PHENOTYPE

Issue 36 | Hilary & Trinity Terms 2021
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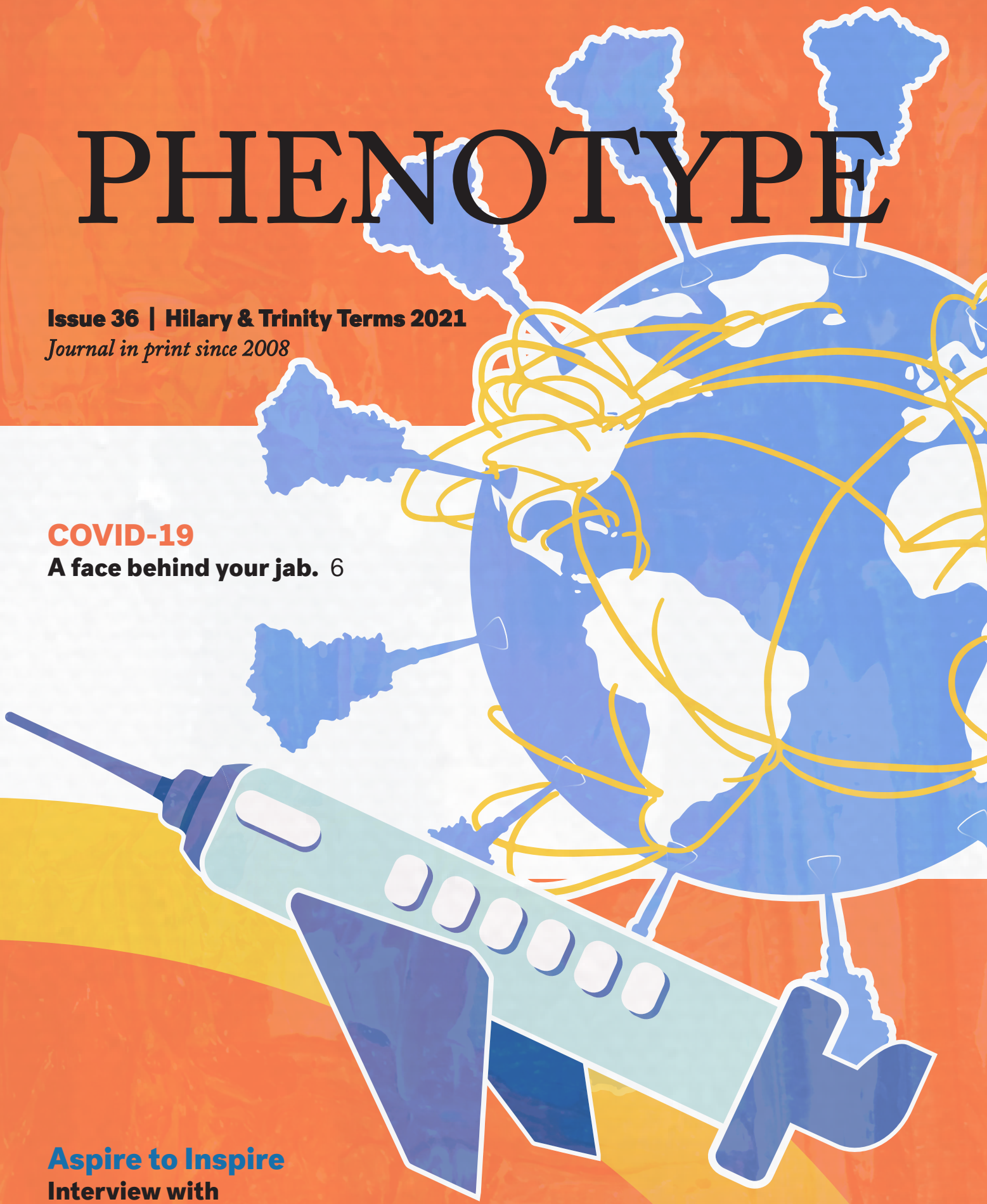


LETTER FROM THE EDITORS

Dear Readers,

If you are picking up a copy of *Phenotype* for the first time, Welcome! We are a student- and postdoc-run Life Sciences Journal that aims to reach scientists and the general public. We started in 2008 as a Newsletter of the Oxford University Biochemical Society, and now, after 13 years in print, our readership spans the globe.

We are unique: we won't charge you for publishing with us, for printed copies, or for subscription. Our journal is supported by the generosity of our sponsors and by the tireless work of passionate, dedicated, and talented volunteers.

In this 36th Issue of *Phenotype* we start with an interview with Ciaran Gilbride, conducted by our editor Laura Steel. Ciaran is supervised by Professor Teresa Lambe and Professor Sarah Gilbert at the Jenner Institute. Ciaran takes us on a journey of development of the Oxford COVID-19 vaccine (p. 6).

For those of you interested in academic paths we interviewed former Oxford DPhils who provide their unique perspective and share their experience starting their labs in the USA (Professor Keary Engel, DPhil 2013), in the UK (Dr Mattéa Finelli, DPhil 2010) (p. 8).

Tired of academia? Want to start a spin-off? Leah Thompson is a Senior Knowledge Exchange Officer, leading the Enterprising Oxford programme at the University. Leah provides step by step advice on how to start and what mistakes to avoid (p. 10).

On p. 12, a recently born team, share their tips and experience of founding a start-up, in a journey from ideas to a concrete project.

Read about the exciting journey of Dr Regenbrecht (a former group leader at the Charité University) in transitioning to industry and founding his successful company ASC Oncology GmbH (p. 14).

As part of our Aspire to Inspire feature, we interviewed Professor Jana Wolf (Free University Berlin, Max Delbrück Center for Molecular Medcine). Find out what it takes to be a computational biologist! (p. 16).

Have you always assumed that healthy lungs support a sterile environment? Find out about the diverse microbiome in healthy lungs and contribution of dysbiosis to asthma (p. 18).

On p. 20, we discover how flies use their memory, what are the mechanisms involved in their learning and why this is important to us.

On p. 23, there's an answer to a compelling question: is it possible to mend a broken heart? See how blood vessels can have an important role in this process.

In our Opinion section, Atreyi Chakrabarty tackles a pertinent topic of fake news and infodemic, specifically in relation to the current pandemic of COVID-19. (p. 25).

On p. 26, we can find out how blood vessels organise in a complex and amazing network, in order to provide an efficient supply of oxygen and nutrients to the body.

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

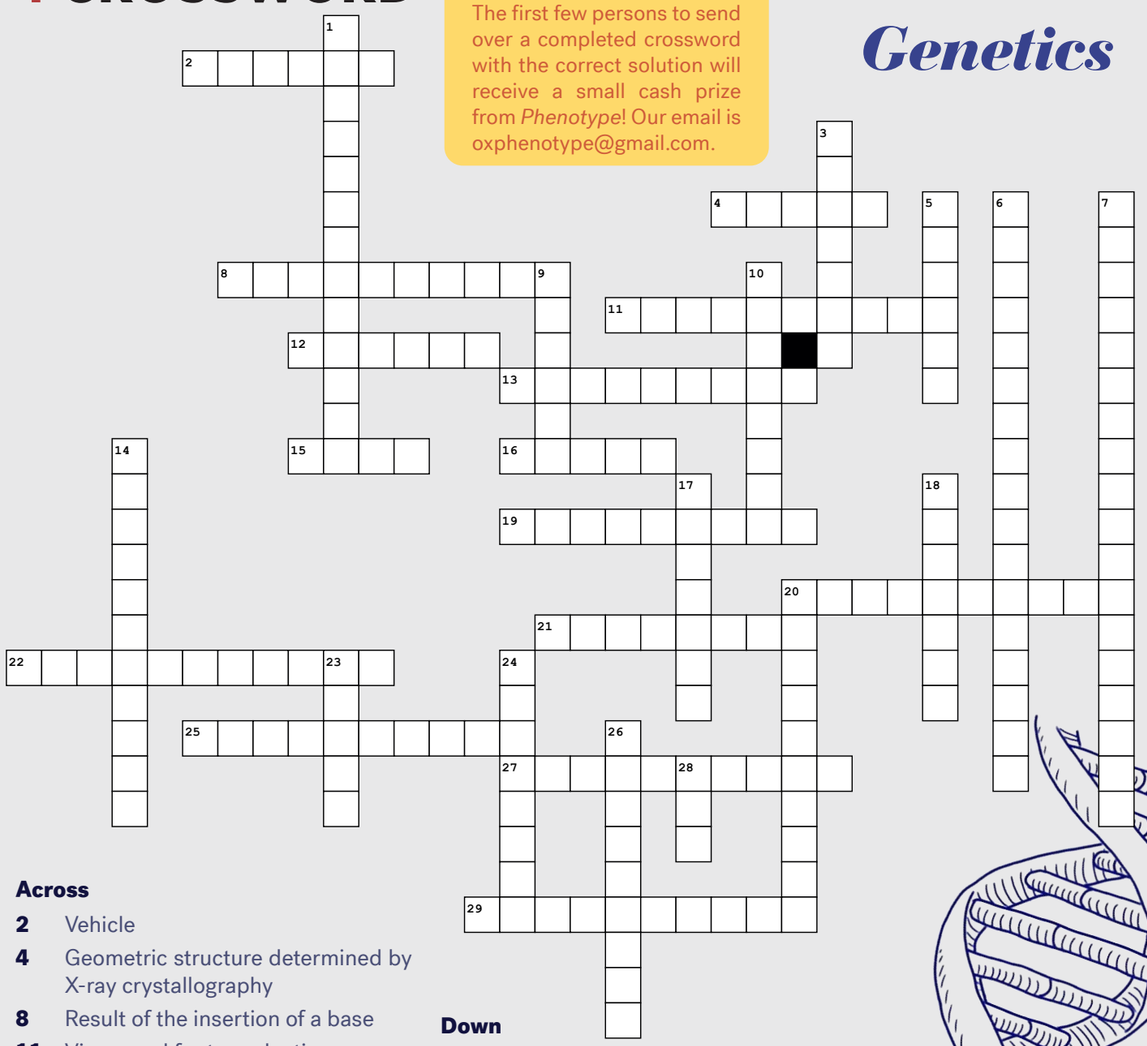
Are you interested in submitting a story to Phenotype or reading our past issues online? Visit our website www.phenotypejournal.org.

CROSSWORD

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: Genetics



Across

2 Vehicle
4 Geometric structure determined by X-ray crystallography
8 Result of the insertion of a base
11 Virus used for transduction
12 Famous repeats in *E. coli* K12
13 How is the knockout in a CD4-Cre/ER transgenic mouse induced?
15 First human cell line (abbrev.)
16 Group of three
19 Holds the chromatids together
20 A lot of non-human cells in our body
21 Phenotype
22 Syndrome where a man has an additional X chromosome
25 Model organism popular in genetics
27 Why some corn kernels have a different colour
29 Non functional region of a DNA, which looks like a gene

Down

1 Enzyme for overwinding or underwinding
3 Can be used to tie your hair
5 5' to 3' strand
6 Genetic disorder leading to blue skin
7 Nucleotides used for Sanger sequencing
9 First genetic modified food sold
10 Number of times a gene has been sequenced
14 Process by which genetic information is changed
17 Mutation acquired by a cell
18 Animal from which the first gene was cloned
20 Start of the translation
23 1.1% of the human genome
24 Animal with most sex chromosomes
26 Technique by which the expression of a gene is reduced
28 Discovery which got the nobel prize in 1993 (abbrev.)

