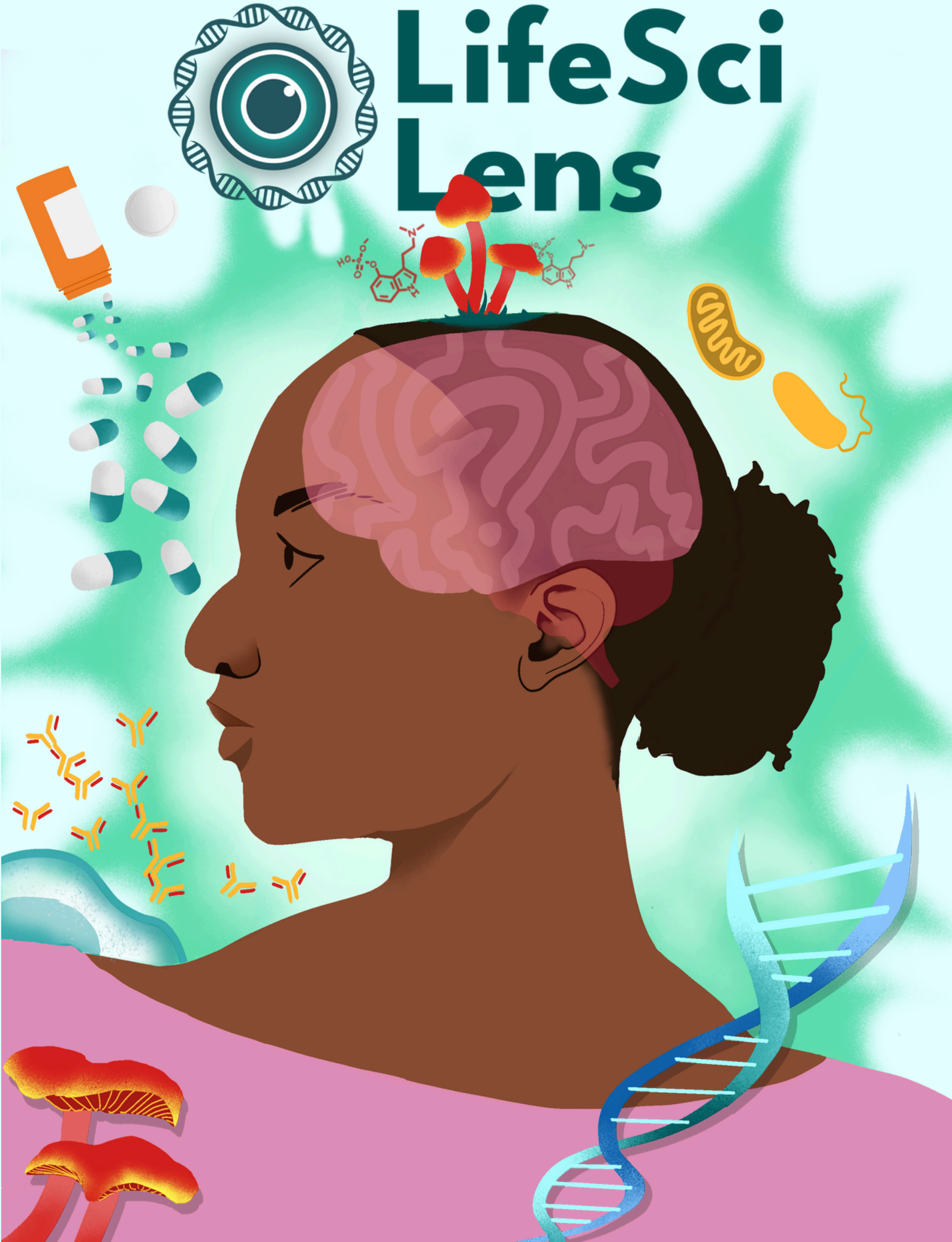
Issue #3 November 2025

LifeSci Lens



Editorial

Welcome to Issue #3 of LifeSci Lens!

With 8 new and original articles written by students, this issue zooms in on the building blocks of life and the brain, before introducing bigger picture ideas about health and sustainability.

Foundations of Life

If we want to design new, synthetic biological systems, we have to understand the essential mechanisms leading up to the evolution of the multicellular biological machines that inhabit the Earth today. This section looks back at the humble origins of cellular complexity in our single-celled ancestors through endosymbiosis and goes on to explore the principles of genetic circuits, which are revolutionising the future of cellular engineering.

Plus check out our first ever art feature!

Unlocking Mental Health

Mental health diagnoses have been steadily rising over the past few decades, putting pressure on the mental health workforce. This section examines how researchers are working to address the issue, turning to previously unexplored and even taboo sources of therapeutic compounds, such as magic mushrooms, in the search for novel drugs that could tackle treatment-resistant cases. But while these results are promising, it is important to consider patient heterogeneity; psychedelic therapies may not be suitable for patients with a history of psychosis, which can be influenced by complex environmental factors such as early childhood adversity.

Biomedical Advances

Recent discoveries are shedding new light on the molecular and immunological mechanisms behind diseases that affect millions worldwide. This section explores beta-amyloid accumulation in Alzheimer's disease through *in situ* studies, revealing new insights into neurodegeneration, alongside research into immune thrombocytopenic purpura, where understanding platelet regulation and immune responses is paving the way for more precise and personalised therapies. By uncovering these underlying processes, researchers are opening doors to targeted interventions and potential treatments.

Drugs in Development

As new therapies emerge, understanding and managing side effects is becoming just as important as their clinical benefits. This section explores innovative research into GLP-1 mimetics, examining how scientists are working to outsmart the nausea caused by semaglutide, with insights into neural pathways and dosing strategies that could make these transformative treatments safer and more effective.

Health and Our Environment

Urban air pollution remains a pressing threat to public health, contributing to millions of premature deaths worldwide and increasing the risk of lung disease and cancer. This section examines a two-year study of Bristol's Clean Air Zone using Palmes diffusion tubes, showing how traffic patterns, green spaces, and local interventions influence nitrogen dioxide levels, and highlighting areas where further action is needed to protect vulnerable populations.

Ana Miletić, *President*
Kerry Shen, *Senior Editor*

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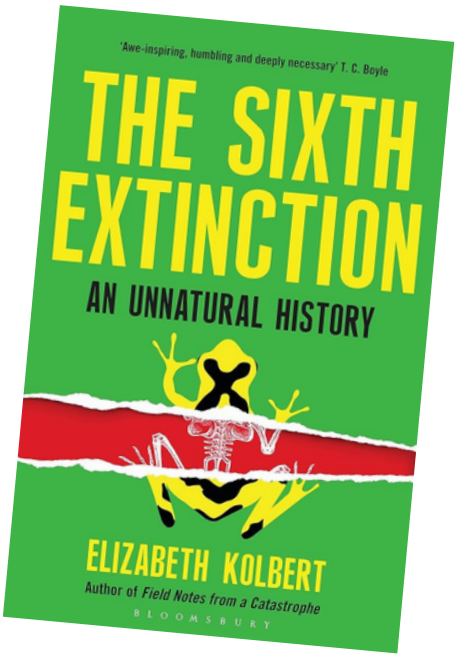
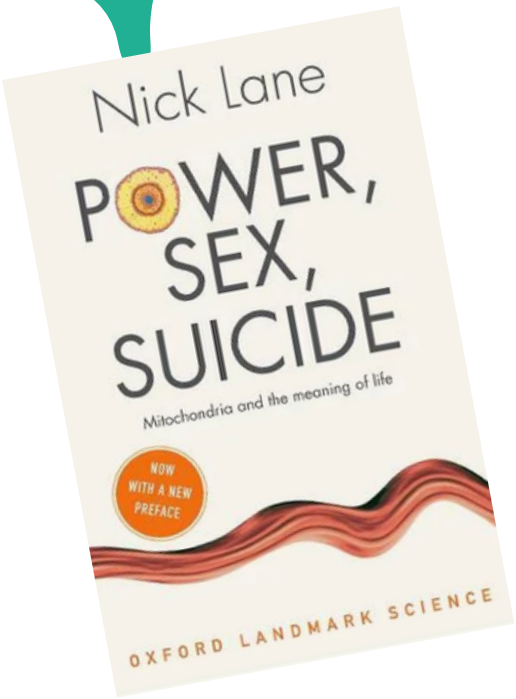
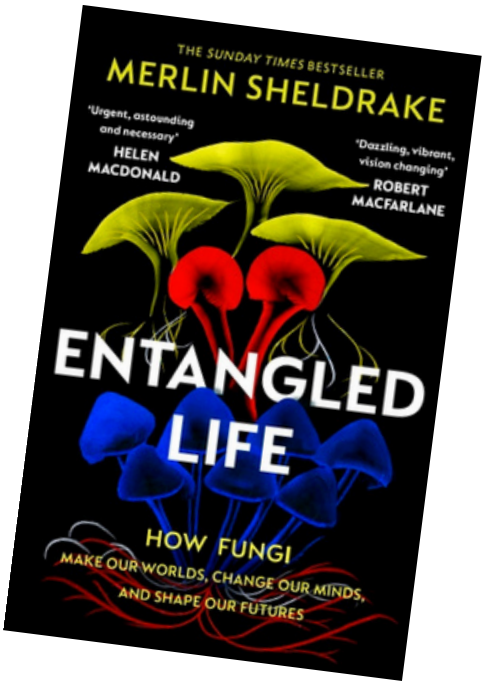
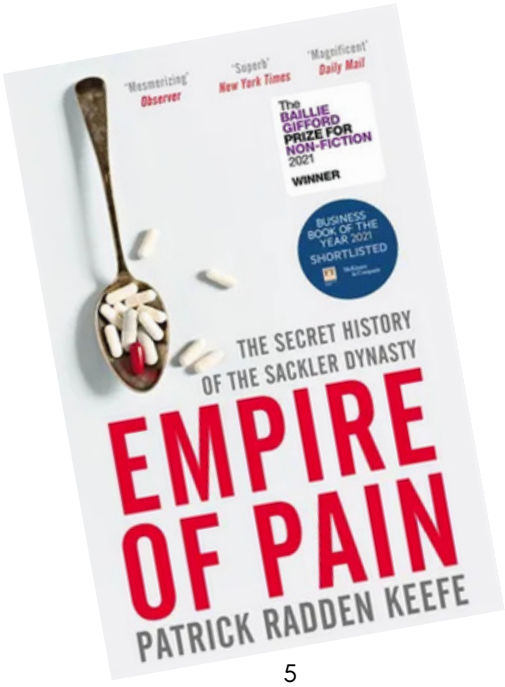
What we're reading









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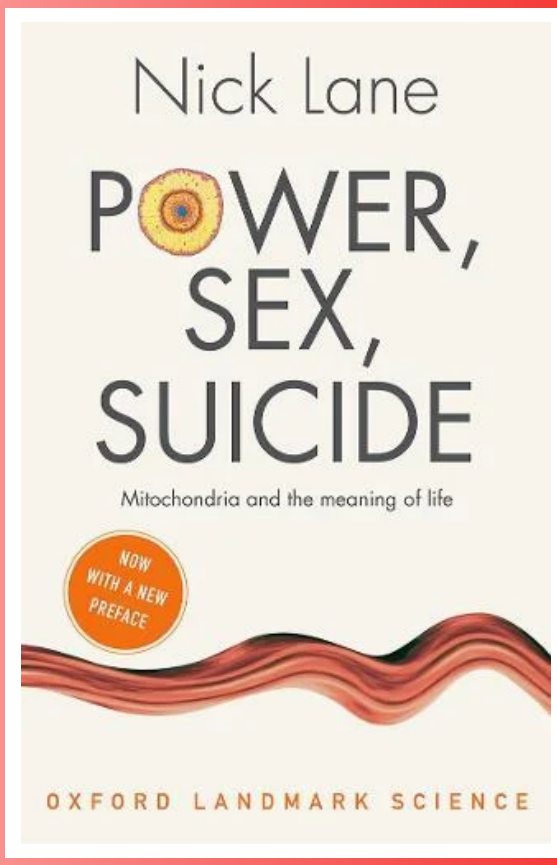
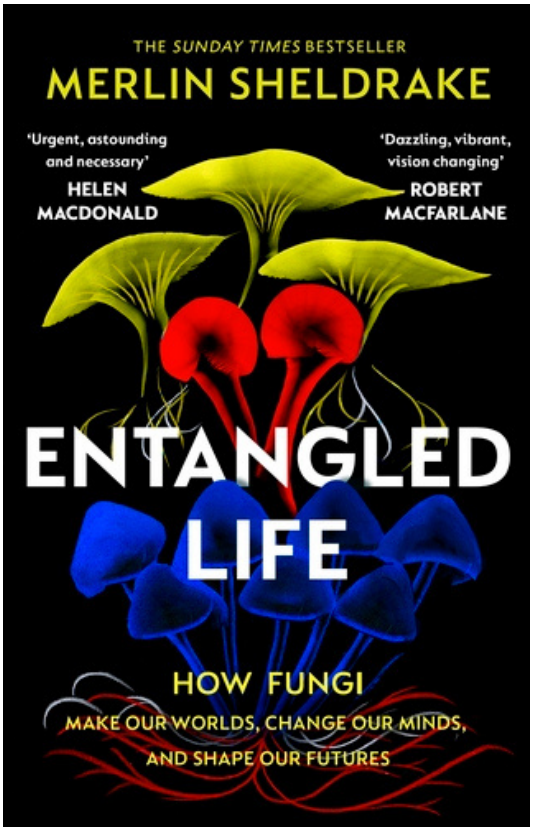
A powerful account of the most important organelle in our body, how it got there and what it does.

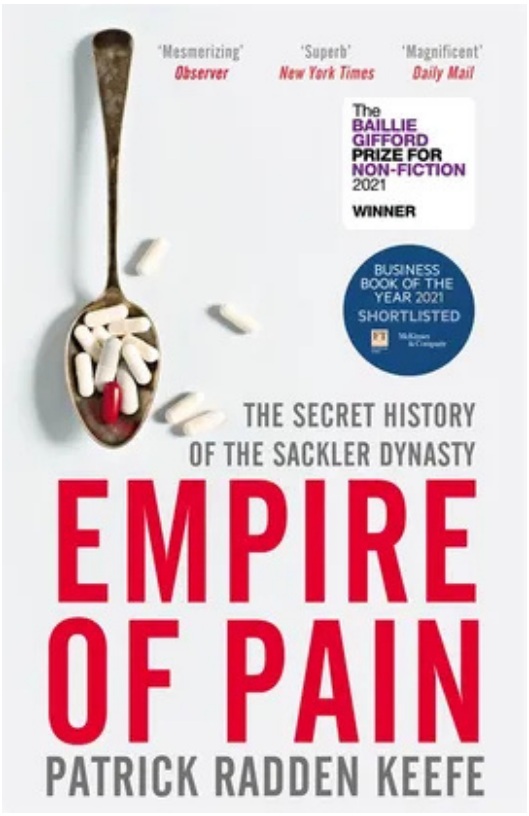
Head to pg 11 to find out about the unlikely endosymbiosis that drove eukaryotic origins.





If watching *"The Last of Us"* left with you with a fear of fungi, this fascinating deep dive into their role in our world might help amend that.

Head to page 24 to read more about the therapeutic potential of magic mushrooms.

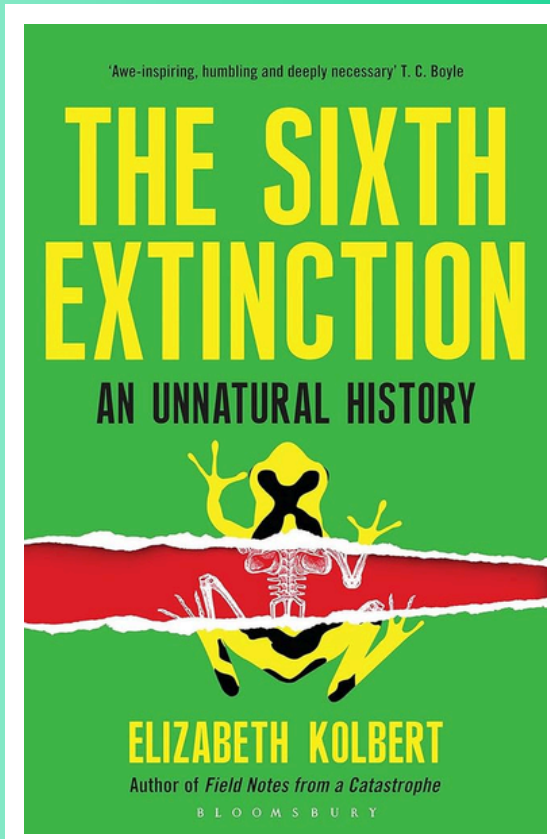


This informative piece brings you up to date on the horrifying tale of the Sacklers' role in the OxyContin epidemic currently gripping the US.

