ScienceMind

SUMMER 2021

KING'S College LONDON

STAFF

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THIS ISSUE

Dear Reader,

I hope you have enjoyed your summer and are ready to get back into the year with a clear headspace and motivation. During the summer Science Mind welcomed new members, meaning we now have a team of 50. In this issue we have introduced **new** sections, in order to make the magazine more inclusive of general science. More specifically, the new sections introduced include Physics, Pharmaceuticals, Business & Law, Technology, Neuroscience and Virology. In this publication you will also read the interview of Professor Manuel Mayr, where he will be discussing his novel Covid-19 research.

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.

Each new issue features an interview with a King's College London researcher to discuss their current research and how they were introduced to their field, providing valuable networking opportunities. We ask that you keep in mind that this is a **sample** and the full version can be found using the QR code below, hence the splicing of some of the page numbers and slight disjointedness.

Yours faithfully,

The Deputy Editor-in-Chief
Rosa Tsucala

Reference lists:

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FUCOXANTHIN: NATURE'S MOST VERSATILE PANACEA

WRITTEN BY RAOUL PISCHEDDA
EDITED BY KANNA KODEMA

THREADING WATER

The latest Health Survey for England estimates that **30%** of adults in the UK are obese. This condition is often accompanied by numerous medical sequelae looming over a haplessly overstretched health system. Focusing on the impact of nutrition, researchers have brought attention to an underappreciated staple of healthy diets. From nori wrapping up sushi and wakame served in miso soup, to laverbread in a traditional Welsh breakfast, edible seaweed has long been noted for its **salubrious effects**. One compound stands out for its versatility.

Fucoxanthin is the most abundant carotenoid in nature. It is an orange-coloured pigment, contained within chloroplasts and extracted from brown algae or Phaeophyta, which are multicellular photosynthetic organisms inhabiting marine environments. The molecule itself is a polyene, a chain made up of alternating single and double bonds terminating in rings at either side. This structure is known as a **conjugated system**, characterized by highly delocalized electrons across multiple connected p orbitals that stabilize the overall compound. Moreover, strong oxygen-containing nucleophilic moieties adorn the molecule like hydroxyl and epoxy groups. Finally, an unusual allenic bond further promotes delocalization. This "freedom of movement" enjoyed by electrons is mainly employed by algae for **absorbing excitation energy** from light as part of photosynthesis. However, it also allows Fucoxanthin to act as an ideal **antioxidant** by reducing highly reactive molecules. Specifically, the molecule scavenges **free radicals**, including reactive oxygen species, forming bonds that transfer energy across the polyene tail as electrons smoothly rearrange themselves in the most stable positions. The compound was also shown to promote the activity of both **catalase** and **glutathione transferase**. These enzymes are involved in reducing radicals and electrophilic compounds that can otherwise cause chain reactions of oxidative degeneration among cellular tissues. Excess glucose and fatty acid blood levels, key symptoms of obesity-related metabolic syndromes, are known to engender such oxidative stress. In turn, this can lead to the development of chronic conditions such as **diabetes mellitus**.

Research has long highlighted the link between **obesity** and **insulin resistance**. Excess fat is prone to **inflammation**, which leads to the dysregulation of adipokine production by adipocytes and further inflammation in a destructive vicious cycle. Furthermore, high blood levels of **saturated fatty acids** promote **macrophage** infiltration and subsequent **TNF-α** secretion, key elements in the development of insulin resistance. Owing to its antioxidant effects, Fucoxanthin has been shown to attenuate the overexpression of **proinflammatory cytokines** and moderate harmful **autoimmune responses**. At the same time, the compound upregulates the expression of **GLUT4 receptors** in skeletal muscle cells, aiding in the maintenance of physiological blood glucose concentration. Studies have demonstrated the ability of the compound to improve **hyperglycaemia** and **hyperinsulinemia** in mice treated with a high-calorie diet.

Whilst antioxidant effects are shared among different carotenoids, Fucoxanthin is unique in its capacity to **directly ameliorate** excess weight gain. Fucoxanthin promotes energy expenditure at rest within **white adipose tissue** or WAT via a process called **adaptive thermogenesis**. Normally occurring within brown adipose tissue or BAT, thermogenesis consists in the uncoupling of oxidative phosphorylation triggered by **UCP**, a family of inner mitochondrial proteins. This is achieved by allowing protons to bypass ATP synthase when moving down their electrochemical gradient through the mitochondrial membrane: energy is thus dissipated as **heat**. UCP itself is regulated through **β3-adrenergic receptors** on BAT adipocytes responding to noradrenaline-dependent sympathetic stimulation. Fucoxanthin has been shown to **upregulate** the expression of those same receptors on WAT adipocytes, which make up most of **human fat**, effectively increasing the activity of UCP and thus promoting **lipid oxidation** at rest.

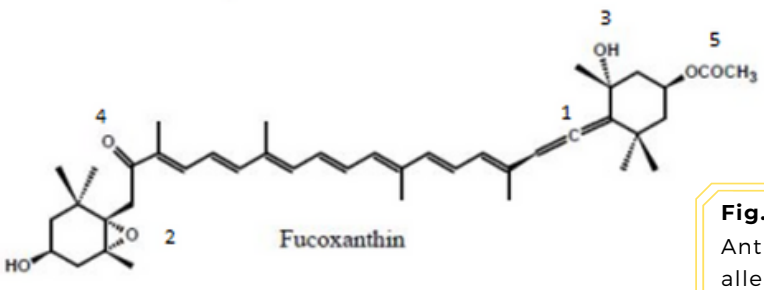

Fig.1 Molecular structure of Fucoxanthin. Antioxidant activity is correlated to the allenic bond (1); it is also favoured by epoxide (2), hydroxyl (3), carbonyl (4) and acetyl groups (5), due to oxygen's sensitivity to radicals in virtue of its nucleophilic nature. Adapted from [1].

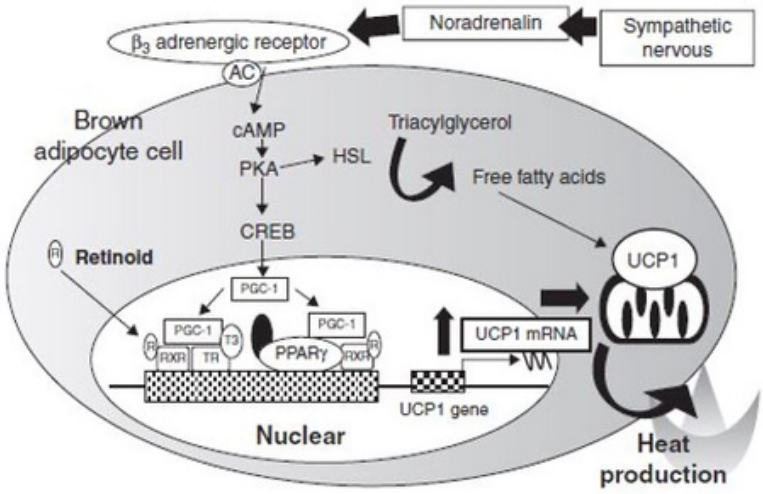

Fig.2 Mechanism of uncoupling protein 1 (UCP1) expression and activity within adipocyte, Promoting energy expenditure via triglyceride oxidation without production of ATP; note the Retinoid binding sequence on the UCP enhancer element, recognized by Fucoxanthin and allowing upregulation of the UCP1 gene. Adapted from [2].

Despite promising pre-clinical trials in animal models, data about the efficacy of Fucoxanthin in human subjects is scarce. Research is still uncovering the far-ranging **clinical potential** of the molecule, from obesity to autoimmune disorders and even cancer treatments. The compound currently lacks any widespread formulation, although it has been recommended as a dietary supplement by the **FDA**. Further studies are expected to be directed at this and similar compounds found in microalgae, in line with a global shift towards sustainable diets and environmentally focused research.

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DEEP DIVE

The Aging Phenomenon

WRITTEN BY HELENA BRADBURY
EDITED BY HUDA HAMMAD RATTU

It is an accepted fact for humans that from the point of conception there is a **limit** to longevity. From infants to now we have familiarised ourselves with the effects of **aging** by witnessing those around us to experiencing it ourselves. Aging can be defined as the time-related **deterioration** of **physiological functions** necessary for survival and fertility. It is what fundamentally governs our life. Scientifically aging is a **biological phenomenon**, whose precise cause and mechanism remain the subject of widespread speculations, despite our familiarity with its emotional and societal impact. In this article, we will review the notable theories of aging and the link of **epigenetics** and **genetics** in its variability.

The theories of aging can be subdivided into two main categories. **Programmed theories** suggest senescence and death to be an inevitable and necessary process for evolution and reproduction, whereas; the **Damage Error theories** propose the accumulation of DNA damage and cellular biochemical products to be the determinant of aging.

First introduced by **August Weismann**, a German evolutionary biologist, the 'programmed death' theory argued limited life span to be advantageous for a species, as from an ecological standpoint it prevented overpopulation and competition for resources following procreation. Supporting evidence revealed that in certain species aging is **delayed** prior to reproduction and accelerated following it. For example, Bamboo grows for 5-10 years without apparent aging, yet after seed formation it withers away allowing new seeds to germinate. Similarly, salmon die soon after migrating from pacific oceans to rivers to spawn eggs.

The **Mitochondrial Free Radical theory** (MFRT) proposes that Reactive Oxygen Species (ROS), such as hydrogen peroxide, produced as by-products of normal metabolism cause **oxidative damage** and hence reduction in longevity. Mitochondria's primary function in the cell is to produce energy in the form of **Adenine Triphosphate** (ATP) through oxidative phosphorylation. Protons are released via the oxidation of coenzymes NADH and FADH2 creating a relatively positive charge in the inner membranal space and in contrast a negative charge in the mitochondrial matrix.

Additionally, electrons are transferred along the respiratory protein complexes I-IV in a series of **redox reactions** until accepted by oxygen resulting in the production of **water**. In contrast to the common sequence of respiration, oxygen can occasionally react with reduced components of the electron transport chain to form **superoxide species**. These can induce significant **mutations** in the mitochondrial genome - theorised to cause **aging**. Despite only correlative data, studies reveal longer-lived rodents express lower levels of free radicals and hence lower oxidative tissue damage.

Furthermore, a short nucleotide sequence (TTAGGG) - 12kbp in length known as a **Telomere** - is present at the terminus of all human chromosomes. Consisting of non-protein coding genes, it primarily **prevents** genomic instability but **shortens** through each mitotic division. Once the telomere becomes too short a DNA damage response is induced and the cell undergoes **replicative senescence**, where it no longer divides to prevent possible DNA damage.

The **Hayflick's limit** is defined as the total number of cell divisions before the cell loses it capacity to divide. In contrast to mitotic cells, non-mitotic cells such as neurons do not possess a Hayflick's limit as the presence of telomerase enzyme ensures any telomere lost is replaced following each division.

Illustrated in Figure 1 the rate of Telomere shortening is greater in **somatic cells** where telomerase is absent compared to **germline stem cells** where it is not. Therefore, an inverse relationship is theorised between **telomere length** and **lifespan**, as through aging the cell becomes more prone to mutation and the number of mitotic cells able to divide and replace those that are damaged decreases. This genomic instability is also associated with **increased cancer risk**. In one study telomere length was measured from various cancer patients (92 head and neck, 135 bladder, 54 lung, 32 renal cell carcinoma) and found be statistically shorter (6 kbp) on average compared to their control subjects.

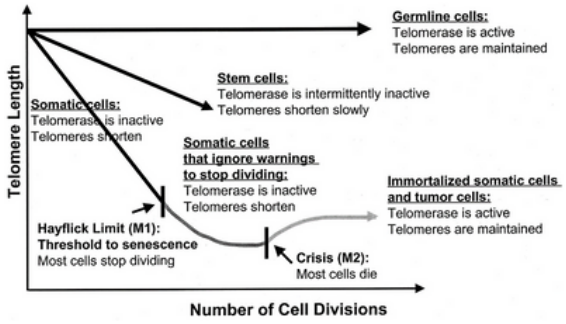

Fig.1 Graph comparing number of cell divisions for mitotic cells (no telomerase) and non-mitotic cells (telomerase present).

It is important to mention the genetic component to aging as statistically **more genes**, and their **mutant variants**, are being linked to **age-related disorders**. For instance, **Hutchinson Gilford Progeria Syndrome**, a genetic condition causing rapid aging in children, is caused by a dominant mutation of a single base substitution on the LMNA gene. Similarly, genome wide studies have identified APOE and PCDH11X gene mutants to be associated with early onset **Alzheimer's**. Two main classes of genes have been strongly linked to increased lifespan. Firstly, is the **clk-1 gene** that encodes for **Coenzyme Q** in the respiratory electron transport chain and secondly is the **isp-1 gene** that encodes an **iron sulphur protein** in the mitochondrial complex III. Mutations in both weaken electron transport chain function and hence limit mitochondrial respiration. As a result, **fewer Reactive Oxygen Species** (ROS) **accumulate**, minimising oxidative tissue damage and aging.

In conclusion, the process of aging is an intricate mechanism and remain the subject of exciting scientific discovery. It is more plausible that all factors such as genetic mutation, oxidative stress, environmental damage, and telomere shortening all work in conjugation to cause aging instead of a single determinant.

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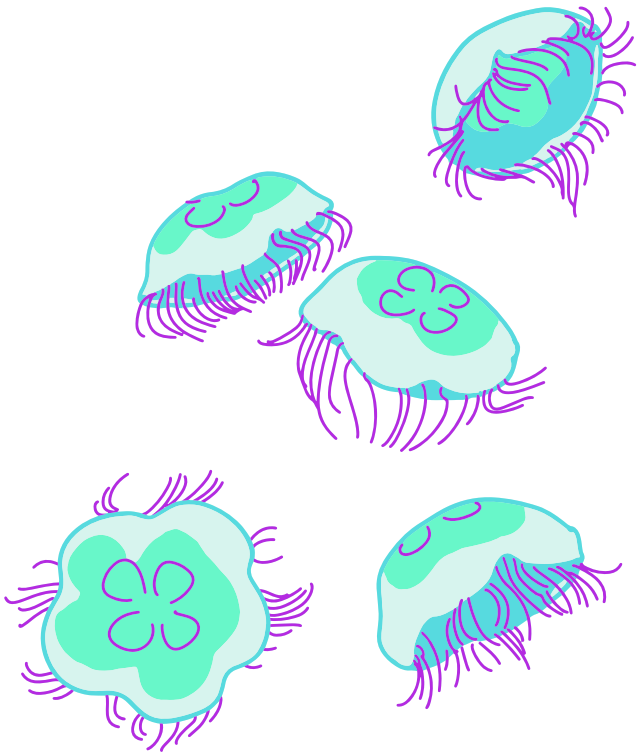
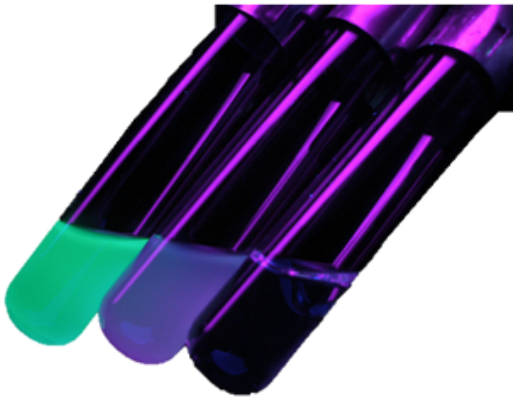
THREADING WATER

From Jellyfish to Cancer Cells: A History of Biology's Most Beautiful Research Tool



WRITTEN BY MAYA ROWLEY
EDITED BY ROSA TSUCALA

In the cold waters of the Pacific Ocean, off the West coast of North America, drift serenely **Aequorea victoria**, also known as the **crystal jellyfish**. Small, translucent, and lacking the long, stinging tentacles that make other species infamous, they may look unremarkable at first glance. However, when stimulated, they emit an eerie, **green glow** along the lining of their 'bell'. The protein responsible for this fluorescence is **GFP**, which, since its discovery, has quickly become one of the most distinctive and indispensable tools in biology.



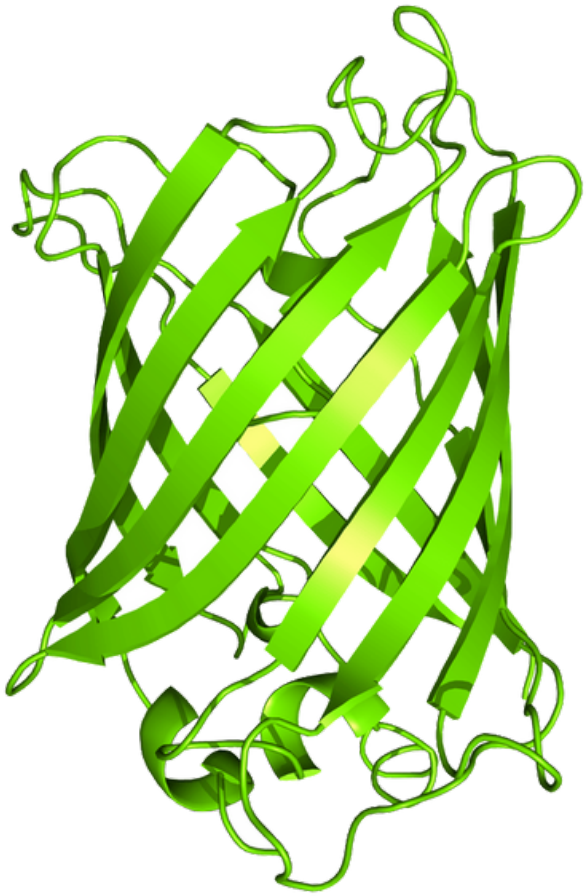
Images of cells brightly illuminated by GFP are popular both within and outside of the scientific community, often used to provide an eye-catching visual for what may otherwise be a dull or abstract topic. From textbook pages to news articles, the protein has become ubiquitous, even if not a household name. GFP has even found its way to the general market in the form of **GloFish**, a brand of strikingly colourful zebrafish genetically engineered to be fluorescent and sold as pets.

However, before becoming a tool for creating aesthetic fish, GFP was simply a mystery compound found in trace amounts in A. victoria. Studying the jellyfish was **Osamu Shimomura**, a Japanese organic chemist, who moved to the U.S. to work on bioluminescence in Aequorea with **Frank H. Johnson** at Princeton University.

From 1961 to 1988, Shimomura estimates their lab collected 850,000 Aequoria specimens total for this research. It was labour-intensive work, travelling across the country to collect then manually process thousands of jellyfish. Through this, they found the main luminescent component to be **aequorin**, a protein which undergoes a calcium-dependent chemical reaction to emit blue light. This was the first photoprotein ever discovered, and its potential for acting as a calcium probe in cell culture quickly became realised. However, what would take much longer to be characterised was another protein found with aequorin that glowed green. In 1971, it was named **green fluorescent protein**, or GFP.

