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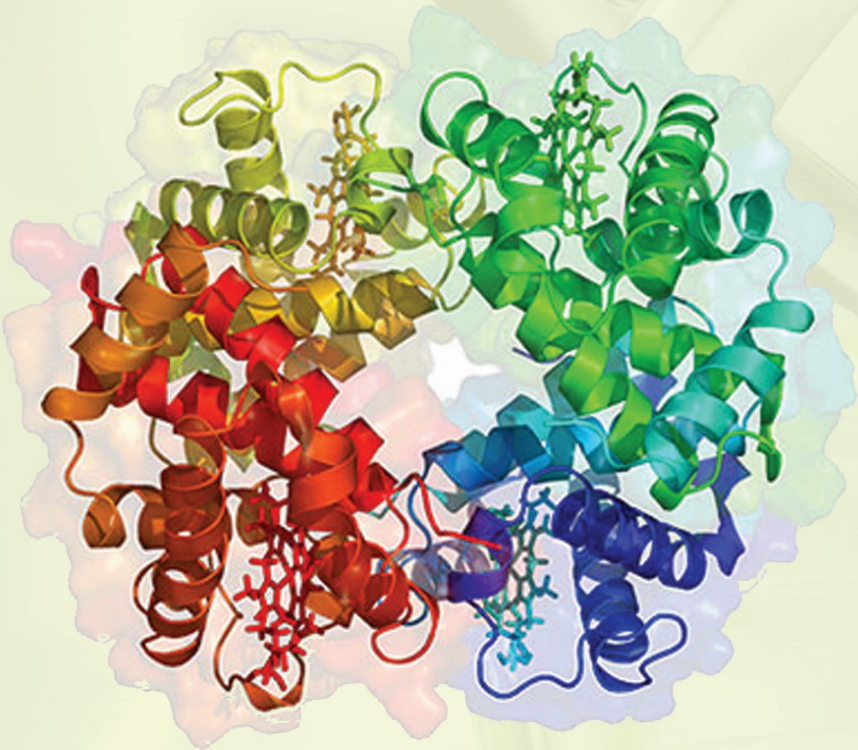

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PHAGE THERAPY

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ABSTRACT

With increase in human population and diseases, care of human health is of utmost importance. From last centuries, antibiotics are used mostly which is used to kill or stop the growth of pathogenic microorganisms. However, it has certain disadvantages such as its broad-spectrum capability i.e., it can kill bacteria other than its target bacteria which can lead to serious damage to human health causing side effects. Bactericidal antibiotics which are used to stop the growth of bacteria instead of killing them which can lead to increase in antibiotic resistance of the bacteria. To cope up all these issues, bacteriophage can be used for the therapy. They are type of virus which infects bacteria which with further modification can be used for treatment. Bacteriophage therapy is cost effective, can easily penetrate biofilm, etc. In this review, types of proteins and advantages of bacteriophage are discussed briefly.

Keywords: Bacteriophage, phage therapy, antibiotics, antibiotic resistance.

INTRODUCTION

Bacteriophage, is a type of virus which infects a bacterium. It is also known as phage and are one of the most abundant organisms found in the biosphere. It was first discovered by W. Twort in 1915 and its potential to infect bacteria was identified by Felix d'Herelle in 1917 (Clokie et al., 2011). The use of bacteriophage was not given any priority post antibiotic era since antibiotic was much easier to administered as compared to bacteriophage but research related to phage used to take place for various fields such as identification of restriction enzymes, basis of genetic material, etc which was of great help in today's molecular biology techniques and research (Clokie et al., 2009). Antibiotics, which are considered as one of the greatest discoveries in the human history is used for treating variety of diseases and illness. Any known disease in the history of humankind can be treated with the help of antibiotics. Based on the spectrum of action, antibiotics are of two types: broad spectrum and narrow spectrum (Rocha et al., 2021). But there are certain complications related to antibiotics such as antimicrobial resistance (AMR) which is one of the greatest threats to the human health which can lead to formation of superbugs which are harder to kill, thus can cause harmful effects to human. For instance, methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant tuberculosis are responsible for deaths of many people around the world (Llor & Bjerrum, 2014). In addition to that, antibiotics are broad spectrum which means it can spread the resistance to both the target of antibiotics as well as other bacteria which were exposed to broad spectrum antibiotics. It can lead to increase in ROS, detrimental effect on gut microbiome, disturb normal body functions such as protection against pathogens and production of vitamins and many other side effects (Sannasimuthu et al., 2020). There are many alternatives to antibiotics such as use of probiotics, Phyto biotics, gene therapy, phage therapy, competitive exclusion of pathogens and many more (Allen et al., 2014; Reid & Friendship, 2002; Vidanarachchi et al., 2005). One of which is phage therapy, in which virus infects bacteria leading to neutralisation of bacteria. It is one of the most researched alternatives to antibiotics. It can be used

because of its target specificity and its efficacy towards mucosal infections (S. Abedon, 2011). In this review, we are going to discuss about preparation of phage for therapy, its advantages and disadvantages and how it can change the face of antibiotic industry.

IMPORTANT PHAGE LYTIC ENZYMES AND THEIR TARGET PATHOGEN

Phage lytic enzymes are enzymes produced by bacterial viruses, either as soluble proteins to induce massive cell lysis at the end of the lytic replication cycle or by facilitating bacterial infection through local peptidoglycan degradation (Briers, 2019). Viral enzymes or proteases are essential for processing encoded polyproteins during replication, in co- and post-translational steps (Mesters et al., 2006). Some important lytic enzymes which are used for phage therapy are listed below.

Lytic enzyme	Target Pathogen	References
ABgp46	*Acinetobacter baumannii, Pseudomonas aeruginosa,*	(Oliveira et al., 2016)
PlyF307	*Acinetobacter baumannii*	(Lood et al., 2015)
Cpl-1	*Streptococcus pneumoniae*	(Witzenrath et al., 2009)
PlyCD	*Clostridium difficile*	(Wang et al., 2015)
PlySs2	*Streptococcus pyogenes*	(Gilmer et al., 2013)
CHAPK	*MRSA*	(Keary et al., 2016)
Artilysins	*Pseudomonas aeruginosa*	(Briers et al., 2014)

APPLICATIONS

Against plant pathogens: Phages have the potential for controlling plant pathogens in the phyllosphere or rhizosphere. However, it requires high amount of both bacterium and phages to initiate a reaction of bacterial lysis. Phage selection is important when treating rhizospheric bacteria because there are many factors such as presence of biofilms, low soil pH which can lead to inactivation of phages. It can be used as a disease control agents against many crops related diseases and various management strategies (Jones et al., 2014).

In Animal Disease: Bacteriophages kill bacteria, are safe, natural, self-limiting, self-replicating, can be used to specifically target pathogens without disruption of commensal bacteria, and have diverse biological properties. All these properties make bacteriophages an attractive alternative to antibiotics, especially broad spectrum and bacteriostatic antibiotics. The effectiveness of bacteriophages to treat and prevent animal diseases has been shown in almost all production animals in both commercial field and laboratory studies. Moreover, combination of phage and antibiotics can be used to enhance the function of phage in disease control (Huff & Huff, 2014).

