BIOKEMI

2024

SIXTH EDITION

DEPARTMENT OF BIOCHEMISTRY
SHIVAJI COLLEGE
UNIVERSITY OF DELHI

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BIOKEMI 2024

Sixth Edition

Departmental Scientific Magazine

DEPARTMENT OF BIOCHEMISTRY

SHIVAJI COLLEGE

UNIVERSITY OF DELHI

MESSAGE FROM THE PRINCIPAL

It gives me immense pleasure to note that the Department of Biochemistry of Shivaji College is bringing out the fifth edition of its annual departmental magazine: BIOKEMI 2024. The motto of Shivaji College Amritam tu vidya (knowledge is eternal) and it is our constant endeavour to transcend knowledge beyond books and classroom.

In sync with this motto, I believe that BIOKEMI provides the students with a priceless opportunity to traverse beyond their textbook-based curriculum and study and write about the scientific phenomena of their interest. It also provides a means to nurture and hone their writing skills and to integrate those skills with art and photography. These experiences not only contribute to their holistic development as students of science but also prepare them better for continuing their quest for knowledge.

I congratulate the editorial board of BIOKEMI 2024 consisting of faculty members and students of the Biochemistry Department, for marching ahead on this journey of enhancing the scientific aptitude of students. I wish you all the very best for all future ventures.

Prof. Virender Bhardwaj
Principal, Shivaji College
University of Delhi

MESSAGE FROM EMINENT SCIENTIST

It is heartening to witness the release of the 6th edition of Biokemi 2024. This annual magazine by the department of biochemistry at Shivaji College is a testament of the continual pursuit of its teachers and students for new knowledge.

In the ever-evolving global scientific landscape, Biotechnology stands as a beacon of innovation, delivering promising solutions to some of the most pressing challenges facing humanity today. The advent of RNA-based therapeutics has emerged as a revolutionary paradigm, holding immense potential for the treatment of diseases that continue to plague us for centuries. From the targeted delivery of therapeutic molecules to the modulation of gene expression, technologies that enable manipulation of our genome are moving us towards a future where personalized medicine will become a practice.

As aspiring scientists and future leaders in the field, it is nice to see that the students of Shivaji College have researched and penned down their perspective on diverse topics with great clarity and precision. In the pages that follow, the readers will be able to explore the myriad facets of science and envision the transformative impact that our collective efforts can have on the world.

I congratulate the entire team for this edition of the college student magazine and wish them success with more scientific endeavors in the future.

Dr. Amita Gupta
HoD, Department of Biochemistry
University of Delhi, South Campus

MESSAGE FROM THE EDITOR'S DESK

*It gives me great pleasure to present to you the sixth edition of the **annual departmental scientific magazine - Biokemi 2024**. I believe that the art of scientific writing plays an important role in enabling researchers to present their works in the form of treatises and publications. It is important to not only make discoveries in the field of science but also lucidly explain the findings through oration and publication.*

Endeavors like BIOKEMI can facilitate the students in developing these skills and preparing them to contribute meaningfully to the frontiers of scientific research. By writing articles on topics of their scientific interest, the students get an opportunity to explore science for the love of it, rather than as a means to score well in the exams. The student editors of Biokemi gain experience in scientific writing and editing, which expands their horizons in expressing scientific work.

It has been possible for us to have come out with the sixth edition of Biokemi solely because of the dedicated faculty members and students of the editorial team. I extend my heartfelt thanks to the entire editorial team of Biokemi 2024 for the wonderful team effort. I would also like to acknowledge all our authors, for submitting interesting scientific articles and other content. As this was the first time for many authors to write an original scientific article, their efforts are particularly appreciated. I would like to take this opportunity to thank our Principal, Prof. Virender Bhardwaj, for his kind support.

We look forward to continuing the legacy of BIOKEMI for the years to come and evolving for the better with every new edition.

Dr. Jayita Thakur
Editor-in-Chief, Biokemi
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1. Interaction of Dietary Polyphenols and Gut Microbiota

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Introduction

Polyphenols are secondary plant metabolites found in fruits, vegetables, wine, green tea, olive oil, and cocoa products. They have been shown to alter brain function by disrupting cerebral circulation, affecting neurogenesis and synaptic plasticity, affecting abnormal protein aggregation, and modulating neuroinflammation, mitochondrial dysfunction, and oxidative stress. However, polyphenols have no bioavailability in the body and are divided into two groups: phenols and free phenols. While free phenols constitute 5-10% of all phenols, 90-95% are bound phenols that must be broken down by intestinal microorganisms into small molecule metabolites. Most metabolites can be fully absorbed and their biological activities improve after biotransformation from the intestines. The composition of the gut microbiome is greatly affected by nutrition, disease, and medications. Gut dysbiosis has been observed in patients with neurodegenerative diseases that reduce the richness and diversity of the gut microbiota, decreasing beneficial bacteria and increasing disease-associated bacteria (1,2,3).

Polyphenols stimulate beneficial bacteria to produce metabolites, including short-chain fatty acids (SCFA), and play an important role in preventing and treating neurodegenerative diseases by stimulating the release of hormones and neurotransmitters. It affects the microbiota-gut-brain axis. The human gut microbiome is a complex ecosystem with trillions of microorganisms that interact with the host system. It regulates food levels, controls immunity, and affects the health of the host. Factors such as age, diet, antibiotic use, and probiotic intake can affect growth. Prebiotics, such as dietary fiber and polyphenols, provide health benefits by promoting the growth and activity of host-microbial species (4). The effect of polyphenols on human health is based on the action of intestinal microorganisms, which can slow down neurodegenerative diseases by improving the intestinal microbiota. This article examines the metabolic processes of polyphenols in the intestine and the effects of polyphenols on brain function through the regulation of the intestines and their metabolites. It also provides insight into the role of polyphenols in slowing neurodegenerative diseases and the impact on immunity via the microbiota-gut-brain (MGB) axis (1,2,3).

Classification of dietary polyphenols

Dietary polyphenols are natural products that are abundant and widely distributed in plants. They are divided into four groups: phenolic acids, flavonoids, polyphenolamides and non-flavonoids. Phenolic acids can be divided into benzoic acid and cinnamic acid derivatives. Flavones include flavones, flavanones, isoflavones, chalcones, flavanols, flavonols, flavanonols, and anthocyanins. Polyphenylamines have nitrogen-containing substituents, while nonflavonoids include stilbenes and

lignans. Non-flavonoid polyphenols found in foods include resveratrol, ellagic acid, and curcumin, and are important for human health. The chemical structure of dietary polyphenols consists of phenolic monomers and polymerized polyphenols (5,6).

Effects of polyphenols on gut microbiota

Gut microbiota is important for health and diseases, including obesity, diabetes, inflammatory bowel disease, and neurodegenerative diseases. Diet can change the composition of the gut microbiota and affect the host's metabolism. Probiotics, prebiotics, and microbiota from fecal matter can also change the intestinal microbiota. Polyphenols can directly alter the gut microbiome, making it beneficial or reducing harmful bacteria. *In vitro* and *in vivo* studies indicate that polyphenol supplementation may affect the gut microbiota.

SCFA are frequently found in the intestine and are produced as a result of incomplete metabolism of plant-derived carbohydrates. EGCG (Epigallocatechin Gallate), a type of catechin under the category of polyphenol, increases SCFA-producing bacteria such as *Akkermansia muciniphila* and supports the immune system and intestinal bacteria. Dietary polyphenols can increase the production of propionic acid and butyric acid by bacteria, reduce stomach acid, increase bile acid, cholesterol, and all lipids, and also reduce metabolic abnormality and fatty liver (5,6).

Table 1. The transformation of polyphenols by gut microbiota

Polyphenols	Composition of Gut Microbiota
Curcumin	firmicute *Blautia* sp. *(MRG-PMF1)*, *Escherichia fergusonii* (ATCC 35469), and two *E. coli strains* (ATCC 8739 and DH10B)
Quercetin and rutin	*Eubacterium ramulus*, *Clostridium orbiscindens*, *Eubacterium oxidoreducens*, *Butyrovibrio* spp., *Bacteroides fragilis*, *Eubacterium ramulus*, *Clostridium perfringens*, *Bacteroides JY-6*, *Bifidobacterium B-9*, *Lactobacillus L-2*, and *Streptococcus S-2*
Daidzein and genistein	*Lactobacillum*, *Bifidobacterium* and *Bacteroides;* *Lactococcus strains*, *E. faecium* INIA P455 and *L. paracasei* INIA P461; *Eggerthella* sp. YY7918, *Eubacterium ramulus* and *Clostridium* sp. HGH 136
Resveratrol	*Bifidobacteria infantis* and *Lactobacillus acidophilus*; *Slackia equolifaciens* and *Adlercreutzia equolifaciens*
Anthocyanins	*Lactobacilli* and *Bifidobacteria* increased; *Staphylococcus aureus* and *Salmonella typhimurium* reduced; *Eubacterium ramulus* and *Clostridium saccbarogumia*
Ellagitannins	*Gordonibacter* genus and *Clostridium coccoides* group
Proanthocyanidins	*Adlercreutzia equolifaciens JCM 14793T*, *Eubacterium* sp. *SDG-2*, *Eggerthella lenta rK3*, *Eggerthella lenta CAT-1*

Source: Zhang Y *et al.*, Nutrients. 2022; 14(24):5373

Effect of polyphenols on neurodegenerative diseases

Patients with neurodegenerative diseases like Alzheimer’s disease and Parkinson’s disease may have intestinal microecological dysfunction, which may cause more intestinal diseases and lowered amounts of beneficial bacteria. Polyphenolic compounds and their metabolites can slow down neurodegenerative diseases by improving the effect of the gut microbiota, thereby slowing down neurodegenerative diseases. They exhibit neuroprotective effects, due to their possible roles in inhibiting oxidative stress and inflammatory cytokines. Taxa of gut microbes associated with decreased synthesis and increased inflammation influence the pathology of neurodegenerative diseases (1).

Biological Significance

Polyphenols are bioactive nutrients obtained from the plants we eat. They have antibacterial and

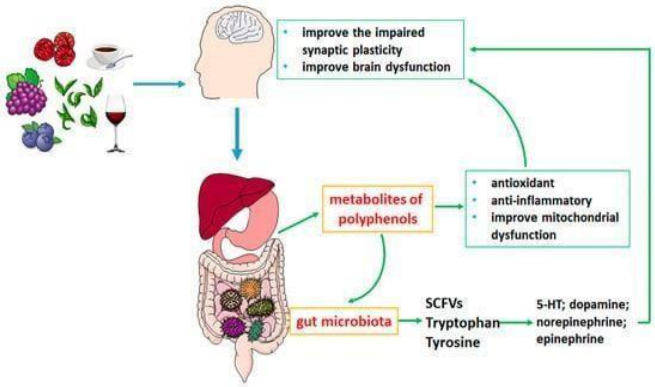

Figure 1. Effects of polyphenols on neurodegenerative diseases by gut microbiota metabolism

Source: Zhang Y *et al.*, Nutrients. 2022; 14(24):5373

antioxidant properties that help the plant recover from infection and protect tissues from reactive oxygen species. Its health-promoting effects, including antioxidant, anti-inflammatory, anti-adipogenic, and neuroprotective activities, are being widely studied for benefitting human health (5,6). The gut microbiota and the host control intestinal function and morphology through an intimate relationship. The gut microbiota helps digest food complexes and produce short-chain fatty acids to maintain human health. Most polyphenols are transported to the human large intestine and only a small portion is absorbed in the intestine. The intestinal microbiota converts polyphenols into bioavailable metabolites, increasing their bioavailability (5).

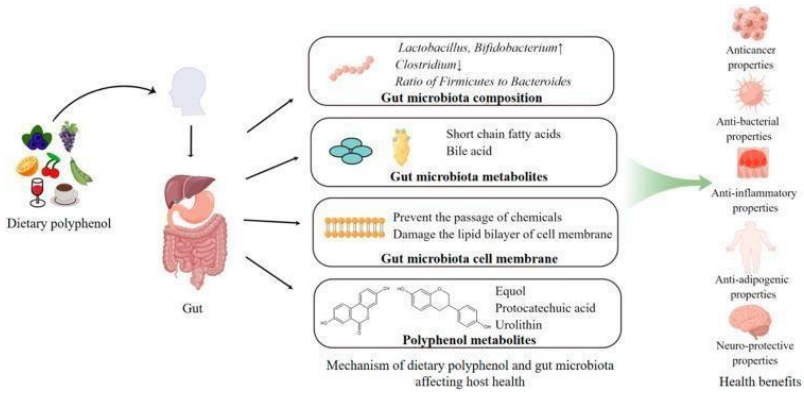

Figure 2. Possible mechanism among dietary polyphenols, gut microbiota, and host health.
Source: Wang X. *et al*., Antioxidants (Basel). 2022 Jun 20;11(6)

Conclusion

Eating foods rich in plant-derived polyphenols have a highly beneficial impact on human health, through interaction with gut microbiota. The metabolites of polyphenols have also been shown to have neurological implications. Recent studies have indicated a potential role of polyphenols in the treatment

of neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. Polyphenol can significantly impact gut microbiome and regulate them functionally and structurally.

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2. Bioluminescence: Nature's Living Symphony of Light

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Biochemistry of Bioluminescence

Bioluminescence is a fascinating phenomenon in many organisms, including fish, jellyfish, insects, and fireflies. (1,2) The biochemical process behind bioluminescence involves the interaction of a light-emitting molecule called luciferin, an enzyme called luciferase, oxygen, and other cofactors. Here is a simple explanation of the process:

- Luciferin: This is a molecule that emits light when a reaction occurs. Different organisms use different types of luciferins, and their structure and function may differ.
- Luciferase: Luciferase is an enzyme that catalyzes the oxidation of luciferin, which causes the release of energy in the form of light. This enzyme facilitates the reaction between luciferin and oxygen, which is necessary for bioluminescence to occur.

- Coenzymes and cofactors: Luciferase often requires many coenzymes and cofactors to function properly. These molecules facilitate energy transfer during exposure and are important for the functioning of the bioluminescence process.
- Oxygen: Oxygen is required for the oxidation reaction that produces light.

Generally, organisms take in oxygen from their environment and use it as a substrate for bioluminescent reactions. When luciferin interacts with luciferase in the presence of oxygen and cofactors, it undergoes oxidation, resulting in the release of photons of light. Specific color and light intensity may vary depending on the type of luciferin and other factors. The multistep oxidative decarboxylation process in the bioluminescence cycle involves several enzymatic reactions that ultimately result in the emission of light. While the exact mechanism can vary among different bioluminescent organisms, a generalized overview includes

- Substrate Binding: Luciferase enzyme binds to luciferin, typically in the presence of oxygen.
- Oxidation: Luciferin undergoes an oxidation reaction, facilitated by luciferase and oxygen, leading to the formation of an excited-state intermediate.
- Decarboxylation: In this step, an enzyme catalyzes the removal of a carboxyl group from the excited-state intermediate, resulting in the release of carbon dioxide.
- Further Oxidation: The decarboxylated intermediate undergoes further oxidation reactions, leading to the formation of a highly reactive intermediate.
- Regeneration reaction: Luciferin is regenerated from oxyluciferin in a subsequent series of reactions.
- Emission of Light: The highly reactive intermediate releases energy in the form of light as it returns to a more stable state, often accompanied by the regeneration of the luciferin substrate.

This multistep process efficiently converts chemical energy into light energy, enabling organisms to produce bioluminescence. Different organisms may utilize variations of this basic mechanism, but the fundamental steps typically involve oxidation, decarboxylation, and the emission of light Bioluminescence reactions cycle. The reaction rate for the luciferin is controlled by an enzyme, either a luciferase or a photoprotein, which is a luciferase variant in which factors required for light emission (including the luciferin and oxygen) are bound together as one unit. Photoproteins are triggered to produce light upon binding another ion or cofactor, such as Ca2+ or Mg2+, which causes a conformational change in the protein. This gives the organism a way to precisely control light emission.

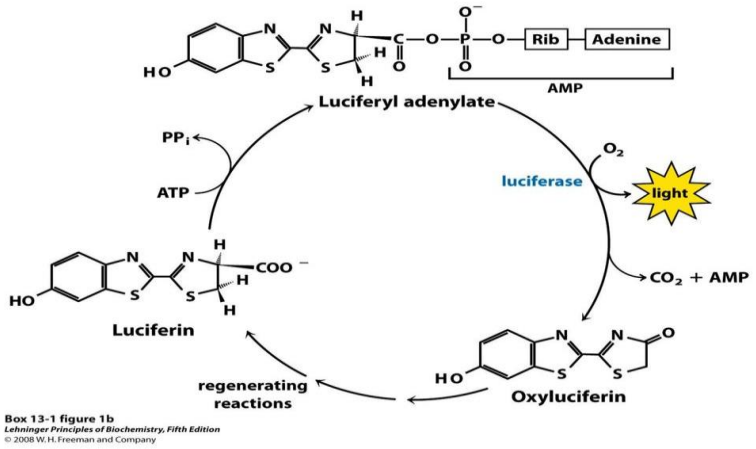

Figure 1. Depicting how light is produced by the Luciferin enzyme

(Source: "*Lehninger* Principles of Biochemistry", 6th Edition by D. L. Nelson and M. M. Cox, 2017, p. 525)

Examples of Bioluminescent Organisms: (4,5)

Imagine a world where the light comes alive and moves like sparkling stars. This is the magic of bioluminescence. Bioluminescence is nature's way of lighting up which is shown by many different kinds of organisms from bacteria to fungi to aquatic animals. Some of them are:

- Fireflies: They are also known as lightning bugs and are maybe the most famous bioluminescent organism. The light is produced by controlled chemical reactions, mainly to attract mates.
- Deep sea fishes: The region of the ocean that never receives any form of light is a home to a multitude of bioluminescent creatures. Angler fish is one of the most famous deep-sea creatures. The female anglerfish possess a bioluminescent lure called esca which it uses to attract prey, while male anglerfish lack bioluminescence. Fishes belonging to the Anomalopidae, also known as Flashlight fishes use bioluminescence produced by a bacterium, symbiotically associated, living underneath their eyes. organs located underneath their eyes showing symbiotic bioluminescence in which the light is produced with the help of bacteria living in the organ.
- Jellyfish: Several species of jellyfish show bioluminescence. For example, the crystal jellyfish produces green fluorescent protein (GFP), a bioluminescent protein that emits a glow when stimulated.
- Dinoflagellates: They are intriguing single-celled organisms that may be facultative heterotrophs. They are known for their ability to show bioluminescence in certain species, making the ocean glow at night.
- Glow worms: They are not actual worms but the larvae of various species of flies or beetles. They produce bioluminescent light to attract prey.

This light show can easily be observed in the night or deep within the sea where no light ever reaches.

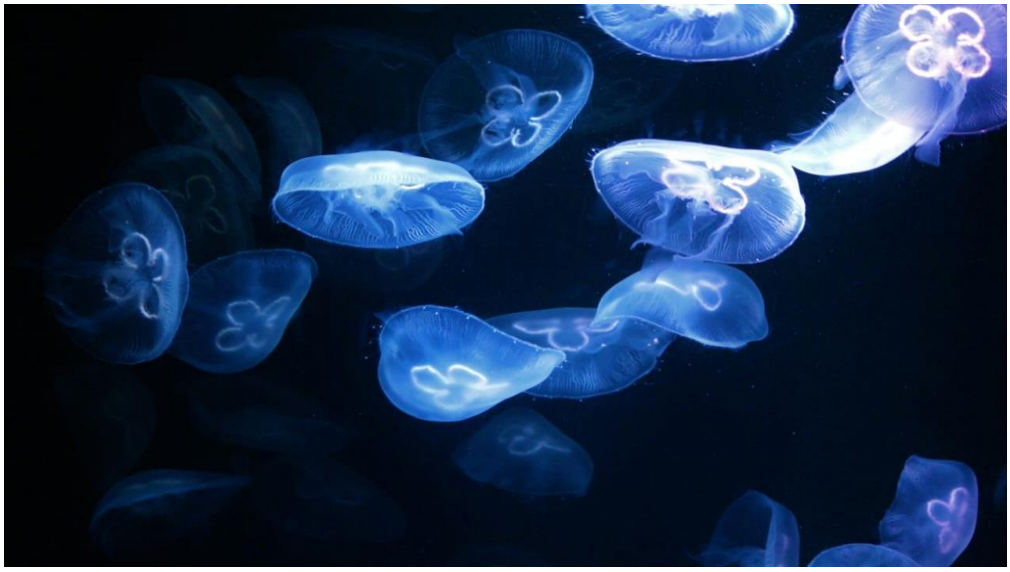

Figure 2. Jellyfish depicting bioluminescence
(Source: https://vocal.media/earth/this-freaky-deep-sea-fish-can-see-colors-that-other-fish-can-t)

Bioluminescence's Evolutionary Significance (3)

There are different theories and reasons so as to why does an organism light out in the dark. A few of these include:

- Luring prey: It serves as a predatory tactic, enabling animals like anglerfish to lure and capture prey effectively. These fishes possess glowing lures that attract smaller fish, which are swiftly captured.
- Defense mechanism: Marine plankton emit sudden flashes when disturbed, startling predators and facilitating escape. Firefly larvae combine light emission with bitter-tasting chemicals, warning predators of their toxicity. Certain squids and fish utilize bioluminescent patterns to confuse prey or predators, reducing their visibility.
- Camouflage: It aids in camouflage and counter-illumination, helping organisms blend into their surroundings or avoid detection by predators. Deep-sea creatures, for instance, emit light from their undersides to match the faint surface light, staying hidden from predators below.
- Communication: It plays a crucial role in animal communication, aiding in mate attraction, group co-ordination, territory establishment, and conveying species-specific information. Fireflies exemplify this, as males use distinct flashing patterns to attract potential mates.
- Attract mate: Organisms often utilize the intensity of their bioluminescent displays to attract potential mates. This luminous emission serves as a visual indicator of the mate's health and vitality, with higher intensities suggesting greater fitness.

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3. Liberation From Schizophrenia's Grip

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Schizophrenia is a severe and extremely persistent mental disease that changes a person's thoughts, emotions, and behaviors dramatically. The condition is described as a complex of symptoms that can be very counterproductive and severely reduce a person's ability to deal with their daily problems. Schizophrenia usually starts to develop in late adolescence and early adulthood, but anybody can have it.

Also, the exact cause of schizophrenia is still unknown.

This multifaceted disease is the result of the joint action of the genetic background, environment, and neurobiology of a person. Schizophrenia is a complex disease with multiple aspects such as gene or biological factors, and environmental stressors. Through genetic research, scientists have identified numerous risk genes linked to schizophrenia, suggesting the genetic component of the disorder. Various environmental conditions, for example, exposure to prenatal toxins, the stress of the mother during pregnancy, or childhood trauma may be another factor that is involved. During the pathophysiology of Schizophrenia, there is a neurobiological abnormality, which can be expressed in structural alterations of the brain, and the imbalance of the neurotransmitters, particularly dopamine and glutamate. (1,2,3)

The symptoms of schizophrenia may be treated in three categories, which are positive, negative, and cognitive symptoms. Such symptoms of belief involve distortions of perception and thought and may involve hallucinations (perceiving things that are not present), delusions (false beliefs), disorganized speech, and disorganized behavior. Negative symptoms are connected with above typical mood and behavior such as low motivation levels, social isolation, and reduced capacity to express emotions, hence lessened talk. Cognitive symptoms cover, attention, memory, and higher executive functioning referring to the level of planning, organizing, and decision-making in the individual.

Often schizophrenia is divided into a lot of subtypes due to the different symptoms that prevail and the clinical impression. The various types of schizophrenia subtypes are paranoid which features prominent delusions and hallucinations, disorganized that is defined by disorganized speech and behavior, catatonic that is characterized by motor disturbances and motor rigidity or immobility, undifferentiated that does not fit into the other types, and residual which becomes prevalent even though the symptoms are not intense. Classification of schizophrenia can be early-onset (before 18 years old) or late-onset (after 40 years old) while these types of distinction are less used in usual clinical practice.

The evolution in treatment methods has been from classical approaches to famous methodologies due to profound knowledge of the disorder's basic science. The brief history is mentioned below:

Classical Approaches:
The way schizophrenia has been traditionally tackled consists of the dopaminergic hypothesis that argues the critical role of dopamine dysregulation in the disease process. As for first-generation antipsychotic drugs, such as chlorpromazine, their mechanism of action is based on antagonism of the dopamine D2 receptors which results in a reduction of positive symptoms like hallucinations and delusions (2,3,4). On the other hand, the development of EPS and tardive dyskinesia due to their action mechanism has also decreased the efficacy and tolerability.

Second-generation antipsychotics:
The arrival of so-called second-generation antipsychotics – risperidone, olanzapine, and quetiapine – provided another treatment option based on dual dopamine and serotonin receptors' involvement (5,6). These medications showed a wide spectrum of receptor activity that included a blockage of dopamine D2 receptors while also being antagonistic to the serotonin 5-HT2A receptors. This approach which had a two-pronged approach, that is, positive symptoms efficacy and EPS risk reduction when compared with the

earlier generation antipsychotic drugs, was greatly successful. Therefore, SGAs were found to be still endangering the cardiometabolic system such as weight gain and blood glucose disturbances (7).

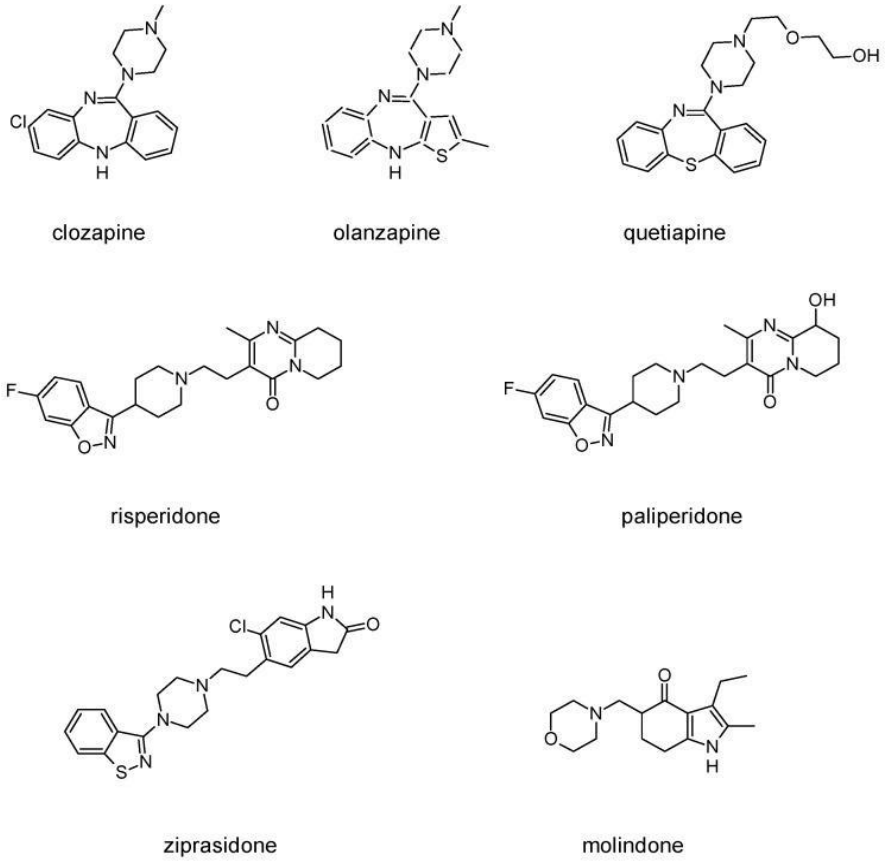

Figure 1. The chemical structures of second-generation antipsychotic drugs.
(Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6222385/figure/molecules-23-02087-f001/)

Third-generation antipsychotics

The latest therapeutic breakthroughs in schizophrenia treatment provide us with the third generation of antipsychotics including aripiprazole, brexpiprazole, and cariprazine (8,9). Instead of blocking the dopamine D2 receptors like they used to, the new medications have been carefully engineered to work as dopamine D2 receptor partial agonists which results in a more delicate regulation of dopamine neurotransmission. To illustrate, (for example) aripiprazole stabilizes levels of dopamine by imitating a partial D2 phenomenon with more and more changed characteristics depending on dopamine concentration. This is achieved through a distinctive inherent mechanism that favors fixing the symptoms, of metabolic disorders to be found in the majority of patients.

