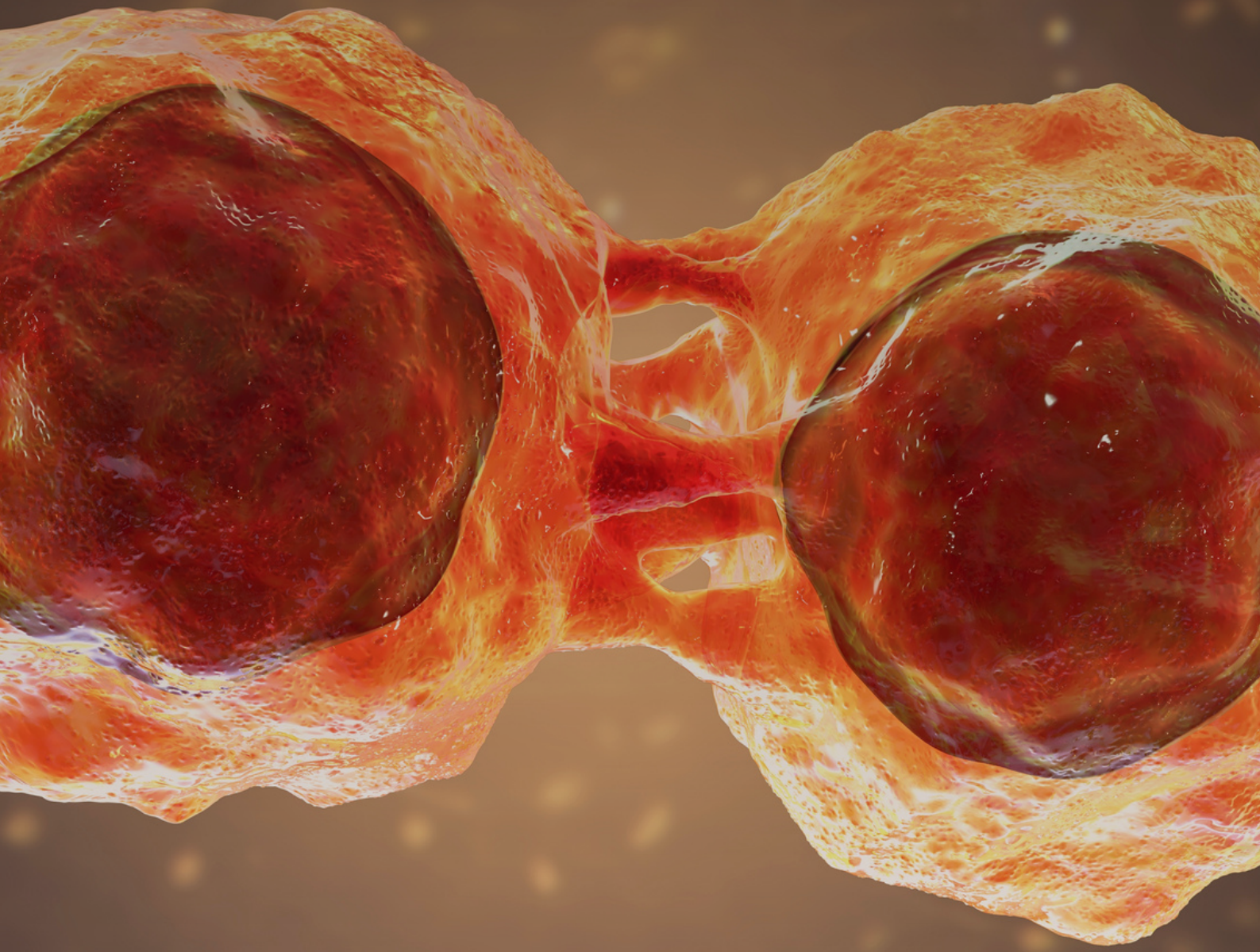
ScienceMind

OCTOBER 2020



KING'S College LONDON

STAFF

THIS ISSUE

Dear Reader,

Welcome to the first issue of ScienceMind (previously KCL Pharmacologist). A big thanks to the writing, editing and media teams for helping to contribute to this first issue.

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

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

Yours faithfully,

The Editor-in-Chief
The Founder

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THREADING WATER

NO BLOOD AND NO VAMPIRES HERE!

TWILIGHT TRIAL DISCOVERS NOVEL TREATMENT TO REDUCE DUAL THERAPY ASSOCIATED MORTALITY FOLLOWING PERCUTANEOUS CORONARY INTERVENTION

WRITTEN BY FATIMAH PATEL & RACHEL BRADY

Cutting-edge research funded by AstraZeneca has shown that treatment with a single antiplatelet drug, Ticagrelor, could be superior to the standard dual treatment of Ticagrelor and Aspirin. The alternative therapy aims to keep the affected blood vessel unblocked after percutaneous coronary intervention (PCI), while also reducing the chance of bleeding.

