ScienceMind

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KING'S College LONDON

STAFF

THIS ISSUE

Dear Reader,

Happy Halloween! Welcome to another issue of ScienceMind. With the beginning of the new academic year, we welcomed over 30 new members including article designers, writers and editors. I would like to thank everyone who supported us at the welcome fair and give a warm welcome to our new members. This is a very exciting issue with interesting topics ranging from freshers flu to the Halloween Genes. More specifically, you will read articles in the topics of Biochemistry, Cardiology, Immunology, Neuroscience, Psychiatry, Mycology, Genetics, Virology and an Interview with Seven Kings School.

ScienceMind is King's College London's student science magazine. We focus on making science accessible to everyone by covering a diverse range of topics. It's why each article has a difficulty level: Shallow dive, threading water and deep dive (easy, medium, hard).

At ScienceMind, we have a passion for showcasing and developing the talents of our members by giving them the opportunity to write articles, edit them, and design them. Flexibility is key to us, which is why members at ScienceMind are not obligated to participate in each of our monthly issues if it doesn't work with their schedule. We also interview members of the scientific community to discuss the work they do, whilst providing valuable networking opportunities.

Yours faithfully,

The Deputy Editor-in-Chief
Rosa Tsucala

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THREADING WATER

THE ROAD TO A GREENER FUTURE... OR IS IT?

WRITTEN BY SOPHIA STEBLINA
EDITED BY ANOUCHKA AZRIA
DESIGNED BY SAMARA SINGH

How many cars are there in the UK? 32,697,408 cars, as of 2020 and 9,068 buses in London alone as of March 2021. When discussing crude oil depletion and pollution in relation to cars, the usual culprits are thought to be petrol and other fuel-associated applications. Nonetheless, an overlooked yet no less culpable component exists – **rubber tires**. Regardless of how eco-friendly transport is, from diesel-run trucks to bicycles, most vehicles drive on tires. **40 million tires** are put on cars each year, three-quarters of which are replacements. Tires are made of a mixture of both natural rubber - found in rubber tree bark - and synthetic rubber - made from **crude oil derivatives**.

Biosynthetic plastics

Crude oil is a valuable but finite resource that sustains our lifestyles. Its derivatives are used to produce fuels and materials. To combat inevitable fossil fuel depletion, the United Nations have publicised environmental sustainability goals and guidelines, encouraging companies and institutions to move away from crude oil refining to sources of **synthetic plastics.**

A team of researchers at the **RIKEN Centre for Sustainable Resource Science** in Japan have risen to the challenge of engineering *Escherichia coli* bacteria to **synthesize 1,3-butadiene** - a key component of rubber and other plastics. Over 12 million tonnes of 1,3-butadiene are produced annually from naphtha cracking. Yutaro Mori and his team of scientists have incorporated rational enzyme design and directed evolution methods to create an **artificial metabolic pathway** that converts glucose to 1,3-butadiene.

The researchers optimised ferulic acid decarboxylase (FDC), an enzyme that catalyses the decarboxylation of phenyl acrylic acid derivatives to terminal alkenes, to recognize the *cis,cis*muconic acid (ccMA) precursor and produce 1,3-butadiene. They engineered a **ccMA producing strain of *E.coli*** to convert glucose into a usable substrate with the shortest production pathway and maximum yield.

Scientists then introduced the optimised FDC protein to the bacteria and fermented them in a jar fermenter. The complete 1,3-butadiene production reaction is only a two-step process: ccMA is converted to pentadienoic acid and then further **decarboxylated** to 1,3-butadiene.

Figure 1. Jar fermenter for Escherichia coli at RIKEN Centre for Sustainable Resource Science.

Around 2g of 1,3-butadiene was produced **over 96 hours.** While this amount seems infinitesimal compared to the millions of tonnes produced in factories each year, this production process has the advantage of being entirely biological.

Environmental impact

It is important, however, to recognize that even biologically derived 1,3-butadiene can be a pollutant.

Regular tires are estimated to be responsible for 0.81 kg of microplastic pollution per year. An estimate of 3-7% of air pollution and 5-10% of ocean plastic pollution has been attributed to microplastics released from tired wear and tear. The presence of tire microparticles places a burden on our health through inhalation and food intake, the severity of which depends on particle size and abundance.

The technology pioneered at **RIKEN** is far from implementation partially due to the infancy of the technique. This offers us a window of opportunity to consider the uses of such technology what measures can be taken to reduce its potentially adverse impact on the environment and us.

DEEP DIVE

Could Athletes Die in Their Sleep?

WRITTEN BY IRIS ZIELER | EDITED BY ROSA TSUCALA
DESIGNED BY TAMARA YAP

Bradycardia is a very common occurrence among endurance athletes. In fact, at rest, some may experience a heart rate **below 30 beats per minute** (bpm), putting them at risk of heart failure. Heart rate is controlled by intrinsic and extrinsic mechanisms. Intrinsic control is mediated by the pacemaker cells of the sinus node. These undergo cyclic depolarisation, established by the funny current, which arises due to sodium ions slowly passing through hyperpolarisation-activated cyclic nucleotide (HCN) channels.

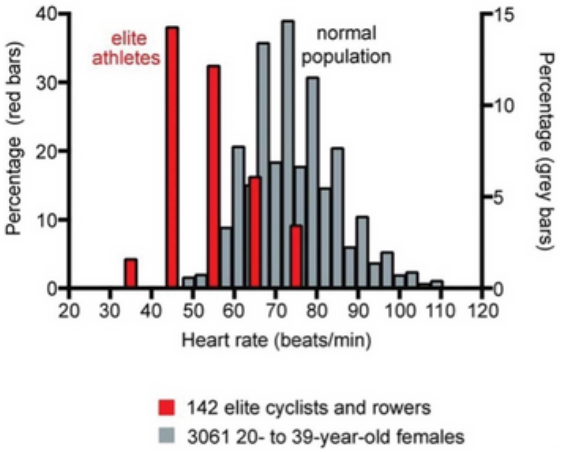


Figure 1. This graph shows the average resting heart rates of elite athletes compared to the normal population. The striking reality is that the values for athletes are significantly skewed to the lower end of the spectrum.

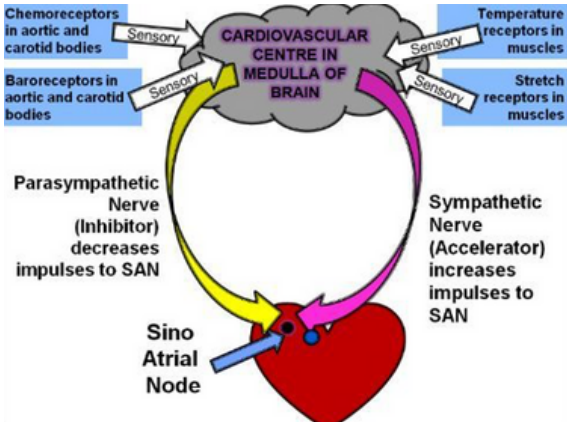


Figure 1. Cardiovascular centre in the medulla of the brain

Once the funny current depolarises the cell enough to reach threshold, L-type calcium channels will begin to open, initiating an action potential. The **extrinsic control** mechanism is dominated by the parasympathetic nervous system at rest, which acts on muscarinic receptors via the vagus nerve to decrease the funny current. The sympathetic nervous system has the opposite effect, releasing catecholamines onto ß-adrenergic receptors to increase the heart rate.

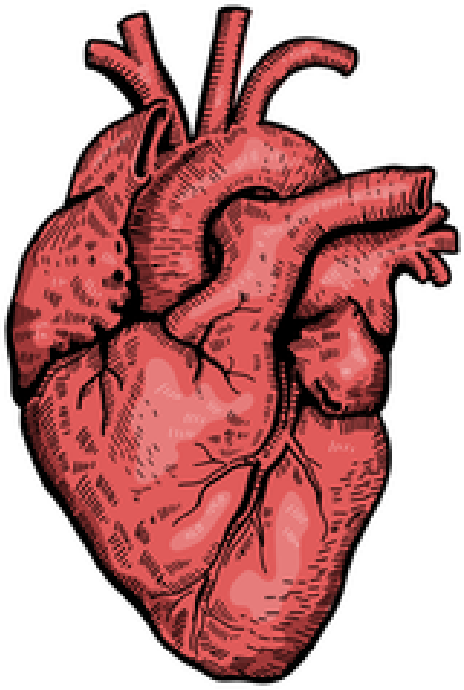
During exercise, the body's response with regards to mediating heart rate can be divided into three processes.

Cardiology

Firstly, there is the **central command**, involving the autonomic nervous system. As vagal tone dominates at rest, the body's initial response to exercise is a decrease in parasympathetic input. This is the main mechanism up to about 90bpm, after which the subsequent increase in heart rate is due to increased sympathetic input stimulating: heart rate, contractility, and peripheral vasoconstriction. The autonomic nervous system will also play a role in resetting the baroreceptor set point to a higher blood pressure.

Secondly, **arterial baroreceptors** can sense the increase in blood pressure caused by exercise. This will lead to an augmented firing rate to the brain, causing an increase in parasympathetic and decrease in sympathetic activity to lower the blood pressure. Thirdly, **neural feedback mechanisms** such as chemo- and mechano-receptors also play a key role in regulating heart rate in response to exercise. They do so via vagal and sympathetic signalling.

How do these short-term control mechanisms add up over time? The long-term adaptations to exercise causing bradycardia in elite endurance athletes go beyond the 'simple' physiological responses seen acutely. One of the main drivers of bradycardia in elite athletes is **cardiac remodelling**. As they train, the heart is chronically being challenged to produce a very large cardiac output to supply the active tissues with sufficient oxygen.

