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COVID-19 mRNA Vaccine: A Milestone in Science and a Game Changer in Medicine

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Contents

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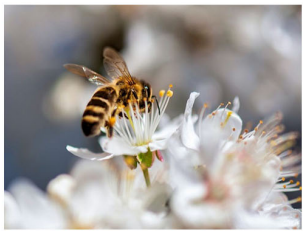

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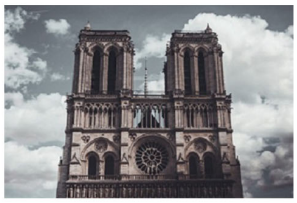

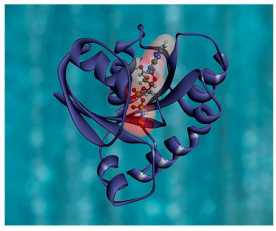

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New Strains of SARS-CoV-2 (the virus responsible for COVID-19): Could 'Neutralising Antibodies' Approach be Answer to Rapid Mutation?

Several new strains of the virus have emerged since the pandemic began. New variants were reported as early as February 2020. The current variant that has brought the UK to standstill this Christmas is said to be 70% more infectious. In view of emerging strains, will several vaccines being developed worldwide still be effective enough against the new variants as well? 'Neutralising Antibody' approach targeting the virus seems to offer a hopeful option in this current climate of uncertainty. The status is that eight neutralizing antibodies against SARS-CoV-2 are currently undergoing clinical trials, including trials of 'antibody cocktails' aimed at overcoming possibility of the virus developing resistance to a single neutralizing antibody by accumulating spontaneous mutations.tt

The SARS-CoV-2 virus responsible for COVID-19 pandemic belong to the betacoronavirus genus in the coronaviridae family of viruses. This virus has a positive-sense RNA genome, meaning strand RNA act as messenger RNA while directly translating into viral proteins in the host. The genome of SARS-CoV-2 encodes four structural proteins {spike (S), envelope (E), membrane (M),

and nucleocapsid (N)} and 16 non-structural proteins. While the structural proteins play role in receptor recognition on the host cell, membrane fusion, and subsequent viral entry; the non-structural proteins (NSPs) play crucial role in replicative functions such as RNA polymerization by the RNA-dependent RNA polymerase (RdRp, NSP12).

Significantly, RNA virus polymerases do not have proofreading nuclease activity, meaning there is no mechanism available to check for the errors during transcription or replication. Therefore, viruses of this family display extremely high rates of variation or mutation. This drives their genome variability and evolution thereby providing them extreme level of adaptability and helping the virus escape the immunity of the host and developing resistance against the vaccines (1,2,3). Obviously, it has always been nature of RNA viruses, including coronaviruses to undergo mutations in their genome at extremely high rates all the time due to the reasons mentioned above. These replication errors that help the virus overcome negative selection pressure, lead to adaptation of the virus. In the long run, more the error rate, more the adaptation. Yet, COVID-19 is the first documented coronavirus pandemic in history. It is the fifth documented pandemic since the 1918's Spanish flu; all of the earlier four documented pandemics were caused by flu viruses (4).

Apparently, human coronaviruses have been building up mutations and adapting in the last 50 years. There have been several epidemics since 1966, when the first epidemic episode was recorded. The first lethal human coronaviruses epidemic was in 2002 in Guangdong Province, China that was caused by the variant SARS-CoV followed by 2012 epidemic in Saudi Arabia by the variant MERS-CoV. The current episode caused due to SARS-CoV-2 variant started in December 2019 in Wuhan, China, and subsequently spread worldwide becoming the first coronavirus pandemic leading to COVID-19 disease. Now, there are several sub-variants spread across different continents. SARS-CoV-2 has also shown inter-species transmission between humans and animals and back to humans(5).

