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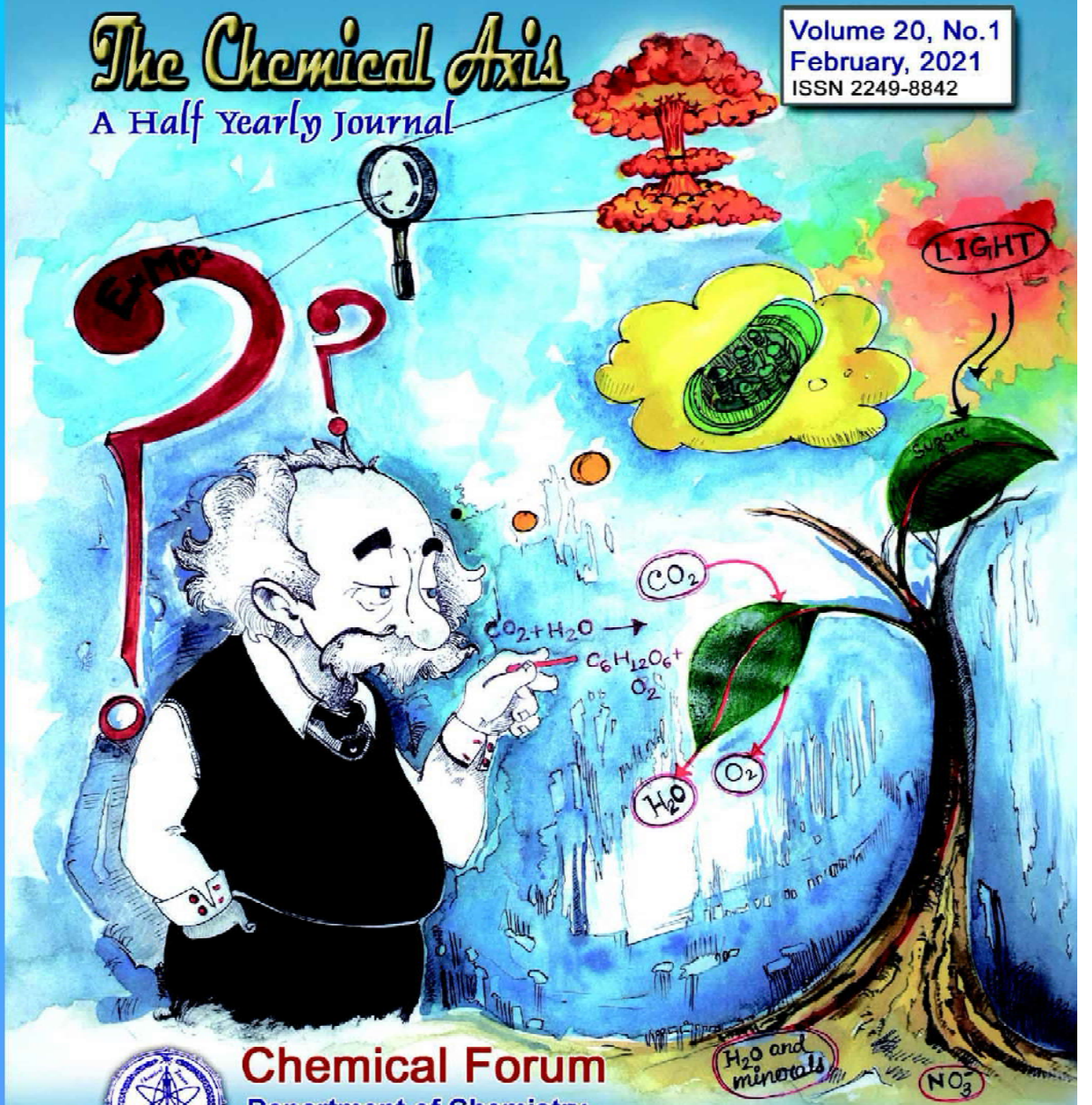

Chemical Forum

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Editorial ...

"Do not wait; the time will never be just right. Start where you stand, and work with whatever tools you may have at your command, and better tools will be found as you go along."

- George Herbert

What a year 2020 has been! The COVID - 19 has been a seismic event, even for the people who managed not to catch the virus. Now as we have left 2020 behind and stepped into 2021, the rate of COVID - 19 has decreased significantly and the world is slowly returning to its normal state. However it's going to be a long time before things return to whatever it is that we envision is normal. But, will we ever get back to where we once were, or at least to the paths we thought we were on? The timeline is going to be long, and it's going to be bumpy. But as countries rebuild their shattered economies, there is an opportunity to build back better and live in a more sustainable, "greener" way.

Though the earth is rebooting itself, and we humans are too, we can't get back the life where we left. The truth is we won't ever get a perfect time to start again. We may feel like we aren't prepared and the time is not right. But it never will be. We won't have all the stars aligned. But when we start, something happens. Something occurs in the mind, and an evolution of ideas and actions begin to unfold. Pushing ourselves forward is what we have to do. We can't suppress our goals or dreams waiting for the perfect time and hinge

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our happiness. That's no way to live. Because, nothing is going to make us happy; happiness comes from within us. So, don't wait and get out there and do the one thing that we've been putting off the longest.

Throughout this pandemic the development of science and technology has been going on to fight the virus. Similarly, our curiosity for science and technology hasn't stopped. Needless to say that though COVID-19 was at its peak, we still continued the journey of 'The Chemical Axis'. The motto of 'The Chemical Axis' has always been to ignite, inspire and nurture the creative instincts of young minds to mould them for a better tomorrow. In this regard, various articles that concur with the present scenario of the research field are enlisted.

The series on Bhatnagar awardees, Nobel Prize in Chemistry, History of Chemistry and Chemistry in movies has been continued through this edition too.

We hope that this edition of The Chemical Axis would jazz up the reader and provide them with various information.

Date: 16-02-2021
Place: Guwahati

The abstract sketched on the cover page has been designed by ***Yoshita Chakravarty*** *on the quotation,*

"The important thing is not to stop questioning. Curiosity has its own reason for existing."

- Albert Einstein

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Students' Section

COVID-19 Vaccine: mRNA Loaded Liposome

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Prologue

On Tuesday (December 8, 2020) 90-year-old Margaret Keenan of UK received Pfizer's COVID-19 vaccine.[1] Both Pfizer (plus BioNTech) and Moderna pharmaceuticals of the United States reported messenger-ribonucleic acid (mRNA) based vaccines against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which causes COVID-19. These companies claimed the vaccines are 95% effective and they activate whole-body immunity against the antigen: receptor-binding domain (RBD) of the viral spike protein.[2] The vaccines instruct antibody production and cures COVID-19.[3,4] However, a critical concern is the storage temperature of these vaccines: Pfizer vaccine needs -70 °C (dry ice temperature) and Moderna vaccine requires -20 °C.[5] The storage temperature can impact the logistics of packaging and distribution of the vaccines throughout the world. But, why do these vaccines need such low temperatures for storage? The answer might lie in the structure-stability relationship of the mRNA, the genetic code for the spike protein on the surface of SARS-CoV-2.

Vaccine Action

In January 2020, China released the genome sequence of the SARS-CoV-2 virus.[6] The pharmaceutical companies have used this genome data to develop multiple vaccines-Pfizer and Moderna pharmaceuticals have developed the vaccines in an unprecedented 10 months' time. Until now, Merck's DNA vaccine (rVSV-ZEBOV) against Ebola is the only genetic vaccine in the market.[7] Both COVID-19 vaccines consist of two parts- lipid nanoparticle or liposome shell and its interior mRNA (not DNA) cargo.[4,5] The mechanism of vaccine action follows multiple steps starting from intradermal injection in the arm to the whole body immunity.[8] At the cellular level, the vaccine first enters a human cell through endocytosis. Next, the vaccine fuses with endosomes in the cytoplasm. The endosome journeys various stages starting from early endosome to lysosome. The acidic pH of the endosome breaks open the liposome and spills the viral codes (mRNAs) onto the ribosomes.[9] The ribosomes then process the viral codes and translate them into SARS-CoV-2 viral proteins. The proteasomes trim the viral proteins into smaller peptides or antigens (receptor-binding domain (RBD) of the spike protein). The major histocompatibility complexes (MHCs) present the RBD peptide antigen on the cell

surface of both normal and immune cells, activating the whole body immune response. Finally, immune cells (B cells) produce antibodies against the viral RBD peptide antigen and protect humans from SARS-CoV-2 infection by neutralizing the invading viral antigens **(Figure 1**).

Modified mRNA

The mRNA vaccine gene therapy has multifold advantages over DNA-1) mRNA's inability to integrate into the host cell's chromosome and thus evades dangerous health effects of 'rogue' proteins, 2) mRNA transfer into the cytoplasm is more efficient than DNA transfection into the cell's nucleus, and 3) mRNA instructs protein synthesis immediately after its cell entry.[10] The mRNA gene directs the expression of the receptor-binding domain (RBD) of the spike protein, which undergoes intracellular processing. The RBD decorates the cell surfaces (mainly professional antigen-presenting cells) and activates the immune system to produce antibodies **(Figure 1)**. But, the structural fragility of mRNA (ubiquitous ribonucleases can chop the gene off), its low translational yield (low protein production capability), and its inherent immune stimulation (suppresses antigen expression and potentially induces severe side-effect due to antibodies against itself) are critical problems.11-13 The solutions to these problems involve the structural modification of the mRNA, its delivery vehicle, and low storage temperature.

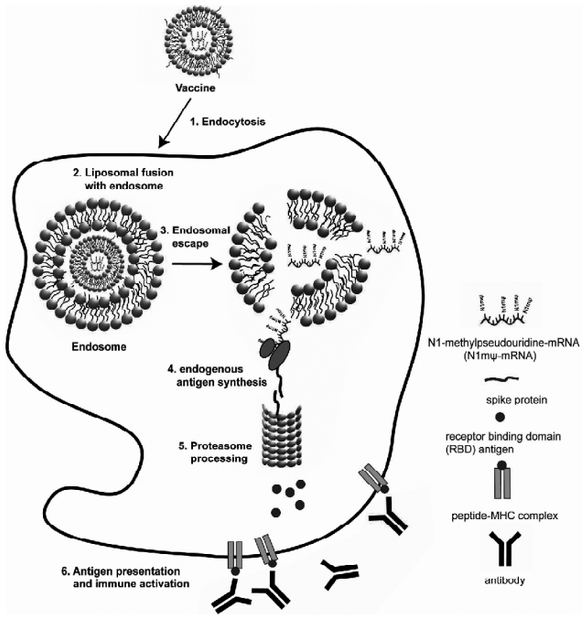

Figure 1 : Mechanism of vaccine action in a human cell

The liposome based vaccine enters a cell through endocytosis (step 1), the vaccine then fuses with endosome (step 2), the acidic pH of the endosome breaks open the liposome releasing N1mΨ-mRNAs code (step 3), the ribosomes translates the single strand viral mRNA into SARS-CoV-2 proteins (step 4), proteasomes trims the viral proteins into smaller peptide (receptor binding domain of the spike protein) (step 5), the major histocompatibility complexes (MHCs) presents these peptide on the cell surface, activating the body's immune response (step 6). Finally, antibodies produced against the viral peptide can neutralize the same peptide present on the SARS-CoV-2.

In both vaccines, chemical structures of the nucleosides determine the stability of the mRNA structure. The pharmaceutical companies replaced the uridine nucleoside (U) of mRNA with pseudouridine (Ψ), the 'fifth nucleoside' or N1-methylpseudouridine (N1mΨ).[14,15] The N1mΨ modification in the Pfizer vaccine likely imparts rigidity to the phosphodiester bond through altered stereo-electronic properties and enhanced local base stacking in the secondary and tertiary structures mediated through RNA-RNA and RNA-protein interactions (**Figure 2**). This mRNA modification exerts significant ripple effect-high translation into COVID-19 spike protein through increased ribosome loading and low immunogenicity.[16,17]

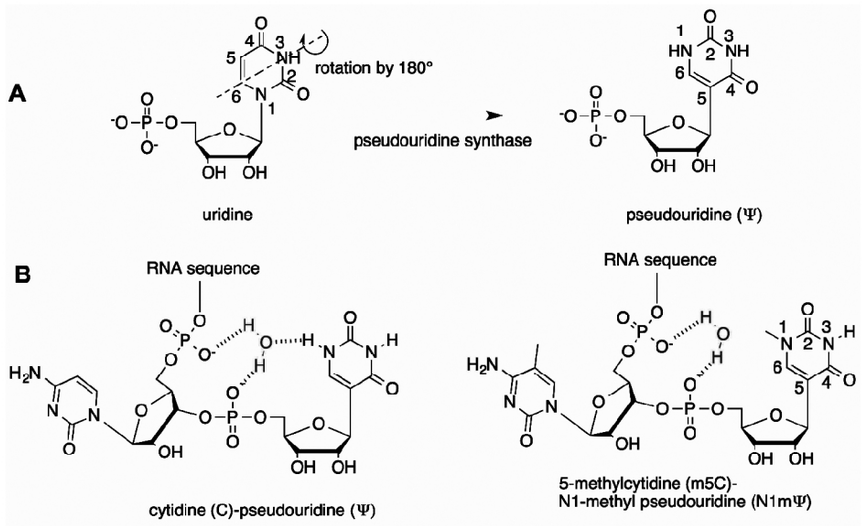

Figure 2 : modified nucleosides in the mRNA of the vaccine

A) uridine base undergoes 180° rotation about C6-N3 bond to form pseudouridine (Ψ). **B)** The pseudouridine (Ψ) supplies an additional hydrogen bonding that stabilizes the phosphodiester bonds through water bridge. The N1-methyl group

of N1-methyl pseudouridine (N1mΨ) eliminates the H-bond but potentially achieves improved steric interaction with other nucleosides.

Liposomes

The vaccines use lipid nanoparticles or liposome vehicles to drive the mRNA genes through blood and deliver them into the cytoplasm of a cell. The liposome covers the mRNA and prevents the enzymatic (ribonucleases) degradation in blood and efficient targeted delivery into a cell. The low temperature is hypothesized to stabilize liposome-mRNA conjugate. The liposomes must exhibit minimum surface charge in the blood (pH 7.4) to minimize the non-specific binding with tissue and proteins and maximum positive charges inside acidic endosome (pH 5.5) to maximize its integration into the negatively charged lumen of endosome (**Figure 3**).[18]

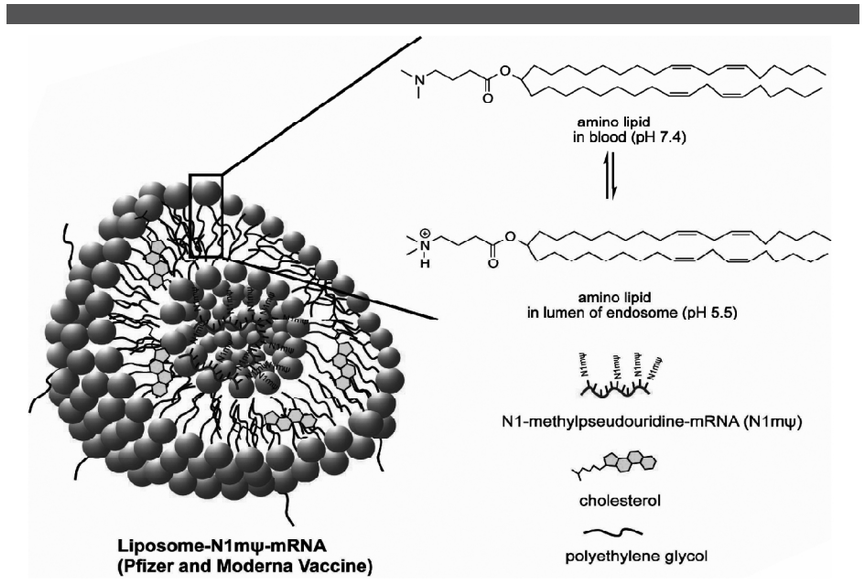

Figure 3 : Structure of liposome-N1mΨ-mRNA vaccine

The cationic amino lipid constitutes the outer lipid bilayer. Cholesterol stabilizes this bilayer and polyethylene glycol (PEG) enhances the half-life of the vaccine in blood. The viral proteins are encoded in the N1mΨ-mRNA, which occupy the hydrophilic core of the liposome. The liposome diameter varies between 70 nm and 90 nm.

The liposome in the Pfizer (and most likely Moderna) vaccine used the following formula- amino lipid,distearoylphosphatidylcholine (DSPC), cholesterol and (R)-2,3-bis(octadecyloxy) propyl-1-(methoxy poly(ethylene glycol)2000)

propylcarbamate (PEG-lipid) in the molar ratio 40/10/40/10, respectively, and a COVID-19 mRNA/total lipid ratio of approximately 0.05 (w/w).[4]

Conclusion

Pfizer and Moderna have introduced a liposome-N1mΨ-mRNA vaccine, which has many potential therapeutic advantages-(I) protection of fragile mRNA from the storm of pH variance, immune cells, and ribonucleases with liposome, (II) shuttle polyanionic mRNA through the lipophilic cell membrane, (III) improved safety due to mRNA's inability to integrate into the genome, thus preventing dangerous side effects, (IV) lack of inflammatory response to N1mΨ-containing mRNA, thereby dampening innate immune inflammation.[10] In a nutshell, these beneficial attributes make N1mΨ-containing mRNA an excellent tool for vaccination. When this article is published, countries around the world will start mass vaccination programs and our lives will slowly become normal again.

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■ ■ ■

Solid Crystalline Drug Formulations

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Inventor of prominent drugs like Propanolol (a beta-blocker) and Cimetidine (an anti-ulcer), Nobel laureate James Black said, *"The most fruitful basis for the discovery of a new drug is to start with an old drug."* The development of novel drugs is extremely expensive and too time consuming to counter the ever-evolving dynamics of diseases and physiological conditions affecting humankind. From drug discovery to drug development, it consists of a sequence of complex events to reach the clinical trials, which on an average takes 12-15 years on time scale and costs million$ per drug to reach the shelves of a medical store[1]. As a response, the scientific community at various disciplines are guiding their efforts to somehow bring down the time and cost involved in developing a drug. Drug repurposing, drug repositioning, therapeutic switching, change in routes of administration etc.at the clinical level and Crystal Engineering at molecular level are the front runners in providing efficient ways to cost and time effective manufacturing of drugs with better or new therapeutic potentials. The concern is not only limited to look out for novel compounds but also to develop on the various parameters which plays a starring rolein defining the efficacy, efficiency and bioavailability for the already existing class of therapeutic compounds.