CONTENTS

PHENOTYPE
Issue 36 | Hilary & Trinity Terms 2021

Words from our cover contributor

Around the World in 126 Days: This pop-art piece reflects on how globalisation facilitated both the rapid spread of SARS-CoV-2 and the efforts to control it. From the first known case (as of writing) on November 17, 2020 in Wuhan, China to the early success of Moderna's phase I/II clinical trials reported July 14, 2020, much of the pandemic and its ongoing resolution has thrived on the ever-growing interconnectedness of the world.

Cover design by **Hailee R. Perrett**, PhD Candidate at Scripps Research in La Jolla, California, USA.

THE FACE BEHIND YOUR JAB

Working on COVID-19 Vaccine

Interview by Laura Steel. Laura is a DPhil student in the Peirson Circadian and Visual Neuroscience group at the University of Oxford, supervised by Professor Stuart Peirson and Professor Russell Foster.

Ciaran Gilbride is a fourth year DPhil Candidate on the Interdisciplinary Biosciences DTP, working in the Emerging Pathogens Group at the Jenner Institute. He is supervised by Professors Teresa Lambe and Sarah Gilbert, and Dr Dalan Bailey of the Pirbright Institute.

What was your individual research focus prior to the pandemic and how has this changed since the emergence of Covid-19?

My individual research was focused on the nairoviruses, particularly Crimean-Congo Haemorrhagic Fever Virus and Nairobi Sheep Disease Virus. These viruses can cause severe disease in humans and animals, and are potential public health threats. I focused on developing and testing ChAdOx vaccines against these diseases, so my work was quite relevant to the trial.

Could you give a brief description of how the Oxford vaccine, ChAdOx1 nCov-19, works?

The Oxford vaccine is a viral vectored vaccine. This means that the antigen, which we develop immunity to, is delivered by a virus. ChAdOx1 is an adenovirus which is modified so that it cannot replicate inside human cells and therefore only acts as the delivery mechanism. ChAdOx1 delivers DNA encoding the SARS-CoV-2 spike protein, which is the part of the virus that is used to bind and infect human cells. Your cells then produce the spike protein in a safe manner, and develop immunity. The advantage of the ChAdOx1 system is that it produces comparatively better T-cell immunogenicity than previous generation vaccines.

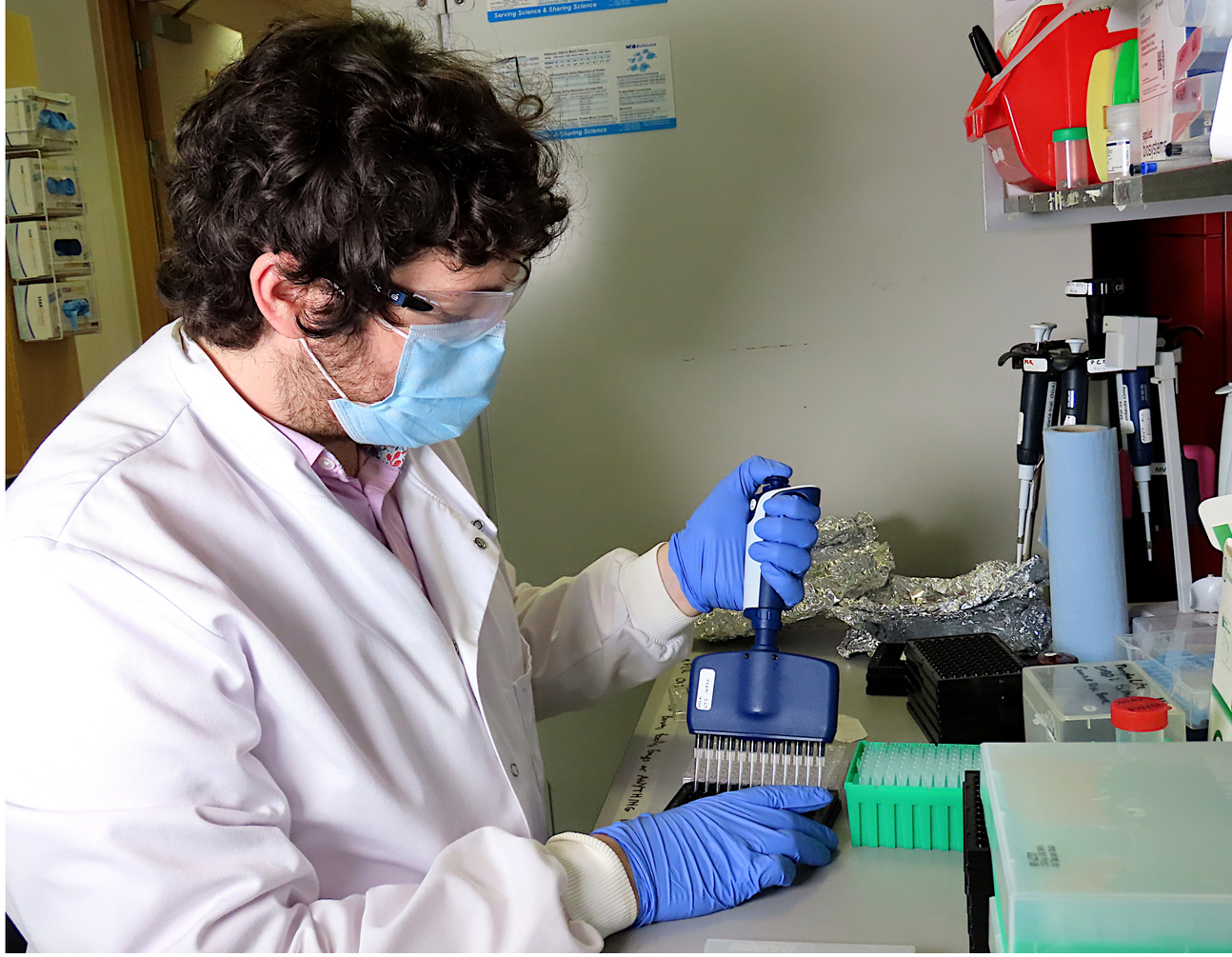
How has the search for the Covid-19 vaccine differed to the development of other vaccines that your group has focused on? In particular, how has the team managed to develop this vaccine and conduct the trial so rapidly?

The main difference has been the funding and manpower which has helped us develop and rollout the vaccine at such a fast pace. Most of our vaccines can be developed very quickly in pre-clinical trials, but then meander for a long time whilst trying to find funding to take them further. Since the financial risk was taken out of the equation in this trial, we could plan phase 2 before phase 1 was even finished, as well as launch into phase 2 the day after the results of phase 1 were known.

It has also been a period of unprecedented collaboration particularly between the Jenner Institute and the Oxford Vaccine Group in the early trial. Whilst we normally work relatively closely, now almost everyone in both departments has been focused on delivering the vaccine trial. Furthermore, the backing of and collaboration with a large multinational pharmaceutical company helps to speed things along, but I haven't been involved on that side of things.

What were the main turning points of the vaccine trials?

The major turning points were almost always the milestones. The first was the vaccination of the initial volunteers. I think that was when the magnitude of what we were involved with hit home. Then there was the release of our pre-print article which showed that the vaccine provoked an immune response. Finally, the day we celebrated the most, was when we found out the vaccine was effective at preventing infection –that was a really proud moment for the whole team.



To what extent have you experienced either collaboration or competition with other research groups developing different vaccines?

I think there has been a huge degree of collaboration with a lot of other groups developing vaccines. For example, we recently published a pre-clinical study comparing our vaccine to one produced by Imperial College. In addition, AstraZeneca are collaborating with the Sputnik vaccine team to look at mixed dosing, and the Oxford Vaccine Group and the Jenner Institute are investigating mixing ChAdOx1 and mRNA vaccines.

It is going to be really important to have many vaccines in order to vaccinate the whole world. Each will have different advantages and disadvantages, affecting their capacity to reach every location. There is also an issue of production capacity. It is really crucial to have a range of vaccines produced in different manners so they can be synthesised in parallel, as this is the only way we will be able to produce enough doses for 7 billion people by the end of 2021.

What has been the most significant challenge in the process to date, for you as an individual and for the team in general?

The early days of the trial were extremely tough: the whole team were working seven days a week, taking and processing samples, and running assays. I think I had two days off in May and June and I was one of the lucky ones!

There were also some notable occasions where my team were waiting anxiously for reagents to arrive, whilst frantically calling around the whole of our building to see if anyone else had what we needed to use. This was due to a lot of scientific companies furloughing staff, resulting in a severely disrupted supply chain. We definitely had times where we had to set up our assays and hope we didn't have to throw everything away at the end of the next day if things did not arrive.

What are your plans for after the PhD? Has working on the vaccine trial encouraged you to pursue this or to change course?

I have to be honest, with the pandemic being so disruptive to my DPhil, I have avoided thinking about future plans. Ask me again in a year and I will probably be able to tell you what I am doing next! ■

A TALE OF TWO COUNTRIES

Stories of landing the first PI position

We interviewed Dr Mattea Finelli (Oxford, DPhil, Neuroscience 2007–2010), to ask her about her journey from being a DPhil student and a postdoc at the Department of Physiology, Anatomy and Genetics, to secure her own first fellowship and start an independent career at the University of Nottingham.

***Phenotype*:** When did you start developing the idea to become a PI?

Mattéa: I think I started to develop the idea of becoming a PI very early on. Even when I was a little girl, I was already leading 'research expeditions' outdoors, with my younger brother and sister as my teammates, taking notes and samples in the hope of finding new species of animals or plants. Then, much later, when I was doing my DPhil in Oxford, I always had in mind to have my own research group one day.

***Phenotype*:** What experience(s) at university do you think prepared you best for this position?

Mattéa: I was lucky enough to have, early on in my career, supervisors who gave me the freedom and independence to be creative in my research and to explore new ideas. This helped me develop my confidence and an unshakable can-do attitude, and taught me how to design and drive research projects. I also learnt how to troubleshoot failed experiments and to handle manuscript rejection. All these early experiences really built my resilience and perseverance, shaped me as a scientist and prepared me for my role as a junior PI.

***Phenotype*:** Was there something you realised you were not prepared for at all?

Mattéa: I was not really prepared to start my own research group in the middle of a global pandemic! But I tried to take it in my stride and make the best of a bad situation. I had to adapt my research plans, focusing on the most critical experiments and being even more efficient and organised. When designing experiments, I now keep in mind that they may have to be stopped at any time, at short notice, depending on our own health and on changes in governmental regulations and lockdown rules.

***Phenotype*:** Is there anything you miss of your previous phase, when you were still at University?

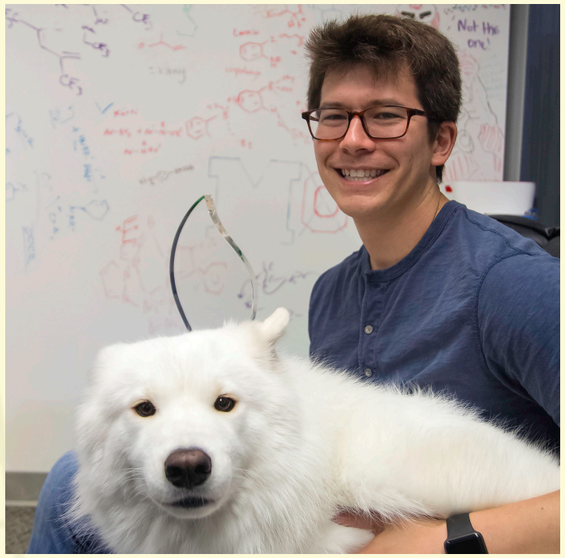
Mattéa: PIs in academia have to divide their time between research, grant and manuscript writing, teaching, mentoring and administrative duties to name a few. However, when I was a postgraduate student at University, my working time was focused mainly on my research project and on carrying out experiments, I did not have to divide my time as much, which I sometimes miss. But I do really enjoy the variety of activities of a PI job, this makes this job very exciting and fulfilling.