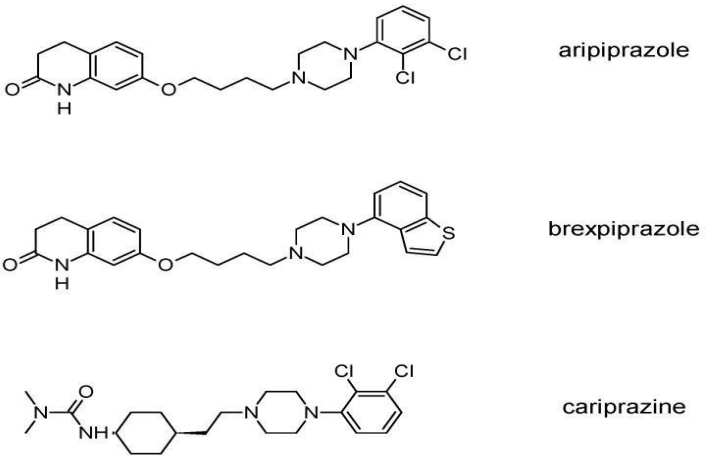

Figure 2. Structures of third generation antipsychotic drugs
(Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6222385/figure/molecules-23-02087-f002/)

Innovative Ongoing Approaches:

Although traditional antipsychotic medicines have been used to treat schizophrenia, ongoing research is investigating novel therapies as complementary models for the management of this condition. Gamma-aminobutyric acid (GABA) system, glutamate neurotransmission, glycine transporters for the glycine cycle, and nicotinic receptors are among the directions that are being explored vigorously (11). The action-selective modulators and biased ligands for the G-protein-coupled receptors (GPCRs) incorporate the precision and tailored therapy that minimizes the side effects and maximizes the desired treatment at the same time (10). As an example, agonists acting as positive allosteric modulators on metabotropic glutamate receptors (mGluRs) underlie the mechanism through which neuronal transmission gets improved, which is beneficial in terms of treating symptoms like cognitive deficits associated with schizophrenia.

Future Prospectives on Treatment:

As medical scientists gasp fast the knowledge of schizophrenia, the same will be the case with its treatment methods. The development of classical antipsychotics to third-generation drugs shows the development process with painted with the progress brought by neuroscience and pharmacology. Yet we notice at the same time that such difficulties still might be there and the most vital of them is to form an appropriate therapy to handle the full range of the symptoms as well as to improve long-term results. Future studies will probably concentrate on honing the existing therapeutic strategies, designing interventions possibly targeting symptom clusters in a personalized type, and exploring novel treatment strategies with the aid of promising neurobiological literature (12,13,14).

In a nutshell, the treatment of schizophrenia has enormously changed the course from the classical period of dopamine antagonists to the era of the development of new mechanisms and precision medicine. Through the years with the development of each generation of antipsychotics, there is a smooth progress that leads to better outcomes for patients, however, the journey of searching for the most effective, safer, and personalized treatment has not ended yet. We do this by technology and interdisciplinary collaboration which allows people struggling with schizophrenia to see that some bright future is ahead of them.

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4. Arsenic Poisoning in the Gangetic plains of Indian Subcontinent

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"No one can avoid a challenge in life without breeding a regret, and regret is the arsenic of life"

Arsenic poisoning casts a Thala-sized shadow over the world, threatening the wellbeing of millions. This silent killer infiltrates our daily lives mainly through polluted water, contaminated soils, and tainted food products, despite the frequent sensationalized stories of arsenic-related homicides. Arsenic's pervasive presence demands utmost attention, as communities across the globe grapple with the devastating consequences of this global health emergency. (1)

High doses of arsenic can be inhaled or consumed, which can result in arsenic poisoning, also known as arsenicosis. Although arsenic occurs naturally, it may also be found in inorganic, or "man-made," formulations. Humans that are employed in mining, manufacturing, and agriculture are at higher risk. The United States, India, China, and Mexico are among the nations with elevated concentrations of groundwater contaminated by arsenic. (2) Arsenic poisoning is classified as a sub-metallic toxicity. Metallic arsenic itself is not hazardous. However, when heated, it reacts with oxygen to produce arsenic trioxide vapours, which are highly lethal. Arsenic is considered a potent poison. Its odourless and tasteless nature made it a favoured choice for political assassins. The potent toxin's use as a murder weapon contributed to its notoriety over the centuries, even up to the modern era.

Mobilization of Arsenic into The Environment

Arsenic contamination is amplified by natural occurrences like volcanic activity, weathering, and biological processes. Human activities such as ore smelting, mining, well drilling, and fossil fuel combustion also contribute to the spread of arsenic into areas inhabited by people. Arsenic's poisonous nature makes it a hazard not just to humans, but also to other living organisms.

Arsenic is largely deposited in the lithosphere and reaches the atmosphere through natural and human activities. Weathering of rocks, geothermal, and volcanic events are all natural processes that cause arsenic poisoning in the environment. Arsenic concentrations in freshwater typically vary from 0.01 to 2 μg L^{-1}, and surface water pollution without anthropogenic arsenic input is rare. Nonetheless, rivers and lakes with headwaters in arsenic-rich sediments may have extremely high arsenic concentrations. Chilean rivers with volcanic deposits can have arsenic concentrations surpassing 2000 mg As L^{-1}. On the other hand, mining and the combustion of fossil fuels are the primary anthropogenic causes of arsenic pollution in the environment.

Arsenic occurs as a byproduct of gold and coal extraction. Furthermore, arsenic is mined and extracted from mineral ores for use in a variety of contemporary applications, including electronics, batteries, paints, wood preservatives, insecticides and medicines. Water bodies that absorb mining and industrial effluents frequently contain increased arsenic concentrations, which can harm local animals. Arsenic values of up to

583 and 18,910 μg L−1 in surface water were observed from the mining districts of Ron Phibun in Thailand and Obuasi in Ghana, respectively. Mining activities can also result in high amounts of arsenic in soil and plants in nearby terrestrial systems. Arsenic levels in surface soil and vegetation near Giant Mine, a decommissioned gold mine in Yellowknife, Canada, have been reported to be 75-400 and 22-725 mg kg−1 dw, respectively, compared to 1-10 and 0.001-0.6 mg kg−1 dw in reference areas. (3)

Arsenic Exposed States in The Ganga-Brahmaputra Fluvial Plains

The rising prevalence of arsenic in ground water, particularly in floodplains, is a serious concern for India and its South Asian neighbours such as China, Bangladesh, and Taiwan.

Arsenic pollution in groundwater exceeds permitted levels in West Bengal, Jharkhand, Bihar, Uttar Pradesh, Assam, Manipur, and Chhattisgarh. (4)

Groundwater is critical in India for meeting the water demands of numerous sectors, including household, industrial, and irrigation. The Ganga and Brahmaputra rivers' alluvial plains constitute the country's richest groundwater region. The majority of the extraction occurs throughout the Indo-Gangetic basin in Northern and Northwestern India, resulting in considerable drawdown and water table drop in several areas. (5)

According to reports, nearly 50 million people in India are presently at risk of arsenic pollution in their groundwater. Workers conducted research on arsenic pollution in groundwaters in India, particularly in the Ganga basin. The Ganga River basin comprises roughly 26% of India's area and has a population of over 500 million.

The Ganga River basin is one of the most fertile and heavily inhabited regions in the world. The Ganga is currently one of the world's most polluted rivers, including a number of poisons such as chromium, arsenic, cadmium, lead, copper, and mercury, as well as pesticides and pathogenic bacteria approximately 3000 times greater than the acceptable level established by the World Health Organization.

Groundwater with high arsenic levels (>10 ppb) has been observed in shallow aquifers in ten Indian states; nevertheless, India's deeper aquifers (>100 m) are arsenic-free. The first occurrence of arsenic pollution in groundwater was recorded in the Chandigarh region of north India, followed by a second case in West Bengal's lower Gangetic plain. Following that, reports came in from West Bengal, Bihar, Uttar Pradesh, Jharkhand, Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim, Tripura, Punjab, Himachal Pradesh, Chhattisgarh, and Andhra Pradesh.

In India, elevated arsenic groundwater falls into two categories:

1. alluvial terrane and
2. hard rock terrane.

In India, alluvial aquifers account for 90% of arsenic. Hard rock aquifers account for just 10%, which includes states such as Karnataka and Chhattisgarh. In Karnataka, arsenic has been linked to sulphide mineralization, particularly arsenopyrite. It is primarily confined to gold mineralized sites in Raichur and Yadgir districts. It has been documented in Chattisgarh from acid volcanics connected with the Kotri lineament. (6)

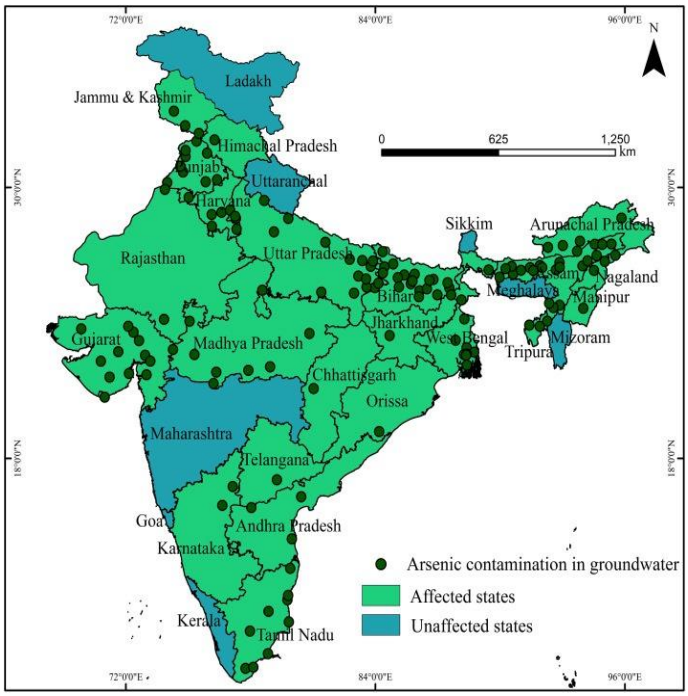


Figure 1. Arsenic affected States and Union Territories in India

(Source: Shaji, E., Santosh, M., Sarath, K., Prakash, P., Deepchand, V., & Divya, B. (2021). Arsenic contamination of groundwater: A global synopsis with focus on the Indian Peninsula. *Geoscience Frontiers*, *12*(3), 101079. https://doi.org/10.1016/j.gsf.2020.08.015)

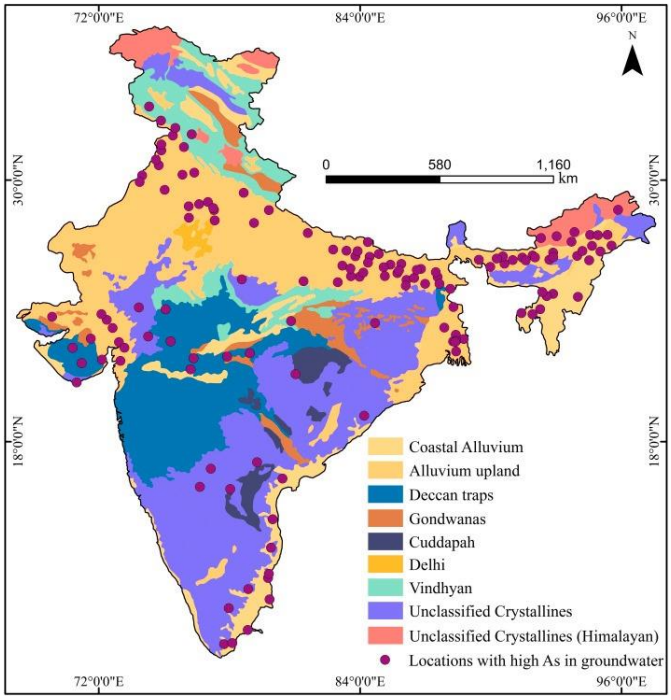


Figure 2. Areas impacted by arsenic placed on India's overall geology. Modified diagram of India's aquifer systems showing that 90% of arsenic comes from alluvial aquifers and 10% comes from hard rock aquifers

(Source: Shaji, E., Santosh, M., Sarath, K., Prakash, P., Deepchand, V., & Divya, B. (2021). Arsenic contamination of groundwater: A global synopsis with focus on the Indian Peninsula. *Geoscience Frontiers*, *12*(3), 101079. https://doi.org/10.1016/j.gsf.2020.08.015)

Findings from Ballia district, Uttar Pradesh (Upper-middle Ganga Plains)

An examination was conducted to determine the impact of arsenic in the blocks of Ballia district in Uttar Pradesh's upper and middle Ganga plains, India. The analysis of 100 drinking water samples found that arsenic content was below 10 μg l^{-1} in 60%, 10-50 μg l^{-1} in 6%, 100 μg l^{-1} in 24%, and 200 μg l^{-1} in 10%, respectively. The arsenic levels in drinking water varied from 12.8 to 132.2 μg/l. The drinking water source depth (10-60 m) was found to have a mean arsenic value of 36.12 ± 13.61 μg/l.

The average arsenic content was 17.398 ± 21.796 μg l^{-1} at 10-20 m depth, 39.685 ± 40.832 μg l^{-1} at 21-40 m, and 46.89 ± 52.80 μg l^{-1} at 41-60 m. The study found a substantial positive connection ($r = 0.716$, $t = 4.215$, $P < 0.05$) between depth and arsenic levels in drinking water. The age of the water sources varied from zero to thirty years. According to the study, older drinking water sources were more likely to be contaminated. The group aged 21-30 had the highest arsenic content, with a mean of 52.57 ± 53.79 μg l^{-1}. The association analysis revealed a substantial positive association ($r = 0.801$, $t = 5.66$, $P < 0.05$) between the age of drinking water sources and their arsenic content (μg l^{-1}). The average arsenic content in blood was 0.226 ± 0.177 μg dl^{-1}, which was substantially higher than the control group. Blood arsenic levels were strongly linked ($r = 0.6823$, $t = 3.93$, $P < 0.05$) with drinking water arsenic levels and exposure duration ($r = 0.545$, $t = 3.101$ & $*P < 0.05$) among Ballia district residents. Observations and correlation analysis suggested that those who drank water from depths of 20-30 m were less harmed by arsenic exposure. (7)

Correlation between arsenic concentration and depth of the drinking water source

Out of 100 drinking water samples tested, 24% had arsenic concentrations of 100 micrograms per litre (ug/L) and 10% had arsenic concentrations of 200 ug/L. The remaining 60% of samples had arsenic concentrations within the acceptable range of 10 to 50 ug/L. This means that 34% of the samples had concerning arsenic levels, which is significant given the population of the Uttar Pradesh (UP) region. The depth and age of the water source directly correlates with the arsenic concentration - the deeper the well, the higher the arsenic level. Individuals using a water source with a depth of 20-30 metres were less affected by arsenic exposure compared to those using a well depth of around 60 metres.

Measures for improving conditions in Ballia

- ➢ Rainwater harvesting
- ➢ Arsenic purifiers installation in the aquifers or RO on personal level
- ➢ Using surface run-off
- ➢ Using alternate water sources

Findings from Murshidabad, West Bengal (Lower Ganga Plains and Delta)

Out of the 26 blocks in Murshidabad, 24 of them were found to have arsenic levels exceeding 50 micrograms per litre (ug/L) in the hand tubewell water samples.

The study screened a total of 25,274 people, and 4,813 (19%) of them were found to have developed

arsenical skin lesions. The researchers also documented a number of cases where these skin lesions had progressed to cancer and gangrene. Histopathological analysis of skin biopsies from different types of lesions was presented as part of the study. Out of 2,595 children examined, 122 (4%) were found to have arsenical skin lesions, including melanosis with or without keratosis. The arsenic-affected villagers also exhibited a range of neurological features, both clinically and through electrophysiological assessments. The study suggests that both the arsenic content in the drinking water and the duration of exposure may increase the risk of adverse pregnancy outcomes in the affected population, such as spontaneous abortions, stillbirths, preterm births, low birth weights, and neonatal deaths. Additionally, the study recorded other multisystemic effects in the affected population, including weakness, lethargy, chronic respiratory problems, gastrointestinal symptoms, and anaemia.

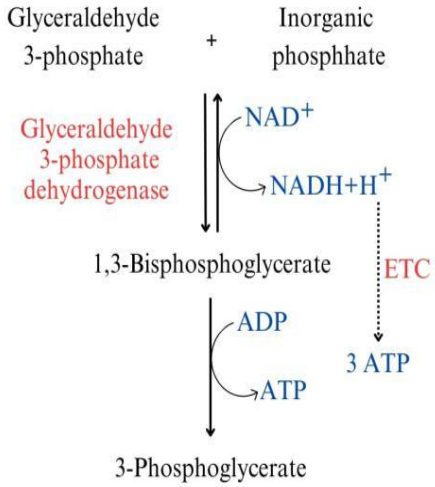
The analysis of total 3800 biological samples from arsenic-affected villages revealed that 95% of the nail and 94% of the urine samples contained arsenic above the normal levels and 75% of the hair samples were found to have arsenic above the toxic level.

More than 3.5 million villagers would suffer from arsenical skin lesions and cancer. (8)

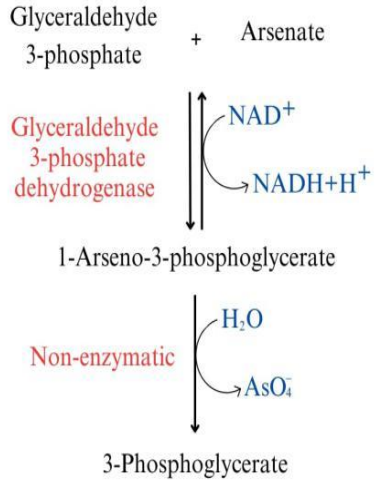
Mechanism of Arsenic Poisoning

1. Glycolysis (Arsenate)

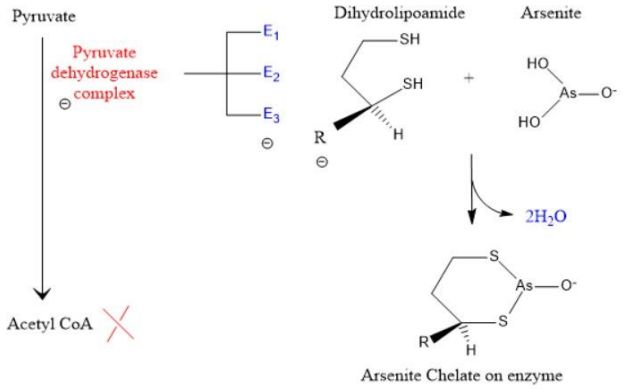
Normal Glycolysis Step



Arsenate Poisoning in Glycolysis



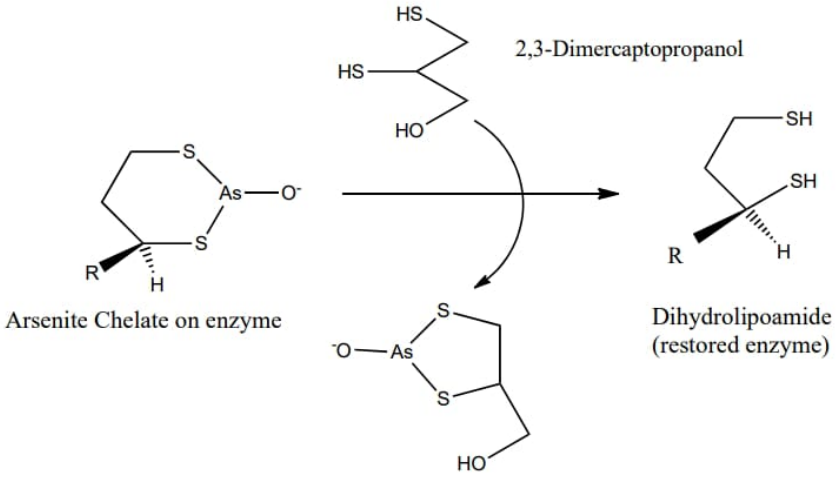
2. TCA Cycle (Arsenite)



BAL Chelation Therapy

British anti-Lewisite (BAL) or dimercaprol offers therapeutic benefits for patients intoxicated by arsenic poisoning. It was the first therapeutic agent found to reverse the neurological symptoms suffered by patients with hepatolenticular degeneration, also known as Wilson's Disease. During World War II, BAL helped reduce the risk of injury or death to Allied infantry from exposure to Lewisite, a highly potent arsenic-based chemical weapon. (9)

Restoration of E_3 using BAL



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5. What Am 'I' (A study on the nature of human consciousness and its neural correlates)

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When defining what the collective experience we as Humans all feel and inherit as the most intelligent species on the planet, we tend to look at the concept of the 'conscious self', this distinguishable factor can be observed only in humans. A form of consciousness can be observed in animals which they express through complex behaviors, including empathy and planning, and animals use facial expressions and sounds to communicate along with each other. On the other hand, when describing consciousness in humans it is characterized by a "subjective point of view" on the world around them and the body in which they reside, encompassing various sensory experiences and responding to them.

During the past thirty years, the emergence and progress of novel scientific methodologies, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have enabled neuroscientists to investigate the functioning of the living brain. These techniques have been widely employed to ascertain the activation of specific brain regions with particular cognitive processes. Researchers from various regions of the world have utilized these approaches to accurately identify the neural correlates of any facet of mental activity. The success of this extensive undertaking depends not only

on the technological capabilities of these instruments but also on our accurate interpretation of the findings obtained through neuroimaging. A precise analysis of experimental data holds meaningful significance, especially in the examination of human cognitive functions.

It is a widely acknowledged fact that our consciousness is what governs our behavior. A prime example of this is the requirement of consciousness to learn new languages or play musical instruments. Without being conscious of our actions, these tasks would be impossible. The significance of consciousness becomes evident in its role in handling unexpected situations, adapting to new stimuli, and performing novel tasks. Additionally, it is crucial to note that unconscious individuals are incapable of appropriately assessing complex emotional experiences. Furthermore, consciousness plays a vital role in decision-making, voluntary control of actions, planning for the future, recalling memories, and constructing a sense of self. Consciousness is integral to numerous fundamental mental functions such as reasoning, creative thought, imagination, empathy, evaluation of intricate emotions, memory retrieval, and action planning (2).

The repeated emphasis on the relationship between consciousness and synchronous neural activity has been observed by several researchers (3). Consequently, it can be inferred that the process of brain synchronization plays a crucial role in integrating various attributes into a unified conscious experience.

The neural bases of consciousness have been identified as the minimal neural mechanisms that are both necessary and sufficient for the perception of any conscious experience (4). The search for the neural structures that play a crucial role in the level of consciousness has been driven by both traditional and contemporary investigations of brain damage, as well as functional magnetic resonance imaging (fMRI) studies, which demonstrate that consciousness is supported by a complex interplay of various networks, including the ascending reticular activating system (ARAS) in the brainstem, the non-specific nuclei of the thalamus, and the extensive thalamocortical connections to the anterior cingulate, posteromedial cortex, and frontoparietal association cortices. (2)

The matter of consciousness is undoubtedly a complex phenomenon that exists in varying degrees. The construction and refinement of the phenomenal content of consciousness occur progressively through the involvement of different brain areas. This process involves the primary and secondary sites of perception, which contribute to an initial and preconscious draft of the content. Subsequently, this "protocontent" is transmitted to higher cortical areas for further processing until it reaches its final stage. At this stage, the content is disseminated throughout the global workspace of the frontoparietal system, leading to its eventual conscious awareness. To explain this elaboration process, three stages have been proposed: subliminal, preconscious, and conscious. The subliminal stage, although insufficiently strong, does not generate conscious experiences. The preconscious stage, on the other hand, is strong enough but requires attention to enter the global workspace. It is believed that the preconscious stage is limited to sensory-motor processors within occipitotemporal loops, and while its contents can prime multiple levels, they cannot be verbally reported. Finally, the conscious stage possesses sufficient strength to produce reportable content that enters the global workspace when attended to. In this model, we can assume the existence of consciousness is based on attention which decides what is given priority for a time being when being played like a movie in our conscious self's brain. **[Central model of consciousness]** The second model suggests that instead of being represented in a singular central system of the brain or a global workspace, the content of an experience may achieve consciousness within the neural structure that analyzes its attributes. The

primary cortex would generate a series of micro-consciousnesses that are specific to each sensory modality; subsequently, these micro-consciousnesses would be united by the secondary cortical areas into a macro-consciousness, always specific to each sensory modality, and, ultimately, the various macro-consciousnesses would be amalgamated into a fully developed conscious landscape. [**Modularity model of consciousness]**

Another theory proposes that the brain's networks are in a state of dynamic criticality, where there's a higher likelihood of both long periods of synchronized activity and sudden changes in global synchrony. Network hubs, particularly "connector hubs" that link different networks, may regulate synchronization by adjusting the connectivity of neighboring regions to facilitate information integration. When discussing brain areas crucial for consciousness, only two areas—the ascending reticular activating system (ARAS) and the intra-laminar nuclei of the thalamus—have been identified. These thalamic nuclei are extensively connected with the ARAS and much of the brain, suggesting a pathway that may influence consciousness by coordinating synchronous oscillations across the brain to establish a coherent baseline of neural activity. The thalamic nuclei, in conjunction with the brainstem arousal system, are believed to regulate

thalamocortical synchronization at different frequencies, such as 40 Hz during wakefulness or much lower frequencies during sleep. Evidence from neurological and neuropsychological conditions supports the idea that consciousness can be specifically impaired. For example, patients with epilepsy, particularly during focal seizures, can exhibit selective disruption and preservation of cognitive functions, behaviors, and conscious experiences. Studies on split-brain patients have shown that certain aspects of consciousness can be limited to one hemisphere. Similarly, conditions like blindsight, anosognosia, prosopagnosia, and neglect demonstrate that specific features of conscious experience can be damaged or lost.

