Prof. Sarman Singh, Director, AIIMS, Bhopal

Statement of Research Achievements for which Sun Pharma Award is Claimed

Tuberculosis is the main killer infectious diseases in India. On the top of that multi-drug resistant (MDR) and extensively drug resistant (XDR) forms have emerged. Diagnosis of TB still remains a major challenge. Prof. Singh has done outstanding work in the field of TB diagnostics.

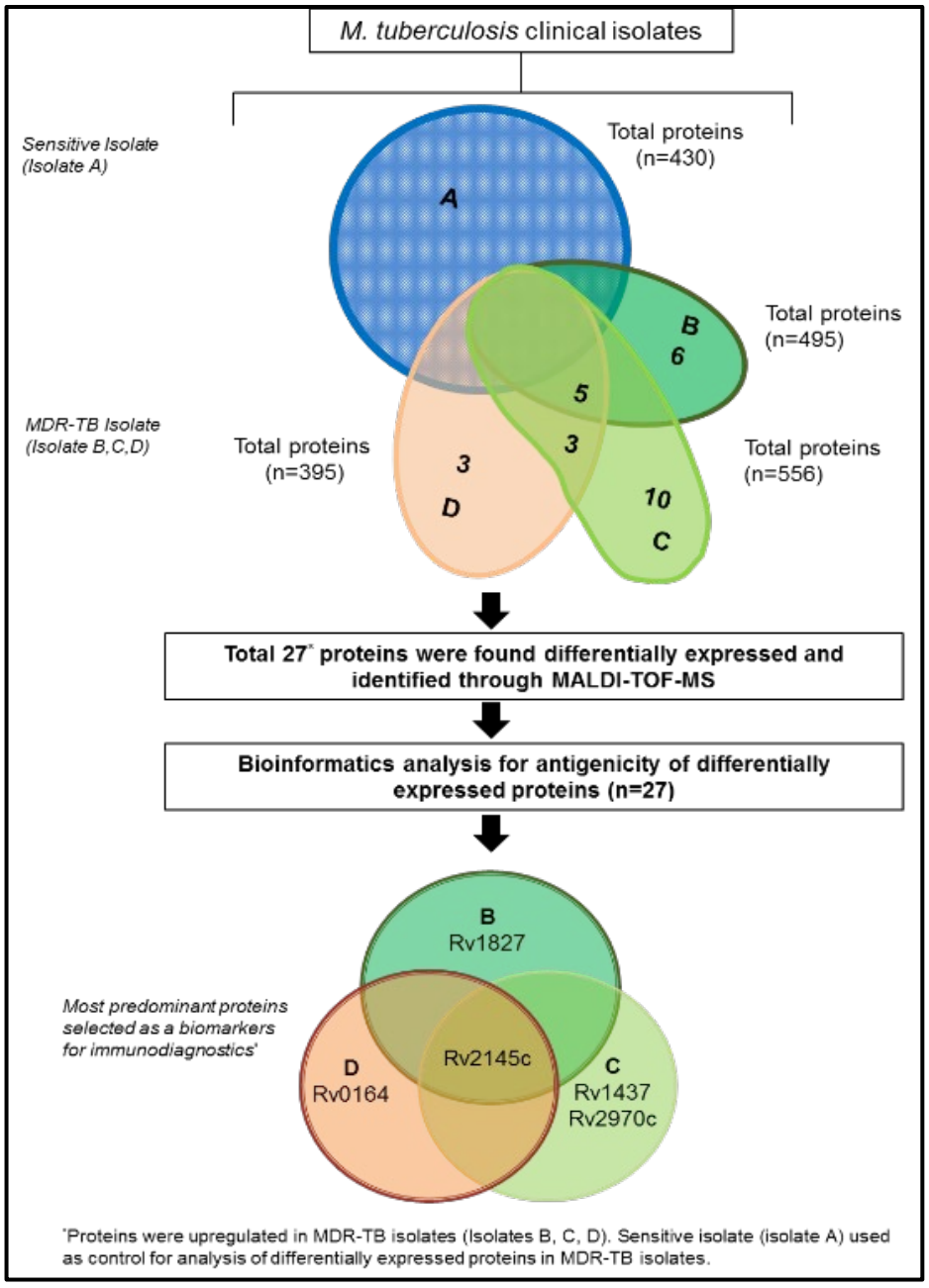
In the last 20 years several serological test kits were dumped in the Indian market for the diagnosis of PTB and EPTB. But these kits gave highly inaccurate results, leading to unnecessary treatment to hundreds of thousands of patients, and leaving several thousands of TB patients untreated, leading ban on these kits.

