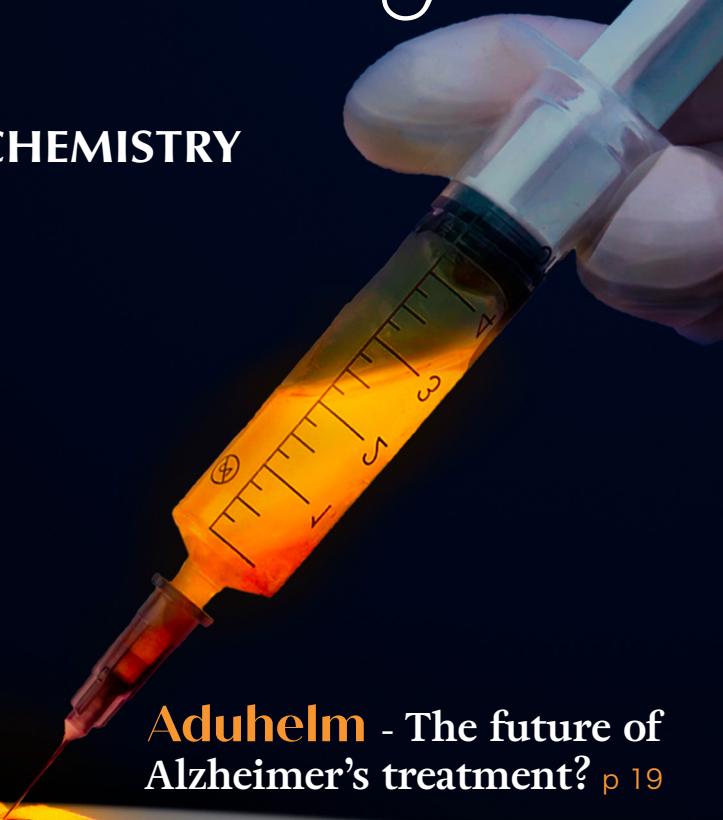




The Catalyst

connecting chemists

THERAPEUTIC CHEMISTRY



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Note from the Co-Founders

This September 2021 issue of The Catalyst takes you on a journey through pharmaceutical treatments from a chemistry perspective. Covering a range of well-known diseases, this issue gives you a diverse compilation of articles including newly discovered treatments, unfamiliar but must-have drugs, and even an insight into the darker past of drug development. On the occasion of Spinal Cord Injury Awareness Month, The Catalyst also features a collaboration with King's College London's very own iGEM team. A variety of other topics are also at your disposal, informing you on environmental changes during COVID-19, how the future of electric cars could look like, and what safety measures make your household more breathable. Our writers and proofreaders joined efforts to provide you with a wide assortment of topics, alongside our editors, who have worked tirelessly to complement each article with the right balance between chemistry and art.

We hope you enjoy!

The Founders



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Author: Paul Amar

The cost of caution

When the words "drug development" are mentioned, what comes to mind? Years of research? Rigorous testing phases? These may be true, some more than others, but we often take for granted the systems that are in place today to ensure that the medication we have access to is safe and effective. Let us then rewind the clock to a time before this, to take a small glimpse at the unfortunate tragedy that inspired the profound change in the regulations and monitoring of pharmaceuticals: Thalidomide.

1950s, West Germany: The head of research at the German pharmaceutical company, Chemie-Grunenthal, Heinrich Mückter, had just tasked his assistant with preparing simple peptides for antibiotic production. In doing so, a by-product was formed and isolated; and upon inspection by Grunenthal pharmacologist Herbert Keller, deemed to be a structural analogue of glutethimide, a hypnotic sedative. This was of great interest at the time, as glutethimide was the only non-barbiturate sedative available in a post-war world hooked on "sleeping pills". Due to the potential financial gain, a series of similarly modified compounds were synthesised and examined, with one seeming most promising, "Candidate K17".

Testing of K17's effectiveness ensued, and although it didn't inhibit the righting reflex of rodents (a laboratory test to determine hypnotic activity), further more complex mobility tests were developed and positive results were finally acquired. Subsequent toxicology tests were performed; the results reported that "no dose used could kill a rat!" hence branding it a safe, non-toxic sedative. Soon after this, in 1957, α -(N-phthalimido)glutarimide, more commonly known as thalidomide, was brought to the East German market, as an over the counter medication, under the brand name Contergan.

Advertised as a miraculous safe hypnotic by its manufacturers, said to alleviate ailments from insomnia to the common cold, the "wonder drug" boomed, and soon turned the heads of pharmaceutical companies all over the world. By 1960, due to lack of regulatory guidelines, thalidomide was sold in over 35 countries, under approximately 40 different names; and had become the 2nd most sold pharmaceutical in Germany after aspirin. In the meantime, further research/ off-label recommendation of thalidomide by doctors, indicated it had antiemetic properties, especially alleviating morning sickness in pregnant women, and was hence recommended for such; yet no reproductive toxicology study had ever been performed, a grave mistake we ought not repeat.

Fast forward to 1961, the non-toxic claims of Grunenthal were questioned as reports started to flood the German conglomerate about adverse undisclosed side-effects, which were ignored. It was only when over 10 000 infants around the world had been born with phocomelia, a rare disease causing the limbs to be abnormally short, that action was taken. After the overwhelming outcry by mothers and doctors, a German newspaper linked thalidomide to these birth defects, finally prompting Grunenthal to remove the teratogenic drug from the market. By 1962 most other pharmaceutical companies had followed suit (again).

Leaving in its wake thousands of dead (~ 40%) and impaired infants, not omitting many adults who had developed peripheral neuritis due to long-term exposure, the thalidomide scandal catalysed a much-needed change in drug manufacturing regulations. Over the following decade, many bodies had been created, among them the World Health Organisation, and formal guidelines were refined, resulting in the International Conference of Harmonisation Guidelines of 1990 which all pharmaceutical companies must abide by today. This tragedy was fortunately avoided in the USA due to the stricter regulations in place by the Food and Drug Administration, the only government regulatory body of the time.

Over a half century after the tragedy, we still do not fully understand the pharmacology of thalidomide. However, it has returned to the market, for treatment of multiple myeloma, and HIV, among other diseases, as it does have therapeutic benefits. Celebrating the 70th anniversary of its removal from shelves, let us explore

what we have learned. Thalidomide is a racemic glutamic acid analogue, hence existing as both R(+) and S(-) enantiomers, which have the ability to racemize in vivo. Study of the S(-) enantiomer indicates it is a powerful inhibitor of the tumour necrosis factor (TNF) from peripheral mononuclear blood cells, while the R(+) enantiomer acts as a sedative, potentially by the mediation of sleep receptors in the forebrain.

The mechanisms of action of thalidomide still remain unclear as research continues, over 30 hypotheses have been proposed as to elucidate the mystery of its teratogenicity alone; the most prevalent of which propose mechanisms through inhibition of angiogenesis, DNA intercalation, and cereblon binding.



Figure 1.
Map of the world showing highlighted some of the countries that sold Thalidomide.

All of these hypotheses have evidence to support them, and it is most likely that these mechanisms may be acting synergistically with each other to create its effects.

Moreover, thalidomide is also believed to function through anti-inflammatory and immunomodulatory mechanisms, which make it a viable candidate for treating diseases such as multiple myeloma, and HIV - which is marked by an increase in TNF, which can be inhibited by thalidomide. Research demonstrates that thalidomide may affect the transcription factor, nuclear factor kappa-B (NF-B), a key regulator of TNF. This factor is bound to inhibitory proteins, such as, I-B, then dissociated by inducers such as TNF in a phosphorylation which results in the activation of genes that are

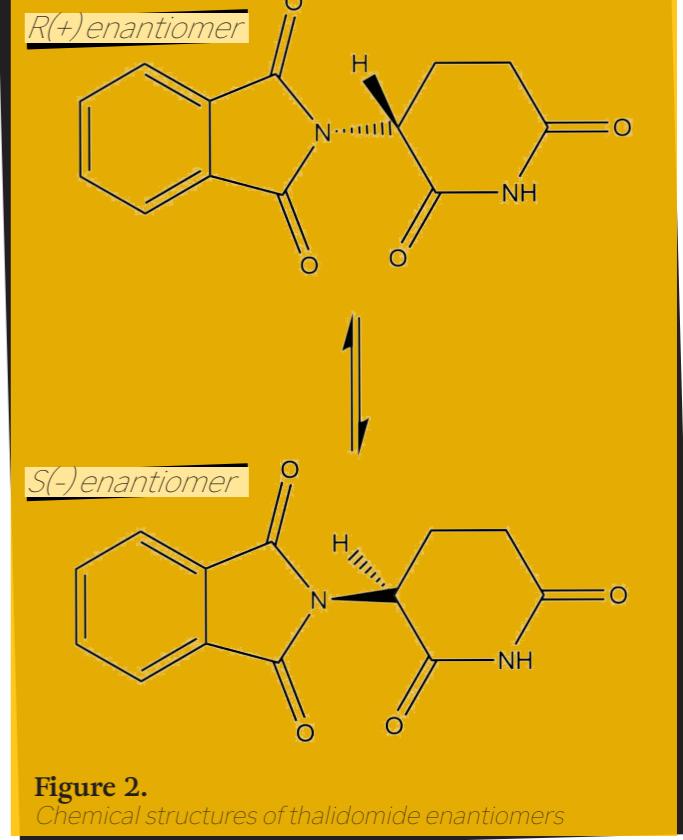
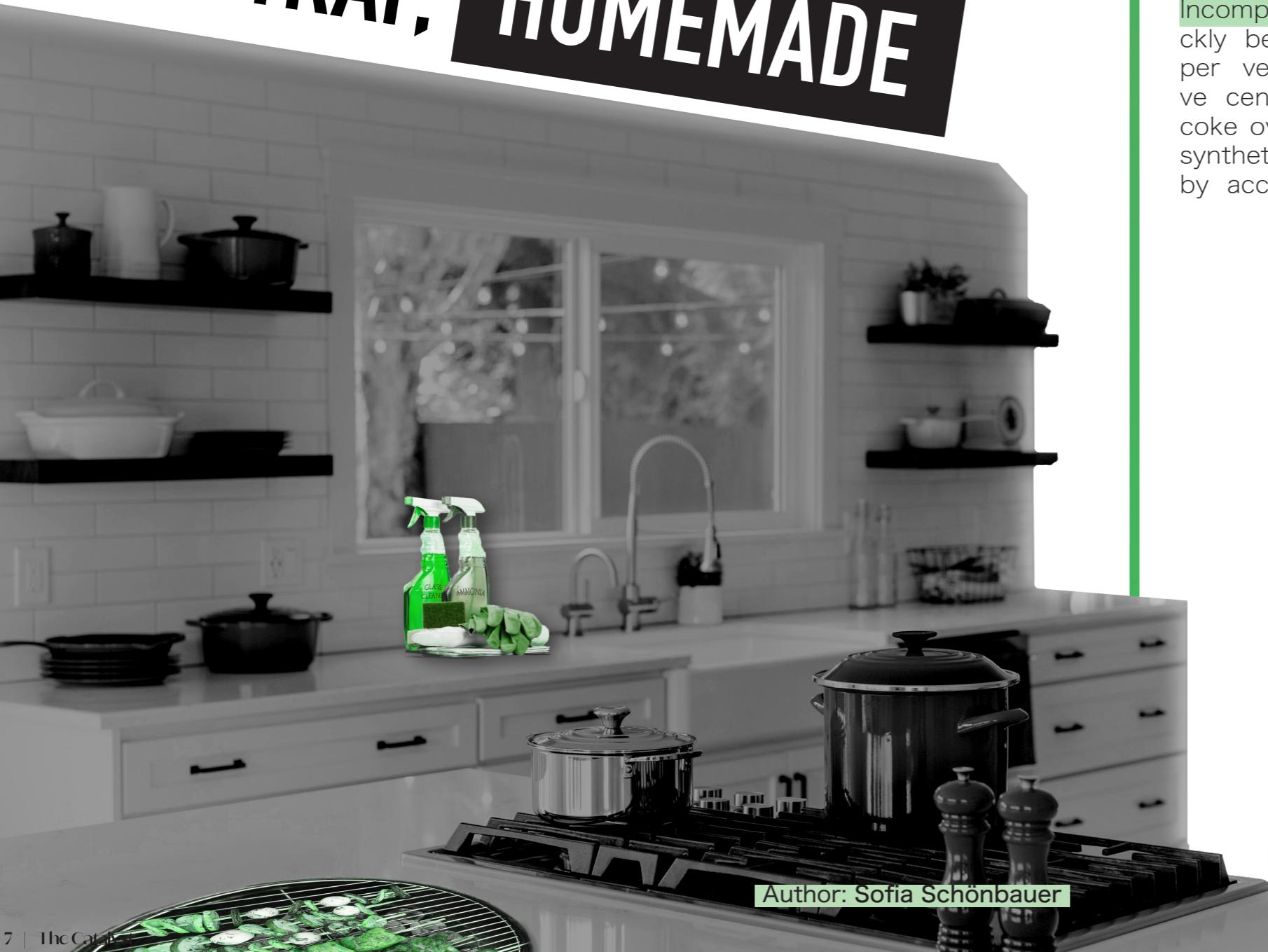


Figure 2.
Chemical structures of thalidomide enantiomers

responsible for immune and inflammatory responses but also cell growth, and possibly mediation of the redox regulation of limb growth. By inhibition of TNF and possible suppression of I-B kinase activity, preventing phosphorylation altogether, thalidomide hence can potentially deactivate NF-B, making it a good candidate for certain therapeutic applications.

