GEOMAR

Helmholtz-Zentrum für Ozeanforschung Kiel

FB3 - RU Marine Natural Product Chemistry - Seminar

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Innovative antibiotics from microorganisms: Some case studies

Natural products continue to be a major source for novel antibiotic lead structures often exhibiting new mode of action(s). In this presentation I will describe our efforts to identify innovative sources of antibiotics and the path from microbial extracts to promising lead structures for pharmaceutical development.

As a first example for entirely new structures I will describe the recently identified cystobactamides as a new class of natural products with broad activity against gram-negative ESKAPE pathogens. The ESKAPE panel of bacteria represents the currently most difficult to treat causative and often multiresistant agents of nosocomial infections. The current status of our efforts to further develop cystobactamid gyrase inhibitors in preclinical studies will be presented.

As second example an update on our efforts to identify novel tuberculosis agents will be given. Despite modern antibiotics and the development of a curative regimen for this devastasting disease, tuberculosis remains a worldwide problem and the emergence of drug-resistant *Mycobacterium tuberculosis* has prioritised the need for new drugs. We show that new and optimised derivatives from *Streptomyces*-derived griselimycin are highly active against *M. tuberculosis*, both *in vitro* and *in vivo*. After identification of the griselimycin biosynthetic gene cluster we were able to clarify the biosynthesis of the biosynthetic precursor methyl-proline which is incorporated into the natural product at the site of metabolic lability. This finding opened up opportunities to improve the ratio of metabolically stable versus unstable griselimycin derivatives. Based on self-resistance studies in *Streptomyces* and genomic analyses of resistant mycobacteria, we found that griselimycins inhibit the DNA polymerase sliding clamp DnaN; these interactions were characterised by surface plasmon resonance and crystal structure analysis. Furthermore, we discovered that infrequent resistance to griselimycin is associated with highly unusual target amplification in mycobacteria. Our results demonstrate that griselimycin and its derivatives have high translational potential for tuberculosis, validate DnaN as an antimicrobial target and capture the process of antibiotic pressure-induced target amplification.

Date: Wednesday, 18th January 2017, **15:00 pm**
Venue: GEOMAR Westshore, Large Conference Room, DW 20
Host: Prof. Dr. Deniz Tasdemir