As Biocontrol Agents in Foods: Phages can be used to control the growth of bacteria both in food products and on food contact surfaces. Phages were successfully used against *Yersinia enterocolitica*, *Shigella spp., Bacillus cereus*, and *Cronobacter spp*. The use of phages resulted in significant, log-fold reductions in the bacterial counts in foods; such reductions are known to substantially decrease a risk of foodborne infections. Recent clearance by FDA of four bacteriophage preparations for food applications shows that bacteriophages are gradually gaining acceptance as a means of prevention of foodborne infections (Borysowski & Górski, 2014).

ADVANTAGES

Safety: Adverse reactions to antibiotics are well documented which include anaphylaxis, nephrotoxicity, cardiotoxicity, hepatotoxicity, and many more. By the use of phage in place of antibiotics, host cell can be easily treated without any harmful side effects. Further study needs to be done regarding the effects of phage therapy (Lin et al., 2017).

Phage as bactericidal agents: Many antibiotics such as tetracycline, chloramphenicols, etc are bacteriostatic in nature i.e., they stop bacterial growth for certain time. This can lead to bacteria gaining resistance towards the antibiotics. Whereas with the help of lytic phages, bacteria have been successfully infected and it was observed that bacteria were unable to regain their viability (Carlton, 1999).

Cost effective: Production of phage's involves a combination between host growth and phage's followed by purification. With the improvement in technology, it is now easier to identify and purify a phage at a very low cost which is low as compared to the industrial production of drugs. The cost of production of phage's can varies depending upon the bacterial species to which it needs to be infected (Skurnik et al., 2007).

Low environmental impact: Phages are made up of nucleic acids and proteins and are mostly specific to certain types of hosts, unlike broad spectrum antibiotics/chemicals which can kill others bacteria other than its target. Phages can be rapidly inactivated with various environmental factors such as temperatures, sunlight, pH, etc and thus have less impact on environment (Ding & He, 2010).

Clearance of Biofilm: A biofilm is a grouping of surface-associated microbial cells that is walled in an extracellular matrix. They protect microbes from the host's immune system and increase their resistance to antibiotics. However, phages have an ability to clear such biofilms by lysing one layer of bacteria at a time and thus have a potential to actively penetrate through the biofilms (S. T. Abedon, 2011).

Rapid Discovery: Unlike antibiotics, phages can be easily discovered from waste products or sewage that contains high bacterial concentration. Although, the process and the cost may be highly demanding when the host bacteria are difficult to culture (Clokie & Kropinski, 2009).

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THE ROLE OF PROBIOTICS ON THE SARS-CoV-2 SYMPTOMS

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ABSTRACT

Saving the lives and reducing the infection rate have become the foremost priorities since the ongoing pandemic spread of SARS-CoV-2. Inspite of strategies based on maintaining social distancing, hygiene, wearing mask, and screening, COVID-19 is rapidly progressing throughout the world with the entire healthcare systems at risk. Though additional effective drug therapies and vaccines research are going on, still certain additional preventive strategies are at urgent need. For these reasons, non pharmacological supplements, probiotics with numerous advantages, easy availability, and negligible side effects are administered to be a beneficial one in mitigating the symptoms of SARS-CoV-2 infection. Thus, rigorous clinical trials to confirm the putative benefits of diet supplements, probiotics in current situation is a must.

Keywords: probiotics, supplements, SARS-CoV-2, COVID-19

INTRODUCTION

The novel coronavirus pandemic of 2019 (COVID-19), a global pandemic caused by multiple strains of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is causing thousands of victims every day around the world with its unexpected infectious spreading capacity, which has not allowed an adequate preparation. Since its first detection in Wuhan, China, SARS- CoV-2 has had a dramatic worldwide diffusion. At the time of writing this review, SARS-CoV-2, has caused well over 109 million infections and more than 2.4 million deaths. The clinical seriousness of the disease ranges from severe pneumonia to asymptomatic cases and sometimes even leading to multi organ failure (MOF). Thus, COVID-19 has arisen as a multi-system, multifaceted, multi-organ disorder infecting individuals irrespective of age groups and sex. Notably, elderly patients with comorbidities (especially diabetes) are more likely to experience a severe illness. Despite of several scientific efforts focused on producing a vaccine and effective antiviral drugs to halt the pandemic, it is difficult to guarantee the marketing of a safe product in a short time without any prior evidence of proper clinical trial of targeting the molecular pathways of SARS-CoV-2 (Cao et al., 2020). However, only remdesivir has shown to be effective in shortening the recovery period of hospitalized COVID-19 patients (Beigel et al., 2020). Also, treatment with chloroquine and hydroxychloroquine has shown mixed benefits, but according to some researches it may even be harmful due to cardiac toxicity (Funck-Brentano & Salem, 2020). Apart from a pharmacological therapy, many are wondering if some non-pharmacological substances can be used to strengthen their immunity. The pharmacological properties of probiotics have gained immense attention in the field of alternative therapeutic approaches to several diseases.

INTESTINAL INVOLVEMENT IN SARS-CoV-2

Infected individuals with COVID-19 usually manifest fever and respiratory symptoms. However, a typical symptom, diarrhoea and other gastrointestinal (GI) manifestations in the first US case of COVID -19 have attracted more attention in the scientific community (Holshue et al., 2020).The binding of virus

surface spike proteins to Angiotensin-Converting-Enzyme-2 (ACE2) mediates SARS-CoV-2 infection in human cells (Hoffmann et al., 2020). High expression of ACE2 is observed not only in AT2 lung cells but also in oesophagus epithelial cells and enterocytes in the ileum and colon (Zhang et al., 2020). A protein named TMPRSS2, responsible for the priming of the viral spike protein is also expressed in absorbent enterocytes (Bertram et al., 2012). In some COVID-19 patients, SARS-CoV-2 RNA is detected in faeces even after the clearance of the virus in the upper respiratory tract (Gu et al., 2020; Holshue et al., 2020). GI tract can be a potential route to SARS-CoV-2, due to the presence of the ACE2, the viral host receptor was demonstrated in the cytoplasm of GI epithelial cells, while the viral nucleocapsid protein was identified in the cytoplasm of rectum, duodenal, and gastric epithelial cells (Xiao et al., 2020). Hence, it is possible that viral replication in the intestine may result in an exponential growth of the viral load in the digestive mucosa. Thus, leading to a loss of barrier integrity, with an imbalance of the microbial flora and its metabolites, which could lead to a strong production of cytokines. This to a certain extent may justify the appearance of acute respiratory distress syndrome (ARDS) and Multiple organ failure (MOF) following interstitial pneumonia.

PROBIOTICS AND VIRAL INFECTION

Probiotics are live microorganisms associated with health benefits to the host, has experienced a renewed interest in society. The idea of treatment with probiotics dates back to 1907. There has been a renewed interest in probiotics not only for improving digestive health, but also in management of inflammatory diseases. *Lactobacillus* and *Bifidobacterium* have evolved as two most commonly used probiotics, *Lactobacillus* (commonly found in curd) is a popular diet supplement in every household for maintaining a healthy gut.