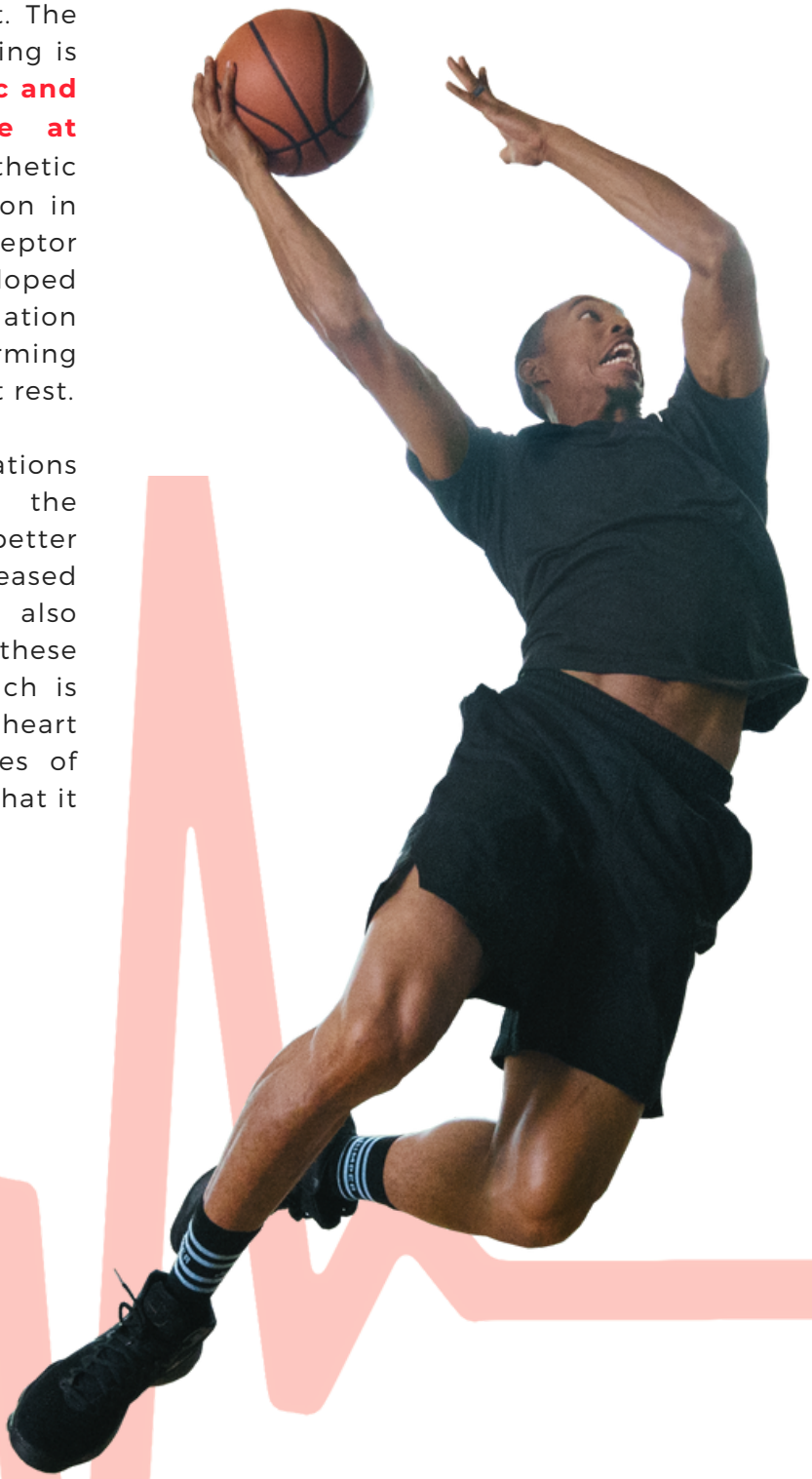


Cardiac output can be measured by the formula: **Cardiac Output = Stroke Volume x Heart Rate**. This indicates that cardiac output is directly proportional to stroke volume and heart rate. Cardiac remodelling involves an enlargement of cardiac cavities with a proportional increase in thickness of the walls, which promotes a better stroke volume during exercise. At rest, as the cardiac output should remain at 5L/min, this augmented pumping and contraction capacity of the heart means that the heart doesn't need to beat as frequently. Furthermore, there is some evidence suggesting **modification of the sinus node**. This manifests as a reduction in HCN4 channel expression, resulting in a lower depolarisation slope, thereby slowing the intrinsic heart rate. In addition to cardiac remodelling, chronic endurance training also increases the **aerobic capacity** of the exercised musculature. This is

achieved by increasing the number of capillaries, the number and size of mitochondria, as well as the vasodilatory capacity of vessels supplying the active muscles.

These act in synergy to augment parasympathetic activity at rest. The final adaptation worth mentioning is the **increased parasympathetic and decreased sympathetic tone at rest**. The decreased sympathetic input may be due to a reduction in baroreceptor and mechanoreceptor sensitivity, which will have developed due to their chronic stimulation accompanying the training, forming a new set-point for both, even at rest.

Cumulatively, all these adaptations allow better oxygenation of the working tissue, leading to better performance and increased endurance. They do however, also cause bradycardia amongst these trained individuals at rest, which is not to be taken lightly, as the heart rate may drop so low in cases of extreme rest, like during sleep, that it could lead to cardiac failure.

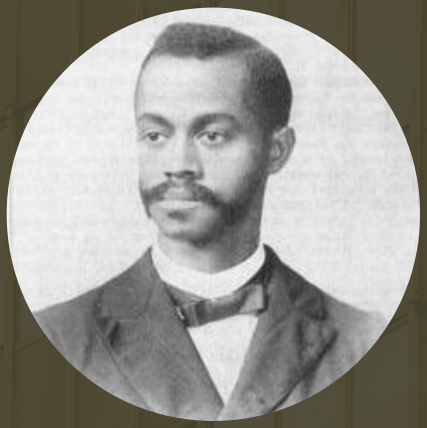


How Black Scientists have Shaped Scientific Discoveries

Alice Augusta Ball (1892-1916)
Chemist: Extracted chaulmoogra seed oil for the treatment of Hansen's disease (leprosy).

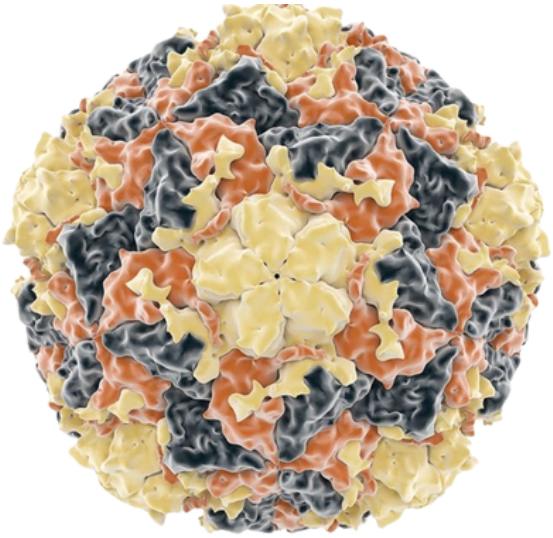
George Carruthers (1931-2020)
Astrophysicist: Invented ultraviolet camera/spectrograph; used by NASA when it launched Apollo 16 in 1972.

James A. Harris (1932-2000)
Nuclear Chemist: Co-discovered Rutherfordium (element 104) and Dubnium (element 105).



Charles Henry Turner (1867-1923)
Zoologist: Proved that insects can hear and can distinguish pitch, that cockroaches can learn by trial and error, and that honeybees can see colour.

Kerrie Holley (1954-present)
Computer Scientist: Inventor of software engineering techniques: system and methods for locating mobile devices using location and presence information.



THREADING WATER

Freshers Flu Or FRESHERS RHINOVIRUS?

WRITTEN BY ZETA IOANNOU
EDITED BY SOPHIA STEBLINA
DESIGNED BY SAMARA SINGH

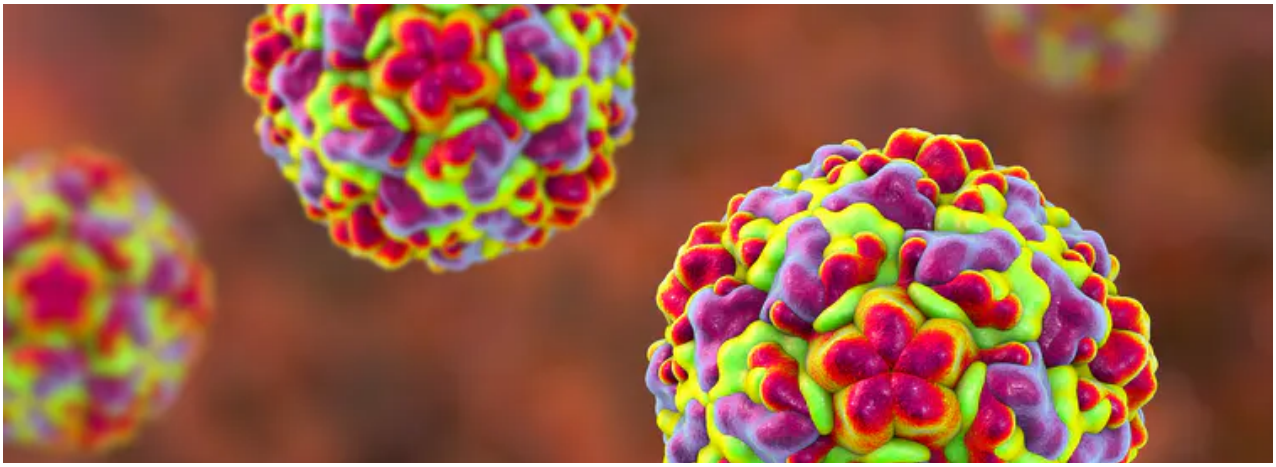
Now that we are all back at university, with various events underway, I am sure that everyone is familiar with 'freshers' flu. Did you, however, know that freshers flu may not necessarily be caused by the influenza virus? In fact, it's just a bad cold, brought on by a range of factors that you are exposed to in the first few weeks at university. These elements work together to weaken your immune system and make you more susceptible to a range of viruses that target your **respiratory tract**; the most common of which is the human rhinovirus.

The main factor responsible for fresher's flu is the convergence of thousands of new students at the start of term. This makes freshers' week a **melting pot of various new and exotic viruses**, leaving people susceptible to infection. These viruses spread when students mingle in large groups at events like the freshers' fair and club nights. Before you know it, nearly everyone is feeling under the weather.

Drinking culture during freshers' week also plays a key role in getting sick. Alcohol is a known **immunosuppressant** that damages cells within the respiratory tract and stomach by causing **pH imbalances** and playing a role in impairing immune cells throughout the body. The food we eat also matters. Unhealthy foods that newcomers at university tend to eat contributes to this immunosuppressive effect. Through this article, I will explore one of the common viruses responsible for the 'freshers' flu - the **human rhinovirus**. I will cover its symptoms, both typical and rare, as well as ways to treat them before they become severe.

Human rhinoviruses (RVs) are small non-enveloped ssRNA viruses of the Picornaviridae family. They come in more than 160 identified strains. RV infections are mainly transmitted through direct contact or via fomite, with inoculation to the eye or nose from the fingertip.

Figure 1. Rhinovirus protein



RV infections compromise epithelial barrier integrity, which may lead to an increased translocation of pathogens and complications of respiratory diseases.

RV serotypes display a propensity for huge antigenic diversity, and as a result are **susceptible to mutations** and the emergence of new variants. This contributes to the persistence of freshers' flu and poses a significant challenge to effective universal vaccine development.

Common symptoms that one might experience with a human rhinovirus infection, include **nasal dryness** or irritation as well as **nasal congestion** and a **sore throat**. Even though mild, there is a variety of medicines available to tackle them; from decongestants such as pseudoephedrine to paracetamol and ibuprofen. What happens, however, when the symptoms worsen and persist for longer periods?

Severe symptoms include difficulty **breathing** and **chest pain**.

Unfortunately, there are currently no direct medicines on the market for this condition. With patients suffering with the same symptoms for 2-3 weeks, the healthcare sector has demonstrated an urgent need for the development of medication able to tackle these more severe forms of the rhinovirus.

Host defence peptides such as **cathelicidins** are key components of the mammalian immune system and many display powerful antiviral activity. Vitamin D supplementation and in particular, vitamin D metabolites, can upregulate these defence molecules. In vitro supplementation studies have shown to reduce viral replication in RV infected models.

At present, virtually nothing is known about the determinants for cathelicidin binding to the viral capsid and a full understanding of this will require fine mapping of cathelicidin binding sites and identification of the active peptide region.

Figure 2. Red seaweed found to have antiviral activity against RV

Currently there are no drugs licensed for use against RV infections, yet a number of promising therapeutics have been demonstrated to have antiviral activity against certain RV serotypes. While no drug has been singled out as a perfect solution, **combinatorial treatment** with selected compounds seems attainable.

Ribavirin - a drug that has been used to treat severe lower respiratory tract infections caused by respiratory syncytial virus (RSV), has been shown to have moderate antiviral activity against serotype RV-13. While others, such as RV-14, have not shown favourable response. patients exhibiting enhanced clearance of RV infections following treatment.

Pleconaril is known to display broad spectrum antiviral activity against a range of viral pathogens. The drug functions by binding to hydrophobic pockets within viral capsids, altering interactions of the viral pathogens to host cell receptors and blocking the uncoating of the virus; it has demonstrated antiviral activity against five RV serotypes.

Interestingly, in vitro studies and clinical trials have suggested that the red seaweed (Figure 2) **polysaccharide, carrageenan**, has antiviral activity against RV both in vitro and in vivo. Iota-carrageenan, a sulphated variety, was demonstrated to prevent the replication of various serotypes including RV-1A, 2, 8, and 84 in the nasal epithelium. A study by Koenighofer et al., investigating carrageenan nasal sprays, found that patients suffering from RV infection and treated with the nasal spray experienced a significant reduction in the symptom duration and enhanced resolution of the infection when compared with placebo controls.

