SIR P. T. SARVAJANIK COLLEGE OF SCIENCE
DEPARTMENT OF PHYSICS

SPECTRUM

Special Issue, June-2021

Nobel Prize in Physics and Chemistry

Editorial

"Every great and deep difficulty bears in itself its own solution. It forces us to change our thinking in order to find it." - Niels Bohr (Nobel Laureate-Physics 1922)

The COVID-19 pandemic has completely transformed our thoughts about the world around us. It had posed an unprecedented challenge to the entire mankind. The word has bounced back on the track and so we are..! Yes, we are back with an exclusive issue of the SPECTRUM inscribed to Nobel Prize -2020. Alfred Nobel was a great visionary who believed that people are capable of helping the society to improve society through their knowledge, science and humanism. Therefore, he bequeathed all his fortune to establish a prize that would honor the discoveries that have conferred the greatest advantage to mankind. The issue of SPECTRUM contains two article by Dr. Pruthul Desai. First Article describes "Nature's Enigma: the Black Holes". The 2020 Nobel Prize in Physics was awarded with one half to Roger Penrose and the other half jointly to Reinhard Genzel and Andrea Ghez, for advancing our understanding of black holes, the all-consuming demon that prowl in the darkest parts of the universe. "Violet CRISPR: A wonder Tool" - Second article by Dr. Pruthul Desai narrates the story of discovery of CRISPR. Emmanuelle Charpentier and Jennifer Doudna played a pivotal role in the development of the wonder tool and were awarded the Nobel Prize in Chemistry 2020 for discovering one of gene technology's sharpest tools: the CRISPR/Cas9 genetic scissors. CRISPR/Cas9 technology has introduced new opportunities in cancer therapies, curing inherited diseases and also in plant inbreeding. As Dr. Desai has mentioned in one of his article, there's nothing more inspiring than our capacity to look up, to wonder, and to have the ingenuity and dedication to see a little farther. Technologies enable us to fathom profound mysteries of the universe. Only time will tell whether these technologies would turn out to be a boon or bane..!!! We also welcome your feedback and creative contribution for the magazine on spectrum@ptscience.ac.in – we look forward to hearing from you!

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1. Nature's enigma: the Black Holes

Dr. Pruthul Desai

Black holes are one of the most enigmatic objects in the Universe whose very existence has been a matter of debate for fifty years. This year's Noble prize recognizes the work of one, Sir Roger Penrose, who ingeniously showed that given certain conditions, a black hole is a logical necessity as per the Einstein's General Theory of Relativity. The other half of the prize recognizes the revolutionary findings of Prof. Reinhard Genzel and Prof. Andrea Ghez, who independently discovered the existence of a monstrous black hole named Sagittarius A^* which is 4 million times, the mass of the Sun. All the three laureates with their amazing work finally silenced the sceptics and black holes now are widely accepted as being truly "there." A brief account of the pioneering work of the trio which paved the way for them to win the coveted Nobel Prize is presented.

1.1 Introduction

Einstein's century old *chef-d' oeuvre* - 'the General Theory of Relativity' with its numerous predictions such as the existence of black holes, binary stars, neutron stars, worm holes has caught the imagination of public at large since its genesis. During the past half century, painstaking efforts have yielded evidences of some of these fanciful predictions and have opened up a new era in out long-standing quest to comprehend cosmos.

On October 6, the Nobel Committee announced that the Nobel Prize in Physics - 2020 will be awarded to three scientists: Sir Roger Penrose (University of Oxford, UK), Reinhard Genzel (Max Planck Institute for Extraterrestrial Physics, Germany) and Andrea Ghez (University of California, Los Angeles) (fig.(5)), for their discoveries about one of the most exotic structures in the Universe - the black hole. Mathematical physicist Roger Penrose was awarded half of the approximately $1.1 million prize for his "discovery that black hole formation is a robust prediction of the general theory of relativity" and erstwhile adversaries, astrophysicists Andrea Ghez and Reinhard Genzel shared equally the remaining half "for the discovery of a supermassive compact object at the center of our galaxy." It is the first Nobel given specifically for black holes — an acknowledgement of their unmistakable existence (notwithstanding the hedging in the language of the second half of the award) [1]. It extends the recent streak of prizes for astrophysics.

Black holes are astoundingly massive objects whose gravitational tug does not allow even light to escape. Therefore, black holes have always remained shrouded in mystery and not amenable

Figure 1: Winners of the Nobel Prize in Physics-2020
(Source: IOP Publishing/Tushna Commissariat; CC-BY-SA H Garching;UCLA/Christopher Dibble)

to direct detection. In his autobiography, *Geons, Black Holes, and Quantum Foam: A Life in Physics*, Prof. John Wheeler, a leading general relativist and who gave black hole its name, writes, “[The black hole] teaches us that space can be crumpled like a piece of paper into an infinitesimal dot, that time can be extinguished like a blown-out flame, and that the laws of physics that we regard as ‘sacred’, as immutable, are anything but."

“The discoveries of this year’s laureates have broken new ground in the study of compact and supermassive objects. But these exotic objects still pose many questions that beg for answers and motivate future research,” says David Haviland, chair of the Nobel Committee for Physics, in a press release.

Penrose 89, told *The Guardian* it was a “huge honor" to win the prize, and that it was wonderful to hear that the award had gone to a woman. But somewhat sheepishly, he added that the win was likely to disturb his current work for few days. “In some ways it is a distraction, I hate to say this," he said, adding that he’d been making the most of lockdown to develop new ideas.

Asked about the discovery of a massive yet invisible object at the heart of the Milky Way, Ghez said “the first thing is doubt." “You have to prove to yourself that what you are really seeing is what you think you are seeing. So, both doubt and excitement," she said in a call with the committee after receiving the award [2].

Incidentally, Prof. Ghez is only the fourth woman ever to have won the Nobel Prize in Physics. The other three illustrious women companions are: Marie Curie (1903), Maria Goeppert-Mayer (1963), and Donna Strickland (2018).

The details of the seminal work by the trio and the story of how they eventually reached their epochal discovery is presented.

1.2 Einstein's Equations and its Solutions

Einstein's *tour de force* - 'the General Theory of Relativity' published in 1915, is considered to be the greatest creation of the human mind and was decades ahead of its time. In this theory, gravity is not a force - a difference from Newtonian mechanics- but a manifestation of the curvature of spacetime, the curvature being caused by the presence of mass [3]. In General Relativity, space and time are truly dynamic quantities. They are no longer mere backdrops in which the drama of life ensues, but respond to the presence of matter and energy, bending, contracting, or even expanding in the presence of appropriate forms of matter or energy [4]. Planets as well as light beams follow curving paths, like balls going around a roulette wheel. As John Wheeler puts it, "spacetime tells matter how to move, and matter tells spacetime how to curve." In the absence of mass the spacetime is flat.