Besides being beneficial bacteria, probiotics also possess antiviral activity, including against coronavirus (Chai et al., 2013). Probiotics, act as an alternative to natural immune enhancer (Lakshmi et al., 2013). Probiotics and their metabolites stimulate innate or adaptive immunity by indirectly interfering with the virus through altering the state of cells. They exert antiviral activity by (1) direct probiotic-virus interaction, (2) production of antiviral inhibitory metabolites, and (3) stimulation of the immune system. Probiotics can interfere with ACE2, the primary host receptor of the SARS-CoV-2. Certain strains of *Lactobacillus* (*L. helveticus*and *L. casei*) during milk fermentation release peptides with high affinities for ACE. Bovine milk fermented with *Lactobacillus* species yields fermented products enriched with ACE-inhibitory peptides (Li et al., 2019), some of which are resistant to GI digestion and inhibit ACE in the rennin-angiotensin system (RAS).

Oral uptake of *L. brevis* in mice is found to enhance antiviral IFN-α as well as production of specific-IgA antibodies against the virus (Waki et al., 2014). Interestingly, Lactobacilli showed to be protective against viral respiratory infections, influencing innate immune responses directly in the airway epithelium upon intranasal administration (Harata et al., 2010). *Bifidobacterium animalis* subspecies *lactis* BI-04, in an experimental rhinovirus infection, have shown to reduce the pro-inflammatory cytokine IL-6 levels, along with nasal lavage virus titer (Turner et al., 2017). The same when administered in the respiratory tract of mice infected with pneumonia virus (PVM), increased mice survival and reduced IL-6 levels. *Lactobacillus gasseri* shows antiviral activity against respiratory syncytial virus (RSV), administration of this in mice results in reduction of the RSV titer in the lungs (Eguchi et al., 2019). COVID-19 patients needing intensive care has higher plasma levels of many cytokines such as IL-6, IL-1, IP-10, MCP-1, MIP-1A, and TNFα (Prompetchara et al., 2020) with respect to non-intensive care unit subjects, increasing the severity and progression of the disease.

Moreover, a large infiltration of inflammatory cells has been observed in the lungs of severe patients (Tian et al., 2020; Z. Xu et al., 2020) which along with inflammatory monocytes, may cause an immune injury with consequent respiratory disability in lungs and increased rate of mortality. The alteration of the cytokine cascade exerted by probiotics may represent therapeutic approach for severe infections, making it permissible to hypothesize that probiotics administration influences the immune response in patients infected with COVID-19. Although solid evidence for the possible role of probiotics on SARS-CoV-2 infection is still lacking (Mak et al., 2020), probiotics could represent an alternative tool to decrease SARS-CoV-2-related inflammation and favour the recovery of intestinal mucosa damage by gut dysbiosis. It is possible that probiotics might play a role in preventing the cytokine cascade and related ARDS or MOF in high-risk individuals with confirmed SARS-CoV-2 infection, but the opposite may also be true, and the lack of sufficient evidence should be considered. Henceforth, safety measures need to be considered while administering bacterial supplements.

COVID-19 AND PROBIOTICS: CURRENT PROSPECTS

A report from China suggests that COVID-19 patients suffer microbial dysbiosis due to imbalance of Lactobacillus and Bifidobacterium, with more than 60% patients expressing GI symptoms (K. Xu et al., 2020), which may also imply greater severity. Reinforcement of colonic microflora using probiotics reduces secondary infection and diarrhoea in patients receiving antibiotics. A meta-analysis revealed that the effect of probiotics such as *Lactobacillus* and *Bifidobacterium* produce a modest decrease in common cold, a symptom of COVID-19 (Kang et al., 2013). Furthermore, meta-analysis of Random Controlled Trial (RCTs) suggests probiotics decrease ventilator-associated pneumonia (VAP)(Su et al., 2020) and duration of antibiotic use for VAP. The excessive release of inflammatory cytokines is the cause for severity and death of COVID-19 patients (Daneshkhah et al., 2020). Therefore, to treat COVID-19, anti-cytokine therapy for suppressing the hyper-inflammatory states is recommended. Moreover, probiotics' ability in balancing the composition of gut microbiota (Dhar & Mohanty, 2020), along with the immunomodulatory potential, helps improving the cytokine storm. Therefore, the use of probiotics with anti-inflammatory effects could maintain the equilibrium of intestinal microbiome and prevent secondary infection in SARS-CoV-2 patients.

CONCLUSION

The potential possible role of probiotics has been demonstrated by numerous clinical studies. Lactobacilli and Bifidobacteria have shown a promising beneficial impact in overcoming gut dysbiosis induced by SARS-CoV-2 infection. The application of probiotics in modulating the gut microbiome and its interactions with the respiratory system is going to increasingly expand the use of probiotics as adjunctive treatment for COVID-19 with time. As of now, when drugs are being used with little anti- COVID-19 data by doctors, probiotics with ability to reduce the severity of COVID-19 morbidity, mortality and inhibit cytokine storm by influencing the innate immunity and evading the exaggeration of adaptive immunity should become a part to reduce the burden and severity of this pandemic.

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MELATONIN AS IMMUNOMODULATOR AND ITS CONTRIBUTION IN IMMUNITY AGAINST ORAL MICROBIOME AND COVID-19

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ABSTRACT

In this review, the immunomodulatory effects of melatonin are discussed, along with how melatonin control the timing and release of certain hormones in human, circadian system, how it helps to strengthen the immune system and how it may help in contributing to COVID-19. Melatonin is a pineal indolamine that is primarily secreted by pineal gland participates in the different body functions such as angiogenesis inhibition and anti-tumor action. Melatonin has demonstrated to have beneficial effects on dental pathologies, exert immunological, antioxidant and anti-inflammatory effects, which can be serviceable in certain dental diseases.

Keywords: melatonin, immunomodulator, oral diseases, antiviral, cytokine storms.

INTRODUCTION

Melatonin is a chemical compound which has the chemical formula of $C_{13}H_{16}N_2O_2$ having melting point of 117°C. This compound is most often suggested as "Off-white powder" which has amino acid tryptophan as an important precursor. It is present both in unicellular prokaryotes such as bacteria and other eukaryotes, vertebrates and invertebrates, fungi, algae, other floras and are also found in various edibles such as fruits, herbs vegetables. Hydroxy indole-O-methyl transferase and tryptophan hydroxylase are enzymes that is able to transfer the methyl group of S-adenosylmethionine to the hydroxy group of N-acetyl serotonin by decarboxylation to form melatonin hormone (Axelrod & Weissbach, 1960). Melatonin was first isolated back in 1960s when this compound was considered to be the substance that by causing aggregation of granules of melanin, can lighten the color of frog's melanocytes. Back then, noradrenaline (synonymous with norepinephrine), the main neurotransmitter of the sympathetic nervous system, is responsible for tonic and reflexive changes in cardiovascular tone, was recognized to be the most active lightening agent, but after the discovery of melatonin revealed that it is 10,000 times more powerful than noradrenaline (Goldstein, 2010). An experiment with Bovine pineal glands and skin of *Rana pipiens* was conducted. They isolated the skin and darkened it with caffeine, as soon as the pigment disseminate throughout the cell, light was allowed to transmit in. After 10 to 20 minutes of addition of melatonin, the skin lightened (Lerner et al., 1960). The physiological effects of melatonin were not yet discovered back then. But now Melatonin is known for its diversity and variability. The production of melatonin is favorably at night because it is exclusively associated with the cAMP mechanisms and NAT activity, while the pattern of production seems species specific, while in vertebrates particularly mammals, MT is secreted in a robust circadian rhythm, from the pineal glands at night (Reiter, 1991). In fact many papers suggested that MT is a, clock and a calender at the same time as its biological rhythm marks 24 hours a day, a sleep hormone or darkness hormone and a chronobiotic substance which helps to regulate the improvement of non-24 hour sleep wake disorder (Arendt & Skene, 2005).

