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THIS ISSUE

Dear Reader,

Happy late St Patrick's Day! This month we've welcomed a number of new talented editors and media officers to our team and we're already impressed with how quickly they have adapted. For this month's issue, I'll be interviewing Dr Peter Giddings to give an insight into careers in patent law after working at GlaxoSmithKline (GSK) for 27 years before retiring. So for those interested in careers outside of academia, you can read our interview to see if the day to day life of a patent attorney sounds like something you'd like to do!

If this is your first time reading our magazine...
Science Mind is the award-nominated, student-led science magazine of King's College London, which focuses on reporting recent findings in the main branches of science to students and the wider community. We aim to showcase and develop the written and oral communication skills of students interested in research by concisely explaining complex scientific concepts in the form of lay articles and conducting interviews. Authors can also broaden their knowledge by writing articles for different sectors between issues.

If science communication is a concept that interests you, I encourage you to join the dynamic and constantly expanding team of ScienceMind. We would love to have you on our team!

Yours faithfully,

The Editor-in-Chief
The Founder

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THREADING WATER

THE SILENT KILLER

WRITTEN BY SEAN CRAWFORD
& AAIMAN BHARMAL
EDITED BY IRIS ZIELER

Cardiovascular disease remains the UKs second largest killer after dementia despite the emergence of COVID-19. In the UK, 160,000 people lose their life to cardiovascular disease every year. To some extent, cardiovascular disease is an inevitable part of ageing but current treatments can delay the progression of cardiovascular disease, as can adopting a healthier lifestyle.

What is cardiovascular disease?

Cardiovascular disease refers to the dysfunction of the circulatory system; it is a disease of the heart and blood vessels. Although the disease takes on many manifestations such as heart attacks, stroke and blood clots, the main pathology remains the stiffening and occlusion of the blood vessels. This is known as atherosclerosis, where fatty substances, such as cholesterol, become deposited in blood vessel walls. The result is that the blood vessels become inflamed, stiffen, and develop plaques that partially block the blood vessels. This process is mostly asymptomatic until significant damage of the blood vessels has already occured. This happens to everyone but our diet, physical activity, and genetic makeup determine the rate at which this process occurs. These dysfunctional, stiff arteries will often cause high blood pressure. When a person has high blood pressure the atherosclerotic plaques can rupture and completely block the blood vessels. This is a medical emergency starving the affected organ of vital oxygen and nutrients. A **heart attack** is when the plaque of a coronary artery ruptures and the blood supply to the heart muscle is cut off. Inadequate oxygen supply makes the heart prone to beat abnormally and the person can go into cardiac arrest, causing the heart to stop beating which often results in death. A **stroke** is when the blood vessels

supplying the brain become damaged due to cardiovascular disease. Obstruction or rupture of the vessels can occur and areas of the brain start to die. Most brain neurons cannot be replaced once lost, making stroke a significant cause of mortality but also the biggest cause of severe disability relating to physical mobility as well as the ability to communicate.

A glass of wine to keep the cardiologist away?

It has long been thought that drinking a glass of red wine is beneficial for the heart and wards off blood vessel dysfunction because grape skin is a source of **natural antioxidants.** Conventional wisdom would have the public believe that oxidants are bad and antioxidants are good. However, it is the controlled regulation of oxidation reactions in the body that is needed for healthy function and it is this regulation that certain 'antioxidants' found in red wine ensure.

A chemical called **resveratrol** is of particular interest in research identifying whether red wine is actually protective of the cardiovascular system. It is a so-called antioxidant but should more correctly be termed a regulator of oxidation processes. It has been found to increase the activity of protein kinase G, an enzyme responsible for relaxing smooth muscle lining the blood vessels. Relaxation helps to lower the pressure of blood inside the vessels and should help to prevent rupture of plaques leading to heart attack and stroke.

Resveratrol in red wine is in its antioxidant form. The molecule is thought to soak up potentially dangerous reactive oxygen molecules generated by inflammation but also from the diet and the environment and prevent them from causing the further development of inflamed, plague ridden arteries. When resveratrol has scavenged these reactive oxygen species it itself is converted to an oxidant. Resveratrol in its oxidant form is then able to oxidise protein kinase G in the artery smooth muscle, converting the enzyme to its more active form that acts to relax the artery walls and lower blood pressure.

Through this **mechanism**, resveratrol could be considered for its ability to prevent the formation and rupture of blood vessel plaques and the prevention of potentially fatal blood clots that lead to heart attack and stroke.

The experimental data in mice published by KCL scientists in 2017 showed that resveratrol could lower high blood pressure in hypertensive mice but had no effect on the blood pressure of mice which were not hypertensive. This is ideal as a clinically useful drug should preferably not cause hypotension as this would be associated with fainting and the possibility of serious head injury. However, concentrations of resveratrol equivalent to that found in about 100 bottles of wine would have to be consumed daily, so while the proof of concept is supported, it remains unlikely a single glass of red wine would have any significant effect on mortality from cardiovascular disease.

In fact, a Global Burden of Disease study in 2016 established that no consumption of alcohol is without an **increased risk of cancer**, leading to the conclusion that consumption of alcoholic drinks for marginal cardiovascular benefits are likely outweighed by the risk of carcinogenesis.

An analysis of human clinical trials of resveratrol in 2019 showed that the chemical only lowered high blood pressure in those who were also diabetic and this decrease was slight but significant (2mmHg). **Diabetes** is known to accelerate the process of plaque formation and blood vessel dysfunction. Resveratrol as a dietary supplement could prove to be a useful adjuvant therapy in diabetics who continue to struggle to regulate their blood sugar but this wine derived molecule is unlikely to revolutionise anti-hypertensive therapy as once thought.

The Use of Antiplatelets as preventive therapy for Cardiovascular disease!

High blood cholesterol often leads to atherosclerotic plaques caused by the aggregations of cholesterol and calcium. The plaques can form in the larger arteries of the heart and narrow their diameter. This reduces the amount of nutrients and oxygen received by the cardiac cells and can lead to acute coronary syndrome (ACS). This is an umbrella term for diseases such as angina, ischemia and ST segment elevation (can be observed on an ECG trace).

The severity of the problem increases when the plaque ruptures. This will lead to a condition called atherothrombosis. It is the uncontrolled formation of blood clot or thrombus inside the artery, blocking it completely. The rupture is seen as a vascular injury. Platelets stick to the site, change shape and release molecules such as Adenosine diphosphate (ADP), Thromboxane A2 and thrombin. These bind to other free circulating platelets and promote their aggregation. This aggregation can be prevented by using antiplatelet therapies, often using a combination of drugs. The combination reviewed here is that of Prasugrel and Aspirin.

Prasugrel is a third generation thienopyridine. Other similar drugs belonging to this class are Clopidogrel and Ticlopidine. These are prodrugs (inactive form of drug) which are readily absorbed in the small intestine and broken down by enzymes present in the blood plasma.

The process produces the active form of the medicine. After activation, the medication binds to P2Y12 receptors such that in the event of rupturing of the plaque, ADP cannot bind to P2Y12 receptors and therefore cannot cause platelets to aggregate. The process of absorption and metabolism is slow and this delays the process of P2Y12 blocking. Of the cohort, Prasugrel has the most rapid onset of action producing a peak concentration of the active metabolite within 30 minutes of administration. Post absorption through the digestive tract it is converted to an active metabolite by a two step pathway involving enzymes called carboxylesterases in the liver followed by conversion by cytochrome P450 found in the blood plasma.

Aspirin is usually given in combination with Prasugrel and it inhibits a different class of receptors called prostaglandins H-synthase-1 and 2 which are both enzymes. These have cyclo-oxygenase activity and Aspirin permanently blocks the COX channel by acetylating it. When aspirin is given in low doses it inhibits all COX-1 sites on the platelet and this is used in the prevention of ACS. High doses of aspirin are only used to treat hyperalgesia and inflammation and increase its toxic effects in the digestive tract. The factor thromboxane A2, which is derived mainly from COX-1 activity, is responsible for platelet aggregation, so blocking COX-1 activity with aspirin, prevents the release of thromboxane A2. This will avert platelet aggregation.

In addition to inhibiting COX-1 on platelets, aspirin also permanently inhibits COX-1 on megakaryocytes such that newly formed platelets are also unable to aggregate.

This dual therapy will prevent platelets to aggregate and hence prevent atherothrombosis.

It is also worth viewing the clinical pharmacology of the drugs which give important findings about the interactions of drugs with the body, and vise versa.

Since the genome of one individual differs from another slightly, genes encoding for these enzymes have also shown variations among individuals which can affect the ability of the enzymes to convert thienopyridines to their active metabolites. Overall due to conservation of genes, the extent to which Prasugrel is metabolised is not affected as compared to Clopidogrel which shows wide variability in effectiveness amongst patients. Treatment with Prasugrel has shown consistent responsiveness amongst patients. The extent to which Prasugrel asserts its protective effects is also dependent on the oral dose administered. Clinical trials have shown that a 60mg dose of Prasugrel resulted in inhibition of platelet aggregation up to 54% within 30 minutes. This indicates the high potency of Prasugrel in comparison to the 600mg dose of clopidogrel needed to reach 69% inhibition at 6 hours.

Another way to judge the effectiveness of Prasugrel is to measure the mean bleeding time (time until blood clot formation). This was done by animal experiments using rats. The rats were administered with a 3mg/kg dose of Prasugrel and after 4 hours, they were given general anaesthesia. Their Jugular and carotid blood vessels were cannulated with a tube containing a silk thread and the amount of platelet aggregation was weighed. It was found that the aggregation was 10% in the rats administered with Prasugrel as compared to the vehicle group at 45% at 8 hours post cannulation. This proved that prasugrel is an **effective antiplatelet therapy.**

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SHALLOW DIVE

The Widespread, and More Difficult to Target, Effects of Cardiovascular Drugs

WRITTEN BY DANIELIUS PAVILONIS
EDITED BY TAMAS BODO

A **drug** is defined as a chemically known substance that is neither a nutrient nor an essential dietary component, which is able to induce a biological response when administered. Cardiovascular drugs, evidently, affect the cardiovascular system and do so in **many ways.** Before considering the effects of cardiovascular drugs, and how many people are prescribed these without actually being diagnosed with heart problems, it is **important** to understand their mechanisms of action. Drugs may act on receptors, of which, there are many. Adrenoreceptors are G protein-coupled receptors that are the target of many catecholamines, such as noradrenaline. Adrenoreceptors include the following: **Alpha 1 receptors** are post-synaptic, and are found on vascular smooth muscle, whereas **alpha 2 receptors** are more widespread, found in the brain and in the periphery. The function of alpha 2 receptors is still not fully understood, though we know that they modulate sympathetic outflow in the brain stem. **Beta 1 receptors** are post synaptic, and found in the heart, and when stimulated through the sympathetic nervous system, increase both force of contraction and heart rate in order to maximise cardiac output. **Beta 2 receptors** are found in the bronchioles of the lungs and in the arteries of skeletal muscles, stimulation of these dilates the bronchioles and also dilates the arteries.

Drugs target these receptors, as well as affect the synthesis, storage and release of catecholamines in presynaptic neurones. It is important to consider that a drug that affects one beta 2 receptor, will **affect all** beta 2 receptors, which are found in arteries that deliver vital substances across the whole body. With that in mind, a prescribed cardiovascular drug will have impacts across the **whole body**, resulting in the many side effects. These side effects may be drastic enough that the drug could be prescribed for the sole purpose of a side effect.

An example of such a drug and its mechanism of action is **Propranolol**. This is a **beta- blocker**, which is also known as a beta adrenoreceptor antagonist. It **decreases** heart rate, force of contraction, conduction velocity and relaxation rate. This is achieved by **preventing** catecholamines such as adrenaline binding to the receptors. Although it can be used to treat patients with **tachycardia** (an irregular, increased resting heart rate), its widespread effects allow it to be possibly prescribed as an **anti-depressant**.

Symptoms of anxiety include an **increased** heart rate, shaking of the hands, dizziness and sweating. The use of beta-blockers allows us to **control** the physical symptoms of anxiety and depression, these drugs also happen to be used in treating cardiovascular disorders. This outlines how cardiovascular changes can have **widespread impacts**, and how many of the drugs prescribed in everyday life may not actually be used for their intended purposes, demonstrating the **true complexity** of cardiovascular pharmacology.

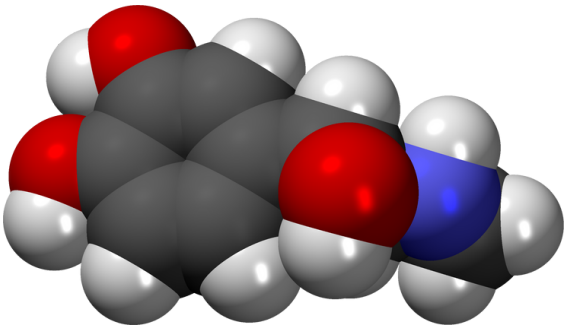

Figure 2. An adrenaline molecule.

About the Author

Danielius Pavilonis is a 1st year neuroscience student, interested in the study of neurodegenerative disorders.

About the Editor

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THREADING WATER

The Mechanism of Action and Therapeutic Potential of Psilocybin

WRITTEN BY HELENA BRADBURY
EDITED BY CONSTANCE PAYAN D'AGOSTO

Psilocybin is a psychoactive **pro-drug** as well as the main hallucinogenic component found in over 100 species of **psychedelic mushrooms** worldwide. Originally isolated from the mushroom **P.mexicana** by Swiss chemist Albert Hofmann and his colleagues in 1959, Psilocybin has gained considerable recognition within the research community and was used in conjunction with **psychotherapy**. However, in 1970, Psilocybin alongside other hallucinogenic drugs such as **LSD and ecstasy**, was classed as a Schedule 1 drug, carrying a high abuse risk and its therapeutic prescription stopped.

