: **Do you believe good mentorship can transform careers? If yes, could you elaborate a bit more on that.**

JM: Absolutely! I've been both a mentor and mentee, which has given me the opportunity to learn from a talented and diverse group of individuals – some of whom I wouldn't have worked with closely otherwise. Mentorship has profoundly expanded my perspective, helping me envision new possibilities. When I consider all of the mentorship relationships I've enjoyed, it's really wonderful to feel as if I have the support of a global village and, in turn, to be able to provide that same support for others and celebrate their successes. Along the way, I've received indispensable career advice on everything from overcoming day-to-day obstacles to rethinking my approach to career development.

Phenotype: **Finally, do you have any suggestions for scientists, especially women, who are interested in taking up editorial roles. What sort of skills and experience are you looking for in prospective candidates?**

JM: My advice is: go for it! Especially for women: Cell Press's professional editorial team currently comprises 67% women, and 61% of our editorial leadership roles are held by women, so you will be in good company.

You don't need previous experience in publishing – we will make sure you get the training and development you need. We look for PhD-trained candidates with a passion for science and communication. Since our teams work closely with authors, we particularly value strong interpersonal skills and the ability to work collaboratively to solve problems. Candidates with these characteristics come from many different backgrounds, so we're more interested in a prospective candidate's commitment and capability than in that person's specific skills and experiences. ■

CellPress
Science that inspires

Returning to Graduate School after 7 Years in Industry

By Grace Pixton. Grace is a PhD student at Scripps Research, La Jolla, California.

Bluntly speaking, leaving a job with a high salary and competitive benefits for the uncertainty and near minimum wage stipend of graduate school was difficult. I was comfortable working for a large biotechnology company. I enjoyed hour-long workout sessions at the complimentary gym, company sponsored volunteer opportunities that connected me with my community, and countless company accolades that rewarded even small victories. Offering programs that promote flexible work-life balance has become pivotal in attracting and retaining talent [1]. This company, like many large biotechnology firms, strives to provide a balanced atmosphere for employees at every level, allowing them to achieve personal goals alongside career successes. During my employment, I was able to coordinate the fundraising of thousands of dollars for local charities, negotiate materials transfer agreements to access first-in-class technologies, and deliver engineered monoclonal antibodies to dozens of internal immuno-oncology research initiatives. While amassing these professional achievements, my schedule allowed for daily fitness, meal preparation, and time with family and friends. Thanks to a competitive compensation package I was able to meet my financial goals while still having extra left over to take yearly trips abroad.

The holistic atmosphere at this company allowed employees to flourish and inspired me to have a greater impact on the biotechnology industry. But despite repeatedly seeking opportunities to spearhead new research initiatives, I was redirected to routine tasks. Many of my post-baccalaureate colleagues experienced the same limitations. **While our freshly minted doctoral colleagues were enjoying trips up the career ladder, we were stuck on the proverbial monkey bars.** Lateral movements within the company were welcome. But it was clear that less than a decade into my career, I had hit a ceiling. The biotechnology industry, particularly in research and development, is highly credential-driven, and without an advanced academic degree, it is difficult to progress beyond a junior level. Some of my colleagues gambled on dedicating years of reliable work to the company, hoping they would be rewarded with a more challenging role. But the majority who take this route will see yearly cost-of-living and title increases, with no real change to their responsibilities. Those who are promoted to senior positions without a doctorate degree are often underestimated by their coworkers and must outperform their peers just to be seen as equals.

One option for the brave among us is to take an entirely different gamble with a startup company. Larger firms compete for the same talent pool, and often offer very similar benefits packages [2]. Startups, however, are as variable as they are many. In the lean business model of a startup, employees who demonstrate aptitude are quickly awarded commensurate title and responsibilities, regardless of credentials. This offers a path for some to amass experience in a senior position and expand their skills [3]. However, new companies can be mired with inefficiency and uncertain futures. Without a human resources department fluent in unconscious bias, many startups suffer from various "isms" among leadership that blind them from recognizing talent. Even in the results-driven environment of startups, employees with a doctorate are more likely to navigate these pitfalls successfully.

This degree demarcation can be frustrating from the post-baccalaureate perspective, but it serves a useful purpose in industry. There is high demand for qualified employees at every level and companies invest heavily in training new talent to excel in their role [4]. However, filling an advanced position with an untested employee is not a risk companies are eager to take. The preference is to recruit talent with a demonstrated record of high achievement to fill the senior ranks. It is the crucible of doctorate-level education that demonstrates a scientist's mettle. By earning a doctoral degree, a scientist builds a trusted reputation as a leader in the field. It demonstrates a growth mindset and resolute determination in the face of challenges. I understand the value of talented employees in biotechnology and I am willing and able to invest in myself. So, while the transition was hard, the rewards will be worthwhile. Completing my PhD opens the pathway of advancement and ensures that exciting opportunities await me at all levels of my career to come. ■

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#STANDWITHUKREAINE

Science Amid the Terror of War

Alina Frolova obtained Bachelor's and Master's degree in Computer Sciences from National University of "Kyiv-Mohyla Academy" in Kyiv. Currently she is a Junior Research Fellow in the Systems Biology Group at the Institute of Molecular Biology and Genetics of National Academy of Sciences of Ukraine, Kyiv. She also holds the same position in Kyiv Academic University, where she teaches at the Department of molecular biology and biotechnology. She is a member of MetaSUB international consortium and founding member of MetaSUB Europe society. Her research interests include integrative analysis and regulatory networks inference of gene expression data, human placenta development in health and disease, single-cell sequencing, and environmental metagenomics.

Phenotype: **What was your lab and group like before the war?**

Alina Frolova: Our lab has operated since 2009 and was the first laboratory of Systems Biology in Ukraine (https://sysbio.org.ua/), organised by Prof. Maria Obolen'ska (Maria) in the Institute of Molecular Biology and Genetics in Kyiv. Back then, it was quite a novel direction, and I think it remains novel, because it's harder to model biological systems as a whole, as opposed to studying its parts separately. I expect Systems Biology is going to develop even more rapidly now, because of all the new high-throughput methods, which allow us to study molecular processes at very high resolution. Personally, I like that we conduct both wet and dry lab research. It makes me feel more connected with the data, even though I'm focused more on computational analysis. Usually, I also try to understand wet lab protocols precisely, despite my pure Computer Science background. This makes it possible to plan our experiments as a whole or explain artifacts we see in data. At the moment, we have 5 permanent employees and 8 students.