Head to pg 43 to learn about other drugs you might also have seen in the news recently.

Is the natural world as we know it nearing its unnatural end due to human interference?

Head to pg 48 to find out how effective Bristol has been at dealing with the climate crisis.



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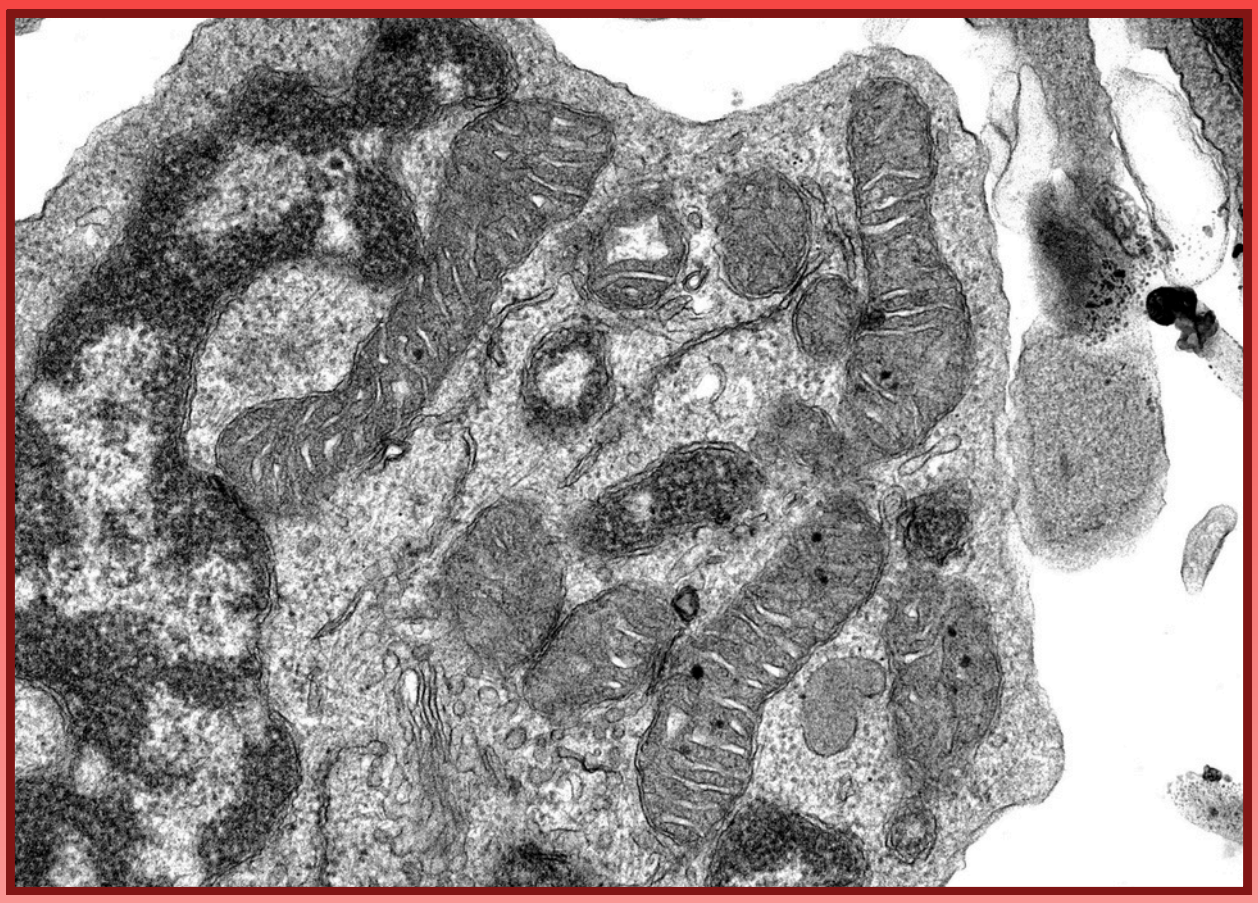
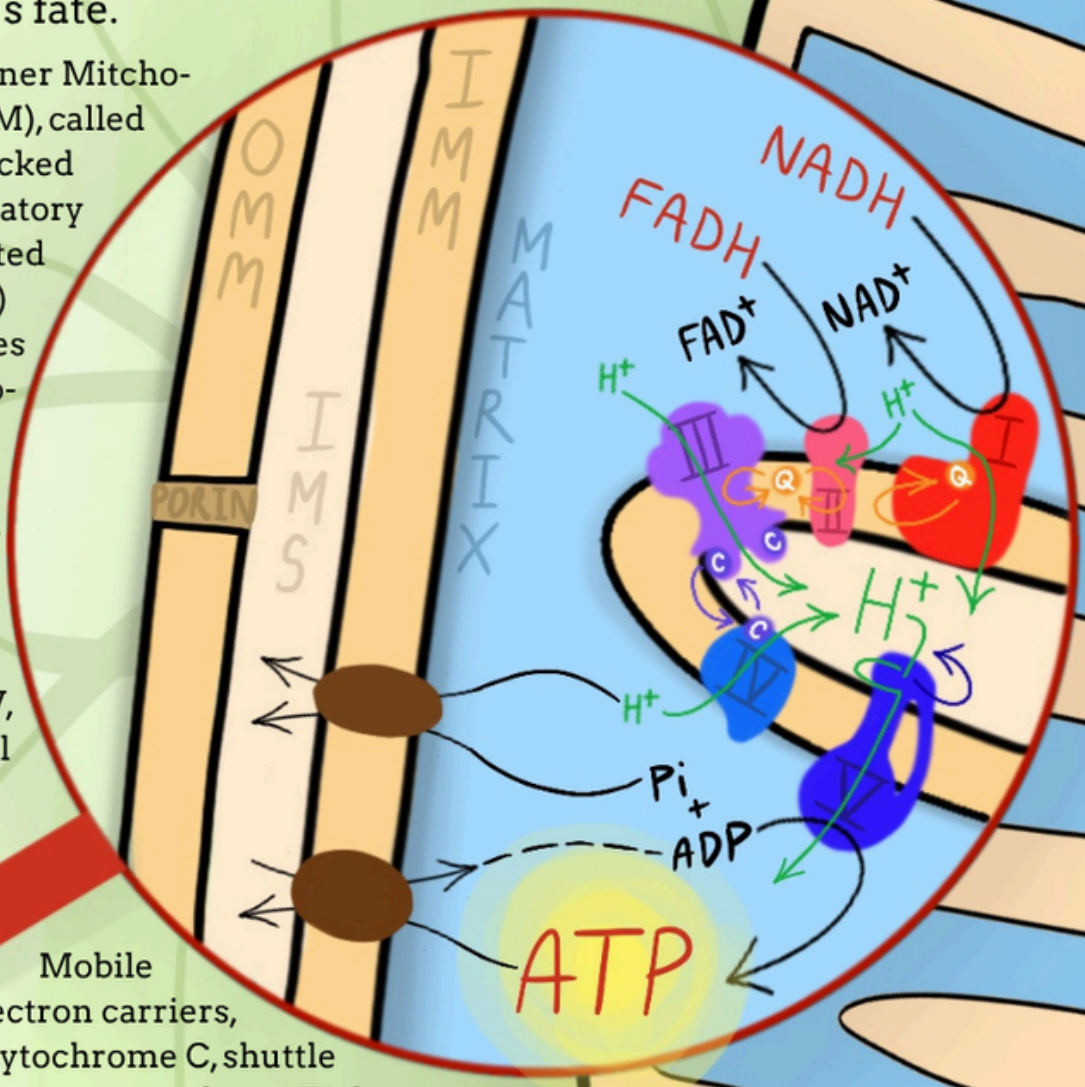


Foundations of Life

MITOCHONDRIA: in Life...

Casually referred to as the 'powerhouse of the cell', these highly adaptable organelles integrate signals from the outside world, acting as a key deciding factor in the cell's fate.

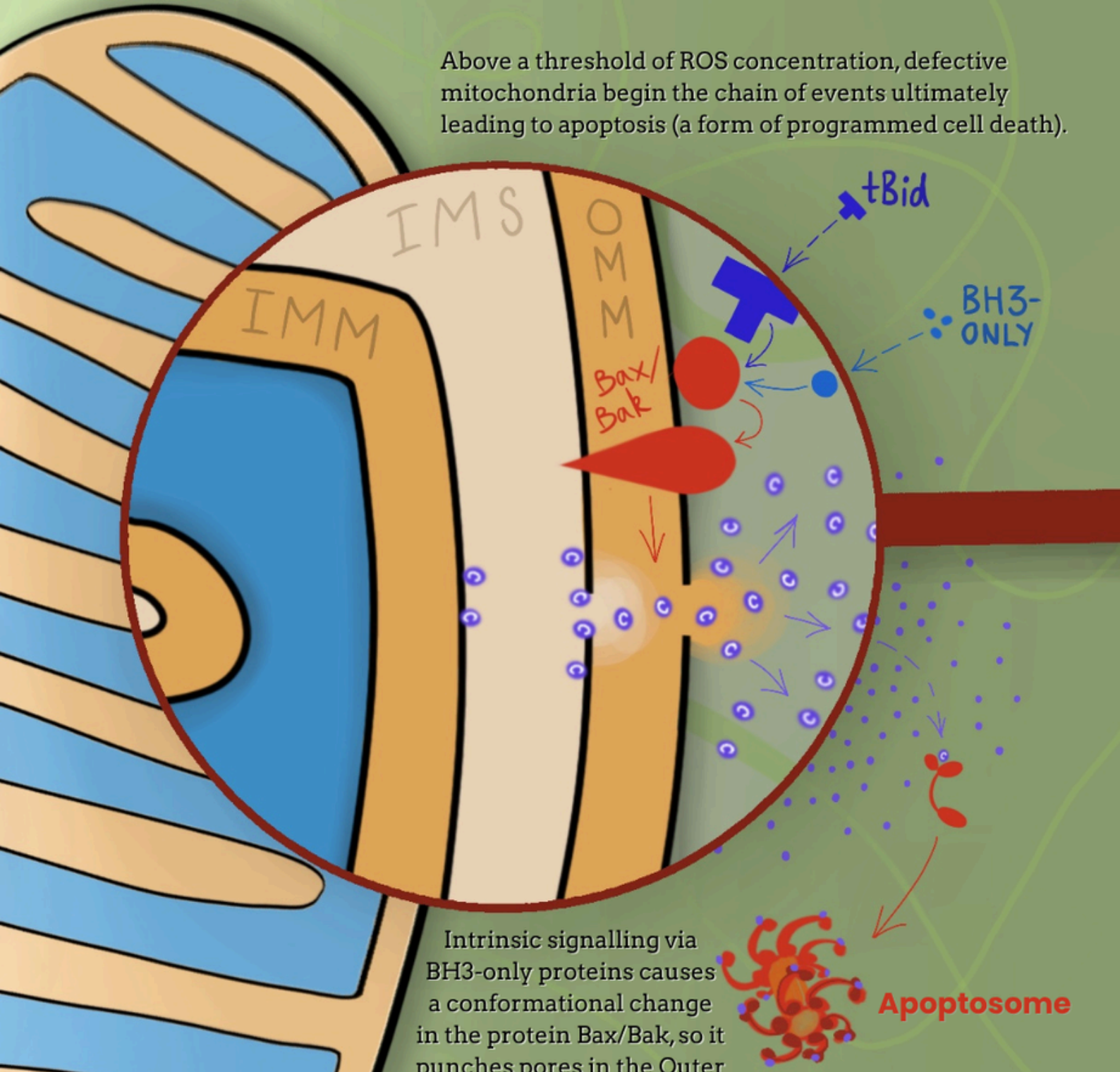
Invaginations of the Inner Mitochondrial Membrane (IMM), called cristae, are densely packed with units of the respiratory chain. Electrons (donated by specialised carriers) pass through complexes I-IV, which pump protons (H+) into the Inner Mitochondrial Space (IMS), to reach oxygen. Stored protons flow back through the otherwise impermeable IMM via complex V, which uses mechanical movement to drive creation of ATP - a usable form of energy for the cell.



Mobile electron carriers, such as cytochrome C, shuttle electrons between complexes. Tight arrangement into supercomplexes increases the transfer efficiency and limits production of damaging Reactive Oxygen Species (ROS). At low concentrations, ROS act as signals that promote transcription of genes required for autophagy ('cell eating') in an attempt to prolong life.

Guan, S. et al. Mitochondrial Respiratory Chain Supercomplexes: From Structure to Function. *Int. J. Mol. Sci.* **23**, 13880 (2022)

Above a threshold of ROS concentration, defective mitochondria begin the chain of events ultimately leading to apoptosis (a form of programmed cell death).



Intrinsic signalling via BH3-only proteins causes a conformational change in the protein Bax/Bak, so it punches pores in the Outer Mitochondrial Membrane (OMM); a similar outcome occurs following extrinsic signalling via cell surface receptor activation of caspase proteins that cleave Bid into its functional form, tBid. Cytochrome C is released into the cell cytoplasm, where it interacts with other proteins (Apaf-1 and caspase-9) to assemble the apoptosome. This machine activates many effector caspases so they can digest the cell interior. Changes in cytoskeletal dynamics causes membrane 'blebbing' into smaller parts that can be cleared safely by the immune system. Defective death signalling could prevent this process of self-sacrifice by cells with cancerous mutations.

Hall-Younger, E. & Tait, S.W. Mitochondria and cell death signalling. *Curr. Opin. Cell Biol.* **94**, 102510 (2025)

...and Death.

By Sophie Bloom

Mitochondria: the Powerhouse of Eukaryotic Evolution?

By Aliki Allagianni

How did complex life begin on Earth? Eukaryogenesis, the origin of eukaryotic cells, is believed to have constituted a significant leap in cellular complexity, acting as a key step in the evolution of multicellularity[1]. Not much is certain regarding how this transition took place, however, increasing evidence points to mitochondria playing an important role.

"Mitochondria's importance for cellular function led researchers to believe that their acquisition was a key event in the transition from prokaryotic to eukaryotic life."

Mitochondria are semi-autonomous intracellular organelles which are present in the majority of eukaryotic cells[2,3]. Bound by a double phospholipid membrane, they possess their own genetic material - the mitochondrial DNA (mtDNA)[3]. Mitochondria are known for their role in the cell's energy metabolism, producing adenosine triphosphate (ATP), which drives cellular activities[4,5]. For this reason, they are often referred to as the 'powerhouse of the cell'[3]. Besides energy production, mitochondria are also intimately involved in apoptosis, calcium homeostasis, and haem synthesis, among other functions[3,5].

Mitochondria's importance for cellular function led researchers to believe that their acquisition was a key event in the transition from prokaryotic to eukaryotic life[1]. However, there is an ongoing debate about the exact conditions and order in which events occurred during eukaryogenesis[6]. The present article aims to examine the role of mitochondria in the evolutionary transition to complex life.

Endosymbiotic Theory

Endosymbiosis refers to the relationship between two organisms in which one lives inside of the other, resulting in a mutually beneficial outcome[7]. Endosymbiotic theory, the notion that some organelles in eukaryotic cells arose through endosymbiosis, was first proposed by Konstantin

Mereschkowski at the beginning of the 20th century[8]. Mereschkowski supported the idea that the chloroplasts in plant cells were the result of an endosymbiosis with heterotrophic amoeboid cells, contradicting the popular view at the time that plastids were autogenous in origin[9]. In support of his theory, he cited the morphological similarities between plastids and free-living algae, as well as the existence of symbiotic photosynthetic microorganisms such as chlorella cells[11]. However, he did not consider the possibility that mitochondria also arose through endosymbiosis.

"Though the idea was initially faced with scepticism, the discovery of archaea helped endosymbiotic theory to grow in popularity."

In the 1970s, Lynn Margulis repopularised endosymbiotic theory, suggesting that mitochondria (as well as chloroplasts) originated from prokaryotes[9]. She proposed that mitochondria were naturally selected for their role in the transition to aerobic metabolism, following the rise of atmospheric oxygen levels[9]. Though the idea was initially faced with scepticism, the discovery of archaea helped endosymbiotic theory to grow in popularity[8]. Archaea are prokaryotic cells, similar to bacteria in size and shape, but possess simplified informational machinery, similar to eukaryotes[9]. In the present, researchers widely agree that mitochondria arose from an endosymbiosis between an alphaproteobacterium and an archaeal cell, though the exact mechanism underlying this endosymbiosis remains under debate[6,11].

