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Tuberculosis - Present Scenario and Strategies

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Dr. Peyush Goyal is presently working as Senior Scientific Officer and Scientist - C in Department of Biotechnology (Govt. of India), New Delhi. During his research tenure the work was carried out on virus profiles for accomplishment of teaching & research particularly in transmission studies of hepatitis viruses, their profiles, histopathological, immunological and epidemiological markers, and detection of viruses in serum samples infected with liver diseases both in human and animals infected with HBV and DHBV. Dr. Goyal is having association with few scientific bodies and published around 15 research papers & article. He has contributed to organising DBT exhibitions, training in different Universities/Organisations for strengthening the activities in Biotechnology & Bioinformatics. The work credited with the honour of awards & Certificates both in organising DBT activities, writing skills and participation through various program conducted inside and outside DBT.

Bioinformatics using computational biology engross the development of techniques by using applied mathematics, physics, informatics, biochemistry, statistics and molecular biology etc helps for exploration of proteins for various humans and animal diseases and to cure for various ailments. Bioinformatics through *in silico* approaches are mainly used to identify the possible drug targets through which structural and functional predictions can be made and to constrict the molecules for drug leverage for various pharmaceutical applications. In many of the past and current researches "genomics" has manifestation in solving various problems including 'tuberculosis' - a well known infectious disease, now emerging as a multi drug resistant forms. Studies revealed that the inflammation caused in different immunological response in humans, is not so far predicted through animal studies, hence *in silico* approach will be useful for treatment and cure regimen and also to find out possible drugs through drug discovery process. It is important to know that the key elements, which can evolve various biochemical questions for its lesion and pathogenecity through which protection can be ascertain can be addressed by establishment of possible drugs/molecules for which genomic/proteomic comparison can be assessed between the two strains and can be addressed using bioinformatics approaches in protein sequences.

In India the first TB patient was found in 1906 in Tiluania, near Ajmer city of Rajasthan, followed by first TB dispensary established in Bombay in 1917. By 1925 chest radiology started diagnosing deep-seated area for TB consolidation and later in 1945 the capability of x-ray was too enhanced to MMR (mass miniature radiography), but the real genuine success in immunizing/cure against TB was occurred with the development of attenuated bovine strain of tuberculosis discovered by Albert Calmette and Camille Guerin in 1906 known as BCG (bacillus of Calmette and Guerin), which was first used on humans in France on July 18, 1921. In India a BCG vaccine production centre was set up with the support of WHO and UNICEF in Guindy, Madras during 1948 and later in 1951, a mass BCG campaign was started in India to control TB for public health and prevention of disease even to the remotest parts of the country. In 1961, a district Tuberculosis Program was too started in Anantpur district of Andhra Pradesh with a first model district TB Centre (DTC) with an aim at integration of TB control schemes mitigating the community problems. During 1959, National Tuberculosis Institute (NTI) was established in Bangalore for practicing research, teaching and training to medical and paramedical workers etc. In 1962, Indian Government launched the National TB Control Program (NTCP) and a collaborative effort is in progress between NTCP and National Rural Health Mission (NRHM) to achieve the goals and to improve primary health care leading to wide spread irrational use of first line and second line anti TB drugs.



In India many parts of the country people are in under impression that TB is a disease of poor people mostly of those living in slums, but it affects the affluent persons by asymptomatic carriers. India's DOTS (directly observed treatment –short course) program was initiated in terms of patient care, initiation on treatment and to cover the larger population in the country with a challenge to control TB in India and to strengthen poor primary health care and unregulated private health care. It has been observed that there is a need to develop first line and second line anti- TB drugs, which is a challenge in present scenario for TB Control program. World Health Organisation (WHO) with its “STOP TB” strategise has a vision to eliminate TB as a public health problem by the end of 2050. During 2007-08, WHO under its Global Response Plan has strategise to implement and to save the lives of 134,000 multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) patient over the next two years and under its revised Global Plan to Stop TB 2006-2015 WHO has strategise the full implementation to access of MDR-TB & XDR-TB patients for their diagnosis, treatment and saving lives of 1.2 million people worldwide. India has proposed to set up a digital database for its 1.4 million people being treated for tuberculosis under the National TB Control program under its Revised National TB Control Program (RNTCP) (HT., March, 24, 2013) to ensure better treatment and compliances which enable to real time reporting and case management studies especially in inaccessible areas and places with high mortality and morbidity. This will ensure the better compliance with drug regimen and reduce transmission and prevalence and to support prevention with the emergence and spread of multidrug – resistant TB (MDR-TB). It is to ensure to provide 200 districts with DNA based MDR and XDR testing equipments in 2013 - 14.