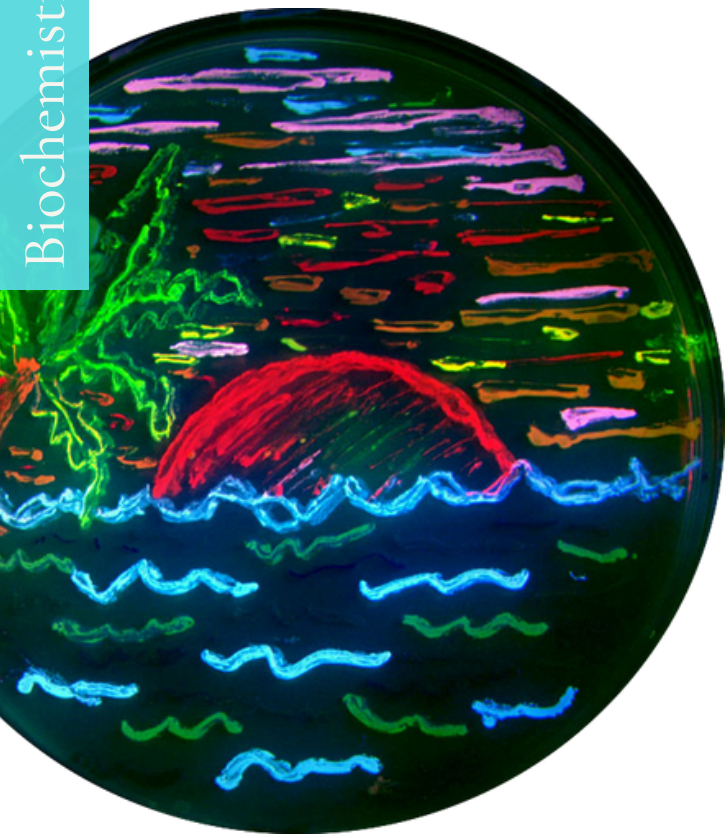
As GFP only exists in trace amounts in A. victoria, Shimomura and Johnson's team had to accumulate the tiny amounts of the protein they acquired in their studies over several years, and it was only in 1979 that they had gathered enough to work with it extensively. Following this, GFP research gathered speed, with the structure being identified, its gene cloned and sequenced, and the protein expressed in **nematodes** by Dr Martin Chalfie. Cloning of the GFP gene, Gfp, meant the protein could be synthesised in labs, eliminating the need for jellyfish harvesting.

GFP contains **238** amino acids of which numbers **65-67** (Ser-Tyr-Gly) form the chromophore: the structure that absorbs and emits specific wavelengths of light, resulting in **fluorescence**. These three amino acids interact to create GFP's distinctive green glow.



GFP also has one of the most recognisable protein structures, consisting of a **beta barrel** made up of **11 beta sheets** with the **chromophore** in the centre, enclosed by the barrel. This arrangement helps prevent the light emitted being absorbed by the environment and thereby quenched.

GFP is unique in that its **fluorescent component** is part of the protein peptide itself and not separate from the protein complex. It can fluoresce without co-factors, enzymes, or other external substrates and is formed in an autocatalytic reaction. This makes it an incredibly useful research tool as the Gfp gene can be inserted on its own to **induce fluorescence** in a sample, whether that be in certain organelles, individual cells, or multicellular organisms.



In 2008, Osamu Shimomura, Martin Chalfie and Roger Y. Tsien jointly receiv ed the **Nobel Prize** in **Chemistry** for isolating and identifying GFP (Shimomura), developing it into a tool of biological study and applying it to visualise cells (Chalfie), and research on the mechanisms of GFP fluorescence as well as development of colour variants (Tsien). Due to the work of these scientists and countless more unnamed, GFP has become an essential tool in visualising the cellular world. From its humble beginnings in A. victoria to its use in laboratories around the world, GFP has contributed an immense amount to biology, and because of it, the future of biological research shines bright, and green.

Genetic engineering of the Gfp gene has been extensive, with many improvements being made such as **increased stability**, **heat resistance**, and **length of fluorescence**. The development of various GFP colour variations (e.g. cyan and yellow, CFP and YFP respectively) has been pioneered by **Roger Y. Tsien**, an American biochemist, providing a rainbow colour palette for scientists to paint cells with. The protein can also be customised to suit the needs of a particular study, such as being able to bind to a specific substrate to act as a **marker**. GFP has been used to visualise and study gene expression, embryo development, cancer metastasis and many other cellular processes in vivo.

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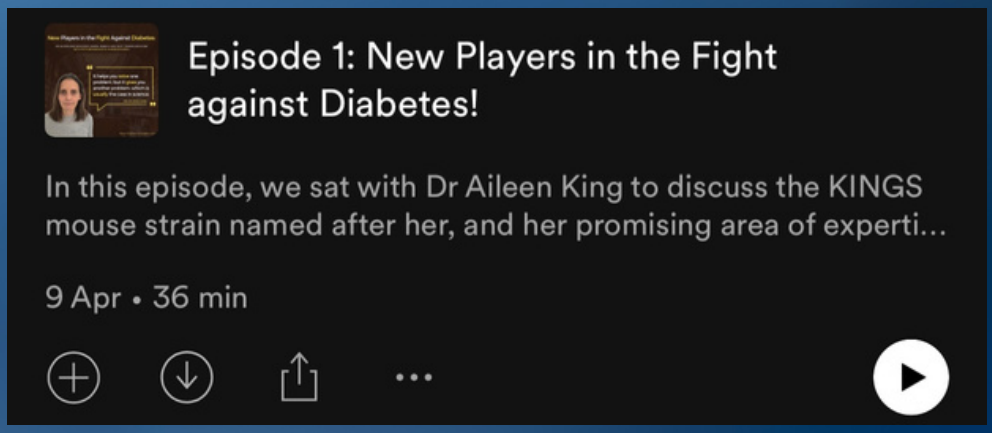

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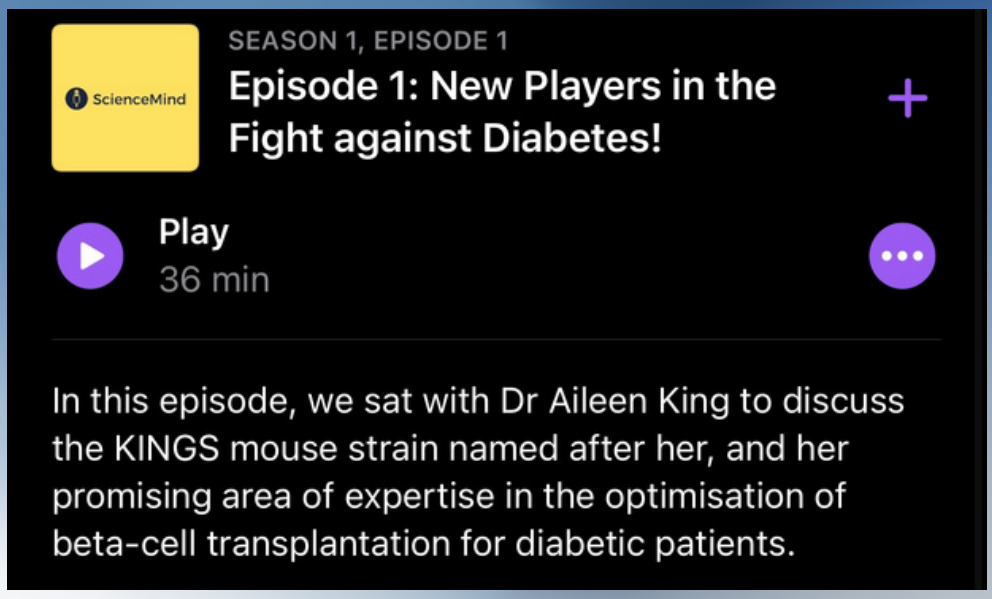

SHALLOW DIVE

Maternal Genetic Predisposition to **Inflammation** May Lead to **Autism-related Traits**

WRITTEN BY JULIET CHEN
EDITED BY MAHIMA KOTECHA

A recent study has unveiled the possibility that women who are genetically predisposed to inflammation may be more likely to have children with symptoms of autism.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder which is often characterised by its phenotypic and aetiological complexity. Through early twin studies, autism has been established to be highly heritable, with its aetiology containing a large genetic component. Despite this, roughly 80% of cases still cannot be explained by a single genetic cause. Therefore, the risk of autism is thought to be a result of multiple mutations and environmental factors, each possessing a minor additive effect.

Previous research has already suggested that **maternal inflammation during pregnancy,** resulting from conditions such as infection or autoimmune disorder, is a causative factor of increased autism risk. The new study uses PTEN, a tumour-suppressing gene that's strongly associated with ASD, to investigate the role that maternal genetics may have in inflammation-related autism risk. PTEN mutations possess approximately 23% penetrance and account for up to 2% of all autism cases.

The researchers developed a transgenic line of mice that had a heterozygous loss-of-function mutation of PTEN, containing only one functional PTEN gene compared to the two in normal wildtype mice. To investigate the impact of maternal genetics on offspring, the litters of PTEN vs wildtype mothers were compared. Offspring of PTEN mothers, even those that do not possess the autism-associated genotype, show increased autism-like behaviour compared to those from wildtype mothers. On the other hand, offspring that were actually genetically predisposed to autism showed less prominent symptoms of autism when born from a wildtype mother. The researchers explain that maternal genetics may not only lead to neurodivergent traits, but also play a protective role against autism predisposition.

Regarding maternal predisposition to inflammation, PTEN mothers showed significantly lower levels of the anti-inflammatory immunosuppressant IL-10 during pregnancy, which directly correlated with a decreased expression of complement proteins in their foetuses. Additionally, these foetuses also had signs of neuronal loss and increased breakdown of the blood brain barrier which would normally protect the brain from harmful substances. This shows a direct impact of maternal immunosuppression on foetal physiology, fundamentally uncovering a potential relationship between maternal genetic factors, in-utero immunosuppression, and foetal neurodevelopment.

This exciting discovery can pave the path for future work in understanding the complex genetic aetiology of autism, showing that **neurodevelopment can be indirectly influenced by genetics in many ways.** The researchers suggest the possibility of future genome-wide association studies to identify specific relevant IL-10 genes in mothers, with the ultimate aim of being able to predict and treat women with such genetic predispositions in clinical applications (Jaini et al., 2021).

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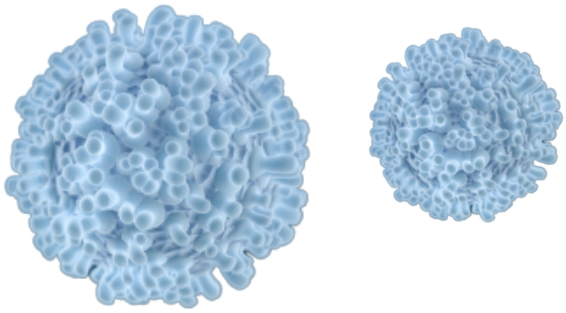
THREADING WATER

The Effect of Environmental Exposures on the Prevalence of Autoimmune Diseases

WRITTEN BY ROSA TSUCALA
EDITED BY HUDA HAMMAD RATTU



An autoimmune disease is characterized by the over-activity of the immune system and the consequential attack on self- antigens, resulting in tissue damage. Common autoimmune diseases include but are not limited to: Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA) and Type I Diabetes Mellitus (T1DM). A common misconception about autoimmune diseases (AD's) is that their development is only due to genetic factors and heritability. Although this statement isn't false in its entirety, there are other factors that come into play in the development of an AD (see Figure 1), such as epigenetic changes.

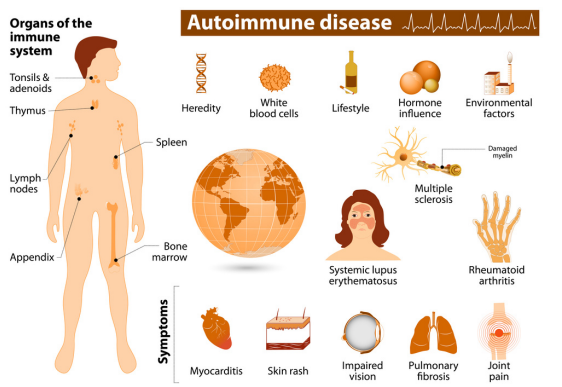


Figure 1. Risk factors for autoimmune diseases. Epigenetic changes are represented by environmental factors and hormone influence.

Conrad Waddington introduced the term epigenetics in the early 1940s. He defined epigenetics as ''the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being.'' In other words, epigenetic modifications are structural changes that occur to the DNA without changing its base sequence, that may influence gene expression and result in changes of the phenotype (see Figure 2).

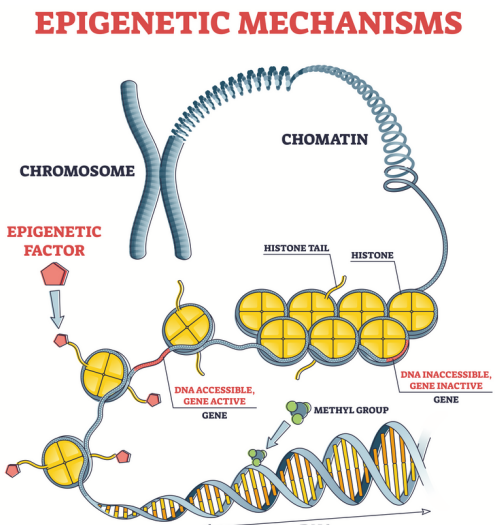


Figure 2. The effect of epigenetic factors on the accessibility of the DNA. The addition of an epigenetic factor such as a methyl group can deactivate the gene by causing it to supercoil and therefore making it inaccessible.

Evidence suggests that epigenetic changes can serve as an on-off switch mechanism for genes involved in the autoimmune response. An individual that possesses a gene for a specific disease is more prone to develop it. However, the individual is more likely to develop the disease when an environmental trigger such as a hormonal - microbial imbalance or psychosomatic stress is introduced. This trigger will lead to the loss of immunological self-tolerance and the initiation of an immune response against self-antigens, which will eventually be expressed as an autoimmune disease. However, if a trigger is not introduced it is likely that the disease will not be expressed. Therefore, it can be derived that environmental factors play a crucial role in the development of an autoimmune disease in combination with genetic biomarkers and can be targeted for effective treatment and prevention.

Which environmental factors play a role in the development of an autoimmune disease?

1.Human Microbiome

Research regarding AD's has dramatically shifted since the discovery that the human microbiome plays a pivotal role in their development. The human microbiome comprises of the aggregate of symbiotic microbial cells that are found within bodily tissues and fluids. Many AD's such as inflammatory bowel disease (IBL), multiple sclerosis (MS), and SLE have disease-related microbiome profiles. The gut microbiome, which is normally tightly regulated by homeostatic mechanisms such as intestinal barrier maintenance, is involved in both adaptive and innate immune responses. However, an underlying genetic defect in combination with environmental exposures can result in the disruption of homeostasis and therefore lack of microbiome regulation. This interaction can have systemic effects on immunity and lead to chronic inflammatory and autoimmune diseases.

2.Oxidative Stress

Oxidative stress is defined as "a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses" Low amounts of reactive oxygen species (ROS) have beneficial effects on the organism including wound healing, killing of pathogens and tissue repair activation. The presence of excessive amounts of ROS has effects on cellular responses and can induce apoptosis and gene activation (epigenetic change). More specifically, research has shown that oxidative stress in combination with UV radiation

increases the expression of an autoantigen on the surface of keratinocytes. Moreover, the investigation of patients with RA, SLE, and Sjögren's syndrome indicated that they were in excessive oxidative stress.

3.Micronutrient deficiencies

Vitamins and nutrients such as Vitamin D, Vitamin C and omega-3 are crucial for the
normal functioning of the immune system. Nutrient deficiencies can be very detrimental to the immune system and are linked to insufficient leukocyte maturation and decreased ability to defeat exogenous pathogens. They are also linked to over-activity of the immune system on the body's own tissues and fluids. Micronutrient deficiencies can be restored by the improvement of diet and the administration of nutritional supplements.

4.Mental Stress

Although not sufficient to cause an AD on its own, mental stress causes hormonal and metabolic imbalances that may lead to autoimmunity. It can act as a trigger for AD's such as SLE, psoriasis and T1DM.

5.Insulin resistance

Consumption of foods high in sugar cause the organism to produce higher levels of insulin to maintain blood sugar levels constant. This can cause increased inflammation and deregulation of the immune system

6.Cigarette Smoking

There is a causal link between cigarette smoking and autoimmune disease development.

AD's linked with cigarette smoking include RA, SLE, MS, Graves' hyperthyroidism, and primary biliary cirrhosis.
Having in mind the aforementioned, we can come to the conclusion that the development of an autoimmune disease is not only due to heritability. Epigenetic changes and environmental exposures play a significant role in autoimmunity. This gives individuals the ability to control their own health through a healthy lifestyle, even though they might be genetically predisposed to a certain disease. Research regarding AD's is ongoing, and its findings keep improving treatment and prevention strategies for patients.

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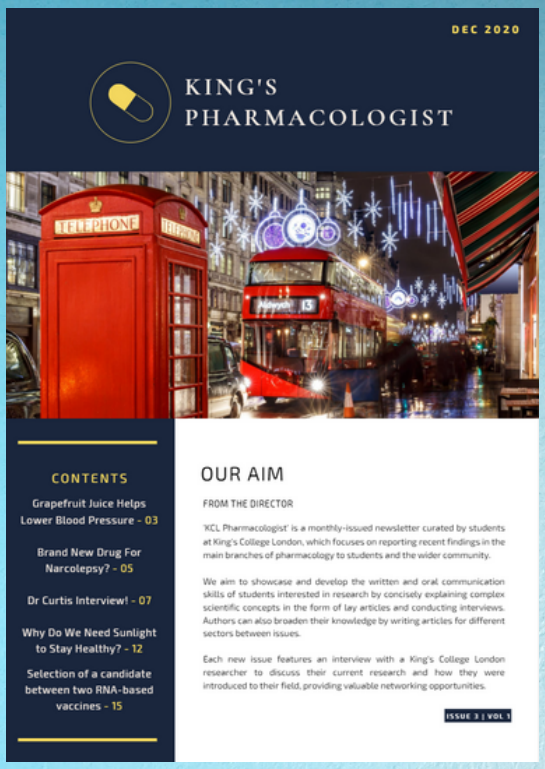
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OUR AIM

FROM THE DIRECTOR

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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.

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ISSUE 2 | VOL 1

Here is a look at all our old issues, we have now remastered all ScienceMind magazine issues.

SHALLOW DIVE

The Complex **Human History** found in Dirt

WRITTEN BY KIRA LINKE
EDITED BY AMINA IGENBEK

Over 100 000 years of human history are represented in the Denisova Cave in southern Siberia. It is named after a hermit, Dyonisiy, who sheltered in it in the 18th century, but ancient artifacts of needles, tools, decorative bone, and jewellery found here prove that the cave sustained creative human life long before that. Dozens of hominid remains have been excavated from the site, including Denisovans, Neanderthals, a child of a Neanderthal and Denisovan (the discovery of which was only published in 2018), and modern humans. However, a dozen remains is far too insufficient to be able to reconstruct an even somewhat exact timing and sequence of occupation. So, as a pilot study, archaeologists took 52 sediment samples and were successful in extracting mitochondrial DNA (mtDNA) from 12 of them. This was followed by a great collaboration between German, Australian, Russian, and Israeli scientists to analyse 728 more samples, taken in a grid-like pattern from exposed Pleistocene epoch deposits of all chambers of the cave. The 685 samples that were found to contain animal and human mtDNA were enriched, and the biological-family level of each mtDNA ascertained.

