

RENEWED INTEREST IN MICROBIAL NATURAL PRODUCTS IS TRIGGERING RESEARCHERS TO EXPLORE MICROBIAL COMMUNITIES AS POTENTIAL SOURCES OF NOVEL COMPOUNDS

# Untapped microbial diversity

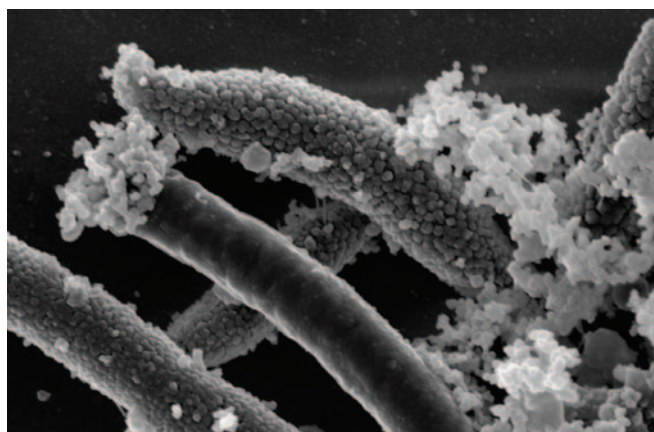
**M**icrobial natural products (NPs) have been exploited during previous decades as one of the most prolific sources of new leads in modern drug discovery, especially in the case of antibiotics. Intensive sourcing programmes were focused on the isolation of huge numbers of strains from a limited number of microbial groups such as actinomycetes, myxobacteria, cyanobacteria and fungi, all known to be prolific producers of secondary metabolites. Discovering new types of natural products from these few taxa has become very challenging given the high rediscovery rates of known compounds.

## Investigating unexplored potential

Recent genomic data derived from massive, whole-genome sequencing projects have shown the untapped metabolic capabilities of microbial sources and are fostering a new interest in the exploitation of these secondary metabolite producers. In fact, microbial whole-genome sequencing programmes have been increasing exponentially in the last few years and have become available to the research community, revealing not only the broad diversity of gene clusters involved in the biosynthesis of NPs of unknown function, but the high numbers of microbial taxa where they were not expected to be found.

The unnumbered cases of silent biosynthetic gene clusters potentially involved in the production of still undetected novel natural products identified among a largely untapped and previously unexplored microbial diversity of taxa suggest that new opportunities to discover novel natural product gene clusters exist.

Prokaryotes are the most abundant and most diverse microbial community on Earth, but less than 1% has been cultivated using standard laboratory conditions. More than half of the recognised bacterial phyla contain uncultured representatives, including many dominant taxa in communities



Scanning electron micrograph of *Longimicrobium terrae*, a new genus from uncultured taxa



where the traditional isolation techniques have failed to culture them. Despite the recent advances in accessing under-represented taxa, vast numbers of taxons await isolation and a deeper investigation of their roles in the biogeochemical cycles, their ecological significance in bacterial communities, and their potential industrial applications. These microbial communities are metabolically active in their natural environment and remain untapped sources of new compounds.

New approaches aiming at isolating these previously uncultured microbial strains are now being pursued by the research community and paralleled by intensive genome mining campaigns from which novel taxa and novel gene pathways are regularly being reported. These efforts are also supported by the development of synthetic biology disciplines and, more specifically, by the metabolic engineering tools and new chassis for the expression of biosynthetic pathways that aim to overcome the limitations of the structural complexity of NPs and help to develop new ways to increase chemical diversity from strains that are difficult to manipulate in laboratory conditions. These new synthetic biotechnology approaches are tackling former limitations and managing the efficient exploitation of these unique resources to express new pathways in laboratory conditions.

## Discovering novel bioactive molecules

In this context the organisation focuses on drug discovery from microbial NPs, and is actively contributing to the research and development of potential novel natural products in collaboration with industrial and academic partners. Established as a public private partnership between the government of Andalucía, the University of Granada, and Merck Sharp and Dohme de España SA – ensuring a follow-up from the former natural products research programmes developed at Merck's Basic Research Centre and leveraging more than 50 years of NP drug discovery expertise inherited from the pharma sector – the organisation has developed a model of public private collaborations enabling the discovery of potential new leads from its natural products libraries.

It is widely accepted that the successful discovery of novel bioactive molecules is dependent on the chemical diversity of NP collections and the capacity of the selected strains to produce novel compounds. Microbial collections were built from the broadest diversity of sources and to ensure the exploitation of their potential to deliver novel scaffolds for the development of novel drugs. The unique microbial NP libraries (130,000 NP extracts) and strain collections (190,000 microbial strains) at the researchers' disposal are enriched in new microbial and chemical diversity, taking into account that the discovery of a novel natural product class is a rare event and the success of any NP screening approach is completely dependent on the capacity of the selected strains to produce novel compounds.

## Developing novel natural products

The researchers contribute to the exploration of novel approaches to mine previously uncultured microbial communities, and to isolating and domesticating in laboratory culture conditions new taxa previously reported only from metagenomic libraries. The organisation has developed new devices inspired on the iChip method with miniature diffusion chambers that permit the isolation of novel bacterial taxa,

**Bacterial conjugation in the new species *Luteolibacter gellanilyticum***



including under-represented phyla in laboratory simulated or real environments.

The system combines the strengths of two previous strategies for the isolation of difficult-to-culture micro-organisms, dilution-to-extinction and incubation of cells and culture media in natural or simulated natural conditions, and unifies the methods using a physical platform amenable to high-throughput microbiology. These new devices have enabled an increase in the numbers of cultured microbial cells that can be recovered from the environment and, more importantly, to culture bacterial lineages in laboratory conditions that were previously only reported as un-cultured bacteria detected from environmental metagenomics analyses and to get access to their metabolic potential. Whole-genome sequencing of these new isolated taxa have confirmed the extraordinary richness in secondary metabolite biosynthetic pathways of these unexplored bacterial groups, opening new opportunities for future natural products research.

Exploring the new chemical diversity of microbial NPs will take advantage of the development of new synthetic biology platforms that will permit the heterologous exploitation of these cultivated and un-cultivated resources.

In this context, the microbial collections are enriched by novel microbial diversity. The new libraries are integrated into new research programmes aimed at discovering new classes of natural and biotechnology products with potential applications in human and animal health, agriculture and other biotechnology sectors as part of its collaborative public private innovation models.

Committed to NP research and the exploitation of these untapped microbial communities, the research organisation supports the renewed interest in fostering research and innovation in the discovery of new NPs, as well as in training support to ensure the future generation of scientists in the field.

**Olga Genilloud**  
**Scientific Director**  
**Fundación MEDINA**

**+34 958 993 965**

**[olga.genilloud@medinaandalucia.es](mailto:olga.genilloud@medinaandalucia.es)**  
**[www.medinadiscovery.com](http://www.medinadiscovery.com)**