Phenotype: **What were your plans for 2022?**

AF: We had lots of plans! Many talented students joined this year and we started new collaborations. We also started teaching a Systems Biology course, since our institute opened a new department together with Kyiv Academic University. Maria was particularly excited about this, as it's hard to recruit people in the lab who have experience in bioinformatics (more common is pure biology or math background), so we need to educate more people if we want to nurture the scientific community.

Additionally, I was planning to submit a paper with my students right before the war. I was extremely happy and proud about this, because we had only Ukrainian authors and the work was presented at a prestigious conference in the field of computational biology - ISMB/ECCB. However, we obviously couldn't meet the fast track deadline – it's impossible to concentrate while you're being bombed or displaced.

As a MetaSUB PI in Kyiv, I was also planning to continue metagenomics studies within the consortium (http://metasub.org/). We collect surface samples every year in Kyiv metro (at the stations and inside trains) during City Sampling day. One of our most recent MetaSUB papers was chosen as the Best of Cell Press 2021 and I'm particularly proud that I represent Ukraine in this consortium. In the paper, we presented the first systematic, worldwide catalog of the urban microbial ecosystem with a focus on antimicrobial resistance and novel viruses. This type of study is especially important in the COVID-19 era. But unfortunately, I don't think we will be able to collect any samples this year...

Phenotype: **Where were you when the invasion started? Did you believe it would happen? How did you inform your lab?**

AF: I was at home and woke up at 5AM when it started because of loud explosion noises. I live between Kyiv and Vasylkiv, so we heard lots of shelling. Vasylkiv has a military airport and there were some heavy fights there in the beginning of the war. A few times, the missiles

Photo by Alina Frolova – a destroyed Russian tank, taken on a volunteer mission in Ukraine

fell quite close, but luckily we are safe and no property was damaged... for now, at least. I kind of believed the invasion would happen, but I was still slow to prepare, as I didn't think it would reach all of Ukraine; rather, we expected it to start from the East and South. For example, I was planning to buy a new electricity generator in case we would be cut from the main power line, so clearly I had the inclination to prepare. I don't think the invasion is possible to explain to people who didn't experience it firsthand (and I hope never will), but we are extremely stressed. For the first few hours, it was hard to stop shaking. Now, I'm not bothered by artillery or missile sounds. It's very scary - to get used to war.

We didn't really have to inform people because within a few hours most Ukrainians knew what happened. However, I contacted my students to double-check their phone numbers and later, I tracked if they relocated or needed any help. All of them are safe and some are already back in Kyiv.

***Phenotype:* What is your day life now?**

AF: My day is not very exciting. Since the beginning of the war, we need to turn off the lights when it gets darker and adjust our schedules, for safety reasons. So I have finally fixed my sleeping schedule to go to sleep and wake up early. Now, what bothers me the most is that I can no longer walk my dogs in the forest (it's now prohibited since forests could be mined). We are limited physically despite living in a nice green area. I did some volunteer work, but I don't have a car, so I'm not very efficient at this. Instead, I decided to focus entirely on what I do best: science and helping scientists. However, people need to understand that it was almost impossible to focus on anything during the first month of the war. We had to adapt somehow to insane levels of stress. Despite all of that, I didn't want to leave the country. I wanted to support my family (who can't leave) and at least be useful somehow to people around me. Although I might consider visiting my collaborators in Europe when the situation is more stable in Kyiv.

At the moment, I'm trying to get back to some regular schedule with my students (albeit remotely). I'm also organising external (non-Ukrainian) mentors for them, as I'm afraid I no longer have the mental capacity to supervise them myself. I want them to finish their Bachelor and Master's diplomas successfully.

I would like to emphasise that all of my colleagues, friends, and other Ukrainians are doing amazing things: volunteering, donating, and helping people in need. It's a daily norm for us now, so I don't consider myself any different. Besides, I know extremely brave scientists who have literally risked their lives to save people from occupied cities, despite constant shelling. For example: Anton Senenko and his colleagues. They motivate me to do more.

***Phenotype:* What do you want people outside of Ukraine to know? And scientists to know?**

AF: First of all, I want people to understand that only a small fraction of scientists can leave Ukraine. I'm really surprised that people do not understand martial law. In particular, it prevents any male between ages 16–60 to leave the country. There are exceptions (e.g. single father), but only a small portion of scientists are among them. In other words, it's not enough to be a scientist, to be able

to cross the border. Even with students it's not clear. Officially, foreign university students who have student ID cards may continue their studies abroad, but this does not always work in practice. It's still poorly regulated and I hope it will improve, but for now, 75–80% of scientists remain in Ukraine. **Many don't want to leave, either because they want to support their families or they strongly believe it's their duty to stay and defend our people and territory, or volunteer in any way possible.** At the same time, many researchers require support of different kinds. Those researchers who have lost their workplace, had to stop their research and change their job to a non-scientific field.

Phenotype: **How can the scientific community help Ukraine and Ukrainian scientists?**

AF: It's now very important to create new grant programs and non-residential fellowships to support Ukrainian scientists remotely, and, if possible, remote positions and internships. As I explained before, many scientists can't leave and on top of that, I think that even after the war ends we will still need remote opportunities. This is because we will have to basically restart our science from scratch, both physically (because some institutes' buildings were destroyed, especially in Kharkiv), and mentally (because it's extremely hard to get back to normal life with PTSD and facing financial problems).

There are at least two volunteering organisations that try to help researchers:

1. https://scienceforukraine.eu/ - They focus on helping researchers and students who had to flee Ukraine, but also have a filter for remote positions that are available for researchers staying in Ukraine.

2. https://www.uascience-reload.org/ – A group of Ukrainian researchers (myself included) who try to support scientists in Ukraine in many different ways: both now, as well as working on a plan to relaunch science when the war is over. Personally, I'm searching for ways to establish digital fellowships through various NGOs.

Phenotype: **What are the hardest things both personally and professionally?**

AF: The hardest thing to see is how many people die in the cruelest way possible: being tortured, raped, and humiliated by Russians. Also to receive news about how your colleagues were killed by Russian bombs and coming to the realisation that it won't stop anytime soon.

Phenotype: **How can we, as readers and junior researchers, help?**

AF: I want people to understand that what is happening in Ukraine is pure genocide. I'm not saying this based on news, but rather on the stories of people I know. We are being killed simply because we are Ukrainian and we dared to choose freedom and European values, such as human rights, free speech and democratic society. Sadly, many fall victim to Russian propaganda, even within Europe, and even among scientists. As researchers and human beings, we must always stay critical, not only in science but in politics and everyday life. We can't abstain from politics completely, because we shape our society and we are responsible for the choices we make. So, I hope the readers stay informed on what's happening in Ukraine and think critically about the news they're receiving. I'm extremely grateful for all the help we received so far, and I think I've been particularly blessed with my foreign colleagues, who are extremely supportive. I'm looking forward to many more connections that we may establish in the future. ■

OPINION

The Disabled Academic: An Endangered Species

Opinion piece – An anonymous contribution from a DPhil student at the University of Oxford.

