Researcher helps develop new technique to explore oceanic microbes

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A new compound, dubbed cabrillostatin, was discovered using SMIRC in a protected marine reserve at Cabrillo National Monument. Credit: SMU

When Southern Methodist University (SMU) researcher Alexander Chase was a young boy, the sheer diversity of plants in Earth's tropical

rainforests fascinated him. He found himself wondering what new species were out there, waiting to be unearthed. That curiosity is why Chase now collects samples from Earth's oceans using a new technique called small molecule in situ resin capture (SMIRC), which could be the first step in uncovering compounds that lead to next-generation antibiotics.

Microbial natural products come from microorganisms (microbes), and account for many of today's essential medicines, including most antibiotics. Microbes are too small to see without a microscope and produce a wide variety of chemical compounds as part of their lifespan, some of which are useful for pharmaceutical applications. Traditionally, these compounds are discovered using a "microbe-first" approach, where individual strains are cultured in the laboratory from a sample picked up in the wild.

While this method has been effective, it has become increasingly difficult for researchers to use it to uncover new chemical "scaffolds," which serve as the foundation upon which chemical compounds are built. Chemical scaffolds are a critical resource for drug discovery.

"Right now, when we collect new samples and culture the microbes, we're discovering scaffolds that essentially are very similar to the ones we already know about," explains Chase, an assistant professor in the Roy M. Huffington Department of Earth Sciences.

"It's been really difficult over the last few decades to find something that is new with the 'microbe-first' approach, which essentially limits us to the same or similar bacterial strains and their chemical compounds that represent only a fraction of the natural diversity out in the ocean. That's where SMIRC comes in, it allows us to explore the unknown."

A recent study in the journal *Nature Communications* by Chase and

researchers at the University of California San Diego and University of California San Francisco explains how SMIRC made possible the collection of microbial natural products where they are produced in the wild, without the need to be cultured in a lab. It used an absorbent resin called HP-20, which acts like a sponge to capture the chemicals released by microbes.

As a test, the researchers used SMIRC in areas covered in seagrass near San Diego. From the chemicals collected, they found an antibiotic compound and also a chemical called chrysoeriol, which is plant-based that has antibacterial properties. A modified version of SMIRC was then used by mixing the HP-20 with agar, a substance that encourages the growth of microbes. This second experiment uncovered aplysiopsene A, which showed continued success of the SMIRC technique for recovering compounds.

A third test used SMIRC in a protected marine reserve at Cabrillo National Monument. Here the technique collected larger samples that contained more complex chemical mixtures. While the reason the site is rich in novel compounds is currently unknown, the researchers speculate it could be because this specific area is exposed to little human traffic.

Although none of the new compounds proved to be a path to new antibiotics, one of the compounds discovered, dubbed cabrillostatin, does show bioactivity and is being pursued as a possible new approach to cancer and heart care.

"The ocean is one of the least explored areas on Earth, especially the deep ocean," said Chase. "There's so much we don't understand about marine microorganisms and the compounds they produce. Because of antibiotic resistance and other health challenges, there is a high priority for natural product research. With SMIRC, we now have an easily deployable system that makes it possible for researchers to study

compounds previously out of reach."

More information: Alexander Bogdanov et al, Small molecule in situ resin capture provides a compound first approach to natural product discovery, *Nature Communications* (2024). DOI: 10.1038/s41467-024-49367-x

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