Biosortia Pharmaceuticals
www.biosortia.com

Biosortia—at scale mining of nature's metabolite bounty

Biosortia is building the world's largest library of microbiome-derived compounds for therapeutic and other applications, by leveraging the company's microbial harvesting platform to sample and mine aquatic microbiomes at unprecedented scales with sustainable and environmentally friendly approaches. Biosortia is seeking partners interested in accessing compounds and chemistries to develop biologically relevant small molecule leads.

Biosortia Pharmaceuticals, a microbiome company founded in 2012, has developed a unique platform for accessing the hidden chemistry of aquatic microorganisms to generate new opportunities for drug discovery. With more than 25% of all marketed drugs over the past 50–60 years having been inspired by or developed from natural products obtained from cultured microorganisms, further exploitation of this approach seems an obvious path. However, the pipeline of compounds is rapidly running dry—only about one percent of microorganisms in all environments have been cultured. Unlocking the chemistry of the remaining 99% of microorganisms, the 'unculturable' fraction, to obtain drug-like natural compounds could have a substantial impact on multibillion-dollar industries, including biopharma, agriculture, and consumer/cosmetic applications.

Biosortia has developed an unconventional approach to tapping into the potential treasure trove of novel compounds 'locked' in the unculturable fraction of aquatic microorganisms: it has developed an environmentally friendly microbiome prospecting platform designed to collect microbiomes from large water volumes in situ while preserving their physical and chemical integrity. The large-yield harvest (typically ~1,000 kg of dry weight microbiome from $20x10^6$ l of sea- or freshwater) provides the company with development scale amounts of natural compounds and patentable derivatives. Rigorous refining of the metabolome results in libraries of novel natural drug-like small molecules that serve as starting points for preclinical drug discovery research by providing access to sources researchers had always wanted to capitalize on but only had very limited access to (Fig. 1).

"Microbes have always been chemical researchers and factories of life," said Ross Youngs, founder and CEO of Biosortia. "But while microbes have consistently proven to be one of the most valuable sources of new drug leads, only about 1% of this resource could be directly explored until now. Biosortia's breakthrough technology now effectively opens the door to all microbes, making thousands of novel chemical entities available for therapeutic and other applications."

Biosortia is developing an internal pipeline of immunological therapeutics, including immuno-oncology leads, and a robust network of external collaborations and licensing opportunities to help maximize the potential of its unique value proposition. The company is seeking new partners interested in exploring its vast and growing library of novel chemistries optimized by nature.

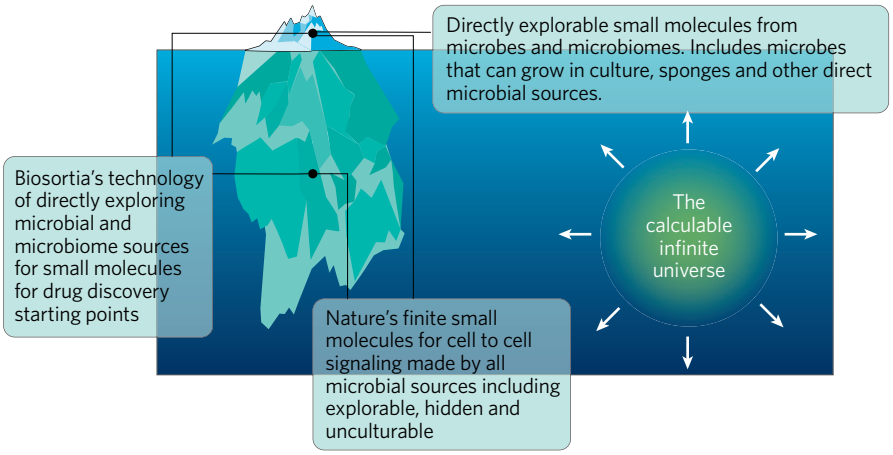

Fig. 1 | Biosortia—unlocking the therapeutic potential of the aquatic microbiome. Biosortia's microbiome mining platform provides access to the finite hitherto hidden drug-like small molecules from the world's fresh- and saltwater microbiomes.

