Patenting Opportunities for Synthetic Biology Products in India

While some are still fishing to find a suitable definition for the term “synthetic biology”, we may be content to look for the patent eligibility of its application spanning everything from genetic engineering to synthetic chemistry. It is not surprising to find that the first most valuable patent that appeared on the landscape of synthetic biology was for the synthesis of ‘Artemisinin’ (an anti-malarial lactone) from yeast cells by turning up the controls on the yeast genes that make FPP (a precursor molecule) and turning down the genes that convert FPP into ergosterol. Jay Keasling, the inventor in the patent “Metabolic Engineering of The Shikimate Pathway”, played a key role in inventing the synthesis of artemisinin.

Interestingly, the US Patent No. 9540652 for “Metabolic engineering of the shikimate pathway” is valued at $120,000. The second most highly valued patent in the area of synthetic biology is “US20160281113A1” for “Compositions and Methods for Producing Isoprene” (valued at $2,550,000). Curiously, Indian Patent IN284097 for this PCT application was also granted, but with only eleven claims. Originally, 105 claims were filed in India based on PCT applications.

However, the granted 1-6 claims in India were limited to recombinant microbial cells and claims 6-11 were for a method for producing isoprene using recombinant cells. The remaining claims for plant cells were deleted when the Section 3(j) objection was raised by the patent office. Another US10934226B2 patent for “Method and composition for improving plant traits” by Pivot Bio is revolutionising the nitrogen fixation process of non-leguminous crops by providing a microbial solution that enables crops to fix their own nitrogen from the atmosphere.

Synthetic Biology and Startups

Some of the synthetic biology inventions are disrupting traditional Industries. For example, new entrepreneur Ginkgo Bioworks is aspiring to produce high-quality fragrances by using the power of genetic engineering. Another synthetic biology entrepreneur, Zymergen, was not successful in launching Hyaline (bio-manufactured polyimide film made from diamine monomers). Hyaline, a polyimide film material, was transparent and flexible, and it was marketed for use in flexible smartphones and tablets. This product was withdrawn as Hyaline was not successful with customers, and its foldable screen did not have as large of a market as anticipated.

Ginkgo, in view of its drug and vaccine development potential, later acquired Zymergen. In the agriculture field, synthetic biology entrepreneur Pivot Bio provides a microbial solution that enables crops to fix their own nitrogen from the atmosphere, thereby eliminating the need for synthetic fertilisers. Another US10934226B2 patent for ‘Method and composition for improving plant traits’ by Pivot Bio is revolutionising the nitrogen fixation process of non-leguminous crops by providing a microbial solution that enables crops to fix their own nitrogen from the atmosphere.

In the leather industry a synthetic biology startup Modern Meadow is successful in production of lab-grown leather by using biofabrication techniques to grow collagen, the main component of leather, in the lab. Likewise, many other synthetic biology startups are pushing the boundaries of what is possible and creating a more sustainable and innovative

future for synthetic biology. A list of the commercially available synthetic biotech products is given below.

Product	**Company**	**Synthetic biological method**
1. Soy Leghemoglobin (Burgers that bleed) Leghemoglobin is a protein that carries heme, an iron-containing molecule that gives a blood-red colour similar to that of meat.	**Impossible foods**	Produced by engineered Pichia pastoris (yeast) was leghemoglobin, which improves meaty flavours and aromas when added to a plant-based burger.
2. Januvia (Sitagliptin)	**Merck**	Produced by engineered enzymes transaminase from Arthrobacter sp., the computational design was applied.
3. Hyaline is a polyimide film made from bio-sourced monomers	Zymergen	This film was made from diamine monomers produced by engineered organisms that were optimised using a suite of robotics.
4. PROVEN (biological nitrogen fertiliser for corn)	Pivot Bio	Synthetic biology was used to turn the genes on, which guided the remodelling of the (γ-proteobacterium) KV137 genome
5. Kymriah (Tisagenlecleucel) -for treatment of B-cell acute lymphoblastic leukaemia	Novartis	By use of engineered living cells. CAR-T cells are manufactured by isolating the patient's T cells, genetically modifying them to express a chimeric antigen receptor (CAR) and reintroducing them into a patient.
6. Calyno n-a high-oleic oil from soybeans	Calyxt	Product from a genome-edited soy plant

Synthetic Biology Tool: CRISPR/Cas-9 System

The role of gene editing technologies in medicine has greatly impacted future therapies to treat debilitating conditions. Gene editing can modify genes of living organisms and help to improve our understanding of gene function. This would lead to the development of ways to use it to treat genetic or acquired diseases. One such gene editing tool is the CRISPR/Cas-9 system (Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated protein 9). This tool allows for precision genome editing by cutting DNA in targeted locations for replacement. CRISPR Infographic would be the future of genome editing. The first gene editing therapy utilising CRISPR/Cas-9, named "Casgevy", got approval from the FDA in the US in December of 2023.