***Phenotype*:** What is good about doing science in the country you work in? Is there anything that could be improved?

Mattéa: There is quite a good and diverse funding landscape in the UK, where I have been working for many years now. For instance, there are national funding agencies, independent charities, as well as schemes targeted at different career stages. However, many of these schemes are extremely competitive, which can make securing funding for research projects quite challenging.

***Phenotype*:** What advice would you give to grad students who want to become PIs?

Mattéa: You have to wholeheartedly love Science and truly be enthusiastic about your research, because this is the light that will guide you through the difficult times and setbacks you may encounter along the way. I would also recommend discussing your research with scientists from other fields and disciplines, and building collaborations. An active and strong collaborative network can really help elevate your research and make it more impactful. ■



We sat down with Keary Mark Engle (Oxford, DPhil Biochemistry 2008-2013) to talk about his meteoric rise to full professorship at Scripps Research. Keary was a Skaggs-Oxford Scholar on a joint DPhil/PhD program between the University of Oxford and Scripps Research. As an NIH Postdoc Fellow, Keary carried out research at the California Institute of Technology, and then in 2015 returned to Scripps as an Assistant Professor. In 2020 he was appointed full professor in the department of Chemistry.

Keary was awarded numerous top fellowships and awards, including Fulbright, NSF Graduate Research Fellowship, Roche Excellence in Chemistry Award, Donald E. and Delia B. Baxter Foundation young faculty award, and he has already published over 80 papers. At Scripps, Keary and his lab aim to advance the efficiency, effectiveness, and sustainability of chemical synthesis.

***Phenotype*:** When did you decide to become a scientist? A PI?

Keary: I decided to attend graduate school to pursue my DPhil during the senior (fourth) year of my undergraduate studies, even though I wasn't exactly sure what I would do with it. I then decided that I would aim for a career as a PI in academia during my second year of graduate school (I completed a five-year joint program coordinated between Oxford and Scripps in La Jolla, California).

***Phenotype*:** Can you use three words to describe your lab?

Keary: Determined, collaborative, creative.

***Phenotype*:** What experience(s) at grad school prepared you best for this position?

Keary: A few stand out. First and foremost are my experiences mentoring younger students, which included younger PhD students, undergraduates, and even high school interns. Thinking about how to design projects that were tailored to each of them was challenging and exciting, and this is a central part of my current position. Second would be different writing and editing tasks. As a grad student, I wrote anything I could; be it papers, fellowship applications, or review articles, and I assisted with editing a huge number of documents for my colleagues. This was great exposure to thinking critically about who the target audience is, what the goal of the document is, and how to effectively deliver the desired message, and now I am in a position where I try to instill these lessons into my own trainees.

***Phenotype*:** What was something you were not prepared for at all?

Keary: Personnel management. As mentioned previously, I had worked with a number of different mentees during my time as a grad student and postdoc, but even still I wasn't well prepared for leading a group of the size of my lab (15–25 people), understanding different personality types and motivations, and resolving the inevitable conflicts that arise.

***Phenotype*:** One thing you miss about Oxford is...

Keary: Too many to list! If I have to pick one, I'll go with Friday evenings at the Uni Club with my friends and labmates... followed closely by Thursday evenings at the Uni Club.

***Phenotype*:** What is good about doing science in your country? Could be improved?

Keary: A good aspect of working in the US is the can-do attitude that US-based scientists bring to research. People aren't afraid to tackle hard but important problems. The downside is that funding availability doesn't always match our collective ambition (particularly in more fundamental and less translational research areas).

***Phenotype*:** What advice would you give grad students who want to become PIs in your country?

Keary: Seek out experiences mentoring younger students, and see if you enjoy it. It's not for everyone, and that's okay. If you enjoy it, try to get more granular. Do you enjoy working with undergraduate level mentees, or collaborating with other graduate students and postdocs? Do you enjoy the research aspect of these interactions or the educational aspects of these interactions? In the US one benefit is that there are many and different types of universities. For example, some only teach undergraduates, whereas the extreme opposite is a place like Scripps, where I work, where we have only PhD students and postdocs (along with the occasional undergrad or high school intern). Ask a mentor to connect you to folks working at different types of educational institutions, and learn what they like and dislike about their work. See what resonates with you, and then start formulating a plan to develop the skill, experiences, and network that will make you competitive for your target position. When in doubt, send me an email (keary@scripps.edu), and I'm happy to get you started! ■

So you want to start a spin-off

Enterprising Oxford
Supporting Entrepreneurial Connectivity

I am Leah Thompson, and I am a Senior Knowledge Exchange Officer at the University of Oxford. I lead a programme called **Enterprising Oxford**, which connects all the entrepreneurship activities happening across the university and the local community. I am kind of like a concierge; it is my job to know as many people and opportunities in the ecosystem as possible to be able to help people find the resources they need right now, no matter what stage they are at. I am also leading **IDEA (Increasing Diversity in Enterprising Activities)**, a University-wide initiative to increase diversity in enterprising activities. We are looking at how we can create culture change in the University, while providing better support and opportunities for the under-represented groups in entrepreneurship: Our first area of activity is around women.

My background is quite diverse – I studied Biology back in Canada where I grew up and worked mainly in horticulture for many years, before moving to UK and getting involved in IT, consulting, and small business operation and management. I have been at Oxford for almost 7 years now, supporting entrepreneurship in various ways during that time.

So I have an idea for a start-up or a spin-off. What should one know or prepare before approaching you? (i.e. market research, outline, pitch).

Do your homework! It is very easy to come up with an idea, but much harder to actually make a business with it. I always tell students to take a look at the Business Model Canvas and fill in all the boxes as a starting point. It is also very important to understand what need you are filling or problem you are solving; all too often solutions are developed and then retrofitted to a problem. You need to understand your customer, and do your market research.

I am still a student or a postdoc, can I apply in parallel to my current position? Do I need to check with my PI?

Many students and post-docs start businesses in parallel to their work or studies. However, it is always a good idea to understand your rights and responsibilities as a student or staff member in your University before starting a business. Does your contract allow you to do so? Are you on a visa, and if so, does your visa allow you to start a business? Who owns the IP (intellectual property) that arises from any ideas you have? All these questions should be evaluated and answered before jumping in – this will save you from future issues! A discussion with your PI, others who have started businesses, your tech transfer office or entrepreneurship centre helps you determine if this is the right path for you.

I will probably require funds in order to pay my salary, if I decide to pursue full time. Is there something available? If so what is the application process?

It depends on what your idea is. If it is related to your studies or research, you may be able to find grants or translational funding which could include salary. The best place to start is your tech transfer office, who will be able to point you in the right direction.

If your idea is unrelated to your studies or research, you will probably need to raise investment or start trading before you will be able to pay yourself. It will completely depend on your idea and how long it takes to find customers or win grants and competitions.

I've heard most start-ups fail. How can one increase chances of success?

Build your network. Be prepared, ask lots of questions, take advices from others who have been here already. Build your network. Do your homework. Build your network (said three times for emphasis!)

There is also an element of luck or serendipity here; being in the right place at the right time can be hugely advantageous. There are many stories of start-ups who failed because the timing was not right or circumstances prevented it. Equally, the success of companies like Zoom or Hopin may not have been the same if we weren't all working from home in the middle of a pandemic!

Is this open only to current students, staff?

Most of the programmes and support the University offers are open to current students, staff and/or alumni. However many events are open to all, and initiatives like Enterprising Oxford help to showcase the opportunities for anyone.

What is a typical mistake that people make?

I guess something I have seen is either trying to move too fast (and not doing enough research) or those who move too slow (trying to perfect things before sharing). There are great stories in the Entrepreneurs Uncovered series on Enterprising Oxford, including a specific question on mistakes or lessons learned.

Where can I find out more about this process?

In Oxford, as it is a small(ish) place, pretty much everyone knows each other so you can start anywhere.But places like Enterprising Oxford, Oxford University Innovation, Oxford Foundry (and many others) can help direct you to the most relevant places. The key thing is to ask! There is also a big scary map on Enterprising Oxford for those who want to see everything. ■

A COLLABORATIVE STARTUP

Mathematics meets Neuroscience

Interview with Arkady Wey & Dr Pavandeep Rai— Entrepreneurs and co-founders of a start-up team

When did you start thinking about a start-up and how did you choose your partners?

Pavandeep and Arkady: We have always been interested in creating something of our own and not staying in academia. We joined a program called EPL-HIT (Enterprise Process Labs High Intensity Training), which is a program, set up by Erfan Soliman and Ti Xu, to train scientists as innovators, and provide a platform for entrepreneurship within the University. After a few interviews, students with STEM backgrounds meet like-minded people who are interested in entrepreneurship and in creating a start-up. We got to know each other, took personality tests and tried to match with people with similar interests. For us though, it was much more a case of happening to sit next to each other during the first meeting and finding we could be a good match - despite the structured program for forming a team, the process actually ended up being quite organic.

Arkady: I am an applied mathematician working within the EPSRC CDT in Industrially Focused Mathematical Modelling (InFoMM) in the Mathematical Institute at University of Oxford. My academic work is in partnership with an American materials manufacturer that supplies other companies with parts for medical devices, amongst other things. I'm generally interested in problems within medicine and biotechnology. This start-up project is the next step for me, as I move further towards real-world challenges.

Pavandeep: I was confused about what I wanted to do after my postdoc. I knew I wanted to stay within healthcare and life sciences but wasn't sure where to apply my skills. So I did many different things to try and understand what would interest me. That's why I participated in the EPH-HIT program.

Choosing the team is really crucial and it was not an easy task to decide if another person could be the right partner for your team. It was quite intense, and we did a lot of exercises together for this. This was really the purpose of the program, rather than the venture building. It lasted about 2–3 months, with the summer semester being more technical.

How did you find the right idea for the project and what is it about?

Arkady: Our focus has been on "Needs-Led innovation". We started by thinking about problems within our everyday lives and researching large real-world challenges on the internet. It's important to do lots of reading, listening to podcasts and thinking. We spent about six months doing that, in order to choose the right problem, and we're still doing that now—you never really stop researching the problem, and reshaping the solution based on this research.

Pavandeep: With my background in Parkinson's and rare diseases I had experience with working with people with dementia and other neurological conditions. We realised that patients' support groups are very common out there, but what about the people who look after patients? What about the support they need to provide, despite not having a scientific background or any understanding of their new responsibility? They are also isolated from each other and don't feel supported themselves. So, we felt we could do something there.

What was the first thing you did in order to put this idea into a project?

Pavandeep and Arkady: First of all, you have to believe in your idea, to have passion for it and think there is really a need there. Thanks to the program we got in touch with experts who could advise and give feedback. We have spoken to mentors and prepared a business plan. We did a market segmentation, to find competitors etc. Then, we got in touch with a charity to start testing our idea. We are working with a charity called The Lily Foundation, and we will test our MVP with them, and find out if it works and if something has to be changed. The process will be extremely iterative. We have prepared and sent surveys to reach as many people as possible, to obtain feedback and obtain a better understanding of the problem and the associated needs. Once tested, we can pitch the idea to get more funds. It's so useful being part of the University of Oxford, as there are so many useful contacts within the University. We also applied for and successfully joined ImagineIF, a global accelerator for early-stage ventures, which is run by the Innovation Forum. It has made it possible for us to develop our idea into a venture and we will be pitching the concept to gain investment in the coming months.