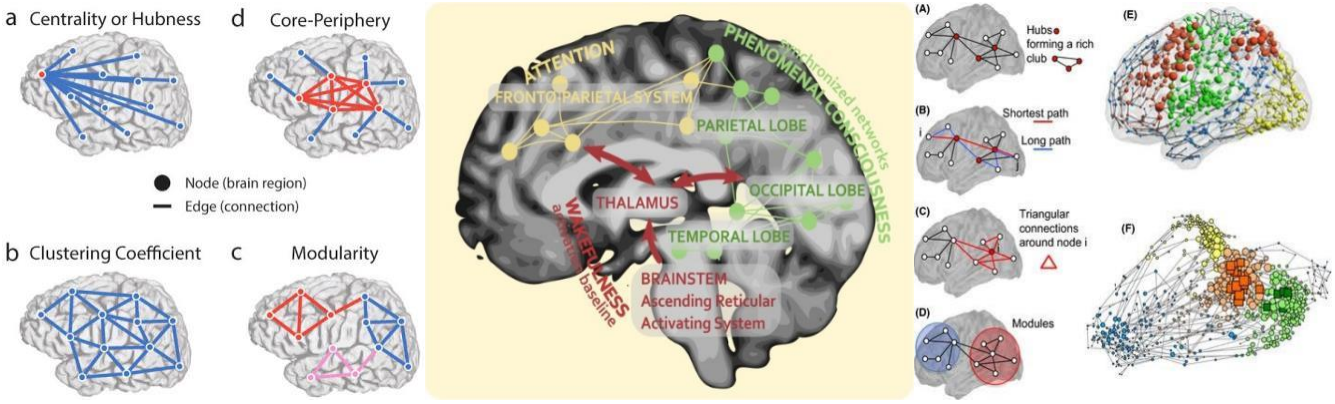

Figure 1. Network metrics illustrating degree, hubs and rich clubs, Path length and efficiency, Clustering and local efficiency, Modularity and topological space.

(Source: Network metrics commonly used to quantify the topology of. . . (n.d.). ResearchGate. https://www.researchgate.net/figure/Network-metrics-commonly-used-to-quantify-the-topology-of- networks-A-Degree-hubs-and_fig5_269174455?_tp=eyJjb250ZXh0Ijp7ImZpcnN0UGFnZSI6InB1YmxpY2F0aW9uIiwicGFnZSI6InB1YmxpY2F0aW9uIiwicHJldmlvdXNQYWdlIjoiX2RpcmVjdCJ9fQ,

Bassett, D. S., Khambhati, A. N., & Grafton, S. T. (2017, June 21). Emerging Frontiers of Neuroengineering: A Network Science

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While the two main models discussed give us, valuable insights into the functionality and the neurophysiology of the brain while it produces the 'conscious self', the Modularity model seems to be more clinically viable and it emphasizes the specialization of different brain regions in conscious experience, although it may oversimplify the interactions between the modules of conscious experience. Consciousness is likely a result of complex and dynamic interactions between various brain regions, which the Modularity Model may not fully capture. When discussing the Central model it proposes a central source of consciousness, the model implies that all aspects of conscious experience are integrated and arise from this central source. This can help in understanding how different aspects of consciousness, perception, memory, and emotion, are related and interact with each other. One major criticism of the Central Model is that it oversimplifies the complexity of consciousness. It suggests that consciousness arises from a single, centralized source in the brain, which may not fully account for the distributed and integrated nature of conscious experience.

Conclusion:

In conclusion, while both models provide valuable insights into the neurological basis of consciousness, consciousness is likely a complex and dynamic phenomenon that involves interactions between centralized and modular processes in the brain. Further research is needed to fully understand the nature of human consciousness and how it emerges from the brain's neural networks.

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6. Aortic Valve Stenosis

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Introduction

The heart is a powerful muscle that pumps blood throughout the body, ensuring that oxygen and nutrients reach all organs and tissues. The pumping action of the heart involves a series of coordinated events, including the opening and closing of heart valves. The aortic valve is one of these valves and is crucial for proper blood flow.

Aortic stenosis is a common valvular disorder leading to left ventricular outflow obstruction. [1] A condition where the aortic valve becomes narrowed, restricting the flow of blood from the left ventricle into the aorta. This narrowing can occur due to the thickening or calcification of the valve leaflets. The restricted opening impedes the normal flow of blood and puts additional strain on the heart. Aortic valve stenotic disease is the most commonly occurring valvular pathology in developed nations (afflicting 9 million people worldwide) and its prevalence has been increasing with population aging and the increased prevalence of atherosclerosis.[2]

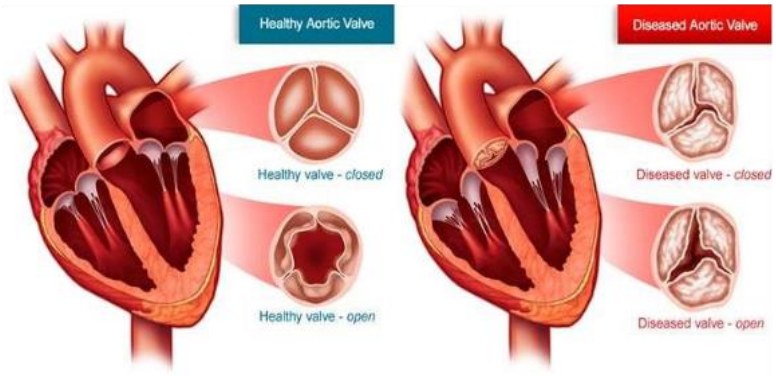

IMAGE: What is aortic stenosis? | St. Joseph's/Candler. (2020, February 4). SJC. https://www.sjchs.org/living-smart-blog/blog-details/blog/2020/02/04/what-is-aortic-stenosis

Causes and Risk Factors:

A. Congenital Valve Abnormalities: Some people are born with aortic valve abnormalities, such as a bicuspid aortic valve (two leaflets instead of the normal three). Bicuspid valves are more prone to calcification and stenosis over time.
B. Age-Related Calcification: The most common cause of aortic valve stenosis in adults is age related calcification of the valve. As people age, calcium deposits can accumulate on the aortic valve, causing it to become thickened and less flexible.
C. Rheumatic Fever: Rheumatic fever, a complication of untreated strep throat or scarlet fever, can lead to damage and scarring of the aortic valve. This scarring may eventually result in stenosis.

D. Calcium Buildup: In some cases, calcium deposits can build up on the aortic valve without an apparent underlying cause. This calcification can stiffen the valve and reduce its ability to open and close properly.
E. Radiation Therapy: In rare cases, exposure to chest radiation therapy, particularly in the treatment of certain cancers, can contribute to the development of aortic valve stenosis. [3]

Symptoms

- Chest discomfort: The chest pain may get worse with activity and reach into the arm, neck, or jaw. The chest may also feel tight or squeezed.
- Cough, possibly bloody.
- Breathing problems when exercising.
- Becoming easily tired.
- Palpitations
- Fainting, weakness, or dizziness with activity.

In infants and children, symptoms include:

- Becoming easily tired with exertion (in mild cases)
- Failure to gain weight
- Poor feeding
- Serious breathing problems that develop within days or weeks of birth (in severe cases)

Children with mild or moderate aortic stenosis may get worse as they get older. They are also at risk for a heart infection called bacterial endocarditis. [4]

Diagnosis

1. Echocardiography: Echocardiography is a key diagnostic tool for aortic valve stenosis. It uses ultrasound waves to create images of the heart and can assess the structure and function of the aortic valve. Transthoracic echocardiography (TTE) is the most common type and is performed by placing the ultrasound transducer on the chest. [5-7]
2. Transoesophageal echocardiography (TEE): TEE is a medical procedure that uses a specialized ultrasound probe. The probe is inserted into the esophagus to obtain more detailed images of the heart structures, including the aortic valve. TEE is particularly useful when a clearer view of the aortic valve is needed. [8]
3. Cardiac Catheterization: Cardiac catheterization involves threading a thin tube (catheter) through blood vessels to the heart, usually from the groin or arm. Contrast dye is injected, and X-ray images are taken to visualize the aortic valve and assess the degree of stenosis.
4. CT scan or MRI: Computed tomography (CT) scans or magnetic resonance imaging (MRI) can provide detailed images of the heart and valves, assisting in the evaluation of aortic valve stenosis.
5. Electrocardiogram (ECG or EKG): An ECG records the electrical activity of the heart and can help identify irregularities or signs of strain on the heart muscle.
6. Exercise Stress Test: A stress test may be performed to assess the heart's function during physical activity, providing information on the impact of aortic valve stenosis on exercise capacity.
7. Medical History and Physical Examination: The healthcare provider will inquire about symptoms, medical history, and risk factors for heart disease. A physical examination may involve listening to the heart with a stethoscope to detect abnormal heart sounds, such as a heart murmur.

Treatment

The treatment options for aortic valve stenosis depend on the severity of the condition, the presence of symptoms, and individual patient characteristics. Here are the main treatment modalities for aortic valve stenosis:

- Medical Management: Mild cases of aortic valve stenosis without significant symptoms may be managed with regular monitoring and medications. Medications may include diuretics and medications to control blood pressure. [7]
- Balloon Valvuloplasty: Balloon valvuloplasty is a procedure where a catheter with a balloon at its tip is used to open a narrowed aortic valve by inflating the balloon. This technique is less common for aortic valve stenosis compared to other interventions but may be considered in specific cases. [8]
- Aortic Valve Repair: In some cases, surgical techniques may be used to repair the aortic valve. This is less common than valve replacement and may involve procedures to address congenital anomalies or damage to the valve leaflets.
- Aortic Valve Replacement: Aortic valve replacement is a standard and effective treatment for severe aortic valve stenosis. During this surgical procedure, the diseased valve is replaced with either a mechanical or biological (tissue) valve. [9]
- Transcatheter Aortic Valve Replacement (TAVR): TAVR is a less-invasive alternative to traditional open-heart surgery for aortic valve replacement. A catheter is used to deploy a replacement valve without the need for open-heart surgery. TAVR is often considered for high-risk or inoperable patients. [9]
- Medication After Valve Replacement: Following valve replacement, patients may be prescribed medications to manage symptoms and reduce the risk of complications. Anticoagulant medications may be needed for those with mechanical valves.
- Lifestyle Changes Adopting heart-healthy lifestyle changes, such as a balanced diet, regular exercise, and smoking cessation, can help manage overall cardiovascular health and improve outcomes.

Conclusion

Aortic stenosis is a condition that is becoming more common as the population ages. In most patients, the primary cause of aortic valve stenosis is an underlying bicuspid aortic valve. However, in older patients, degenerative remodeling of a tricuspid valve is a common cause of Aortic Stenosis. The clinical risk factors for the development of AS are similar to those for atherosclerosis, including hypertension, hyperlipidemia, and diabetes.

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7. The mRNA Revolution: Unraveling the Potential of mRNA Vaccines

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Introduction

In the domain of contemporary healthcare, the advent of messenger RNA (mRNA) technology has instigated a significant transformation in the field of vaccine advancement. Conventional vaccines typically depend on attenuated or inactivated pathogens to elicit an immune reaction. In contrast, mRNA vaccines introduce a pioneering methodology that exploits genetic material to direct cells to generate antigens, thereby eliciting an immune response targeted at specific pathogens. Delivery of naked modified mRNAs is characterized by inefficiency, leading to diminished levels of antigen protein synthesis. Consequently, lipid nanoparticles have been harnessed to enhance the delivery process and safeguard the mRNA payload against degradation in the extracellular environment. This progression marked a significant milestone in the evolution of mRNA vaccines. Subsequent to the remarkable triumph of mRNA vaccines against COVID-19, numerous other mRNA-based therapeutics have been suggested for the management of diverse medical conditions. mRNA-based pharmaceuticals have surfaced as a compelling novel category of therapeutics, poised to transform the landscape of cancer therapy via a range of strategies including therapeutic vaccinations, monoclonal antibodies, immunomodulatory agents, and chimeric antigen receptor (CAR) cell therapy [1]. This paper delves into the complexities of mRNA technology, investigates the evolution of mRNA vaccines, and scrutinizes their implications for public health.

Understanding mRNA Technology

Messenger RNA (mRNA) is a form of single-stranded ribonucleic acid derived through transcription from a DNA strand, containing the genetic instructions for protein synthesis to be subsequently translated and modified into active proteins [2]. An mRNA-centric strategy has the potential to generate

a wide array of proteins and peptides by leveraging the cellular mechanisms of protein synthesis within transfected cells, whether in an in vitro or in vivo setting [3]. Furthermore, mRNA presents no possibility of genomic integration, a concern that is not purely hypothetical for DNA. mRNA does not pose any foreseeable risk of inadvertent transmission or chance insertion-induced mutagenesis [4]. This characteristic grant mRNA a fundamental safety edge when compared to DNA-derived therapeutics. Also, the expenses associated with the production of mRNA at a considerable magnitude are anticipated to be less compared to those required for the synthesis of DNA owing to the high yields of *in vitro* transcription reactions. [5]. Moreover, mRNA undergoes degradation via typical cellular mechanisms, and its in vivo stability can be modulated by employing diverse alterations and transportation techniques [6]. mRNA transcripts, in contrast to DNA- based pharmaceuticals, exhibit a notably heightened transfection efficacy and minimal toxicity owing to their independence from nuclear entry for functionality [7]. A previous study showcased the potential of mRNA-lipid nanoparticle (mRNA-LNP) technology in efficiently generating monoclonal antibodies (mAbs) directed towards the receptor binding domains (RBDs) of SARS-CoV-2 spike (S) proteins originating from various variants [8].

Synthesis and Development of mRNA Vaccines

Eukaryotic RNA experiences multiple post transcriptional modifications prior to its transportation from the nucleus to the cytosol for protein synthesis, with the initial modification being 5′ capping. The process of capping is essential for improving mRNA stability, processing, export, and translation, involving a three-step mechanism facilitated by RNA triphosphatase, guanylyltransferase, and methyltransferase. This process results in the production of a 7-methylguanosine (m7G) at the 5′ terminus of the mRNA, followed by a triphosphate linkage to the initial nucleotide (m7GpppN, Cap0) [9]. The N6, 2′-O-dimethyladenosine (m6Am) cap, cap 0, cap 1, and cap 2 are the four recognized cap structures. Cap 1 is created by methylating the 2′-hydroxyl group on cap 0, while cap 2, which is found on approximately 50% of transcripts, is created by 2′-O-methylation of the second nucleotide. Retinoic Acid Inducible Gene-I (RIG-I), a cytosolic innate immune receptor, can detect RNAs that are uncapped or have a cap 0, but it cannot recognize RNAs that have a modification on their cap 1 [10]. Capped RNAs are currently made using two different techniques:

- The first, and more costly, method involves utilizing vaccinia virus capping enzymes to create cap 0 or cap 1 RNAs [11].
- Using a cap analogue such as ARCA (anti-reverse cap analogue), which has a methoxy group (- OCH3) in place of the 3′ hydroxyl group (-OH closer to m7G), is the second way to accomplish RNA capping during transcription. The translation efficiency of ARCA-capped mRNAs in rabbit reticulocyte lysates was double that of mRNAs capped by a traditional cap analogue [12].

The poly (A) tail can be added post-transcriptionally by enzymatic polyadenylation, which produces poly (A) tails of varying lengths, or it can be integrated into the plasmid template or added via PCR. As opposed to using traditional homogeneous poly (A) tails, a segmented poly (A) strategy that adds shorter spacer lengths between poly (A) segments in the DNA template can increase translation efficiency and decrease plasmid recombination in E. coli [13]. It has been discovered that optimizing mRNAs with aGC-rich sequence and adding 5-methylcytidine (m5C) and pseudouridine (ί) reduces immunogenicity and boosts translation efficiency [14,15]. N1-methylpseudouridine (m1Ψ) has been utilized recently in SARS- CoV-2 mRNA vaccines due to its ability to produce abundant protein and induce a reduced immunogenic response. Neither during translation nor during the creation of an RNA duplex does m1Ψ generate miscoded peptides

[16]. In order to enhance translation efficiency during mRNA construction, the Kozak sequence (gcc) gccRccAUGG is typically positioned following the 5′-UTR sequence [17]. Sequences can be sourced from genes including globin, Hsp70, axon dynein heavy chain 2 (DNAH2), and hydroxysteroid dehydrogenase (3β-HSD) [18,15]. A 3′-UTR from the hemoglobin subunit α (HBA) and subunit β (HBB) genes [19], albumin (ALB), heat-shock protein 70 (Hsp70), tyrosine hydroxylase (TH), or collagen alpha 1 (COL1A1) gene [20, 21] may be changed to enhance mRNA stability.

Delivery Mechanisms of mRNA Vaccines

mRNA therapeutics are often much larger than other molecules that readily move into cells, and naked mRNA is also susceptible to destruction by nuclease. Given below are some of the mRNA delivery systems:

- Lipids
  Cationic lipids, such as DOTAP and DOTMA, can form complexes with negatively charged nucleic acids, promoting the formation of liposomes for efficient mRNA delivery [22]. However, these lipids can be immunogenic and toxic, leading to interferon-gamma secretion and liver damage [23]. To increase delivery efficiency, researchers are using ionizable lipids, which are neutral at physiological pH but become positively charged at low pH. These lipids can be further complexed with other lipid components to form ionizable LNPs, which are well-suited for efficient mRNA delivery. Some FDA-approved ionizable lipids have been applied to clinical applications, such as the BNT/Pfizer vaccine Comirnaty and the Moderna vaccine Spikevax [24].

- Polymers
  Cationic polymers can condense nucleic acids into polyplexes, improving the delivery of mRNA-based therapeutics. Studies have shown that polyethyleneimine (PEI) can induce immune responses in mice [25], while PEG-PAsp (DET) can repair neurological function in nasal neurons [26]. However, most synthesized polymers have high cytotoxicity issues, leading researchers to sign biodegradable polymers using natural biopolymers or surface modification techniques. Cationic polymeric nanoparticles have advantages like simplicity of synthesis, long-term storage stability, and ability to carry large nucleic acids. However, their high cytotoxicity and low transfection efficiency have limited their clinical application [27].

- Peptides
  Positively charged amino acids can improve mRNA delivery by electrostatic interactions with nucleic acids. Some cationic peptides can form stable nanoparticles, protecting mRNA from degradation. Protamine, an arginine-rich peptide, has been used in cancer and viral vaccines [28]. Cell-penetrating peptides (CPPs) with membrane-penetrating capabilities have been used for mRNA delivery [29]. However, tight binding with peptides can affect mRNA release and endosome escape ability, lowering target protein expression [30]. Therefore, designing peptides with balanced positive charges is crucial to improve therapeutic applicability of peptide-based mRNA delivery technologies.

mRNA Vaccines/Drugs Administration Routes

- Intramuscular: Recruit different types of immune cells and recycle them to the injection site.

- Intradermal: Deliver directly into the dermis and induce potent immune response.
- Intravenous
    1. Send directly to APCs and lymphoid organs.
    2. Rapid onset of action.
- Intranasal
    1. Induce potent immune responses.
    2. Quick absorption and ease of distribution.
- Subcutaneous
    1. Have a larger injection volume and reduce local adverse reactions.
    2. Easy to administer with minimal skills.

Applications

- mRNA vaccinations have already shown to be a secure and successful method of stopping the COVID-19 virus from spreading [31]. BNT/Pfizer (BNT162b2) was the first to get authorization for emergency use of an mRNA vaccine, and Moderna (mRNA-1273) was approved shortly after. In terms of preventing wild-type SARS-CoV-2 infection in completely immunized persons, each of these vaccinations was approximately 90% effective, and in partially immunized adults, it was approximately 80% effective.
- Furthermore, a growing number of mRNA-based medications are being developed for use in clinical therapy, and the methodology has even been used in the treatment of illnesses linked to immune cells. There are currently five FDA-approved RNAi drugs in clinical use, namely Patisiran (2019), Givosirna (2020), Lumasiran (2020), Lnclisirna (2021), and Vutrisirna (2022) [1].
- Since mRNA vaccines are very desirable for next-generation cancer therapies, they are being studied for cancer treatment. Tumor genomic mutation produces neoantigens, and erroneous RNA splicing and unexpected post-translational protein modification will translate unique antigen. By comparing these neoantigens with their whole-genome and mRNA sequencing, or with dysregulated protein from normal and tumor tissues, sophisticated techniques like next- generation sequencing (NGS) or mass spectrometry could be used to discriminate these neoantigens. Certain algorithms may find potential candidates for major histocompatibility complex (MHC) binding epitopes to identify neoantigen mRNA for use in cancer vaccines [32]. One RNA-lipoplex (RNA-LPX) can be used to successfully deliver mRNAs to DCs and macrophages in lymphoid tissues by merely modifying the net charge without altering the well- characterized composition [33].

  In a different investigation, graphene oxide (GO) and polyethyleneimine (PEI) were combined to create an injectable hydrogel. This hydrogel was injected with mRNA antigen and an adjuvant (R848, a TLR7/8 agonist modified by palmitic acid), and it continued to target skin dLN-DCs for at least 30 days following subcutaneous injection. Strong production of particular antibodies and antigen-specific CD8+ T cells was made possible by this prolonged exposure, and the vaccination was able to stop tumor progression with just one injection [34].
- Many mRNA-based cell therapies, such as autologous cell therapy CAR-T MCY-M11 (MaxCyte), TriMix-based immunotherapy (ECI-006), and Cartesian therapy, are currently undergoing clinical studies [35]. Clinical application of such mRNA-based therapeutics, such

as CAR-T cell therapy, in the prevention and treatment of numerous diseases is highly promising.

- Treatments for disorders brought on by deficits or mutations in certain proteins may involve protein replacement therapy. With the help of mRNA technology, proteins of interest can be expressed in vivo for longer periods of time, resolving issues with the delivery of protein therapeutics that may be big, unstable, or expensive to produce [36].

Conclusion

The expeditious progression and authorization of mRNA vaccines for COVID-19 underscore the transformative capacity of mRNA technology in the realm of healthcare. Evidencing heightened efficacy and safety in comparison to conventional vaccines, mRNA vaccines epitomize a pioneering strategy for disease prevention. Moreover, the adaptability of mRNA transcends the scope of vaccines, presenting potential uses in diverse therapeutic domains such as cancer immunotherapy and protein replacement therapy. The domain of mRNA research is swiftly evolving with numerous enterprises and academic establishments actively engaged in exploration. Envisioned advancements in artificial intelligence and high-throughput technologies are set to propel further creativity, opening pathways for personalized medicine and enhanced healthcare.

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. 8. CAR T Cell Therapy: A Versatile Living Drug

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Introduction

CAR T Cell Therapy i.e. Chimeric antigen receptor (CAR) T cell therapy. In this therapy

T cells can be functionally reprogrammed by chimeric antigen receptors (CARs), which are special receptors that are made to target a particular tumor antigen. This form of therapy may be referred to as immunotherapy, gene therapy, or cancer therapy. The immune system of humans is capable of effectively recognising both self and non-self substances, such as bacteria, viruses, and aberrant cancer cells. Tumor cells are distinguished from other types of cells by their increased immunogenicity and acquired antigenicity through the production of foreign antigens. On the other hand, cancer cells possess the ability to manipulate the immune system to their benefit, leading to insufficient immunity against tumors, as well as their survival and advancement.Considering the immune system in the body is naturally equipped to identify infections and malignant cells, immunotherapy is also known as biotherapy. Immunotherapy has been a significant area of treatment for diseases of a similar nature in recent years. Its defense system, though, might be different. While some immunotherapies target the cancer cells directly, others strengthen the immune system. Depending on the type of sickness, each treatment option has pros and cons. Up to the age of 25, patients with acute lymphoblastic leukemia (ALL) can be treated with tisagenlecleucel (Kymriah). Similarly, individuals with big B-cell lymphomas, such as non-Hodgkin lymphoma (NHL), and those whose malignancy is unresponsive to other treatments or recurs frequently are approved to use axicabtagene ciloleucel (Yescarta).

Different Generations of CARs Models [1]

First-generation CARs

A CD3 chain functions as a crucial transmitter of signals from endogenous TCRs in the first-generation CAR T model. This kind of medication went into phase I clinical trials for leukemia, lymphoma, and several other cancers, such as neuroblastoma and ovarian cancer, after showing promise in preclinical testing. Patients treated with α-CD20-CD3ζ CAR T cells for B-cell lymphoma and several patients with neuroblastoma treated with scFv-CD3ζ CAR T cells have shown sustained therapeutic effects, even though the antitumor action was insufficient due to the lack of activation.

Second-generation CARs

Second-generation CAR T cell treatment was made possible by the first-generation CARs' triumph in phase 1 clinical trials.In phase I clinical studies, this CAR T cell model produced complete remission rates of up to 90% in patients with recurrent B-cell ALL (B-ALL), suggesting a more potent anti-leukemic response. In this instance, the CD3 domain-attached m4-1BB or CD28 costimulatory domain was combined with the second-generation anti-CD19 T cells.However, there are still a lot of unanswered questions about its robustness, safety, and effectiveness.In response to these worries, second-generation CARs added intracellular signaling domains from various co-stimulatory molecules to the cytoplasmic tail of the CAR, thereby enhancing the signal. Examples of these molecules include CD28, 4-1BB or CD137, inducible T cell costimulator (ICOS) or CD278, OX40 or CD134.

Third-generation CARs

Third-generation CARs, such as CD3ζ-CD28-OX40 and CD3ζ-CD28-4-1BB, combine two signaling domains with the CD3ζ chain to increase antitumor efficacy. These combinations result in enhanced activation signals, longer proliferation, increased cytokine secretion, and effective function. In patients with chronic lymphocytic leukemia, for instance, a third-generation CAR composed of α-CD19-CD3ζ-CD28-4-1BB showed 100% remission rates by infiltrating and lysing cancer tissue. Furthermore, certain CAR T cells have memory functions that stop tumor recurrence.

Fourth-generation CARs

Prior generation CARs aided in mediating the T cell anticancer response and were predicated on a precise strategy. However, these have drawbacks, such as degradation linked to antigen-negative cancer cells and a lack of antitumor effect against solid tumors because of their significant phenotypic variability. A fresh CAR strategy was developed as a result of these flaws. Induced expression of transgenic immune modifiers, such as interleukin (IL)-12, which stimulates innate immune cells and increases T cell activation to decrease antigen-negative cancer cells in the indicated lesion, is how fourth-generation CARs were introduced to create the tumor backdrop.