Whilst the precise **mechanism** of psychedelic-induced hallucinations is unknown, it has been theorised that stimulation of **serotine 5HT2AR receptors** causes hyperactivation of the cortical neurons within the cerebral cortex. This mechanism induces the drug's characteristic euphoric sensation and time distortion. This article will outline Psilocybin's **signalling pathway** alongside its therapeutic effects for the treatment of depression, anxiety, and OCD.

Once ingested, Psilocybin is distributed to every tissue including the brain. Psilocybin is termed as a 'pro-drug' as it only elicits **psychoactive** properties once metabolised to its active form Psilocin. This conversion is achieved by the **dephosphorylation** of Psilocybin in the mucosal layer of the ileum by alkaline phosphatase and esterase enzymes, thus making Psilocin more lipid-soluble with the removal of the highly hydrophobic phosphate group. This initial step is vital as the **increased lipid solubility** of Psilocin allows it to cross the blood-brain barrier, triggering a response. Additionally, accumulating evidence suggests Psilocin as an agonist has a **higher affinity** than Psilocybin to the target serotine receptors (5-HT2A, 5-HT1A, 5-HT2C) located in the thalamus and cerebral cortex. It is suggested that **overactivation** of these serotine receptors also disrupts the cortico-striato-thalamo-cortical pathway (CSTC); a circuit within the brain linking the cortex, basal ganglia, and thalamus, controlling movement and behaviour. Upon oral administration, the effects of Psilocybin typically last **2 to 6 hours.** However, this can vary depending on the dosage taken, species of mushroom, and the individuals' physiology and tolerance. The subsequent Pharmacokinetics and **metabolism** of Psilocybin occur predominantly in the liver; Monoamine oxidase breaks down Psilocin to several metabolites; 4-hydroxylindole-3-acetaldehyde, 4-hydroxytryptophol, and 4-hydroxyindole-3-acetic acid that are carried in the **blood plasma** to the kidneys. Psilocin additionally undergoes glucuronidation, a metabolic pathway used to excrete toxic substances, whereby glucuronic acid binds to Psilocin substrate via a glycosidic bond. Glucuronosyltransferase enzymes then catalyse the formation of psilocin-O-glucuronide which is excreted in the urine.

Many **conventional treatments** for depression are based on the theory that it is caused by a deficiency in monoamine neurotransmitters such as serotine, noradrenaline, and dopamine. Medications like antidepressants inhibit neurotransmitters reuptake, thus prolonging their effects and enhancing mood. However, those medications can also cause adverse effects such as sexual dysfunction and **weight gain**. In a double-blind, placebo-controlled study, 29 patients with cancer-related anxiety or depression received a single dose of psilocybin.

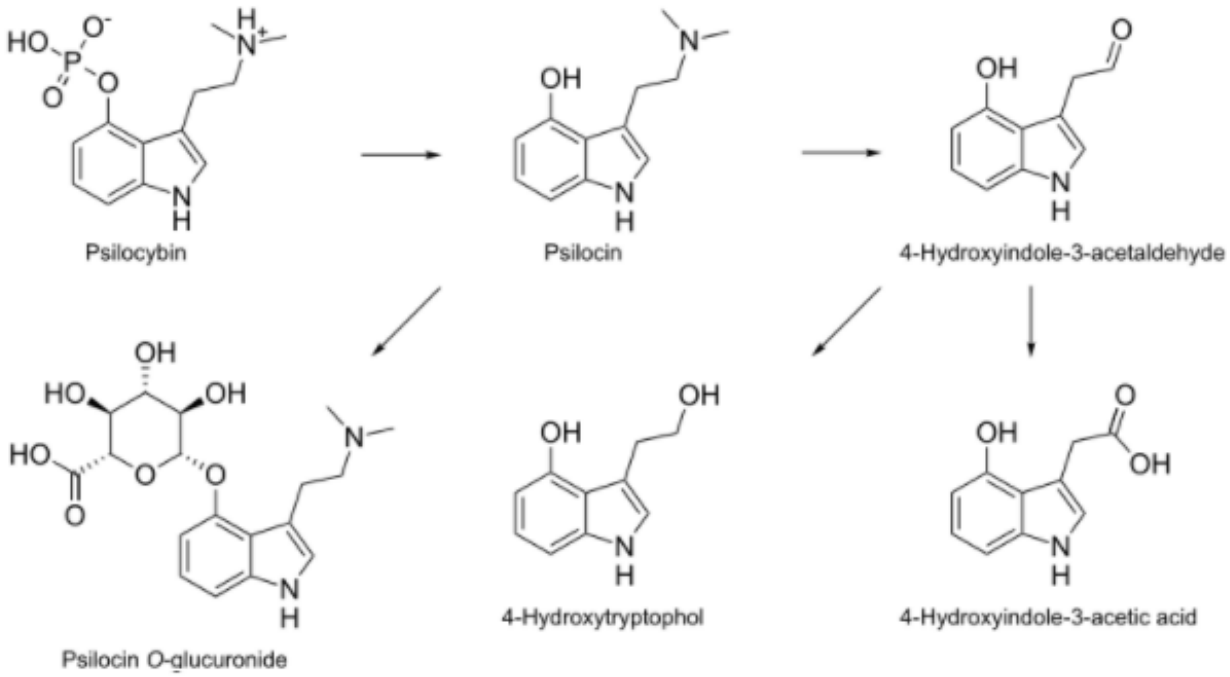

Figure 1. A schematic outlining the conversion of Psilocybin to Psilocin to its metabolites 4-hydroxylindole-3-acetaldehyde, 4-hydroxytryptophol and 4-hydroxyindole-3-acetic acid.

Results showed an immediate significant improvement in mood and overall wellbeing that was sustained at the 6.5-month follow-up. Approximately **60-80%** of participants also reported continual reductions in anxiety after long-term use. Similarly, a study involving 9 patients with OCD showed a **25%** decrease of symptoms after receiving Psilocybin, which was maintained for **66.7%** of participants after 24 hours.

Whilst Psilocybin exhibits promising benefits with limited safety concerns, further experimentation of larger-scale studies is required to fully understand the drug in a therapeutic setting. However, based on this data it serves as a compelling argument to question why Psychedelic drugs are not taken more seriously and are instead **stigmatised.**

About the Author

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DEEP DIVE

INVESTIGATING CAFFEINE AS A TREATMENT FOR PARKINSON'S DISEASE

WRITTEN BY CHARLINE HENDRICKX | EDITED BY AMINA IGENBEK

Parkinson's Disease (PD) is an incapacitating, **neurodegenerative** condition that causes tremor, postural instability, muscle stiffness, bradykinesia, and akinesia. Other symptoms include anxiety, sleep disruption, dementia, psychosis, and reduced cognition, making daily life extremely difficult for those who suffer from it. These symptoms occur due to a **progressive degeneration** of dopaminergic neurons in the substantia nigra pars compacta and corpus striatum with the manifestation of aggregated a-synuclein proteins in neuronal cells known as **Lewy bodies**. There are currently **no disease modifying treatments** and the treatments available are symptomatic.

In the early 2000s, evidence emerged displaying the inverse relationship between **caffeine** and the risk of developing PD. It was shown that coffee drinkers were **5 times less likely** to develop it compared to non-coffee drinkers. Caffeine therefore attracted attention as a potential neuroprotective treatment for Parkinson's disease. A large study from the Honolulu Heart Program was the first to show evidence of caffeine's role in reducing the risk of developing the disease. It demonstrated that the risk of developing PD was decreased fivefold in people who consumed coffee daily as opposed to non-coffee drinkers. Numerous **follow-up studies** further confirmed the inverse correlation between the consumption of caffeine and the onset of Parkinson's. The beneficial effects were confirmed to be due to caffeine as these results were not observed in people that consumed **decaffeinated coffee.**

In order to understand caffeine's protective role, its effects were investigated at a molecular level. Caffeine holds its benefits due to its antioxidant and neuroprotective ability. In PD, the monoamine oxidase B (**MAO-B**) enzyme, which catalyses the oxidation of dopamine to generate hydrogen peroxide (**H2O2**), a reactive oxygen species, is known to be overactive. Caffeine inhibits MAO-B, thus preventing the increased oxidative stress caused by the over production of H2O2.

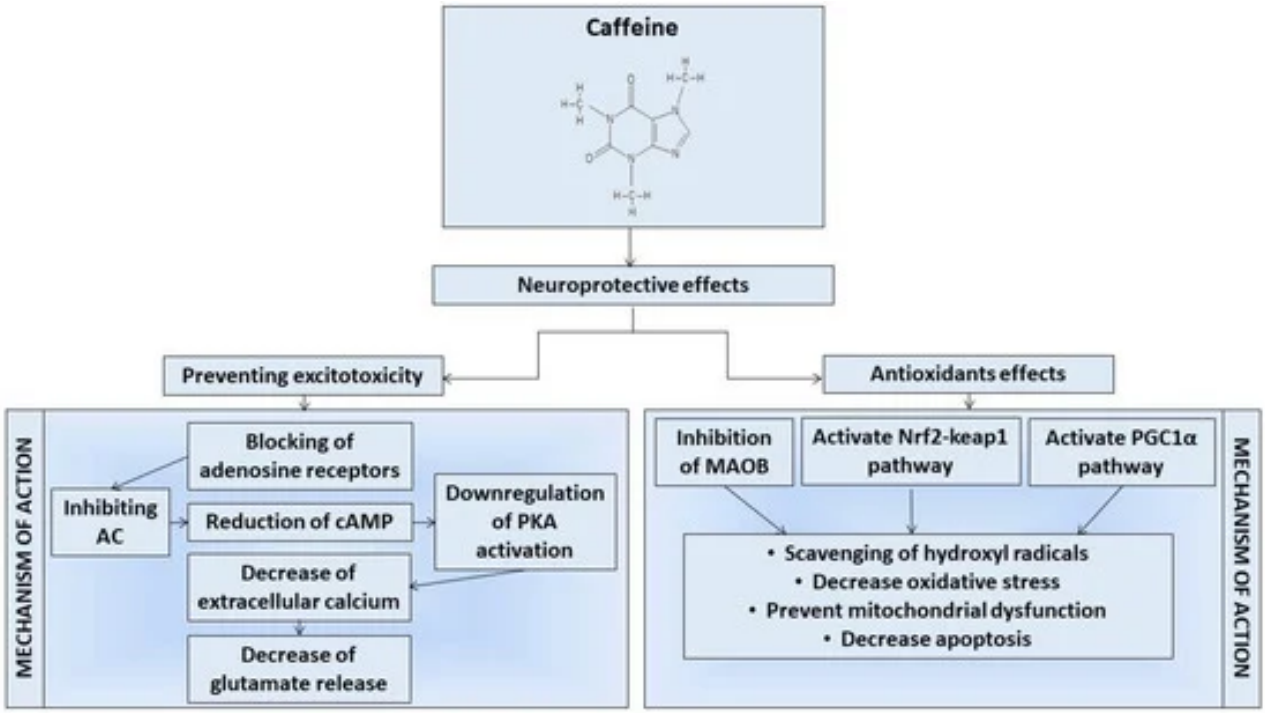

Figure 1. Caffeine's effects at the molecular level; how it exerts neuroprotective effects through antioxidative abilities and preventing excitotoxicity.

It also holds its antioxidant effects by its ability to activate anti-oxidative and anti-inflammatory signalling pathways. Meanwhile, its action on GABA receptors, regulation of intracellular calcium, and promotion of the inhibition of phosphodiesterase (**PDE**) and adenosine receptors (AR) allows for its neuroprotective characteristics (see figure).

Many studies have been conducted in animal models of PD such as the 6-OHDA lesioned and MPTP-treated rats to further test caffeine's beneficial effect and all showed promising results. Caffeine treatment led to a reduction in motor deficits and **increased dopamine** and monoamine levels. Studies showed that caffeine's neuroprotective effects and ability to prevent the aggregation of a-synuclein, a hallmark of PD, was due to its **antagonism** at the adenosine 2A receptor (A2AR). The antagonism of A2AR was shown not to cause **dyskinesia** which occurs with the current L-DOPA treatment. Studies have also shown encouraging results with a combined caffeine and L-DOPA administration to reduce the **levodopa-induced dyskinesia** (LID). It has therefore been proposed that blockade at this receptor could help prevent LID.

Unfortunately, clinical trials yielded poor results demonstrating that caffeine cannot be used as a treatment for Parkinson's as it did not provide **motor improvements**. Nevertheless, there is still clear evidence that caffeine does have neuroprotective effects and thus can reduce the risk of developing PD. Overall, caffeine does indeed have beneficial effects against Parkinson's disease before its onset but is not effective enough as a treatment.

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DEEP DIVE

CAN E-CIGARETTES REINFORCE NICOTINE ABUSE?

WRITTEN BY ZAHRAA BHATTI | EDITED BY FATIMAH PATEL

E cigarettes are smoking cessation tools that were introduced in the early 21st century and have currently soared their way up in the market. A survey from 2017 showed that approximately **8 million** Europeans regularly used e-cigarettes, and there are now over **15,000 e-cigarettes** flavours ranging from 'crazy berry' to 'tropical blue slushie'. Although e-cigarettes are not harmful, the appealing flavours cause nicotine to be more rewarding and addictive, thus altering the nicotine **reinforcement**.

