Antibiotic team building

By Chris Cain, Senior Writer

The **National Institute of Allergy and Infectious Diseases** has awarded a 5-year, $26 million grant to a center for antibiotic development that brings together researchers from **Rutgers University**, **The Rockefeller University** and **Cubist Pharmaceuticals Inc.** The goal is to take discovery-stage programs through lead optimization and preclinical development to a partnering event.

The award marks the 13th Center for Excellence in Translational Research (CETR) funded by the National Institute of Allergy and Infectious Diseases (NIAID) in 2014.

The center will be led by David Perlin, executive director of and a professor at **The Public Health Research Institute at Rutgers University**. He told *SciBX* that the regulatory hurdles and financial disincentives to antibiotic development have stymied industry interest in early stage projects—a gap the center hopes to bridge.

Indeed, antibiotic developers and infectious disease specialists have repeatedly told *SciBX* that there is a dearth of new antibiotics in the pipeline capable of dealing with emerging drug-resistant bacterial threats.[1,2]

"There is a big gulf to cross from fundamental discovery and identification of small molecule inhibitors to refining and validating antibacterial compounds," Perlin said. "Companies have not been as patient to go through this early process—they essentially want molecules ready to go into preclinical assays. By having this center, we can advance molecules to that point."

The funding will support projects from five labs as well as their use of associated core facilities. These include a medicinal chemistry core with a structural biology subcore to optimize molecules; a pharmacokinetic and toxicology profiling core; an *in vitro* screening core to assess compound potency and spectrum of activity; and an animal model core that provides disease models for skin and soft tissue infections and systemic and pulmonary infections, and that permits an analysis of markers of disease progression.

The center has biosafety level 3 capabilities and access to a regional biocontainment laboratory that can handle multidrug-resistant pathogens including *Mycobacterium tuberculosis*, *Bacillus anthracis* and *Yersinia pestis*.

Perlin said that Rutgers is well equipped in part because it has been a member of the NIAID-funded Northeast Biodefense Center. Regional Centers for Excellence are consortiums that have been funded by large NIAID grants since 2003, although funding for the program expires this year. The CETR is a follow-on NIAID program.

The academic research teams participating in the CETR are led by Sean Brady, an associate professor at Rockefeller; David Alland, associate dean for clinical research and a professor of medicine at **Rutgers New Jersey Medical School**; Joel Freundlich, an assistant professor of pharmacology and physiology and medicine at the medical school; and Richard Ebright, a professor of chemistry and chemical biology at Rutgers University and lab director at the **Waksman Institute of Microbiology at Rutgers University**. Cubist is the lone industry member.

Mechanism scattershot

Perlin told *SciBX* that the projects being developed by the center include a mix of chemical classes that hit validated targets as well as new antibiotic mechanisms of action.

For example, Brady's lab will be developing compounds sourced from peptidic libraries derived from environmental samples of bacteria. He has published extensively on using sequencing, computational methods and *in vitro* analysis to identify new antimicrobial natural products.

A second project will be focused on compounds that inhibit mycolic acid synthesis, a key component of the cell wall in mycobacteria including *M. tuberculosis*. A third will work on developing Bayesian modeling to accelerate antibacterial discovery.

Ebright told *SciBX* that his lab will pursue a project focused on optimizing new arylpropionyl-phloroglucinol–based inhibitors of bacterial RNA polymerase (RNAP). The inhibitors bind to a site on the protein that is distinct from that of existing inhibitors such as rifampicin. The project is one of many in his lab that is investigating drug discovery against RNAP.

In a separate, non-CETR project published last month in *eLife*, Ebright used extensive crystallography and other *in vitro* studies to show that the natural product antibiotic GE23077 binds to yet another site on RNAP that is distinct from that bound by rifampicin.[3]

His team further showed that bipartite inhibitors linking GE23077 to rifampicin had activity against strains resistant to either compound alone. Patent applications covering the bipartite compounds have been filed and are available for licensing. Composition-of-matter patents covering GE23077 are owned by **Naicons s.r.l.**

Cubist input

The fifth and final project in the center comes from Cubist, which inherited its role in the CETR through its 2013 acquisition of Trius Therapeutics Inc. The deal's most visible asset was tedizolid, an oxazolidinone that is under FDA review to treat acute bacterial skin and skin structure infections (ABSSSI). However, Cubist also gained Trius' DNA gyrase inhibitors, which were included as part of the CETR application.

Cubist's EVP of R&D and CSO Steven Gilman told *SciBX* that the gyrase program caught the company's attention at an early stage. "One of the things we looked at in Trius when we were starting to talk with them about a relationship was the DNA gyrase program. We had been interested in DNA gyrase for a long time—quinolones had been very useful drugs for many years with a good spectrum of activity against

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Gram-positive and Gram-negative bacteria, and most of the problems with resistance are related to the quinolone structure. This program could offer quinolone-like efficacy with a scaffold that is distinct."

Gilman acknowledged that Cubist has significantly more in-house resources than Trius and thus may not rely as heavily on the center's chemistry capabilities as Trius might have.

Thus, he said, "the benefit of this consortium is more of an intellectual exchange—the researchers are well-known scientists with whom we'd like to collaborate more deeply. We bring years and years of biopharmaceutical industry experience to this consortium. Cubist has a wealth of experience, understands what companies are looking for, and can help groups create a package of information that is strong and comprehensive and could open up additional funding and partnerships."

Perlin agreed and said that he had originally specifically sought out Trius before it was acquired to join the CETR to get industry input on projects. He added that the DNA gyrase inhibitor program was further along than other projects, and its inclusion helped balance the stage of development of projects at the center and improve their chances of accelerating a program into the clinic.

Perlin added that the regulatory environment for antibiotic development is improving. "There is money to be made with anti-infectives; we know there is a need for them, and companies will in fact get back into it," he said.

Indeed, in the past six months **Roche** has entered into at least three antibiotic discovery partnerships with biotechs.[4]

Although this CETR is focused on antibiotics, the larger NIAID CETR program is casting a broad net for anti-infective strategies. Two centers established so far this year include a $32 million project to study the role of autophagy in pathogen-host defense with researchers from the **Washington University in St. Louis School of Medicine**, **Massachusetts General Hospital**, the **Broad Institute of MIT and Harvard** and **The University of Texas Southwestern Medical Center**.

The other center involves 15 institutions and received a $28 million grant to develop Ebola treatments.

NIAID intends to commit $75 million to the CETR program in FY2014 and to fund a total of 10–20 awards.

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COMPANIES AND INSTITUTIONS MENTIONED

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National Institute of Allergy and Infectious Diseases, Bethesda, Md.
The Public Health Research Institute at Rutgers University, Newark, N.J.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
The Rockefeller University, New York, N.Y.
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