The vaccine development against human coronavirus did start after 2002 epidemic. Several vaccines against SARS-CoV and MERS-CoV were developed and underwent preclinical trials but few entered human trials. None of them received FDA approval though (6). These efforts came handy in vaccine development against SARS-CoV-2

through usage of existing preclinical data including those relating to vaccine design performed during development of vaccine candidates for SARS-CoV and MERS-CoV (7). At this point of time, there are several vaccines against SARS-CoV-2 at a very advanced stage; few have already been approved as EUA (Emergency Use Authorization). About half a million high-risk people in the UK have already received Pfizer's mRNA vaccine. And, here comes the report of newly emerged, highly infectious strain (or, sub-strain) of SARS-CoV-2 in the UK this Christmas time. Temporarily named VUI-202012/01 or B117, this variant has 17 mutations including one in spike protein. More infectious doesn't necessarily mean that the virus has become more dangerous for humans. Naturally, one wonders if these vaccines will still be effective enough against the new variants as well. It is argued that a single mutation in the spike should not make vaccines ('spike region' targeting) vaccine ineffective but as the mutations accumulate over time, vaccines may need fine tuning to accommodate antigenic drift (8,9)

Antibody approach: renewed emphasis on neutralising antibodies may be imperative

It is in this background that the 'antibody approach' (involving 'neutralizing antibodies against SARS-CoV-2 virus' and 'therapeutic antibodies against COVID-19-associated hyperinflammation') gains significance. Neutralizing antibodies against SARS-CoV-2 virus and its variants may serve as a 'ready to use' passive immunity tool.

The neutralising antibodies target the viruses directly in the host and can provide quick protection especially against any newly emerged variants. This route has not shown much progress yet but has the potential to address the problem of antigenic drift and possible vaccine mismatch presented by the fast-mutating and evolving SARS-CoV-2 virus. As on 28 July 2020, eight neutralizing antibodies against SARS-CoV-2 virus (namely LY-CoV555, JS016, REGN-COV2, TY027, BRII-196, BRII-198, CT-P59, and SCTA01) were undergoing clinical evaluation. Of these neutralising antibodies, LY-CoV555 is monoclonal antibody (mAb). VIR-7831, LY-CoV016, BGB-DXP593, REGN-COV2, and CT-P59 are other monoclonal antibodies being tried as neutralising antibodies. Antibody cocktails can overcome any possible resistance developed against a single neutralising antibody, hence cocktails such as REGN-COV2, AZD7442, and COVI-SHIELD also are undergoing clinical trials. However, strains may gradually develop resistance to cocktails as well. Further, there may be risk of antibody-dependent enhancement (ADE) due to antibodies that only bind to the virus and are incapable of neutralising them, thereby worsening disease progression (10,11). A continuum of innovative research work is needed to address these issues.

Related article: COVID-19: 'Neutralising Antibody' Trials Begins in the UK

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COVID-19: 'Neutralising Antibody' Trials Begins in the UK

University College London Hospitals (UCLH) has announced neutralising antibody trial against COVID-19. The announcement on 25 December 2020 says "UCLH doses first patient in the world in Covid-19 antibody trial" and " Researchers in the STORM CHASER study led by UCLH virologist Dr Catherine Houlihan have recruited the first participant in the world to the study" (1).

The antibody under clinical trial in UCLH is AZD7442 which is a combination of monoclonal antibodies (mAbs) developed by AstraZeneca. This combination is already undergoing clinical trials in the USA since December 2, 2020 (2) . Several other 'antibodies' and 'antibody cocktails' are undergoing clinical trials elsewhere (3). The combination of antibodies in AZD7442 have been modified to extend their half-life to afford protection for six to 12 months. More importantly, they have been engineered for reduced Fc receptor binding that aims to minimise the risk of antibody dependent enhancement of disease- a phenomena in which antibodies to the virus promote, rather than inhibit infection (4).

These neutralising antibodies are an important tool for providing protection in patients with a weak immune system and where the disease has already progressed far (3). Vaccines provide active immunity, however immunity development through vaccines may take some time and may be ineffective after infection has been contracted. Providing passive immunity through ready-made, exogenous antibody is the way forward to give quick protection to immune compromised patients and patients with full blown disease.

Two studies are planned. The STORM CHASER study aims to evaluate effectiveness of monoclonal antibody AZD7442 for immediate protection to people who have been recently exposed to the SARS-CoV-2 virus, to prevent them developing Covid-19; while the other study namely PROVENT aims to evaluate the antibody AZD7442 in people who has a compromised immune system who will

not respond to vaccines or are at higher risk due to factors such as age and existing conditions.

