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Structure of mycobacterial ATP synthase with the TB drug bedaquiline

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Tuberculosis (TB), the world's leading cause of death by infectious disease, is increasingly resistant to current first line antibiotics. The bacterium Mycobacterium tuberculosis that causes TB can survive low-energy conditions, which allows infections to remain dormant and decreases their susceptibility to many antibiotics. Bedaquiline was developed in 2005 from a lead compound identified in a phenotypic screen against M. smegmatis. It can sterilize even latent infections and has become a cornerstone of treatment for multidrug-resistant and extensively drug-resistant TB. Bedaquiline targets the mycobacterial ATP synthase, an essential enzyme in the obligate aerobic Mycobacterium genus, but how it binds the intact complex is unknown. We determined structures of M. smegmatis ATP synthase with and without bedaquiline. The drug-free structure suggests how hook-like extensions from the alpha subunits prevent the enzyme from running in reverse, inhibiting ATP hydrolysis and preserving energy in hypoxic conditions. Bedaquiline binding induces large conformational changes, creating tight binding pockets at the interface of subunits a and c that explain the drug's potency as an antibiotic for TB.

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