The rhythmic production of melatonin in the pineal gland is under the control of norepinephrine synthesized and released from commiseration endings that terminate on pinealocytes. Information related to the light: dark cycle is transferred from the eye, via the retino hypothalamic tract to the suprachiasmatic nucleus (SCN); these nuclei constitute the biologic clock and synchronize circadian melatonin synthesis. The SCN deliver a neural signal to the pineal gland via pre and post ganglionic neurons with the final synapse in the superior cervical ganglia. Melatonin was found to have adverse promising effect on the maturation of oocyte, fertilization, and quality of embryo (Zhao et al., 2021). It was also proved that when melatonin is consociated with hyperprolactinemia, shows harmonious result and it is also a dominant factor for maintenance of progesterone levels (FdCAM et al., 2020).

IMMUNOMODULATING EFFECTS OF MELATONIN

The immune system is a versatile defense system that has evolved to protect animals from being invaded by pathogenic microorganisms and cancer by maintaining tissue homeostasis and system integrity. It can generate an enormous variety of cell molecules capable of specifically recognizing and eliminating a good number of foreign invaders. The immune system can acknowledge the subtle differences that distinguish one foreign pathogen or any unknown cell from another. Once foreign molecules have been recognized the immune system recruits a variety of cells and molecules to defend. Functionally, an immune response can be categorized into two related activities recognition and response. Immune recognition is unusual for its specificity. The immune system is able to recognize subtle chemical differences that differentiate one foreign pathogen from another. Furthermore, the system is able to differentiate between foreign cells and the body's own cells and proteins. Once a foreign organism or cell has been recognized, the immune system inducts a variety of cells and molecules to mount an appropriate response, called an effector response, to eliminate or neutralize the organism. In this way the system is able to convert the initial recognition event into a variety of effector responses, each uniquely suited for eliminating a particular type of pathogen. Later, exposure to the same foreign organism or induces a memory response, characterized by a more rapid and heightened immune reaction that serves to eradicate the pathogen and prevent disease (Sattler, 2017). To enhance or modify the various logical and non-specific responses of our immune system, the use of variety of agents like interferons, drugs like thalidomide, amantadine and tilorone are certainly exciting development of immunopharmacology, and are termed as immunomodulators or immunostimulatory. They may act either by increasing the humoral antibody responses, or by increasing the phagocytic activity of the macrophages, and modifying the cell mediated responses. The Melatonin along with its diverse pleiotropic properties, elevate an increase in the weight of thymus and spleen of distinct rodents, and it also provides compelling protection against injurious effects of dexamethasone including a decrease of body weight, and degeneration of thymus and adrenals. Melatonin take part in an immunomodulatory role, by stimulating the secretion of interleukin-2 (IL-2) and interferon-a (INF-a) and the consequent activation of $CD4^+$ lymphocytes. Furthermore, melatonin reportedly stimulates the proliferation and synthesis of type I collagen and promotes bone formation. In general, MT expresses adverse positive effects on the humoral and cell-mediated responses under basal or immunosuppressed conditions. Back in 1986, Melatonin, alone or in combination with dehydroepiandrosterone (DHEA), suppress Th2 cell cytokines such as IL-10, improving cellular immune function. This results in the increment of the IL-2 and IFN-gamma in old mice (Inserra et al., 1998).

CONTRIBUTION OF MELATONIN IN ORAL CAVITY

The introductory part of the digestive tract is the oral cavity, which includes the lips, the bony front

portion of the roof of the mouth called hard palate, the muscular back portion of the roof of the mouth called soft palate, retromolar trigone which is located in the area behind the wisdom teeth, gums or gingiva buccal mucosa, the inner lining of the lips, the floor under the tongue and the front two-thirds of the tongue. Melatonin plays an important role in providing protection from the tissue damage caused by oxidative stress. Various studies were reported that melatonin is an important mediator in bone formation and impulsion (Witt-Enderby et al., 2006). MT might play a important role in the physiological role in tooth maturation by mediating the cell functions of the odontogenic cells (Kumasaka et al., 2010). A human dental papilla cell line, DP-805 cells, exhibited Mel1aR. The level of expression of mRNA for Mel1aR in DP-805 cells shoot up rapidly until few days after reaching conflux and decreased thereafter. Melatonin also enriched the mineralized matrix formation in DP-805 culture cell lines in a dose-dependent manner (Tachibana et al., 2014). In Hamsters, when the level of melatonin levels is maximum, caries occurs less frequently, but in the spring and summer, when the level of melatonin is minimum, more caries lesions seems to appear (Mechin & Toury, 1973). Periodontitis which is serious gum infection that damages gum as well as jawbone, which results in swelling and reddening of gums. Melatonin affects the activation of fibroblast and bone regeneration by inducing the osteoblast differentiation and bone formation, and additionally, it stimulates the synthesis of type I collagen fibers. Melatonin mediates these effects through receptors accumulation on preosteoblasts, which results in the production of bone sialoprotein, alkaline phosphatase, osteopontin and osteocalcin in these cells, thus significantly diminishing the time needed for their differentiation into mature osteoblasts (Cutando et al., 2006).

Oral Candidiasis or Oral thrush is a fungal infection where the fungus *Candida albicans* accumulates in the mouth. Melatonin as the immunomodulator protects in severe shock induced by bacterial liposaccharides. Melatonin reduced IL-6 levels and diminished time to improve in animals with Candida sepsis. The level of TNF-alpha and adhesion molecules in melatonin- untreated septic rats were increased compared with those in melatonin-treated septic rats (Yavuz et al., 2007).

MELATONIN AS AN ANTIVIRAL FOR COVID-19

As mentioned above, melatonin has intrinsic anti-oxidation, anti-inflammation, immune stimulating qualities which have the capacity to inhibit nlrp3, due to which it can act as antiviral indirectly. Some studies were conducted right after the discovery of this virus COVID-19, that pregnant ladies and newborns are less infected due to presence of the high level of melatonin. An experiment was conducted where *Selmiki forest* virus (enchaphalities causing arbovirus) is administered into the muscle and subcutis (Ben-Nathan et al., 1995). This virus invades the CNS and then gradually replicates in the encephalon leading to death of the host. Melatonin was diluted in phosphate buffered saline and injected to the subcutis and Dexamethasone was diluted in saline buffer and injected into the muscle. CD1 female mice were taken of age 6 to 11 months. The main goal of this experiment is to observe the effect of melatonin in protection against viruses. Clearly it does not help in inhibiting the viral replication but it certainly affects the host resistance. The protective effect of melatonin might be through peripheral immune stimulation.