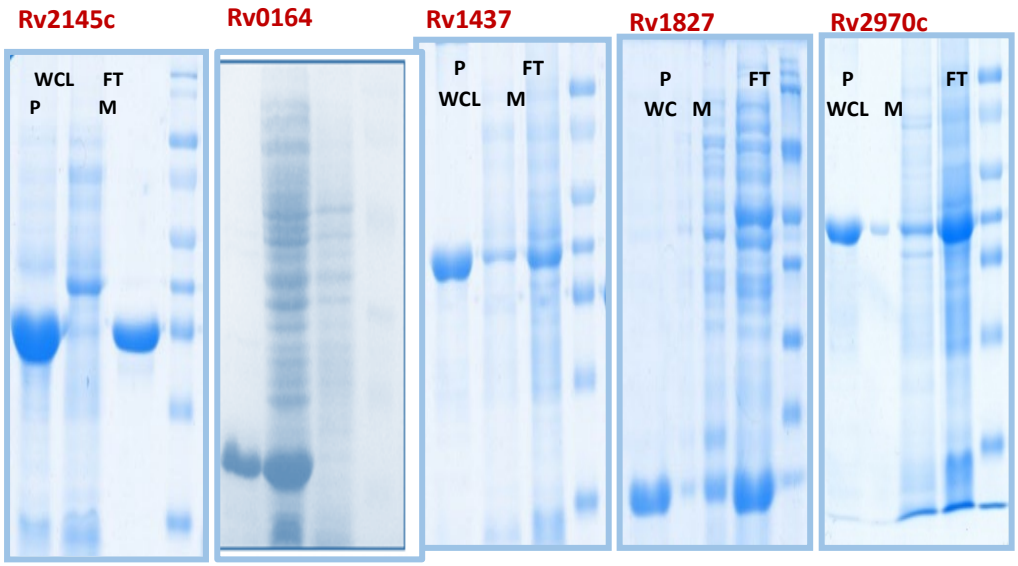
However, the ban on serology has created a complete gap in the TB diagnostic field. Dr. Singh worked untiringly to find out novel molecular tools and biomarkers for the diagnosis and differentiation of drug susceptible and drug resistant Mycobacterium tuberculosis. His laboratory made a revolutionary discovery in this field by screening hundreds of proteins of MTB, *his team identified 5 novel proteins/antigens which are over-expressed only during the in-vivo drug resistance developme*nt. The genes were cloned and proteins expressed, purified and used on various categories of patients showing the sensitivity and specificity of these proteins between 98.2% -100% and 89.1 - 98.2%, respectively (Singh et al, 2015, Singh et al, 2017). Using these novel proteins, development of a point-of-care (POC) rapid test is underway. *This innovation is expected to be a **game changer** in the area of TB diagnostics not only for India but globally. The Foundation for Newer Innovative Diagnostics (FIND) evaluated these antigens and has shown interest in this innovation. The prototype ICT based RDTs prepared in the laboratory (**images shown below**) have shown excellent results and technology is ready for transfer to a commercial partner for marketing this innovation.*

Dr. Singh has also done pioneering work in the field of non-tuberculous mycobacteria (NTM) often neglected by clinicians and medical microbiologists as contaminants. In AIDS era these NTM have gained much importance but the conventional methods of identification are neither reproducible nor very specific. *His team has developed novel multiplex-PCR (**images shown below**) for the diagnosis and differentiation of Mycobacterium tuberculosis, M. avium, M. kansasii and other NTM, directly from the clinical samples in a single tube (PCT/IN2004/000396).* These PCR primers and the process have been found highly sensitive and specific and are being routinely used at various laboratories throughout the country including AIIMS (Singh et al, 2006, Gopinath et al, 2009, Kumar et al 2014a). *This has made a paradigm shift in the understanding of NTM disease in India. Using the same gene targets, a new technology known as loop mediated isothermal amplification (LAMP) assay (**images shown below**) have also been developed by him.. The technology is being evaluated across the country through ICMR and DBT, Government of India.*

Currently molecular tools have become essential to understand the pathophysiology and drug targets. Dr. Singh has moved with the time. His laboratory is equipped with all modern tools including 6 laser flow cytometer and New Generation Sequencer (NGS), beside all routine diagnostic tools and services. *We have done WGS of more than 200 MTB clinical isolates and have submitted several Genome projects and several thousands of the gene sequences in the GenBank for the benefit of other researchers.*

Therefore, my contribution of research has been highly significant and ground breaking. I could translate my research into application for the patient care, justifying for this recognition.