The Einstein field equations are ten tensor equations which describe gravity as a result of spacetime being curved by mass and energy. These equations are notoriously difficult to solve unless the simplifying assumptions are made. Just a few weeks after the publication of the General Theory of Relativity, German astrophysicist, Karl Schwarzchild, took up the challenge of solving these complicated equations for the case of a spherical non-rotating stationary star whose spherical symmetry simplified the mathematical calculations.

Undeterred by the pounding mortar shells in his immediate vicinity on the eastern war front during the World War - I, Schwartzchild, who, despite being above 40 years had voluntarily enlisted himself for the military service, pointed out an apocalyptic solution: In effect, cramming too much matter and energy inside too small a space would cause space-time to collapse into a point of infinite density called a singularity. In that place — if you could call it a place — neither Einstein's equations nor any other physical law made sense [5]. His work predicted a "Schwarzschild radius"— a radius that denotes how compact an object would need to be to prevent light from escaping its gravitational pull. The sun, for example, has a real radius of nearly 700,000 kilometers, but its Schwarzschild radius is only three kilometres [1]. Thus, Schwarzchild laid the foundation of the theory of black holes. The question: whether the resulting singularity was simply an artefact of that perfect spherical symmetry — something possible on paper, but preposterous in nature, lingered on.

Sadly, Schwarzchild contracted an autoimmune disease of skin while serving on the eastern front. Within a few months of his revolutionary prediction, Schwartzchild breathed his last. He was 42. But the quest triggered by Schwarzchild has continued to attract some of the best scientific brains of the century and has eventually led to this year's Nobel Prize.

The idea of a superheavy star encapsulating infinity, despite being mathematically permissible,

was unpalatable to Einstein's taste. How could the laws of physics lead to a dire possibility for a star and for physics itself? For Einstein, the idea of a singularity where laws of physics break down was a bit too much and therefore, he contemptuously dismissed it. Deep down his heart Einstein believed that nature would find a way to steer clear of such a calamitous scenario.

1.2.1 Further Insight!

Though the idea of a black hole existing out there in the Universe is a commonplace today with the stunning pictures of black hole's silhouette captured by the Event Horizon Telescope in 2019, splashed across the front pages of the majority of the newspapers around the world, it certainly was not so in the past. The concept of the black hole which was then called 'dark stars' was first mooted by the British philosopher and Mathematician John Mitchell in 1783 and later on by the renowned French polymath, Pierre Simon de Laplace in 1793. They envisaged a massive star whose gravitational pull would be so strong that even light would not be able to escape.

After Schwarzchild's prescient idea, an American Physicists, Robert Oppenheimer and Hartland Snyder calculated the dramatic collapse of a spherically symmetric matter distribution in 1939. He gave a full geometrical spacetime picture of such a cataclysmic event. He showed that when a massive star runs out of nuclear fuel, it first explodes as a Supernova shedding mass and energy. Whatever matter that is left at the end of the cataclysmic event would implode to form a small, ultra-dense region called singularity which bends the space-time continuum infinitely at its centre. A gossamer veil known as event horizon will encapsulate the singularity. An event horizon is the 'point of no return,' kind of one way traffic and anything entering it, including light, would not be able to escape from it. For a non-rotating star its event horizon is same as its "Schwarzchild radius."

In spite of these developments, most of the leading scientists of the time were sceptical of the existence of the black hole. They believed that the black hole was a mere mathematical artefact sans real existence and should be studied only satiate the curiosity of mathematics wizards. This notion resulted in a hiatus of nearly three decades till a fortuitous discovery brought black hole physics back to the lime light and what was regarded as a mere mathematical curiosity suddenly became one of the hottest topics of research.

1.3 The First Hint: Quasars

In 1963, the Dutch astronomer Maarten Schmidt discovered the first quasar which was named 3C273. From its evident great distance from us (as ascertained by redshift measurements), the intrinsic brightness of this object was judged to be extraordinary, over 4×10^{12} times the

brightness of the Sun, so that its output is about one hundred times the total output of our own entire Milky Way galaxy [6]!The discovery of quasars - brightest objects in the Universe provided the first indirect evidence of possible black hole out there in the Universe. “Quasars are among the brightest and most distant known celestial objects and are crucial to understanding the early universe," an astronomer Bram Venemans of the Max Planck Institute for Astronomy in Germany said in a statement [7].

Quasars spew out tremendous amount of light (energy)- something rarely observed in umpteen other stellar objects. To explain this extraordinary mass output from the inexhaustible inferno, the scientists conjured up the concoction of outrageous-seeming idea that the central object responsible for these emissions would have to involve a huge, yet extremely compact mass, devouring gas and dust to generate light. An in-depth understanding of the behaviour of quasars was an intriguing problem for theorists and and the problem, to accurately measure the radiation effusing out as jets, was an equally challenging one for experimentalists.

Soon after the discovery of quasars, the scientists started to model the dynamics of the ultra-compact objects with humongous gravity. The solutions of Einstein’s equation leading to a singularity worked out by Schwarzchild were under simplifying assumptions that the material undergoing gravitational collapse is a perfect sphere. The question was whether the resulting singularity was a mathematical artefact caused by the spherical symmetry or extends to the actual asymmetric cases which are usually observed in nature. How to avoid the singularity? Any theoretical model of black hole would inevitably be required to circumvent singularity. This tricky scenario provided an ideal opportunity to Roger Penrose to wave his magic wand.

1.4 Dying Stars form Black Holes

“[Physicists] would argue. They would get answers that didn’t agree with each other," says Daniel Kennefick, an astrophysicist and historian of science at the University of Arkansas. “It turned out the reason was that they didn’t really understand the structure of infinity, and Penrose solved that problem." In 1965, exactly ten years after Einstein’s death, Penrose generalised Oppenheimer’s idea and showed that collapse to a singularity always happens when there’s enough mass/energy packed together, regardless of the symmetry of the collapse.

As Penrose put it in his 1965 paper, “deviations from spherical symmetry cannot prevent space-time singularities from arising.” In other words, what Penrose was saying that given enough mass, even when a star is distorted and asymmetric, it will still collapse down to a point. The fate of the star is sealed and nothing can prevent this cataclysmic slump. Thus, Penrose was first to prove mathematically that the black holes are a natural consequence of the relativity theory and not just science fiction. Ironically enough, Penrose presented the path-breaking

paper at a conference in Poland, which was attended by the physicist Richard Feynman who wrote to his wife to remind him not to go to conferences on general relativity [8].