In India, TB has been mentioned in the Vedas and the old Ayurvedic scriptures and fight against TB can be broadly classified in to three periods like early period, before the discovery of x-ray and chemotherapy; post-independence period during which nationwide TB control program was initiated and implemented and the current period during which new researches and bioinformatics applications can be used as an arena to combat with this dreaded disease using drug discovery process which will help not only to cut the cost of its manufacturing but will also help in saving time through bio-computing facilities established at various places in India under Bioinformatics Program. It is well known that the principal cause of human tuberculosis is *Mycobacterium tuberculosis*, discovered in 1882 by Robert Koch who later awarded with Nobel Prize in 1905. Tuberculosis is one of the most ancient diseases worldwide and considered among the top 10 killer infectious diseases, second only to HIV. The disease caused by *Mycobacterium Tuberculosis* is an air borne disease can infect large number of people in the community. Other members of the Mycobacterium tuberculosis are *M.bovis*, *M.microti*, and *M. africanum*. *M.bovis* has a wider host range is the main cause of tuberculosis in animal species. *M.microti* is not known to cause TB in Humans and *M. africanum* is very rare. Infection in humans through *M.bovis* is usually via milk, milk product or meat from infected animals even consumption of unpasteurized milk or dairy products made from raw milk can be a potential source of TB, as it has ample evidence that bovine TB (*Mycobacterium bovis*) gets transmitted to humans. In India there have been 66,000 cases of MDR TB and 22 of extreme drug resistant (XDR) have been reported. One in three people in the world is infected with dormant TB germs, and once it becomes active, as a result of anything it can reduce the Person's immunity such as HIV. MDR-TB takes longer to treat with second line drugs, which are more expensive and have more side effects.

Tuberculosis is remain a major public health threat declared as Global emergency by WHO in 1993 as multi drug resistance (MDR) and extensive drug resistance (XDR) are now a serious concern for its spread and control, hence there is a need to develop new methods to be explored for its control and diagnosis, cure and prevention. Malignant child hood tuberculosis particularly affecting pleural lymph nodes, bone and joints including meningitis are also now a serious concern. Even today, two deaths occur every three minutes from TB with lack of proper care and treatment. *M. tuberculosis* strains that are resistant to two most potent anti – TB drugs viz., Rifampicin and Isoniazid are termed as multidrug resistant TB (MDR-TB) strains. However, Extensively drug resistant TB (XDR-TB) is a form of TB caused by bacteria that are resistant to Rifampicin and Isoniazid as well as to any fluoroquinolone and any of the second-line anti –TB injectable drugs like amikacin, kanamycin or capreomycin. These forms of TB do not respond to the standard six month treatment with first- line anti TB drugs



and can take up to two years or more to treat; hence both MDR-TB and XDR-TB are emerging threats to the success of anti-TB program. Drug resistance may be broadly classified as primary and acquired. WHO and IUATDL have now replaced the term 'primary resistance' with the term 'drug resistance' with the term "drug resistance among new cases", and acquired resistance, with the term "drug resistance among previously treated cases".

Modern biotechnology started in Research laboratories, came to an attention that there is need of debate that what new knowledge and techniques that helps with the growing experience in the country. Till 1986, there is no scientific basis for specific legislation that helps to regulate the use of recombinant DNA organisms. Scientifically it was favoured to develop new vaccines, foods, seeds and industrial enzymes, but in 1990 resulted in contained use of genetically modified organisms and debate continued thereon. India being a part of Asian Biotechnology Scenario has grown up many folds both in Pharmaceutical and Agriculture field with diversified applications and expansion through industry and academia interactions, hence, in 1992, Asian Biotechnology and Development Review (BDR) has developed for cross-sectoral approach and formed a Research and Information System (RIS), an autonomous research institution with a mandate to function as an advisory body to the GOI including sub-regional cooperation with various Govt. bodies, Research Institutions, Academicians, Policy makers etc in India and abroad.

Pharmaceutical industries have been a major player since the early 19th century developing several life saving drugs such as antibiotics. Till middle of the 20th Century there are no drugs or treatment with combination of drugs was available effective against TB. In past few years Pharmaceutical Industry has changed radically with the spectrum of disease on rise with the quality of human life. Now the use of *in silico* approach emerged as a viable alternative with the knowledge of specific chemical responses in the body or target organism tailoring treatment regimen. Unravelling the blue print of human life through outcome of Human Genome Project has given the birth of a whole new discipline called "Bioinformatics" which is now being a driving force in drug discovery and validating potential drug targets and in screening molecules before entering the drug development process. 3D structures of number of bio-molecules are deposited in public domain like protein data bank (PDB) which helps targeting to receptor proteins using *in silico* approach. Software packages capable of modelling large number of compounds predicting drug-target interaction through molecular simulation are now commonly used for docking studies in structure based drug design. It has always been a quest in medicinal and computational chemists to be able to gain insight in to protein structure from legend information alone and Pharmacophore modelling, 3D QSAR (quantitative structure activity relationship) are some method that allows scientific community to gain valuable information of how ligands bind in 3D space in the protein site and also helpful in understanding the lead optimization. As clinical research improves, now in the 21st century, the scientific community is trying to focus on the use of Phylodynamics to find out how pathogen genetic variation is altered by host immunity, transmission and epidemics. However, it is critical to understand the control methods for some of the important human and animal diseases. Many Pharmaceutical companies have established high through put screening to screen large compound libraries enabling genome-wide investigations for a wide range of applications in research fields. Bioinformatics in drug discovery research may not help to cut the cost of production to approximately 33% but also in time saving which can be minimized to 30% what we does usually through general wet lab experimentations.

