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MOLECULAR MEDICINE FOR DISEASE DIAGNOSIS; EMPHASIS ON TUBERCULOSIS**Dr.Dhammika Magana-Arachchi,**

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Molecular Medicine is a science that seeks to comprehend disease causes and mechanisms at the molecular level, and to apply this basic research to the prevention, diagnosis and treatment of diseases and disorders. Global travel, the threat of new pandemics, and the spread of re-emerging infectious diseases highlight the need for comprehensive pathogen detection. Identification of the infectious agents is critical to provide a precise diagnosis, properly manage patient care and reduce the risk of transmission within the community and health care settings. To meet these challenges, inventive technologies have to be developed that detect single pathogens, multiple syndromic related pathogens and genotypic drug resistance. However the translation of novel discoveries from basic research to clinical application is a long, often inefficient, and thus costly process.

Tuberculosis (TB) remains one of the major unresolved global health problems, causing high mortality and morbidity with eight million new TB cases and two to three million deaths annually. The emergence of drug resistant and multidrug-resistant (MDR) tuberculosis i.e., resistance to at least rifampin (RIF) and isoniazid (INH) makes the situation even worse. In the community, MDR TB originates from two possible sources, either from the spread of previously, resistant strains or by the selection of resistant bacteria due to suboptimal treatment.

One of the most important challenges in the control of TB is a rapid diagnosis of cases and the optimization of anti tuberculous treatment, mainly to prevent the development of resistance and the dissemination of resistant strains. XDR TB has emerged worldwide as threat to public health and TB control, raising concerns of a future epidemic of virtually untreatable TB. Therefore new anti TB drug regimens, better diagnostic tests, and international standards for SLD – susceptibility testing is needed for effective detection and treatment of drug resistant TB. Phenotypic drug susceptibility testing by conventional methods on solid media requires 10 to 30 days after the primary culture has been isolated. Despite the use of new liquid medium

cultures, the isolation of *Mycobacterium tuberculosis* still time consuming and leads to delays in obtaining susceptibility patterns.

Substantial progress has been made in the understanding of the molecular basis of *M. tuberculosis* drug resistance and understanding the genetic events that lead to drug resistance in clinical *M. tuberculosis* isolates is important for the development of genetic assays, elucidation of the mechanisms of action of antimicrobial agents, and the design of novel antibiotics that are active against drug-resistant strains. The knowledge of the genetic basis of resistance to RIF and INH has provided molecular tools to rapidly detect the principal mutations conferring resistance to INH and RIF. Analysis of ~ 500 RIF strains from global sources has found that 96% of RIF resistant clinical isolates of *M. tuberculosis* have mutations in the 81-bp core region of *rpo* gene, which encodes the B subunit of RNA polymerase. It is estimated that 90% of RIF resistant isolates are also resistant to INH, making RIF resistance a useful surrogate marker for MDR resistance. Investigators on several continents have reported that many (50-60%) INH resistant patient isolates have mutations, small deletions or insertions that are not represented among INH sensitive control strains. Mutations leading to INH resistance have been identified in different gene targets including *KatG*, *inhA* and other genes that remain to be established. Most studies have examined the mutations present in these genes by DNA sequencing. However these methods are labour intensive and require well grown cultures.

Molecular methods have been developed to detect resistance to INH and RIF because of their ability to provide results rapidly. Upon the elucidation of the genes involved in resistance to INH and RIF, several studies describing various PCR based molecular genetic techniques for the detection of resistance have been published.

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