History

- **Pioneering CAR-T Cells** : In the late 1980s and early 1990s, researchers Zelig Eshhar and Gideon Gross developed a revolutionary idea: T cells equipped with a special chimeric molecule, now known as CAR-T cells.
- **Early Clinical Trials**: Fast forward to 2011, Carl June, David Porter, and Stephan Grupp at the University of Pennsylvania and Children's Hospital of Philadelphia made history by initiating the first clinical trials of CAR-T cell therapy in humans.
  These trials targeted chronic lymphocytic leukemia (2011) and acute lymphoblastic leukemia (ALL) (2012).
- **Gaining Approval**: The success of these trials paved the way for regulatory approval. In 2017, the US FDA and in 2018, the European EMA greenlit the first two CAR-T cell therapies, including tisagenlecleucel (Kymriah) for treating young patients with leukemia.[2]
- **India Joins the Fight**: More recently, in October 2023, India's Central Drugs Standard Control

Organization (CDSCO) approved NexCAR19, the nation's first CAR-T cell therapy. Developed through a collaborative effort by ImmunoAct, IIT Bombay, and Tata Memorial Hospital, NexCAR19 has already been administered to 15 patients in India.[3]

Structure of Chimeric Antigen Receptor

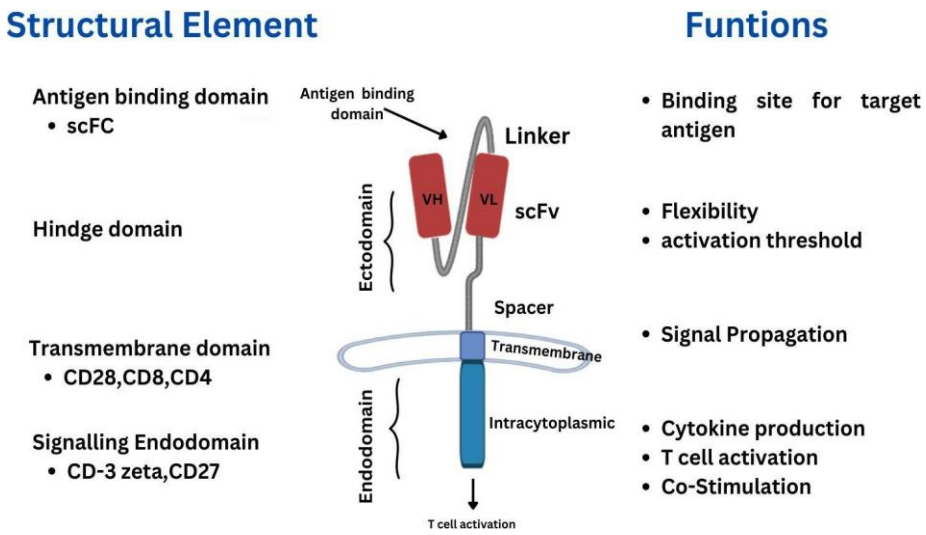


Figure 1: Structural element of Chimeric Antigen Receptor and their functions [4]
Source: https://doi.org/10.1016/j.adcanc.2022.100035

Signaling Cascade for Second-Generation Car T Cell

T cell therapy utilizes genetically engineered T cells equipped with chimeric antigen receptors (CARs) to target cancer cells. CARs are constructed by combining an antigen-binding fragment (scFv) derived from a monoclonal antibody with T cell signaling machinery. The scFv, formed by linking the variable regions of the antibody's heavy and light chains, recognizes specific antigens on tumor cells. Upon binding, the hinge region of the CAR transmits an activation signal through the transmembrane domain and into the T cell. Inside the cell, co-stimulatory domains like CD28 or 4-1BB trigger distinct signaling pathways.[4]

These pathways, involving molecules like TNF receptor-associated factors (TRAFs) and nuclear factor-κB (NF-κB) for 4-1BB, ultimately lead to T cell activation. The activated T cell then releases cytotoxic molecules like perforin and granzyme, inducing apoptosis (programmed cell death) in the targeted tumor cell. Interleukin-2 (IL-2) might also play a role in this process.[5]

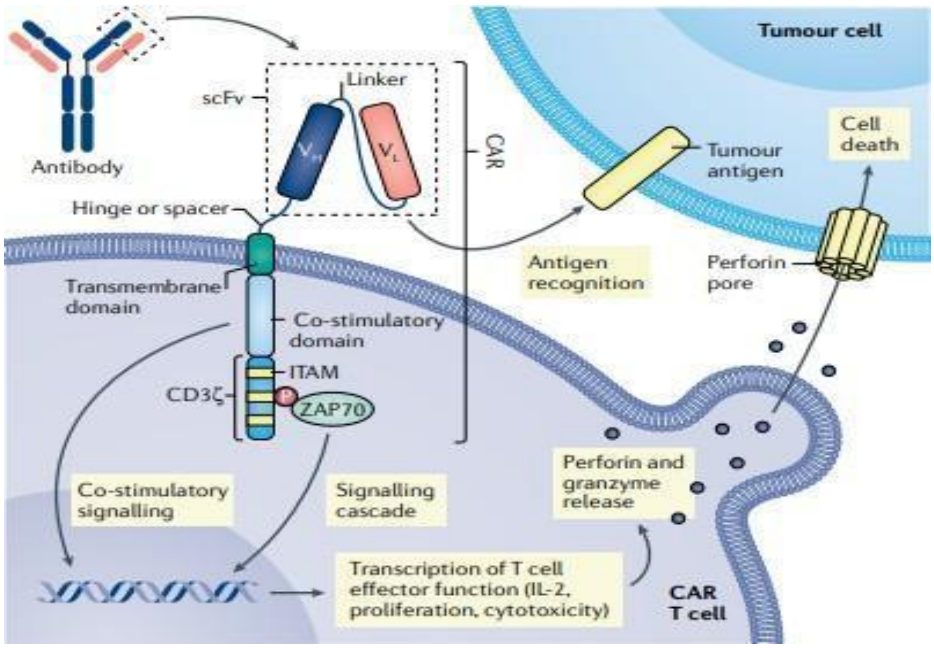
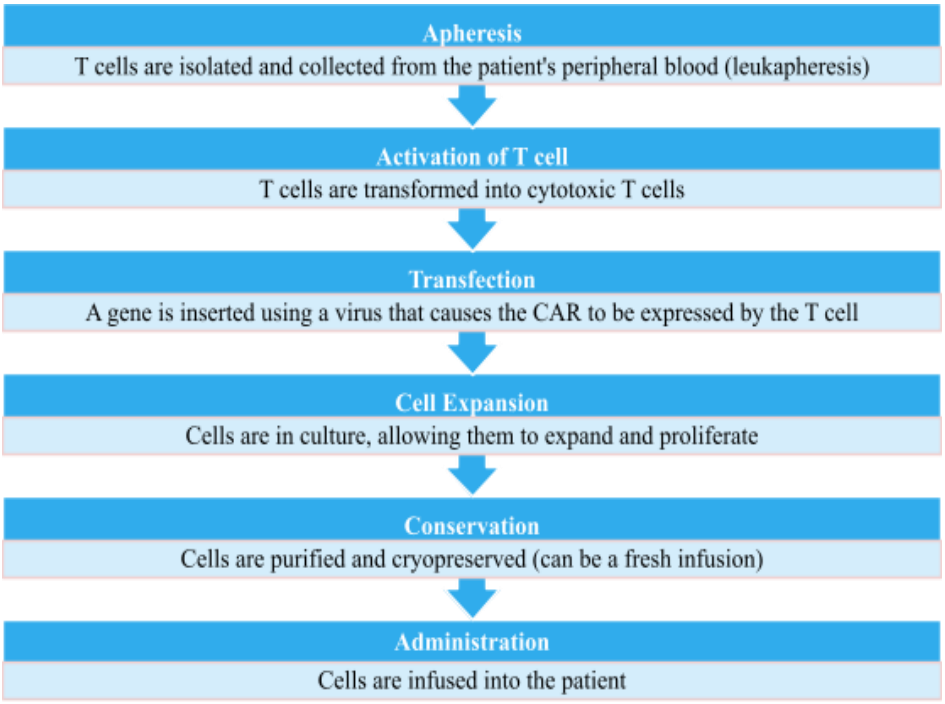


Figure 2: Schematic of a basic second-generation CAR T cell.[5]
Source: https://www.nature.com/articles/s41568-020-00323-z/figures/1

Procedure for the Production of Chimeric Antigen Receptor Cell Therapy



Advantages

CAR T cell therapy is considered a "drug of the present day" because the cells can survive in the host body for an extended period of time and have the constant ability to locate and destroy cancer cells during relapse. This is the therapy's most notable advantage over other cancer therapies. Additionally, the patient only needs to receive proper care and observation for two to three weeks.Patients who have not responded well to transplantation or who relapse after receiving a transplant are currently eligible to receive CAR T cell treatment. It is anticipated that CAR T cell therapy would replace several transplant kinds. Clinical trials on blood cancer have demonstrated that CAR T cell therapy is effective in eradicating the illness entirely, even in individuals with a refractory condition, meaning that the cancer returned after multiple transplants. Additionally, patients can benefit from a sanitary treatment like stem cell transplantation and enjoy their lives without the fear of relapsing thanks to CAR T cells. As a result, CAR T cell therapy may be described as a "living medication."

Conclusion

CAR T-cell therapy, a revolutionary innovation in bioengineering, offers exciting possibilities for cancer treatment. It's giving new hope to patients with advanced leukemia and lymphoma, even when traditional treatments haven't worked. As our understanding grows and technology advances, this approach holds promise for tackling solid tumors as well. Additionally there are 20 different ongoing CAR gene-engineered T-cell immunotherapy clinical trials.[6]

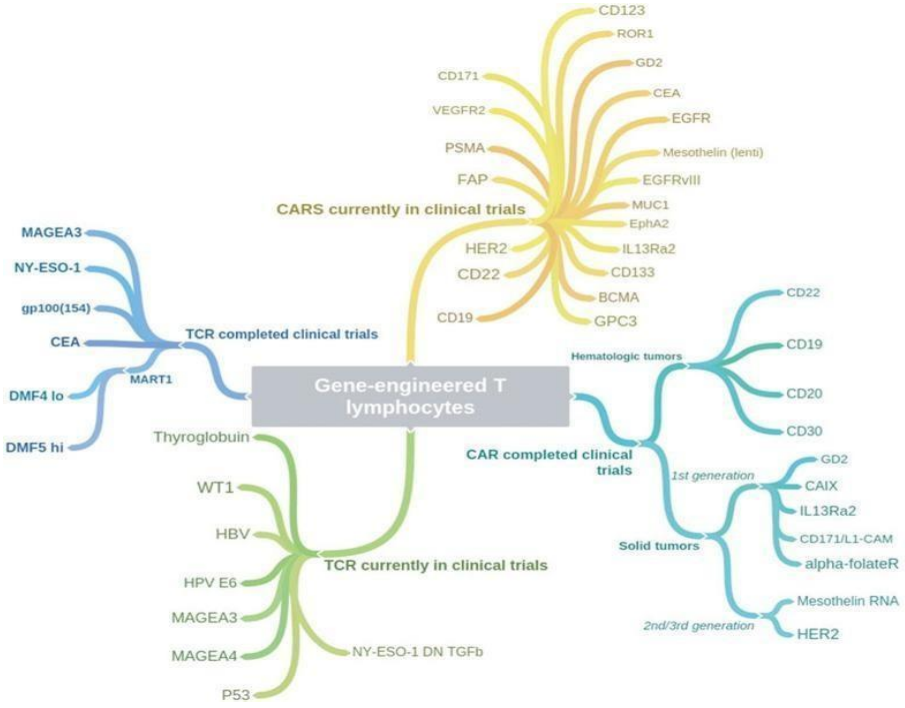


Figure 3: Coggle diagram of completed and ongoing TCR and CAR gene-engineered T-cell immunotherapy clinical trials

Source: https://pubmed.ncbi.nlm.nih.gov/28025979/#&gid=article-figures&pid=figure-4-uid-3

Challenges remain, such as overcoming treatment resistance and managing side effects. However, the ability to engineer CAR T cells in various ways and develop clever strategies paves the way for continuous improvement. This cutting-edge research is sure to push the boundaries and lead to incredible

breakthroughs in cancer treatment.

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9. Bio Nano Technologies & Covid-19 Pandemic

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Bio-nanotechnology is defined as the incorporation of biological molecules into nano artifacts. The science of bio-nanotechnology is all-pervasive and promises a sustainable alternative for restoring and recreating physiological functions with a "systems approach" comprising structural and functional forms. Bio-nanotechnology integrates insights from diverse fields including physical sciences, molecular engineering, biotechnology, nanotechnology, chemistry, and medicine, leveraging the evolutionary adaptations of living organisms to advance technological applications.

It derives inspiration from human physiology to evolve complex artificial systems, through the fusion of biological systems with nanotechnology. It applies the concept and techniques of molecular biology to engineering objectives by fabricating devices at the nanoscale, we gain the capacity to replicate biological

structures with meticulous precision at the molecular level.

Covid 19 Pandemic

In December 2019, the novel coronavirus, known as SARS-CoV-2, emerged in Wuhan, China, marking the beginning of the COVID-19 pandemic. This virus, belonging to the coronavirus family, quickly spread globally, leading to significant health and economic impacts worldwide. Unlike previous coronaviruses like SARS-CoV and MERS-CoV, SARS-CoV-2 exhibits higher transmissibility, posing a greater challenge in controlling its spread. The most common symptoms of COVID-19 include fever, dry cough, difficulty breathing, fatigue, and muscle pain, with varying degrees of severity from mild respiratory illness to acute respiratory syndrome.

Additionally, COVID-19 can affect multiple organs and systems in the body, leading to complications such as cardiovascular issues, neurological problems, kidney and liver damage, and gastrointestinal symptoms. One common cause of death is an uncontrolled immune response known as a cytokine storm, which can lead to organ failure or cardiovascular events.

In response to the pandemic, various strategies have been implemented, including social distancing, lockdowns, and improved disinfection protocols.

Nanotechnology has emerged as a promising avenue for combating COVID-19, offering innovative approaches for prevention, diagnosis, and treatment. Nanotechnology enables the development of novel antiviral treatments and vaccines, as well as improved diagnostic methods and delivery systems for therapeutics, contributing to the global effort to contain and manage the pandemic.[4]

Bionanotechnology in Covid 19 Pandemic

- **Nanotechnology based Vaccines**

Nanotechnology offers promising advancements in vaccine development, especially in the fight against COVID-19. Traditional vaccine types like live attenuated, inactivated, subunit, and gene-based vaccines are undergoing extensive testing globally. However, they face challenges such as safety concerns, weak immune responses, and the need for multiple doses. Nanovaccines, utilizing nanotechnology, aim to overcome these limitations.

One approach involves using nanocarriers like solid lipid nanoparticles (SLNs) or polymeric nanoparticles to deliver vaccine components, ensuring their stability and targeted delivery. For instance, SLNs functionalized with viral antigens have shown enhanced cellular uptake and immune responses against hepatitis B virus.[1] Similarly, poly(lactic-co-glycolic acid) (PLGA) nanoparticles can carry antigens and adjuvants, mimicking whole-cell vaccines without the risk of active infection.

Additionally, virus-like particles (VLPs), ranging from 20-100 nm, self-assemble and mimic viral structures, inducing robust immune responses without causing infection. Several VLP-based vaccines against hepatitis B and human papillomavirus are commercially available. Similarly, genetically engineered VLPs targeting SARS-CoV-2 are under development and in clinical trials.

Another innovative approach involves nucleic acid-based nanovaccines, utilizing genetic fragments to encode viral antigens. These vaccines offer scalability, safety, and prolonged expression of antigens, eliciting both antibody and cellular immune responses.[3] However, challenges in cellular uptake efficiency and stability have been addressed using nanocarriers like gold nanorods or lipid nanoparticles. For instance, lipid-nanoparticle-encapsulated mRNA vaccines have shown promising results in inducing immune responses against SARS-CoV-2 in preclinical studies.[1]

Several companies and research institutions worldwide are developing nanotechnology-based COVID-19 vaccines, with some already in clinical trials. These include DNA vaccines delivered using nanovehicles to enhance immunogenicity and mRNA vaccines formulated with lipid nanoparticles for stability and efficacy.[3] Overall, nanotechnology holds immense potential in revolutionizing vaccine development, offering safer and more effective solutions to combat infectious diseases like COVID-19.

- **Nano Coating based PPE**

The search for effective treatments and vaccines against COVID-19 has led scientists to explore alternative approaches to contain the pandemic. One crucial strategy is reducing the risk of virus transmission through physical barriers, such as personal protective equipment (PPE) like gloves, face masks, face shields, and gowns. However, the global shortage of PPE has forced many to reuse their equipment, posing significant safety risks. Nanotechnology presents a solution by enhancing the performance of PPE, making them reusable and washable without compromising safety.

Researchers at the University of Central Florida (UCF) have developed washable and reusable nano-coatings for PPE. These coatings, made of alternating layers of cationic and anionic nanoparticles, effectively trap and destroy viruses, including SARS-CoV-2. Additionally, zinc-oxide nanoparticles have been used to create face masks with strong antimicrobial properties, expected to be available by the end of 2020. This technology aims to revolutionize PPE production by offering washable, reusable, and antimicrobial options.

Face masks play a crucial role in controlling the spread of COVID-19, prompting nanotechnologists to focus on enhancing their performance. Rainy et al. have developed highly-breathable masks using cellulose nanofibers, ensuring comfort even during long hours of use and suitable for individuals with respiratory issues or in hot and humid conditions. Furthermore, various companies are leveraging nanotechnology to design innovative face masks.[1]

- **Antiviral Nanomaterial for Inanimate Surface Coatings**

SARS-CoV-2, unlike many other viruses, can persist on surfaces like plastic, fabrics, wood, glass, and metal for extended periods, contributing to its spread. Nanotechnology offers innovative solutions to develop anti-coronavirus coatings, drawing from experience combating other contagious diseases and introducing novel approaches to antiviral design.

Various nanomaterials have been proposed for incorporation into anti-COVID-19 coatings, including silver nanoparticles, cuprous oxide nanoparticles, gold nanoparticles on silica nanoparticles, zinc oxide nanoparticles, and quaternary ammonium cations (QUATs). Researchers have synthesized SARS-CoV-2-coated cuprous oxide particles bound onto polyurethane, maintaining antiviral activity even after prolonged exposure to water or the virus.

Conventional disinfection methods like bleach and alcohol have limitations, such as impractical real-time sanitization and the risk of recontamination. Nanomaterial-based coatings offer smart solutions to these challenges. For instance, researchers at the Hong Kong University of Science and Technology (HKUST) developed a smart antimicrobial coating based on heat-sensitive polymers and slow-release disinfectants, effectively inactivating viruses and preventing their adhesion to surfaces for up to 90 days.[1]

Another approach involves polymer-based coatings containing copper and other metal nanoparticles, ensuring controlled and sustained release of antiviral agents over time. Photoactive antimicrobial nanomaterials utilize light of specific wavelengths to kill germs through photodynamic killing, photothermal lysis disinfection, and photocatalysis. Canadian scientists created a self-sterilizing nano-

coating, NanocleanSQ, capable of killing 99.99% of viruses upon contact and remaining effective for weeks or even years, particularly when exposed to light.
Furthermore, modifying frequently touched surfaces like bed rails, bed surfaces, supply carts, and doorknobs with highly-repellent nanomaterials can help deter germs and viruses. These advancements in nanotechnology hold promise for developing long-lasting, effective, and sustainable solutions to mitigate the transmission of SARS-CoV-2 and other pathogens on various surfaces.

- **Bionanotechnology in Diagnosis of Covid 19**

Viruses have posed significant health threats throughout history, but advancements in understanding their biological structure have enabled more accurate diagnosis. With the emergence of COVID-19, scientists have been striving to develop reliable, sensitive, and scalable diagnostic tests. While the standard method, reverse transcription-polymerase chain reaction (RT-PCR), is widely used, its limitations in sensitivity have prompted exploration into nanobiosensors for rapid and real-time detection of SARS-CoV-2.
Optical biosensors, utilizing biorecognition elements coupled with optical transducers, offer advantages such as small size, high specificity, sensitivity, and cost-effectiveness. Plasmonics-based optical sensors, particularly localized surface plasmon resonance (LSPR), have demonstrated efficacy in detecting specific viral strains. Optical sensors enable high-resolution imaging of viruses, facilitating rapid diagnosis. Recent developments include optical sensors for imaging viruses based on laser diode excitation, achieving imaging resolutions of less than 50 nm. Additionally, gold nanoparticle-based sensors with laboratory-designed DNA receptors have been designed for detecting SARS-CoV-2 RNA strands.
Dual-functional plasmonic photothermal biosensors functionalize gold nanoparticles with complementary DNA receptors, enabling specific hybridization with virus RNA strands. These biosensors measure local refractive index changes upon virus binding to the sensor surface, aiding clinical COVID-19 diagnosis. Point-of-care (POC) biosensors are crucial for community-based COVID-19 diagnostics. Chip-based and paper-based biosensors offer rapid detection using nucleic acids and antibodies, providing early and late-stage infection screening. Colorimetric biosensors, coupled with loop-mediated isothermal amplification (LAMP), offer low-cost, highly efficient virus detection suitable for lab-on-a-chip (LOC) devices. Miniaturized nanobiosensors integrated into smartphones enhance their utility for virus detection. Fluorescence-based digital nanosensors and cellulose-based biosensors coated with silver and fullerene nanoparticles enable rapid and cost-effective detection of viruses like Ebola and Mycobacterium tuberculosis. [5]

Field-effect-transistors (FETs), three-electrode potentiometric sensors, and amperometric systems offer low-cost, miniaturized platforms for COVID-19 detection. FET biosensors constructed from antibody-modified graphene sheets detect SARS-CoV-2 proteins in clinical samples. Electrochemical biosensing approaches, utilizing surface-modified gold nanoparticles, provide label-free detection of viral RNA or cDNA, offering smartphone-based readouts for point-of-care healthcare.

Microfluidics, particularly lab-on-a-chip (LOC) technology, holds promise for rapid and accurate diagnostic tests. Nanochip systems, like the Nanochip 400, enable multiplexed detection of various viruses using PCR chemistry and electronic microarrays. Another example is the micro/nanofluidic chip (MNC), offering rapid screening for influenza viruses. Novel LOC designs, such as those utilizing magnetic nano-beads, facilitate the isolation and detection of SARS-CoV-2 and other viruses.
Nanopore sequencing addresses the challenge of viral genetic diversity by enabling real-time reading of long DNA or RNA segments. For SARS-CoV-2 detection, LamPORE integrates nanopore sequencing with

loop-mediated isothermal amplification, providing scalability and high sensitivity.
Other nanotechnology-based strategies include colorimetric tests utilizing plasmonic gold nanoparticles for rapid virus detection. Colloidal gold-NP-based lateral-flow tests detect anti-nucleoprotein IgM antibodies with high specificity and rapid response. Porous nanomaterials, like metal-organic frameworks (MOFs), offer sensitive pathogen recognition, while CRISPR-based platforms, such as SHERLOCK and DETECTR, enable rapid and specific detection of SARS-CoV-2 sequences with high sensitivity.[1]

These nanobiosensor technologies hold promise for widespread, rapid, and sensitive detection of SARS-CoV-2, aiding in effective management and control of the COVID-19 pandemic.

Conclusion

Nanotechnology has become a crucial tool in the fight against the COVID-19 pandemic, drawing on lessons learned from previous outbreaks such as SARS and MERS. One significant contribution is in vaccine development, where nanotechnology has accelerated the creation of stable, scalable, and self-administered vaccine formulations. These nanoplatforms enable the design of single-dose vaccines, easing distribution efforts and reducing strain on healthcare systems. Additionally, nanomaterials have revolutionized personal protective equipment (PPE) by enhancing its efficacy even after multiple uses and washes. This addresses the global shortage of PPE while minimizing environmental impact. Furthermore, antiviral and antibacterial nano-coatings on surfaces help maintain sterile environments, particularly in high-risk settings for viral transmission.

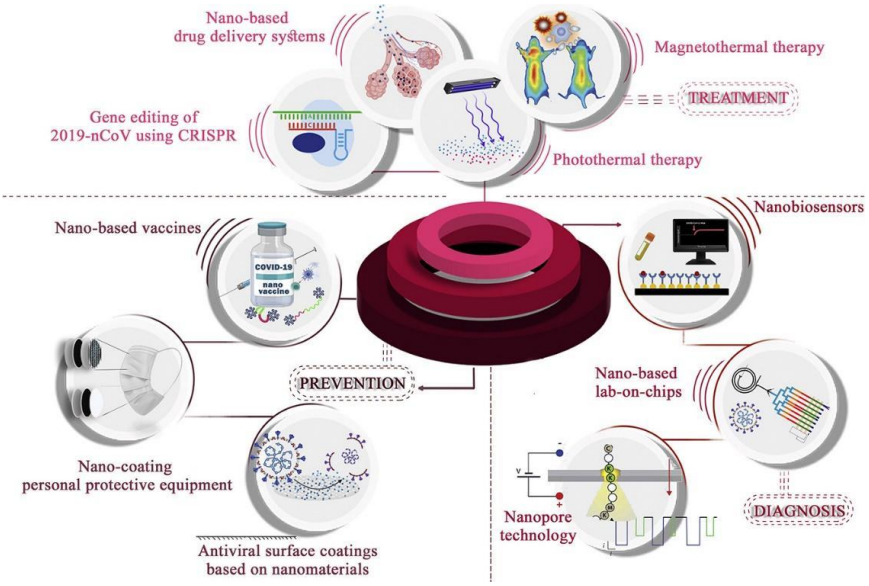

Figure 1. Nanotechnology against covid-19
Source: https://www.sciencedirect.com/science/article/pii/S0168365921003345

In diagnostics, nanobiosensors, lab-on-a-chip nanosystems, and nanopore technology have facilitated the development of highly accurate, real-time, and cost-effective COVID-19 tests. These advancements enable early detection and containment of the virus, crucial for effective pandemic management. Moreover, nanoparticles are being incorporated into therapeutic applications such as magnetothermal therapy, photothermal therapy, drug delivery systems, and gene-editing platforms like CRISPR/Cas9. These therapies offer promising avenues for treating COVID-19 infections with minimal side effects, showing

early potential in clinical settings.
Overall, ongoing research leveraging nanotechnology not only aims to halt the current pandemic but also seeks to enhance preparedness for future viral outbreaks. By continuously improving our understanding and application of nanotechnology, we can better mitigate the impact of emerging infectious diseases and prevent future pandemics.

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10. Metabolic changes in aging humans

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Metabolism is the intricate network of chemical processes within an organism that sustains its living state. These processes involve both the breakdown and synthesis of energy, crucial for maintaining life functions in animals. Basal Metabolic Rate (BMR) quantifies the energy necessary to support the body's basic functions while at rest.

The Harris-Benedict equation utilizes factors such as height, weight, age, and sex to determine Basal Metabolic Rate (BMR). This calculation serves as a key indicator of an individual's health status and provides guidance on weight management, calorie intake, and expenditure. For both women and men, BMR is determined separately using the following equation –

BMR (women) = 655.1 + (9.6 × weight in kg) + (1.8 × height in cm) - (4.7 × age in years)

BMR (men) = 66 + (13.7 × weight in kg) + (5 × height in cm) - (6.7 × age in years) [1]

Aging and metabolism are intricately connected, with age-related alterations in body composition, such as heightened central adiposity and sarcopenia, stemming from underlying aging mechanisms. Sedentary lifestyles intensify these changes, but maintaining physical activity can partially mitigate them. This study digs into the specific metabolic tissue alterations (meaning the progressive loss of physiological integrity of tissue which often leads to compromised functioning of the tissue, often leading to death) is observed in aging individuals, including adipose tissue, muscle, and liver, as well as broader metabolic shifts in older adults, which is the primary risk factor for cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases.

Mammalian research has provided a comprehensive understanding of age-related pathological changes. Certain interventions that prolong lifespan have been found to enhance health span, as long-lived mutants often display resilience against age-related chronic illnesses. Furthermore, the global population is aging rapidly, with significant economic and societal consequences. Despite the continuous increase in life expectancy, health span is not progressing at the same rate due to current disease treatments primarily focusing on reducing mortality rather than addressing overall health decline. Consequently, older individuals are enduring prolonged periods of illness, often managing multiple chronic conditions simultaneously. [2]

Aging is marked by an increase in fat accumulation, particularly visceral fat, which correlates with heightened cardiometabolic risk. Additionally, hormonal shifts occur with age, including a decline in dehydroepiandrosterone sulfate (DHEA-S) levels in both men and women, plummeting to approximately 20% of peak values by the seventh decade of life. Low DHEA-S and/or dehydroepiandrosterone (DHEA) levels are associated with increased adiposity. Furthermore, testosterone levels decrease in aging men, with total serum testosterone inversely linked to body fat levels, and bioavailable testosterone inversely correlated with visceral fat mass. Given these established connections between aging, alterations in DHEA and testosterone, and adiposity, it is plausible to theorize that hormone replacement therapy in elderly individuals could potentially yield favorable outcomes in terms of body fat distribution and metabolic health. [2]

The balance between fatty acid storage and release dictates total body and regional fat composition. Dietary fat serves as the primary source of fatty acids for storage in adipose tissue for most individuals, and various methods have been devised to quantify this process accurately. Similarly, adipose tissue lipolysis liberates free fatty acids (FFAs) into the bloodstream to fuel lean tissue, with release rates correlated with resting energy requirements in post-absorptive adults. [3]

However, there remains limited information regarding the mechanisms underlying the effects of dehydroepiandrosterone (DHEA) and testosterone on adipose tissue in humans. Recent research indicates that testosterone administration for five days led to a decrease in meal fat storage specifically in visceral adipose tissue, while having no significant effect on subcutaneous abdominal fat. Additionally, the same study found that a two-month course of testosterone treatment resulted in reduced meal fat storage in abdominal adipose tissue, with no significant impact on femoral subcutaneous fat, compared to a placebo.