Recent studies have provided further insights on eukaryogenesis. Phylogenetic analyses by Santana-Molina *et al.* provided strong evidence that *Asgardarchaeota* made contributions to the central carbon metabolism of the last eukaryotic common ancestor (LECA), which was previously thought to be bacterial in origin[12,13]. Bernabeu *et al.* found significant genetic contributions to LECA from three non-alphaproteobacterial individuals, as well as signs that gene transfer was facilitated by *Nucleocytoviricota* viruses[14]. These findings suggest that eukaryogenesis likely involved a series of sustained interactions between an archaeon and multiple bacteria[14]. Nevertheless, more research is required to further validate these ideas[6].

Mitochondria and Cell Bioenergetics

Regardless of how mitochondria entered the archaeal host cell, they have made significant contributions to the complexity and evolutionary trajectory of eukaryotic cells. In line with the predominant view, the archaeal host was likely an anaerobe, living in anoxic marine sediments, as do its closest living relatives, the *Asgardarchaeota*[6] (Figure 1). Through an endosymbiosis with alphaproteobacteria—themselves likely facultative anaerobes—the archaeal host is thought to have developed aerotolerance, allowing it to accommodate increasing atmospheric oxygen levels[11]. The switch to aerobic respiration might have also enabled early eukaryotes to occupy more diverse environments, allowing further diversification and eventually multicellularity to develop[15].

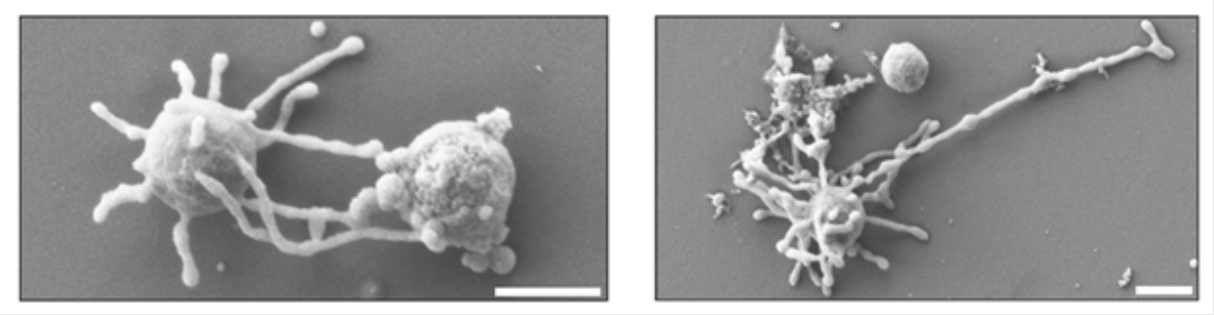


Figure 1. *Lokiarchaeum ossiferum* cells, a member of the *Asgardarchaeota*, and the closest known relatives of modern-day eukaryotes[16]. Scale bars: 500 nm.

Nevertheless, aerobic respiration does not necessarily explain the increase in complexity and genome size observed in eukaryotes, as both aerobic prokaryotes and anaerobic eukaryotes are known to exist[16]. Lane and Martin postulate that the answer lies in energy, arguing that the energy required to express new proteins greatly surpasses the cost of carrying the genes that encode them[16]. A large genome, and by extension a large proteome, has significant energetic costs attached[15]. This, they argue, is also the reason why complexity is often selected against in organisms[15]. This phenomenon is evident in bacteria, whose DNA is gene-dense, polycistronic, and lacks introns, in the interest of energy efficiency[16]. Eukaryotes, however, in large part due to the ATP generated by oxidative phosphorylation, are able to express tenfold the number of proteins compared to prokaryotes, which likely allowed them to become more complex[5,16].

A counterpoint that is often brought up against the notion that mitochondria were a prerequisite for cellular complexity are anaerobic eukaryotes, some of which have lost their mitochondria entirely[15]. These eukaryotes can occupy both nutrient-poor and -rich anaerobic environments and typically rely on fermentation for energy[5,15]. However, aerobic respiration is a far more efficient method of energy production[15]. How, then, are anaerobic eukaryotes capable of cellular complexity when they have a less efficient metabolism? Lane and Martin argue that in terms of bioenergetics it is easier to retain ancestral structures rather than to create them anew[17]. Therefore, as anaerobic eukaryotes evolved reductively from aerobes, it would not be particularly energetically costly to retain some of the complex structures they inherited[17].

"How, then, are anaerobic eukaryotes capable of cellular complexity when they have a less efficient metabolism?"

Lane and Martin's claims were challenged by Lynch and Marinov, who determined that the ATP requirements of cells, both bacterial and eukaryotic, declined with increased cell volume[17,18]. They claim that bioenergetics, as described by Lane and Martin, do not appear to act as a barrier to cellular complexity[18]. Nevertheless, they offer no alternative 'barrier' to the evolution of eukaryotes, failing to explain why eukaryotic cells haven't evolved multiple times in evolutionary history[19]. Moreover, they do not address that amitochondriate eukaryotes must compensate for their lower energy yields with slower growth rates, a practice that likely constrains their macroevolutionary potential[15].

Conclusion

The answer to the central question of this article – what was the role and importance of mitochondria in eukaryogenesis? – lies in the ways in which mitochondria altered the pre-eukaryotic energy metabolism. Aerobic respiration is more efficient and has a higher energy yield than anaerobic methods. Therefore, the transition to an aerobic energy metabolism following mitochondrial acquisition allowed pre-eukaryotic ancestors to function more efficiently. The aerobic metabolism also coincided with increasing atmospheric oxygen levels, broadening eukaryotes' ecological

and evolutionary potential[15]. Moreover, the influx of energy from mitochondria enabled eukaryotes to significantly amplify their protein production, likely resulting in increased cellular complexity[9].

Although recent discoveries have provided new insights into eukaryogenesis, many questions remain unanswered. Researchers have emphasized the need for better and more accurate phylogenetic models. Even so, it is evident that mitochondria played an important role in the evolutionary history of eukaryotes, with future research likely further highlighting the significance of this vital organelle.

References

Primary editor: Alex Papasavvas
Peer-reviewer: Kerry Shen

Programming the Cell: How Genetic Circuits Work

By Ethan Foddy

Introduction

Genetic circuits are engineered biological systems of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and proteins that function analogously to electronic circuits within living cells. They control how genetic information is processed and perform specific functions, building cells to execute a user-defined function. They program the cell so that a predefined stimulus (input) results in a desired response (output)[1]. This can have significant impacts across many fields. Microbes could produce pharmaceuticals or biofuels, cells could be designed to fight certain diseases, and organisms could be engineered for sustainable agriculture. This article provides an overview of the fundamentals of genetic circuitry and its future.

Core Components and Design

The core components of genetic circuits can be broadly categorised based on their molecular nature (Figure 1):

- DNA elements include promoters, coding sequences, terminators, and ribosomal binding sites (RBS) that adjust and control protein synthesis.

- RNAs; mRNAs for protein synthesis. Regulatory RNAs (small RNAs, small interfering RNAs and ribozymes) control gene expression by binding to and affecting mRNA's translation or stability[2,3]. Catalytic ribozymes can function enzymatically or through self-cleavage[4]. Post-transcriptional mechanisms in eukaryotes (splicing, polyadenylation, and capping) can also be implemented for gene expression.

- Proteins produced include regulator proteins that transcriptionally inhibit (such as LacI and TetR) or enhance gene expression by binding to DNA or other molecules[5]. Enzymes (such as recombinases and polymerases) catalyse specific reactions critical for the circuit's function or output[6].

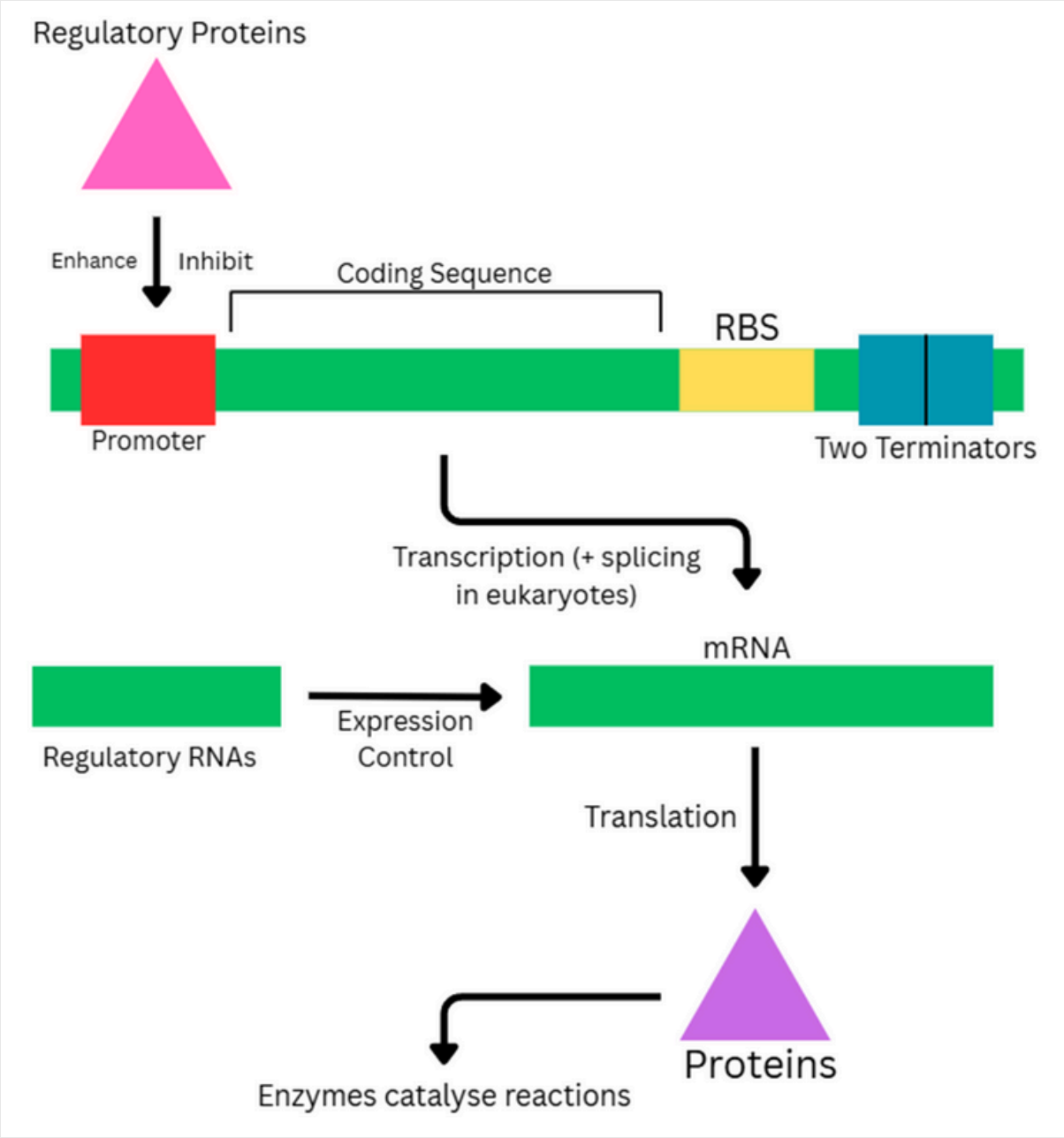


Figure 1. Simplified Core Components of a Genetic Circuit. Regulatory proteins, a promoter, and insulators control transcription of a coding sequence into mRNA. A ribosomal binding site (RBS) and regulatory RNAs guide the final steps of creating a functional protein through translation.

- Insulators include two consecutive terminators and ribozyme-based sequences. They minimise the frequency of erroneous transcription. During transcription, terminators do not always function properly, resulting in transcriptional read-through, which can lead to unintended expression and interference[7,8].

Fundamental design principles emphasise modularity, tunability, and orthogonality. Modularity encompasses standardised modules with well-defined functions, allowing customisation of complex genetic circuits. Tunability aims for precise control over the cell's output by modifying genetic circuit constituents to tune the cell's behaviour. Orthogonality is the exclusive interaction between the genetic circuit's components, critical for optimising the circuit's modularity and tunability[9,10].

Examples of Genetic Circuits

Based on electrical circuits, genetic circuits also constitute exemplary parts, including logic gates, memory/switches, and oscillators (Figures 3, 4, and 5, respectively). Logic gates in electrical circuits process inputs of 1s and 0s to provide an output. An **OR** gate receives two signals; if either one or both is a 1, it outputs a 1; if both are a 0, then the output is 0. An **AND** gate requires both signal inputs to be 1s to output a 1; otherwise, the output is 0. A **NOT** gate only has one input and outputs the opposite of this input. The **NOR** gate outputs a 1 only when both inputs are a 0; otherwise, the output is 0 (Figure 2).

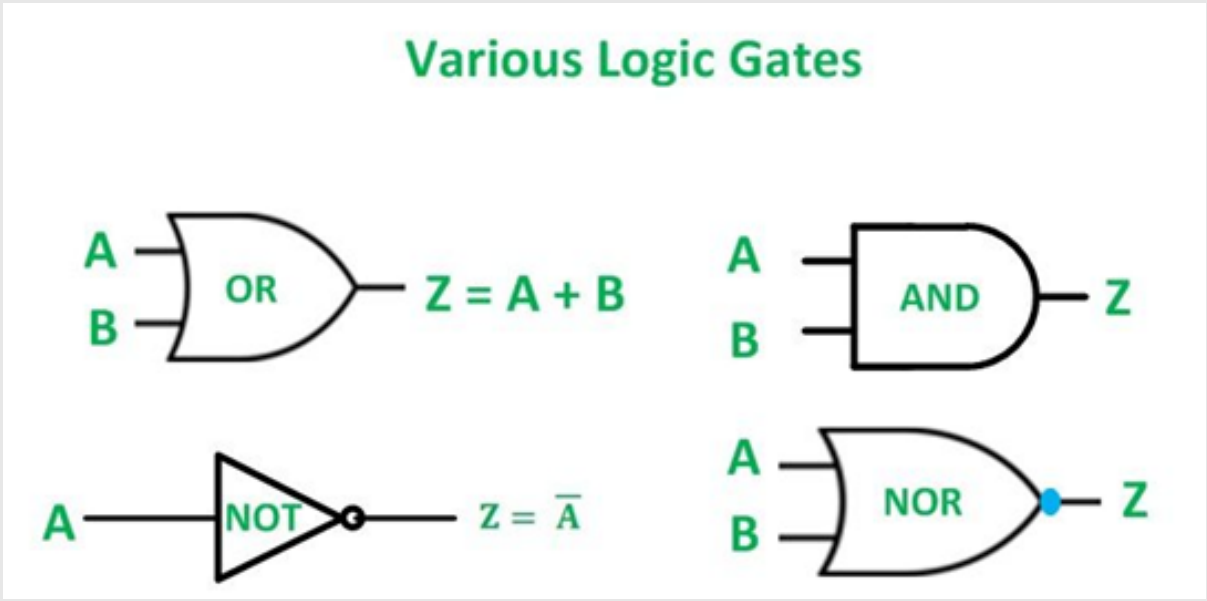
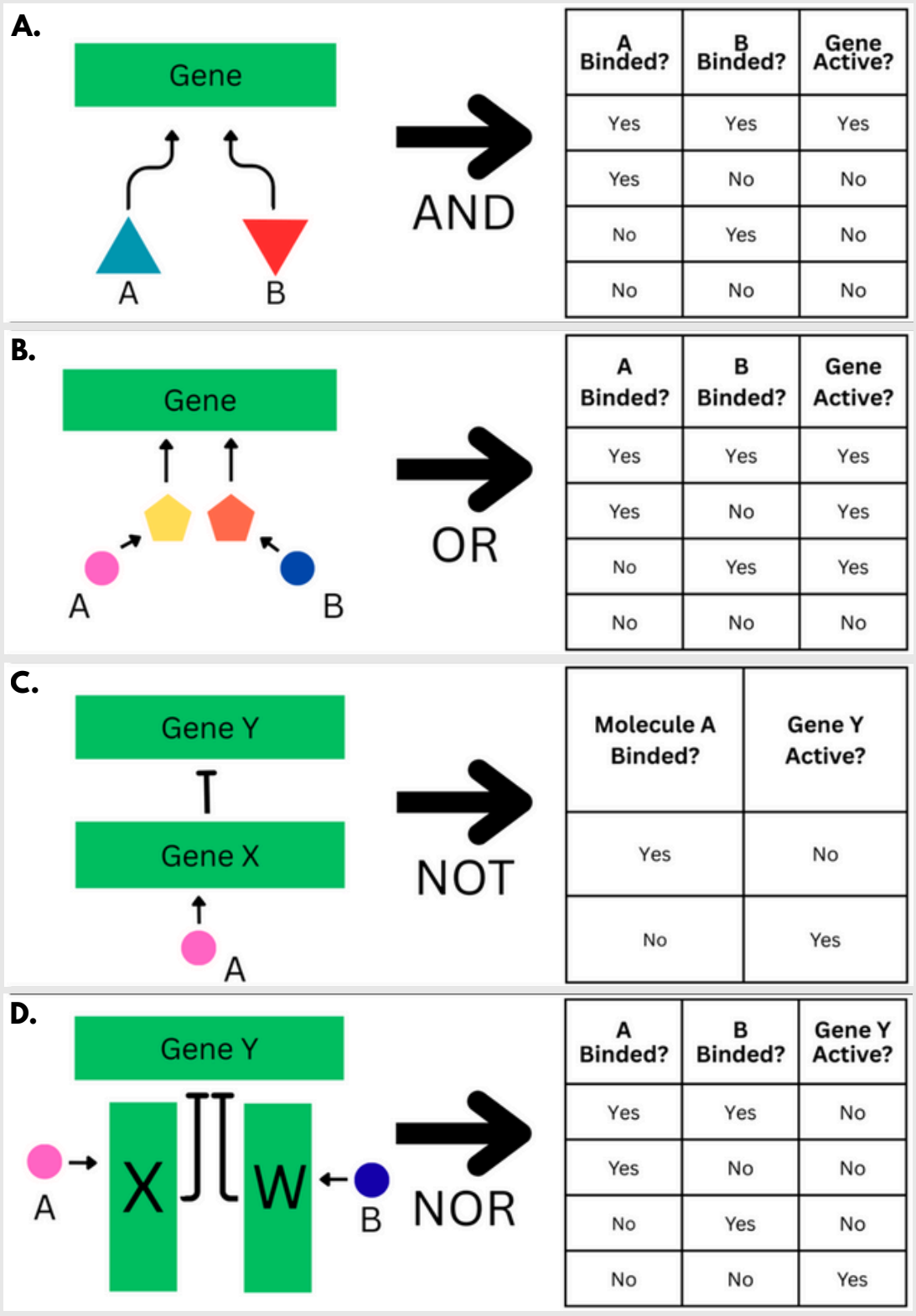