As time progressing the field of Bioinformatics and Computational Science has important distinction now for the students having studied molecular biology, and biotechnology and moving towards computational biology which includes Bioinformatics as a core subject. Biology and Biotechnology is now become more progressive quantitative science as it was earlier in the past three centuries. Bioinformatics approaches now helps transforming experimental research to new innovations and discoveries available in a big data set by applying advanced analytical methods, tools and software. Through chemoinformatics approach (analysis of complex relations between the component inside a given biological system), one can study the genomic changes for identifying new therapeutics through the new software and tools and programmed designed in JAVA, Perl and Python are the current valuable advances for the study of drug discovery by QSAR and Protein-Protein interactions.

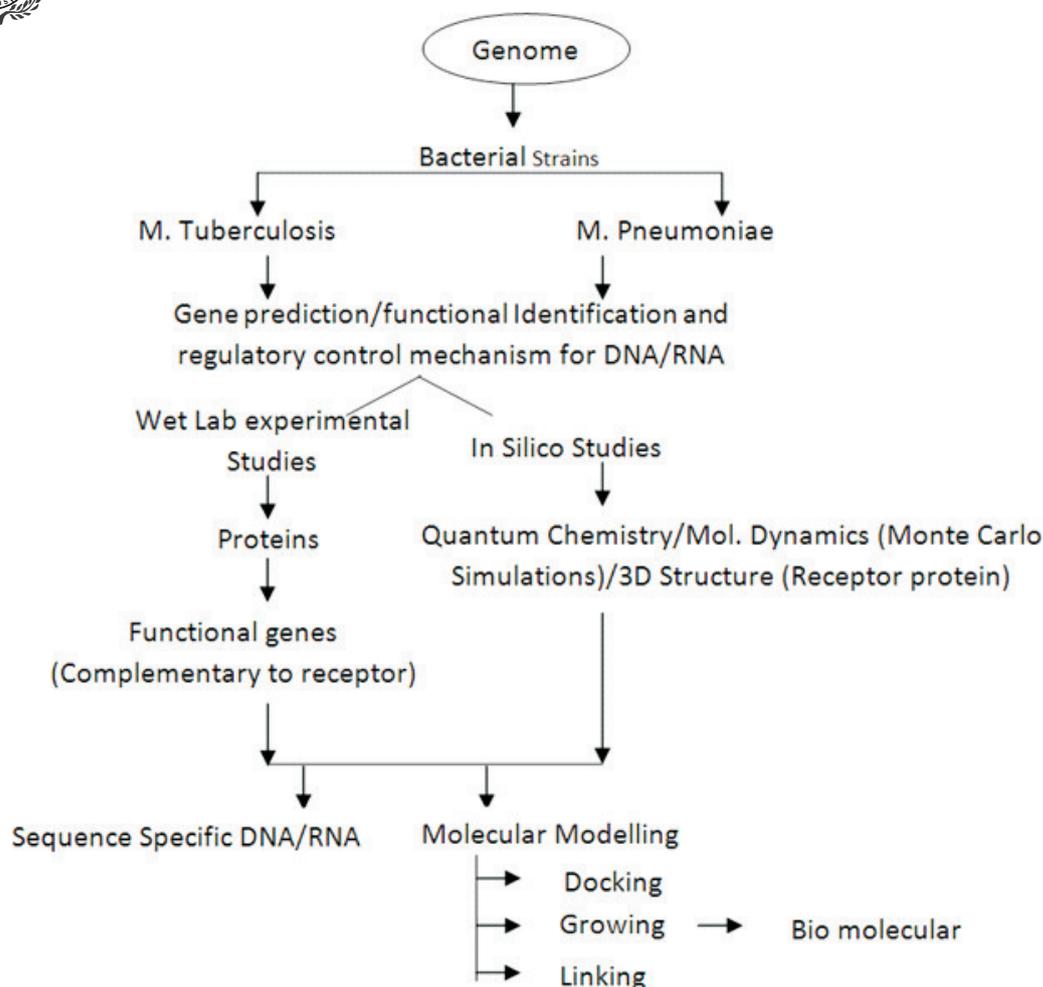


Fig: Diagram showing wet lab and *in silico* approaches for study of molecules

Whole genome sequencing technology has provided information for the identification of new therapeutic targets in pathogens and till December 2009, the complete genome sequence is known of about 1007 bacterial species roughly 56 eukaryote of which about half are fungi and genome sequence of 2274 viruses and numbers of Bioinformatics tools are also developed to analyse those genome (Kaminski, 2000; & Galperin and Koonin, 1999). There are many approaches to identify potential drug targets and comparative genomics provide a new approach to identify novel drug target among previously known targets.

According to Medilexicon's medical dictionary, tuberculosis is "A specific disease caused by infection with *Mycobacterium tuberculosis*, the tubercle bacillus, which can affect almost any tissue or organ of the body, the most common site of the disease being the lungs". Hence, much effort is needed with all advanced practices and techniques for useful product (s) to fight with the disease to save lives among the masses.

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