Natural product discovery—closing the circle

Starting with penicillin in 1929, drug discovery has relied heavily on new chemical activities and entities derived from natural products. While this pipeline of compounds turned out to be bountiful, supporting the growth of the industry and the development of countless breakthrough therapies, it also turned out to be finite due to its reliance on the one percent of organisms generally regarded as culturable. This limitation has been offset by two key technological advances.

First, the development of combinatorial chemistry opened countless new chemical scaffolds and variants that could be assembled from known building blocks using existing and novel chemical processes. A research and commercial ecosystem was created that provided a boon for synthetic chemistry, and the basis for countless drug development programs. But while very prolific, combinatorial chemistry also turned out to be limited, in this case, by the number and diversity of starting chemistries and the 'optimization by nature'. Unlike natural compound chemistries, which have been optimized over evolutionary timescales to interact with nature, combinatorial chemistry products need to be optimized in the laboratory to interact with nature.

A second advance came with the sequencing of the human genome and the ensuing sequencing of thousands of other organisms. The genomic revolution was heralded as an endgame of sorts, in terms of advancing our understanding of human physiology and the inner workings of the natural world. But while the genomic revolution has unequivocally advanced insights into health and disease, as well as supported efforts to identify new chemistries and pathways of interest in a wide range of organisms, it has also raised more questions than it has answered.

The unfulfilled promise of both the combinatorial chemistry and the genomic revolutions has created urgency within the biopharma industry to find alternative ways of identifying new bioactive chemical entities. Against this background, Biosortia has focused on opening a third path in the quest to reinvigorating the biopharma pipeline. The company's strategy consists of returning to the approach that supported the growth of the biopharma industry in the first place, the identification of natural products with activities of interest, but with a twist. Biosortia has scaled up and optimized the extraction and identification of new chemical entities directly from the environment. By extracting compounds at development scale levels, Biosortia has for the first time been able to uncouple the discovery of new natural products from the need to cultivate individual organisms. In addition, the company has capitalized on many of the technological advances

brought about by the combinatorial chemistry and the genomic revolutions to streamline the analysis and characterization of the novel therapeutic lead compounds it isolates.

"We have created technologies to deeply explore microbiome habitats, an approach that is more closely related to previous culture-based drug discovery approaches and avoids the high costs associated with the development of de-risked assets via combinatorial chemistry and/or genomics," said Youngs. "Small molecules accessed directly from the microbiome are more likely to be successful in clinical development than non-natural molecules from purely infinite indirect omics, combinatorial, or computational approaches. Nature's small molecules are very relevant and ready to be explored"

Mining the microbiome

While small molecules with new modes of action continue to be identified from aquatic microorganisms, their rate of discovery has fallen over the past few decades. Current approaches tend to be inefficient due to limitations with culturing conditions and extraction. Typically, natural product programs obtain samples via expeditions where organisms are collected and used as direct sources for natural product isolation, or further cultured to obtain compounds in larger quantities. This process is however far from comprehensive and is highly biased toward compounds present at the highest concentrations and microorganisms that grow under standard culturing conditions. Obtaining large amounts of biological material directly from the environment without having to resort to culturing would address both issues.

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> Ross Youngs, founder and CEO, Biosortia

Biosortia focused on developing an easy to implement solution: microbiome mining

Microbiome mining can be most simply defined as the process of collecting a very large sample of all the living microbes from an active habitat in ways that do not damage or degrade the collected organisms. The goal is to rapidly preserve a snapshot in time of the chemical molecules, genomic information, and environmental conditions of the sample.

Devices for collecting biomass from aquatic samples at large scales, in particular of microalgae, have been in use for some time for applications ranging from biofuels to high added value nutraceutical products. Such applications, however, do not require preserving the molecular integrity of the cells because the goal is to extract a particular compound—an oil, a vitamin, a protein—that is usually produced at high concentrations. By contrast, microbiome mining seeks to identify the entire spectrum of compounds and pathways in the microbes, which requires preserving the integrity of the cells and their chemistry.