Further research and clinical investigations using different combinations of neutralising antibodies to SARS-CoV-2 virus would pave the way for providing protection to not only the vulnerable population with a weak immune system and people having the disease but will also protect otherwise healthy individuals from contracting the disease when administered with these antibodies.

Related article: New Strains of SARS-CoV-2 (the virus responsible for COVID-19): Could 'Neutralising Antibodies' Approach be Answer to Rapid Mutation?

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COVID-19, Immunity & Honey: Recent Advances in Understanding Medicinal Properties of Manuka Honey

Anti-viral properties of manuka honey are due to the presence of methylglyoxal (MG), an arginine directed glycating agent that modifies sites specifically present in the SARS-CoV-2 genome, thereby interfering with its replication and inhibiting the virus. In addition, manuka honey also exhibits strong anti-bacterial and anti-cancer properties. For now, manuka honey can be the ambrosia that may be consumed to boost the immunity against infections, including COVID-19 thereby promoting health.

In the current climate of COVID-19 pandemic especially when SARS-CoV-2 is mutating at an increasingly pace, giving rise to more infectious variants raising concern, it may be pertinent to explore and leverage resources that may have potential to boost immunity and contribute in combating against COVID-19 to reduce morbidity and mortality, thereby improving health.

In addition to consumption of Vitamin C and D to boost the immune system, honey, particularly Mānuka honey (a monofloral honey produced from the nectar of the mānuka tree, Leptospermum scoparium by European honey bees (Apis mellifera) is understood to be providing health benefits as immune booster in terms of fighting against infections. This article shall analyse,

review and evaluate evidences from recent research with respect to manuka honey and its medicinal properties. Manuka honey is made from flowers of manuka tree that it is a native of Australia and New Zealand.

The major component of manuka honey that is responsible for its antibacterial and anti-viral properties is the presence of high amounts of methylglyoxal (MG). While MG is present in all types of honey at varying concentrations, it is present at a very high concentration in manuka honey. Higher MG results from conversion of dihydroxyacetone that is present in flowers of manuka tree at a high concentration. Higher the MG, higher the antibiotic effect. Manuka honey is rated using a rating factor known as UMF (Unique Manuka Factor). Higher the UMG, higher the antibiotic properties of manuka honey and higher its price.

It has been shown that MG, present in significant concentration in manuka honey, can act as an arginine-directed glycating agent, for selective toxicity to SARS-CoV-2. Sequence analysis of SARS-CoV-2 proteome revealed the presence of 5-fold enrichment of methylglyoxal modification sites in the SARS-CoV-2 proteome, compared to the human host – indicating selective toxicity of methylglyoxal to the virus (1). Manuka honey can interfere with the virus replication and inhibit the growth of enveloped virus (2). Anti-viral and immunomodulatory effects of manuka honey can also be ascribed to the presence of phenolic compounds that act as anti-oxidants (3). The presence of phenolic compounds, flavonoids such as quercetin may inhibit 3-chymotrypsin-like cysteine protease, an enzyme that plays an important role in viral life cycle (4), thereby exhibiting anti-viral effects of manuka honey.

The antibacterial property of manuka honey comes from the presence of Hydrogen peroxide, low pH and high sugar content, characteristics that are found on other honey types as well. The antibacterial effect of manuka honey has been demonstrated by significantly reducing MRSA cell viability in a biofilm (5). This was due to the significantly reduced expression of genes encoding laminin- (eno), elastin- (ebps) and fibrinogen binding protein (fib), and icaA and icaD, involved in biosynthesis of polysaccharide intercellular adhesin in both weakly and strongly adhering strain, compared to the control. Manuka honey also exhibited activity against Escherichia coli O157:H7 in biofilms (6) as well as bactericidal and anti-spore formation activity against Clostridioides difficile (7).