Biopharmaceutical classification system (BCS) classifies all drugs into four different classes on the basis of their solubility and permeability (Figure 1).

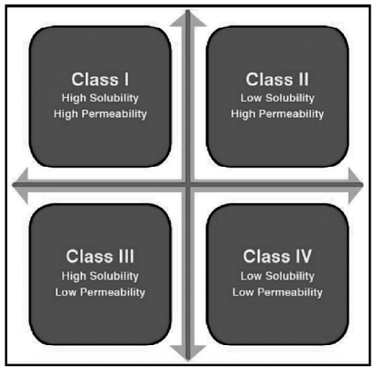

Figure 1 : Biopharmaceutical classification system (BCS) classification of drugs into four quadrants.

The solubility and permeability parameters of a drug are of extreme importance considering its oral administration into the patient's body which is the most popular route due to ease of ingestion, ease to self-administer, pain avoidance, versatility (to accommodate various types of drug candidates), and, most importantly, patient compliance[2]. Besides, these systems do not require sterile conditions and are, therefore, easy to finances on a large scale.However, about 50% of the approved active molecules have poor aqueous solubility and permeability issues, resulting in limited gastrointestinal absorption and poor bioavailability[3]. That is why limited solubility of drugs is a major challenge in development of oral dosage forms. Although numerous strategies exist for enhancing the bioavailability of drugs with low aqueous solubility, the success of these approaches cannot be quantified and is greatly dependent on the physical and chemical nature of the molecules being developed.[4]

Crystal Engineering acts as a portal to a number of routes to enhance the solubility and dissolution rate, depending upon molecular properties of active pharmaceutical ingredients(API) present in a drug. The main advantage of this technique is that it offers a plethora of biopharmaceutical and physicochemical enhancements to a drug molecule without the need of any pharmacological change in the drug.[5] An active ingredient is the ingredient in a pharmaceutical drug or pesticide that is biologically active. APIs are most commonly formulated in the solid-state for an obvious reason of better physical and chemical stabilities. Moreover, the ease of handling, processing, and packaging during the various stages of drug development and preparation promotes the solid preparation of APIs.[6] The structure of an API is core factor of its property, as inherent structural change can modify its unique property and crystal engineering exploits this property to bring about changes in the associated functionality of the drug molecules. G.R. Desirajuin 1989 defined Crystal Engineering as "the understanding of intermolecular interactions in the context of crystal packing and in the utilisation of such understanding in the design of new solids with desired physical and chemical properties".[7] Contemporary to the idea of Crystal engineering was the development of a new distinct field in chemistry known as Supramolecular Chemistry[8] - chemistry beyond molecule; which led to a synergistic effect between these two fields to design large functional structures at molecular level with the aid of weak intermolecular forces such as hydrogen bonding and van der Waals interactions as the two important components in addition to some newer ones such as halogen bonding and C–H···π interactions.

During crystal formation, molecules are assembled via ordered repeating units of non-covalent interaction to form structural motifs in the crystalline lattice and G. R. Desirajuused the term 'supramolecular synthon' for the first time to describe

these interaction motifs in crystal structures.[9] Supramolecular synthons are spatial arrangements of intermolecular interactions that describe recognition events that take place when molecules assemble into supra molecules. The overall goal of crystal engineering is to recognize and design synthons that are robust enough to form new crystals with desired properties.[9-10]

Crystalline Organic Solid States

The very basic idea of solids refers to a degree of arrangement at its atomic or molecular level. Crystallization is the process by which a solid forms, where the atoms or molecules are highly organized into a structure known as a crystal. Crystallization occurs in two major steps. The first is nucleation followed by crystal growth as the second step. Crystallisation of organic solids is functions of weak inter- and intramolecular interactions compared to the inorganic systems involving strong electrostatic interactions at large. Hence the ability to tune the structure-property analogy of organic solids is at considerable focus to the expanding pharmaceutical industries. A solid is categorized as a single component or a multi-component system depending upon the components present in building units of a crystal lattice. Single component solids include amorphous forms and polymorphs. Polymorphs are substances with the same chemical composition, but show different crystal packing or molecular conformations in the crystalline state. Multicomponent solids can be cocrystals, salts, amorphous solids, solvates/hydrates, and continuous solid solutions or discontinuous solid solutions/eutectics.[11] Although these differentiations are generalized but many a times the studied systems are a blend of such states.

Most of the marketed APIs are crystalline rather than amorphous because of the thermodynamic standpoint. Organic molecules, including APIs, generate polymorphic crystals through two mechanisms, first is the packing polymorphs mechanism, in which molecules with relatively rigid conformations can be assembled into different three-dimensional structures whereas the second mechanism occurs when a flexible molecule bends into different conformations to subsequently be packed into alternative crystal structures.[12] The different types of solid formulations being studied for various pharmaceutical advances are described below

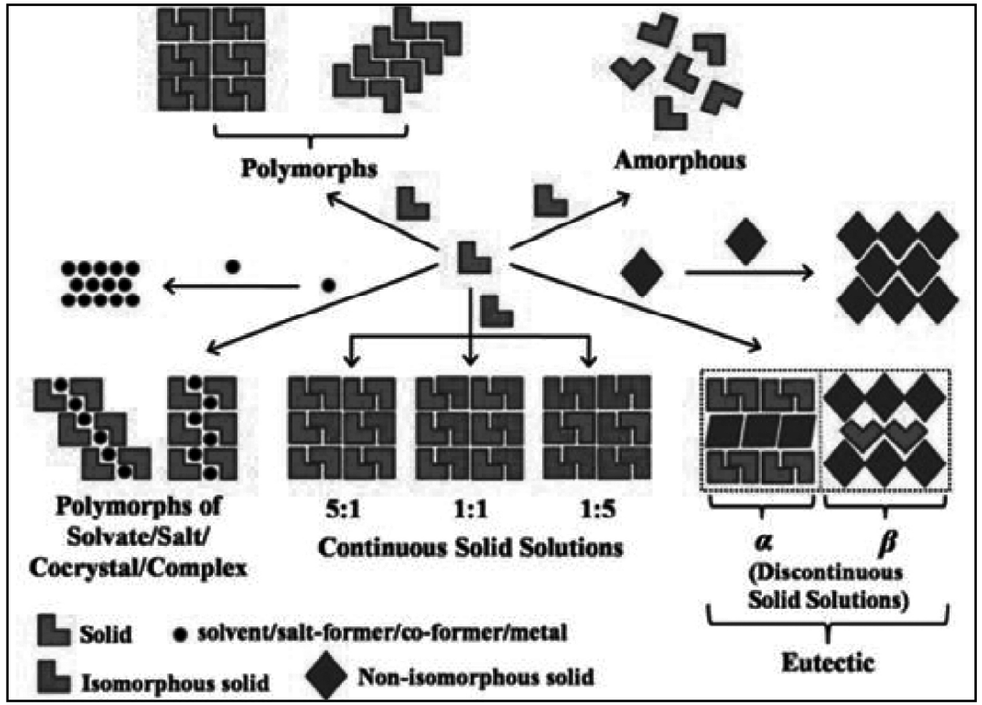

Figure 2 : Schematic representations of various single and multi-component forms. *Adapted from Chem. Commun., 2014, 50, 906-923 by Nangia and coworker.*[13]

Polymorphism

It is defined as the ability of a substance toexist as two or more crystalline phases that have different arrangements or conformations of the molecules in the crystallattice. In different polymorphs, the samemolecule can exists in different ways resulting in packing polymorphism. If the polymorphism is due todifference in conformation, it is called conformational polymorphism and synthon polymorphism is due to different hydrogen bond synthons present in different polymorphs. As results of molecules have differentarrangements in the unit cell of its crystals, it offers different physical properties. These include different packingproperties, thermodynamic properties such as solubility, free energy, melting point, etc.,spectroscopic properties, kinetic properties such as dissolution rate, stability, and mechanicalproperties such as hardness, compatibility, tableting, tensile strength, etc. Polymorphism is extremely important in the development of a desired form of a drug. It is equally important in pigment research, agrochemicals,explosives and fine chemical industries.

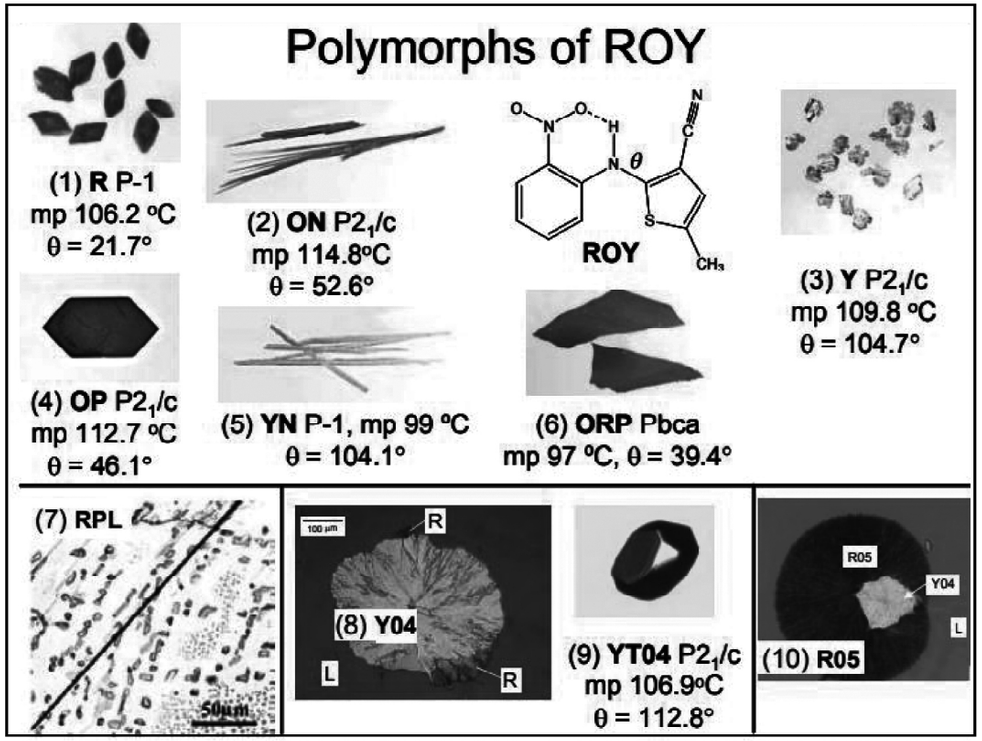

Figure 3 : The 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile also known as ROY has been crystallized in over 14 polymorphs. These polymorphs are crystallized in mainly three different colours Red (R), Orange (O) and Yellow (Y). Reproduced with permission from the web pages of Prof. Lian Yu ofUniversity of Wisconsin-Madison (see: http://www.pharmacy.wisc.edu/SOPDir/PersonDetails.cfm?&ID=32)

Hydrates, Solvates and Network Solids

Crystals with solvent molecules incorporated into its crystal lattice are known as pseudo polymorphs. Hydrates are the largest classes of pseudo polymorphs which are crystalline materials with water molecule incorporated into their lattice. In case any other solvent is incorporated it is termed as solvate. Crystalline hydrates are classified into three types. Class I refers to the isolated site hydrates e.g. cephradinedihydrate where the water molecules inside the lattice are isolated and intervened by the drug molecule. Class 2 hydrates are channel hydrates where water molecules in adjoining cell units lie along an axis e.g. ampicillin trihydrate. The Class 3 hydrates are ion associated hydrates where a metal ion remains co-

ordinated to the water molecule e.g.calteridol calcium.The presence of water molecules affects the level of intermolecular interactions (internal energy and enthalpy) and the degree of crystalline disorder (entropy). Hence, it impacts the free energy, thermodynamic parameters, solubility, dissolution rate, solid state stability, and bioavailability of hydrated APIs.Various types of phase changes are possible in solid-state hydrated or solvated systems in response to changes in environmental conditions, such as relative humidity, temperature and pressure, hence any improvement in different parameters to the drug if induced are subjective to a number of other variables which are very often difficult to control.[14]

Salts

The presence of ionizable moieties in the APIs provides an excellent opportunity to develop new formulation of drugs termed as salts which can be used to address physicochemical and biological concerns such as stability, toxicity, poor absorption, and issues related to manufacturing processes.Half of the top 200 prescription drugs in the United States consist of pharmaceutical salts. The solubility of weakly acidic and basic drugs is seen to be very well mediated by salt formulation of APIs. Salt formation has also been utilized to increase transdermal permeability of ointments, gels or creams.Various salt formulations are observed to generate different conducive effect in terms of dosage forms, route of administration, scaling up of synthesis and enhancement of pharmacokinetic attributes. For example, benzylpenicillin-a drug to treat syphilis was co-formulated with benzathine-a counterion and a local anaesthetic that numbs the intramuscular (IM) injection site thereby reducing the pain associated with a very high IM depot dose of benzylpenicillin.Dramamine® (diphenhydramine + 8-chloro theophylline), where 8-chloro theophylline acts as a stimulant to counteract the drowsiness caused by diphenhydramine is another example of progressive effect of salt formation.[15]

During salt formation, a complete transfer of proton takes place between acid-base pairs. The ΔpKa value has been used to predict proton transfer between multicomponent forming pairs. The parameter is also used as a criterion for selecting counter ions for salt formation. When the difference between the pKa values of API and coformer, $\Delta pKa < 0$, there will be no proton transfer andcocrystal formation is expected. Salt formation is observed due to completion of proton transfer if ΔpKa value >3.7. In the ΔpK_a range of 0 to 3.7, its prediction accuracy is poor. In this range, complexes between acids and bases can still form, although they can be salts or cocrystals or mixed ionization states that can't be assigned to either category. Nangia and coworkers have reported salt formation at ΔpKa value for the system was 0.93 while they were attempting to synthesize clotrimazole cocrystals with malic acid. The correctness of this approach is confirmed when the structure of the crystal system is solved from single-crystal data.

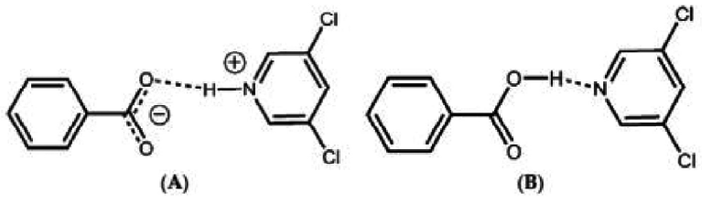

Figure 4 : Schematic representation of difference between a salt **(A)** and a cocrystal **(B)** Adapted from *Molecular pharmaceutics,* 2007, 4, 317-322 by Aakeroy and coworkers.

Cocrystals

Friedrich Wohler in the year 1844.[16] synthesized the first known cocrystal called 'quinhydrone' using benzoquinone and hydroquinone.In 2004, the term pharmaceutical cocrystals was introduced by Zaworotko and Almarsson.[17] The first cocrystal drug, Entresto, for the treatment of chronic heart failure wasapproved by the U.S. Food and Drug Administration, USFDA in 2015 resulting in a 20% reduction in cardiovascular deaths.[11] In pharmaceutical industries, the field of cocrystals is one of the most sought forbecause of its ability to fine-tune the physicochemical properties of drugs. The previous few decades have witnessed a revolution in this genre at an industrial scale. Indeed, there were four new product approvals from 2014 to 2017 and more are in the pipeline. Pharmaceutical cocrystals belong to the sub-class of multicomponent crystals in which one component is an API and the coformer is selected from the Generally Recognized as Safe (GRAS) list of substances.[18] Although there are no commonly accepted definitions for the term cocrystals but those by USFDA and EMA represents the subject concisely. The most recent and ground breaking success is an antidiabetic formulation- Steglatro1, a molecular cocrystal of ertugliflozin and L-pyroglutamic acid, possible by crystal engineering principles in a collaborative effort by Merck and Pfizer.[19] There are two main classifications of cocrystals, ionic cocrystals (or charge assisted) and molecular cocrystals. Molecular cocrystals generally consists two components, a biologically active molecular compound and a pharmaceutical acceptable molecular coformer. On the other hand,ionic cocrystals must have an additional variable because they comprise at least three moieties: an anion, a cation, and a neutral component, one of which is biologically active. This additional variable creates an exponentially widermatrix of possible compositions and many folds increase in the probability ofdeciphering new solid form with desirable characteristics.[19] Ionic cocrystals are sustained by charge-assisted supramolecular synthons, which are more open to property variations as they are very less likely to be affected by solvent. In a nutshell, cocrystals with suitable coformers canact as a tool to maneuverthe physiochemical properties of a medicine provided thecoformersused are, pharmaceutically

acceptable, of low molecular weight, and have multiple API-binding sites with the ability to form strong intermolecular interactions.Although the findings in chemical and biochemical laboratories are greatly promising but still there persists an uncertainty on scaling up the manufacture of cocrystal drugs with concerns of higher mass of dosage forms, mechanical stability and tabletability.[19]

Summary of cocrystal products currently in clinical trials or in the market as a new drug[19]

Drug	Phase	Company	Clinical trial identifier
TAK-020 (TAK-020-gentisic acid)	Phase I	Takeda Pharmaceuticals	NCT02723201
E-58425 (tramadol hydrochloride-celecoxib)	Phase III	Esteve	NCT03108482
CC-31244 (non-nucleoside polymerase inhibitor)	Phase IIa	Cocrystal Pharma	NCT0276075
T121E01F/T121E02F (zoledronic acid cocrystal)	'Phase III ready'	Thar Pharmaceuticals	NCT01721993

Solid Solutions and Eutectics

Cocrystallization of molecules that have complementary functional groups to form cocrystal may sometimes give new solid forms of drugs like solid solution, a eutectic, or even a simple physical mixture of unreacted compounds.Crystalline solid solutions are characterized by a structural disorder that enables the variation of stoichiometry in continuum. A solid solution is a variable stoichiometry multi-component crystalline solid formed when one component is incorporated in the crystal lattice of another component homogeneously. Eutectic mixtures or discontinuous solid solutions are multicomponent crystalline materials that are formed between two or more non-isomorphous compounds. They possess a melting point less than the melting point of the pure components and their structures lack a unique lattice arrangement that is distinct from the individual components.Eutectic mixtures may be prepared with a drug and an inert carrier (usually a highly hydrophilic compound) or by combining two drugs with different solubilities. The main advantage of such systems is thatthey are not considered as new chemical entities or new crystal form and consequently do not require clinical trials.[21] The most detailed description of pharmaceutical solid solutions is related to the separation and purification of enantiomers and racemic mixtures. The thermal and mechanical response of a drug are observed to be improved by the exploration and possible association of solid solutions of drugs to delivery systems, which in a way are adding to the literatures to impact the manufacturing, tableting and storage. Braga, Grepioni and co-workersreported binary and ternary solid solutions of chloro-, bromo- and methyl- para substituted benzyl alcohol that raised the melting point of

the product from 53 to 80 °C.[20] Desiraju observed that omeprazole crystallizes as a tautomeric solid solution, the relative tautomeric composition of which can be controlled by varying the crystallization temperature which in a way affects the hardness of the crystals.[20] Non-stoichiometric hydrates are another type of solid solutions that are sometimes encountered amongst pharmaceutical crystals.In LY297802 (Vedaclidine) tartrate the water content varies in continuum, from anhydrous to the hemihydrate form, as function of external humidity.[20] In comparison, the resultant crystal packing in a cocrystal is distinct from the parent components so the X-ray diffraction pattern and spectroscopic signature peaks of a cocrystal, with its unique crystalline arrangement is different from that of the individual components. In contrast, solid solutions and eutectics exhibit close similarity to the patterns of the pure constituents.