PCI is a non-surgical procedure that involves unblocking a blood vessel; using a metallic mesh known as a stent. It is performed on patients whose arteries have been obstructed by fatty deposits and small blood cells called platelets. Clotting around the stent is a severe complication of PCI as it can lead to a heart attack or a stroke. Clot formation is likely to occur as a result of the body's immune response to foreign objects.

In the case of PCI, the blood circulating in the body would come into contact with the stent and respond by sending platelets to coat the mesh. Clinically, dual antiplatelet therapy is given to patients following PCI to reduce the risk of clotting around the stent. However, these drugs can result in increased bleeding around the body as the platelets would not be able to form a 'plug' around any damaged vessels.

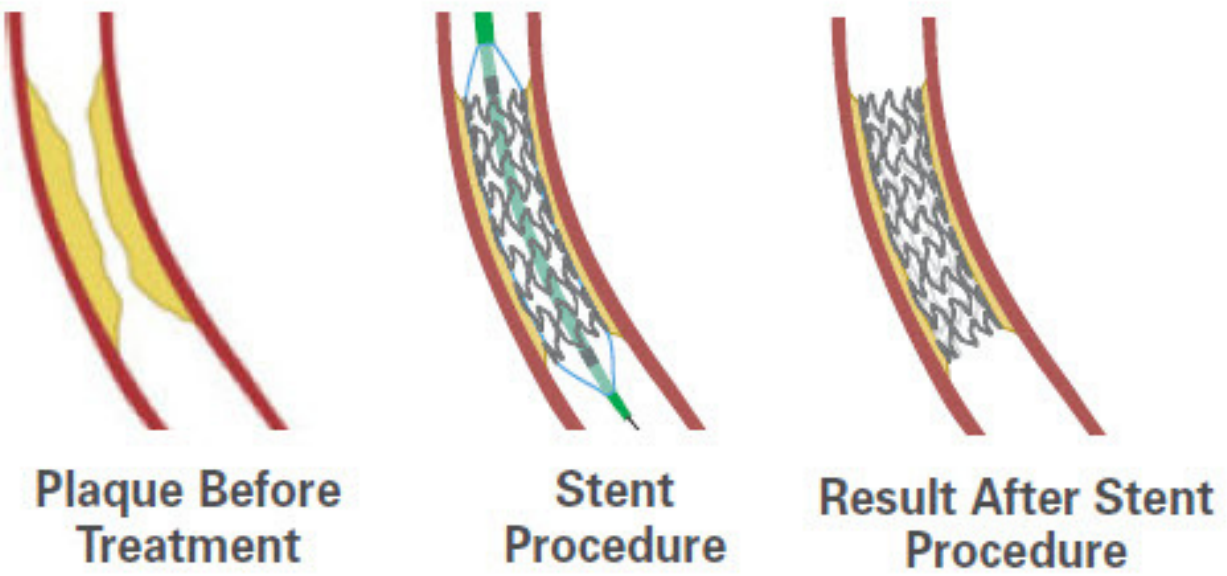

Figure 1. A before and after comparison of the stent procedure on blood vessels.

The 'Ticagrelor with Aspirin or Alone in High Risk Patients after Coronary Intervention' (TWILIGHT) trial was designed to test whether patients who underwent PCI would benefit from ticagrelor monotherapy following 3 months of plus aspirin dual therapy. This treatment was compared to patients who continued ticagrelor plus aspirin therapy after 3 months. The study looked at PCI patients who were at high risk for ischemic events, such as a heart attack, or a major bleeding event.

The trial found that after dual antiplatelet therapy, patients treated with only Ticagrelor reduced their risk of major bleeding by 44% over 12 months. A concern with the use of only one antiplatelet drug is the increased risk of death due to clotting. However, the study found no evidence of an increased risk of death, heart attacks or stroke when comparing Ticagrelor monotherapy to Ticagrelor and Aspirin dual therapy.

This shows that transitioning to ticagrelor monotherapy after 3 months of ticagrelor and aspirin dual therapy reduces bleeding and does not increase the chance of ischaemic harm. Although more trials need to be carried out with a diverse patient population, the TWILIGHT trial showed that this reformed style of treatment has clinical benefits, primarily for those who were already at a high risk of bleeding. This study opens the door to new and improved therapies which can reduce the incidences of blood loss fatalities whilst lowering the chance of blood clot formation.

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Fatimah Patel is a 3rd year BSc Pharmacology student with a strong interest in neuropharmacology.