Casgevy is a potential treatment for patients suffering from sickle cell disease, known as genetically inherited blood disorder. The emergence of synthetic biology patents relating to CRISPR has led to much talk about the CRISPR-Cas9 battle between the Massachusetts Institute of Technology Broad Institute Inc. and the University of California and others. A quick glance at the litigation chart relating to synthetic biology patents reveals that much talked about the CRISPR-Cas9 patent battle does mark the realisation of the opportunities for synthetic biology innovators to commercialise their inventions in adjacent markets.

US patent US8697359B1 for "CRISPR-Cas systems and methods for altering expression of gene products" obtained by Massachusetts Institute of Technology Broad Institute Inc. was opposed by the University of California, Berkeley, and the University of Vienna with Emmanuelle Charpentier (CVC) on the ground that the patent (filed earlier) by CVC covers methods and compositions for use of CRISPR/Cas9 and chimeric Cas9 in all cell types including eukaryotic cells. Federal Circuit confirmed the PTAB's finding that the Broad Institute's claims were non-obvious regarding "the extent to which the art provided instructions for applying the CRISPRCas9 technology in a new environment".

The court upheld the Patent Trial and Appeal Board (PTAB) decision that Charpentier and Doudna's patent application of May 2012 demonstrated the use of this technology but did not go so far as to claim its use in eukaryotic cells (i.e. CRISPR/Cas-9 gene editing in human cells). Whereas the Broad Institute demonstrated the use of this technology specifically in eukaryotic cells in their December 2012 patent application. The Broad Institute's patent received its first patent on April 15, 2014, for a method of altering eukaryotic cells using technology.

It is interesting to know that both of the research groups have engaged in a continuous battle over many patents over the last 10 years. Both have appealed various patent decisions, with the Patent Trials and Appeals Board (PTAB) and the Federal Circuit continually ruling in favour of the Broad Institute. For instance, in 2017, in one appeal, the Federal Circuit confirmed the PTAB's finding that the Broad Institute's claims were non-obvious regarding *"the extent to which the art provided instructions for applying the CRISPRCas9 technology in a new environment".* In another decision on February 28, 2022, the Federal Court confirmed that the Broad Institute's team was the first to invent the technology for modifying genomes in human cells.

Under this ruling, Broad's thirteen patents and one application remain in force. At the same time, CVC's fourteen applications with claims directed to gene editing of eukaryotic systems were rejected for lack of priority. This decision favoured Broad as it was able to provide "sufficient evidence to show that its claims, which are all limited to CRISPR-Cas9 systems in a

eukaryotic environment, are not drawn to the same invention as [University of California's] claims, which are all directed to CRISPR-Cas9 systems not restricted to any environment."

Indian Patents on CRISPR/Cas9 and Chimeric Cas9

The ripple effect of synthetic biology patents was also felt in India, as many patent applications were filed in relation to CRISPR/Cas9 and chimeric Cas9 inventions. For instance, India Patent No. 397884 was granted for '*Methods and compositions for RNA directed target DNA modification and for RNA directed modulation of transcription*' to the Regents of the University of California, University of Vienna and Charpentier, Emmanuelle (Assignee: ERS Genomics Limited) on May 27, 2022. This patent covered methods and compositions for the use of CRISPR/Cas9 and chimeric Cas9 in all cell types, including eukaryotic cells. It is interesting to note The Broad Institute Inc. is also actively pursuing granting patents on this synthetic biology field in India.

For instance, Indian patent 403134 for *'Delivery use and therapeutic applications of the CRISPR CAS systems and compositions for targeting disorders and diseases using viral components"* (granted on August 5, 2022), Indian patent 479497 for '*Novel CAS13B orthologues CRISPR enzymes and systems*' (granted on February 8,.2023), Indian patent 418414 for 'A composition for treating an ocular genetic disease comprising a CRISPR-Cas system' (granted on January 18, 2024) and Indian patent 508237 for 'A composition for treating an ocular genetic disease comprising a CRISPR-Cas system' (granted February 7, 2024) were obtained by The Broad Institute Inc. and others. It may be noted that all these PCT applications were examined under the scanner of Sections 3(J) and 3(i) of the Indian Patent Act, 1970, as amended in 2005.