Summary

Multiple strategies towards the understanding of new crystalline drug formulations have been adopted. Polymorph, cocrystal, salt, solvate and eutectic solutions are some of the critical crystalline modifications of different organic molecules and are the logical outcome of the subject 'crystal engineering'. In the resulting phases or complexes, the forces between the component molecules can vary in magnitude and directionality and thereby changing the molecular arrangements in the lattice. Indeed such distinct molecular arrangement commandsfor a suitable preparation of an active ingredient.

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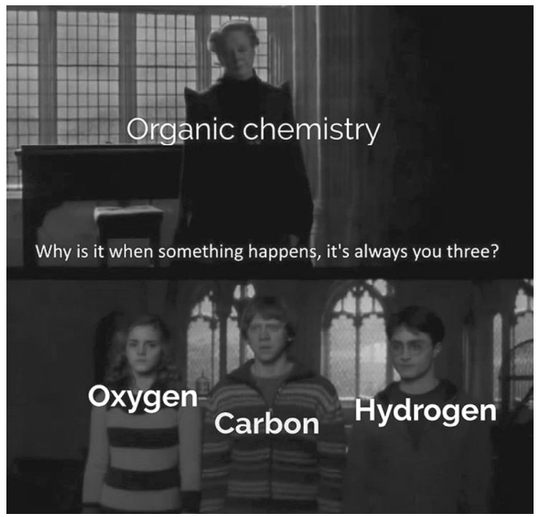

Cyclic Peptide Nanotubes: A Brief Overview of Structure and Application

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Cyclic peptides (CPs) belong to an interesting class of peptides that have been widely studied over the past decades due to their ease in synthesis, modifications, and vast applications in different fields. They are applied in the pharmaceutical industry (due to their antibacterial or antitumor activity), the agricultural sector (as fungicides), diagnostics, and vaccines. CPs has attracted a great deal of attention from the scientific community as they avoid the drawbacks of linear peptides, which include poor oral bioavailability, poor membrane permeability, vulnerability to proteolytic degradation, and lack of a rigid three-dimensional structure.

Cyclic peptides are generally defined as polypeptide chains where the linear peptide is pinned into one or more macrocycles by the addition of chemical bond(s). These bonds can be between amino acid side chains or the peptide N- and C-termini, or a combination thereof. Different chemical strategies are employed to synthesize these cyclized peptides. Some of these include (1) disulfide bonding via the thiol side chain of two cysteines, common in natural proteins; (2) head-tail bonding, where the peptide N-terminus forms a peptide bond with its C-terminus, effectively removing the peptide termini; (3) N-terminus to acidic side chain; (4) C-terminus to basic side chain; (5) side chain to side chain; and (6) more complex modifications, such as the cysteine bridging to serine or threonine seen in lanthipeptides. Typically, cyclic peptides are at least four amino acids in length to be practically synthesizable, except for the special structure of the diketopiperazines lactam ring formed from two amino acid head-tail-bonded peptides.

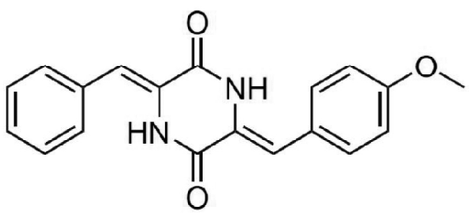

Figure 1: A diketopiperazine molecule that acts as a PAI 1 inhibitor

A class of cyclic peptides is the self-assembled cyclic peptide nanotubes (SCPNs) that have recently drawn particular attention as one of the most intriguing nanostructures in the field of nanotechnology. The interest is largely related to

their technological possibilities as biosensors, photosensitive materials, antimicrobial agents, molecular electronics components, drug delivery, and gene delivery vectors, and ionic or molecular channels. Cyclic peptide nanotubes are hollow cylindrical-shaped supramolecular structures formed by the stacking of cyclic peptides (CPs) in a flat conformation. Their unique features include high surface area, increased drug loading, environmental stability, enhanced permeation, and modifiable drug release. These hollow tubular structures can be constructed with cyclic di-, tri, tetra-, hexa-, octa-, and decapeptides with various amino acid sequences, enantiomers, and functionalized side chains.

In the year 1993, Ghadiri and his team had first reported the structure, synthesis, and characterization of nanotubes based on rationally designed cyclic peptides. On protonation, these compounds crystallize into tubular structures of hundreds of nanometres long, with internal diameters of 7-8 Å. These SCPNs are open-ended, with uniform shape and internal diameter. Subsequently the following year they had demonstrated that the internal diameter of the nanotubes can be rigorously controlled simply by adjusting the ring size of the peptide subunit employed. To prove that they had designed and synthesized a 12-residue cyclic peptide structure and documented its utility in the construction of nanotube ensembles having a uniform 13 Å van der Waals pore diameter.

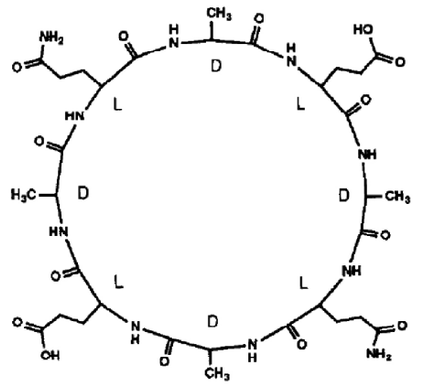

Figure 2: Primary structure of the amino acid which assembled to form the first reported nanotube.

One of the key facts of the design principles of the nanotubes is that the cyclic peptide structures are made up of an even number of alternating D- and L-amino acid residues which tend to minimize nonbonded intramolecular transannular side chain-side chain and side chain-backbone interactions by adopting (or sampling) a flat ring-shaped conformation in which all backbone amide functionalities lie approximately perpendicular to the plane of the ring structure. Furthermore, the local conformational and steric constraints imposed by the alternating amino acid backbone configuration forced the amino acid side chains to point outward away from the center of the peptide ring structure, thus leaving it free to form a tubular hollow-core structure. Some of the factors which directly affect the peptide self-assembly process are the ring size of the peptide subunit, preference for a particular ring stacking arrangement, relative sheet register, and identity of the amino acid side chains.

Apart from the structure of the cyclic peptide, the backbone-backbone intermolecular hydrogen-bonding interaction for the ring stacking arrangement plays a vital role in the self-assembly of the nanotubes. The H-bonding interactions can proceed via either parallel or antiparallel ?sheet-like ring stacking arrangements (Figure 3). However, molecular modelling suggests a marked preference for an antiparallel arrangement that creates the best alignment between backbone amide NH and carbonyl groups.

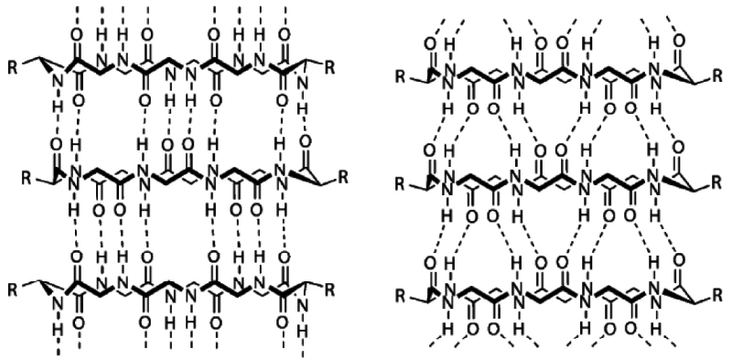

Figure 3: Cyclic octapeptides with alternating D and L amino acids can potentially stack to form anti parallel or parallel nanotubes

Mostly three types of SCPN structures have been studied: cyclic D,L-α-peptides, cyclic β-peptides, and cyclic α-γ-peptides. Recently in 2020 itself Insua and Montenegro have reported the design of the first cyclic peptide capable of undergoing sequential 1D-to-2D self-assembly in an aqueous medium to produce dynamic and giant two-dimensional supra-molecular structures. These ultrathin supra-molecular assemblies constitute one of the largest fully organic 2D structures ever assembled in solution.

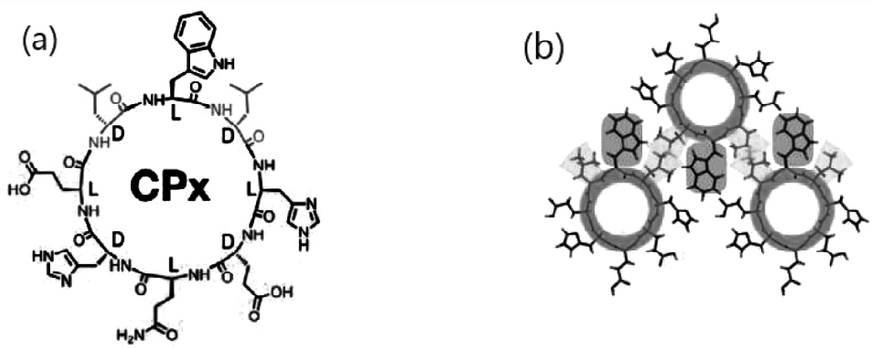

Figure 4: Proposed model for 1D-to-2D self-assembly of cyclic peptide. (a) Primary structure of the amino acid sequence of the cyclic peptide. (b) 2D self-assembly of the cyclic peptide.

One of the most attractive features of SCPNs is their surface properties: their charge, size of the radius of the nanotubes, and hydrophobicity/hydrophilicity that can be easily altered by changing the amount and type of amino acids, pH, or polymeric conjugation without additional chemical functionalization. SCPNs constructed with an even number of alternating D- and L-α-amino acids have been reported to exert antiviral activity. Hore *et al.* found that an eight-residue cyclic D,L -a-peptide, cyclo-(Ser-D-His-Lys-D-Arg-Lys-D-Trp-Leu-D-Trp) with antitype A influenza viral activity and IC_{50} of 5 mM acts by preventing HeLa cells from forming low-pH endocytic vehicles and further inhibiting viral escape from endosomes. On the other hand, these nanotubes are also used as antimicrobial agents. In this context, Fernandez-Lopez *et al.* demonstrated in 2001 that six- and eight-residue amphipathic cyclic D,L -α-peptides with appropriate amino acid sequences for stacking into hollow and β sheet-like cyclic peptide nanotubes bearing suitable outer surface properties could potentially act against either gram-positive or gram-negative bacteria. it was proposed that this involves a carpet-like mechanism that enhances membrane permeability and causes rapid cell death. Coming to the use of cyclic peptide nanotubes in drug delivery, there are several examples of its application as anticancer drugs. Chen *et al.* found that the liposomal membrane release of anticancer drug 5-FU was enhanced by the addition of a highly hydrophobic cyclic peptide, namely, cyclo-[Gln-(D-Leu-Trp)4-D-Leu], in a dose-dependent manner. Cyclic peptide nanotubes have also been revealed to function as gene delivery vectors and can be also used as artificial ion channels that cross lipid bilayer membranes for efficient transport of ions and molecules vital for cell functioning. Moreover, studies have revealed that these nanotubes have potential as materials for organic electronics in the fabrication of nano-electronic sensors for the ultrasensitive detection of protein and viral particles, as well as for recording, simulation, and inhibition of neuronal signals in nanowire-neuron hybrid structures.

Apart from the mentioned applications, these SCPNs have a range of applications in the vast field of nanotechnology. There are many such information and uses of these nanotubes that are yet to be explored. Nonetheless, the versatility and tunability of these structures would pave the way for new exciting applications in the near future.

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Series

Shanti Swaroop Bhatnagar Awardees in Chemical Science: Nanduri Atchuta Ramaiah; The Eight Recipient

The Shanti Swaroop Bhatnagar Award for Science and Technology is a science award in India given annually by the Council of Scientific and Industrial Research (CSIR). The award was instituted in 1958 with the objective to recognize conspicuously important and outstanding contribution to human knowledge and progress - fundamental and applied. The award is named after the founder director of the CSIR, Shanti Swaroop Bhatnagar. It was first awarded in 1958. Any citizen of India engaged in research in any field of science and technology up to the age of 45 years is eligible for the award.

In 1966, Nanduri Atchuta Ramaiah was awarded the prestigious Shanti Swaroop Bhatnagar Award for his contribution to chemical science. Herein, brief information of the great scientist is given.

Nanduri Atchuta Ramaiah is an Indian physical chemist, sugar technologist and the director of National Sugar Institute, Kanpur. He was an elected fellow of the Indian National Science Academy, The National Academy of Agricultural Sciences and the Royal Institute of chemistry. The CSIR, the apex agency of the Government of India for scientific research, awarded him the Shanti Swaroop Bhatnagar in 1966.

N.A. Ramaiah born on 26 August 1923 in the South Indian state of Andhra Pradesh passed his master's degree from Banaras Hindu University and continued there to secure Ph. D.

Academic Work:

N. A Ramaiah's career started at his alma mater where he joined as a member of faculty but later shifted to University of Delhi. In 1956, joining government of India service, he began an association with the National Sugar Institute, Kanpur (NSI) which would last almost a quarter of century. Starting as a professor of physical institution in 1974 and stayed there till his superannuation in 1981.

When the sugar industry enquiry commission was constituted by the Union Government in 1969,he was made the Secretary of the Commission and he stayed at the assignment, on deputation from NSI, till 1974.Vasantdada Patil and his

comrade, Shankarrao Mohite-Patil, Vishwanath Anna Kore, Ratnappa Anna Kumbhar, Yashwantrao Mohite and Shankarrao Kolhe, founded the Deccan Sugar institute in 1975 and his association with them during the tenancy of the commission gave him an opportunity to join them as the director of the institute in 1981.

Scientific work:

- Ramaiah developed several analytical methodologies for colour assessment and for the production of active carbon which assisted the industry to lessen their dependence on sulphur thereby making the processing more cost effective.
- He serves as the chairman of the ICAR committee and there he prepared a project report for the manufacture of ethanol form sugarcane in which he proposed the use of ethanol as motor fuel.
- Ramaiah's researches during his doctoral studies were on electron triggering.
- Ramaiah has written extensively on sugar technology by way of over 325 articles.

Awards and honours:

- The Council of Scientific and Industrial Research awarded Ramaiah the Shanti Swarup Bhatnagar Prize, one of the highest Indian science awards, in 1966.
- The Sugar Technologists Association of India (STAI) honoured him with the Noel Deer Gold Medal and followed it up with the Lifetime Achievement Award in 2005.
- He is an elected fellow of the Indian National Science Academy, National Academy of Agricultural Sciences and the Royal Institute of Chemistry.
- A street, Atchuta Ramaiah street, in Kakinada in East Godavari district in Andhra Pradesh has been named after him.

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Note: For information about the 1st to 7th recipients of Shanti Swaroop Bhatnagar Awards, refer to previous editions of *'The Chemical Axis'*.

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Artificial Intelligence - The New Paradigm Shift in Healthcare

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The definition of **Intelligence** in the **Oxford Dictionary** is something like this "the ability to learn, understand and think in a logical way about things; the ability to do this well" and it is mostly referring the cognitive ability of living-beings, or more specifically the humans, for the past centuries. However, human civilization is evolving and so does their cognitive ability. The most widely spoken type of intelligence in the world is now the 'Artificial Intelligence' or in short AI. As its name goes, AI is the ability of an artificial system to perform tasks with intelligence similar to the human being. Although many of you have heard this terminology and are aware of all the discussions going on around you regarding the use and ability of AI, this isn't 21st-century terminology. The concept and the terminology both were actually originated way back in the middle of the 20th century[1]. The simple concept of AI is all about feeding tons of data to a computer system and developing an algorithm to receive, analyze, and react to those data automatically by the system. To enable this, fast computing facilities with more storing capacities are the prime requirement. From its inception to the current stage, AI has seen its ups and downs. The concept flourished at the beginning, but it received several setbacks due to a lack of funding as well as limitations in the computing facilities. Nevertheless, recent advancements in computing technologies, as well as storage capabilities, have shifted the paradigm of AI and we can see more and more individuals, as well as organizations, are flexing their muscles to get a piece of this pie.

In a discussion about AI, most of the time we stumble upon few other terminologies such as 'Machine Learning (ML)', 'Deep Learning (DL)', and 'Neural Networks (NN)'. People also often mix AI, ML, DL, or NN while they are not the same. To understand the concept, you can visualize them as the concentric circles where AI is the largest circle with ML inside, DL fitting inside ML, and NN fitting inside DL [2,3]. Thus, each of the terms is a component of the prior term and all of them are the way of feeding information and train the algorithm to self-perform an automated decision-making process like a human, but DL and NN are more

advanced than ML by the fact that the former can autocorrect its error whereas ML needs human guidance in such instances[3]. Since the purpose of this article is not to get a deeper insight about AI, ML, DL, and NN but to learn how they are influencing our daily lives and more specifically the healthcare system, I will use the term AI only to refer to the concept irrespective of the learning method used to achieve that decision-making process.

AI is everywhere now, from your cell phone to your watch almost every electronic gadget is now getting its own intelligence for better performance to match growing human needs. One such example is the Google Maps, and it has uplifted the comfort of our daily commute by many folds. But have we ever thought about how Google Maps is predicting our Estimated Time of Arrival or ETA! It is a very simple answer; they are using data, such as the speed of travel, from other smartphone users who have used your route within a recent time frame. And by feeding those data to their AI system, it can easily predict the traffic congestion at that given time in that particular route and hence can quickly estimate your ETA. Similarly, an app-based taxi service like Uber is also using AI technology to provide its users a better-quality service with higher accuracy in finding the nearest taxi as well as calculating the most reasonable fare for their users. Another fine example of your daily usage of AI is Facebook. Whenever someone uploads a picture on Facebook, the AI-based technology immediately scans the picture to detect any face in it and quickly match that face with your friend accurately in most of the cases. Similar technologies are also being used in smartphone cameras to detect faces or to detect smiles etc.

