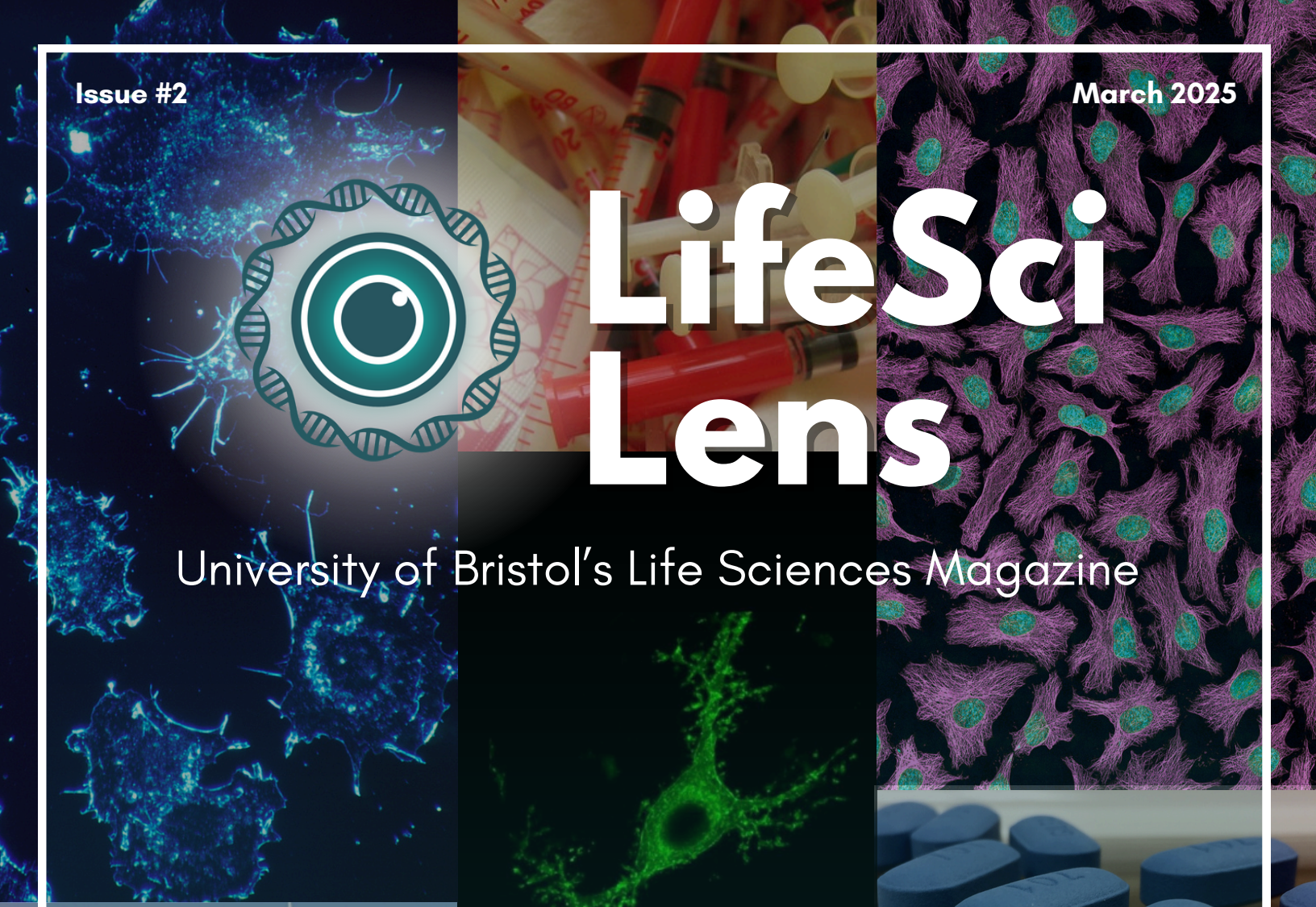
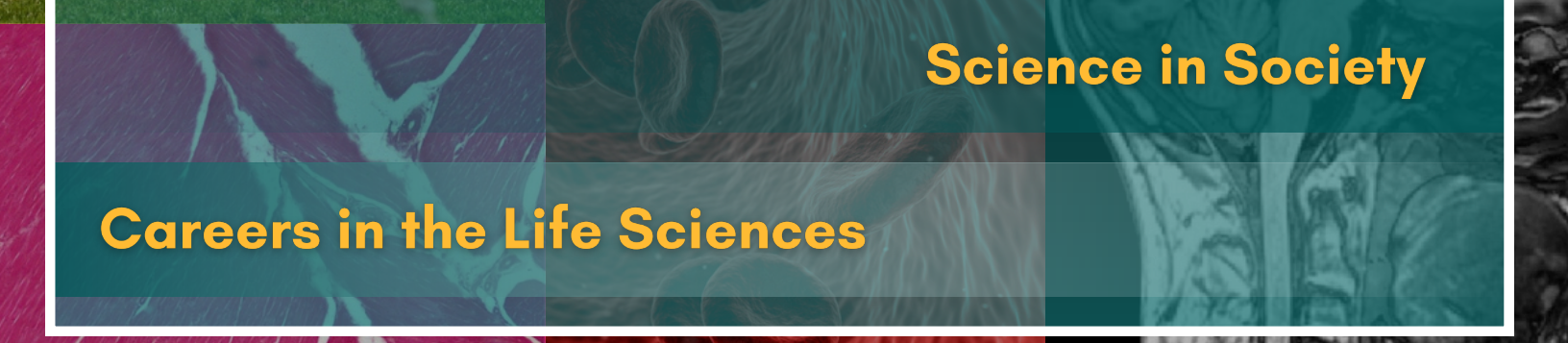
Issue #2

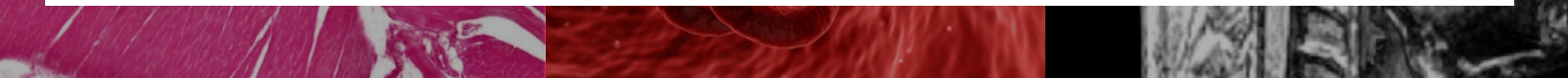
March 2025

LifeSci Lens

University of Bristol's Life Sciences Magazine







Biomedical Advances

Membrane Matters

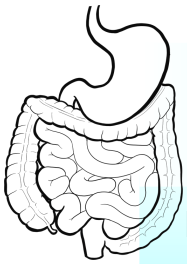
Drugs in Development

Science in Society

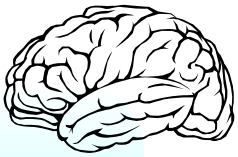
Careers in the Life Sciences

Editorial

Welcome to Issue 2 of LifeSci Lens: the University of Bristol's life sciences magazine, written and run by students, for students. In this issue we have 9 original articles covering a diverse range of topics. We have reprised the themes of Drugs in Development and Science in Society from our first issue, as well as introduced 3 new and exciting sections.



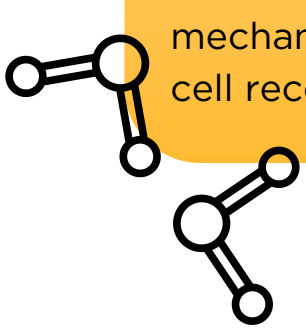
Biomedical Advances



In the last few decades, the drive for personalised medicine has encouraged studies targeting underrepresented groups, alongside the use of bioengineered approaches. This section explores the cutting-edge research paving the way for more equitable healthcare, with novel findings on gestational brain changes in women, a previously neglected area of research, as well as the growing potential for immunocompatible bioengineered organs that could cut transplant wait lists.

Membrane Matters

Cellular membranes are a vital component of life, with roles in compartmentalisation, controlled transport, and signalling, both between and within cells. This section investigates how membrane processes can work for or against an organism, discussing current theories behind an essential bacterial protein translocation mechanism, while illustrating the potential for cancer cells to hijack cell recognition and signalling systems to evade immunity.



Drugs in Development

Following on from our first issue, we continue our review of drugs and their development. This single article takes a detailed look at lenacapavir, a new long-acting drug used to treat and prevent HIV.

Science in Society

While Western medicine is often considered the gold standard, Western contributions to medical science should not be seen as infallible, nor be the only style of treatment relevant in the modern world. This section scrutinises the history of past ethical violations within medical studies, and underlines how culturally diverse medical knowledge should not be disregarded, especially when considering roles in patient adherence or potential alternative advantages stemming from whole-body approaches.

Careers in the Life Sciences

In the competitive environment of the science industry, it is important to reduce career barriers and learn from the experience of peers. This section shares the accounts of two students throughout either their PhD or internship, discussing the challenges and rewards associated with lab research, and giving specific details of the studies they were involved in.

Ana Miletić and Alex Radlett, *LifeSci Lens Co-founders*

@lifescilens
LifeSci Lens
UoB SU Webpage
lifesci.lens@gmail.com

In this issue...

Biomedical Advances

Membrane Matters

Drugs in Development

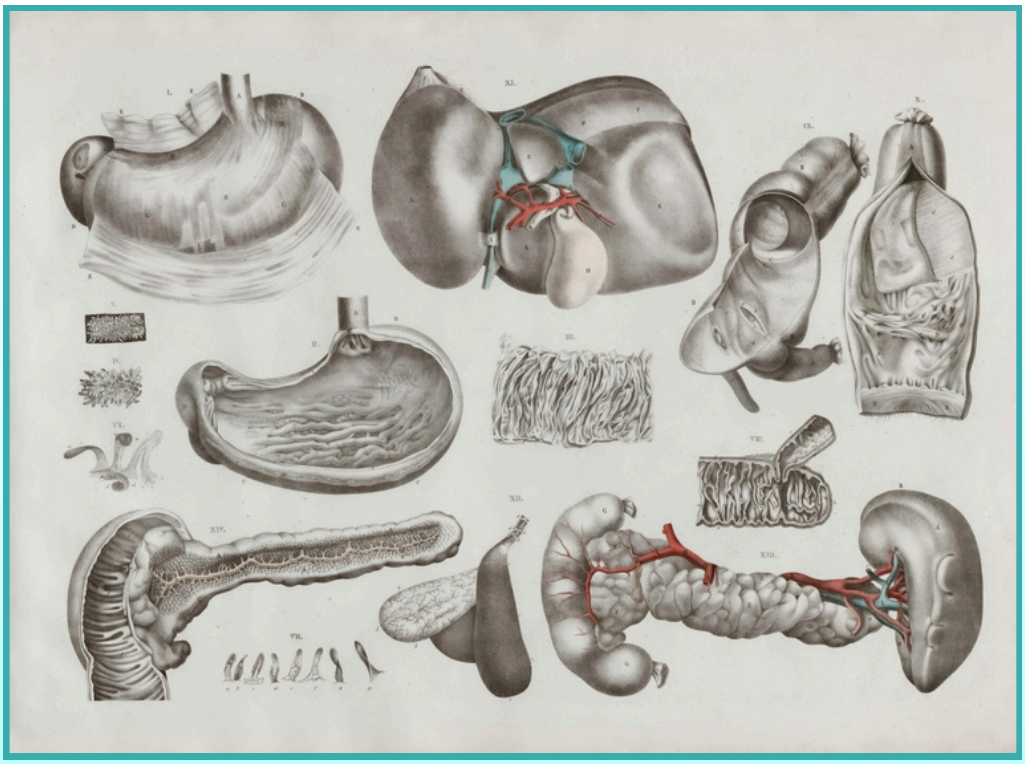
Science in Society

Careers in the Life Sciences

References

Credits

Back to contents



Biomedical Advances

Inside the Pregnant Brain:
New Study Reveals How the Brain Changes During Pregnancy

page 6

Bioengineered Organs:
Cutting-Edge Approaches in Regenerative Medicine to Transform Disease Treatments

page 9

Image credit: 1

Inside the Pregnant Brain: New Study Reveals How the Brain Changes During Pregnancy

By Annabel Thomas

For the first time, scientists have mapped brain changes across the entire span of pregnancy, addressing a gap left by previous research that only scanned the brain before and after, without capturing changes during pregnancy itself. Research by Pritschet *et al.* revealed the structural and electrophysiological changes the brain undergoes during pregnancy[1] (Figure 1). This study tracked MRI scans of Dr Chrastil, a neuroscientist who became pregnant through IVF, from three weeks before conception to two years postpartum[2,3].

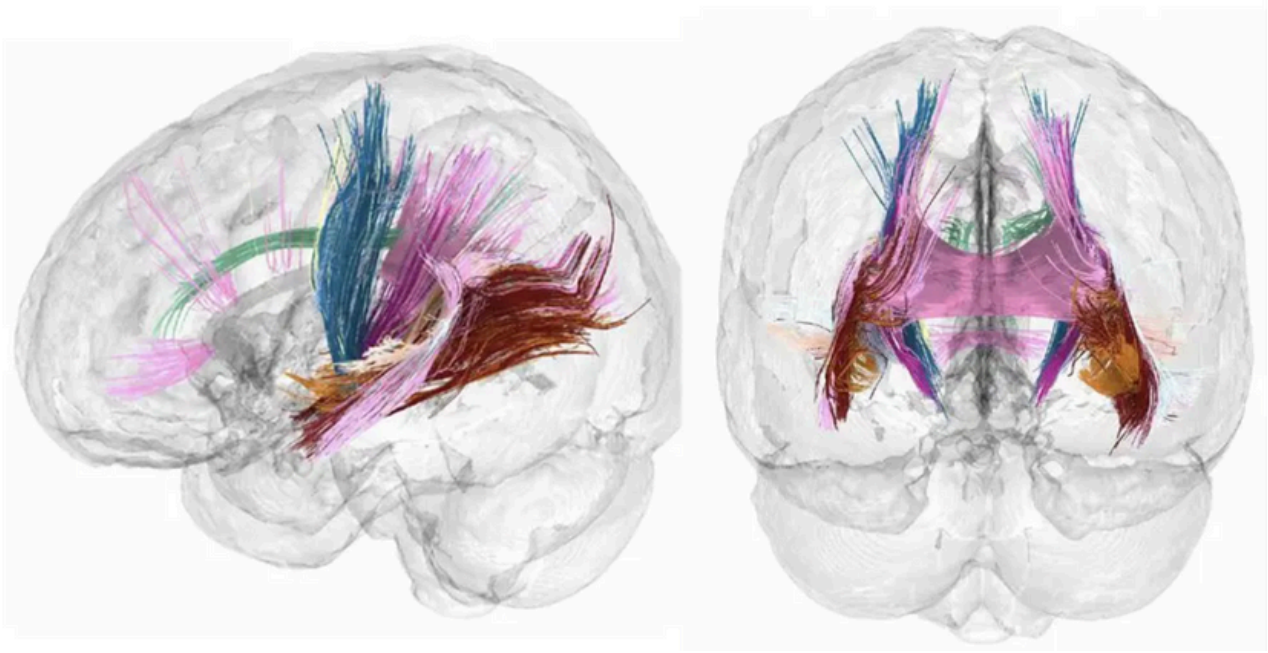


Figure 1. White matter tracts, which connect regions of grey matter, showed increased structural integrity during pregnancy[1,2].

Pregnancy triggers substantial hormonal increases that drive widespread physical changes, including transformations in the brain. Comparing scans taken before and after pregnancy, researchers observed a reduction in grey matter volume — a tissue that contains neuronal bodies, synapses, and glial cells — primarily located in the brain's outer cortex. Notably, reductions in grey matter became evident only after pregnancy, with no significant changes detected during pregnancy itself[3].

The research team observed consistent decreases in grey matter volume and cortical thickness throughout pregnancy, with only partial recovery after birth. This reduction affected most areas of the cerebral cortex and several deep brain regions, with changes surpassing those seen in non-pregnant women over similar timeframes[2].