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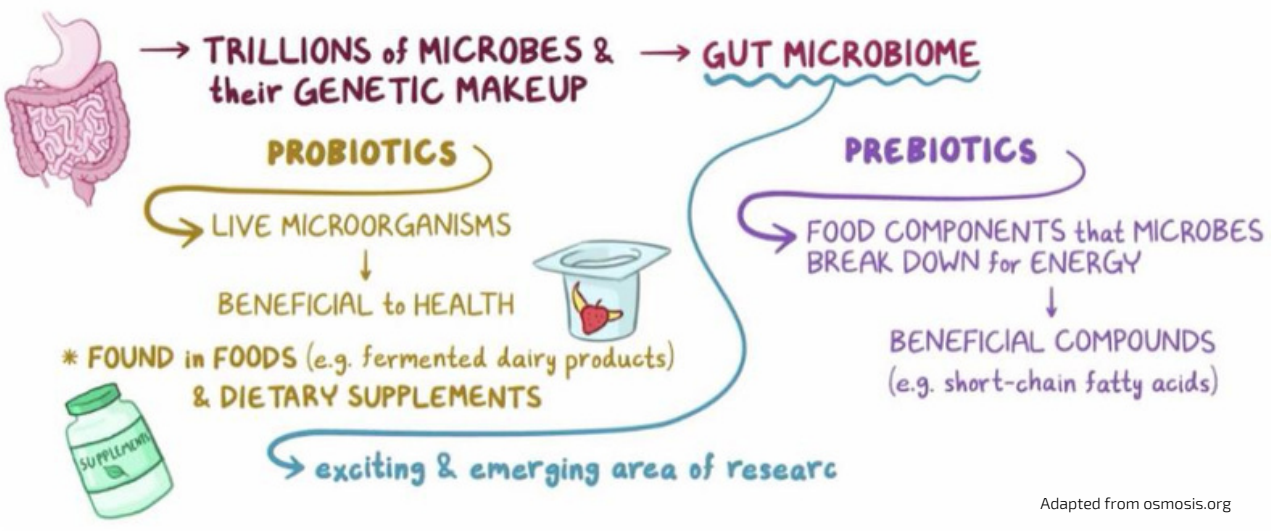

SHALLOW DIVE

GUT MICROORGANISMS AFFECT MENTAL HEALTH IN ADULTS?

WRITTEN BY SOUMIYA DRIR SADAOUI

There is a one-to-one ratio of microbial cells to human cells, with the scale tipping slightly toward the microbe side, making us more microbe than human. The gastrointestinal tract is home to trillions of microbes collectively called the gut microbiome. A function of the gastrointestinal system is to absorb gut products which may reach the brain through the blood circulation. Recent studies in the last two years have proven that gut microbiota may influence the brain's responses through the neural, endocrinological, and immunological systems.

A 2020 review from Järbrink-Sehgal and Andreasson had reported an improvement in anxiety and stress levels with the use of probiotics; dietary supplements that contain beneficial microorganisms.

The studies reviewed were centralized around the following four divisions: brain imaging studies, depression, bipolar disorder, and anxiety, or stress.

As part of the brain imaging studies, two healthy individuals were put on a 4-week probiotic treatment. The participants disclosed higher positive behaviour which was reflected in their blood-oxygen level-dependent (BOLD) imaging; a magnetic resonance image (MRI) which shows the contrast of haemoglobin without oxygen in the brain.

Several studies on depression such as an 8-week trial of probiotics on patients who were taking Selective Serotonin Reuptake Inhibitors (SSRI) antidepressants showed to relieve depressive symptoms and improve cognitive capabilities.