These findings shed light on the potential influence of testosterone on fat distribution, particularly within the abdominal region, suggesting a complex interplay between hormones and adipose tissue metabolism. Further research is needed to elucidate the precise mechanisms involved and explore the implications for metabolic health and disease management in humans. [4]

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11. Unlocking Hope: The Promise of Vaccines in Cancer Treatment

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Introduction

Because of its intricacy and adaptability, cancer has long been one of medicine's most difficult enemies, posing a challenge to both researchers and physicians. But new developments in immunotherapy have sparked renewed optimism in the fight against cancer. Among these developments, cancer vaccines are particularly noteworthy as a potentially effective method of using the body's immune system to target and eliminate cancer cells. This article delves into the rapidly changing field of cancer vaccines, examining their current state, potential applications, and processes.

Cancer vaccines are made to precisely boost the immune response against cancer cells, in contrast to regular vaccines that prevent infectious diseases by preparing the immune system against infections. They function by teaching the immune system to identify and target proteins or antigens specific to cancer cells, all the while preserving healthy, normal cells.

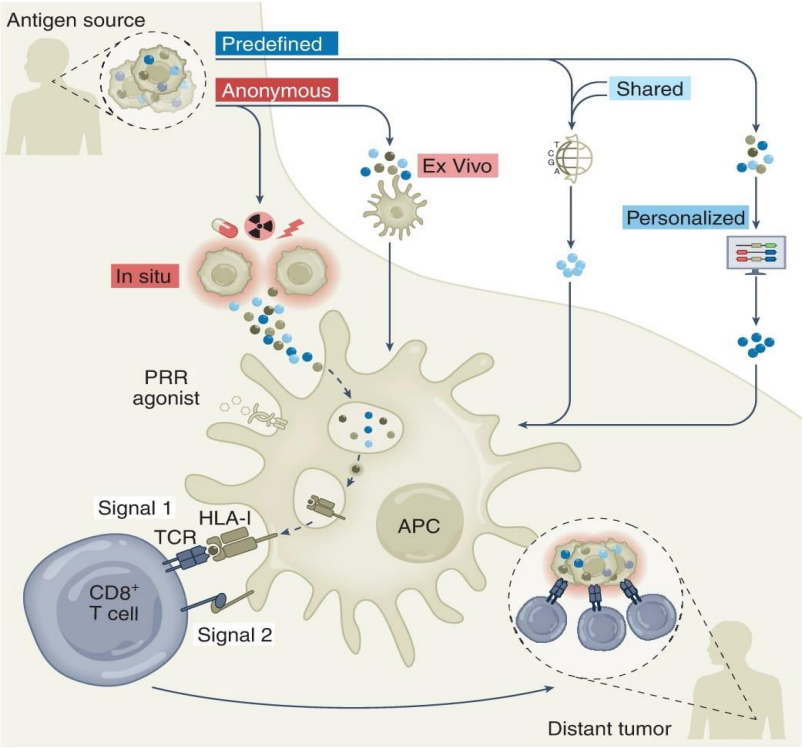

Fig 1. Cancer Vaccine type.
Source: https://www.nature.com/articles/s43018-022-00418-6/figures/1

Preventive Cancer Vaccines

Many malignancies are brought on by viral infections, and vaccinations that lower the risk are crucial in lowering that risk. For example, hepatitis B virus, or HBV, can cause liver cancer, whereas human papillomavirus, or HPV, can cause cervical and head and neck cancer. Numerous vaccinations have been created to guard against the development of malignancies linked to HPV and HBV and to prevent HBV and HPV infection. **(7)** The US Food and Drug Administration (FDA) has licensed four of these cancer vaccinations that can be used as preventative measures.

Mechanism

1. Vaccination: The targeted antigen, which may be a virus or a tumour-associated antigen, is injected into the body by the vaccine.
2. Antigen presentation: The antigen is taken up and broken down into smaller pieces by antigen-presenting cells (APCs), such as dendritic cells and macrophages. (5)
3. T cell activation: The antigen fragments complexed with MHC molecules are then presented by the APCs on their surface. T cells, cytotoxic T lymphocytes in particular, are able to identify these complexes (CTLs).
4. Immune response: The CTLs multiply and become activated upon recognition, creating a vast army of immune cells that are particular to the target antigen. (5)
5. Immune memory: A small percentage of activated T cells develop into memory T cells, which stay in

the body for a considerable amount of time and offer long-term protection against the targeted antigen.

6. Cancer prevention: The immune system can quickly mobilise memory T cells and freshly activated CTLs to eradicate the virus if the (person) comes into contact with it or develops precancerous cells expressing the targeted antigen. This will stop the development of cancer.

Therapeutic Cancer Vaccines

Immunotherapy in the form of therapeutic cancer vaccines teaches the body's immune system to identify and combat cancer cells. Therapeutic cancer vaccines are administered to patients who already have cancer, as opposed to preventive cancer vaccinations, which are given to healthy individuals in an effort to prevent cancer.

Therapeutic cancer vaccines come in two primary varieties:

1. Vaccines developed from tumours: These shots are created using tumour cells that have been extracted from the patient's body. The compounds that the immune system detects as foreign are called antigens, and they are separated from the tumour cells in a laboratory setting. After that, the patient receives another injection of the antigens, which are subsequently absorbed by immune cells. Upon learning to identify the antigens, the immune cells proceed to target any cancer cells within the body that express them.
2. Vaccines derived from dendritic cells: Dendritic cells are an immune cell subtype that aids in the activation of other immune cells. After being extracted from the patient's blood, dendritic cells are subjected to tumour antigens in a lab setting. After that, the patient receives another injection of dendritic cells, which can now stimulate additional immune cells to combat the cancer cells.

Mechanism

1. Antigen Delivery: Tumour antigens, or chemicals unique to cancer cells, are injected into the body by vaccination. Among these antigens are:

- peptides or proteins derived from tumour cells.
- DNA or RNA-based genetic material that codes for tumour antigens.
- whole tumour cells that have been destroyed or rendered weak.

2. Presentation of Antigens: Tumour antigens are taken up by antigen-presenting cells (APCs), such as dendritic cells. After processing, they display the antigens on MHC (major histocompatibility complex) molecules on their surface.

3. T Cell Activation: The MHC-antigen complex on the surface of the APC is recognized by T cells, a subset of white blood cells engaged in the immunological response. The T cells become activated as a result.

4. Tumour Cell Attack: The activated T cells then multiply and migrate throughout the body. They recognize and attack cancer cells that express the same antigen.

5)Memory T cells: They are developed from activated T cells in the immune system. These cells stay in the body and have the ability to react fast when the cancer cells reappear.

Personalised vaccine

One form of immunotherapy called personalised cancer vaccines aims to teach a patient's immune system to identify and target their particular cancer cells. Personalised cancer vaccines target neoantigens, which are mutations specific to a patient's tumour, as opposed to standard immunizations that target common antigens

shared by many people.

Mechanism

1)Tumour sample collection: During a biopsy or surgery, a little sample of the patient's tumour is taken.

2)Neoantigen identification: To determine which particular neoantigens are present in the cancer cells, a laboratory analysis of the tumour sample is conducted. Next-generation sequencing is one approach that can be used for this.

3)Development of vaccines: Following their identification, neoantigens are employed in the creation of a customised vaccination. **(6)** There are various platforms available for this, including:

- Vaccines against dendritic cells (DC): T cell activation is aided by DCs, which are immunological cells. This method involves taking the patient's own DCs, loading them in the lab with neoantigens, and then injecting the DCs back into the patient to trigger an immune response.Vaccines utilising modified viruses to transfer neoantigens into the patient's cells are known as viral vector vaccines. The neoantigens are produced by the cells under the direction of the viral vector once they are within the cells and are subsequently exposed to the immune system.
- Vaccines containing DNA or mRNA: These vaccines provide the patient's cells with the genetic instructions needed to produce the neoantigens. Neoantigens are subsequently produced by the cells and reintroduced to the immune system.

4)Vaccination: The patient is subsequently given the customized vaccination.

5)Activation of the immunological response: The introduction of the vaccination triggers the immune system's defence against the neoantigens. **(4)** This comprises:

- T cell activation:-When antigen-presenting cells (APCs) offer neoantigens, the T cells in the immune system identify them and become activated.
- T cell proliferation:- Activated T cells proliferate and undergo differentiation into T helper cells and cytotoxic T lymphocytes (CTLs).
- Killing tumour cells:- The CTLs have the ability to identify and eliminate cancer cells that display the neoantigens.
- Immune memory:- In order to help stop the cancer from coming back, the immune system also produces memory T cells.

Current Status and Challenges

While the concept of cancer vaccines holds

great promise, their clinical success has been variable, with few vaccines receiving regulatory approval. Challenges such as tumour heterogeneity, immune evasion mechanisms employed by cancer cells, and immunosuppressive tumour microenvironments have hindered the effectiveness of cancer vaccines in some cases. Additionally, optimising vaccine design, identifying ideal patient populations, and determining the most effective combination strategies with other treatments like checkpoint inhibitors are ongoing areas of research.

Conclusion

A promising strategy for utilising the immune system to combat cancer is the use of cancer vaccines. Even though the creation of vaccines has advanced significantly, further study and clinical testing are required to reach the full potential of these efforts. Cancer vaccines may someday become a mainstay of individualised cancer treatment, providing patients fighting this aggressive illness with hope for better prognoses and a higher quality of life with sustained investment and interdisciplinary teamwork.

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12. Efficacy Of DNA Polymerase in The Treatment of Cancer

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DNA polymerase: An enzyme with multiple roles

DNA polymerases are enzymes with play a pivotal role in DNA replication. The process of replication involves the duplication of genetic information stored in DNA. They are mainly responsible for the replication of DNA before cell division which in turn helps to maintain the integrity of genetic information. This process involves the action of multiple enzymes to carry out the process efficiently. Before the process of replication, an enzyme called helicase is responsible for unwinding the double-stranded (ds) DNA molecule which leads to the formation of a single strand where each strand can act as a template (1, 2, 3). This in turn is followed by the action of DNA primase which works by placing primer on the template DNA strand which favors the attachment of DNA polymerase which works by adding nucleotide to the 3' end of the newly forming strand leading to elongation in 5'-3' direction (4, 5).

DNA polymerases have mechanisms for proofreading the newly synthesized DNA molecule in case the replication process is subjected to any kind of error. These enzymes are capable of proofreading in the direction of 5'-3' direction. If in case any error is found the misplaced nucleotide is cleaved off. This activity is referred to as 5'-3' exonuclease activity. Exonucleolytic correction leads to a slowdown of the process of DNA replication in the presence of lesions in the DNA template but they make the process of replication more accurate thus reducing the probability of mutagenesis and carcinogenesis (2). They can also function as sensors in the cell cycle checkpoint where they work by delaying the cell division till the time the DNA damage is repaired (5, 6).

Translesion DNA polymerase follows a quite precise mechanism in which they rescue the stalled DNA polymerases at the site of damage followed by replacing the replicative polymerase which in turn is followed by installing nucleotide across the site of damage. So, TLS provides additional time for the cell to repair the damage before the continuation of replication (3).

Types Of DNA Polymerases

Out of 15 DNA polymerases 5 DNA polymerases are involved in chromosomal synthesis. Polymerase δ and polymerase ε are the two DNA polymerases that are mainly responsible for chromosomal DNA synthesis (1). Moreover, these polymerases also play an important role in various DNA repair pathways such as base excision repair (BER), nucleotide excision repair (NER), and mismatch repair. (1)

Table 1. Types of DNA polymerase and their functions

TYPE OF DNA POLYMERASE	FAMILY	FUNCTION
α (alpha)	B	DNA replication, DSB repair: HR S-phase checkpoint
β (beta)	X	BER
γ (gamma)	A	mitochondrial replication and repair
δ (delta)	B	replication, repair: MMR, BER, NER, DSBs
ε (epsilon)	B	replication, repair: BER, NER DSBs HR, S-phase checkpoint
ζ (zeta)	B	TLS, ICL repair somatic hypermutation
η (eta)	Y	TLS, somatic hypermutation, HR
θ (theta)	A	somatic hypermutation, BER, TLS
I (iota)	Y	TLS, BER ,Specialized MMR
κ (kappa)	Y	TLS, NER
λ (lambda)	X	DSB repair, BER
μ (mu)	X	DSB repair, recombination
ν (nu)	A	ICL repair
Rev1	Y	TLS
TdT	**X**	**Recombination**

Source: Pavlov, Y. I. *et al.*, International review of cytology, 255, 41–132.

How is DNA polymerase activity targeted to prevent carcinogenic cells?

DNA polymerase activity is a major target of therapeutic agents to prevent hyperproliferative diseases like cancer. The targeting DNA polymerase works in two major ways. It can occur by either directly inhibiting the DNA polymerase activity which in turn inhibits the DNA replication, such therapeutics mainly include purine and pyrimidine nucleoside analogs. The second way to target DNA polymerase is by the use of DNA damaging agents which work by modifying the composition and structure of nucleic acid substrate which in turn inhibits

DNA synthesis indirectly (1, 6).

Therapeutics targeting of DNA polymerase activity

1. Purine and pyrimidine analogs

This works by terminating the DNA synthesis. In this method, a polymerase is provided with a nucleotide analog which comprises simple alterations to the deoxyribose moiety. The 3' OH moiety which is required for elongation of DNA is substituted with non-reactive functional groups like hydrogen halogens and azides. Also, there are analogs in which the entire deoxyribose moiety is replaced with arabinose sugar that has halogen at 2' or 3'. The nucleobase component is left unaltered which permits the polymerase to form base pairs with a templating base. This leads to the successful incorporation of the suicide analog successfully into the DNA. As the analog is devoid of 3'OH forming a substrate that cannot be elongated by the polymerases. -This in turn leads to the induction of apoptosis by termination of DNA synthesis. These suicide analogs are also referred to as anti-metabolites and are representative of the largest class of antineoplastic agents used clinically.

a. Purine Nucleoside analogs *fludarabine (9-β-D-arabinoside-2-fluoroadenine), cladribine [2-chlorodeoxyadenosine (2-CdA)], clofarabine [2-chloro-9-(2'deoxy-2'-fluoroarabinofuranosyl) adenine]*

This works by the competitive inhibition using F-ara ATP. Once this substrate is incorporated opposite to thymine the DNA polymerases do not cause elongation beyond the modified nucleotide and this ultimately leads to chain termination. (1)

b. **Pyrimidine nucleoside analogs** *gemcitabine [2', 2'-difluorodeoxycytidine (dFdc)*

The triphosphate form dFdCTP functions as a substrate for DNA polymerases involved in wide array of functions like chromosomal replication, Trans lesion DNA synthesis, and DNA repair. This analog competes with dCTP for binding opposite to guanine. Due to the incorporation of dFdc, the Pyrimidine is modified which can be elongated by only one additional nucleotide before the DNA synthesis is terminated. This method of DNA synthesis termination is called masked chain termination. It is called so because the addition of a nucleotide masks the analog from various enzymes which could excise it thus causing reversal of its effect on DNA synthesis. (1)

2. The DNA-damaging agent

Cisplatin, oxaliplatin, etc. are metal complexes that act by distorting DNA structure and indirectly inhibit DNA synthesis. The metal-containing compounds are electrophilic in nature, and they readily react with nucleophilic DNA moiety and disturb the hydrogen bonding potential of DNA by modifying its composition and structure. The formed lesion acts as a physical barrier to the movement of DNA polymerase, resulting in the inhibition of DNA synthesis. Also, the difference created in hydrogen bonding increases the chances of miscorporation events. The resulting mispair acts as a substrate for the action of enzymes involved in DNA repair, that can either correct damaged DNA or cause apoptosis (8).

Combination Therapy Strategy

A new innovative approach was elucidated that includes the combination of drugs (one from purine/ pyrimidine analog and the other, being DNA damaging agent). Various trials were conducted to study the efficacy of different drug combinations, out of which one successful approach was to combine gemcitabine (pyrimidine analog) with cisplatin (DNA damaging agent) (1). Cisplatin is the most potent chemotherapeutic drug, widely used in the treatment of patients with solid tumors. Besides its excellent efficacy in inducing apoptosis, it is cytotoxic in nature. Also, many cases have been reported in which patients develop resistance to cisplatin in short intervals of the treatment plan, affecting the prognosis of the disease (7).

Therefore, cisplatin is generally used in combination with gemcitabine (pyrimidine nucleotide analog). This combination has been proven to be highly effective in the treatment of gall bladder, ovarian, and pancreatic cancer. This combination provides a therapeutic option in the treatment of patients having a dismal prognosis. Gemcitabine and cis Latin shows synergistic effects. Toxicity due to cisplatin was easily manageable, and no treatment-related deaths occurred (9). Certain other combinations such as Fludarabine along with chlorambucil are not as effective as the action of individual monotherapies of these drugs. This combination also resulted in hematological toxicity deteriorating the condition of the patient (1).

Conclusion

Limiting the activity of DNA polymerase can be used as a method to limit the growth of carcinogenic cells. This may either be achieved by limiting the DNA polymerase activity itself, or by damaging the template DNA and preventing DNA synthesis. A combination of both, in a targeted manner, would be the ideal way to achieve maximum efficacy.

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13. The Cancer Vaccine Race: Revolutionising Treatment and Prevention

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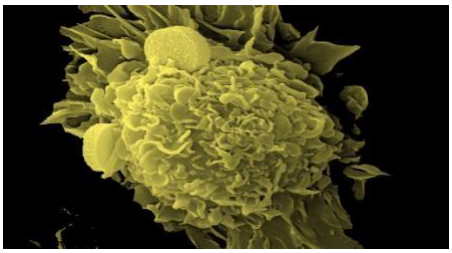

Figure 1. Developing novel vaccine delivery systems for cancer therapy
Source: https://www.flickr.com/photos/nihgov/28432767823

The world of medicine has always been a battlefield, with researchers and scientists who constantly screeching to find new ways to treat and prevent diseases. One of the most formidable adversaries in this ongoing war was Cancer, a disease that affects millions of lives worldwide. In recent years, the focus has shifted towards a promising solution: the development of a cancer vaccine. This article explores the ongoing race to create a cancer vaccine and its potential to revolutionize treatment and prevention.

What is Cancer?

When the normal cells of our body are affected by various physical and chemical carcinogenic factors, then the normal cells get converted into cancerous cells, which results in a lack of contact inhibition (Which means, the cells continue to grow and divide even when they contact surrounding cells, unlike normal cells which stop dividing when they come into contact with other cells). and metastasis (Which means when cells spread from the primary tumor to the other part of the body, forming a secondary tumor).

Understanding cancer vaccines

Cancer vaccines come in various forms, but they generally fall into two categories:

1. **Preventive vaccines**: These vaccines are designed to prevent cancer from developing in the first place by targeting specific viruses known to cause cancer, such as the human papillomavirus (HPV) and hepatitis B virus (HBV).
2. **Therapeutic Vaccines**: Therapeutic cancer vaccines are aimed at treating existing cancers by stimulating the body's immune system to recognize and attack cancer cells.

The Race for Breakthroughs

The quest for effective cancer vaccines has spurred a global race among researchers, pharmaceutical companies, and biotech startups. This race is driven by the recognition of the immense potential of cancer vaccines to transform cancer treatment and prevention.

Key players and innovations

1. **Immune Checkpoint Inhibitors:** These drugs, such as pembrolizumab and ipilimumab, work by releasing the brakes on the immune system, allowing it to recognize and attack cancer cells more effectively. While not traditional vaccines, they have revolutionized cancer treatment and are often used in combination with other therapies, including vaccines.
2. **mRNA vaccines**: The success of mRNA vaccines, notably in the context of COVID-19, has sparked interest in applying similar technology to cancer vaccines. mRNA vaccines can be quickly designed and manufactured, offering a flexible platform for targeting a wide range of cancers.
3. **Personalized Vaccines**: Advances in genomics and immunology have paved the way for personalized cancer vaccines tailored to the individual's unique genetic makeup and immune profile. These vaccines hold the potential to improve efficacy and minimize adverse effects by focusing on the specific vulnerabilities of each patient's cancer.

Clinical Progress and Challenges

While the field of cancer vaccines has witnessed significant progress, several challenges remain:

- **Tumor Heterogeneity**: Cancer is highly heterogeneous, meaning it can vary widely from one patient to another and even within the same tumor. Developing vaccines that can effectively target this diversity poses a formidable challenge.
- **Immune Evasion**: Cancer cells have developed sophisticated mechanisms to evade the immune system, making them difficult to target with vaccines. Overcoming these immune evasion strategies is essential for the success of cancer vaccines.
- **Clinical Trials and Regulatory Hurdles**: Conducting rigorous clinical trials to demonstrate the safety and efficacy of cancer vaccines is a time-consuming and resource-intensive process. Regulatory approval can also be a significant barrier to bringing new vaccines to market.

The promise of cancer vaccines

Despite the challenges, the promise of cancer vaccines looms large on the horizon.

- **Improved Survival Rates**: Successful cancer vaccines have the potential to significantly improve survival rates and quality of life for cancer patients, particularly those with advanced or metastatic disease.
- **Reduced Treatment Toxicity**: Unlike traditional cancer treatments such as chemotherapy and radiation therapy, which can cause significant toxicity and side effects, cancer vaccines offer a more targeted and potentially less toxic approach to treatment.

Prevention of Cancer: Preventive cancer vaccines targeting viruses like HPV and HBV have already demonstrated remarkable success in reducing the incidence of cervical and liver cancers. Expanding the use of preventive vaccines could further decrease the burden of cancer worldwide.

Cancer prevention encompasses lifestyle choices and regular screenings. Here are some key points:

1. **Healthy Diet**: Consuming plenty of fruits, vegetables, whole grains, and lean proteins while limiting processed foods, red meat, and sugary drinks can reduce cancer risk.
2. **Regular Exercise**: Aim for at least 150 minutes of moderate aerobic activity or 75 minutes of vigorous activity weekly to maintain a healthy weight and reduce cancer risk.
3. **Avoid Tobacco**: Tobacco use increases the risk of various types of cancer. Quitting smoking and avoiding

second-hand smoke can significantly decrease cancer risk.

4. **Limit Alcohol**: Excessive alcohol consumption is linked to several cancers, including liver, breast, and colorectal cancer. Moderation is key.
5. **Sun Protection**: Limit exposure to ultraviolet (UV) rays by wearing sunscreen, and protective clothing, and seeking shade to prevent skin cancer.
6. **Screening Tests**: Regular screenings for breast, cervical, colorectal, and prostate cancers can detect abnormalities early when treatment is most effective.
7. **Vaccinations**: Vaccines like HPV and hepatitis B can prevent infections that increase the risk of certain cancers, such as cervical and liver cancer.
8. **Maintain a Healthy Weight**: Obesity is associated with an increased risk of several cancers, so maintaining a healthy weight through diet and exercise is important.

By adopting these preventive measures, individuals can significantly reduce their risk of developing cancer and lead healthier lives.

The Cancer Vaccine Race

As we know, it's a leading cause of death worldwide; it accounted for nearly 10 million deaths in 2020, which is one in six deaths in the world. over cancer by killing Cancerous cells and reducing the risk of it coming back. Several countries and companies are working on cancer vaccines.

Current scenario

- **Russia** made a big claim; it says that the Russian scientists are close to the goal of creating the vaccines for cancer that will soon be available to patients. However, it did not specify which type of cancer the proposed vaccine would target or how. (1,2)
- Last year, the **United Kingdom** government agreed with BioNTech, headquartered in Germany, with aspirations to reach 10,000 patients by 2030.
- Various pharmaceutical giants, such as Moderna and Merck & Co., are progressing in the development of experimental cancer vaccines. Encouraging results from a mid-stage study
  showcased Moderna and Merck & Co.'s vaccine's potential, demonstrating a 50% reduction in the risk of recurrence or mortality from melanoma, the deadliest skin cancer, after three years of treatment.

Notably, the World Health Organization reports the availability of six licensed vaccines targeting human papillomaviruses (HPV), known to cause various cancers, including cervical cancer, along with vaccines combating hepatitis B (HPV), which can lead to liver cancer.

Figure 1. Cancer vaccines

It is a type of vaccine that works by stimulating an immune response against four different antigens, like four different viruses or other microorganisms.

- Another breakthrough in the race to treat cancer: India's **starter hospital and IIT Mumbai** have invented a new technology called the **Car-T** to treat blood cancer.

  Two phases of the trial have been completed and the results are very promising, having been found to be 99% effective on children. This could not cause as much pain as in case of chemotherapy (4).
- The researchers at **TATA Memorial Hospital** in India claim that they have found an extremely affordable tablet-a ground breaking-tablet that-can prevent the recurrence of cancer. This tablet is called **R+CU,** and the research was carried out by Mumbai's TATA Memorial Hospital. It took the researchers 10 years to come up with this tablet. They basically inserted human cancer cells in rats, tumours were formed, and the rats were then treated with radiation therapy, chemotherapy insurgency followed with this research. When cancer cells die, they break down into pieces called chromatin particles. When these particles enter the bloodstream and then travel to other parts of the body, they enter Healthy cells and turn them cancerous. This is what researchers involved in the study found. They treated the rats with prooxidant tablets with resveratrol and CU, which is copper. The tablet helps to destroy the dangerous particles and prevents a relapse or recurrence of cancer.

  The researchers claim that the tablet also reduces the side effects of cancer treatments like radiation and chemotherapy (5).

So, progress has been made, but cancer is a tough enemy because of its diversity and the ability of cancer cells to adapt and resist treatments.

Conclusion

The race to develop effective cancer vaccines represents a beacon of hope in the fight against cancer. While significant challenges remain, the rapid pace of innovation and the growing understanding of the immune system's role in cancer hold promise for the future. With continued investment, collaboration, and scientific discovery, cancer vaccines have the potential to revolutionize cancer treatment and prevention, offering new hope to millions of patients around the globe.

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14. CRISPR Cas9 Assisted Gene Editing

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Gene editing is a method to modify the nucleotide sequence of the genome with base pair specificity and thus represents true genetic precision therapy (1) Modification of specific sites within a gene of interest is considered to be a standard approach to elucidate gene function, to cure disease like SCD, cystic fibrosis and more or to improve the characteristics of animals and plants. CRISPR Cas9 stands for Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated protein 9 has provided a much simpler and more economical method for gene-targeted modification.

The CRISPR–Cas system was initially identified as an adaptive immune mechanism in bacteria and archaea, and has now been engineered as RNA-guided endonucleases (RGENs) for genome editing. (2) The CRISPR system was adapted from a natural defense mechanism found in bacteria and archaea, where it functions as a kind of immune system against invading viruses as this mechanism defends from recurrent viral attacks via three basic stages:

- adaptation (spacer acquisition),
- crRNA synthesis (expression), and
- target interference.

Cas9 is the first Cas protein used in genome editing and was extracted from *Streptococcus pyogenes* (SpCas-9). It is a large multi-domain DNA endonuclease with 1368 amino acids responsible for cleavage of target DNA and introducing double-stranded break it is called a genetic scissor which is guided by two RNAs

(3) Cas9 is supposed to be involved in crRNA maturation and crRNA-guided DNA interference. The addition of Trans activating crRNA (tracrRNA), which can pair with the repeat sequence of crRNA is essential to crRNA maturation in this system, as it triggers Cas9 to cleave plasmid DNA which requires both magnesium and the presence of a crRNA sequence which is complementary to the DNA (4).

