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Gene Therapy: The Current Codon Status

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Scenes of scientists exploiting the genetic material from an amber trapped mosquito which had apparently sucked the blood of a ferocious dinosaur to finally create a monster had captured the imagination of audience world wide. Genetic engineering has since then gradually emerged from the shadows of fantastic and novelistic ideas depicted in the wildly successful *Jurassic Park* to the box-office flop *Alien: Resurrection*. The image of creating a seemingly flawless piece of genetic thread finely entwined following years of research spent in solving the genetic jigsaw has captured the imagination of the world. The implications are huge and often exaggerated but never thought to be beyond the reach of the ever-so impatient man. The impact of genetic engineering on the society is often debated but a final decision will unfortunately have to wait.

Generally branded as monolithic, by the common man, genetic engineering is just a catchall phrase that depicts the tools used to efficiently and appropriately manipulate an organism's hereditary material. The plethora of information released into the public domain from the human Genome project proved to be the lifeline for a therapy now touted to be the 'medicine of the future'. What would appear to be a seemingly innocuous alteration in the nucleotide of a person's genome (genetic make-up) has now been proved to be the underlying cause of thousands of genetic disorders. Most diseases can now be explained as manifestations of gene disorders. Herein lies the huge implications of a therapy that aims to set right the disorder/s caused due to genetic alterations.

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Gene therapy involves the insertion of correct genes into an individual's cell to treat a disease. This could be a hereditary disorder in which a functional gene/allele replaces a dysfunctional one leading to corrections in a person's genetic make-up. Extensive studies worldwide have led to the identification of exact genetic alterations in the genome sequence that contributes to an array of diseases like Glaucoma, rheumatoid arthritis and schizophrenia. This therapy assumes huge significance given the prevalence of monogenic disorders like hemophilia, sickle cell anemia, muscular dystrophy and cystic fibrosis. Gene therapy could either refer to Germ line gene therapy or Somatic gene therapy. Germ line therapy refers to the introduction of functional genes into sperms or eggs hence; the change due to therapy is heritable. However, given the ethical and technical hurdles in this form of gene therapy applications in human beings has been prohibited. On the other hand Somatic gene therapy involves the transfer of therapeutic genes into somatic cells of a patient and will not be heritable.

Worldwide experts are of the opinion that gene therapy's current status is similar to that of monoclonal antibodies 15 years ago and that the net market worth is estimated to be over $ 20 billion. The world's first commercialized gene therapy drug is Gendicine made by China's Shenzhen SiBiono Gene Tech. Gendicine is now being reviewed by the Drugs Controller General of India (DCGI) which would then decide on allowing clinical trials in India. Known as Recombinant Ad-p53 Anti-cancer injection this drug is used to treat head and neck squamous cell carcinoma. Data from Indian clinical trials could help significantly in obtaining regulatory approvals in other developing and developed nations. The only other commercialized gene therapy product is Rexin G from Epeius Biotechnologies in California, currently approved for use only in the Philippines for treatment of metastatic breast cancer, pancreatic cancer, Osteosarcoma and soft tissue sarcoma. HGF DNA plasmid, a drug from Sosei and Daiichi Sankyo investigated for treatment of peripheral vascular disease was filed for approval in Japan. Success in discrete medical trials has also been witnessed in treating conditions like myelination disorder X-linked ALD (adenoleukodystrophy), ADA-SCID (adenosine deaminase deficiency-related Severe Combined Immunodeficiency) and Leber congenital amaurosis).

Although gene therapy failed to live up to its promise in early 1990s, it was generally accepted that the discouraging outcome was not due to an adequate insights into the genomics involved rather due to the lack of an optimal gene delivery system. Success in gene therapy has now been acknowledged as an outcome determined by optimal gene delivery systems. Retroviral vectors have long been used in gene therapy clinical trials. However, this system suffers from serious setbacks such as weak titers and inefficient encapsidation of the therapeutic gene, thus decreasing their therapeutic value. Unlike retroviruses, lentivectors do not necessarily require cell division for proviral integration. Lentivectors couple the advantage of facilitating a highly efficient and stable transgene expression to its ability to transduce a variety of cell types that are not amenable to transduction by other vectors. Although several clinical trials are currently on in several parts of the world, gene therapy still appears to be in the infancy stage in India. Studies are however being conducted for oral cancer at the Tata Memorial Hospital, Mumbai. Narayana Nethralaya, a speciality eye hospital in Bangalore is in the process of using gene therapy to treat inherited retinal disorders in children. Although a recent Financial Express report indicates that Intas Pharma will launch Gendicine in India, there appear to be no reports of any company in India that has taken the initiative to invest in and explore the potential of this remarkable technology. It is of paramount importance that gene therapy strategies and regulatory approvals be put in place urgently. This will facilitate appropriate therapeutic interventions that could potentially prove to be a boon to the millions that suffer from genetic disorders.