National Institute of Technology Rourkela

Departmental Seminar

Seminar Title	: Is the Aspartate pathway Achilles heal?: Mtb as a case study
Speaker	: Dr. Neeraj Kumar Mishra, Gitam University
Supervisor	: 2787
Venue	: Civil Department Seminar Room
Date and Time	: 31 Jul 2025 (16:00 hrs)
Abstract	: Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), remains one of the most persistent and deadly infectious diseases globally. A major challenge in treating TB is the bacterium's ability to survive in a dormant or persistent state inside the human body, where conventional antibiotics often fail. This study focuses on a critical metabolic pathway in Mtb — the aspartate pathway — which is responsible for producing essential amino acids like methionine, threonine, lysine, and isoleucine, as well as key molecules for cell wall and protein synthesis. Using genetic, biochemical, and structural biology approaches, researchers investigated two key enzymes in this pathway: ThrA (homoserine dehydrogenase) and MetX (homoserine transacetylase). They found that deleting these enzymes in Mtb leads to rapid bacterial death, both in lab cultures and in infected mice. This confirms that the aspartate pathway is essential for Mtb survival, especially during chronic infection. Further analysis revealed that blocking this pathway causes a metabolic imbalance, particularly an overproduction of lysine, which becomes toxic to the bacteria. Mtb tries to manage this stress by exporting lysine and breaking it down through a unique degradation pathway. These responses act like a "relief valve" to prevent metabolic collapse. In parallel, structural studies of MetX revealed how it works at the molecular level. The enzyme follows a ping-pong mechanism, where it first binds acetyl-CoA, forms an intermediate, and then transfers the acetyl group to homoserine. Key amino acids in the enzyme's active site were identified, and their roles confirmed through mutational studies. The enzyme also shows substrate and product inhibition, suggesting a built-in feedback regulation system. Importantly, since the aspartate pathway is absent in humans, targeting these enzymes offers a promising strategy for developing new TB drugs that are both effective and selective. The findings provide a strong foundation for future drug design efforts aimed at eradicating persistent TB infections.