Figure 2. Logic gates process an input of A and B, each representing 1 or 0, to provide an output Z, representing 1 or 0. The **OR** gate outputs a 1 if either A or B is a 1. The **AND** gate outputs a 1 if both A and B are a 1. The **NOT** gate outputs the opposite of A. **NOR** outputs a 1 when both A and B are a 0; if either or both are a 1, then the output is 0[11].



A Binded?	B Binded?	Gene Active?
Yes	Yes	Yes
Yes	No	No
No	Yes	No
No	No	No

A Binded?	B Binded?	Gene Active?
Yes	Yes	Yes
Yes	No	Yes
No	Yes	Yes
No	No	No

Molecule A Binded?	Gene Y Active?
Yes	No
No	Yes

A Binded?	B Binded?	Gene Y Active?
Yes	Yes	No
Yes	No	No
No	Yes	No
No	No	Yes

Figure 3. A) AND gate: a gene is expressed when two specific inputs, A and B, are both present. **B) OR** date: a gene is expressed if either input A or B (or both) is present. **C) NOT** gate: a gene is not expressed when a specific input A is present; its absence leads to gene expression. D) **NOR** gate: a gene is expressed only when inputs A and B are absent[12].

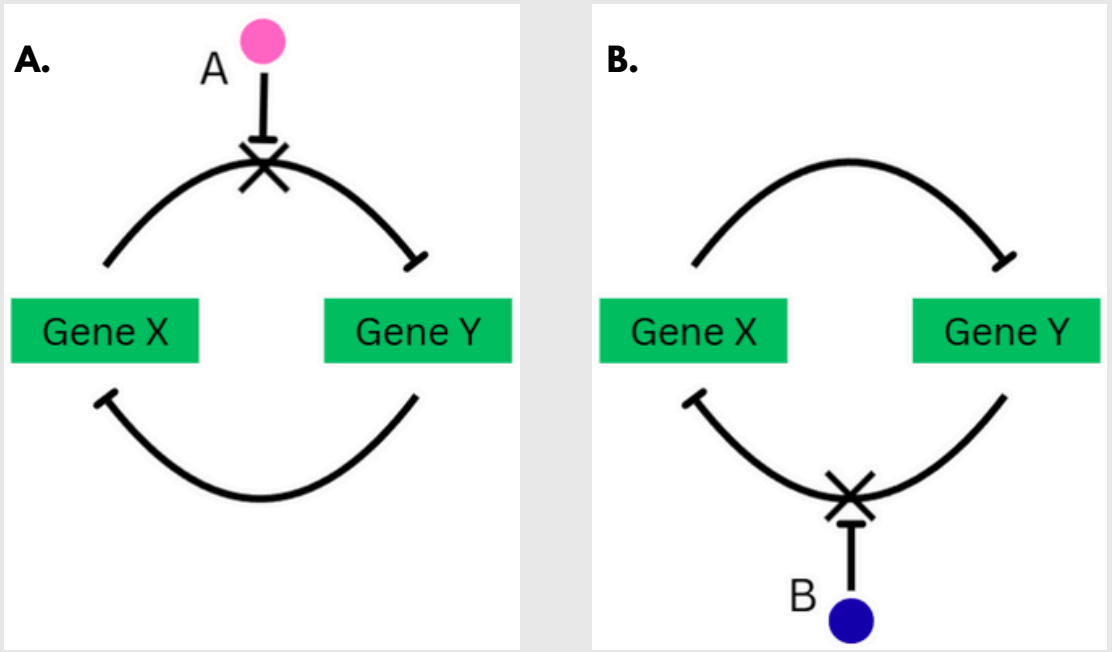


Figure 4. Genetic switch of two mutually repressive genes, X and Y. A) Introduction of molecule A inactivates repressor X, allowing gene Y to turn on and switch the cell's state. **B)** The opposite occurs if molecule B is introduced. This enables cells to "remember" an event through a stable ON or OFF state[13].

Building and Studying Genetic Circuits

DNA assembly techniques, including Gibson Assembly, are used to join DNA fragments and create a genetic circuit. It is then cloned into a plasmid and inserted into host cells for replication and expression[15]. Thereafter, fluorescent proteins (FP) are used as reporters to measure the activity of a genetic circuit: the brighter the signal, the more activity there is. This fluorescence is measured using instruments such as a fluorometer or a flow cytometer[16,17].

Before any circuits are built, computational models are used to design and test them by predicting how a circuit will behave, saving time overall. Different types of models are used for varying purposes:

- Boolean models use logic gates to describe circuit function.
- Ordinary Differential Equations (ODEs) predict how the circuit will respond to different inputs.
- Stochastic models analyse how random fluctuations affect the circuit[18].

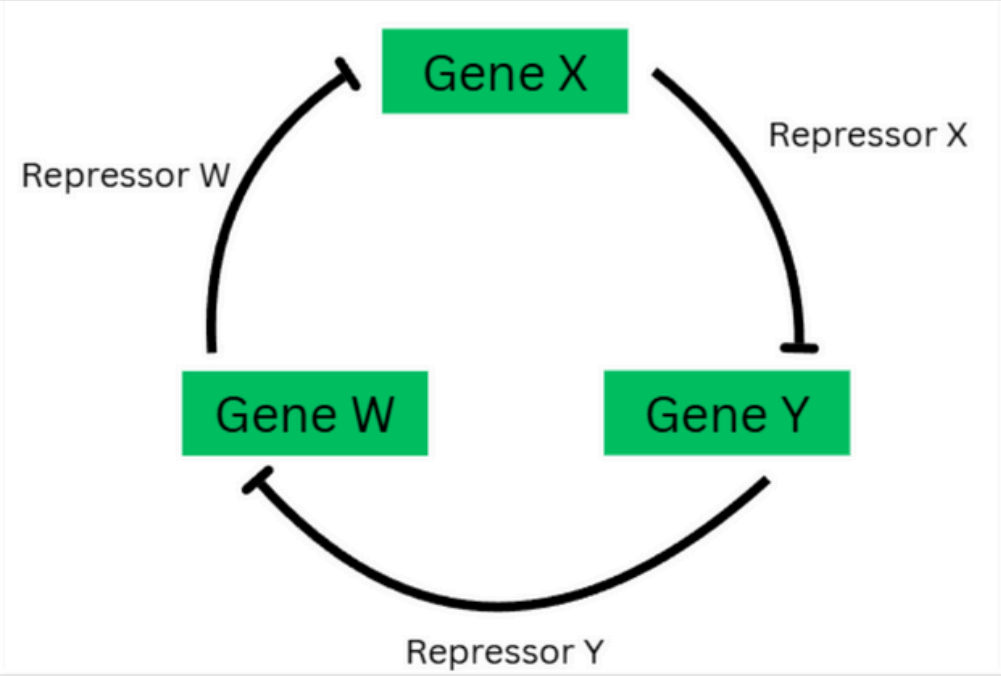


Figure 5. An oscillator is a genetic circuit that produces a repetitive output. The Repressilator, a classic example, consists of three genes in a ring, where each gene's protein product represses the next gene in the sequence. This creates a cycle of repression and derepression, allowing the circuit to act as a cellular clock or synchronise cellular processes[14].

Challenges and Future Outlook

Future challenges include the inherent internal noise of cells. Orthogonality minimises this issue by separating the genetic circuit from the original components of the cell. Additionally, resource loading is the competition between genetic circuits and host processes for limited cellular resources. It can potentially damage the host cell fitness and unpredictably alter the circuit's behaviour, making predictions harder[19].

Consequently, larger libraries of reliable, predictable, orthogonal parts need to be developed, along with principles and methods for creating circuits capable of long-term stability. Computational models need to be designed to better account for noise, resource loading, and host internal climates. AI and machine learning could be utilised when designing, simulating, and verifying larger, more complex circuits[20]. Crucially, there have to be proactive discussions and studies around safety, environmental impact, ethics, security, and public perception regarding engineered genetic circuits outside of research[21].

Conclusion

Genetic circuits are biological systems designed and engineered to perform a desired function within living cells. The study and refinement consist of core components, design principles, computational modelling, assemblies, and methodologies simplified in this article. The path forward still necessitates significant research around the inherent variability and complexity within cells, including resource loading, noise, and consequent unintended interactions. Advancing design robustness, predictability, orthogonality, computational tools, and responsible innovation will majorly drive future progress. Still, genetic circuits promise remarkable applications in medicine, manufacturing, agriculture, and the environment.

References

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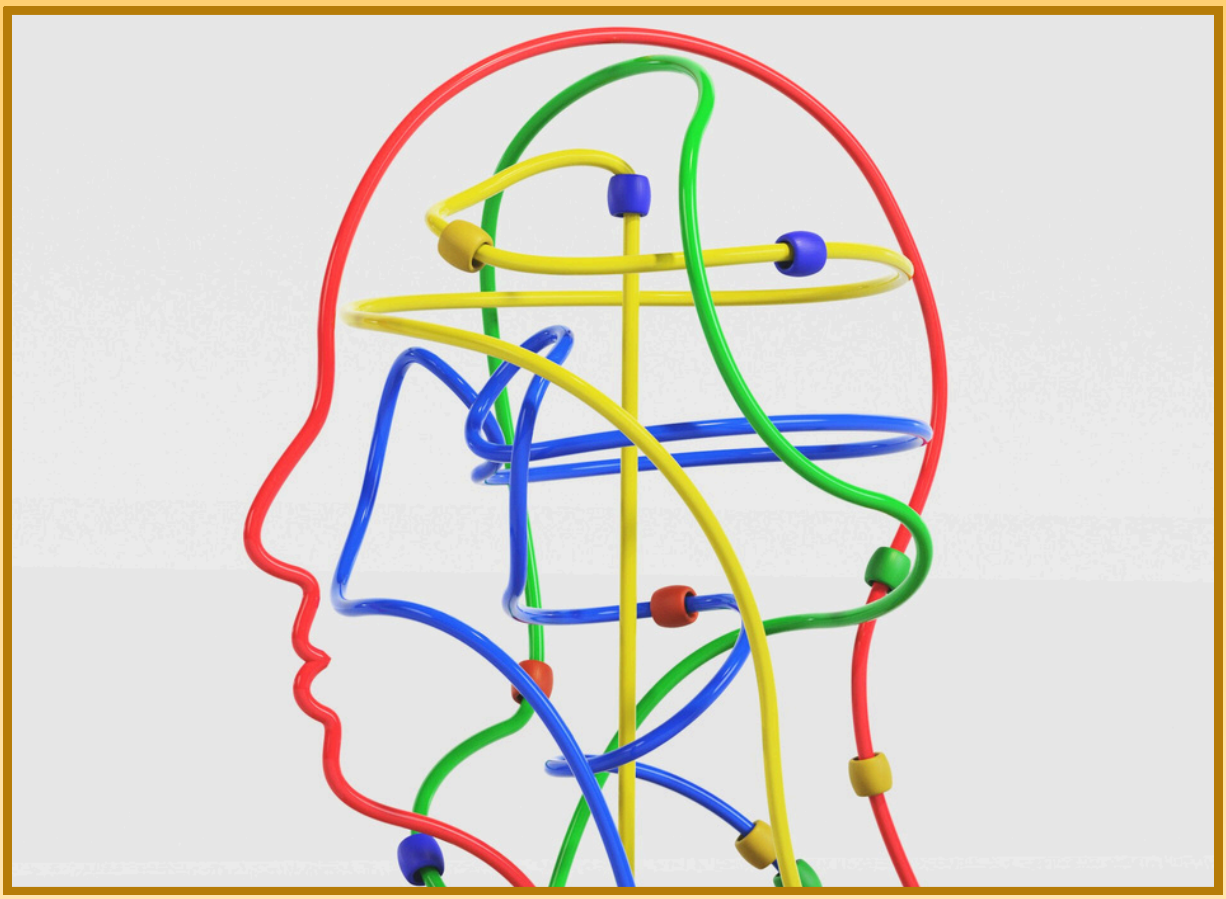

Unlocking Mental Health

Towards Efficient Psilocybin Synthesis for Rapid-Acting Antidepressant Research

By Sammy Bakewell and Dylan Li

Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, are the most prescribed antidepressants today[1]. SSRIs are ineffective for approximately 30% of patients, and even among responders, clinical improvements often take 4-6 weeks to emerge[1,2]. Consequently, there is a growing and urgent focus on developing rapid-acting antidepressants (RAADs). Psilocybin, a natural psychedelic from the *Psilocybe* genus of mushrooms, has emerged as a potential RAAD[2]. As interest in psilocybin continues to grow, the rising demand for this compound highlights the need for more efficient methods of synthesis.

"Since major depressive disorder (MDD) remains poorly understood [...], these findings highlight psilocybin's promise as a novel therapeutic avenue."

Multiple clinical trials involving psilocybin have been conducted over the past decade, indicating its potential antidepressant effects[2]. Notably, these effects were also observed in patients with treatment-resistant depression[3]. Since major depressive disorder (MDD) remains poorly understood, largely due to the absence of reliable biomarkers and the wide variability in patients' symptoms, these findings highlight psilocybin's promise as a novel therapeutic avenue. While early psilocybin antidepressant findings are promising, the precise mechanisms underlying psilocybin's antidepressant effects remain under investigation. As a serotonergic agonist acting primarily on 5-HT2A receptors, psilocybin is thought to attenuate the monoamine deficit in the prefrontal cortex of patients, potentially through mechanisms like those of SSRIs[4]. Additionally, psilocybin is believed to exert neuroplastic effects similar to other RAADs, such as ketamine, a process attributed to its activation of glutamatergic synapses in the prefrontal cortex[4] (Figure 1). Glutamate, the brain's primary excitatory neurotransmitter, plays a crucial role in strengthening neuronal connections and promoting synaptic plasticity. Evidence suggests that a single dose of

psilocybin can produce antidepressant effects lasting up to three months, supporting the idea that it may promote durable neuroplastic changes[3].