"The study presents a detailed map of brain changes throughout pregnancy, serving as an open-access resource for the brain imaging community to deepen their understanding of the maternal brain."

White matter, which connects regions of grey matter, showed increased structural integrity during the first two trimesters but returned to baseline levels after birth. Additionally, cerebrospinal fluid in the brain's lateral ventricles increased in the second and third trimesters which then sharply declined postpartum[3]. These changes appear to be linked to shifts in steroid hormone levels, with the results showing nearly weekly brain transformations. This underscores pregnancy as a period of high neuroplasticity - the brain's capacity to reorganize and adapt. The study presents a detailed map of brain changes throughout pregnancy, serving as an open-access resource for the brain imaging community to deepen their understanding of the maternal brain. This could be utilised to explore the maternal brain's associations with health outcomes like postpartum depression. Future research with a larger sample of pregnant women will help determine whether these findings are typical and how they may relate to maternal health conditions[2,3]. The study offers insight into "pregnancy brain" or "baby brain" — the forgetfulness and

mental fog many expectant mothers report; though it stops short of confirming this effect as it was not directly assessed in the participant[3].

Overall, this research is groundbreaking, opening new pathways for understanding the maternal brain. By mapping changes that occur during pregnancy, scientists may gain a deeper understanding of brain changes. This could help researchers identify neural markers that predict postpartum depression, leading to earlier interventions and improved treatment strategies[3]. Furthermore, this research may shed light on how conditions like pre-eclampsia impact the brain, offering the potential for more targeted and effective approaches to maternal health[2].

References

Primary editor: Meredith Lott
Peer reviewers: Rezanë Kajashi, Roshni Chadha

Bioengineered Organs: Cutting-Edge Approaches in Regenerative Medicine to Transform Disease Treatments

By Sarah Al-Shahabi

The organ transplant waiting list is long, and it does not always accommodate everyone due to the need for immunological compatibility between patients and the shortage in the number of donors. According to the NHS, around 7,898 individuals were awaiting organ transplants in 2024 in the UK[1]. Additionally, about 106,000 people in the United States were awaiting kidney transplants in 2024[2]. Therefore, the necessity for new organs that are immunologically tolerable or autologous is necessary to overcome organ shortages. This will help in reducing mortality rates due to organ failures. A solution to organ transplantation is the application of regenerative medicine. Some of the main approaches to creating bioengineered organs include the use of stem cells, scaffolds, and biomaterials. Parallel advancements like disease-modelling organs are serving as foundational frameworks for the development of fully functional complex organs. Bioengineered organs have the potential to mitigate the organ shortage while also modelling different diseases to serve research purposes. Remarkably, there are engineered tissues such as cartilage, bone and skin that have been successful in treating diseases or injuries primarily due to their relatively simple structure. However, can complex organs such as the heart, lung, and liver be bioengineered successfully in the lab?

"Some of the main approaches to creating bioengineered organs include the use of stem cells, scaffolds, and biomaterials."

Designing Bioengineered Organs

Bioengineered organs are typically sourced from autologous cells, such as tissue-specific cells or stem cells like induced pluripotent stem cells (iPSCs) or bone marrow-derived mesenchymal stem cells (Figure 1), to prevent immunological rejection. Biomaterials, scaffolds such as collagen and

hydrogels, and decellularized organs serve as distinct platforms for cellular integration and attachment, each used differently to support bioengineered organs. Bioreactors (e.g. perfusion bioreactors) are machines which can help in replicating the natural differentiation of the cells within the body in order to help in producing bioengineered organs *in vitro*. They contain pumps and fluids to help in circulating nutrients and oxygen as well as in waste removal. Additionally, 3D cultures are widely used for bioengineering as they support a dynamic environment to help in growing organoids. The aim of bioengineering organs is to mimic the complexity of the human tissues, including oxygen exchange within the tissues, the vasculature and the different cell types.

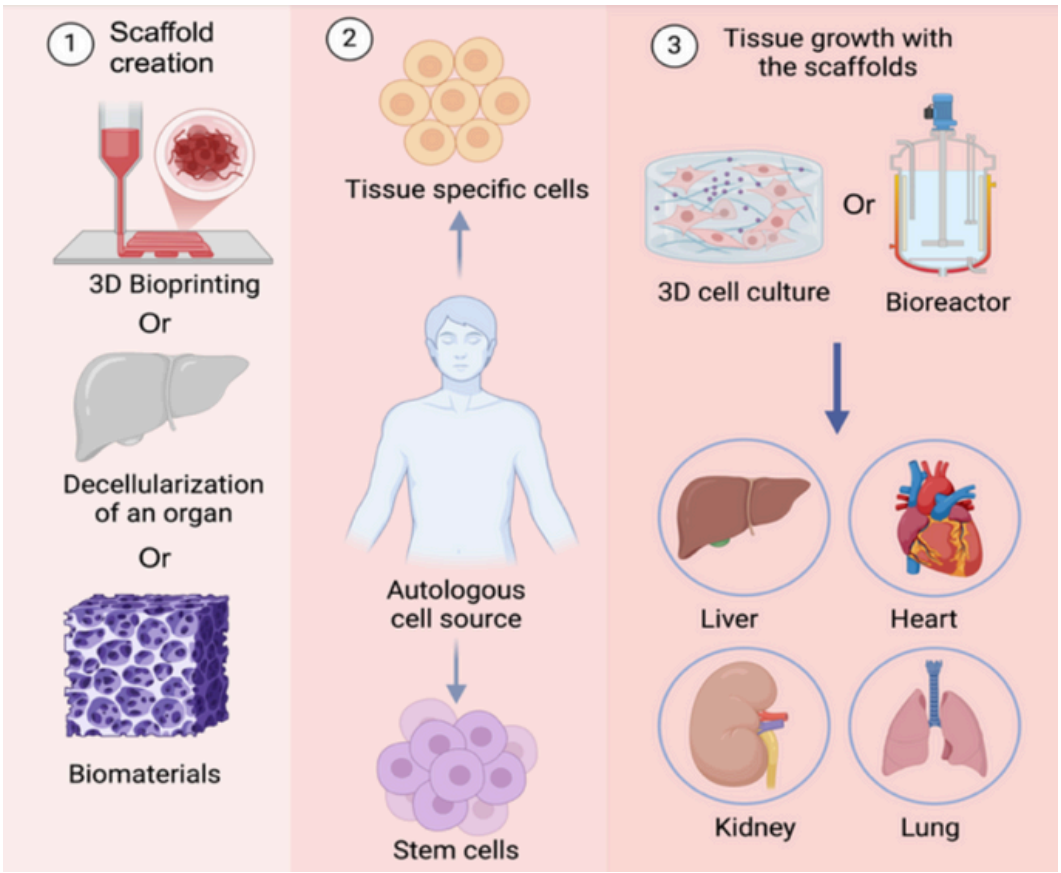


Figure 1. A simple overview of the process of bioengineering organs.

Diverse Outcomes of Applying Bioengineered Organs

Success stories in the field of tissue engineering are remarkable. For instance, a tissue engineered bladder made from autologous urothelial and muscle cells seeded into a scaffold made from a composite of collagen and polyglycolic acid was successful in treating seven patients with end-stage bladder disease and resulted in improved continence[3]. Recent clinical trials demonstrate promising outcomes in the restoration of vision for corneal diseases and blindness via the use of bioengineered corneas which replace the damaged cornea[4].

When it comes to more complex organs like the heart, the efficacy of bioengineered organs remains a significant challenge. However, in 1969 the first artificial heart was transplanted using a "cardiac prosthesis" and the artificial heart was able to support the circulation[5]. Unfortunately, the patient died three days post-procedure as a result of the invasive nature of the open-heart surgery and a *Pseudomonas* pneumonia infection. The patient received immunosuppressive medications and thus, immune cells were unable to eliminate the infection. On the other hand, the efficacy of bioengineered trachea for pulmonary diseases has been controversial, primarily because of Dr Paolo Macchiarini, who claimed that he had successfully transplanted functional bioengineered trachea into many people. However, most of the artificial tracheal transplants were made of plastic scaffolds seeded with stem cells, which resulted in the deaths of many of his patients[6].

"The aim of bioengineering organs is to mimic the complexity of the human tissues, including oxygen exchange within the tissues, the vasculature and the different cell types."

As a proof of concept, iPSC-derived hepatocytes along with other cells successfully replaced the decellularised liver scaffold and led to the formation of a miniature liver that is significantly comparable to the a liver with non-alcoholic fatty liver disease[7].

Although this approach is used to study liver disease and test various drugs in vitro, it is a crucial step towards bioengineered organs in the future. Similarly, kidney organoids or miniature kidneys are still being tested, and they aim to replicate the architecture of the natural kidney by mimicking the vasculature and filtration processes by specialised endothelial cells[8,9]. The transition from kidney miniature to fully functional bioengineered kidneys has the potential to reshape the treatment of renal failure by addressing the critical shortage of donated organs, as kidneys are the most in-demand organ on transplant waiting lists. In addition, it will reduce the need for kidney dialysis. Other studies in animal models have tested bioengineered ovaries made from follicles, ovarian stromal cells and biodegradable chitin-based hydrogels[10], as this can potentially replace hormone replacement therapies for post-menopausal women. Surprisingly, there are bioengineered models that replicate central nervous system (CNS) diseases, including Parkinson's disease (PD). Functional organoids, such as those which model the dopaminergic neurones impacted by PD, can help in testing different drugs on CNS disorders[11,12].

"The transition [...] to fully functional bioengineered kidneys has the potential to reshape the treatment of renal failure by addressing the critical shortage of donated organs..."

Ethical Considerations in Bioengineering Organs

Given the many benefits of bioengineered organs, there are some considerations that need to be met to ensure their successful development and implementation, particularly in terms of safety, efficacy, and ethical standards. Tissue engineering needs to be ethically conducted with many *in vitro* studies, followed by animal studies and safety studies. For the development of intricate bioengineered organs, the organisational structures of the tissues need to be optimised as well as mimic the natural function and molecular biology of the organ in the human body. There are other considerations that need to be accounted for, such as using the appropriate scaffolds and biomaterials.

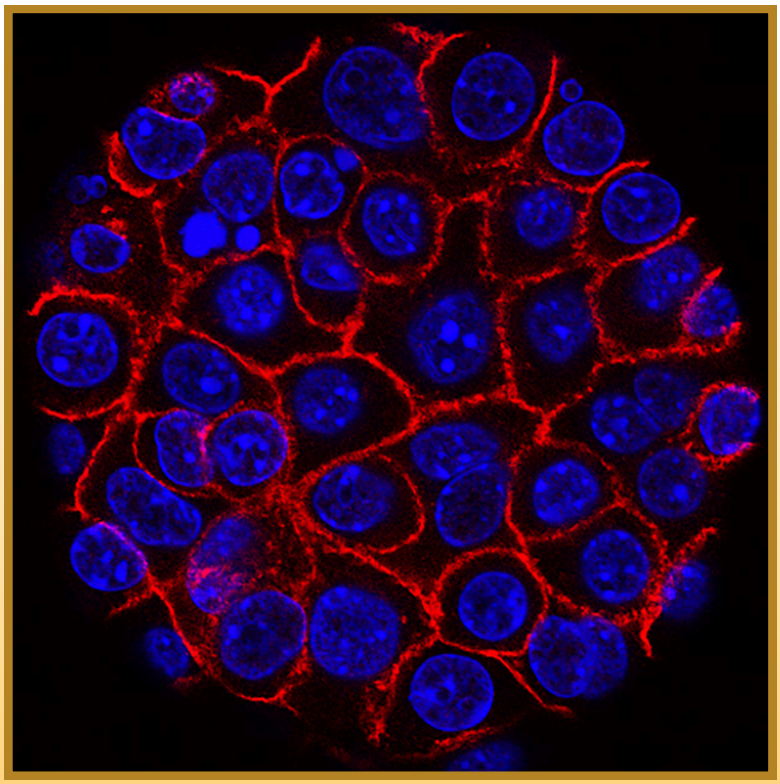
Future Perspective

The field of regenerative medicine is paving the way for sustained, long-term treatments for organ failures. The utilisation of autologous cells in tissue engineering eliminates the necessity for immunosuppressants, resulting in cost-effective, enduring treatments. Additionally, bioengineered organs offer significant advantages in modelling diseased tissues for drug testing, contributing to faster, more efficient therapeutic development. Given these benefits, one can envision a future where bioengineered organs revolutionize organ transplantation, potentially replacing the current organ waiting lists.

References

Primary editor: Rebecca Lin
Peer reviewers: Alexa Lopez, Lauren Cozens

Back to contents



Membrane Matters

New Discovery:
How Cancer Cells Use Lipids to Evade the Immune System

page 15

SecA's Role in Sec-Mediated Translocation:
Exploring the Brownian Ratchet and Power Stroke Models

page 19

Image credit: 2

New Discovery: How Cancer Cells Use Lipids to Evade the Immune System

By Tara Maziliauskas

What if cancer cells had a secret weapon that lets them hide in plain sight, even when the immune system is actively hunting them down? A groundbreaking study from Rockefeller University has revealed that cancer cells have a clever trick up their sleeve — they use lipids to shield themselves from immune detection and weaken the body's natural defences. By adjusting the structure of their cell membranes, cancer cells create a habitable environment that allows them to flourish undisturbed. Understanding how cancer cells leverage lipids for survival might just lead to breakthroughs in the way we fight the disease, opening the door to more effective cancer treatments[1].

"By adjusting the structure of their cell membranes, cancer cells create a habitable environment that allows them to flourish undisturbed."

Altered Lipid Metabolism and Tumour Progression

Lipids are the fundamental building blocks of a cell's plasma membrane and their metabolism plays a major role in the proliferation of cancer cells. These cancer cells can attract certain checkpoint proteins such as Programmed Death-Ligand 1 (PD-L1) which upregulate the production of lipids and affect signalling pathways[2].

PD-L1, specifically on liver cancer cell membranes, activates epidermal growth factor receptor (EGFR) and combines it with ITGB4 to produce a complex. This interaction activates a PI3K/mTOR/SREBP1c signalling pathway involved with changing lipid metabolism and other metabolic processes. These *in vivo* experiments confirmed that altering lipid metabolism supports tumour growth[3].

Additionally, binding between PD-L1 and its receptor Programmed Death 1 (PD-1) on a T cell induces many chemical alterations leading to the inactivation of tumour-infiltrating lymphocytes (TIL) via apoptosis (Figure 1), allowing the cancer cell to successfully evade the immune system[4].

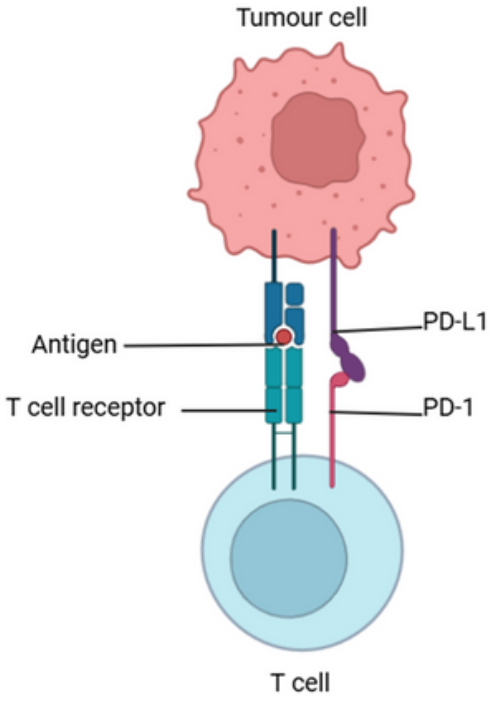


Figure 1. When the programmed death receptor (PD-1) on a T cell binds to programmed death-ligand 1 (PD-L1) on a tumour cell, the T cell becomes deactivated, allowing the cancer cell to evade immune detection. T cells are crucial immune cells that target and destroy infected or cancerous cells, defending the body against disease.