List of a few more presentative patents granted in India for synthetic biology-related inventions

Patent No/Granted on	**Tille**	**Assignee/applicant**
IN259538 15.03.2014	A portable microorganism assay device	BATEC Bio Analytical Ltd
IN209305 12.09.2007	Method of producing lgG	GE HEALTHCARE BIO-SCIENCES AB
IN394534 08.04.2022	Production of succinic acid from organic waste or, biogas or methane using recombinant methanotrophic bacteria	String Bio Private Limited
397713 26.05.2022	Whole cell methanotroph based biostimulant compositions, methods and applications thereof	String Bio Private Limited
IN 394533 15.04.2022	Recombinant microorganisms for converting organic waste to lactic acid and method of use thereof	String Bio Private Limited

Patentability Issues under Section 3(j) and 3(i)

Since patent laws in India do not consider method treatment as patentable subject matter, objections to such claims are invariably raised by the examiners in India. Section 3(i) reads as follows

> *"(i) any process for the **medicinal,** surgical, curative, prophylactic **diagnostic, therapeutic or other treatment of human beings** or any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products. "*

Similarly, the patentability of '*plants, animals and part thereof'* is questionable under Section 3(j), and patenting of cells, genes, DNA, etc., is also subjected to closer scrutiny by the Indian patent office. Section 3(j) reads as follows.

> *(j) **plants and animals in whole or any part thereof** other than microorganisms but including seeds, varieties and species and essentially biological processes for production or propagation of plants and animals;*

If we see the prosecution history of granting the Indian patent IN397884, we will find that this patent was allowed only when the applicant amended the claims (1-5,11, & 38) to recite the invitro and remove the negative limitations. To meet the objections under Section 3(j) claims, the applicant deleted claims 42-43 (for cells). Claims (61) for method of treatment were also deleted as they fall under Section (i) exceptions. The final granted patent had method claims (1-34). composition claims (35-38), claim 39 for nucleic acid, and claims 40-41 were for Kit. Claims 44 to 59 are for composition, nucleic acids, kit and cells, claims 60-61 are for composition for use in treatment, while claims 62 to 68 are for engineered and/or non-naturally occurring DNA-targeting RNA. This scrutiny clearly reveals that the patentability of synthetic biology-related inventions is subjected to an exception to patentability as stated under Sections 3(j) and 3(i). There was no difficulty in obtaining a patent for claims for method, composition, nucleic acid and kits.

Again, if we look at the prosecution history of IN 479497, the following objections were raised regarding 150 claims (original):

- *Claim(s) (40-42, 42-43, 36-48) are statutorily non-patentable under the provision of clause (3(j), 3(d)) of Section 3 for the following reasons:*

  > *" 1. Claims 42-43, 40-42 are directed to plants and animals in whole or any part thereof other than microorganisms. Hence not patentable u/s 3(j) of the Patents Act, 1970 (as amended).*
  >
  > *2. Claims 36-48 are directed to mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant, is not patentable u/s 3(d) of the Patents Act, 1970 (as amended)."*

When the applicant amended claims 1-7, as stated below, the patent was granted.

Claim 1-3 were also amended to recite 'non-naturally occurring or engineered composition' and claim '4-5 were for delivery system configured to deliver a Cas13b effector protein and one or more nucleic acid components of a non-naturally occurring or engineered composition. The applicant deleted all the other claims which fall under Section 3(i) and Section 3 (j).

Claims as granted reads as

"*We Claim:*

1. A non-naturally occurring or engineered composition comprising

i) a Cas13b effector protein from Bacteroidetes bacterium GWA2_31_9 of Table 1A, optionally comprising one or more mutations and having a sequence identity of at least 90% with a Cas13b effector protein from Bacteroidetes bacterium GWA2_31_9 of Table 1A, and

ii) a crRNA, wherein the crRNA comprises

a) a guide sequence that is capable of hybridising to a target RNA sequence, and

b) a direct repeat sequence, capable of forming a CRISPR complex comprising the Cas13b effector protein complexed with the guide sequence capable of hybridising to the target RNA sequence, optionally which comprises an accessory protein that enhances Cas13b effector protein activity, preferably wherein the accessory protein that enhances Cas13b effector protein activity is a csx28 protein, or which comprises a accessory protein that represses Cas13b effector protein activity, preferably wherein the accessory protein that represses Cas13b effector protein activity is a csx27 protein, wherein the target RNA is a pathogen derived target, preferably viral RNA.