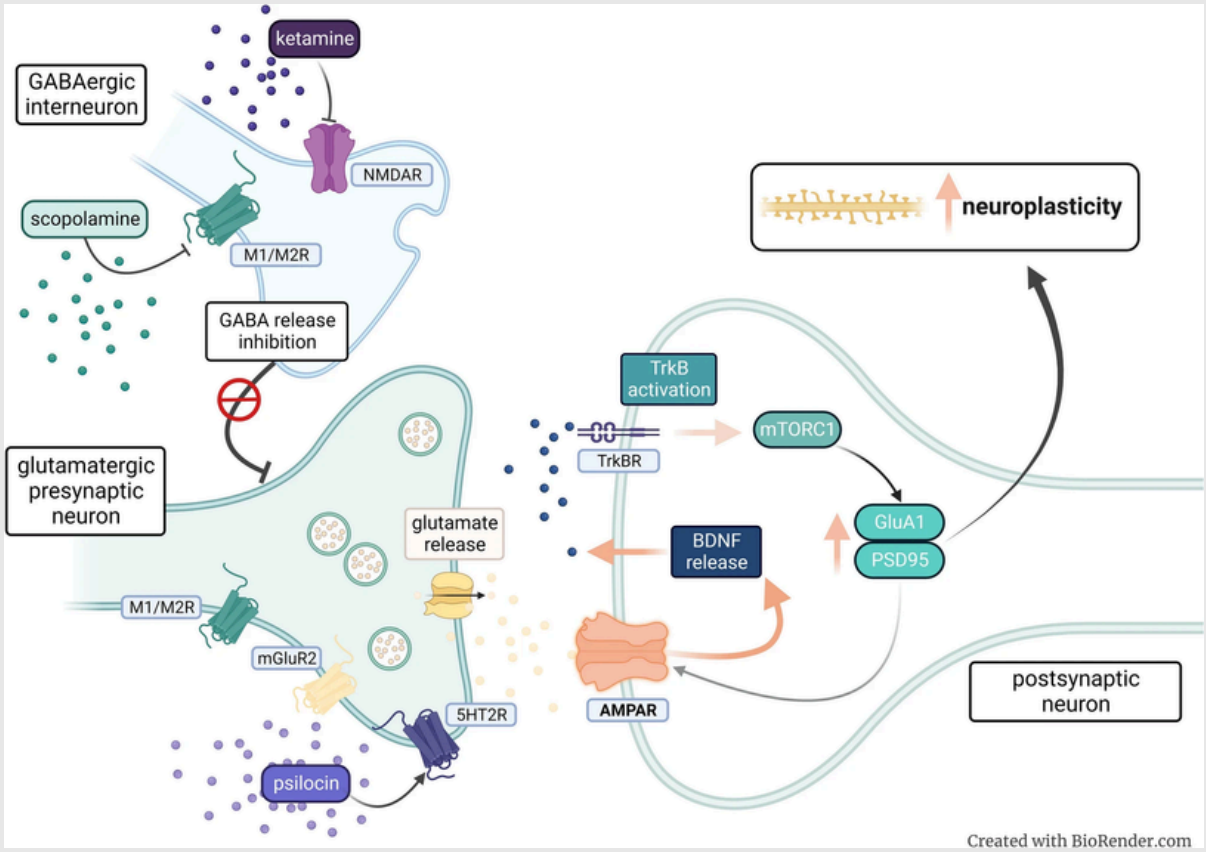

Figure 1. Postulated mechanisms of rapid-acting antidepressants action. RAAD efficacy is related to glutamate, an essential player in antidepressant (AD) action. Specific receptors on GABAergic interneurons that innervate glutamate pyramidal cells are blocked by RAADs, leading to blocked neurotransmission. This leads to activation of the pyramidal cells and release of glutamate into the synaptic cleft, fostering enhanced AMPA receptor function and the release of brain-derived neurotrophic factor (BDNF), activating TrkB receptors and stimulating the AKT/ERK/mTOR pathway. This sequence of events results in the local synthesis of synaptic proteins (PSD95, GluA1), which is accompanied by dendritic spine growth and improved connectivity in the brain. Psilocin, the active metabolite of psilocybin, exerts similar behavioural and cellular AD-like effects. This may suggest overlapping mechanisms initiated by the modulation of serotonin receptors, predominantly the postsynaptic 5-HT2 receptors, which may affect a glutamate-dependent increase in the activity of pyramidal neurones in the pre-frontal cortex. [Adapted from Chruścicka-Smaga *et al.*, 2023]

Furthermore, several limitations and challenges remain regarding the use of psilocybin as an antidepressant. Firstly, as a controlled substance in many

regions, psilocybin is difficult to obtain for research purposes[5]. Additionally, its history as a recreational drug and potential for its misuse complicate psilocybin's path to regulatory approval and raise cultural and political concerns[5].

"...its history as a recreational drug and potential for its misuse complicate psilocybin's path to regulatory approval and raise cultural and political concerns."

Psychotherapy can be both overwhelming and expensive for patients; however, these costs might be offset by less frequently used treatment options[2]. Longer and larger clinical trials are still necessary to fully understand psilocybin's antidepressant effects, its safety profile, and how it interacts with existing therapies[2]. Consequently, increased production of the compound will be essential to meet research and clinical demand. Finally, the absence of a recurring treatment model may further deter pharmaceutical companies from investing in psilocybin research, particularly given the compound's limited availability and the complexity of its synthesis[6].

Determining the structures of the enzymes responsible for psilocybin production is vital for identifying highly efficient enzymes that can improve psilocybin yield. Researchers recently resolved high-resolution crystal structures of L-tryptophan decarboxylase PsiD, both in its apo form and bound to tryptamine[6]. They also characterised 4-hydroxytryptamine kinase PsiK with its substrate and multiple structural states of the methyl-transferase PsiM from a psilocybin-producing mushroom[6]. This has opened new frontiers in the scalable, reproducible production of psilocybin.

The structural elucidation of these key enzymes has provided crucial insights at the molecular level into substrate recognition, active site architecture, and reaction mechanisms, thereby enabling precise, rational enzyme engineering. This has led to improvements in both catalytic efficiency and protein stability under varying reaction conditions, which are essential for reliable and scalable biosynthesis. These structural insights have also facilitated the reconstruction of psilocybin's biosynthetic pathway

in vitro through multi-enzyme "one-pot" systems, allowing for streamlined conversion from inexpensive, commercially available precursors such as 4-hydroxy-L-tryptophan[6] (Figure 2). Such systems not only reduce the need for complex purification steps but also minimise product loss due to the instability of intermediates like psilocin. By mitigating bottlenecks found in traditional chemical synthesis, specifically the historically low-yield and poorly reproducible phosphorylation of psilocybin, these advancements enable high-yield, efficient, and potentially more sustainable production of psilocybin for pharmaceutical applications.

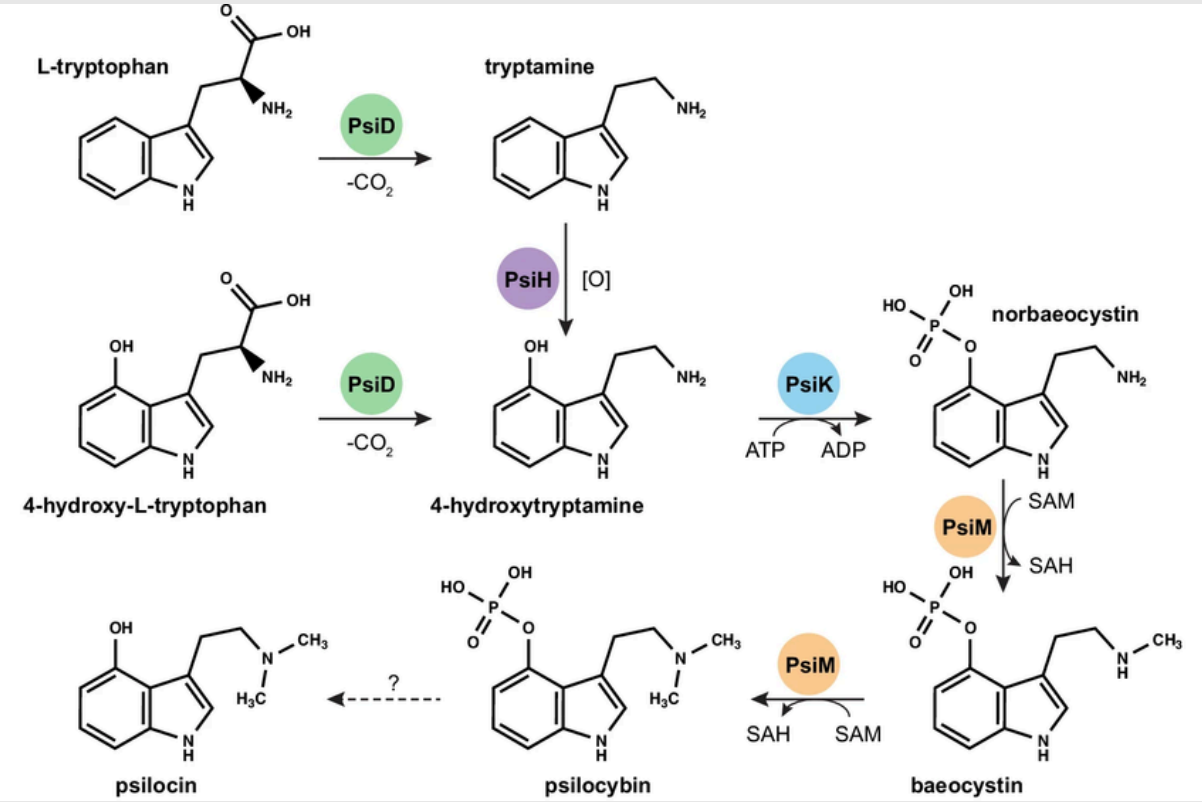

Figure 2. Enzymatic synthesis pathway of psilocybin in *P. cubensis*. [Adapted from Meng *et al.*, 2025]

Moreover, structural characterisation has catalysed progress in heterologous biosynthesis by guiding the functional integration of psilocybin pathways into microbial hosts such as *Escherichia coli* and *Saccharomyces cerevisiae*. Understanding enzyme structure-function relationships has allowed researchers to optimise expression systems and explore biosynthetic flexibility for the generation of novel analogues. This structural foundation not only supports the cost-effective biotechnological

production of psilocybin but also opens pathways to the rational design of new tryptamine-based therapeutics with tailored pharmacological profiles.

Together, these developments demonstrate how advances in structural biology and molecular pharmacology are driving a new era of precision biosynthesis for psilocybin. By enabling scalable and cost-effective production, these breakthroughs address key limitations in research access and pharmaceutical development. As a result, these findings will support the increasingly promising research into psilocybin as a RAAD.

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How Early Life Adversity Affects Adult Mental Health

By Hannah Carpenter

Early life adversity refers to negative experiences that occur in childhood or adolescence that have profound impact on individual's physical or emotional health. This term encompasses a variety of adverse events such as abuse, war, poverty, and parental death. It is estimated that 40% of people will experience a form of adverse childhood event (ACE)[1].

ACEs have been demonstrated to increase the risk of and correlate with developing mental health conditions, as well as the severity of symptoms associated with these disorders[2]. Here, the focus will specifically be on the risk conferred to schizophrenia and the potential neurobiological mechanisms.

"It is estimated that 40% of people will experience a form of adverse childhood event"

Schizophrenia is a neuropsychiatric condition which affects around 23 million individuals globally[3]. Symptoms include hallucinations, loss of motivation, and cognitive impairment such as memory decline[4]. Men are more commonly diagnosed than women, with the disorder emerging in late adolescence to early adulthood[5]. In the development of schizophrenia, there is the "two-hit" hypothesis which suggests that ACEs combined with genetic risk factors and a second adverse incident later in life may result in schizophrenia[5].

Studies have shown that ACEs can affect the severity and risk of schizophrenia symptoms[6–8]. Risk of symptoms such as hallucinations and depressive mood were increased in individuals who have experienced more than four ACEs[6]. Individuals with schizophrenia that had experienced higher levels of neglect had more severe symptoms, such as deficits in emotional processing[7]. Higher levels of ACEs were also reported in schizophrenic patients[7]. Additionally, trauma exposure up to 17 years old increased the risk of experiencing a psychotic episode in adulthood[8]. The

following sections will discuss how specifically ACEs could be contributing to the development of schizophrenia.

How is the Brain Changed?

Adverse life events have been shown to alter the brain both structurally and on a molecular level. Structural studies can be done in humans using imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET). These techniques allow changes to both the white matter (myelinated axons) and grey matter (neuronal cell bodies) of the brain to be observed.

Individuals with schizophrenia had smaller grey matter of the amygdala and hippocampus – brain areas heavily involved in memory and anxiety circuits[9]. Additionally, it was found that the more significant the childhood trauma, the more severe the clinical symptoms of schizophrenia[9]. Overall, hippocampal and amygdala volume was reduced in a population of individuals who had a higher genetic risk of schizophrenia and had experienced an ACE throughout childhood[10]. An analysis of neuroimaging studies supported that childhood trauma was associated with decreased grey matter in the prefrontal cortex and changes in circuitry in key brain regions involved in schizophrenia[11]. All of this leads to the hypothesis that early life adversity can affect overall brain structure in schizophrenic individuals.

"...it was found that the more significant the childhood trauma, the more severe the clinical symptoms of schizophrenia."

Molecular pathways

To study the molecular pathways that may contribute to brain changes, animal models such as maternal separation are used to demonstrate an early adverse event, typically in rodents. One important neurobiological pathway being investigated for schizophrenia is the hypothalamus-pituitary-adrenal (HPA) axis. The HPA axis is a neuroendocrine system involved in controlling the stress response. When activated by stress, there

is an increase in the amount of corticotropin-releasing hormone (CRH) produced by the hypothalamus, which triggers increased production of adrenocorticotrophin hormone (ACTH) secreted from the pituitary gland. ACTH travels through the circulation to the adrenal cortex, where it stimulates production of glucocorticoids – the body's stress hormones (Figure 1)[12]. The most common stress hormone is cortisol, which regulates blood glucose availability to the brain.

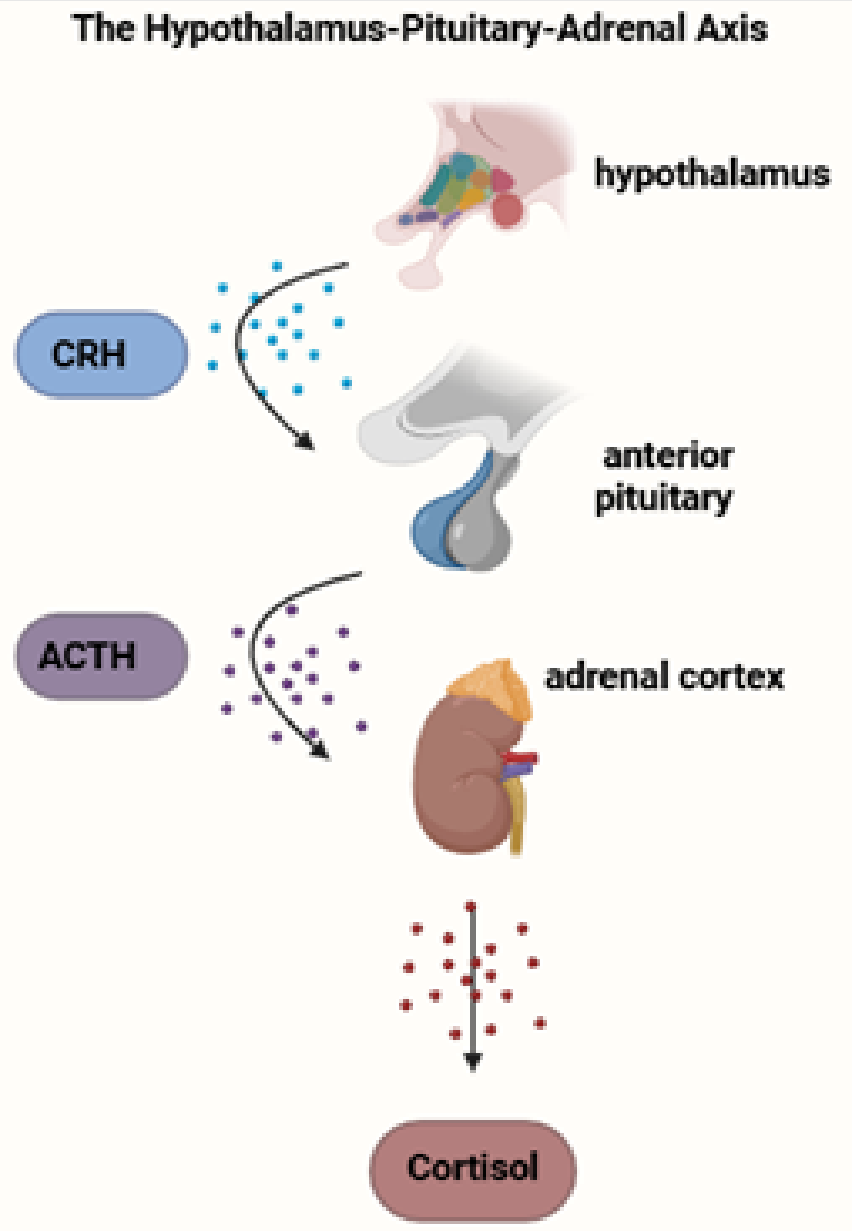

Figure 1. Mechanism of the Hypothalamus-Pituitary-Adrenal (HPA) Axis. CRH = corticotropin-releasing hormone. ACTH = adrenocorticotrophin hormone [BioRender].