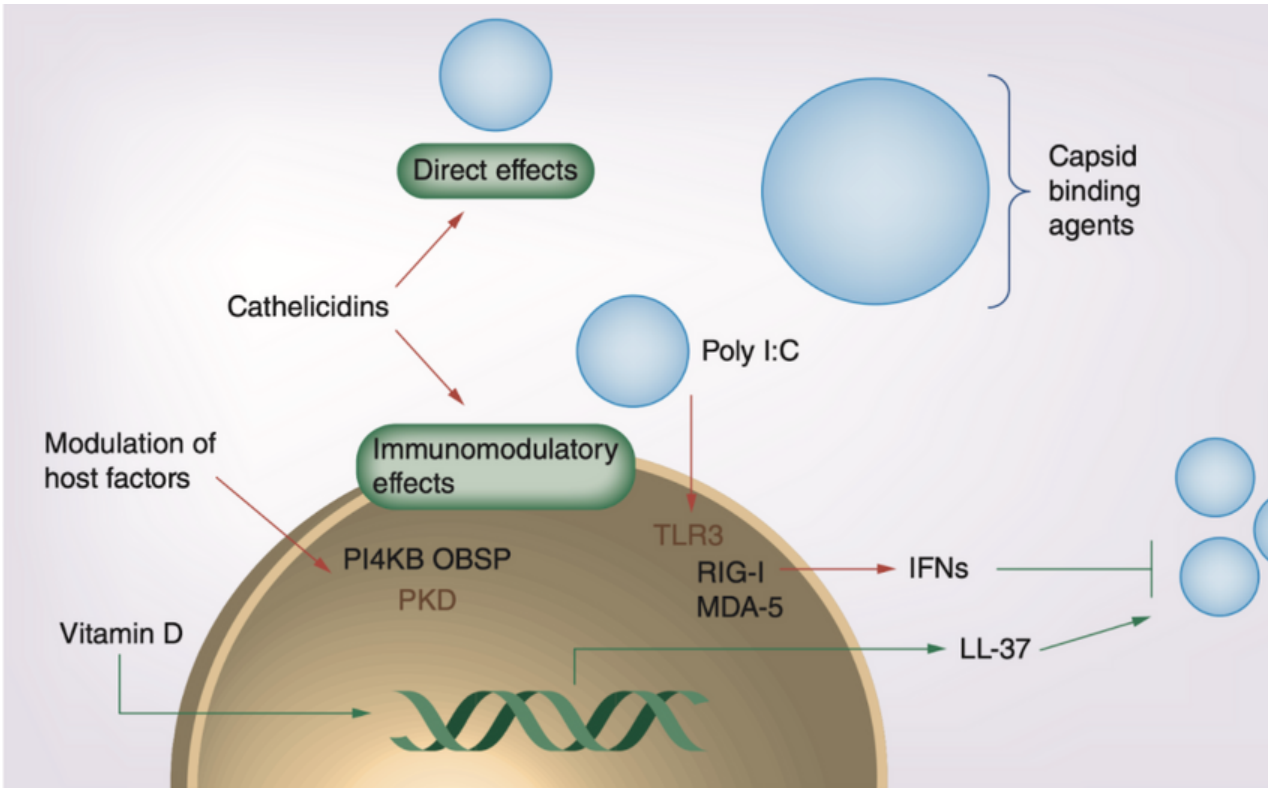
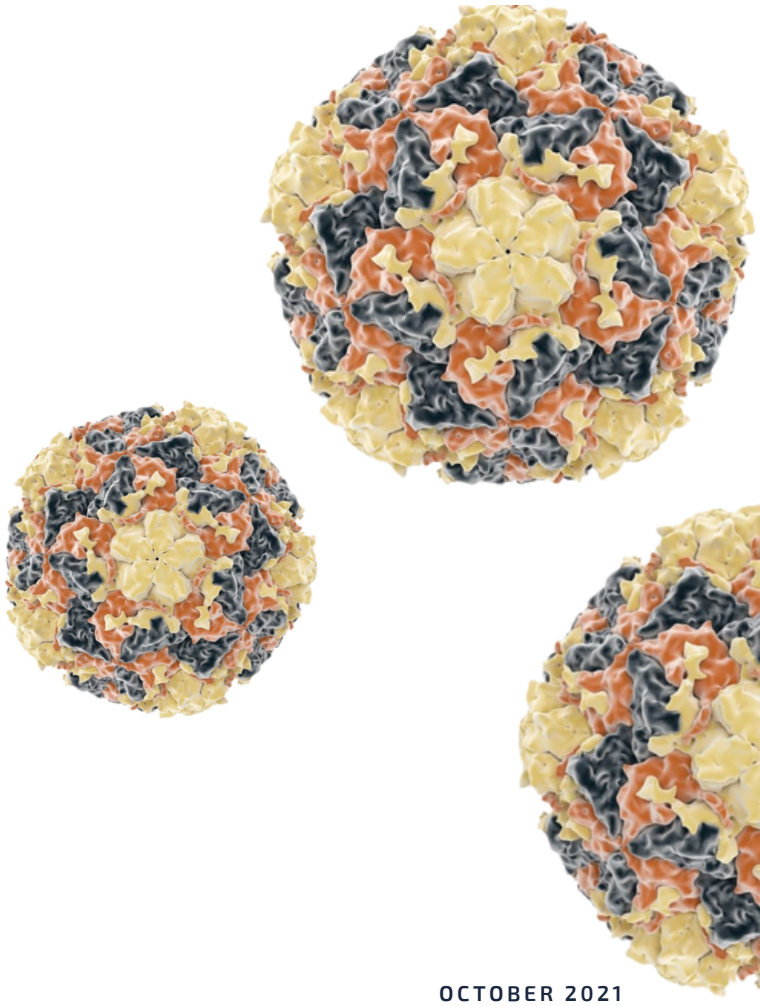


Figure 3. Schematic representation of targets for development of antiviral therapeutics against human RV

Final thoughts

Many of the therapeutics described herein have been under investigation for decades, but the challenges posed by this particular pathogen have, thus far, been insurmountable. Encouragingly, a new wave of antiviral peptides and compounds has been characterized over the past 2–3 years, and thus the potential for developing novel and effective treatments for targeting RV infection may be closer than ever before (Figure 3).



Studying at University: Expectations vs Reality

SEVEN KINGS SCHOOL STUDENTS DISCUSS STUDYING SCIENCE AT UNIVERSITY WITH THE FOUNDER

Students from Seven Kings Sixth form sat with ScienceMind to discuss their concerns and queries about going to university next year. According to their website, Seven Kings School is a co-educational comprehensive primary, secondary school and sixth form located in Ilford in the London Borough of Redbridge, England. It caters for pupils aged 4–18 years old. In this day and age, without the right connections or guidance, it's difficult for young people from disadvantaged backgrounds to get an idea of what university is actually like if they don't have older siblings that went to university or if they are the first in their family to go to university. This interview occurred during a work experience event organised by us and Dr Aileen King at King's College London where a number of panels attended by PhD students were organised so that students could learn more about studying science at university.

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> I think that it would be quite difficult to get your head around all the facts and information at first but you can quickly find a system of getting through it without it being too stressful.
>
> SEVEN KINGS STUDENT

We asked: "What is your biggest concern about uni?" Understandably, the main concern we found was that students were concerned about the 'increased workload' as well as the 'jump in difficulty' from sixth form. Regarding workload, it's really down to your time management. You'll have to strike a balance between your social life and your academics. Yes, it's a big jump as your 1st year studying biosciences is often where you are taught the basics and there is little time to go over things in detail. Therefore, my advice is to not worry if you don't understand things the first time round. Also, try to save time on making flashcards as Quizlet has tons of flashcard sets that other students have made in previous years. The content is unlikely to change! Many students regrettably sell their textbooks, not realising that everything you need is on the slides.

Other concerns included things such as: "not knowing anyone" to "being worried about finances once I move out". Most are in the same boat in 1st year, it's really up to you to go up to people at events, lecture halls and even in societies. Friendships will not fall out of the sky, you have to make an effort! As for finances, many students say that it's important to keep to a budget and to learn to live within your means. Follow shows on YouTube such as 'Millennial Money' to see how people budget their expenses daily. But what if your 'course just isn't right for you?' I'd sit down with careers advisors who would be better suited to answer this but know that many have been there before and that it's never too late.

We then asked: "What do you think studying a science subject at university is like?". Whilst one person put 'it will be very interesting going into further detail on concepts we went through in school quite briefly', others simply put that they thought it would be 'exciting', 'difficult', and 'competitive and stressful'. I agree. When I was in 1st year, I found it hard due to the depth of some subjects but as time went on, I found my own ways to manage my workload. Others thought that science students would be 'doing lots of practicals, exams and essays' which is also true to an extent. As time went on during my degree, we did less practicals and more in-depth research but it certainly felt like a lot at first. I've found that those practicals give a good basic understanding of lab techniques that come in handy when you end up doing your final year research projects. As for essays and exams, those also decreased with time but the focus on wider reading from scientific papers increased a lot.

"What excites you about going to university?". Students mentioned 'learning new interesting content', to 'making and living with new friends' as well as the 'independence' associated with that. I certainly agree that the sense of 'adventure' and 'discovery' is exciting to new students especially to one who said that it was 'a step closer to my ambitions'.

SHALLOW DIVE

Zombie **Ant-pocolypse:** A **Fungal Tale**

WRITTEN BY KIRA LINKE | EDITED BY ALEX EPSHTEIN
DESIGNED BY ZAHRAA BHATTI

A healthy ant makes its way down the trunk of a tree in a Thai rainforest, and a lone spore drifts onto its body. This is a worker ant of the species *Camponotus leonardi*, about to be infected by the parasitic fungus *Ophiocordyceps unilateralis s.l*, and so its fate becomes sealed [1].

As our ant continues foraging for food for its colony, the fungus enzymatically bores through the exoskeleton [2]. Webs of mycelium branch through the body of our ant, drape over muscle fibres and blood vessels. 40% of the ant's biomass is now the proliferating fungus [3]. It is as familiar with the ant's body as the ant is itself.

Our ant begins straying off path, the first sign it is losing control of its body. It meanders through the forest at random, its little body convulses suddenly. In this state, return to the safety of the colony is impossible [1]. This is a clever tactic of the fungus - if its prey were to die near the colony up in the dry, hot canopy, other workers would safely dispose of the body, in an area not suited to the fungus' germination.

Instead, our little ant is driven into the humid understory of the forest, onto a growing sapling. It accurately climbs to 25±3cm above the soil on the budding plant as it enters the final stage of its life. When the sun is highest in the sky, it clamps its mandibles deep into the underside of a leaf, into the main vein [4]; this is the 'death grip'. The fungus has meticulously grown throughout our ant's whole head in its single-celled stage [1].

Muscles are laced with mycelium and atrophying, but both motor neurons and neuromuscular junctions remain in functional condition - a clue into how the fungus makes our ant's body its own. Even more informative is the lack of fungal matter in the brain. From the moment of infection to the ant's eventual death, our ant's mind is never touched. Instead, extracellular vesicle-like particles hint at the fungus taking over the body's fine-tuned biochemical pathways [3]. The fungus hyper-contracts the mandibular muscles and anchors our ant in death.

The fungus begins to truly flourish here. Decomposition of the body feeds the fungus whilst the exoskeleton protects it. When ready, the mycelium organises into a mushroom that blooms out of the back of our ant's head. A long stalk, the stroma, supports the development of the sexual structure.

The infection cycle begins again. Spores are released, which drift through the understory, prepared to infect the next scavenging ant. The manipulated ants find their way into the same area, and the graveyard fills up. Over 25 ants may die per square meter [1].

A long history of coevolution has led to this moment. Since Tom Petch's description in 1931 we have known about this parasitic relationship [5]. It plays out differently for each species of ant and its corresponding species of Ophiocordyceps. Each produces a compound cocktail personalised for the host [2], so that in this game of fate, our ant could only lose. The earliest evidence of this manipulation is a 48 million year old fossilised leaf with 29 scars distinctive to the death grip induced by Ophiocordyceps [6]. Yet ants are not the only insect susceptible to behaviour-modifying fungal parasites. Cicadas spread Massospora in a hypersexual state, induced by the fungus using psychoactive alkaloids [7].

These parasitic fungi do not have their own brains or even set physical forms, but enact behaviours to ensure their survival with dextrous skill nonetheless.

