NEW BIOACTIVE METABOLITES FROM *ACTINOBACTERIA*

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Introduction. Natural products represent a major source of approved drugs and still play an important role in supplying chemical diversity. Despite a decreased interest by many pharmaceutical companies, the need for novel antibiotics to fight multidrug-resistant pathogens calls for a return to natural product screening, but novel approaches must be implemented to increase the chances of discovering novel compounds against a background of tens of thousands of known natural products.

Methods. Our core technology is represented by a large and diversified collection of actinomycetes and filamentous fungi (over 65,000 strains), which includes many rare and hard to isolate strains. In order to mine this vast potential source of bioactive compounds, while avoiding rediscovering any of the ~10,000 microbial metabolites described in the literature, approaches must be implemented that increase the likelihood of finding new compounds. We are applying a High Quality Screening (HQS) approach, whereby strains are preselected for focussed screening campaigns in which priority is given to chemical novelty of a bioactive compound. This is achieved by mining a databse of high throughput screening data or by screening previously underexplored taxa of *Actinobacteria* by simple growth-inhibition assays, followed by the rapid assessment of chemical novelty by a combination of analytical techniques and database queries.

Results. Naicons' current pipleine includes four compounds, three of which are represented by ribosomally-synthesized, post-translationally modified peptides (RiPPs). The lantibiotic NAI-107, produced by the actinomycete *Microbispora sp.,* has the potential to treat life-threatening infections caused by multidrug-resistant Gram-positive pathogens and is currently undergoing formal toxicology studies. Naicons is coordinating an FP7 project aimed at the optimization of the production process. The semisyntehtic compiund NAI-Acne is a derivative of the thiopeptide GE2270, which exibits a selective antibacterial spectrum covering mostly *Propionibacterium acnes*. For the thiopeptide GE2270, which is produced by the genetically intractable actinomycete *Planobispora rosea*, we have successfully expressed the gene cluster in the heterologous host *Nonomuraea* sp., thus enabling the generation of analogues by appropriate manipulation of the cluster. The third RiPP is represented by the lanthipeptide NAI-112. This compound, although identified in the same screening program that led to NAI-107 and other lantibiotics, is substantially devoid of antibacterial activity, but is effective in animal models of neuropathic pain.

Conclusions. Microbial natural products can provide new classes of bioactive compounds, sometimes with a bioactivity different from the seeked one, highlighting the role played by evolution in making compounds that interact with biological targets. These bioactive, often chemically complex compounds can represent important tools in chemical biology, can be scaffolds for further modification by chemical and/or genetic means or directly become developmental candidates for preclinical studies. In our opinion, the chemical diversity present in most microbial taxa in far from having been exhausted.

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