When I began my DPhil in 2017, I was regarded as a promising and talented student. I know this, as my supervisor wrote this in my first evaluation. I scribbled it down and kept it in my wallet – so I could look at the tiny scrap of paper whenever I felt overwhelmed. I still have it even now, 5 years later.

Around a year into my studies, I noticed I was becoming a bit... odd. My emotions were turbulent and hard to predict. I would feel bright and confident some days, then horrendously tired and grumpy on others. It was like a swing in a playground, pushing me up and down.

As further stress was heaped on, I was yanked out of the playground and thrown onto a rollercoaster. Where I previously felt exhausted, I now spent days weeping in bed. Where I previously felt energetic and sunny, I found myself unable to sleep, with a voice in my head telling me that I'm the next Da Vinci and that my brilliance would be remembered through the ages. Surprisingly, I didn't get much work done during this time.

I was eventually diagnosed with bipolar disorder, and I am now disabled. Even with taking fistfuls of toxic lithium pills every day, I am "better" but will never be "well".

When I began to phase back into my DPhil, I was high with a fresh wave of agony as I realised that things could never be the same again. Having faced the battle of recovery, I saw that I would be facing a never-ending war of being disabled in the workforce.

While 80% of non-disabled people are in employment, only 52.7% of disabled people are (only half! – accordingto the UK Department of Work & Pensions)*. To boil down a dreadfully complex issue: the contemporary workplace, within the capitalist economic structure, is not suited for people who deviate from the "ideal". There are laws protecting disabled people from discrimination during both hiring and working - however there are laws against murder, too. Yet it still happens.

Now disabled, my experience of academia has violently lurched in a new direction. Part of managing my disorder requires reasonable accommodations at work, to which I am legally entitled. Academia however, is survival of the fittest.

Within an academic workplace, it is common to work shockingly late, and also during weekends (then looking down on those who don't). There are high-stress cycles of needing to produce data quickly for tight deadlines, like grants. There is a pervasive culture of shirking health and safety, and ignoring HR. A scientist's career is dead in the water without frequent and regular publishing. Some institutions and buildings I have worked in lacked basic accessible infrastructure. Networking is considered essential to career progression, often at large overseas conferences. All of these features can be not inclusive to a disabled person – someone who needs deliberate and thoughtful inclusion.

I always imagined myself becoming an expert in my field, being in charge of my own lab, and taking on lots of students. As I'm looking at my map through an academic career I feel doomed, despite the skills and talent I bring to the table. What if I can't stay until 10pm every day? What if I need to take extended sick leave, and can't publish for a time? While it's unlikely that I'd be sacked, it's near certain that I'll fall behind.

To conclude: I'm going to give it my best, and then forgive myself when I lose. I'm sure the industry has space for someone like me. ■

YOUNG INVESTIGATOR

"It's a gut feeling" – Journey of a new PI

Georg Busslinger is a group leader at the Medical University of Vienna and an adjunct Principal Investigator at the Research Centre for Molecular Medicine (CeMM), Vienna, where he works on the epithelial cell biology of gastrointestinal organs using human organoids as a model system. We sat down with Georg to talk about his journey from being a student at the ETH Zurich to his PhD at the IMP, Vienna, followed by an exciting postdoc with Hans Clevers in the Netherlands, that recently culminated in the start of his own lab — all in a very short period.

***Phenotype:* What inspired you to become a scientist and how did you embark on this journey?**

Georg Busslinger: Biology has always fascinated me. As a young boy, I watched a lot of documentaries about wildlife and animals so, after high school, when I had to pick a subject to study, I decided to go down the life-science path. I wanted to understand how things work in detail, for example, how a cell does what it does. Particularly, I was advised that to truly understand these processes, it was best to approach them from a chemical point of view, which led me to study Molecular Biology in Vienna, followed by Cell Biology in Zurich. Additionally, as my father was a scientist, it was much easier for me to envision what the life of a scientist would entail compared to other professions.

***Phenotype:* How did you choose where to pursue your PhD studies?**

GB: Broadly speaking, I wanted to focus on signalling pathways, which is not a specific topic; therefore, instead of letting the topic determine my place of study, I placed priority on the work environment. Growing up, America sounded like an exciting place for research, so I pursued an internship at Rockefeller University, where I studied cellular interferon responses and demethylation. The Rockefeller has a rather mature research environment; it is a huge institute with many labs but has very few doctoral students. There I understood I wanted to stay in an environment with more PhD students, with whom I could connect more easily by sharing the same journey. This decision led to the search for European positions, where I knew I could find such environments. I looked at many doctoral programmes, including ETH Zurich, EMBO in Heidelberg and the VBC in Vienna, and finally settled on the VBC programme.

***Phenotype:* What was your PhD experience like?**

GB: During my PhD studies, I went back to what I was originally interested in — how do the cells of our body function in detail? I worked on the cohesin complex, which is best known for its role in cell cycle but interestingly is also present in non-replicating, resting cells. This concept was quite puzzling to me at the time, so I aimed to dissect the function of this complex in both proliferating and non-proliferating cells. Overall, I was quite happy during my PhD Working with murine models involved a lot of planning and foresight, and it was a beautiful albeit slow process. In fact, during previous research internships, I worked with yeast or fruit flies and back then, the waiting time to design experiments felt like ages (replication time of a few hours for yeast or 10-14 days for flies). I was, therefore, convinced that I would never work with higher eukaryotic model organisms. Funnily enough, I ended up working with mice during my doctoral study, and now I use human cells, which are even trickier. If someone had told me this is what I would be doing now, I would have said: "You're crazy."

My big breakthrough discovery came a year after I had

finished my PhD It was quite common for students to defend and stay in the same lab to complete ongoing projects. I approached my PI with an idea for an experiment, and though he did not see its point at the time, he told me to go ahead with it. It turned out that this experiment made the difference between a "nice okay" paper and an outstanding one, which we finalised within a few months.