Thalidomide has marked the history of the pharmaceutical industry forever, and it is too often we think of it as a “bad drug” which killed thousands of innocent lives, but this cannot be said to be the whole story. Thalidomide has potential benefits, but under the appropriate conditions and with careful monitoring. It is the lamentable lack of responsibility, proper testing, and forethought, coupled with the corporate greed of its manufacturers that truly brought this regrettable calamity upon its unsuspecting users; leaving the children to pay the cost of caution.

DEATHTRAP, HOMEMADE



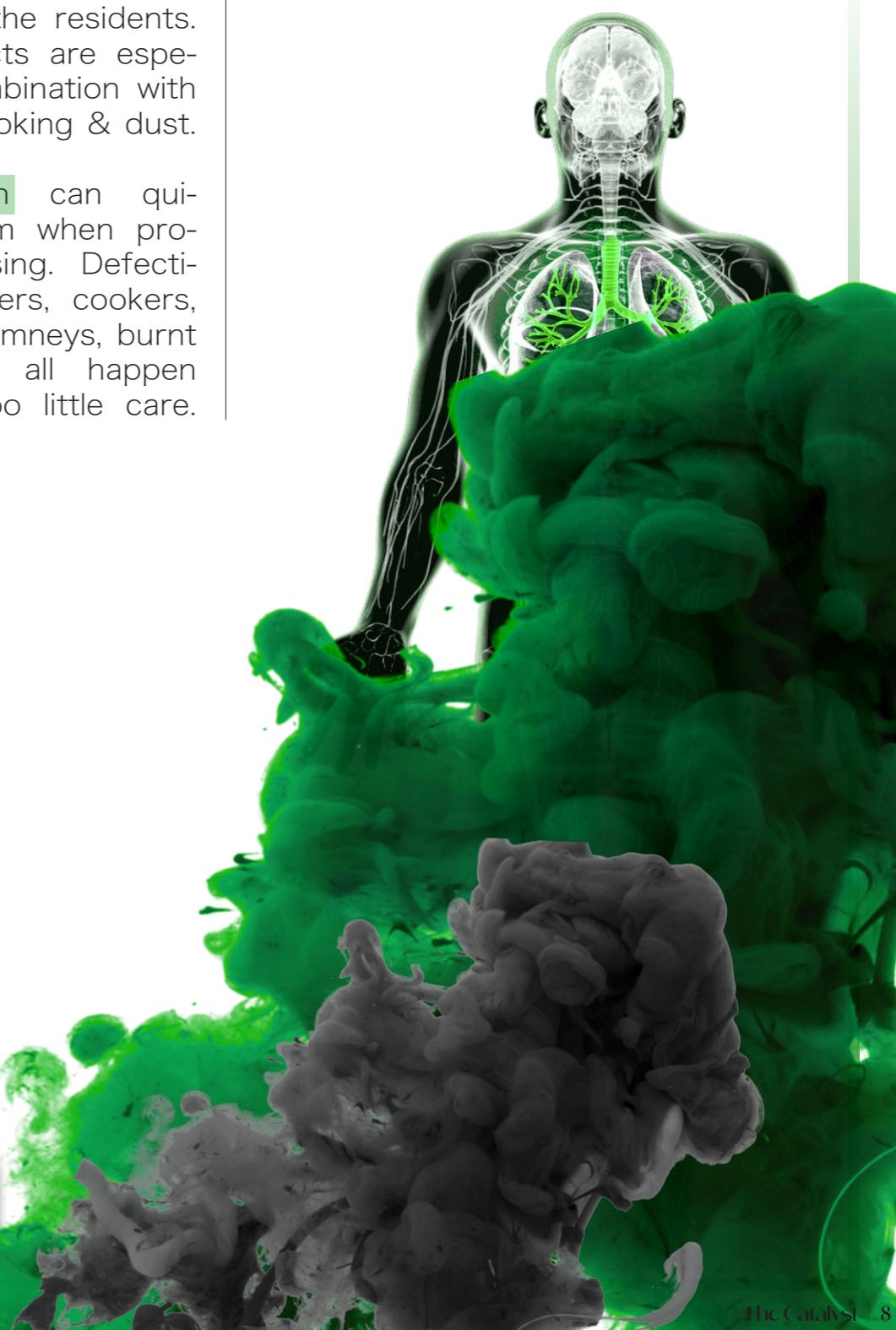
Author: Sofia Schönauer

Have you ever almost asphyxiated from water-proofing shoes? Ever not opened the window for a long time and felt tired and slow? Ever heard of carbon monoxide poisoning and thought you'd never be in that position?

Here's a guide to your household dangers and how to avoid them. Through soil, water, basements and ventilation; uranium decay to radon and its progeny is quite common, and can infiltrate a home without any contribution from the residents. Those decaying products are especially dangerous in combination with risk factors such as smoking & dust.

Incomplete combustion can quickly become a problem when proper ventilation is missing. Defective central heating boilers, cookers, coke ovens, blocked chimneys, burnt synthetics; those can all happen by accident or with too little care.

Running cars or barbecues indoors is less likely an accident, but just as dangerous. All of these actions are likely to produce carbon monoxide, one of the most common deadly gases. Chlorine gas and phosgene can both be set free when exposing chlorinated cleaning products to the wrong conditions: heat, ammonia, acid. These gases might have a tell-tale smell, but are no less dangerous, even being used as chemical weapons in World War I.



Chlorine gas poisons its first contact point in the human system after inhalation: the lungs. It reacts with water in the tissues, giving hypochlorous and hydrochloric acid, as well as a free oxygen radical. As this radical is very reactive, it can't diffuse far away, which is why chlorine gas poisoning is localized to the lungs. The high reactivity also means that the radical will interfere in regular redox reactions involved in electron transport chains and oxidize other cell parts that shouldn't be changed e.g. lipids or proteins. This can cause irritation to the mucosal membrane, edemas and even adult respiratory distress syndrome (ARDS). The acid formed, although not very harmful at physiological condition can result in superficial burns as well.



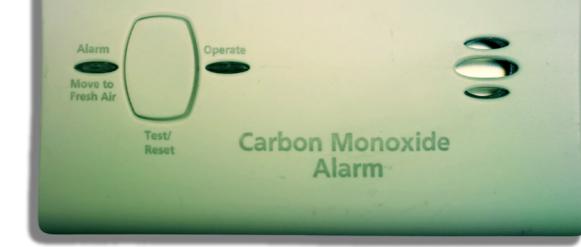
Radon's radioactive isotope ^{222}Rn also localizes its effect in the lungs. It is part of the decay chain from Uranium-238 and ends up decaying to stable lead. Its progeny - the decay products - follow the series: $^{222}\text{Rn}(\alpha) \rightarrow ^{218}\text{Po}(\alpha) \rightarrow ^{214}\text{Pb} \rightarrow ^{214}\text{Bi} \rightarrow ^{214}\text{Po}(\alpha) \rightarrow ^{210}\text{Pb}$. Radon and its progeny are charged and attach to aerosol particles such as dust. When inhaled, they deposit in airways as clusters, while continuing through the decay chain. This exposes adjacent tissues to alpha radiation; very strong and localized predominantly in the tracheobronchial tree. This type of radiation is very concise, inducing ionizations in a highly linear fashion, which can cause DNA molecules to break in both strands. The exposure is much higher in dusty or smoky conditions, as there are more aerosol particles around. The decay of ^{218}Po and ^{214}Po , alongside the initial ^{222}Rn contribute most to its toxicity due to their strong alpha particle emissions. ^{210}Pb has a half-life of 22.2 years and is therefore established as the "stable" isotope which is metabolized to thiocyanate by the enzyme rhodanase, before it can cause any significant radiation damage to the tissues.

Exposure to phosgene can happen through ingestion, inhalation and simple contact as well. It has a smell reminiscent of cut grass and is heavier than air, so more likely to accumulate on the bottom of a room. There are two mechanisms: the less dangerous one occurs upon inhalation and consists of hydrolysis to carbon dioxide and hydrochloric acid. As only a small amount of the latter is produced in physiological conditions, a different mechanism of poisoning is more prevalent.

Phosgene undergoes acylation with functional groups on lipids, proteins and carbohydrates. These reactions cause extreme oxidative damage and increase free radical concentration, with a similar mechanism of disrupting adjacent cells' redox chemistry and compartments. The main effect is an increase in vascular permeability, meaning that the barrier between blood and tissues weakens. This favors the formation of pulmonary edemas, as inhalation exposes primarily the lungs to phosgene.

Hydrogen cyanide is classified as a systemic poison: it affects several organs of the body through the central nervous system. It poisons by non-competitive inhibition of cytochrome c oxidase. Binding to the iron co-factor prevents electron transport to oxygen at the end of the transport chain. This tampers with cellular respiration and ATP production. In brain cells, HCN very quickly affects consciousness, respiration and leads up to death. Other enzymes (iron and copper-containing) can also be affected.

Odorless carbon monoxide poisons through inhibition of oxygen binding to haemoglobin. The heme unit has a much higher affinity for CO than for oxygen, and forms a very stable compound. This mechanism also affects the body on a larger scale rather than just the lungs. Oxygen isn't very soluble in blood, so by preventing the transport to tissues, CO disrupts respiration. CO can also bind to myoglobin, therefore cutting off oxygen transport to brain and muscles. Final result: asphyxiation.



What used to be a canary bird's role in mines nowadays fits into a palm-sized device that continuously measures carbon monoxide levels at home. Airing out rooms every day, and remembering to not burn anything without direct ventilation also goes a long way for your own safety. There are similar detection devices for radon, those however are left in the main living areas - usually for 3 months - then sent in and analyzed. Although more expensive, this test should suffice for a good time as it gives an indication of how strongly your living conditions expose you to radon. HCN is also detected by industrial readers, although these are probably not as necessary as ventilating any open flames, and avoiding plastics and other synthetic fabrics from being combusted. Chlorine leak detection can be done with sensors, or with an ammonia solution close by that reacts with leaks to give off visible vapors. Separating chlorine-containing cleaning products from all other substances and heat exposure is also very recommendable to reduce chances of violent and dangerous reactions. This will also reduce the need for a phosgene detector.

Although scientific research has facilitated safety at home with a variety of detectors for all gases listed, a little trivial knowledge might just come in handy on occasion to avoid unpleasant surprises.

LIQUID GOLD: CANCER

Author: Sofia Schönauer



Chemistry as we know and love it has its own logic. It lets us predict mechanisms, reaction outcomes and physical properties based on what we've learnt in the past. However, for a certain category of particles, that logic seems to fail on occasion. Particles with a dimension or characteristic measured on a scale of nanometers are classified as nanoparticles (NPs), and are available in a variety of shapes and functionalities. This will be a series across future magazine issues that will explore gold NPs and their versatility across a range of topics.

Contrary to the image one might have of a gold bar, colloids - formations of gold that don't exceed nano-scale dimensions - can form solutions of varying shades of red in water.

This class of particles has become more and more researched lately; one focus being the usefulness in cancer imaging and treatment. Different mechanisms allow for an intravenous solution of gold nanoparticles (AuNPs) to accumulate in and around cancer cells. Depending on how they were functionalized, they display different anti-cancerous properties. The passive mechanism (of nano-gold) uptake is quite common, and is also termed the enhanced permeability and retention effect (EPR). It has been shown that given intravenously, the nanoparticles aren't taken up by healthy tissues or cleared by the kidneys due to their size. They can however permeate tumorous vasculature, and accumulate in vicinity to cancerous tissue due to a lack of effective lymphatic drainage (a cell's waste disposal).