What do you think are three qualities that are important for a successful entrepreneur?

Arkady: I would say especially three skills: (1) Multitasking, (2) Patience and (3) Being collaborative. (1) Because you need to learn to do different tasks at the same time, especially if you are doing another job or a PhD; (2) Because it does not happen overnight and takes a very long time to think about the best idea and to put it into practice. You have to be prepared to try things and for them to fail; (3) Because you need to work as a team, and it's also essential to spread the word by networking.

Pavandeep: I would say first of all communication and networking and then a questioning nature; we are lucky in the fact we have mentors we can speak to, but one important thing is being proactive in contacting people; you have to be able to speak about your idea to as many people as possible and listen to feedback. You need to have the ability to communicate what you are doing; then creativity and perseverance are important aspects.

In the team we have different personalities and roles – finding co-founders that can be complementary is also crucial for the success of the project.

What skills from your scientific background and as a post-doc researcher you found helpful?

Pavandeep and Arkady: There are definitely similarities: having ideas, selling them, finding investment to fund your idea, communicating your idea, managing a project; I found it easy to transit, it's just a different language really.

Learning skills of business was tricky but not impossible – I actually googled everything. Then I read lots of articles and resources online.

What do you wish you had known before you started?

Pavandeep and Arkady: I wish I had started this sooner and done the whole thing earlier because it's a long process to verify if an idea works or not. I think it was a lack of confidence that prevented me not starting this before, and a lack of certainty of the process. You have to be willing to take some risks.

What advice would you give to people who would like to embark in a similar project?

Pavandeep and Arkady: Do your research and talk to others; take an idea, play with it, mould it, and figure out early if you are spending time on the right thing; always seek feedback.

Join accelerators if you can. No matter how early you are in the process, it's a good way to start speaking to people, even if you're not fixed on a particular idea. This whole process will help you to determine if there is a need for your idea in the real world. ■

PHENOTYPE MEETS PHENOMICS

Spin-off entrepreneur shares his story

When looking for inspiring young entrepreneur to enlighten our readers about the life in biotech industry, *Phenotype* had to look no further than Christian Regenbrecht, who has emerged as the founder of a successful SME (small-medium enterprise), CELLphenomics, which aims to help the biotech and pharma industries create innovative testings of novel anti-cancer drugs using patient-derived 3D cell culture models. It was an honour to sit down with Christian and have a candid conversation about his journey from academia as a group leader at the Charité University (Berlin) to a successful entrepreneur.

Christian completed his PhD at the University of Bonn and his postdoc at the Max Planck Institute for Molecular Genetics in Berlin. He then moved to the Charité University as a group leader, and was subsequently appointed head of the core-facility for functional genomics. In 2012 Christian was awarded the innovation award from the states of Berlin and Brandenburg for his work on the Oncolyzer, a software to analyse patient data in real-time. Christian is a speaker and a member of numerous national and international societies and advisory committees.

***Phenotype*:** When did you realise you wanted to start your company?

Christian: It was more of a gradually formed decision than an exact moment. Matters at academia became more and more daunting. People without any scientific qualification decided what consumables were ordered based just on price, and not on the purpose. For example, I once ended up with thousands of pipette tips that were useless for my group, as they did not fit on the pipettes we used. The lady in the purchase department happily proclaimed that she had negotiated a great price when I called her to return those pipette tips [Christian was not able to return them]. So I traded pipette tips for useful things the next 2 years.

***Phenotype*:** What surprised you about post academia life?

Christian: Well, first of all, that there actually is a life post academia! I mean let's be honest, people inside academia are arrogant enough to believe that academia is the only true path for a scientist, which is completely wrong. I have had the pleasure of meeting many smart and skilled scientists from pharma and biotech companies. They were not only smart, but great to work with. I was also surprised to see how swiftly things can move when you make your own rules, and hire the people you want without being compelled to consider formal qualification and instead are free to make hiring decisions based on the work ethic and attitude of applicants.

***Phenotype*:** What according to you, are the three most important qualities of a successful entrepreneur?

Christian: Well, to begin with, a certain amount of stubbornness/persistence is good. If you are not willing to fight for your ideas, who will? An ability to tolerate frustration, which I guess, is intrinsic to every good scientist. And the third important quality is good communication. If you cannot communicate your science, or your ideas in general, it will be very difficult to engage investors, customers and clients. You must be able to clearly convey the broad idea without getting into meticulous scientific details, no matter how fascinating YOU think they are.

***Phenotype*:** What should be the first step for someone interested in starting their own company?

Christian: The first step should be self-assessment; asking yourself if you just want to leave academia, or if you truly want to start something new. Just running away from something isn't an excuse enough and won't lead you anywhere. Once you have a clear idea of the "why", you should ask, "which problem do I want to solve?". Once you can phrase this on a napkin – as the best ideas don't need too much explanation – you should find your target market. And by market I not only mean customers and competitors, but all stakeholders. This may be special interest groups, professions, politics, public opinion, etc.

If you still want to carry on after this step, aim for it and be prepared to work harder than ever before. Even harder than on those experiments that "reviewer 3" is always asking for [is laughing].

***Phenotype*:** Did you have any experience in industry before?

Christian: The closest thing I had to working in an industry, was being PI in a large consortium together with some pharma people. In general, I think working for an industry is not much different than working in a competitive research organisation such as Max Planck Society, or Europe's largest university hospital [Charité]. It is mostly about ego, politics and sometimes meeting absurd expectations. So, in terms of the pitfalls I think I was mostly well prepared for challenges that came with founding two companies.

***Phenotype*:** Three words to describe what it is like at your company?

Christian: Best. Job. Ever.

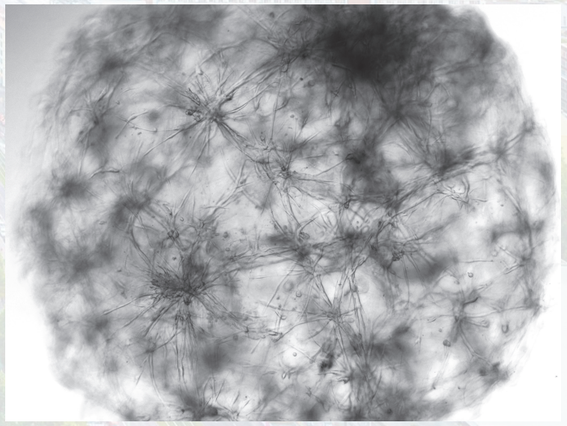
***Phenotype*:** What do you wish you had known before you started?

Christian: I wish I knew some basic principles of business administration. There are so many administrative things you need to keep in mind, approvals for biology labs, tax-related stuff, insurance questions. These matters consumed more time than I was expecting. If you are lucky, you find somebody complementary to your own skill set who will cover this area. I solved the problem by co-funding one of my PhD students for an MBA course; this student was interested in these kinds of things and I trusted them. It is really good, if you don't have to oversee everything.

The second thing that I wish I knew before is the importance of putting things in writing. Contracts last longer than friendships, but I will save that story for my memoirs!

***Phenotype*:** You are very active in outreach and we have just heard a brilliant talk by you about life post academia. You were also on TV where you talked about what you do. What motivates you to address students/postdocs and the public?

Christian: Most of the research in my academic life was paid by the taxpayers. Therefore, I believe they are genuinely interested to know how their money is spent. Also, as most of scientists know, in comparison to other professions like MDs, scientists are poor at lobbying. If we do not raise awareness about the policy issues regarding academic career progression, the general public will never know that there are real people with real struggles behind it, and in turn, will not be able to understand the problems we face during PhD or postdoc time. Specifically, here in Germany, where you have the "Hochschulrahmengesetz", roughly translating into "academic framework law" which basically says, that if you don't have a permanent position after 12 years including your PhD thesis, you have to leave academia, you only can create awareness of the academic precariat. But leaving politics aside – I really enjoy what I am doing and I really enjoy educating people about what I am doing. ■



MODELLING BIOLOGY

In conversation with Prof. Jana Wolf

Forging novel directions by combining research from separate fields requires a vast outlook and a balanced perspective. As science is becoming more and more interdisciplinary, single-track research can soon become a thing of the past.

To provide some inspiration to our readers, Phenotype interviewed Professor Jana Wolf, who seamlessly integrates mathematics, physics, and biology to answer some of the most fundamental questions in science.

Professor Jana Wolf is a theoretical biophysicist who applies her command in mathematical modeling to understand and predict the influence of metabolism to cancer progression. She serves as a Professor at the Institute of Mathematics and Computer Science at the Free University Berlin and a Group leader at the Max Delbrück Centre for Molecular Medicine. Professor Wolf has researched in the UK, in the Netherlands, and in Japan and has experience of working in both academia and industry. Her research interests include mammalian signalling pathways and gene-regulatory networks in health and disease that Jana and her team analyse by mathematical modelling.

Jana has served as an elected member of the MDC supervisory board and board of trustees and was a Member and elected co-speaker of the Scientific Committee of the Berlin Institute of Health.

Jana currently serves as an elected Member of the project committee for the research concept e:Med of the Federal Ministry of Education and Research (BMBF), and as a Member of the Helmholtz Information & Data Science Incubator. Since 2015 Jana is an elected member of AcademiaNet-Excellent Woman Academics Nominated by the Helmholtz Association of German Research.

***Phenotype*:** Thank you, Jana, for agreeing to do this interview with Phenotype. It is very exciting to interview a real mathematician! How did you get into maths?

Jana: Actually, I am not a real mathematician! I studied biophysics — this is a field that combines biology, physics and maths. I would have preferred to study biomathematics, but that was not possible at the time. I studied at Humboldt University, which was one of two universities at the time that offered biophysics. The programme enrolled five students each year.

***Phenotype*:** Is anyone in your family also a scientist?

Jana: No, actually. My mother is a medical doctor and my father was a professional musician. They shared their enthusiasm about their fields and always encouraged us to follow our interests. I was interested in natural sciences quite early on. I loved maths, biology and physics. At first, I was scared of chemistry, but I later found it very fascinating. I went to a school with a specialisation in maths and the natural sciences.

***Phenotype*:** How did you choose your study course?

Jana: After school I was looking for a degree program (or study) where I could combine my interests in various sciences, and the only thing that sounded interesting and cool to me at the time was biophysics. I did a diploma and PhD in theoretical biophysics — which now would be called computational systems biology. I started working on mechanistic questions and became then interested in applying theoretical models and approaches to relevant problems in disease research. Therefore, I first went to the Charité for a postdoc and worked on signal transduction in cancer cells, and then I worked on that at GlaxoSmithKline, where I developed models of the MAPK pathway to analyse how combined drugs would work.

***Phenotype*:** How and why did you come back to academia from industry?

Jana: I really enjoyed working in the pharmaceutical R&D environment, but I was interested in academic research where you can set and address your own questions — which might be hard in industry in the long term.

***Phenotype*:** Did you have mentors or people who have inspired you along the way?

Jana: The first, and a very important one, is my PhD supervisor Reinhard Heinrich — one of first theoretical biophysicists. He always had a very keen interest in understanding design principles in biology; he developed and analysed models for a wide range of systems and so it was always very interesting to work with him. I also learnt a lot from experimental collaborators who taught me about their fields in biology.

I think one always has many mentors because one learns different approaches from different people: colleagues, friends or inspiring scientists from history.