Further reading suggestions:
Extended phenotype

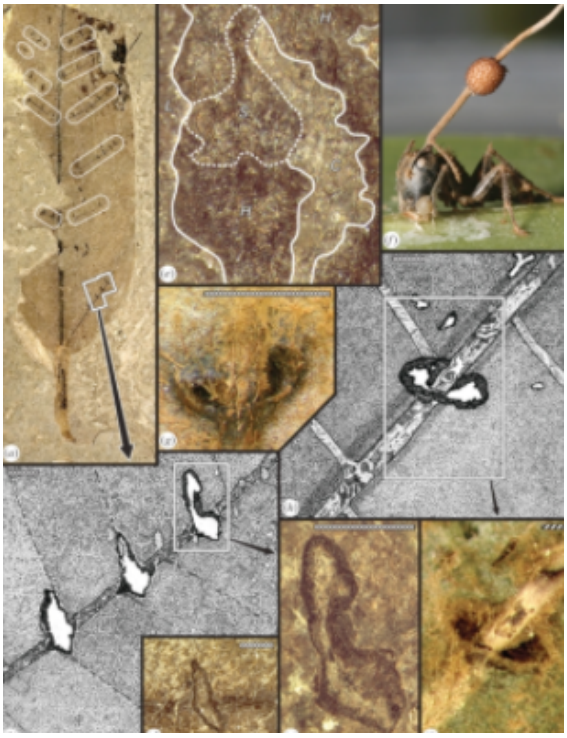


Figure 1. (a-e) Damage to fossilised leaf caused by ants performing 'death grip' caused by Ophiocordyceps infection and greater detail thereof; (f) Fruiting body of Ophiocordyceps on ant; (g-i) Modern ant death grip scar and greater detail thereof. [6]

THREADING WATER

Major Breakthrough: WHO Approves World's First Malaria Vaccine

WRITTEN BY CANSU OZDEMIR | EDITED BY MAYA ROWLEY
DESIGNED BY JENNA KEUNG

The **RTS,S vaccine**, also called **Mosquirix** and developed by UK pharmaceutical giant has just been approved for rollout in areas of high malaria transmission. Malaria is a parasitic disease transmitted to humans via bites from an infected female **Anopheles mosquito**. Its symptoms can range from those of flu-like illness with fever, chills and nausea, to life-threatening complications including respiratory distress and organ failure. The tropical disease can turn fatal, with mortality rates in 2019 estimated to have been **409,000** with the most vulnerable group being children under five, representing 67% of all deaths.

Leading on from the successful pilot programme in Malawi, Kenya and Ghana, the vaccine will be issued to children from five months of age, with a total of four doses. More than 2.3 million doses of the vaccine have been given, with trials showing **30% falls** in severe disease and hospitalisation with severe malaria, and in those who received the full four doses,

Figure 1. Common mosquito bite

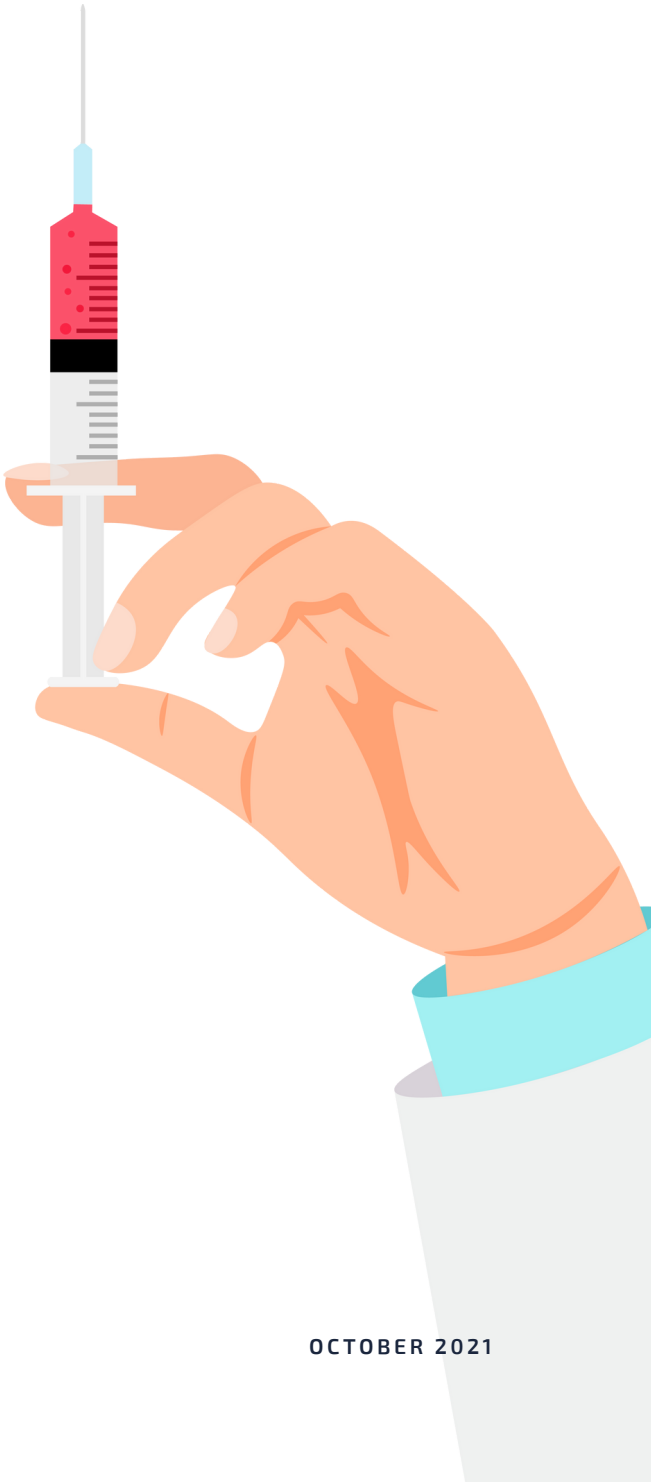
it led to the prevention of 4 in 10 cases.

Whilst these results may not be on par with the effectiveness of other vaccines such as the recent SARS-CoV-2 vaccines which vary from 60-90%, modelling has proposed an estimated prevention of the deaths of **23,000 children** a year if those living in areas of high incidences of the disease are vaccinated. However, recent research showed that using a combination of prophylactic antimalarial drugs alongside the RTS,S vaccine could reduce deaths by 72.9% and clinical malaria by 62.8%.

The RTS,S vaccine is considered a **pre-erythrocytic** vaccine as it attacks the parasite before it invades the red blood cells. It targets the circumsporozoite protein on the sporozoite surface (during the first stage of the parasite's life cycle) before they infect the hepatocytes. Normally, the infected hepatocytes produce 30,000 to 40,000 progeny over a six day period, causing the hepatocytes to rupture and release the progeny merozoites which invade the host's erythrocytes. The erythrocytes also rupture and increase cytokine production in response, which causes clinical malaria symptoms.

Mosquirix triggers the immune system against malaria caused by the predominant species: **Plasmodium falciparum**, which accounts for the highest rates of complications and mortality globally. The vaccine is comprised of the central repeat region of P. falciparum circumsporozoite protein (CSP) and T-cell epitopes of the CSP, fused with the surface antigen from the hepatitis B virus for immune system recognition. The production of a malaria vaccine proved difficult due to the large genetic scale of the parasite: compared to viruses with around 10 genes, Plasmodium falciparum has a larger scale genome, coding for over 5,000 genes. The P. falciparum proteins are also incredibly polymorphic and the malaria parasites have a complex life cycle.

The evaluations for the current **six year trial** are to be completed by 2023 and scientists are hopeful that it will provide evidence to vaccinate more at-risk children across the continent. Data collected from phase 4 trials will be able to provide more information on vaccine effectiveness and side effects. As another malaria vaccine R21 or Matrix-M enters phase 3, it promises that alongside other preventative measures, many more countries can reach zero malaria cases in the near future.



SHALLOW DIVE

Not Guilty by Reason of Insanity

WRITTEN BY ALEX EPSHTEIN
EDITED BY ANOUCHKA AZRIA
DESIGNED BY ANA LINARES

Every crime involves three elements: actus reus, the act or conduct; mens rea, the individual's mental state at the time of the act; and third, the presence of a connection between the act and the effect. According to Cornell Law School, the Insanity Defence **directly** challenges the mens rea: "the intent to commit a crime". It argues that the perpetrator has a particular mental disorder that **prevents** them from forming mens rea, as required by law in order to be persecuted.

Once the individual pleads with the notion of insanity as a defence, concrete evidence is **needed** to prove that the individual is unable to **distinguish** between right and wrong or didn't understand what they did because of a 'disease of the mind'. As stated by the Legal Information Institute, there are **four** different tests designed to prove that the defendant is legally **'insane'**: M'Naghten test, Durham Rule, the Irresistible Impulse Test, and the Model Penal Code. Each test has a set of rules the defendant must follow for a complete psycho-analysis, but the central question still revolves around the notion: **'did the defendant know what he was doing, or, if so, that it was wrong?'**

For someone to be classified as legally 'insane', these tests must come to two conclusions. The first being **'the defendant must be suffering from a mental defect or disease at the time of the crime'** and the second **'the defendant did not know the nature or quality of the criminal act they committed or that the act was wrong because of the mental defect or disease'**. an experienced psychiatrist commonly conducts these tests.

The insanity defence sits at a rare intersection between psychiatry and the justice system. Throughout history, and to this day, medical doctors have frequently appeared in court cases, aiding people who do not fit into the societal "norms". As discussed in Feurestein et al's paper **"The Insanity Defence"** (2005), a psychiatrist can be involved in a case concerning the criminally insane in two ways.

The first being via their patients; if their client has been involved in a criminal matter and chooses to make their case, they can call their treating psychiatrist or physician to **testify** to their defence in court while they are on trial.

The second way is by assuming the role of a consultant, whose aim is to **"evaluate the individual as well as the circumstances of the crime"** (Feurestein et al., 2005). Here, unlike in the previous example, the physician would be examining the person under a court order or at the request of one of the attorneys. This contrasts the first point, as it heavily differs from knowing and having seen the patient regularly, therefore the main concern with this route is the issue of **confidentiality**.

So what happens when a defendant is found **"not guilty by reason of insanity"**? Contrary to popular belief, this does not necessarily mean that the person will **"get away with"** their respected crime. Instead, treatment is sought for the defendant, whether that is through institutionalisation or confinement in a **'prison for the criminally insane'** for a minimum conviction charge. In some cases, using the Insanity Defence has proven to work **against** the defendant, meaning they end up spending more time in confinement than initially intended. However, this **varies** depending on the laws of the region.

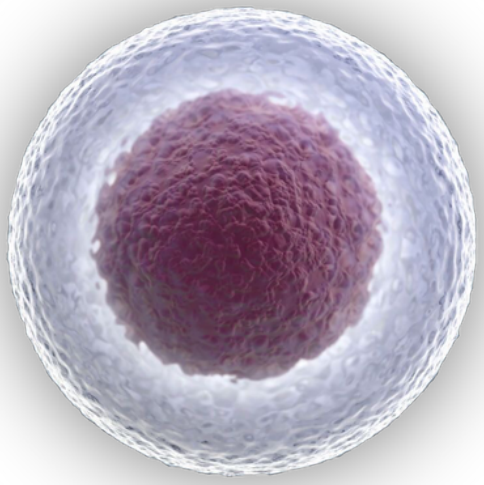
One example where defendants succeeded in using the Insanity Defence includes the case of John Shrank. According to the Smithsonian, Schrank's case began when he appeared in court for **attempted murder** of Roosevelt after deciding to run for his third term in office. Schrank told police that former President McKinley appeared in a dream and said that Roosevelt had **assassinated** him. He told the police that his knowledge of history... convinced [him] that Colonel Roosevelt was engaged in a dangerous undertaking... [he] was confident that if he was **defeated** at the Fall election... his action would plunge the country into a bloody civil war' (O'Toole, 2012). Psychiatrists eventually declared Schrank 'insane', and **unfit** to stand trial with a jury, resulting in a judge sentencing him to life in an asylum.

Although it is a commonly discussed matter, the Insanity Defence is used in **1%** of criminal proceedings. Out of this 1%, **25%** are successful. Therefore, less than 1 in 400 defendants are found not guilty **"by reason of insanity"** in this country. However, the last time the legal definition of insanity changed was 1842. In 1953, evidence was provided to the Royal Commission stating the definition of insanity was **obsolete** and **misleading**. This suggests that the law surrounding insanity is **outdated** and in need of urgent reform, hence this short overview merely scratches the surface of problems surrounding the plea: '**not guilty by reason of insanity**'.

