Existing Parkinson's Disease Drug May Fight Drug-Resistant TB

July 06, 2009 |

Existing drugs used in the treatment of Parkinson's disease could be repositioned for use in the treatment of extreme drug-resistant tuberculosis, which kills about 2 million people each year, according to a study led by researchers at the University of California, San Diego. The rise of these strains of TB throughout the world, including industrialized countries, poses a great threat to human health.

Using a novel computational strategy and subsequent experimental validation, the researchers discovered that two commercially available drugs, currently prescribed for the treatment of Parkinson's disease – entacapone and tolcapone – have the potential to treat multi-drug resistant and extensively drug resistant tuberculosis. The study will be published in the July 3rd issue of the *Public Library of Science (PLoS) Computational Biology* journal.

"We have computational, and experimental data to support this repositioning," said Philip E. Bourne, PhD, professor of pharmacology at UCSD's Skaggs School of Pharmacy and Pharmaceutical Sciences and the principle investigator on the project. "What is exciting about this finding is that the TB target, enzyme InhA, is already well known. But existing drugs are highly toxic and of completely different chemical structure than entacapone and tolcapone. Here we have drugs that are known to be safe and with suitable binding properties which can be further optimized to treat a completely different condition."

Earlier work by Li Xie, Lei Xie, Bourne and colleagues (*PLoS Computional Biology*, May 15, 2009) demonstrated the value of a chemical-systems biology approach to identify off-targets of major pharmaceuticals on a proteome-wide scale. This paper further demonstrates the value of this approach for the possible repurposing of existing drugs that have already gone through the stringent FDA approval process.

The researchers' methodology extends an approach called SOSA (Selective Optimization of Side Activities), which involves the use of old drugs for new pharmacological targets. SOSA involves screening a limited number of structurally diverse drug molecules, then optimizing the hits so that they show a stronger affinity for a new target. Using this method, it is possible for scientists to

derive a whole panel of new, active molecules from a single marketed drug that has already been shown to be safe in humans – drastically reducing the time and cost of drug discovery.

The team extended the scope of this concept across gene families by extracting the binding site of commercially available drugs, then identifying off-targets with similar ligand binding sites using an accurate, functional site search algorithm. Subsequently, working with the TB bacterium itself, they found that the active component in Comtan tablets (entacapone) is effective at inhibiting *M.tuberculosis* in concentrations well below a level that is toxic to cells.

"Although we have demonstrated in the lab that Comtan is active against *M.tuberculosis,* additional studies are required in order to transform it into an anti-tubercular therapeutic," said Sarah L. Kinnings, a graduate student and lead author on the study. "Given the continuing emergence of *M.tuberculosis* strains that are resistant to all existing, affordable drug treatments, the development of novel, effective and inexpensive drugs is an urgent priority."

The researchers believe that the systematic use of small molecules to probe biological systems will provide valuable clues about the molecular basis of cellular functions, shifting the conventional one-target-one-drug discovery process to a new, multi-target-multi-drug approach.

Additional contributors include Nina Liu and Peter Tonge, Stony Brook University; Nancy Buchmeier, UC San Diego Department of Chemistry and Biochemistry; and, Lei Xie, San Diego Supercomputer Center at UC San Diego.

The research was funded by NIH grant GM 078596.

# # #

Media Contact: Debra Kain, 619-543-6163, ddkain@ucsd.edu

Related Specialties

Parkinson's Disease and Movement Disorders

Infectious Diseases

Share This Article

Related News

UC San Diego Health Begins Treating Multiple Myeloma with

CAR T-cell Therapy
6/3/2021

Social Justice as Part of the Remedy for What Ails Us
6/3/2021

Diet Plays Critical Role in NASH Progressing to Liver Cancer in Mouse Model
6/1/2021

Noted Researcher and Scientific Leader Jack E. Dixon Retires
5/27/2021

View All News >

Follow Us

Follow @ucsdhealth