Once in the cancerous tissue, one destructive action these colloids can carry out is creating hyperthermic conditions. This so-called photothermal therapy exposes the tissue to high levels of radiation or heat, destroying them from within. How might that work without exposing a patient completely to those levels of radiation? Only near-infrared (NIR) is used. This region of the electromagnetic spectrum has longer wavelengths than visible light, which can pass through and penetrate up to a few centimeters into the tissue, making that region so important for this therapy to work. As a laser is shone from the outside, electrons on the gold surface layer resonate within the same frequency of the photons that they pick up. As a result, they propagate along the surface of the nanoparticle, which is called surface plasmon resonance (SPR). This enhances the very specific light that is taken up, which collectively creates the hyperthermic conditions that selectively destroys the cells around where the particles have accumulated, and where the NIR laser was shone on.

Because the light reaches this depth, NIR encompasses the best region for SPR absorption of AuNPs. For that very SPR, and for its quick, immediate conversion of light into heat, gold nanoparticles are also a useful tool to enhance radiotherapy.

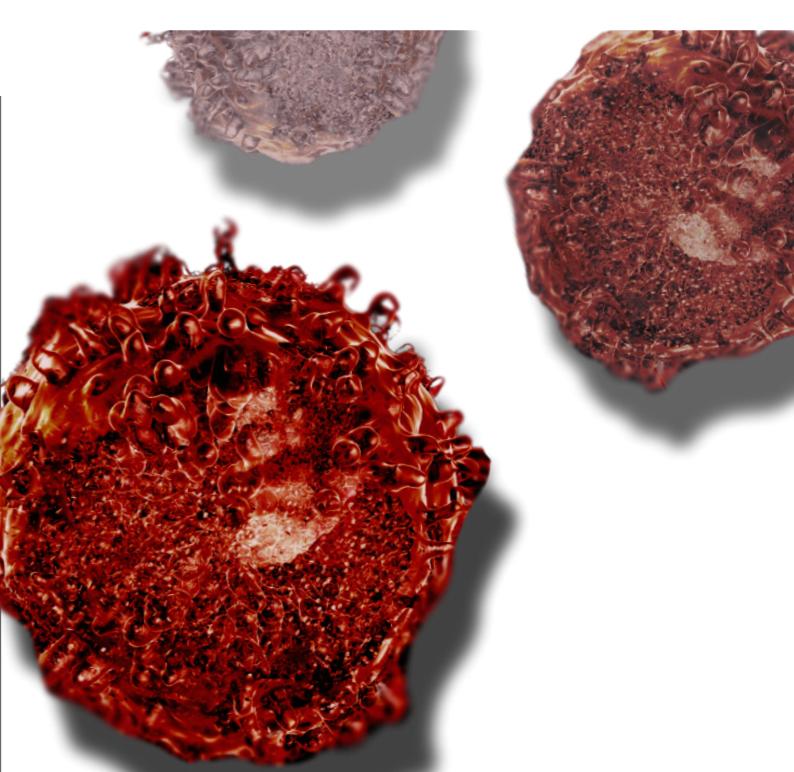
Thermal destruction - through cell membrane disruption, protein denaturation and up to cell death - requires exact knowledge of where the tumor is located, as it is unlikely that 100% of AuNPs would be positioned next to the tumor tissue. Regardless, there is a chance for healthy tissues to get exposed as well, which is why the use of gold nanoparticles in cancer treatment still requires a lot of research and in vivo studies.

The surface of the colloids allows for effective conjugation with a variety of compounds. Conjugated with drugs, gold nanoparticles

can carry them to enhance the targeted uptake of those drugs into the tumor tissue. Controlled release can happen with magnetic AuNPs or hyperthermic stimulation. Similarly, nucleic acids can also be conjugated and delivered on the surface of colloids. Drugs, gold nanoparticles can carry them to enhance the targeted uptake of those drugs into the tumor tissue. Controlled release can happen with magnetic AuNPs or hyperthermic stimulation. Similarly, nucleic acids can also be conjugated and delivered on the surface of colloids.

Different conditions are being explored to figure out how to make the most effective use of the AuNPs. Poly(ethylene glycol) (PEG) is very commonly used for functionalizing nanogold, covalently bound to the gold atoms on the surface of the particle. Its improvement on biocompatibility, blood half-life and escaping the reticuloendothelial system's (RES) clearing through hydrophilicity makes PEG a very interesting conjugation species. Another concern when using nanogold is its cytotoxicity. Certain modifications with folic acid, polyacrylamide and polyvinylpyrrolidone on the surface can reduce (if not eliminate) the possibility of damage to cells from the AuNPs. A coating with poly(acrylic acid) or poly(allylamine hydrochloride) also has this effect.

Apart from the uncertainty of photothermal therapy and the incurring damage on healthy cells, other factors also need accounting for AuNPs to be used on a wide scale. Problems with an optimized synthetic route have yet to be resolved,



to eliminate any chance of contamination with chemicals harmful to the human body when injected. Additionally, the synthesis needs to be able to control nanoparticle size, growth and shape, as a distribution of nanoparticles could complicate dosage and might affect healthy cells. Since the mechanisms listed are mostly based on the passive uptake mechanism, and some conjugated particles even avoid RES elimination, an effective mechanism of clearing the nanoparticles from the blood-stream is still needed.

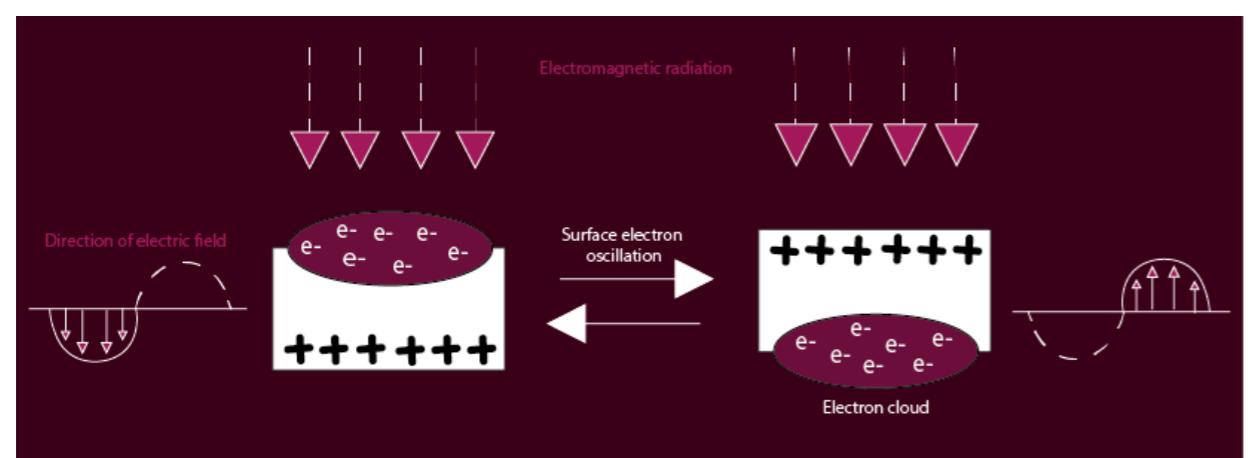


Figure 1.
Diagram showing how Surface Plasmon Resonance (SPR) works.

Some research looks at the use of gold nanoparticles specifically for brain and breast cancer, but a lack of specificity, and the vast variety of shapes, sizes and distributions that can be tested allow for a lot more research to be done on these specific cancer treatments. The nanogold's surface properties that allow for conjugation and for SPR to occur, make this group of molecules so intriguing. They demonstrate high versatility across disciplines. This series on their applications across chemistry will continue soon...

Lithium-ion Batteries

Introduction

For many years scientists have sought greener alternatives of energy to prevent pollution from fossil fuels. In particular battery technologies have been pioneered in order to reduce petrol consumption in transport vehicles (such as cars), as there is a global concern that they are major contributors to atmospheric pollution. To put this into perspective in the EU alone 30% of CO₂ emissions are caused by transport where 72% comes from car emissions.

While global demand for personal cars has increased, so has the demand for electric cars. It is estimated that the global demand for electric cars has increased from only a few thousand to 7.5 million in 2019. Lithium-ion batteries have been the main technology which has powered electric cars, because lithium is a very strong reducing agent. It has one of the highest voltage outputs of -3.4 V, producing the highest amount of electricity.

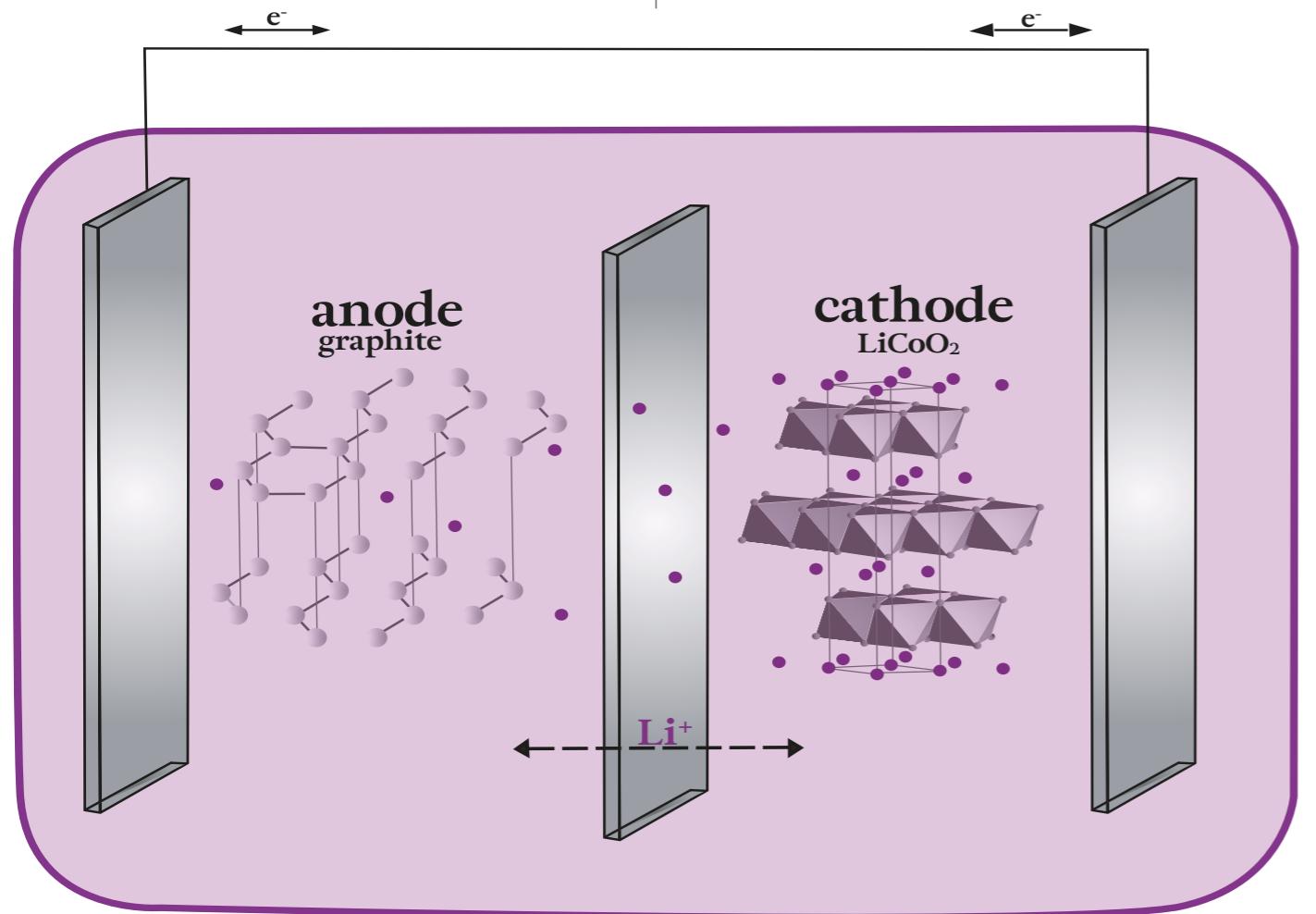


Figure 1.
Diagram showing how the Li battery works.

Author: Radoslav Petkov

But how do lithium-ion batteries operate and are there problems with this technology, which would hinder future advancements?