175 of these samples contained humanoid DNA (79 Denisovan, 47 Neanderthal, 35 modern human), which provides a genetic record of humans in all three major stages of the epoch in all chambers of the cave. Interestingly, four of the genetic sequences could be linked to previously sequenced DNA from actual Neanderthal and Denisovan remains. The most complete mtDNA sequence could be reconstructed to over 99% and was of a Neanderthal, and the eldest mtDNA found was identified as Denisovan in a sediment layer that dates to 250±44 thousand years ago. This is the oldest genetic evidence for hominin occupation of the cave, and suggests that Denisovans were the creators of the oldest artifacts found, as they coincide with Denisovan occupation. According to the DNA record, Neanderthals only started contributing to the creation of artifact assemblages towards the end of the early Middle Palaeolithic era. Later, towards the Initial Upper Paleolithic, nothing rules out that Neanderthals, Denisovans and modern humans all occupied the cave at a similar time.

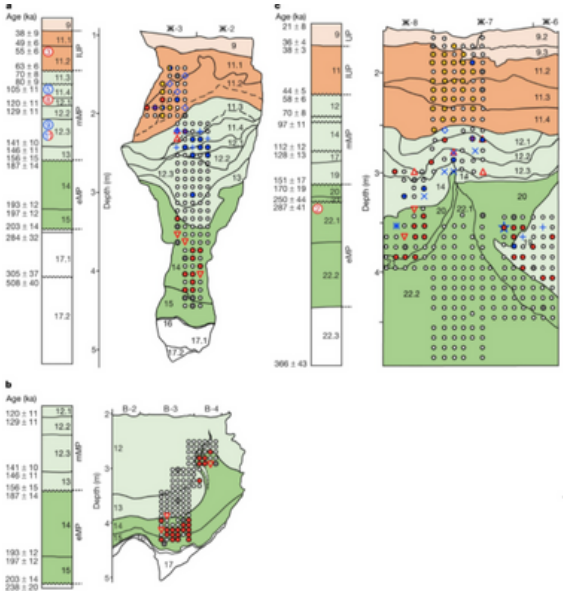

Figure 1. a, East Chamber, southeast profile. b, East Chamber, northwest profile. c, Main Chamber, southeast profile. The time scale is in ka units, meaning thousands of years. Circles on the maps represent the sampling site, and the colour denotes the mtDNA found, where red is Denisovan, blue is Neanderthal, yellow is ancient modern human, and grey is unidentified ancient hominin.

From the Neanderthal DNA, three lineages could be identified: 'typical' Neanderthal DNA, the Sima de los Huesos lineage, which lived 430 thousand years ago around what is now Spain and are closely related to Denisovans, and the Hohlenstein-Stadel lineage, which falls basal to the other lineages, meaning that on a phylogenetic tree, they are the most genetically different while still branching from the same stem ancestor.

The archaeologists also analysed the fauna DNA they isolated. Of the most interesting discoveries:

- Elephantid mtDNA was predominantly woolly mammoth.
- The relative abundance of ursid mtDNA shifted from cave bear to exclusively brown bear around 150 thousand years ago.
- Archaic hyena mtDNA also presented three lineages like humanoids - African spotted hyenas, east Asian cave hyenas, and European cave hyenas. The overlap in time lines suggests that the mountains around the Denisova cave were contact zones between lineages of hyenas, just as for humans.

Changes in relative abundance of fauna coincides with great climatic transitions. Changes in the human population are believed to have been driven either in response to those different fauna, or also been in response to the changing ecological environment.

While the researchers acknowledge the limitations of utilising DNA preserved in sediment to establish a genetic chronology, such as two major time gaps in the stratigraphic record, burrowing animals may have displaced sediment, and the imprecision of the optical layers, this paper demonstrates the remarkable ability of modern scientific techniques. An incredible international effort made this possible. These scientists have constructed detailed phylogenetic trees by means of some dirt samples, and allowed us to marvel at the lives we can imagine were led in that cave by the artifacts found.

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STUDENTS FOR SENSIBLE DRUG POLICY KING'S COLLEGE LONDON

THE WAR ON DRUGS IS A WAR ON US!

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DEEP DIVE

RNA: The Dawn of a New Era

WRITTEN BY RISHA DUGGAL
EDITED BY DRSHIKA MEHTANI

The fight for survival between donors & the availability of desired organs has led to the use of inferior and incongruous organs, thus increasing the risk of developing **ischemia-reperfusion injury** in individuals' manifold. Ischemia-reperfusion is a condition characterised by the reflow of blood to the hypoxic tissues leading to tissue damage. Therefore, researchers have developed **RNA interference (RNAi)** to ensure delivery via the method of organ transplantation.

RNA is also known as ribonucleic acid is a nucleic acid known for its self-replicative property acting as a bridge to convert information into proteins. **Double-stranded RNA** (dsRNA) arising from pre-existing viruses, is sliced by **dicer**, an enzymatic component in eukaryotes, into base pairs of **simple interfering RNA** (siRNA). dsRNA failed in its use as a therapeutic due to its stress mechanism on entering mammalian cells. With the use of siRNA, a protein called **RISC** (RNA-induced silencing complex) unwinds its strands while eliminating the passenger strand; it targets the wanted messenger RNA or mRNA sequence to be silenced (Figure. 1).

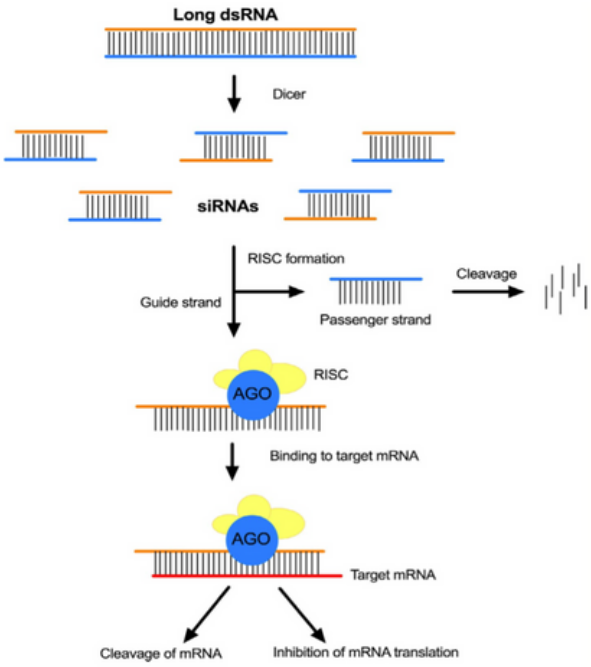

FIgure 1a. Schematic illustration of the mechanism of RNAi

Various variable RNAs, for example, microRNA/siRNA, short hairpin RNA (shRNA), and substrate RNA differ in silencing pathway, RISC molecules involved, and the period required for the silencing process.

siRNA delivered to the host via viral vector express higher efficiency in gene silencing processes as compared to the non-viral vectors like polymeric chains, cationic lipids, and inorganic nanoparticles of matter. The sole disadvantage of this procedure is the activation of oncogenes in the host.

Pre-insertion, the organ is kept externally and is flushed regularly to prevent excessive siRNA to act on undesired recipient receptors. This method is known as **ex-situ machine perfusion** and is highly beneficial to prevent the overexpression of siRNA.

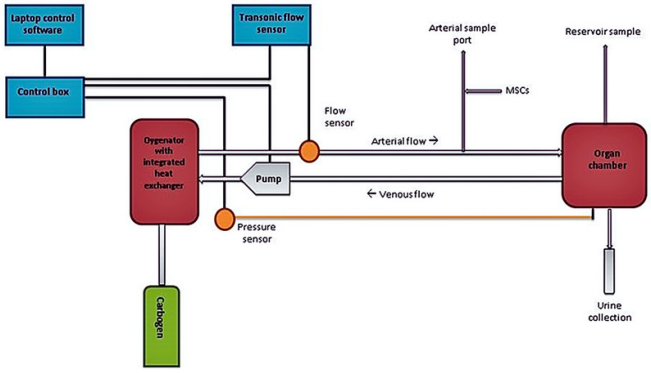

FIgure 1b. Ex-situ method of preservation in the kidney (Taken from Pool et al., 2019).

In the liver, laboratory mice were injected with **caspases 3** and **8 siRNA**, 48 hours prior to the procedure. It was found to have **reduced** Aspartate aminotransferase (AST), inflammatory cytokines of NALP3 (Nucleotide-binding oligomerization domain, Leucine-rich Repeat, and Pyrin domain-containing family pyrin domain 3) release as well as improve histological stress by reducing oxygen demand. Similar effects were spotted on TNF alpha and PHD1 targets. While considering the molecules trigger immune responses in the lungs through pathogenic molecular patterns, interferons and TLR pathways either Beta dependent or independent are triggered.

Restrictions of siRNA are due to its large **molecular size**, **weight**, and its **negative charge** and therefore is repelled by the lipid cell membrane. Due to their unspecific nature, they pose a threat to non-target cells too. The latest success of the use of RNAi in kidney transplantation was when the p53 gene was silenced thus minimising the chances of delayed graft function (DGF) and thereby reducing chances of organ rejection.

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DEEP DIVE

NEOANTIGEN VACCINES: The Future of Cancer Immunotherapy?

WRITTEN BY AMINA IGENBEK
EDITED BY ROSA TSUCALA

Cancer is a disease associated with uncontrollable cell proliferation (tumour formation) and, in some cases, metastasis from the tissue of origin into other tissues. Traditionally, there are **six hallmarks of cancer**: growth signal autonomy, insensitivity to anti-growth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. It is a genetic disease- caused by **mutations** in genes mostly associated with cell division and growth, and DNA repair. Some of the treatments for cancer include surgery, chemotherapy, radiation, and immunotherapy, which is aimed at activating or amplifying the body's **immune response** to tumour cells. With vaccines against SARS-CoV-2 at the forefront of public awareness, it is interesting to consider vaccines that are levelled not at infectious pathogens, but the body's own **malignant cells**.

Cancer vaccines can be divided into two main categories: preventative and therapeutic. **Preventative vaccines** immunize people against pathogens that are known to cause cancer, for example vaccines against carcinogenic types of HPV. Immunization against these viruses protects from developing cervical and other types of cancer. As of right now, there are no preventative vaccines for non-viral-associated cancers.

Therapeutic cancer vaccines aim to potentiate the tumour-specific T-cell response. In order to understand how these vaccines work, we should look at the components of the **tumour microenvironment** (TME) (Figure 1). In the TME, cells of the innate immune system (natural killer cells, macrophages and neutrophils) immediately recognize and attack the tumour, while dendritic cells (DCs) capture and cross-present antigens released by tumour cells undergoing immunogenic cell death on MHC-I and MHC-II molecules.

The antigen-presenting DCs then travel to a secondary lymphoid organ, where interactions between the MHC cells and T cell receptors of naïve CD4+ and CD8+ T-cells triggers T-cell maturation. The **mature T-cells** then travel back to the tumour and control its growth via direct killing and IFNγ-mediated prevention of cancer cell proliferation.

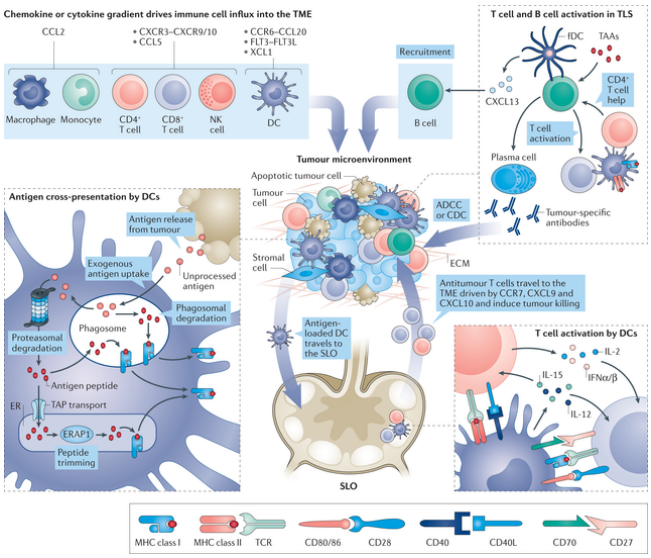


Figure 1. The tumour microenvironment and its components. A chemokine gradient drives immune cells to the TME. Dendritic cells (DCs) take up and cross-present tumour antigens on MHC class II or MHC class I molecules. Antigen-presenting DCs travel to the secondary lymphoid organ (SLO). DCs secrete cytokines and activate T cells due to an interaction between MHC–peptide complex–T cell receptor (TCR) and cognate receptor–ligand pairs. CD4+ T cells secrete IL-2 and amplify CD8+ T cell responses. Activated T cells travel to the TME and induce tumour killing. Antigen-loaded DCs activate T cells and follicular DCs (fDCs) in tertiary lymphoid structures (TLS), facilitating the generation of memory B cells and antibody-producing plasma cells. Activated T cells, B cells and antitumour antibodies cause tumour cell death. (Taken from Saxena et al., 2021).

Cancer vaccines contain **tumour-specific antigens**, which should ideally stimulate the body's adaptive immune system to attack the tumour, preventing its growth and inducing regression. In the past, cancer vaccines mostly contained **tumour-associated antigens** (TAAs), which are self-antigens that are overexpressed or modified in the tumour. Unfortunately, as of right now, only one such vaccine, **sipuleucel-T**, has been approved in the treatment of prostate cancer, and even then, it has a very low efficacy in improving survival. There are many reasons why cancer vaccines have so far been unsuccessful and one of them is the fact that the body has **tolerance to self-antigens**, making it difficult to induce an effective immune response.

Neoantigen Vaccines

This is where neoantigen vaccines come in. Mutations in tumour cells can give rise to **novel epitopes**, which are the parts of the antigen that are recognized by the immune system, that are specific to that particular cancer. The advent of next generation sequencing has made it feasible to develop tumour-specific, personalized cancer vaccines by sequencing the genome of the tumour. Neoantigen vaccines have a number of advantages over the aforementioned type of therapeutic cancer vaccines. Due to the de novo nature of the epitopes, they eliminate the issue of self-tolerance. Furthermore, as neoantigens are only expressed by the tumour, the risk of off-target effects and vaccine-induced autoimmune toxicity, wherein the vaccine causes the immune system to attack non-tumour cells that express TAAs, is decreased.

These vaccines can be administered as peptides, DNA, or mRNA and have been shown to be effective in patients with certain subtypes of melanomas, which form in a subtype of skin cells called melanocytes, and gliomas, which form in the glial cells of the nervous system.

One of the glioma vaccines, called **IDH1-vac**, was targeted at mutated isocitrate dehydrogenase-1 (IDH1) in newly diagnosed gliomas and was shown to be safe and immunogenic (producing an immune response) in a single-arm, first-in-human trial. Another vaccine, **NeoVax**, targets stage III and IV melanomas at high risk of rejection. Other key clinical trials include **IVAC MUTANOME**, an mRNA vaccine against late-stage melanomas, and **GAPVAC**, a peptide vaccine against glioblastomas. The success of these trials and others of this type proves that neoantigen vaccines potentiate T-cell response.

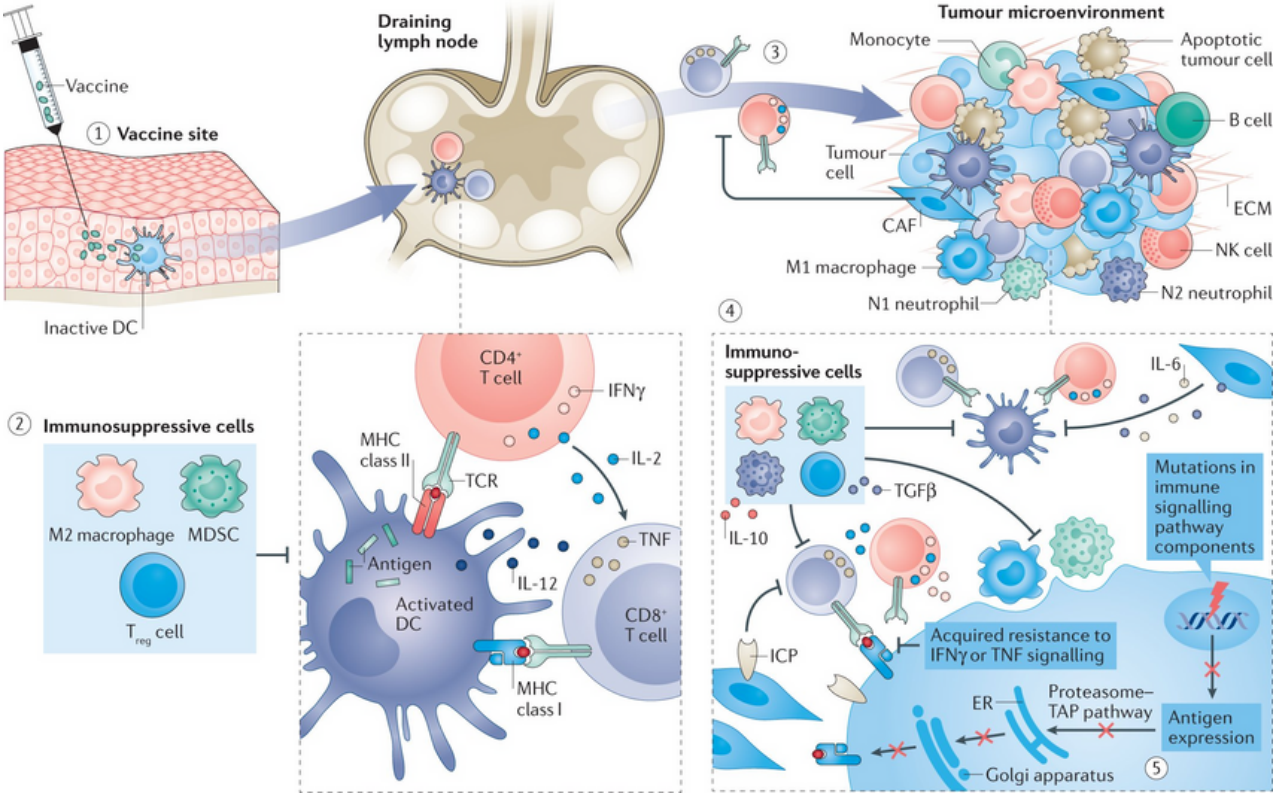
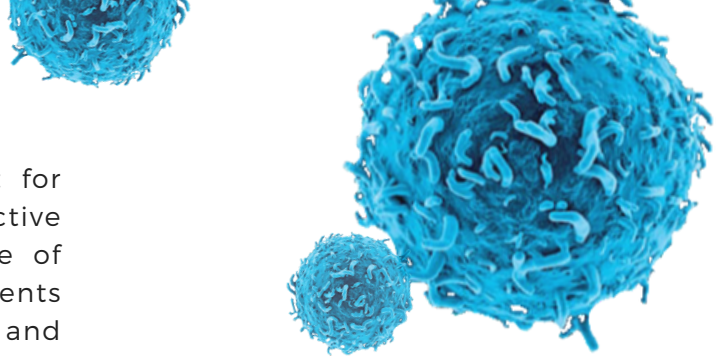
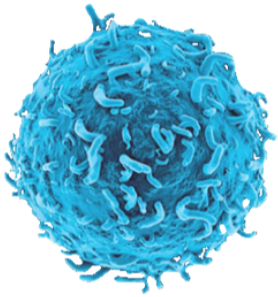


Figure 2. Mechanisms of tumour resistance to vaccines. Tumour extrinsic mechanisms: Excessive levels of immunosuppressive type 2 macrophages (M2 macrophages), myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Treg cells) are present in the TME. These may impair activation or alter the quality of tumour-reactive T cells (2). Chemokine-gradient and cytokine-gradient regulation by cancer-associated fibroblasts (CAFs) and a dense extracellular matrix (ECM) may impair the immigration of the activated T-cells from the lymph node to the TME (3). In the tumour cell bed: CAFs may impair (DC) trafficking via IL-6 and TGFβ. IL-6 and IL-10 secreted by immunosuppressive cells impair DC-mediated local T cell activation and block development of tumouricidal M1 macrophages and N1 neutrophils. Tumour-resident T cells are prevented from exerting their function by arginase 1, inducible nitric oxide synthase (iNOS), reactive oxygen species and immune checkpoint (ICP) molecules (4). Tumour-intrinsic mechanisms: mutations in signalling pathways associated with the immune control of tumours; lowering or loss of tumour antigen expression or alterations in antigen processing pathway. This results in suboptimal recognition of tumour cells by T cells. Moreover, the activation and impact of T-cell function is impeded by constitutive expression of the ligands for ICPs and acquired resistance to TNF and IFNγ. (Taken from Saxena et al.,2021).