Sphingolipids and Immune Suppression

Cancer cells also alter how sphingolipids are produced, using them to create a more favourable environment for tumour growth. One example is the production of sphingosine-1-phosphate (S1P), a lipid metabolite that influences immune functions. S1P can attract T regulatory cells (T-regs), which suppress T killer cells in the tumour area. By drawing in more T-regs, cancer cells create an immune-suppressing environment that shields them from attack. This manipulation of the immune system is one of the key ways cancer cells use lipids to survive[5].

Sphingolipids also affect inflammation in the tumour environment. While chronic inflammation can trigger cancer, established tumours twist inflammatory pathways to weaken the immune response[6]. Lipid-derived signalling molecules can trigger the release of suppressive cytokines, further dampening the immune system and creating a safe zone for the tumour[5].

Glycosphingolipids: A New Target for Cancer Therapy

Given the central role of lipids in cancer's immune evasion, researchers have begun to explore ways to target lipid metabolism as a potential therapeutic strategy. One promising area involves glycosphingolipids, a class of lipids that are essential components of lipid nanodomains. By disrupting the synthesis of glycosphingolipids, it may be possible to impair the formation of these domains and weaken the cancer cells' defences against the immune system[1].

Future research will determine whether this lipid-based mechanism holds true for multiple types of cancer. The team observed this mechanism in various cancer types but noted a particular prevalence in *KRAS*-dependent cancers. Somatic mutations in the *KRAS* gene cause cancers like pancreatic and colorectal cancer. These initial results could have significant clinical impacts, given the aggressive nature of many *KRAS*-dependent cancers[7].

"In experiments on pancreatic, lung, and colorectal cancer models, inhibiting glycosphingolipid synthesis significantly repressed tumour growth."

Researchers have tested this approach using a drug approved for Gaucher disease, a condition involving defective lipid metabolism. This drug blocks the synthesis of glycosphingolipids, preventing the formation of lipid nanodomains. In experiments on pancreatic, lung, and colorectal cancer models, inhibiting glycosphingolipid synthesis significantly repressed tumour growth. The treatment made cancer cells more susceptible to immune responses, suggesting that targeting lipid metabolism could enhance the efficacy of immune-based therapies[1].

Takeaway Messages

Lipids are much more than the mainframe of cell membranes — they are active players in cancer biology. Cancer cells cleverly manipulate lipids, especially through the control of PD-L1 and sphingolipid pathways, to evade

immune attacks and suppress the body's defences. As our understanding of lipids in cancer deepens, therapies that interfere with these processes could become potent weapons in the fight against cancer, helping to restore the immune system's ability to detect and destroy tumour cells.

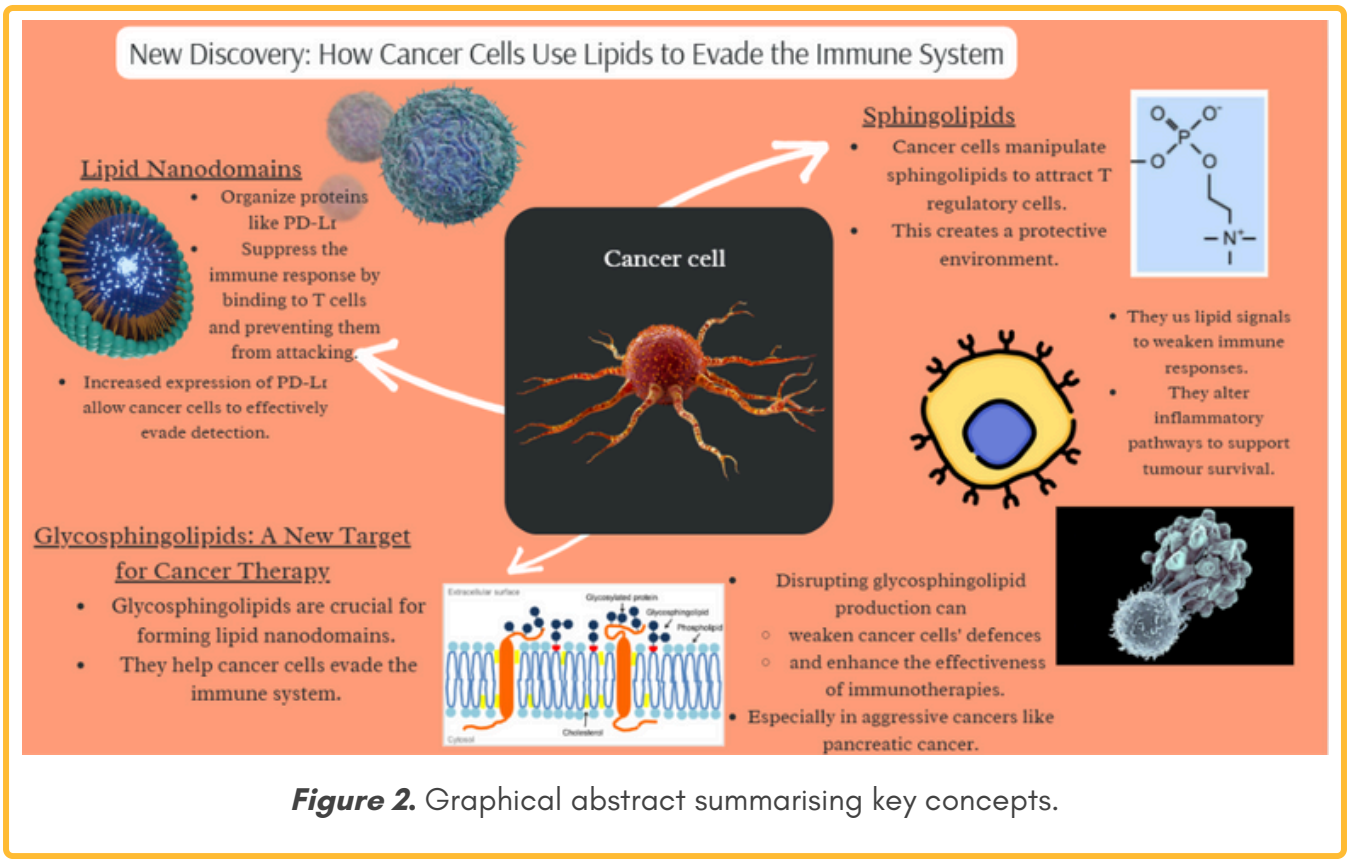


Figure 2. Graphical abstract summarising key concepts.

[References](#)

Primary editor: Cheuk Gi Chloe Lau
Peer reviewers: Defne Kiziltan, Matilda Wicks

SecA's Role in Sec-Mediated Translocation: Exploring the Brownian Ratchet and Power Stroke Models

By Jim Leung

Proteins are essential molecules in all cells, performing vital functions such as regulating biochemical processes and repairing tissues. While many proteins function within the cell, others, like outer membrane protein A (OmpA), play crucial roles externally by anchoring the bacterial outer membrane to the cell wall[1]. For these functions to be carried out, many transmembrane and secreted proteins must be transported across membranes, relying on systems like the highly conserved Sec system. Despite its importance, the exact mechanisms of membrane protein transport remain incompletely understood. In bacteria, the Sec system is responsible for moving proteins across the membrane, yet there is ongoing debate over how this process occurs. Two prominent models of Sec-mediated translocation are currently debated, and this essay will explore these mechanisms.

"Despite its importance, the exact mechanisms of membrane protein transport remain incompletely understood."

The Key Components: SecYEG and SecA

To understand the mechanisms of protein translocation, it is essential to first grasp the roles of SecYEG and SecA. SecYEG is a highly conserved protein complex embedded in inner bacterial membranes, forming a channel through which newly synthesised proteins are translocated or inserted into the membrane[2] (Figure 1).

On the other hand, SecA is an ATPase motor protein that binds to both the pre-protein (a precursor protein with a signal sequence) and the SecYEG complex. SecA uses energy from ATP hydrolysis to push the pre-protein through the SecYEG channel[2]. SecA consists of two RecA-like nucleotide-binding domains (NBD1 and NBD2) that bind and hydrolyse ATP, providing

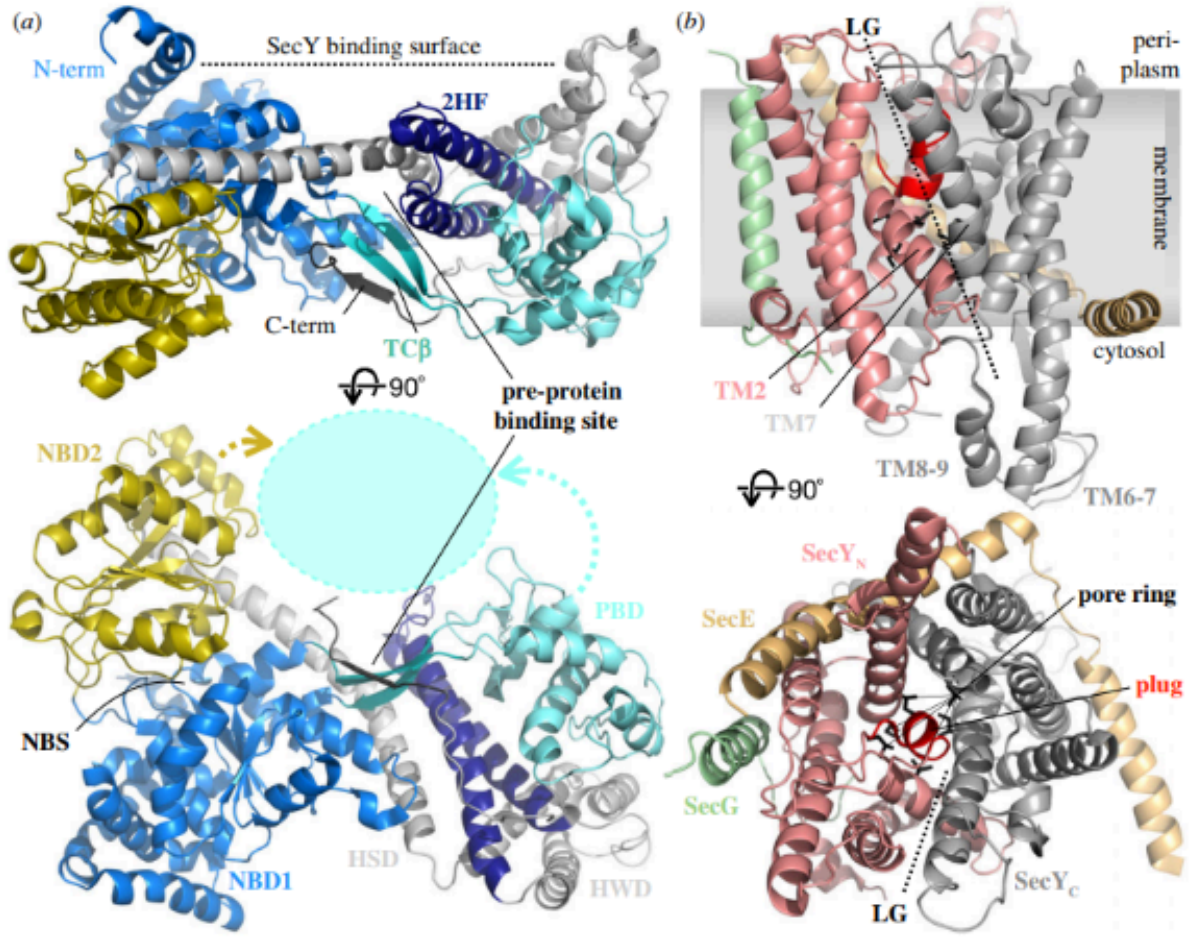


Figure 1. Structures of SecA and SecYEG. **(a)** shows the SecA structure and key domains are highlighted. **(b)** shows the structure of SecYEG and key features are labelled[3].

the energy required for Sec-mediated translocation[1] (Figure 1). It also contains a two-helix finger (2HF) domain, which interacts with the SecYEG complex and plays a crucial role in driving the movement of proteins through the SecYEG channel (Figure 2).

Brownian Ratchet vs Power Stroke Models

The Brownian ratchet model suggests that translocation begins with ATP binding, which induces an "open" conformation in SecA, enabling interaction with the pre-protein and its insertion into the SecYEG channel. As ATP

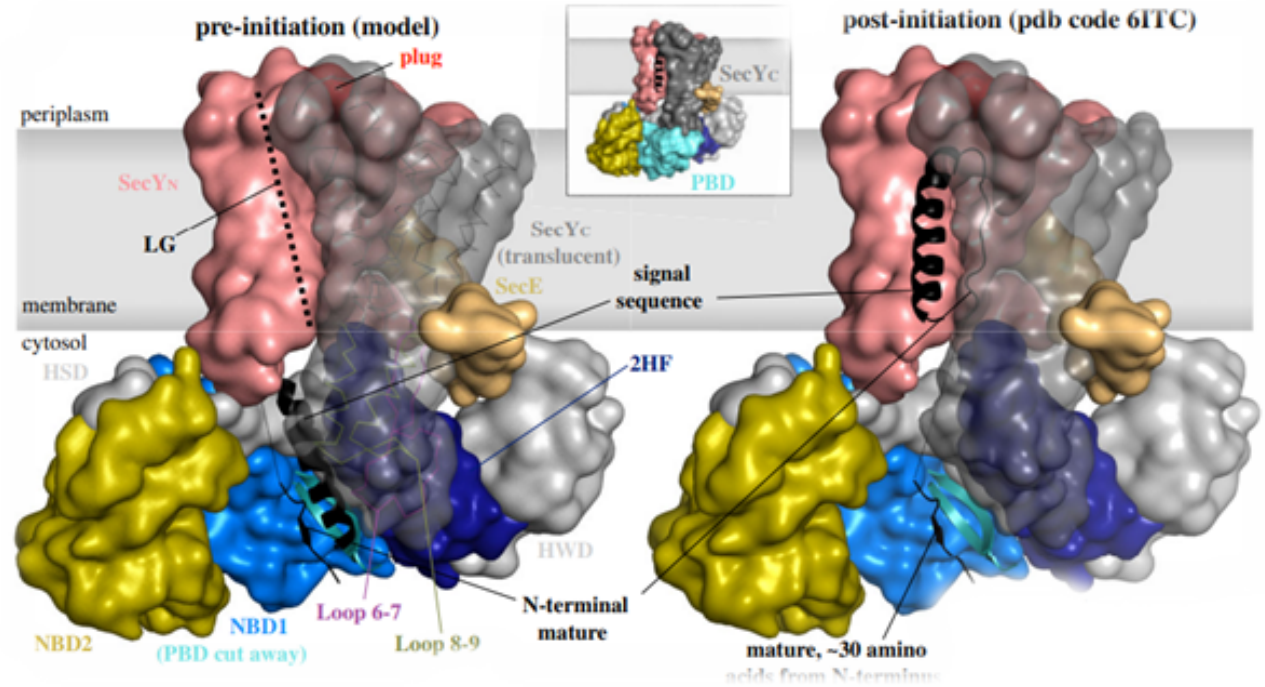


Figure 2. Surface representation of SecYE-SecA with bound pre-protein pre-initiation and post-initiation[3].

hydrolysis occurs, SecA undergoes conformational changes that facilitate a "ratcheting" action, moving the pre-protein stepwise through the channel. In the ADP-bound state, SecA returns to a "closed" conformation, resetting the system for another cycle of ATP binding and translocation[3] (Figure 3). This model emphasises that pre-protein movement is not solely driven by ATP hydrolysis and that Brownian motion also aids pre-protein diffusion through the SecYEG channel, while SecA's ATPase activity ratchets the pre-protein forward and prevents backward slippage to achieve directional movement.

