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DNA, Discoveries and Mysteriesâ€“An Exhibit of Scientific Achievement

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—Dr Gita Sharma, Head-biotech, Xcleris labs

It seems like only yesterday that Watson and Crick published their epoch-making paper on DNA, (Nature (1953) volume 171, page number: 4356), and today no publication, scientific or otherwise is in print without some reference to genes or genomics.

Five decades are truly a short span of time on the scale of knowledge accumulation. This area of science has progressed so rapidly in such strides, the genome of the discoverer himself was the first to be sequenced completely at a cost of a million dollars. After Watson's whole genome sequencing in 2007, the latest news is that the whole genome read can be available at $5,000, the cost could plummet even lower, if it could be done easily and made necessary to have it on your personal ID along with your blood group.

An organism's complete set of DNA is called its genome. Virtually every single cell in the human body contains a complete copy of approximately three billion DNA base pairs that make up the human genome. A gene is the unit of DNA that carries instructions for making a specific protein or set of proteins. If a cell's DNA is mutated, an abnormal protein may be produced, which can disrupt the body's usual processes and lead to a disease, such as cancer.

Darwin's theory of evolution was all about natural selection and survival of the fittest; evolution has occurred throughmutation and selection over millions of years. After 200 years of propagation of the theory of evolution, we are now in a position to accelerate and direct evolution in the way we want, through biotechnology, which impacts all aspects of life, agriculture, food, health, energy, environment and all else.

The fundamental requirements are:

- Know what we have: The genome DNA, the information molecule or whole genome sequence.
- To annotate and derive meaning, information from all this data--Bioinformatics.
- Its function and variation—Functional genomics and single nucleotide polymorphisms (SNIPs).
- Tools to identify and manipulate: Biomarkers and recombinant DNA technology.

These needs are thus dependent on multiple expertises, necessitate teamwork and with technologies evolving so fastmaking them obsolete in such quick succession that to outsource has become a need of the day. Only contract research organizations (CROs) whose very business model is to offer services can ramp up the latest technology with the speed required and there are a few like our own organization in this space to enable progress of science for human betterment.

DNA sequencing

Sequencing simply means determining the exact order of the bases in a strand of DNA. Because bases exist as pairs, and the identity of one of the bases in the pair determines the other member of the pair thus excludes the need to sequence the other strand. Common type of sequencing used today is called the chain termination method. A DNA strand is treated with a variety of nucleotides, a set of enzymes, and a specific primer to generate a collection of smaller DNA fragments. Radiolabelled ATP was used earlier, but today four fluorescent tags, each specific to a given base, are part of the mixture.

Each of the fragments differ in length by one base and is marked as a radiolabel signal on X-ray film and today, using fluorescent tag the last base of the fragment is determined by the mass of the nucleotide. The fragments are then separated according to size and passed by a detector that reads the fluorescent tag. Earlier, the ladder of sequence was manually read. Today, computer reconstructs the entire sequence of the long DNA strand by identifying the base at each position from the size of each fragment and the particular fluorescent signal at its end in platforms such as Applied Biosystems, Inc.(ABI) and by nucleic acid by mass spectrometry in Sequenom platform. Each platform having its own advantage depending on what is the required output. This is indeed a quantum leap from the earlier days. Sanger's chain-termination itself was a leap from cumbersome Maxam–Gilbert technique. Today, with automation in place it seems a cake walk in comparison.

Although biologist have studied the genomes of numerous organisms for decades the last ten years have brought an enormous increase in the pace of genomics research with next generation sequencers from ABI and Illumina, which increase the data acquisition capacities and reduce the time and cost.

This has had a profound impact on the scope of interrogation and finding solutions. At present, this technology only can determine the order of up to 800 base pairs of DNA at a time. So, to assemble the sequence of all the bases in a large piece of DNA, such as a gene, researchers need to read the sequence of overlapping segments. This allows the longer sequence to be assembled from shorter pieces, somewhat like putting together a linear jigsaw puzzle. In this process, each base has to be read not just once, but at least several times in the overlapping segments to ensure accuracy.

Researchers can use DNA sequencing to search for genetic variations and/or mutations, DNA methylation, copy number variation, genotyping, haplotyping, allelotyping, prenatal diagnosis, viral load, quantitative gene expression, allele specific expression, alternative splicing, gene copy number, SNP/mutation detection, pathogen typing, quantitative methylation etc. using systems such as Sequenom or Illumina. The applications of sequence information could be in human health, food safety, agriculture, industry and last but not the least in biodefence. An achievement indeed!