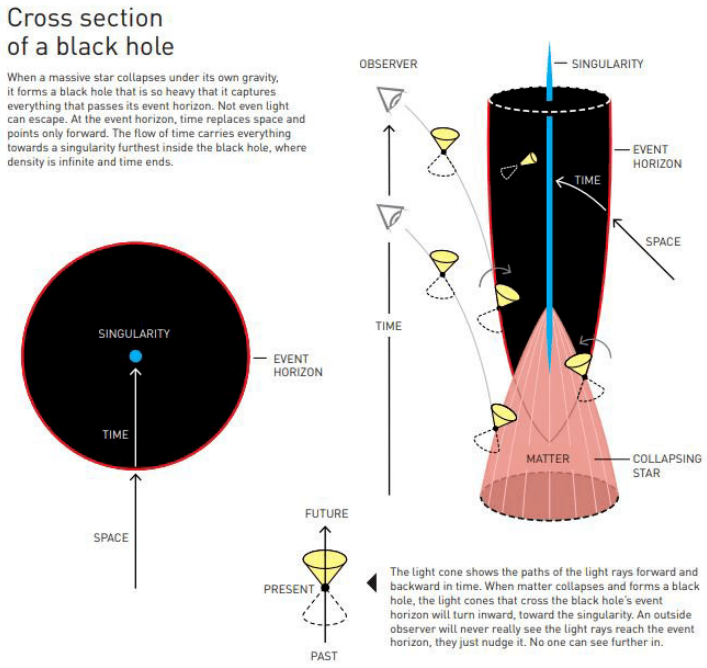

Figure 2: Spacetime in the vicinity of a Singularity
(Source: ©Johan Jarnestad/The Royal Swedish Academy of Sciences)

Armed with an expertise in topology - the branch of mathematics that describes the properties of geometric objects as they are twisted or stretched, and inspired by the work of Dutch graphic artist M C Escher, Penrose devised a diagrammatic scheme to analyse the spacetime near singularity which helped him to arrive at his outlandish conclusion. Penrose invented a mathematical notion named “trapped surfaces." Unlike a regular surface, which can have light rays shooting away from it in any direction, a trapped surface is a closed two-dimensional surface that — even when distorted so it’s no longer a sphere — only allows light rays to go one way: towards the center point.

Penrose found that the dimensions of space and time switch roles inside a trapped surface. Time is the direction pointing toward the center, so that escaping a black hole is as impossible as going back in time. The path inward is as inexorable as the forward arrow of time outside the black hole: one-way traffic only [9] as shown in the fig.(6). Although we don’t have any idea of what the singularity is, we know for sure, that at singularity, our very conceptions of

space, time and matter fall apart and the laws of physics simply break down. Singularity points at new laws of physics which have to be churned out to understand it.

“We really don’t like having singularities,” Stein says. “In fact, we could cut out the inside of the black hole spacetime and replace it with ... pink elephants or what have you. And from the outside, you would never be able to tell the difference, because it’s all hidden behind the horizon." Penrose’s idea of “cosmic censorship" was that there could be no “naked" singularities: all of them would have to be “clothed" by an event horizon. Even when black holes crashed together and merged, the singularities—or pink elephants—would remain hidden by their event horizons, preventing their existence from throwing the outer cosmos into chaos [1].

Penrose, together with Stephen Hawking, soon showed that a similar analysis applies to the entire universe: A singularity would have inevitably existed when matter and energy were densely packed together in the Big Bang [10]. This pioneering work by the duo tilted the balance in the favour of the Big Bang Theory which is based on the premise that the Universe had a beginning and it sounded death-knell for the Steady State theory which assumed that the Universe is everlasting with no beginning.

The fact that mathematics demonstrated that astrophysical black holes may exactly exist in nature is exactly what has energised the quest to search for them using astronomical techniques. Indeed, since Penrose’s work in the 1960s, numerous black holes have been identified [11].

1.5 Black Hole in the Backyard

Scientists were on a cosmic scavenger hunt for more than half a century which culminated in an epic scientific quest of observing the existence of “exotic" black holes outside the Milky Way. Today, the existence of black holes is a foregone conclusion. These giant monsters are ubiquitously common occupying the centres of billions of galaxies interspersed in the cosmic void. Some of these behemoths are as large as million times or even billion times the mass of the Sun.

But closer home, one of the most likely places to search for these monsters is at the galactic centre of the Milky Way. The first hint about a possible black hole at the galactic centre was the detection of the radio signals by the radio astronomer Karl Jensky in 1931, coming from the direction of the constellation Sagittarius. With much improved telescope, the astronomers Bruce Balick and Robert Brown could locate the galactic centre in the Sagittarius constellation and named it Sagittarius-A^*. In 1971, Lynden-Bell and Martin Rees, of the University of Cambridge, compared a map of quasars to radiation coming from the Milky Way. Based on their analysis, they predicted that the Milky Way should also host a massive black hole at its

centre [12].

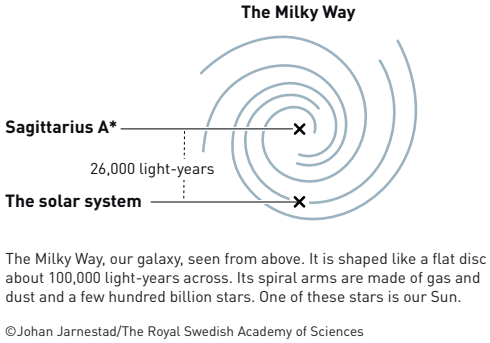

Figure 3: Top view of the Milky Way
(Source: ©Johan Jarnestad/The Royal Swedish Academy of Sciences)

In the mid-1990s, though the resolution of telescopes had increased by leaps and bounds during the late twentieth century it was not yet good enough to spatially resolve objects separated by distance of the order of the Schwarzchild radius of the purported black hole at the galactic centre. The Earth is surrounded by a blanket of atmosphere extending to about 100 kms. The disturbance and turbulence created in the atmosphere limits the resolving power of the telescope.

The promethean astronomers Reinhard Genzel and Andrea Ghez embarked on a mission to do the unthinkable - peer across a distance of nearly 2600 light years to detect a black hole with the ground based telescope whose technology, most believed, was inadequate for the herculean task at hand. Undeterred by the daunting task, both Genzel and Ghez listened to their apparently vague intuitions and convinced themselves that the persistent, yet sagacious probing, would force nature to reveal its profound secret. Genzel and his group worked with Very Large Telescope (VLT) facility in Chile operated by the European Southern Observatory (ESO) and Ghez used the Keck Observatory in Hawaii.

The two groups were competing for the elusive prize and this healthy competition fuelled remarkable findings. Over two decades, the two groups tried hard to outrun the other by producing research papers one after the other, often within six months of each other.