What does the battery contain?

Lithium-ion batteries have the same basic components as a voltaic cell.

■ ANODE

A layered structured compound such as graphite.

■ CATHODE

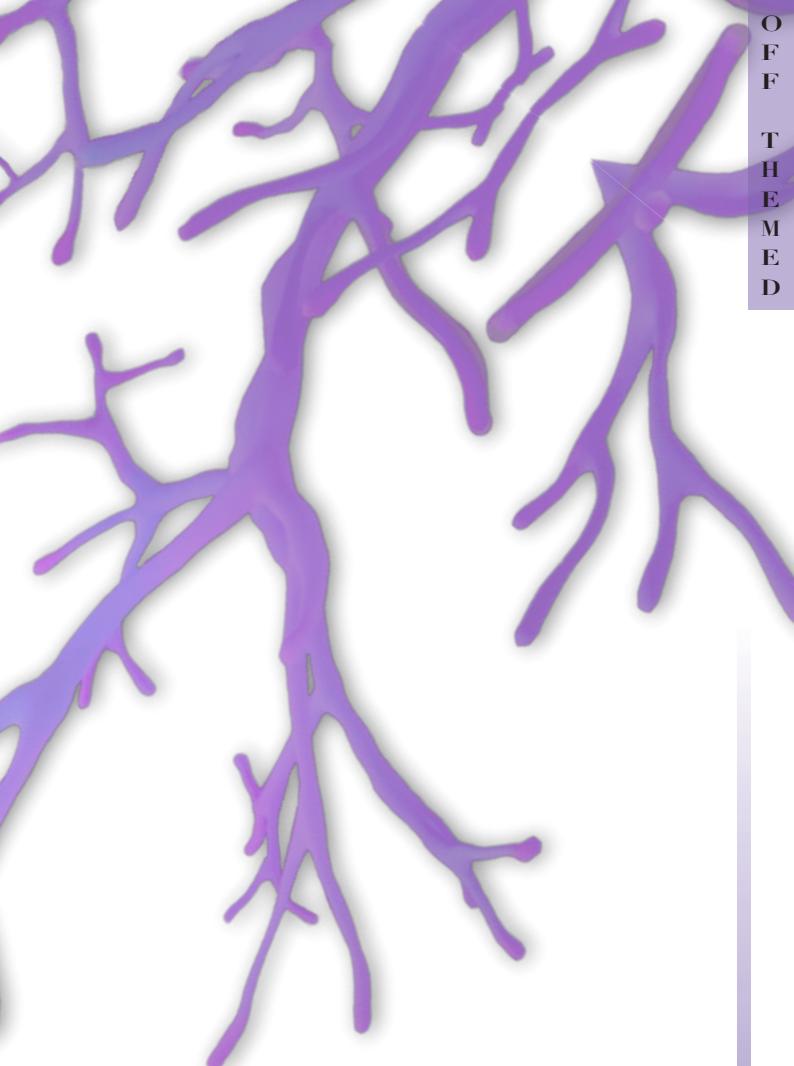
A lithium oxide compound (lithium ions by themselves will be too reactive).

■ ELECTROLYTE

A lithium compound dissolved in organic solvent (such as lithium hexafluorophosphate dissolved in ethylene carbonate).

■ POLYMER MEMBRANE (separator)

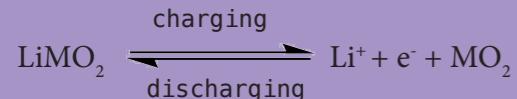
Provides a physical barrier so that the anode and cathode do not mix.



How does the battery work?

Initially, lithium becomes oxidised and forms lithium ions in the cathode. The lithium-ions will diffuse through the electrolyte through the separator, into the anode and fit in between the ordered graphite layers. The graphite itself is an inert compound and does not take part in the reaction as it only accommodates the lithium ions. The electrons cannot pass through the electrolyte, because the separator has a property called microporosity, meaning that it is only permeable to lithium-ions. Electrons will therefore pass through the external circuit and into the graphite layers. This process is called charging and the half-equations are represented in the diagram on the next page.

● Cathode



● Anode

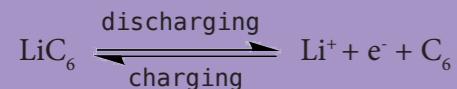
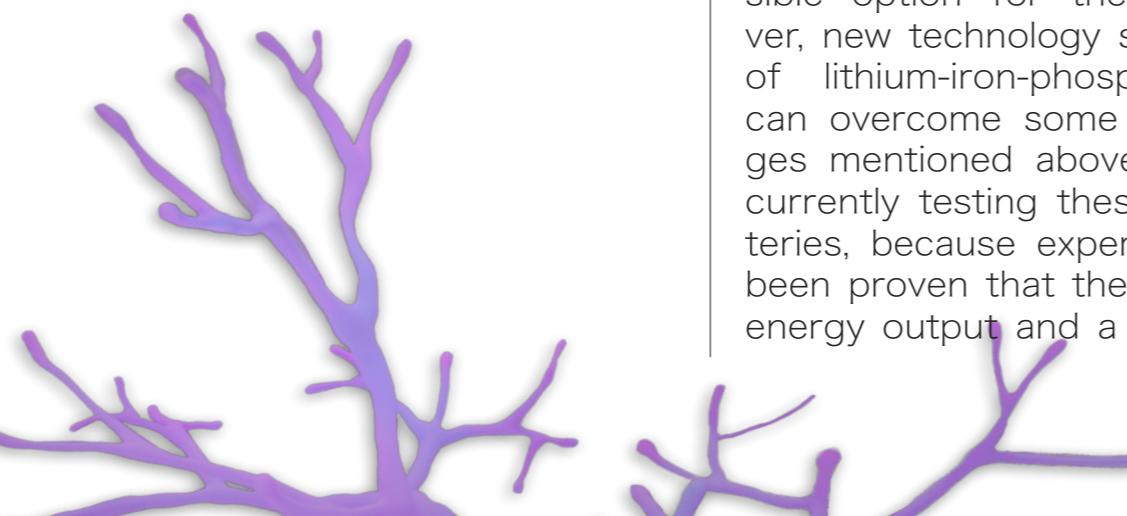


Figure 2.
Half-equations for charging and discharging processes.

During the discharging process the lithium-ions become reduced by the incoming electrons and diffuse through the electrolyte and back into the cathode. The environment inside the battery is very reducing and this could cause the breakdown of products in the electrolyte to form LiF, LiP etc. These compounds accumulate around the electrodes and form the separating electrolyte interphase (SEI). This layer is very important, because it allows for redox processes to occur, by the diffusion of lithium ions.² through the electrolyte. However, at the same time the SEI layer prevents electrons from migrating to the anode, which will have destructive effects on the electrolyte.

Over time, the thickness of the SEI naturally increases, reducing the storage capacity of the battery. This would mean that lithium ions become trapped in the SEI layer, instead of diffusing.



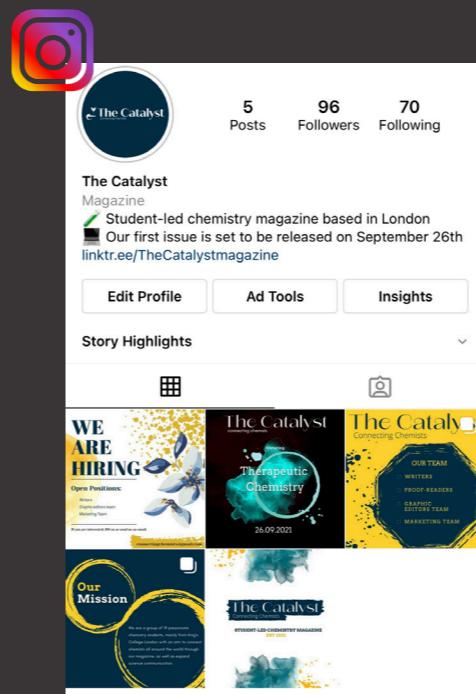
Problems with lithium-ion batteries?

The increase in the thickness of the SEI is not the only problem in lithium-ion batteries. One of the major problems is the accumulation of lithium dendrites on the surface of the cathode. Lithium dendrites are accumulation of lithium metal into tree-like structures which greatly reduce the capacity of the battery to generate energy. If the dendrites grow for too long, they can pierce the separator and allow the electrolyte in the cathode and anode to make contact. This could lead to cell explosions. While efforts have been made by scientists to reduce the amount of lithium dendrite formation, this problem has still not been overcome partially because of the lack of understanding of dendrite formation, how it is governed (thermodynamic or dynamic control) and methods of dendrite deposition.

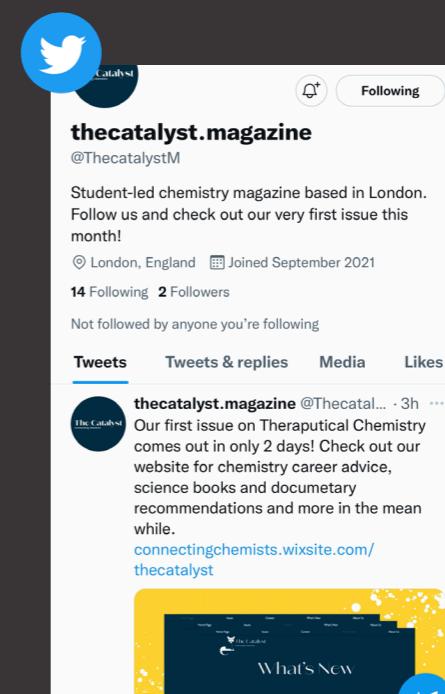
Conclusion

While lithium-ion batteries show a promising alternative to providing clean energy, the complications which arise from dendrite growth and SEI, makes them a less scientifically feasible option for the future. However, new technology such as the use of lithium-iron-phosphate batteries can overcome some of the challenges mentioned above. Tesla is even currently testing these types of batteries, because experimentally it has been proven that they have a higher energy output and a longer life-time.

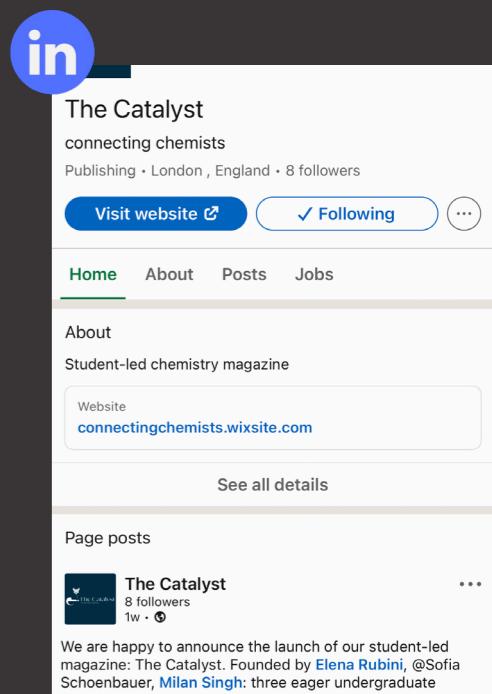
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ADUHELM.

The *newest* treatment for Alzheimer's?

Author: Matt Dagwell

For decades, Alzheimer's disease (AD) has been eluding scientists and medical professionals alike, affecting almost 40 million people worldwide. From the moment the amyloid hypothesis was proposed in 1984 scientists have tried to find ways to combat the disease using many different types of drugs but to little avail. But could we now be on the break-through of a drug that will finally effectively treat AD?

Alzheimer's disease is described as a progressive brain disorder first discovered on 3rd November 1906 by clinical psychiatrist, neuroanatomist and lecturer at Munich University, Dr. Alois Alzheimer. Dr. Alzheimer first discovered the cause of AD following an autopsy of a patient who had been experiencing paranoia, problems with sleep and memory, aggression, and confusion.



From this autopsy, both plaques and neurofibrillary tangles were found to be present in the patients histology. In order to understand how to tackle AD we must first understand its pathophysiology. AD has two main pathophysiologies associated with it: the formation of plaques and neurofibrillary tangles.

The plaques formed in AD occur due to an abnormal post-translational modification of the amyloid precursor protein (APP). The amyloid precursor protein is found as a transmembrane protein in the cell membranes of neurons and is used to help grow and repair neurons in the brain. It is normally cleaved using two enzymes α -secretase and γ -secretase forming a soluble molecule of sAPP α that is unable to cause any damage to the brain.