Dysregulation of the HPA axis has been shown in schizophrenia. An increase in volume of the pituitary gland was observed in people who have experienced an episode of psychosis or high risk individuals[13]. Increased cortisol reactivity is also seen in people with high risk of schizophrenia[14]. However, decreased cortisol response has been seen in chronic schizophrenia, suggesting that it may mark a transition point in the disorder[15]. Berger *et al.* performed a meta-analysis to investigate this using the cortisol awakening response[16]. This refers to the spike in cortisol that occurs after wake. It has been suggested as a biomarker for schizophrenia due to its association with risk factors of the disorder. They found a decrease in response in individuals with schizophrenia but a normal response in people at risk and suggest it may reflect a transition[16].

"Further studies are needed to fully understand the interconnected role of the HPA axis and adverse events in schizophrenia."

Aes *et al.* used enzyme-linked immunosorbent assays to measure cortisol levels from hair in participants with schizophrenia[17]. They found that those who had experienced childhood mistreatment had higher cortisol levels. Additionally, they found that higher hair cortisol significantly impacted working memory – a cognitive symptom of schizophrenia[17]. Finally, physical abuse was slightly associated with increased cortisol metabolism[18]. Further studies are needed to fully understand the interconnected role of the HPA axis and adverse events in schizophrenia.

To conclude, early life adversity has been shown to impact long-term outcomes in mental health conditions, but more research is needed to fully elucidate the underlying neurobiological mechanisms which can contribute to the development of future therapies.

References

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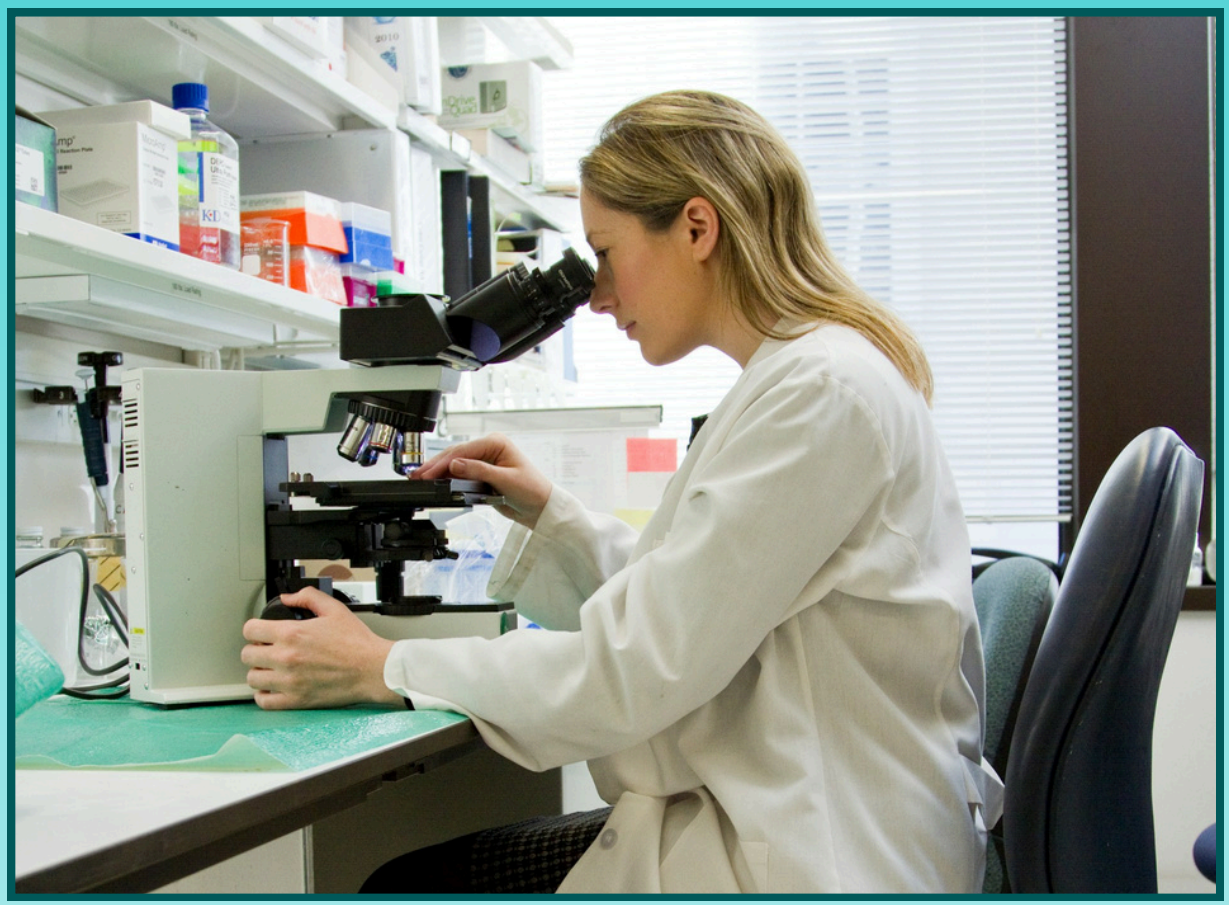

Biomedical Advances

Beta-Amyloid: *in situ* Insights into Alzheimer's Disease

By Gabrielle Williams

Amyloid is an insoluble aggregate of protein formed from soluble monomers. Many different protein monomers can form amyloid; one of the most clinically relevant monomers is β-amyloid. The process by which amyloid aggregates form is as follows: multiple monomers combine to form oligomers; multiple oligomers come together to form protofilaments; many protofilaments coalesce to make fibrils; then both protofilaments and fibrils cluster to form β-amyloid aggregates (Figure 1)[1,2]. These oligomers are the toxic species while the fibrils help to promote the spread of amyloid formation[3].

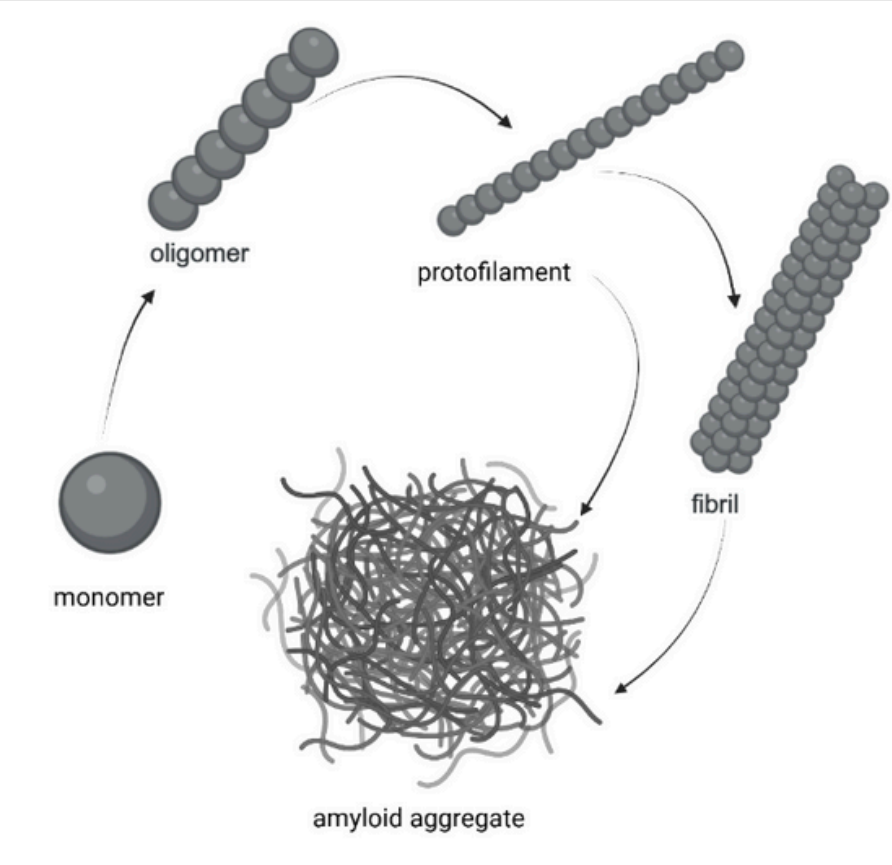

Figure 1. Schematic showing the process through which amyloid aggregates form from protofilaments and fibrils [BioRender].

Diseases associated with amyloid are often incurable, such as the debilitating neurodegenerative condition Alzheimer's disease. Due to an ageing population, the numbers of patients with such diseases are currently on the rise, making it increasingly urgent to understand the molecules implicated in their progression[4]. There are limited treatments for these diseases, and many have been taken off the market due to their lack of efficacy, further highlighting the need to better characterise the architecture of β-amyloid and tau[5].

"...there is reason to believe that *in situ* amyloid structures differ from their *in vitro* counterparts, likely due to factors such as the interaction of amyloid with lipids."

Alzheimer's disease is associated with two key pathogenic protein aggregates: β-amyloid and tau[2]. Amyloid has been historically challenging to study due to its non-crystalline structure and heterogeneity[6]. Nevertheless, *in vitro* amyloid structures have been resolved using techniques such as cryogenic electron microscopy, X-ray diffraction, and solid-state nuclear magnetic resonance spectroscopy[7–9]. However, until recently, the *in situ* structure of amyloid in the human brain remained elusive. That is until a publication by Gilbert *et al.* emerged last year, leveraging the recent resolution revolution for techniques such as cryogenic electron tomography (cryo-ET), to produce structures of amyloid *in situ*[2]. Interestingly, there is reason to believe that *in situ* amyloid structures differ from their *in vitro* counterparts, likely due to factors such as the interaction of amyloid with lipids[2,10]. Frieg *et al.* found that amyloid formed *in vitro* in the presence of lipids more closely resembled brain-derived amyloid compared to amyloid formed in the absence of lipids[10]. This suggests that amyloid is interacting with other molecules in the brain to achieve its structure. Therefore, it is of increasing interest to determine what these molecules are and what effect they exert on amyloid structure.

In the paper by Gilbert *et al.*, postmortem samples from a human brain with Alzheimer's disease were used and studied by a variety of biophysical techniques, such as cryo-ET, to produce images of the in-tissue architecture of β-amyloid and tau[2]. A key finding from this paper is the discovery that in situ β-amyloid is surrounded by non-amyloid constituents, such as extracellular vesicles and cuboidal particles (Figure 2). It is thought that

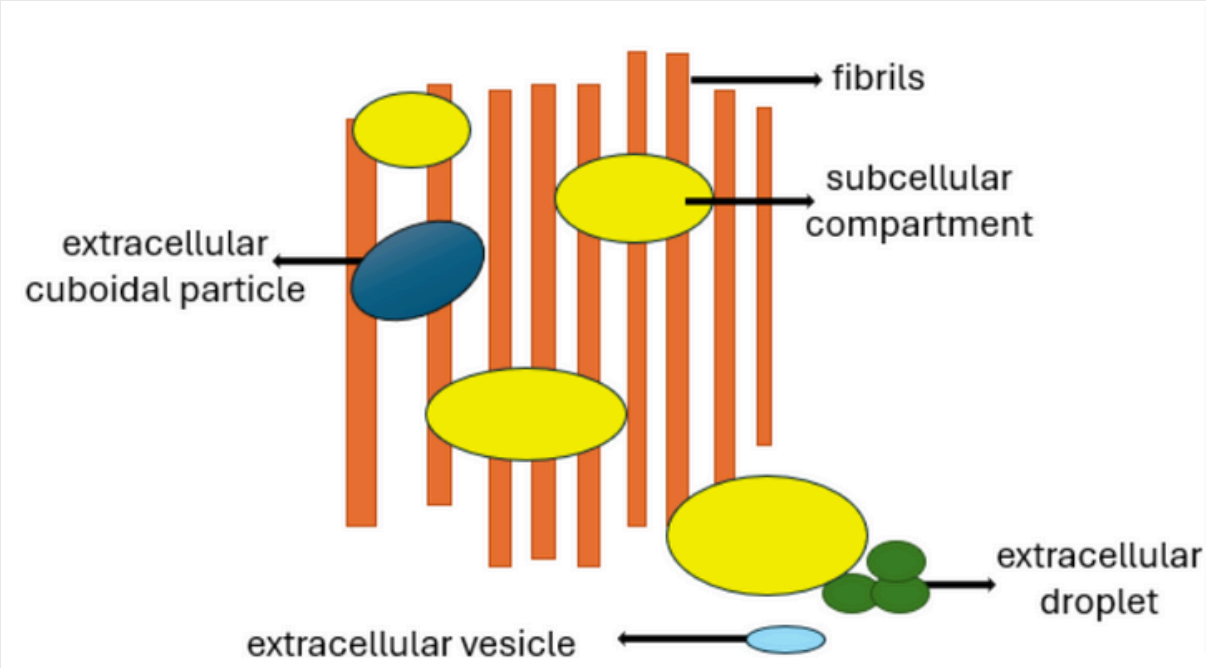

Figure 2. Schematic of a tomograph of β-amyloid pathology in a postmortem Alzheimer's disease brain cryo-section [PowerPoint].

these non-amyloid constituents are related to the formation of β-amyloid, or they might instead be a cellular response to amyloid[2]. Furthermore, Frieg *et al.* found that the aggregation of β-amyloid can lead to lipid extraction from vesicles; this is thought to be a key process in the pathology of Alzheimer's disease[10]. Understanding how amyloid interacts with other molecules may elucidate druggable targets. In addition, future research may identify small molecule inhibitors of amyloid formation that could be used to treat Alzheimer's disease as well as other neurological conditions associated with amyloid. These small molecule inhibitors could work by stopping cell-to-cell transmission of plaque-causing species such as amyloid fibrils. Such a therapeutic would work in concert with other drugs to target oligomers as they are the primary toxic species, not the amyloid fibrils.

Another key discovery from Gilbert *et al.* is that amyloid aggregates are composed of structures resembling lattices and parallel arrays of branched and unbranched fibrils, as well as protofibrils, while tau aggregates consist of unbranched filaments[2]. This increased structural understanding of β-amyloid and tau might be used in the future to better understand the kinetic processes by which the aggregates assemble. An additional key finding by Gilbert *et al.* is that amyloid heterogeneity was shown to be

spatially organised by subcellular location, with filaments within one cluster being similar to one another but different to other clusters. Future research using the same techniques used by Gilbert *et al.* but on a larger variety of Alzheimer's disease brain samples may illustrate how amyloid architecture relates to individual disease profiles. This research has reshaped our understanding of amyloid aggregates and will have implications for the design of future treatments, possibly employing a personalised medicine approach.

"This research has reshaped our understanding of amyloid aggregates and will have implications for the design of future treatments, possibly employing a personalised medicine approach."

Work by Gilbert *et al.* has helped understand the relationship between amyloid structure and the cellular context. These new structures have the potential to improve therapies for diseases associated with amyloid, which are currently limited. The *in situ* β-amyloid fibrils analysed by Gilbert *et al.* resembled *ex vivo* β-amyloid fibrils form previous research. This suggests that although cryo-ET has developed as a technique to study the architecture of β-amyloid fibrils *in situ*, previous *ex vivo* experiments may remain a relevant method to study amyloid fibril structure. But using solely *ex vivo* methods to study amyloid fibril interactions in the cellular context remains out of reach, because removing fibrils from their biological context removes interactions with other molecules such as lipids, therefore changing the fibril structure. Forthcoming experiments may look to understand how small molecules interact with lipids and amyloid to reveal druggable targets, as well as possible small molecule inhibitors of amyloid growth. In addition, the *in situ* structural techniques used by Gilbert *et al.* can be used to learn about other neurodegenerative diseases such as Parkinson's disease[2].