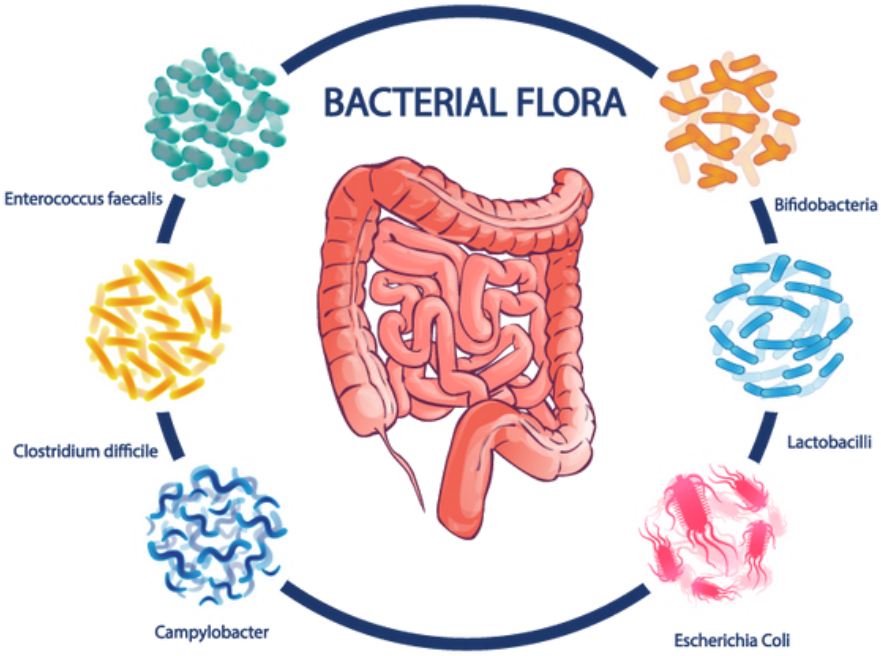

Figure 1. A visualisation of common bacterial species present within the microbiome

Unfortunately, the use of probiotics in Bipolar Disorder is an underexplored research sector and only one trial of probiotics in patients with Bipolar Disorder has been published, which was found to positively impact the nervous system. Lastly, the studies on anxiety were carried out among college students who were given multiple species of probiotics. Students showed ameliorated conditions of mood, state, and worry.

Overall, the studies that have been carried out show a positive response to the use of probiotics with regard to the mental health state of people. Many of the studies are limited to certain populations and sample sizes, therefore making use of brain imaging as a tool for investigating the connection between gut microorganisms and cognitive function avoids significant research bias.

In addition, the analysis of mucosal microbiota biopsies (the gut microbiota from human tissues) would give a better representation of the organisms' present in the gut. Both techniques could be considered for future studies to achieve accurate results.

ABOUT THE AUTHOR

Soumiya Drir Sadaoui is a 2nd year BSc Pharmacology student. Her main focus is on mental health and neuropharmacology in general..

" I got into this field because my grandmother had been diagnosed with Parkinson's "

FEATURED INTERVIEW

Dr Duty's interest in Parkinson's disease piqued during her time working on her PhD in cardiovascular pharmacology at the University of Manchester. Her PhD looked at how drugs that open ATP sensitive K+ channels in cardiovascular smooth muscle could be used as hypertensives. Her grandmother developing Parkinson's and her colleagues' research in this area were the two most influential reasons why she delved into Parkinson's research.

THREADING WATER

NEUROPROTECTIVE DRUG STRATEGIES TO BOOST PROTEIN LEVELS FOR PARKINSON'S DISEASE.

WRITTEN BY CHETANA PRABHU

Dr Susan Duty and her research team at King's College London have recently been working on neuroprotective drug strategies primarily using targeted repositioning of existing drugs to boost levels of fgf20 (fibroblast growth factor-20) protein in the brain for Parkinson's disease.

The primary pathology responsible for Parkinson's is the degeneration of the nigrostriatal dopamine containing neurons in the brain and by boosting the levels of fgf20, this provides significant protection against the loss of dopaminergic neurons. However, at present there is no medication to stop or slow down the degeneration of these neurons.

'Repositioning or repurposing' refers to the approach where existing medication is used to treat a disease other than the one it was initially designed for. 'Targeted repositioning' uses specific drugs in order to boost or inhibit a molecular target, in this case, the desired protein. This method is currently becoming attractive in the industry as the coveted drug has already undergone modifications for proper absorption and has been checked out for its safety aspects.

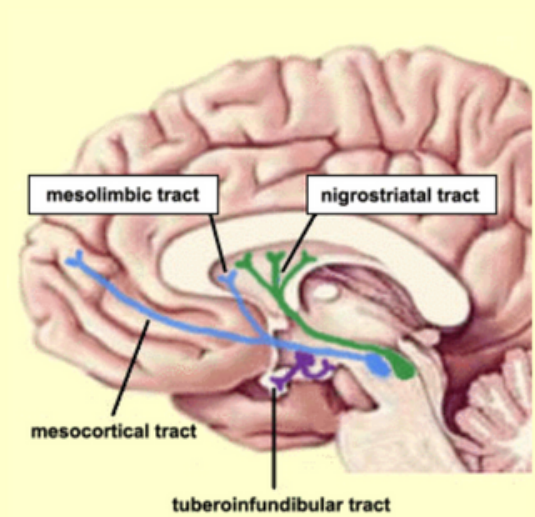

Figure 1. Illustration of the different dopamine pathways in the brain

Therefore, the long drug discovery process which normally lasts 10 to 15 years is shortened by 5 years or more.

The research includes several techniques ranging from Insilco to In-vivo models. Previous research has shown that boosting the levels of fgf20 in the brain can protect the dopamine containing neurons and prevent motor impairments in a rat model. However, the only downside is that fgf20 is a huge protein and must be delivered directly to the brain, which is not easily accessible to patients.