Effects of e-cigarettes are population demographic

Men are more likely to consume e-cigarettes than females, but females are more drawn to the attractive flavours and packaging. According to one survey, the inclusion of "appealing flavours" was stated by **89.23%** of women as a justification for using e-cigarettes, compared to **74%** of males. Females are more vulnerable to the sensory aspects of cigarette smoking instead of the pharmacological effects of nicotine. Males, on the other hand, are more likely to consume higher nicotine doses, **regardless of the flavour**.

Supporting this, an animal study by Avelar et al found that male mice, rather than than female mice, were prone to the nicotine reward-enhancing effect of **farnesol**, an organic compound used to improve the odor in green-apple flavouring. Days after the male mice were treated with farnesol, they displayed more dopaminergic firing in the ventral tegmental area due to the **decrease of GABAergic** firing on inhibitory interneurons, compared to their female counterparts. However, more research is needed to support the hypothesis of sex differences.

Adolescents consume more flavoured e-cigarettes (**63-66%**) compared to tobacco-flavoured cigarettes (**4.8-5.1%**). fMRI scans have shown greater activity of the nucleus accumbens (NAc) when college students watched an advertisement for flavoured e-cigarettes as opposed to tobacco flavoured e-cigarettes.The variety of different flavours are becoming increasingly popular, encouraging more young adults to consume e-cigarettes. The **enhanced NAc activity** was positively correlated with decreased memory for health warnings on advertisements for sweet-flavored products.

This implies that the characterisation of e-cigarettes as having 'fun flavours' can reduce young people's perceptions of harm. A theory has been proposed that young adults who consume flavoured e-cigarettes may associate nicotine to being pleasurable. Subsequently, they're more likely to smoke regularly. However, the role of flavoured e-cigarettes in the ability to cause progression to combustible cigarettes is still unclear.

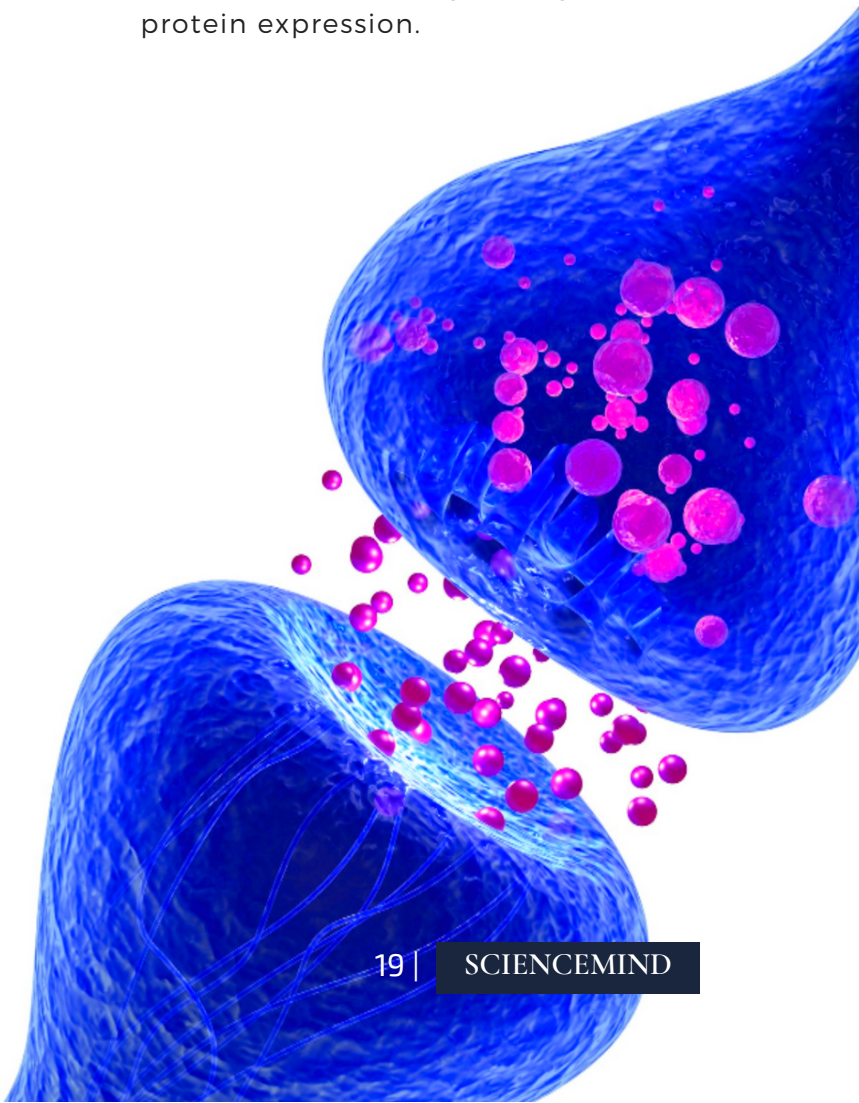
E-cigarette's flavouring can affect the nicotine reward and reinforcement

It's apparent that flavoured e-cigarettes appear to be rewarding, even in absence of nicotine. Supporting this, up to **60%** of young adults only vape for its flavour. If characterised flavouring has its own reward, it could potentially interact with the nicotine reward to further reinforce **vaping**, and, as a result, increase nicotine consumption. A clinical study assessed the reinforcement of flavoured e-cigarettes, and found that participants performed **4x harder** to receive puffs from their chosen flavoured e-cigarette than puffs from an unflavored e-cigarette. 'Sweetness' seems to be enhancing nicotine reinforcement the most, as **sucrose and saccharin** resulted in high dopamine release in the NAc. This enhancing effect is only achieved at low doses of nicotine. The leftward shift of the **drug-response** curve provides an explanation of the presence of reward at lower concentration of nicotine.

Nonetheless, it's necessary to understand that age can contribute to reinforcement, so the reward effect is subjective.

Pharmacological effects of flavoured e-cigarettes

Vanillin is one of the most common e-cigarette flavour volatiles. This organic compound increases cellular activity and **downstream signaling** by activating phospholipase C and releasing calcium ions from the endoplasmic reticulum. Vanillin also inhibits **monoamine oxidase** (MAO), an enzyme which breaks down monoamine neurotransmitters such as dopamine. By inhibiting MAO, dopamine remains active in the synapse, which increases nicotine reward. **Linalool** is another common volatile in e-cigarettes. It is an anxiolytic drug, which prevents stress-induced changes in gene and protein expression.



Linalool alters the activity of cytochrome P450 enzymes so that it can no longer metabolise nicotine, thereby increasing nicotine concentration. Other components of flavoured e-cigarettes include ethyl butyrate, ethyl acetate and ethyl maltol. Although these chemicals can alter the pharmacology, it's unknown if the concentrations are high enough to produce a **significant** effect.

Flavour depends on the stimulation of chemosensory nerve endings in the mouth, nose, and airways, which incorporates tactile sensations into **taste perception.** Whilst nicotine is the primary reinforcer in cigarette smoking, the sensory component of smoking is also important for nicotine addiction.

Supporting this, participants from a study gained more pleasure from smoking a **denicotinized cigarette** than from receiving nicotine intravenously. Therefore, blocking the sensory experience significantly reduces the satisfaction of smoking. The ratio and concentration of the e-cigarette flavour volatiles, determine the sweetness and sensory experience, thus can alter the neuropharmacological effects.

There are limited studies analysing the **pharmacokinetics effects**, but one study indicates that flavoured e-cigarettes can increase nicotine absorption. Strawberry flavoured liquids are more acidic (pH = 8.29) than tobacco-flavours (pH = 9.10). This increase of acidity elevates the rate of **nicotine absorption** as well as the subject's heart rate. Acidic vapor is absorbed more rapidly into the blood than **basic vapors**, due to the structural complexity of the alveoli. As a result, the maximum concentration is reached at an earlier time.

Overall, flavoured e-cigarettes are skyrocketing in the market due to its appealing sensory experience. However, there's a rising concern that this pleasant experience can be associated with smoking regularly during their **adulthood**. The risk of e-cigarette consumption by young adults needs to be addressed alongside the benefits it has on adults to quit smoking.

It's still unclear how potent the volatiles are, so more research is needed to achieve a greater understanding of the effects of the chemical composition of the e-cigarette vapes. There are a range of **mechanisms**, such are sensory stimulation which contribute to pharmacokinetics and neuropharmacology. By studying these mechanisms, nicotine abuse can be better understood.

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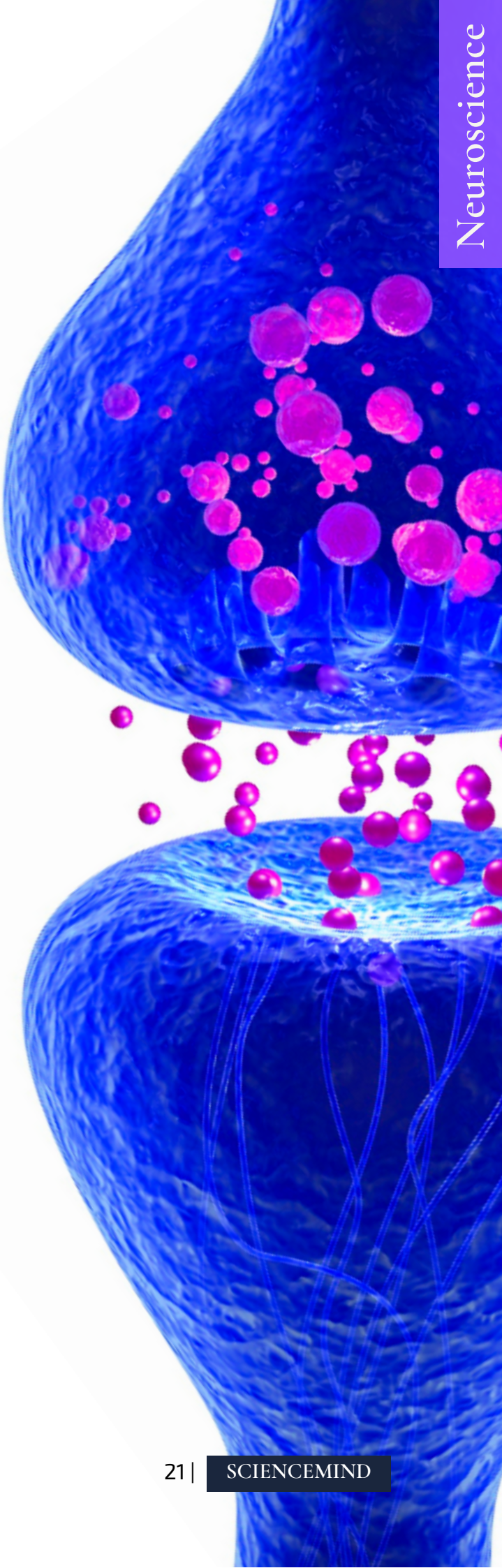
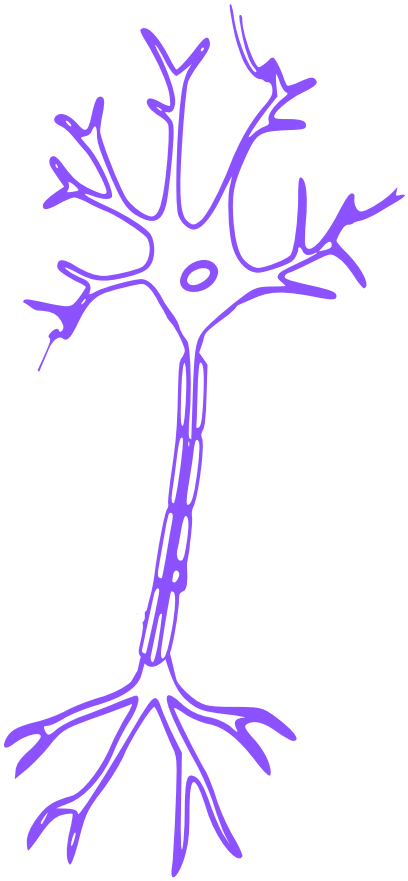


DEEP DIVE

COULD TARGETING FIBROBLAST GROWTH FACTOR 21 TREAT PARKINSON'S DISEASE?

WRITTEN BY JAMILA CHOUDHURY
EDITED BY MAHIMA KOTECHA



What is Parkinson's Disease?

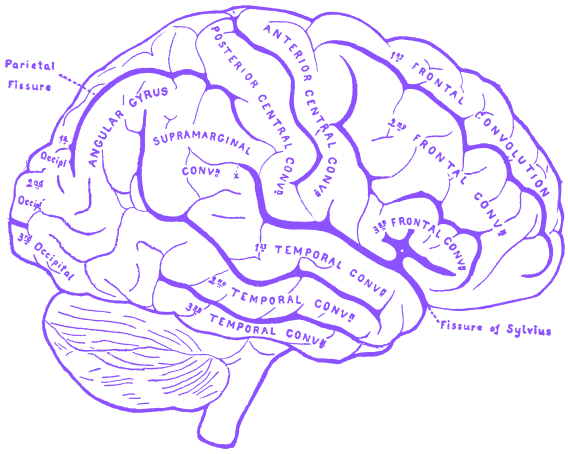
Parkinson's Disease is a commonly known age-related neurodegenerative disorder that worsens with time. It is characterised by the degeneration of dopaminergic neurons in the **substantia nigra pars compacta** (SNpc) and the accumulation of misfolded alpha-synuclein in **Lewy Bodies**, which are found in many regions of the brain. Current therapies such as Levodopa focus on symptomatic relief, for example, alleviating symptoms such as tremors and stiffness, but fail to prevent further **neurodegeneration** of **dopaminergic** neurons. Therefore, new therapeutic targets and drugs are being sought to stop the progression of PD. For example, neurotrophic factors are being investigated in connection with neurodegenerative diseases. They play an important role in the survival, maintenance, and regeneration of neurons. The levels of certain **neurotrophic factors** and their receptors appear to be altered in neurodegenerative diseases. These factors are believed to prevent cell death in degenerative processes and promote both the **growth** and **function** of the affected neurons in neurodegenerative disorders. (Connor and Dragunow, 1998; Sullivan and O'Keeffe, 2016).