Support for the Brownian ratchet model comes from observations that ATP binding opens the SecYEG channel, activating the SecYEG rather than directly driving movement[4]. Furthermore, all-atom molecular dynamics simulations and smFRET experiments demonstrated that pre-proteins move through the SecYEG channel in random, discrete steps rather than steps synchronised with the ATP hydrolysis cycle. This behaviour aligns with the

model's prediction of random diffusion, coupled with ATPase-mediated trapping of pre-protein segments[5].

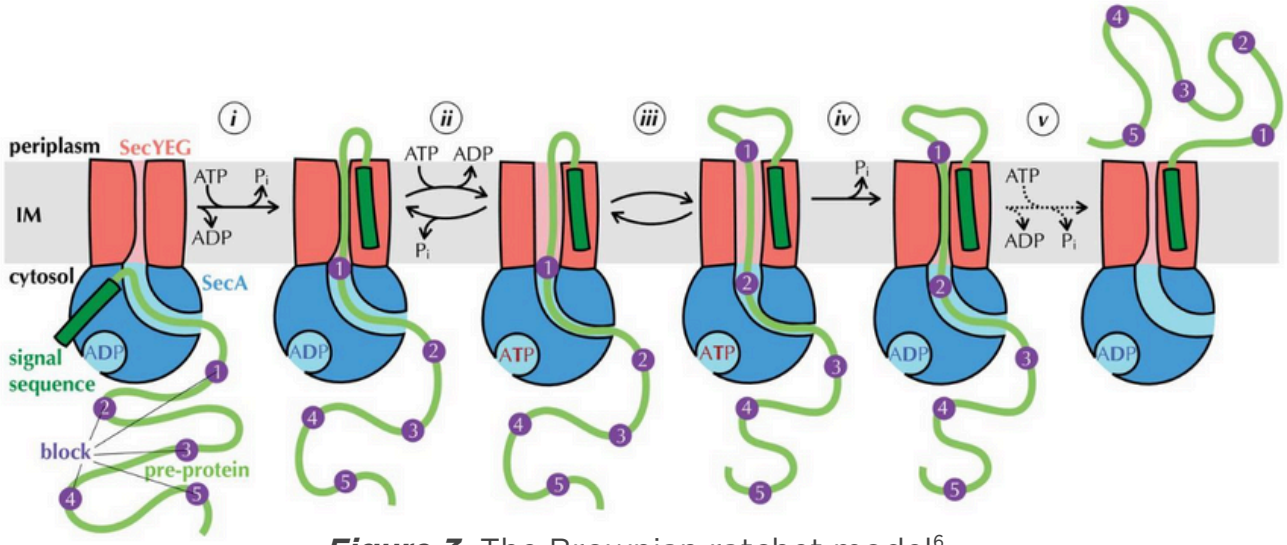


Figure 3. The Brownian ratchet model[6].

In contrast, the power stroke model proposes that the energy released from ATP binding and hydrolysis is directly converted into mechanical force, pushing the pre-protein through the SecYEG channel. In this model, SecA functions as a motor protein, where its two-helix finger (2HF) domain physically pushes the pre-protein forward. Each cycle of ATP hydrolysis generates a "power stroke," progressively moving segments of the pre-protein through the channel until complete translocation[7].

Evidence supporting the power stroke model includes structural studies, such as X-ray crystallography and cryo-electron microscopy, which reveal significant conformational changes in SecA upon ATP binding and hydrolysis. These changes, particularly in the 2HF domain, suggest that SecA mechanically pushes the pre-protein forward[7]. However, as discussed in the following section, the crosslinking of 2HF to SecYEG does not appear to block translocation, making this evidence inconclusive.

However, the same study shows that during ATP hydrolysis, 2HF retracts

while SecA's clamp domain tightens around the polypeptide, ensuring the translocation process continues[7]. This synchronised movement supports the idea of a power-stroke mechanism rather than a purely diffusive one.

Limitations of the Models

Both models offer insights into pre-protein translocation, but they also have limitations. While there's no definitive evidence disproving the Brownian ratchet model, it's clear that it doesn't work well in every situation. For instance, in crowded environments, random diffusion slows down and becomes less effective, meaning more ATP needs to be used to make progress. This makes the model less efficient and unsuitable for processes that require speed or precision. The Brownian model works well in the right context, but its limitations mean it's not the best solution for every scenario[8].

On the other hand, the power stroke model faces structural challenges. Studies show that the 2HF domain of SecA moves less than 1 nm, which may be insufficient to produce the force required for translocation as suggested by the model. Additionally, when the movement of the 2HF domain is inhibited by covalent crosslinking to SecYEG, translocation is not blocked, implying that significant movement of the 2HF domain may not be necessary, contradicting key aspects of the power stroke model[9].

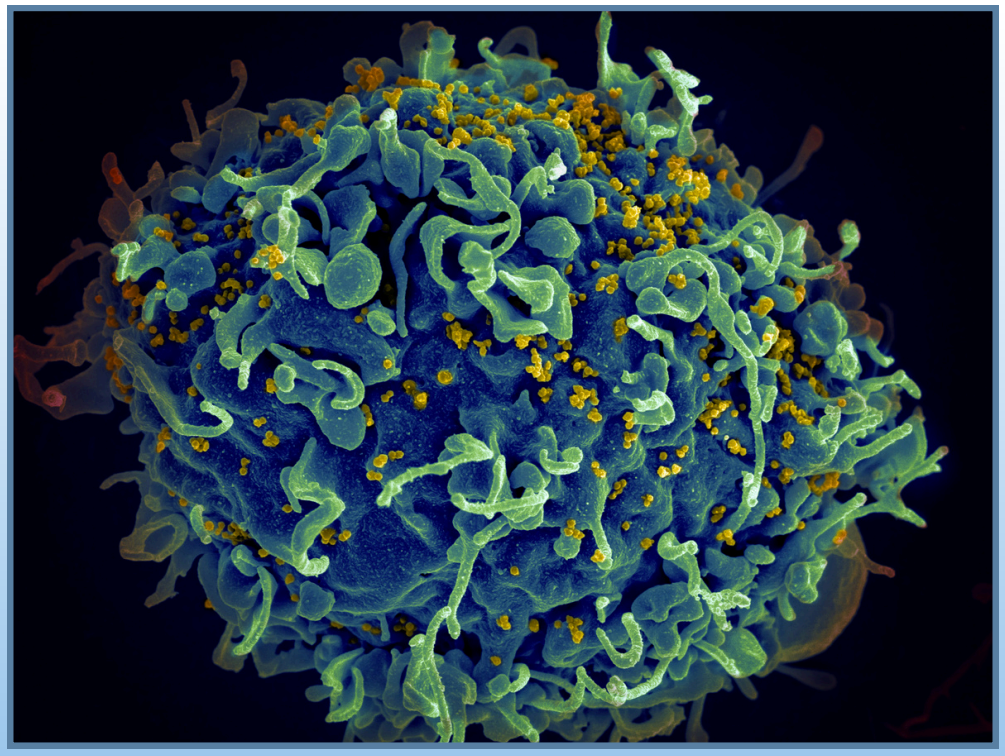
Conclusion

The Sec system is essential for protein translocation across bacterial membranes, yet its precise mechanism remains unclear. Both the Brownian ratchet and power stroke models offer valuable insights but have limitations, indicating the need for a more comprehensive explanation. One approach is the proposed hybrid "push and slide" model, which suggests that ATP-driven power strokes are complemented by diffusion[10]. Future research will likely uncover more details that will help identify the unifying mechanism, leading to a clearer understanding of the complex dynamics involved in SecA-SecYEG-mediated protein translocation.

References

Primary editor: Zihan Deng
Peer reviewers: HanSheng Ang, Uthra Mandi

Back to contents



Drugs in Development

Revolutionising HIV Prevention:
The Promise of Six-Month Injectable PrEP

page 25

Image credit: 3

Revolutionising HIV Prevention: the Promise of Six-Month Injectable PrEP

By Klaus Wang

Despite significant advancements in medical science, Human Immunodeficiency Virus (HIV) remains a formidable global health challenge. Antiretroviral therapy (ART) has transformed HIV from a fatal disease into a manageable chronic condition[1–3], enabling millions to lead longer, healthier lives. However, ART requires lifelong daily medication and strict adherence[1–3], and it does not eliminate the risk of virus transmission to others. According to the World Health Organisation (WHO), approximately 39.9 million people are currently living with HIV, with around 630,000 fatalities reported in 2023. While a complete cure for HIV remains elusive, nearly 100% effective prevention methods are available to stop its transmission[4]. One such revolutionary strategy is Pre-Exposure Prophylaxis (PrEP). Unlike ART, which treats the virus after infection, PrEP prevents the infection from occurring in the first place. The current PrEP is available as a daily pill and requires nearly-perfect adherence to prevent the development of drug resistant variants[4–7]. However, a groundbreaking injectable form of PrEP, effective for up to six months with just a single dose, offers a promising advancement in HIV prevention[4–7].

"Unlike ART, which treats the virus after infection,
PrEP prevents the infection from occurring in the first place."

The Evolution of HIV Prevention

Introduced in the 1980s, HIV initially had no effective treatment or preventative options. This landscape transformed in 2012 with the approval of Truvada, a daily oral PrEP that combines two nucleoside reverse transcriptase inhibitors (NRTIs), tenofovir (TFV) and emtricitabine (FTC)[7–9]. These drugs inhibit HIV's essential reverse transcriptase enzyme, preventing the virus from replicating by terminating the DNA chain during viral transcription[7,9]. Clinical trials have shown that consistent daily intake of TFV and FTC reduces the risk

of getting HIV by over 99%, particularly among high-risk groups such as sexually active individuals with multiple partners and intravenous drug users[8,10]. However, the daily regimen of traditional PrEP poses significant adherence challenges, especially among populations with limited healthcare access or those facing stigma associated with HIV/AIDS[7,9]. The necessity for daily intake highlights the critical need for more adaptable and durable prevention methods that reduce the burden of daily medication.

"However, the daily regimen of traditional PrEP poses significant adherence challenges, especially among populations with limited healthcare access or those facing stigma associated with HIV/AIDS."

A New Era with Long-Acting Injectable PrEP

Recent innovations have led to the development of long-acting injectable medications, offering extended protection against HIV infection[5,11]. Lenacapavir (LEN), a novel antiretroviral agent and capsid inhibitor, has shown substantial promise in both the treatment and prevention of HIV[5,6]. LEN specifically targets the HIV capsid, a protein shell crucial for the virus's replication and assembly[5,6,12]. By binding to a unique site on the capsid protein, LEN interferes with the capsid's stability and function throughout the viral life cycle[5,6,12]. This includes hindering the transport of viral DNA into the nucleus, and impairing the assembly and maturation of new viral particles[5,6,12] (Figure 1). By interfering at multiple stages, LEN effectively inhibits the virus's ability to replicate and infect new cells[5,6,12]. Gilead Sciences used advanced technologies to enhance LEN's particle size, release rate and solubility[4–6]. This optimisation ensures extended stability and efficacy within the body[4–6]. Administered subcutaneously every six months, LEN creates a depot in the tissue from which the drug is gradually released, maintaining therapeutic levels in the bloodstream and reducing the frequency of dosing[4].

LEN's efficacy in preventing HIV infection is currently being evaluated in Phase III clinical trials, such as the PURPOSE 1 and PURPOSE 2 studies[13]. These are randomised, double-blind, placebo-controlled trials designed to

assess the safety and effectiveness of LEN as a long-acting PrEP option. Participants are randomly assigned to receive either LEN injections or a placebo, allowing for a rigorous comparison between the two groups. The

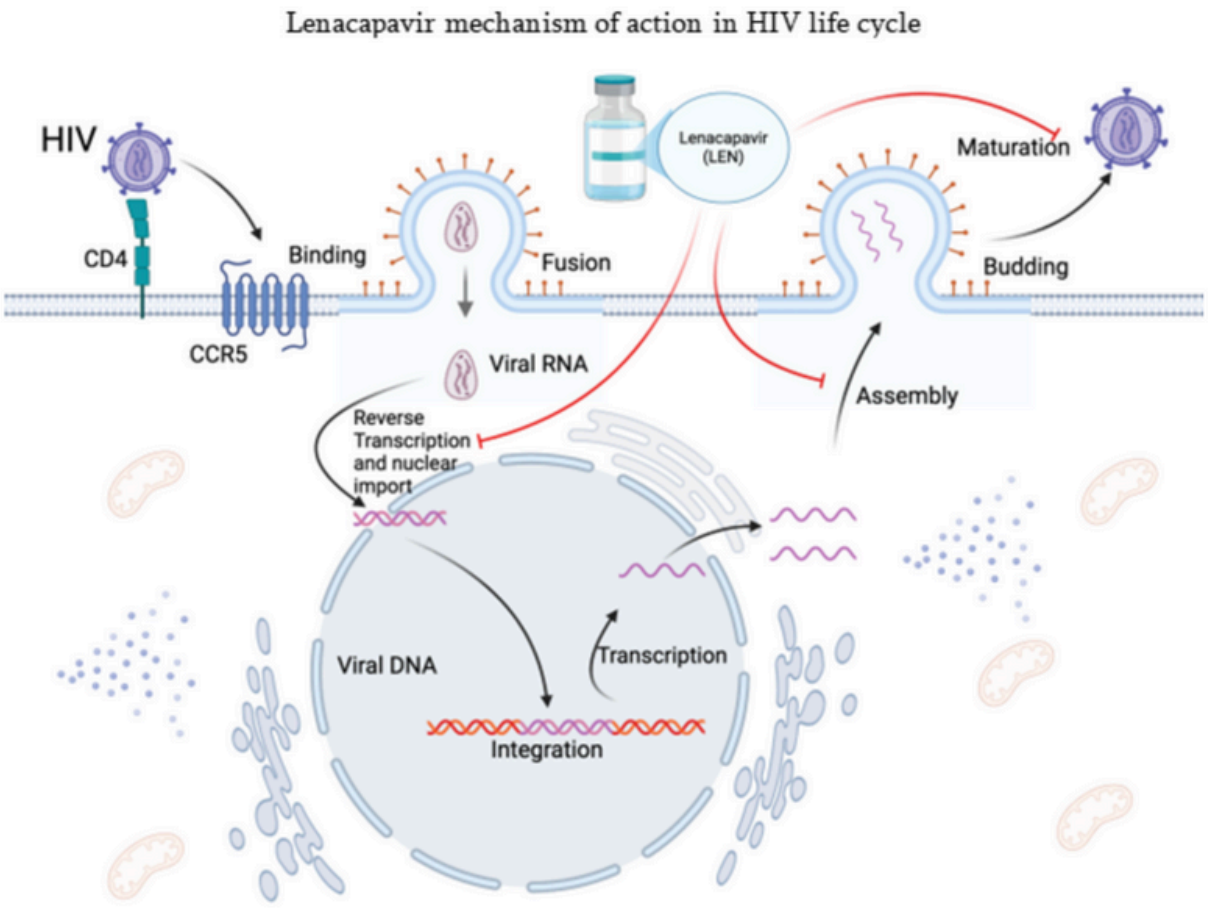


Figure 1. Illustrates how LEN disrupts multiple stages of the HIV replication process. HIV begins its infection by binding to the CD4 receptor and CCR5 co-receptor on the host cell surface, facilitating viral entry. Once inside, the virus releases its RNA, which is reverse transcribed into DNA and transported into the nucleus to integrate with the host genome. LEN disrupts this process at three critical stages indicated by red inhibitors: **1. Reverse transcription and nuclear import:** it prevents the transport of viral DNA into the nucleus, blocking integration into the host genome; **2. Assembly:** it interferes with the assembly of new viral particles, hindering the formation of functional capsids; **3. Maturation and release:** it disrupts the maturation process of newly formed viruses, preventing them from becoming infectious.

trials involve diverse populations, including cisgender men who have sex with men, transgender women, and other individuals at high risk of HIV infection[4,13]. The primary endpoint is the incidence of HIV infection over the study period, which enables researchers to determine LEN's protective efficacy compared to the placebo[13]. While early results have shown promising trends in HIV prevention[13], with LEN demonstrating strong potential in reducing new infections[13], final efficacy data will be available upon the completion of these trials.