2. The non-naturally occurring or engineered composition as claimed in claim 1, wherein the Cas13b effector protein is associated with one or more functional domains, optionally wherein the functional domain cleaves the target RNA sequence or wherein the functional domain modifies translation of the target RNA sequence.

3. The composition as claimed in claim 1, wherein the Cas13b effector protein is associated with one or more functional domains; and the effector protein contains one or more mutations within an HEPN domain, whereby the complex can deliver an epigenetic modifier or a translational activation or repression signal.

~~*4. A Cas13b vector system for providing the composition as claimed in claim 1, which comprises one or more vectors comprising:*~~

~~*a first regulatory element operably linked to a nucleotide sequence encoding a Cas13b effector protein from Bacteroidetes bacterium GWA2_31_9 of Table 1A, optionally comprising one or more mutations and having a sequence identity of at least 90% with a Cas13b effector protein from Bacteroidetes bacterium GWA2_31_9 of Table 1A and capable of forming a CRISPR complex comprising the Cas13b effector protein complexed with a guide sequence capable of hybridising to a target RNA sequence, and a second regulatory element operably linked to a nucleotide sequence encoding the crRNA, optionally wherein the nucleotide sequence encoding the*~~

~~*Cas13b effector protein is codon optimised for expression in a eukaryotic cell, wherein the target RNA is a pathogen derived target, preferably viral RNA.*~~

~~*5. The vector system as claimed in claim 4, which further comprises: a regulatory element operably linked to a nucleotide sequence of an accessory protein.*~~

~~*6. The vector system as claimed in claim 4, wherein the one or more vectors comprise viral vectors, optionally wherein the one or more vectors comprise one or more retroviral, lentiviral, adenoviral, adeno-associated or herpes simplex viral vectors.*~~

4. A delivery system configured to deliver a Cas13b effector protein and one or more nucleic acid components of a non-naturally occurring or engineered composition as referred to in claim 1, comprising i) Cas13b effector protein from Bacteroidetes bacterium GWA2_31_9 of Table 1A, optionally comprising one or more mutations and having a sequence identity of at least 90% with a Cas13b effector protein from Bacteroidetes bacterium GWA2_31_9 of Table 1A, and ii) a crRNA,

wherein the crRNA comprises

a) a guide sequence that is capable of hybridising to a target RNA sequence in a cell, and

b) a direct repeat sequence, wherein the Cas13b effector protein is capable of forming a complex with the crRNA, wherein the guide sequence is capable of directing sequence-specific binding to the target RNA sequence, capable of forming a CRISPR complex comprising the Cas13b effector protein complexed with the guide sequence ***in in vitro cell*** ~~*capable of hybridising to the target RNA sequence,*~~ *wherein the target RNA is a pathogen derived target, preferably viral RNA.*

5. The delivery system as claimed in claim 47, which comprises one or more vectors or one or more polynucleotide molecules, the one or more vectors or polynucleotide molecules comprising one or more polynucleotide molecules encoding the Cas13b effector protein and one or more nucleic acid components of the non-naturally occurring or engineered composition.

~~***9***~~*.6. The delivery system as claimed in claim 47, which comprises a delivery vehicle comprising liposome(s), particle(s),* ~~***exosome(s),***~~ *microvesicle(s), a gene-gun or one or more viral vector(s).*

~~*10. An in vitro or ex vivo method of modifying expression of a target gene of nterest, the method comprising contacting a target RNA with one or more non- naturally occurring or engineered compositions as referred to in claim 1, comprising i) a Cas13b effector protein from Bacteroidetes bacterium GWA2_31_9 of Table 1A, optionally comprising one or more mutations and having a sequence identity of at least 90% with a Cas13b effector protein from Bacteroidetes bacterium GWA2_31_9*~~

~~*of Table 1A, and* ***ii) a crRNA,***~~

~~*wherein the crRNA comprises a) a guide sequence that is capable of hybridising to a target RNA sequence in a cell, and b) a direct repeat sequence, wherein the Cas13b effector protein is capable of forming a complex with the crRNA, wherein the guide*~~

~~*sequence is capable of directing sequence specific binding to the target RNA sequence in a cell, whereby there is formed a CRISPR complex comprising the Cas13b effector protein complexed with the guide sequence that is capable of hybridising to the target RNA sequence, whereby expression of the target locus of interest is modified, optionally which further comprises contacting the target RNA with a accessory protein that enhances Cas13b effector protein activity, preferably wherein the accessory protein that enhances Cas13b effector protein activity is a csx28 protein, or which further comprises contacting the target RNA with a accessory protein that represses Cas13b effector protein activity, preferably wherein the accessory protein that represses Cas13b effector protein activity is a csx27 protein, wherein said method is not a method for modifying the germline genetic identity of human beings, wherein the target RNA is a pathogen derived target, preferably viral RNA.*~~