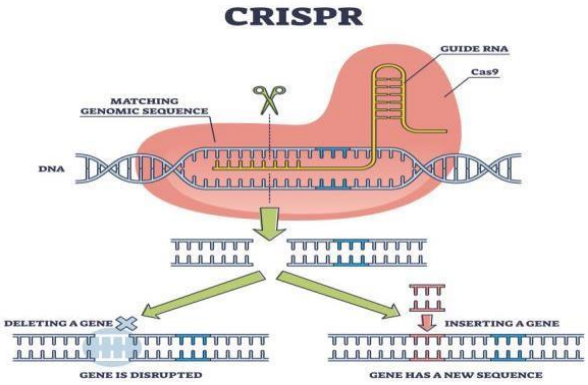

Figure 1. Crispr, a genetic tool
Source: https://images.app.goo.gl/GsbnsSrpRb1na4jF8

Components of CRISPR Cas9 system

Based on the structural characteristics and functional roles of Cas proteins, the CRISPR/Cas system is categorized into distinct classes:

Class I – It consists of multi-subunit CRISPR RNA Effector complexes and includes type I, III, and IV CRISPRs

Class II – It consists of a single subunit Crispr RNA Effector complex and includes type II and recently classified type V Crispr systems.

- Cas-9 is comprised of two domains: the Recognition (REC) lobe and the Nuclease (NUC):
- The REC lobe is composed of two subdomains, REC1 and REC2, which play crucial roles in the association with guide RNA.
- The NUC lobe encompasses the RuvC, HNH, and Protospacer Adjacent Motif (PAM) interacting regions. The RuvC and HNH regions facilitate the cleavage of each strand of the DNA, whereas the PAM interacting domain imparts specificity to the PAM sequence and plays a pivotal role in the initial binding with the target DNA.
- Guide RNA consists of two parts:
    1) CRISPR RNA (crRNA): It is an 18–20 base pair in length that specifies the target DNA by pairing with the target sequence
    2) Trans-activating CRISPR RNA (tracrRNA): It is a long stretch of loops which serve as a binding scaffold for Cas-9 nuclease.

In prokaryotes, the guide RNA is used to target viral DNA, but in the gene-editing tool, it is synthetically designed to form a single guide crRNA by combining crRNA and tracrRNA to target gene sequence which is supposed to be edited.

Mechanisms of CRISPR/CAS-9 Genome Editing

Three steps comprise the general mechanism of CRISPR/Cas-9 genome editing:

- Recognition: sgRNA directs Cas 9 to recognize the target sequence present in the gene of interest by its 5'-crRNA complementary base pair components.
- Cleavage: Cas 9 nuclease introduces double-stranded breaks at 3 base pair upstream to PAM (Protospacer Adjacent Motif) which is a short 2-5 bp length sequence. Cas 9 protein recognizes PAM sequence at 5'-NGG-3' and triggers local DNA melting which is followed by the formation of RNA -DNA hybrid. Cas 9 protein is activated by DNA cleavage HNH domain cleaves complementary strands while RuvC domain cleaves the non-complementary strand of DNA to produce blunt-ended double-stranded breaks.
- Double Stranded Break Repair Mechanism: DSBs created by Cas-9 protein can be repaired using two mechanisms: Non-homologous end joining and homologous-directed repair.

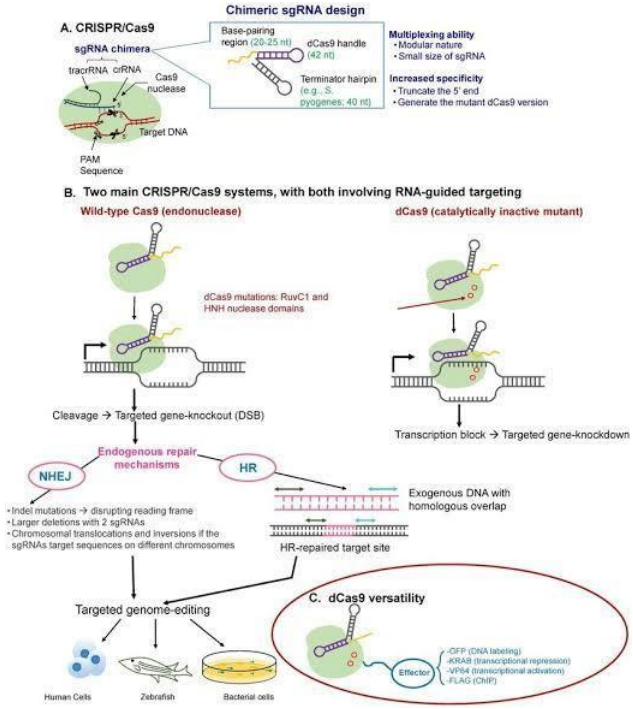

Figure 2. Mechanism of Crispr Cas 9
Source: https://images.app.goo.gl/8mASu6we5gEKAf436

Non-homologous end joining mediates the reparation of double-stranded breaks through an enzymatic mechanism that ligates DNA fragments without the need for an external homologous DNA template. This pathway operates ubiquitously throughout all stages of the cell cycle.

Homology-directed pair: It is highly a precise pathway that requires the use of a homologous DNA template. It is found to be most active in the late S and G2 phases of the cell cycle.

In CRISPR-gene editing, the homology-directed repair (HDR) process necessitates an extensive quantity of donor (foreign) DNA templates that carry the desired sequence for the purpose of accurately executing gene insertion or replacement. This is achieved by incorporating a donor DNA template, which shares sequence

similarity, at the designated site of the double-strand break (DSB).

Conclusion

CRISPR-Cas9 is a powerful and versatile genomic editing tool that has revolutionized the field of molecular biology. Its applications range from basic research to clinical trials, with the potential to treat a wide variety of diseases, including single-gene disorders, complex diseases like cancer and HIV infection, improving agricultural practices, and understanding the fundamental processes of life.

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15. The Ever-Present Shadow: Understanding Bioterrorism

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The use of infectious diseases as weapons of warfare has been a grim strategy throughout history, dating back to as early as 600 BC. This form of biological warfare aimed to weaken or eliminate enemy forces by deliberately spreading disease. One of the most notorious examples occurred during the siege of Caffa in 1346, when Tartar forces, afflicted by the plague, catapulted the bodies of their dead into the city. This act of biological warfare precipitated a plague outbreak within the city walls, significantly contributing to the spread of the Black Death across Europe, the Near East, and North Africa, resulting in the deaths of millions and becoming one of history's deadliest pandemics. The deliberate use of disease as a weapon was not unique to the siege of Caffa. Throughout history, similar tactics have been employed in various conflicts, including the use of cadavers to spread disease among enemy ranks. This strategy was observed again during the battle in Karolstein in 1422 and the conflict between Russian and Swedish forces in 1710. These incidents underline the strategic deployment of disease as a means to gain military advantage, showcasing a dark aspect of warfare where victory was sought at the cost of unleashing widespread suffering and death. These historical episodes of biological warfare highlight the catastrophic potential when infectious diseases are weaponized. The impact of these tactics extended far beyond the immediate military outcomes, contributing to some of the most severe epidemics and pandemics in history. The use of biological agents in warfare serves as a stark reminder of the devastating consequences that can arise from the intersection of human conflict and disease.

Table 1: Examples from the last two millennia of the employment of chemical and biological weapons

Year	Event
600 BC	During Krissa's siege, Solon employs the purgative herb hellebore.
1155 AD	In Tortona, Italy, Emperor Barbarossa poisons water wells containing hum an corpses.
1146 AD	Bodies of plague victims are thrown over the city walls of Caffa, Crimean Peninsula, by Tartar soldiers (today Feodosia, Ukraine)
1495 AD	In Naples, Italy, the Spanish mixed wine with the blood of leprosy victims t o sell to their French enemies.
1675 AD	The French and German armies decide against using "poisoned bullets."
1710 AD	Russian soldiers launch plague victims' corpses onto Swedish cities with great force.
1763 AD	Native Americans get blankets from British smallpox patients.
1797 AD	Napoleon increases the malaria epidemic by inundating the lowlands surrounding Mantua, Italy.
1863 AD	During the US Civil War, Confederates sold garments to Union troops who had smallpox and yellow fever.
World war 1	Anthrax and glanders are used by French and German spies.
World war 2	Japan employs anthrax, plague, and other illnesses; a number of other nations conduct biological weapons research and development projects.
1980–1988	During the Persian Gulf War, Iraq utilizes mustard gas, sarin, and tabun against Iran and ethnic groups within Iraq.
1995	Aum Shinrikyo uses sarin gas in the Tokyo subway system.

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(Source: Riedel S. (2004). Biological warfare and bioterrorism: a historical review. Proceedings (Baylor University. Medical Center), 17(4), 400–406)

World War I

In the 19th century, advances in microbiology, including Koch's postulates, enabled the isolation and production of specific pathogens, leading to more sophisticated biological warfare.

After World War I, Germany faced accusations of trying to use biological warfare by spreading diseases like anthrax and glanders, alongside attempts to infect populations in Italy and Russia with cholera and plague. Germany denied these claims, including the alleged dropping of biological bombs on British troops. A 1924 League of Nations investigation found no conclusive evidence of biological warfare use, though it did confirm chemical warfare's deployment. This prompted the 1925 Geneva Protocol, which prohibited the use of asphyxiating gases and bacteriological methods in warfare, although it lacked mechanisms for verification and enforcement. Despite the protocol, several countries, including major powers and the eventual ratification by the USA in 1975, began developing biological weapons programs.

World War II

During World War II, several countries, including Japan, launched extensive research into biological weapons. Japan's efforts, which spanned from 1932 to 1945, were led initially by Shiro Ishii and later by Kitano Masaji. The epicenter of their biowarfare research was Unit 731, located in Manchuria, near Pingfan. This program

had over 150 facilities, several satellite sites, and employed over 3,000 scientists. Their research focused on pathogens like anthrax, meningitis, cholera, and plague, among others. It's estimated that over 10,000 prisoners, including soldiers from Korea, China, Mongolia, the Soviet Union, America, Britain, and Australia, died from experimental infections. Victims were exposed to deadly diseases like gas gangrene, anthrax, and cholera through experimental procedures. There were also tests conducted with tetrodotoxin, a highly toxic substance. Japanese officials later expressed deep regret over these human experiments, acknowledging their severe impact on humanity.

During World War II, Japan's biological warfare efforts involved infecting fleas with the plague in labs and then releasing them over Chinese cities to start epidemics. These actions led to significant casualties, including among Japanese troops, due to poor preparation for biological warfare's risks. The program ended in 1942 after causing around 10,000 deaths in one city alone.

In 1949, a Soviet tribunal tried Japanese war prisoners for using biological weapons, revealing that Unit 731 killed hundreds annually through experiments. Meanwhile, Germany, despite initiating some biological research and facing accusations from both sides, did not fully develop a biological weapons program. Adolf Hitler had banned such weapons, citing his aversion to chemical warfare from World War I.

The British conducted experiments with anthrax spores on Gruinard Island, which led to long-term contamination. Only in 1986 was the island decontaminated.

In the aftermath of World War II, the media extensively covered outbreaks of diseases attributed to foreign actors wielding biological weapons. During the Korean War, allegations surfaced, with the Soviet Union, China, and North Korea accusing the United States of employing biological warfare tactics against North Korea. While the US admitted its capability to produce such weapons, it vehemently denied their actual utilization. However, the credibility of the US was compromised due to its failure to ratify the Geneva Protocol of 1925, acknowledgment of its offensive biological warfare program, and suspicions of collaboration with former Unit 731 scientists.

Amid the Korean War (1950–1953), the US expanded its biological warfare program, establishing a novel production facility in Pine Bluff, Arkansas. Concurrently, a defensive program commenced in 1953, aimed at developing countermeasures, including vaccines and therapeutic agents. By the late 1960s, the US military boasted a diverse biological arsenal, encompassing pathogens and toxins capable of targeting agricultural crops.

At Fort Detrick, experiments involved the detonation of biological munitions within an aerosolization chamber colloquially termed the “eight ball,” exposing volunteers to pathogens such as Francisella tularensis and Coxiella burnetii. These endeavors sought to elucidate human vulnerability and assess the efficacy of medical countermeasures. Despite reports of occupational infections at Fort Detrick, these incidents remained within established safety thresholds.

Between 1951 and 1954, covert experiments were undertaken in US urban centers to evaluate aerosolization and dispersal techniques employing simulant organisms like Aspergillus fumigatus and Bacillus subtilis var globigii. Apprehensions were raised following a urinary tract infection outbreak linked to Serratia marcescens experiments at Stanford University Hospital.

Furthermore, other nations, including Canada, Britain, France, and the Soviet Union, persisted in biological weapons research. The UK inaugurated the Microbiological Research Department in 1947, conducting trials with biological agents before discontinuing offensive research in 1957. Conversely, the Soviet Union intensified both offensive and defensive biological warfare research, despite officially disavowing possession of such armaments.

Allegations of biological weapons employment persisted post-World War II, encompassing accusations against Great Britain, the USA, and the Soviet Union by the Eastern European press, China, and Egypt,

respectively.

Nation	Numbers of workers (estimated)	Focus
Germany	100-200	Research on offenses is prohibited.
Canada	small	Illnesses of animals and crops, rinderpest, and anthrax
United Kingdom	40-50	Foot and mouth disease, anthrax, animal and agricultural illnesses
Japan	several thousand	Vast; official information was hidden by a pact with the United States of America that dropped all war crime accusations in exchange for the sharing of experimental data.
Soviet Union	several thousand	Typhus, plague
USA	1500-3000	Chemical herbicides, anthrax

Table 2: Programs for biological warfare in World War II.
(Source: Riedel S. (2004). Biological warfare and bioterrorism: a historical review. Proceedings (Baylor University. Medical Center), 17(4), 400–406. https://doi.org/10.1080/08998280.2004.11928002)

The 1972 Biological Weapons Convention

During the late 1960s, escalating global apprehension emerged regarding the indiscriminate and unpredictable attributes of biological weapons, coupled with the absence of robust epidemiological control mechanisms. This concern prompted initiatives by both Great Britain and the Warsaw Pact nations, spearheaded by the Soviet Union, to propose the prohibition of biological weapons' development, production, and stockpiling at the UN Committee on Disarmament in 1969. Consequently, the 1972 Biological Weapons Convention (BWC) was instituted, aiming to outlaw the development, production, and accumulation of pathogens or toxins for non-peaceful objectives. The BWC also prohibits the advancement of delivery systems and the dissemination of biological warfare technology. Under the BWC, signatories are mandated to dismantle stockpiles, delivery systems, and production infrastructure. Despite widespread ratification, the BWC suffers from ambiguous guidelines regarding inspections, enforcement mechanisms, and the management of breaches. Instances of purported violations are reported to the UN Security Council; however, the ability of permanent members to veto proposed inspections complicates enforcement efforts.

In the United States, President Nixon initiated the termination of the offensive biological weapons program in 1969 and 1970, directing the obliteration of the biological weapons cache while permitting ongoing research for defensive purposes. Subsequently, the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) was established to conduct research on medical defense against biological weapons, operating within an unclassified framework.

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Table 3: The number of people that a hypothetical biological attack could potentially kill.

Agent	Downwind reach (km)	Number killed	Number incapacitated
Rift Valley fever	1	400	35000
Tick-borne encephalitis	1	9500	35000
Typhus	5	19000	85000
Brucellosis	10	500	125000
Q-fever	>20	150	125000
Tularemia	>20	30000	125000
Anthrax	>20	95000	125000

(Source: Riedel S. (2004). Biological warfare and bioterrorism: a historical review. Proceedings (Baylor University. Medical Center), 17(4), 400–406)

The Biological Warfare Program of the United States

The US Biological Warfare (BW) program originated during World War II in response to suspicions of Germany and Japan developing such capabilities. Key figure George W. Merck advised President Franklin Roosevelt and initiated the program, which was overseen by the Army Chemical Warfare Service. Initiated in 1941 under tight security, BW research remained undisclosed to the public until after the war in 1946. Secretary of War H. Stimson highlighted German use of glanders against Rumanian cavalry and sabotage of horses in World War I, prompting the need for significant research efforts beyond initial university and private institutes collaboration.

In 1943, BW agent research commenced at Fort Detrick, Maryland, with the US program gaining high priority. Germany's apprehension of US BW capabilities reportedly deterred their pursuit of BW, unbeknownst to the Allies. A notable achievement was the development of small-particle aerosol dissemination of pathogen preparations during World War II. The US negotiated immunity for Japanese BW program leaders in exchange for experiment data. Preparation for the Korean War included making wheat rust available as a potential agent against the Soviet Union. The Pine Bluff Arsenal in Arkansas opened the first bacterial agent production facility in 1950, scaling up Brucella suis production to 650 tons/month by 1954. Throughout the 1950s and

1960s, the program expanded to involve about 3400 personnel and various agents, including Bacillus anthracis, Francisella tularensis, and Coxiella burnetii.
In 1969, President Nixon halted offensive BW development, redirecting facilities for peaceful or bio-defense purposes. Reasons included preventing proliferation of BW technology and advancing negotiations for a convention banning biological and toxin weapons. Disinformation was spread to the Soviet Union by the FBI regarding covert offensive BW activities in the USA. Recent revelations discredited allegations by China, North Korea, and the Soviet Union during the Korean War regarding US BW use. Cuba also accused the USA of using BW agents, notably in 1997, leading to consultations under the Biological and Toxin Weapons Convention in Geneva (2).

The Biological Warfare Program of the Soviet Union

In September 1981, the US Secretary of State accused the Soviet Union of providing mycotoxins to its communist allies in Vietnam and Laos for military purposes against resistance forces in Laos and Cambodia, as well as using these agents in combat operations in Afghanistan. This allegation, if accurate, would mark the first instance of toxin warfare. The US also suggested that the Soviet Union was violating the 1925 Geneva Protocol and the 1972 Biological and Toxin Weapons Convention (BTWC). The evidence presented led to extensive discussions. An alternative explanation for the alleged 'yellow rain' phenomenon was proposed by a group of researchers, suggesting that the colored rain reported by refugees could be harmless showers of yellow bee feces, given the prevalence of mycotoxins in the region. Despite this, the US has not retracted its claim regarding Soviet engagement in toxin warfare from 1975 to 1984, leading to the continued inclusion of trichothecene mycotoxins on lists of possible BW agents. This underscores the importance of promptly deploying scientifically trained teams to respond to allegations, gather evidence rigorously, and preserve it at the site of alleged use.
The Soviet BW program began in the mid-1920s and expanded during the 1930s and 1940s with research at the Red Army Bacteriology Institute in Vlasikha, near Moscow. Limited information exists about this early period, which involved work on various pathogens and methods for warfare. World War II saw the development of typhus as a BW agent and the invention of an aircraft dispenser for plague bacteria. Captured Japanese BW program members provided data and plans for Soviet BW facilities. Post-war, new BW research and production facilities were established in the 1950s, driven by concerns about potential US BW use. The Soviet Union ratified the BTWC in 1975 but significantly expanded its BW program, possibly influenced by US disinformation efforts (2). The creation of Biopreparat aimed to leverage advances in microbiology and biotechnology for BW purposes. Field testing of BW agents occurred on Vozrozhdeniye Island. At its peak, the program involved around 60,000 individuals across 40-50 facilities, focusing on agents such as plague, anthrax, and smallpox.
Efforts to end the Soviet/Russian BW program began in 1989, with the US and UK launching a trilateral process involving mutual inspections. President Yeltsin's 1992 decree banned further offensive BW work, though suspicions persist about ongoing activities. Western support now aims to redirect BW expertise in Russia and CIS countries toward peaceful pursuits through financial aid. The 1979 anthrax outbreak in Sverdlovsk, resulting in 69 deaths, was a significant incident implicating Soviet violation of the BTWC. President Yeltsin later acknowledged an aerosol release from a military facility, but recent military representatives have reverted to attributing the outbreak to contaminated meat, highlighting the need for international investigation mechanisms.

Conclusion

Biological weapons possess distinct characteristics, including their invisible nature and delayed effects, which

instill fear, confusion, and uncertainty among victims while allowing perpetrators to evade detection. Such attacks not only lead to widespread sickness and death but also aim to disrupt social and economic activities, undermine government authority, and impair military responses. The psychological impact of even a small number of infections, as exemplified by the "anthrax letters" following the September 2001 World Trade Center attack, can be immense, instilling a sense of threat and unpredictability.

The choice of biological warfare agents depends on the resources and capabilities of the state or organization involved. Highly lethal agents like smallpox, Ebola, and Marburg virus may be favored due to their reputation for causing terrifying illnesses. Images of healthcare and law enforcement personnel in full protective gear can exacerbate public anxiety and distraction.

Biological warfare attacks are now a realistic threat, necessitating increased awareness and preparedness within the medical community and among the general public. Understanding epidemiology and control measures is crucial for mounting a calm and rational response in the event of an outbreak. Education on recognizing and responding to this threat is essential for healthcare professionals.

Preventative measures include establishing global norms rejecting the development of biological weapons, early detection, and prompt treatment of diseases. The medical community plays a pivotal role in disease surveillance and reporting, providing crucial early indicators of biological weapons use. Continued research to enhance surveillance, diagnostics, therapeutics, and response plans is vital for strengthening prevention efforts. Additionally, efforts to minimize the disability caused by disease, known as tertiary prevention, should not be overlooked. Despite these efforts, the imperfections of preventative measures highlight the importance of readiness to address the consequences of biological weapons use should it occur (1).

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16. Prostate Cancer

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Prostate cancer ranks fifth among all cancer-related deaths in males and is the most frequently diagnosed malignancy in this age group in the world. 1,414,249 newly diagnosed cases and 375,000 fatalities globally were attributed to this illness in 2020.In more than half of the world's countries, prostate cancer is the most often diagnosed cancer. (1)

The prostate is an exocrine gland situated above the penis and below the bladder, with a size similar to a walnut. It generates seminal fluid, which during ejaculation feeds and moves sperm. Prostatic fluid's alkalinity shields sperm from the acidic vaginal environment. Benign prostatic hyperplasia (BPH) is the term for the natural enlargement of the prostate with aging. This illness affects around one-third of males over 60 and half

over 80. Symptoms include frequent urination due to bladder constriction. Because of their similar histology and molecular causes, BPH and prostate cancer have been proposed as possible precursors, though this link is still up for debate. (2)

Symptoms of Prostate Cancer

1. Urine passage difficulties
2. Regular urge to urinate, particularly at night
3. Weak or erratic urination
4. Urinating with pain or burning
5. Blood in the semen or urine
6. Ejaculation that hurts
7. Nagging discomfort in the pelvis, hips, or back

Prostate cancer can spread to the prostate gland. Or it may spread throughout the body. It often spreads to the bones. Therefore, bone pain, especially back pain, maybe a symptom of prostate cancer (4).

Risk Factors

Age: Prostate cancer is more common in men 50 years of age and older

Race: Prostate cancer in African-American males is most common; it often develops earlier in life and spreads more quickly than in men of other races. Prostate cancer is most common in white males, second only to African-American men, then in Hispanic and Native American men. Prostate cancer is least common in Asian-American men.

Diet: Prostate cancer risk has been linked to diets low in selenium and alpha-tocopherol and high in dairy and calcium.

Family history: A man's chance of developing prostate cancer is two to three times greater than that of a man without a family history of the disease if his father or brothers have had the condition. A man's chance of developing prostate cancer is approximately ten times higher if he has three close family members who have the disease than if he does not. A man's chance of getting prostate cancer increases with the age of his relatives who have the condition. Men from families with a history of breast cancer seem to have a somewhat increased risk of prostate cancer as well.

Smoking: Due presumably to cigarette mutagens that encourage prostatic carcinogenesis, tobacco smoking raises the incidence and death of prostate cancer. Smokers were more likely to be diagnosed in middle-aged men by 1.4×, and by 1.6× if they had more than 40 pack years. Additionally, smokers' risk of prostate cancer mortality was 1.6× higher. The incidence and mortality of smoking were found to be positively impacted by quitting, and these effects increased over time.

Prostatitis: Chronic prostatitis increases overall prostate cancer risk in the general population but not among African Americans, as indicated by another meta-analysis. (2)

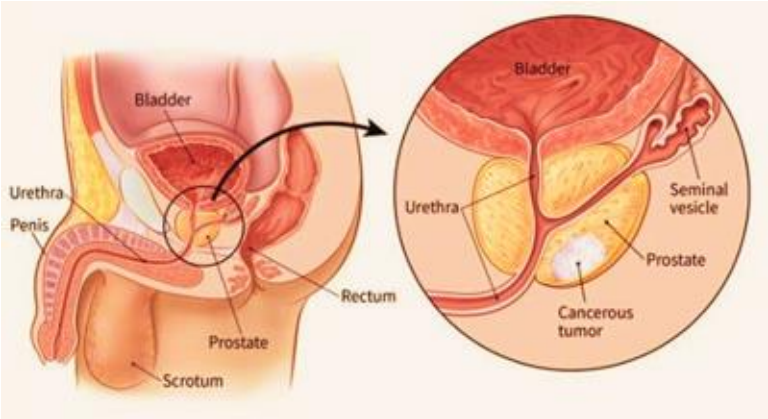

Figure.1: prostate cancer
(Source: https://www.cancer.org/cancer/types/prostate-cancer/about/what-is-prostate-cancer.html)

Diagnosis

PSA (Prostate-Specific Antigen) Test:

A PSA level of 4-
10 ng/mL indicates a 25% risk, while a PSA level of >10 indicates a >50% risk. Although the age-related increase in PSA is normal, this value is borderline and requires further evaluation of cancer risk (2).
Early diagnosis by PSA test can increase survival rate and aid timely treatment. However, over ten years, 15% of patients experience negative results, leading to unnecessary interventions. 20% - 50% of malig nancies detected by PSA may be overdiagnosed. According to research, African Americans should have a PS A test at the age of 45, middle-aged men at the age of 50, and high
risk men at the age of 40. American Cancer Society. On the other hand, the US Preventive Task Force does not recommend routine PSA tests on the grounds that they may do more harm than good (4).
A biopsy is usually recommended after a positive PSA reading; The risk of hospitalization due to surgery-related complications is 1%. Imaging techniques such as transrectal ultrasound or MRI-guided biopsy and Gleason score are good. (6)

Digital Rectal Exam (DRE)

A good way to check the prostate is DRE. The doctor uses gloved, lubricated fingers to feel the prostate throug h the rectum. This test takes ten to fifteen seconds.
This test checks:
1) The size, firmness, and texture of the prostate.
2) Hard, lumpy, or enlarged areas that spread beyond the prostate
3) The prostate any pain caused by touching or pressure (4)

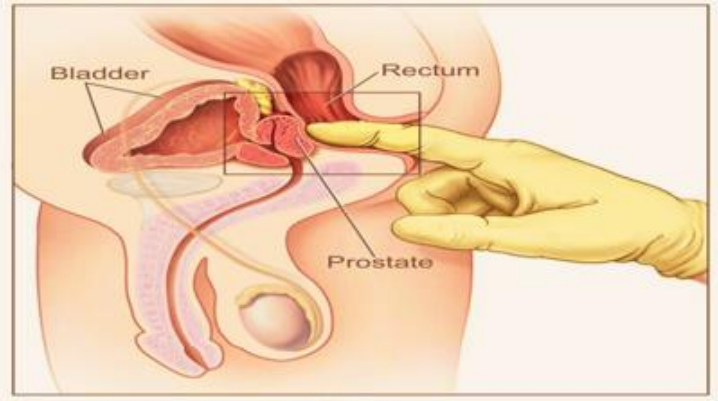

Figure.2: Digital rectal exam
(Source: https://www.cancer.gov/types/prostate/patient/prostate-screening-pdq (2023)

Grading

Prostate cancer is classified histopathologically using the Gleason score, which goes from 2 to 10. It helps with risk assessment by classifying malignancies as low-grade (<6), intermediate-grade (7), and high-grade (8–10) diseases.(1)

Grade Group 1 (Gleason ≤6): Well-formed glands
Grade Group 2 (Gleason 3+4=7): Mostly well-formed with some poorly-formed or fused glands
Grade Group 3 (Gleason 4+3=7): Mostly poorly-formed or fused with some well-formed glands
Grade 4 (Gleason 8): Only poorly formed/fused/cribriform or mostly well developed with a component lacking glands
Grade Group 5 (Gleason 9 or 10): Lacks gland formation (or with necrosis)

Histologically speaking, Grade Group 1 is "low grade," Grade Group 2 is "intermediate grade," and Grade Group 3 or higher is "high grade" disease in clinical practice. (2)

Treatment:

1) Localized Prostate Cancer Treatment:

- Radical prostatectomy or radiotherapy for localized disease.
- Observation for low-risk or intermediate-risk patients with a life expectancy of <5 years.
- Robotic or laparoscopic prostatectomy is preferable for fewer complications, especially for older men. (2)

2) Radiotherapy Approaches:

- External beam radiotherapy as monotherapy for low-risk patients and adjuvant for high-risk patients post-prostatectomy.
- High-dose rate brachytherapy as monotherapy or in combination with external beam radiation. (3)

3) Androgen Deprivation Therapy (ADT):

- Standard for initial castration-sensitive prostate cancer treatment.
- GnRH agonists/antagonists replace surgical orchiectomy, reducing symptoms and slowing tumor progression. (5)

4) Castration-Resistant Prostate Cancer (CRPC) Treatment:

- Next-generation endocrine agents (abiraterone, enzalutamide, apalutamide, darolutamide).