"The biannual subcutaneous administration of LEN could substantially enhance patient adherence compared to more frequent dosing schedules required by other treatments"

Benefits and Challenges of Lenacapavir

LEN, a novel capsid inhibitor designed for the treatment of multi-drug resistant (MDR) HIV-1, represents a significant advancement in the management of HIV. Its unique mechanism disrupts the virus's replication process by targeting the capsid protein, setting it apart from traditional antiretrovirals[14]. The biannual subcutaneous administration of LEN could substantially enhance patient adherence compared to more frequent dosing schedules required by other treatments like ibalizumab or daily oral regimens like fostemsavir[14]. However, there are limitations. LEN's efficacy depends crucially on the concurrent use of an optimised background regimen (OBR)[14]. An OBR is a tailored combination of other antiretroviral medications selected based on the patient's specific resistance profile and treatment history[14]. By customising the regimen to include drugs that the virus has not developed resistance to, the OBR works alongside LEN to prevent resistance development and achieve maximum viral suppression[14]. This highlights the need for rigorous patient management strategies to ensure adherence[14]. Additionally, LEN's interaction with other medications, particularly strong CYP3A inducers, and its unestablished effects on pregnant or breastfeeding women demand meticulous medical attention[14]. CYP3A inducers are drugs that increase the activity of the CYP3A enzyme in the liver, which can accelerate the metabolism of LEN and reduce its effectiveness[14]. Common

CYP3A inducers include certain anticonvulsants like carbamazepine and phenytoin and antibiotics like rifampin[15]. Patients taking these medications may require dosage adjustments or alternative treatments to maintain LEN's efficacy[14,15]. Common side effects such as injection site reactions and systemic effects like nausea, along with more severe but less common issues such as changes to liver enzymes and muscle pain, further underscore the need for ongoing monitoring and management to maximise the therapeutic benefits of LEN whilst minimising its risks[14]. Moreover, the costs and infrastructure needed for biannual injections could limit accessibility, especially in low-resource settings.

Implications for the Future

LEN signifies a paradigm shift in HIV prevention. Its extended dosing schedule reduces the physical and psychological toll of daily medication, fostering greater adherence and broader uptake among diverse populations. However, addressing barriers such as cost, access to injection facilities and awareness campaigns remain critical. Additionally, ongoing clinical studies, like ARTISTRY-1, are critical for further clarifying LEN's role in various patient populations and in combination with other drugs, aiming to develop integrative HIV treatment protocols for disease management[16].

The transition from daily oral PrEP to extended-release injectable formulations like LEN could significantly alter HIV prevention strategies. By addressing the limitations of current therapies and providing new, adaptable treatment options, LEN has the potential to dramatically enhance the quality of life for millions at risk of or living with HIV. As we continue to tackle this persistent health challenge, continued innovation is essential for moving towards an HIV-free future.

References

Primary editor: Sanya Saxena
Peer reviewers: Roop Chahal, Yun Shen

Back to contents

Science in Society

Unethical Experiments that Shaped Modern Medicine

page 31

Cultural Differences in Diagnosing and Treating Diabetes

page 36

Image credit: 4

Unethical Experiments that Shaped Modern Medicine

By Zhi Yuek Chung

Throughout history, the pursuit of medicine was thought to be a virtuous and significant endeavour. However, visionaries sullied the legacy with dark and unethical practices. These controversial and tragic mistakes force us to reflect deeply on our moral principles and develop ethical standards to ensure such transgressions are not to be repeated.

The Beginning of Ethical Research Principles

The Nuremberg Code was a document established in 1947 during the hearings of 23 Nazi doctors which built the foundation of medical ethics standards[1,2]. The document focuses on 10 points mandating that medical experiments conducted on human beings must adhere to clearly defined humane and ethical standards[1]. The principles of the Nuremberg Code were crucial in the development of the Declaration of Helsinki in 1964, which further expanded on the obligation of complete transparency of experiments to human subjects[1]. The declaration written by the World Medical Association has been amended multiple times, with its latest edition completed recently in October 2024, containing 37 elements in total[1,3].

"The whole discipline of biomedical ethics rises from the ashes of the Holocaust. The Nuremberg Code, which was created in response to the atrocities committed by Nazi doctors, laid the foundation for modern biomedical ethics. It mandates that medical experiments conducted on human beings must conform to well-defined, humane, ethical standards, with the foremost being the immutable standard of voluntary consent."

Figure 1. Quote from Dr Arthur Caplan, a renowned medical ethicist, during a biomedical ethics conference[4].

The result of the Nazi's medical experiments performed in the concentration camps made it painfully clear that the justification of mass killing for the greater good of society was just a façade for their twisted pseudo-science and eugenics[4,5]. More importantly, our medical ethics foundation was built upon the blood of many, and we must ensure to never follow in their footsteps.

"...our medical ethics foundation was built upon the blood of many and we must ensure to never follow in their footsteps."

Tuskegee Syphilis Experiment

30 years after the establishment of the Nuremberg Code, the United States faced the scandal of the infamous Tuskegee Syphilis experiment[1]. The initial study was to observe the pathological differences of "Negro vs White" in patients with a long history of syphilis for a year and then provide them with adequate treatment[6]. This study ended up recruiting 399 infected men and 201 healthy males for controls, all of whom were at least 25 years of age[6,7].

Figure 2. An African American male is tested and treated during the Tuskegee Study of Untreated Syphilis in the Negro Male. According to the Centres for Disease Control and Prevention, the study began in 1932 and U.S. Public Health Service medical personnel conducted these tests without patients' informed consent[8].

Even after the initial study was completed, men continued to attend "physical check-ups" unaware that the examination had no help in mitigating their disease[6,7]. Some men underwent lumbar punctures, mistakenly believing they were receiving therapeutic "spinal shots"[6]. The side effects were torturous, having to endure severe back pain, headaches, and even temporary paralysis for years, hidden behind the name of "research purposes"[6].

This study continued for three decades, despite penicillin being introduced 20 years prior which was cheap and an effective drug to administer against syphilis patients[6]. However, none received the proper treatment due to the belief in "Race Medicine" where "Blacks" with infections were more indolent than "Whites"[6].

"The side effects were torturous...severe back pain, headaches, and even temporary paralysis"

The tragedy of the study can be attributed to the arrogance and ignorance of those running, funding, and supporting it[6]. The implicit duty of doctors to prevent disease, the responsibility of peer reviewers to halt unethical studies, and the obligation to administer penicillin once it became widely available were all neglected[6]. This lesson remains effective today for us involved in the biomedical field to be obligated and fully inform others of the truth and complications of studies[6].

Henrietta Lacks – HeLa Cells

One of the most common cell lines used to study various biological processes are HeLa cells[9]. They have been instrumental in numerous scientific breakthroughs, including the development of the polio vaccine, advancements in cancer research, and most recently used for research in COVID-19 vaccines[9,10]. However, did you know HeLa cells originated from Henrietta Lacks, a Black woman who suffered from cervical cancer[9,10]?

When scientists attempted to culture her cells, they were astounded to find that they were able to survive and reproduce at an extraordinary rate in the

petri dish, which had not been seen before[10]. The manufacturing and distribution of her immortal cells worldwide has helped launch thousands of studies, resulting in over 110,000 research publications revolving around the use of HeLa cells[10].

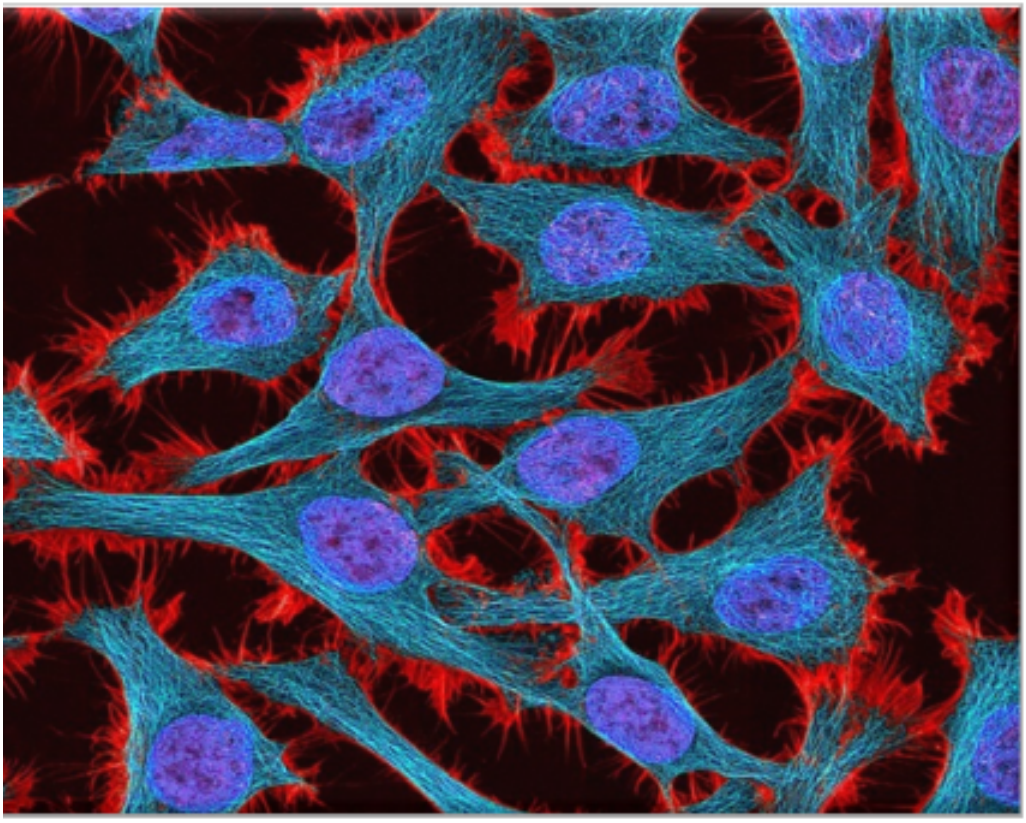


Figure 3. Multiphoton fluorescence image of HeLa cells stained with the actin binding toxin phalloidin (red), microtubules (cyan) and cell nuclei (blue).

Despite the monumental impact of HeLa cells, Henrietta Lacks's family did not benefit financially and did not provide consent for the use of Henrietta's cells[10]. Furthermore, not only was her identity revealed, but her medical records were also provided to the media, and her cells' genome was even published online[10].

The ethical concerns surrounding the use of her cells have sparked debates about consent and justice[10]. Recent efforts by the scientific community and Lacks's family have pushed for stronger established guidelines for governing, consent, and use of biological specimens[10]. While attempts to revise the Common Rule — a set of policies protecting human research participants — failed in 2017, efforts in advocating for change persist[10]. The injustices she endured were indefensible, but they helped highlight the need for continued ethical reforms[10]. We cannot change the past, but recognising and addressing these wrongs is a vital step towards justice[10].

Figure 4. Statue of Henrietta Lacks by Helen Wilson-Roe, outside Royal Fort House, Bristol.

References

Primary editor: Jasmine Abdy
Peer reviewers: Hithrisha Sree Pillai and Kelsey Abellana

Cultural Differences in Diagnosing and Treating Diabetes

By Aliese H W Fan

Diabetes mellitus is a condition where patients have high blood glucose levels with lowered insulin sensitivities or deficiencies. Patients may experience symptoms like excessive thirst, frequent urination and constant tiredness. It was reported that it ranked 8th amongst the 10 most common causes of death globally in 2021[1]. The medical field around the world has put in the effort and performed continuous investigations into diagnoses and treatments of diabetes to tackle this increasing trend, with newer effective methods. Being raised in a diverse cultural background, I became curious about the differences between the medical systems (Chinese vs Western); how one may be better and the possibility of combining the medical systems/theories to benefit the general diabetic population.

HbA1c	Range
<42mmol/mol	Normal
42-47mmol/mol	Pre-diabetes
>48mmol/mol	Type 2 Diabetes

Figure 1. Recommended blood glucose range and their representation, adapted from Forth (2024)[4].

Differences between the Traditional Chinese Medical system (TCM) and Western Medicine (WM) begin with the diagnostic skill of diabetes. In the West, most patients are diagnosed by the HbA1c blood glucose test. Blood test results are compared with the recommended ranges as shown in Figure 1 for diagnosis. However, with TCM, a relatively subjective approach is made through observation. If the patients present symptoms of excessive thirst, practitioners may consider that the patient has diabetes[2]. However, the symptom may also be regarded as internal disharmony[3], leading to patients getting the wrong treatments. Acknowledging that early management is key

to better monitoring and potentially getting cured of the condition, TCM thus may not provide a timely diagnosis of diabetes or the correct treatments, making it less effective than WM.

Treatment follows from the point where a patient is confirmed to have diabetes. In WM, direct insulin doses are given, targeting the liver and muscle cells, converting glucose in blood to glycogen for storage. Patients using TCM, on the other hand, would be given herbal medications and/or acupuncture. Both methods used are quite effective in alleviating symptoms and helping patients with their conditions, yet concerns are raised regarding their affordability. As illustrated in Table 1, TCM is generally more expensive than WM. This may discourage patients from using TCM and are forced to switch to use WM. This shows the lowered feasibility of TCM when used on a large scale.

	Western Medicine (WM)	**Traditional Chinese Medicine (TCM)**
Consultations	Multiple consultations All free at the GP surgery in the NHS	60-minute consultations costing £110 £45 per subsequent consultation
Medication	Free from the NHS Online platforms e.g. Amazon, eBay: average cost of £6.18	Prescriptions cost £1 - £15 per day Certain species with medicinal use are banned under the UK laws

Table 1. Price comparisons between TCM[5] and WM[6].

Discussions above tend towards and have proven that WM is better for diagnosing and treating diabetes than TCM. However, is TCM as useless as it seems? The effects of TCM are not rapid, yet they are not negligible. TCM focuses on recuperating the whole body, addressing both the target problem and the functioning of other organs in the body at the same time.

Successful cases have been identified as scientists tested the effects of combining the use of WM and TCM. A systematic review and meta-analysis conducted by Liu *et al.* concluded that combined TCM and WM treatments improved patient's conditions more than using WM only[7]. However, the reliability of these studies is often doubted. An evaluation conducted by Chen *et al.* shows that TCM studies usually lack placebo and blinding, thus introducing possible bias with the unintentional influence of results to fit into the researcher's hypothesis[8]. The personalisation of TCM treatments also leads to inconsistencies within the research[9]. The inability to use reliable scientific methods to conduct research lowers its reliability and validity, suggesting more clinical-based studies may be needed to agree that TCM can be used together with WM for treating diabetes.

To conclude, WM and TCM both have their advantages and disadvantages. Until now, WM is still considered to be better than TCM in terms of effectiveness, feasibility and reliability. Yet, there are successful cases where a combination of treatments is used. It is still questionable whether the combination treatments will work in a wide-scale application around the world, hopefully, with further research, we will be able to find the best way of diagnosing and treating diabetes.