Phenotype: **How did you decide your next steps?**

GB: I started developing an interest in stem cell research, and I wanted to go abroad. Hans Clevers was working on exciting stem cell frontiers and a new organoid system, so I decided to give it a shot and contacted him. I honestly had no expectations, but he was one of the quickest to respond to my emails and invited me over for a meeting. After that, it felt like a whirlwind with wrapping up my PhD project, submitting my paper and beginning my postdoc in the Netherlands.

Phenotype: **How did you experience the transition from PhD student to postdoc, especially since you had switched fields?**

GB: People surrounding me always argued that, in science, one should not change too many things at a time. "There are three pillars - the topic, the model, and the methodology. If you change too much, you will have to start from scratch." I had changed pretty much all three. However, I considered switching fields a clever move as it forced me to face new challenges. At the same time, I must admit that I, in parts, regretted my decision as it took me almost a year to adjust to the new model and methodology, obtain access to human tissue samples and properly get started.

Phenotype: **Did you always want to become a PI?**

GB: I was always open to a variety of career paths. Although I had the traditional 'PhD to Postdoc to PI'-route at the back of my mind, I was willing to branch off into any direction my work would have taken me.

Phenotype: **When you become a PI, you have different responsibilities and need to learn several new things quickly. What was the process of setting up a new lab like?**

GB: Yet again, everything happened quite quickly. I was trying to juggle a multitude of tasks at once — finishing up my publications, organising my lab, ordering reagents, hiring new employees — all in the midst of a pandemic! I always felt that I was too slow. When you focus on one task, you think you should be working on another instead. However, while it might feel like you are doing everything wrong, you suddenly see the progress you have made and that you have set up a whole new lab in just a few months!

Phenotype: **What experiences best prepared you for your position as a PI? What was unexpected?**

GB: Although I used to work in big labs with established systems, I often felt "in my very own niche" within these labs. For instance, in Hans' lab, I was the only one working on stomach and oesophagus organoids, which meant I had to work independently for the most part. This environment, therefore, fostered my independence and gave me the confidence to undertake different projects and establish new protocols. However, as group leader, I have to learn to hand over these projects I used to do myself and it is necessary for me to understand that my employees will approach challenges and problems in a different way than me.

Phenotype: **How did you decide on the research that your lab would focus on?**

GB: I drew on aspects from my PhD and Postdoc that interested me the most. I wanted to continue working with human organoids but delve into the molecular aspects. I aim to achieve the differentiation of human cells in-vitro as this will open up a world of possibilities. Next, I also plan to study inflammatory diseases of the gastrointestinal tract. Importantly, as I am situated within the Medical University, I can shape my research on current medical needs.

Phenotype: **What do you think of the research environment in Vienna?**

GB: I am placed in the gastroenterology department at the Medical University with an adjunct position at CeMM, which I think is perfect; On the one hand, it provides me with access to the clinics and human samples, which can be quite difficult to obtain, and on the other hand, I benefit from the molecular advances and technologies available at CeMM. In other words: "I get the best of both worlds!".

Phenotype: **Finally, what advice would you give students who aspire to become PIs?**

GB: Follow your heart and do what you like to do. At the same time, it is important to be persistent. You need to assess if you are having fun with your work and if the results of an experiment excite you enough to carry you forward. It's all a gut feeling after all! Importantly, don't regret missed chances as they might not have been the best path for you. Make the most of the opportunities you do have instead. In the end, if you give it your best, your best must and will be good enough.

Phenotype: **Thank you for this interesting and inspiring interview!** ■

CeMM

SCIENCE IS OUR MEDICINE

ASPIRE TO INSPIRE

From Oxford to Berlin: In Conversation with Prof. Ana Pombo


Photo by Felix Petermann

Prof. Dr. Ana Pombo is a senior group leader at the Max Delbrück Center for Molecular Medicine (MDC) in the Helmholtz Association, Vice-speaker of the Systems Medicine and Cardiovascular Disease Program at the MDC, and appointed Professor of Biology at Humboldt University. Prior to Ana's scientific career in Berlin, she was a group leader at the MRC London Institute for Medical Sciences, and a PhD student at the Sir William Dunn School of Pathology, University of Oxford.

Phenotype: **Can you give a quick summary of your research?**

Ana Pombo: Our lab is very interested in understanding how information stored in the genome is organised within the nucleus and decoded into gene expression. Particularly, we want to understand how genome organisation and gene expression differ in different cell types and disease states. We study this in two opposite extremes of biology: In early development, we want to determine how one cell acquires different identities as it divides, and how genome folding regulates this process. We study the same concepts in cells that are already very specialised – neurons, to learn how genome organisation responds to the distinctive functions of these cells. Also, we develop new technologies to address these questions as we go along – primarily, the growing family of Genome Architecture Mapping (GAM) technologies.

Phenotype: **When/how did you first realise that you wanted to be a scientist?**

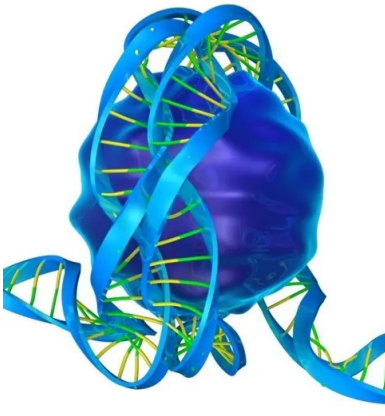
AP: I would not say there was one particular moment, but I can remember some moments throughout different phases of my education:

I was fascinated when I first learned about cells in secondary school. I remember thinking it was a great puzzle to discover how the different types of cells performed diverse jobs, despite containing the same basic components.

In my teens, I was further inspired by the scientific process depicted by "The Story of Louis Pasteur" and the discovery of insulin by Sir Frederick G. Banting, Charles H Best and JJR Macleod in Toronto.

Later in university, I remember wandering into the library, opening scientific journals, and feeling very motivated by scientific manuscripts. I was fascinated by how much work must have gone into them and impressed by the knowledge and rigor. I knew it was something I wanted to be a part of.

Phenotype: **What was your favorite aspect of scientific life in Oxford?**



AP: I found it incredible to be amongst the scientists I admired most and whose work, papers, and textbooks most excited me. I was suddenly able to share ideas with them and have them as my mentors. It was also then that I realised the scientists I admired so much were not so different than I was.

Phenotype: **What was your favorite aspect of life outside the lab in Oxford?**

AP: I enjoyed the beautiful scenery of the city and that everything was nearby. For example, I could bike to the lab to set up an experiment, go out to eat, and come back to finish my work. I also enjoyed having a very international group of colleagues and friends as Oxford has a diverse community of people.