The interstellar dust obscures the visible light received on the Earth. Therefore, both the teams took observation in the near-infrared region centres at $\lambda = 2.2\mu$m. They used an innovative technique: speckle imaging which involves combining multiple brief exposures, each short enough to avoid the extended atmospheric distortion. Images of star with a very short exposure

time of just about a tenth of a second were captured using very sensitive detectors. The series of short exposures were spatially shifted to align the pattern of stars and added. The stack of shifted images provided a sharper and deeper image [13]. A more refined image with much higher spatial resolution was obtained by combining it with adaptive optics technique.

In their mission to find the purported black hole languishing at the galactic centre, both the teams zeroed in to observed the motion about 100 stars crowded near Sagittarius A^*. Both Grenzel and Ghez were particularly interested by S2 or S-O2, a star with short elliptical orbit with time period of less than 16 years around Sagittarius A^*. We can compare it with the time period of 200 million years that the Sun takes to revolve round the galactic centre once as shown in fig.(7). Dinosaurs were walking on the Earth when we started our lap [14].

They were able to map the entire orbit of S2 as shown in the fig.(8)and during the 16 years of its journey, they continued to develop and refine technology to get clearer and sharper image of the reclusive star. This high precision measurement of the orbit of S2 helped to estimate the mass of the putative black hole. It was found that at the perigee the star S2 whisks around Sagittarius A^* at a breathtaking speed of nearly 8000 km/s.

Ultimately, their observations of bright stars grooving around an unknown mysterious object known as Sagittarius A^* revealed that their movements were guided by the powerful gravity of what could only be a super massive black hole - an object with a mass of 4 million suns crammed into an area of the size of our solar system [15]. That both the groups working independently arrived at the same results, gave greater credence to their findings and confirmed beyond doubt that a monstrous black hole of mass nearly 4 million times the mass of the Sun is languishing at the centre of Milky way.

“The scientific audience was in a perfect position to see us perform the same exercise and judge if the outcome was the same," said Genzel. “It’s the perfect science principle — when two observers agree, then the audience would believe what we saw [15]."

Daniel Holz, an astrophysicist at the University of Chicago who wasn’t part of either team, said the fact that the two groups used different telescopes with different capabilities added another layer of credibility to their findings.

“All of these breakthrough techniques bring us closer than we have ever come to the edge of the unknown, offering novel ways to study the most mysterious objects in the cosmos and to test our most fundamental theories,” Shep Doeleman, project director for the Event Horizon Telescope and astronomer with the Harvard-Smithsonian Center for Astrophysics, tells *Scientific American* [16].

“The story of the discovery of black holes demonstrates vividly how powerful pure mathe-

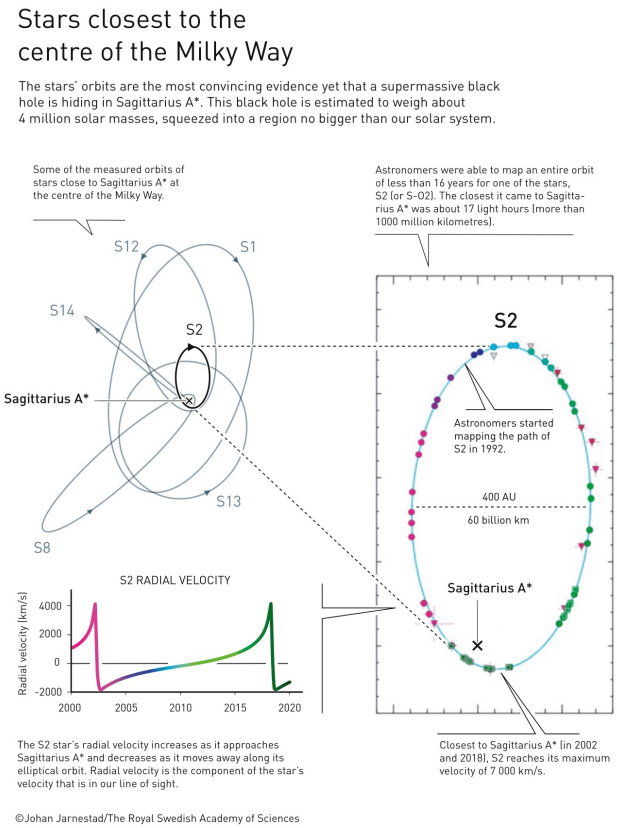

Figure 4: The orbit of the star S2
(Source: ©Johan Jarnestad/The Royal Swedish Academy of Sciences)

matics can be in the quest to understand nature [16].” “We already know Einstein's theory of gravity is fraying around the edges," Dr. Ghez said in an interview a couple of years ago. “What better places to look for discrepancies in it then a supermassive black hole," said Dr. Ghez.

1.6 Conclusion

Einstein's theory has withstood the test of time for over a century, but as more and more black holes are observed and studied, deep within, the Physicists know that Einstein's theory will have to be modified to cope with extreme situations such as the Big Bang or whatever happens inside the black holes.

For astronomers and astrophysicists these “exotic" objects are an incredible sight to behold.

Many of the nature's deepest secrets lay hidden in these enigmatic behemoths. There's nothing more inspiring than our capacity to look up, to wonder, and to have the ingenuity and dedication to see a little farther. We sincerely hope that the mother nature would bestow her blessings which will unable us to fathom its profound mysteries.

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2. CRISPR: A Wonder Tool

Dr. Pruthul Desai

Two women who played a pivotal role in developing the CRISPR-Cas9 technique - a powerful tool which has allowed the researchers to modify and investigate genomes with unprecedented precision were awarded the Nobel Prize in Chemistry - 2020. Owing to its simplicity, the technique has taken the world of biogenetics by storm and has seen a copious surge in its use, across the diverse fields such as agriculture, therapeutics, biotechnology etc. The road to the successful development of the CRISPR technique and the crucial role of the two Nobel laureates is presented. A brief overview of the inextricable ethical issues surrounding the technique and its potential applications is also vividly discussed.

2.1 Introduction

On October 7, the Nobel Committee announced that the Nobel Prize in Chemistry - 2020 will be awarded to two women scientists: Emmanuelle Charpentier, a microbiologist at the Max Planck Unit for the Science of Pathogens, Berlin, Germany and Jennifer A. Doudna, a biochemist at the University of California, Berkeley, USA (fig.(5)), "*for the development of a method for genome editing.*" Specifically, they've been awarded the prize for their discovery of the CRISPR–Cas9 genome editing technique which allows the scientists to alter the genome of any organism with unprecedented ease and finesse. Yet the technology that came out of their work, revolutionary as it is, springs from an innovation that first evolved in bacteria, probably more than a billion years ago, and went unnoticed until recently [1]. It provides an excellent example of a humbling lesson of science in the sense that, even when it comes to many of humanity's most brilliant inventions, nature got there first.