DEEP DIVE

Clonal Haematopoiesis: How Ageing Influences Our Risk for Cardiovascular Disease

WRITTEN BY TREASA JIANG
EDITED BY JULIET CHEN
DESIGNED BY TAMARA YAP



Clonal haematopoiesis is an age-related phenomenon in which a **haematopoietic stem cell (HSC)** acquires an advantageous mutation that allows its clones to prevail in the bone marrow. It was known to be present in patients with leukemia, but it wasn't until the 1990s that clonal haematopoiesis was discovered in healthy, non-cancer individuals and shown to play a prevalent role in **ageing**.

As we age, our cells accumulate more and more mutations, the majority of which have no functional impact. However, on the rare occasion a mutation may arise that confers a **survival advantage** to the cell, allowing it to 'win' over other cells that do not have the mutation. In the haematopoietic system, this would manifest as a large proportion of circulating blood cells carrying the same mutation. This expansion of blood cell clones derived from a single mutated stem cell is known as clonal haematopoiesis (Figure 1).

Because a sufficient number of mutations need long periods of time to **accumulate** and **expand**, clonal haematopoiesis is much more prevalent in the elderly population. Following whole-exome sequencing studies in 2014, it was estimated that around 10-20% of people over 70 years old have detectable clonal mutations, while less than 1% of people under 40 do. The advancement of next generation sequencing in the last decade has also allowed scientists to identify the specific somatic mutations driving clonal haematopoiesis at the population level. Some of the most commonly mutated genes include DNMT3A, TET2 and PPM1D.

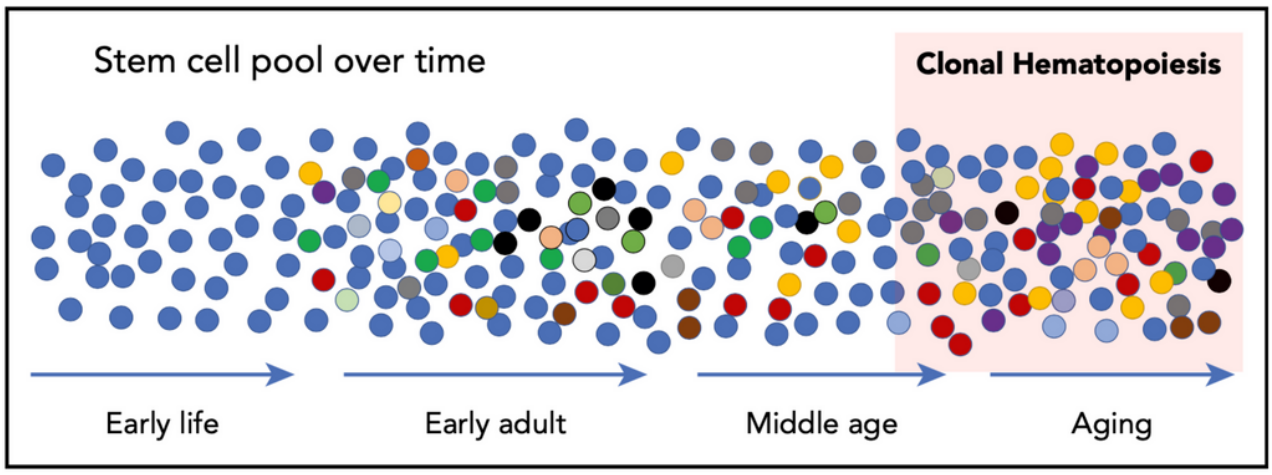


Figure 1. Development of clonal haematopoiesis over time. Adapted from Challen and Goodell, 2020.

Ageing has been widely linked to inflammation, such that the term '**inflammaging**' was coined to describe the systemic inflammation that accompanies advanced age. **DNMT3A** and **TET2** mutations are highly responsive to changes in an inflammatory environment. DNMT3A encodes DNA methyltransferase 3 alpha, an enzyme responsible for adding methyl groups to DNA to promote HSC differentiation.

Mice with knockout DNMT3A show loss of pro-differentiation genes and suppression of apoptosis when subject to infectious stress, leading to the expansion of DNMT3A loss-of-function HSC clones under inflammatory conditions. TET2 encodes an enzyme that catalyses an important step in myelopoiesis. Similar to DNMT3A, TET2 knockout HSCs obtain a growth advantage after inflammatory insult due to elevated levels of signalling factors that promote resistance to apoptosis.

CRISPR-induced deletion of DNMT3A and TET2 resulted in cardiac hypertrophy and increased fibrosis in mice with angiotensin II-induced heart failure, as well as greater macrophage accumulation. This suggests that DNMT3A- or TET2-mediated clonal haematopoiesis may lead to cardiovascular diseases via disruption of the inflammatory response in myeloid cells.

The vast amount of studies looking at clonal haematopoiesis has given scientists new insights into the mechanisms underlying age-related diseases. Through harnessing the power of novel sequencing technologies, this phenomenon has the potential to be used for identifying and preventing blood cancers and cardiovascular diseases in at-risk individuals. However, much more research is required to elucidate the link between specific genetic variants and disease before this can be realised.

SHALLOW DIVE

No More 14-day Rule for Embryos

WRITTEN BY VIDUR TANDON
EDITED BY TREASA JIANG
DESIGNED BY TAMARA YAP

Up until recently the growth of human embryos in labs was restricted to 14 days.

Ethical issues prohibited research to continue past this point, especially due to the central nervous system initiating growth and allowing the embryo to feel pain. However, in May of this year, the International Society for Stem Cell Research (ISSCR) relaxed this legislature, causing a massive relief for many scientists.

The 14-day rule was followed almost globally and was first brought up around the 1980s, subsequently being included as an official regulation in the UK's **Human Fertilisation and Embryology Act in 1990.**

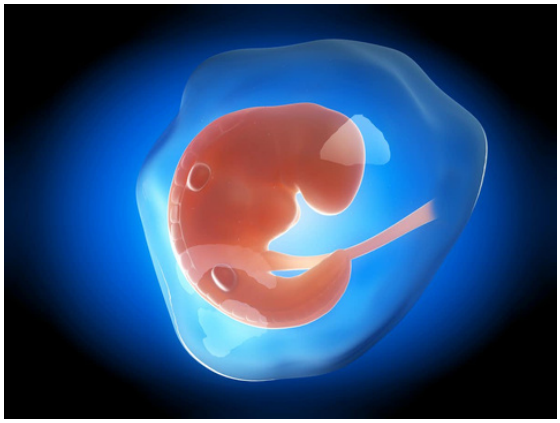
Since at that time embryonic research was not as advanced as today, embryos were not even able to survive close to two weeks. With major scientific advancements in the past 40 years, it is now realistic for embryos to survive 14 days and potentially even longer, which explains why scientists have been appealing for an extension of this legislature these past few years.

To understand why the period after the 14 days is so critical, one must understand what occurs to the embryo at that point in development. During the first 14 days, the embryo undergoes several cycles of **cell division** until it reaches the **blastocyst** stage, after which it implants into the uterine wall.

From day 15 onwards **gastrulation** in the embryo begins, meaning the three types of germ cells start differentiating, creating the **ectoderm**, **mesoderm** and **endoderm** alongside the primitive streak which is essential in determining the body axes and in preparing for organogenesis. These steps in the development are absolutely critical and need to occur flawlessly, since any malfunction during this period can lead to developmental issues. If that were to occur, the embryo would likely not survive.

16-cell human embryo on a pin

The relaxation of the 14-day rule has opened the door to major research opportunities, yet must be treated with caution and respect. Concern has been raised about the **ethical correctness** of experimenting on gastrulating embryos, arguing that from this point onwards they should be seen as proper individuals. In addition, looser restrictions allow possibilities of experimenting with **germline gene editing** which is a very fickle field and could easily lead to ethical misconduct.



one-month-old fetus © The Conversation

However, a majority of **miscarriages** and **congenital birth defects** originate in the time span following the first 14 days. Scientists haven't had the chance to properly investigate many of the causes and processes, and hence to come up with ways to avoid these occurrences. To replace the 14 day rule, the ISSCR proposes to have each project considered individually to determine the time frame permitted for the embryos to develop. The projects will have to undergo a number of reviews to eventually be accepted.

Overall, this extension allows an insight into the development of the **nervous system** and **organogenesis** as well as potentially aiding in **IVF procedures** and reducing the rate of miscarriages. While being a pivotal step in research, it will take some time until we see the actual impact of it.

THREADING WATER

The Halloween Genes: Genetics' Spookiest Discovery

WRITTEN BY AMINA IGENBEK | EDITED BY EMMA VON SETH
DESIGNED BY TAMARA YAP

If you are not an insect geneticist, "The Halloween Genes" may just sound like the name of a subpar horror flick, but they are actually a very real gene family with an important role in insect development.

These genes were first discovered in the 1980s by a team of German scientists who conducted a large-scale mutation screen for mutants that result in embryonic lethality in ***Drosophila melanogaster***. They identified a number of mutations which led to **embryonic deformities**, giving the *Drosophila* embryos a rather ghastly appearance. Gerd Jürgens, who was tasked with the nomenclature, rather aptly named the genes in question: **disembodied**, **shadow**, **shade, spooky** (mutant phenotype with no differentiation of cuticle and head skeleton), and **haunted** (mutant phenotype with only head skeleton visible). Two of the collaborators, Christiane Nüsslein-Volhard and Eric F. Wieschaus, went on to win the Nobel Prize in Physiology or Medicine along with Edward B. Lewis for their discoveries concerning the genetic control of early embryonic development. Some time later, Michael O'Connor and Lawrence

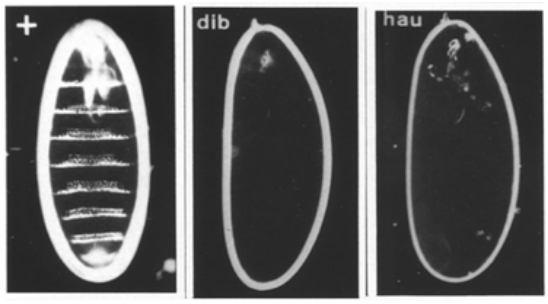


Figure 1. Drosophila melanogaster embryonic mutant phenotypes. + wild type, dib-disembodied, hau-haunted. Adapted from Jurgens et al.

Gilbert began to elucidate the function of a group of genes including disembodied, shadow, shade, phantom, spooky, and spookier, which O'Connor famously, and fittingly, dubbed the Halloween genes. To make matters even more fun, the transcription factors that control their expression are called seance and ouija board!

So what exactly do these genes do and why do their mutants have such a frightful appearance? It has been discovered that the Halloween gene products are **cytochrome P450 enzymes** that catalyse reactions in the 20-hydroxyecdysone(20E) biosynthetic pathway. **20E** is the principal molting hormone which plays an important role in insect growth and development, including cuticle formation, explaining the