Phenotype: **What is your favorite aspect of scientific life in Berlin?**

AP: My favorite aspect of scientific life in Berlin has been becoming more closely connected with the medical research community. Our work is very basic – we could work with any cell, any genome – but here in Berlin, we have some amazing colleagues working at the intersection between research and medicine. This has been a very positive influence on the model systems we choose to work on. It makes our work much more exciting as our discoveries become useful, and potentially translational.

Phenotype: **What is your favorite aspect of life outside the lab in Berlin?**

AP: Berlin is a beautiful city with many gardens and parks. Life is also much more affordable than in Oxford or London, so we have more access to culture. However, it has also been difficult to connect and integrate in Germany since my family and I do not speak German.

Phenotype: **What would be your advice for current students?**

AP: I would say to start learning computational skills as early as possible, especially if you do not have the opportunity to learn this during university. We see recently that the recruitment process favors students who have both computational and experimental skills.

Additionally, keep in mind that a career in science can lead to different opportunities because there are various skills that we acquire as scientists such as; writing, interpreting, presenting, discussing, analysing, etc. Do not only associate success with becoming an academic scientist.

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As budding scientists, it is also crucial to have a broad set of mentors and continually test your ideas with them, both in terms of promise and feasibility, especially to learn to brave inevitable peer challenges. You have to enjoy the process of continuous learning and criticism.

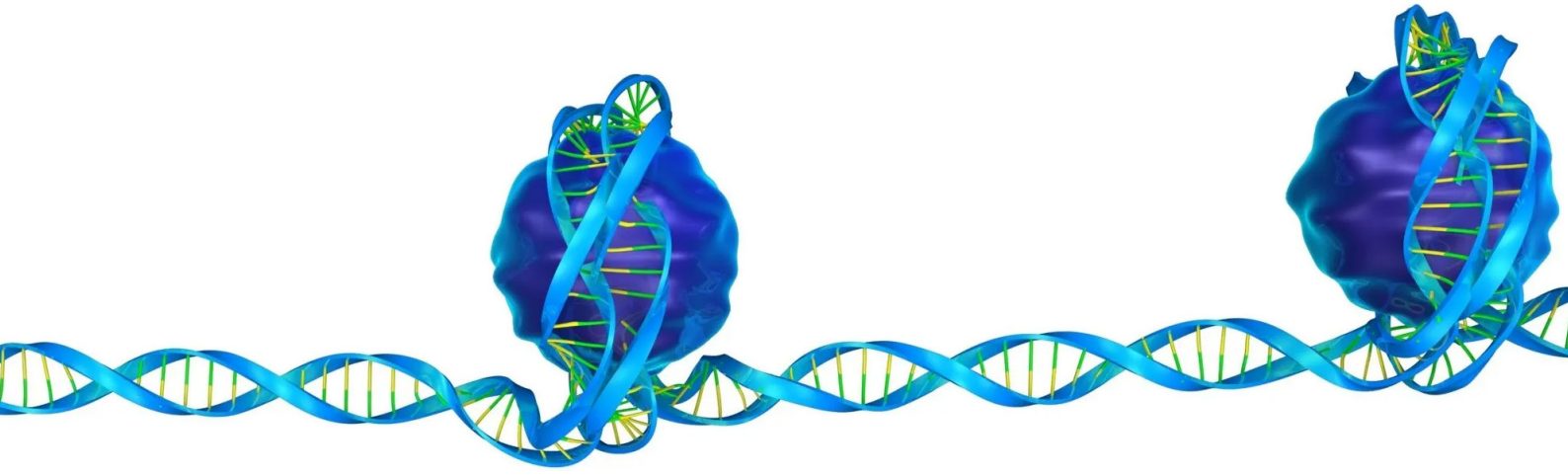
Phenotype: **What are you most looking forward to for the future of the lab?**

AP: I am excited to explore multi-omic techniques and analyses where we can simultaneously measure different facets of the same single cell such as, chromatin state, transcription, and protein expression. In this way, we expect to get closer to cause-effect relationships of how 3D genome structure impacts cellular function.

Phenotype: **Who is your favorite scientific role-model and why?**

AP: Peter Cook was a wonderful mentor for showing me how to nurture innovation in research. In Portugal, I had excellent university professors who trained me to do robust research, yet it was hard to make a completely novel discovery and be supported. When I moved to Oxford, I was looking for a mentor who – should I ever be lucky enough to discover something entirely new – would know how to support me. Not only did Peter Cook nurture big discoveries, however unlikely, but he also taught me how to nurture discovery in others.

A more senior role model of mine is Mandy Fisher. She showed me the importance of defending horizontal (less hierarchical) organisational structures in research institutions. Horizontal structures are more creative and can be more effective, and I was inspired to see her defend that. ■



MINI REVIEW

Maintaining Membrane Integrity with Protein Transport

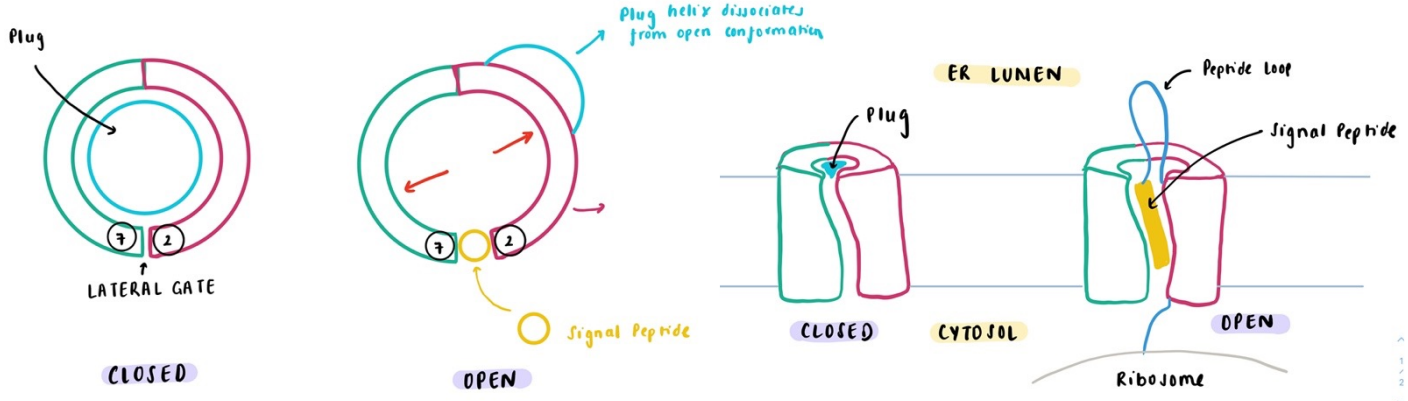
By Rebecca Harry. Rebecca is a second-year undergraduate in Biochemistry at the University of Oxford.