References

Primary editor: Saniyah Khan
Peer reviewers: Cherub Cheuk Hang Poon, Scarlet Siu

Back to contents

Careers in the Life Sciences

Gene Editing to Combat Soil Erosion in the Fight for Food Security:
An Interview with PhD Student Emily Carr

page 40

The Science Behind Healing Hearts:
My Laboratory Internship at the Bristol Royal Infirmary

page 45

Image credit: 5

Gene Editing to Combat Soil Erosion in the Fight for Food Security: An Interview with PhD Student Emily Carr

By Ana Miletić

The 2024 Cabot Annual Research Showcase on Planetary Health featured the work of Emily Carr, a plant biologist at the University of Bristol. Currently, she is completing a Southwest Biosciences-funded PhD on root secretions with the potential to fight soil erosion, one of the key threats to food crops worldwide. I spoke to Emily *(direct quotes in italics)* to find out more about how her work can support more sustainable food production, her personal experience working in research, and the future of gene editing in agriculture.

Inspired by her undergraduate lectures on the challenges facing global food security, Emily chose to specialise in plant biology to tackle them from the ground up.

"I just had no idea [...] how much work needs to be done in terms of the fact that: the population is growing at a fast rate, with climate change we're facing all these uncertainties in the weather patterns, diseases are spreading into different locations, there's less land to be growing plants on just because buildings are popping up all over the place. [...] I think [the lecturers] described it as the perfect storm."

Within this perfect storm, the loss of arable land through soil erosion is as much a consequence as it is a contributing factor. Soil erosion is exacerbated by the use of intensive farming driven by increasing food demands, as well as the higher intensity rainfall brought about by climate change[1,2]. While it might not be the most obvious threat to planetary health, compared to infamous greenhouse gases or deforestation, soil erosion has been estimated to cost the UK around £150 million yearly due to the cost of treating water affected by soil leaching[1]. But the rich underground landscape of the rhizosphere, the region of soil surrounding roots, may already hold a solution in the form of

root exudates. These secretions not only support a network of communication between soil microbes of neighbouring plants[3], but also contain a variety of polysaccharides that help hold soil together, like the pectin that makes jam sticky[4].

Despite this potential, Emily explains that the field of root biology in crop plants is relatively under researched, represented in only a minority of talks held at the 2024 International Wheat Congress she attended. Working to fill this gap, her project utilises mutant lines formed either by targeting induced local lesions in genomes (TILLING) or CRISPR gene knockout. These methods of mutagenesis allowed her to produce mutations in selected genes of interest that were implicated (by preceding bioinformatic searches) in the production of soil-binding root exudates in wheat. Responsible for approximately a fifth of calories consumed each day[5], wheat is one of the most essential crops worldwide, but working with it in the lab can be challenging.

"To make a mutant in wheat is really difficult because it's hexaploid, so there's six copies of every gene because of ancestral hybridisation. So, it's got three ancestors each of which have two sets of genes, and now there's six. And to create a mutant to look at the effects of the genes that I'm interested in, you need to get rid of all six copies."

To create wheat mutant lines for her gene of interest, Emily used a one-pot reaction known as Golden Gate cloning to produce CRISPR constructs[6]. These were then transformed into wheat embryos using biolistics, a term literally derived from "biological ballistics" as the method involves shooting DNA directly into cells using a gene gun (Figure 1). Adapting to new lab techniques like these has been a big part of her PhD, and she emphasises that resilience is key.

"You definitely always learn something the first time you do something. It doesn't usually go well, you've just gotta not get too frustrated and go: 'I still learned something'. That's the whole point of a PhD. It's a really steep learning curve."

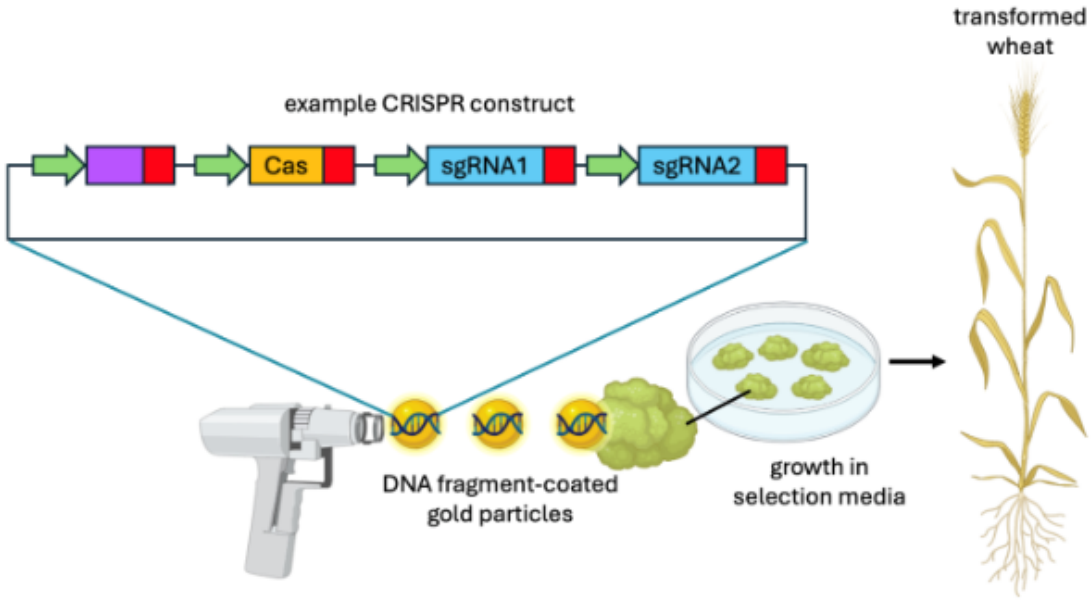


Figure 1. Biolistic transformation of CRISPR construct into wheat embryos[6]. *Example of a CRISPR construct formed by seamless Golden Gate cloning is shown. The construct includes CRISPR building blocks such as the Cas9 endonuclease, single guide RNAs (sgRNAs), and a selectable marker gene conferring PPT herbicide resistance. Gold particles are coated with the DNA and shot into wheat embryos, which are grown in PPT to select only the successful transformants that will grow into wheat with the desired mutations.*

But the obstacles are also what make the successes all the more rewarding, like achieving her first full CRISPR knockout line. Initially, while waiting for the knockout DNA sequencing results, Emily used gel electrophoresis to separate her DNA sample by size as a simple way of confirming she had generated her desired mutation. She had incorporated a 500 base pair deletion so that the mutated DNA would form a distinct band on the gel, however due to innate DNA repairs she did not observe the characteristic deletion. This meant that, although she might have achieved small edits of one base pair difference in size, she had no way of knowing from the gel.

"I was obviously not holding out hope [...] and then the sequencing came back after ages as well, because the primers weren't working. I think it was around

5pm [in the life sciences building] on a Friday, and no one was [there]. And I was so excited but thinking 'I've got no one to tell!' and had to message the postdoc who helped me make the CRISPR mutants saying: 'We've got a child!'."

After obtaining her gene knockouts, her next step is to validate their success using reverse transcription PCR, which will allow her to analyse the mRNA expressed by the mutant lines as a measure of gene expression. She then plans to study the root exudates of the mutant lines, measuring their level of 'stickiness' using soil binding and uprooting assays. If the results of those assays go on to confirm that the edits to her genes of interest improve the soil binding of wheat root exudates, Emily hopes they will be recommended to plant breeders as desired traits for enhancing soil health. Nonetheless, it can often take years for elite varieties with these selected mutations to be obtained via traditional breeding, which tends to rely on the random process of spontaneous mutation and requires breeding multiple generations[7]. The pressure of rising global food demands raises the question of why the comparatively faster and more precise method of CRISPR gene editing is not being used in the industry.

In 2023, the Precision Breeding Act approved the use of gene editing in agriculture in England[8], allowing any genetic changes that could be obtained by traditional selective breeding methods, like those created by Emily in her mutant lines. However, tougher restrictions on gene editing still remain in Scotland and Wales due to concerns about the risks to health and the environment, and the EU has only recently begun negotiations around easing its strict regulations on gene editing[9], meaning traditional breeding continues to be favoured.

"We have more obstacles than just legalising [gene edited] plants to be sold for food in the UK. We need our neighbouring countries to legalise [gene editing] as well, to allow for trade and economic growth, which will then result in widespread food security. This is an obstacle that requires scientists, economists and politicians to work together, and is a perfect example of why cross-discipline collaboration is so important in modern day science."

Ultimately, more widespread science communication is needed to improve awareness of gene editing, which is often perceived by consumers as "unnatural"[10]. A survey conducted in 2020 found that most consumers lacked an understanding of gene editing but became more accepting of its application in food production upon becoming more informed[10]. With more outreach events showcasing research like Emily's, public perspectives may shift in favour of gene editing, promoting changes in government policy that could allow for more sustainable global food production in future.

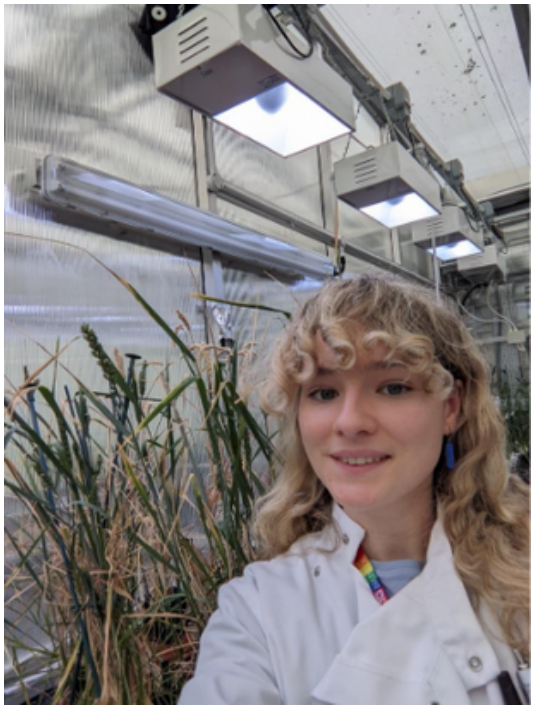


Figure 2. *Emily Carr with her transformed wheat plants.*

References

Primary editor: Jing Ying Tong
Peer reviewers: Annabel Thomas, Alex Gabriel Chong

The Science Behind Healing Hearts: My Laboratory Internship at the Bristol Royal Infirmary

By Soham De

My name is Soham De and I am currently a third-year mature student studying Cancer Biology and Immunology. In my second year, I undertook an internship at the Bristol Royal Infirmary (BRI). From February to May 2024, I observed and worked in research related to congenital heart disease (CHD) culminating in a 4-week project. My time spent learning both widely used and specialised laboratory techniques, attending lab meetings, and working independently further reinforced my interest in pursuing a research-based career. This experience also gave me crucial experience to help guide my decisions.

"My time spent learning both widely used and specialised laboratory techniques, attending lab meetings, and working independently further reinforced my interest in pursuing a research-based career."

Congenital Heart Disease and Biological Scaffolds

My internship took place in Professor Massimo Caputo's lab where I worked with Dr Amy Harris — at the time a final-year PhD student — who supervised my work experience and project which was centred around paediatric CHD.

CHD is the most common birth defect and while huge improvements have been made in several aspects of diagnosis and treatment, for example in surgical methods, CHD is still the leading cause of death in children with congenital birth defects (Figure 1)[1].

A number of biological scaffolds, structures made from extracellular matrix materials, exist and can be used to surgically repair congenital heart defects, including scaffolds derived from both human (homograft) or animal (xenograft) origins[2]. One of the key obstacles in paediatric CHD is graft rejection, where xenografts used for surgical reconstruction of the heart

defect are often rejected by the recipient's immune system[3]. Additionally, a section of the heart known as the right ventricular outflow tract (RVOT) can have impaired function in several types of CHD pathologies such as pulmonary valve stenosis and tetralogy of Fallot[4].

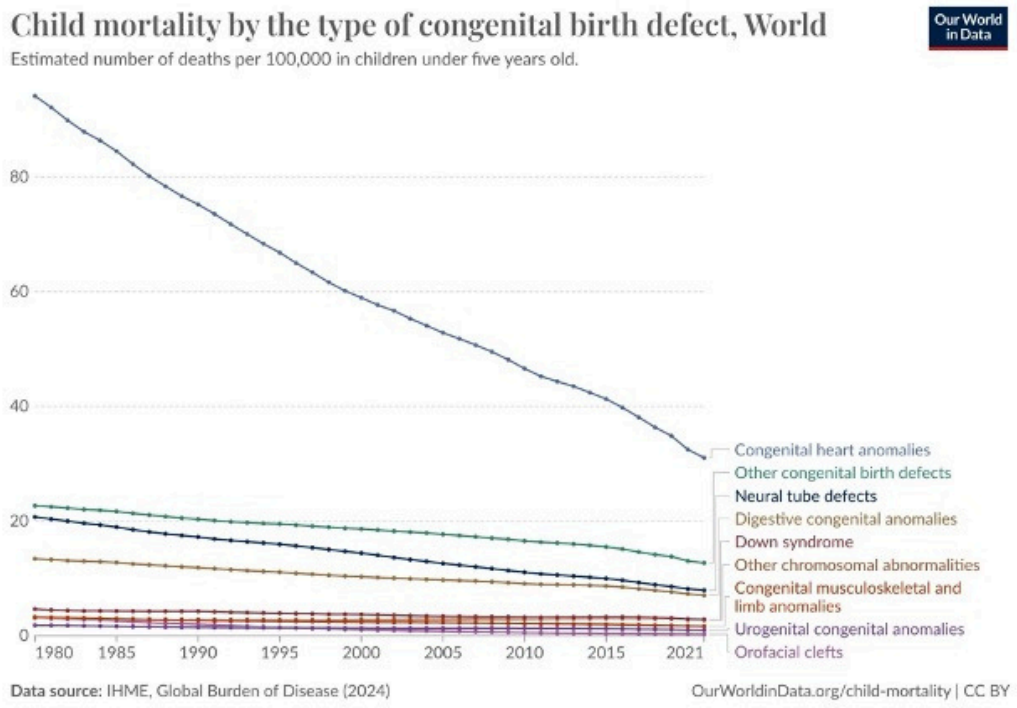


Figure 1. Worldwide trends in childhood mortality from 1980–2021, by type of congenital birth defect.

Dr Harris' research focused on utilising a porcine RVOT as a biological xenograft scaffold to treat paediatric CHD. Amongst other procedures and experiments, this research involved dissecting the porcine heart to isolate the RVOT, removing all of the cells of the RVOT in a process called decellularisation to leave an acellular collagen and elastin structure, and seeding this structure with different kinds of stem cells. The resulting product was assessed for properties such as acellularity, mechanical integrity, and

seeded cell viability. My internship focused on techniques and procedures related to the dissection and decellularisation of the porcine RVOT.

Working in a Research Active Laboratory

My internship at the BRI can be split into two main parts: a few months of ad-hoc work experience at around 8-10 hours/week and a 4-week project.

"I had a chance to apply techniques I had learned in my course so far such as buffer preparation, as well as learn a range of foundational lab skills."

Work experience

During the work experience, Dr Harris introduced me to various laboratories and equipment as well as taught me laboratory techniques. This consisted of essential skills needed when working in a wet lab as well as methods more specific to her research. I had a chance to apply techniques I had learned in my course so far such as buffer preparation, as well as learn a range of foundational lab skills. This included using a microtome, a machine that slices tissues embedded in paraffin wax into very thin sections, automatically labelling multiple slides with LabWriter, a software designed to quickly name and print multiple slides, and imaging stained tissues. I also experienced some specialised techniques such as porcine heart dissection and the setup of RVOT decellularisation which gave me an opportunity to work in a tissue culture room, something I now do in my third-year research project. Furthermore, I practised reading and applying scientific protocols, such as Dr Harris's newly developed STAR protocol for decellularising porcine RVOTs which discusses procedures such as porcine RVOT dissection, preparation of the decellularisation process, and quantification and statistical analysis of the decellularised RVOT[5].