M. tuberculosis clinical isolates
Sensitive Isolate (Isolate A)
Total proteins (n=430)
A
B
6
5
3
3
D
10
C
Total proteins (n=495)
MDR-TB Isolate (Isolate B,C,D)
Total proteins (n=395)
Total proteins (n=556)
Total 27* proteins were found differentially expressed and identified through MALDI-TOF-MS
Bioinformatics analysis for antigenicity of differentially expressed proteins (n=27)
Most predominant proteins selected as a biomarkers for immunodiagnostics*
B
Rv1827
D
Rv0164
Rv2145c
C
Rv1437
Rv2970c
*Proteins were upregulated in MDR-TB isolates (Isolates B, C, D). Sensitive isolate (isolate A) used as control for analysis of differentially expressed proteins in MDR-TB isolates.


Rv2145c
WCL
P
FT
M
Rv0164
Rv1437
P
WCL
FT
M
Rv1827
P
WC
M
FT
Rv2970c
P
WCL
M
FT

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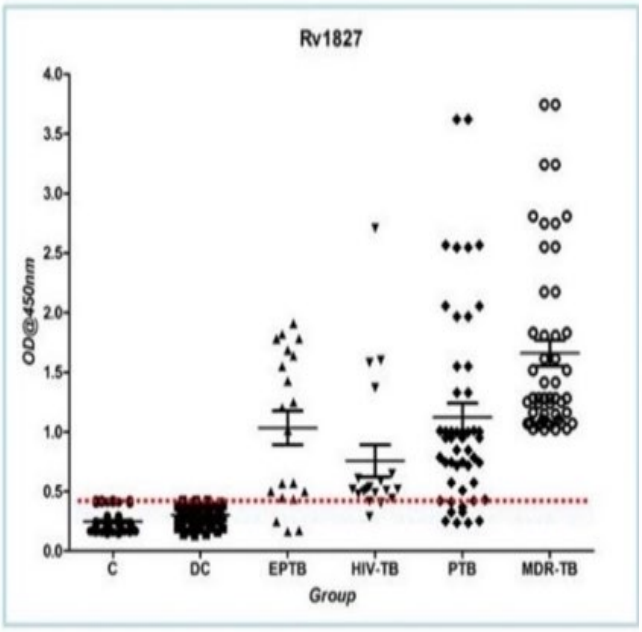
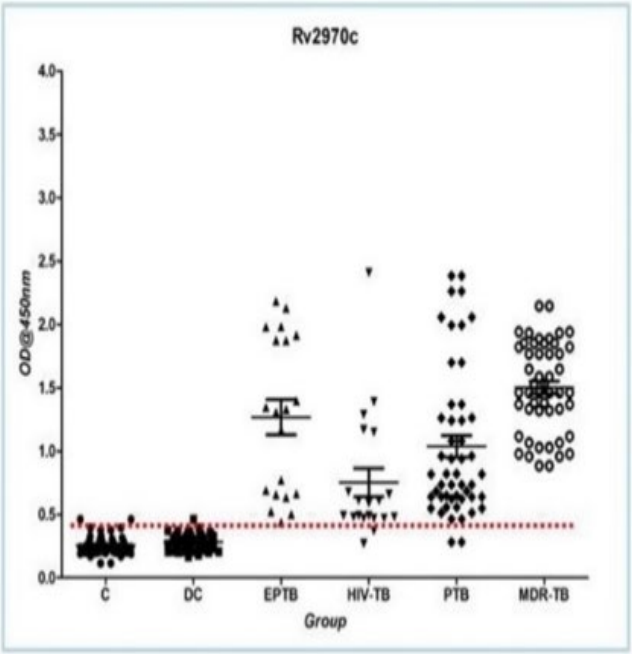
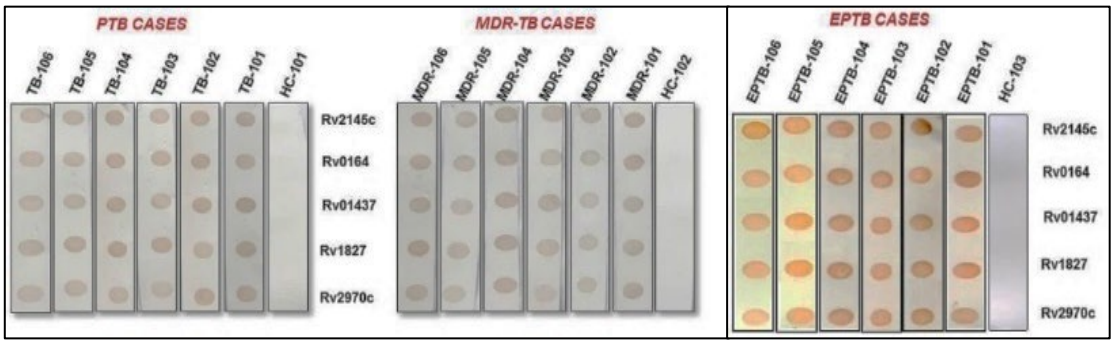
Evaluation of 5 Novel protein biomarkers for the rapid diagnosis of pulmonary and extra-pulmonary tuberculosis: preliminary results