AFFECT OF MELATONIN IN CYTOKINE STORMS

“Cytokine storms” often refer to as Cytokine release syndrome (CRS) which is very similar to macrophage activating syndrome (MAS), certainly not happening in all the patients suffering from COVID-19 have CS, proved by a lot of findings of severe ill COVID infections, that appear to have the clinical and laboratory findings of cytokinin phase. In Cytokine Storm, dysregulated immune response

occurs, unexpected rise in immune response ramp up more than it should which may lead to a local and systemic inflammatory response. This may be due to release of large amount of proinflammatory cytokine release, which is proportional to the morbidity and mortality of the patient. Starting, with Alveoli, pneumocyte type II (which is responsible for producing the surfactant) the virus infects via ACE-2 receptors, and replicates inside one of these cells. Human body stimulates humoral or cell immune response along with the release of IgM antibodies, which results in huge amount of release of cytokines in the body in some patients. Typically, it begins in the lungs causing inflammation and edema which can lead to respiratory distress like ARDS and secondary bacterial infection (Zhang et al., 2020). Natural killer cells and are major contributors of the cytokines which effects the vasodilation leading to ultimate increase of extra vascular pressure, decreased tissue perfusion, often leads to endothelial dysfunction, and compromise the integrity of endothelial cell junctions. Severe infected patients have increased level of proinflammatory cytokines, IL-6, necrosis factor – Alpha, IL-1 beta and some chemokines leading to multi organ failure. The properties of Melatonin can potentially help during the cytokine storm phase of the Covid-19 by generated free radicals and neutralizing them, reducing proinflammatory cytokines and protect the lungs. Melatonin reacts upon necrosis factors-alpha, IL-2, IL-10, IL-6 and other inflammatory factors that weigh in inflammation (Reiter et al., 2020). An exclusive study, determined that Melatonin suppresses the angiogenesis and reproduction (rapid) of Human umbilical vein endothelial cells (HUVECs), which have reduced the formation of tubes, also alternated the entire condition in hypoxia. MLT suppresses the expression of VEGF induced hypoxia group (Cheng et al., 2019).

AVAILABILITY OF MELATONIN

Melatonin is widely popular dietary supplement used by many who struggle to sleep with nights of insomnia. A study was conducted where Rob L. DeMuro et.al picked up, some healthy people, with proper sleep-wake cycles. A clinical crossover trail, was conducted in three- phases. In phase 1-2mg of melatonin was subjected to the veins. The Parental dose was prepared in powder form and stored at 4°C for maximum 6 months. The individuals fasted for 8 hours prior to each dose and 4 hours after dosing. 2mg and 4mg of melatonin drug is administered on each individual, orally. The result elaborates about the pharmacokinetic analysis, concentration of both doses and half-life (DeMuro et al., 2000).

CONCLUSION

Melatonin is not effective for all the patients and it's not FDA regulated. People who are 70 or older cannot produce enough melatonin, jetlagged individuals, people having night-shifts can be benefited from this drug. Melatonin has a wide dose range in which 0.2-0.5 mg is ideal for the beginners. Despite of having huge positive effects, some individuals reported to have dizziness, drowsiness, headache and fatigue.

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THE CATASTROPHIC PHENOMENON OF MODERN TIMES: ANTIMICROBIAL RESISTANCE

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ABSTRACT

Antimicrobial Resistance (AMR) is among the most serious global health threat of present time. Overuse or misuse of antimicrobial agents could lead to exposure of microorganisms to these drugs which may result in development of a mechanism by the microorganisms to survive making the drug ineffective which was once used to kill or inhibit the growth of same microbes. AMR microbes has extremely ill-impact on human health whether it is related to infections, risks associated with medical procedures, increase in mortality rates of human or some other issues. There is no such well-established treatment for AMR. Hence, we need to be extremely careful while taking any antimicrobial drugs as it might knowingly or unknowingly induce the chances of AMR. Preventive measures for AMR should always be followed as there is no such effective cure of the problem and consequences can be dangerous, so preventive measures are a necessity.

Keywords: Antimicrobial resistance, microbes, human health, infections

INTRODUCTION

The term “Antimicrobial” belongs to Greek origin where Anti means Against, micro means little and bios means life, altogether meaning those which acts against microorganisms (Asif, 2017). These antimicrobial agents can either be natural or synthetic substances that are used to kill or inhibit the growth of microorganisms (Mikšik et al., 1998). Antimicrobial Resistance (AMR) is a phenomenon or a property of microbes where microorganisms develop mechanisms to protect themselves from the effects of antimicrobial drugs. Microbes including bacteria, viruses, fungi, and parasites may develop such mechanism and become resistant to antimicrobial agents which makes it difficult to treat infections with such drugs, making the scenario vulnerable. Bacteria which are totally drug- resistant are often referred to as “superbugs” (Magiorakos et al., 2012), which may occur due to random natural genetic mutation or by misuse of antimicrobial drugs. AMR is becoming a major concern worldwide. At present, it is estimated to have 700,000 deaths every year due to AMR infections but could lead to 10 million in near future if we do not take any precautions (O'Neill, 2016) and steps to deal with this problem.

MECHANISMS OF ANTIMICROBIAL RESISTANCE

Antimicrobial agents generally have different working mechanisms to kill or inhibit the growth of microbes by its interference with cell wall synthesis, nucleic acid synthesis or protein synthesis; by metabolic pathway inhibition or by disrupting microorganism's membrane structure. But due to AMR, microorganisms may become resistant against antimicrobial drugs or agents by acquired resistance mutation in which microorganism may generate enzymes to destroy the drug or agent, undergoes modification of drug's target site, production of an alternative pathway or prevention of the drug to reach its intracellular target; acquisition of genes which are resistant from other organisms may also occur through conjugation, transformation, transduction (Tenover, 2006); it may also takes place due to overuse of antimicrobial drugs/agents. This global threat makes the situation worse for medical sciences.

ROOTS OF AMR

Antimicrobial resistance may occur naturally either by mutation due to natural selection to become resistant against a particular drug (Holmes et al., 2016) or by acquisition of resistant genes from other organism (Tenover, 2006). One of the most common causes of AMR is taking medicines on our own without consulting any professional physician which is often referred to as self- medication. This is because people with lack of knowledge in medicinal field may mistreat themselves by consuming antimicrobials unnecessarily or in excess, which in long run may result in antimicrobial resistance (Rather et al., 2017). Unnecessary uses of antimicrobials in clinical operations (Ventola, 2015) or through prescribed medicines like broad spectrum medications by professionals, whether due to their own benefit or without knowing the consequences leading to AMR (Harris et al., 2019). Untreated medications from pharmaceutical industries, hospitals and laboratories gets disposed in the surrounding may interact with the environmental microbes increasing the chances of AMR (Ahmad et al., 2017). Treating livestock with antimicrobial agents or using these agents for plants may lead to large yields and high-quality products (Michael et al., 2014), but with time, some microbes may become resistant to those agents and when these products are consumed by humans, it increases the risk of transfer of resistant microbes to human body which has the potential to cause infections or other health related problems (Piddock, 2012). Sometimes Laboratory carelessness may also lead to AMR, when the microbes are kept for a longer time with antibiotic discs in the media without discarding them either due to carelessness or due to lack of knowledge about the serious consequences of the action. In some cases of AMR, these infections have no treatment options. However, to treat such conditions, new antimicrobial drugs can be used which could act against the microbes.