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Understanding Immune Thrombocytopenic Purpura

By Aliese H W Fan

Immune thrombocytopenic purpura (ITP) is a rare acquired autoimmune disorder. Individuals suffer from a low platelet count due to immune destruction, with only 3000-4000 patients in the UK affected at any one time[1]. It can also be called idiopathic thrombocytopenia, highlighting the condition's asymptomatic clinical presentations and spontaneous nature until discovered via routine blood tests. If left untreated, patients face risks of excessive blood loss when injured, causing potential organ failure and even death. It is thus necessary to understand the condition's cause and its categorisation, allowing the development of relevant treatments and possible preventive measures, which could halt ITP progression.

To understand ITP, it is first important to understand what an autoimmune disorder is. According to the National Cancer Institute, autoimmune disorders are conditions where the body's immune system mistakes healthy tissues as foreign and attacks them across various body parts[2]. In the case of ITP, the circulating platelets are targeted. Although the cause of ITP is still unknown, scientists have proposed various mechanisms that may lead to the development of thrombocytopenia and ultimately ITP (Figure 1).

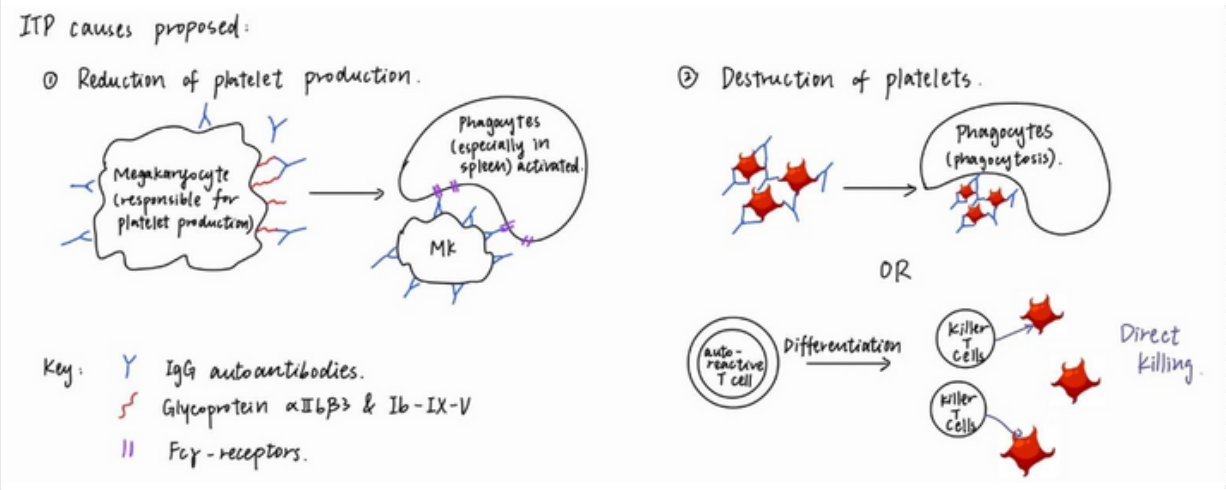

Figure 1. Hand-drawn graphical representation of causes of ITP.

One of these possibilities is a reduction of platelet formation induced by the production of IgG autoantibodies. These autoantibodies bind to the membranes of megakaryocytes (MKs), cells that are responsible for synthesising and assembling platelet components and organelles. This binding activates phagocytes via Fcγ-receptors, inducing phagocytosis and inhibiting the maturation of MKs. Another possibility is the increased destruction of platelets via either IgG antibodies or the activation of autoreactive T cells. An increased expression of cytotoxic genes, such as Apo-1/Fas and genes involved in the Th1 cell response (e.g. interferon-γ), can be found in ITP patients compared to controls[3]. The overstimulation of cytotoxic components can lead to heightened interactions with platelets, potentially causing the accidental elimination of platelets through phagocytosis. This lowers the platelet count in the blood, thus increasing the risk of ITP development.

"...it is difficult to identify ITP patients [...] due to the asymptomatic disease course. [...] Only when patients show no sign of recovery will the doctor [...] conduct additional blood tests to further differentiate the disease that may be mistaken for ITP."

Clinically speaking, it is difficult to identify ITP patients with a platelet count of 50-100x10^9 L^{-1} due to the asymptomatic disease course[4]; only those with a platelet count below this range may show symptoms such as easy bruising, fatigue, and petechiae (pinpoint blood spots under the skin). Despite patients presenting characteristic symptoms, the condition remains a diagnosis of exclusion based on the patient's medical history, family history, further examination, and tests such as the full blood count. Only when patients show no sign of recovery will the doctor take small bone marrow samples and conduct additional blood tests to further differentiate the disease that may be mistaken for ITP[5].

There are two types of ITP: primary ITP and secondary ITP, which are differentiated depending on how ITP develops in individuals. Primary ITP (also known as acute ITP) is the most common form of ITP and typically arises without a detectable underlying cause. Its development is often considered multifactorial, involving genetic variants and environmental factors.

Single-nucleotide polymorphisms and copy number variations have been identified in several immune-related genes, such as Fcγ receptor genes and T-cell co-stimulation genes[6]. The overstimulation of these genes leads to an increase in protein production, increasing the concentration of pro-inflammatory factors. These produce an excessive immune response, which may accidentally target and eliminate platelets, initiating the development of ITP. In addition to genetic predisposing factors, long-term exposure to ambient nitrogen dioxide, nitrogen oxides, and fine and coarse particulate matter produced from human activities is also associated with increased ITP risk[7]. As urbanisation and environmental pollution increase, this evidence could explain the increasing cases of ITP: an average annual percentage increase of 4.3% between 2003 and 2014[8]. However, further research is required to clarify causality, thus allowing informed strategies to be implemented to reduce the risk of developing ITP.

"After bacterial *[H. pylori]* eradication, 63.2% of patients had a significant increase in platelet count and a significant decrease in autoantibodies within the 5-year follow-up period."

Secondary ITP, on the other hand, occurs in conjunction with or because of other identifiable conditions. One common example is viral infections, especially human immunodeficiency virus (HIV). Due to the viral mechanisms, the production of reactive oxygen species accelerates platelet clearance and suppresses platelet production in infected MKs. This induces ITP-HIV (platelet count $<150 \times 10^9$ L^{-1}) in 5-30% of HIV patients before any treatment is given[9]. Bacterial infections can also cause secondary ITP, with *Helicobacter pylori* being the most studied. Molecular mimicry is involved: bacteria derive molecules, such as CagA, which have a similar composition to platelet surface glycoproteins[10]. The adaptive immunity initiates the production of anti-CagA antibodies, aiming to bind to *H. pylori* to remove the bacteria. Instead, some antibodies react with circulating platelets, leading to platelet aggregation and destruction. After bacterial eradication, 63.2% of patients had a significant increase in platelet count and a significant decrease in autoantibodies within the 5-year follow-up period[11]. A link could thus be drawn between *H. pylori* elimination and platelet recovery, which may clarify how secondary ITP is developed as more research is conducted.

Once diagnosed, treatments are determined based on various markers. Age, a significant marker in the development of ITP, would be considered first due to the possibility of the disease becoming incurable, especially in those with primary ITP. The most common first-line treatment is corticosteroids, which reduce the rate of platelet destruction, slowing ITP development. Sometimes intravenous high-dose immunoglobulins (IVIg) would also be given if patients are at high haemorrhagic risk. This quickly increases the concentration of platelets in their circulation, allowing blood clots to form and thus preventing excessive blood loss. These treatment options, however, only induce transitory beneficial effects and have adverse side effects (e.g. weight gain, hyperglycaemia, insomnia)[12]. Second-line treatments include rituximab, thrombopoietin receptor agonists, and immunosuppressants (e.g. ciclosporin A) when first-line treatments have little to no effect on patients' condition[13]. Some may also consider splenectomy (i.e. removing part of the spleen) if the individual has chronic ITP or has failed multiple lines of medical treatment. Still, it is only suitable for certain patients. Thus, many can only rely on long-term application of existing treatments, changing their diets and lifestyle to maintain platelet counts and avoid bleeding risks.

In conclusion, ITP is largely considered an autoimmune disorder, with classifications of primary and secondary depending on the patient's clinical presentation and medical history. Understanding the mechanisms of ITP pathogenesis can help us improve diagnostics and subsequent treatment strategies. As research progresses, ITP therapies are likely to become more personalised and precise, ultimately improving efficacy with a better safety profile, curing those affected, and improving their quality of life.

References

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Drugs in Development

Can We Outsmart the Nausea Caused by GLP-1 Mimetics?

By Mia Jojic

Understanding how GLP-1 analogues cause nausea and how recent research fuels hope of dissociating the groundbreaking therapeutic benefits of semaglutide from its adverse effects.

Marketed under brand names including Ozempic and Wegovy, semaglutide has rapidly gained global recognition as a leading anti-obesity medication. Initially developed for the management of type 2 diabetes, Ozempic's impressive appetite-suppressing effects paved the way for Wegovy's approval as a weight loss treatment in 2021[1]. However, its increasing popularity has also unveiled its significant adverse effects – most notably, gastrointestinal manifestations such as persistent nausea and vomiting.

"...enhancements make GLP-1 mimetics highly effective for both glycaemic control and appetite suppression."

Semaglutide mimics glucagon-like peptide-1 (GLP-1), an endogenous incretin hormone that regulates insulin secretion and signals satiety to the brain – the feeling of 'fullness' in response to food intake. However, due to the rapid degradation and short half-life of endogenous GLP-1, synthetic analogues have been engineered to resist enzymatic breakdown and prolong pharmacological activity[2]. These enhancements make GLP-1 mimetics highly effective for both glycaemic control and appetite suppression. While several GLP-1 analogues preceded it, semaglutide distinguished itself through superior weight-loss efficacy and convenient once-weekly dosing[3,4]. This, combined with intense media coverage, propelled the drug into the spotlight to become one of the first true household names in its class. Nonetheless, it may be the very same mechanisms responsible for these therapeutic benefits that induce the drug's undesirable effects.

One hypothesis underlying the nausea and gastrointestinal discomfort is the drug's capacity to delay gastric emptying, thereby prolonging the sensation of fullness[5]. Whilst this pharmacological effect helps reduce overall calorie intake, a key goal in weight management, it may also intensify symptoms including bloating, abdominal discomfort, and nausea. To mitigate this, clinicians advise changes in eating habits, such as eating more slowly and consuming smaller, more frequent meals. Medical recommendations also encourage a slow and gradual increase in the drug's dosage when users begin their course, to allow the body to adjust to the medication[6]. While these strategies can mellow gastrointestinal concerns, adverse effects remain one of the leading reasons for premature discontinuation of treatment[7]. Therefore, understanding the more intricate pharmacological mechanisms of the drug is key to minimising dropout rates among patients and improving long-term adherence.

"While these strategies can mellow gastrointestinal concerns, adverse effects remain one of the leading reasons for premature discontinuation of treatment"

Recent research has also focused on semaglutide's mechanism of action, specifically its preferential targeting of GLP-1 receptors in the dorsal vagal complex (DVC) at the level of the caudal nucleus of the solitary tract (NTS) and area postrema (AP) (Figure 1). This part of the DVC is well-established as the satiety centre of the hindbrain, critical for integrating autonomic signals and regulating appetite[8].

The AP and NTS of the DVC both express GLP-1 receptors but mediate distinct physiological responses. A 2024 study demonstrated that activation of GLP-1 receptors within the NTS alone can effectively suppress appetite without inducing nausea[9]. However, access of the drug into the brain is largely restricted to circumventricular organs like the AP, where the blood-brain barrier is fenestrated[9]. As such, GLP-1 analogues reach the NTS through the specialised glial barrier at the AP-NTS border[9].

Notably, the AP is a well-established chemoreceptor trigger zone for nausea and emesis[10], and activation of GLP-1 receptors in this region has been directly associated with the gastrointestinal side effects reported with anti-obesity medications. Importantly, Huang *et al.* raise the possibility of

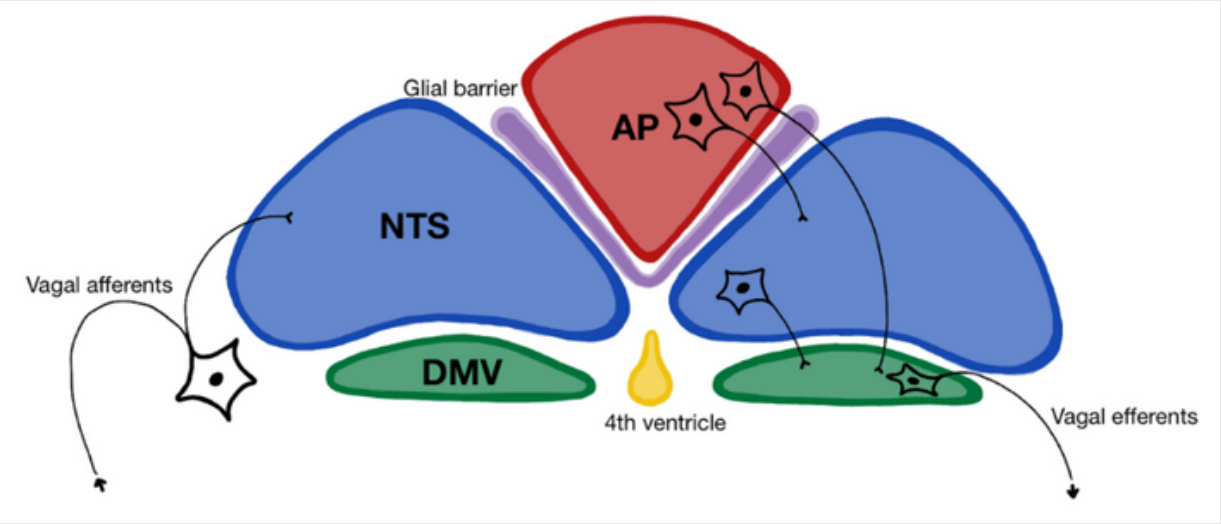

Figure 1. Schematic of the structures that comprise the dorsal vagal complex (DVC): the area postrema (AP; red), nucleus solitary tract (NTS; blue), and dorsal motor nucleus of the vagus (DMV; green). The NTS receives signals from the AP, across the specialised glial barrier, and gut information from vagal afferents, helping integrate signals that regulate appetite and digestion. Vagal efferents from the DMV send messages back to the stomach to form the gut-brain axis, allowing the DVC to communicate back to the stomach to create a sensation of fullness [Adapted from Chrobok *et al.*, 2022].

developing pharmacological strategies to selectively target NTS GLP-1 receptors to harness weight-loss benefits without provoking adverse effects[9].

Emerging research has further highlighted the potential role of circadian rhythms to utilise this delivery pathway. As mentioned, semaglutide crosses from the AP into the NTS through a specialised glial barrier, and recent findings suggest this barrier exhibits time-of-day-dependent changes in permeability. Chrobok *et al.* investigated the circadian regulation within the DVC and found that, in male mice, the permeability of the AP-NTS barrier increased during the early dark phase (the onset of the active period) compared to the early light phase[11]. These findings imply that access to the NTS may be more efficient during specific phases of the circadian cycle. If validated in both sexes and extended to human physiology, this discovery could open new avenues in chronopharmacology, aligning semaglutide administration with our natural body clocks. Administering GLP-1 analogues during windows of increased NTS accessibility could facilitate preferential activation of NTS satiety-related pathways, enabling reduced dosing and improved drug tolerability.

Ultimately, these emerging insights offer a novel and promising path forward for optimising the efficacy of GLP-1-based therapies and reducing treatment discontinuation due to gastrointestinal discomfort. By dissociating the therapeutic benefits from the intolerable side effects, it may indeed be possible to outsmart the nausea caused by GLP-1 mimetics and revolutionise the treatment of conditions like obesity and beyond.

