BioMAP screening procedure could streamline search for new antibiotics

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Researchers at the University of California, Santa Cruz, have developed a new strategy for finding novel antibiotic compounds, using a diagnostic panel of bacterial strains for screening chemical extracts from natural sources.

Public health officials warn of a looming antibiotic crisis due to the steady increase in antibiotic resistance and a dramatic decline in the development of new antibiotics. Most currently available antibiotics are derived from natural compounds produced by microorganisms such as bacteria and fungi. New antibiotics developed by drug companies are often synthetically tailored variations of existing classes of antibiotics. To combat the problem of antibiotic resistance, however, researchers desperately want to find antibiotics with completely novel structures and modes of action.

The new screening procedure, called BioMAP (antibiotic mode of action profile), promises to streamline the discovery of new antibiotics from natural sources by providing a low-cost, high-throughput platform for identifying compounds with novel antibiotic properties.

"If you take a library of natural product extracts and screen them against a bacterial target, you will find a lot of antibacterial compounds, but almost all of them will be known structures," said Roger Linington, assistant professor of chemistry and biochemistry at UC Santa Cruz. "BioMAP is a new way to look at antibiotic activity so that you're not wasting time and energy chasing things that turn out to be well-studied

compounds of little therapeutic value."

Linington's lab focuses on marine natural products—mostly microorganisms isolated from marine sediments—as a source of lead compounds for drug discovery. The BioMAP project was led by Weng Ruh Wong, who joined the lab as a postdoctoral fellow in the QB3-Malaysia Program. Wong is first author of a paper presenting the BioMAP screening procedure published in the November 21 issue of *Chemistry & Biology*.

The researchers started with a training set of 72 commercially available antibiotics and tested them all against a panel of 15 bacterial strains, including a broad range of clinically important pathogens. The commercial antibiotics were chosen to include multiple members of all of the main classes of antibiotics. Parallel screening of the antibiotics against all 15 strains was performed using robotic equipment at the UCSC Chemical Screening Center.

The tests yielded a characteristic pattern of activity, or BioMAP profile, for each antibiotic, and antibiotics within the same class had similar profiles. Analysis using hierarchical clustering methods showed that the BioMAP profiles are highly diagnostic for the known structural classes of antibiotics. The researchers then showed that the procedure could be used to classify compounds present in natural product extracts and identify novel antibiotics.

"The first step was to profile a lot of known drugs and see if BioMAP profiles were diagnostic for specific structural classes. The second step was to profile a library of unknowns from our natural product collection, eliminate all extracts with profiles that matched known classes of antibiotics, and focus on those that look unique," Linington said.

One extract from the lab's natural product library looked particularly

interesting and led to the isolation of a novel antibiotic compound. Named arromycin, the compound is a napthoquinone antibiotic with a number of unusual structural features.

"Arromycin probably won't lead to a new antibiotic drug—there are a number of structural liabilities from a drug development standpoint—but its discovery is a proof of principal that the BioMAP platform works for finding novel compounds," Linington said. "Our library has tens of thousands of chemicals. If we want to find new antibiotics, this is an excellent way to do that without wasting time rediscovering known structures."

It makes sense to look for antibiotics in environments where bacteria compete with one another, he said. About 80 percent of currently available antibiotics are derived from natural products, mostly from soil microorganisms. But because natural products have been studied so extensively, the rate of return in terms of novel chemistry has decreased precipitously.

"Almost all of the new antibiotics are 'me too' drugs that work in the same way as an existing drug," Linington said. "The paucity of new therapeutic options for bacterial infections is a well-recognized and ongoing issue, and it is a major emerging threat to public health, both nationally and on a global scale."

Provided by University of California - Santa Cruz