***Phenotype*:** How did you come to work on the topic you are working on right now?

Jana: I was always interested in using mathematical and computational tools to bring new insights into the experimental biological field. The theoretical community before 2000, which was very small, had a keen interest in analysing fundamental phenomena — like biological rhythms or switch-like behaviour and regulatory properties. This was often studied in small example systems, but at the same time it became clear that diseases like cancer were determined by the signaling pathways and gene expression — and these are rather complex networks. So, I thought that one has to apply the theoretical approaches that had been established in cancer research to develop models for these pathways — that's what I have also done at GlaxoSmithKline. Therefore, I ended up modelling MAPK, NF-κB and Wnt signaling, which are prominently disrupted in cancer. It is becoming increasingly clear that metabolism plays a big role in cancer, and our aim is to combine the analyses of these networks to come to an integrative understanding.

***Phenotype*:** What would you recommend to people who want to pursue computational biology as their field of research?

Jana: I think biology as a field is changing and becoming even more interdisciplinary. Whatever people are most interested in, they should follow it further — whether they study biochemistry, physics, engineering or maths. There are many ways to enter the field [of computational biology]. You should follow your own interests in your studies because, ultimately, the computational biology groups are mostly composed of people with different expertise and it is that multidisciplinarity that creates the best ideas.

***Phenotype*:** What is the most rewarding thing about what you do?

Jana: What I really like the most is developing ideas by discussing with colleagues or students.

***Phenotype*:** So for potential collaborators — what kind of data should they give you and what kind of outputs are they going to get?

Jana: This is not the way it works! Usually, people are approaching us with a certain question and what we are doing using models is formalising hypotheses about biological mechanisms that can be tested based on data. So, it is not most important what kind of data potential collaborators already have to hand over, since its not a pure data analysis where you get a parcel back with some analysis results. It is rather a very interactive discussion about which kind of question you would like to address, what kind of hypotheses and data are there and if there is a way to develop a model to solve that question.

The model then allows to answer questions which cannot be answered by experiments alone — and that is usually the point.

***Phenotype*:** That's a huge advantage, of course, because there are many things which cannot be answered by experiments.

Jana: Yes, for example one can predict the time course or concentrations of metabolic intermediates that cannot be measured. Or one can discuss different molecular mechanisms or cross talk among networks and which ones fit better to the data. There are different ways of doing it. So, it is not [about] the kind of data you have, but it is an interactive process to come to a new insights in biology.

***Phenotype*:** What is the most common misconception that biologists have about modelling?

Jana: A common misconception is that modelling is always very fast and another, that people doing theory are scary!

***Phenotype*:** What is your lab like?

Jana: It is an interdisciplinary crowd. We have people from physics, bioinformatics, biophysics, or bioengineering. We also have people from biochemistry who are trained in modelling — there you need a really good background in maths.

***Phenotype*:** Where do you see the field going in the next ten years?

Jana: I think we will see a revolution of biological and medical understanding due to extensive data collections on various levels and comprehensive analyses of these. It will be possible to investigate these complex systems in great detail, both with respect to their spatiotemporal resolution which allows for a deeper characterisation of the networks and the occurrence of perturbations in different diseases or individual patients. This will lead to a new understanding of health and disease and will open new avenues for a truly personalised treatment of patients. ■

Photo by Heidi Scherm

BREATHTAKING MICROBES

Linking the lung microbiome to asthma

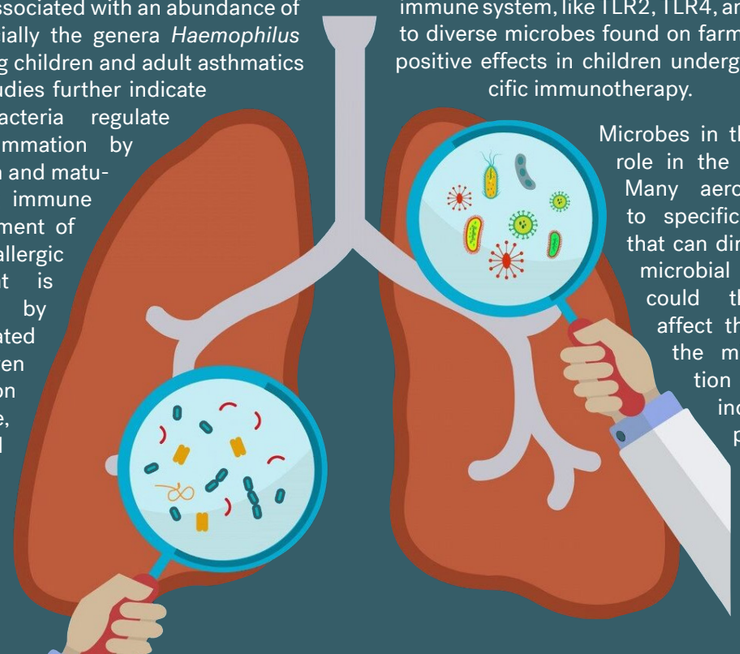
By Vinaya Roehrl. Vinaya is an undergraduate in Biology at St Peter's College, University of Oxford.

Asthma is the most common chronic respiratory disease, affecting more than 300 million people worldwide and killing about 250,000 each year [1]. It also poses a substantial socioeconomic burden. It is a multifactorial and heterogeneous disease characterised by diffuse narrowing of the bronchi and includes several disease phenotypes and endotypes. As with many other respiratory diseases, asthma is associated with altered microbiota.

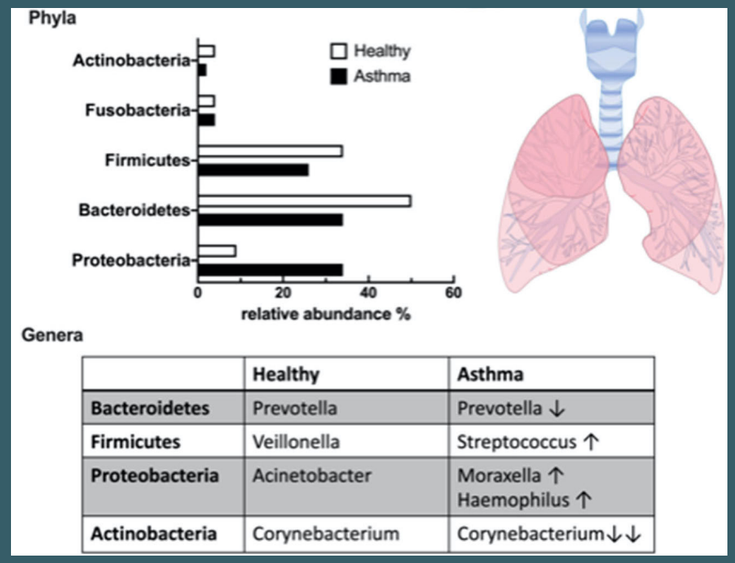
Contrary to the previous belief that healthy lungs are sterile environments, it is now unequivocal that they harbour a dynamic ecosystem composed of diverse microbial communities. This was confirmed by sequencing 16S ribosomal RNA. Lung microbiota play a significant role in the regulation of immunophysiological functions, and as with every lung disease studied to date, the lung microbiome is altered compared to that of healthy controls [2]. In the case of asthma, disease development is influenced by environmental and other exogenous factors synergising with genetic predisposition. The shaping of the lung microbiome during birth and very early life seem to play a role in the onset of allergic asthma [2]. The healthy lung microbial composition is characterised by a prevalence of bacteria belonging to the phyla *Bacteroidetes*, *Actinobacteria*, and *Firmicutes* [3]. However, viral respiratory infections are associated with an abundance of *Proteobacteria*, especially the genera *Haemophilus* and *Moraxella* in young children and adult asthmatics [4]. Immunological studies further indicate that commensal bacteria regulate allergic airway inflammation by altering the population and maturation status of lung immune cells [5]. The involvement of resident microbiota in allergic asthma development is primarily supported by data showing exaggerated Th2 immunity-driven airway inflammation in germ-free mice, whereby the total numbers of lymphocytes and eosinophils were also elevated [6].

Evidence arising from both human and animal studies suggests that the development of allergic diseases, including asthma, may be dependent on the bacterial communities residing in the gut supported by the gut-lung axis [1]. The use of antibiotics during maternal and early life stages has been shown to disrupt gut microbiota. Apart from antibiotic exposure, formula feeding [7] and Caesarean-section delivery [8] have been correlated with differences in infant gut microbiota composition, which pose a heightened childhood asthma susceptibility compared with breastfeeding and vaginal delivery.

Other environmental exposures during early life create differences in microbiota diversity. It has been shown that dust from households with pets enriched cecal microbiota and downregulated Th2-mediated airway inflammation. An experiment where mice were exposed to dust caused by living with dogs indicated a change in lung microbiome, when compared to mice kept separate from dogs [9]. Similarly, the environment provided by growing up on a farm and consuming raw milk has been shown a two-fold reduction in the incidence of asthma and diseases [10]. The optimal farm effect for children seems to correlate with a higher number of different animal species encountered already during pregnancy, supporting the expression of receptors of the innate immune system, like TLR2, TLR4, and CD14. Exposure to diverse microbes found on farms has even shown positive effects in children undergoing allergen-specific immunotherapy.



Microbes in the air also play a role in the onset of asthma. Many aeroallergens belong to specific protein families that can directly interact with microbial constituents and could therefore directly affect their virulence and the microbial composition of the lungs. This includes certain pollen types, which have their own microbiome and could interfere with allergic sensitisation and lung inflammation. Additionally, air pollution is associated with the worsening of lung infections as they can increase free radical production in the lung, consume antioxidant ingredients, and cause oxidative stress [11]. It has been shown that air pollutants decrease the relative abundance of *Bacteroidetes* and *Fusobacteria* but also increase the relative abundance of *Firmicutes*, *Proteobacteria*, and *Actinobacteria* in the oropharyngeal mucosa.



Genera

	Healthy	Asthma
Bacteroidetes	Prevotella	Prevotella ↓
Firmicutes	Veillonella	Streptococcus ↑
Proteobacteria	Acinetobacter	Moraxella ↑ Haemophilus ↑
Actinobacteria	Corynebacterium	Corynebacterium ↓↓

Relative abundance of the five most common bacterial phyla in the lungs of healthy and asthmatic subjects. Phyla *Actinobacteria*, *Firmicutes* and *Bacteroidetes* are less abundant in airways of asthmatics, while *Proteobacteria* are enriched. The dysbiosis of the lung microbiome is caused by some bacterial genera having a growth advantage (*Moraxella*, *Haemophilus*), while some are less abundant (*Prevotella*, *Corynebacterium*). Credit: Hufnagl *et al.* (2020) [4]

Several clinical strategies have been proposed to treat and prevent asthma. Probiotics have been shown to induce positive effects against asthma [12]. Lactic acid bacteria in particular seem to have a direct effect on the maturation of the gut barrier and development of tolerogenic dendritic cells, which counteract microbiome dysbiosis in allergy and asthma. Bacterial lysates may also reduce respiratory tract infections and influence asthma via immunoregulatory mechanisms, but their influence on lung microbiota is still unclear.

Overall, microbe-depleting drugs and environmental factors in utero and in early life stages are the main contributors in the development of asthma. They are also associated with induction of lung microbiome dysbiosis and inflammatory pathway activation. As there is great variability in lung and gut microbiota among humans, it has been difficult to make definitive conclusions on the mechanisms by which microbial dysbiosis contributes to severe asthma and how much of a role environmental factors play. Further study of the gut-lung axis will therefore allow for a deeper understanding of these mechanisms and more impactful prevention and treatment methods for asthma and other respiratory diseases. ■

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TINY BRAINS, HUGE INSIGHTS

Memory: a fly's eye view

By Dr Aditi Mishra. Adita is a postdoctoral research at Prof. Scott Waddell's group at the Centre for Neural Circuits and Behaviour (CNCB), University of Oxford.

