New Study of FDTS Enzyme Pathway Identifies New Target for Antibiotics

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Despite the advances of modern medicine, certain pathogens, including tuberculosis, continue to avoid the effects of antibiotics.

The work of Amnon Kohen, University of Iowa professor of chemistry, uncovers what gives these pathogens the ability to resist antibiotics and cause disease.

Kohen's research group delves into the details of the reaction path taken by biomolecules called enzymes, which accelerate crucial chemical transformations in cells.

"Enzymes are the micro-entities in every organism that are responsible for all the metabolic pathways and chemical processes that happen in all organisms," Kohen said.

Knowledge of enzyme mechanisms can allow for design of better drugs and therapeutic compounds to inhibit enzymes whose actions are undesirable or associated with disease.

Of particular interest to Kohen and his student Kalani Karunarante, UI graduate student in chemistry, is the mechanism of flavin-dependent thymidylate synthase (FDTS), a recently discovered enzyme that is essential for the biosynthesis of DNA in pathogens.

"FDTS is present in a subset of pathogens that cause dangerous diseases, and a drug that blocks FDTS action is likely to kill the pathogens without side effects for human cells," Karunarante said.

The FDTS enzyme is used by certain pathogens to bypass antibiotics. Thus, better understanding of the enzyme reaction mechanism can provide new insights for drug discovery.

"Once we understand how the enzyme [FDTS] works, then we can think about synthesizing small molecules that would mimic certain steps in a fashion that would stop the enzyme," Kohen said.

The mechanism of the FDTS enzyme was originally unknown.

"Other groups have reported that current drugs and antibiotics do not inhibit this enzyme," Kohen said.

Kohen and his group used a variety of standard biochemical techniques to successfully obtain a basic understanding of how the enzyme works. Essentially, they were able to observe and determine the fates of certain atoms, enabling them to map the mechanism of the FDTS enzyme. Their work was recently published in the scientific journal *Molecules*.

“The good news is that this mechanism is completely new and different than the mechanisms used for DNA biosynthesis in other humans or humans,” Kohen said. “This means that if we can stop this enzyme with a small molecule that targets its unique mechanism, then there is a good chance that such a therapeutic will not be toxic.”

Thanks in part to Kohen’s work, FDTS is now recognized as a new target for antibiotics that will have love toxicity and bypass the resistance that tuberculosis and other pathogens have developed against current pathways.

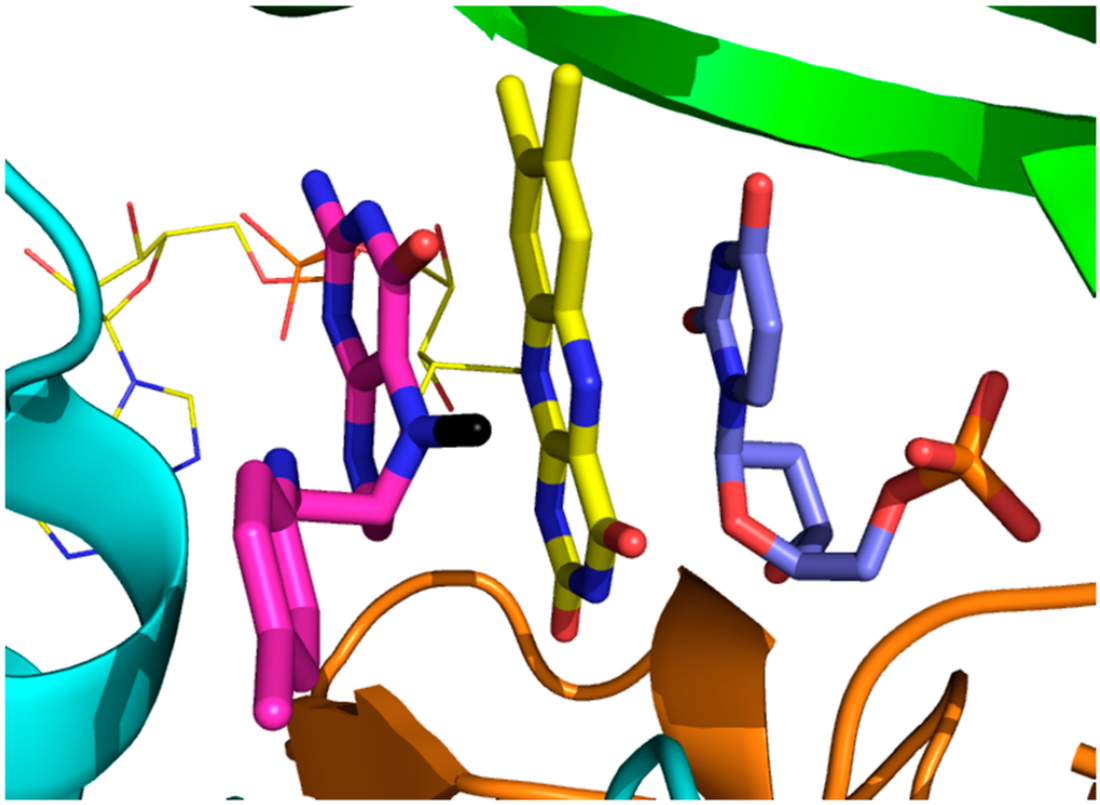
Both academia and industry have the capacity to screen or look for families of compounds that can mimic specific steps of the enzyme’s mechanism and serve as a therapeutic.

“There are at least six different steps in this mechanism and each step can be targeted for small molecules that will specifically bind to the enzyme and stop it,” Kohen said.

According to Svetlana Kholodar, UI research scientist in Kohen’s lab, some of the lab’s current studies are aimed at searching for these enzyme inhibitors as potential novel therapeutics.

“After developing analogs of intermediates of the enzyme’s reaction, we can then test their potency as inhibitors specific for the enzyme of interest,” Kholodar said. “In the long-term we can test certain molecules as potential treatments at the cellular level.”

Kohen and his lab’s continued work will reveal any likely reaction intermediates and thereby provide insights into drug development against FDTS and other enzymes used by pathogens.



Active site of the FDTS enzyme that Kohen and his group studied.