Fibroblast Growth Factor 21

One neurotrophic factor is Fibroblast Growth Factor 21 (**FGF21**). This one endocrine hormone plays several roles in metabolism and is highly synthesised in the **liver** and other regions, namely the midbrain, which contains the dopaminergic neurons that degenerate in Parkinson's Disease (Mäkelä et al., 2014). Its **receptors** are widespread in the central nervous system (CNS).

A key receptor located in the brain is the **co-receptor β-klotho**. The co-receptor lacks the heparin-binding domain, which means that FGF21 has a low heparin-binding affinity (Kakoty et al., 2020). It is therefore able to cross the **blood-brain barrier** (BBB) to reach the brain directly by simple diffusion. For these reasons, FGF21 synthesised peripherally or centrally could potentially play a role in the CNS.

Studies suggest that this factor may be a potential candidate for **neuroprotection** in Parkinson's. Recent data has shown that FGF21 treatment had beneficial effects in PD model mice, for example, an improvement in **motor behaviour** and a reduction in the loss of tyrosine hydroxylase, a marker for dopaminergic neurons in both the SNpc and striatum regions of the brain (Fang et al., 2020). In addition, FGF21 treatment has been shown to significantly reduce dopaminergic **neuron loss** and **alpha-synuclein abnormalities** in PD model mice (Chen et al., 2020).



Although these preclinical models have demonstrated the therapeutic potential of FGF21, their effectiveness in clinical trials remains to be confirmed (Pramanik et al., 2016; Sullivan and O'Keeffe, 2016). The **mechanism** of action and the specific role of FGF21 in relation to PD will need further clarification.

Previous growth factor clinical trials have proven problematic owing to the difficulty of targeting delivery of the **exogenous growth factor** where it is needed. While this might be less of a problem if FGF21 is indeed able to cross BBB in humans, the approach taken in this project sets out to bypass the need for using FGF21 itself.

This project will be completed at the end of April. The aim is to identify **drug candidates** with the potential to increase endogenous FGF21 levels in the brain, in the hope of potentially slowing or stopping PD progression. The strategy that will be used is called **targeted repositioning**, a process that identifies new therapeutic applications for existing FDA-approved drugs.

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THIS ARTICLE IS BASED ON JAMILA'S FINAL YEAR BSC RESEARCH PROJECT WITH DR SUSAN DUTY.

TO FIND OUT MORE, CHECK OUT OUR OCTOBER 2020 INTERVIEW WITH DR SUSAN DUTY.

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ScienceMind

INFLUENCE OF CIRCADIAN RHYTHM OVER GLUCOSE METABOLISM

WRITTEN BY CHETANA PRABHU
EDITED BY JABARI LAMBERT

Circadian rhythm originates from Latin – circa diem meaning about a day. It is a part of the body's internal clock that helps in regulating various essential functions and processes which repeats approximately every 24 hours, in accordance with the Earth's rotation. This **rhythm** ensures that the body's functions are optimised at various points during the day. It was discovered that in animals active during the day (**diurnal**) and at night (**nocturnal**), who were kept in total and constant darkness displayed a 24-hour regularity in behaviour and physiology. Unlike metabolic rhythms that depend on the fasting-feeding cycles and temperatures, and other bodily functions that do not show a 24-hour cycle, circadian rhythm shows a constant 24-hour cycle. The **sleep-wake cycle** is important for maintaining the circadian rhythm.

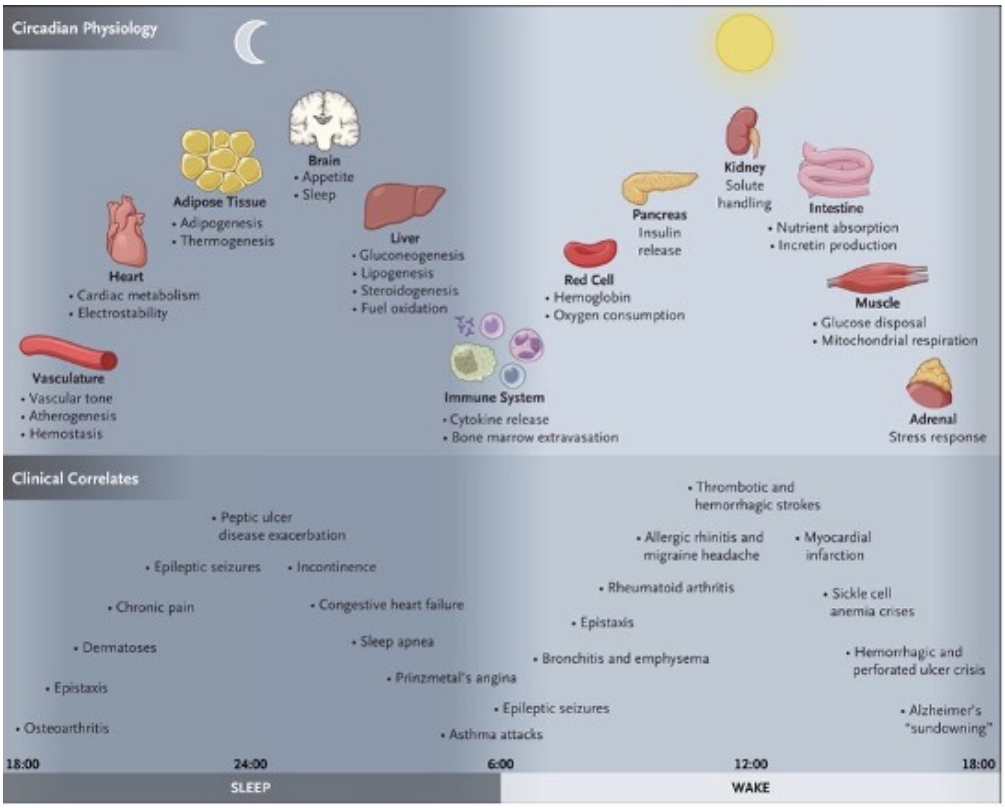

Figure 1. The circadian physiology and its clinical correlates

PACEMAKER NEURONS- MASTER NODE OF THE CIRCADIAN CYCLE

These neurons are the master node in the network of **internal clocks- circadian clocks**. They drive the sleep-wake rhythms and coordinate the peripheral tissue clocks. Present in the **SCN** (hypothalamic suprachiasmatic nucleus), these neurons exhibit large day and night variations in their spontaneous firing rates and resting membrane potentials (**-60mV**). The suitable activity of sodium and potassium currents allow the necessary exhibitory and inhibitory drives for **activity rhythms**. Specialised retinal ganglion cells, rod and cone photoreceptors that express a photopigment called **Melanopsin** which senses light and relays said information to the SCN clocks. Pacemaker neurons regulate various **physiological processes** such as the feeding time, temperature, sleep, mood and movement.

HOW DOES THE CIRCADIAN CLOCK "TICK"?

Understanding circuitry of the circadian clock was made possible by the discovery of the genes Period (Per) in **Drosophila melanogaster.** The Per gene controls the repression of its own transcription by oscillating the level of its product PER during **different** points of the day, which then results in a daily Per rhythm. Increasing the level of PER inhibits the transcription of Per gene, lowering the PER level. Subsequently, the Per activator was discovered in mammals and was named **Clock**.

This clock gene can thus induce its own repression by forming a negative feedback loop just like the Per gene in **drosophila**. The timing of the feedback loop is controlled by the post-transcriptional and especially post translational **modifications**. The activators such as PAS (Per-Arnt-Sim) and BMAL1 (brain and muscle Arnt protein 1) bind to core repressors Period (Per1, Per2 or Per3) or Cryptochrome (Cry1 or Cry2) in mammals which dimerize and provide the **negative feedback** to control their own transcription.

Disruption in this core Clock activity has shown that the rhythmicity of the physiological processes arises from the **oscillating** gene expression of Clock.

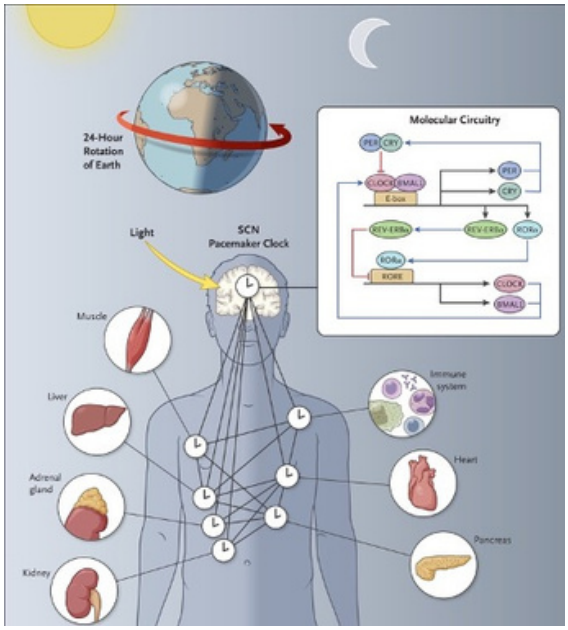

Figure 2. Molecular circuity of the circadian clock

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DISRUPTION OF GLUCOSE HOMEOSTASIS AND TIME RESTRICTED FEEDING

Impaired glucose tolerance is a major systemic effect of disturbed circadian rhythm because insulin release by the **beta cells** in pancreas requires the expression of clock genes within the glucose sensing islet cells. Clock genes regulate the genes involved in insulin secretion and increase their secretory capacity to coincide when the person is awake. However, the alpha cells are important in **regulating** the glucose levels at night. The autonomic nervous system determines the insulin and **glucagon** release by conditioning the local alpha and beta cells to the light-dark cycles by signalling it using the hormone melatonin which is typically produced in response to darkness. **Melatonin 1B receptors** are associated with the glucose regulation, however, it's not clear whether they act on the islet or brain cells. Melatonin rises at night due to lack of light and increases insulin production in the morning. The circadian system is essential for glucose production, disposal and cycles of storage and usage of energy using glucose.

Disruption of meal timings in animals and humans leads to weight gain and impaired glucose tolerance. Melanopsin absorbs the blue light more readily than broad-spectrum light. Exposure to light at the wrong time of the day such as blue light emission from electronic devices can delay the circadian clock. This misaligns it from the environmental cycle and leads to a **high risk of sleep disorders**, impair cognitive function performance as the phases of pacemaker neuronal clocks and peripheral tissue clocks. This can also misalign the metabolic clock and lead to obesity and diabetes.

In contrast, time restricted meals lead to decreased chances of metabolic disorders related to diet induced **obesity**. Time restricted feeding protects from obesity and may also promote healthy aging. Continuous disruption to the light-dark cycle while administering nutritional supplement to a patient could result in inflammation and insulin resistance.

Emerging research has indicated that synchronising delivery of drugs with a person's endogenous physiological rhythm can **optimize** the efficacy of the drug.
The frequency of side effect caused by some drugs varies according to the time of day it was administered. Some drugs when administered during the day **reduces** off target side effects. Whereas some drug targets peak at different times during the day. Therefore, treatments can also be most effective if synchronised with the daily changes.

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DEEP DIVE

ADRENAL ANDROGENS: PREVENTING DEGENERATIVE EFFECTS WITH OLD AGE

WRITTEN BY ZETA IOANNOU
EDITED BY ROSA TSUCALA

Dehydroepiandrosterone (DHEA) and its active metabolite DHEA Sulphate (DHEAS), are **cholesterol-derived hormones** produced and released by the adrenal cortex in response to adrenocorticotropic hormone (ACTH). These steroid hormones exert weak androgenic effects and therefore are considered as **pro-hormones** with a need to be transformed to more potent androgens such as testosterone, to exert their effects (Figure 1). It is worth noting that levels of DHEA and DHEAS deteriorate with old age and their reduction has been associated with a higher prevalence of **degenerative disorders**. In this article, I will be exploring the potential roles of these androgens in longevity and their potential **'anti-ageing' properties.**

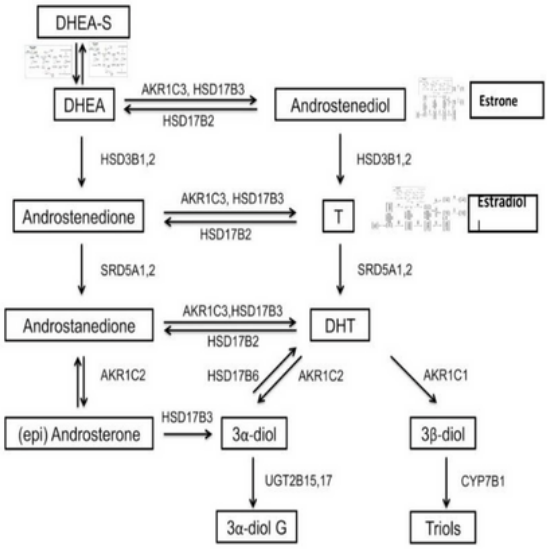

Figure 1. Metabolism of adrenal androgens from less potent (DHEA/DHEAS) androgens, to more potent ones (androsterone). Adapted from: Lois et al., 2014)

As previously mentioned, the adrenal cortex and more specifically the adrenal fasciculata and adrenal reticularis, are responsible for the release of most abundant adrenal androgens DHEA and DHEAS via ACTH regulation (see Figure 2). They are secreted in an unbound state until their binding to plasma proteins; predominantly **albumin**, to be transported to various organs and tissues utilising them.

