

# Basic microbiology, chemistry and synthetic biotechnology to identify and characterize antibiotics from microbes

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Amongst the well-established bacterial producers myxobacteria have a great track record for the discovery of entirely new natural product scaffolds exhibiting promising bioactivities<sup>1</sup>. This is at least in part due to the fact that they have been much less studied in the past in comparison to other traditional sources such as actinomycetes and bacilli. Nevertheless, the issue of rediscovery is a major hurdle for myxobacterial extracts as well. I will discuss recent results from our efforts to culture previously uncultured myxobacteria and to connect phylogenetically distant clades to novel metabolites by metabolome and genome mining<sup>2</sup>. Examples of novel and genetically engineered natural products in preclinical development as broad spectrum antibiotics exhibiting novel mode of action(s) will be shown<sup>3,4,5,6</sup>. In addition, I will show examples of heterologous expression of myxobacterial compounds yielding producer strains making production of lead compounds for pharmaceutical development feasible<sup>7</sup>.

<sup>1</sup>Herrmann, J., Abou Fayad, A. and Müller R. (2017) Natural products from myxobacteria: novel metabolites and bioactivities, *Nat. Prod. Rep.*, 34 (2):135-160.

<sup>2</sup>Hoffmann, T., Krug, D., Bozkurt, N., Duddela, S., Jansen, R. Garcia, R., Gerth, K., Steinmetz, H. and Müller, R. (2018) Correlating chemical diversity with taxonomic distance for discovery of natural products in myxobacteria, *Nat. Commun.*, 9 (1): 803.

<sup>3</sup>Baumann, S., Herrmann, J., Raju, R., Steinmetz, H., Mohr, K.I., Hüttel, S., Harmrolfs, K., Stadler, M. and Müller, R. (2014) Cystobactamids: myxobacterial topoisomerase inhibitors exhibiting potent antibacterial activity, *Angew. Chem. Int. Ed.*, 53 (52): 14605-14609.

<sup>4</sup>Kling, A., Lukat, P., Almeida, D.V., Bauer, A., Fontaine, E, Sordello, S., Zaburannyi, N., Herrmann, J., Wenzel, S.C., König, C., Ammerman, N.C., Barrio, M.B., Borchers, K., Bordon-Pallier, F., Brönstrup, M., Courtemanche, G., Gerlitz, M., Geslin, M., Hammann, P., Heinz, D.W., Hoffmann, H., Klieber, S., Kohlmann, M., Kurz, M., Lair, C., Matter, H., Nuermberger, E., Sandeep T., Fraisse, L., Grosset, J.H., Lagrange, S. and Müller, R. (2015) Targeting DnaN for tuberculosis therapy using novel griselimycins, *Science*, 348 (6239): 1106-12.

<sup>5</sup>Lesnik, U., Lukezic, T., Podgorsek, A., Horvat, J., Polak, T., Sala, M., Jenko, B., Harmrolfs, K., Ocampo-Sosa, A., Martinez Martinez, L., Herron, P.R., Fujs, S., Kosec, G., Hunter, I.S., Müller, R. and Petkovic, H. (2015) Construction of a new class of tetracycline lead structures with potent antibacterial activity through biosynthetic engineering, *Angew. Chem. Int. Ed.*, 54 (13): 3937-40.

<sup>6</sup>Hüttel, S., Giambattista, T., Herrmann, J., Planke, T., Gille, F., Moreno, M., Stadler, M., Brönstrup, M., Kirschning, A. and Müller, R. (2017) Discovery and total synthesis of natural cystobactamid derivatives with superior activity against Gram-negative pathogens, *Angew. Chem. Int. Ed.*, 56 (41): 12760-64.

<sup>7</sup>Sucipto, H., Pogorevc, D., Luxenburger, E., Wenzel, S.C. and Müller, R. (2017) Heterologous production of myxobacterial  $\alpha$ -pyrone antibiotics in *Myxococcus xanthus*, *Metab. Eng.*, 44:160-170.