What CRISPR offers, and the biologists desire, is specificity: the ability to target and study particular DNA sequences in the vast expanse of a genome [2]. In the 8 years since its creation, the scientists have published thousands of experiments using CRISPR to alter DNA in organisms across the tree of life, including butterflies, mushrooms, tomatoes, and even humans [3].

They are the first two women to jointly win the Nobel and only the seventh and eight women ever to win it for Chemistry in the illustrious history of the Nobel prizes spanning more than a century. The two women will equally split the prize money of $1.1 million. The prize to CRISR-Cas9 is also unusual for it is rare for a method to be announced and conferred with Nobel within the decade of its discovery.

The Nobel Committee said in a statement, “Using these (CRISPR), researchers can change the DNA of animals, plants, and microorganisms with extremely high precision. This technology has had a revolutionary impact on the life sciences, is contributing to new cancer therapies, and may make the dream of curing inherited diseases come true."

“The number of discoveries in biomedicine that have had the impact that Jennifer’s and Emmanuelle’s had can be counted on the fingers of one hand: recombinant DNA, PCR, DNA sequencing, and now CRISPR,” says Fyodor Urnov, a gene-editing scientist at the University of California, Berkeley. “We have never had a technology as powerful and versatile as genome editing with CRISPR, and it is a thrill to work with it daily.”

“My wish is that this will provide a positive message to the young girls who would like to follow the path of science, and to show them that women in science can also have an impact through the research that they are performing," said Emmanuelle Charpentier when she heard about the good news.

Figure 5: Winners of the Nobel Prize in Chemistry-2020

When the news of winning of the Nobel Prize were broken to via a phone call, Doudna, who was in “deep sound sleep" said,"I grew up in a small town in Hawaii and I never in a 100 million years would have imagined this happening. I am really stunned, I’m just completely in shock." “I know so many wonderful scientists who will never receive this, for reasons that have nothing to do with the fact that they are wonderful scientists," says Doudna. “I am really kind of humbled."

2.2 What is CRISPR-Cas9?

Prokaryotes - bacteria and less well-known single-celled organisma called archea, many of which live in extreme environments - face a constant onslaught of genetic invaders. Viruses

outnumber prokaryotes by ten to one and are said to kill the half of the world's bacteria every two days [4]. Prokaryotes have developed the slew of weapons to cope with these threats. They are armed with restriction enzymes which can cleave a DNA at or near a specific sequence. But the defence mechanism is static in the sense that it is potent only if the bacteria has a right copy of the gene of the invading virus - a rarity in the cesspool of countless viruses. A much more dynamic system which could provide a robust adaption to the intruder is required for a long term protection and survival. The CRISPR-Cas9 mechanism aptly serves the purpose and is the most potent weapon in the armoury of the prokaryotes which has impeded their obliteration from the Earth.

The term CRISPR is an acronym for Clustered Regularly Interspaced Short Palindromic Repeats. These are short, partially palindromic repetitive clusters in a DNA sequence which are separated by unique intervening sequences of constant length. CRISPR-associated (cas) genes are a group of genes only present in CRISPR-containing prokaryotes and are always adjacent to CRISPRs as shown in the fig.(6). Combined together they are called CRISPR-Cas9 and form an inbuilt mechanism to counter any viral attack. Much like what Microsoft (MS) Word does for writing, the CRISPR-Cas9 system allows for adding, altering and deleting the genomic code in living beings. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) are pieces of DNA that bacteria snip off from viruses that once attacked them, much like file names used to store various documents we write in MS Word [5].

2.3 Editing Letters in the Book of Life

Long back in 1987, the Japanese molecular biologist Yoshizumi Ishino and his co-workers at Osaka University, while studying the most common gut microbe *E. coli*, serendipitously observed something unusual - palindromic sequence of a *iap* gene. A palindromic sequence is a nucleic acid sequence on double-stranded DNA or RNA wherein reading 5' to 3' forward on one strand matches the sequence reading backward 5' to 3' on the complementary strand with which it forms a double helix. For example, a sequence may be CAAGCTTG in the 5' to 3' direction on one strand, and therefore it will be GTTCGAAC in the 3' to 5' direction on the complementary strand.

When they studied the neighbouring sequences they were aghast with what they found. Near the *iap* gene there were five identical segments of DNA. The five segments were each composed of the same 29 bases. Each sequence had a gap of 32 bases called spacers. In other words, each 29-base sequence was separated from the other by 32-base block called spacers. Unlike the repeat sequences, each of the spacers had a unique sequence. Due to lack of homology to other known sequences, they were clueless about the genetic sandwich and left to wonder why

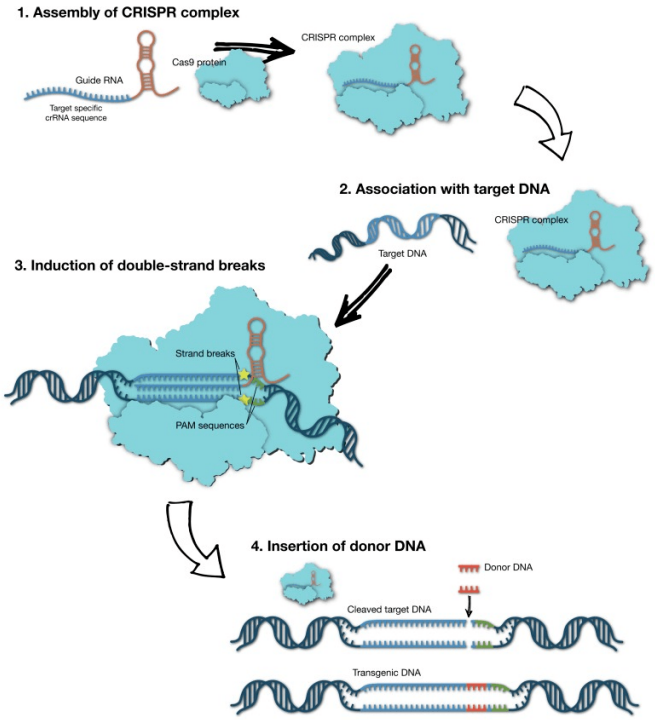

Figure 6: CRISPR
(Source: https://www.ncbi.nlm.nih.gov/books/NBK464635/figure/gen_edit.F2/)

would such a strange structure be present in the first place and what would be its biological significance. They could not conclusively say whether the repeated sequences were unique to *E. Coli* or were prosaic and universal amongst all microbes.

