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Novel Cure for TB

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Multi drug resistant tuberculosis (MDR-TB) is a major public health problem that threatens progress made in TB care and control, worldwide. WHO estimates that around 0.5 mn cases of MDR-TB are reported each year, of which nearly 10 percent die every year. MDR-TB is difficult to diagnose and treat, leading to increased transmission and mortality.

By 2015, it is estimated that $2 billion will be needed for the diagnosis and treatment of MDR-TB. Many cases of resistant tuberculosis go undiagnosed, this increases the threat of large scale dissemination of the bacteria in the population.

Many research experts across the globe have begun their hunt for newer drugs with the bacteria exhibiting increased resistance to existing antibiotics. Indian Institute of Science's (IISC) latest discovery could break new grounds in the treatment of the disease and provide relief to numerous patients worldwide. The nine-membered research team comprised of PhD students and professors, was led by Prof. V Nagaraja of the Department of Cell Biology and Microbiology.

Speaking exclusively to Bio spectrum, he explains the novel cure in sight for TB and how MDR-TB has gripped the world with fear.

1. In your opinion, how did the multi drug resistant strain of TB evolve and spread in the population?
Tuberculosis affects nearly one third of the world's population and is the number one killer disease in the world. Currently, the treatment for TB involves a combination therapy where patients are treated with four front line drugs. However, many patients do not complete their drug regime. This results in the remaining population of the bacteria developing drug resistance, which then spreads in the population making it tough to eradicate the disease. MDR-Tb is difficult to diagnose and many cases go undetected. Close contact with such patients also spreads the bacteria. Poor patient management by healthcare practitioners is also responsible for increasing numbers of these bugs in the population.

2. Please tell us about your novel compound developed for Tuberculosis, in detail?

With the bacteria developing resistance to existing drugs, understanding the biology of the pathogen is very important and our work is aimed in that direction. In our approach, we discovered a vulnerable 'hotspot'- certain histone like nucleoid association proteins, (HU) which are very important in the life cycle of the bacterium. The HU proteins are global regulators of gene expression. Blocking these proteins from binding to the DNA altered the expression. To identify the small blocking molecules that can bind to the histone protein, we first cloned the HU-encoding gene. The protein that got expressed in large quantities was then purified. The physics department in IISc under Prof. Ramakumar derived the 3D structure of the protein using X-ray crystallography. The next step involved the identification of the core region in the DNA that interacted with the histone proteins. The bound histone proteins made the DNA more compact resulting in deregulation, affecting the expression of many genes and killed the bacteria. This molecule can be further studied and developed into therapeutics that can cure the disease.

3. What is the mode of action of the 'molecule'?
The molecule targets a pathway in the cell cycle of the bacteria. The chemical compound is bound to proteins in the organism affecting the normal replication of DNA. This caused several genes to be turned off, hindering the normal life processes of the bacteria.

4. Can this molecule treat MDR-Tb as well?
These molecules have been tested only in drug-sensitive TB. But in principle, drug-resistant TB bacteria should be equally vulnerable. For example in organisms like E. coli, there are 12 genes encoding for HU proteins that play a key role in DNA compaction, and there are many genes that can act as a backup in case one gene is compromised. So HU protein is not essential for cell survival in the case of E. coli. However in the case of MDR-Tb bacteria only five histone-like proteins have been identified and there seems to be no additional gene that is similar to that of HU protein. Hence, if the HU protein is knocked off, the bacteria dies.

5. How is this discovery unique?
With this discovery, IISc is first in the world to identify histone proteins as potential targets to kill TB bacterium. Current available drugs focus on different pathways like cell wall inhibition, replication of the bacteria etc. The discovery is also unique as the molecule can kill many other bacteria, which have similar vulnerable targets. The compound can then be developed into newer therapeutics that can combat not only TB but also many other diseases. This research uses major disciplines of science like NMR, Microbiology, Bio Physics, Chemistry, and Molecular Biology together to identify this 'killer molecule.'

6. How effectively can the molecule be converted into therapeutics?
This discovery is only lab scale and is not a magic bullet to get rid of Tb right away. Lot of research needs to be done before converting this molecule into therapeutics. Better compounds that are smaller and act more efficiently need to be identified. IISc is looking for some other research collaborators to partner with and who will accept this tough challenge.