Nevertheless, there is hope yet for the formulation of clinically effective cancer vaccines. Our knowledge of the TME and the way its components interact is increasing every day, and this will lead to a better understanding of what is needed for a cancer vaccine to be successful. Thus, despite the seeming lack of success in this branch of cancer treatments, the future is fraught with possibilities for new cancer immunotherapies.



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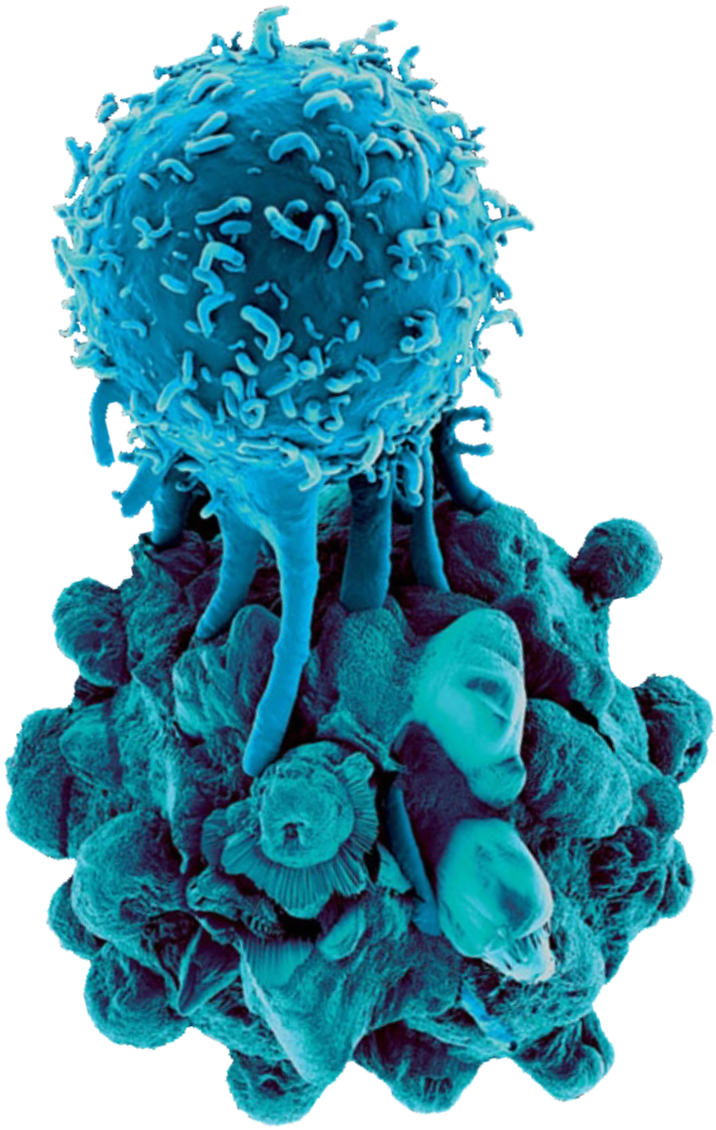
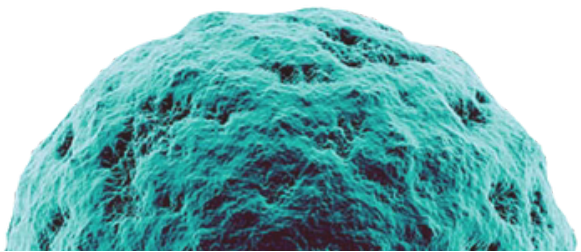


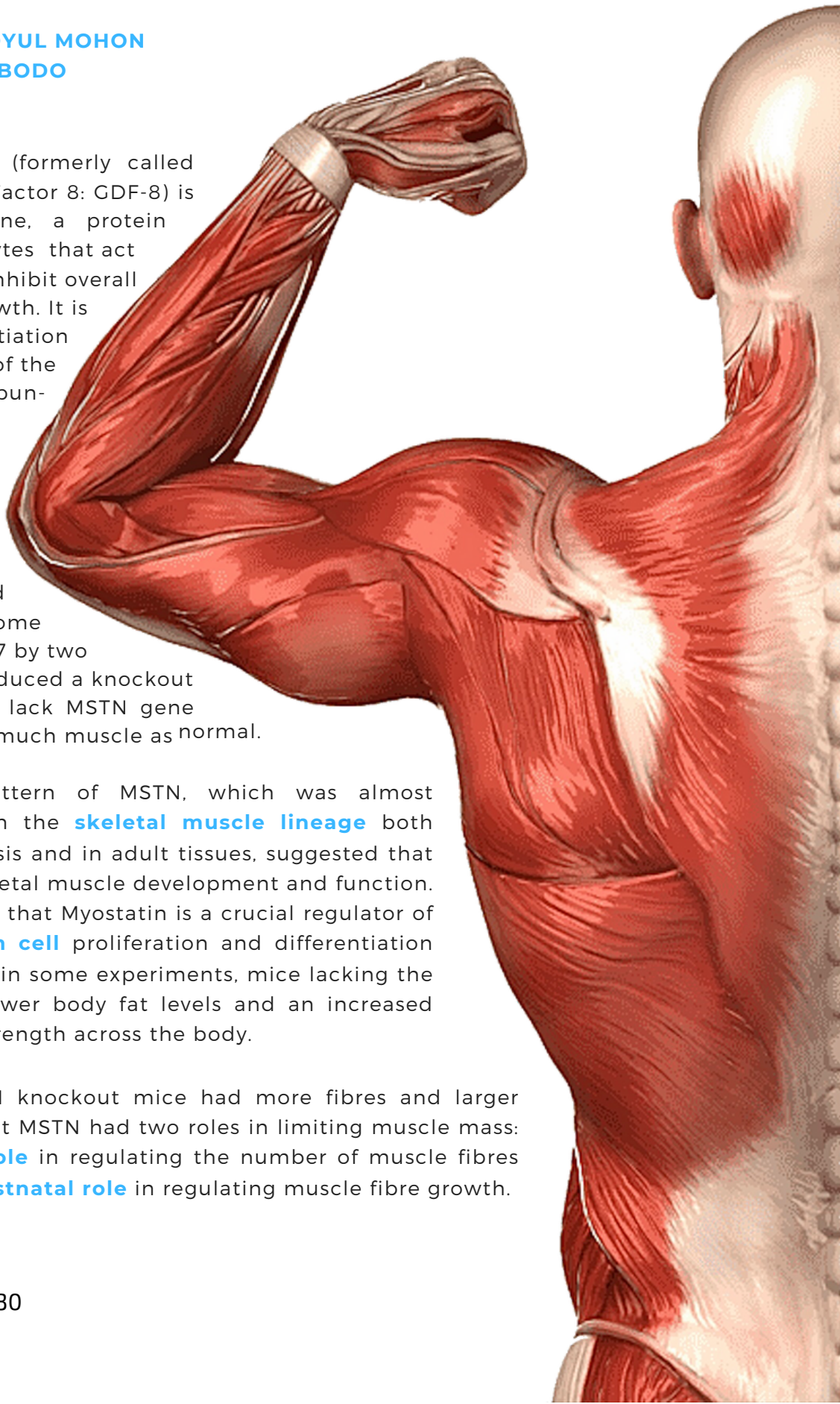


THREADING WATER

HERCULE'S GENE

WRITTEN BY ANMOYUL MOHON
EDITED BY TAMAS BODO

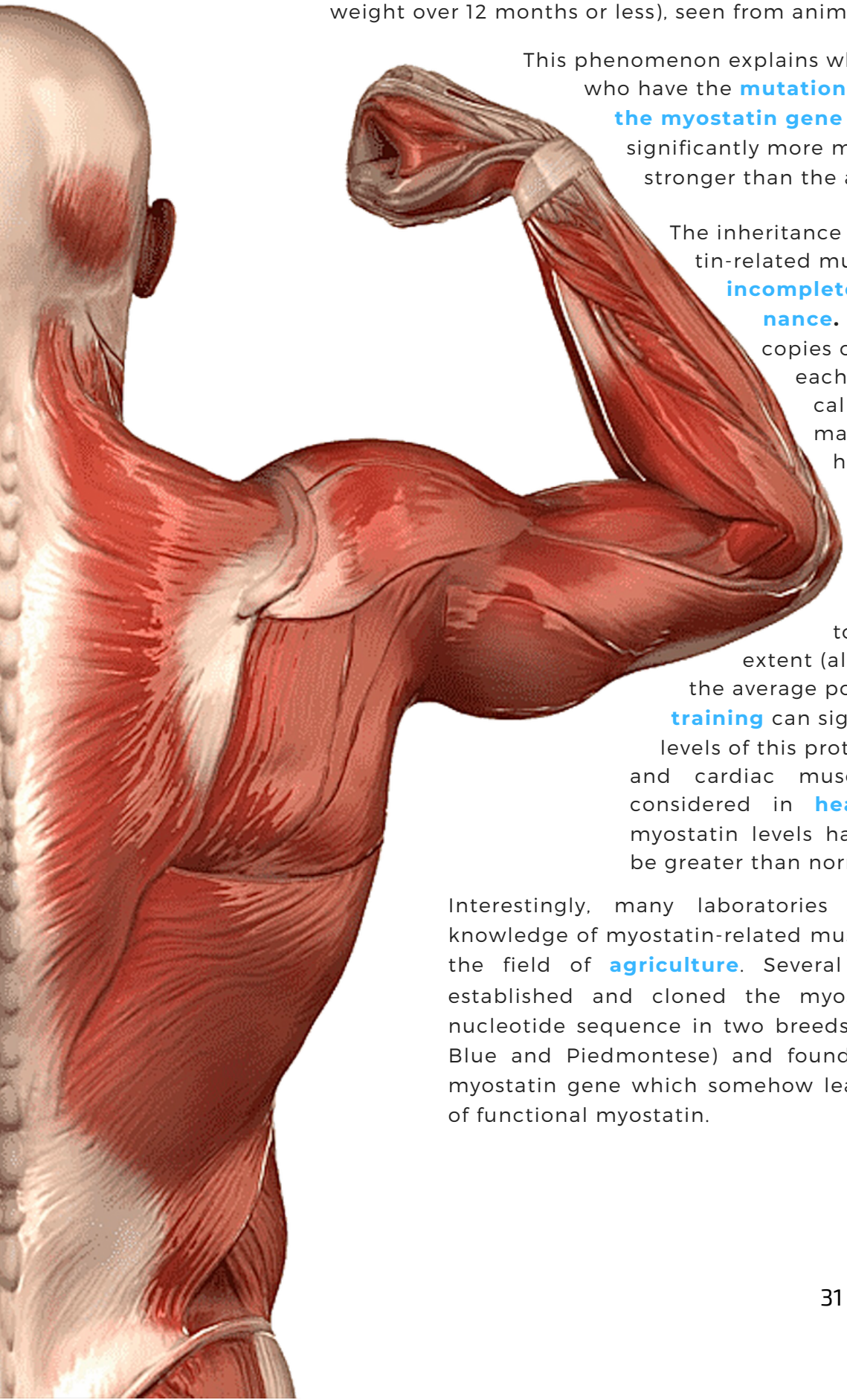
Myostatin (formerly called Growth Factor 8: GDF-8) is a myokine, a protein produced by myocytes that act on muscle cells to inhibit overall muscular tissue growth. It is a growth differentiation factor that is part of the **TGF beta-1** family abundantly expressed in skeletal as well as striated muscle cells. In humans, myostatin is encoded by the **MSTN gene** (located on human chromosome 2) discovered in 1997 by two geneticists who produced a knockout strain of mice that lack MSTN gene leading to twice as much muscle as normal.



The expression pattern of MSTN, which was almost exclusively found in the **skeletal muscle lineage** both during embryogenesis and in adult tissues, suggested that it may a role in skeletal muscle development and function. It is now recognised that Myostatin is a crucial regulator of **mesenchymal stem cell** proliferation and differentiation which explains why in some experiments, mice lacking the MSTN gene have lower body fat levels and an increased bone density and strength across the body.

The fact that MSTN knockout mice had more fibres and larger fibres suggested that MSTN had two roles in limiting muscle mass: a **developmental role** in regulating the number of muscle fibres generated and a **postnatal role** in regulating muscle fibre growth.

Similarly in other organisms, this myostatin **deficiency** (or even loss-of-function) causes a dramatic muscle mass increase leading to an overly muscular appearance. Conversely, an **overabundance** of this myostatin protein causes a delay in muscle development which can go as far as cachexia (the loss of more than 5% body weight over 12 months or less), seen from animal models.



This phenomenon explains why some individuals who have the **mutations in both copies of the myostatin gene** (homozygous) have significantly more muscle mass and are stronger than the average population.

The inheritance pattern for myostatin-related muscle hypertrophy is **incomplete autosomal dominance.** Homozygotes (both copies of the MSTN gene in each cell) have dramatically increased muscle mass & strength whilst heterozygotes (those who have a mutation in 1 copy of the MSTN gene in each cell) have more muscle mass too, albeit to a lesser extent (although higher than the average population). **Physical training** can significantly lower the levels of this protein in both skeletal and cardiac muscle. This can be considered in **heart failure** where myostatin levels have been shown to be greater than normal.

Interestingly, many laboratories have taken their knowledge of myostatin-related muscle hypertrophy to the field of **agriculture**. Several laboratories have established and cloned the myostatin gene MSTN nucleotide sequence in two breeds of cattle, (Belgian Blue and Piedmontese) and found mutations in the myostatin gene which somehow leads to the absence of functional myostatin.

The discovery of regulatory and signalling components of the **MSTN pathway** (Figure 1) has also led to the creation of a number of pharmacological drugs (such as follistatin) capable of inhibiting MSTN function in vivo. With this said, animals lacking myostatin or treated with substances that block the binding of myostatin to its receptor have significantly larger muscles (although no more than 40% of muscle increase).

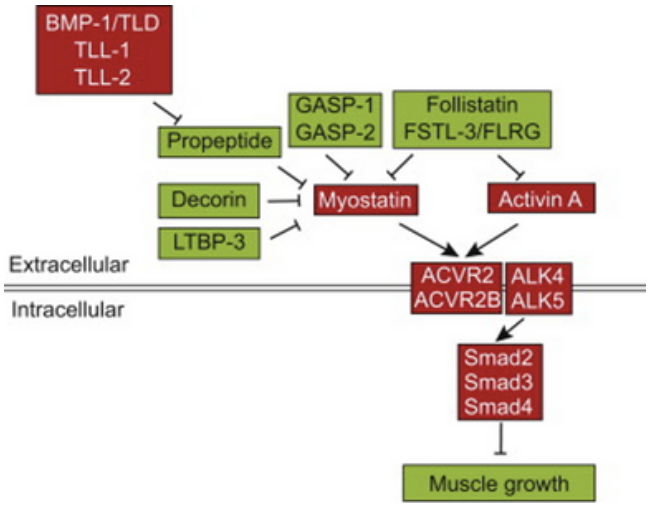
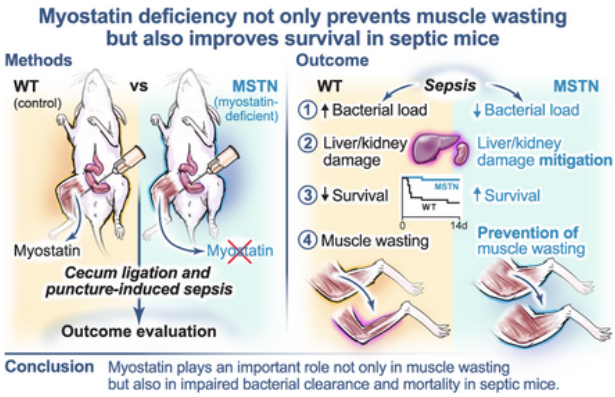


Figure 1. Regulatory and signaling component. Signaling through this pathway is promoted by the components outlined in red, which suppresses muscle growth. Components in green inhibit signalling in this pathway, which stimulates muscle growth.

Lowering myostatin levels could, in theory, benefit the livestock business, proposing future studies over such practices. Unfortunately it has been seen that homozygous animal breeds for myostatin deficiency suffer reproductive challenges (birthing difficulties) requiring particular care due to excessive size, or an overly expensive diet to attain a higher yield mainly due of their exceptionally hefty and bulky progeny which has a negative impact on the economics aspect of myostatin-deficient breeds to the point that they no longer present a clear advantage. Nonetheless, there is still hope that studies on myostatin and its gene may provide potential therapeutic application in **treating muscle wasting diseases** such as muscular dystrophy.

Over a two-week treatment, normal mice with **soluble activin type IIB receptor**, a molecule that is associated with cells and binds to myostatin, gain much more muscle mass. Myostatin's attachment to the soluble activin type IIB receptor is hypothesised to prevent it from connecting with cell-bound activin receptors.

Scientists reported in September 2020 that inhibiting the activin type 2 receptors-signalling proteins myostatin and activin A with the activin A/myostatin inhibitor, **ACVR2B**, can protect mice from both muscle and bone loss. The mice were transferred to the International Space Station and due to genetic engineering for targeted deletion they were able to maintain their muscle weights - nearly twice that of wild type mice.



As **myostatin inhibitors** might cause muscular hyperplasia, hypertrophy and to a certain extent boost athletic performance there is concern that they will be **overused in sports**. The World Anti-Doping Agency (WADA) has banned the use of myostatin inhibitors, though in contrast, the legal supplement Creatine remains approved which also effectively lowers myostatin levels.

Altogether from various data, Myostatin appears to be an essential **regulator of muscle mass** and **bone density** according to evidence from human trials and animal models. The mechanisms by which myostatin affects bone formation are unknown, although it is apparent that myostatin has direct impacts on mesenchymal stem cell proliferation and differentiation, and that myostatin and its receptor are expressed during bone regeneration. As a result, myostatin appears to be a **potent anti-osteogenic factor** that inhibits osteo- and chondroprogenitors' proliferation and perhaps survival. Other data believe that enhanced bone mineral density observed in many parts of the skeleton are more likely to represent direct effects of myostatin deficiency on bone rather than mechanical reactions or adaptations to increased muscle mass.

Once proven that myostatin has direct anti-osteogenic actions in bone, then **myostatin inhibitors** could be the key to increase bone density, strength, and muscle mass. Recent studies reveal that a recombinant decoy myostatin receptor greatly boosted bone growth and bone mass in mice, confirming this prediction.