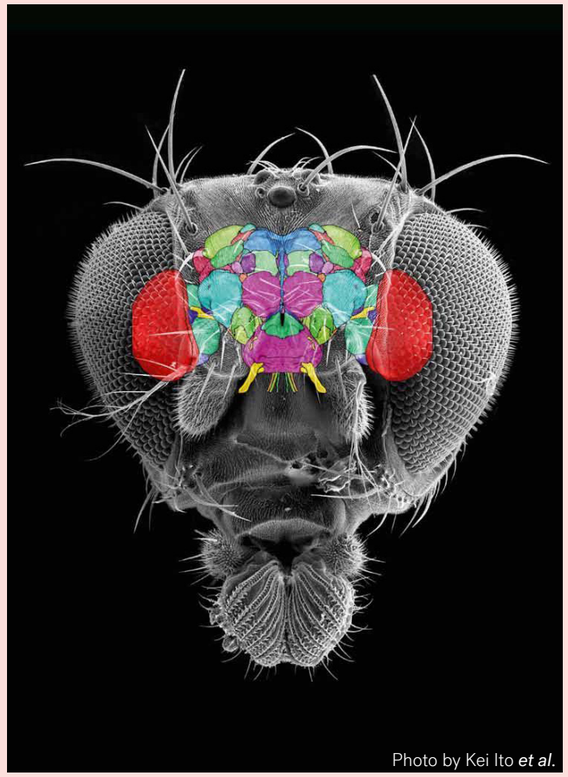

Photo by Kei Ito *et al.*

Invertebrate model systems such as fruit flies have played an important role in determining the molecular mechanisms of learning and memory. Extensive knowledge of the fly brain, from small molecules and neuronal networks to behavioural assays and genetic tools to investigate behaviours, makes fruit flies an apt model system to investigate how the brain forms, stores and retrieves memories.

This article highlights memory processing in the fly, and provides insights into the methods used to probe neuronal function.

Fruit flies can learn to associate an odour with punishment, such as electric shock or quinine, or reward such as sucrose [1–4]. Olfactory memory in fruit flies is assayed using a T-maze **(Figure 1)**. Naïve untrained flies (2–5 days old) in groups of ~100 are exposed to an odour with simultaneous, either appetitive (sucrose) or aversive (electric shock) reinforcement for one to two minutes. After a brief rest, they are exposed to a second odour without any reinforcement for one to two minutes. Memory is measured as a choice between the reinforced and the unreinforced odours. Typically, flies that are trained with electric shock avoid the associated odour while flies trained with sugar prefer the associated odour **(Figure 1)**.

In the fly brain, the anatomical structure of neurons called the Mushroom Body (MB) is required for olfactory memory consolidation and retrieval [5–7]. The L-shaped MB is comprised of approximately 5000 largely parallel Kenyon cell (KC) axons that form two branched lobes; αB and α'β', and a horizontal lobe; γ [8] **(Figure 2)**. The KCs form a tripartite synapse with the dopaminergic neurons (DANs) and the MB output neurons (MBONs) [8–10]. The MBONs receive cholinergic inputs from the KCs and convey information to downstream systems via acetylcholine or glutamate [11–13]. MBONs can be broadly categorised as approach promoting or avoidance promoting **(Figure 2)** [14,15]. In naive flies, output from both approach promoting and avoidance promoting MBONs are balanced such that prior training the flies have equal preference towards both odours used in the assays.

During training, the odour information relayed to the KCs converges with activation of specific DANs that assign values (attractive or aversive) to the odour [16,17]. Typically, DANs in the PPL1 region in the brain are activated by aversive reinforcement and DANs in the PAM region are activated in appetitive reinforcement [18–22] **(Figure 2)**. The dopamine thus released alters the KC-MBON synapse and skews output from the MBON network to result in avoidance of or approach to the odour [23,24]. For instance, pairing of sugar with an odour activates the PAM DANs which depress the odour drive to the avoidance promoting MBONs, resuting in approach to the odour **(Figure 2)** [25].

To decipher the role of a specific neuron in memory processing, synaptic transmission from the neuron is blocked and the consequence on memory is examined [26,27]. This can be done, for instance, via blocking synaptic transmission from a pair of dorsal paired medial (DPM) neurons in between training, and then measuring memory [7,28]. This intervention significantly reduces memory measured three hours after training [7,28]. Although DPM neurons project to all MB lobes, their projections to the α'β' MB lobes are crucial for memory consolidation. When output from neurons in the MB α'β' lobes is blocked, flies cannot consolidate aversive and appetitive memories [5]. Similarly, blocking output from the αβ lobes during testing, impairs retrieval of appetitive and aversive memories when measured after three hours [5].

The fly community boasts a fully sequenced fly genome, and a database of connectomes and transcriptomes of the brain that permits in-depth investigations into the function of neurons in different memory mechanisms [29–33]. The neuronal connections identified in the connectomes inform on the neurons that might be relevant to a behaviour, just as transcriptomics endeav-

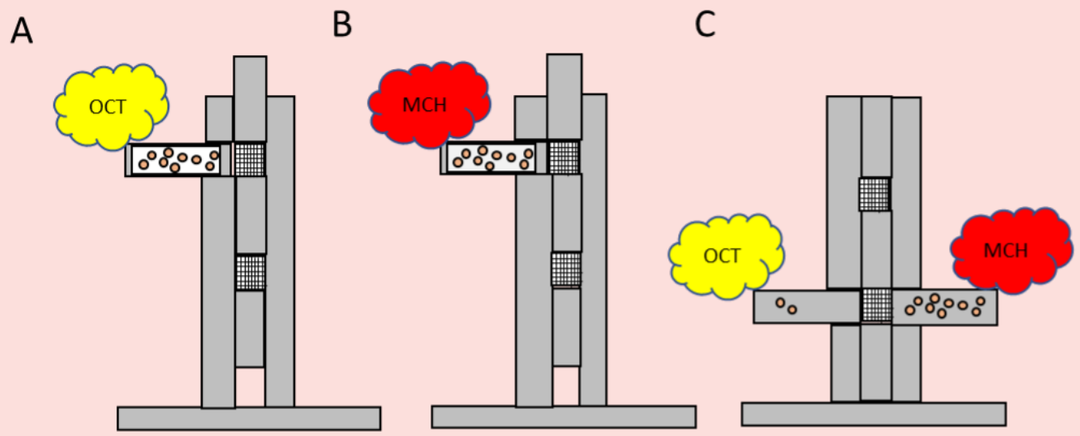

Figure 1. Schematic of appetitive olfactory memory in the T-maze. (A) Groups of ~100 starved flies are trained to associate an odour (here, Octanol) with a filter paper for 2 minutes. (B) After a 30-second break, they are trained for a further 2 minutes to associate a second odour (here, 4-Methylcyclohexanol) with sucrose. (C) Flies are allowed to choose between OCT and MCH. A preference towards MCH indicates positive appetitive memory.

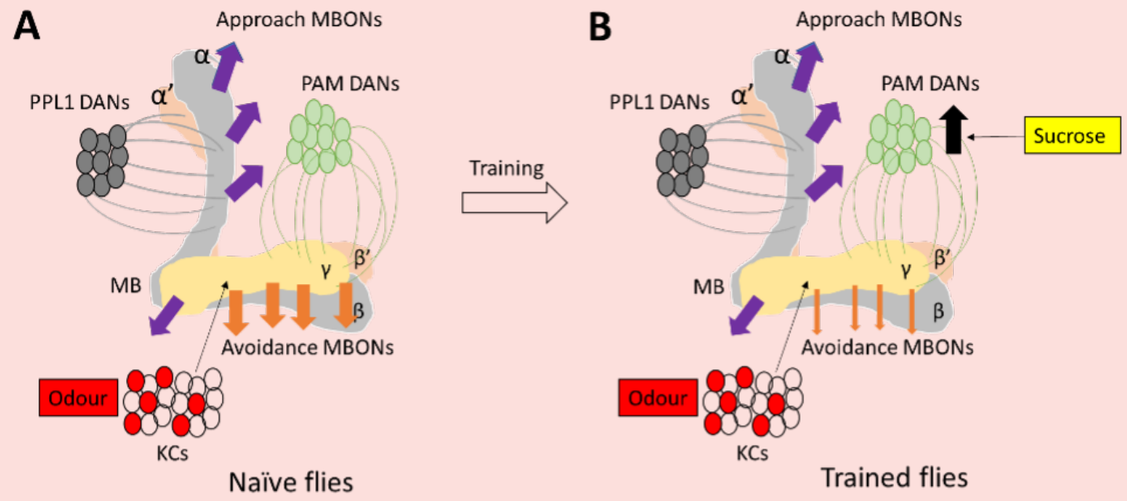

Figure 2. Learning skews the MBON output network. (A) Naïve flies: Odour information is conveyed by KCs (red cells) that form a tripartite synapse with the DANs (PPL1 cluster in red and PAM cluster in green) and the MBONs (avoidance promoting in orange and approach promoting in purple arrows) in the MB. The MBON ouputs are balanced. Thus, flies do not have a preference towards the odour used. (B) Trained flies: Upon pairing an odour with sucrose, the PAM DANs are activated (black arrow), leading to depression of the avoidance promoting MBONs (orange arrows) and enhancement of approach promoting MBONs (purple arrows). Thus, the flies approach the odour associated with sucrose.

ours to target individual neurons by their expression patterns. By using the fly brain connectomes, researchers could determine that activation of rewarding DANs underlies aversive memory extinction in flies [3]. Interestingly, extinction of the odour associated with shock reduces avoidance towards that odour, by forming a parallel extinction memory trace [3]. In a recent study, repeated spaced aversive training sessions produced two long term memories, an aversive memory encoded in the α lobe, and a "safety memory" encoded in the β' lobe [4,34]. These studies show that odour-specific memories co-exist in flies and have thus provided a window into studying how these memories interact to generate behaviours.

In summary, future research into the fly brain will provide a multifaceted view into the mechanisms of memory and psychological principles that underlie various brain functions. ■

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HACKING HEARTBREAK

Can we mend a broken heart?

Will the vessels rescue the starved heart?

By Dr Vignesh Murugesan. Vignesh is a postdoctoral vascular scientist in the research group led by Dr Nicola Smart at the Department of Physiology, Anatomy and Genetics, University of Oxford.

Heart disease is the major cause of death worldwide with a tragic figure of 17.9 million deaths each year. The heart relies on a continuous supply of fresh oxygen from the coronary arteries. When a coronary artery is obstructed during the course of a myocardial infarction (MI), the blood supply to parts of the heart is cut off, resulting in irreversible damage to the cardiac muscle cells **(Figure 1a)**. Consequently, the formula to regenerate and prevent cardiomyocyte death is still a holy grail. In general, cardiomyocytes have a very low turnover rate of 0.5–1% per year and, following an ischemic injury, an adult human heart with 2-3 billion cardiomyoctyes could lose up to a staggering 1 billion of these cells if the blockage is not dealt within an hour. Eventually, a non-contractile fibrotic scar replaces the dead cells leading to impaired function/contractility of the entire organ. In contrast, a neonatal mouse heart efficiently regenerates healthy tissue by replacing scarred regions with new cardiomyocytes, enabling the heart to function efficiently post injury. Interestingly, these regenerative components undergo a maturation process and this capability is lost after the first week of life.