As the technology got advanced, the DNA sequencing became cheaper and widely available. By early 2000s, the homological sequence in a gamut of microbes was identified and astonishingly, most of them exhibited similar genetic sandwiches ensconced in their genes. Though the repeat sequences were common place, its function and biological significance was yet poorly understood! A need was felt to give a name to these sequences and out of various names suggested by the researchers, the name, "Clustered Regularly Interspaced Short Palindromic Repeats" — CRISPR for short, given by Francisco Mojica at the University of Alicante, Spain and Ruud Jansen of Utrecht University in the Netherlands was unanimously adopted and is in use till date.

Jansen's observation that the prokaryote repeat cluster was accompanied by a set of homologous genes that make up CRISPR-associated systems or Cas genes, was a major and significant

advancement of the understanding of the CRISPR system. Initially, four Cas genes (Cas 1-4) were identified. In 2005, it was discovered that the spacers matched sequences present in phages and plasmids, and that the more spacers are present, the fewer phages that were able to infect them [6]. It unequivocally pointed to something hitherto unheard off - the role of CRISPR-Cas in the prevention of phage infection and plasmid conjugation. In effect, the spacers are fragments of DNA gathered from viruses that previously tried to attack the cell. The acquired spacers serve as DNA records of prior infections that are passed to the host's progeny. The source of the spacers was a sure sign that the CRISPR-Cas system could have a role in adaptive immunity in bacteria [7]. Thus the quintessential feature of CRISPR-Cas system was adaptive immunity - a revolutionary finding indeed. Till then, the immunological memory was regarded as a feature unique to vertebrates and the scientists ridiculed at the idea that bacteria might be able to 'remember' viruses that attack them.

Mojica and collaborators at the University of Alicante, predicted a role for the RNA transcript of spacers on target recognition in a mechanism that could be analogous to the RNA interference system used by eukaryotic cells. RNA interference is a biological process in which RNA molecules inhibit gene expression or translation, by neutralizing targeted mRNA molecules. In 2006, Eugene Koonin and colleagues showed that the CRISPR-Cas is a genetic defence system analogous to RNA interference in eukaryotic cells. The system serves to protect cells from the foreign genetic elements, such as viral DNA, by remembering the elements and using them as the guides to destroy invading DNA or RNA.

2.4 Role of Cas Genes

Jennifer Doudna was leading a research group at the University of California, Berkeley. She was working with RNA and in 2006, started to work in an exciting new field: *RNA interference*. One day, she got a phone call from her colleague who divulged her latest findings which were nothing short of being called baffling. When the genetic material of vastly different bacteria, as well as archea (a type of microorganism) was compared, they found repetitive DNA sequences that were surprisingly well preserved. The same code appeared over and over again, but between the repetitions there was unique sequences that differ as shown in the fig.(7). It is like the same word was being repeated between each unique sentence in a book [8].

What was eye-catching was the fact that the repeated sequences in CRISPR appear to match the genetic code of various viruses. It soon became clear that bits of genetic material extracted from the virus which tried to infect the bacteria, was snugly ensconced between these repeats. It meant that for some unknown reasons, the bacteria were plucking bits of viral genes and storing them away between the repeats. It was as if they were creating an archive of past

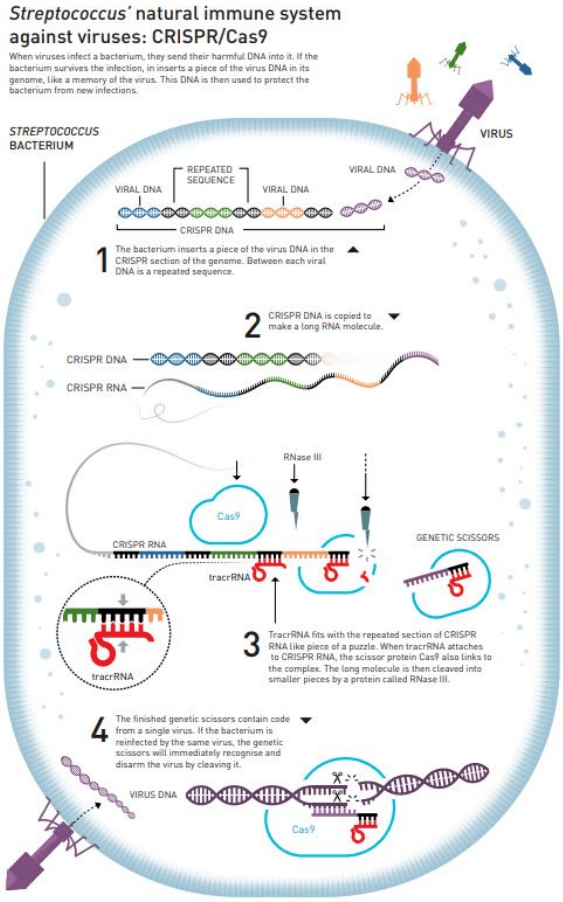

Figure 7: Repetitive DNA Sequences
(Source: The Royal Swedish Academy of Sciences)

infections, which they could later use to defend against the future attacks [9].

Her colleague hinted that the mechanism used by bacteria to neutralise a virus is similar to that studied by Doudna: *RNA interference*. The hint was more than enough to attract Doudna's attention. Immediately, she undertook concerted efforts to understand thoroughly the CRISPR mechanism. Doudna found that Cas genes were similar to the genes that code known proteins which specialise in unwinding and cutting up DNA. Doudna asked a pertinent question: Do the Cas proteins have the same function? Do they cleave virus DNA [8]? She dedicated herself to find an answer to these puzzling questions.

Five years of painstaking efforts yielded the fruitful results. Doudna and her coworkers were

successful in finding the function of several different Cas proteins. It was soon realised that the bacterial immune system was of two types viz. class 1 and class 2. The CRISPR-Cas system studied by Doudna and her group belonged to class 1; it is a complex machinery that requires many different Cas proteins to disarm the virus. The class 2 systems are significantly simpler because they need fewer proteins. Across the Atlantic, in Europe, Emmanuelle Charpentier just came across such a system viz. class 2 which uses RNA molecules transcribed from spacer sequences to direct an enzyme to cleave invading viras or plasmids. It is prized for its simplicity and versatility in genome editing.

2.5 Discovery of TracerRNA

Emmanuelle Charpentier focussed on one of the bacteria that causes the greatest harm to humanity: *Streptococuus pyogenes*. She was interested in identifying sites in the genome of *S. pyogenes* that made regulatory RNAs. She collaborated with the molecular biologist Jorg Vogel, then a junior group leader at the Max Planck Institute for Infection Biology, who had developed methods for large-scale mapping of RNAs in a genome. By 2008, the collaboration mapped sequences of all the small RNAs generated by *S. pyogenes*.