In addition, manuka honey has also been shown to exhibit anti-cancer activity. This was demonstrated by the ability of manuka honey to induce apoptosis in a cancer cell line by maintaining high permeability of hydrogen peroxide against intracellular reactive oxygen species (8) . The antitumor effect of manuka honey is due to inhibitory effects on the inflammatory and oxidative stress signalling as well as inhibition of proliferation and metastasis component activities (9).

There seems to be enough evidence to suggest that consumption of honey, especially manuka honey may help people improve their immunity due to the anti-viral and anti-bacterial properties caused by the presence of MG. In addition, consumption of manuka honey as part of life-style management may also help in cancer prevention. Is it worthwhile to surmise that manuka honey is a panacea for all ills inflicting mankind? Time will tell and the answer will lie in the analyses of data generated from more studies on consumption of manuka honey. However, for now, manuka honey seems to be the ambrosia that may be consumed for its medicinal properties to prevent severity of bacterial and viral infections including COVID-19.

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Understanding Life-threatening COVID-19 Pneumonia

What causes severe COVID-19 symptoms? Evidences suggest inborn errors of type I Interferon immunity and autoantibodies against type I Interferon are causal for critical COVID-19. These errors can be identified using whole genome sequencing, thereby leading to proper quarantine and treatment.

A recent paper throws light on causal mechanism underlying severe COVID-19 pneumonia.

More than 98% of the infected persons do not get any symptoms of the disease or develop mild disease. Less than 2% of the infected persons develop severe pneumonia 1-2 weeks after infection and need to be hospitalised for acute respiratory distress and/or organ failure. Less than 0.01% of the infected persons develop severe systemic inflammation resembling Kawasaki disease (KD).

Advanced age was found to be major risk for life-threatening COVID-19 pneumonia. Most of the persons requiring hospitalisation are more than 67 years of age – critical disease was found to be 3.5 times higher in persons more than 75 years of age than persons less than 45 years. Men are at higher risk of developing severe symptoms.

People with comorbidities like hypertension, diabetes, chronic cardiac disease, chronic pulmonary disease, and obesity are at higher risk of developing severe symptoms.

Some genotypes were causal for the severe COVID-19 phenotype. Inborn errors of interferon immunity play key role in development of severe symptoms. Patients with deleterious variants at 13 loci (that code for immunologically connected proteins) have defective interferons. These errors disrupt type I Interferon immunity thus causing-

excessive inflammation and critical COVID-19 symptoms. Further, neutralising autoantibodies against type I interferons are present in at least 10% of patients with severe life-threatening illness.

This paper concludes that inborn errors of type I Interferon immunity and autoantibodies against type I Interferon are causal for critical COVID-19.

Perhaps identifying people with such genotypes will go a long way in preventing and treating severe outcome of the disease. Whole genome sequencing of people can be used to identify the vulnerable patients leading to their proper quarantine and treatment.

Source(s):

Zhang Q., Bastard P., Bolze A., et al., 2020. Life-Threatening COVID-19: Defective Interferons Unleash Excessive Inflammation. Med. Volume 1, Issue 1, 18 December 2020, Pages 14-20. DOI: https://doi.org/10.1016/j.medj.2020.12.001

COVID-19 mRNA Vaccine: A Milestone in Science and a Game Changer in Medicine

Viral proteins are administered as antigen in the form of a vaccine and the immune system of the body forms antibodies against the given antigen thus providing protection against any future infection. Interestingly, this is first time in human history that the corresponding mRNA itself is being given in the form of a vaccine that uses the cell machinery for expression/translation of the antigen/protein. This effectively turns cells of the body into factory for producing antigen, which in turn provides active immunity by generating antibodies. These mRNA vaccines have been found to be safe and effective in human clinical trials. And, now, the COVID-19 mRNA vaccine BNT162b2 (Pfizer/BioNTech) is being administered to the people as per the protocol. As the first duly approved mRNA vaccine, this is a milestone in science that has ushered in new era in medicine and drug delivery. This could soon see application of the mRNA technology for cancer treatment, range of vaccines for other diseases, and thus possibly changing practice of medicine and shape pharmaceutical industry altogether in future.

If a protein is needed inside a cell for treating a diseased condition or to act as an antigen for development of active immunity, that protein needs to be delivered into the cell safely in the intact form. This still is an uphill task.