Looking at the limitless utility of AI, the healthcare sector is also gearing up to accept it passionately as it has just opened up another dimension for innovation. Although numbers are yet to be multiplying, AI technology has already been able to make some remarkable progression. However, so far it is mostly limited to the field of In-vitro Diagnostic or IVD devices and with some limited exemplary progress in the field of therapeutic medical devices. Those who are not familiar with this field may get perplexed with the idea of utilizing AI for diagnostic or therapeutic purposes in the healthcare system, now however it is a reality rather than a concept from any sci-fi movie. To simply this, I would like to put some examples here.

The IDx-DR Device[4]: A very well-known disease of the modern age is Diabetes Mellitus or more commonly "Diabetes" which is a group of metabolic disorders characterized by a high blood sugar level. One of the complications associated with this disease is 'Diabetes Retinopathy' where the blood vessel of the retinal light-sensitive tissue gets damaged resulting in blindness over the long run. The IDx-DR device contains an algorithm constituted of detectors to detect different biomarkers such as microaneurysm, hemorrhages, protein deposits, etc., and those detectors work either individually or overlapping with each other while diagnosing

a patient. Additionally, this device is autonomous (thanks to its AI capability) and it can predict the results of the diagnosis within minutes without any human intervention in interpreting the data. As a result, this device would reduce the human error margin while detecting patients with or without the progression of Diabetes Retinopathy. This will prevent patients with Diabetes Retinopathy from losing their eyesight by detecting the disease progression at a very early stage.

QuantX Device[5] **:** QuantX is a diagnosis software as a medical device used to assess and characterize breast abnormalities using Magnetic Resonance Imaging (MRI) data. It includes the AI technique to process the acquired images of the patient and help the radiologist to make a better decision. The device is intended to perform as follows; at first, the MR images of the patient's intended area of investigation are captured, then the images are autonomously registered by the software, later it segments and analyzes the Radiologist (user) selected regions of interest (ROI) on the images. The software extracts image data from the ROI to provide analytical outcomes, morphological, and enhancement characteristics of the target region on the patient. The AI algorithm then synthesizes the imaging features and provides a single score based on the available database of previously known abnormalities in the intended patient population.

Caption Guidance or Caption AI[6] **:**The Caption Guidance or Caption AI is another software as a medical device that assists the healthcare provider for proper maneuvering of the Ultrasound transducer (or probe) to acquire a better quality cardiac (heart) ultrasound, or echocardiography images. The Ultrasound technique or sonography is very familiar to us as it is one of the most preferred methods in the field of diagnosis with minimum to no side effects and it produces dynamic visual images of our organs, tissues or blood flows inside the body by using high-frequency sound waves only. However, like other diagnostic techniques, the medical professional utilizing the Sonography also needs to have extensive experience to handle the device and to capture diagnostic quality images for the cardiologists. The Caption AI is developed using the ML technique by feeding information from thousands of patients to differentiate between acceptable and unacceptable image quality. This intelligence of the software has provided its manufacturer to prepare an interactive user interface (UI) to deliver prescriptive guidance to the users on how to maneuver the ultrasound probe to achieve standard echocardiographic images and video clips of diagnostic quality. Additionally, this software provides real-time feedback on the image quality as well as can auto-capture video clips and decides by itself to save the best video clip acquired from a particular view. Although the software does almost everything on behalf of a human, it still keeps the acquired information for the cardiologists for a final assessment of the images and videos for patient evaluation. The smart interactive user interface with the

Caption AI software has enabled even the medical professional without any previous experience in sonography to capture diagnostic quality images. This usability of the software was evaluated in two different studies where images captured by nurses who are not experts in Sonography were compared with the images captured by trained sonographers. The result showed that Caption AI software enabled the nurses to capture echocardiography images and videos with diagnostic quality. This enhancement in diagnosis by empowering more medical professionals will directly help the patients with heart diseases to receive proper treatment without any delay in the event when there is a lack of trained medical professionals to help facilitate the diagnosis of the patients.

AI in Diagnosing COVID-19

Since December 2019, the new type of coronavirus, COVID-19 has been creating havoc all around the world. In my assumption, directly or indirectly, there is no one left on earth without being affected by this pandemic. People are affected either mentally, economically, socially, or physically. According to the Worldometer[7], as of January 8th, 2021, there are 88,528,033 no. of confirmed COVID-19 cases worldwide where more than 1.9 million people have lost their lives and this trend is still increasing exponentially. This depicts how fast this viral species can spread from human to human. With this fast spreading of the COVID-19 virus, it needs a robust healthcare system to diagnose and treat the patients at the earliest so that it can be contained quickly. Over time people are getting more information about COVID-19 and thus its diagnosis has been improving. However, this has been achieved at a cost, the death of healthcare providers. The healthcare providers around the world have sacrificed everything in this war against COVID-19 and they are the most vulnerable ones when it comes to diagnosing/treating a potential patient infected with COVID-19. When a person gets infected with this virus, in a conventional way it's the healthcare provider who needs to collect the biological samples from the patient to conduct the testing. But not all those testing are effective enough as reported in studies[8].Additionally, whenever a healthcare provider approaches one prospective patient they are exposed to that deadly virus and this process repeats every day as in many countries the healthcare system is overwhelmed with growing numbers of COVID-19 patients. Thus, for the healthcare providers the chance of getting the virus increases by many folds. Alongside working on finding a vaccine candidate for COVID-19, scientists across the globe are also working on approaches in order to help the healthcare provider to limit their exposure to the prospective patient. One such approach is the application of AI in diagnosis and over the course of a year, since the onset of this pandemic, a plethora of scientific articles has been published. Few of those articles are[8,9,10] and the referenced articles therein. The overall idea in these studies is to improve existing

or develop a new algorithm by feeding either Computer Tomography (CT) or X-Ray images of the chest region. They selected images taken from a patient infected with COVID-19 virus, other viruses, or other bacteria as well as healthy people. The authors were able to train their algorithms in such a way that it could determine and categorize patients with COVID-19 pneumonia, other bacterial or viral pneumonia, and normal people. It is a significant milestone as this has the potential to provide critical information regarding the progression of the disease at the very early stage even when the laboratory testing fails to do so. Another major benefit of such a diagnosis is that with the advancement in IVD medical devices, the healthcare providers now can stay at a remote distance and capture the patient images. Additionally, imaging techniques such as X-Ray are readily available at a cheaper cost and thus it will be beneficial to the developing nations also. Although there is a possibility of utilizing AI in diagnosing COVID-19 with greater benefits, it is still far from becoming the major diagnostic technique. Intervention from a healthcare provider is still required, but they can consider the results from these techniques as the 'Second Opinion' to come to a robust conclusion much faster than usual. In the event when a 'mass rapid screening' to track infected people in possible hotspots is required and there is an insufficiency of resources, in my opinion, I see huge applicability of this technique for faster tacking and quarantining purposes.

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Progress on iron catalyst employed nucleophilic substitution reactions of alcohols and future aspects: an illustrative review

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Nucleophilic subtitution reactions have great importance in fundamental transformation of organic synthesis. Generally, these transformations are done by direct substitution of hydroxyl groups by incoming nucleophiles. Although bimolecular nucleophilic substitution of alcohol is found to be important in organic synthesis, but due to bad leaving character of -OH, the substitution is hindered and become complicated. In some cases, deprotonation of alcohol is also found by the ligand as ligand are one type of bronsted base.[1] These limitations can be defeat unless we transform this bad leaving group to a more active functional groups. It can be achieved by employing an active transition metal catalyst like iron.[2]

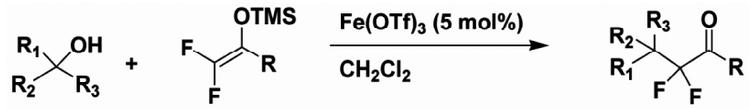
Before entering into the experimental procedure, we have to consider some key challenges that required achieving great implementation if we use the procedure of transformation of -OH to a more active functional group at first.[3] These are-

(a) Unwanted interaction of catalyst with the nucleophiles,
(b) Regeneration of the catalyst via cleavage of the oxygen-catalyst bond in presence of the nucleophiles,
(c) Bronsted acid catalyzed direct substitution reaction,
(d) The indium catalyzed direct chlorination reactions etc.

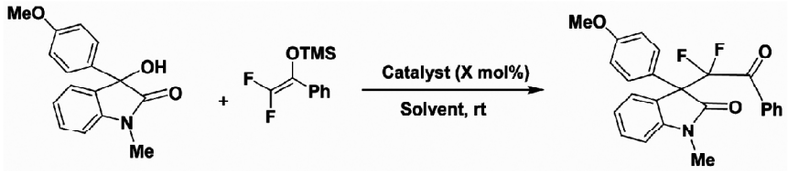
There is another way in which pre-activation of the alcohol is not required, so on demand for economic, efficient and ecologically valuable process, it is an environmentally benign protocol.[4] Depend on these points and key challenges, the idea of catalysis in direct nucleophilic substitution in organic transformations are contemplated and here we discussed some of theses recent developments on catalytic nucleophilic substitution of alcohols.

β-Quarternary α, α-Difluoroketones can be constructed through catalytic nucleophilic substitution of tertiary alcohols with difluoroenoxysilanes.[5,6] The

substitution of tertiary alcohols (cyclic or acyclic) with difluoroenoxysilanes can be carried out by efficient catalysis of $Fe(OTf)_3$, which provides a excellent yields under a mild conditions.

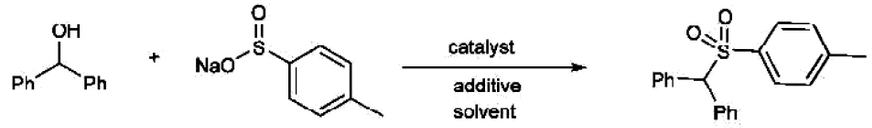


The use of iron triflates as a catalyst highly succeed the transformation where the reaction of 3-hydroxyoxindole with difluoroenoxysilane in CH_2Cl_2 at room temperature produce 91% yield of the desired product.



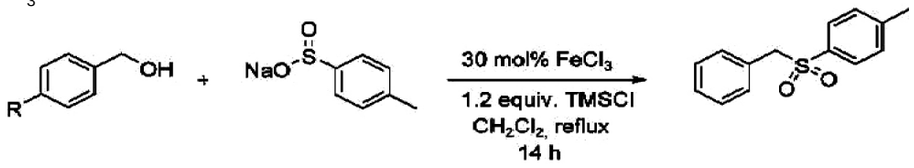
This study revealed that $Fe(OTf)_3$ act as a hidden Bronsted acid in this reaction, which actually enhance the efficiency of this reaction. The difluorinated tricyclic indoline derivatives constructed by above scheme has great importance in drug discovery.

In a study, direct sulfonylation of benzylic, allylic and homoallylic alcohols with Sodium Arenesulfinates was carried out by introduced $FeCl_3$ as a catalyst and chlorotrimethylsilane as an additive[4]. By utilized this path way, 96% yield can be achieved if we optimized the condition, where the best way found to be used of 15 mol% $FeCl_3$ and 1.2 equivalent of TMSCl.

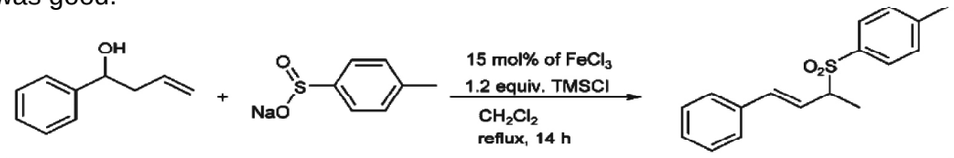


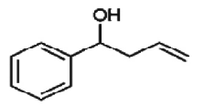
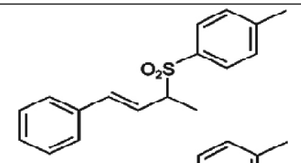
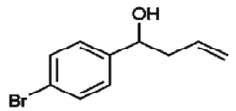
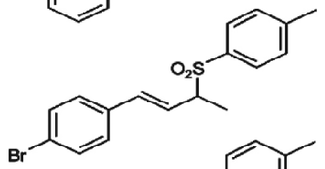
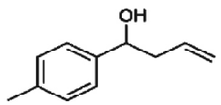
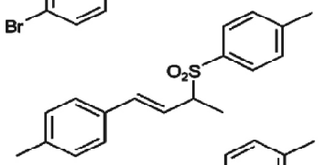
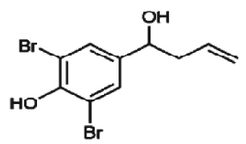
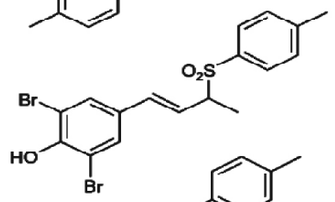
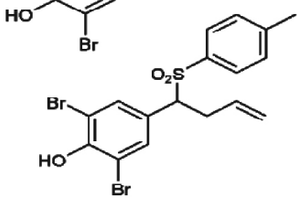
In this reaction, TMSCl plays an important role since it extracts nucleophilic sulfinate anion from its salts, in addition having Lewis acidity can activate the alcohol too.

Non-benzylic alcohols such as cyclohexanol and 4-tert-butylcyclohexanol can be substituted directly by using sodium p-toluenesulfinate salt with the help of $FeCl_3$ and TMSCl.



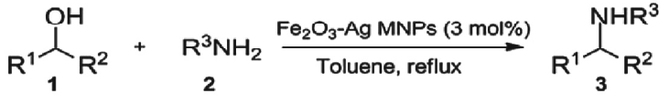
In further study, the importance was on allylic sulfonylation of different types of alcohols. The result shows similar activity of them with benzhydrols, also the yield was good.



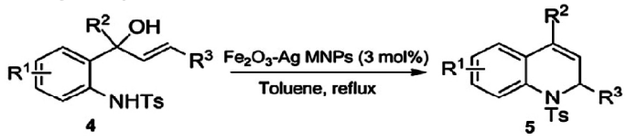
Entry	Homoallylic alcohol	Product	Yield [%]
1			55
2			60
3			58
4			8
			52

In a study, development of bimetallic iron oxide-silver magnetic nanoparticles (Fe_2O_3-Ag MNPs) as a catalyst provides an efficient heterogeneous synthetic pathway to allylic amines and 1,2-dihydroquinolines in which the direct inter/intramolecular nucleophilic substitution of π-activated alcohols with electron-deficient amines occurs.[7] Due to some factors like wide availability of substrate, simple separation of product, low catalyst loading, magnetically recyclable catalyst etc., this protocol become more efficient and beneficial. The allylic amines and 1, 2-dihydroquinilines obtained about 98% by this process.

Fe_2O_3-Ag MNPs catalyzed intermolecular nucleophilic substitutions with a alcohols and amines.

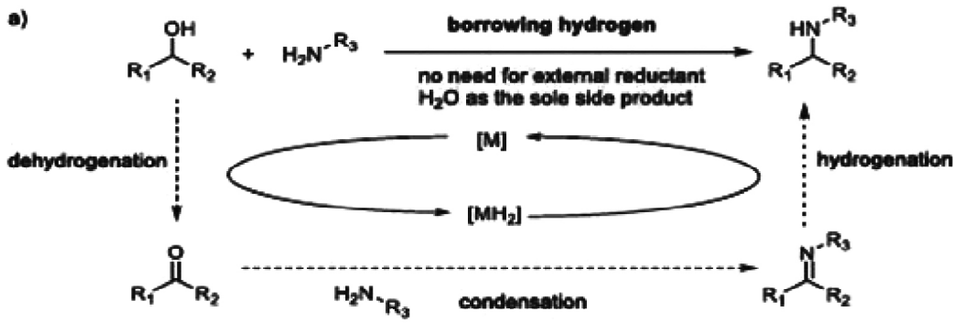


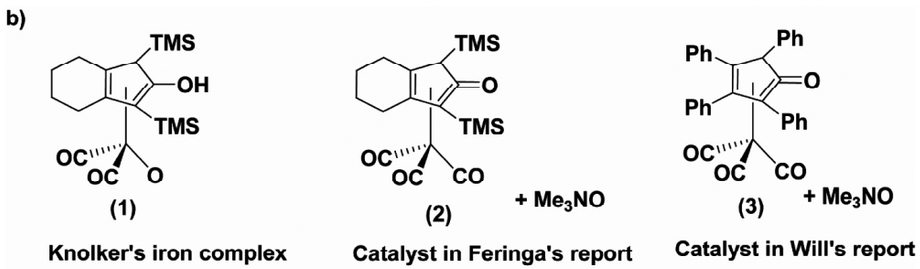
Fe_2O_3-Ag MNPs catalyzed intramolecular nucleophilic substitutions for the synthesis of 1, 2-dihydroquinilines.



Another experimental methodology shows iron-catalyzed amination of alcohols.[8] An efficient Lewis acid-assisted, borrowing hydrogen methodology was introduced in this process.

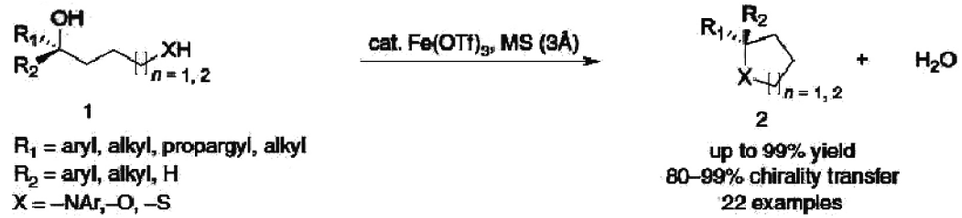
Silver fluoride was identified to be a highly effective additive to overcome the low efficiency in the amination of secondary alcohols catalyzed by the Kn?lker's complex. In this overall redox-neutral process, the alcohol substrate serves another important role as the hydrogen donor so no external reductant is needed, and water is generated as the only side product.