Charpentier and her coworkers found that the novel and hitherto unknown variants of RNA (small RNA), were profusely produced by the bacterium. To Charpentier's great surprise the genetic code of small RNA matched the peculiar repeated sequence in CRISPR in the bacterium's genome. From its sequence and position on the genome - it was at a location that Charpentier's Bioinformatics had predicted as being close to the CRISPR site - they realized that it was highly likely to be involved in a CRISPR system that had not previously been described [2]. The new variant was called tracer RNA (tracrRNA). The similar genetic code made Charpentier wonder about the possible link between small RNA and CRISPR.

Charpentier and her coworkers started working on the trail. To their astonishment, the CRISPR system seemed to be made up of three components - tracrRNA, CRISPR RNA and Cas9 protein - something unheard off back then. "Other CRISPR systems involved just one RNA and many proteins, and no one really thought that two RNAs might be involved," said Charpentier. The system was so exceptionally simple that she realized that it might one day be harnessed as a powerful genetic engineering tool. If the components could be controlled, it might provide the long-sought ability to find, cut and potentially alter DNA at a chosen, precise site in a genome [2].

But how exactly was this CRISPR system working? Instead of working independently, Charpentier suspected that the two RNAs might be working in tandem to guide Cas9 protein to a particular DNA sequence in the virus. This seemingly outlandish idea was Charpentier's ge-

nius. At the behest of Charpentier, her graduate student, Elitza Deltcheva, reluctantly agreed to perform targeted experiments to check the veracity of her prescient idea. In June 2009, after intensive experimentation, Deltcheva finally confirmed her hypothesis which came as a shot in the arm for Charpentier. She immediately realized that her findings were going to be game-changer in the field and published her findings in *Nature* [10].

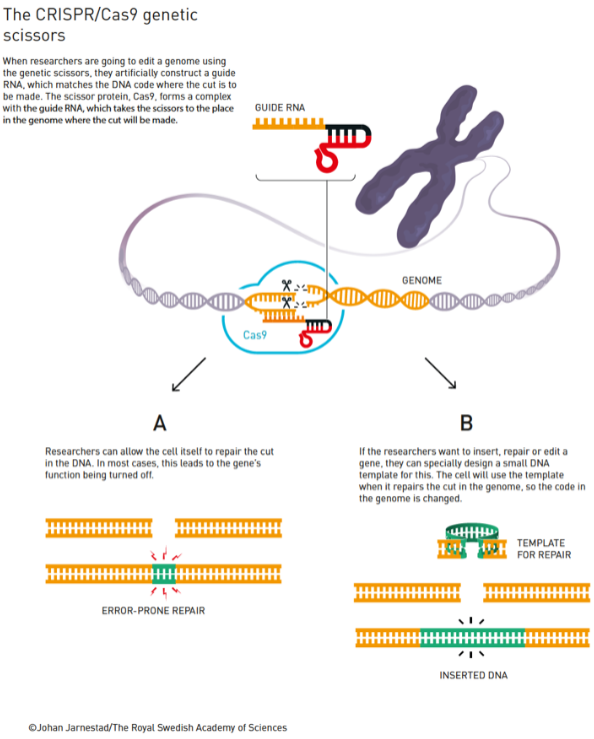

Figure 8: The CRISPR-Cas9 genetic scissors
(Source: ©Johan Jarnestad/The Royal Swedish Academy of Sciences)

The last missing clue in the jigsaw puzzle was to decipher the covert mechanism which assisted the dual-guide RNA system to cleave DNA. The problem at hand required an expert in Biochemistry. Meeting Jennifer Doudna was Charpentier's tryst with destiny. Doudna, a Biochemist from University of California, Berkeley, with an experience of two decades of working with RNA under her belt, was a tailor-made expert for the task that Charpentier set out for. The scenario was an ideal setting for a blooming collaboration to ensue.

2.6 Conference in Puerto Rico

In 2011, a conference was organized by the American Society for Microbiology in San Juan, Puerto Rico. On the second day of the conference, Charpentier met Jennifer Doudna who was charmed by the ebullience of the Frenchwoman. “I loved her intensity, which was apparent from the moment I met her," said Doudna. Charpentier made an offer which Doudna just couldn’t refuse. Charpentier asked “would she like to participate in studying the function of Cas9 in *S. pyogenes*?"

A plan was hatched up to organize regular online meetings to chalk out the design of the experiment which would unravel the mystery. After a great deal of brainstorming and failed experiments, they could observe beyond doubt that in the presence of tracrRNA, Cas9 gene cleaved the DNA in two pieces. In other words, the Cas9 protein acts as a “genetic scissors" as shown in fig.(8).

Could ‘genetic scissors’ be simplified? How could one mimic the bacterial immune system with controlled targeted delivery of Cas9 protein at a particular location in DNA sequence? Building on their insights about the function of Cas9, they conjured up a mechanism which they believe will do exactly what they desired. In order to cleave DNA at a particular location, first essential step was to deliver Cas9 protein to that location. In other words they required a ‘guide.’ They figured out how to fuse the tracrRNA and CRISPR-RNA into a single molecule which they named guide RNA [8]. If the guide RNA worked as desired then Cas9 would be delivered to a particular location and on reaching the site, the Cas9 protein would cleave the DNA at that exact location. The idea was miraculous. But the million dollar question was: would it work?

To find out, they needed to set up an ingenious and revolutionary experiment. They took a gene that was already in a freezer in Doudna’s laboratory and selected five different places where the viral gene should be cleaved. Using the guide RNA, they programmed Cas9 to reach those chosen sites. To their utter surprise, yet elation, the DNA molecules were sliced in exactly the predecided places. In other words, they recreated the bacteria’s genetic scissors in a test tube and simplified the tool to make it easier to programme the system to precisely cut specific sites of interest in any DNA, including humans. To put it figuratively, they could engineer a “guide” RNA molecule with a target genetic sequence that serves like a GPS and zooms in on a location on the DNA where a Cas protein, a pair of molecular scissors, can cut at the desired location. They published their findings in their landmark paper in *Science* in 2012.

While the tool is most often used to make a cut in the DNA, newer approaches are being attempted to add or make minor changes to the DNA. All these approaches may at some time

in the future make it easy to “rewrite the code of life”.

2.7 The Patent Controversy

Over the years the Nobel Prizes across all disciplines have, occasionally, courted controversies and this year,s prize in no exception. Many believed that a Nobel for CRISPR technique would not be awarded for many years to come owing to the long-running patent battle in the US over the technique. One name which many believed should have received the Nobel is Feng Zang from Broad Institute, MIT’s genetic research centre. Zang’s conspicuous absence has raised eyebrows.

Needless to say, the research by the two scientists who were awarded the Nobel Prize in Chemistry has the potential to change the course of humanity. And with that potential comes lots of capital investment and companies vying for patents on techniques and therapies derived from Charpentier’s and Doudna’s research. Given the world-changing applications — and the amount of revenue such CRISPR therapies could bring in — it’s no wonder that such rivalry is often heated and in some cases has led to lawsuits over the technology and its patents [11].