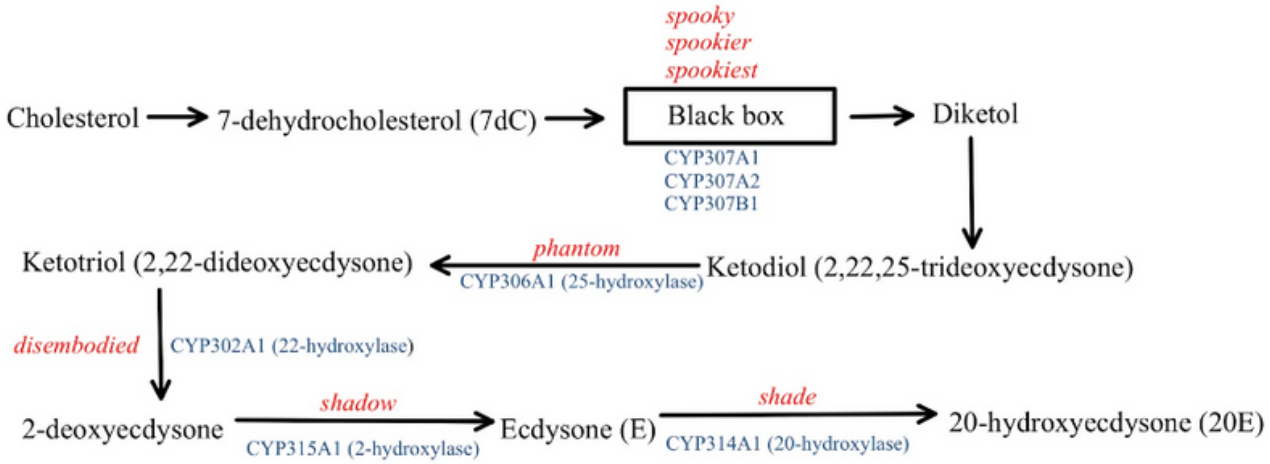
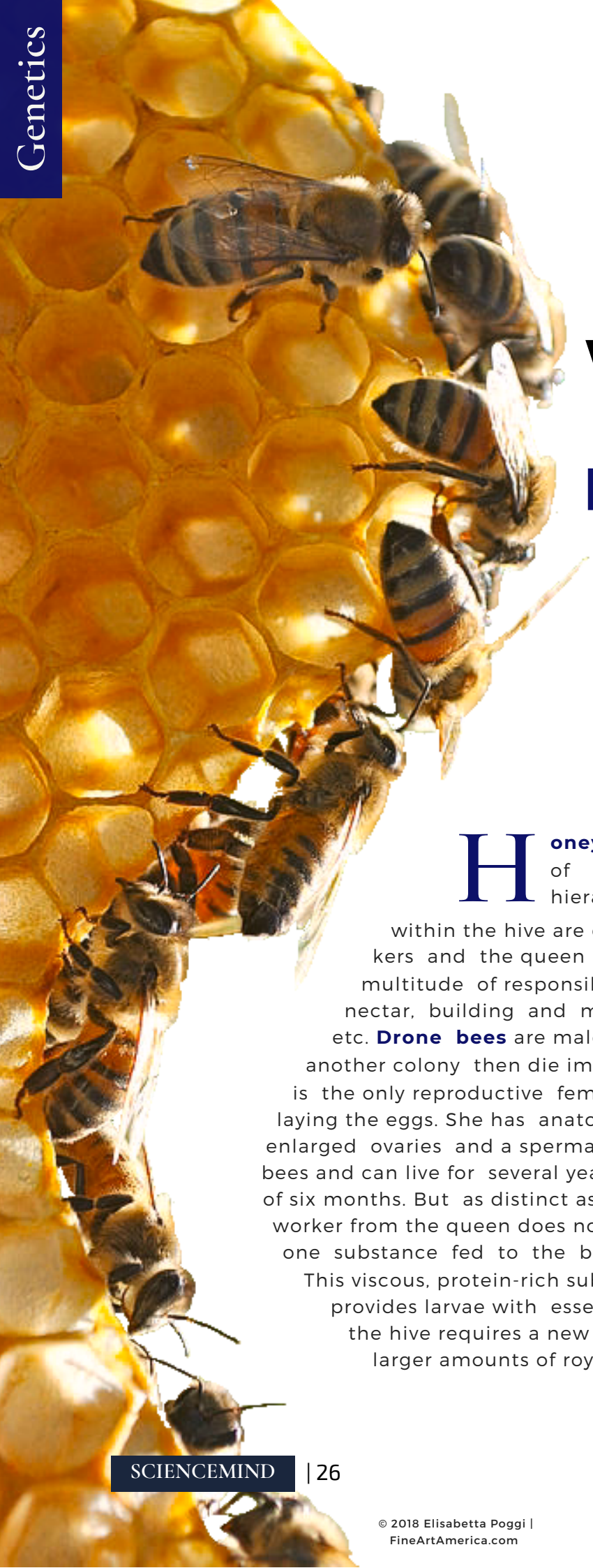


Figure 2. The roles of the Halloween genes in the biosynthetic pathway of 20E.

severe disruptions in morphogenesis in Halloween gene mutants. In the 20E biosynthetic pathway, cholesterol is converted to 7-dehydrocholesterol, which then undergoes a series of hypothetical reactions known as the **black box**, leading to the formation of diketol, which is then reduced to ketodiol. The **spooky** and **spookier gene** products act somewhere in the black box, but their definitive function is uncertain. Next, a series of hydroxylation reactions occur, ultimately leading to the formation of 20E. **Phantom**, **disembodied**, **shadow** and **shade** each code for a hydroxylase that mediates each subsequent conversion. Not so creepy after all!

And so, a catchy name made embryonic ecdysteroid synthesis in *Drosophila melanogaster* a tad mysterious and the scientists behind it a little more famous. Happy Halloween!

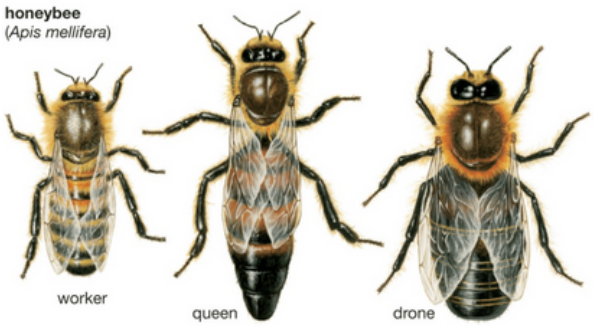


DEEP DIVE

To Be or Not to Be: The Search for What Decides the Development of a Queen Bee

WRITTEN BY MAYA ROWLEY
EDITED BY KANNA KODAMA
DESIGNED BY TAMARA YAP

Honeybees are well known for having one of the most sophisticated social hierarchies in the insect world. Roles within the hive are divided into three 'castes': drones, workers and the queen bee. **Worker bees** are females with a multitude of responsibilities including collecting pollen and nectar, building and maintaining the hive, nurturing larvae, etc. **Drone bees** are males that mate with a queen bee from another colony then die immediately after. Finally, the **queen bee** is the only reproductive female in the colony and is responsible for laying the eggs. She has anatomy specialised for this role, including enlarged ovaries and a spermatheca. She is also larger than the other bees and can live for several years while worker bees live a maximum of six months. But as distinct as these castes are, what separates the worker from the queen does not lie in their DNA sequence, rather just one substance fed to the bee during its larval stage: **royal jelly**. This viscous, protein-rich substance is secreted by worker bees and provides larvae with essential nutrients for development. When the hive requires a new queen, a few female larvae are fed larger amounts of royal jelly, triggering **epigenetic changes** that form a queen bee.



© Bhokray, Ketan. (2016). Artificial Bee Colony Optimization.

Epigenetics refers to the modifications made 'on top of' an organism's DNA that affect gene expression. These changes can include how the DNA is packed (histone acetylation and deacetylation), use of non- coding RNAs as gene regulators, and DNA methylation. These changes affect how the DNA is transcribed and thus can have a distinct effect on the phenotype, while maintaining the original genetic code. In honeybees, significant changes are made in the **physiology** and **anatomy** of larvae destined to be queens that are not hardwired into their DNA; their DNA sequences are **indistinguishable** from those of worker bees. Only through changes in gene expression brought about by high consumption of royal jelly do the characteristics of a queen bee start to develop.

While the exact composition of royal jelly is yet to be determined, it is known to contain the protein family, **Major Royal Jelly Proteins**, or MRJPs. These proteins are thought to be crucial in queen bee development. In particular, **MRJP-1** or **royalactin** was thought to be the main determinant of whether a queen bee develops or not. In the now controversial 2011 paper 'Royalactin induces queen differentiation in honeybees', researcher Masaki Kamakura argues that royalactin is the 'master inducer' of this caste differentiation by triggering a signalling cascade mediated by the **Epidermal Growth Factor Receptor (EGFR)**. These results were surprising as it was unheard of that a single compound could so drastically alter an organism's developmental fate. However, this paper has since been refuted by other researchers, notably Anja Buttstedt et al. in their 2016 paper, 'Royalactin is not a royal making of a queen'- a title in direct opposition to that of Kamakura's.

Buttstedt et al. stated that the amount of royal jelly the larvae were fed was essential in deciding queen bee formation and that other nutrients in the jelly are also crucial for this process, **e.g. 10-hydroxy-2-decenoic acid**, which inhibits histone deacetylase to regulate DNA transcription, as well as various sugars that collectively act as a switch for biochemical pathways. Buttstedt et al. repeated Kamakura's experiments, but were not able to replicate his very high rates of queen bee development (100% in some cases). They also found that feeding honeybees a royalactin-free diet did not have an effect on the proportion of queen bees developed.

Their results strongly suggested that a **variety of substances** were needed to induce the queen bee phenotype, not just royalactin.

Although royal jelly's exact chemical composition and its effects remain elusive, it has been the subject of many studies due to its intriguing properties.

When scientists fed Drosophila melanogaster, a species with a much less sophisticated social hierarchy royal jelly from honeybees, it also produced the same physiological changes found in queen honeybees, such as **increased body size** and **ovary development**. Other studies using *Caenorhabditis elegans* have shown that feeding royal jelly can **increase lifespan** and **tolerance to environmental stresses** by activating certain transcription factors. These effects have even been shown in mammal cells, with one study showing that the substance can prolong pluripotency in mouse embryonic cells. It is clear royal jelly has **potent regulatory effects** on evolutionarily conserved biochemical pathways.

There is still much to be discovered about the mechanisms of caste differentiation in honeybees. As the scientific literature continues to build, we can expect to see many more discoveries relating to the complex epigenetic workings of royal jelly and perhaps its applications in **ageing** and **stem cell research**. This topic is also a crucial reminder that biological systems are more often than not, far more intricate and multi-faceted than they appear and a nuanced understanding of the various interplaying factors is needed when discussing them.

From their epigenetic modifications on the atomic level to the elaborate societies they form, honeybees have proven to be a prime example of the fascinating complexity of the natural world.

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THREADING WATER

DNA is the New Flash Drive

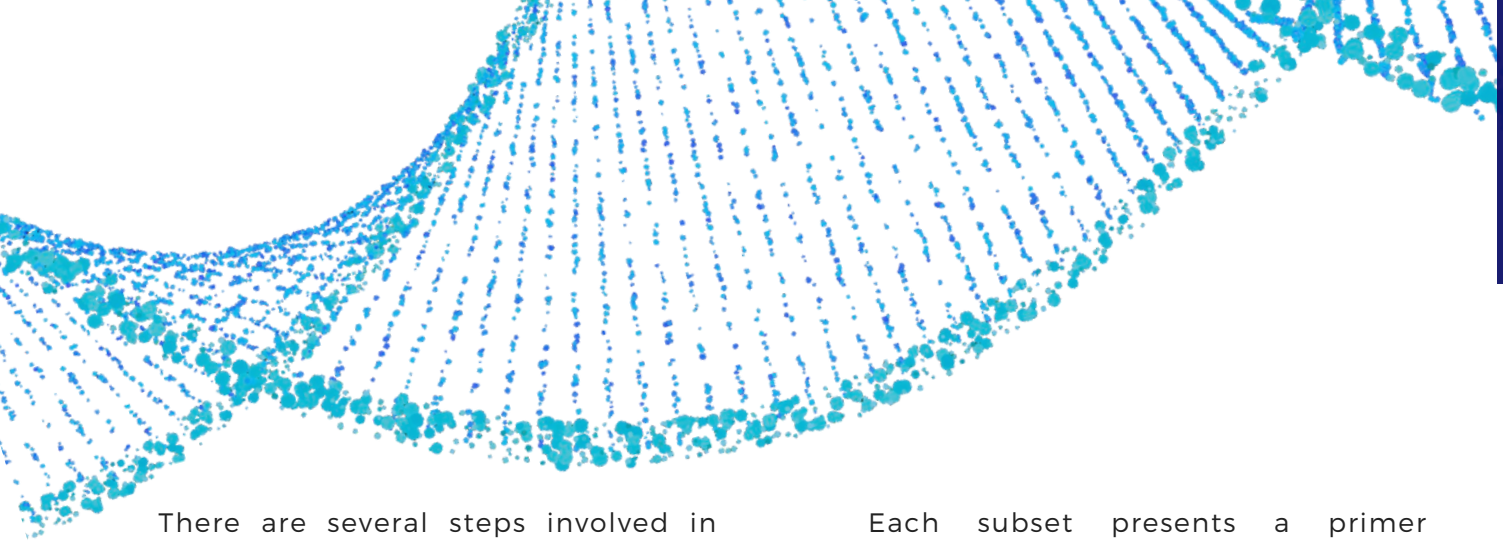
WRITTEN BY RAOUL PISCHEDDA
EDITED BY ANDREA MAZGALEVA
DESIGNED BY TAMARA YAP

They call it the "zettabyte era", a world dominated by its most valuable commodity: **data**. In a single day we collect data comprising more information than the entire recorded human history up to the 21st century: from demographic surveys to sophisticated machine learning algorithms, the applications seem endless. Data centres spanning multiple football fields bear the challenge of storing this growing swathe of knowledge, pushing the limits of modern technology. But we may only have to look inside of us to find a tried-and-tested solution to our storage issue.