Future studies utilizing conditional knockout mouse models with targeted deletions of either myostatin or its receptor in osteoblasts, chondrocytes, or bone marrow stromal cells may shed light on the underlying molecular mechanisms by which myostatin influences bone and cartilage formation. Moreover, **systematically given myostatin** has been shown to cause muscle wasting and transgenic mice overexpressing myostatin have lower muscle mass, the exact skeletal phenotype(s) associated with persistently high myostatin levels has yet to be elucidated. Equally in clinical situations such as with muscular dystrophy , anorexia nervosa, HIV, and cancer-related cachexia, myostatin levels are likely to rise and cause significant loss of both muscle and bone.

It is therefore important to gain a better knowledge and fully elucidate all facets of **myostatin-induced osteopenia** and **sarcopenia**, as it holds great potential for the development of novel therapeutic interventions and use in many different fields of science.

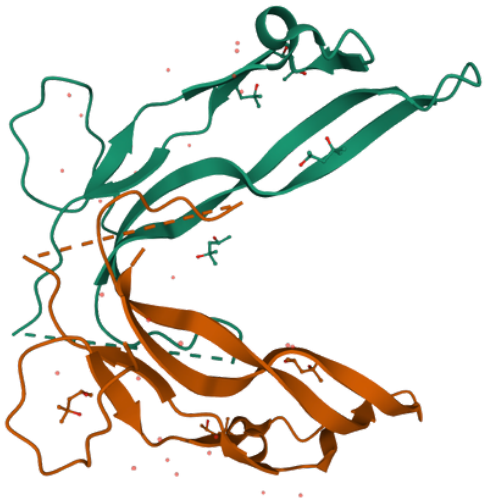
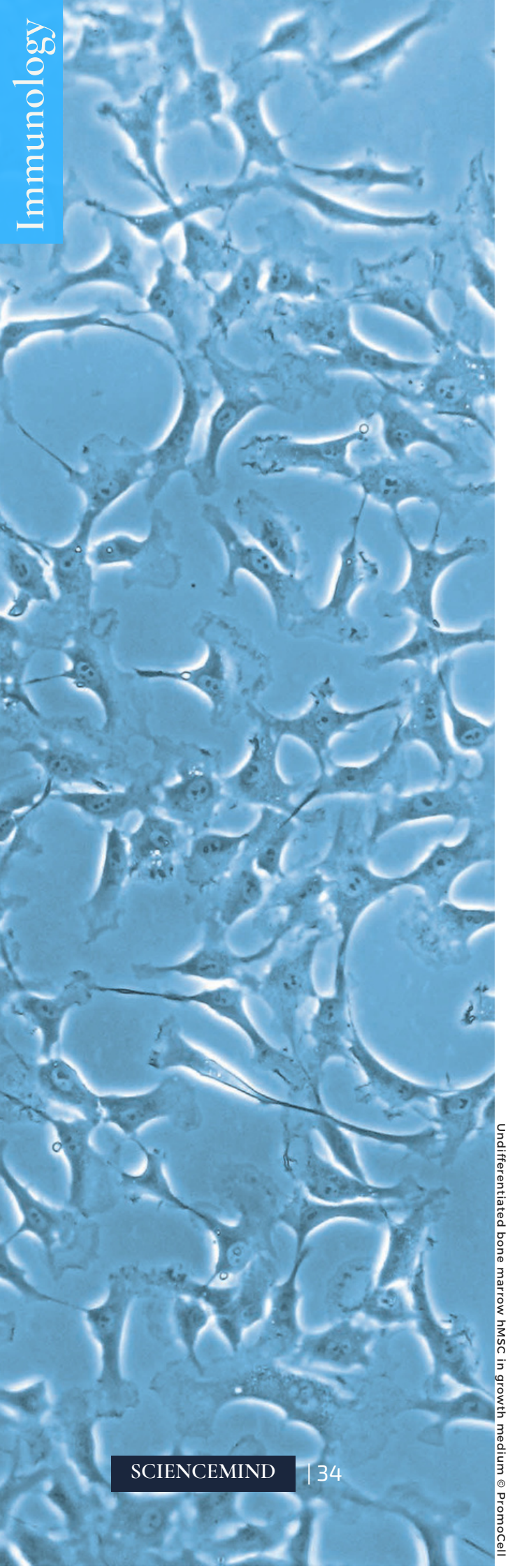


Figure 2. Crystal structure of mouse (Mus musculus) myostatin (RCSB PDB, 2019)



Undifferentiated bone marrow hMSC in growth medium © PromoCell

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THREADING WATER

COVID-19: Shifting from Proteomics to Virology

PROFESSOR MANUEL MAYR DISCUSSES HIS NOVEL COVID-19 RESEARCH WITH ZAHRAA BHATTI

Professor Manuel Mayr is a British Heart Foundation Professor of Cardiovascular Proteomics. He studied Medicine at the University of Innsbruck, Austria in 1999 and has always had a great interest in biology and medical research. He then moved to London to complete his PhD in Cardiovascular Proteomics at St George's University. Due to the coronavirus pandemic, Professor Mayr shifted his research to viral diseases to understand the molecular mechanisms of the SARS-CoV-2 spike protein. He aimed to research the different molecules which contribute to deterioration in COVID-19 patients and to comprehend why some patients develop a more severe form of the disease. We sat down with him to gain an insight on new anti-viral treatments for COVID-19 and the presence of viral RNA as an indicator of mortality.

There are 20,000 protein coding genes, why would I spend my career studying one of them and never having the possibility to studying many others?

PROFESSOR MANUEL MAYR

Professor Mayr worked alongside clinicians and PhD students to look for circulating virus RNA, stating, "One good outcome of the pandemic is that it forced a relationship between clinicians and scientists". The clinicians collected approximately 500 blood samples from patients admitted to Guy's and St Thomas' and King's College Hospitals. They compared plasma samples between COVID-19 patients admitted to intensive care units (ICU) with COVID-19 patients not admitted to ICU and non-COVID-19 ICU patients. Analysis of the samples showed that approximately 25% of the ICU patients had detectable levels of virus RNA within the first week of testing positive for COVID-19. They concluded that most patients do not have detectable circulating virus RNA unless severely ill. Patients with high levels of the virus RNA are at a higher risk of developing a severe form of the disease, which is more likely to result in death.

Professor Mayr also studied the immune responses to the virus RNA and analysed which proteins interacted with the SARS-CoV-2 spike protein. He explained, "We used proteomics to identify proteins that would bind to the spike protein through pull-down experiments". Through this, they identified galectin-3-binding protein (LGALS3BP) as a binding protein for the SARS-CoV-2 spike protein. High levels of this protein in the lungs were found to provide protection against cell deterioration caused by the SARS-CoV-2 spike protein. LGALS3BP was previously known only as a potential anti-viral protein for human immunodeficiency virus (HIV) but could now be a therapeutic anti-viral target for COVID-19.

After conducting his research, Professor Mayr established surprising results; protein markers can rise or fall depending on COVID severity. From this, he wondered whether protein markers associated with severity could also predict patient mortality. He discovered that very few proteins which rise with severity correlate with the predicted outcomes of COVID-19 patients. He also concluded that ICU patients have a very strong antibody response within the first few weeks of developing COVID-19 symptoms. However, the rise in antibody levels didn't correspond to patient outcomes. Research in this field is still ongoing as this is the first-time circulating proteins have been shown to bind to the SARS-CoV-2 spike protein. Even with the immense time pressure, Professor Mayr highlighted how crucial it is to ensure his experiments are performed to a high standard so there is no inaccurate data. He also explained how the technology used to study viral diseases is also used for proteomics, demonstrating how flexible medical research can be.

Professor Mayr now focuses his research on the delta variant, a highly contagious SARS-CoV-2 virus strain originating in India. The variant is now responsible for the vast majority of UK COVID-19 cases. He aims to collect samples of the delta strain from India and the UK to compare responses in different geographical areas, accounting for factors such as obesity, age and having a weak immune system that could also affect the severity of COVID-19.

Professor Mayr is also looking at non-coding proteins called microRNAs. microRNA regulates gene expression by binding with messenger RNA (mRNA) in the cytoplasm and thus is a potential therapeutic target. He is researching how microRNAs can be used as specific biomarkers in panel testing for organ damage, a kind of diagnostic test used to evaluate a particular organ or organ system.

Aside from further COVID-19 experiments, Professor Mayr is now focusing on how drugs could be tailored when treating cardiovascular patients. Statins are commonly used to help lower the level of low-density lipoprotein (LDL) cholesterol. However, patients can still have high levels of LDL cholesterol even when on statins. In this case, drugs called PCSK9 inhibitors are used to reduce circulating cholesterol. PCSK9 inhibitors are expensive compared to statins, so biomarkers could be used to subgroup patients to identify who would benefit most. Through tailoring treatments, both patients and the economy are positively affected. Professor Mayr notes, "By tracking these lipoproteins, we can find the most beneficial treatment".

Professor Mayr continues his research in cardiovascular proteomics and proceeds to find more about COVID-19. We thank him for his time during this busy period.

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ASK US ANYTHING

WHAT DO YOU DO AS A WRITER? HOW MUCH TIME DO YOU NEED TO DEDICATE?

ANSWER

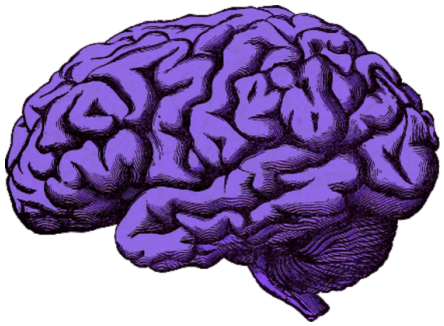
AS AUTHORS, WE WANT OUR ARTICLES TO DESCRIBE THE TOPIC IN DEPTH, WHILE STILL BEING UNDERSTANDABLE AND, ULTIMATELY, ENGAGING TO THE READER. HENCE, IT SHOULD COME AS NO SURPRISE THAT WRITING FOR SCIENCEMIND TAKES CONSIDERABLE EFFORT.

THROUGHOUT THE WHOLE PROCESS – FROM CHOOSING AN INTERESTING TOPIC, TO EXTRACTING KEY INFORMATION FROM OUR RESEARCH, TO PRESENTING IT IN WRITING – IT'S EASY TO STUMBLE ACROSS MULTIPLE TIME-CONSUMING ROADBLOCKS. AS CLICHE AS IT MAY SOUND, STARTING EARLY IS KEY FOR MINIMIZING THE IMPACT OF SUCH OFTEN INEVITABLE HURDLES.

IN ADDITION, CLEARLY DEFINING AND LIMITING THE SCOPE OF THE ARTICLE IS IMPORTANT TO AVOID THE RESEARCH DEATH SPIRAL. FINALLY, WHEN FACING OBSTACLES, IT'S IMPORTANT TO REACH OUT TO OUR COLLEAGUES AND SUPPORT SYSTEM! A FRESH PAIR OF EYES CAN OFTEN SAVE HOURS THAT WOULD HAVE OTHERWISE BEEN SPENT STARING AT A WORD DOCUMENT.

DEEP DIVE

Light at the End of the Tunnel for ALZHEIMER'S DISEASE?



WRITTEN BY EMMA SALMELA
EDITED BY CONSTANCE PAVAN D'AGOSTO

Alzheimer's disease (AD) affects millions of people worldwide, and as the number of cases keeps on increasing, the development of **new treatments** has not been following a similar trend. Many underlying mechanisms of the disease remain **unknown**, and finding a cure persist an unmet challenge. However, aducanumab, **a new drug** developed by the American biotechnology company Biogen, was approved by the United States Food and Drug Administration (FDA) in June 2021 for the **treatment** of AD. It is the first drug introduced into the market in over **20 years**, marking a milestone in the development of new treatments for AD. **Aducanumab** is also the first treatment targeting the potential causes of AD, rather than simply its symptoms. But the reception for aducanumab has been highly **controversial**, with some experts contending its approval.

One of the most popular theories to explain the development of AD is the amyloid hypothesis. This theory suggests that amyloid β (Aβ), a neurotoxic protein leading to cell death is accumulating in the extracellular space, causing synaptic dysfunction and neurodegeneration. Aβ is cleaved from a transmembrane protein called amyloid β precursor protein (APP) by β- and γ-secretases as illustrated in Figure 1.

Normally, the Aβ fragments are rapidly
degraded and cleared, making them **harmless**. However, in AD the metabolism of these fragments is **insufficient**, which results in aggregation and thus in cognitive decline, principally in **memory loss** (Kametani & Hasegawa, 2018).

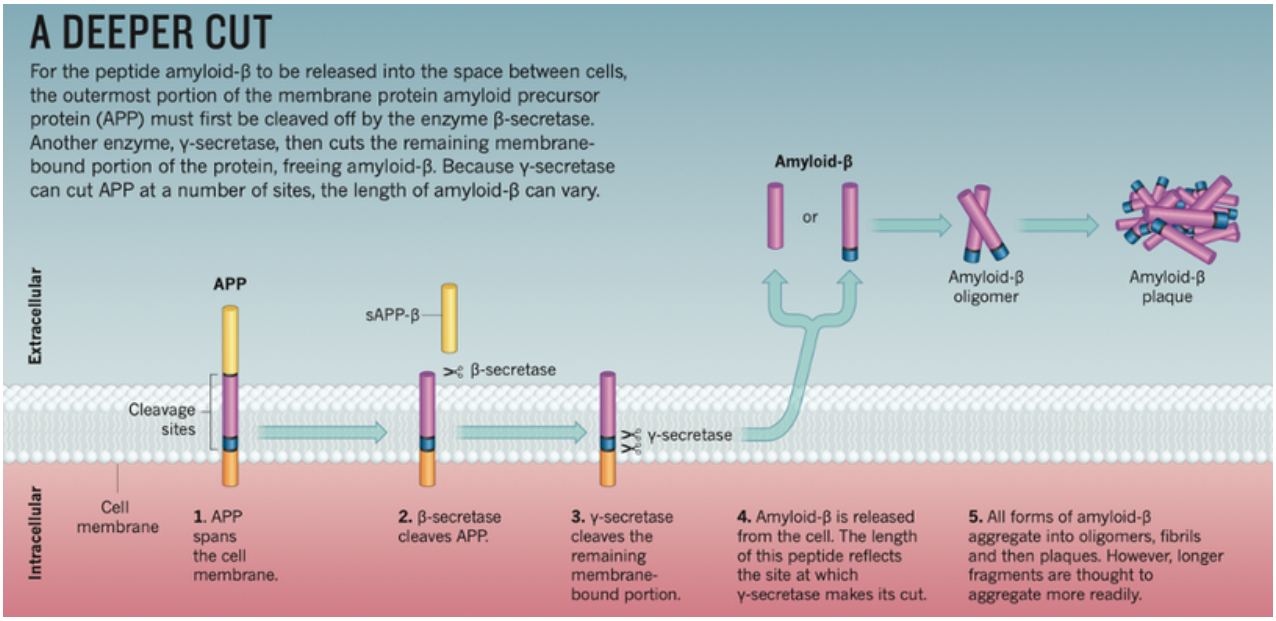


Figure 1. Cleavage of amyloid β from amyloid β precursor protein (APP). Adapted from (Makin, 2018).

In simple terms, Aβ causes a traffic jam in the highway of neuronal connections, ultimately blocking the roads and disrupting the transportation of information.

This theory is supported by many genetic mutations. Some pathogenic mutations occur in the APP transmembrane protein, specifically in the β- and γ-cleavage sites and some can occur in the γ-secretase. As these mutations are linked to the cleavage process of Aβ, it would add up that they are a central component in the development of AD. However, as usual, things are not as straightforward. It has been found that many healthy elderly people also have Aβ aggregates in their brains to the same extent as dementia patients. In addition, some AD patients have been observed to have very few amyloid deposits.

These findings suggest that the aggregation of Aβ and cognitive decline are completely independent, and unrelated phenomena (Kametani & Hasegawa, 2018). This would mean that the amyloid deposits are not the cause of AD.

Aducanumab is a **monoclonal antibody**, which recognises and removes the Aβ aggregates. Interestingly, aducanumab can differentiate between the **Aβ monomers** and **oligomers**. It is highly selective for the oligomers and has a weak affinity for Aβ monomers. This represents a **great potential**, as Aβ monomers are thought to have neuroprotective properties, and oligomers being the neurotoxic ones (Arndt et al., 2018). Therefore, the lack of success for other Aβ targeting therapeutics might be due to the **insufficiency** to distinguish between different **Aβ fragments** (Sevigny et al., 2016).

Despite the uncertainties around the amyloid hypothesis, an **"accelerated approval"** was given to aducanumab by the FDA.

Therefore, Biogen needs to provide further evidence on the effectiveness of the drug in the following years (Mullard, 2021a). The American biotech giant performed two clinical trials for aducanumab, ENGAGE and EMERGE, which comprised individuals suffering from AD with mild cognitive decline and dementia. These trials were both **ceased** in March 2019 because the scores defining participants' cognition kept falling in both groups despite the treatment. However, following a closer look at the **EMERGE trial**, evidence showed that cognitive decline was slower in the group receiving **high dose** aducanumab. Nonetheless, both studies showed a clear **dose-dependent reduction** in Aβ levels (Fillit & Green, 2021).

After the approval by the **FDA**, there has been a lot of debate about the decision based on these results, especially because the effectiveness of aducanumab was not **properly demonstrated**. FDA approved aducanumab based on the drug's ability to clear Aβ deposits from the brain. However, as there still are **gaps** in the amyloid theory, it is not fully established whether it actually is the cause of cognitive decline associated with AD. Before the **approval**, drug development started to drift towards **other targets**, such as another neurotoxic protein tau. **Sceptics** of the amyloid theory, such as George Perry, a neurobiologist from the University of Texas, who argues that the approval is "going to set the research community back 10–20 years". Furthermore, the results from the EMERGE/ENGAGE trials did not unanimously support the effectiveness of aducanumab.

Scott Emerson, a **biostatistician** from the University of Washington in Seattle, said that the interpretation of the results was like "firing a shotgun at a barn and then painting a target around the bullet holes" (Mullard, 2021b). In other words, many experts believe that the evidence supporting aducanumab is on **thin ice**.

On the other side of the debate, some believe that the **approval** of a new drug will revitalise the field, which has not seen a lot of **success** in the past 20 years. Maria Carrillo, the chief science officer for **Alzheimer's Association**, a patient-advocacy group, says that in the past, approval of new drugs has attracted **new investments** and innovations for research (Mullard, 2021b). This is of **great importance**, especially as big pharmaceutical companies, such as Pfizer and Amgen, have recently shut down their neuroscience programmes due to a **lack of success** (Mullard, 2021b). However, whether or not the approval of aducanumab was the right decision, this debate has already **accelerated** conversation in the field. This will not only attract investment to AD research, but also **encourage** the researchers to have constructive conversation, and share opinions about this **devastating disease**, bringing us closer to new treatments.

References

Refer to QR code for full reference list

ASK US ANYTHING

WHAT DO YOU DO AS A GRAPHIC DESIGNER?

ANSWER

GRAPHIC DESIGNERS CAN DESIGN ARTICLES, INSTAGRAM POSTS AND PODCAST EPISODE COVERS. VIDEO TUTORIALS ARE AVAILABLE TO TEACH NEWCOMERS.