The levels of DHEA and DHEAS in the blood vary along the life of an individual. Their peak levels occur during the third decade of life; after which the serum levels of DHEA and DHEAS **progressively** decline with advancing age (approx. by 2-5% per annum) (Labrie et al., 2003). By the 80th and 90th decade of life, their levels drop by around 80-90% of the peak production (Baulieu et al., 2000 and Mazat et al., 2001). This decline has been referred to as **adrenopause** (Heaney et al., 2012). There appears to exist inter-individual variability within the age-related decline of DHEA and DHEAS levels (Parker et al., 1999).

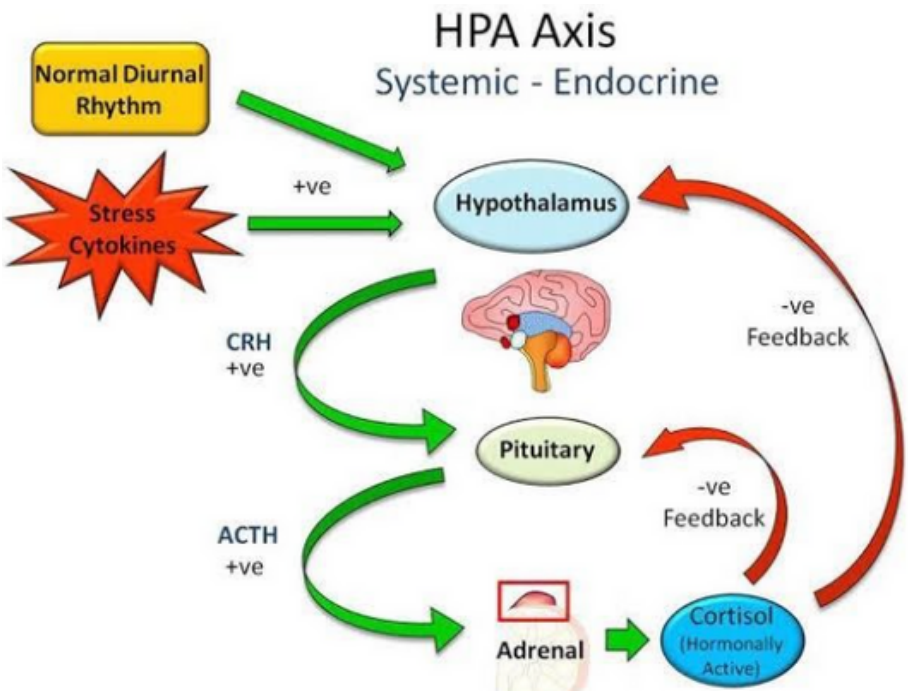

Figure 2. Adapted from: https://drjohnhwi.medium.com/physiology-and-clinical-relevance-of-salivary-adrenal-steroids-cortisol-dhea-dheas-in-natural-2d79cd8f4e90

Widely known in the scientific community is the Free Radical Theory of Ageing (Biesalski, 2002). With increasing age, **mutations** in the mitochondrial DNA accumulate due to reactive oxygen-free radicals, ultimately leading to cell death and a critical role in the development of cancer, atherosclerosis and Alzheimer's disease (Biesalski, 2002 and Lois et al., 2014). To combat this, there is a great volume of data suggesting antioxidant properties of DHEA. The **pro-hormone** appears to inhibit glucose-6-phosphate dehydrogenase (G-6-PDH) and NADPH production (Levy et al., 1979 and Schwartz et al., 2004). The reduction in **NADPH levels**, results in reduction in the formation of oxygen-free radicals via the mechanism involving NADPH oxidase (Schwartz et al., 2004). Low levels of DHEA and DHEAS have also been associated with ageing-related pathologies such as poor muscle strength and a reduction in bone mass leading to an increased occurrence of fractures, as well as **cardiovascular disease** (CVD) and mortality from CVD (Valenti et al., 2004, Baulieu et al., 2000 and Ohlsson et al., 2010).

According to a study assessing physical conditioning of elderly individuals, higher DHEAS levels were associated with increased bone mass density (BMD) in both men and post-menopausal women (Nawata et al., 1995). It is worth noting that the increase in BMD was more obviously observed in the **lumbar spine area** as well as the hip area (Villareal et al., 2004 and Weiss et al., 2009).

In a study administering DHEA and DHEAS to elderly individuals, DHEA exerted **positive** effects on muscle strength, body composition as well as physical performance (Villareal et al., 2004 and Kenny et al., 2010).

Regarding CVD, some preliminary data in patients with type 2 Diabetes Mellitus (condition most prevalent with advancing age), suggest that the **adrenal androgens** may increase the generation of activated protein C; important in anticoagulation and protecting from acute coronary events (Suzuki et al., 2012). There is also data suggesting a positive correlation between an increased concentration of DHEA and DHEAS in the blood and neuroprotective effects (Lois et al., 2014).

In summary, in older individuals, lower than normal levels of DHEA/DHEAS are related to ageing-associated degenerative disorders. However, despite this, DHEA is considered as a hormone in Europe and thus becomes available only by prescription as opposed to the precursors in the United States, where they're considered nutritional supplements. DHEA supplements are generally well **tolerated**. However, in women, DHEA upon administration is converted to androgen metabolites; producing some minimal androgenic adverse effects including mild acne, seborrhoea and ankle swelling (Traish et al., 2011, Legrain et al., 2000 and Panjari et al., 2009). Despite increasing evidence for the positive pharmacological effects of DHEA and DHEAS, consensus has not yet been reached. **Further clinical trials** are necessary to better identify the clinical role of DHEA supplementation and for its wider distribution and use more globally.

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SHALLOW DIVE

Patent Pending: What on Earth is a Patent Attorney?

DR PETER GIDDINGS DISCUSSES CAREERS IN PATENTS AND LIFE AT GSK
WITH THE FOUNDER | EDITED BY VIRGINIA BALDI

Dr Giddings is a retired patent attorney that worked at GlaxoSmithKline (GSK) at their Brentford centre for 27 years from 1983-2010. Dr Giddings is also a KCL alumnus, having completed a BSc in biochemistry from 1973-76 and did a PhD in chemistry, finishing in 1979. His PhD project focused on trying to find new antibiotics (derivatives of penicillin products). In my time as a student at King's, a lot of career advice from the bioscience departments at King's mostly focus on routes into academic research and industry but we don't tend to hear a lot about other career paths relevant to a life science degree and I find that to be quite a shame. And so, my hope for this session is to provide some context on careers in patents and to ask Dr Giddings about his experiences on working in this field.

> It's an interesting life, it's a fulfilling life as a patent attorney and it's well worth the initial effort of taking on board some extra exams. It's worth it in the end and a very worthwhile thing to do.
>
> DR PETER GIDDINGS

Q: What motivated you to pursue a career in science before you came to study at King's?

A: I suppose as with anyone in school, there are certain things you like, and I liked science. I liked chemistry in particular and I liked biology as well and I just thought "well biochemistry sounds like it might be interesting" so I applied to do Biochemistry as an undergraduate. I didn't know what it would particularly be like. I knew I wanted to do something scientific, had no idea what I'd do with it once I was finished. I grew up in the West Country originally, near Bath, and I just liked the look and feel of King's as a College.

Q: What was your PhD project?

A: When I graduated, I didn't really have any great plans of what to do but I quite enjoyed the research part and being in the lab and although there were no opportunities for a PhD in biochemistry, I did know some people in the chemistry department and there was a PhD in organic chemistry that opened there with an industrial placement for 3 months at Beecham Pharmaceuticals which today no longer exists as it had been consumed under GSK.

So, for those who may not be familiar with patents, a patent is a document which protects an invention and gives the holder the right to take legal action against anyone who makes, uses, sells or imports it without their permission. In the pharmaceutical industry this could be a new way to treat something, a small drug molecule or a new type of medical device.

Usually for a patent to be granted, it must follow the criteria of being something that can be made or used, new, and inventive (not just a simple modification to something existing already – this is called prior art). To become a patent attorney, the most important thing to take into account is that one, you don't need to have a law degree and two, your degree must be from a technical background (engineering, IT, pharmaceutical).

Q: What was your first encounter with patents and what inspired you to pursue this career path?

A: It was sort of accidental back when I worked down at Beecham! Some of the experimental work I did on preparing some new semi-synthetic penicillin-type compounds was included in a patent. I didn't really think much of it and I sent off my experimental description, and it was put into this patent and I had been given a copy to check it over and I was intrigued by the patent document. I didn't understand at all the way it was written. At some point, a colleague of mine told me all about the patent profession and was very enthusiastic at how the whole job is and it sounded like something I wanted to do. So when I completed my PhD, I looked around for vacancies in the profession to start as a trainee patent attorney (they used to call them patent assistants) and there was a position at the welcome foundation. So I did 2 years there before joining Smith Kline and French, which became GlaxoSmithKline. I sort of stumbled into it and that wasn't that unusual at the time; it wasn't easy to find out about things like this.

Figure 1. Dr Peter Giddings in a King's College London chemistry lab during his PhD days, back in 1975.

If you thought it was hard now, it was pretty impossible when there was nothing online so there wasn't a way of finding out about it unless you knew somebody. I also feel I wasn't cut out for research.

For those wondering, pharmaceutical companies (which have their own team of patent attorneys) tend to do things differently from private IP firms (the case being that pharmaceutical companies tend to patent their own discoveries whereas private IP firms tend to have individual clients that they provide services to).

Q: What was your day to day life like as a patent attorney?

A: My day to day life basically revolved around managing different areas of patents related to different areas of research. So when you become a trainee, you work together with a patent attorney and are assigned to various areas of research and to work in conjunction with the scientists to identify any patentable inventions coming out of their R&D. So you will start to get involved with things like giving an assessment as to whether or not what they're doing might be patentable.

They might want to come to you to ask "we want to work in this area, are there any other patents from other companies that get in the way?" so you're doing that assessment of patentability and checking it against other company patents. And if all of that looks okay, they would have found some new compounds that have some interesting activity and this was usually in the early stages of in vitro screening just to look for basic activity.

There are many years from that point before you might get something onto the market. Then you work with them to draft the patent description document which details how to make and use the product, how to put it into practice basically. This is with the intention that once the patent has expired, there should be enough information in there for people to be able to copy your product. So once you get into it, you'll get all sorts of different inventions and problems coming to you which you need to manage and handle on a day to day basis.

A lot of the work in the early days involved prosecuting patent applications so once you've drafted your patent, you need to file it in every patent office around the world where you want to get a patent and once you do that, each of those patent offices may raise objections to it (not new, not inventive, other application problems). They might write to you and say "we think there's this problem" and you have to write back to them arguing the opposite saying that you disagree and that it should be patented.

That written exchange of correspondence can take several years to complete because they will write to you in the first place and tell you that you have 6 months to reply and because you're very busy with all sorts of things, you generally don't respond until right before the end of those 6 months. Then another period of time will go by before they write back to you to either continue the argument or grant the patent. So when you file hundreds of cases, you'll get hundreds of letters coming in at different times constantly and so you're managing all those correspondences.

So your day to day life is a lot of written work and argumentation work to get and secure a patent. It is quite intensive at first because you need to develop the written argumentative skills (writing the patent application clearly and arguing about its patent ability in written form). That is not a skill which comes instantly, most people take time to develop those skills and as you're practicing for the exams as well as they test your ability to draft patents and you need to be able to argue the patentability of something.

Q: How were your patent attorney exams? Did you find them difficult?

A: They were difficult, but I think that if you have good training, and you've picked up what to do, then they shouldn't be so daunting. I think part of the problem used to be that people just didn't get much training but I think that's changed completely.

And of course, the UK has 2 exams, a foundation exam, and the final exams. The foundation exams can be done by a postgraduate course in intellectual property law. This can be done at Queen Mary's College in London. The finals themselves really just need practice and you need to be able to write clearly and concisely. If you can do that and you're getting the training and enjoying the job, then it shouldn't be so difficult.

Some people find great difficulty in passing and other people don't, so it's difficult but it's a challenge. I think one of the biggest achievements I had was passing all of those exams the first time round so I'm quite proud of that. They are testing your ability to write but if you can't write it down in a clear and concise way and you're not analysing the document or noticing the key points, then you'll find difficulty in that. But equally, if you can't do that, then you're probably not in the right job.

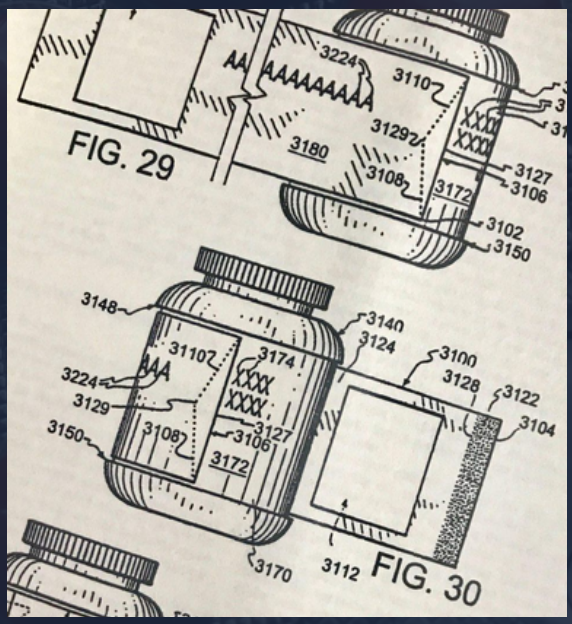
Q: What was your role at GSK towards the end of your career and how different was it from when you first joined?

