MedicalXpress

TB-drugome provides new targets for anti-tuberculosis drug discovery

November 8 2010

Researchers at the University of California, San Diego School of Medicine and the University of Leeds have linked hundreds of federally approved drugs to more than 1,000 proteins in Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), opening new avenues to repurpose these drugs to treat TB.

The study was published Nov. 4 in PLoS Computational Biology.

"Tuberculosis is currently one of the most widely spread infectious diseases, with an estimated one-third of the world's population infected and between one and two million people dying each year from the disease," said Philip Bourne, PhD, professor of pharmacology at UCSD's Skaggs School of Pharmacy and Pharmaceutical Sciences. "The continuing emergence of M. tuberculosis strains resistant to all existing, affordable drug treatments requires the development of novel, effective and inexpensive drugs.

The newly developed TB-drugome may help that effort, Bourne said, by identifying new M. tuberculosis protein targets that can be perturbed by a variety of existing drugs prescribed for other purposes.

Sarah Kinnings at the University of Leeds and a team of scientists at UC San Diego, led by Bourne (who is also associate director of the RCSB Protein Data Bank) and research scientist Lei Xie, PhD, used a novel computational strategy to investigate whether any existing drugs were able to bind to any of the approximately 40 percent of proteins in the M.

tuberculosis proteome with decipherable three-dimensional structures.

The researchers not only discovered that approximately one-third of the drugs examined may have the potential to be repurposed to treat tuberculosis, but also that many currently unexploited M. tuberculosis proteins could serve as novel anti-tubercular targets. This finding led the investigators to construct a complex network of drug-target interactions – a TB-drugome available to all scientists.

While this new computational, high-throughput process of drug discovery is promising, Xie cautioned that "only experimentation can validate the most promising drug-target combinations, and there will be many failures along the way."

Kinnings added that any drugs subsequently confirmed to bind to M. tuberculosis proteins may need to be modified to increase their ability to penetrate the bacterial cell membrane, reduce their required dosage, and improve other pharmacological properties. The screening of a large collection of analogs to known drugs will be the next step towards anti-tuberculosis drug discovery.

Provided by University of California - San Diego