DEEP DIVE

Understanding Regenerative Medicine: ChABC

WRITTEN BY BEATRIZ LAUREANO, QURRATU AINI BINTI HASHIM & KATE FLANAGAN

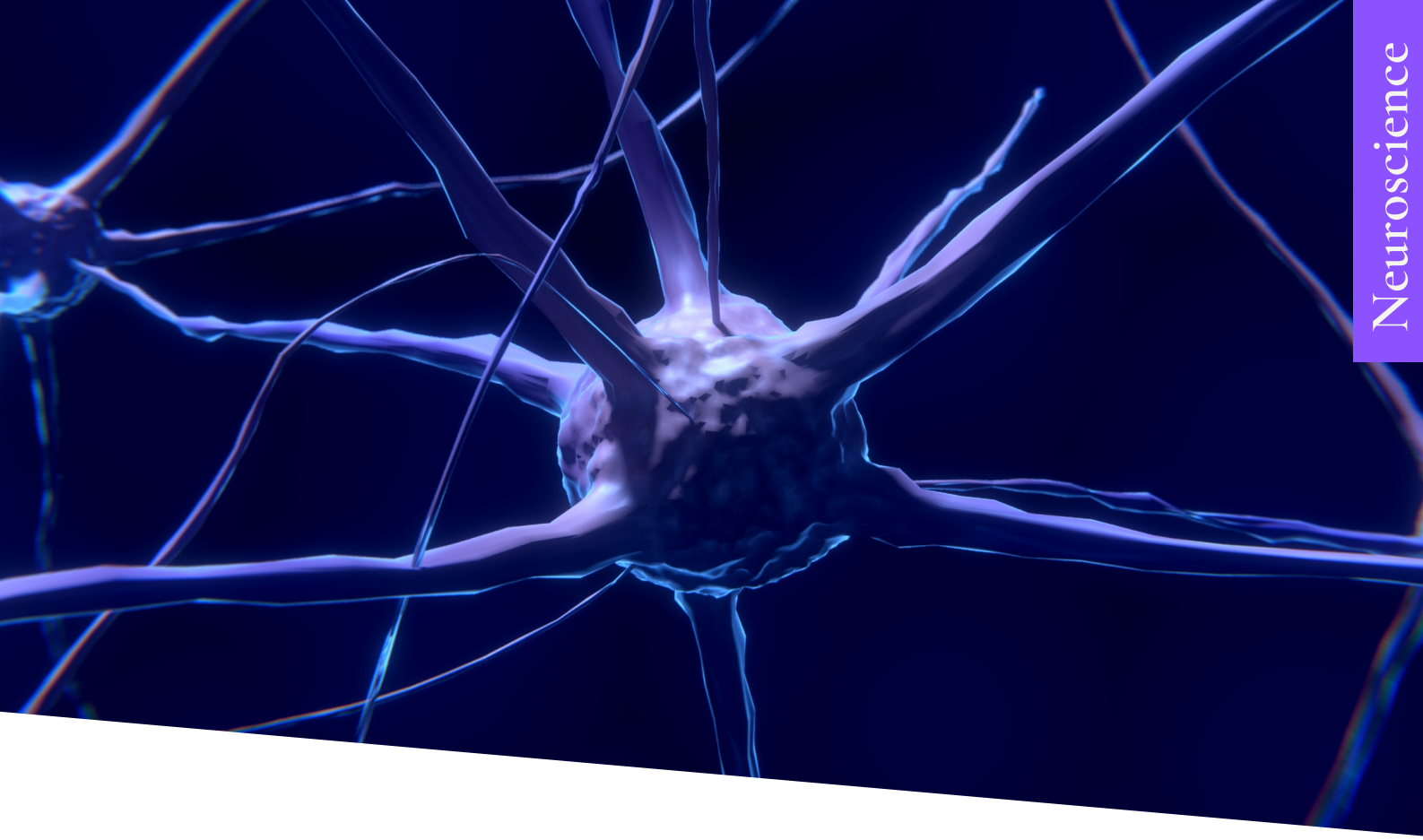
Regenerative medicine can be found at the exciting crossroad between engineering and the life sciences (Mao and Mooney, 2015). These two disciplines are intertwined through the common thread of encouraging restoration and/or replacement of cells within diseased and injured tissues & organs (Mason and Dunnill, 2007). The general strategy entails the implementation of materials and de novo generated cells which have scope to be used in combination (Mao and Mooney, 2015).

Therapeutic applications of regenerative medicine - categorised broadly into biologics, medical devices, and biopharmaceuticals - cover a broad spectrum of disorders. Wound healing and orthopedics have a particularly robust profile amongst FDA-approved therapies. Examples include Epicel which utilises the patient's own keratinocytes to create a graft for recovery of severe burn wounds (Mao and Mooney, 2015).

The role of this field within neuroscience and neurosurgery, however, is particularly intriguing due to the severe outcomes of central nervous system (CNS) disorders ranging from Parkinson's disease to spinal cord injury (SCI) and its notorious resistance to repair (Burns and Quinones-Hinojosa, 2021).

Regeneration in the CNS is no easy task with most pharmacological treatment options available only delaying the progression of CNS diseases (Tam et al., 2013). Functional axonal regeneration rarely occurs due to multiple factors including the presence of inhibitory components at lesion sites and overall in the CNS (Cullen et al., 2015). To overcome these obstacles researchers have focused on developing drug delivery strategies to target many of the mechanisms of growth inhibition including the presence of inhibitory molecules (Lu and Tuszynski, 2008).

One enzyme in specific has demonstrated considerable success in this regenerative process: **ChABC is an enzyme** that has been having lots of attention recently in the regenerative world due to its regenerative abilities from restoring plasticity in the CNS and memoryto promoting functional recovery after SCI (Yang et al., 2015). The potentials of this bacterial enzyme are countless.



One specific area in which ChABC has a **potential therapeutic application** is in SCI. The pathophysiology of a SCI, particularly the extracellular matrix (ECM), is very inhibitory for axonal regeneration. A mixture of inhibitory molecules both bound and secreted **creates** a hostile environment that is detrimental to functional recovery (Fan et al., 2018). Examples of these inhibitory molecules include the membrane protein enriched in **CNS myelin**, Nogo-A, and proteoglycans.

Chondroitin sulphate proteoglycans (CSPGs) are one such inhibitory component of the ECM that **prevent** neurite sprouting and the formation of new connections. ChABC, as a chondroitinase, cleaves the long unbranched carbohydrate glycosaminoglycan (GAG) side chains of the proteoglycan, releasing growth factors bound to the CSPG and promoting axonal regrowth. This enzyme recognizes the heterodimers that make up the GAG chains and cleaves them where they attach to the core protein by O-linkage. Removing the **inhibition** of CSPGs is an effective way to **promote** neurite sprouting and therefore new connections which can lead to functional recovery (Crespo et al., 2007). ChABC is an example of the potential power of regenerative medicine, particularly in the face of the extreme adversity of SCI.

If you are interested in further understanding the possibilities of regenerative therapies and synthetic biology, follow KCL iGEM on their social media to learn more about how the team will be continuing their research into novel therapies that can promote regeneration post-SCI.

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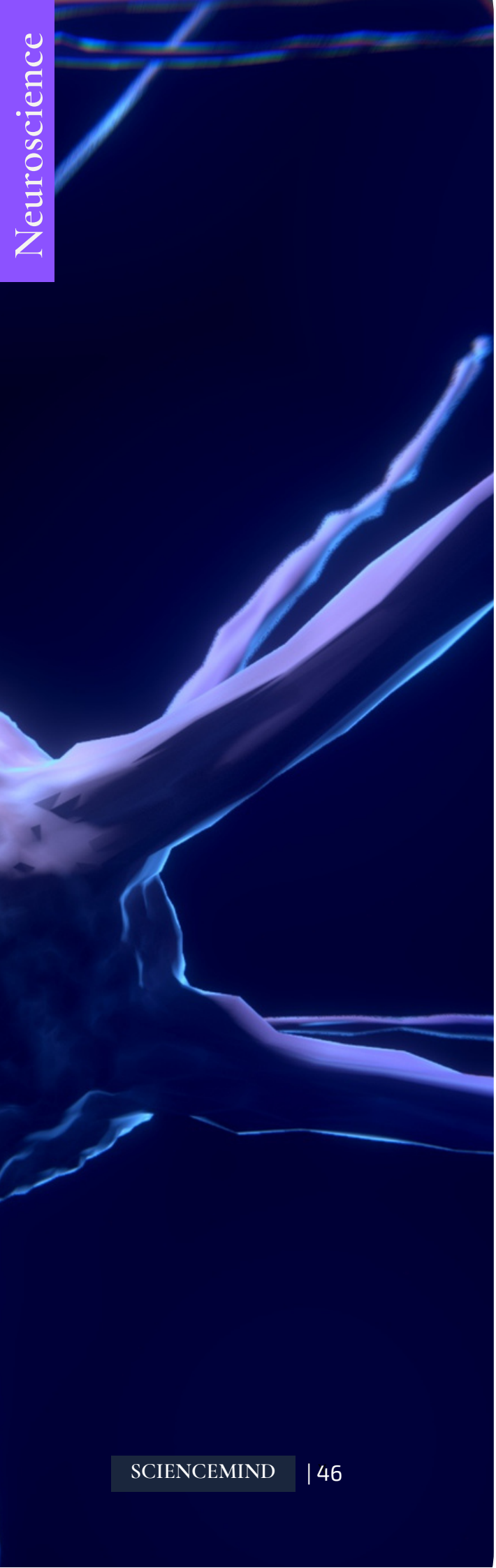

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ASK US ANYTHING

WHAT DO YOU DO AS AN EDITOR?

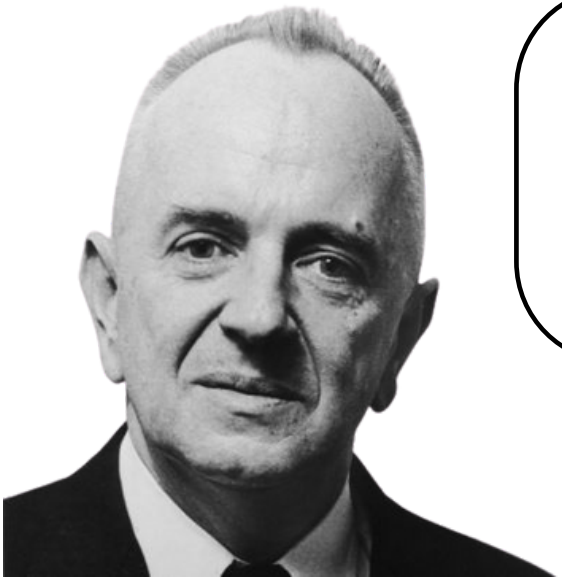
ANSWER

CHECK FOR ACCURATE SCIENTIFIC CONTENT, TYPOS, GRAMMATICAL ERRORS IN THE ARTICLE BEFORE SENDING IT BACK TO WRITERS.

SHALLOW DIVE

KNOWLEDGE OF CANCER EVOLUTION AND DRUG DISCOVERY

WRITTEN BY MADIHA MOHSEN
EDITED BY IRIS ZIELER



> Nothing in biology makes sense except in the light of evolution.
>
> THEODOSIUS DOBZHANSK

Cancer always seems to find a way out to escape the wrath of anticancer drugs. Every time, it evades our attempts to eliminate it, and comes back stronger yet. To develop new drugs and combat this dynamic behaviour, it is extremely important to understand the principles of this evolution.

To survive, cancer cells inside a tumour start to mutate. Mutation is the process by which genetic diversion takes place so that the fittest cells survive. The selection pressure from the surrounding environment stimulates this evolution, resulting in mutation. Self-evolution concepts cannot be explained without the CSC (Cancer stem cell) theory. In normal cells, stem cells are the cells that can undergo self-renewal. However, as with everything "normal," this is regulated tightly by genetic control systems. With cancer cells, the stem cells are the origin of the tumour and can propagate uncontrollably. This explains why cancer cells often develop innate resistance to radiotherapy and chemotherapy. The only positive aspect in this case is that, unlike normal cells, the natural repair machinery of cancer cells is not controlled and, as a result, cancer cells cannot repair themselves. This can work both for, and against us. Against us, because they can ignore the signals for self-

destruction or repairs, thereby increasing the number of faulty genes. For us, because this characteristic can be used against them by manipulating and interfering with certain pathways.

Cancer cells have developed an important pathway to get rid of the drugs targeting them. The result is a decreased concentration of the therapeutic drugs in the cells and subsequent failure of the cancer treatment. The 'clever' cells increase the expression of certain pumps on their cell membranes. These pumps, called "family of ABC" (ATP-binding cassette) transporters, are normally responsible for getting rid of toxins in normal cells. Cancer cells utilize these pumps to get rid of the drugs that enter the cells passively by actively pumping them out using energy from the breakdown of ATP. This in turn leads to drug resistance, not to just one drug but several different drugs.

In depth studies of ABC transporters is required to understand these pathways and how to manipulate them. The ultimate goal is to find a way to keep the drugs inside the target cells. Currently, inhibitor drugs are administered together with therapeutic ones to prevent the ABC transporters from performing their excretion function. One well known example is Tariquidar, however, it comes with concern of unwanted side effects and is therefore not a first-line treatment for all cancer patients . (2)

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SHALLOW DIVE

New Merger Event Provides Insight Into Gravitational Waves

WRITTEN BY CHETANA PRABHU
EDITED BY DRSHIKA MEHTANI

The **gravitational wave** detectors recently observed a new type of event in the cosmos. A black hole and a neutron star hybrid collision. Black holes are regions in spacetime where the gravity is so strong that even light cannot escape their pull and are formed due to the gravitational collapse of massive stars (usually of more than 8 solar masses). Neutron stars are also produced during a supernova explosion however, despite being dense they are not large enough to turn into black holes. Gravitational waves are oscillations or invisible ripples caused in space when a massive body comes into motion.

The gravitational waves are usually very faint to be noticed, but their effects are amplified when two large bodies orbit each other. This is usually very faint to be noticed but becomes strong when two bodies orbit each other. These waves pass at the speed of light and stretch or squeeze anything in their paths. There certainly have been collisions of 2 black holes or 2 neutron stars, but the neutron star-black hole merger was the first of its kind.
Einstein's theory of general relativity associates the force of gravity

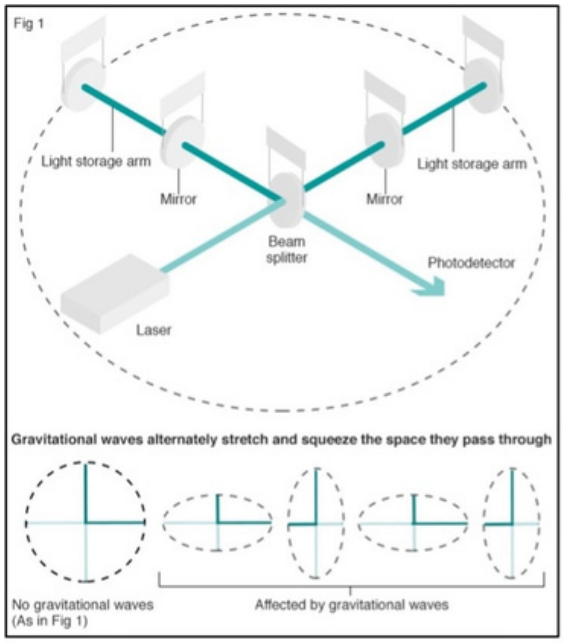
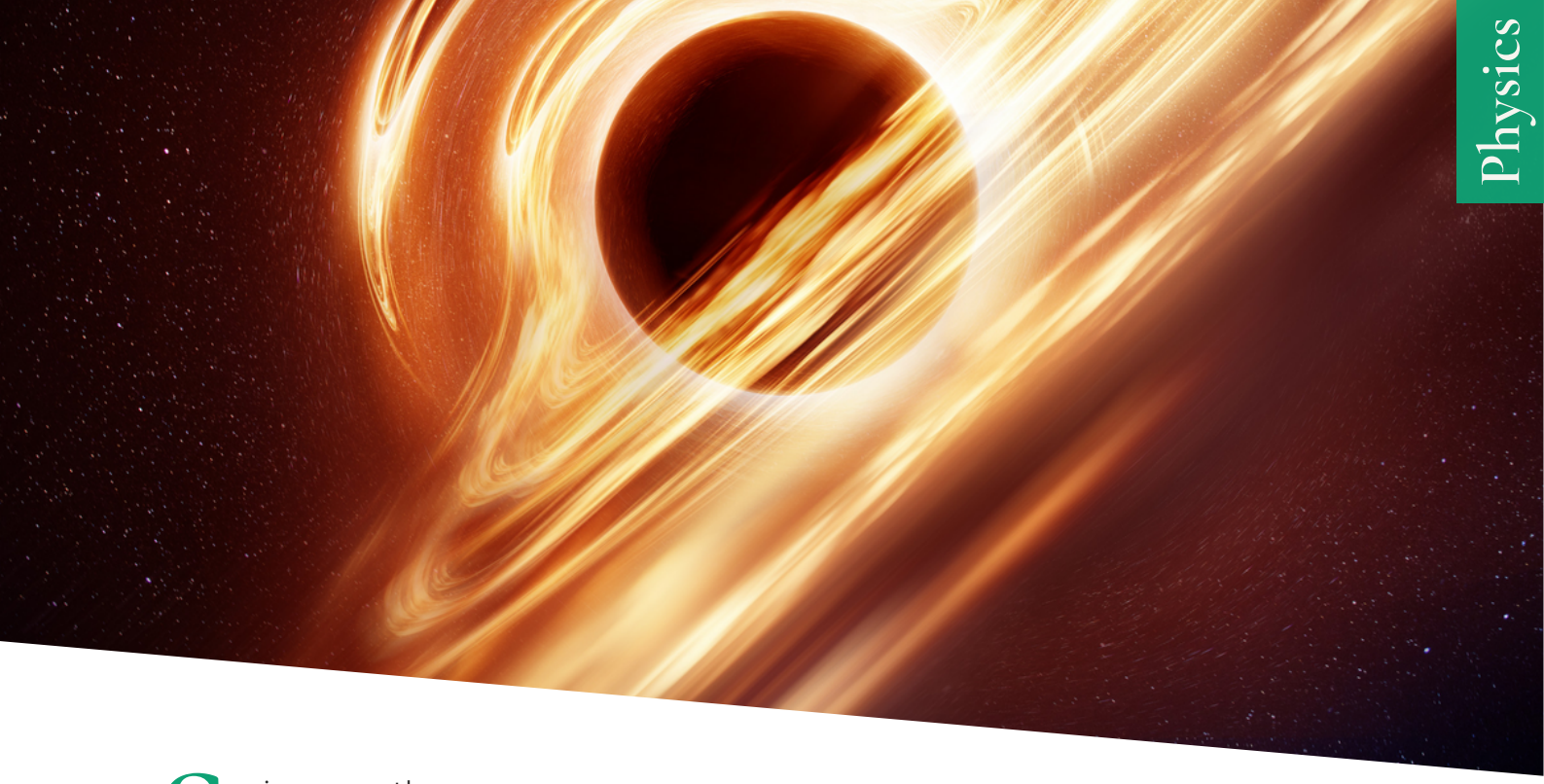


Figure 1. Showing how a gravitational wave detector works (source LIGO/NSF)

with the changing geometry of the space-time.
This also predicts that when a massive body comes into motion, due to the curvature of the spacetime around it, the oscillations produced would be at the speed of light. Gravitational waves generated from the collision of the black hole and neutron star proves this. Generally, when there are mergers between two neutron stars or black holes, they give out a stream of electromagnetic radiation which helps to identify the type of cataclysmic event.