A: I took over the responsibility for managing all the paralegal people who managed all of our data and all the documentation that goes along the individual patent filings so they keep all the data to ensure fees are paid on time, actions are all taken on time and that we prepare and sign all the application forms that need to go with each patent application so that was quite a big operation, especially near the end.

I had people who worked in the UK and the US for me who did that, so I had to then go and see them every week or so to keep that going so that was quite a challenging part of the role as well.

Q: What skills, in your opinion, make a great patent attorney?

A: I think you need to be analytical and curious as well. You need to be able to ask the right questions, and you need to be able to write clearly and concisely and you need to have an eye for detail. You need to have a good understanding of the science and be able to apply it to law.



Q: What advice would you have for undergraduate students considering this as a career now?

A: I would say if you are interested in patents, then go for it but don't expect to know everything in a few months or a year. It takes time, it takes time to develop into the role, it takes time to develop your skills and so on, but it's very much worth sticking at and I think if you are interested in it, then do it. I think you would find either you really like it or you just hate it; I don't think it's the sort of job that you can just go into half-interested in and think "oh well I'll just do this for the rest of my life", it's not an easy way but I don't want people to think it's impossible because that's not the case.

It's new skills, it's a different type of work and it's worth sticking at; it's worth doing it. There's not many people that do it (1500 qualified UK attorneys vs 150,000 general lawyers) so that gives you the sense that it's a small profession and actually, you can get a pretty good career out of it if it's something you want to do. So don't think it sounds as though it's all too much, because I don't think it is in the end because when you're in it, you're building up your portfolio of work, you're doing things step by step and suddenly you're in there, you're qualified and you're moving on.

You also need to keep learning about the law as it develops and you need to keep in touch with developments and it's interesting as you feel you're making a contribution and you're doing something useful.

Certainly, continuous learning is a good thing to have with any subjects. Patent matters matter! You only have to see in the press about how Apple and Samsung often have patent battles together, they end up licensing things from each other where they pay hundreds of millions of dollars because of the patents they have so it is something that does matter, it is something that is important in industry.

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DEEP DIVE

CHRYSANTHEMUM POLYSACCHARIDES AS VACCINE ADJUVANT

WRITTEN BY KIRA LINKE | EDITED BY HUDA HAMMAD RATTU

Nature is often the initial source of important medical compounds, and recent studies have found **benefits** in extracts derived from Chrysanthemums. Chrysanthemum zawadskii Herbich var. latilobum leaves are used as a **source** of extracted saccharides, mainly glucose and glucose derivatives, and a yet unspecified group of acidic polysaccharides called CP (Chrystanthemum zawadskii Herbich var. latilobum polysaccharides). CP has **previously** demonstrated anti-inflammatory properties, and protective effects against chemokine-induced liver damage in mice. New research published in the June volume of the journal 'International Immunity' shows promising results that CP can be **beneficial** as a vaccine adjuvant for cancer vaccines that utilise dendritic cells as antigen presenters.

As an initial control experiment, CP was found to be **not cytotoxic** to dendritic cells even at 30μg/mL; the highest concentration used in any subsequent experiment. CP induced production of co-stimulatory molecules (Figure 1) intracellularly and significantly **increases** secretion of pro-inflammatory cytokines.

However, anti-inflammatory IL-10 was **not** significantly affected by CP. These effects attest that CP accelerated the maturation of dendritic cells, which is confirmed by tests of endocytic activity and antigen-presenting ability. Data suggests that CP acts by phosphorylating MAPKs - a **key** pathway for cell proliferation - and translocating NF-κB, which has a role in transcription and cytokine production. Thus, CP acts directly on pathways involved in **activating** the immune response, allowing it to **increase** the effectiveness of vaccines.

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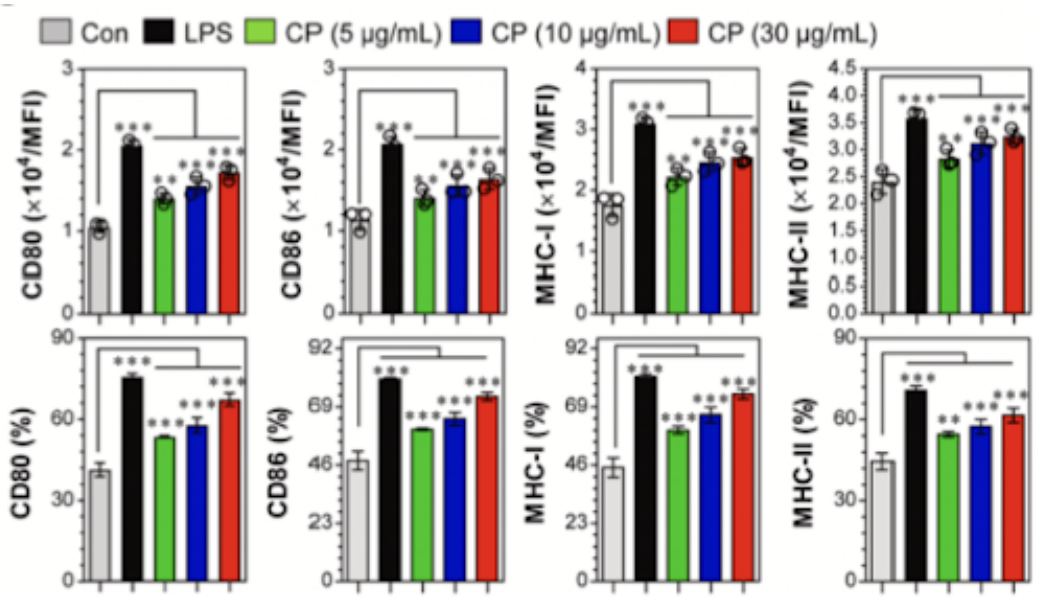


Figure 1. CP Dose-dependent increase of co-stimulatory molecules, compared to LPS (endotoxins that stimulate immune response) and control.

Previous studies have demonstrated that a **more effective** immune response is carried out by polyfunctional cells. In particular, T cells that co-produce various immunological signalling and stimulatory factors. CP particularly enhances activation of polyfunctional CD4+ and CD8+ T cells.

Furthermore, of significant relevance to vaccine research was the experiment examining the extent to which CP is **effective** in preventing cancer growth in vivo. Mice were injected with cancer cells expressing ovalbumin (OVA) as a marker after immunisation with CP and OVA stimulated dendritic cells (OVAs-DC) as well as various controls were also studied. 35 days after tumour implantation, the CP/OVAs-DC immunised mice had **significantly** the smallest tumour size (see figure 2). The polyfunctional T cells **activated** by CP are believed to also play a role in this.

Since this paper has demonstrated CP's potential as a cancer suppressant and immune system activator, the **increased** maturation of dendritic cells due to CP may prove **very beneficial** in the future for vaccine adjuvants. However, only mouse models have been explored, and future research must **identify** the specific polysaccharides in CP that contribute to its effects. Overall, CP is proving to be yet another avenue of **utilising** nature for medicinal benefit.

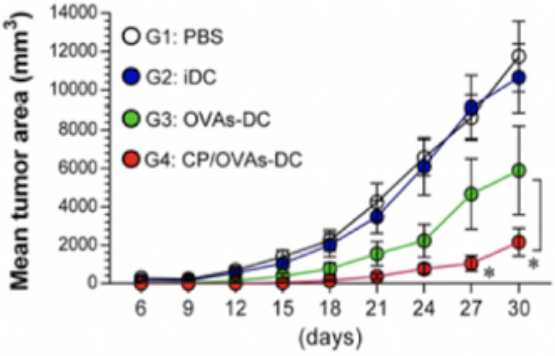


Figure 2. Changes in tumour size after injection. 10 mice per group. CP/OVAs-DC has the most significant tumour suppressant effect.

DEEP DIVE

BREAKTHROUGH in the Quest for Better, Cheaper Cancer Vaccines

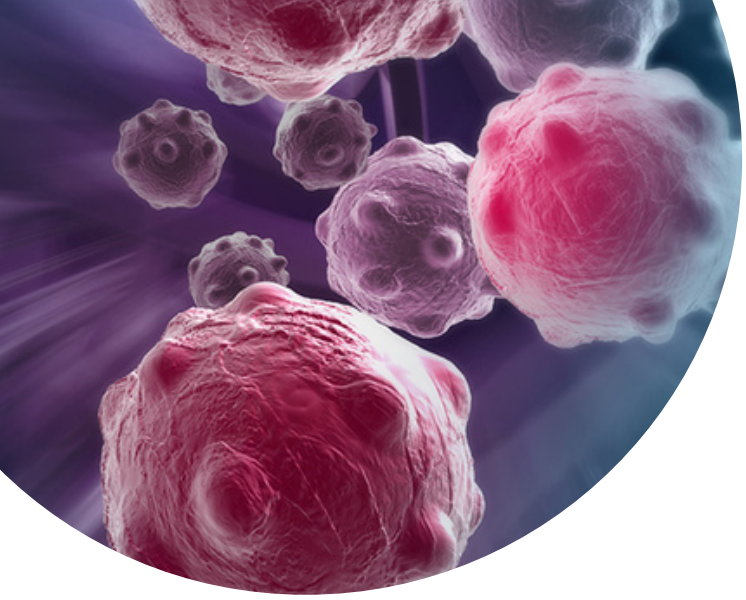
WRITTEN BY OLIVERA MITEVSKA | EDITED BY JULIET CHEN

Two brand new "off the shelf" vaccines currently underway for early Phase I clinical trials show preclinical immunological efficacy in vivo, while escaping comparatively **high** production costs. Researchers at the University of Queensland and the Translational Research Institute in Australia show that the chimeric vaccines, comprised of an antigen-carrying IgG4 antibody (Ab) **specific** for the C-type lectin-like transmembrane receptor CLEC9A unique to CD141+ Dendritic cells (DCs), effectively **activate** CD8+ T-cells against epitopes of the Wilms' Tumour 1 (WT1) and the New York esophageal squamous cell carcinoma 1 (NY-ESO-1) tumour-associated antigens (TAAs). The vaccines were tested in **humanized mice** reconstituted with human CD141+ DCs, ensuring greater generalizability to humans. The results have been corroborated by multiple different research groups in mice and non-human mammals in vivo.

After the reign of checkpoint-inhibitors, DC cancer vaccines are making a **comeback** with over 200 registered clinical trials. Early Phase II trials for similar formulations based on the CLEC9A receptor against **melanoma** are already in action.

The new CLEC9A-specific Ab vaccines are **more economical** than their polypeptide-based and monocyte-derived DC cell-based vaccine counterparts, which require specialized facilities and are more labor-intensive. Unlike the others, CLEC9A-Abs also achieve **long-term** memory responses with high-avidity TAA-specific CD8+ T-cells.

The improvements evidenced in the novel vaccines are linked to their **structural composition**. The TAAs, WT1 and NY-ESO-1, are overexpressed in many hematological and solid malignancies, such as acute myeloid leukemia, multiple myeloma, non-Hodgkin lymphoma, breast cancers and pancreatic cancers, and are **restricted** by multiple antigen-binding HLA haplotypes found on CD8+ T-cells. This cross-cancer prevalence is thought to make the vaccines **widely applicable** to many patients.



CLEC9A plays a **critical role** in cross-presenting these TAAs to CD8+ cells. Taking the aforementioned into consideration, specifically targeting CD141+ DCs using WT1- or NY-ESO-1-conjugated CLEC9A-specific IgG4 Ab successfully primes naïve and mature CD8+ T-cells, the specificity of which produces a targeted humoral response with **high efficacy** that yields synergistically with other traditional cancer therapies such as chemotherapy, surgery, and checkpoint-inhibitors. The vaccine's high efficacy is thought to lie in the favorable retention of IgG4 in the bloodstream, and the basic environment of the early endosomes wherein CLEC9A **traffics** the TAAs, both of which assist cross-presentation. Furthermore, it is hypothesized that because of the specificity of this process, the vaccines would exhibit **minimal side effects** in humans.

While presently the formulation only targets either WT1 or NY-ESO-1, the researchers note that the Ab backbone, which conjoins the TAAs at the heavy chains via an alanine-linker (thus, each Ab carries 2 TAAs), could reasonably be **altered** to accommodate multiple different or identical TAAs.

Additionally, other research groups have reported that generating adjuvant-CLEC9A-Ab vaccine cocktails may **increase** immunological responses in vivo, such as with Fms-related tyrosine kinase 3 ligand (Flt3L) or poly-ICLC. For instance, **administering** Flt3L in addition to CLEC9A-Ab **increases** otherwise sparse levels of CD141+ DCs in patient blood. However, the researchers caution that due to the potential of high-titer Ab humoral response, as evidenced in mice and macaques, implementing the vaccine in the multiple cycles required for human treatment could potentially be **challenging**.

CLEC9A-specific Ab carrying WT1 or NY-ESO-1 epitopes **successfully** induce immune responses in humanoid mice models, however, their efficacy and safety in humans is yet to be ascertained. Answers will hopefully follow as the clinical trials progress.