An ideal scenario for functional regeneration of the injured heart involves clearing of dead tissue, restoring lost muscle and, most importantly, rapid vascularisation of the injured tissue to prevent further cell death and regenerate the injured area. A classic example to illustrate the importance of revascularisation (among other regeneration strategies) is that when vessel growth in an injured zebrafish is hindered, its natural ability to regenerate is impaired [1]. In most cases, patients who suffer an acute MI will be rushed to hospital to impart timely reperfusion therapy by virtue of coronary interventions, such as angioplasty and thrombolysis, which limit the extent of injury. Albeit a successful reopening of the occluded artery (typically major epicardial vessels), there is still evidence of compromised zones constituting severe myocardial hypo-perfusion at the microvascular level, referred to as microvascular obstruction. This is due to damage or obstruction to the microvasculature after initiation of reperfusion, a so called "re flow phenomenon".

Clinically, attempts to therapeutically stimulate vascularisation have led to minimal success. Examples involve Angiogenic therapy – the VIVA and FIRST trials, using VEGF-A and FGF-2 respectively. Poor understanding of

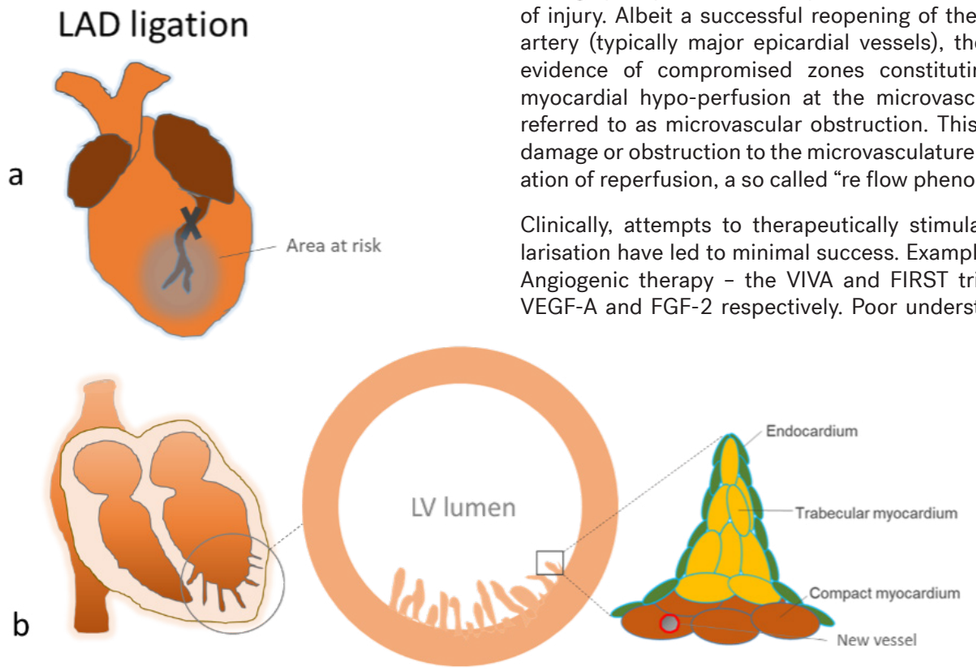

Figure 1. LAD ligation, Trabeculation and Compaction. (a) Permanent occlusion of the left anterior descending coronary artery (LAD) leads to irreversible damage within the left ventricle (LV). (b) Injury induces hypertrabeculation and compaction of the myocardium, which give rise to new vessels. Figure by Vignesh Murugesan.

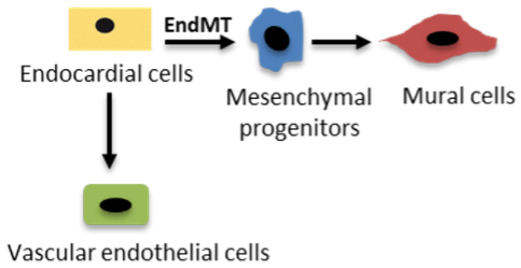

Figure 2. Endothelial to mesenchymal transition (EndMT). Endocardial cells through EndMT in the adult may give rise to Endothelial or Mural cells. Figure by Vignesh Murugesan.

the intrinsic processes that form coronary vasculature, such as the underlying endogenous mechanisms that gives rise to or that can be stimulated to generate new vessels post MI, is the prime reason for ineffective stimulation of new vessels. Previous work from our lab has unveiled that a significant proportion of the neo-vascular response post MI in adult mice arise via de-novo vessel formation. The study revealed that endocardium (the innermost thin layer of tissue that lines the chambers of the heart) is apparently one of the major contributing sources, although an endocardial specific lineage trace at the time was unavailable [2].

During perinatal development, the endocardium contributes to 60% of coronary vessels. This is possible largely via a distinct mechanism of compaction of the trabeculated endocardial surface **(Figure 1b)**. The compaction traps the endocardial cells within the muscle layer and a subsequent coalesce generates new vessels, facilitating perfusion of the nearby myocardium. However, concurrently trapping of the endocardial surface in the myocardium via compaction can trigger endocardial cells to further change their fate to become coronary endothelial cells or mural cells – which support new vessels, through the process of endothelial to mesenchymal transition (EndMT) **(Figure 2)**. After all, we know that the endocardium has been described as the major contributor of coronary vessels within the myocardium perinatally and the injury responses in the adult heart usually recapitulate developmental processes; my project aims at investigating how to reactivate the endocardium in the adult setting and to examine the neo-vascular process after myocardial infarction.

To understand how endocardial remodelling contributes to subendocardial vessels, we contemplated the mechanisms influencing endocardium during development. One such regenerative signalling pathway, which is influential for both trabeculation and compaction during development, is the NOTCH pathway. Injury has been shown to induce hyper trabeculation of the endocardial surface and, to determine whether this can be further augmented, we constitutively activate NOTCH1 signalling and examine whether there is any increase in new vessels formed post MI from endocardium.

So can we mend a broken heart? Driven by the dire need for better treatments for heart failure, I am confident that results gleaned from our ongoing research can one day salvage the oxygen-starved heart by revealing the secret source to therapeutically initiate the rescue vessels for effective myocardial perfusion. The heart can then vascularise itself to protect vulnerable cardiomyocytes and support newly formed cells. ■

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MISINFORMATION

Understanding a dangerous disguise

Opinion Piece by Atreyi Chakrabarty. Atreyi is a DPhil student at Prof. Colin Akerman's group at the Department of Pharmacology, University of Oxford.

The World Health Organisation claims we are in the middle of an infodemic. From racist conspiracies that the "China virus" was concocted in a lab, to rumours that the vaccines were a pharmaceutical profitmongering hoax, to fake ads marketing Miracle Mineral Solutions — which the FDA warned was the "same as drinking bleach" — misinformation has become part and parcel of the pandemic, and grown stronger as we have become more vulnerable.

Misinformation thrives on our anxiety. Human decision researchers, Valerie Reyna and David Broniatowski, found that misinformation framed using emotive language with a simple, coherent gist — such as the message, "vaccines cause autism" — is more likely to be re-tweeted than facts and statistics [1]. States of extreme emotional arousal such as fear, anxiety and shock are powerful motivators for spreading information regardless of its veracity. Just as Vervet monkeys have elaborate alarm calls to warn conspecifics of a predator nearby, we humans use social media to warn our social circle about perceived threats.

We tend to imitate those in our social network — a phenomenon termed "social contagion". In the monotony of lockdowns and quarantines, we have been cemented to our screens, compulsively consuming information online. Social media platforms provide a breeding ground for a vortex of information sharing among friends and followers with similar perspectives, and personalised algorithms create echo chambers which drive a positive feedback loop.

Twitter believes user-controlled fact-checking could be an effective means to tackle the spread of misinformation. On 25 January, Twitter launched its new @BirdWatch pilot feature to enable a "community-driven solution" [2]. Complex information is often condensed into over-simplified messaging that is easy to share and disengages from critical thinking. BirdWatch will enable verified participants to flag potentially misleading tweets and write notes to add context.

However, in a paper recently published in Proceedings of the National Academy of Sciences, MIT scientists showed people were more likely to respond to fact-checking tags if they were presented once the reader had evaluated the accuracy of a headline, rather than if the information was presented before they had read it [3,4]. Crucially, the study suggests that the timing of correction matters, and feedback to action (the digestion and evaluation of information) makes the correct information "stick". Rather than labelling false information, it might be more effective to show the tag after a user has liked or shared a post. However, these interventions may not work for passive engagement, such as scrolling through a newsfeed.

Even if misinformation is corrected, it still influences our decision-making and information recall. Other experts propose a more preventative intervention: "cognitive inoculation" to increase immunity to false claims. Finland, for example, has deployed this form of anti-fake news training since 2014, and its citizens ranked first for media literacy in 2018. Other imaginative strategies might include games, such as the one created by Sander van der Linden, a University of Cambridge psychologist. In his online game Bad News, players collect points by maximising misinformation spread in a social media ecosystem. Data showed that the players of Bad News were better able to detect misinformation and had improved confidence in their evaluation of fake news.

Although disinformation is targeted, misinformation can inadvertently slip through the gaps in our understanding. Melinda Mills, Professor of Sociology at the University of Oxford, speaking at a Royal Society event about COVID vaccines, suggested a more inclusive approach. "People may have really legitimate questions, so it's important to not dismiss that as misinformation or disinformation... but actually engage with people where they are," she said [5].

The pandemic may also have a silver lining: it has bootstrapped concerted and multi-disciplinary research to identify the underlying pathology behind the infodemic, and this will further inform interventions to tackle the veil of misinformation. ■

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Forming a Functional Vasculature: Organisation is Key to Success

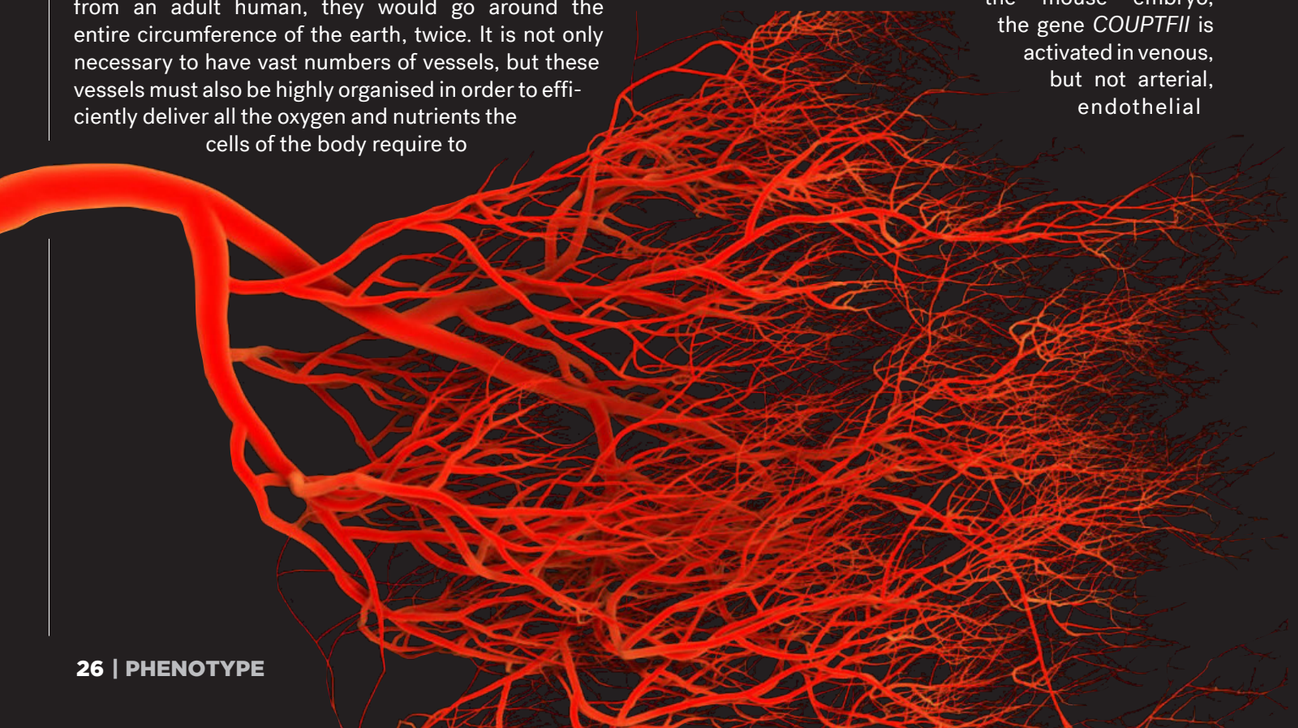
By Alice Neal. Alice is a postdoctoral scientist in the lab of Prof. Sarah De Val in the Department of Physiology Anatomy and Genetics and the Ludwig Institute for Cancer Research, University of Oxford.