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Health and Our Environment

Investigating the Effectiveness of Bristol's Clean Air Zone on NO_2 Concentration: a Two-year Post-implementation Study using Palmes Tubes

By Kerry Shen

Nitrogen dioxide (NO_2) exposure is linked to severe respiratory and cardiovascular diseases, making its monitoring critical for evaluating the impact of air pollution policies such as low-emission zones. This research investigates the effectiveness of Bristol's Clean Air Zone (CAZ) in reducing NO_2 pollution using Palmes diffusion tubes. NO_2 levels were measured at four Bristol sites, both inside and outside the CAZ. Results showed higher NO_2 levels within the CAZ, with Marlborough Street exceeding the UK's legal limit of 40 µg m^{-3}. However, St. Stephen's Street experienced a 50% reduction in NO_2 since 2022. Green areas such as Royal Fort Garden and Berkeley Square demonstrated mitigation effects. A 2024 pollution map revealed reduced emissions within the CAZ since 2023, likely due to diverted traffic. However, areas near hospitals require stricter policies to address persistent high pollution levels.

"Air pollution, primarily from transport and fossil fuel combustion, is the second leading cause of global mortality."

Introduction

Air pollution, primarily from transport and fossil fuel combustion, is the second leading cause of global mortality, causing 8.1 million premature deaths in 2021, including 300 annually in Bristol[1–4]. NOx emissions, mostly from motor vehicles, consist of NO and NO_2, with NO_2 forming via NO oxidation[5,6]. Exposure to a concentration of NO_2 greater than 200 µg m^{-3} can cause inflammation of the airways, increase susceptibility to respiratory infections, and exacerbate the symptoms of those with pre-existing lung or heart conditions[7]. The UK's annual legal NO_2 limit is 40 µg m^{-3} [5,8]. In 2022,

Bristol exceeded this threshold[5,8]. To address this, the CAZ was introduced, aiming to reduce non-compliant vehicle use[9,10]. In its first year, NO_2 dropped by 4.3 µg m^{-3} inside the CAZ and 2.6 µg m^{-3} outside[9,11]. Palmes tubes, chosen for cost-effectiveness, simplicity, and accuracy, were used to assess CAZ effectiveness[12].

Methodology

Palmes tubes were placed at four sites (Figure 1): two inside the CAZ (Marlborough Street, St. Stephen's Street) and two outside (University Walk, Berkeley Square). Sites near Bristol Council's monitors were selected for comparison. Data was collected, processed using Beer-Lambert Law, and compared with previous years' reports and international data.

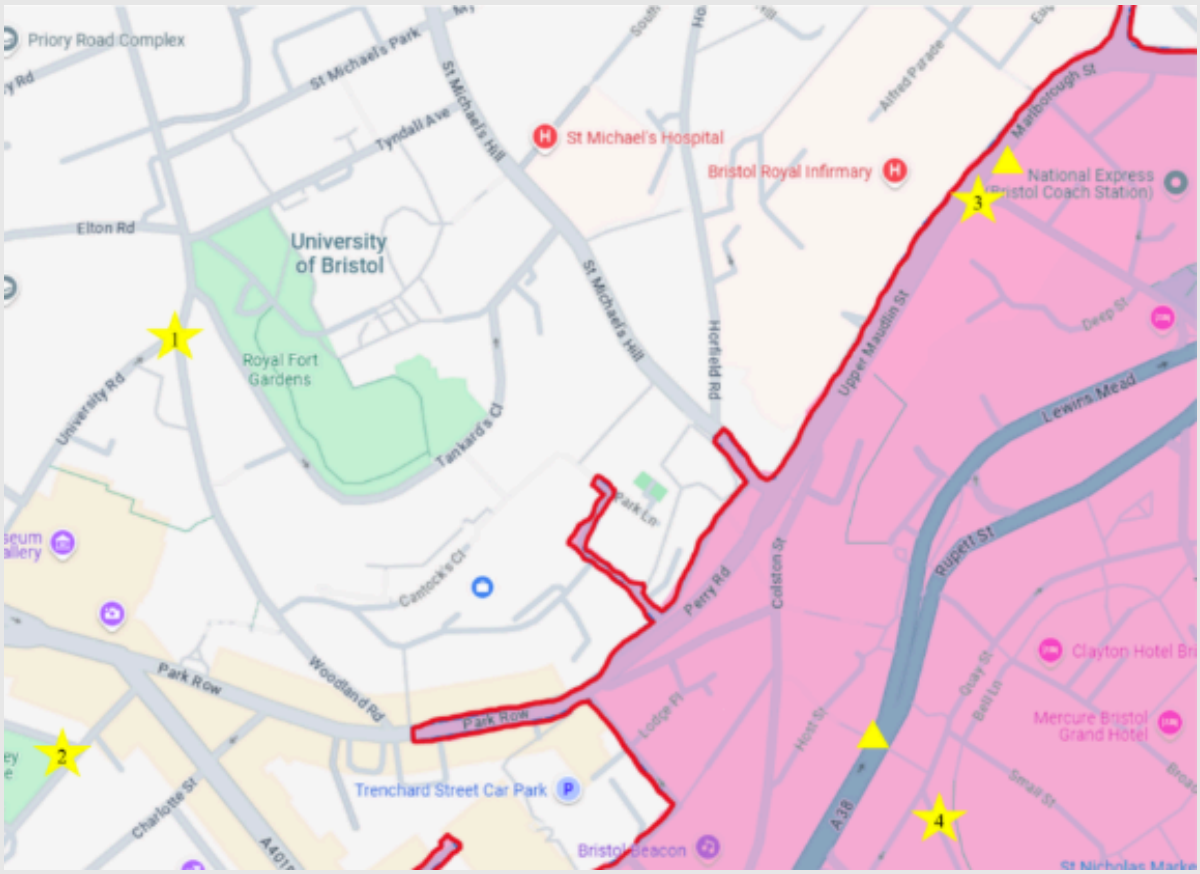

Figure 1. Four Palmes tubes (yellow star) were located at University Walk (1), Berkeley Square (2), St. Stephen's St (3), and Marlborough St (4). Tubes 1 and 2 were placed outside the CAZ, and tubes 3 and 4 were positioned within the CAZ (pink shaded region with red outline) adjacent to continuous monitors (yellow triangle)[13].

Discussion

The calibration curve (Figure 2) showed strong correlation ($R^2 \approx 1$), indicating reliable field data. Among the four locations, University Walk (19.02 µg m^{-3}) and Berkeley Square (23.07 µg m^{-3}) recorded the lowest NO_2 levels. This may be due to low traffic from green commuting and nearby parks, especially Royal Fort Garden. In contrast, St. Stephen's Street (32.61 µg m^{-3}) showed a notable improvement from 2022, with levels halved and below the legal limit. However, Marlborough Street measured 40.89 µg m^{-3}, still above the limit, likely due to hospital traffic, roadworks, and a fire-related road closure.

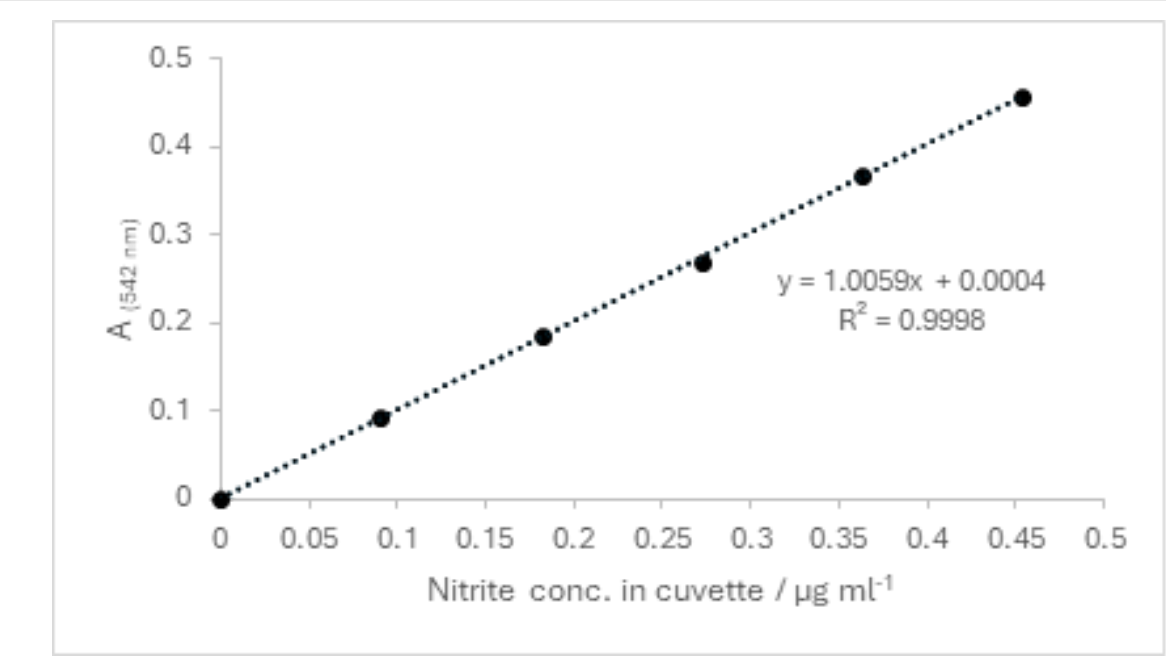

Figure 2. Calibration curve showing the absorbance of ultraviolet radiation measured at 542 nm plotted against the concentration of nitrite in cuvettes in (µg ml^{-1}) using Beer-Lambert Law[14,15].

While the CAZ appears to have reduced NO_2 levels inside the zone since 2023, some measurements outside the CAZ now exceed the limit, suggesting traffic may be displaced rather than reduced (Figure 3). Portway, in particular, saw elevated levels, indicating a northwest traffic shift compared to northeast trends in previous years.

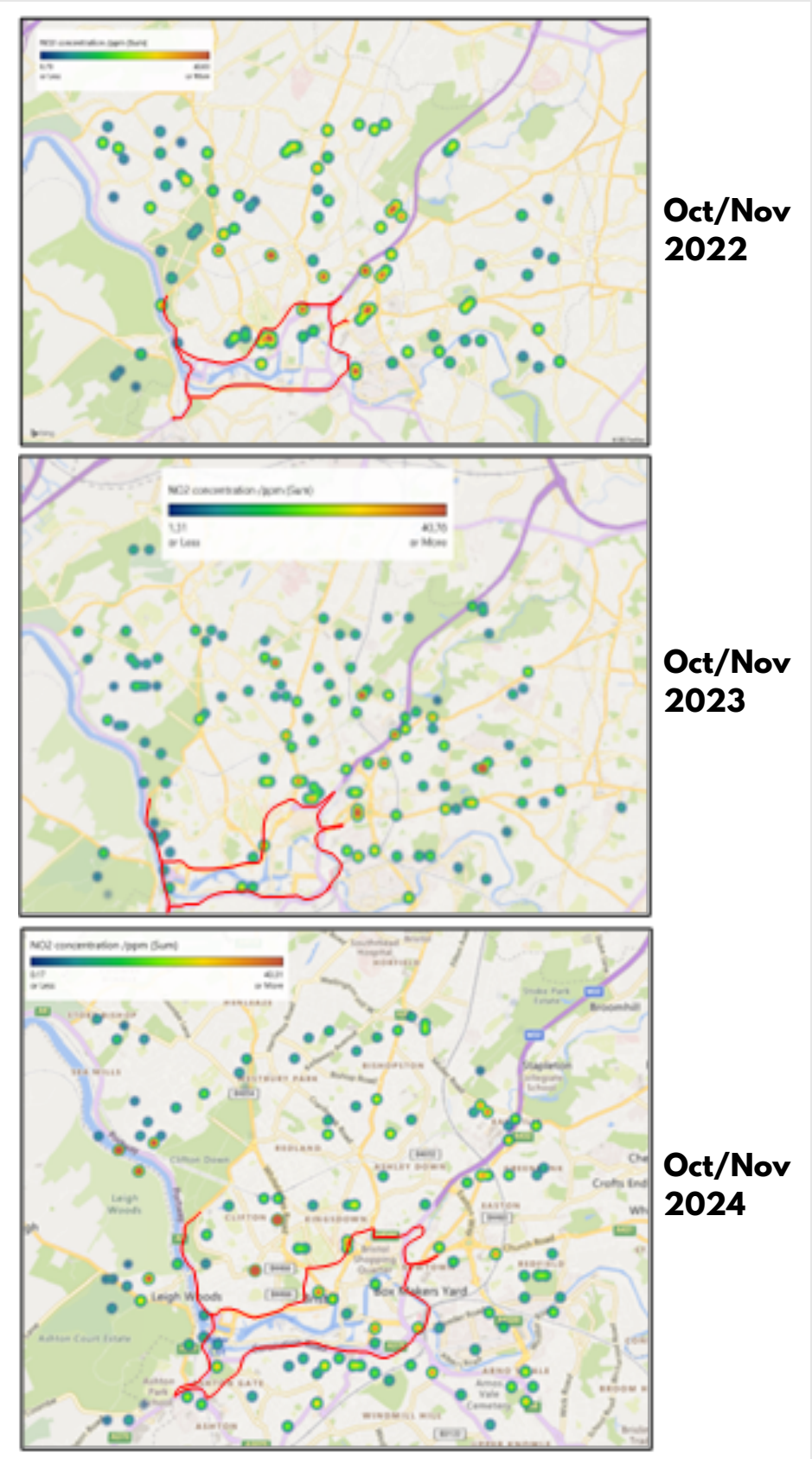

Figure 3. Maps of NO2 levels in Bristol from 2022 to 2024. Areas enclosed by the red solid line indicate the CAZ. NO_2 concentrations were measured in parts per million (ppm)[16].

Comparison with other cities

Sheffield and Rotterdam, cities with similar population densities and low-emission policies, exhibit comparable NO_2 trends[17,18]. Sheffield's CAZ (introduced three months after Bristol's) showed NO_2 levels of 38 µg m^{-3} at Pond Street, similar to Bristol's St. Stephen's Street. However, Western Bank (outside Sheffield's CAZ and near a children's hospital) exceeded 45.9 µg m^{-3} in 2022, reflecting Marlborough Street's ongoing challenges[19]. Similarly, Rotterdam's low emission zone (LEZ) (launched in 2020) targeted vehicle emissions, showing that such policies can reduce NO_2 but require supportive urban planning to prevent pollution displacement[20].

"Elevated levels inside the zone and the rise of pollution in surrounding areas underscore the need for continued monitoring, policy adjustment, and enhanced support for green urban infrastructure."

Conclusion

Two years after implementation, Bristol's CAZ shows promising results in reducing NO_2 pollution in specific locations. However, elevated levels inside the zone and the rise of pollution in surrounding areas underscore the need for continued monitoring, policy adjustment, and enhanced support for green urban infrastructure. Areas near hospitals require urgent attention to ensure cleaner air for vulnerable populations. Although the error in the measurements was relatively low, improvements and further work could still be implemented to increase the accuracy of the measurements. The diffusion coefficient of NO_2 has not been directly measured; the preferred value for NO_2 in air has an uncertainty of ± 10%, which cannot be eliminated [21]. Under sunlight, NO can react with O_3 to produce NO_2, leading Palmes tubes to overestimate NO_2 levels by up to 40% compared to continuous analysers[21]. While continuous analysers are significantly more expensive, they provide more accurate measurements and additional data for analysis. Balancing cost with accuracy will be critical to ensuring robust evidence for future air quality policies and the continued effectiveness of Bristol's CAZ.

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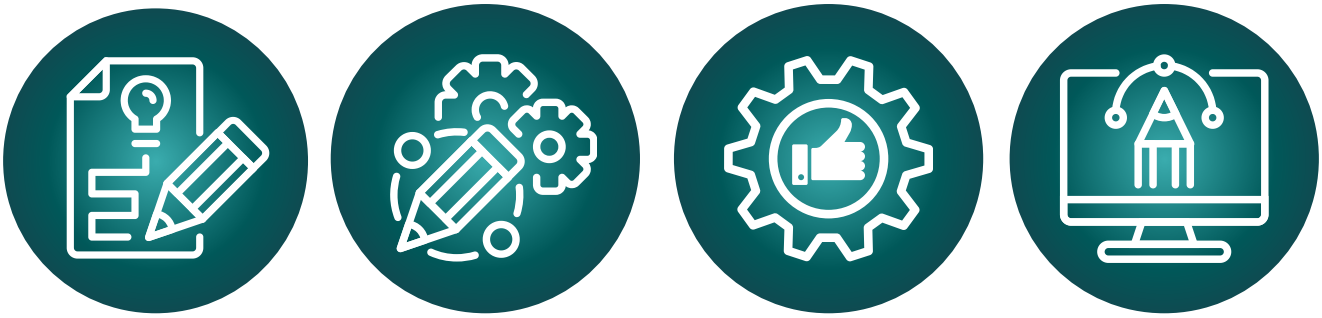

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