However, in AD the β -secretase-1 (BACE1) enzyme is used over the α -secretase enzyme causing the formation of an insoluble protein monomer called Amyloid- β . These monomers are insoluble in the brain and bind together to form amyloid- β plaques that can interrupt neuronal function and lead to cerebral amyloid angiopathy.

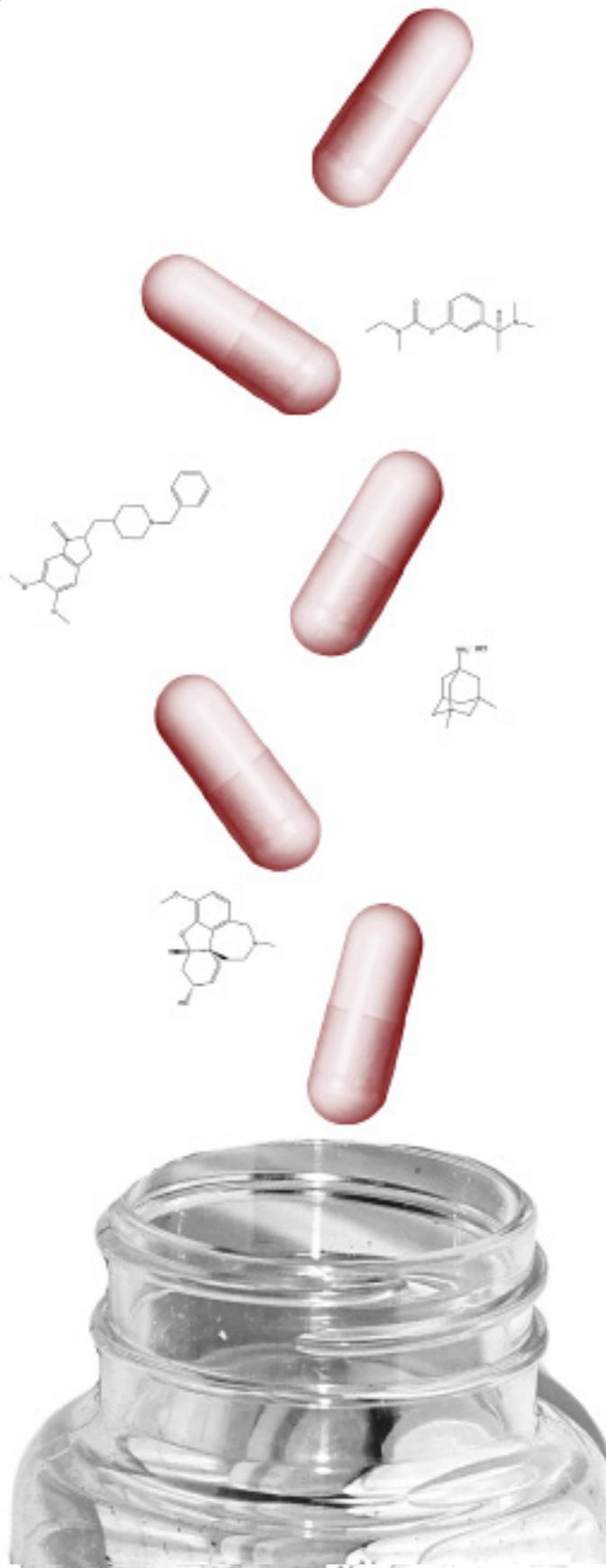
Neurofibrillary tangles

Neurofibrillary tangles are another characteristic pathophysiology of AD. The way by which these tangles are formed is debated, however a key process of hyperphosphorylation of the microtubule associated protein (MAP) Tau in the cytoskeleton of the neuron is thought to be the main cause of these tangles.

The Tau protein holds together the microtubules that make up the cytoskeleton of the neuron, however when these are hyperphosphorylated by the protein kinase, it is thought that the tau protein undergoes allosteric changes to cause a lower binding affinity of tau to the microtubule. This causes it to detach and instead aggregate outside of the microtubule and consequently triggers the degeneration of the neuron's cytoskeleton and therefore its structure. This loss of structure subsequently leads to a loss of signalling efficiency of the neuron as well as cellular apoptosis. These further regress to brain atrophy causing the gyri to degrade and sulci to expand; this leads to the degradation of brain function and problems with speech and memory.

THE HISTORY OF ANTI-ALZHEIMER'S DRUGS

There are currently five main drugs used to treat AD that are approved by the FDA, which utilise two different mechanisms of action; cholinesterase inhibitors (AChEIs) such as Aricept (approved in 1996), Exelon (approved in 2000) and Razadyne (approved in 2001) as well as an N-methyl-D-aspartate (NMDA) channel blocker known as Namenda (approved in 2003). There is additionally a fifth drug, Namzaric, which utilises a combination of these two mechanisms of action.



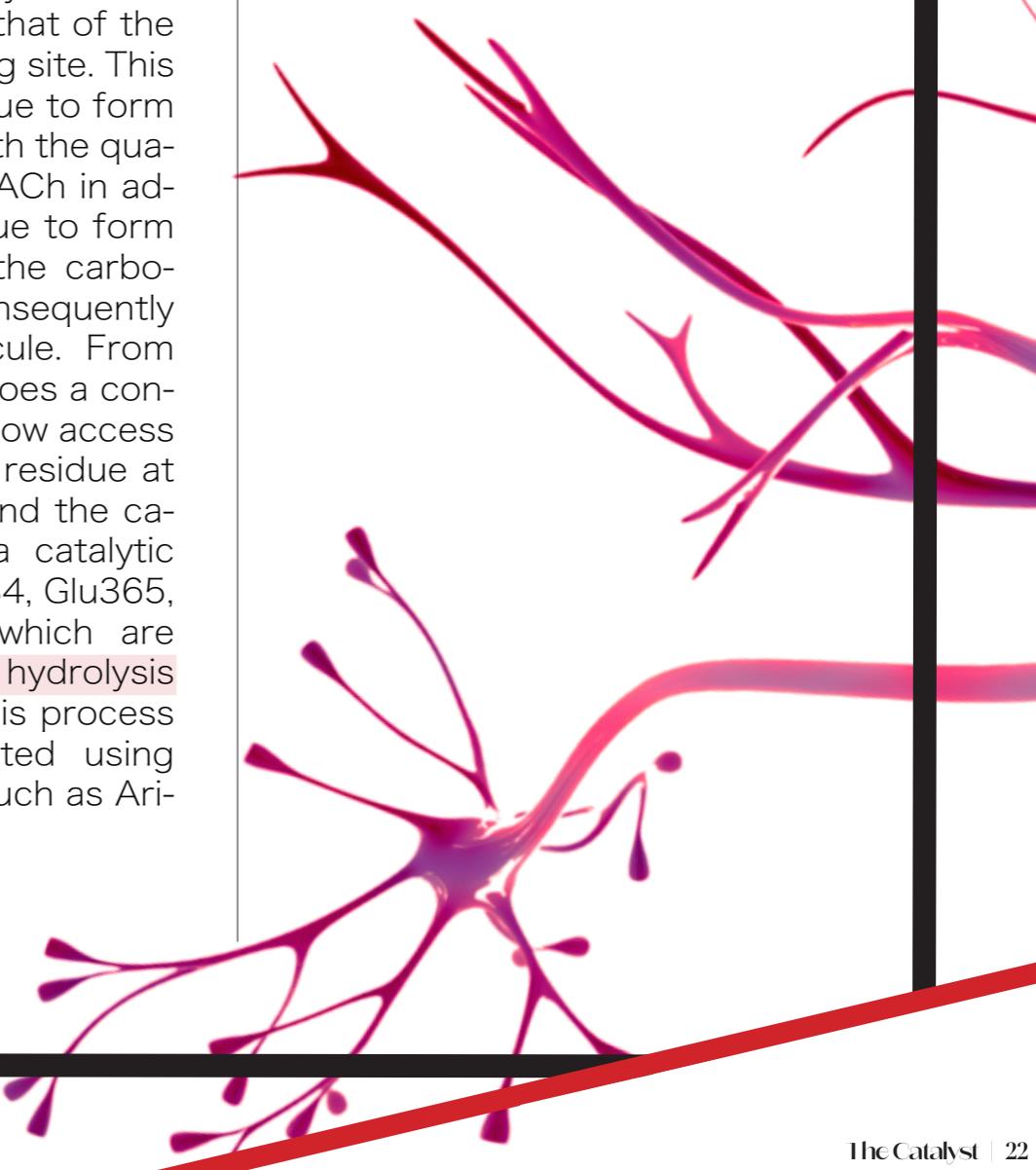
Acetylcholine and Acetylcholinesterase inhibitors

To understand how these drugs work, we first must understand the neurochemistry of both acetylcholine and glutamate. Acetylcholine (ACh) is a neurotransmitter found throughout the body in the cholinergic nervous system and in the central nervous system, with many different functions from muscle contraction to processing memory. As such, this neurotransmitter plays an important role in the treatment of memory processing disorders and maintenance of brain function in patients with mild to moderate AD.

This treatment functions by increasing the amount of ACh present in the synaptic cleft to increase neuronal signal transduction. Since ACh is not reabsorbed into the presynaptic neuron like other neurotransmitters and is instead hydrolysed by the enzyme Acetylcholinesterase (AChE), the main drug target has been the active site of this enzyme to inhibit its catalytic activity and consequently increase the amount of ACh in the synaptic cleft.

The AChE enzyme has three main active sites present in a 20 Å long hydrated gorge, the catalytic site, the acyl pocket, and the peripheral anionic binding site, all of which are important in its catalytic activity. The first site used is that of the peripheral anionic binding site. This site uses a Trp317 residue to form a π -cation interaction with the quaternary amine group of ACh in addition to a Tyr372 residue to form a hydrogen bond with the carbonyl group of ACh, consequently sequestering the molecule. From here the enzyme undergoes a conformational change to allow access to a second tryptophan residue at the base of the gorge and the catalytic site containing a catalytic triad consisting of Ser234, Glu365, and His478 residues, which are then able to perform the hydrolysis of the ACh molecule. This process can however be inhibited using many different AChEIs such as Aricept.

Aricept functions as a mixed competitive and non-competitive inhibitor by being able to both block the main catalytic site of the enzyme and thus block the hydrolysis of ACh but also by binding to the enzyme once it is loaded with the substrate leading to unequal stability of the enzyme thus preventing the hydrolysis from occurring. Razadyne works in a similar fashion to Aricept in that it reversibly inhibits the function of AChE, however this molecule is also believed to enhance the intrinsic action of ACh on nicotinic receptors, leading to a further increase in cholinergic neurotransmission. The mechanisms of action of the final AChEI - Exelon - are however still unclear.



GLUTAMATE AND THE NMDA CHANNEL

In addition to acetylcholine, another neurotransmitter is believed to be important in the progression of AD. Glutamate is one of the most abundant excitatory neurotransmitters in the brain and plays a key role in neuroplasticity and enhancing neuron strength. It does this by binding to the Mg²⁺ gated N-methyl-D-aspartate (NMDA) receptors on the postsynaptic neuron, causing an influx of Ca²⁺ ions triggering a signalling cascade which enhances the signalling strength of the neuron. However, the abundance of glutamate in the brain must be carefully moderated, as too much can lead to excessive stimulation of the neurons. Excitotoxicity follows closely, where nerve cells are either damaged or killed. In AD, the system responsible for the reuptake of the glutamate from the synaptic cleft has been shown to be severely weakened, meaning more glutamate is present in the cleft and thus excitotoxicity increases, leading to the symptoms characteristic of AD. Drugs such as Namenda have been used to prevent excitotoxicity from occurring by blocking the NMDA channels and thus preventing the flow of Ca²⁺ ions into the postsynaptic neuron.

From here the channel is then able to close, thus entrapping the drug in the receptor and preventing the over-stimulation of the postsynaptic neuron.

However, despite these treatments being effective in the treatment of AD (slowing the disease progression), there is yet to be a treatment that prevents the formation of AD in the first place until 2021.

INTRODUCING ADUHELM

Aducanumab marketed under the name Aduhelm is a human monoclonal antibody that has been shown to decrease the presence of A β plaques in patients with prodromal or mild AD with a visibly positive A β PET scan and is currently in stage three clinical trials with approval by the FDA along its accelerated approval pathway. Aducanumab was first resolved from a blood lymphocyte library of a sample of elderly people who showed no signs of cognitive impairment or with an unusually slow decline in cognition. After undergoing phase one trials with promising results, researchers set out to find out how aducanumab functions in the treatment of A β plaques in patients with AD.