COMPLICATIONS RELATED TO AMR

This can have serious side effects like organ failure and other health issues. Presence of effective antibiotic drugs are essential for many medical procedures such as chemotherapy for cancer treatment, organ transplantation and many more which could not be performed without any effective antibiotics. Infections caused by multi-drug resistant microorganisms may lead to high rates of mortality (Prestinaci et al., 2015). Antibiotic-resistant infections adds more monetary burden to health care system of the countries and it may lead to complicated illnesses.

PREVENTIONS OF ANTIMICROBIAL RESISTANCE

Consumption of antimicrobials as prescribed by doctors routinely without any self-medication can be a good initiative against AMR. These preventive measures may also include not using antimicrobial drugs that was prescribed to another person just because of the similarities in the symptoms of diseases faced by two individuals. We should avoid taking antimicrobials for mild illnesses and spread awareness regarding the harmful effects and consequences of misuse or overuse of antimicrobial agents. We should definitely stop the overuse or misuse of antibacterial drugs by using it for viral infections as it will not be effective (Gallagher et al., 2018) but many consume it without knowing the fact. It will also be far better if there occurs minimization of the usage of antimicrobial drugs at clinical level (Prestinaci et al., 2015).

CONCLUSION

Antimicrobial resistance is an emerging problem and a global threat which needs to be monitored or prevented due to its extremely ill-impacts in recent times. It can create a lot of problems and increase the mortality rates, if AMR continues to emerge. Preventive measures of AMR should be taken and along with that spreading awareness is also important to control antimicrobial resistance.

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NANOTECHNOLOGY IN BIOLOGICAL SCIENCES: A REVIEW

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ABSTRACT

Nanotechnology is an integrative scientific field undergoing explosive development. The genesis of nanotechnology can be traced to the promise of revolutionary advances across communications, medicine, genomics and robotics. On the surface, miniaturization provides cost effective and more rapidly functioning mechanical and biological components. Nanometer sized objects also possess remarkable self- ordering and assembly behaviors under the control of forces quite different from macro-objects. These unique behaviors which make nanotechnology possible, and by increasing our understanding of these processes, new approaches enhance the quality of human life will surely be developed. Its impact on our society and economy in the 21st century is comparable to that of semiconductor technology, information technology, or cellular and molecular biology. The integration of nanotechnology into larger systems has provided breakthrough solutions to many current medical, environmental and industrial problems, including smart materials, nano manufacturing, electronics, drug delivery, energy and water, biotechnology, information technology, and national security. Nanotechnology has a profound impact on our economy and society; it is a modern industrial revolution. Nanotechnology represents a megatrend by bringing disruptive innovation. It has become a general purpose technology and is being applicable across various industrial sectors. This field is opening new path in science and technology.

KEYWORDS: Nanotechnology, nanoparticles, nanomaterials.

INTRODUCTION

Nanotechnology deals with the various structures of matter having dimensions of the order of a billionth of a meter. While the word *nanotechnology* is relatively new, the existence of functional devices and structures of nanometer dimensions is not new (Poole Jr & Owens, 2003). Nanotechnology is considered to be the key technology at the 21st century (Chen et al., 2016). The ideas and concepts behind nanotechnology started with a talk entitled *"There's plenty of room at the bottom"* by physicist Richard P. Feynman, 1959 (Khan et al., 2017). Nanotechnology is a technology that deals with nano-meter-sized objects. It is expected that nanotechnology can be developed at several levels; materials, devices and systems. At present, the nanomaterials level is the most advanced, both in scientific knowledge and in commercial applications. In the past, nanoparticles were studied because of their size-dependent physical and chemical properties. Now, they entered a commercial exploration period (Salata, 2004). Nanotechnology refers to any technology that is implemented at nanoscale and has applications in the real world. When the dimensions of a material are reduced from a large size, the properties of material remain the same at first, and then small changes occur. The physical and chemical properties of nanomaterials can be exploited for commercial applications and for novel performance that benefits society. The discovery of novel materials, processes, and phenomena at the nanoscale and the development of new experimental and theoretical techniques for research provide fresh opportunities for developing innovative nano systems and nanomaterials (Bhushan, 2017). "Nanomaterials (NMs)" can be defined as materials that exist in an unbound state or aggregates with one or more external dimensions. Depending on the overall shape, these materials can be 1D, 2D, or 3D. Researchers found that the size of

these materials can influence the physicochemical properties of the substances (Khan et al., 2017). The material property changes as their size approach the atomic scale. This is due to the increasing surface-area-to-volume ratio, resulting in the material's surface atoms dominating the material performance. Nanoparticles have a very large surface area to volume ratio as compared to bulk material, such as powders, plates and sheets. This feature enables nanoparticles to possess unexpected optical, physical and chemical properties, as they are small enough to confine their electrons and produce quantum effects. Nanoparticles are widely used due to their low cost and compatibility, and they are more preferred in industries, agriculture, medicine, and cosmetics (Chen et al., 2016).

APPLICATIONS OF NANOTECHNOLOGY

After more than twenty years of basic nanoscience research, applications of nanotechnology are delivering its potential in many ways, especially in the field of information technology, homeland security, medicine, transportation, energy, food safety, and environmental science. Nanotechnology is widely being used in medical tools, drug delivery and therapies. Nano based solutions are used for disease diagnosis, prevention and treatment. Nanotechnology can help improve energy efficiency, as well as it helps in detecting and cleaning-up of environmental contaminants. Researchers have developed a nano fabric "paper towel" woven from tiny wires of potassium manganese oxide, which can absorb 20 times its weight in oil for cleanup applications (Souzandeh et al., 2017). Nanotechnology also showed excellent potential in the production of mimetic enzymes, known as Nanozymes. These nanozymes have intrinsic enzyme-like activity and can efficiently catalyze the conversion of a substrate and follow the same kinetics and mechanism of natural enzymes under physiological conditions (Lizeng & Xiyun, 2016). It has the ability to create and manipulate materials at nanoscale levels to create products that exhibit novel properties and have a promising effect on disease prevention, diagnosis, and treatment. Cancer nanotechnology is emerging as new interdisciplinary research across biology, chemistry, engineering, and medicine. It plays a vital role in cancer detection, diagnosis, and treatment (Misra et al., 2010). Nanoparticle also plays an important role in agricultural and crop science research, especially to combat various biotic and abiotic stress-related problems. Studies have demonstrated enhanced seed germination, crop growth, and quality enrichment. In a recent study conducted by Kumar et al. (2018), multi-walled carbon nanotubes positively affect seed germination and plant growth.