Therefore, the research team screened for the drugs that switch on the fgf20 gene in the transcriptional databases (A database which stores information on the genes that are switched 'on or off' by drugs that are in clinical use), using bioinformatics.

This was made possible by a mathematical algorithm generated by Dr. Gareth Williams, also based in King's College London. The drugs that came up in the searches were screened in a cell-based system to check if they could boost the levels of protein in the cell culture itself. The two best drugs namely - salbutamol (bronchodilator used in asthma inhalers) and triflusal (anticoagulant) were put in another cell line which was physiologically relevant, to check their activity.

For preclinical trials, naïve rats were dosed and measured for fgf20 protein levels using a computer program- ELIZA. This was followed by chronically dosing rats using a toxin that induced Parkinson's disease. While the lesion was developing, the successful drug was used and the rat's brain was taken out to measure the number of neurons left in the particular nigrostriatal area to check the drug's effectiveness. In the pilot study, it was also shown that taking salbutamol as an oral infusion, could protect the dopaminergic neurons.

To the team's surprise, they witnessed that drugs like beta blockers and beta agonists (which have completely different pharmacology) switched on the fgf20 encoding gene directly instead of activating a receptor at first, concluding that salbutamol and triflusal possess the ability to boost fgf20 levels.

"Whether these candidates will be able to provide long-term protection against the degeneration of the dopaminergic neurons and preserve movement in animals"

is a question for the next stage in their research. In the future we can hope for this to become very successful in order to finally obtain a medication for such a daunting disease.

ABOUT THE AUTHOR

Chetana Prabhu is a 1st year BSc Pharmacology student. Her current areas of interest include neuroscience, genetics and pharmacology.

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DEEP DIVE

TEST TUBE BABIES, NOW FOR VIRUSES

WRITTEN BY KIRA LINKE

ABOUT THE AUTHOR

Kira Linke is a 1st year BSc Pharmacology student and is notably fascinated by immunopharmacology.

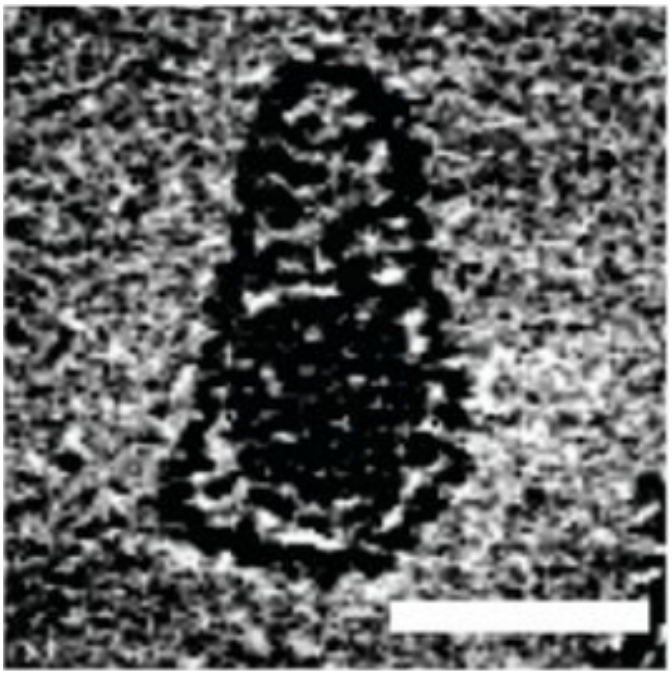
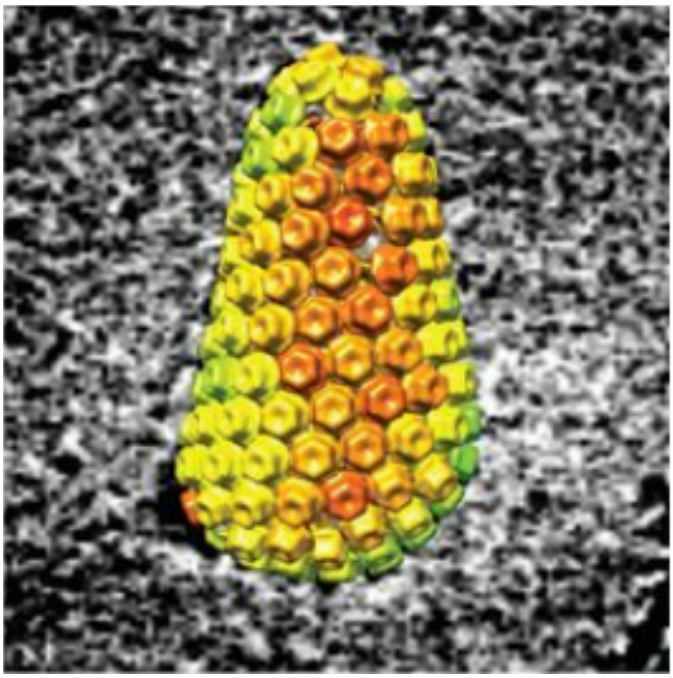


Figure 1. Top: a scan of the capsid, Bottom: model of the structure overlaid on the scan



HIV can now be induced to perform the process of infection without an actual host cell present. A team of scientists from the University of Utah School of Medicine and University of Virginia managed to observe the virus' attempts to replicate in a test tube by delivering the bare essential compounds necessary for the virus, instead of a complete cell. They call it the 'cell-free model'. The paper proposes that the virus capsid provides previously undervalued, but essential functions.

