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Unique collaboration holds potential for life-giving drugs for tuberculosis

Dr. David Russell, of Cornell's College of Veterinary Medicine, has established a paradigm-shifting collaborative relationship with Vertex Pharmaceuticals, of Cambridge, Mass., opening a door for novel tuberculosis (TB) drug discovery. Dr. Russell's long-term goal is to help the many millions around the world who suffer from tuberculosis, the disease caused by Mycobacterium tuberculosis, by finding new compounds that can reduce the treatment time and also be effective against drug resistant TB. The collaboration will provide access to the pharmaceutical company's drug library, comprised of hundreds of thousands of compounds. Many of these compounds have not yet been screened for anti-tuberculosis activity.

Historically, most pharmaceutical companies dedicate their compound libraries to in-house testing that focuses on target-based screening: working with molecules that have known applications for particular diseases. In target-based drug screening, tests are usually developed for a specific enzyme, receptor or other specific protein target in a pathway known to be necessary for pathogen survival. Libraries of compounds are analyzed, with the goal of finding inhibitors of an already known and characterized target.

Russell, professor of molecular microbiology, is looking for drugs with the capacity to shorten the treatment regimen by identifying compounds that can kill the TB bacterium quickly and also prevent it from persisting in the host by hiding out in a virtually dormant state. To accomplish this goal, he will use cell-based assays when screening the compounds in Vertex's library. Although less commonly employed than target-based screening, cell-based screening has an increasingly important role in research and drug discovery, because it interrogates the pathogen in its true host environment. Cell-based screening offers several advantages: A compound's usefulness is often best predicted by measuring the biological behavior inside living cells, where the molecular interactions can be evaluated within the context of the cellular environment. In addition, the potential toxicity and side effects are also more readily detected. Cell-based screening therefore offers an avenue to the discovery of truly novel drugs and targets.

"For decades, we have been remodeling known compounds," said Russell. "We have pretty much exhausted all of the logical solutions in the world of drug remodeling for tuberculosis. We need to find new options, which can only be done if we introduce new compounds and new assays into the equation. Vertex has been incredibly generous, extremely flexible, and has shown tremendous foresight, and we hope that their compound collection may yield a novel new approach to the

treatment of TB. They've thrown open the doors both for scientific discovery as well as the opportunity to eradicate a terrible disease."

According to the World Health Organization, a person contracts the tuberculosis bacterium every second, and fully one-third of the world's population is currently infected with this pathogen. Although drugs for tuberculosis have only been available for about 50 years, some strains of the bacterium have already adapted, making them resistant to all major anti-tuberculosis drugs.

"Drug-resistant TB is caused by failure of treatment, either when patients do not take all their medicines regularly for the required period because they start to feel better, or because doctors and health workers prescribe the wrong treatment regimens, or do not have access to sufficient supplies of the drug," said Russell.

Russell will use high-throughput, bacterial survival assays to run two types of cell-based screens in M. tuberculosis-infected host cells. The first will check for the survival of the tuberculosis bacterium inside macrophages (white blood cells within tissues that eat bacteria and where the tuberculosis bacteria can persist for decades) by reading a luminescence signal generated by bacteria expressing the luciferase enzyme from fireflies. If a compound introduced into the infected macrophage culture kills the tuberculosis bacterium, the signal will be reduced. The second type of screen focuses on pathways that are important for M. tuberculosis to survive within the macrophage, through exploitation of the genes known to be expressed inside the host cell.

"When the tuberculosis bacterium enters a macrophage, it turns on certain genes," Russell said. "For example, we've focused on one gene that is expressed in response to an acidic environment. When the pH level in the vacuole containing the bacterium drops, the gene is expressed. We have linked this regulatory pathway to the expression of the Green Fluorescent Protein (GFP) so that bacteria going into macrophages turn green. Compounds that kill the bacterium will prevent this increase in fluorescent signal coming from intracellular bacteria."

The beauty of the cell-based screen is that it targets the entire unit of infection, where the bacterium persists inside its host cell, rather than focusing on the function of a single enzyme or protein target. Russell believes that this greatly increases the chance of success and the discovery of truly novel drugs against this infectious agent.

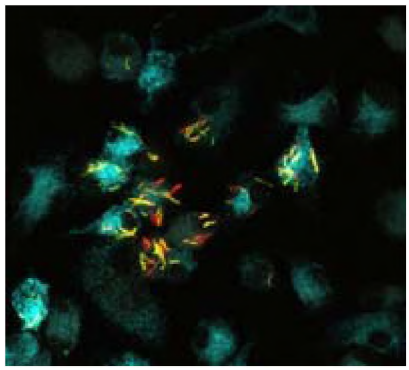
"However, the delay between getting an initial hit and developing a drug is years," said Russell. "Once the activity of a compound is validated, we will send it to synthetic chemists at Vertex who will aim to make a family of compounds to test for activity. Beyond that, Vertex will engage scientists to study the efficacy of the compound's ability to be absorbed in the body and conduct additional research. We believe that our collaboration with Vertex may enable this complex series of scientific and logistical requirements to take place in a highly efficient and effective manner."

Facilitated by JoAnne Williams, the director of Cornell's Office of Sponsored Programs, the unique collaboration represents an unusual twist in the drug discovery paradigm. Pharmaceutical companies regard their compound library as their "lifeblood," and it is rare for them to allow these collections to be screened outside their own facilities, according to Russell. In the collaboration, Vertex will control the future application of discoveries in tuberculosis, with a vision of developing therapies aimed at benefiting people with TB around the globe. The rights to apply these discoveries more broadly, outside the field of TB, will be shared by Vertex and Cornell.

"Our collaboration with Cornell underscores Vertex's commitment to innovative science aimed at the discovery of new treatment options for serious diseases," said John Thomson, Vice President of Strategic Research and Development Networks for Vertex. "Dr. Russell and his team are at the cutting edge of innovation in the fight against TB, and we look forward to working with them as part of this unique collaboration."

"This is a measure of trust that has never been established before," said Russell. "And it is our hope that people suffering around the world will be the beneficiaries."

For more information on Vertex Pharmaceuticals, visit www.vrtx.com/. For more information on Cornell's College of Veterinary Medicine, visit www.vet.cornell.edu.



The image shows Mycobacterium tuberculosis transformed to express mCherry (red) constitutively, and GFP (green) under regulation of a pH-sensitive promoter. The bacteria are in macrophages that have endocytosed fluorescent dextran to label their lysosomes (blue). The picture was taken by Robert Abramovitch.