With Dr Harris' guidance, I got more comfortable week to week and started to work more independently. I began to appreciate how these techniques did not exist in isolation but worked together and required coordination, time management, and planning. For example: before dissecting porcine hearts,

you should first prepare the buffer that you want to store them in. Additionally, collaboration with the abattoir is essential to harvest the required waste tissue and then immediately process the hearts for dissection. Understanding both the research and logistical context of why I was doing these tasks made me better appreciate each day I spent in the lab. This made each task, no matter how basic, feel important.

The Project

In the final month of my internship, Dr Harris offered me a part-time 4-week project where I could put together what I'd been learning. My project was focused on verifying the decellularisation of the tissues in the RVOT with an additional goal of helping increase the sample size for some of Dr Harris's results which would help improve their reliability. My project was split into 4 main parts:

1. **Section different tissues in multiple RVOTs**. There were three types of tissues: the pulmonary artery, right ventricle, and the pulmonary valve leaflet. This involved using LabWriter to label each set of slides and a microtome to give 5 µm sections of each tissue (Figure 2).

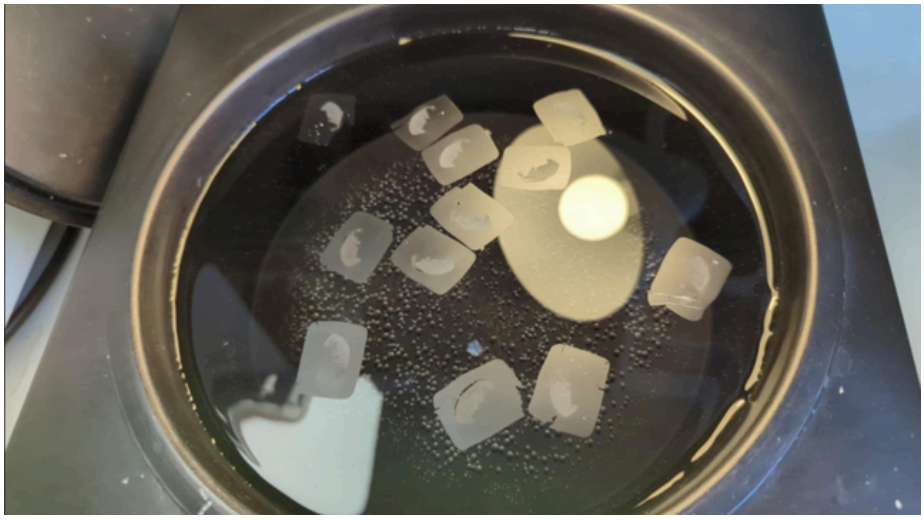


Figure 2. 5 µm sections of porcine right ventricle suspended in water.

2. **Dewax and stain each of the tissue sections** separately using three different stains — haematoxylin and eosin (H+E), 4′,6-diamidino-2-phenylindole (DAPI), and Elastin van Gieson (EVG). H+E and DAPI were used to check that the tissue had been decellularised (via staining cytoplasm, nuclei, and DNA) and EVG, which stains for elastin and collagen, was used to check the integrity of the biological scaffold.

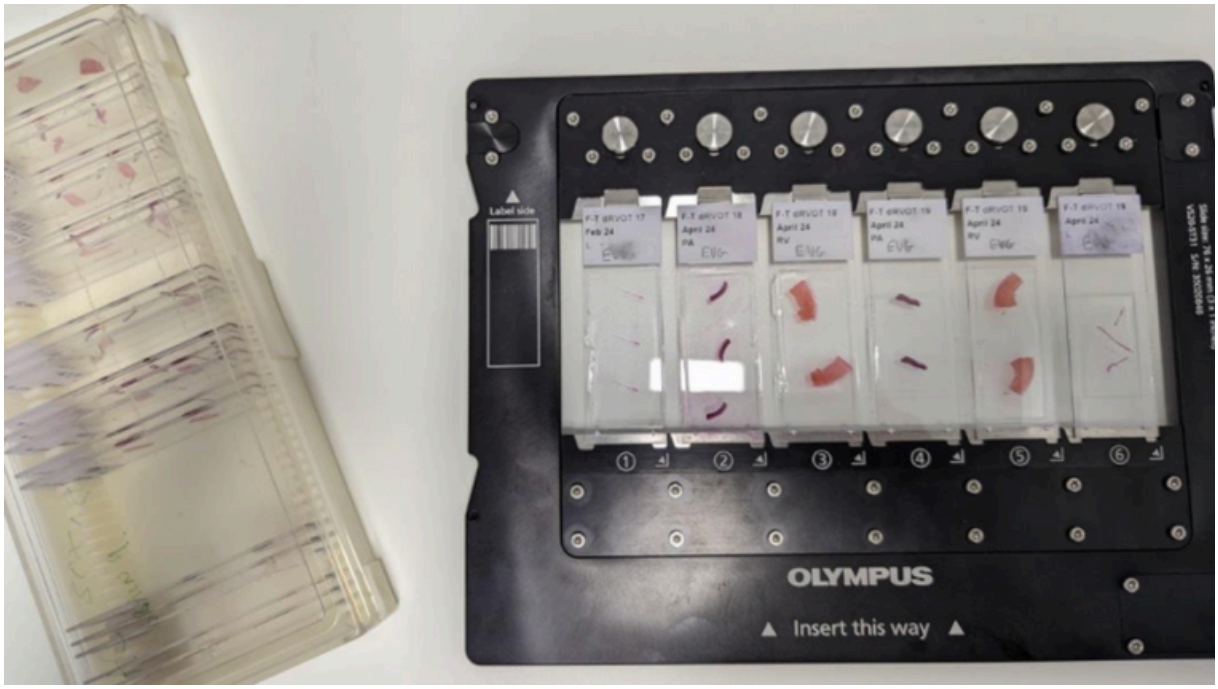


Figure 3. EVG-stained sections on a tray before being loaded onto the slide scanner.

3. **Image each section** to give an accurate representation of the success of the decellularisation procedure. This involved using a slide scanner to image each slide and then QuPath to process images (Figure 3).

4. **Collate the data** (i.e., the images) into clear sets of tables using PowerPoint (Figure 4).

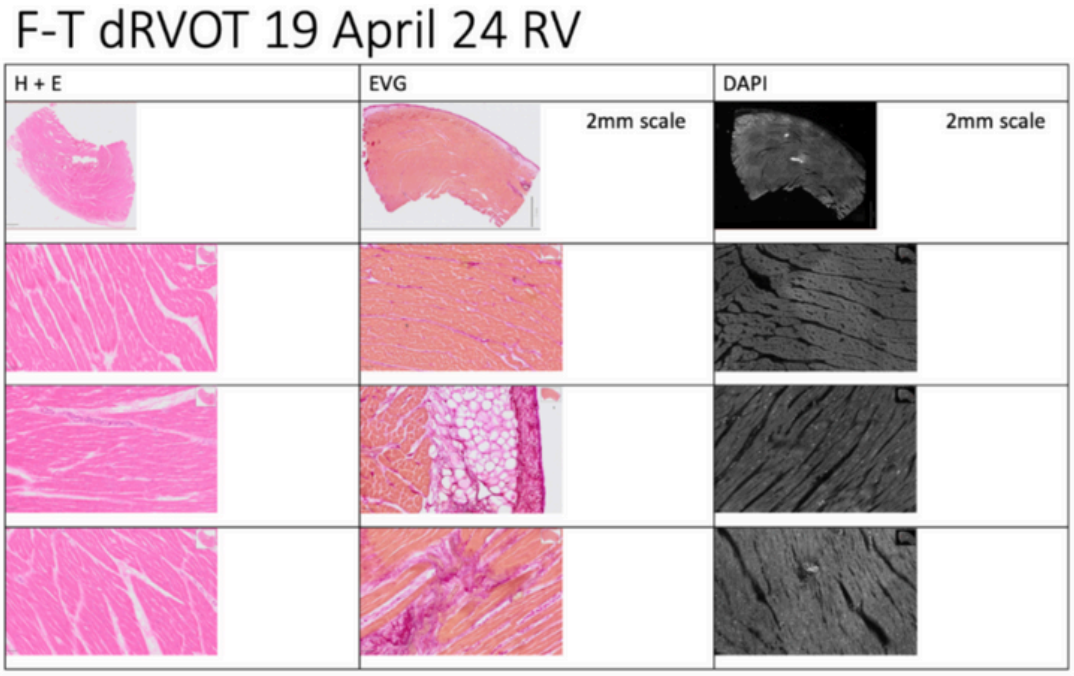


Figure 4. A slide as part of the data collation part of my project showing the right ventricle (RV) of a freeze-thawed (F-T) decellularised RVOT (dRVOT) stained with H+E, EVG, and DAPI.

Meaningful Research Informs Life-Changing Therapies

My experience at the BRI really helped me understand what working in a research laboratory entails and whether this would be something I would enjoy doing. My project allowed me to build on what I had been learning over the past months alongside learning new techniques like dewaxing samples, DAPI staining, and using a slide scanner. I got the opportunity to work as independently as possible which helped me gain confidence in working on my own in a lab, troubleshoot problems, and set deadlines for different parts of the project.

I also better appreciate why research can be both stepwise and complex. Dr Harris' research, for example, created a foundation for future researchers to build on; a potential outcome being developing a novel seeded biological xenograft possessing growth potential, not limited by graft rejection problems. With further research, perhaps this novel seeded xenograft might

one day allow children with CHD to live much longer and healthier lives. Understanding why this research was happening gave me a sense of purpose and motivation to contribute, however small, to it and to one day carry out my own research in the field I'm most passionate about, cancer immunology.

I am extremely grateful to Dr Harris who offered me this opportunity and provided excellent guidance and support throughout. I believe that through the kindness of such scientists, enthusiastic and dedicated students are given a unique opportunity to engage with laboratory research, which can only impact their future — and the future of scientific research — for the better.

References

Primary editor: Sarah Alshahabi
Peer reviewers: Imogen Joseph, Jaya Veronique Richardson

References and Figure Credits

Inside the Pregnant Brain: New Study Reveals how the Brain Changes During Pregnancy

1. Pritschet, L. *et al.* Neuroanatomical changes observed over the course of a human pregnancy. *Nat Neurosci* **27**, 2253-2260 (2024).
2. Roxby, P. *Pregnancy brain changes revealed in detailed scans*. [online]. BBC News. https://www.bbc.co.uk/news/articles/ (2024).
3. *Brain changes observed during pregnancy*. [online]. NIH Research Matters. https://www.nih.gov/news-events/nih-research-matters/ (2024).

Bioengineered Organs: Cutting-Edge Approaches in Regenerative Medicine to Transform Disease Treatments

1. *Statistics about organ donation*. [online]. NHS Organ Donation. https://www.organdonation.nhs.uk/ (2024). Accessed: 26/11/ 2024.
2. *Transplant Waiting List*. [online]. American Kidney Fund. https://www.kidneyfund.org/ (n.d.). Accessed: 26/11/2024.
3. Atala, A., Bauer, S. B., Soker, S., Yoo, J. J. & Retik, A. B. Tissue-engineered autologous bladders for patients needing cystoplasty. *The Lancet* **367**, 1241–1246 (2006).
4. Rafat, M. *et al.* Bioengineered corneal tissue for minimally invasive vision restoration in advanced keratoconus in two clinical cohorts. *Nat Biotechnol* **41**, 70–81 (2023).
5. Cooley, D. A. *et al.* Orthotopic cardiac prosthesis for two-staged cardiac replacement. *Am J Cardiol* **24**, 723–730 (1969).
6. Vogel, G. *Transplant surgeon sentenced to prison for failed stem cell treatments*. [online]. ScienceInsider. https://www.science.org/content/article/ (2023). Accessed: 27/11/2024.
7. Collin de l'Hortet, A. *et al.* Generation of Human Fatty Livers Using Custom-Engineered Induced Pluripotent Stem Cells with Modifiable SIRT1 Metabolism. *Cell Metab* **30**, 385-401.e9 (2019).
8. Cintron Pregosin, N., Bronstein, R. & Mallipattu, S. K. Recent Advances in Kidney Bioengineering. *Front Pediatr* **9**, 743301 (2021).
9. Ciampi, O. *et al.* Engineering the vasculature of decellularized rat kidney scaffolds using human induced pluripotent stem cell-derived endothelial cells. *Sci Rep* **9**, 8001 (2019).
10. Xiang, D. *et al.* Artificial ovaries constructed from biodegradable chitin-based hydrogels with the ability to restore ovarian endocrine function and alleviate osteoporosis in ovariectomized mice. *Reprod Biol Endocrinol* **21**, 49 (2023).
11. Abdelrahman, S. *et al.* A Parkinson's disease model composed of 3D bioprinted dopaminergic neurons within a biomimetic peptide scaffold. *Biofabrication* **14**, 044103 (2022).
12. Rouleau, N., Murugan, N. J. & Kaplan, D. L. Functional bioengineered models of the central nervous system. Nat Rev Bioeng 1, 252–270 (2023).

Figure 1: Created by Sarah Al-Shahabi using BioRender.

New Discovery: How Cancer Cells Use Lipids to Evade the Immune System

1. Rockefeller University. *Cancer cells may be using lipids to hide from the immune system* [online]. ScienceDaily. https://www.sciencedaily.com/releases/ (2024). Accessed: 26/10/2024.
2. Han, Y., Liu, D. & Li, L. PD-1/PD-L1 pathway: current researches in cancer. *Am J Cancer Res* **10**, 727 (2020).
3. Zhao, M. *et al.* Tumour cell-expressed PD-L1 reprograms lipid metabolism via EGFR/ITGB4/SREBP1c signalling in liver cancer. *JHEP Rep* **6**, 101009 (2024).
4. Jiang, Y., Chen, M., Nie, H. & Yuan, Y. PD-1 and PD-L1 in cancer immunotherapy: clinical implications and future considerations. *Hum Vaccin Immunother* **15**, 1111–1122 (2019).
5. Sattar, R. S. A. *et al.* S1P signaling, Its Interactions and cross-talks with other partners and therapeutic importance in colorectal cancer. *Cell Signal* **86**, 110080 (2021).
6. Yi, M. *et al.* Targeting cytokine and chemokine signaling pathways for cancer therapy. *Sig Transduct Targeted Ther* **9**, 176 (2024).
7. Soula, M. *et al.* Glycosphingolipid synthesis mediates immune evasion in *KRAS*-driven cancer. *Nature* **633**, 451–458 (2024).

Figure 1: Created by Tara Maziliauskas using BioRender.

Figure 2: Created by Tara Maziliauskas using Canva.

SecA's Role in Sec-Mediated Translocation: Exploring the Brownian Ratchet and Power Stroke Models

1. Park, J. S., *et al.* Mechanism of anchoring of OmpA protein to the cell wall peptidoglycan of the gram-negative bacterial outer membrane. *FASEB J* **26**, 219-228 (2012).
2. Rusch, S. L. & Kendall, D. A. Oligomeric states of the SecA and SecYEG core components of the bacterial Sec translocon. *Biochim Biophys Acta* **1768**, 5-12 (2007).
3. Allen, W. J. & Collinson, I. A. Unifying mechanism for protein transport through the core bacterial Sec machinery*. Open Biol* **13**, 230166 (2023).
4. Crossley, J. A. *et al.* Dynamic coupling of fast channel gating with slow ATP-turnover underpins protein transport through the Sec translocon*. EMBO J* **43**, 1-13 (2024).
5. Allen, W. J. *et al.* Two-way communication between SecY and SecA suggests a Brownian ratchet mechanism for protein translocation*. Elife* **5** (2016).
6. Allen, W. J. et al. Rate-limiting transport of positively charged arginine residues through the Sec-machinery is integral to the mechanism of protein secretion. Elife 11 (2022).
7. Catipovic, M. A. *et al.* Protein translocation by the SecA ATPase occurs by a power-stroke mechanism. *EMBO J* **38**, (2019).
8. Allen, W. J. *et al.* Refined measurement of SecA-driven protein secretion reveals that translocation is indirectly coupled to ATP turnover*. Proc Natl Acad Sci U S A* **117**, 31808-31816 (2020).
9. Collinson, I., Corey, R. A. & Allen, W. J. Channel crossing: how are proteins shipped across the bacterial plasma membrane? *Philos Trans R Soc Lond B Biol Sci* **370** (2015).
10. Bauer, B. W. *et al.* A "push and slide" mechanism allows sequence-insensitive translocation of secretory proteins by the SecA ATPase*. Cell* **157**, 1416-1429 (2014).