About the Author

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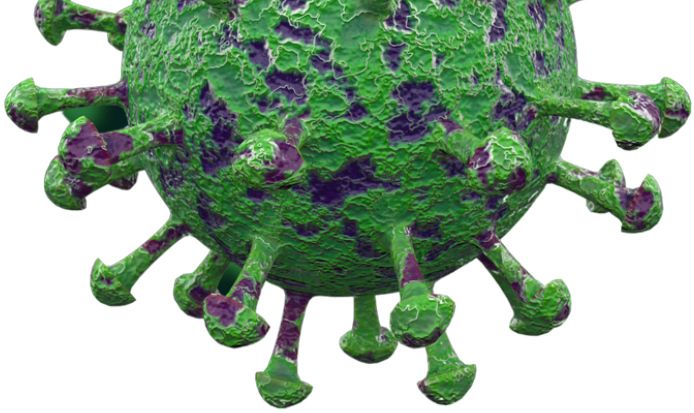
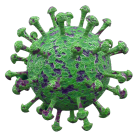
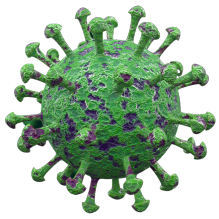


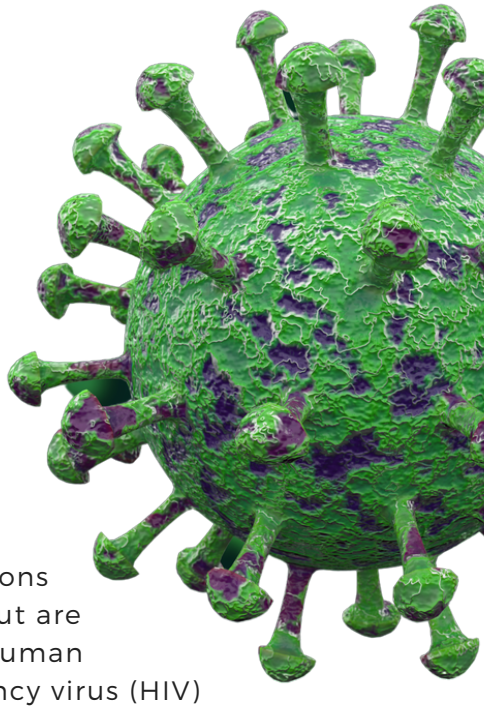




DEEP DIVE

WRITTEN BY DRSHIKA MEHTANI | EDITED BY TAMAS BODO

How Safe and Effective is the Pfizer-BioNTech BNT162b2 COVID-19 vaccine?



COVID-19 caused by the SARS-CoV-2 virus has affected tens of millions of people all over the world. Safe and effective vaccines are being developed as they are urgently needed to combat the disease world-wide. One such potential vaccine candidate is the **Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine**.

The safety and efficacy findings discussed here are from phase 2/3 of the clinical trial of the vaccine.

BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified RNA encoding the SAARS-CoV-2 full-length spike, modified by two proline mutations to **lock it** in the perfusion conformation. The trial was multinational, placebo-controlled and observer-blinded. People of age 16 years or older were randomly assigned in a **1:1 ratio** to receive two doses which were 21 days apart of either the placebo (saline) or the vaccine candidate (30 µg of BNT162b2) to be administered **intramuscularly**. People of age 16 years or older were only eligible if they were healthy or had stable chronic medical conditions that included but are not limited to human immunodeficiency virus (HIV) or hepatitis C virus infection. People were **not eligible** if they had a medical history of COVID-19, immunosuppressive therapy or were **diagnosed** with an immunocompromising condition. Of the 43,548 participants that underwent randomisation, 37,706 were given either the vaccine (18,860) or the placebo (18,846) for the **first** dose.

18,556 participants then received the **second** vaccine dose, and 18,530 participants received the second placebo dose. Participants of the trial were followed up for a median of 2 months for the symptomatic development of COVID-19.

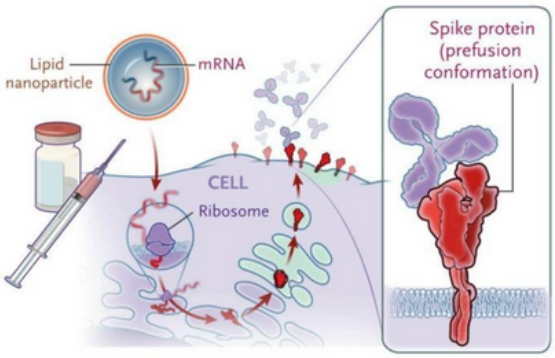


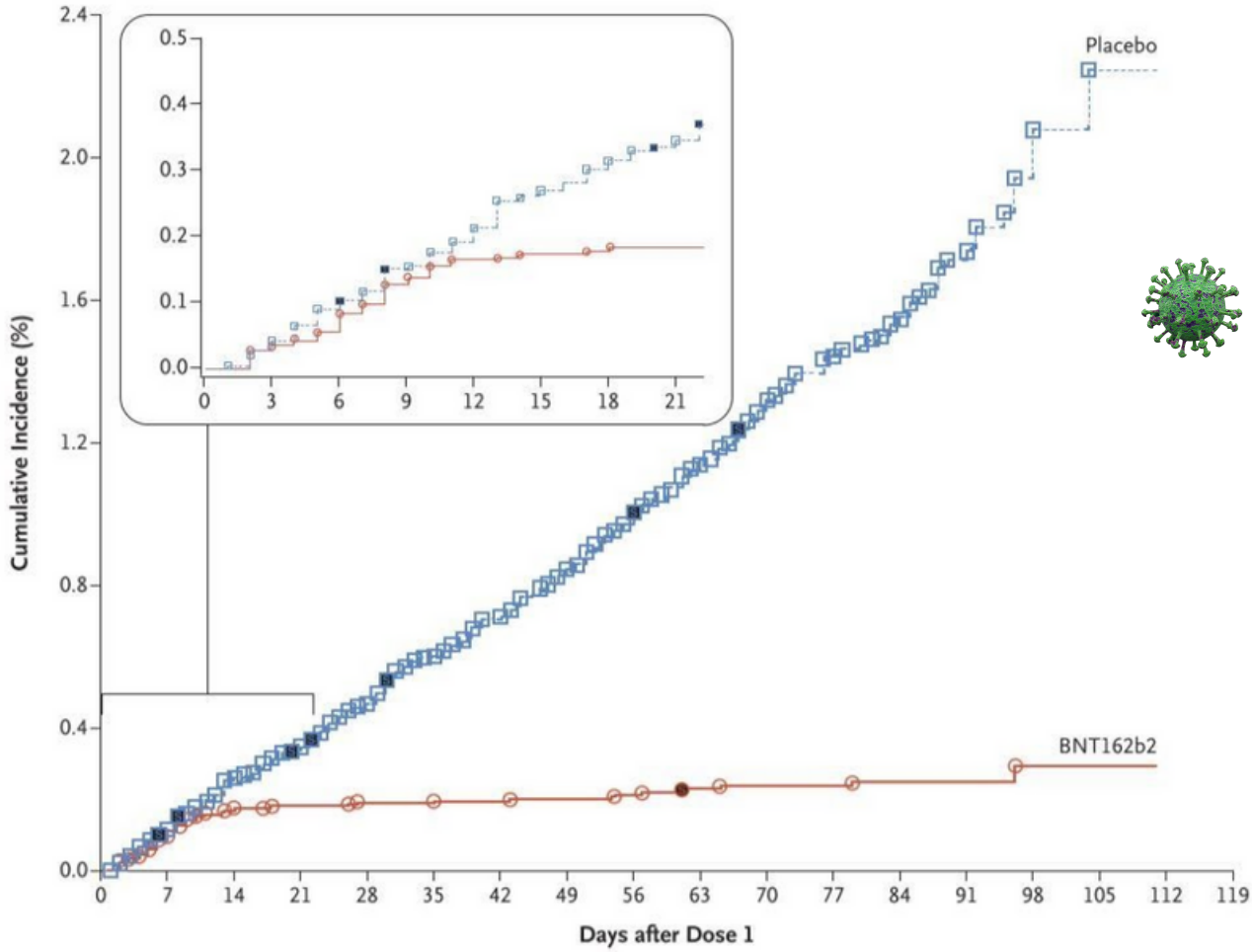
Figure 1. How the COVID-19 vaccine works in the body.

There were 10 **severe** COVID-19 cases after the first dose was administered, of which 9 were from the placebo group and **one** from the BNT162b2 group. There were 8 positive cases of COVID-19 with a minimum of 7 days after the second dose was administered in the BNT162b2 group and 162 cases in the placebo group. BNT162b2 was shown to be **95%** effective at **preventing** the onset of COVID-19. Analogous vaccine efficacy (90% to 100%) was shown across subgroups that were established by age, sex, race, ethnicity, baseline body-mass index and the presence of coexisting conditions.

Vaccine recipients showed both local (pain, swelling, erythema) and systemic (fever, headache, myalgia, etc.) reactions at **higher rates** than placebo recipients. These reactions were **more severe** after the second dose was administered. However, those that were of mild to moderate severity resolved after a day or two.

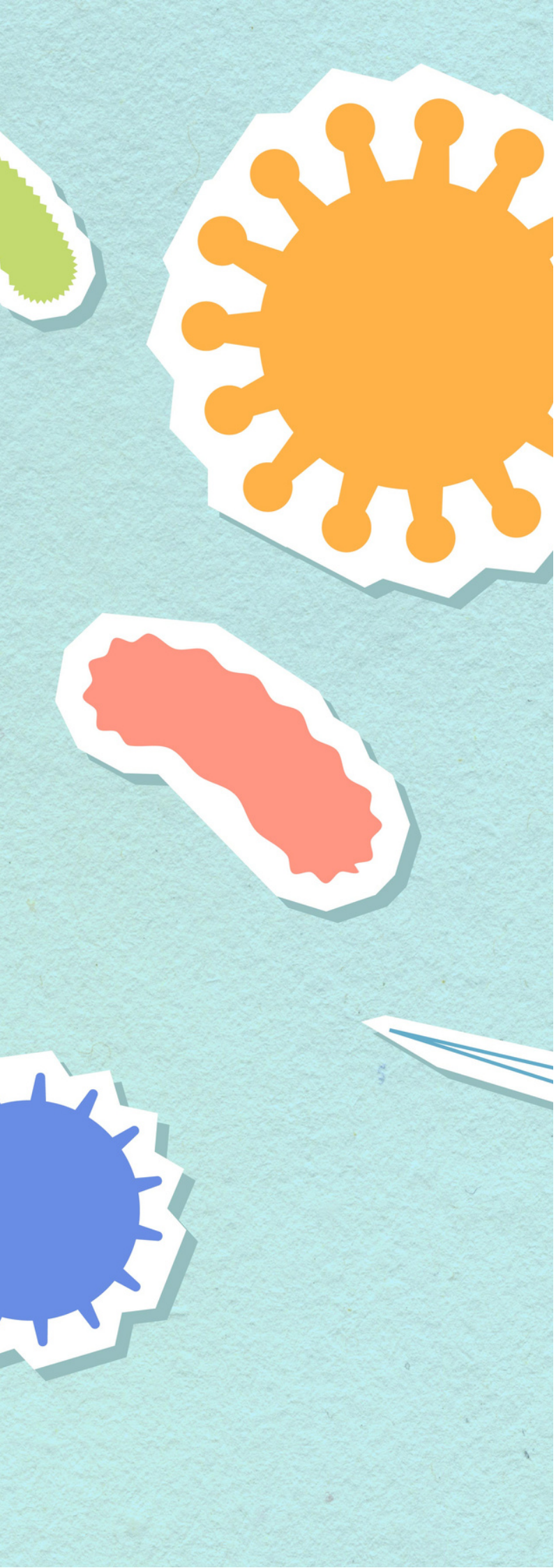
Further analysis is required to address several concerns regarding the effects of the vaccine in **unstudied groups** such as children and immunocompromised persons. It is also required to understand whether the vaccine protects against asymptomatic infection and the **transmission** of the virus to uninfected people.

Nevertheless, a two-dose administration BNT162b2 provides **95% protection** against COVID-19 in people aged 16 years or older. The immunogenicity of the vaccine and the **durability** of the immune response to immunisation is still currently in investigation within trials, and once understood, it might offer **clearer insights** concerning the **overall efficacy** and **safety** of the vaccine.



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Figure 2. Cumulative incidence (%) of BNT162b2 versus placebo



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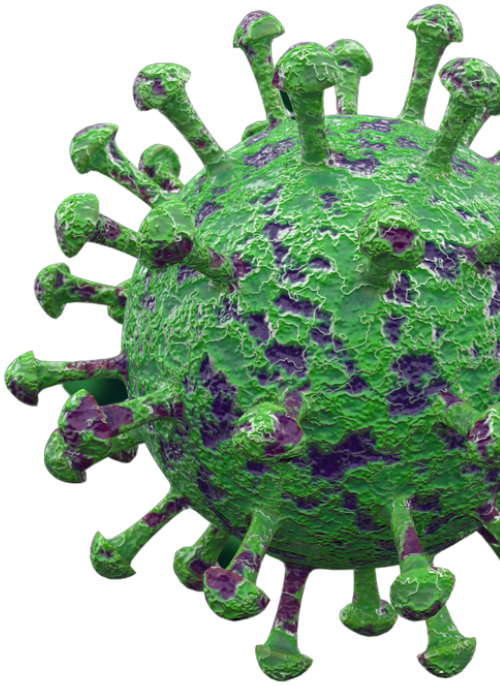
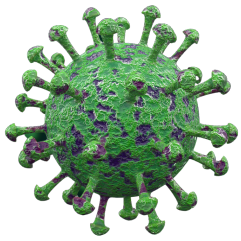
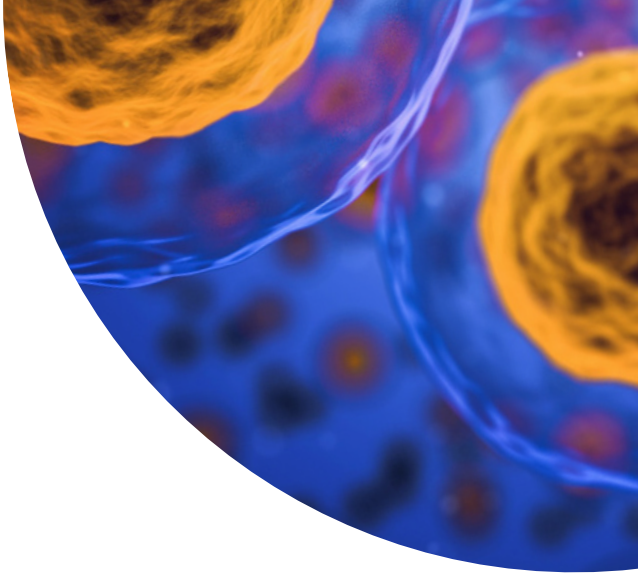






THREADING WATER

CAN HUMAN CELLS BE IMMORTALIZED?