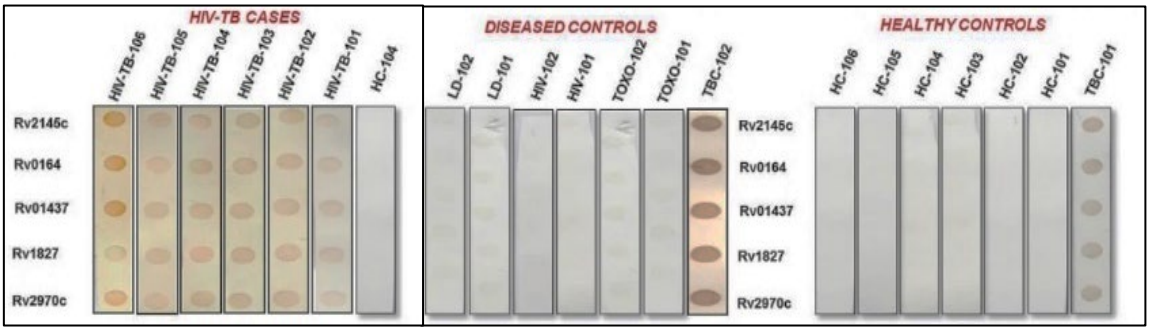
Amit Singh[1,*], Anil Kumar Gupta[1,*], Krishnamoorthy Gopinath[1,†], Pawan Sharma[2,‡] & Sarman Singh[1]

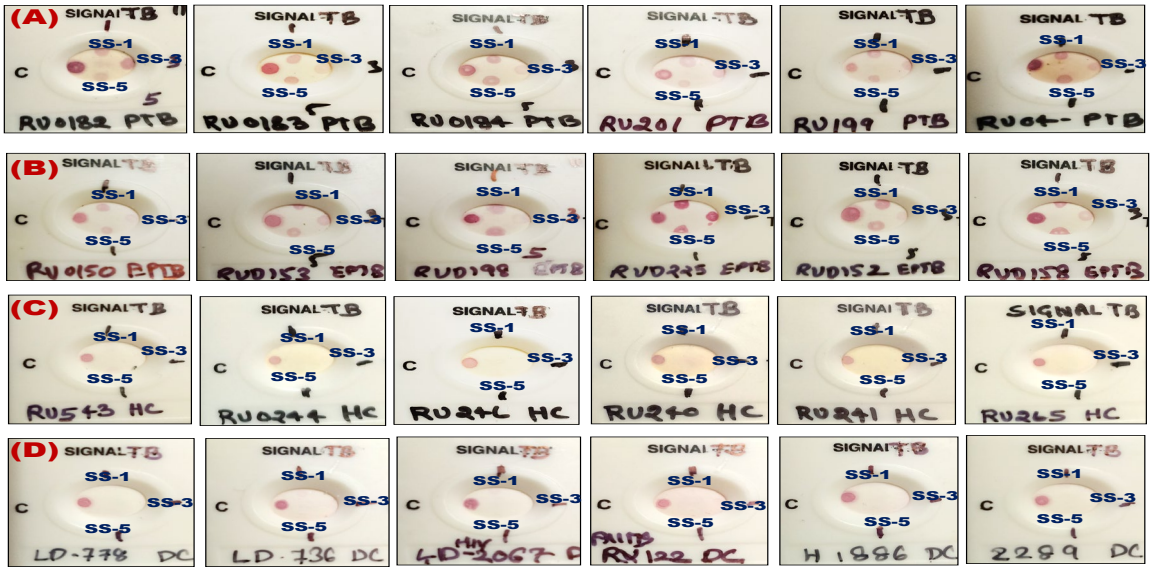
Improved methods are required for the early and accurate diagnosis of tuberculosis, especially in the patients with smear-negative disease. Several biomarkers have been tried but most have shown poor sensitivity or specificity. In present study we aimed to evaluate the diagnostic utility of five novel antigens identified earlier by us. This is an initial study conducted on 250 subjects. The five recombinant antigens, named as rSS1 (Rv2145c), rSS2 (Rv0164), rSS3 (Rv1437), rSS4 (Rv1827) and rSS5 (Rv2970c), were expressed in pQE-30 expression vector, purified and their sero-diagnostic efficacy was evaluated in an unblinded manner using dot-blot and ELISA methods. The sensitivity and specificity of these