Revolutionising HIV Prevention: The Promise of Six-Month Injectable PrEP

1. Buck, A. M., Deveau, T. -M., Henrich, T. J. & Deitchman, A. N. Challenges in HIV-1 Latent Reservoir and Target Cell Quantification in CAR-T Cell and Other Lentiviral Gene Modifying HIV Cure Strategies. *Viruses* **15**, 1126 (2023).
2. Brockman, M. A., Jones, R. B. & Brumme, Z. L. Challenges and Opportunities for T-Cell-Mediated Strategies to Eliminate HIV Reservoirs. *Front Immunol* **6**, 506 (2015).
3. Kim, Y., Anderson, J. L. & Lewin, S. R. Getting the "Kill" into "Shock and Kill": Strategies to Eliminate Latent HIV. *Cell Host Microbe* **23**, 14-26 (2018).
4. Bekker, L. -G. *et al.* Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women. *N Engl J Med* **391** (2024).
5. Dvory-Sobol, H., Shaik, N., Callebaut, C. & Rhee, M. S. Lenacapavir: a first-in-class HIV-1 capsid inhibitor. *Curr Opin HIV AIDS* **17**, 15-21 (2022).
6. Prather, C., Lee, A. & Yen, C. Lenacapavir: A first-in-class capsid inhibitor for the treatment of highly treatment-resistant HIV. *Am J Health Syst Pharm* **80**, 1774-1780 (2023).
7. John, S. A. *et al.* Exploring preferences and decision-making about long-acting injectable HIV pre-exposure prophylaxis (PrEP) among young sexual minority men 17–24 years old. *Sci Rep* **13**, 5116 (2023).
8. Molina, J. -M. *et al.* Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. *Lancet HIV* **4**, e402-e410 (2017).
9. Straubinger, T., Kay, K. & Bies, R. Modeling HIV Pre-Exposure Prophylaxis. *Front Pharmacol* **10**, 1514 (2020).
10. Murchu, E. O. *et al.* Oral pre-exposure prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations. *BMJ Open* **12** (2022).
11. Liegeon, G. & Ghosn, J. Long-acting injectable cabotegravir for PrEP: A game-changer in HIV prevention? *HIV Med* **24**, 653-663 (2023).
12. Bester, S. M. *et al.* Structural and mechanistic bases for a potent HIV-1 capsid inhibitor. *Science* **370**, 360-364 (2020).

continued...

13. *Gilead Presents Full PURPOSE 2 Data Results for Twice-Yearly Lenacapavir for HIV Prevention at HIV Glasgow*. [online]. Gilead Sciences. https://www.gilead.com/news/ (2024).
14. Hitchcock, A. M., Kufel, W. D., Dwyer, K. A. M. & Sidman, E. F. Lenacapavir: A novel injectable HIV-1 capsid inhibitor Author links open overlay panel. *Int J Antimicrob Agents* **63**, 107009 (2024).
15. Wieczorek, S. J. & Tsongalis, G. J. Pharmacogenomics: will it change the field of medicine? *Clinica Chimica Acta* **308**, 1-8 (2001).
16. Mounzer, K. *et al.* Efficacy and Safety of Switching to Daily Bictegravir Plus Lenacapavir From a Complex Human Immunodeficiency Virus Treatment Regimen: A Randomized, Open-Label, Multicenter Phase 2 Study (ARTISTRY-1). *Clin Infect Dis* **ciae522** (2024).

Figure 1: Created by Klaus Wang using BioRender.

Unethical Experiments that Shaped Modern Medicine

1. *Introduction: Unethical Medical Experiments 1980–2010.* [online]. Alliance for Human Research Protection. https://ahrp.org/ (2015). Accessed: 25/10/2024.
2. Stewart, K. *Nuremberg Code*. [online]. Britannica. https://www.britannica.com/topic/Nuremberg-Code (2024). Accessed: 25/10/2024.
3. Resneck, J. S., Jr. *Revisions to the Declaration of Helsinki on Its 60th Anniversary: A Modernized Set of Ethical Principles to Promote and Ensure Respect for Participants in a Rapidly Innovating Medical Research Ecosystem*. [online]. JAMA https://jamanetwork.com/journals/ (2024). Accessed 25/10/2024.
4. Bekier, M. Human Experimentation in *Medical Ethics* (ed. Pecorino, P. A.). [online]. https://www.qcc.cuny.edu/socialSciences/ppecorino/ (2010). Accessed: 25/10/2024.
5. Burbach, K. *Deadly medicine: How the Nazis influenced modern medical ethics.* [online]. University of Nebraska Medical Center. https://www.unmc.edu/newsroom/ (2005). Accessed: 25/10/2024.
6. Brawley, O. W. The Study of Untreated Syphilis in the Negro Male. *Int J Radiat Oncol Biol Phys* **40**, 5–8 (1998). Accessed: 25/10/2024.
7. Nix, E. *Tuskegee Experiment: The Infamous Syphilis Study*. [online]. HISTORY https://www.history.com/news/ (2023). Accessed: 25/10/2024.
8. *About The Untreated Syphilis Study at Tuskegee*. [online]. Centers for Disease Control and Prevention. https://www.cdc.gov/tuskegee/about/ (2024). Accessed 27/10/2024.
9. *What are the common cell lines?* [online]. AAT Bioquest. https://www.aatbio.com/resources/ (2023). Accessed: 25/10/2024.
10. Henrietta Lacks: science must right a historical wrong [online]. Nature Editorials. Nature 585, 7 (2020). Accessed 25/10/2024.

Cultural Differences in Diagnosing and Treating Diabetes

1. *The top 10 causes of death*. [online]. World Health Organization. https://www.who.int/news-room/fact-sheets/ (2024). Accessed: 14/10/2024.
2. Maggie, B. & Covington, M. B. Traditional Chinese Medicine in the Treatment of Diabetes. *Diabetes Spectrum* **14**, 154–159 (2001).
3. Chen, J. J. & Bertrand, A. *Excessive Thirst according to TCM*. [online]. Me & Qi. https://www.meandqi.com/symptoms/ (n.d.). Accessed: 15/10/2024.
4. *Pregnancy With Diabetes*. [online]. NHS Forth Valley. https://nhsforthvalley.com/health-services/ (n.d.). Accessed: 24/11/2024.
5. *Our Prices*. [online]. Lily Lai Acupuncture and Chinese Herbal Medicine. https://www.acupunctureandherbs.co.uk/prices (n.d.). Accessed: 19/3/2023.
6. *ATCM*. [online] The Association of Traditional Medicine & Acupuncture UK. https://www.atcm.co.uk/ (2015). Accessed: 19/10/2023.
7. Liu, H. *et al*. Chinese herbal medicine combined with western medicine for the treatment of type 2 diabetes mellitus with hyperuricemia: A systematic review and meta-analysis. *Front Pharmacol* **14**, 1102513 (2023).
8. Chen, Q. *et al*. Problems lowering the study quality in traditional medicine, introspection from an example of meta-analysis of acupuncture. *BMC Complement Med Ther* **20**, 41 (2020).
9. Zhang, J. & Zhang, Z. M. The Challenges of Ethical Review in Clinical Research of Traditional Chinese Medicine. *Evidence-Based Complementary and Alternative Medicine* **2021**, 6754985 (2021).

Gene Editing to Combat Soil Erosion in the Fight for Food Security: An Interview with PhD Student Emily Carr

1. Graves, A. R. *et al.* The total costs of soil degradation in England and Wales. *Ecological Economics* **119**, 399–413 (2015).
2. Nearing, M. A., Pruski, F. F. & O'Neal, M. R. Expected climate change impacts on soil erosion rates: A review. *Journal of Soil and Water Conservation* **59**, 43-50 (2004).
3. Bais, H. P., Weir, T. L., Perry, L. G., Gilroy, S. & Vivanco, J. M. The role of root exudates in rhizosphere interactions with plants and other organisms. *Annu Rev Plant Biol* **57**, 233–266 (2006).
4. Galloway, A. F. *et al.* Cereal root exudates contain highly structurally complex polysaccharides with soil-binding properties. *Plant J* **103**, 1666–1678 (2020).
5. Shiferaw, B. *et al.* Crops that feed the world 10. Past successes and future challenges to the role played by wheat in global food security. *Food Security* **5**, 291–317 (2013).
6. Hahn, F., Korolev, A., Loures, L. S. & Nekrasov, V. A modular cloning toolkit for genome editing in plants. *BMC Plant Biol* **20**, 179 (2020).
7. Wolter, F., Schindele, P. & Puchta, H. Plant breeding at the speed of light: the power of CRISPR/Cas to generate directed genetic diversity at multiple sites. *BMC Plant Biol* **19**, 176 (2019).
8. Department for Environment, Food & Rural Affairs. *Genetic Technology Act key tool for UK food security*. [online]. GOV.UK. https://www.gov.uk/government/news/ (2023). Accessed: 06/01/2025.
9. *New Genomic Techniques: MEPs back rules to support green transition of farmers*. [online]. European Parliament. https://www.europarl.europa.eu/news/ (2024). Accessed: 06/01/2025.
10. Mori, I. *Consumer Perceptions of Genome Edited Food*. [online]. Food Standards Agency. https://www.food.gov.uk/research/ (2021). Accessed: 06/01/2024.

Figure 1: adapted from Hahn, F., Korolev, A., Loures, L.S. & Nekrasov, V., created by Ana Miletić using BioRender.

Figure 2: photographed by Emily Carr.

The Science Behind Healing Hearts: My Laboratory Internship at the BRI

1. Bouma, B. J. & Mulder, B. J. Changing Landscape of Congenital Heart Disease. *Circ Res* **120**, 908-922 (2017).
2. Harris, A. G. *et al.* Biological Scaffolds for Congenital Heart Disease. *Bioengineering (Basel)* **10**, 57 (2023).
3. Harris, A. G., Iacobazzi, D., Caputo, M. & Bartoli-Leonard, F. Graft rejection in paediatric congenital heart disease. *Transl Pediatr* **12**, 1572-1591 (2023).
4. Arunamata, A. & Goldstein, B. H. Right ventricular outflow tract anomalies: Neonatal interventions and outcomes. *Semin Perinatol* **46**, 151583 (2022).
5. Harris, A. G. *et al.* Protocol to decellularize porcine right ventricular outflow tracts using a 3D printed flow chamber. *STAR Protoc* **5**, 102899 (2024).

Figure 1: "Child mortality by the type of congenital birth defect, World" by Our World in Data, licensed under CC BY 4.0. Retrieved from: https://ourworldindata.org/grapher/. Accessed: 22/01/2025.

Figures 2, 3, 4: created and photographed by Soham De.

Front cover images

1. "MRI brain sagittal section' by Everyone's Idle, licensed under CC BY-SA 2.0. Retrieved from: http://commons.wikimedia.org/wiki/. Accessed: 08/01/2025.
2. "Multiphoton fluorescence image of HeLa cells" by Tom Deerinck (NIH), licensed under CC BY-NC 2.0. Retrieved from: https://www.flickr.com/photos/nihgov/. Accessed: 08/01/2025.
3. "A close up of a bunch of sylls" by Pixabay, licensed under CC0 1.0. Retrieved from: https://boudewijnhuijgens.getarchive.net/media/. Accessed: 08/01/2025.
4. "Pre-Exposure Prophylaxis (PrEP)" by National Institute of Allergy and Infectious Diseases, licensed under CC BY-SA 2.0. Retrieved from: https://www.flickr.com/photos/niaid/. Accessed: 08/01/2025.
5. "Herd of cows grazing on a lush green field" by Pixabay, licensed under CC0 1.0. Retrieved from: https://picryl.com/media/. Accessed: 08/01/2025.
6. "Muscle Tissue: Cross Section Whole Skeletal Muscle" by Berkshire Community College Biosciences, licensed under CC0 1.0. Retrieved from: https://www.flickr.com/photos/. Accessed: 08/01/2025.
7. "Human red blood cells" by Arek Socha, licensed under CC0 1.0. Retrieved from: https://www.flickr.com/photos/. Accessed: 08/01/2025.
8. "Cancer cells" by Cecil Fox, licensed under CC BY 1.0. Retrieved from: https://commons.wikimedia.org/wiki/. Accessed: 08/01/2025.
9. "Mossy brain cell" by Ivan Soltesz, licensed under CC BY-NC 2.0. Retrieved from: https://www.flickr.com/photos/nihgov/. Accessed: 08/01/2025.

Title page images

1. “Anatomie der Ernährungsorgane” by Universitätsbibliothek Heidelberg, licensed under PDM 1.0. Retrieved from https://www.europeana.eu/item/. Accessed: 04/03/2025.
2. “Pancreatic cancer cells” by National Cancer Institute, licensed under Unsplash License. Retrieved from https://unsplash.com/photos/. Accessed: 13/03/2025.
3. “HIV, the AIDS virus (yellow), infecting a human cell” by National Cancer Institute licensed under Unsplash License. Retrieved from https://unsplash.com/photos/. Accessed 04/03/2025.
4. “Algo-r-(h)-i-(y)-thms, 2018. Installation view at ON AIR, Tomás Saraceno's solo exhibition at Palais de Tokyo, Paris, 2018″ by Alina Grubnyak, licensed under Unsplash License. Retrieved from https://unsplash.com/photos/. Accessed: 04/03/2025.
5. “DNA Fragmentation. A dye marker on agarose gel used to separate DNA by a female scientist” by National Cancer Institute, licensed under Unsplash License. Retrieved from https://unsplash.com/photos/. Accessed: 04/03/2025.

Back to contents

Our Editorial Team

Thank you to all the Editorial Team members who contributed to this issue.

Editors:

Jasmine Abdy
Kelsey Abellana
Sarah Alshahabi
Han Sheng Ang
Roshni Chadha
Roop Chahal
Alex Gabriel Chong
Lauren Cozens
Zihan Deng
Imogen Joseph
Rezanë Kajashi
Saniyah Khan
Defne Kiziltan
Cheuk Gi Chloe Lau
Rebecca Lin
Alexa Lopez
Meredith Lott
Uthra Mandi
Hithrisha Sree Pillai
Cherub Cheuk Hang Poon
Jaya Veronique Richardson
Sanya Saxena
Yun Shen
Scarlet Siu
Annabel Thomas
Jing Ying Tong
Matilda Wicks
Ana Miletić *(Senior Editor)*
Alex Radlett *(Senior Editor)*

Designers:

Sophie Bloom *(Senior Designer)*
Yasmin Abdrakhmanova
Roshni Chadha
Defne Kiziltan
Cheuk Gi Chloe Lau
Hannah McDickson
Ozioma Onyeama
Hithrisha Sree Pillai
Michael Wong

Proofreaders:

Jessica Loong *(Senior Proofreader)*
Hannah Carpenter
Olivia Cocks
Tanya Gunnarsdóttir
Erin Johnston
Nelly Kobrzynska
Andrea Polomcic
Esther Riddy
Henry Spearing

Senior Team:

Yasmin Abdrakhmanova
Sophie Bloom
Jessica Loong
Ana Miletić
Alex Radlett
Michael Wong

With additional thanks to Hithrisha Sree Pillai for designing the front cover.