To mimic endocytosis, the compound melittin (the protein in bee venom that causes pain) was added to lyse the lipid envelope that normally fuses with the human lipid bilayer. Thus, the capsid containing RNA is released. The capsid consists of hexagonal structures, which are stabilised by the addition of IP6 (inositol hexakisphosphate). IP6 carries a negative charge, which attracts the positive side chains pointed inwards in each hexagonal subunit and pulls the subunits together. In a cell, the capsid would pick up free nucleotides from the cytoplasm through pores, so a mixture of dNTPs (like in PCR) is added.

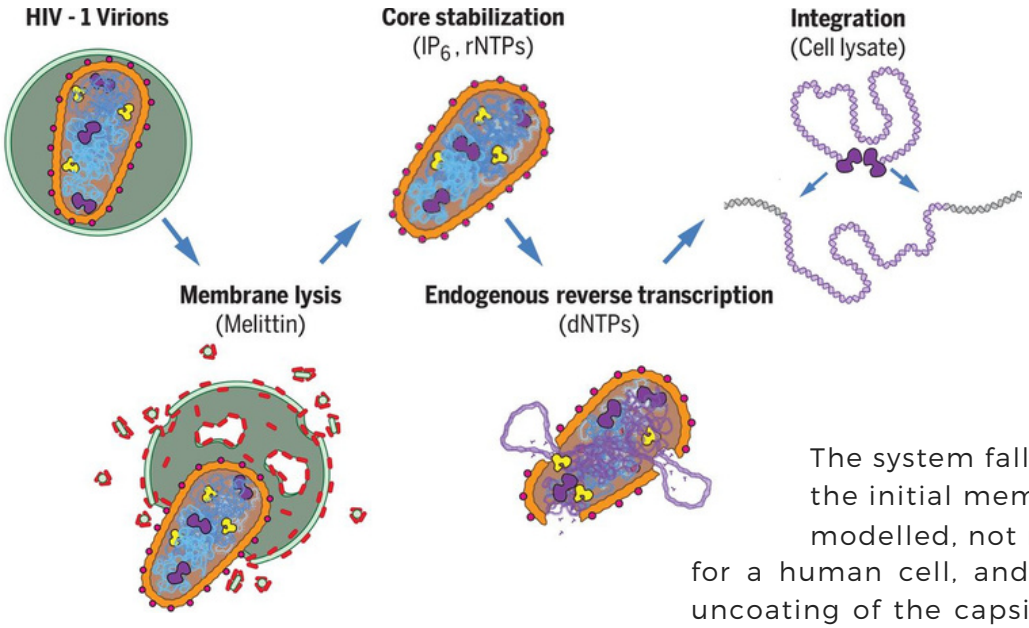


Figure 2. "Reconstitution and visualization of HIV-1 capsid-dependent replication and integration in vitro"

For reference, dNTPs are nucleotides with a tri-phosphate chain, so it can be rapidly added to a replicating strand whereas PCR is a procedure used to mass replicate DNA for analysis. Reverse transcriptase within the capsid converts the viral RNA into DNA that can be integrated into the host genome. IP6 largely maintains the capsid, despite the increasing pressure from the synthesised DNA, presumably to ensure that the enzyme and nucleotides continue to react instead of diluting in the cytoplasm. The capsid does need to be uncoated for the viral DNA to exit and integrate into the host DNA. The ingredients for this have not been perfected for the cell-free model, as the team discovered that varied levels of stabilising and destabilising agents impacted the effectiveness of integration of viral DNA into host DNA, despite the capsid being uncoated. The cell-free system uses more general cell extracts which include DNA plasmids amongst other proteins and compounds. PCR analysis revealed the success of the system.

The system falls short in that the initial membrane lysis is modelled, not replicated as for a human cell, and the complete uncoating of the capsid continues to be a mystery. However, the study, published 09. Oct. in Science Magazine provides a steppingstone for the development of a full understanding. The success of the cell-free system shines a new light on the importance of the viral capsid for infection. Compositional changes for the various stages suggest that interruption of the morphology can easily incapacitate the infection process. Additionally, the process simplifies the study of reactions that normally occur deep within the nucleus.