~~*11. An isolated eukaryotic cell comprising a Cas13b effector protein from Bacteroidetes bacterium GWA2_31_9 of Table 1A, optionally comprising one or more mutations and having a sequence identity of at least 90% with a Cas13b effector protein from Bacteroidetes bacterium GWA2_31_9 of Table 1A, and capable of forming a CRISPR complex comprising the Cas13b effector protein complexed with a guide sequence capable of hybridising to a target RNA sequence as referred to in claim 1, or a nucleic acid encoding said Cas13b effector protein.*~~

7. A non-naturally occurring or engineered composition comprising

i) an mRNA encoding a Cas13b effector protein from Bacteroidetes bacterium GWA2_31_9 of Table 1A, and capable of forming a CRISPR complex comprising the Cas13b effector protein complexed with a guide sequence capable of hybridising to target RNA sequence, optionally comprising one or more mutations and having a sequence identity of at least 90% with a Cas13b effector protein from Bacteroidetes bacterium GWA2_31_9 of Table 1A, and

ii) a crRNA, wherein the crRNA comprises

a) a guide sequence that is capable of hybridising to a target RNA sequence, and b) a direct repeat sequence, wherein the target RNA is a pathogen derived target, preferably viral RNA."

This analysis also reveals that claims for only non-naturally occurring or engineered composition were allowed, and where claim 5 for A delivery system configured to deliver a Cas13b effector protein and one or more nucleic acid components of a non-naturally occurring or engineered composition was made same was amended to include 'a CRISPR complex comprising the Cas13b effector protein complexed with the guide sequence in **in vitro cell** ' and claim 6 was amended to delete 'exosome(s)",

"The delivery system as claimed in claim 47, which comprises a delivery vehicle comprising liposome(s), particle(s), ~~***exosome(s),***~~ *microvesicle(s), a gene-gun or one or more viral vector(s)."*

This clearly indicates that the Indian Patent Office's position is consistent for synthetic biology inventions as only claims for method, non-naturally compositions, and systems where the procedures are performed in in vitro cells are allowed. The patent claim for

genes, exomes, vectors, DNA fragments, cell lines and similar products are objected to and not permitted under Section 3(j).

Approval from NBA Necessary Where Cell Used Obtained from India

In the Indian context, the applicant is also required to disclose the source of origin of the biological material used in the invention. Section 6, read with Section 19 of the Biological Diversity Act, 2002, mandates that if a biological material procured from India is used in an application for a patent, permission and other information for making an application for the patent should be obtained from the National Biodiversity Authority. If the biological material procured from India is used in an application for a patent per, a mission to use the biological material from the National Biodiversity Authority is essential for the grant of a patent. For instance, in the 1910/CHE/2014 case, String Bio Private Limited received a grant (IN 394533) only after the required permission from the NBA and the agreement had been uploaded by the applicant.

Looking Forward

The potential of synthetic biology products as an alternative process of synthesis of natural or known products is immense, and many products are commercially successful. However, patenting biosynthetic inventions in India and elsewhere is not without its challenges. A brief analysis of selected patent applications in India showed that the Indian patent office position is clear for synthetic biology inventions as only claims for method, non-naturally compositions, and systems where the procedures are performed in vitro cells are allowed. The claim for genes, exomes, vectors, DNA fragments, cell lines and similar products are objected to and not permitted under Section 3(j). Additionally, under Section 3(i) claims for medical method of treatment may not be allowed.

However, claims for in vitro treatment of cells outside the body are permitted. Unlike the US, we have not seen any patent dispute relating to synthetic biotech patents in India. We look for more synthetic biology patent applications in India in rapidly emerging fields like pharmaceuticals, carbon capture, biofuels, flavours, fragrances, vaccines, syn-enzymes etc. Synthetic biology has revolutionised the process of drug discovery and development, bringing about significant advancements in healthcare. By leveraging the power of genetic engineering and DNA manipulation techniques, scientists can now design and create novel molecules with specific therapeutic properties.

It is not surprising to know that synthetic biotech has the potential to touch upon virtually every aspect of our lives. Like any other inventions, biosynthetic processes and products also require patent protection to stay competitive in this emerging market space. The patent applicant in this field may face a few of the hurdles discussed above, and they must navigate with the assistance of an expert to overcome these obstacles to build and consolidate a strong patent portfolio in the new era of biosynthesis innovation in India as well.