HOW DOES IT WORK?



The human monoclonal antibody was found to bind to the beta amyloids plaques predominantly by the first 3-7 amino acids of the polypeptide chain with some key residues in the epitope being present that allow for efficient and effective binding: Glu3, Asp7, Phe4 and His6. Upon mutagenesis of these key residues, a decreased binding affinity was found, with substitution for alanine residues in positions 3 and 7 moderately reducing aducanumab binding. The same mutagenesis at positions 4 and 6 lead to a complete reduction and subsequently no binding of the aducanumab fragment to the beta amyloid plaque, indicating that residues Phe4 and His6 are instrumental in the binding of the Fab fragment. The binding of aducanumab has predominantly been shown to comprise several hydrogen bonds with an additional salt bridge and extensive hydrophobic interactions occurring via multiple different amino acid side chains present on the Fab fragment. Once this antibody is bound to the plaque using its binding sites, the immune system can take over in breaking down the neurotoxic plaque oligomer and thus treat the disease.

SO,
IS IT EFFECTIVE?

In a phase 1b PRIME (prospective research in memory) clinical trial of aducanumab, it was found to be effective in penetrating the brain and removing beta amyloid plaques within the sample population, with doses of 3, 6 and 10 mg/kg significantly decreasing the amyloid PET SUVR, while patients in the control group receiving the placebo showed no change in their mean PET SUVR composite scores. In addition to this at this stage of trial the use of aducanumab also showed a decrease in the CDR-SB (Clinical Dementia Rating scale Sum of Boxes) and MMSE (Mini Mental State Examination) scores of patients, indicating a clinical benefit of decreasing the amount of beta amyloid present in the brain. Despite the reduction in beta amyloid being seen after 6 months, the actual clinical effects of the antibody were not observed until one year after first administration. However, the sample size used in this trial was quite small and was only performed in the USA and so may not be representative of the global population.

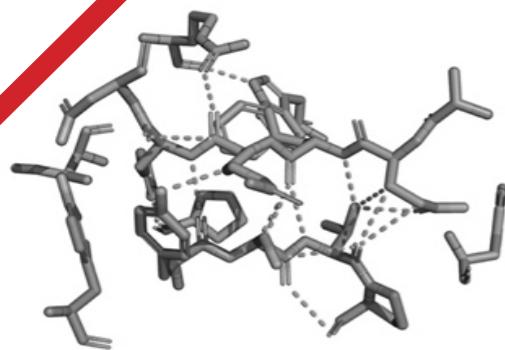


Figure 1.

3D model representing the hydrogen bonds between the aducanumab Fab fragment with the key epitope of the beta amyloid protein.

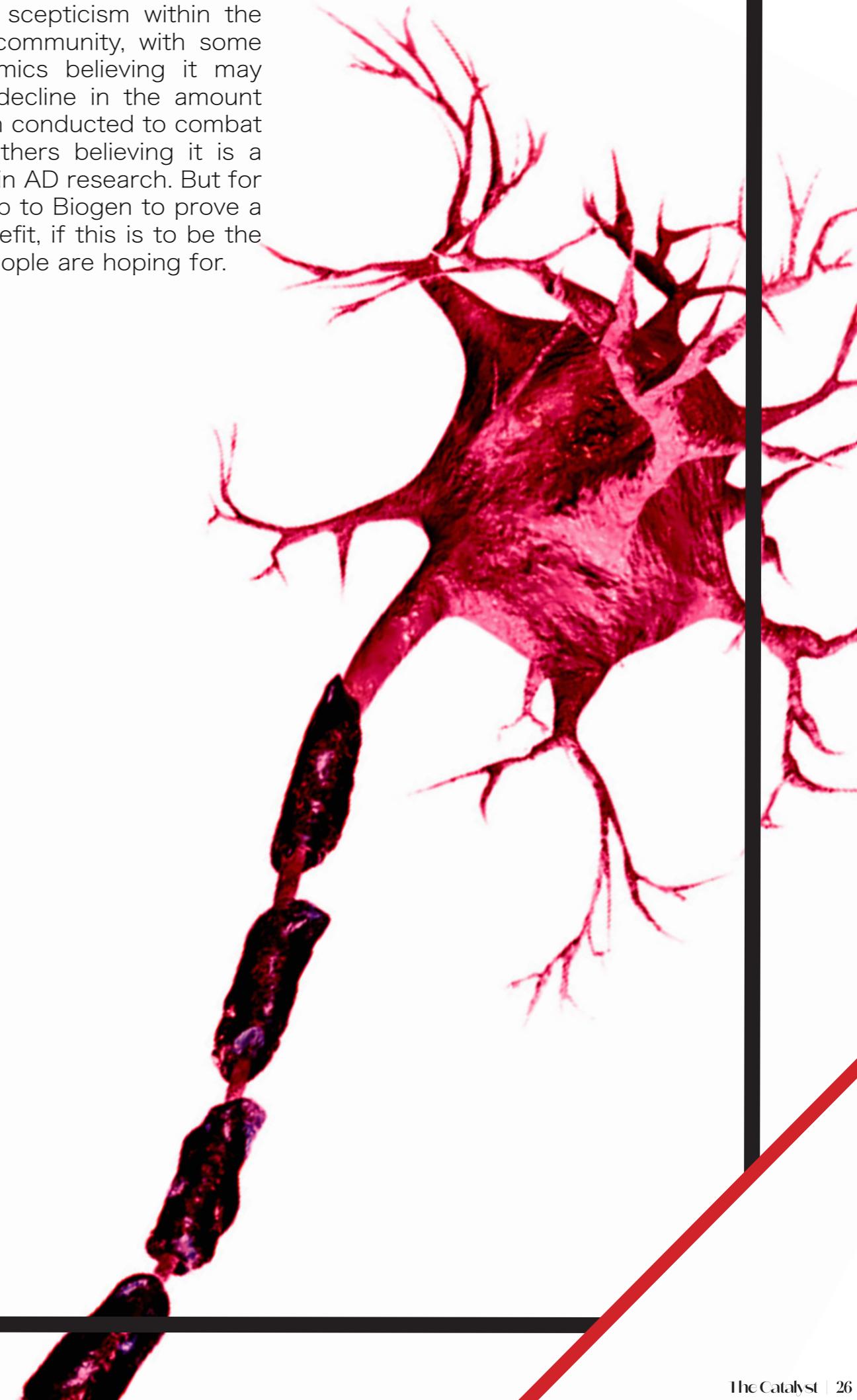
When taken to a global scale in phase three clinical trials, the results became more conflicting in the use of aducanumab to effectively treat AD. The main company sponsoring the production and research into aducanumab - Biogen - halted stage three clinical trials of the antibody due to futility, but went on to suggest efficacy of the drug 7 months later. These reports come from two sets of opposing data found during trial 1 of phase 3 from the "EMERGE" data set and one from the "ENGAGE" data set. The EMERGE study showed benefits of aducanumab as represented by the CDR-SB and MMSE scores obtained during this trial when aducanumab was used at a high dosage. However, little difference to the placebo group was seen when a low dose was used.

In keeping with the theme, there was also little difference shown between the placebo group and the group receiving aducanumab at both high and low doses in the ENGAGE trial, with this trial not reaching an endpoint. Because of this, the company Biogen went on to say that this trial had been a failure after citing that both trials had to reach an endpoint for the trial to be a success, however this did not occur.

Its approval overall has been met with some scepticism within the academic community, with some top academics believing it may lead to a decline in the amount of research conducted to combat AD, with others believing it is a great step in AD research. But for now, it is up to Biogen to prove a clinical benefit, if this is to be the big step people are hoping for.

IS ADUHELM THE FUTURE OF ALZHEIMER'S TREATMENT?

There have been many different antibodies tried in Alzheimer's research in an attempt to decrease the pathological beta amyloid plaques that develop in patients with AD, but most tend to fail. The FDA have approved aducanumab as of this year using its accelerated approval pathway that allows for drugs to be approved using a surrogate endpoint where the drug is then expected to have a clinical benefit. In the case of Aducanumab the endpoint of decreasing the amount of beta amyloid present in patients had been met and so approval by the FDA was achieved, but with stipulation that Biogen need to prove its clinical benefit.



LA - ICP - MS

Who hasn't seen them? Dozens of criminal and forensics investigation series on TV demonstrate how they caught an arsonist by traces of accelerant, a kidnapper by a single fiber of his hoodie, and arrested a murderer by the mud in one of his footprints. Extensive work is required to derive the bigger picture and ulterior motive from the crime scene alone, however it is crucial for identifying and charging the criminal. Nowadays, a lot of the analytical work is done by machines and computer programmes, although the conclusions are still drawn by humans to avoid any errors. To reduce margins of error, or account for lack of sufficient evidence, there is a need for more evolved devices.

Laser Ablation Inductively Coupled Plasma Mass Spectroscopy, a technique just as complex as it is a mouthful to say. Shortened to LA-ICP-MS, this analytical method was developed to require less sample, and to be less destructive during the analysis process. Deconstructing its name reveals how this technique has the ability to match a tiny glass shard on clothing to the crime scene from which it originated.

Component 1.
laser source

Component 2.
laser beam

inert gas →

Component 3.
Sample

Component 4. and 5.
ICP + Mass Detector

During laser ablation, a nanosecond-pulsed **laser beam** is directed onto the sample, creating an aerosol in the process. The high electric field of the laser frees electrons from the bulk, which subsequently collide with the atoms in the bulk, and through transfer of energy, the surface heats up and evaporates. A stream of **inert gas** (usually helium or argon) carries the sample particles and ions through to the ICP-MS. The plasma element happens through a coil coupling to the argon gas via a generator. This atomizes and ionizes all particles through a cascade of collisions and ionizations, reaching temperatures of up to 10,000 K. As different elements have different first ionization potentials, and the sample was atomized almost completely, the ICP-MS can measure and distinguish almost all elements on the periodic table. The separation and detection happens via the **mass-to-charge (m/z) ratio** - this is the mass spectroscopy aspect of the technique. The number of elemental ions detected correlate directly to the concentration of that element or ion in the original sample.

Another benefit that this method brought to **forensic investigations** is its capacity to analyze many solid samples without needing any preparation, making it easier and less time consuming, as well as less destructive, eliminating the need for strong solvents or corrosives.

In forensic science especially, this still-developing technique allows for many improvements in the analytical field. Not only is the detection limit as low as 10 parts per billion, the amount of sample needed can be on as little as the picogram or femtogram scale, a factor of 10¹² smaller than what the traditional ICP-MS needs. It is most commonly used for glass and paint samples, but more materials are also being found suitable, including fibers, cannabis, certain minerals, stones and metals. Another use in forensics and materials science alike is the ability to determine trace elements and to analyze the surface to such a small scale. As conventional ICP-MS requires a liquid sample, contamination during sample preparation is a common error. As a result, determining where traces came from originally doesn't work efficiently upon dilution.

POTASSIUM IODIDE

A key ingredient to *radiating* health

Present-day UK is host to 15 operable reactors, with 6 further ones in construction or planning stages. (Figure 1) They require more than 1800 tonnes of uranium every year, and generate a fifth of the UK's electricity needs. This has been reduced from 25% in 1990 and is set to be halved again by 2025. The reactors currently working are well distributed along the UK's coastline.

In uranium fission and decay, the radioiodine ^{131}I , is one of the main fission products. Its relatively short half-life of 8 days and its numerous physical barriers usually prevent the release of any radioactive iodine into the environment. Given severe damage to reactor core and facilities, there is a good chance of exposure or leakage, as history has shown.

Author: Sofia Schönauer

One of the most famous disasters - among many others - happened in Chernobyl releasing 1.8 EBq of radioactive iodine. This was caused by a faulty reactor design alongside a lack of appropriate safety measures or staff. However, less extensive accidents happen on a much larger scale: In the UK alone there has been one every 6 years on average. Exposure to radioactive iodine is directly correlated with thyroid cancer.

The thyroid concentrates iodine from the bloodstream after uptake (through sodium/iodide symporter (NIS)), the protein TPO reduces hydrogen peroxide to oxidize the iodine to become an iodinating species, which then attaches to Tyrosyls in Thyroglobulin (Tg). This iodination of Tg initially gives monoiodotyrosine (MIT) and diiodotyrosine (DIT), and subsequent iodinations couple these to give hormones L-triiodothyronine T3 and L-thyroxine T4 that regulate metabolism and energy.