Life as we know it is based on the preservation and propagation of information. This data is primarily preserved in our **DNA**. With over 3 billion base pairs making up our genome, all the instructions that build us can be contained in merely **5µm of a cell's nucleus**. Tempered by millions of **years of evolution**, DNA has been recognized as a potential data storage form of unparalleled efficiency/versatility.

Numerous are the challenges this unique molecule can overcome compared to mainstream forms of storage, such as magnetic hard drives and solid-state flash drives.

DNA can maintain its structure for thousands of years with minimal intervention: a dry and sterile environment is enough to prevent degradation by hydrolytic enzymes. Moreover, unlike obsolete media formats, the structure of the molecule is **constant** and **universal**, allowing future users to read it with any technology available. Another advantage is its ease of **replicability**, as making copies of itself constitutes the DNA's metier. However, it's most attractive feature is the sheer **density** of data it can encode. Given that 8 bits are required to code for a single letter on a computer, DNA's density has been estimated at 4.9 * 1020 B/g (bytes per gram), six times denser than the most efficient artificial device. A single gram of DNA could store more than 200 million gigabytes of data: that's 25 million movies or almost 40 billion pictures!



There are several steps involved in the creation and use of a DNA-based storage medium. The first one involves converting digital information, written at its most basic level in binary, into **base pair sequences**. Although various algorithms have been proposed for this purpose, one simple way is to proceed base by base: Adenine could read '00', Cytosine '01', Guanine '10' and Thymine '11'. The synthesis of oligonucleotides is achieved through ***phosphoramidite* building blocks**, that is nucleoside analogues added alongside reversible protective groups inhibiting the molecule's reactivity. Finally, **unique RNA primer binding sequences** are added to each fragment's ends. To retrieve a specific piece of the code, a **PCR** reaction is run to amplify the sequences of interest through the appropriate primers. These will then be sequenced and translated back into the original code.

While sequences encoding different files should vary enough to prevent cross-interaction, recent research has shown how **non-specific interactions** between a single primer and similar DNA molecules can be used to **preview data**. Each file is encoded in different subsets of a single strand, amounting to fractions of the file.

Each subset presents a primer binding site with various degrees of affinity: for example, one subset could be perfectly complementary to the primer, whilst another could have a few differing nucleotides. By manipulating thermodynamic parameters during PCR amplification, the specificity of the primer binding DNA can be regulated.

A higher annealing temperature and a lower concentration of the primer favour binding between sequences with the highest affinity. Lowering the temperature and increasing the amount of primer instead lead to 'promiscuous' binding. Thus, different resolutions of the file are read based on how many subsets of the same strand are amplified.

Costs associated with reading and writing DNA remain the limiting factors for its usage as a data storage. However, a growing interest in the field of genomics has led to developments in both sequencing and synthesis technologies, driving down costs and accelerating the collection of genetic information. The solution to the **zettabyte era dilemma** might depend on the inauguration of a genomic era of DNA manipulation: a solution based on life's oldest creation.

SHALLOW DIVE

Let's Get this **Ball** Rolling!

WRITTEN BY REBECCA HAMMERSLEY
EDITED BY DRSHIKA MEHTANI
DESIGNED BY TAMARA YAP

In the recent decades, with the constant progress of scientific research, ethics have been questioned for the use of embryonic stem cells. Many people believe that they are living and should not be experimented on in this way, but others can see the vital aspect they hold in modern day scientific research. But is there a way to satisfy both arguments? For this we will need to delve into the world of epigenetics.

In the world of epigenetics, **Waddington's landscape** is a very important concept. When the ball is at the top of the hill it can be rolled down into any of the valleys below, meaning it has the potential to become any cell; this is a pluripotent stem cell. As the ball rolls down the hill, the cell becomes more **specialised**. Sometimes this ball will stop in an indent mid-slope; this represents adult stem cells as they can specialise into other stem cells. However, unlike embryonic stem cells, they do not have the ability to differentiate into every cell possible. If the ball passes this point, the cell is fully specialised and cannot become another cell.

In summary, the positions of the divots in Waddington's landscape represents the potency of stem cells and the valley at the bottom represents a fully specialised cell.

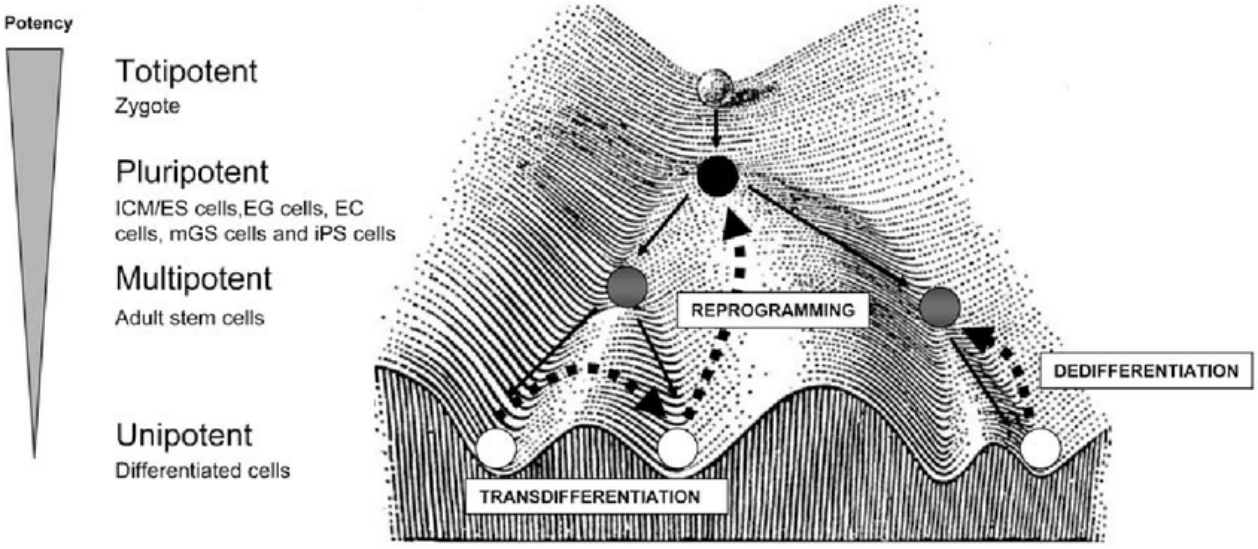
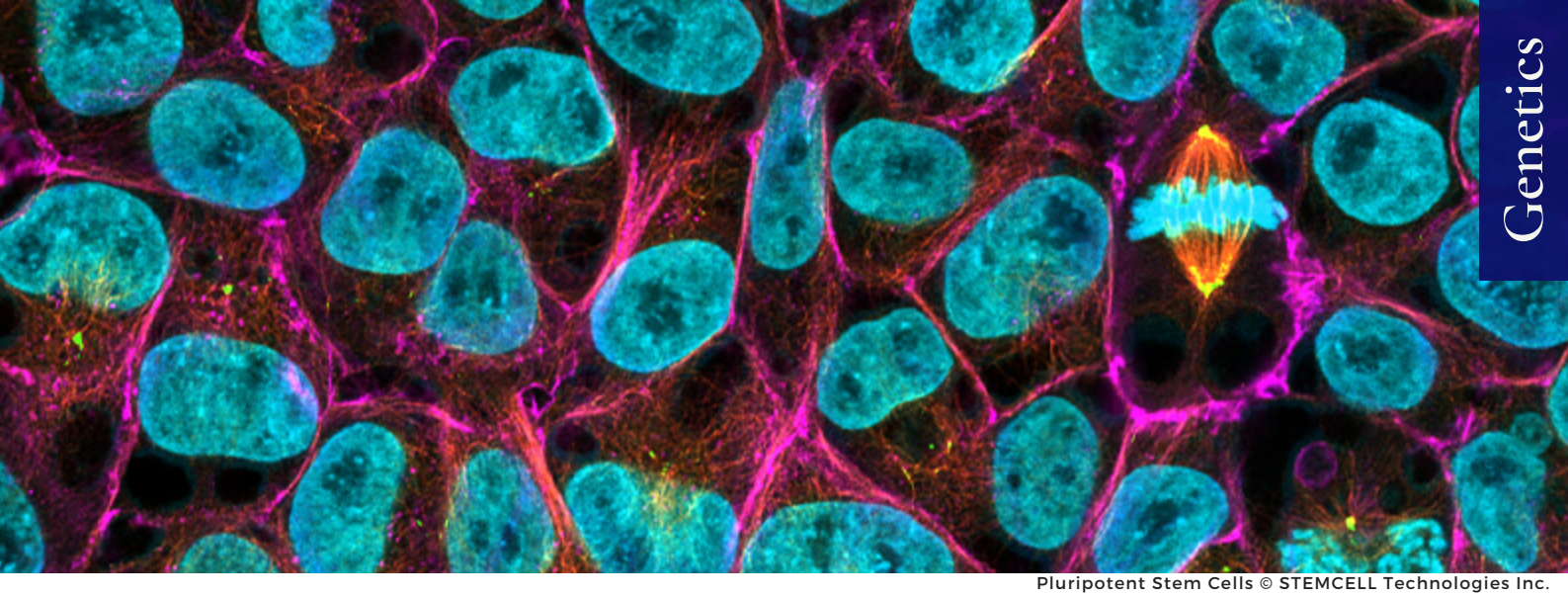


Figure 1. This image is an adaptation of Waddingtons original landscape, showing the stages a cell can go through on its descent down the valley.



Pluripotent Stem Cells © STEMCELL Technologies Inc.

So, is it possible to roll the ball back up the hill to a state of pluripotency? In 2006, Shinya Yamanaka and his research assistant Kazutoshi Takahashi answered this question. Yamanaka used the list of 24 already known genes to create the first **induced pluripotent stem cell (iPSC)**. These 24 genes are called the **pluripotent genes**, which means that the regulations of these genes keep an embryonic stem cell in a state of pluripotency. Through various experiments they managed to identify a combination of the four key genes that can make a fibroblast act as an embryonic stem cell. The genes were **oct4**, **sox2**, **klf4** and **c-Myc.** These were the specific genes that brought about induced pluripotency in stem cells.

So how can we use these today? iPSCs could **replace the use of embryonic stem cells** in modern research. In order to model disease more effectively, human stem cells are required. This is because they can be specialised into all types of human cells, meaning we can see the effect of the disease in question on different cells and thus model how it may affect the body. iPSCs can be used in this case as they are cells that can be reproduced and then specialised into the specific cells needed.

This reduces the task at hand as they do not have to collect multiple different tissue samples to gain the cells and neither do they have the ethical debate of using embryonic stem cells. iPSCs can also be very useful in **patient specific treatment** as specific cell types can be created that are genetically identical to the patient so that there is no form of rejection by the host.

The discovery of the iPSC changed medical research and still holds so much potential to revolutionise patient specific medication while simultaneously eradicating the use of embryonic stem cells, making it worth all the hassle to roll the ball uphill.

THREADING WATER

Closed-loop Neuromodulation: A New Approach to Treating Treatment-resistant Depression and Other Psychiatric Disorders

WRITTEN BY DRSHIKA MEHTANI
EDITED BY TRIPTI SINGH
DESIGNED BY CELESTE COCKMARTIN

Major depressive disorder (MDD) is a common disorder that has significant rates of treatment resistance. Deep brain stimulation (DBS) is a promising treatment for MDD but the individuals' heterogeneity in portraying MDD has resulted in inconsistent findings from clinical trials. Researchers at the University of California, San Francisco have now been able to successfully treat a patient with **severe** treatment-resistant depression using DBS. The study is a milestone in the long-time efforts to apply the advances in neuroscience to treat psychiatric disorders.

While open-loop DBS based therapy has shown therapeutic benefits in patients with Parkinson's disease and epilepsy, treating MDD requires a **personalized** approach due to individual differences in symptomatic neural circuits. For **open-loop therapy**, parameters such as amplitude, frequency and duty cycle are used to adjust the stimulation and deliver it at a scheduled time. Closed-loop systems on the other hand have a stimulation current that can change **automatically** according to the recorded brain pathological state. Fig. 1 compares a closed-loop system with an open-loop one.