For a protein to be transported across a membrane or inserted into it, there is implied risk of ion leakage across that membrane, and loss of electrochemical and/or concentration gradients as a result, which the cell and organelles rely on for proper function. However, since the cytosol is the site of protein synthesis, but proteins are needed in all organelles, there must be suitable mechanisms in place to reduce or prevent ion leakage, allowing for the sustainable transport of proteins. Here, we focus on mechanisms within the Sec translocon and the Tat transport method.

Sec Translocon

The Sec translocon is the key complex that transports nascent polypeptides with a targeting signal sequence from the cytosol into the luminal space of the endoplasmic reticulum (ER). This translocation process requires the protein to cross a hydrophobic lipid bilayer. The same complex is also used to integrate nascent proteins into the plasma membrane. Ten transmembrane helices form a non-covalently sealed ring with a lateral gate at the sealing point, with helices two and seven being the ones at the gate. The Sec translocon acts as channel when moving proteins across the bilayer. This channel has a constriction point known as the pore ring, made up of inward facing hydrophobic residues being plugged by an alpha helix in closed conformation. Proteins are targeted for transport through the Sec translocon via a short helical peptide. It is the insertion of this signal peptide in-between helices two and seven (the lateral gate) that moves the Sec translocon from a closed conformation to an open one. Once the signal peptide is inserted, we have an eleven-helix ring, causing the plug helix to dissociate, opening the aqueous channel through the membrane. Proteins are threaded through this channel in an unfolded state, in an active process.

Since there is an open channel through the membrane, one might assume that ions can freely move through the Sec translocon along with the peptide, or even when the translocon is in a closed state, as there are still transient gaps of 1–2 Å, the ideal size for an ion, that open up around the channel during natural flexing. However, there are mechanisms in place to prevent this, as it would be detrimental for the cell to have uncontrolled ion exchange between the ER and the cytosol. The channel is always narrowest around the pore ring, even when in the open state, and surface mesh models show that the narrow point of the channel packs extremely tightly around the translocated polypeptide, which is the primary method of preventing leakage. The tight fit around the polypeptide means that there is no "easy" pathway through for ions. At the constriction point within the channel there is a ring of isoleucines pointing inwards from helices 2, 5, 7, and 10. As hydrophobic residues they reduce friction for the polypeptide in the channel, but they also have a second purpose. Ions with hydration shells have a diameter of ~10 Å, far too large to fit through any transient gaps that arise during protein flexing. There is an energy barrier for the ions to shed their hydration shells in the hydrophobic environment of the channel, so the ions remain hydrated and unable to pass through the channel. Although the incoming peptide also has charged groups, it is being actively threaded through the translocon, so there is energy for the hydration shells of charged residues to be shed, allowing passage.



Top (left) and side (right) views of the insertion of the signal recognition sequence into the lateral gate of the Sec translocon, facilitating the threading through of the unfolded protein.

Bacterial Mechanisms: Tat Transport

The Tat pathway is a protein export system found in the cytoplasmic membrane of prokaryotes which operates in parallel with the Sec pathway but differs in that the Tat pathway transports folded proteins, whereas Sec transports unfolded proteins. Substrates of the Tat pathway have an N-terminal signal peptide that is used to target the substrate protein to the Tat apparatus. One reason proteins may have to be transported as already folded could be that they contain cofactors that must be within the folds, such as iron-sulphur complexes, cytochromes and respiratory complexes. Tat is an active transport system, driven by proton motive force (PMF). This contrast the Sec translocon, where substrate diameter remains consistent as peptide chains all have a diameter of 12–14 Å. The Tat system is capable of moving substrates with diameters ranging from 25-70 Å, therefore cannot maintain membrane integrity in the same way that as above.

Tat transport is initiated when the signal peptide of a substrate protein is recognised and bound by a multisubunit TatBC complex located in the membrane- a PMF independent event. This binding event then triggers PMF dependent recruitment and oligomerisation of TatA from a pool in the membrane to form the active TatABC containing translocation site. Transport of the folded passenger protein across the lipid bilayer is assumed to be mediated by the assembled TatA oligomer. When transport is complete, the signal peptide is cleaved from the substrate by signal peptidase and the translocation site disassembles, unlike Sec, where the translocon is a permanent feature of the membrane and its open/closed state is what changes.

A distinct feature of the Tat system is that it can operate at PMFs that are considerably smaller than the physiological proton gradient, but the threshold PMF for transport does differ significantly between proteins. To be able to use the PMF at all, the Tat apparatus must be allowing protons to diffuse across the membrane, so must be able to assemble a proton-conducting pathway composed of protonatable amino acid side chains and buried water molecules in a proton wire. There is a transient aqueous channel seen in the structure of TatC which extends into the central cavity of its 'glove' shaped structure as far as key conserved glutamate which is believed to make up the cytoplasmic half of this pathway. It is also thought that proton movements in the periplasmic half of the membrane might be mediated by TatA family proteins using the conserved transmembrane helix polar residue and other hydrophilic amino acids that are located close to the periplasmic side of the membrane. Although proposals for proton route remain unconfirmed, it is clear that the pathway is not made up of a single component of the Tat pathway.

There is a two-step mechanism for Tat transport: TatA oligomerisation and then substrate transport across the membrane by the assembled TatABC complex. Even though the movement of the protein only takes milliseconds, the second step of this process is on the minute scale, likely due to a high activation barrier to moving the protein. The Tat method of protein transport is not well understood, but there are several hypotheses for how it works to prevent detrimental ion leakage while transporting proteins. One of these theories is that the reason why the translocon only assembles when needed, is to minimise leakage, as the assembled complex may permanently consume the PMF even when there is no protein to be transported. Most protein transporters have an aqueous transmembrane channel to transport the protein, however, as discussed above, this would not be suitable for Tat and no evidence has been found to support this. Instead, it is theorised that the concentration of TatA molecules in the membrane causes a local weakening. In this case, substrate movement would occur through physical driving through the weakened bilayer or rupturing and resealing of the bilayer. This is consistent with the strong influence the bilayer composition has on Tat transport. It is also likely that the cell would tolerate this very brief ion leak, particularly compared to that which might occur if Tat did work via aqueous channels.

