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SMALL-MOLECULE INHIBITORS OF ANTHRAX LETHAL FACTOR IDENTIFIED
Findings Hold Promise for Developing New Anthrax Therapies

Scientists have identified several compounds that block the activity of a key anthrax protein called lethal factor (LF)—an important first step in developing therapeutics to counter the disease.

Anthrax, a disease caused by the spore-forming bacterium *Bacillus anthracis*, is most deadly when exposure occurs through inhalation. Prompt diagnosis and antibiotic treatment during the early stages of infection are critical. In many cases, however, antibiotics may not be effective—particularly when bacterial overload causes large amounts of anthrax toxin to be released in the body.

Anthrax toxin consists of three proteins: lethal factor, protective antigen, and edema factor, all of which work in concert to kill host cells. While the exact mechanism of anthrax toxin is not yet well understood, it is clear that developing methods to inhibit toxin assembly and/or function is critically important.

In an article published in this month's issue of *Nature Structural and Molecular Biology*, investigators from the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), the National Cancer Institute (NCI), the Burnham Institute, and the Harvard Institutes of Medicine report using a high-throughput assay to screen a group of 1,990 compounds known as the NCI diversity set. The molecular properties of this group are predictive of a larger set of more than 100,000 compounds.

Using a two-stage screening assay, the team identified a number of compounds that inhibited the activity of LF. All inhibitors were further verified by high-performance liquid chromatography and their efficacy was validated in cell culture. Finally, molecular modeling techniques were used to predict structural features that contribute to inhibitor binding and potency.

These techniques revealed a common pharmacophore—a "scaffold" upon which future therapeutics can be built. This pharmacophore will serve as a basis for directing future efforts to develop LF inhibitors with enhanced potency.

"These studies have provided us with a road map to the rational design of more potent, highly selective lethal factor inhibitors," said lead author Sina Bavari of USAMRIID. "I believe this team has quickly answered the urgent call for novel anthrax inhibitors."

Bavari's collaborators were Rekha G. Panchal, Ann R. Hermone, Tam Luong Nguyen, Douglas Lane, Connor McGrath, James Burnett, Edward A. Sausville, Dan W. Zaharevitz, and Rick Gussio of NCI; James Schmidt, M. Javad Aman, and Stephen Little of USAMRIID; Thiang Yian Wong, Robert Schwarzenbacher, and Robert C. Liddington of the Burnham Institute; and Benjamin E. Turk and Lewis C. Cantley of the Harvard Institutes of Medicine.

"This work is an example of the types of interactions we are seeking at the new Fort Detrick National Interagency Biodefense Campus," said Colonel Erik A. Henchal, commander of USAMRIID. "By working together, the federal partners will be able to develop the products the nation needs for biodefense."

USAMRIID, located at Fort Detrick, Maryland, is the lead laboratory for the Medical Biological Defense Research Program, and plays a key role in national defense and in infectious disease research. The Institute's mission is to conduct basic and applied research on biological threats resulting in medical solutions (such as vaccines, drugs and diagnostics) to protect the warfighter. USAMRIID is a subordinate laboratory of the U.S. Army Medical Research and Materiel Command.

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