Could the protein be expressed directly into the cell by injecting the corresponding nucleic acid (DNA or RNA), which then uses the cellular machinery for expression?

A group of researchers conceived the idea of nucleic acid encoded drug and demonstrated for the first time in 1990 that direct injection of mRNA in to mouse muscle led to expression of encoded protein in the muscle cells(1). This opened up the possibility of gene-based therapeutics, as well as gene-based vaccines. This development was considered as a disruptive technology against which future vaccine technologies will be measured (2).

The thought process quickly shifted from 'gene- based' to 'mRNA-based' information transfer because mRNA offered several advantages compared to DNA as mRNA neither integrates in the genome (hence no detrimental genomic integration) nor does it replicate. It has only elements directly required for expression of protein. Recombination between single stranded RNA is rare. Moreover, it disintegrates within few days within the cells. These features make mRNA more suitable as a safe and transient information carrying molecule to act as vector for gene-based vaccine development (3). With advances in technology particularly relating to the synthesis of engineered mRNAs with right codes that could be delivered into the cells for protein expression, the scope further broadened from vaccines to therapeutic drugs. Use of mRNA started getting attention as a drug class with potential application in the areas of cancer immunotherapies, infectious disease vaccines, mRNA-based induction of pluripotent stem cells, mRNA-assisted delivery of designer nucleases for genome engineering etc. (4).

Emergence of mRNA-based vaccines and therapeutics got further fillip by results from pre-clinical trials. These vaccines were found to elicit potent immune response against infectious disease targets in animal models of influenza virus, Zika virus, rabies virus and others. Promising results have also been seen by using mRNA in cancer clinical trials (5). Realising the commercial potential of the technology, industries made huge R& D investments in mRNA-based vaccines and drugs. For example, until 2018, Moderna Inc. may already have invested more than a billion dollars while still years away from any marketed product (6). Despite concerted efforts towards use of mRNA as a therapeutic modality in infectious disease vaccines, cancer immunotherapies,

treatment of genetic diseases and protein replacement therapies, the application of mRNA technology has been restricted due to its instability and proneness to degradation by nucleases. Chemical modification of mRNA helped a bit but intracellular delivery still remained a hurdle though lipid-based nanoparticles are used to deliver mRNA (7).

Real thrust to the progress of mRNA technology for therapeutics came, courtesy unfortunate situation presented by the worldwide COVID-19 pandemic. Development of safe and effective vaccine against SARS-CoV-2 became the topmost priority for everyone. A large scale multicentric clinical trial was conducted to ascertain safety and effectiveness of COVID-19 mRNA vaccine BNT162b2 (Pfizer/BioNTech). The trial started on January 10, 2020. After about eleven months of rigorous work, the data from the clinical study proved that COVID-19 is preventable by vaccination using BNT162b2. This provided proof of concept that mRNA-based vaccine can provide protection against infections. The unprecedented challenge posed by the pandemic helped prove that a mRNA-based vaccine can be developed at fast pace, if sufficient resources are made available (8). Moderna's mRNA vaccine also received emergency use authorisation by FDA last month.

Both the COVID-19 mRNA vaccines i.e., BNT162b2 of Pfizer/BioNTech and Moderna's mRNA-1273 are now being used to vaccinate people as per the national protocols for administration of vaccine (9).

The success of two COVID-19 mRNA (BNT162b2 of Pfizer/BioNTech and Moderna's mRNA-1273) vaccines in clinical trials and their subsequent approval for use is a milestone in science and medicine. This has proved a hitherto unproven, high potential medical technology that scientific community and pharmaceutical industry has been pursuing for almost three decades (10).

The new enthusiasm following this success is bound to gather energies after the pandemic and mRNA therapeutics would further prove to be a disruptive technology ushering in a new era in medicine and the science of drug delivery.

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Notre-Dame de Paris: An Update on 'Fear of Lead Intoxication' and Restoration

Notre-Dame de Paris, the iconic cathedral suffered serious damages due to fire on 15 April 2019. The spire was destroyed and the structure considerably weakened due to flames that raged for hours. Some amount of lead volatilized and deposited in the surrounding areas. This had given rise to suspicion of intoxication.