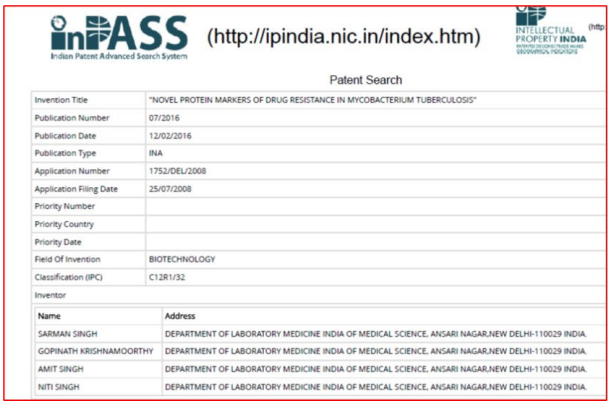








Laboratory Scale preparation of ICT Based RDTs for the TB diagnosis



inPASS (http://ipindia.nic.in/index.htm)

Indian Patent Advanced Search System

Patent Search

Invention Title	"NOVEL PROTEIN MARKERS OF DRUG RESISTANCE IN MYCOBACTERIUM TUBERCULOSIS"
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Priority Number	
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Priority Date	
Field Of Invention	BIOTECHNOLOGY
Classification (IPC)	C12R1/32
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(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2007/0072188 A1**

Singh et al. (43) **Pub. Date: Mar. 29, 2007**

(54) **METHODS FOR DETECTION OF MYCOBACTERIUM TUBERCULOSIS**

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(51) **Int. Cl.**
C12Q 1/68 (2006.01)
C07H 21/04 (2006.01)