- Cytotoxic agents (docetaxel, cabazitaxel) improve survival when added to ADT upon progression.
- Sequencing therapy lacks consensus, and alternating chemotherapy and anti hormonal drugs might be promising. (4)

5) Immunotherapy and Targeted Therapies:

- Pembrolizumab approved for high PDL-1 expression and microsatellite instability in later-line treatment.
- Sipuleucel-T for minimally symptomatic patients.
- Radium-223 for bone metastases without visceral involvement. (2)

Conclusion

Facing prostate cancer is like navigating a personal journey, considering factors unique to each individual—race, genetics, and lifestyle. Think of diagnostics, like the Gleason score, as personalized roadmaps guiding treatment decisions. While PSA testing was a game-changer, we now approach it with caution, aiming for accuracy. National guidelines encourage a thoughtful approach, suggesting watchful waiting for some, allowing for a balance between treatment and quality of life. Innovative treatments, such as robotic prostatectomy, offer hope, symbolizing a shift towards care that recognizes the person behind the diagnosis. It's about tailoring the path to ensure not just survival but a meaningful and human experience.

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17. Intruder Alert: The Exclusome's Mission to Safeguard Genetic Integrity

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Introduction

The eukaryotic genome is encapsulated within a double-membraned nucleus, separating the nucleoplasm from

the cytoplasm. The nuclear envelope (NE) comprises various proteins binding to chromosomal DNA and nuclear pore complexes (NPCs) regulating compartmental flux. Although disassembled during mitosis and reassembled at mitotic exit (1), it remained unclear if this process exclusively involved chromosomal DNA (2). Extrachromosomal DNA in mammalian cells, whether endogenous (e.g., circular, linear, mitochondrial) (3) or exogenous (e.g., viral or bacterial infections, DNA transfection) (4), poses a risk of integration into chromosomes (5).
Enter the Exclusome: a membrane-bound container that selectively segregates extrachromosomal DNA from chromosomal DNA by exiting the nucleus and confining itself to the cytoplasm (2), thus safeguarding the nucleus (5).

Nuclear Reassembly

At the Telophase's end, spindle disassembly, recruitment of NE proteins, ER membrane, and NPC assembly occur to form the interphase nucleus (1). The Barrier-to-Autointegration Factor (BAF) saturates chromosomal DNA by sequence-nonspecific binding (6), then links to ER membrane proteins like Lap2, Emerin, and LEM domain proteins, recruiting the ER membrane to form the nucleus (7). NPC assembly coincides with chromosome-membrane contact, contributing to membrane sealing (8).
Notably, while the process of nuclear reassembly has been extensively studied, it has remained unclear whether this process exclusively involves wrapping around chromosomal DNA or encompasses other DNA entities within the nucleus (2).

The Exclusome Discovery

Upon transfection of a LacO-LacI system plasmid into HeLa cells via electroporation or polymer-based transfection, Live Cell Imaging was employed to track the fate of the plasmid focus. The majority of plasmid foci were observed in the cytoplasm post-transfection. Interestingly, those that entered the nucleus were swiftly sorted from chromosomal DNA and transported to the cytoplasm within 1 hour (2).
Furthermore, it was noted that the formation of plasmid foci within the nucleus occurred predominantly during interphase, with some instances during mitosis. Suggesting there are two instances where the DNA is expelled from the nucleus- During the interphase sorting or the mitotic sorting. Notably, transfected cells tended to form only one plasmid focus, with multi-focus cells observed to degrade over time.
Continued observation revealed intriguing dynamics regarding the fate of cytoplasmic plasmid foci. A significant portion (two-thirds) remained segregated from chromosomes for extended periods without re-entering the nucleus. In contrast, approximately one-third of foci degraded after more than 10 hours of observation (2).
To validate these findings across different cell lines and transfection methods, a similar experiment was conducted on MDCK cells using a different plasmid. The results mirrored those observed in HeLa cells, demonstrating consistent preferential maintenance of plasmid DNA in a single cytoplasmic focus across different experimental conditions (2).
Further investigation into the association of plasmid DNA with ER markers shed light on the structural characteristics of the Exclusome. High-resolution visualization using Correlative Light and Electron Microscopy (CLEM) revealed a double-membraned organelle resembling the endoplasmic

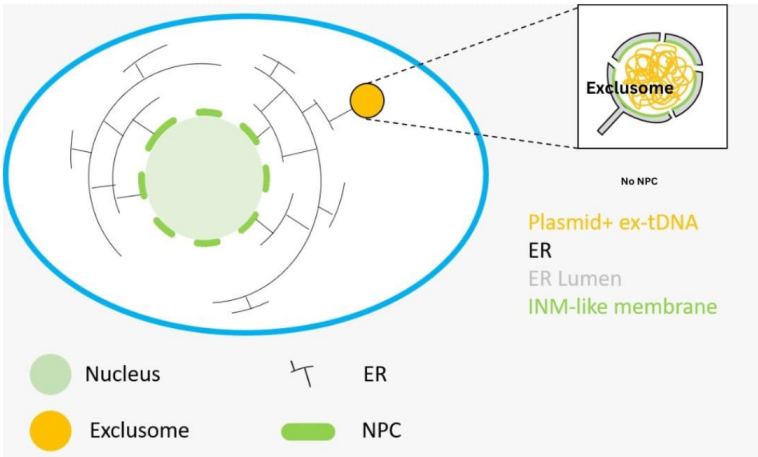

Figure 1. Diagram of exclusome as observed in an interphase cell
Source: Schenkel, L., Wang, X *et al.*, Molecular Biology of the Cell, 34(11)

reticulum (ER), with fenestrations and connections to the ER network. Importantly, the absence of nuclear pore complex (NPC) and Lamin B Receptor (LBR) proteins at the foci distinguished the Exclusome from the nuclear envelope (2).

Probing the Exclusome for similarities with the nuclear envelope, various protein markers were utilized, including inner nuclear membrane proteins (e.g., Emerin, Lap2β), DNA-membrane tethering proteins (e.g., Barrier-to-Autointegration Factor, Lamin B Receptor) (9), and NPC-related proteins(FG-NUP, ELYS) (10). Cytoplasmic foci consistently exhibited the presence of BAF, Emerin, and Lap2β, with ER proteins highly enriched. Notably, no NPC proteins were detected at the foci, confirming the absence of functional NPCs in the Exclusome membrane (2).

Intriguingly, the Exclusome was found to not only contain exogenous plasmid DNA but also endogenous extrachromosomal DNA of telomeric origin (tDNA). Fluorescently labeled telomeric probes revealed the colocalization of tDNA and plasmid DNA within the same Exclusome, suggesting a broader role in DNA segregation and maintenance of nuclear integrity (2).

Discussion

The discovery of the Exclusome unveils a previously unrecognized mechanism for distinguishing and segregating extrachromosomal DNA in mammalian cells. This organelle's ability to selectively maintain plasmid DNA in a single cytoplasmic focus, independent of cell cycle stage or transfection method, underscores its fundamental role in safeguarding nuclear integrity.
Investigating the molecular machinery involved in Exclusome formation and maintenance could provide insights into the mechanisms underlying DNA segregation and organelle biogenesis and may shed light on other functions it may exhibit such as degradation of ex-DNA.
Lastly, exploring the evolutionary conservation of the Exclusome across different organisms and its implications for genome stability could offer evolutionary insights into cellular defense mechanisms and organelle evolution, as it has a striking resemblance to the ‘core region’ of the nuclear envelope (7). Comparative studies in model organisms and human cells may reveal conserved features and divergent adaptations, providing a deeper understanding of the Exclusome's evolutionary origins and adaptive

significance.

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18. The evolution of vaccine

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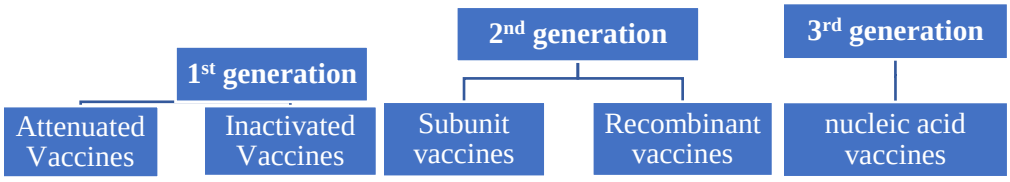
Throughout the evolution of medicine, humans have endeavoured not just to treat diseases but also to prevent them and bolster immunity, with vaccines emerging as one of their most utilized tools in this endeavour.

According to World Health Organization, Vaccination is a simple, safe, and effective way of protecting you against harmful diseases, before you come into contact with them. It uses your body's natural defences to build resistance to specific infections and makes your immune system stronger. Vaccines educate your immune system to produce antibodies, much like it naturally does when encountering a disease. However, since vaccines consist of only inactive or weakened versions of pathogens such as viruses or bacteria, they do not induce the illness or expose you to the risks associated with its complications.

1. The chronicle of vaccine advancement.

Although Inoculation practices initiated in China and the Middle East from the 12th to the 15th centuries, The term "vaccine" was initially coined in the 18th century by Edward Jenner. Edward Jenner pioneered the concept of utilizing cowpox as a preventive measure against smallpox, he administered cowpox lesions obtained from the hands of milkmaids to an eight-year-old boy through inoculation, resulting in immunity against smallpox. In 1885, Dr. Louis Pasteur demonstrated the prevention of disease by employing weakened germs. This was exemplified when he utilized a vaccine to effectively prevent rabies in a young boy named Joseph Meister, who had been severely bitten by a rabid dog. In 1931, Louis Pasteur's significant research on cultivating viruses in chicken embryos ushered in a new era of mass vaccine production, utilizing various techniques. This resulted in the development of influenza and yellow fever vaccines. Advancements in cell culture technology during 1940s culminated in the development of the polio vaccine, heralding the onset of a golden age in vaccine innovation. During this era vaccines targeting Measles, Rubella, and Mumps were developed. It progressed with the development of the Chickenpox vaccine and the inactivated Japanese encephalitis vaccine in the 1970s. During the 1990s, the progression of vaccine technology led to the emergence of a novel vaccine type called DNA vaccines (1,2,3,5).

2. Different Types and Generations of Vaccines



2.1. First-generation vaccines

Attenuated and inactivated vaccines belong to the first generation of vaccines, characterized by their primary method of production.

2.1.1. Live-attenuated vaccines

Live-attenuated vaccines contain a weakened (or attenuated) form of the pathogen that causes a disease. These vaccines are valuable because they mimic the infection process, potentially triggering robust antibody responses and cellular immunity. They elicit a robust and enduring immune response. Typically, just one or two doses of most live vaccines can provide lifelong protection against both the pathogen and the associated disease.

Live vaccines are used to protect against Rotavirus, smallpox, chickenpox and yellow fever. The combination vaccine for measles, mumps, and rubella (MMR) is a notable example of an attenuated vaccine.

2.1.2. Inactivated Vaccines

Inactivated vaccines use the killed or inactivated form of pathogen that causes a disease. Because inactivated vaccines contain killed virus there is no risk of reversion and hence no threat to human health. Inactivated vaccines typically offer less potent immunity compared to live vaccines so they need regular booster injections. Inactivated vaccines are used to protect against hepatitis A, rabies and flu. (1.1,7)

2.2. Second-generation vaccines

This generation was discovered based on subunit elements, recombinant or synthetic proteins, non-protein antigens, and expressed bacterial or viral immunogens. These components encompass a multitude of molecules and epitopes derived from various species and strains of pathogens. Subunit, recombinant, polysaccharide, and conjugate vaccines belong to this generation of vaccine. As these vaccines utilize specific segments of the pathogen, they elicit a highly focused immune response directed toward critical components of the pathogen.

2.2.1. Subunit vaccine

Subunit vaccines consist of one or more protein-peptide or polysaccharide components naturally present in the pathogen's structure. By utilizing only a portion of the pathogen, subunit vaccines cannot replicate, thereby reducing the likelihood of unintended immune responses.

The bacterial subunit vaccines are categorized into Toxoid vaccines and polysaccharide vaccines. Toxoid vaccines primarily target toxins, which serve as the main pathogenic factor. Toxins are rendered harmless by treating them with formaldehyde to convert them into non-toxic forms, known as toxoids. Following the transformation into toxoids, they can be utilized for vaccination purposes. Antibodies initiate the neutralization of toxins due to the structural similarity between the toxin and toxoid. Polysaccharide vaccines are derived from the polysaccharide capsules found on encapsulated bacteria. These capsules serve to increase membrane hydrophilicity and anti-phagocytic properties.

2.2.2. Conjugated vaccines

Polysaccharide antigens are large molecules with repetitive epitopes. These antigens cannot be processed by antigen-presenting cells, leading to an antibody response independent of T cells. Such responses are incapable of forming immune memory or facilitating affinity maturation for these types of infections. In 1929, Avery and Goebel were the first to employ proteins to boost the immunogenicity of polysaccharide antigens. They noted that the low immunogenicity of the polysaccharide antigen from Streptococcus pneumoniae type 3 was enhanced when linked to a carrier protein in rabbits. These findings laid the groundwork for the development of modern conjugate vaccines. The inaugural glycoconjugate vaccine intended for human use, targeting Haemophilus influenzae type b (Hib), received licensure in the USA in 1987. Shortly thereafter, it was incorporated into the US infant immunization schedule.

2.2.3. Recombinant vaccines

Progress in immunology, molecular biology, biochemistry, genomics, and proteomics has brought fresh insights to the field of vaccinology. At present, it is feasible to obtain the sequence of pathogenic protein antigens by sequencing the genes encoding the primary antigen, and subsequently synthesizing them synthetically using recombinant DNA technology. Employing recombinant proteins enables the direction of immune responses toward specific protective antigens. Hepatitis B stands as the premier and one of the most triumphant instances of synthetic vaccines. The surface antigen of the hepatitis B virus (HBsAg) exhibits exceptional immunogenicity and efficacy, capable of eliciting high levels of antibody production within the body. To produce recombinant hepatitis B vaccine, recombinant HBsAg is expressed in cells with robust expression systems, such as yeast. This results in the generation of virus-like particles by HBsAgs, which are highly immunogenic. As these particles lack a genome, they are incapable of causing disease, thereby eliciting a robust and potent immune response against the primary pathogen. Other common vaccines include those targeting herpes simplex virus, rotavirus, and human papillomavirus (HPV) (1.1,4,7,8,).

2.3. Third-generation vaccines

Genetic vaccines, which utilize DNA or RNA plasmids as antigen precursors for immunization or immunotherapy, are classified as third-generation vaccines. The gene sequence encoding the antigen of interest

is taken up and translated into protein by host cells. The third-generation vaccine technology, often regarded as innovative among vaccine platforms, saw widespread utilization in combatting COVID-19. Various names have been assigned to this type of vaccine, including DNA vaccines, RNA vaccines, and plasmid vaccines.

In recent times, mRNA vaccines have garnered particular interest and demonstrate several advantages over DNA vaccines. These include precise delivery exclusively to the cell cytoplasm, eliminating the risk of genomic integration, and functioning autonomously regardless of cell division. Nonetheless, RNA vaccines necessitate additional steps in their production and are vulnerable to degradation both ex vivo and in vivo. In contrast, DNA vaccines exhibit greater thermostability, simplifying their storage requirements.

DNA vaccines consist of synthetic DNA sequences encoding antigens from the targeted pathogen, which are cloned into expression vectors. Following in vivo transfection, the vaccine plasmid must reach the nucleus, where transcription into mRNA occurs, followed by translation of vaccine antigen peptides in the cytoplasm. Following translation, these intracellular antigens undergo processing within the proteasome, resulting in the generation of vaccine epitopes. Subsequently, peptides are transported to the endoplasmic reticulum via the TAP transporter, where they bind to MHC-I molecules and are presented to T cell surface receptors, thereby activating cytotoxic responses.

The mechanism of action of mRNA vaccines closely resembles that of DNA vaccines. The primary distinction lies in the fact that after immunization, mRNA vaccines are transported directly to the cell cytoplasm, where they are poised for translation, eliminating the necessity to reach the nucleus. There are two types of mRNA vaccines: non-replicating mRNA vaccines, which encode solely the target antigen, and self-replicating RNA vaccines that contain the replication machinery of positive-stranded RNA viruses like alphavirus, flavivirus, measles virus, and rhabdovirus, facilitating intracellular replication of the vaccine. Third-generation vaccines signify a significant leap forward in the realm of vaccinology. The COVID-19 pandemic underscored the significance of this vaccine platform, offering a remarkable illustration of how pioneering studies initiated decades ago could be swiftly, efficiently, safely, and cost-effectively applied—unprecedentedly—in combating the pandemic (4,6,7,8,1.1).

3. Conclusion

Third-generation vaccines signify a significant leap forward in the realm of vaccinology. The COVID-19 pandemic underscored the significance of this vaccine platform, offering a remarkable illustration of how pioneering studies initiated decades ago could be swiftly, efficiently, safely, and cost-effectively applied—unprecedentedly—in combating the pandemic.

In conclusion, the evolution of vaccines has been a remarkable journey marked by continuous innovation and advancement. From the earliest forms of variolation to the cutting-edge technologies of genetic and mRNA vaccines, the field of vaccinology has witnessed transformative developments. These advancements have not only enabled the prevention and control of infectious diseases but have also revolutionized public health on a global scale. As we move forward, the COVID-19 pandemic serves as a poignant reminder of the vital role vaccines play in safeguarding human health and well-being.

In pursuit of enhanced safety, efficacy, and stability, future vaccine strategies aim to leverage our expanding understanding of microbiology, immunology, molecular biology, genetic engineering, and manufacturing techniques. This collective knowledge paves the way for the development of advanced generations of vaccines capable of preventing and treating a wide array of diseases. As we continue to push the boundaries of scientific discovery, the path towards these novel vaccine solutions becomes increasingly accessible. With concerted efforts and interdisciplinary collaboration, we stand poised to usher in a new era of vaccines that promise to profoundly impact global health outcomes for the better.

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19. Unlocking the Secrets of Gut Microbiota

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Introduction

Ever wondered why we feel a flutter in our stomach when we're nervous or why certain foods seem to affect our mood?

The answer lies in the intricate world of our gut microbiota- the trillions of microorganisms living in our digestive systems. Our bodies are home to trillions of microorganisms, collectively known as microbiota, which plays a crucial role in maintaining our health. Among these the gut microbiota, residing in our gastrointestinal tract, have attracted significant attention due to their profound impact on various aspects of human health. Recent biochemical studies have shed light on the pivotal role these tiny inhabitants play in maintaining our overall health and well-being. Our gut microbiota is like a bustling metropolis, with diverse communities of bacteria, viruses,

fungi and other microbes working together in a delicate balance. These microscopic organisms interact with each other and with our body and influence digestion, immune function, metabolism and even brain health.

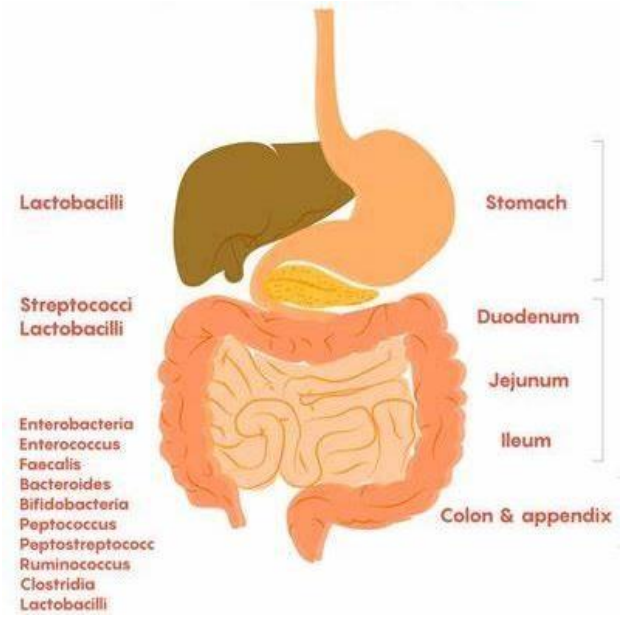

Figure 1. Gut microbiota

Biochemical studies have uncovered fascinating details about how gut microbes communicate with our body and impact our health:

1) **Metabolism regulation**: Gut microbes produce enzymes that help break down complex carbohydrates and fiber, releasing nutrients that our body can absorb. This process not only aids digestion but also influences our metabolism and energy levels. [1] Certain gut bacteria produce short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate, which have been linked to reduced inflammation, improved insulin sensitivity, serve as energy source for colonocytes and contribute to overall gut health and lower the risk of metabolic disorders like obesity and type 2 diabetes. [1,2]

2) **Immune System Modulation**: Gut microbes interact with immune cells in our gut, influencing the development and function of our immune system. This interaction helps regulate immune responses, preventing inflammatory diseases like inflammatory bowel disease (IBD) and allergies. Some gut bacteria produce molecules that stimulate the production of regulatory T cells which play a crucial role in maintaining immune tolerance and preventing autoimmune diseases.[5]

3) **Neurotransmitter Production**: Gut microbes can produce neurotransmitters, such as serotonin, dopamine, and gamma-aminobutyric acid (GABA), which are known to affect mood, behavior, and cognitive function. The gut-brain axis, a bidirectional communication system between the gut and the brain, allows gut microbes to influence brain health and mental well-being.

4) **Protection Against Pathogens**: By producing antimicrobial substances, gut microbes help protect against the colonization and overgrowth of harmful pathogens. Certain species of gut bacteria can outcompete pathogens for nutrients and space in the gut, reducing the risk of infections and maintaining a healthy microbial balance.

GUT- BRAIN AXIS

The bidirectional communication between the gut and the brain, known as the Gut- brain axis, namely through signaling between gut microbiota and brain and with brain to gut microbiota through neural, endocrine or humoral means which helps helps in maintaining neuroendocrine and neuroimmune homeostasis. [3] Emerging evidence suggests that gut microbiota derived metabolites including gammaaminobutyric acid, exert neuroactive effects and modulate brain function. GABA, a major inhibitory neurotransmitter in the Central Nervous System (CNS) is produced by certain gut bacteria through decarboxylation of glutamate. This microbial derived GABA can cross the blood-brain barrier, influencing neuronal excitability, neurotransmission and behaviour.

The mechanism underlying the gut microbiota brain axis involves multiple pathways. Vagus nerve signaling facilitates bidirectional communication between the gut and the brain, transmitting sensory information and modulating autonomic functions. Moreover gut microbiota-derived metabolites, such as SCFAs and GABA interact with neuronal receptors, including GABA receptors, and influence neurotransmitter synthesis and release.[3]

Diseases associated with dysregulation of gut microbiota

Dysbiosis of the gut microbiota has been linked to various diseases, including inflammatory bowel diseases (IBD), irritable bowel syndrome, obesity, metabolic disorders, autoimmune diseases and neurological conditions such as depression and anxiety. Studies have shown that dysbiosis- induced reductions in SCFA production are linked to increased susceptibility to inflammatory conditions.[5] Altered microbial composition and dysregulated immune responses contribute to pathogenesis of these disorders.

Therapeutic potential: The insights gained from biochemical studies have paved the way for innovative therapeutic interventions targeting the gut microbiota. Probiotics, prebiotics and fecal microbiota transplantation (FMT) (insight gained from biochemical studies) have shown promise in treating various conditions, including antibiotic-associated diarrhea and Clostridioides difficile infection (CDI). [1,4]

CONCLUSION

The gut microbiota plays a crucial role in human health, influencing metabolism, immune function and neurological processes through intricate biochemical interactions. Dysregulation of the gut microbiota has been implicated in various diseases, underscoring the importance of maintaining microbial balance for optimal health.

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20. Painless Innovation: The Future of Needleless Injections

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Introduction

Are needles becoming relics of the past in the realm of drug delivery? In a world where innovation knows no bounds, needle-free injection systems have emerged as pioneers in revolutionizing drug administration. The landscape of drug delivery is undergoing a remarkable transformation, propelled by advancements in needle-free injection technologies. Needle-free injection systems have emerged as a groundbreaking innovation in the field of drug delivery, offering numerous advantages over traditional needle-based methods. They utilize various mechanisms to deliver medication into the body without the need for traditional needles.

The growing demand for needle-free injection systems is driven by several factors, including the rising prevalence of needle phobia and the need for improved safety in healthcare. The Needle-free technique was first described in 1936 by Marshall Lockhart in his patent jet injection (1). The NeedleFree Injection Technology (NIFT) employs a diverse range of techniques to deliver the target drug beyond the epidermis (2).
In recent years, significant advancements have been made in the development of needle-free injection technologies, ranging from jet injection systems to micro-needle arrays and powder injection devices.

Mechanism and Working Principle:

1. **Jet Injection**: One of the most commonly employed mechanisms is the jet injection. In jet injection systems, a high-pressure stream of liquid, typically propelled by a gas or spring mechanism, is used to penetrate the skin and deliver medication into the underlying tissues. The process begins with the loading of the medication into a sterile chamber within the injection device. When activated, the device rapidly pressurizes the medication, forcing it through a narrow orifice at high velocity. This creates a fine stream of liquid that penetrates the skin, depositing the medication into the targeted tissue layers. Jet injection systems can deliver medication subcutaneously, intramuscularly, or intradermally, depending on the device design and application technique (2, 3, 4).

2. **Micro-needle Arrays**: Another mechanism employed in needle-free injection systems is the use of micro-needle arrays consisting of micron-scale needles or projections arranged on a patch or array. The working principle of micro-needle arrays involves the gentle insertion of the micro-needles into the skin, where they create microscopic channels for the efficient delivery of medication, making this process virtually painless and minimally invasive (4, 5).