Since there was no electromagnetic radiation given out in this particular merger, it was instead only characterised by the gravitational waves that were generated which made the scientists sure that it was a black hole-neutron star collision. However, it cannot be completely concluded that light-based mergers could not occur since that depends on the mass, velocity, orientation, and the cosmic environs of both the astronomical objects.

The waves have travelled 900 million light-years for us to witness the first-evercollision on 5th January 2020 between a 9 solar mass black hole and a 1.9 solar mass neutron star. Whereas it travelled 1 billion light-years for the second collision on 15th January 2020 between a 6 solar mass black hole and a 1.5 solar mass neutron star. These gravitational waves have been of great assistance to the scientists to get a glimpse of the past by providing insights into mere moments after the big bang and the deep interior of supernovas. Going forward, these waves can be a huge window into answering the big questions of the universe.

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SHALLOW DIVE

Dark Matter Slowing the Spin of the Milky Way's Galactic Bar ?

WRITTEN BY DRSHIKA MEHTANI
EDITED BY JULIET CHEN

Astrophysicists have long predicted that dark matter may be responsible for slowing the spin of a galaxy's galactic bar. The first evidence of this phenomenon has recently been observed (Chiba and Schönrich, 2021). Many spiral galaxies such as the Milky Way have a spinning bar at their centres which is made up predominantly of stars, and these bars serve as stellar nurseries. These galaxies also have postulated dark matter halos (Knapen et al., 2002). Figure 1. shows the structure of a galaxy ("ESA Science & Technology - Anatomy of the Milky Way," n.d.).The nature of dark matter and its constituents are not well understood, but it has been well established that its composition is unlike regular matter. Dark matter is studied by examining the visible effects it has on regular matter; by mapping the gravitational potential of galaxies and eliminating the contribution of visible matter from the potential. The photometric data that the researchers used for the study is publicly available; provided by the Gaia space telescope (Chiba and Schönrich, 2021).

Analytically, the study shows that the galactic bars encounter dynamic friction with postulated dark matter halos, causing the transfer of energy and angular momentum to the halo, slowing the bar's spin. Measurements from the study show that the spin of the Milky Way's galactic bar has slowed approximately 24% since it was first formed. As the spin of the bar slows, it grows in volume while resonance moves radially outwards. The effect of this is seen the best when examining stars at points in the stellar disc that are gravitationally trapped by the spinning bar. The pattern speeds of these stars are in proportion with the pattern speed of the galactic bar.

With the bar's deceleration, stars at these gravitationally locked points sweep outwards towards the stellar disc. As these stars migrate outwards, the space volume grows, and surrounding stars then become trapped in resonant orbits. To understand this phenomenon better, picture the rings of a growing tree and how new layers of cells form radially outward to keep the bark continuously growing. The resonance builds up layers of trapped stars that are analogous to the way a tree builds rings at its centre (Chiba and Schönrich, 2021).

A large group of moving stars, known as the Hercules stream, are resonantly locked with the galactic bar. It was found that these stars carry chemical clues that aid in proving the slow bar theory. The metallicity (abundance of heavier elements) of these stars is unusually high compared to the other stars in their environment and their relative position withing the galaxy.

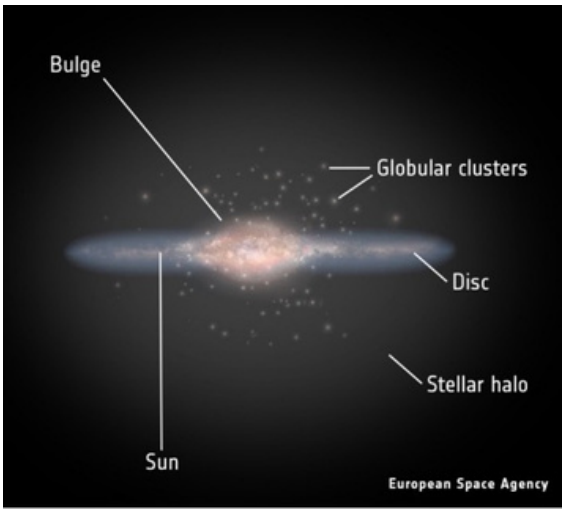

Figure 1. Anatomy of the Milky Way Galaxy ("ESA Science & Technology - Anatomy of the Milky Way," n.d.)

It is known that the metallicity of a star and the star's distance from the centre of the galactic bar are inversely related. The galactic bar is rich in stars and star-forming gas, contributing to its high metallicity. The unusually high metallicity of the stars in the Hercules stream shows that this group travelled away from the galactic centre due to the described phenomenon. This is the only suitable argument available for explaining the high metallicity of these stars (Chiba & Schönrich, 2021).

The study provides valuable insight in measuring dark matter as its inertial mass is considered and not its gravitational energy. Along with supporting the slow bar theory, the calculations from the study also support the existence of the 'hypothetical' dark matter halo rather than having to alter other known models of gravity to account for discrepancies (Chiba and Schönrich, 2021).

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SHALLOW DIVE

Is ARTIFICIAL INTELLIGENCE artificial life?

WRITTEN BY VIRGINIA BALDI
EDITED BY INES KUSEN

Artificial Intelligence (AI) is a term coined by John McCarthy in 1956, who believed that "every aspect of learning or any other feature of intelligence can in principle be so precisely described that a machine can be made to simulate it." (Childs, 2011).

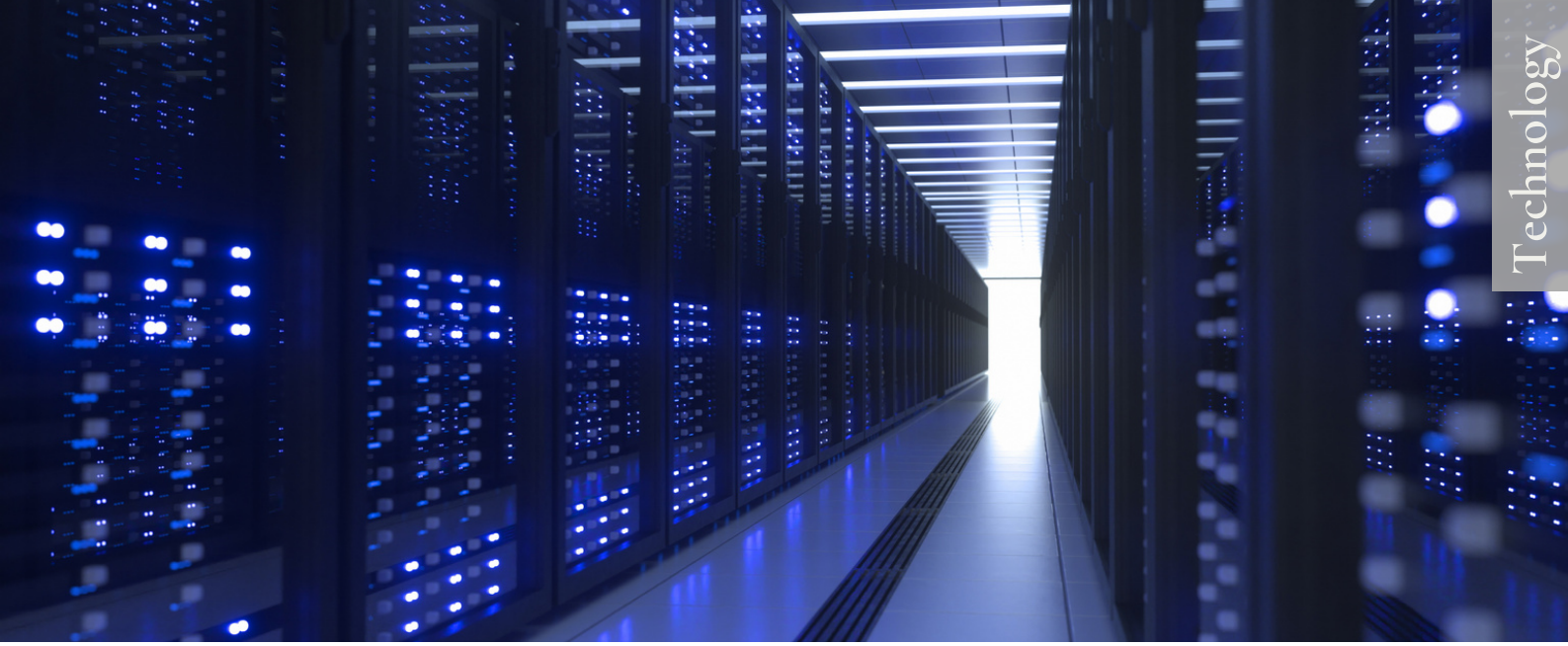
AI is evolving and developing at a seemingly exponential rate and as such we have integrated it into our culture, in movies, and everyday life without realising it (Siri, email spam, apps like maps, weather, Google Translate, etc.) (Urban, 2015). To monitor its progression in the UK, the Royal Society published a major policy study on machine learning with the aim of implementing this technology as quickly as possible for the benefit of humanity. There is even a specialised national institution for AI and data science in the Alan Turing Institute (The Royal Society, 2018).

Due to the extensiveness of AI, we categorise it based on an its calibre. The classification is as follows:

Artificial Narrow Intelligence (ANI)/ Weak AI/Calibre 1: AI that specialises in one area, such as a system built to exclusively play chess which would not be able to predict the weather.

Artificial General Intelligence (AGI)/Strong AI/Human-Level AI/Calibre 2: refers to a computer that is as smart as a human, performing any task a human could. Alan Turing set up the 'Turing test' in the 1950's to evaluate if AI could be AGI (Urban, 2015; Sysiak, 2021).

Artificial Superintelligence (ASI)/Calibre 3: which will surpass the intelligence of all humans combined. Oxford's leading AI thinker Nick Bostrom defines superintelligence as "an intellect that is much smarter than the best human brains in practically every field, including scientific creativity, general wisdom, and social skills." (Bostrom, 2012).



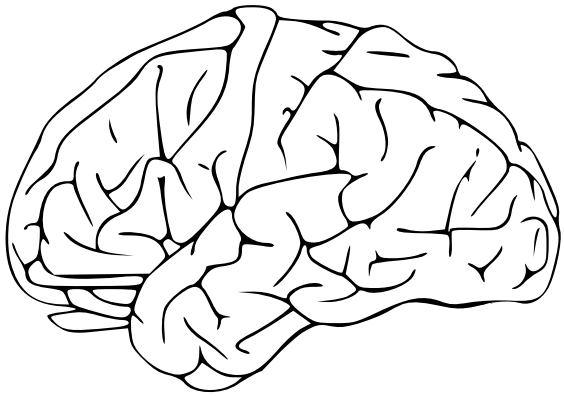
Momentarily we only have access to the lowest calibre of AI in **ANI**, and it is ubiqu-itous. AI can, and will, have a plethora of applications, ranging from characterising dark matter, modelling and predicting complex biosynthetic pathways of molecules, understanding the effects of climate change on the world, finding patterns in astronomical data, nanotechnology, and many more (The Royal Society, 2018). This is directly related to **Moore's Law**, which states that "the world's maximum computing power **doubles** approximately every two years, meaning computer hardware advancement, like general human advancement through history, grows exponentially" (Urban, 2015). Therefore, life will dramatically change as the AI Revolution unfolds, ergo the road from ANI, through AGI, to ASI. Transitioning from **ANI to AGI** is not only complex, but extremely controversial since the human brain is currently the most complex entity in the known universe.

What computers find so difficult to mimic are those actions we do subconsciously, which seem trivial to us, but in reality are not (Sysiak, 2021). What is also contentious to realise is that the aforementioned law which dictates how quickly such an impacting change will come to fruition, will possibly be in our lifetime, approximately around **10-50 years away** from now. (Urban, 2015). Ultimately, we also have no idea how **ASI** will decide to behave once it is fully functional. Since **ASI** will inevitably surpass our intellect, they may experience their own 'life' at unimaginable rates, possibly moving atoms, curing aging, death and any disease or pestilence known to man, if not obliterate humanity itself.

To accomplish this transformative but forthcoming advancement, researchers have therefore devised different mechanisms which can mimic the brain as **artificial neural networks.** This is done using a web of transistor "neurons" which do not store any information (Urban, 2015). By a process of trial and error, it makes connections in the firing pathways, which result in being stronger when correct and weaker when mistaken, thus optimizing the machine for the task. Although our brain is more sophisticated, it works somewhat similarly and, with time, we will manage to uncover its neural circuitry. Even though **data sets** are often too modest, we can use computers to select useful data for experiments, notwithstanding the fact that we might ultimately not know how they were generated, since they are devised by the computers themselves (Urban, 2017; The Royal Society, 2018).

Alternatively, we could slice a human brain into layers, scan them and reconstruct a model via software and implement it onto a computer: this is **"whole brain emulation".** The computer would be able to execute anything the brain is capable of after gathering this information (Urban, 2017; Sysiak, 2021).

Evolution is also considered since the brain is not easily emulated and machines might operate at different capacities in comparison to biological systems. To do this we use **"genetic algorithms"** via natural responses produced by biological creatures. This process would involve "breeding" the most successful computers with each other by merging half of each of their programming into a new computer and eliminating the least successful (Urban, 2015). Nevertheless, **evolution** is a long process, and we aim to achieve all this in a few decades. Evolution is also prone to random mutations, but this could be controlled, directing it towards a higher intelligence. However, such a procedure would use a lot of energy, thus naturally opposing the advancement towards ASI. Accomplishing this would mean needing to innovate the machines in different ways, such as modifying how the systems produce energy, to facilitate intelligence itself, but it is not clear if we will be able to tweak it enough to achieve this (Sysiak, 2021).



Furthermore, researchers could develop AI which would be built to analyse **its own functions and capabilities**, and simultaneously code changes into itself, thus improving on its own. We would teach computers to be computer scientists so that they could enhance their development and therefore further progress our knowledge on AI. Once it gets to AGI, systems that were developed through methods that do not involve self-improvement would also now be smart enough to begin self-improving if they so wished (Urban,2015; The Royal Society, 2018).

As a result, the next few decades might bring about the development of ASI, which will be the most powerful being in the history of life on Earth, and with this intelligence comes immense responsibilities. Thus, we will be forced to reconsider how we perceive ourselves and the world we built, fundamentally changing it for better or for worse. The computers will possibly have enough domain knowledge built-in that they will make their own breakthroughs. Whichever way AI develops it will greatly impact our future, leading to a profound **AI and human revolution**.

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SHALLOW DIVE

BIOPRINTING using pluripotent stem cells, the application of the 3D PRINTER in medicine

WRITTEN BY JABARI LAMBERT | EDITED BY TREASA JIANG

Is it possible for man to replicate biological systems?
Given the composite biological materials and a 3D printer it may be.

Biofabrication or 3D Bioprinting refers to the process in which biocompatible materials and biological materials are used to 3D print structures which **mimic living systems**. The birth of 3D technology in the 1980s was kicked off by Charles Hull's stereolithographic manufacturing device, which was capable of manufacturing three dimensional objects. Building upon Charles' invention, researchers first demonstrated the concept of bioprinting in 1988.

Bioprinting biological systems works by stacking clumps of cells suspended in **bioink** layer by layer onto biopaper gel to build said tissue. Bioink consists of growth factors and nutrients needed for the specific cell type. These layers are held in place by a gel paper to allow the cells to fuse. The thickness of a layer tends to be **0.5mm or less**. As the layers are stacked the bioink takes shape solidifying and allowing the cells to fuse in a process called **crosslinking**.

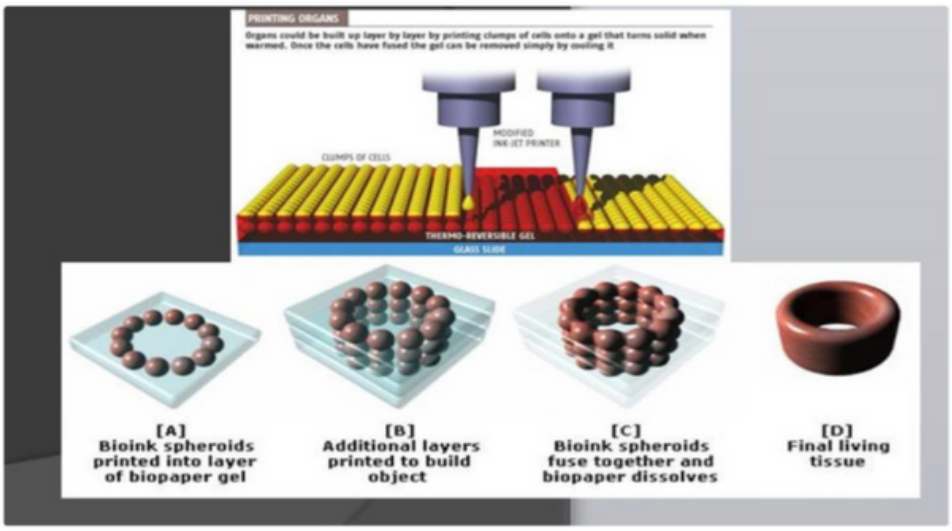

Figure 1. Bioprinter stacking cells.

Stem cells are **undifferentiated cells** from which all other cells in the body are derived, through a process called cellular differentiation. Stem cells are arguably the best composite material to use in bioprinting complex tissue. Specifically, pluripotent stem cells which have the ability to self-renew and differentiate into any of the three embryonic germ layers granting them the ability to in theory differentiate into any tissue in the body.

Bioprinting has been successfully done using **cultured multipotent adult stem cells** (stem cells which can differentiate into a specific range of cells) however, it has been unsuccessful using **pluripotent** stem cells.

The use of pluripotent stem cells in bioprinting is currently limited by three factors: **physical printing technology, bioink properties** and **biological challenges**.

Pluripotent stem cells are sensitive to cell manipulation, and the fragile nature of the cell makes it vulnerable to cell death from the shear stress during printing. Due to this the cells are often damaged when leaving the nozzle of the printer.

Current formulations of bioink struggle to find to the balance between adherence and porousness causing **anoikis** (a form of programmed cell death which occurs in anchorage dependant cells) of the cells due to issues with waste and nutrient transfer or a weak structure from poor adherence.

The use of pluripotent stem cells is limited by the available cell differentiation protocols i.e. we can't successfully induce differentiation into the wanted tissue. Most cell differentiation protocols are optimized for 2D structures and need to be changed for the 3-dimensional plane.

Pluripotent stem cells are still a relatively new and poorly understood field of science. However it does show great promise for the future and if utilized properly with bioprinting may lead to breakthroughs allowing fabrication of more tissue like structures, perhaps even organs.