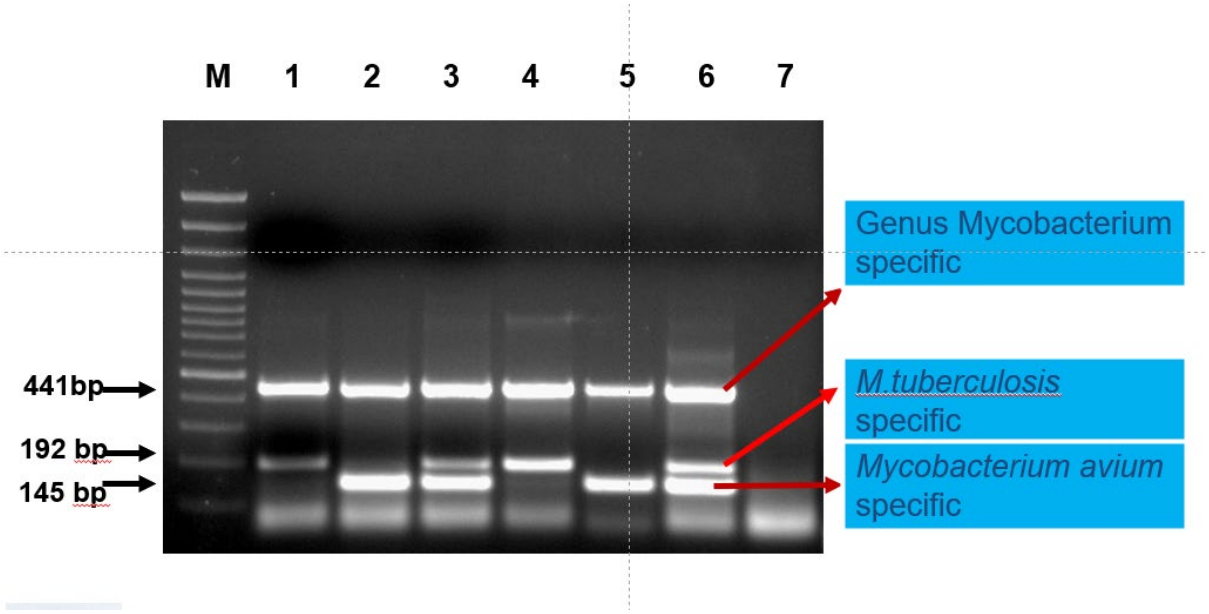
(52) **U.S. Cl.** **435/6**; 536/24.1

(57) **ABSTRACT**

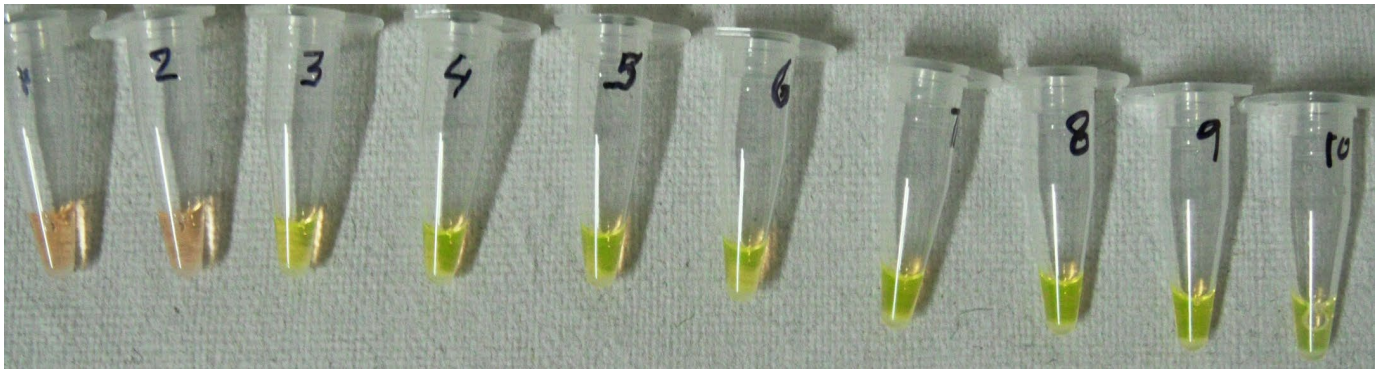
The present invention provides an oligonucleotide primer pair having SEQ ID NO: 3 and SEQ ID NO: 4 for amplification of Early Secretory Antigenic Target (esat)-6-gene of *Mycobacterium* species. The invention also provides a method for detecting *M. tuberculosis* in a sample based on the amplification of esat-6 gene, comprising isolating DNA template from the sample, amplifying with the above oligonucleotide primer pair and subjecting the amplified DNA product to separation and staining to detect the presence of amplified DNA product for identifying Mycobacterium tuberculosis in the sample. The invention further provides a diagnostic kit for detection of *Mycobacterium tuberculosis*. The invention also provides a method of detecting *Mycobacterium tuberculosis* from a sample by amplifying the 16s rRNA region from the isolated DNA template by conventional methods to detect *Mycobacterium* species and further amplifying the positive sample contains Mycobacterium species using primers positive for ESAT-6 region detection of *Mycobacterium tuberculosis*.