The CRISPR technology is at the core of one such patent dispute involving Charpentier and Doudna’s group at the University of California, Berkeley, and a team at MIT and Harvard’s Broad Institute in Cambridge, Massachusetts.

Broadly speaking, CRISPR-Cas9 as a technology was discovered by University of California, Berkeley (UC Berkeley), professor Jennifer Doudna and Emmanuelle Charpentier and they hold the patent rights for it. Doudna went on to publish a paper in 2013 using the same technique to make gene edits in animal cells. But Feng Zhang, a scientist at the Broad Institute, MIT’s genomic research center, had published a similar paper four weeks earlier, making him the first to prove the tool could be used in human cells. This was the beginning of what has become a yearslong legal battle over who owns the CRISPR Cas-9 editing system.

The current litigation is over the conflicting patents that lay claim to the use of CRISPR Cas-9 to edit genes in human cells. The University of California at Berkeley and the University of Vienna were the first to file patents on the gene-editing process, but the Broad Institute paid to fast-track its patent review. In 2014, the U.S. Patent and Trademark Office awarded several patents to the Broad Institute. A party led by UC Berkeley subsequently filed an interference claim. The Patent Trial and Appeal Board is still in the process of determining which party was first to invent the editing framework.

The argument over who gets to profit from CRISPR has been extremely public, a function of how game-changing the initial discovery was. At the heart of the argument is whether or not it

was clear that Doudna's and Charpentier's method would work in human cells. This has been the subject of both the litigation over CRISPR-Cas9 and debate among scientists [12].

The litigation has glaringly brought to the fore the politics of turning science into a for-profit venture is becoming more powerful than the science itself. As Michael Eisen, a biologist at UC Berkeley, put it at that time, the business of science is increasingly becoming a part of the scientific process, where experiments, papers, and discoveries are being used to further commercial ends rather than the scientific ones.

Nobel's choice of Doudna and Charpentier seems to refute that trend, illustrating and emphasising that science can prevail over politics.

2.8 Applications

The gene-editing technology has opened up a vast window of opportunity. CRISPR is causing a major upheaval the in biomedical research. Within eight years of its discovery in 2011, the tool has enabled the scientists to edit human DNA in a dish and early-stage clinical trials are being attempted to use the tool to treat a few diseases, including inherited disorders/diseases and some types of cancer.

Unlike in the case of humans, the tool is being extensively used in agriculture. It is being tried out in agriculture primarily to increase plant yield, quality, disease resistance, herbicide resistance and domestication of wild species. The huge potential to edit genes using this tool has been used to create a large number of crop varieties with improved agronomic performance; it has also brought in sweeping changes to breeding technologies.

Food allergies affect a huge percentage of the population, and can be life-threatening in some cases. With CRISPR, it could be possible to make milk, eggs or peanuts that are safe for everyone to eat. "There are four proteins within egg white that cause allergy," Tim Doran, researcher at Australia's CSIRO, explained in a podcast. "We're essentially rewriting those regions of the gene that are recognised by the immune system and cause an allergic reaction."

The gene-editing tool has indeed taken "life sciences into a new epoch."

2.9 Ethical Issues

CRISPR-Cas9 technology is the biggest game-changer to hit Biology since long. But with its huge potential comes pressing concerns. The uncanny ability to edit "genomes" with relative ease has sparked lots of hand-wringing over the ethics of using CRISPR for creating "designer humans."

In 2018, a Chinese researcher caused an international furore when he announced that he had used CRISPR technology to create the world's first genetically edited babies. He claimed to have modified a particular gene in the embryo to make babies immune to HIV infection. Though no guidelines have been drawn up so far, there is a general consensus in the scientific and ethics communities that the gene-editing technique should not be used clinically on embryos.

Such incidents, though uncommon today, involve ethical issues. If allowed unchecked, it may raise serious issues on equality and justice. Therefore, there is an urgent needs to put in place appropriately robust checks and balance mechanism so that such stray incidents don't reoccur. If we fail in this sacred duty then the CRISPR technology would turn into Frankenstein's monster - something its creators never craved for.

2.10 Conclusion

CRISPR-Cas has been the biggest revolution in the field of genetics since the discovery of DNA structure by Watson and Crick in 1953. Charpentier and Doudna showed how the Cas system could be turned into a universal 'cut and paste' tool for editing gene sequences with far-reaching consequences. This year's prize is about rewriting the "code of life."

The CRISPR-Cas9 is an excellent example of how humans have learnt from the workings of mother nature. The development of this powerful tool was inspired by the observed mechanism of the immune system of prokryotes.

Eight years since CRISPR-Cas technology burst onto the scene, the researchers have officially recognized 6 different types of CRISPR system, with 19 subtypes. The diversity of CRISPR-Cas systems is mind-boggling. We really only know how a fraction of them work. Unravelling those mechanisms could hold the key to finding new biotechnological applications.

There are many more profound and fundamental questions which are mysteriously subtle and out of grasp for us right now. How did CRISPR evolve, and how did it shape microbial evolution? Why do some microbes use it, whereas others don't? Where would the tinkering of genes lead us all to? The answer: we simply don't know.

The CRISPR technology has put a powerful tool capable of meddling with the nature's own creations, into the hands of mere mortals - a scary scenario, to say the least. Doudna explained in her book, *A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution*, cowritten by Samuel H. Sternberg, "Within a few decades, we might well have genetically engineered pigs that can serve as human organ donors—but we could also have woolly mammoths, winged lizards, and unicorns."

Only time will tell whether CRISPR technology would eventually turn out to be a boon or bane. I am keeping my fingers crossed!!!

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Emmanuelle Charpentier and Jennifer Doudna

Winners of Nobel Prize in Chemistry 2020

Famous Quotes

- Armed with the complete CRISPR toolkit, scientists can now exert nearly complete control over both the composition of the genome and its output.
- The first monkeys were born with genomes that had been rewritten through precision gene editing, bringing the steady march of CRISPR research right to Homo sapiens' evolutionary front door.
- The power to control our species' genetic future is awesome and terrifying. Deciding how to handle it may be the biggest challenge we have ever faced.
- Tomatoes that can sit in the pantry slowly ripening for months without rotting. Plants that can better weather climate change. Mosquitoes that are unable to transmit malaria. Ultra-muscular dogs that make fearsome partners for police and soldiers. Cows that no longer grow horns. These organisms might sound far-fetched, but in fact, they already exist, thanks to gene editing. And they're only the beginning. As I write this, the world around us is being revolutionized by CRISPR, whether we're ready for it or not.