Increased understanding of the initial stages of infection may present new opportunities for treatment of the disease and provides a new environment for drug testing. HIV continues to afflict 38 million people globally, with 1.7 million new infections over the last year. The distribution of cases illustrates the continued impact of colonialism, with 54% of cases in eastern and southern Africa. The burden is carried socially and financially, and new developments provide hope for cheaper, more potent treatment and perhaps an eventual cure.

CAN A DRUG USED TO TREAT RHEUMATOID ARTHRITIS SAVE LIVES FROM COVID-19?

WRITTEN BY SEAN CRAWFORD & AAIMAN BHARMAL

The COVID-19 pandemic has cost the lives of over 1 million people worldwide with over 40,000 dying from the disease in the UK. Artificial intelligence has predicted that Baricitinib, a drug licensed for treating rheumatoid arthritis, could save lives from life threatening inflammation seen in the lungs of severely ill COVID-19 patients. Initial clinical trials led by the Hospital of Prato in Italy have shown a reduction in mortality as well as a quicker discharge from hospital in those admitted with moderate COVID-19 pneumonia.

In February 2020, at the beginning of Europe's COVID-19 outbreak, bioinformatics experts at London-founded BenevolentAI analysed clinical data from COVID-19 patients in northern Italy. Using artificial intelligence, they suggested the anti-inflammatory pill Baricitinib may be useful in combating the disease. This area of therapeutics has already yielded results with the WHO naming the cheap anti-inflammatory steroid dexamethasone as the only drug proven to reduce death in those admitted to intensive care units with COVID-19.

Figure 1. Baricitinib, marketed as Olumiant by manufacturer Eli Lilly, was approved in the EU in 2017 for tackling joint damaging inflammation in rheumatoid arthritis. It is administered orally.

Mortality from COVID-19 disease (estimated 1-3% of cases) is associated with both SARS-CoV-2 coronavirus damage to human cells and the immune system reacting to the presence of the virus by damaging human tissue. Severe acute respiratory syndrome (SARS) occurs when the coronavirus as well as the patient's own immune response have inflamed the alveolar air sacs in the lungs to the extent sufficient oxygen can no longer be absorbed.

How Baricitinib helps the body from being damaged by it's own defence mechanisms

Baricitinib is thought to reduce the excessive and uncontrolled release of pro-inflammatory cytokine proteins which are responsible for the damaging inflammation seen in COVID-19 patients admitted to intensive care. Particularly in the elderly or those who are classified as immunosuppressed, the immune system is sometimes unable to mount an efficient and swift response to the early stages of coronavirus infection.

In those individuals, their condition will often worsen 8-10 days from the infection onset - this is because the immune system then goes into overdrive and causes damage to the body. This is known as the cytokine storm. Cytokines are proteins in the blood that are immune system activators. In mild COVID cases they cause fever.
In high amounts seen in severe COVID cases they cause the excessive recruitment of neutrophils – the so called 'suicide bomber' white blood cells of the immune system. Neutrophils secrete damaging enzymes which destroy lung tissue in the hope of also killing present coronavirus. Immune cell movement from the circulation into the alveoli makes the blood capillaries leaky and the inflamed alveoli fill with fluid.

Ultimately, death through suffocation can result as oxygen can no longer enter the blood through the fluid filled lungs.

Looking at the mechanisms resulting in the cytokine storm, scientists have discovered a pathway called the JaK-STAT signalling cascade. As a Janus kinase (JaK) inhibitor, Baricitinib blocks the beginning of the intracellular JaK-STAT signalling cascade used by cytokines to cause more immune cell involvement and greater tissue damage. It is proposed that the blocking of this cascade could prevent lung alveolar air sac damage that is often responsible for COVID-19 mortality.

