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Tapping into personalized chemistry

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Abstract

By integrating metagenomics, spectroscopy and synthetic biology, the individualized chemistry of small reef-dwelling organisms and their associated microbiota can be characterized in exquisite detail, unlocking a wealth of structural diversity for the development of new drugs.

Since Fleming's discovery of penicillin from the fungus *Penicillium notatum*, compounds purified from natural sources have provided a wealth of bioactive molecules, many of which comprise our current stash of pharmaceuticals. This is especially true for antibiotic and anticancer agents, for which upwards of 70% of small-molecule drugs are traceable to a natural product¹. Though the majority of natural product-derived drugs originate from terrestrial microorganisms, resampling of common species eventually stymied the pipeline². Compared to terrestrial settings, the diversity of the world's oceans remains largely untapped, and ecosystems rich with microbes, like sediments and coral reefs (Fig. 1a), provide novel chemistry for those with the tools to exploit them. In this issue, Smith *et al.* have shown that an integrative approach using the latest tools of metagenomics, spectroscopic analyses, and synthetic biology can interrogate the bioactive chemistry of reef-dwelling populations with an unprecedented level of detail³.

Marine invertebrates such as sponges or sea squirts (tunicates) are known to produce bioactive compounds, but they host dense microbiomes that often contain the true producers of observed chemistry⁴. The complex requirements of these symbioses make them challenging to reproduce under laboratory conditions, leaving chemical synthesis as the major means for production of lead compounds observed in the field—a tall order given the intricate structures typical of these natural products⁵. More rapid development requires the identification of the structure of bioactive molecules isolated in minute quantities and a means for producing the compound and structurally related analogs in the laboratory for testing. The approach detailed by Smith *et al.*³ demonstrates such a way forward for unlocking the pharmaceutical potential of marine ecosystems.

The authors started small, using individual specimens of the solitary tunicate *Didemnum molle*, a sedentary filter-feeding animal picked from a Papua New Guinean reef. Saving part of each sample for genomic sequencing, the remainder was chemically extracted and tested

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Competing financial interests

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for antiviral activity. Though one tunicate sample neutralized HIV infection *in vitro*, a visually identical neighbor was inactive (Fig. 1b). As only nanomole quantities of the active component could be isolated, typical spectroscopic techniques were unable to fully identify the chemical structure. However, a tetrapeptide motif and two atypical amino acid residues suggested a ribosomally synthesized and post-translationally modified peptide (RiPP) natural product. The primary sequence of a RiPP is directly encoded in the genome, thus the partial sequence was used to probe the metagenome of the tunicate to identify a single candidate in the genome of its symbiotic cyanobacterium *Prochloron didemni*. Analysis of colocalized genes allowed structural prediction of the encoded product consistent with the unassigned spectroscopic data (Fig. 1c). In the third part of their approach, the authors engineered an *Escherichia coli* strain to express the cyanobacterial genes in the laboratory, producing the expected compound alongside several analogs at a scale amenable to detailed structural assignment and further testing of antiviral and drug-like properties.

The insights gained from this work were made possible by the maturity of understanding typical natural product biosynthetic pathways alongside the accessibility of metagenome sequencing, which informed spectroscopic analysis of chemical structure on a scale that was previously impossible. This approach allows characterization of the chemistry of individual tunicates, uncovering minor structural variations that determine activity. Such variation would be lost in larger scale studies that necessitate pooling of similar organisms to achieve sufficient scale. Instead, this work reveals a rich resource for identifying chemical and functional diversity among bioactive scaffolds occurring within the multitude of marine organisms that host personalized and spatially distinct microbiomes⁶.

Notably, although other genomic approaches aim to exploit the chemical structure space encoded by marine microorganisms on a large scale, they cannot initially discriminate between bioactive and inactive compounds⁷. By contrast, in this study, bioactivity was paramount from the initial screens, and synthetic biology produced a small suite of analogs from which initial structure-activity relationships could be inferred. In this way, the classic drug-discovery paradigm of activity screening and compound development was maintained, but driven by a modern approach to unlock new chemistry. In the future, it is likely that this integrated strategy will speed the discovery and development of novel peptide drugs, and it may be applied to other natural product classes as our ability to predict their biosynthesis steadily improves.

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Figure 1 |.

A bioactivity-driven drug-discovery approach to exploiting the full diversity of complex ecosystems. **(a)** The enormous biodiversity found on coral reefs is revealed in this underwater photo. Numerous individual *D. molle* specimens appear in the center. Photo credit: C. Bewley. **(b)** Following biological screening of individual specimens, structural assignments of active compounds are determined by combined interpretation of metagenomic and spectroscopic data. Synthetic biology is then used to confirm structure predictions and produce active compounds at a preparative scale. **(c)** Using this approach, two related lanthionine-bridged peptide natural products were discovered, produced and tested, revealing sequence and structural features required for anti-HIV activity. Differences between the two peptide sequences are highlighted in red and blue.