The use of 1 for hydrogenation and transfer hydrogenation of carbonyls is well established.[9,10] Very recently, the Feringa group and the Wills group reported successful amination of alcohols catalyzed by iron complex 2 (precursor to Knölker's complex) and the analogous complex 3 respectively.[11,12] It is important to note that Fe-catalyzed amination reactions through a borrowed hydrogen process is highly successful for only primary alcohols and selected symmetrical secondary alcohols. On the other side, secondary alcohols are in most cases remain unreactive. But silver fluoride as an effective additive can enable highly efficient amination of secondary alcohols catalyzed by Knoiker's iron complex.[8]

One illustrative study explains on intramolecular substitutions of secondary and tertiary alcohols with chirality transfer by an iron(III) catalyst.[13] This process demonstrate a simple, inexpensive, and environmentally benign iron(III) catalyst promotes the direct intramolecular substitution of enantiomerically enriched secondary and tertiary alcohols with O-, N-, and S-centered nucleophiles to generate valuable 5-membered, 6-membered and aryl-fused 6-membered heterocyclic compounds with chirality transfer and water as the only byproduct.



The power of the methodology is demonstrated in the total synthesis of (+)-lentiginosine from D-glucose where iron-catalysis is used in a key step. Adoption of this methodology will contribute towards the transition to sustainable and bio-based processes in the pharmaceutical and agrochemical industries. Iron-catalyzed intramolecular substitution with chirality transfer of the OH groups of enantioenriched secondary and tertiary alcohols.

In conclusion, it can be asserted that great progress has been already achieved in the last two decade in nucleophilic substitution reaction of alcohols.. The wide substrate scope, simple product separation, low catalyst loading, and magnetically recyclable catalyst make this protocol attractive to the chemistry community. However, there is still room for improvement in various aspects of this transformation. Though the direct substitution methodologies provides an economic, efficient and ecologically valuable process, but there is still room for minimize the use of organic solvents. In this sense, the use of recyclable solvents like water or ionic solvents will have great importance to fulfill the dream of introduces highly environmentally benign protocol.

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THE NOBEL PRIZE IN CHEMISTRY, 2020

Emmanuelle Charpentier and Jennifer Doudna are awarded the Nobel prize in Chemistry 2020 for discovering one of the gene technology's sharpest tools: the CRISPR/Cas9 Genetic Scissors.

The gene editor called CRISPR - Cas9 is one such unexpected with breath-taking potential. When Emmanuelle Charpentier and Jannifer Doudna started investigating the immune system of a Streptococcus bacterium, one idea was that they could perhaps develop a new form of antibiotic. Instead, they discovered a molecular tool that can be used to make precise incisions in genetic, making it possible to easily change the code of life.

In 2011, March, Emmanuelle published the discovery of tracrRNA. and in collaboration with Doudna they study the function of Cas9 in S. pyogenes. Their suspicion is that CRISPR RNA is needed to identify a virus DNA, and that Cas9 is the scissor that cuts off the DNA molecule. However, nothing happens when they test this in vitro. The DNA molecule remain contact. But after a great deal of brainstorming and numerous failed experiments, the researchers finally add tracrRNA to their test. Previously, they believed that tracrRNA was only necessary when CRISPR-RNA was cleaved into its active form, but once Cas9 had access to tracrRNA what everyone was waiting for actually happened: the DNA molecule was cleaved into two parts. The weapon that Streptococci have developed as a protection from viruses is simple and effective. Soon after Charpentier and Doudna publishes their discovery of the CRISPR/Cas9 genetic scissors in 2012.

The Nobel Prize in Chemistry 2020 rewards the development of such technique that can be used to change the DNA of animals, plants, and microorganisms with extremely high precision. This technology has revolutionized the molecular life sciences, brought new opportunities for plant breeding, is contributing to innovative cancer therapies and may make the dream of curing inherited diseases come true.

ABOUT THE LAUREATES:

Jennifer Anne Doudna (19thFebruary,1964): Jennifer Doudna was born in Washington, DC. Doudna developed her interest in science and mathematics in school. Doudna was an undergraduate student at Pamona College in Clarement, California, where she studied biochemistry. She chose Harvard Medical School for her doctoral study and earned a Ph.D. in biological chemistry and molecular pharmacology in 1989.She held research fellowship in molecular biology at the Massachusetts General Hospital and in genetics at Harvard Medical School. She started research on ribozyme structure and functions at the Cech lab in 1991 and finished it at Yale University in 1996.

AWARDS AND HONOURS:

- In 1996, Beckman Young Investigators Award.
- In 2016 Received Doctor of Science as an honorary degree from Yale University.
- In 2014, Jacob Heskel Gabbay Award (jointly with Feng Zhang and Emmanuelle Charpentier).

- In 2015, Gruber Prize in Genetics (shared with Charpentier).
- In 2016, L'Oréal-UNESCO Award for Women in Science (jointly with Charpentier).
- In 2017, F. Albert Cotton Medal.
- In 2017, Japan Prize (jointly with Charpentier).
- In 2019, Received Doctor of Science as an honorary degree from the University of Oxford.
- In 2019, Nierenberg Prize.
- In 2020, Nobel Prize in Chemistry (jointly with Emmanuelle Charpentier) for the development of a method for genome editing.

EMMANUELLE CHARPENTIER (11th February, 1968):

Emmanuelle Marie Charpentier is a French professor and researcher in microbiology, genetics and biochemistry. After serving as a director at the Max Planck Institute for Infection Biology in Berlin from 2015, she founded an independent research institute, the Max Planck Unit for the Science of Pathogens in 2018. Charpentier studied biochemistry, microbiology and genetics at the Perrie and Marie Curie University (today the Faculty of Science of Sorbonne University) in Paris. Her PhD project investigated molecular mechanisms involved in antibiotic resistance. Charpentier is best known for her Nobel winning work of deciphering the molecular mechanisms of a bacterial immune system called CRISPR/Cas9 and repurposing it into a tool for genome editing.

AWARDS AND HONOURS:

- In 2014, the Paul Janssen Award for biochemical research (shared with Jennifer Doudna).
- In 2015, Gruber Foundation International Prize in Genetics (shared with Jennifer Doudna).
- In 2015, the Breakthrough Prize in Life Sciences (shared with Jennifer Doudna).
- In 2016, Leibniz Prize from the German Research Foundation.
- In 2016, Tang Prize (shared with Jennifer Doudna and Feng Zhang).
- In 2017, BBVA Foundation Frontiers of Knowledge Award (jointly with Jennifer Doudna and Francisco Mojica).
- In 2017, Japan Prize (jointly with Jennifer Doudna).
- In 2018, Kavli Prize in Nanoscience.
- In 2019, Scheele Award of the Swedish Pharmaceutical Society.

CONCLUSION:

There is no other prize in the intellectual realm with the prestige of the Nobel prizes. They also have a visibility that can hardly be compared to any other. In an age in which we are gradually losing whole sets of values fundamentally humanistic ones, the Nobel prizes are one of the last bastions. We seek them in a reference, not only of excellence, but of honesty, enthusiasm, commitment to ideals that inspires both laymen and professionals.

Copper-related Disorders and their Protection by Sulfur and Selenium based Compounds

Rakesh Kumar Rai
Department of Chemistry
Shiv Nadar University, India

1.1 Introduction:

Copper, an essential element for life, is utilized by the endogenous system as an electron exchange pool because of its ability to flip its oxidation state between cuprous and cupric (Cu^{+}/Cu^{2+}) state.[1] Copper is used by the cells in structurally-constrained binding sites in metalloproteins to carry out the structural, regulatory or catalytic functions due to its high redox potential of Cu^{+}/Cu^{2+}.[2] However, despite the several applicability of the copper in the human body, it has a pernicious effect of promoting cytotoxic reactions due to its redox-active nature and so needs to be tightly regulated to confine it to only vital roles. The cytotoxicity of copper mainly results because of the dysfunction of the copper chaperones and the transporters in the copper-trafficking pathway, leading to the accumulation of an excess copper in the liver or brain.[3] As copper is redox-active and are prone to oxidation, so it readily reacts with the hydrogen peroxide (H_2O_2) present in the cells to generate free radicals such as hydroxyl radical (OH^{o}) and hydroperoxyl radical (OOH^{o}), and the phenomenon is commonly termed as the Fenton-like reaction. The Fenton-like reaction is a category of Fenton's reaction developed by Henry Fenton in 1890s to catalyze the oxidation of organic contaminants with a solution of H_2O_2 and Fe(II) ion.[4] Additionally, the reactive oxygen species (ROS) are also formed as natural by-products of cellular respiration and NADPH oxidases.

1.2 Copper-homeostasis:

As the free copper is toxic to the human body, so its homeostasis is carefully modulated in the cytosol through a system of protein transporters and chaperones as shown in Figure 1.1. The concentration of copper in the mammalian cells predominantly depends on its metabolism rate, as it is incapable of synthesizing copper by biochemical processes. The dietary intake copper is absorbed by our digestive system, enters the blood stream by copper carrying proteins such as ceruloplasmin and Human Serum Albumin (HSA), and ultimately distributed to the various organs and tissues such as liver, kidney, brain, lungs, etc.[5] The consumed copper(II) from the dietary sources is always associated with the protein transporters

as they travel across membranes, traverse intra-cellular space, and while present extracellularly. The Cu(II)-HSA complex is reduced to Cu(I) form by the copper-reductases present in the apical membrane, and then is delivered to the high-affinity cellular copper acquisition protein, human copper transporter Ctr1. The plasma membrane proteinCtr1 forms ahomotrimeric pore around the Cu(I) and assist its importin the enterocytes, as shown in Figure 1.2b.[6] Unlike Iron, where the status of excess cellular iron is reflected by the higher ferritin (Iron storage protein) content, copper has no such known storage proteins. In case of copper, this function is carried out by the cysteine-rich metallothionein protein, which binds to the majority of the cytosolic copper. In addition to this, the sulfur-containing small molecules such as Glutathione (GSH) forms a stable complex (K_d = 9.13 x10^{-12} M) with the cytosolic copper.[7] The three copper chaperones CCS (chaperone of superoxide dismutase 1), COX17 (chaperone for cytochrome coxygenases), and ATOX1 (chaperone for ATPases – ATP7A and ATP7B) compete for copper from Cu-GSH pool and metallothionein to deliver it to the specific proteins and enzymes.[8]

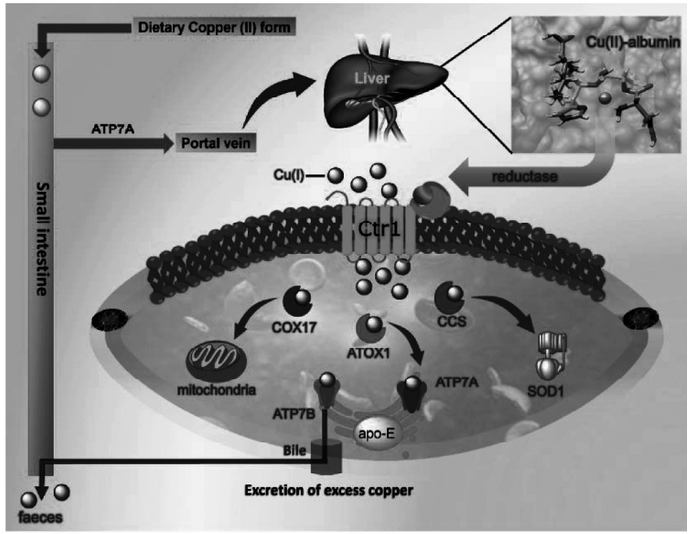

Figure 1.1: The proposed pathway of copper 2008). 9a metabolism in human. (Adapted and modified from D. J. Thiele et al.[6]

1.3 Copper cytotoxicity and related diseases: The presence of an adequate amount of copper is very crucial for the proper biological functioning of the metalloenzymes such as tyrosinase, Cu/Zn-SOD, ceruloplasmin, cytochrome-c oxidase, and metallothionein. Defects or blockages in the Cu-trafficking proteins may prevent Cu from reaching its cellular target and results in the localized accumulation or deficiency leading to the pathological conditions. The defect in the copper homeostasis may cause neurodegenerative disorders such Wilson's disease (WD), Menkes disease (MD), Parkinson's disease (PD), Alzheimer's disease (AD), etc. Wilson's disease (autosomal recessive) and Menkes disease are considered as the most well understood and recognized copper disorders. They are caused by the recessive defects in the ATP7A and ATP7B genes, as shown in **Figure 1.2.**

MD is an X-linked inherited disorder, caused by the mutation in the copper transport protein ATP7A leading to the copper deficiency in the body.[9] This disease mainly causes hypothermia neuronal degeneration, bone fractures, mental retardation abnormalities in the hair (scalp hair called kinky), and aortic aneurysms. In contrast to the MD, the root cause of Wilson's disease is the copper overload in the various parts of the human body. This genetic disorder happens due to the mutation in the ATP7B genes (P-type ATPase), responsible for copper transfer into the secretory pathwayfor both bindings into ceruloplasmin and excretion into the bile.[10] Alzheimer's disease is another copper-overload related neurological disorder causing memory loss and psychiatric disorders in human beings. This disease is related to the progressive brain cell death and disrupts a person's ability to think and function independently.

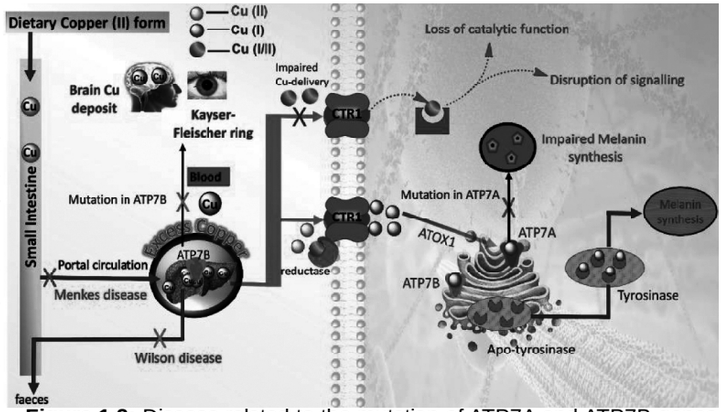

Figure 1.2: Disease related to the mutation of ATP7A and ATP7B genes (X-corresponds to the major steps impaired in the copper distribution). (Adapted and modified from Delangle. P. et al. 2012).[16]

Excess copper accumulation in the body may also participate in the free radical generation by reacting with the H_2O_2, and may eventually lead to damage of proteins, DNA, and cell death.[11]

1.4 Chemical detoxification of copper-related disorders:

The copper overload in the human body has been a major problem from the long past, and is the reason for the ailments such as Wilson's disease. The Wilson disease was discovered since the early 1900s, but there were no major symptoms found to identify this disease. The rings in the corneal pigmentation (Kayser-Fleischer ring), named after the two German doctors, were the only clear-cut diagnosable sign at that time. The link of Wilson's disease to the copper overload was found later in the year 1940, yet the gene responsible for it (ATP7B) was discovered in 1993. Due to the lack of adequate knowledge at that time, it was very difficult to design an appropriate chelating drug for removing excess copper with fewer side effects. Amidst this discovery of the reason behind Wilson's disease and the responsible gene for its cause, many chelating agents, as shown in Figure 1.3, have been tested to rectify this problem.

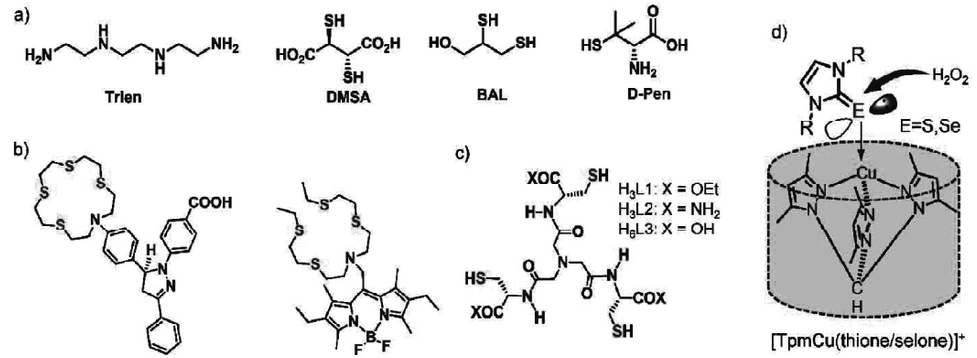

Figure 1.3 : (a) Chemical structures of the chelating agents employed for the treatment of copper toxicity. (b) Intracellular Cu(I) fluorescence sensors with a remarkable selectivity for Cu(I) over Cu(II). (c) NTA-cysteine tripodal derivatives and their Cu(I) complexes. (Delangle, P. *et al. DaltonTrans.* 2012).[16] (d) Representational figure showing the protection of copper from H_2O_2 by metal-bound thione/selone.

British anti-lewisite (BAL) was the first molecule that has relieved the neurological symptoms of the patients due to Wilson's disease.[12] Later on, it was found that BAL has many unforeseen side-effects due to its highly chelating nature, and it has to be administered intramuscularly causing a lot of pain. To overcome this problem, some of the derivatives of BAL such as DMPS (DL-2,3-dimercapto-1-propanesulfonic acid) and DMSA (meso-2,3-dimercaptosuccinic acid) has been tested for treating the copper overload toxicity.[13] These drugs come up with some additional features including more hydrophilicity and reduced toxicity and have been continued for some years, particularly DMSA was used in China for over 40 years. But, over the time these drugs were found to causeallergic skin reactions, neutropenia, and gastrointestinal discomfort. In a parallel section of time, another drug D-penicillamine ((2S)-2-amino-3-methyl-3-sulfanyl-butanoic acid, D-pen) was introduced by John Walshe in the year 1956, for the treatment of Wilson's disease.[14] D-penicillamine has an added advantage of orally-administrable and accelerating the process of copper removal through urine, but has to face the same allergic problem such as causing vomiting, bone marrow suppression, and diarrhea. To resolve this problem, Walshe pioneered other chelating agents such as triethylenetetramine (TETA) in 1982 and tetrathiomolybdate (TTM);TETA and TTM are used in the USA as a copper chelator but TTM has not obtained FDA agreement.A deeper study of the copper homeostasis with time has shown that the copper mainly accumulates in the liver in Cu(I) form due to the reducing environment of the intracellular medium (presence of a high concentration of Glutathione). This influences the researchers to design chelators, as shown in Figure 1.3b, which could enter the hepatic cells and could specifically bind to Cu(I).