RECENT DEVELOPMENTS

A new inexpensive, fast and accurate nano-sensor based technique, known as Nano2RED was developed to detect infectious diseases. The innovative Rapid and Electronic Readout process ("RED") delivers test results, which are detectable as a colour change in the sample solution, and record the data through inexpensive semiconductor elements such as LEDs and photodetectors. The technology represents a significant advance to fight against infectious diseases as well as detecting viral antigens (Das et al., 2016). It plays an important role in capturing off-target cancer drugs to prevent tissue damage. It prevents the previously unavoidable damage; researchers have developed new nanomaterials engineered to capture chemotherapy drugs before interacting with healthy tissue. The method is based on hairy cellulose nanocrystals-nanoparticles developed from the main component of plant cell walls and engineered to have immense numbers of polymer chain "hairs" extending from each end. These hairs significantly increase the potential drug capture capacity of the nanocrystals (Blumenfeld et al., 2018). For some organs, like the liver, chemotherapy can be locally administered through catheters. A device is placed based on the nanocrystals to capture the excess drugs existing in the liver's inferior vena cava, a major blood vessel.

CONCLUSION

Nanotechnology research is still in its nascent stage and there lies a mammoth arena in its optimisation, development and applications. Nanotechnology will substantially change the manufacturing process of every product in existence. It is likely to be the human race's greatest scientific achievement and will probably change all of our lives. Nanotechnology offers the ability to build large numbers of incredibly powerful products in today's standards. Nevertheless, the expectations of nanotechnology in the near future are high, and the demand for advanced technology is increasing day by day. The benefits of such products and applications in many technological sectors will be significant, and the fields it will be applied will lead to a new generation. The effect of nanotechnology in everyday life is considered to be great, since it will make communications, transportation, data storage, health treatment and many other technological applications faster, safer and cheaper. Some of these developments may not be materialized, but the imagination of scientists has always led technology in new paths.

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WORLD FIRST LIVING BIOLOGICAL ROBOT FROM THE STEM CELL OF *XENOPUS LAEVIS*

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ABSTRACT

The world has got the first living robot which is neither a traditional robot nor a species of animal, it is not made up of any plastic material but entirely made from organic cells. The name of the robot is xenobot, and its size of about less than 1 mm wide because of the small size of xenobot makes it a promising solution against the problem area where other robots cannot perform the function properly. It going to be useful in the design of scientific instrument, disease diagnosis and treatment procedures. It is quite enthralling because this robot was built with a combination of artificial intelligence and cell biology. Xenobot also decreases the boundary between robotics and cell biology.

KEYWORDS *Xenopus laevis*, xenobot, artificial intelligence, stem cell.

INTRODUCTION

Xenobot is a living programable organism from the stem cell of an embryo of an African clawed frog (*Xenopus laevis*) which differentiate into the epidermal cell and cardiac cell (Ashiyani al. 2021). The name xenobot was taken from *Xenopus laevis* from which it was created. Epidermal cells of *Xenopus laevis* can stick together, which provides the architecture to xenobot. In contrast, the cardiac cell has the ability to contract and relax, and it acts as an engine to move xenobot. The xenobot are able to swim through the liquid, navigate through tubes, work together to collect particles into piles, heal themselves when injured, and even store information from their experience.

Fig. Xenobot, in reality, | Source: Douglas Blackiston & Sam Kriegman

CREATION OF XENOBOT

Xenobot was created by scientists at the University of Vermont, Tufts University, and the Wyss Institute for Biologically Inspired Engineering at Harvard University (Brown al. 2021). Scientists first extracted the embryo of *Xenopus laevis* stem cell that differentiates into a cardiac and epidermal cell, followed by providing data of an evolutionary algorithm on a supercomputer. Based on this data, the supercomputer promptly generated millions of cell configurations. Scientists working on the first xenobot were expected to get the desired type of movement. A supercomputer tries to find only the best configuration that could produce the desired locomotion. After running hundreds of tests to get the right configuration, they get only a few computer-generated configurations for the best locomotion of xenobot. Then these stem cells under laboratory conditions, undergo microsurgery with the help of tiny force and tweezers under the microscope (Kanchwala al. 2022). During this microsurgery, scientists took one stem cell at a time and repeated this process for 3000 stem cells together. During culturing of stem cells in saltwater, researchers observed that all the cells clumped together on their own and the cell located outside of the clump developed into cilia. These cilia which are located outside of the clump cell, help in the movement of clump cells from one location to another location (Tenn al.2021). The scientist then uses artificial intelligence to predict and select the most active shapes of xenobots that gives the desired behaviour. The xenobot was then converted into a C-shaped by using artificial intelligence. After putting it into a petridish, scientists observed that the c-shaped tiny xenobots were able to gather hundreds of small stem cells inside its mouth (Hunt al. 2021).

MECHANISM OF XENOBOT

Xenobot is small enough to travel inside a human body for treating and detecting various diseases. It is entirely biodegradable, and after completion of the goal, it changes into a dead cell. It can heal itself and move from one place to another and perform an operation in a group. Xenobots have holes in the centre of the body that can carry a drug to the desired location while treating any patient. The movement of xenobot depends on the biochemical, electrical, and hormonal signals from adjacent cell or information control centres. Xenobot has a short life span of about ten days, and it survives from days to weeks without any nutrients (Ashiyani al. 2021). A messenger RNA molecule for EosFP protein can also be inserted in xenobot for developing molecular memory. Xenobot is a self-replicating biological robot and reproduces by a process called "kinematic replication" (Sharma al.2021).

FUTURE APPLICATION OF XENOBOT

Xenobot will be helpful in the delivery of drugs to the desired location and in treating patients at the cellular level. It can act as a new scientific instrument like microscope and cyclotron, helping scientists to understand cell biology more deeply (Yeung al.2021). It can be used in treatments related to arthritic joints, blocked arteries, sensing trouble, gut and intestine diseases, wound healing, cancer, etc. It may also be used in the xenotransplantation of an organ. Researchers are now focused on creating guidance systems for the bots—sensors to help bring them to a target, or attract them to back a collection point after their work is done.

CONCLUSION

In the days to come, xenobot will be considered the best biological robot. It will be helpful in the medical field with the capability to cure many diseases and make treatment of some illnesses easier.

