# Researchers find new path to antibiotics in dirt

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(PhysOrg.com) -- A teaspoon of dirt contains an estimated 10,000 species of bacteria, but it's only one percent of these microbial bugs — the ones that can be grown easily in a lab — that have brought us antibiotics, anticancer agents and other useful drugs. The odds favor the other 99 percent for clinical promise, too, but scientists have had little success in tapping this unknown majority for new medicines because of the difficulty of analyzing the bugs' DNA.

Now researchers at The Rockefeller University have extracted that genetic material from a lump of earth and turned it into an environmental DNA "megalibrary" that may provide access to many previously unknown organic compounds. The library has already led them to the genetic code for two potential antibiotics; the scientists also used enzymes from one set of cloned genes to produce new antibiotic derivatives as powerful as the strongest drugs we have today.

The research could recharge interest in the search for new compounds in the environment that has flagged over the past decade because of lackluster results. The new findings suggest that all sorts of useful and unknown products are being manufactured by bacteria in the soil that we routinely trample underfoot. And it shows a promising way to get at them. The work was published online Wednesday in *Proceedings of the National Academy of Sciences* Early Edition.

"This proves that you can recover large gene clusters from very complex soil samples," says Sean F. Brady, who heads the Laboratory of

Genetically Encoded Small Molecules. “It suggests that there’s an untapped reservoir out there of variations on many clinically relevant antibiotics, and that by using culture-independent screening strategies, we may be able to gain access to them.”

The search for new antibiotics is increasingly urgent as “drugs of last resort” like vancomycin and teicoplanin are resorted to more commonly these days. Some of the meaner strains of Staphylococcus and other infections, including tuberculosis, have developed resistance to traditional antibiotics after decades of exposure to them.

By heating up about a cupful of soil in the presence of a detergent, Brady and graduate student Jacob Banik were able to separate the DNA from the dirt and scan the genetic material for a gene sequence called OxyC that is common to the family of antibiotics including vancomycin and teicoplanin. In soil samples from Pennsylvania, New Jersey, Massachusetts, Utah, Oregon, North Carolina, Tanzania and Costa Rica, they found that each contained at least one previously undiscovered variant of the OxyC sequence.

Focusing on the sample from Utah, the Brady lab organized all of the genetic material into a 10 million member megalibrary, far larger than any other DNA library of its kind. It contained the rough equivalent of 100,000 bacterial genomes. Banik cloned two unique gene clusters that were associated with new OxyC sequences and used one of the clusters to manufacture a new family of antibiotics. In addition to combating bacteria as well as the most powerful drugs in use today, the new antibiotics have unique structural features that could hold as yet undetermined medical advantages.

“This is just one example of the new, medically relevant structures you can find using this genetic targeting strategy,” Brady says, “It suggests that there are many, many more out there.”

“We can go out and find compounds that have never been seen before, and those are very likely to have some functionalities that are even more useful than the ones we’ve got in the lab already,” Banik says. “If you look at the complexity and elegance of the solutions found by Mother Nature, it just seems incredibly obvious that there are more effective elements to go after than those to which we currently have access.”

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