Based on the intracellular environment, the complexing agent containing multidentate Sulfur donors such as CTAP-1 have been widely studied to design synthetic Cu(I) chelators to overcome the Cu-overload related disorders.[15] Delangle P. *et al.* have designed copper chelators based on the structural and functional aspects of Metallothionein. They have synthesized a series of tripodal ligands by functionalizing the nitrilotriacetic acid (NTA) with cysteine units having different carbonyl groups (ester in L1, amide in L2 and acid in L3), as shown in Figure 1.3c.[16] They observed that the tripodal ligands comprising of L1 and L2 were efficient chelators of Cu(I) (logK = 19.2 for $\mathbf{L_1}$ and 18.8 for $\mathbf{L_2}$), forming CuS_3 coordination with the dissociation constant similar to that of the metallothionein (K_d 10^{-19} M). Moreover, these complexes transform into polymetallic coordination of Cu_6L_3 and Cu_6L_9 core, as described in some metallothionein. Brumaghim and co-workers have implemented the chemistry of cysteine and selenocysteine oxidation in their work to overcome the copper-mediated oxidative damage. For instance, they have coordinated the copper(I) complex, $[TpmCu(CH_3CN)]^+$ with *N,N*-dimethylimidazolethione (dmit), and its selenium analog *N,N*-dimethylimidazoleselone (dmise), as shown in Figure 1.3d, and have performed the NMR study in presence of 2 or 3 equivalent of H_2O_2.[17] They observed that the thione and selone moiety oxidizes in the presences of H_2O_2 and protects the copper oxidation. This phenomena may be termed as the "sacrificial effect" of the thiones and selones and their pioneering work opens a new door to explore this field. The thiones and selones utilized in this study was a derivative of ergothioneine and selenoneine (naturally occurring antioxidant) and may be explored further to design a suitable drug in future.

1.5 Conclusions:

Copper, a redox active metal, plays a crucial role in the proper functioning of the human body and has to be maintained in optimal amount for governing the various metabolic processes of the body. A defect or blockage of the copper-trafficking proteins hinders the copper homeostasis, causing mutation of the essential genes and accumulation or deficiency of copper in localized cellular regions. This condition may give rise to the genetic disorders such as Wilson's disease, Menkes disease or skin diseases (albinism, vitiligo, lentigens, etc.). Moreover, the accumulated free copper may also undergo Fenton-like reaction to catalyze the generation of free radicals leading to cellular damage of biomolecules and other pathological conditions such as cancer, neurological disorders and cardiovascular diseases. A steady effort has been made to resolve this problem from early 1900s and a series of drug has been discovered or invented, but each one of it has its own pros and cons. The valiant effort of the researchers has helped to understand and control the metal-induced damages to a greater extent, yet there are some areas for improvement and some facts that needs to be highlighted for obtaining a better compound.

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Series

History of Chemistry : 21st Century

As the 21st century winds down, it is natural to contemplate the changes that one has seen and experienced during the past 100 years. For a chemist, this reflection brings upon a feeling of wonder and amazement. It is almost impossible to imagine what chemistry was like at the beginning of this century when one ponders the remarkable advances made during this time period. Some of the renowned chemists of the 21st century are :

Ada Yonath (1939-) one of the most revered global scientific personalities, who dedicated her life towards the study of the structure of ribosome. Born in an impoverished family, young Yonath showed traits of making it big since an early age. Despite being born in an underprivileged family, she did not compromise on her education and attained PhD degree in the field of Chemistry. Subsequently, she committed herself to the study of the structure and function of the ribosome. She made a massive contribution in the field of chemistry by introducing the innovative techniques in cryo bio-crystallography for enabling ribosomal crystallography. She was bestowed with Nobel Prize in Chemistry, which she shared with Venkatraman Ramakrishnan and Thomas A. Steitz. She became the first Israeli woman to win the Nobel Prize, the first woman from the Middle East to win a Nobel Prize in the sciences, and the first woman in 45 years to win the Nobel Prize for Chemistry.

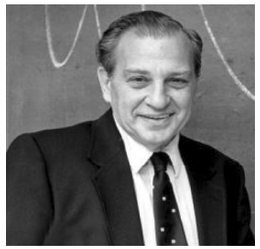
Mario Molina (1943-) a renowned chemist who studied the effects of man-made compounds on the atmosphere and pioneered the theory of CFC and ozone depletion. Ever since his childhood, Molina was attracted towards science. Falling in line with family's practice of studying abroad, Mario attended school in Switzerland. He pursued studies which catered to his goal of becoming a physical scientist. To succeed in his endeavour, he went to the United States and enrolled in University of California, which later became central to his research work. In association with F. Sherwood Rowland, he studied the chemical reactivity of CFC in the atmosphere and came up with startling conclusions. His findings suggested that the CFC's were responsible for the corrosion of ozone layer present in the stratosphere. He was even awarded a Nobel Prize for his work in the field of environmental chemistry.

Thomas Robert Cech (1947-) an American chemist who was jointly awarded the 'Nobel Prize in Chemistry' in 1989 along with American molecular biologist Sidney Altman, for his pioneering discovery of the part that ribonucleic acid (RNA), a polymeric molecule. He found out that RNA, one of the nucleic acids, has the capacity to cut fine threads of RNA, a finding which displayed that there is a possibility that life was initiated as RNA. He received several awards and recognition for his scientific contributions. These included the 'Louisa Gross Horwitz Prize' from 'Columbia University' and the 'Heineken Prize' from the 'Royal Netherlands Academy of Sciences' in

1988; the 'National Medal of Science' from the President of the United States in 1995; and the 'Othmer Gold Medal' in 2007 presented together by the 'Chemical Heritage Foundation', the 'American Chemical Society' (ACS), the 'Société de Chimie Industrielle' (American section), 'The Chemists' Club' and the 'American Institute of Chemical Engineers' (AIChE).

Aaron Klug (1926-) a Nobel laureate in Chemistry who is the man behind the development of crystallographic electron microscopy. His technique of restructuring 2-D image to 3-D has been applied in various arenas, the most prominent one being the CT scan. Born in Zel'va, Białystok Voivodeship, he went on to graduate with a Bachelor of Science degree from the University of the Witwatersrand before completing his Master of Science degree at the University of Cape Town and earned his PhD at Trinity College, Cambridge. Klug went on to study helical viruses to reveal how protein units are formed, investigated the polio virus with J. D. Bernal, and researched the structure and action of transfer DNA (deoxyribonucleic acid). A much renowned chemist, he received several prestigious awards for his development of crystallographic electron microscopy and his structural elucidation of biologically important nucleic acid-protein complexes.

Paul Jozef Crutzen (1933-) a Dutch atmospheric chemist, who won the 1995 Nobel Prize in Chemistry for his work in atmospheric chemistry. He was born in early 1930s. Brought up under a harsh condition by his working-class parents, he managed to complete his schooling in time. He enrolled at a Middelbare Technische School and worked his way up to become a civil engineer. Later he joined the Department of Meteorology at the University of Stockholm as a computer programmer and at the same time began enhancing his academic qualifications, acquiring first a MS and then a PhD on photochemistry of atmospheric ozone. Later while working as a postdoctoral fellow in England he established his theory of ozone depletion and also demonstrated that increased use of nitrogen-rich fertilizers and fossil fuel is responsible for such a phenomenon. The work later earned him the Nobel Prize in Chemistry. He spent his later years working on global warming and is one of promoters of the theory of nuclear winter. He believes that, "Nuclear war could easily mean the destruction of not only our race, but most of the planetary life as well".



Rudolph A. Marcus (1923-) a Canadian-American chemist who received the 1992 Nobel Prize in Chemistry for his work on the theory of electron-transfer reactions in chemical systems. The Marcus theory, named after him, provides a framework for explaining diverse and fundamental phenomena such as photosynthesis, cell metabolism, and simple corrosion. He is also known for his work in areas such as transition-state theory and the theory of unimolecular reactions. Born in Montreal, Quebec, he developed an early interest in science. After completing his high school, he joined the McGill University to study chemistry. He eventually moved to the United States for a postdoctoral research fellowship and ultimately became an American citizen. It was in the 1950s that he began studying electron-transfer reactions and investigated the role of surrounding solvent molecules in determining the rate of redox reactions. He developed Rice-Ramsperger-Kassel-Marcus theory by combining RRK theory with transition state theory.

Carbon nanotube: oil-water separation via its superhydrophobic and superoleophilic properties

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Introduction:

The field of oil-water separation is highly significant as it has direct implications in solving the problems of oil spilling, which is a severe threat to the ecosystem[1-3]. The development of carbon-based carbon nanotubes (CNTs) has shed bright light on the disasters caused by oil spillage and industrial oily wastewater drainage. The superhydrophobicity and superoleophilicity of CNT makes it an ideal fit for oil-water separation. Moreover, CNT is bestowed with many distinctive physicochemical properties such as high surface area, low density, chemical stability, excellent mechanical properties, large pore volume, environment-friendliness and high sorption capacity. The absorption capacity of CNT sponges ranges between 15-50 times of their own weight and can be reused by heating and mechanical squeezing. The theoretical aspect of oil-water separation revolves around the subject matter of water contact angle (CA).

Remarkable development of industries, especially petrochemical and marine industries in the past decades is the major cause of oil-spilling. Leakages during storage and transportation of oil has caused many accidents all over the world. Above this, the planned disposal of oily wastewater into water bodies by mankind is very threatening. Oil-spill in water bodies is more dangerous than on land as oil floats over water blocking large surface, leading to death of many marine life. Separation of oil-water emulsion is even more important, as emulsions are very stable and is a challenging task for the scientists. Emulsions may be of various kinds, including oil-in-water emulsion, surfactant stabilised or surfactant free and of various sizes (micrometre or nanometre).

Amongmany enormous oil spill incidents, thedreadful aftermath of the Persian Gulf War oil Spill incidentin 1991 urges us to learn important lessons from it. Miserably, it was not an accident but a filthy deed of mankind. Approximately,4 million barrels of oil were released into the northern Persian Gulf. The oil penetrated deep down and it persists till date, thereby affecting lives mercilessly.

Principles of oil-water separation by CNT:

The theoretical aspect of oil-water separation revolves around the subject matter of contact angle (CA) θ. CA is the angle measured through theliquid, where the liquid-vapour interface meets the solid surface. It gives a quantitative measurement of the wettability of a surface via the Young equation:

$$cos\theta = \frac{\gamma_{SV} - \gamma_{SL}}{\gamma_{LV}}$$

Here, γ_{SV}, γ_{SL} and γ_{SL} denote the interfacial tension between solid-vapour, solid-liquid and liquid-vapour respectively as shown in Fig 1

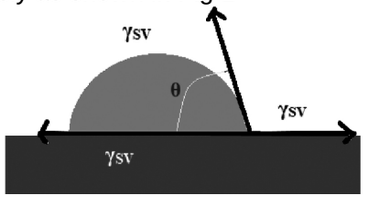

Fig 1: Contact angle

The value of CA categorises a surface into hydrophilic, hydrophobic and superhydrophobic. With the water contact angle (WCA) less than 90°, a surface is defined as hydrophilic, when it is in between 90° and 150° then it is hydrophobic and when it is above 150° it is superhydrophobic. The same description is applicable for all liquids including oil.

Structure of CNT:

As the name suggests, CNT has cylindrical structure (infinitely long) with diameter in the range of nanometers (Fig 2). It has a hollow one-dimensional structure with rolled up graphene layers; graphene has a two-dimensional layered structure with carbon atoms arranged in a hexagonal manner. The diameter of CNT is constrained to a narrow range as the carbon-carbon bond length is fixed.

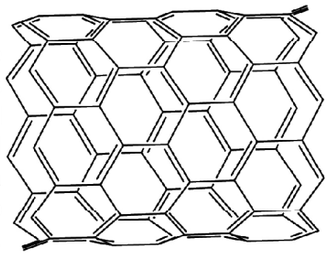

Fig 2: Carbon nanotube

NT may be both single-walled (SWCNT) or multi-walled (MWCNT). In MWCNT the single walled CNTs are nested together bonded by weak vander-waals interaction in a tree-ring like fashion.

Applications-CNT based oil-water separation: In order to increase the efficiency of CNTs, proper functionalisation of CNT wall is required. This lowers the surface energy and impart proper roughness to CNTs. Superhydrophobic CNT films may be produced by the following two main approaches: (a) Adsorption of low surface energy chemicals onto the CNT surface (bounded by vander-waalsor π-π interaction) (b) Covalent attachment of hydrophobic groups. CNTs are used to fabricate many membranes, as the CNTs impart tensile strength, electrical and thermal conductivities, etc. to the membrane.

In 2013, Wang *et al.* coated polyurethane (PU) sponge with the superhydrophobic and superoleophilic carbon nanotube and polydimethylsiloxane (PDMS)[4]. PU sponge has been widely used in the field of oil-water separation as it is easily available commercialy and has the ability to absorb both oil and water. Fabrication of the sponge with various materials can tune its absorption property according to requirement.

Upon fabrication of CNT/PDMS layer onto PU sponge, the wettability of PU sponge

changed from hydrophilic to superhydrophobic nature; thereby repelling water and absorbing oil and organic solvents. Owing to the robust nature of the prepared CNT/ PDMS-PU sponge can be used in conjugation with a vacuum pump for simultaneous removal of oil from water. The CNT/PDMS-PU sponge could separate micrometer sized surfactant free water-in-oil emulsions with very high efficiency (99.97 wt %).

The method of preparing the CNT/PDMS-PU sponge is as follows: A dip-coating method was used to deposit CNT/PDMS suspension on the PU sponge, which was then heated at 120°Cin an oven.

The prepared CNT/PDMS-PU sponge had a water contact angle of 162°±2° (superhydrophobic) and contact angle of n-hexane, n-hexadecane, and gasoline were all close to 0° (superoleophilic). The fabricated sponge could separate oil upto 35000 times of its own weight.

In 2014, another group fabricated a superhydrophobic and superoleophilic Polyurethane (PU) with CNTs for discriminatory removal of oil from water[5]. Apart from superhydrophobicity and superoleophilicity, the prepared sponge had marvellous properties including excellent mechanical strength and elasticity, stability in a temperature range of 50°C to 100°C and selective absorption of oil with a sorption capacity upto 34.9 times of its own weight. A simple squeeze removes all the absorbed oil and the material may be reused for upto 150 times with intact efficiency.

The procedure for synthesis is as follows: Being inspired by the adhesive property of dopamine, they coated CNTs with dopamine film; the dopamine modified CNTs (CNT-PDA) were then anchored on PU sponge through the self-polymerisation of dopamine (PDA). Further, a chemical reaction was carried out where the PDA film was conjugated to octadecylamine (ODA) to give the resultant sponge.

CNTs have also been widely applied for the separation oil-water emulsions. Carbon based-carbon nanotube has flourished as an exceptional tool for oil-water separation in today's revolutionary world6-9. Being environment friendly and biodegradable, it has been widely accepted.

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Molnupiravir (EIDD-2801) inhibits SARS-CoV2 replication

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Abstract

Since its emergence in Wuhan, China in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide resulting in a global pandemic with more than1.5 million deaths until now. In the search for small molecule inhibitors of SARS-CoV-2, drug repurposing is being extensively explored.

Molnupiravir (EIDD-2801) is an orally bioavailable nucleoside analog that possesses a relatively broad-spectrum antiviral activity including against coronaviruses. The effect of EIDD-2801 was studied in a well-established Syrian hamster SARS-CoV2 infection model. Treatment of SARS-CoV-2-infected hamsters with 200 mg/kg BID of EIDD-2801 for four consecutive days, starting from the day of infection, significantly reduced infectious virus titers and viral RNA loads in the lungs and markedly improved lung histopathology. When onset of treatment was delayed until 1 or 2 days after infection, a very modest antiviral effect was observed. The potential of EIDD-2801 for the treatment and or prevention of SARS-CoV2 deserves further attention.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a β-coronavirus that was first identified in Wuhan, China in December 2019[1]. Since then, the virus rapidly spread around the globe with more than 66 million cases reported by the end of 2020, including more than 1.5 million deaths. Infection with SARS-CoV-2 results in COVID-19 which is characterized by a wide range of symptoms including fever, dry cough, muscle and/or joint pain, headache, decreased sense of taste and smell and diarrhea. The disease can also progress into severe complications such as acute respiratory distress syndrome (ARDS), respiratory failure, septic shock and multi-organ failure, which are mainly attributed to a massive cytokine storm and exaggerated immune response[2].

To date, there are no approved, specific antiviral drugs or vaccines available to

treat or prevent infections with human coronaviruses. The use of potent antivirals against SARS-CoV-2 will reduce viral loads and may hence reduce the chance to progress to a severe disease. In addition, such antiviral drugs could be useful to protect for example health care workers and high-risk groups in a prophylactic setting. Since the *de novo* development and approval of (a) specific, highly potent antiviral(s) for SARS-CoV-2 may take years, the main focus for COVID-19 treatment in the current pandemic is to repurpose drugs that have been approved or in clinical trials for other diseases[3].

The ribonucleoside analogue, N4-hydroxycytidine (NHC, EIDD-1931), has broad-spectrum antiviral activity against multiple viruses belonging to different families of RNA viruses. Activity against SARS-CoV and SARS-CoV-2 has been reported in cell lines and primary human airway epithelial cell cultures[4]. Acting through lethal mutagenesis, its incorporation into viral RNA results in the accumulation of deleterious transition mutations beyond a permissible error threshold to sustain the virus population, leading to error catastrophe[5]. The orally bioavailable, pro-drug counterpart of NHC[6], Molnupiravir (EIDD-2801, MK-4482) is currently being assessed for its potential as an antiviral treatment of SARS-CoV-2 infection in Phase 2 clinical trials of infected patients **(NCT04405570, NCT04405739)**

As far the recent information, three very recent studies reported on activity of orally dosed EIDD-2801 in SARS-CoV-2 infected animals. Oral treatment of SARS-CoV2 infected Syrian hamsters with EIDD-2801 resulted in marked reduction of viral loads when administered either in a pre- or post-exposure settings[7]. In a ferret model, EIDD-2801 significantly reduced virus load in a therapeutic setting and blocked SARS-CoV-2 contact transmission[8], while in a humanized mouse model, EIDD-2801 prevented SARS-CoV-2 infection in a pre-exposure prophylaxis setting[9].

Recent Studies

Recently, a Syrian Gold (SG) hamster model for the evaluation of antiviral drugs against SARS-CoV-2 was established and characterized[10,11]. Using this model,it was shown that a high dose of the influenza drug Favipiravir results in a pronounced antiviral activity in SARS-CoV-2 infected hamsters, whereas hydroxychloroquine lacks antiviral activity in this model. The same hamster model was used to assess the anti-SARS-COV2 of EIDD-2801 against SARS-CoV-2 in infected hamsters.