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Nobel Prizes in Physiology or Medicine

NOBLE PRIZE 2001

Leland H. Hartwell, Tim Hunt and Sir Paul M. Nurse "for their discoveries of *key regulators of the cell cycle*"

NOBLE PRIZE 2002

Sydney Brenner, H. Robert Horvitz and John E. Sulston "for their discoveries concerning *genetic regulation of organ development and programmed cell death"*

NOBLE PRIZE 2003

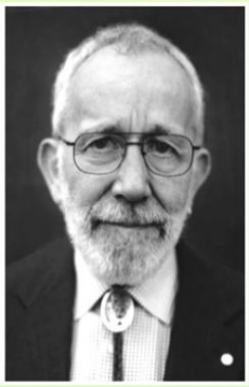
Paul C. Lauterbur and Sir Peter Mansfield "for their discoveries concerning *magnetic resonance imaging*"

NOBLE PRIZE 2004

Richard Axel and Linda B. Buck "for their discoveries of *odorant receptors and the organization of the olfactory system*"

Nobel Prizes in Physiology or Medicine

NOBLE PRIZE 2005

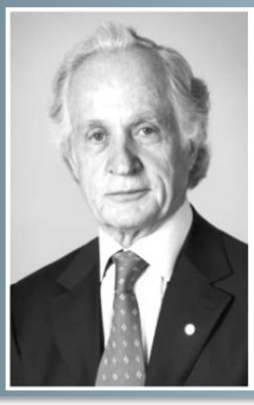


Barry J. Marshall and J. Robin Warren "for their discovery of the bacterium *Helicobacter pylori and its role in gastritis and peptic ulcer disease*"

NOBLE PRIZE 2006

Andrew Z. Fire and Craig C. Mello "for their discovery of *RNA interference – gene silencing by double-stranded RNA*"

NOBLE PRIZE 2007



Mario R. Capecchi, Sir Martin J. Evans and Oliver Smithies "for their discoveries of *principles for introducing specific gene modifications in mice by the use of embryonic stem cells*"

NOBLE PRIZE 2008

Harald zur Hausen"for his discovery of *human papilloma viruses causing cervical cancer*"

Françoise Barré-Sinoussi and Luc Montagnier "for their discovery *of human immunodeficiency virus*"

Nobel Prizes in Physiology or Medicine

NOBLE PRIZE 2009



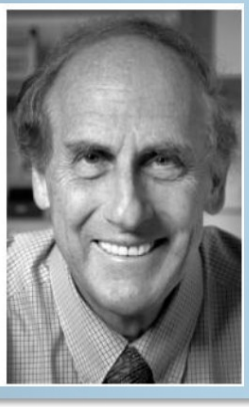
Elizabeth H. Blackburn, Carol W. Greider and Jack W. Szostak "for the discovery of *how chromosomes are protected by telomeres and the enzyme telomerase*"

NOBLE PRIZE 2010

Robert G. Edwards "for the development of *in vitro fertilization*"

NOBLE PRIZE 2011



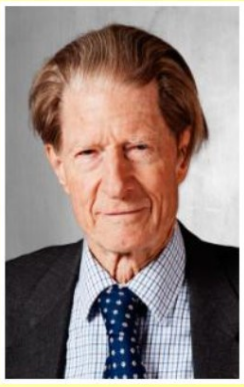


Bruce A. Beulter and Jules A. Hoffmann "for their discoveries concerning the *activation of innate immunity*"

Ralph M. Steinman "for his discovery of the *dendritic cell and its role in adaptive immunity*"

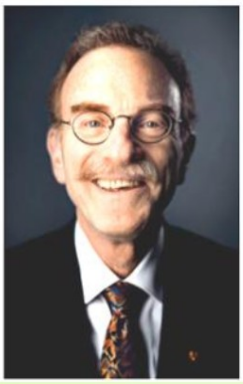
NOBLE PRIZE 2012

Sir John B. Gurdon and Shinya Yamanaka "for the discovery that *mature cells can be reprogrammed to become pluripotent*"




Nobel Prizes in Physiology or Medicine

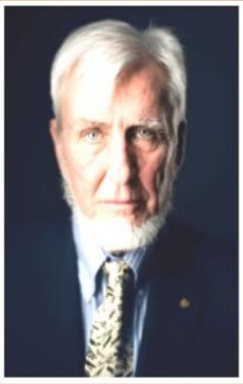
NOBLE PRIZE 2013

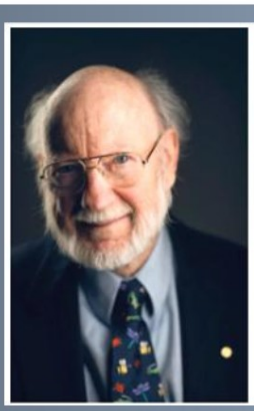

James E. Rothman, Randy W. Schekman and Thomas C. Südhof "for their discoveries of *machinery regulating vesicle traffic, a major transport system in our cells*"

NOBLE PRIZE 2014

John O'Keefe, May-Britt Moser and Edvard I.Moser "for their discoveries of *cells that constitute a positioning system in the brain*"



NOBLE PRIZE 2015

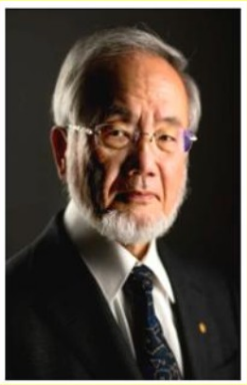


William C. Campbell and Satoshi Ōmura "for their discoveries concerning a novel therapy against infections caused by roundworm parasites"

Tu Youyou "for her discoveries concerning *a novel therapy against Malaria*"

NOBLE PRIZE 2016

Yoshinori Ohsumi "for his discoveries of *mechanisms for autophagy*"



Nobel Prizes in Physiology or Medicine

NOBLE PRIZE 2017



Jeffrey C. Hall, Michael Rosbash and Michael W. Young "for their discoveries of *molecular mechanisms controlling the circadian rhythm*"

NOBLE PRIZE 2018

James P. Allison and Tasuku Honjo "for their discovery of *cancer therapy by inhibition of negative immune regulation*"

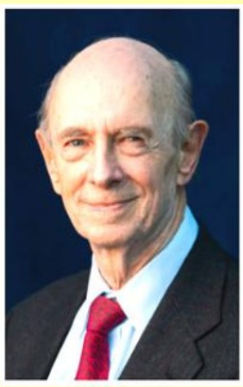

NOBLE PRIZE 2019



William G. Kaelin Jr, Sir Peter J. Ratcliffe and Gregg L. Semenza "for their discoveries of *how cells sense and adapt to oxygen availability*"

NOBLE PRIZE 2020

Harvey J. Alter, Michael Houghton and Charles M. Rice "for the discovery of *Hepatitis C virus*".



Ministry of Health & Family Welfare
Government of India

NOVEL CORONAVIRUS (COVID-19)

Protect yourself and others!

Follow these Do's and Don'ts

Do's

Practice frequent hand washing. Wash hands with soap and water or use alcohol based hand rub. Wash hands even if they are visibly clean

Cover your nose and mouth with handkerchief/tissue while sneezing and coughing

Throw used tissues into closed bins immediately after use

See a doctor if you feel unwell (fever, difficult breathing and cough). While visiting doctor wear a mask/cloth to cover your mouth and nose

If you have these signs/symptoms please call State helpline number or Ministry of Health & Family Welfare's 24X7 helpline at 011-23978046

Avoid participating in large gatherings

Don'ts

Have a close contact with anyone, if you're experiencing cough and fever

Touch your eyes, nose and mouth

Spit in public

Together we can fight Coronavirus

mohfw.gov.in @MoHFWIndia @MoHFW_INDIA mohfwindia

Source: https://www.mohfw.gov.in/