The synthesis of both hormones is iodine-dependent, however it has no way of separating radioactive from stable iodine. Exposure to radioiodine, likely through inhalation of fumes or ingestion, concentrates the medium energy radiation (gamma radiation and beta particles) around the thyroid. Without prophylaxis, the tissue is exposed and damaged by the radiation, with high probability of thyroid cancer especially in children and pregnant women.



Figure 1.
Map of the UK depicting the locations of the 15 operable reactors.

POTASSIUM IODIDE

Potassium iodide is the prophylaxis to take in case of exposure to radiation. It prevents uptake of radioactive iodine, by saturating the body with stable iodine to synthesize its hormones from. The radioactive iodine remains in the bloodstream and is filtered out and secreted by the kidney. (Figure 2) Short-term, KI also decreases the proteolysis of Tg, slowing down the secretion of T3 and T4 hormones. Long-term, the prophylaxis also slows down hormone synthesis. Both effects of the drug decrease the probability for radioactive iodine to be taken up by NIS and subsequently be synthesized into a hormone, exposing the thyroid to damaging radiation.

It seems like a small, insignificant chemical, but potassium iodide can be a life-saver. Especially in Europe, a drug so simple is essential in every household. With 15 reactors in the UK alone there is a significant probability for any part of the country to be affected by an accident. Additionally, any major reactor malfunction in Europe would likely reach the entire continent via smoke distribution.

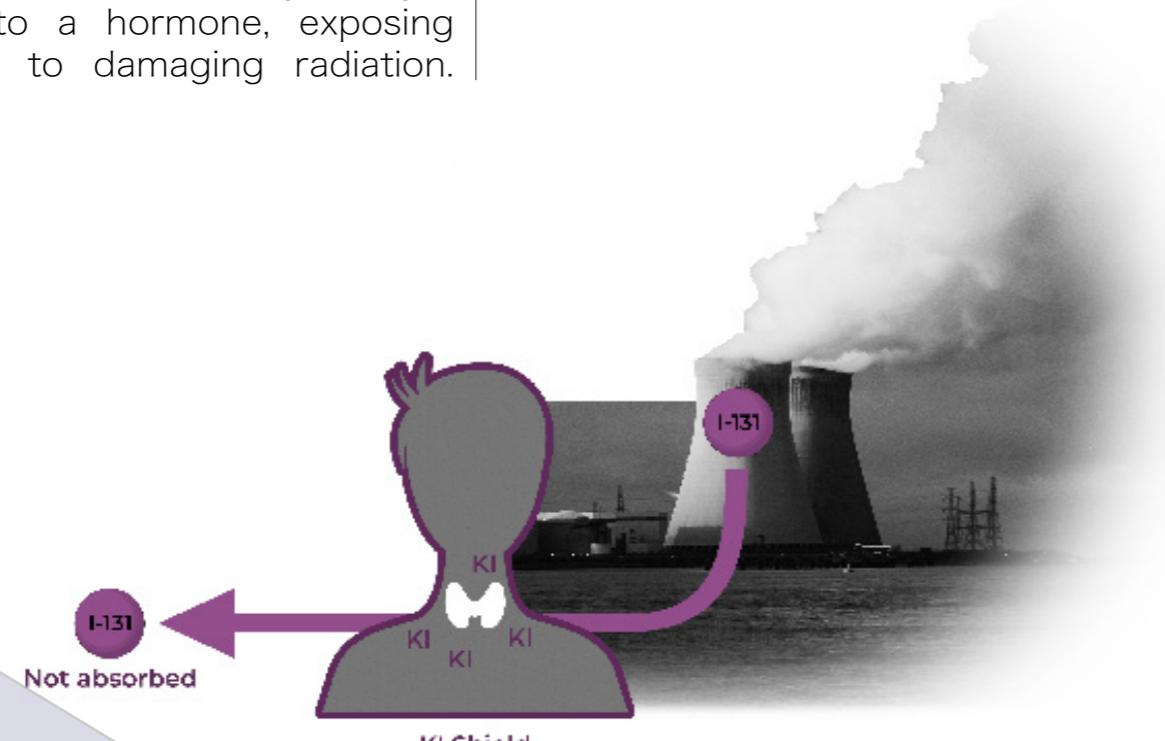


Figure 2.

Potassium iodide (KI) acting as a prophylaxis, resulting in some of the released radioactive iodine-131 to not be absorbed by the thyroid gland upon exposure.



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diabetes treatment advancements

Cases of diabetes have skyrocketed in the past decades, primarily due to a major change in diet and leading more sedentary lifestyles. It is believed that more than 10% of the population in the US, and more than 4.9 million people in the UK suffer from diabetes. Whilst no permanent cure has been formulated, recent advancements in scientific research indicate that science is closing the gap to finding a cure and reducing the more damaging effects of the disease. These include renal failure and cardiovascular disease amongst others. Techniques such as pancreas transplantation, injection of exogenous insulin and immunotherapy are some of the ways in which diabetes is targeted.

Diabetes is an autoimmune disease characterised by lack of insulin production in the body (type 1 diabetes) or the inability of insulin receptors in the cell to recognize the glucose control hormone (type 2 diabetes), which prevents the body from managing hypoglycemic and hyperglycemic control. It is believed that diabetes is caused by the expression of a particular MHC class 2 gene, which causes T-cells to destroy beta-cells in the pancreas. Interestingly, in the last few decades scientists have exploited multiple techniques to treat diabetes; one of them being immunotherapy. This involves suppressing the immune system with various drugs, so that beta-cells producing endogenous insulin can be preserved. The body is able to produce these autoantibodies, prior to any beta-cell destruction. Currently, detection of these antibodies would imply that there is a 100% chance a patient will develop the disease.

Author: Radoslav Petkov

However, if there is a way to surpass the immune system at that point, theoretically speaking onset diabetes could be prevented; but is that really the case?

Coppieters et al. found that there has been a larger effort to develop drugs in the symptomatic stage after a diabetes diagnosis, because of the inherent difficulty in suppressing the immune system in the pre-symptomatic stage. Companies such as Trial Net and Immune Tolerance Network have been pioneers in this field, developing drugs such as the kinase inhibitor imatinib and others (CD-3 teplizumab and Gad-alum). It was surprising for scientists to find that imatinib (brand name Gleevec) resulted in lowering of type 2 diabetes levels, although it is generally used to treat cancer. The drug prevents the phosphorylation of a major transcription factor called peroxisome proliferated-activated receptor gamma (PPRPy). It is responsible for the control of glucose and adipose tissue levels in the body. Imatinib prevents phosphorylation of the protein and a subsequent reduction in glucose levels. It has been reported that the outlined drugs have led to a lower c-peptide detection, however more experimentation is needed for such drugs to be approved in the market, especially with human trials.

Much attention has also been brought to pancreas transplants, which have been portrayed to be the permanent solution to diabetes. Theoretically speaking this should be the case, but there are many hidden practical difficulties. In the US alone there are 50,000 pancreas transplants a year, where 73% patients show insulin independence after 5 years. However, one of the biggest

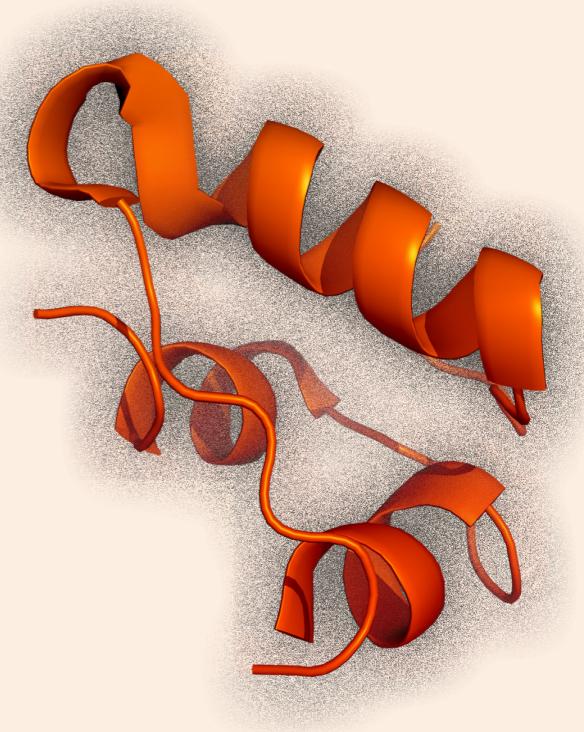


Figure 1.
One unit of insulin drawn with Pymol.

problems is overcoming tissue rejection and so, drugs such as anti-thymocyte are prescribed, reducing the T-cell count in the body. The most invested and researched area on the other hand, is designing formulations for exogenous insulin, which can stay in the blood for a long period of time to minimize daily injections. Insulin is a small protein with the following structure and key features. In recent years scientists have engineered an acylated insulin analogue called Degludec with a mutation at B10 His, which has been reported to stay in the body for 40 hours.

Monomeric insulin is mechanically and thermally unstable, therefore it will be very ineffective if introduced in the body in this form, however it can form hexamers and multihexamers in the presence of zinc ions. Thus acting like a depot, they steadily

release insulin into the bloodstream from the subcutis. The zinc-protein complex is believed to have 3 distinct states. Each zinc ion binds to the substituted B10His from 3 different insulins. In most cases, the packing of the protein causes the zinc to switch from octahedral geometry to a tetrahedral geometry.



Initially zinc binds to the 3 B10His from 3 different insulins and 3 water molecules in an octahedral geometry. As the N-terminus in the B-chain of insulin folds, the zinc ion is pushed down while remaining bound to the 3 histidines. The hydrophobic and narrow space created, allows for the 3 water molecules to be removed and zinc to bind to the carbonyl group of the difatty acid present in the acylated insulin to adopt tetrahedral geometry. This folding opens hydrophobic pockets allowing compounds such as phenols to bind to the insulin. These interactions, together with the binding to the difatty acid adds further allosteric effects, which favors an alpha helix conformation.

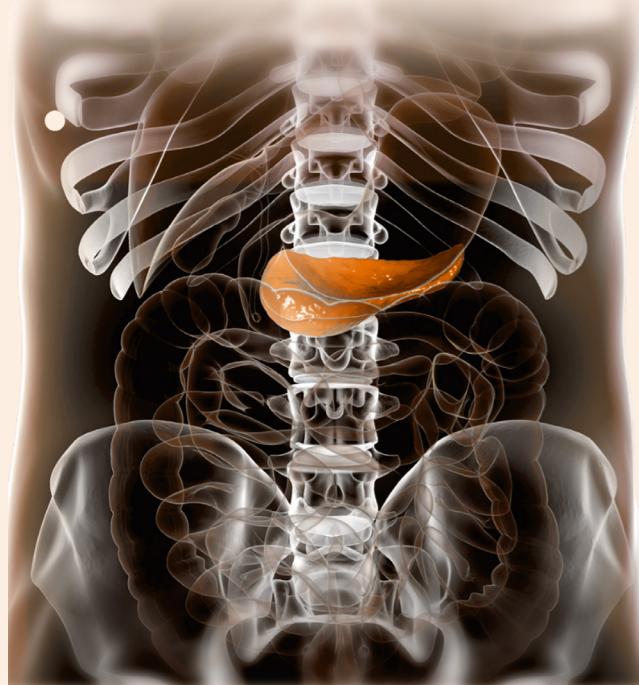


Figure 2.

Image and location of the pancreas within the body.

This manipulation of engineered insulin has been a hallmark in increasing the amount of time insulin can be spent in the body. Recent developments have completely changed their methodology. In fact, only this year a new insulin variant called Icodec, has been reported to stay in the human body for 196 hours, implying that only one insulin injection per week will be required to reach normoglycemic glucose concentrations. A large library of insulin analogues were screened and it was determined that increasing proteolytic stability and albumin binding while decreasing receptor affinity of insulin will optimize its pharmacokinetic profile and increase its half-life.

Advancements in scientific methodologies have meant that we are one step closer to finding a cure for diabetes. While immunotherapy and pancreas transplant treatment can be a permanent solution, there are still inherent problems with the procedures such as life-long immunosuppression. I believe that exogenous insulin formulations such as Icodec are the best option now for diabetic patients. that fewer injections have to be performed annually, which ensures a better quality of life and reduces other fatal conditions from developing. Nevertheless, we need to look for other treatments for a more permanent solution.

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HAVE LOCKDOWNS HELPED tackle THE CLIMATE CRISIS?