Conclusion

There are several effective methods in place across protein transport mechanisms to prevent ion leakage, including size constraints aided by hydrophobic residues, plug domains to ensure a closed channel, and membrane thinning for forced transport of folded proteins with minimal leakage (particularly compared to an equivalent channel for folded proteins). Mutations in Sec have been linked to human disease, such as tubulo-interstitial kidney disease with anaemia in humans. By understanding the normal function of Sec, we can begin to consider how we might tackle conditions related to its malfunction. Additionally, since we also see the Sec system in bacteria, insights into its mechanism tell us more about bacterial secretion. The same can be said of the Tat system. Understanding bacterial secretion is important for a number of reasons, from producing proteins to tackling infection. ■

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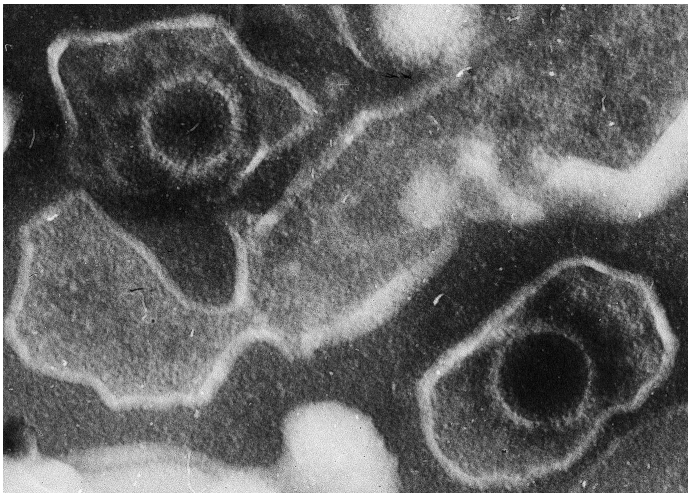
RESEARCH HIGHLIGHT

Viral origin of multiple sclerosis?

By Bakhrom Muinjonov. Bakhrom is a PhD student at the research group led by PD Dr. med. Volker Siffrin at the Max Delbrück Center for Molecular Medicine in Berlin.

Multiple sclerosis (MS) is a chronic inflammatory immune-mediated demyelinating disease of the central nervous system of unknown etiology. **The relative contribution of genetic and environmental risk factors to trigger MS pathophysiology is an area of fertile debate. It is known that a constellation of various factors' interactions might determine susceptibility to develop MS.** These factors include the Human Leukocyte Antigen (HLA) region, Epstein-Barr virus (EBV), vitamin D and smoking [1].



Electron micrograph of two Epstein–Barr virions showing round capsids loosely surrounded by the membrane envelope. Figure from Gross L (2005), doi: 10.1371/journal.pbio.0030430.

EBV is a human herpesvirus that persists in latent form in B lymphocytes after infection. It infects ~96% of adults, and previously, it has been shown in some pathological studies that it exists in MS demyelinated lesions [2]. Indeed, one of the most efficient therapies for MS is depletion of circulating memory B cells, the primary site of persistent latent EBV infection [3].

A recent study by Bjornevik *et al*. published in *Science* [4] showed a remarkable association between multiple sclerosis (MS) and the Epstein-Barr virus (EBV) infection and reported a 32-fold risk for MS after EBV infection.

This observational study longitudinally investigated MS incidence in a cohort of 10 million EBV-negative young adults in US military service, some of whom were infected with EBV during the follow-up from 1993 to 2013. As in the general population, the EBV prevalence was high, with only 5.3% of the samples being EBV negative. In this cohort, out of 801 young individuals who developed MS with the serum samples available to assess EBV infection status, 800 had positive titers against EBV. Most MS cases emerged on average within five years after the first EBV-positive serum samples were identified. Remarkably, while these healthy controls had a seroconversion rate of only 57%, those suffering from MS had an extremely high rate of seroconversion (97%), i.e. they had more antibodies against EBV ($p<0.001$). This is a case-control study and for each person with MS, two matched controls were included who were comparable in terms of age, sex, race/ethnicity, branch of military service, and even dates of collection of blood samples, but did not develop MS.

Authors showed that the signs of neuroaxonal degeneration, measured by serum concentrations of neurofilament light chain, a sensitive, albeit not MS-specific biomarker, were increased only after EBV seroconversion, indicating that EBV infection preceded the first detectable initial symptoms of MS. Conclusively, it has been shown that the EBV infection increased the risk of MS by 32-fold among young adults. None of the known risk factors for MS was previously reported to have such a strong association. The most important known risk factor for MS to date, HLA-DR15, is linked with only three times higher risk of developing the disease. Additionally, there is epidemiological [5] evidence that EBV infection and HLA-DR15 may act synergistically in causing MS.

These data reinforce the hypothesis that there is an association between EBV infection and multiple sclerosis, but do not prove yet that there is a causal relationship. The conclusion that might be objectively drawn is that EBV infection precedes MS onset, and it is associated with markedly higher disease risk. This was much higher than in the control population, while for cytomegalovirus infections, there was no difference.

If the causal relationship will be proven in further studies, future vaccination against EBV would potentially be an option to reduce the incidence of MS. Unfortunately, there is no available vaccination against EBV yet, but different companies are working on it, including Moderna, which has developed an mRNA-1189 vaccine against EBV, currently in phase I of clinical trials [6]. ■