There are a number of clinical situations in which the ability to manipulate the growth or maturation of blood vessels would be of great value. For example, cancerous tumours are sustained via their own tumour vasculature and metastasis is achieved via abnormal, highly permeable endothelial cell junctions. Preventing tumour blood vessel growth and/or normalising tumour blood vessels is a goal for drug developers that is yet to be realised and new targets are greatly needed [1]. In the adult human heart, therapeutic strategies are sought to increase blood vessel growth following a myocardial infarction (heart attack). The heart's limited capacity to regenerate after injury is at least in part due to the failure of the coronary vessels (the blood vessels that serve the heart muscle itself) to effectively regrow once damaged [2]. In order to achieve these goals, it is first necessary to gain a better understanding of the gene regulatory networks and their upstream signalling pathways that govern blood vessel growth and maturation.

If you were to line up end to end all the blood vessels from an adult human, they would go around the entire circumference of the earth, twice. It is not only necessary to have vast numbers of vessels, but these vessels must also be highly organised in order to efficiently deliver all the oxygen and nutrients the cells of the body require to survive. The vascular network begins as an undifferentiated mesh-like structure in the early embryo, which must then be patterned into a functional network. Vascular patterning represents a crucial and mysterious step of embryonic development.

The tubes through which blood flows are created from a highly specialised cell type: the endothelial cell. Endothelial cells are elongated cells that stick together to form a one-cell thick barrier between the blood and the tissue. Endothelial cells can be broadly categorised into three subtypes: those that form the arteries, the veins or the capillaries. It is the endothelial cells themselves that bestow the defining properties of these blood vessel types: regulating smooth muscle coverage of arteries [3], forming the venous valves [4] and establishing the permeability of the capillary bed [5].

Whether an endothelial cell becomes an artery or a vein is dictated in the early stages of development by the expression of fate-determining genes. For example, in the mouse embryo, the gene *COUPTFII* is activated in venous, but not arterial, endothelial cells. If COUPTFII is absent, veins do not form, with arterial-like vessels instead appearing in their place. Conversely, if COUPTFII is overexpressed, venous-like vessels form in the place where arteries ought to be found. Either phenotype leads to early embryonic lethality [6].



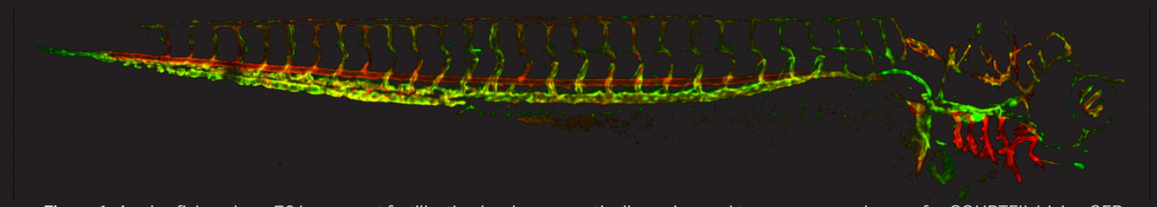


Figure 1. A zebrafish embryo 72 hours post fertilisation has been genetically engineered to express an enhancer for *COUPTFII* driving GFP expression (green) in venous endothelial cells and an enhancer for VEGF receptor 2 driving mCherry expression (red) in both arteries and veins. Yellow shows expression of both GFP and mCherry.

Through our work we aim to understand the gene networks that underpin blood vessel formation and patterning. We start by finding and characterising enhancers, which are short sequences of DNA that contain clusters of binding sites for DNA binding proteins (transcription factors). When these enhancer regions are bound by their requisite transcription factors, they form a physical loop with their target gene promoter. This allows for the assembly of the transcriptional machinery at the promoter region and thereby the expression of the gene. Enhancers and the transcription factors that bind them act as 'on/off' switches for genes, and as such are the gatekeepers of cell fate decisions. Thus the specialisation of an endothelial cell into an arterial or venous fate is governed by the availability and abundance of key transcription factors.

Using fluorescent reporter proteins in zebrafish and mice, we have been able to identify enhancers that drive the expression of crucial venous or arterial specific genes **(Figure 1)**. Analysis of these enhancers has demonstrated that venous endothelial cell fate requires signalling from the Bone Morphogenic Protein (BMP) family of growth factors. *SMAD1/5* is a transcription factor activated by BMP signalling that, by binding to venous specific enhancers, promotes the expression of vein specific genes and thus, the formation of embryonic veins **(Figure 2)** [7]. In contrast, arterial endothelial cell identity depends upon Vascular Endothelial Growth Factor signalling (VEGF), with the requirement for activation by SOX transcription factors and removal of RBPJ-mediated repression [8]. On the other hand, the ETS family of transcription factors, is necessary for both arterial and venous gene expression [9].

Finding and characterising enhancer sequences can uncover the complex regulatory networks that govern time and location dependant patterns of gene expression. By understanding the mechanisms of blood vessel patterning in the embryo, we aim not only to uncover fundamental aspects of development and cell specification, but also to provide novel targets for those wishing to manipulate blood vessel growth for clinical gain. ■

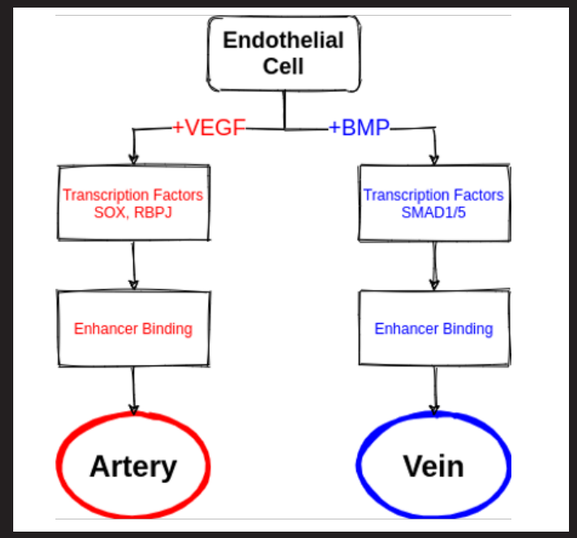


Figure 2. Signalling cascades that lead to the formation of endothelial cells of the artery or the vein. BMP signalling initiates SMAD1/5 binding at venous enhancers and thus the development of veins. VEGF signalling initiates SOX binding and removal of repression from RBPJ at arterial specific enhancers which leads to the formation of arteries.

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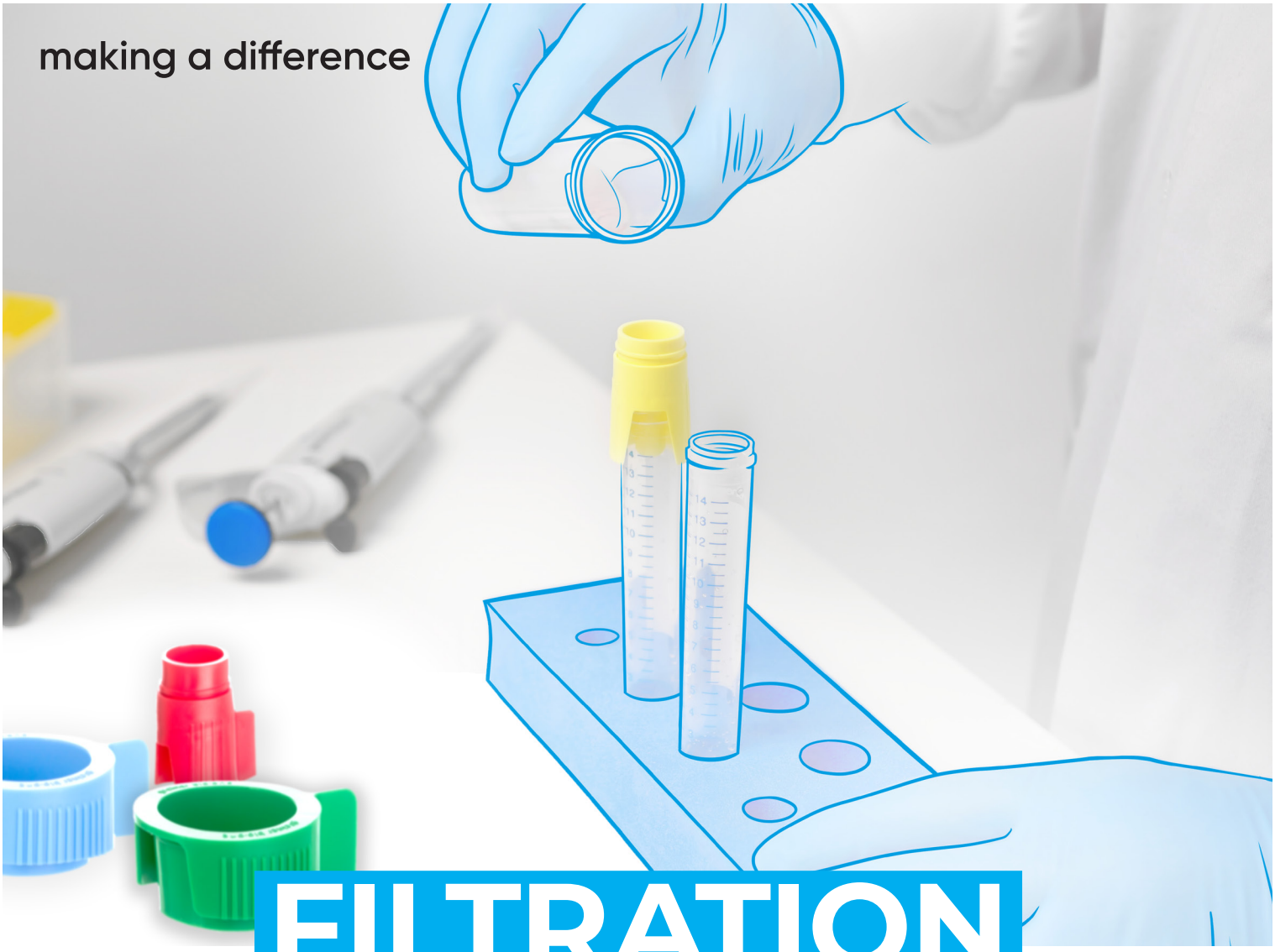
making a difference



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