First, the effect when the drug was administered at a dose of either 75 or 200 mg/kg BID was evaluated. Briefly, 6-8 weeks female SG hamsters were treated with the intended dose of the compound or the vehicle (i.e. the control group) for four consecutive days starting one hour before intranasal infection with 50 µL containing 2×10^6 $TCID_{50}$ SARS-CoV-2 [BetaCov/Belgium/GHB-03021/2020 (EPI ISL 109 407976|2020-02-03)]. At day four post-infection (pi), the animals were euthanized and lungs were collected for quantification of viral RNA, infectious virus

titers and lung histopathology as described previously[10] **(Figure 1A)**. Treatment of hamsters with 75 mg/kg BID EIDD-2801 resulted in 1.2 log_{10} reduction in the viral RNA copies per mg of lung tissue (P=0.01), compared to the vehicle-treated infected hamsters **(Figure 1B)**. On the other hand, in the lungs of hamsters that had been treated with 200 mg/kg BID EIDD-2801 a 3log10 reduction in the viral RNA copies/ mg of lung tissue was noted (P <0.0001) **(Figure 1B)**. A similar pattern was observed for the infectious virus load in the lungs, the high dose of 200 mg/kg, but not the 75 mg/kg dose, reduced infectious virus lung titers by 3.3 log_{10} (P<0.0001) $TCID_{50}$ per mg **(Figure 1C)**.

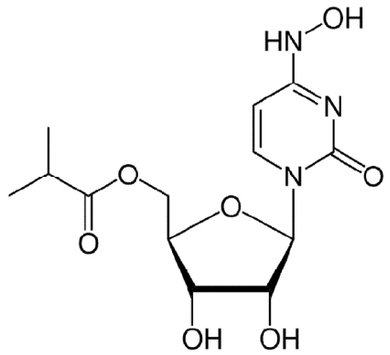
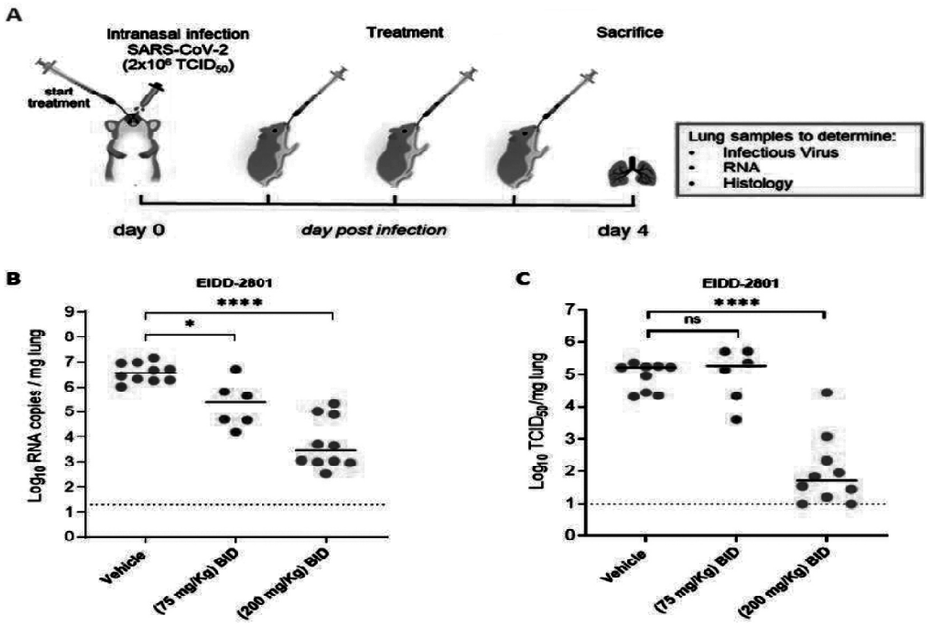


Figure: Structure of Molnupiravir



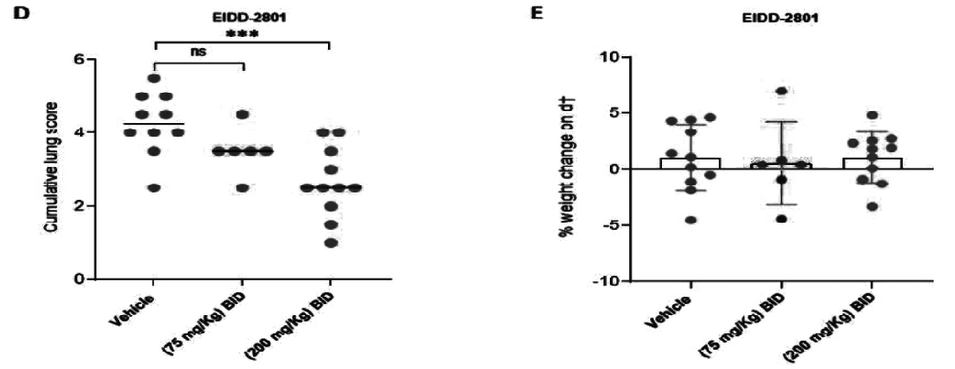
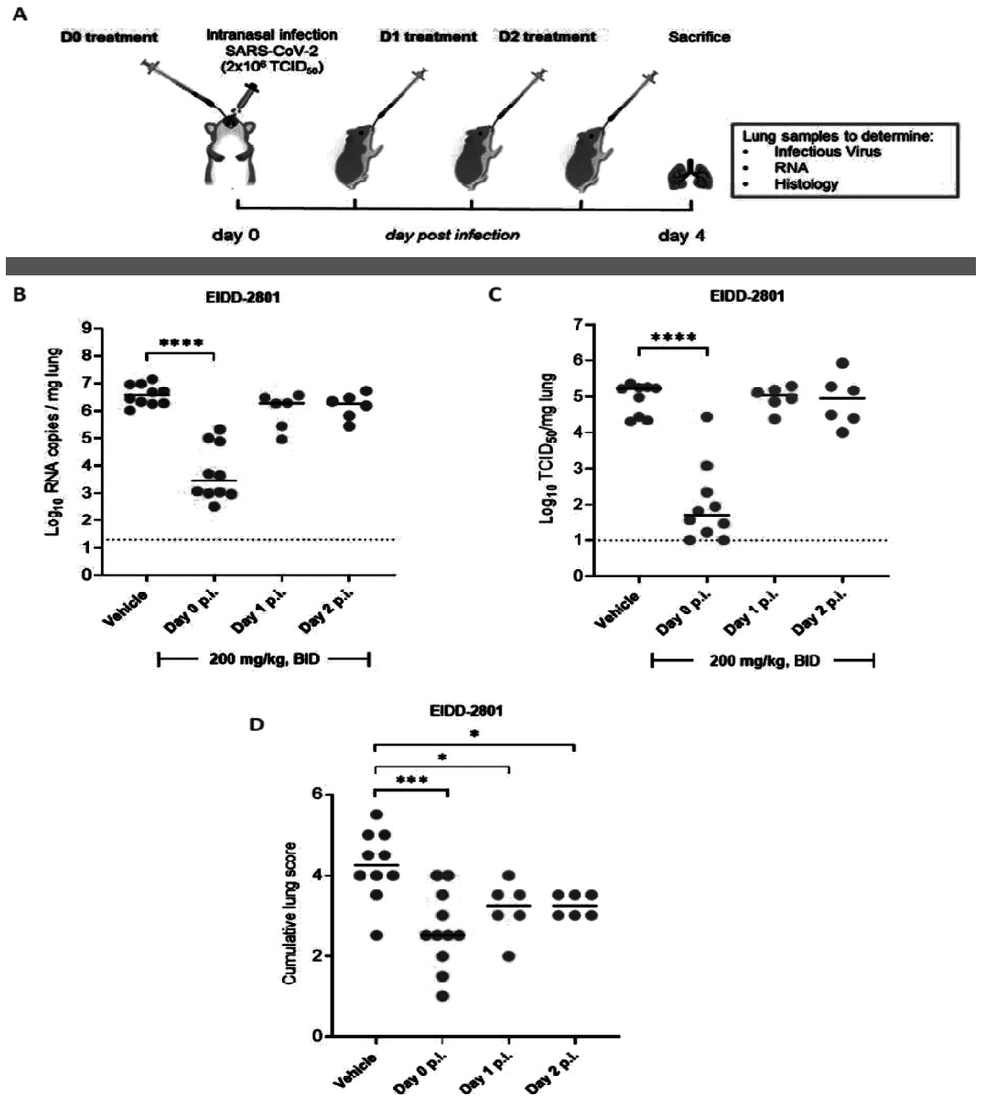


Figure 1: In vivo efficacy of EIDD-2801 against SARS-CoV2 at the time of infection.

(A)Set-up of the study. (B) Viral RNA levels in the lungs of control (vehicle-treated) and EIDD-2801-treated SARS-CoV-2–infected hamsters at day 4 post-infection (pi) are expressed as log_{10} SARS-CoV2 RNA copies per mg lung tissue. The bars represent median values. (C) Infectious viral loads in the lungs of control (vehicle-treated) and EIDD-2801-treated SARS-CoV-2–infected hamsters at day 4 pi are expressed as log_{10} $TCID_{50}$ per mg lung tissue. The bars represent median values. (D). Cumulative severity score from H&E stained slides of lungs from control (vehicle-treated) and EIDD-2801-treated hamsters. The bars represent median values. (E) Weight change at day 4 pi in percentage, normalized to the body weight at the day of infection. Bars represent means ± SD. Data were analyzed with the Mann±Whitney U test. *P < 0.05; ***P < 0.001, ****P <0.0001.

Importantly, treatment with 200 mg/kg EIDD-2801 BID significantly reduced the histological lung disease score (P=0.001), whereas the lower dose resulted only in slight reduction in lung pathology (P=0.05, ns, **Figure 1D**). Both doses were well-tolerated without significant weight loss or any obvious adverse effects **(Figure 1E)**.

Next explored was whether the high dose can also be used in a post-exposure setting, i.e. when treatment is started at 24 or 48 h after infection **(Figure 2A)**. Delaying the start of treatment with EIDD-2801 (200 mg/kg, BID) by 1 or 2 days resulted in a loss of potency with only a rather slight reduction of viral RNA copies/ mg lung [0.3 to 0.4 log10 respectively] **(Figure 2B)**. Similarly, virus titrations of the lung tissues also revealed no significant reduction of infectious virus load in both groups with delayed treatment compared with the vehicle-treated group **(Figure 2C)**. However, a modest but significant reduction of the histological lung disease score was observed in both the day 1 (p=0.016) and day 2 (p=0.01) delayed treatment groups **(Figure 2D)**. These results suggest that even if the delayed treatment with the 200 mg/kg BID dose was not sufficient to efficiently stop the viral replication, it may still able to delay the disease progression in the lung of infected hamsters.



Figuge 2: In vivo efficacy of EIDD-2801 against SARS-CoV2 in a post-exposure setting.

(A) Set-up of the study. (B) Viral RNA levels in the lungs of control (vehicle-treated) and EIDD-2801-treated SARS-CoV-2–infected hamsters at day 4 post-infection (pi) are expressed as $\log_{10}$ SARS-CoV2 RNA copies per mg lung tissue.

The bars represent median values. (C) Infectious viral loads in the lungs of control (vehicle-treated) and EIDD-2801-treated SARS-CoV-2–infected hamsters at day 4 pi are expressed as $\log_{10}$ $TCID_{50}$ per mg lung tissue. The bars represent median values. (D). Cumulative severity score from H&E stained slides of lungs from control (vehicle-treated) and EIDD-2801-treated hamsters. The bars represent median values. Data were analyzed with the Mann–Whitney U test. *P < 0.05, ***P < 0.001, ****P < 0.0001

SUMMARY

In summary, EIDD-2801 is able to markedly reduce SARS-CoV2 infection and virus induced pathology in hamsters, in particular when given at the time of Infection. EIDD-2801 has been previously demonstrated to exert antiviral activity against MERS-CoV and SARS-CoV in cell culture and mouse models. Very recently activity was also reported against SARS-CoV-2[4,8,9]. In another SARS-CoV2 Syrian hamster model, 250 mg/kg of EIDD-2801 was given orally every 12 hours starting either 12 hours pre-infection or 12 hours post-infection[7]. Although a slightly higher compound dose (250 mg/kg, BID) and a much lower virus inoculum (5×10^2 $TCID_{50}$) was used in their hamster study, the observed antiviral effect was less pronounced (1 $\log_{10}$ reduction in viral RNA and 2 $\log_{10}$ reduction in infectious virus titers) than in the study[7].

EIDD-2801 has also been reported to be effective in SARS-CoV infected C57/BL6 mice either when administered prophylactically (start of treatment 2 h before infection) or therapeutically (start of treatment delayed until 48 hpi) at a dose of 500 mg/kg twice daily (Sheahan et al., 2020). In a humanized mouse model of SARS-CoV-2 infection, pre-exposure (prophylaxis) (12 h before infection) with 500 mg/kg of EIDD-2801 twice daily was efficacious in preventing SARS-CoV-2 infection, with a ~6 $\log_{10}$ reduction in virus lung titers[9]. In a very recent report, EIDD-2801 was found to markedly reduce SARS-CoV-2 viral titers in in the upper respiratory tract of ferrets when start of treatment was delayed until 12 hpi to 36 hpi. Moreover, treating SARS-CoV2 infected ferrets with EIDD-2801 starting at 12 hpi prevented contact transmission when they were co-housed with non-infected untreated contact ferrets[8].

The results are consistent with other recent studies (in hamster, mouse and ferret models) showing that pre-emptive and early intervention with oral EIDD-2801 results in antiviral activity. However, at a dose of 200 mg/kg there was no observation in reduction of virus in the lung when treatment was initiated 24 to 48 hpi in our Syrian hamster model (although some improvement in lung pathology was observed in these groups). Further studies are ongoing to explore therapeutic (delayed start of treatment) effect at higher doses.

The antiviral drug, Remdesivir, is the first treatment for COVID-19 to receive

FDA approval for use in hospitalised patients, although the World Health Organisation has recently recommended against its use.

Both Remdesivir and EIDD-2801 are nucleoside analogues acting on the viral RNA replication pathway, with Remdesivir resulting in chain termination and EIDD-2801 in lethal mutagenesis[5,12]. Additionally, both have a high resistance barrier, with resistant viral mutants having a loss in fitness[6,13]. However, Remdesivir needs to be administrated intravenously, whereas EIDD-2801 can be dosed via the oral route. This is a significant advantage in terms of the practicalities of treatment management, where we can envision that asymptomatic patients who have had high-risk contact or patients presenting mild symptoms are prescribed EIDD-2801 pills in a non-hospitalised setting.

By demonstrating the antiviral efficacy of the orally-bioavailable EIDD-2801 against SARS-CoV-2 in the Syrian hamster model, further evidence is provided in support of the ongoing Phase II clinical trials. The outcomes of these trials could play a pivotal role in the control and management of this devastating pandemic.

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Students' Section

The 'Magic Ion' in Tap Water

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What if I said that our drinking water contains an element that's used in batteries and that it could also be affecting our mood?

Sometimes referred to as the Magic Ion, the element is 'Lithium'. In recent review of decades of research has found that trace amounts of lithium found in the tap could be stabilizing our mood and may even have the potential to reduce the risk of suicide.

Of all the elements, lithium is one of the lightest. This soft, silvery-white metal occurs naturally in soil, rocks, and many foods. It's also highly reactive, particularly with water. Varying degrees of lithium can be found in surface water, groundwater, and seawater around the world. Not only is it valued for increasing the energy density of our batteries, but over the past few decades, lithium has gained recognition in the medical community for its powerful impacts on mental health too. Today, lithium is a standard treatment for bipolar disorder, a mental illness categorized by dramatic mood swings of emotional highs and lows that affect roughly 1 in 100 people worldwide. Lithium is also used when patients with depression don't respond to other medications as it is recognized as an effective long-term management tool.

Even though it might have some side effects when taken in high enough doses, the doses prescribed and the amount that we get naturally from the tap water is very different. Used medically, a prescribed dose typically ranges from a couple of 100 milligrams to about 1000, by contrast, the lithium levels found in a litre of drinking water typically measure anywhere between a fraction of 1 microgram to 200 micrograms depending on the source. But this incidental exposure isn't necessarily insignificant.

Over the past few decades, studies have shown evidence of a relationship between higher levels of lithium and drinking water and lower rates of depression, crime, and even dementia in the general population. Some studies have even suggested an association between higher lithium levels and lower rates of suicide, but no comprehensive effort had been made to connect all of this research until now. A recent study led by researchers from King's College London and Sussex

Medical School set out to incorporate all available evidence of the association between lithium and drinking water and suicide rates in total. The team identified 415 articles spanning three decades, comprising data from over 1000 regions, counties, and cities around the world. The average concentration of lithium in the water samples ranged from under 4 to over 80 micrograms per litre. By combining the results of multiple studies, the team was able to statistically analyse the data and search for a link, and a link emerged.

Their analysis showed that areas with higher concentrations of lithium in their public tap had correspondingly lower rates of suicide.

This is the first meta-analysis of its kind so these findings are hugely encouraging, still, the team emphasizes that more work needs to be done to explore this relationship. They note that conducting randomized trials that supplement the water supply with lithium would be a great place to start particularly in communities with a high prevalence of mental health conditions, criminal behaviour, and substance misuse.

But how exactly does this magic ion work? The answer is a little hard to pinpoint. This is because lithium is an ion, that interacts with many different target cells in our body and results in a whole host of side effects making it extremely difficult to identify which interaction affects our mood. However, we do know that lithium interacts with the brain's neurotransmitters, the chemical messengers that help our neurons communicate. When in balance our billions of neurotransmitters manage virtually all of the body's tasks, from our breathing to how we learn, but if their levels become out of sync health problems like depression and anxiety can arise. By modulating the response of our neurotransmitters lithium is thought to restore their proper functioning. The prevailing hypothesis is that lithium promotes inhibitory neurotransmission which regulates anxiety while restraining excitatory neurotransmitters like dopamine and glutamate which are elevated during mania.

Not only does this recent analysis provide us with further incentive to unpack lithium's effects on the body it offers us a chance to appreciate water's overall health benefits as well. Clean healthy drinking water contains all kinds of elements and minerals that are vital to human health, Calcium, and Potassium just to name a few. In fact, water can help us meet up to 20 of our daily dietary intake requirements for different elements, and even just staying hydrated can restore balance of neurotransmitters in our body and calm our nerves.