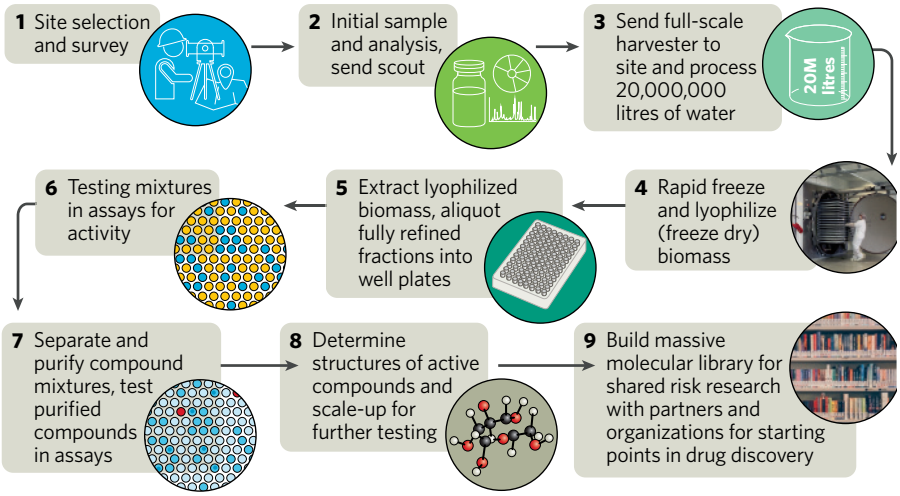

Fig. 2 | The largest library of microbiome-derived compounds. From site selection to harvesting, and testing, the company's microbial harvesting platform provides a molecular library of potential drug candidate starting points.

Biosortia's patent-protected microbiome mining device is based on solid-liquid separation (SLS) technology designed to gently harvest all living microbes between 0.02 µm and 100 µm from any aquatic environment. Biosortia's SLS technology relies on the use of a type of capillary dewatering that facilitates the gentle separation of water from the microorganisms, allowing for multi-phased concentration of the microbiome through the removal of significant quantities of water while preserving microbial integrity. The concentrate is then used as the starting material for further extraction and processing (Fig. 2).

The system is capable of recovering up to 100 kg of microbiome biomass concentrate per day through multi-stage mechanical dewatering. Biosortia has the ability to deploy both scouting systems with a capacity of harvesting 2–4 kilograms dry weight per day and full harvesting systems with a capacity of harvesting 50–100 kilograms dry weight per day.

Once the microbiome concentrate is lyophilized, downstream processing at Biosortia includes extraction and fractionation to isolate compounds for the company's natural product library. Other mining efforts include genomic analysis of the samples, chemical, and computational screening of extracts, providing many opportunities for collaboration with third parties.

"We developed the initial SLS technology and have now advanced to a full-scale fourth generation that dewaters unprecedented amounts of microbiome biomass from aquatic environments, unlocking a whole new universe of opportunities for drug discovery," said Youngs. "Biosortia now has the ability to isolate and identify in excess of 70,000 addressable compounds per habitat sample harvested."

Maximizing the therapeutic potential of aquatic microbiomes in partnership

The therapeutic potential of nature, and more specifically, of the microbial world has been clearly established over the past 100 years, and there is a high likelihood that access to previously inaccessible compounds will be the quickest way to the next blockbuster treatment for conditions from diabetes to Alzheimer's disease.

Biosortia has now established a comprehensive inventory of diverse aquatic microbiomes, proprietary methods to acquire vast quantities of microbiome biomass while preserving its integrity, validated rapid and effective off-the-shelf sorting capabilities, high-throughput screening for drug discovery, and laboratories ready to do custom preclinical and clinical studies. The company's potential libraries represent thousands of species of microorganisms across phylogenetic classes containing more than 100 million genes, and tens of thousands of chemically highly diverse secondary metabolites that include signaling molecules and compounds exhibiting high potencies evolved to maximize activities in highly dilute environments.

Biosortia is seeking to expand its network of partnerships with collaborators interested in gaining access to the company's unique libraries. Biosortia can for example provide pure compound libraries to support pharma screening efforts, or highly refined mixtures for academic researchers interested in deconvoluting novel signals.

Biosortia is building the largest library of unknown natural drug-like small molecules in quantities fit for preclinical drug discovery research.

"Our greatest challenge is also our greatest opportunity—we have set out to find the hidden chemistry of 3.4 billion years of single-cell microorganism evolution that could potentially cure a disease and improve the lives of those impacted," said Youngs. "Success takes time and resources, and Biosortia cannot move fast enough!"

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