Ever since Thomas Newcomen invented the steam engine and paved the way for the industrial revolution in 1712, the use of fossil fuels has increased significantly from only 97 terawatt-hours in the year 1800 to over 136,000 terawatt-hours in the year 2019. However, with the recent COVID-19 pandemic we saw something unprecedented in the history of humankind:

The world stood still.

Around the world, countries were sent into lockdowns to help control the spread of the virus.

So, with fewer businesses open and less people using transport, did these lockdowns influence the climate crisis? And if so, could they be the future of climate control?



Author: Matt Dagwell

In the year 2020 the world was put on hold by a deadly virus circulating the planet with full force, causing the deaths of millions worldwide and economic collapse in most countries. But with this halting of humankind came a strange side benefit: less emissions globally.

The COVID-19 pandemic caused a global decrease in carbon emissions by 6.4% (2.3 billion tonnes), with areas such as the United States, the European Union and the United Kingdom, and India seeing decreases in their carbon emissions of 12.9%, 7.7% and 8.0% respectively. Countries with multiple outbreaks throughout the year saw the largest decrease in carbon emissions. However, many researchers are suggesting that this is not to last for a long period of time, as once the virus is under control, an 'emissions bounce-back' has been predicted, with countries once again burning through billions of tonnes of fossil fuels per year.

WHY KEEP CARBON EMISSIONS LOW?

Increases in carbon dioxide (CO_2) is believed to be responsible for about two-thirds of the total energy imbalance that causes the rise in the Earth's temperature. Carbon dioxide is able to absorb heat in the form of infrared radiation (IR) and then pass on this heat by emitting radiation or via collisions. CO_2 is able to do this for the same reason it is able to absorb in our IR spectrometers; it has a permanent dipole moment, one of the key requirements for IR absorption.

Upon absorption, the molecule can undergo many different deformations including bending and stretching modes of vibration. Whilst undergoing these deformations, the CO_2 molecule is likely to collide with other CO_2 molecules, adding to their speed. This causes an increase in the average speed of the gas molecules in the atmosphere and thus an increase in the temperature of the atmosphere - the greenhouse effect.



However, CO_2 is not the only gas able to cause this greenhouse effect, and is in fact not even the best gas for absorbing heat. Methane and nitrous oxide are much more effective at absorbing IR radiation, but do not contribute as much to the greenhouse effect as CO_2 , due to the sheer abundance of carbon dioxide (Figure 1). Either way, it is important that we do not ignore these gases, as they still contribute to the climate crisis.

HOW HAVE CONCENTRATIONS OF THE OTHER GREENHOUSE GASES CHANGED WITH LOCKDOWN?

The lockdown restrictions brought on by the COVID-19 pandemic haven't only affected global carbon emissions but also the emissions of other greenhouse gases such as nitrous oxides. Overall concentrations of nitrogen dioxide decreased globally by around 20% in comparison to a computer-modelled "COVID-free 2020", with countries such as China seeing an even greater decrease of around 60%.

This is important as it is believed that these nitrogen dioxide molecules aid in the formation of the greenhouse gas ozone. They react with sunlight and oxygen in the troposphere, which results in a photochemical smog, one of the causes of the respiratory condition asthma.

Another potent greenhouse gas is methane. Methane is predominantly produced from three main sources: fossil fuels, agriculture, and waste disposal. One would assume that the concentrations of this greenhouse gas would decrease alongside the consumption of fossil fuels, however a recent study by the National Oceanic and Atmospheric Administration (NOAA) found that there was a surge in the concentration of methane during the COVID-19 pandemic instead. It is difficult however, to attribute these results to one specific source.

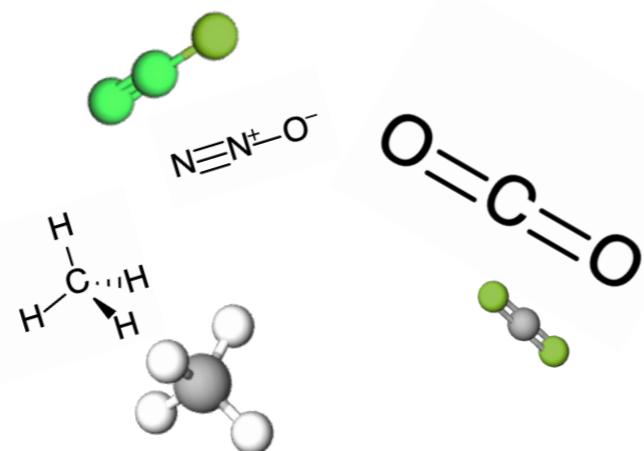


Figure 1.
(Left to right) Diagram depicting molecules of methane, nitrous oxide, and carbon dioxide.

DID LOCKDOWNS INFLUENCE THE CLIMATE CRISIS?

Overall, the research in this area is somewhat conflicting. Most current studies suggest that enforcing coronavirus restrictions has led to a decrease in carbon dioxide and nitrogen dioxide emissions, predominantly due to a drop in overall human activity. However, the research surrounding methane emissions seems to be more unclear, with some research suggesting an overall surge in these emissions but without a clear source.

SO, COULD THESE RESTRICTIONS BE THE FUTURE OF CLIMATE CONTROL?

In conclusion, I doubt it would be possible to implement these restrictions either on an annual basis or for prolonged periods of time, despite their effects on greenhouse gas emissions. This is predominantly due to the massive economic effects they have on many countries.



Instead, I believe more time should be spent researching and developing greener alternatives to tackle the climate crisis in a more permanent fashion, and decrease global emissions by the 7.6% needed to keep the Earth's temperature from increasing by 1.5°C and thus reach the goals set during the 2015 Paris climate accords.



The power of **DOPA**

Author: Milan Singh

ACDEFGHIKLMNPQRSTVWY. At first sight, this might look like an erroneous account of the English alphabet, but a closer look will reveal the unique, identifying one-letter codes of amino acids. At some point in their lives, all science students would have been taught about the importance of this category of molecules which - by definition - are often described as the "building blocks of proteins and of life".

In fact, this standardised model could not be more accurate: amino acids are indeed essential and common to all living organisms. Humans tend to have around 20, some of which are synthesised in the body and others that are supplied to it through our diet. Their biological role makes their understanding essential, as the knowledge of their mechanisms, reactivities and modes of action unlocks secrets that range from disease therapy to pollution control. For these reasons, and to simplify the learning process, they are often divided into groups based on their chemical structure and behaviour. For example, 'neutral', 'aromatic' and 'polar side chains' are all classes that meet the profile description of the amino acid tyrosine (Y).

Here is where things get a little more complicated. Referring back to the example of tyrosine, the amino acid has two possibilities: 1) remain unchanged and eventually form a polypeptide, or 2) undergo post-translational modifications in the cytoplasm of cells, which would alter its side chain and therefore the functionality of the whole protein.

In the case of tyrosine, the latter option would lead to the formation of **DOPA**. At this point, the reader should rest assured that this article will not be the latest review on the central dogma, but instead it will take a turn and later dive into the sea.

DOPA (3,4-dihydroxyphenylalanine) is an amino acid whose side chain is broadly referred to as a catechol, that lies at the foundation of many well-known compounds. Some travel in our bloodstream on a daily basis such as adrenaline and dopamine. Not only is it a constituent of hormones and neurotransmitters, but surprisingly it has also been associated with the flavour and smell of tea and cacao!

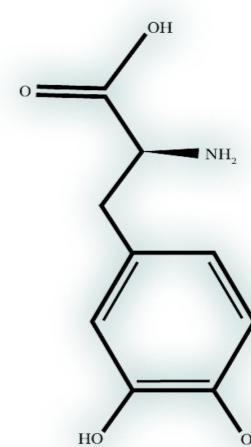


Figure 1.
Structure of DOPA.



Generally, DOPA is a modified amino acid that comprises two vicinal aromatic diols that grant the molecule its peculiar reactivity. With pK_as of 9.19 and 13.09 in an aqueous environment, it can easily interact in a multitude of reactions, the main ones being metal complexation, oxidation and polymerisation. The first reactions are possible due to the bidentate ligand nature of catechols, which are capable of coordinating with a variety of metals such as uranium, copper and most commonly iron. On the other hand, the crucial functionality of the two electron-rich, reactive hydroxyls must be highlighted as they are subject to oxidation, producing another class of significant compounds referred to as quinones. This process is neither elementary nor insignificant; in fact, the oxidation proceeds via an intermediate, semi-quinone, which despite its radical nature can be regarded as a reagent itself, engaging with metals in complex formation. Additionally, quinones have been linked to the reason behind why some people seek sunny destinations: they are biosynthetic bricks involved in the production of melanin pigments and hence the cause of our tans. Lastly, polymerisation reactions can commonly occur between two units of catechols in a reaction known as arylloxyl coupling. Alternatively and more simply, crosslinking can happen between two oxidised DOPA equivalents.

Now, as promised above: the interesting part. DOPA has caught the attention of the scientific community all around the world due to its remarkable adhesive properties.

It can naturally be found in marine organisms that have evolved an extraordinary strategy to survive harsh marine conditions and tidal waves. Often found on fancy dinner tables at seaside locations, mussels are one of these organisms. Their well-adapted foot organ secretes the byssal thread, a structure that is both flexible and stiff, which helps them anchor themselves to underwater surfaces and withstand the extreme conditions. To add some context, one mussel can exert a force equal to 300-400 N, that is to say the gravitational force applied by a 30-40 kg mass. This is astonishing, since the creature only weighs up to a few grams!

Returning back to the secreted structure, the end of the thread consists of plaques that secrete six main proteins responsible for adhesion, called mussel foot protein (Mfps), from 1-6. The adhesion mechanism of Mfps is a complex one, however it has greatly been attributed to the presence of DOPA, which can interact with mineral surfaces in the seabed through the aforementioned metal complexation and cation-π interactions, amongst others. Understandably, this wet adhesion has appealed to many scientists who have been experimenting with the Mfps and applying them to many industries, including medicine.

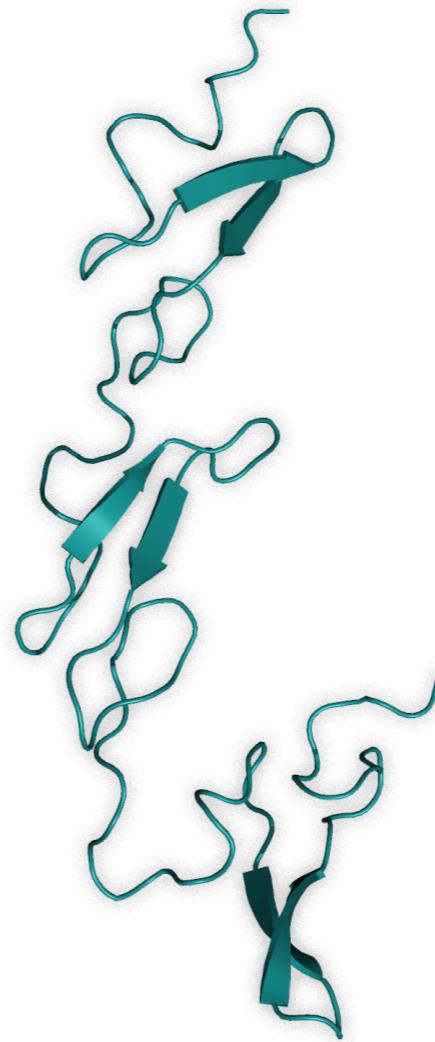


Figure 2.
Structure of the mussel foot protein, Pvfp-5, drawn with Pymol.

Re-emerging back to the United States, Boston. The adhesive potential was recognised by the co-team leaders of the iGEM team at King's College London back in 2019, during the final Giant Jamboree. iGEM is the International Genetically Engineered Machine Competition, a synthetic biology and genetic engineering competition started by MIT and is annually joined by more than 300 schools and universities around the world.

KCL iGEM 2021 team members are working on their Phase II project, focused on improving treatment for spinal cord injury (SCI), which causes nerve damage in the spine and results in life-long consequences for the affected individuals. They have designed and constructed a 3D bio-printed scaffold made with the polymer polycaprolactone (PCL), which will then be coated with their protein of interest that comes from the mussel species *Perna viridis*, termed Pvfp-5. Pvfp-5 has been synthesised through recombinant expression in E.Coli with the addition of tyrosinase, an enzyme that catalyses the conversion of tyrosine to DOPA post-translationally. Exploiting the power of DOPA, the group of 19 students from multidisciplinary STEM backgrounds merged chemistry with synthetic biology and they are working to further the research available on therapies for SCI. They are Renervate Therapeutics.



Figure 3.
iGEM logo.

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