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Students' Section

Synthesis of Bioplastic from Potato Peels

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Introduction

Plastics are more useful than metals, paper in various aspects like lightness, durability, cheapness, etc. Therefore, they have a large use in every field of industry. But the crucial problem with plastic is that it is not biodegradable, for which it gets deposited everywhere and disturbs the surrounding i.e. river, ocean, landfill, etc. Hence its utilization becomes a major issue for us. It is damaging both land and marine ecosystem. Thus, Bioplastic becomes a paramount solution to this burning problem.

What are Bioplastics?

Bioplastics are defined as plastics made from renewable resources, such as potato, corn, sugar, etc. and produced by a range of microorganisms. There are several types of Bioplastic like photo-degradable, compostable and bio based bioplastics. Photo-degradable bioplastics are polymeric structure. However, in absence of sunlight they cannot be disintegrated. Bio based bioplastics are derived from renewable resources containing starch, protein and cellulose. The most known bio based plastic is Polylactic Acid (PLA).

Among the renewable resources potato starch is a potentially useful material for bioplastics because it is inexpensive and easily available. Inspite of its abundance, low cost and natural origin, there is a fundamental concern about its use for bioplastics. Various researches advocates that, when there will be hunger in the world then the potato starch cannot be used in this non-food area. Also bioplastic industry may lessen the land availability for food production. As a solution to this, they started to produce bioplastic from food waste like potato peels, banana peels etc.

Methods of Preparations

First, potatoes are cleaned up and peeled, then the peels are granulated and centrifuged at 15000 rpm for 20 minutes. The supernatant was filtered and starch was obtained. 13g of dried starch was extracted from 330g potato peels. After

filtration, starch was dried at 50°C for 2 hours and kept in a zip-locked airtight environment until processing. Then 135mL of tap water, 16.2mL vinegar, and 10.8mL glycerine was added to the 13g starch. This mixture was heated on a hot plate till to 100°C and kept waiting at that temperature for 20 minutes. The mixture was led to air dry for 48 hours and then the bioplastic was produced in a sheet form. This produced bioplastic from potato peel waste is known as PPB.

Conclusion

Bioplastics are a revolution in the green plastic world. The property of biodegradability is what makes them unique and separates them from the rest of the plastics. Results have also shown that plastics prepared from potato peels can degrade at a comparable rate with paper. They certainly would not cause any pollution as their composition is completely from biomass and do not contain any toxins. Bioplastics could be the next big thing that could actually help in a healthy cancer free and pollution free environment. They would certainly not damage any marine life as they are composed of biomasses. Thus, it can be concluded that for a healthy environment, it is mandatory to reduce the use of petroleum based plastics and begin utilising bioplastic.

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News in Focus

● Chemists Discover a New Form of Ice

Scientists from the United States, China and Russia have described the structure and properties of a novel hydrogen clathrate hydrate that forms at room temperature and relatively low pressure. Hydrogen hydrates are a potential solution for hydrogen storage and transportation, the most environmentally friendly fuel. In their new study, chemists focused on hydrogen hydrates. Gas hydrates hold great interest both for theoretical research and practical applications, such as hydrogen storage. If stored in its natural form, hydrogen poses an explosion hazard. That is why scientists are looking for cost-effective hydrogen storage solutions. The crystal structure of hydrogen hydrates strongly depends on pressure. At low pressures, it has large cavities, which resemble Chinese lanterns, each accommodating hydrogen molecules. As pressure increases, the structure becomes denser, with more hydrogen molecules packed into the crystal structure, although their degrees of freedom become significantly fewer. In the research published, experiments were performed to study the properties of various hydrogen hydrates and discovered an unusual hydrate with 3 water molecules per hydrogen molecule. The reaches simulated the experiment's conditions and found a new structure very similar to the known proton-ordered C1 hydrate but differing from C1 in water molecule orientations. The team showed that proton disorder should occur at room temperature, thus, explaining the X-ray diffraction and Raman spectra data obtained in the experiments.

● Green Hydrogen Is Sparking a Revolution in Sustainable Energy

Sustainable Energy is the hydrogen is one possible answer for our dependence on the fossil fuels that power our cars and buses. Though there are many vehicles today that are run by hydrogen but that technology is still struggling. Many European Union and other countries are now moving towards the use of Green Hydrogen. There are a couple ways of producing hydrogen and not all of them move us toward the goal of cutting down on greenhouse gas emissions today the most common hydrogen is known as gray hydrogen. Green hydrogen could compete with its gray counterpart as soon as 2030 then it could be applied in transportation particularly for large vehicles like buses, trucks and ships where the drawbacks of current batteries make them less

than ideal but hydrogen has potential far beyond trucks or boats. The EU has drawn up a road map of the ways green hydrogen could help them hit emissions targets, it could be used to decarbonise the gas grid and deliver heat and power. Adding it to the grid doesn't require huge upgrades and energy producers could convert to use pure hydrogen essentially hydrogen could be a way to produce energy in one place and then transport it for use or storage somewhere else solving a big problem of renewable. Finally, hydrogen could be used in industrial processes to generate heat or replace coal-based blast furnaces in steel production. It all sounds very tempting enough that the EU proposed investing billions of dollars in green hydrogen. Separately the UK is ramping up their own use of hydrogen with buses and trains powered by the technology just entering service in a few trial cities with re-imagined transportation and a converted grid using hydrogen from clean sources. Europe could be a model for the world to follow.

- **SpaceX's New Rocket Fuel Could Help Us Finally Launch Humans to Mars**

Space X recently launched their Crew 1 mission to the International Space Station using the iconic Merlin Engine. Recently, Space X has developed an entirely new raptor engine to achieve an even further goal, the dream of Elon Musk, i.e., Mars. It starts with a new kind of fuel that's not only less dense but also more efficient and eco-friendlier. Talking in terms of the mixture needed to launch a rocket, we need two things: a fuel which is basically known as propellant and an oxidizer to release oxygen. In 1926, legendary engineer Dr. Robert Goddard used a combination of gasoline and liquid oxygen to launch the very first rocket. Though it was a great starting point, but as new mixtures were developed gasoline its popularity and also since it is an extremely volatile substance it is very dangerous to have it around the crew. In 1981, manned space shuttles were launched using liquid hydrogen in combination with an oxidizer liquid oxygen. Liquid hydrogen has a relatively low density of only 70g/L, due to which engineers had to use bigger fuel tanks. Having a propellant with a higher density means using smaller fuel tank, i.e., a lighter rocket and the ability to go further distances. The currently used propellant is RP-1 ($C_{10}H_{14}O_4$) has some drawbacks that lead leading Space X scientists to look for a different propellant which could be used specifically for mars exploration. So, recently, they developed the latest Space X 'Raptor Engine' and its next generation propeller. This engine uses a combination of liquid methane and liquid oxygen mixture for a reusable vehicle on Mars. Not only is this an efficient fuel but it can easily be created using resources that we can find on the red planet. This could help Space X achieve its main goal, i.e., to create a system that can take humans

to mars and back. Both methane and CO_2 could be extracted from the atmosphere using solar power and water could be mined near the surface of Mars. Recently in Q4 of 2020 Space X's raptor engine passed a major milestone in their engine development process when their chamber pressure reached 330 bar without exploding this beats out the previous record held by the Soviet Union's RD - 701 engine.

- **The World's First Room Temperature Superconductor Is Here**

Superconductors are the secret sauce that many designs for quantum computers, particle accelerators, and fusion reactors. But most superconductors need to be kept at ultra-cold temperatures, a drawback that severely limits their use. Now for the first time, researchers have created a material that acts as a superconductor at nearly room temperature. Superconductors are aptly named; they're materials that conduct electricity with zero resistance, meaning a current can move through the material without losing any energy. They also expel magnetic fields thanks to a phenomenon called the Meissner effect. Quantum computers like the one made by IBM have to keep their handful of quantum bits even colder, just 0.015 Kelvin. These extreme temperatures present extreme problems. For all these reasons, a room temperature superconductor is considered the holy grail. Researchers started with a mixture of carbon and sulphur in between the diamonds of their vise. Next, they piped in the gases, hydrogen, hydrogen sulphide, and methane. When the ingredients were hit with a laser, they reacted to form clear crystals. Then they cranked up the pressure. At 148 gigapascals, the crystals became superconductors at 147 Kelvin. The researchers ratcheted up the pressure even higher, to 267 gigapascals, and found the material had the properties of a superconductor at 287 Kelvin. One very recent proposal for a fusion reactor, MIT's SPARC, could be a huge breakthrough in the field and it's only possible because these materials are just becoming viable for large scale use. In its current state, the superconducting crystals the researchers made in their diamond vise don't really have a practical application. The researchers' ultimate goal is to create a material that keeps its properties even when the pressure is released.

References:

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2. sciencedaily.com

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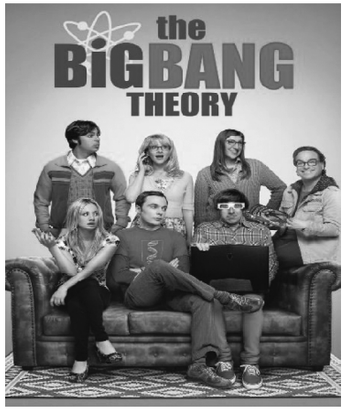
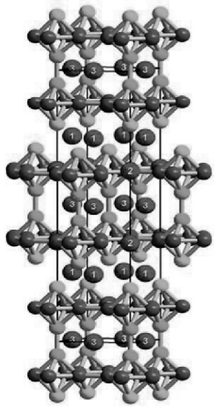
CHEMISTRY IN MOVIES

The Big Bang Theory



The pop culture impact of certain TV shows and movies have been known to seep into the world of science A chemical compound has taken a page from *The Big Bang Theory's* Sheldon Cooper. Within the confines of *The Big Bang Theory,* Sheldon's constant use of the word *"bazinga"* is one of the sitcom's longest recurring jokes. While Sheldon Cooper doesn't enjoy strong personal relationships or understand nuances like sarcasm, he does like to make his own type of practical jokes. And whenever the scene stealer manages to get one over on the rest of the cast, he exclaims *"bazinga",* cueing them into the fact that he got them, and he got them good. Hold on to your comic books, because *bazinga* might just end up in future chemistry books.

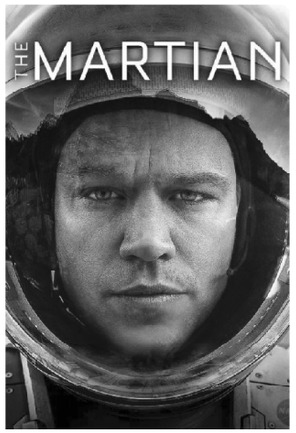
Researchers Paul Canfield and Na Hyun Jo at Iowa State University are attempting to grow the material after watching *The Bing Bang Theory.* In an episode of *Big Bang,* Sheldon let out his signature catchphrase *"bazinga!"*. During this same scene, the nerd's white board contained the elements barium, zinc, and gallium. That's when the researchers decided to combine these elements into a new compound, and see if BaZnGa could somehow contribute to the greater world of science.



Source: Na Hyun Jo et al

The structure of BaZnGa with barium shown in red. The other sites in green, cyan and blue can be occupied by zinc and gallium.

The Martian



In the movie The Martian, Mark Watney made water by taking the excess hydrazine from the lander and using principles of chemistry to convert it into water. Could that actually work? In theory - yes. But not quite like the movie showed. Hydrazine has been used as rocket fuel for Mars landers for a long time. It's a fairly low power, low efficiency fuel for a rocket but it's attractive because it's a monopropellant.

For a rocket engine, hydrazine (N_2H_4) is passed through a catalyst which causes it to decompose into ammonia, nitrogen gas, and hydrogen gas according to the following reaction:

$$N_2H_4 \rightarrow N_2 + 2H_2$$

In the movie The Martian, Mark Watney used that same reaction to produce the hydrogen gas and then, in combination with the oxygen in the lab, he burned the hydrogen and made water.

$$2H_2 + O_2 \rightarrow 2H_2O$$

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In Focus

Artificial Intelligence Solves Schrödinger Equation

A team of scientists at Freie University, Berlin has developed an artificial intelligence (AI) method for calculating the ground state of the Schrödinger equation in quantum chemistry. It seems to ease the difficulties using Schrödinger equation in practice.

Up till now, it has been impossible to find an exact solution for arbitrary molecules that can be efficiently computed. But the team at Freie University has developed a deep learning method that can achieve an unprecedented combination of accuracy and computational efficiency. The team is looking for a significant impact on the future of quantum chemistry by their approach. The results were published in nature chemistry. The deep neural network designed by Professor Frank Noe's team, is a new way of representing the wave functions of electrons.

Prof. Frank and his team designed an artificial neural network capable of learning the complex patterns of electron location around the nuclei which is expected to ease the difficulties faced in the standard approach of composing the wave function from relatively simple mathematical components.

The authors called their method as 'Pauli-net', because of one peculiar feature of electronic wave function i.e., their anti-symmetry. When two electrons are exchanged, the wave function must change their signa and they build this property into the neural network for the approach to work.

Besides Pauli exclusion principle, electronic wave functions also have other fundamental physical properties and much of the innovative success of Pauli-net is that it integrates these properties into the deep neural network rather than letting deep learning, figure them out by just observing the data. Building the physics into the AI is essential for its ability to make meaningful predictions in the field.

There are still many challenges to overcome before the method is ready for industrial application. But it is a fresh approach to an age-old problem in the molecular and material sciences, and the team is excited about the possibilities to open up.

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AMAZING FACTS

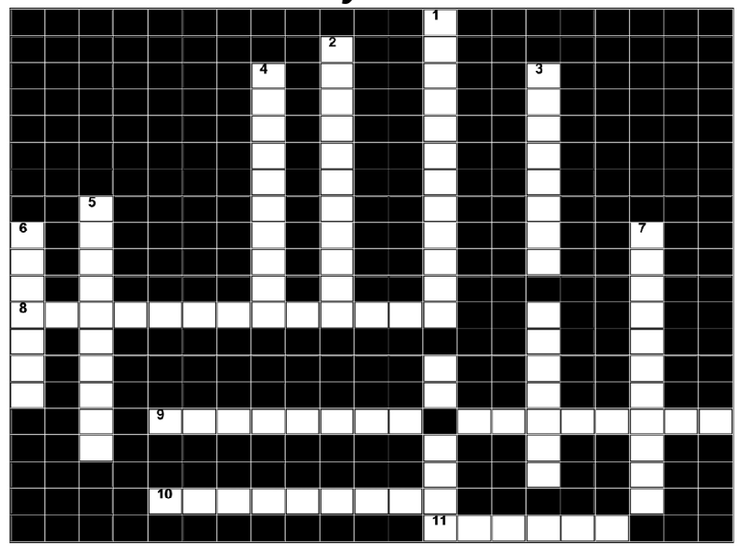
1. Bones, teeth and pearl dissolves in vinegar because it contains acetic acid.
2. Astatine is the rarest element encountered naturally on earth.
3. Secretion of the hormone ghrelin by the stomach leads to the feeling of hunger.
4. One inch of rain is equal to 10 inches of snow.
5. Air becomes liquid at -190°C.
6. 20% of earth's oxygen is produced by the Amazon rainforest.
7. Chalk is made from trillions of microscopic plankton fossils.
8. Polar bears are nearly undetectable by infrared cameras.
9. Venus is the only panet ton spin clockwise.
10. Petrichor is the earthly scent produced when rain falls on dry soil.

Chemistry Puzzle

FIND THE HIDDEN NAME REACTIONS

T	B	O	V	O	N	M	I	Z	I	T	U	F	U	I	X	N
C	O	T	X	B	U	I	T	U	T	N	W	T	X	O	O	E
L	U	W	L	M	W	R	W	N	T	E	D	N	Q	I	N	C
E	V	T	D	T	A	I	C	U	G	M	I	G	T	I	R	G
M	E	O	F	W	E	B	L	G	U	E	Y	A	H	E	A	D
M	A	B	S	A	Z	O	A	L	T	G	S	N	I	Q	P	D
E	U	S	W	G	R	T	Z	S	I	N	H	M	T	C	G	X
N	L	L	U	U	T	C]	L	X	E	A	E	D	D	S	R	G
S	T	Z	H	E	R	E	L	D	K	R	M	X	C	S	E	A
E	B	O	R	Q	K	T	N	E	T	R	U	S	Y	P	B	R
N	L	M	N	N	P	O	Z	I	D	A	M	G	O	Z	M	E
E	A	O	I	G	C	B	E	N	W	E	N	M	W	N	O	N
N	N	F	R	L	I	M	Z	T	H	R	I	K	R	C	G	H
J	C	K	O	A	A	F	Y	O	R	N	E	R	X	K	H	S
X	G	D	Z	N	Z	C	K	J	E	E	A	L	F	B	U	I
M	L	H	N	T	D	I	M	H	C	S	S	E	B	L	O	K
A	B	N	B	D	H	U	N	S	D	I	E	C	K	E	R	F
W	I	T	T	I	G	F	Q	N	Z	A	B	D	E	K	B	F
B	T	H	N	M	E	A	T	A	A	L	C	Q	G	H	G	L
T	Z	K	G	Z	C	A	Z	N	T	C	O	W	P	K	Y	O
R	E	Y	A	M	D	N	A	S	B	K	A	G	Y	I	T	W
H	O	F	M	A	N	N	B	R	O	M	A	M	I	D	E	A

Chemistry Crossword



Down :

1. States that during a chemical reaction, the matter cannot be created or destroyed, so the amount does not change, conserving mass.
2. Type of reaction where elements in different compounds trade places or when an element replaces another in a compound.
3. A combustion of symbols that represent the elements in a compound.
4. Materials or substances that start a reaction.
5. Shows the number of specific atom in a molecule or the ratio of elements in a compound.
6. Material or substance that is produced in a reaction.
7. Is a number place in front of a chemical formula or symbol in a chemical equation.

Across :

8. Type of chemical reaction where a large, complex reactant compound breaks down into smaller, simpler products.
9. A shorter way to show chemical reactions, using symbols instead of words.
10. A type of chemical reaction where two or more smaller reactants combine to form a larger, more complex product.
11. In chemistry is a one-letter or two-letter set of characters used to identify an element.

N.B. Please send the answer to The Editor, 'The Chemical Axis', Department of Chemistry, B. Borooah College, Guwahati, Assam - 781007 on or before 20-03-2021
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Any suggestion regarding the improvement of 'The Chemical Axis' will be solicited. Please send your suggestion to The Editor, 'The Chemical Axis', Department of Chemistry, B. Borooah College, Guwahati, Assam-781007.

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8. Course of study (PG/UG/HS) :
9. Any suggestion regarding development of the Forum :

Date :
Place :

Signature

N.B.

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- *To make necessary arrangement for beneficiary programme for the students.*

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