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A recent study investigated the blood lead levels of adults in Paris. The findings published recently support the view that blood lead levels of adults living and working in the vicinity of the cathedral did not increase as a result of fire thus putting aside the fear of intoxication (1).
Listed as World Heritage site of UNESCO, Notre-Dame was built originally in 12th century and was modified and restored in 18th and 19th century respectively. Its history is closely associated with history of France and is symbol of Christian faith in Paris over long period of time (2) .

Post-fire restoration of Notre-Dame entail issues relating to material science, structural integrity, fire safety and preservation ethics (3) . In July 2020 interview, the director of Historical Monuments Research Laboratory (LRMH) mentioned 'damage assessment' as the main task. The basis of restoration was the status of the cathedral after the fire (4) . A working group is is preparing a "digital twin" (an information system that brings together all technical and scientific data of Notre-Dame cathedral on a digital platform. The data from 3D scan conducted earlier before the fire tragedy would come handy (5) .

The restoration work continues with collabora-

tive efforts of experts from various fields (6). By now, all the burnt scaffolding surrounding the cathedral has been removed. The Grand Organ has been dismantled and removed. The next phase of reconstruction is in progress. The restoration work along with organ reassembly and tuning is estimated to be completed by April 2024 (7).

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Oxford/AstraZeneca COVID-19 Vaccine (ChAdOx1 nCoV-2019) Found Effective and Approved

Interim data from the phase III clinical trial of Oxford University/AstraZeneca COVID-19 Vaccine show the vaccine is effective at preventing COVID-19 caused due to SARS-CoV-2 virus and offers a high level of protection against the disease.

The phase III trial tested two different dose regimens. The higher efficacy regimen used a halved first dose and standard second dose. The interim analysis indicated that efficiency was 90% in higher efficacy regimen and 62% in the other regimen with an overall efficiency of 70.4% when data from two dosing regimens were combined. Further, from those who received the vaccine, none progressed onto severe cases requiring hospitalisation (1).

Upon analysis of the interim data, Medicines and Healthcare products Regulatory Agency (MHRA), the regulating body concluded that the vaccine has met its standards of safety, quality and effectiveness. The government has subsequently accepted the recommendation of MHRA and granted approval (2).

Importantly, unlike earlier approved 'COVID-19 mRNA vaccines', this vaccine has relative advantage because can be stored at regular fridge temperature of 2-8 °C and can be distributed for administration at healthcare facilities using existing logistics thereby making it possible staple vaccine in the fight against the pandemic worldwide. However, mRNA vaccines have far wider potential in therapeutics and infections in the medium and long-term (3).

Oxford/AstraZeneca COVID-19 Vaccine uses the weakened and genetically modified version of common cold virus adenovirus (a DNA virus) as vector for expression of viral protein of novel coronavirus nCoV-2019 in the human body. The expressed viral protein in turn act as antigen for development of active immunity. The adenovirus used is replication incompetent meaning it cannot replicate in human body but as vector it provides an opportunity for translation of incorporated gene encoding Spike protein (S) of novel coronavirus (1,4).