Closed-loop neuromodulation can be personalized to selectively trigger stimulation only when a pathological state is detected. This approach is crucial when treating MDD because the pathological states that affect mood arise at **irregular** times.

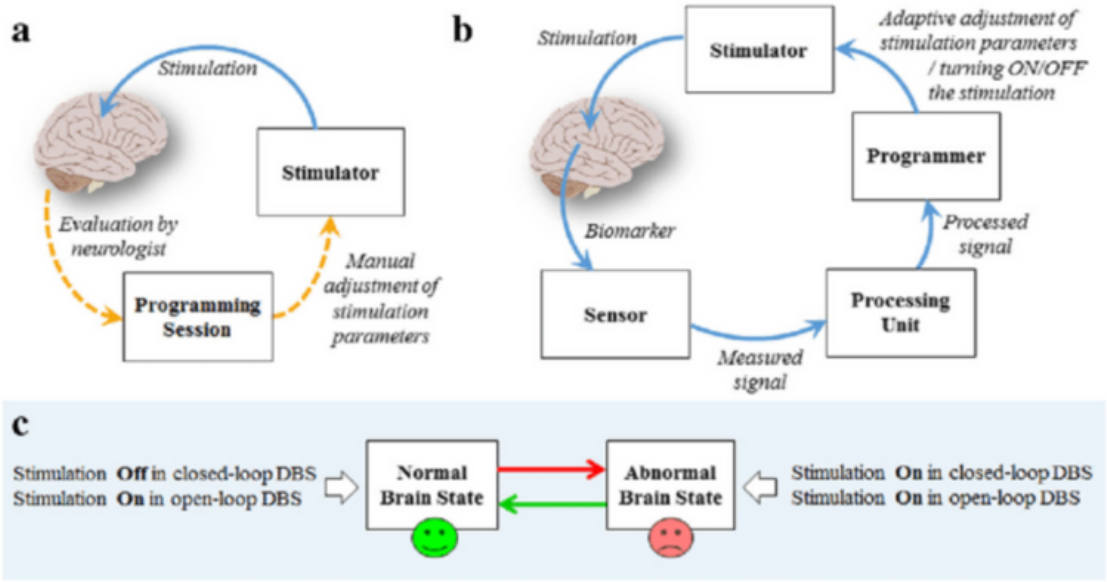


Figure 1. Schematic representation of an open-loop system and a closed-loop system.

It also relieves the problems of neural adaptation, reduces side effects, and preserves the battery life of the device so it **does not** need frequent replacement. For closed-loop therapy to function when a biomarker is detected, intracranial corticolimbic circuitry mapping was conducted to **map the patient's brain** and identify the neural biomarker.

It was found that the amygdala and hippocampus integrated signals from many brain regions and when the ventral capsule/ventral striatum was stimulated, the conjured response was **strongest** in the amygdala. Axonal tracts for this connectivity were then identified. Stimulation across these areas was then tested and once significant therapeutic potential was **identified**, a chronic brain implant was put in place. Fig. 2 shows a representation of the implanted DBS system.

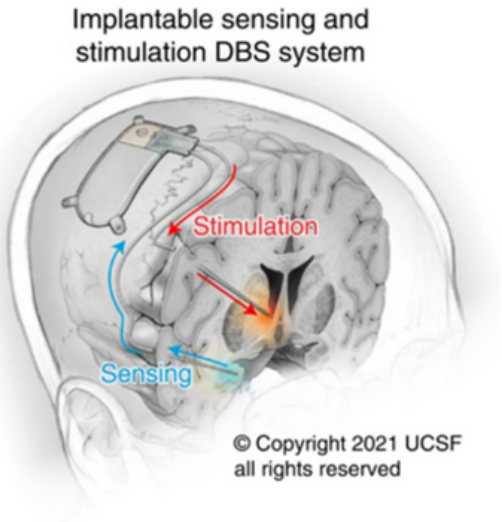


Figure 2. Fully implantable DBS system.

The implant was then used to record and study the **frequency** of occurrence of the pathological biomarker and the mood effects of the stimulation. It was found that 6 seconds of intermittent stimulation at 1 mA was clinically **effective**, and this was below the patient's perceptual threshold.

If the stimulation was increased to 2 mA or the contact leads were changed, the clinical response **worsened**. The therapy rapidly and effectively improved the severity of the symptoms and the patient's depression. The patient's Montgomery-Åsberg Depression Rating Scale (MADRS) score **dropped** from 33 before the trial to 14 after 12 days of stimulation. Furthermore, the score dropped to below 10 after several months of using the implant.

The first author of the paper, Katherine Scangos, said that "The effectiveness of this therapy showed that not only did we **identify the correct brain circuit** and biomarker, but we were able to replicate it at an entirely different, later phase in the trial using the implemented device.

This success in itself is an incredible advancement in our knowledge of the brain function that underlies mental illness." Although, the study does have **several** limitations. The DBS-based therapy was only performed on the right hemisphere while traditional therapies are performed **bilaterally**. This was done based on the biomarker present. Since the study involved a single participant, it cannot be evaluated whether the ventral capsule/ventral striatum-amygdala sub-circuit or the amygdala biomarker is **present** in all MDD patients and further research is required in this area. However, the study has provided valuable insight into the treatment of treatment-resistant MDD and the **future** of DBS based therapies.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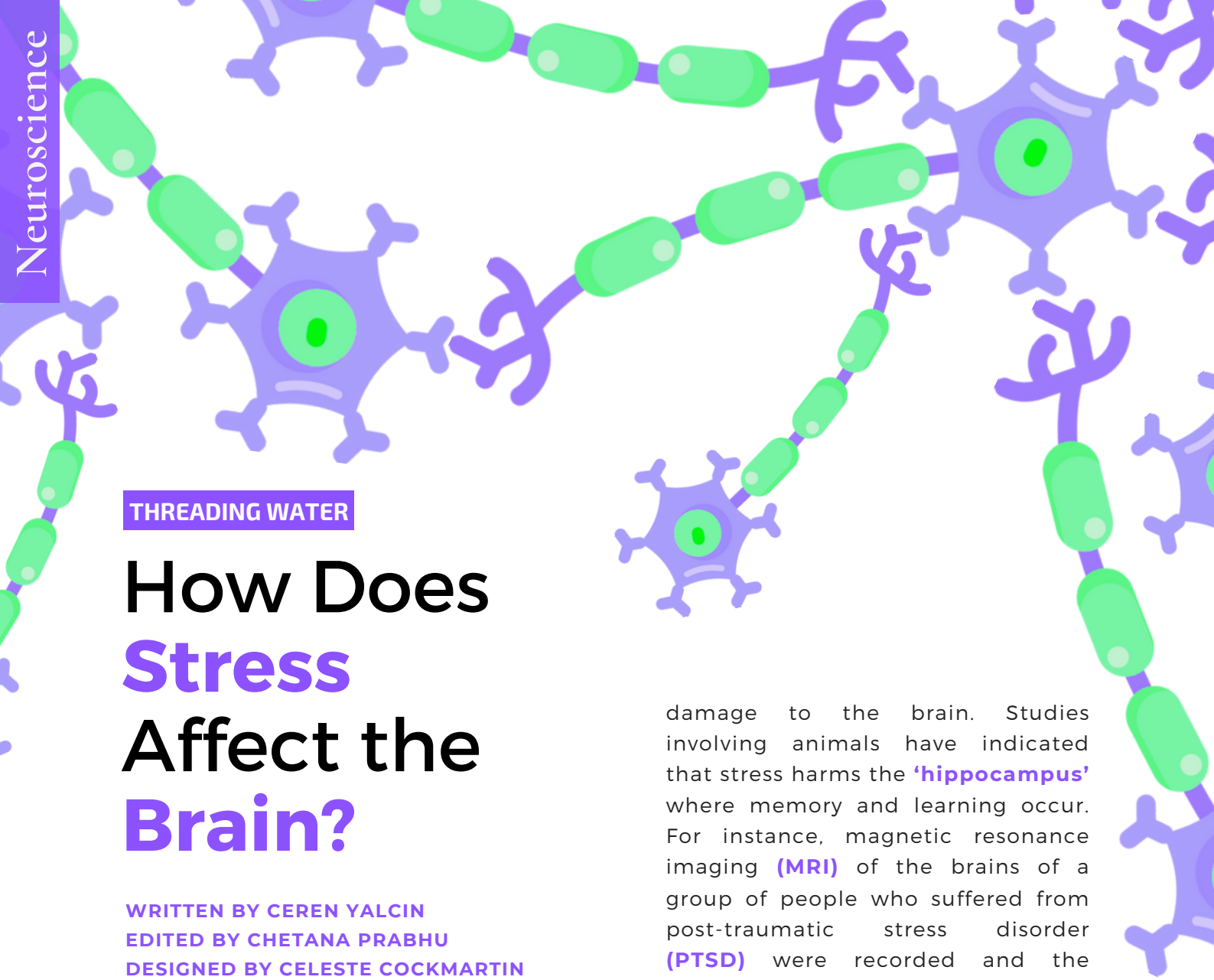

THREADING WATER

How Does Stress Affect the Brain?

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People from most age groups are constantly exposed to stress, making it a common state of mind stimulated by the environment. Stress leads to the body to form **psychological** and **physiological** responses such as anxiety, weakened immune system, rapid heart rate, and so on. In the short term, stress can also be a good tool to **enhance** motivation, maintain emotional well-being, and increase performance to the point where it's called 'eustress'. However, from a neurobiological aspect, prolonged stress actually cause damage to the brain. Studies involving animals have indicated that stress harms the **'hippocampus'** where memory and learning occur. For instance, magnetic resonance imaging **(MRI)** of the brains of a group of people who suffered from post-traumatic stress disorder **(PTSD)** were recorded and the images demonstrated a reduction in the volume of the hippocampus which was projected as impaired verbal memory and other brain dysfunctions.

In a study conducted at Max Planck Institute of Psychiatry, it was observed that the gene 'Drr1' was expressed in mice that were exposed to stress. **Drr1** was examined to cause neuronal projection to decrease, as well as eroding the capability of neurons to properly associate with each other which drew the conclusion of stress being able to **modify** the connections in the brain.

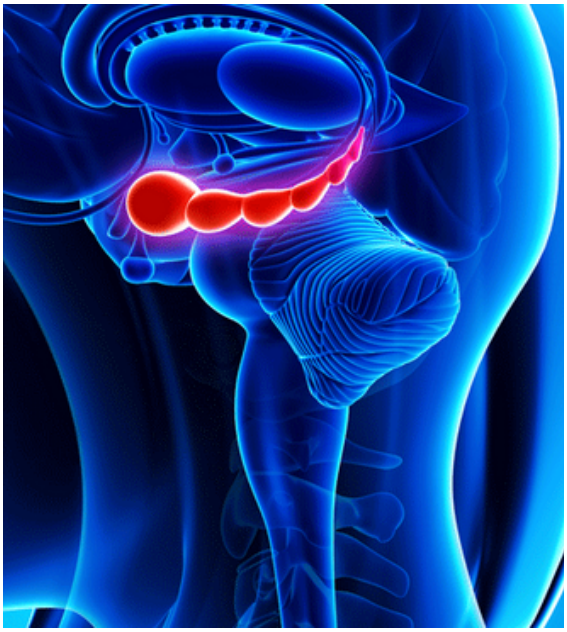

Figure 1. Hippocampus in the brain.

From a more specific point, in another research performed at the University of Pennsylvania, mice were engineered to **concentrate** β-amyloid proteins in their brains like the brains of patients with **Alzheimer's disease**.

Mice were then exposed to experience stress by being isolated within tubes. The β-amyloid **accumulation** in stressed mice brains was greater than the non-stressed mice brains. Stressed mice also ended up having impaired memory as well as **losing** brain tissue meaning that stress expedites neurodegeneration in Alzheimer's disease.

Consequently, stress has a significant impact on how the brain **maintains** its function. And it is crucial to keep up a good mental state and physical well-being to **reduce stress** to avoid the aforementioned harms. It is undeniable that we only have enough reasons to stress over, especially in these unusual pandemic days; however, it is always good to be on the **positive** side. Stay less-stressed!


REFERENCES:
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