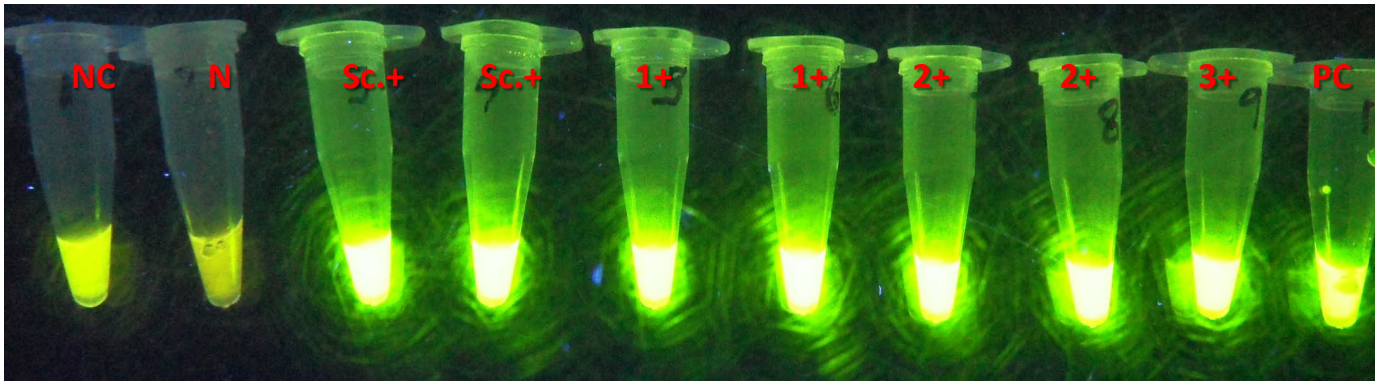
Indian Patent Application for Biomarkers and International Patent for Multiplex PCR

Novel set of PCR primers developed for detecting and differentiating the MTB from *M. avium*, M. *Kansasii* and other NTM in a single reaction tube.



LAMP (Loop Mediated Isothermal Amplification) Test Developed using the same primers and new probes . This test does not require any detection device to report the test results.





Tuberculosis Patents by Inventor Dr. Sarman Singh

Sarman Singh has filed for patents to protect the following inventions. This listing includes patent applications that are pending as well as patents that have already been granted by the United States Patent and Trademark Office (USPTO).

- **Constructing a DNA chimera for vaccine development against leishmaniasis and tuberculosis**

  Patent number: 8299232

  Abstract: A novel recombinant chimera of DNA construct having esat-6 region of Mycobacterium tuberculosis and kinesin region of Leishmania donovani cloned together on two sides of self cleaving peptide in a DNA vaccine vector pVAX-1 wherein the chimeric construct is operatively linked to a transcriptional promoter thus capable of self replication and expression within the mammalian cell, and the process of preparation thereof comprising: analysis of the predicted protein sequence of kinesin motor domain and esat-6 domain using Promiscuous MHC Class-1 Binding Peptide Prediction Servers; amplification of gene coding for kinesin motor domain and esat-6 domain; cloning of kinesin esat-6 gene region in pGEM-T™ vector for sequence analysis; generation of chimeric construct by directional cloning in pVAX-1 vector.

  Type: Grant

  Filed: February 10, 2009

  Date of Patent: October 30, 2012

  Assignees: Department of Biotechnology, All India Institute of Medical Science

  Inventors: Sarman Singh, Ayan Dey

- **Constructing a DNA Chimera for Vaccine Development Against Leishmaniasis and Tuberculosis**

  Publication number: 20110150932
  Abstract: A novel recombinant chimera of DNA construct having esat-6 region of Mycobacterium tuberculosis and kinesin region of Leishmania donovani cloned together on two sides of self cleaving peptide in a DNA vaccine vector pVAX-1 wherein the chimeric construct is operatively linked to a transcriptional promoter thus capable of self replication and expression within the mammalian cell, and the process of preparation thereof comprising: analysis of the predicted protein sequence of kinesin motor domain and esat-6 domain using Promiscuous MHC Class-1 Binding Peptide Prediction Servers; amplification of gene coding for kinesin motor domain and esat-6 domain; cloning of kinesin esat-6 gene region in pGEM-T™ vector for sequence analysis; generation of chimeric construct by directional cloning in pVAX-1 vector.
  Type: Application
  Filed: February 10, 2009
  Publication date: June 23, 2011
  Applicants: DEPARTMENT OF BIOTECHNOLOGY, ALL INDIA INSTITUTE OF MEDICAL SCIENCE
  Inventors: Sarman Singh, Ayan Dey

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