3. **Powder Injection**: Powder injection is accomplished by a light gas gun. An accelerating piston provides enough velocity to the molecules, that carries them along. A deacceleration mechanism slows down the piston and forces the particles carried along with it to leave the piston's surface. This leads to the ejection of particles that act on the target tissue area. It offers increased stability of therapeutic agents (4, 5).

Advantages over traditional needle-based methods

Needle-free injection systems offer several advantages over traditional needle-based methods. Firstly, they

eliminate the risk of needlestick injuries and reduce the associated fear and anxiety among patients, particularly children, and individuals with needle phobia. Additionally, needle-free injection systems minimize the risk of cross-contamination and infection transmission, enhancing safety for both patients and healthcare providers. Furthermore, needle-free injection systems offer improved accuracy and consistency in medication delivery, ensuring optimal therapeutic outcomes. The painless and non-invasive nature of needle-free injections promotes greater patient acceptance and compliance with medication regimens. This can lead to improved medication adherence and better management of chronic conditions. They are user-friendly and easy to administer. provide greater convenience and flexibility in administration, making them suitable for self-administration by patients in home or community settings. This enhances convenience and reduces the need for frequent visits to healthcare facilities (4).

Applications

These injections also find a diverse range of applications across medical fields. They are employed for insulin delivery in the management of diabetes. They offer painless and convenient administration of insulin, improving patient acceptance and adherence to insulin therapy. Needle-free injections are utilized in pain management for the administration of analgesics and local anaesthetics (6). Furthermore, they find applications in emergency medicine for the rapid administration of medications such as epinephrine, naloxone, and antidotes. They enable swift and effective treatment in critical situations without the need for needle insertion (7).

Conclusion

In conclusion, needle-free injection technology represents a monumental leap forward in the field of drug delivery, offering unparalleled advantages over traditional needle-based methods. The evolution of needle-free injection technologies, from jet injection systems to micro-needle arrays and powder injection devices, has revolutionized the way medications are administered, making them safer, more convenient, and less invasive for patients. Their widespread adoption in diverse clinical settings underscores their transformative potential and the profound impact they have on patient care. As we stand on the brink of a new era in drug delivery, fuelled by innovation and technological advancement, needle-free injection systems emerge as the vanguard of change. With continued research and development, these pioneering technologies hold the promise of further enhancing healthcare delivery, improving patient outcomes, and shaping the future of medicine.

Thus, medication can, now, be administered reliably, painlessly, and with precision, all without a single prick.

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2. Patwekar SL, Gattani SG, Pande MM. Needle free injection system: A review (2013) *Int J Pharm Pharm Sci* Vol 5:14-9. https://doi.org/10.55248/gengpi.4.523.44134

3. Tejashree W, Gautam S, Sunil KD, Murali MP, Gaurav G, Mahaveer S, Kamal D. Microneedles: A smart approach and increasing potential for transdermal drug delivery system (2019) *Biomedicine & Pharmacotherapy* Vol 109; 1249-1258. https://doi.org/10.1016/j.biopha.2018.10.078

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5. Anubhav Arora, Murk R, Prausnitz, Samir Mitragotri. Microscale devices for transdermal drug delivery (2008). *Int J Pharm*; 364:227-36. Doi: https://doi.org/10.1016/j.ijpharm.2008.08.032

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7. CynthC. Formulating for Needle-free Jet Injection (2015) *BioPharm International,* Volume

B. SCIENTIFIC GALLERY

1. Guardians of the Garden: “The Remarkable Role of Ladybugs in Nature’s Balance”

Simran Kumari (Batch of 2021-24)

Department of Biochemistry, Shivaji College, University of Delhi

Ladybugs, also known as ladybirds, are not just delightful insects with their vibrant colors and distinctive patterns; they play crucial roles in ecosystems, particularly in agricultural settings. Despite their small size, ranging from 0.8 to 18 mm (0.03 to 0.71 inches), ladybugs live relatively long lives, averaging 2 to 3 years. These petite beetles act as natural pest managers, preying on aphids and other detrimental insects to safeguard plants. Their conspicuous markings serve as a warning to potential predators, signaling that they are unpalatable.

When threatened, certain species of ladybugs employ defensive mechanisms such as reflex bleeding, where they release a yellowish fluid containing toxic alkaloids from their leg joints to deter attackers. Additionally, they can emit a strong odor from these joints as an extra deterrent. Some ladybug species have evolved to mimic the appearance of other insects like ants or beetles, aiding in camouflage. Their bright hues, including red, orange, and yellow, serve as warning signals in nature.

Communication among ladybugs primarily occurs through chemical signals known as pheromones. When in flight, a ladybug's wings beat approximately 5100 times per minute or about 85 beats per second. Although ladybugs possess two pairs of wings, they only utilize one pair for flying, with the front wings providing protection to the rear wings, which are the ones used for flight. Despite having two eyes, ladybugs have limited vision and can only distinguish between light and dark.

- Scientific Name:Coccinellidae
- Camera: MI 11lite NE 5g
- Location: Chuhan, Pathankot, Punjab
- Date: 21st February, 2024

- Captured by: SIMRAN KUMARI
- Reference :https://kids.nationalgeographic.com

2. Life in a Bottle: Drosophila Habitat

Khushi Negi (Batch of 2021-24)

Department of Biochemistry, Shivaji College, University of Delhi

Drosophila melanogaster, commonly known as the fruit fly, is a pivotal organism in scientific research, particularly in genetics and developmental biology. Its small size, short generation time, and well-characterized genome make it an ideal model organism for studying various biological processes. Fruit flies share many genes with humans, making them valuable for understanding fundamental biological principles and disease mechanisms. Researchers have extensively utilized Drosophila to investigate topics ranging from embryonic development and behavior to neurobiology and aging. Moreover, its genetic tractability allows for sophisticated manipulations, such as gene knockouts and transgenic expression, facilitating the elucidation of gene functions and molecular pathways. Consequently, Drosophila serves as an indispensable tool in advancing our knowledge of genetics and biology, contributing to numerous breakthroughs in scientific research.

- Camera: One plus 6T
- Location: Biochemistry lab, Shivaji College
- Date: 2nd March, 2024
- Captured by: Khushi Negi
- Tolwinski, Nicholas S. “Introduction: Drosophila-A Model System for Developmental Biology.” Journal of developmental biology vol. 5,3 9. 20 Sep. 2017, doi:10.3390/jdb5030009

3. Stomata in Tradescantia pallida

Devender Kumar (Batch of 2022-2026)

Department of Biochemistry, Shivaji College, University of Delhi

Tradescantia pallida is a delicate evergreen perennial originating from northeast Mexico, spanning from Tamaulipas to Yucatan. It is cultivated for its striking purple foliage, serving as an ornamental plant. Initially designated as *Setcreasea pallida* by Joseph Nelson Rose in 1911, it was later reclassified under the genus Tradescantia by D.R. Hunt of the Royal Botanic Garden Kew in 1975. Despite this reclassification, the former names S. pallida or S. purpurea are still commonly used. Popularly known as purple heart or purple heart wandering jew (and sometimes referred to as "Moses in the Basket," although this name typically denotes a different species), this herbaceous plant belongs to the Commelinaceae family, also known as the spiderwort family. It is a trailing plant of modest height, resilient in zones 7-10, yet adaptable as an annual or indoor plant in colder regions.

A stomate refers to any of the tiny openings or pores found in the epidermis of leaves and young stems. Typically, stomata are more abundant on the underside of leaves. They facilitate the exchange of gases between the external atmosphere and the intricate network of interconnected air channels within the leaf. Stomata open and close in reaction to the internal pressure exerted by two sausage-shaped guard cells enveloping them. These guard cells have a thicker inner wall compared to the outer one. When the guard cell accumulates water and becomes turgid, the outer wall bulges outward, dragging the inner wall along, thereby enlarging the stomata.

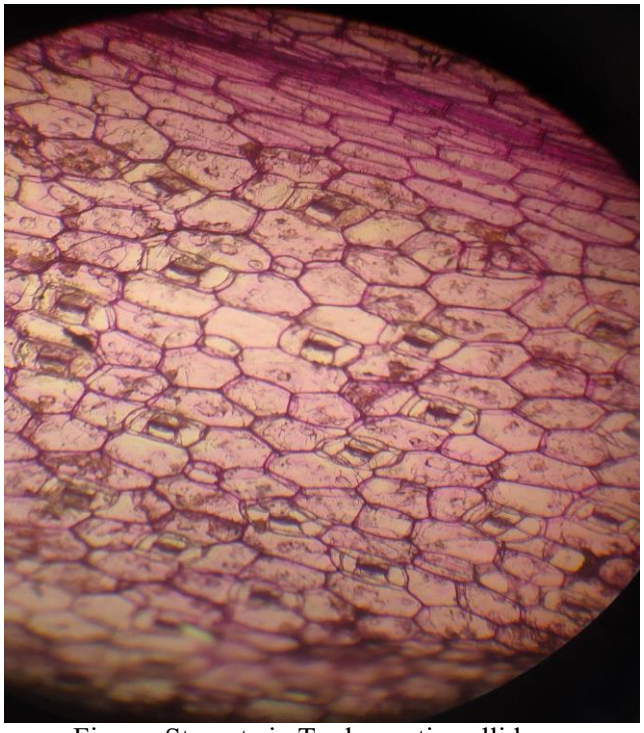

Figure. Stomata in Tradescantia pallida

- Camera- Realme 5 pro
- Location- Shivaji College's biochemistry lab
- Date- 21 April 2023
- Captured by- Devender Kumar
- Reference: https://hort.extension.wisc.edu/articles/purple-heart-tradescantia-pallida/

4. How Yellow Dahlias Bring Sunshine to Your Garden: A Burst of Joy in Petal Form!

Shivangi Aggarwal (Batch 2021-2024)

Department of Biochemistry, Shivaji College, University of Delhi

In the vibrant world of flowers, few blooms can rival the stunning allure of the Dahlia 'Kelvin Floodlight'. With its luminous yellow petals and captivating presence, this cultivar stands out as a beacon of warmth and radiance in any garden. Let's delve into the fascinating characteristics and captivating history of this sunshine blossom.

Interestingly, the cultivar name 'Kelvin Floodlight' pays homage to the renowned physicist and engineer, Lord Kelvin, known for his contributions to the understanding of thermodynamics and light. The choice of name reflects the radiant warmth and luminosity of this dahlia variety.

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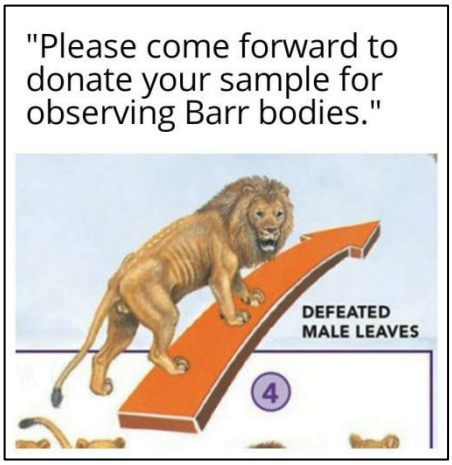
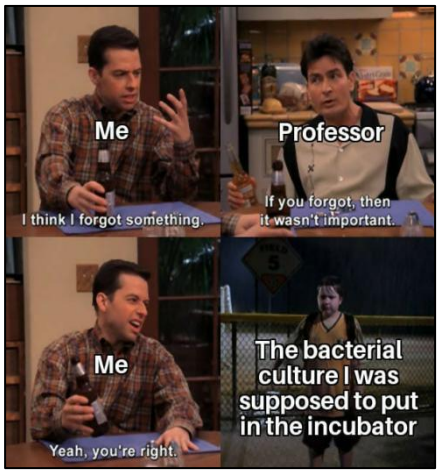
- ***Scientific name-*** *Dahlia*
- ***Camera-*** *OnePlus 7T*
- ***Date-*** *27 February 2024*
- ***Captured by-*** *Shivangi Aggarwal*
- ***Location-*** *Shivaji College Campus, DU*
- ***Reference:****https://www.easytogrowbulbs.com/products/dahlia-kelvin floodlight?variant=31581665804*

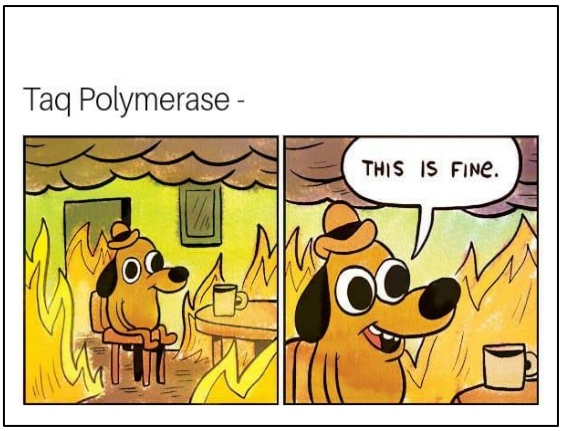
Humour in Science

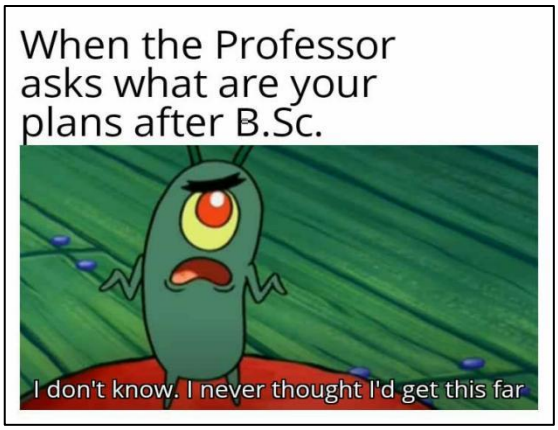
Shivangi Aggarwal (Batch 2021-2024)

Department of Biochemistry, Shivaji College, University of Delhi





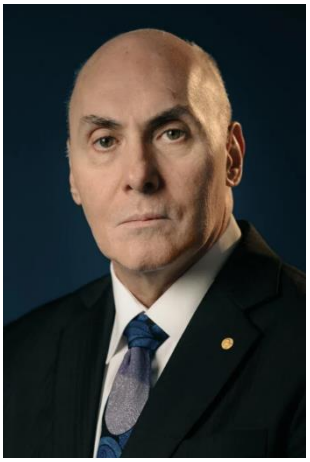




C. NOBEL HALL OF FAME

2023-24

The Nobel Prize in Physiology or Medicine 2023



Katalin Karikó **Drew Weissman**

© Nobel Prize Outreach. Photo: Clément

Nobel Prize in Physiology or Medicine for their discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19.

The Nobel Prize in Chemistry 2023

Moungi G. Bawend **Louis E. Brus** **Aleksey Yekimov**

© Nobel Prize Outreach. Photo: Clément Morin

Nobel Prize in Chemistry 2023 for the discovery and development of quantum dots. These tiny particles have unique properties and now spread their light from television screens and LED lamps. They catalyse chemical reactions and their clear light can illuminate tumour tissue for a surgeon.

D. STUDENTS' PROGRESSION

2020-23

Total Strength of Class: 19			
S. NO.	**NAME OF THE STUDENT**	**NAME OF INSTITUTE/ UNIVERSITY**	**NAME OF PROGRAMME**
1.	Aantra Rao	Christ University, Bangalore	MSc Biotechnology
2.	Dakshita Sehrawat	Department of Anthropology, University of Delhi	MSc Forensic Science
3.	Karishma Lekhwar	Julius Maximilans University of Wurzburg, GERMANY	MSc (H) Biochemistry (Focus: Molecular Oncology)
4.	Mehfooz Helal	Central University of Punjab	MSc (H) Biochemistry
5.	Mitali Singh	National Institute of Technology, Rourkela	MSc Life Sciences
6.	Pooja Gupta	Amity University, Noida	MSc Biotechnology
7.	Sudhanshu Shukla	Indian Institute of Science, Bangalore	MSc Life Sciences (Focus: Peptide Engineering)
8.	Tushar Gupta	Guru Gobind Singh Indraprastha University, New Delhi	MSc Bioinformatics
9.	Vanshika Bansal	All India Institute of Medical Sciences, New Delhi	MSc Biotechnology

E. ENTRANCE EXAMINATIONS/ INTERNSHIPS

I. Entrance Examinations

Tentative dates of some important competitive examinations for students pursuing biological sciences

S. NO.	EXAMINATION NAME	REGISTRATION STARTS FROM (Tentative)	MONTH OF EXAMINATION (Tentative)
1.	TIFR (Tata Institute of Fundamental Research Graduate School Admissions)	October 2024	December 2024
2.	IIT JAM (Indian Institute of Technology Joint Admissions Test for M.Sc.)	September 2024	February 2025
3.	GAT-B (Graduate Aptitude Test Biotechnology)	March 2025	April 2025
4.	AIIMS MSc Biotechnology, Biochemistry, Entrance Exam	February 2025	June 2025
5.	GATE (Graduate Aptitude Test Examination)	August 2024	February 2025
6.	IBAB (Institute of Bioinformatics and Applied Biotechnology Entrance Exam)	January 2025	May 2025
7.	CUCET (Central Universities Common Entrance Test)	March 2025	June 2025
8.	KIITEE (Kalinga Institute of Industrial technology Entrance Exam), M.Sc. Biotechnology	December 2024	February 2025
9.	University of Madras M.Sc. Entrance Exam	April 2025	June 2025
10.	ICAR (Indian Institute of Agricultural Research All India Entrance Examination)	March 2025	June 2025

11.	Punjab University CET-PG	April 2025	July 2025
12	JNTU M.Sc. Biotech Entrance Exam	June 2025	July 2025
13.	Jamia Millia Islamia MSc Biotechnology Entrance Exam	March 2025	June 2025
14.	Hyderabad University, M.Sc. Biochemistry	April 2025	June 2025
15.	HPU Shimla, M.Sc. Biotechnology	June 2025	July 2025
16.	Osmania University, Hyderabad, M.Sc. Entrance	April 2025	July 2025

II. INTERNSHIPS

Tentative Dates of some important Internships/Training programmes for students pursuing biological sciences:

S. NO.	INTERNSHIP/ TRAINING PROGRAMME TITLE	ORGANIZING INSTITUTION	DURATION	ELIGIBILITY (B.SC. BIOSCIENCE COURSES)
1.	Visiting Students Research Programme (VSRP)	Tata Institute of Fundamental Research	8 Weeks	B.Sc. (2nd Year Completed)
2.	Summer Undergraduate Research Programme (SURP)	Dr. B.R. Ambedkar Center for Biomedical Research	6-8 Weeks	B.Sc. in Biomedical Science, Life Science or Related Subjects
3.	Science Academies' Summer Research Fellowship Programme for Students and Teachers	Indian Academy of Sciences, Bengaluru Indian National Science Academy, New Delhi The National Academy of Sciences, India, Prayagraj	8 Weeks	B.Sc. (2nd Year Only)

4.	Project Oriented Biology Education (POBE)	Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR)	6 to 8 Weeks (Over 3 consecutive summers)	B.Sc. (1st Year of Three-Year B.Sc. Programme Only)
5.	Summer Research Fellowship Programme (SRFP)	Indian Academy of Science	8 Weeks (Renewable for a Second Year for Selected students)	B.Sc. (1st and 2nd Year)
6.	Summer Student Programme (SSP)	IISER Pune	4 to 8 Weeks	B.Sc. (2nd Year onwards)
7.	Summer Research Program	IISER Mohali	4 to 8 Weeks	B.Sc. (2nd Year onwards)
8.	Summer Student Research Programme	IISER Kolkata	4 to 8 Weeks	B.Sc.
9.	Summer Visiting Programme	IISER Thiruvananthapuram	8 Weeks	B.Sc. (Preferably 2nd Year)
10.	IARI internship training	Indian Agricultural Research Institute (IARI)	1 to 6 Months	B.Sc. (Any Year)
11.	Summer Internship Programme	NIT, Durgapur	4 Weeks or more	B.Sc. (Any Year)

12.	Bose Institute Summer Training	Bose Institute	8 Weeks	B.Sc. (Only if recipient of KVPY, INSPIRE, JBNSTS, NTSE or Other similar Awards)
13.	Annual Summer School Programme	School of Life Sciences, Jawaharlal Nehru University	8 Weeks	B.Sc. (Any Year)
14.	Summer Research Internship	Regional Centre for Biotechnology, RCB	7 Weeks	B.Sc. (3rd Year)

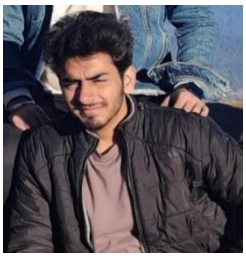
F. MEMORY LANE 2024

Mansi Tanwar (2017-2020), Ph.D. Scholar, 2nd Year, AIIMS Delhi

My time at the biochemistry department of Shivaji College was truly incredible, teaching me patience and resilience. Professors, both in academic and non-academic realms, dedicated themselves tirelessly to imparting knowledge, from fundamentals to advanced topics, along with organizing conferences, fun trips and offering guidance on research articles and journal editing, adding to the comprehensive teaching approach.

Also, don't forget the importance of holding onto your college friendships; they'll be invaluable in the years ahead. And please get involved in every event, whether academic or non-academic, happening in the college or department or any other DU college. This phase is never going to be back. Enjoy your hustle!

Kaushal Grover (2019-22), M.Sc. Computational Biology, JNU



I want to express my heartfelt gratitude to Biochemistry Department for all the amazing experiences, guidance, and support throughout my time as a student. A special thanks to the fantastic faculty, friends, and staff for creating such a supportive and nurturing learning environment. You've all played a huge part in my personal and professional growth!

To the juniors, cherish every moment and seize every opportunity during your time here. I wish you all the best for the future!

Merlin Mathew (2019-22), M.Sc. Biochemistry, South Campus, University of Delhi

As I reflect on my journey through the department, I am flooded with memories of our late-night study sessions for internals, us completing our files while sitting in Hawa Mahal, all the excitement that came with planning a departmental event, and the fun-filled moments with my friends and seniors. From hands-on workshops to online lectures and conferences, our department provided us with an opportunity for all-round development.

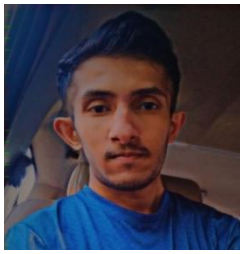
I am grateful for the foundation laid and the memories made that will remain with me for the rest of my life.

Sudhanshu Shukla (2020-23), MS scholar, IISc Bangalore

Three years in the Biochemistry Department of Shivaji College came with a lot of academic and non-academic experiences. It was an honour to be taught by highly qualified as well as skilled professors. Everyone was so helpful and kind, from the faculty to the lab staff, fellow students, and juniors.

Thank you, everyone for making everything so smooth and easy. All the best to my juniors, and remember, “If you can dream it, you can do it.”

Adhbut Jangid (2020-2023), Professional Para-Badminton Player, Preparing for Govt. Exams



In the cacophony of college life, I found myself entwined in a delicate dance between two fervent passion - sports and studies.

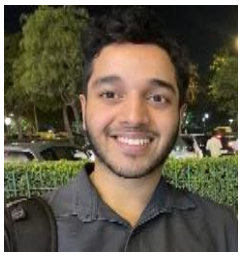
Yet, amidst the chaos and fatigue, there existed a profound sense of fulfilment, a realization that I was living life to the fullest, embracing the challenges with open arms and emerging stronger with each passing day.

As I stand on the precipice of nostalgia, looking back at those formative years with fondness and gratitude, I am reminded of the invaluable lessons learned, the friendships forged in the tapestry of our college memories, your (Teachers) wisdom and dedication shine as beacons of inspiration. Thank you for your unwavering support, your patience, and your tireless efforts in shaping our minds and nurturing our dreams. You have left an indelible mark on our hearts, and we are forever grateful for the invaluable lessons you imparted.

Karishma Lekhwar (2020-23), Master student (Molecular Oncology, Biochemistry) at Molecular Oncology Department, Julius Maximilians University of Würzburg, Germany

Reflecting on my time at Shivaji College fills me with gratitude and nostalgia. The journey through my Biochemistry degree was a transformative one, filled with growth, learning, and cherished memories. As an alumna of Shivaji College, I carry with me not just academic knowledge but also invaluable experiences and friendships that have ignited a Biochemist out of me. From late-night study sessions with friends to prepare for the exams to finally holding a graduate degree in my hand. Shivaji College was more than just an educational institution—it was a second home where I found my passion and purpose. As I embark on the next chapter of my journey, I carry the spirit of my college with me, forever grateful for the foundation it has provided me. Here's to the bonds forged, the knowledge gained, and the countless adventures yet to come. Go, Shivaji! Wishing the college and its current students a bright and promising future ahead!"

Tushar Gupta (2020-2023) Masters of Computer Applications, Indraprastha University



Walking down memory lane brings back so many cherished moments! My journey here was nothing short of transformative. From a shy newbie to a confident individual, this place has shaped me in ways I never imagined. I still remember endless labs and failed experiments and the list goes on but also let's not forget the amazing people I've met along the way – truly the best part of this journey!

TOPPERS

First Year (Batch of 2022-2026)

Priyanka Bisht

I[st] Position

CGPA - 8.82

Gayathry Krishna

II[nd] Position

CGPA - 8.73

Ankita Das

III[rd] Position

CGPA - 8.64

Second Year (Batch of 2021-2024)

Harshita Kohli

I[st] Position

CGPA - 8.86

Simran Kumari

II[nd] Position

CGPA - 8.71

Bhavya Mittal

III[rd] Position

CGPA - 8.64

Third Year (Batch of 2020-2023)

Karishma Lekhwar

I[st] Position

CGPA - 9.189

Aantra Rao

II[nd] Position

CGPA - 9.095

Mehfooz Helal

III[rd] Position

CGPA - 8.919

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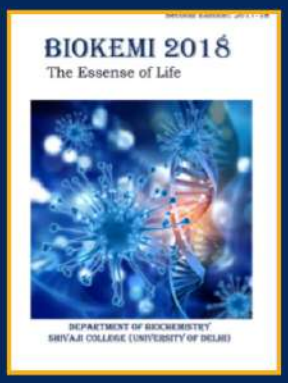
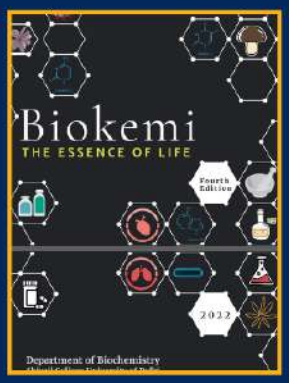
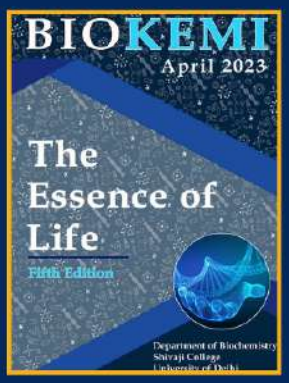
Council of Scientific & Industrial Research
(विज्ञान एवं प्रौद्योगिकी मंत्रालय, भारत सरकार)
Ministry of Science & Technology, Govt. of India

SYMPOSIA GRANT SCHEME

Under the Scheme, financial assistance is provided to Universities, Academic institutions, Colleges, Government Departments, registered societies to organize scientific events such as Symposia/ Seminars/ Conferences/ Workshops or any other similar scientific activity that provides platform/forum to professionals, scientists, research and educational institutions to share knowledge and experience in various fields of Science and Technology. The Scheme provides partial support towards expenses related to organising Scientific events such as Travel support, Registration Fee Waiver, Promotion (web site, brochures, proceedings), Secretarial assistance, Local hospitality, Venue charges.







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