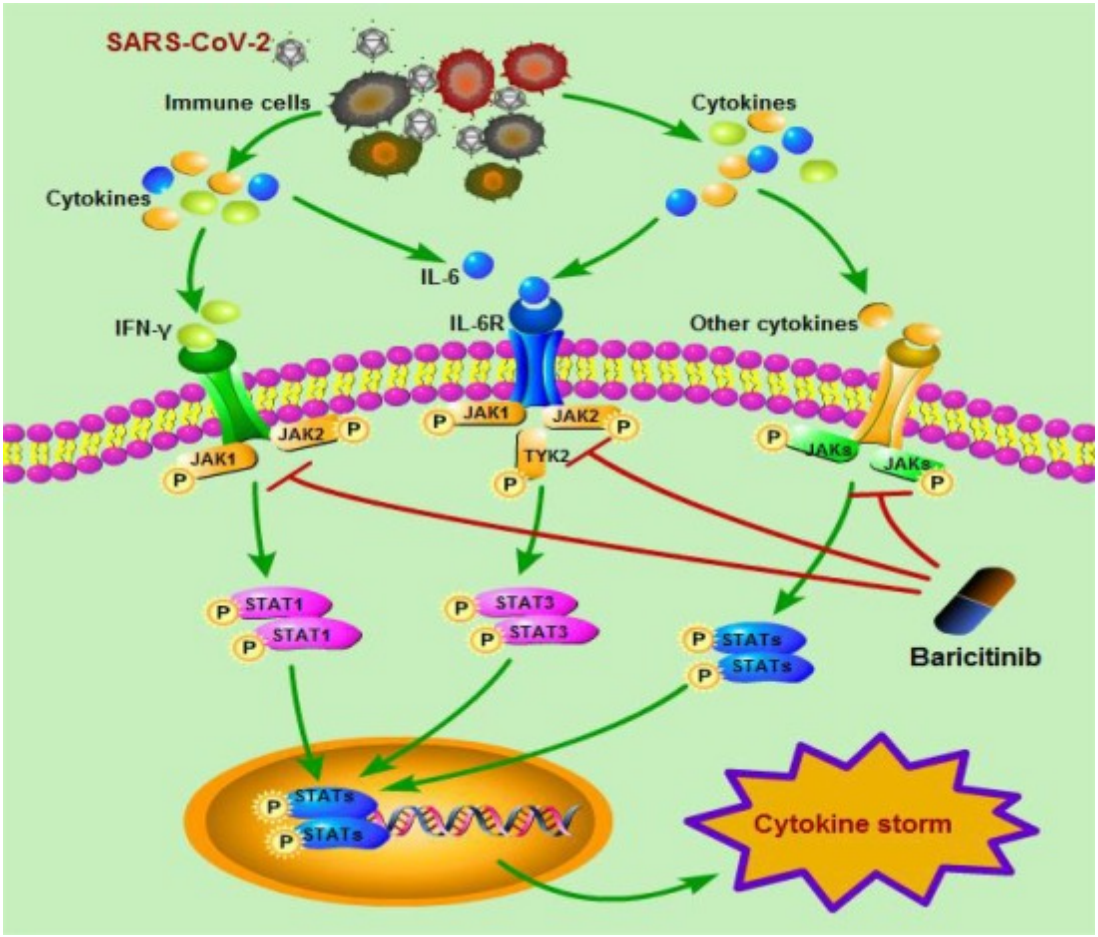


Figure 1. Illustration sourced from Zhang et al. on the cytokine storm

Results of the Baricitinib trial

A clinical trial in northern Italian hospitals, led by the Hospital of Prato compared outcomes of Baricitinib treatment with lopinavir/ritonavir HIV antiviral treatment. The COVID-19 patients participating in the study were admitted to hospital for what was initially pneumonia of a moderate severity and they were given oxygen therapy. 113 were given Baricitinib 4mg/day and 78 were given a control lopinavir/ritonavir antiviral treatment. The Baricitinib group saw no fatalities and only 1 patient's condition required mechanical ventilation. The control group saw comparatively worse outcomes; 14 later required a ventilator of which 5 of the patients died. Baricitinib whilst apparently increasing survival also reduced the duration of time spent in hospital.

A possibility for Baricitinib to have dual benefits

Interestingly, whilst dampening down dangerous levels of inflammation, Baricitinib is thought to prevent entry of the SARS-CoV-2 coronavirus into human cells. The SARS-CoV-2 coronavirus targets and infects human cells by sticking to the ACE2 receptor located in high numbers on cells in the alveolar air sacs of the lungs. Baricitinib may block the SARS-CoV-2 coronavirus from taking over and destroying human lung cells by inhibiting other kinase enzymes which are involved in bringing the coronavirus bound ACE2 receptor inside the cell.

Therefore, Baricitinib is thought to inhibit the cell machinery which is involved in bringing the coronavirus inside the cell, thus preventing the virus from replicating. This suggests it may have potential in more mild cases or earlier stages of COVID-19 infection.

Some updates on the marketing of Baricitinib as a remedy for Covid-19

The pharmaceutical giant, Eli Lilly, is currently leading a global phase 3 clinical trial assessing the impact of Baricitinib compared to and with other treatments in patients with moderate pneumonia, which is due to be published in the coming weeks. Eli Lilly are currently seeking emergency use authorisation from the US Food and Drug Administration (FDA) for the use of Baricitinib in COVID-19 patients admitted to hospital. Currently no issues with its safety in regard to treating COVID-19 have been raised.

ABOUT THE AUTHOR

Sean Crawford is a 3rd year BSc Pharmacology student with interests in neuropharmacology

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