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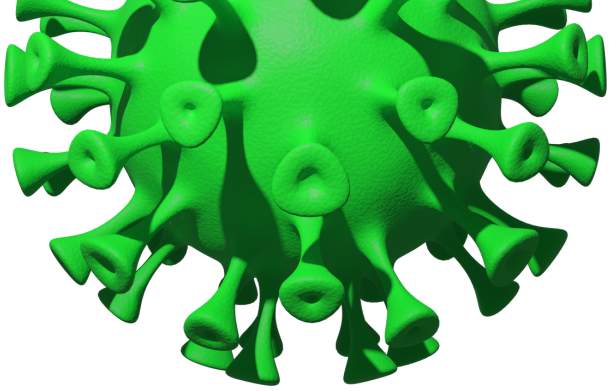
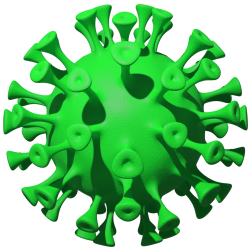
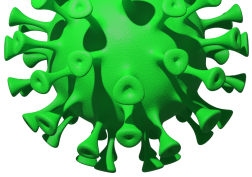


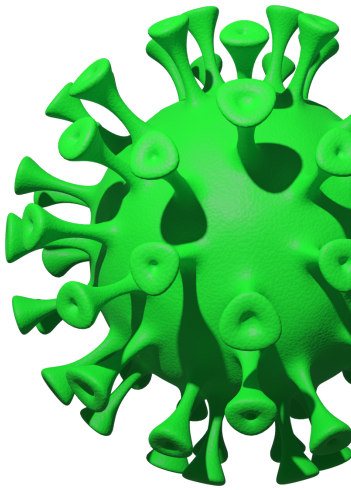




SHALLOW DIVE

WRITTEN BY DRSHIKA MEHTANI | EDITED BY RISHA KAUR DUGGAL

CRISPR and How it Has Been Used to Aid Gene Drive Development in a Highly Resistant Mosquito



Mosquitoes act as disease vectors globally for diseases such as the West Nile virus, lymphatic filariasis and malaria (Feng et al., 2021). While insecticides are being used to control the disease vector, insecticide-resistant lines are emerging that render this method ineffective. As new insecticides are formulated, genetic intervention is necessary for effective control of the vector. Genetic elements are therefore incorporated into vector genomes and these traits portray selection bias in the normal population, being eventually carried by the whole population, causing a 'gene drive'. These introduced genes may either incapacitate the vector's ability to carry the pathogen or may employ the sterile insect technique. The sterile insect technique involves the release of many sterile males that outnumber the number of wild-type males and compete for females. These techniques have been shown to suppress large numbers of mosquito populations in the past (Figure 1.) (Nolan, 2021).

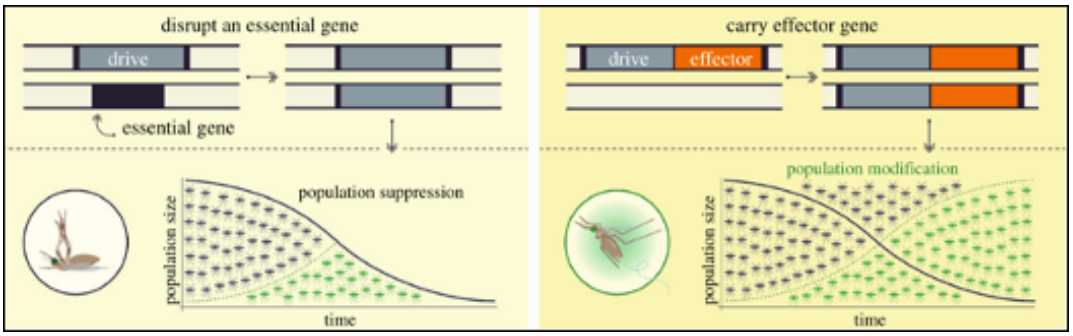


Figure 1. shows how the effects of the gene drive on the vector population when the sterile insect technique is implemented (left) and when the vector is incapacitated to carry the pathogen (right) (Nolan, 2021).

While effective gene drives have been developed for Anopheles and Aedes mosquitoes, studies have been lacking for Culex. Researchers have now been successful in developing a Culex-specific Cas9/sgRNA expression toolkit from scratch by using site-directed homology-based transgenesis. The study has provided valuable insight into the control of the highly insecticide-resistant Culex mosquitoes and has also provided an understanding of how these findings may help improve gene modification in other species (Feng et al., 2021).

'CRISPR-Cas9' stands for 'Clustered Regularly Interspaced Short Palindromic Repeats-Cas CRISPR-associated protein 9'. This technique is used by researchers to carry out precise gene editing. CRISPR employs the use of the Cas9 enzyme and two different RNA molecules: CRISPR RNA (crRNA) and transactivating crRNA (tracrRNA). The crRNA and tracrRNA form a single-stranded guide RNA (sgRNA). The sgRNA helps Cas9 recognise mobile genetic elements (MGEs) and cleave them at the target site creating a double-strand break (DSB) (Barman, Deb and Chakraborty, 2020). DSBs induced by Cas9 have been used to introduce mutations using homology-directed repair (HDR) with both double-stranded plasmid DNA as well as single-stranded oligonucleotide donor templates (Sander and Joung, 2014). Figure 2. Depicts the use of CRISPR-Cas9 to produce genetic modifications in mosquitoes (Nolan, 2021).

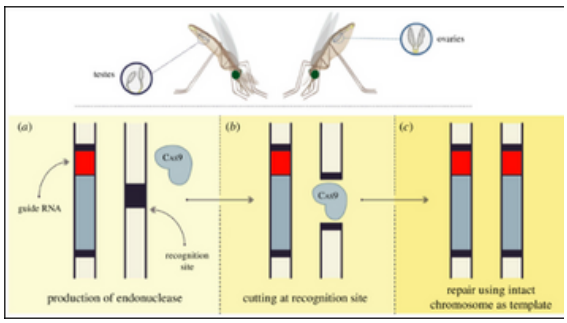


Figure 2. In an individual heterozygous for the gene drive, the wild-type chromosome is cut as the chromosome containing the gene drive is immune. After the wild-type chromosome is cut, homology directed repair pathway is induced in the wild-type chromosome using the chromosome containing the gene drive. This method also induces gene drive development in subsequent generations (Nolan, 2021).

To generate plasmid reagents for competently expressing Cas9 and sgRNA, regulatory gene sequences were identified in Culex quinquefasciatus based on data obtained from other mosquito species. Several genes were chosen for the expression of Cas9 and several U6 promoters were obtained for efficient sgRNA expression. These newly derived CRISPR constructs were then validated using a controlled in vitro cell culture system. After validating high editing efficiencies in vitro, the researchers went onto studying them in vivo. These employed the use of the cardinal locus using a validated sgRNA. Homozygous mutants were known to have a visible phenotype difference as compared to wild-type counterparts, having a lighter red eye (Figure 3.). The genomes of the mutants produced from the use of each construct were studied and varying editing rates from each construct were obtained, the results

being in line with the in vitro results. The viable constructs were then further evaluated in vivo using a previously validated sgRNA at the target cardinal locus. The best Cas9 construct was then identified to establish a transgenic line. A single plasmid that had the vasa-Cas9 transgene, DsRed marker and the sgRNA cassette was created. It was used to create an established transgenic line. This line was also validated by introducing a phenotype disruptive sgRNA source in the transgenic eggs. This newly established transgenic line can therefore be used for future studies to aid gene drive development in the species (Feng et al., 2021).

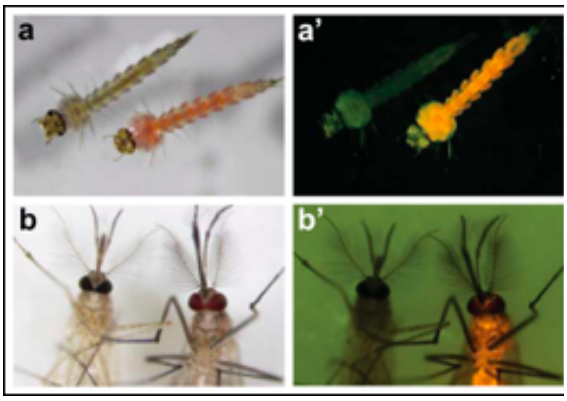


Figure 3. Phenotypic, molecular, and functional validation of the vasa-Cas9 transgene. a, b′ Phenotypes of homozygous vasa-Cas9 (right) compared to wild-type (left). Individuals display the cardinal– eye phenotype and the DsRed fluorescence marking the transgene in both (a, a′) larvae and (b, b′) adults. a, b Brightfield image. Note how the expression of the transgene is visible as pink pigmentation, observable to the naked eye. a′, b′ DsRed fluorescence filter (Feng et al., 2021).

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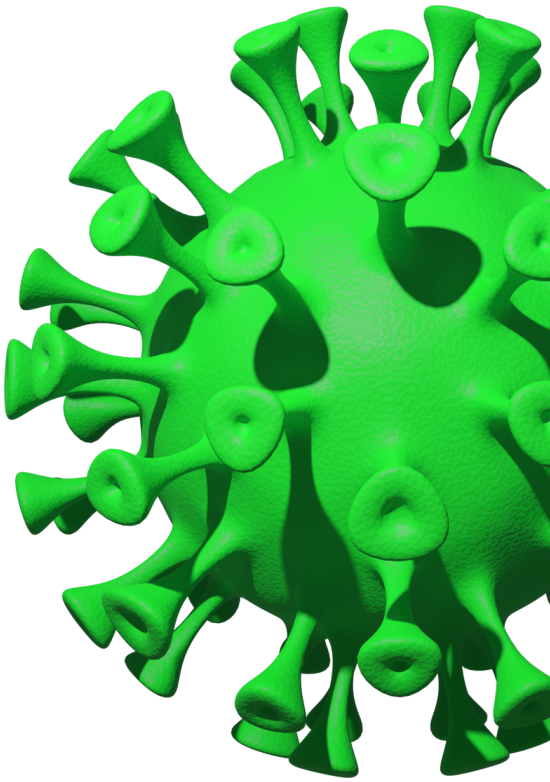
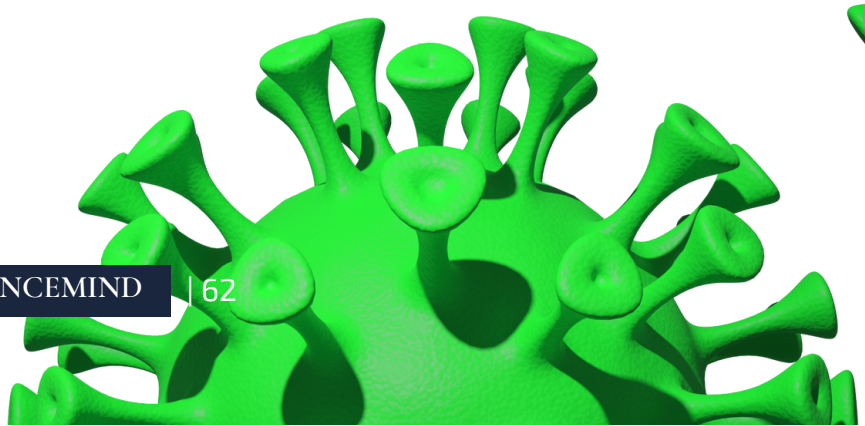




ASK US ANYTHING

DOES THE SOCIETY TAKE PART IN COMPETITIONS?

ANSWER

YES, WE TAKE PART IN REGIONAL (LONDON) AND NATIONAL COMPETITIONS WHERE YOU CAN TAKE PART AND WIN TROPHIES!

DEEP DIVE

A Review of the **Moderna COVID-19 Vaccine** Patent and its Implication on the Global Vaccination Effort

WRITTEN BY LEON ZHANG
EDITED BY JABARI LAMBERT

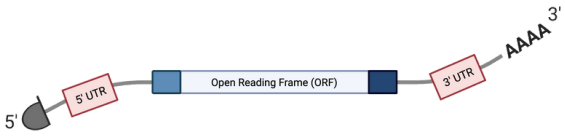
Since the outbreak of the COVID-19 pandemic in 2019, scientists around the world have rushed to sequence the genome of **SARS-CoV-2** leading to the development of vaccines at an unprecedented rate. However, for many reasons the global vaccine supply has been distributed unequally and has led to fears of a **vaccine apartheid**. Consequently, the patent system has undergone scrutiny from the Biden administration, India & South Africa who support the waiving of patents [1]. **Patents** are a form of intellectual property whereby inventors are granted **territorial rights**, to stop others from using their invention without consent for a limited time, by governments in exchange for full public disclosure [2].

How are patents granted?

In general, to obtain a patent, one must successfully argue that their invention is **innovative**, involve an **inventive step** and capable of **industrial application** [2]. However, nuances exist between different patent offices around the globe. For example, the European patent office allows the patenting of inventions containing biological materials, such as nucleic acids carrying genetic information, so long that it is new, involves an inventive step and applies to industries [3]. However, in the US the supreme court has ruled that patents for products of nature, such as isolated DNA segments, are not eligible whereas cDNA is patentable as it is not naturally occurring [4]. Generally, **artificial nucleic acids constructs** can be patented in the EU and the US since they cannot be found in nature. Consequently, pharmaceutical companies, such as Moderna, can patent their COVID-19 mRNA vaccine as the nucleic acid construct is artificial.

The US20200282406 patent

The US20200282046 patent has been granted to **ModernaTX** by the US government which makes the following claims [5]. Firstly, an artificial mRNA construct with an open reading frame (ORF) encoding at least one of the **BetaCoV antigenic polypeptides** in table 1 and is flanked by a **5'** and **3' untranslatable region**. At least 80% of uracil residues must be chemically modified (some examples from a long list of modifications include N1-methylpseudouridine, N1-ethylpseudouridine and 2-thiouridine). Furthermore, the construct also contains a 1-methylpseudouridine or 1-ethylpseudouridine 5' cap and a 3' polyadenine tail. Collectively, this results in the formation of an artificial nucleic acid sequence that will never be found in nature thus ensuring the technology is eligible for patent protection.



Secondly, a **lipid nanoparticle** in which the mRNA is formulated, it is composed of 20-60% ionizable cationic lipid, 25% mol 1,2-distearoyl-sn-glycero-3-phosphocoline (DSPC) (neutral lipid), 25-55% mol cholesterol and 0.5-1.5% mol of 1,2-dimyrisoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG-DMG) (PEG-modified lipid). The nanoparticle has a mean diameter of 50-200nm, polydispersity value of less than 0.4 and a neutral charge at neutral pH.

What are the implications of Moderna's patent?

Moderna's patent prevents others from exploiting their technology, non-consensually. The claims regarding the composition of the lipid nanoparticle are broad and prevent others from using a list of specific chemicals and compounds at specific concentrations. Furthermore, the claims regarding the mRNA construct prevent others from using mRNA that encodes or share at least 80% homology with the polypeptides listed in Table 1. Since filing their application, Moderna has announced that they will be **waiving their patents** to aid the development of other COVID-19 vaccines [6]. Therefore, enabling others to manufacture COVID-19 vaccines using Moderna's lipid nanoparticle and mRNA technology without being sued.

Many vaccine campaigners have supported this decision as it enables poorer countries to produce their own vaccines, at a cheaper price than that offered by pharmaceutical companies [1]. However, pharmaceutical companies have stated that the problem lies within the manufacturing process rather than patents [7]. Naturally, waiving the patents surrounding COVID-19 vaccines will increase global demand for the raw materials, which are in **limited supply**, required to manufacture the vaccines. An increase in demand will result in the cost of production rising thus exacerbating the problem of vaccine distribution inequalities.

Antigenic polypeptide	Amino acid sequence
Human SARS-CoV spike glycoprotein (UniProtKB: P59594, PDB: 1WNC)	MFIFLLFLTLTSGSDLDRCTTFDDVQAPNYTQHTSSMRGVYY PDEIFRSDTLYLTQDLFLPFYSNVTGFHTINHTFGNPVIPFKDG IYFAATEKSNVVRGWVFGSTMNNKSQSVIIINNSTNVVIRAC NFELCDNPFFAVSKPMGTQTHTMIFDNAFNCTFEYISDAFSLD VSEKSGNFKHLREFVFKNKDGFLYVYKGYQPIDVVRDLPSGF NTLKPIFKLPLGINITNFRAILTAFSPAQDIWGTSAAAYFVGYL KPTTFMLKYDENGTITDAVDCSQNPLAELKCSVKSFEIDKGI YQTSNFRVVPSGDVVRFPNITNLCPFGEVFNATKFPSVYAWE RKKISNCVADYSVLYNSTFFSTFKCYGVSATKLNDLCFSNVY ADSFVVKGDDVRQIAPGQTGVIADYNYKLPDDFMGCVLAW NTRNIDATSTGNYNYKYRYLRHGKLRPFERDISNVPFSPDGK PCTPPALNCYWPLNDYGFYTTTGIGYQPYRVVVLSFELLNAP ATVCGPKLSTDLIKNQCVNFNFNGLTGTGVLTPSSKRFQPFQ QFGRDVSDFTDSVRDPKTSEILDISPCSFGGVSVITPGTNASSE VAVLYQDVNCTDVSTAIHADQLTPAWRIYSTGNNVFQTQAG CLIGAEHVDTSYECDIPIGAGICASYHTVSLLRSTSQKSIVAYT MSLGADSSIAYSNNTIAIPTNFSISITTEVMPVSMAKTSVDCN MYICGDSTECANLLLQYGSFCTQLNRALSGIAAEQDRNTREV FAQVKQMYKTPTLKYFGGFNFSQILPDPLKPTKRSFIEDLLFN KVTLADAGFMKQYGECLGDINARDLICAQKFNGLTVLPPLL TDDMIAAYTAALVSGTATAGWTFGAGAALQIPFAMQMAYR FNGIGVTQNVLYENQKQIANQFNKAISQIQESLTTTSTALGKL QDVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDKVEAE VQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSEC VLGQSKRVDFCGKGYHLMSFPQAAPHGVVFLHVTYVPSQER NFTTAPAICHEGKAYFPREGVFVFNGTSWFITQRNFFSPQIITT DNTFVSGNCDVVIGIINNTVYDPLQPELDSFKEELDKYFKNH TSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQE LGKYEQYIKWPWYVWLGFIAGLIAIVMVTILLCCMTSCCSCL KGACSCGSCCKFDEDDSEPVLKGVKLHYT
Noverl_SARS_S2	MFIFLLFLTLTSGSDLDRALSGIAAEQDRNTREVFAQVKQMY KTPTLKYFGGFNFSQILPDPLKPTKRSFIEDLLFNKVTLADAG FMKQYGECLGDINARDLICAQKFNGLTVLPPLLTDDMIAAYT AALVSGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQN VLYENQKQIANQFNKAISQIQESLTTTSTALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRV DFCGKGYHLMSFPQAAPHGVVFLHVTYVPSQERNFTTAPAIC HEGKAYFPREGVFVFNGTSWFITQRNFFSPQIITTDNTFVSGN CDVVIGIINNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLG DISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYI KWPWYVWLGFIAGLIAIVMVTILLCCMTSCCSCLKGACSCGS CCKFDEDDSEPVLKGVKLHYT
Novel_Trimeric_SARS_S2	MFIFLLFLTLTSGSDLDRALSGIAAEQDRNTREVFAQVKQMY KTPTLKYFGGFNFSQILPDPLKPTKRSFIEDLLFNKVTLADAG FMKQYGECLGDINARDLICAQKFNGLTVLPPLLTDDMIAAYT AALVSGTATAGWTFGAGAALQIPFAMQMAYRFNGIGVTQN VLYENQKQIANQFNKAISQIQESLTTTSTALGKLQDVVNQNA QALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQIDRLITG RLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRV DFCGKGYHLMSFPQAAPHGVVFLHVTYVPSQERNFTTAPAIC HEGKAYFPREGVFVFNGTSWFITQRNFFSPQIITTDNTFVSGN CDVVIGIINNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLG DISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYI KWPWYVWLGFIAGLIAIVMVTILLCCMTSCCSCLKGACSCGS CCKFDEDDSEPVLKGVKLHYT

Table 1. A table depicting the amino acid sequences of the three different antigenic polypeptides that is protected by the US20200282046 patent. Taken and modified from [5].

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