WRITTEN BY ROSA TSUCALA
EDITED BY TREASA JIANG

What if we could immortalize human cells and **reverse the aging process?** This might come as a surprise, but advances in the field of molecular anti-aging have indicated the aforementioned could be possible. To understand this, we first need to understand the molecular mechanism of aging. What is aging? The encyclopedia Britannica defines aging as the "progressive physiological changes in an organism that lead to senescence (old age), or a decline of biological functions and of the organism's ability to adapt to metabolic stress." However, what is the underlying molecular **mechanism** that leads to cellular aging?

Telomere length: a marker for cellular aging

A marker for cellular aging is telomere length, which decreases with age and has been associated with age-related diseases. **Telomeres** are nucleoprotein structures, including repeating TTAGGG sequences found at the terminal ends of DNA chromosomes (Figure 1). The word telomere comes from the Greek word "telos" which means "end" and "meros" which means "part," meaning they are the end parts of eukaryotic chromosomes. Chromosomes are supercoiled, replicated DNA consisting of sister chromatids, which acquire this structure during prophase and become more evident during metaphase. The type of chromosomes utilized for **karyotyping** and telomere length measuring are metaphase chromosomes due to their supercoiled structure. Studies have indicated the **correlation** between short telomere length and aging-related diseases such as cardiovascular diseases, stroke, cancer, arthritis, osteoporosis, etc. Factors that affect **telomere length** include environmental factors such as physical activity, body mass index (BMI), **hormone replacement therapy**, smoking, chronic inflammation, oxidative stress, and others.

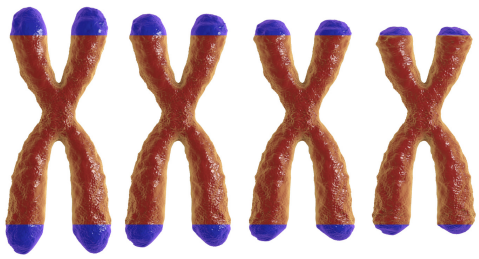
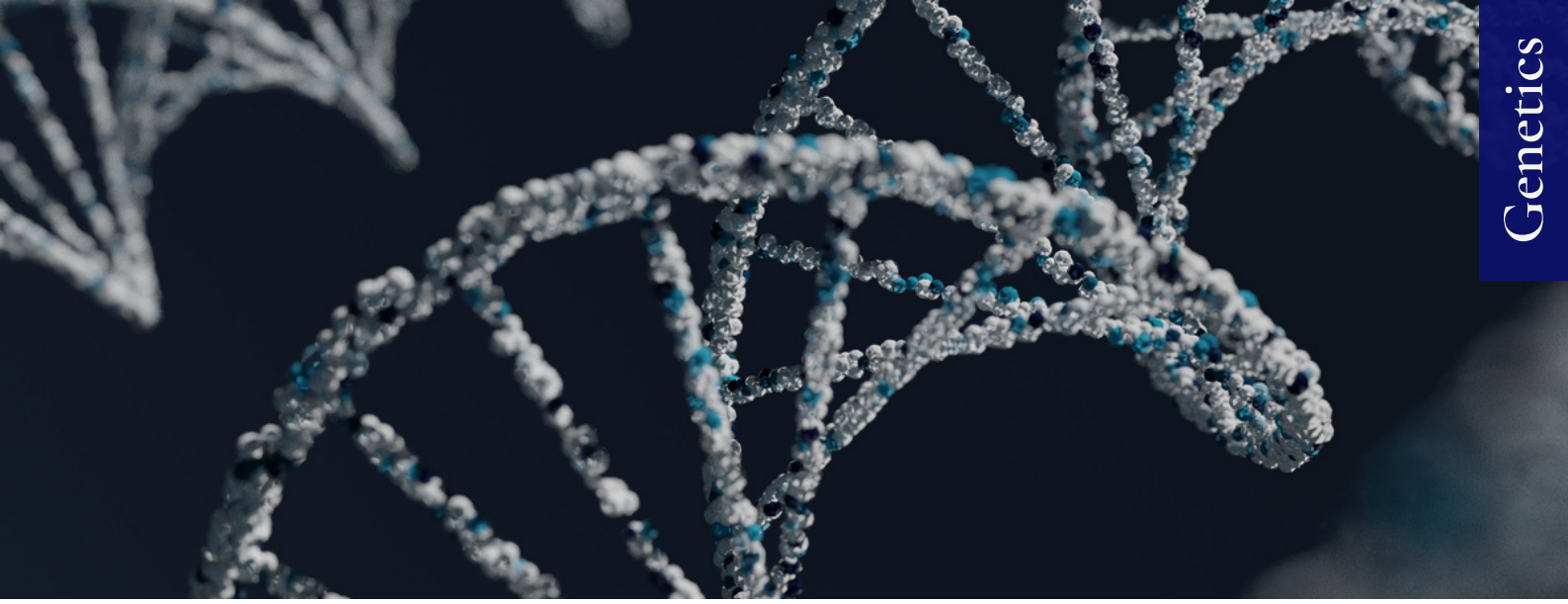


Figure 1. Eukaryotic chromosome telomeres of different length



Telomere elongation and longevity

Keeping in mind the aforementioned, the following question arises "Has telomere elongation been linked to increased life-span?" The answer is that the rate of increase of short telomere length has been linked to **longevity** in mammals.

More specifically, when telomere length decreases below a threshold, cellular **apoptosis** is induced, and cell growth is restricted. A study conducted on mice with hyper-long telomeres indicated the following astonishing results: The mice had longer telomeres and less DNA damage with aging. They were lean and demonstrated low cholesterol and LDL levels and **improved** glucose and insulin tolerance. Hyper-long telomere mice also showed less incidence of cancer and an increased longevity. These findings indicate that longer telomeres than normal in this species show beneficial effects.

Although mice with long telomeres have been linked to increased longevity and decreased **cancer** incidence, these mice were engineered using embryonic stem cells.

Telomerase: telomere repairing enzyme

How could this finding be applied to human telomeres and have the same effect later in an individual's life? The key lies in the discovery of the enzyme telomerase, which was awarded the 2009 Nobel Prize in Physiology or Medicine. Telomerase is a telomere **repairing enzyme** which adds nucleotides at the ends of telomeres and elongates them (Figure 2).

This enzyme is essential for the organism as it has the ability to repair the damage caused by **environmental factors.** However, the rate at which telomeres are shortened is much faster than the rate at which telomerase can repair them. Therefore, the net result is that eukaryotic telomeres decrease in length over time.

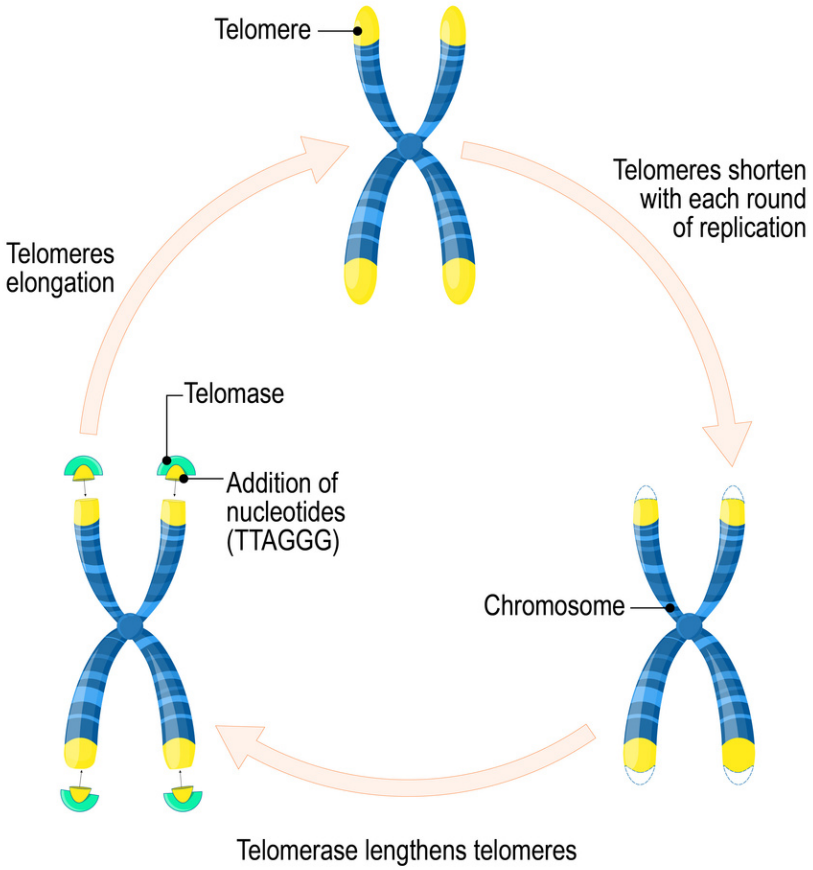


Figure 2. Eukaryotic chromosome telomere cycle and telomerase repair

Telomerase activation using natural molecules

Recent advances in molecular biology have uncovered that telomerase can be activated using natural molecules. More specifically, a study examining the effect of telomerase **activators** on telomerase activity of human peripheral blood mononuclear cells indicated that a formulation including Centella asiatica extract produced a nine-fold increase in telomerase activity. Additionally, a study by Harley B.C. et al. revealed that a formulation including **TA-65®**, a natural product-derived telomerase activator, prescribed with other supplements, improved markers for metabolic, bone and cardiovascular health. Ip F.C.F et al. conducted a study regarding telomerase activation by the substance cycloastragenol (CAG) in human neonatal **keratinocytes** and rat neuronal cells. Keratinocytes are epidermal cells that produce keratin. The study demonstrated that CAG promotes telomerase activity and cell proliferation.

Telomerase activation: anti-ageing applications

Overall, long telomeres have been associated with longevity and decreased incidence of diseases. Intervention studies on humans are required to reveal the application of telomerase activators as an aging prevention tool. Telomerase activators are a potential application for anti-aging and could bring immense change to the future of biomedical science advances.

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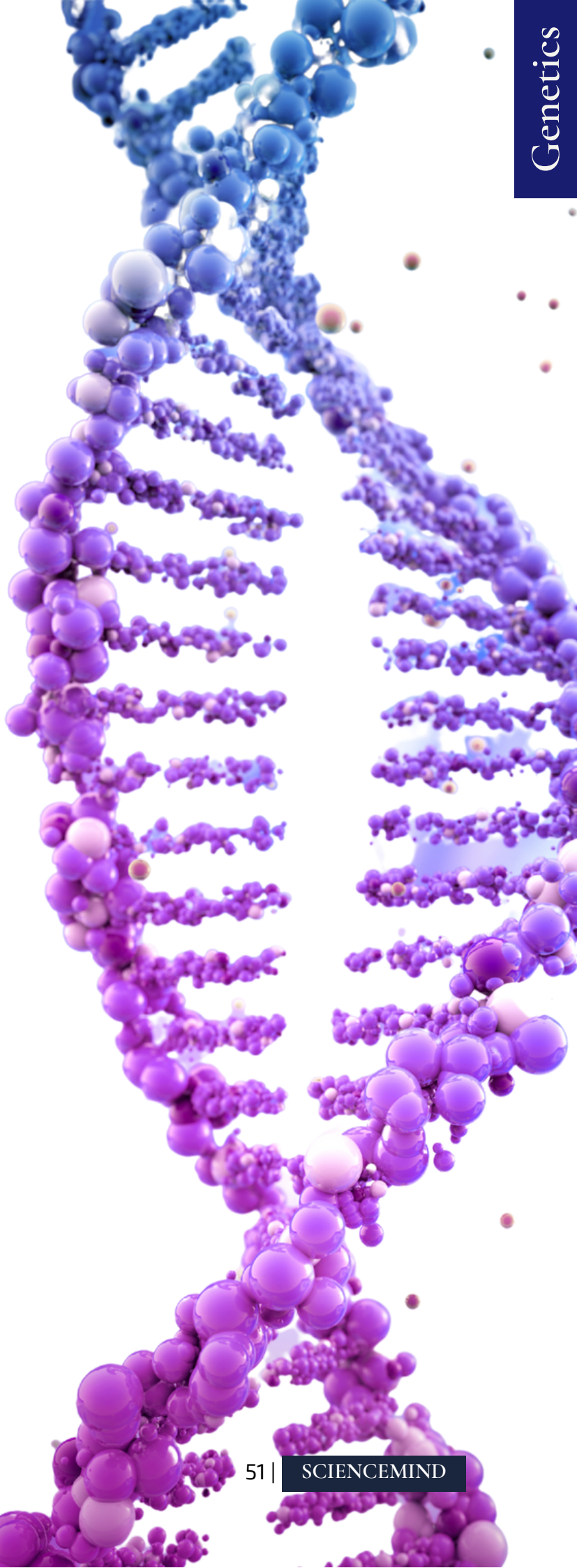

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