Multi-omics, AI and CRISPR join forces to expose new vulnerabilities in Mtb

Oren Tzfadia

Tuberculosis still kills more people than any other bacterial disease, yet most datasets on *Mycobacterium* tuberculosis (Mtb) sit in separate silos. We are knitting them together—genomes, RNA profiles, protein structures and immune data—into an expanding knowledge graph that anyone can query in plain language. More than 32 000 clinical genomes already anchor the resource, and automated text-mining adds fresh studies daily. AI models trained on these layers now rank every Mtb gene by how crucial it is for survival and by how rarely its residues change across lineages. The first insight is a set of "never-mutate" stretches in the ESX-1 secretion system—promising footholds for drugs or vaccines. A second is a global risk map for current subunit vaccines, showing where variation in South and Southeast Asia could erode protection. Multi-omics integration also sheds light on drug resistance. By combining whole-genome and RNA-seq snapshots of bedaquiline-susceptible and -resistant isolates, we uncovered a tell-tale signature: permanently active drug-efflux pumps backed by rewired energy and stress pathways. These fingerprints could power rapid diagnostics and suggest add-on therapies that switch the pumps off. CRISPR editing brings predictions back to the bench. We have already created 25 precise mutants, testing how knocking out top-ranked genes affects growth, secretion and infection. Each experiment feeds new facts into the graph, tightening the loop between data, AI reasoning and wet-lab proof. The same pipeline can be lifted to other pathogens, promising a steady flow of actionable leads for prevention, diagnosis and treatment.

Oren Tzfadia is a computational biologist whose career is driven by the fundamental challenge of linking genes to their functions, addressing gaps in biological knowledge through the development of computational algorithms for big data. He has designed tools for constructing and analysing regulatory networks within specific biological pathways, with the overarching aim of strengthening the integration of computational biology and data science into clinical research, particularly in the context of *Mycobacterium* tuberculosis (MTB) drug resistance.

Since transitioning to clinical sciences in September 2019, Dr Tzfadia has broadened his research interests to include multi-omics, integrating information from orthogonal technologies (such as RNA/DNA next-generation sequencing, proteomics and structural biology) and different molecular layers (including metabolites, proteins and genes). He has also developed expertise in artificial intelligence, notably the application of large language models (LLMs) for the integration and analysis of complex biological datasets, supporting hypothesis generation and accelerating research workflows.

Throughout his career, he has created several user-friendly computational tools designed to unlock biological discoveries from omics datasets.