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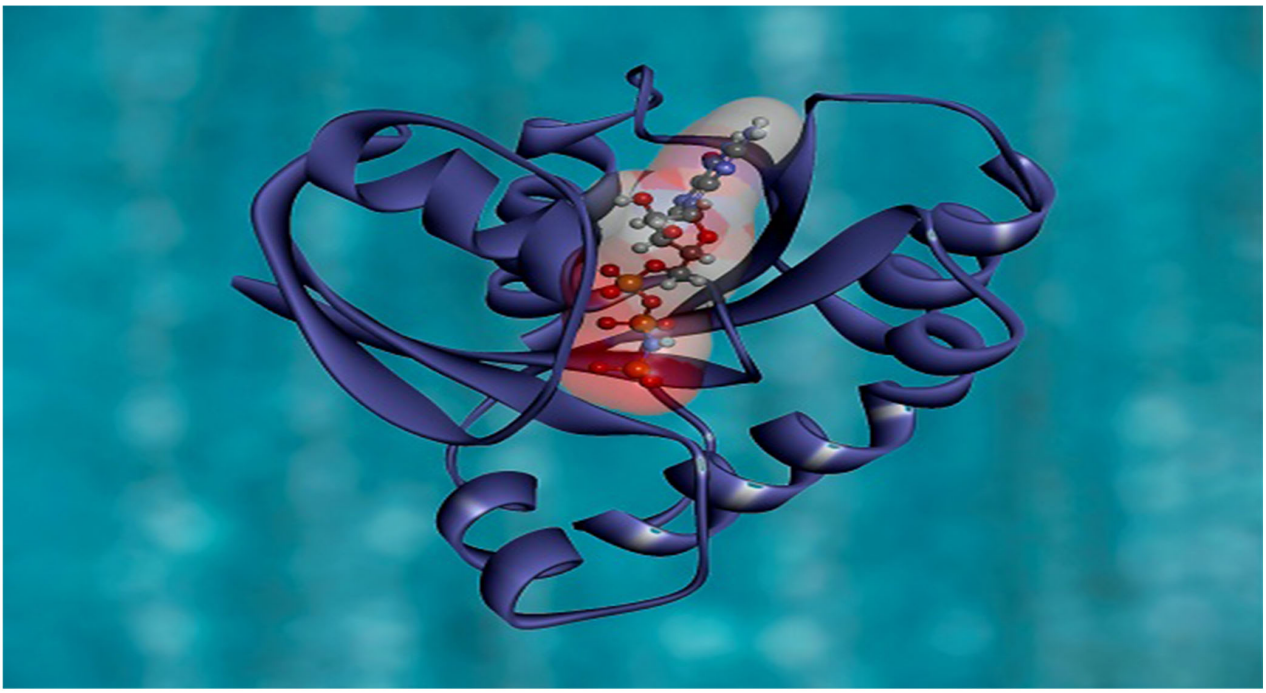
Human Proteome Project (HPP): Blueprint Covering 90.4% of the Human Proteome Released

Human Proteome Project (HPP) was launched in 2010 after successful completion of Human Genome Project (HGP) to identify, characterise and map human proteome (the entire set of proteins expressed by the human genome). On its tenth anniversary, HPP has released the first high-stringency blueprint that covers 90.4% of the human proteome. As the code of life, this milestone has very significant implications for human health and therapeutics.

Completed in 2003, Human Genome Project (HGP) was an international collaboration set up in 1990 with an aim to identify the complete set of human genes and to determine the complete sequence of DNA bases in the human genome. On January 15, 2001, HGP had released initial sequence and analysis of the human genome. Identifying, characterizing and mapping of human proteome (entire complement of proteins coded by the genome) was the next logical step. Therefore, Human Proteome Organization (HUPO) was formed on February 9, 2001 to promote proteomics research. On September 23, 2010 HUPO officially launched Human Proteome Project (HPP) with an aim to prepare a blueprint of the human proteome (1).

The analysis of the human genome predicts around 20,300 protein-coding genes. The entire set of proteins coded by these genes constitute the 'human proteome'. Human proteome is much larger than 'human genome' because one gene can be expressed in range of forms (proteoforms) as a result of chemical modifications during and



after translation. It is estimated that a million proteoforms may coexist in a single individual. In 2010, at the start of HPP, barely 70% of the proteins predicted by the genome analysis were identified. The agenda of the proteome project was to fill this knowledge gap. With the advances in technology, it has become possible to detect and quantify proteins and their forms with higher precision. Still, there are a good number of missing proteins (proteins predicted by the genome analysis, but still undetected) (2,3). The project is still in progress; however, a milestone has been reached.

On October 16, 2020 on its tenth anniversary, HPP released the first high-stringency blueprint that covers 90.4% of the human proteome (1). This considerably improves our knowledge of human biology and understanding of the molecular mechanisms at cellular and molecular level, especially the role played by human proteome which directly leads to performing research and development of diagnostics and therapeutics for cancers, cardiovascular and infectious diseases particularly for personalised and precision medicine (4).
The development of Human Protein Atlas presents a very significant progress for further research in the area of human diagnostics and therapeutics (5,6).

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