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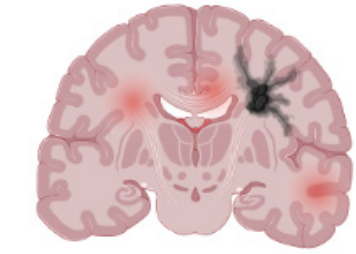
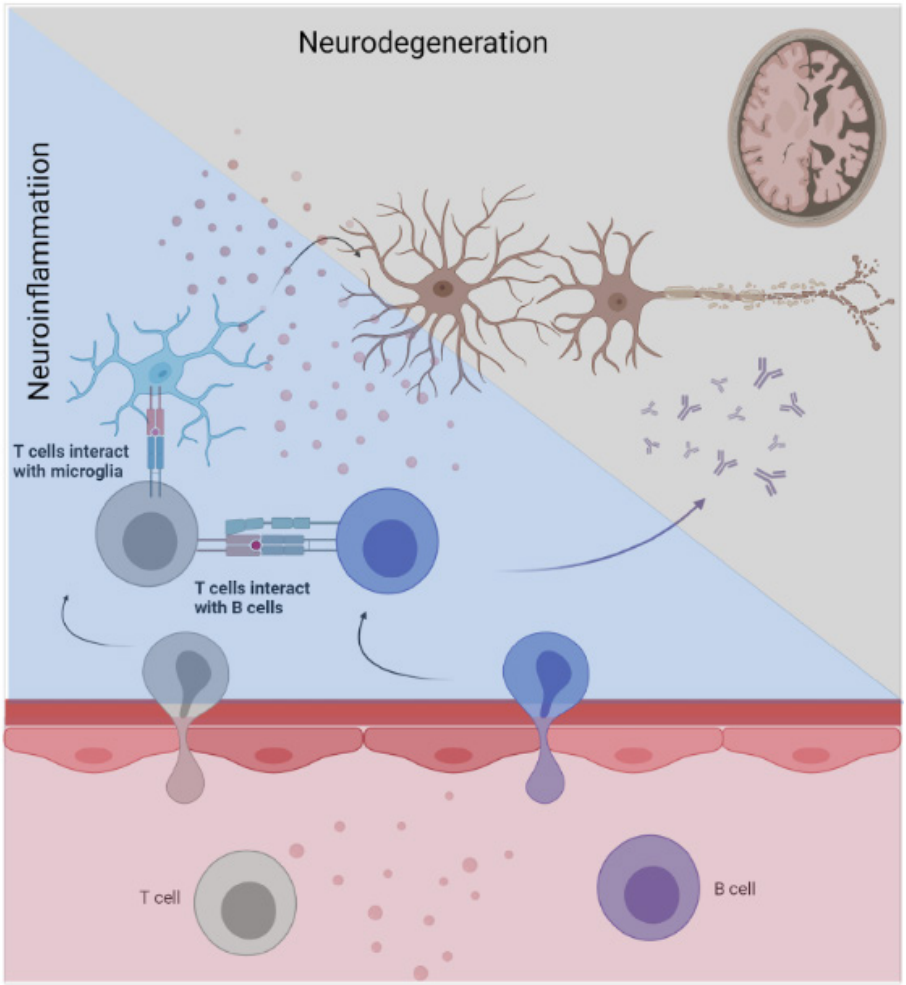


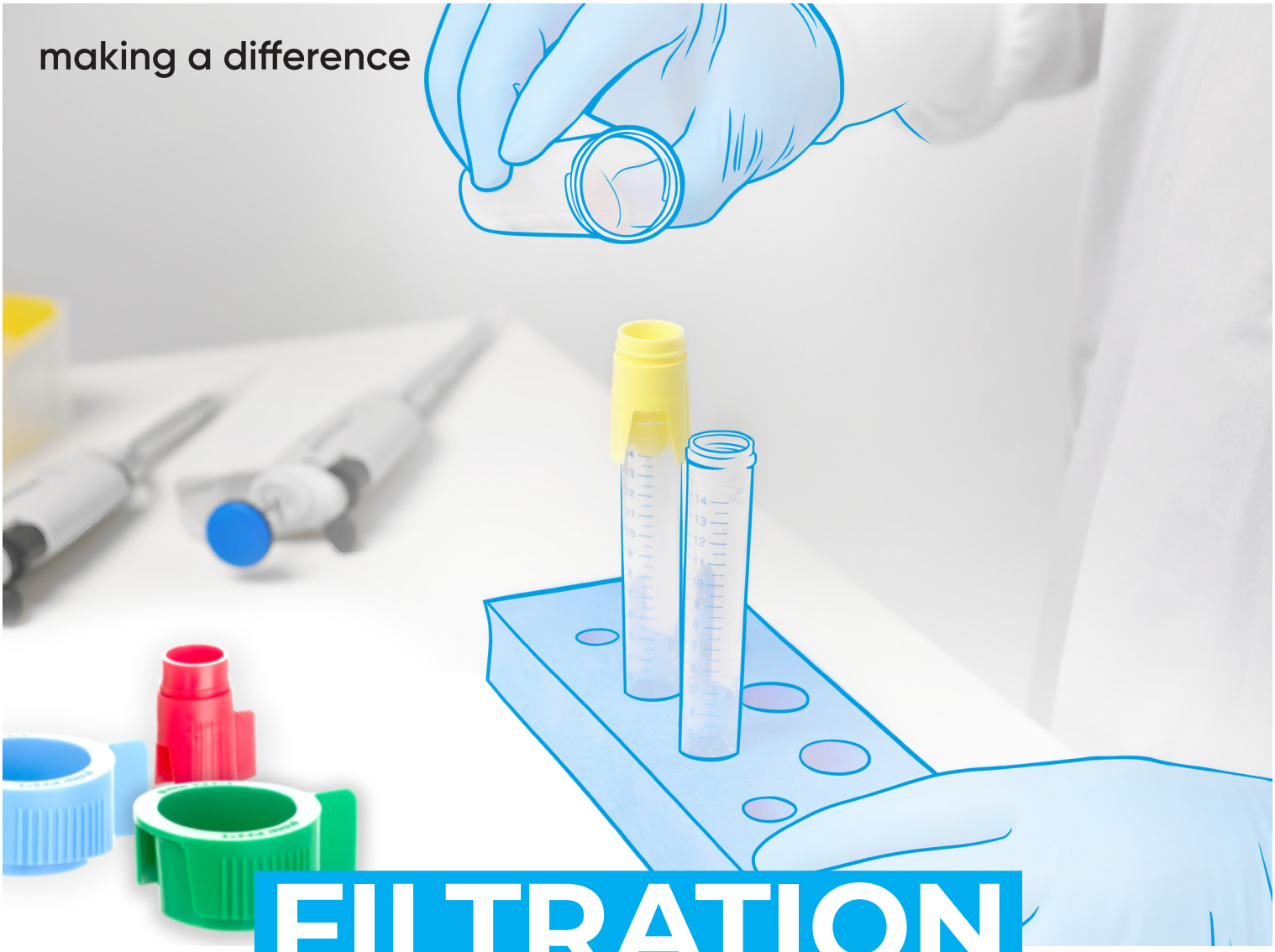
spasticity, mobility problems
ataxia
numbness, tingling
muscle spasms
pain
urinary incontinence or retention
tremor
cognitive problems
fatigue
vision problems
dizziness
constipation



General overview of the mechanism behind multiple sclerosis suggests that the immune system starts to see myelin components as foreign and destroys myelin sheath, thus contributing to disease pathogenesis.

Two mechanisms have been hypothesized to explain it: molecular mimicry and bystander activation. In the initial phase of the inflammatory process, T cells become active in the periphery and migrate to the central nervous system. Inflammation products are important for tissue defense, but in the long-term, the inflammatory response is not self-limiting and triggers neuronal stress response. (Created via biorender.com.)

making a difference



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