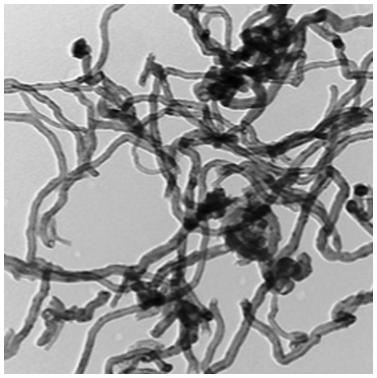
In This Issue

Carbon Nanotubes: Getting into the Biological Swing of Things



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Carbon nanotubes (CNTs) are remarkable materials that exhibit fascinating physicochemical properties, and their use as tools to investigate biological systems has been gaining attention and gathering momentum. Incorporating CNTs into routine biological research will require an integrative approach that crosses disciplines and draws from the efforts of chemistry, physics, and material and life sciences. In this review, Ménard-Moyon et al. provide an overview of recent examples of the use of functionalized CNTs as probes for molecular functions and highlight the potential of expanding and further developing CNT based approaches in life sciences. (Figure credit: Ménard-Moyon et al.)

Chemical Synthesis Meets *Mycobacterium tuberculosis*

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The easy accessibility and availability of a specific substrate is one of the key requirements that needs to be satisfied in order to fully characterize the kinetics of an enzyme. When that enzyme is IspF, a potential drug target due to its critical role in the 2-*C*-methyl-D-erythritol 4-phosphate (MEP) pathway for the biosynthesis of isopentenyl diphosphate and dimethylallyl diphosphate, two major building blocks of isoprenoid compounds, the need to investigate its kinetics in detail is further emphasized. Here, Narayanasamy et al. design a synthetic strategy to easily prepare a enantiopure 4-diphosphocytidyl-2-*C*-methyl-D-erythritol 2-phosphate, IspF sustrate, and use this compound to initate IspF characterization.

Killing Two PI3Ks with One Stone

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Williams et al. describe the discovery of small molecule inhibitors of unusual potency and selectivity for the immune-cell-expressed PI3Ks δ and γ. The compounds selectively target PI3Kδ and PI3Kγ but have over 1000-fold less activity against the ubiquitous PI3Kα and PI3Kβ. The authors discovered that PI3Kδ/γ dual inhibition provides a more desirable anti-inflammatory profile than either PI3Kδ inhibition alone or pan-PI3K inhibition and uncovered some functional antagonism of further PI3Kα/β inhibition in TNFα release. The work also revealed a previously unknown level of functional similarity between this dual inhibitory profile and that of the glucocorticoid agonist prednisolone.

Activating TRPML3

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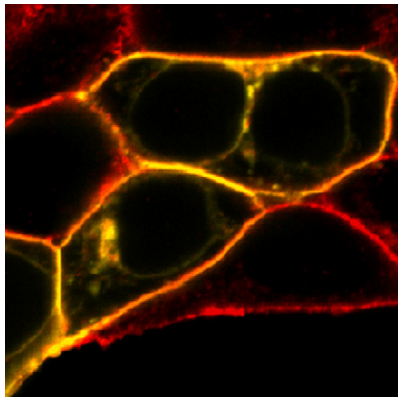
Transient receptor potential (TRP) channels are a large family of ion channels that conduct cations, including sodium, calcium, and magnesium. TRPML3 is one the family members, and a study by Grimm et al. now reports on the identification of 53 small molecules that selectively activate this channel. The compounds activate TRPML3 with different kinetics and maximal response levels, offering an unprecedented collection of tools to study activation mechanisms of TRPML3. Surprisingly, cells that natively express TRPML3 showed only weak or no responses to the activators. These results suggest that TRPML3 in native cells is either not present in the plasma membrane or that the protein heteromerizes with other subunits, leading to channels that are not or only weakly responsive to the compounds identified in this screen. (Figure credit: Grimm et al.)



Discovery of Kalimantacin/Batumin-Related Polyketide Antibiotic

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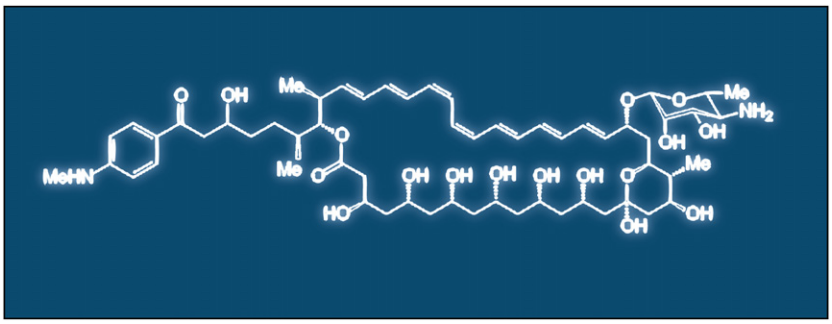
In the antibiotic resistance age, marked by an increasing need for novel compounds, secondary metabolites continue to play a major role in antibacterial drug discovery and development. Polyketides represent a major class of antibiotics, amenable to rational antibiotic design, by genetic modification within the modular biosynthesis operon. Research by Mattheus et al. focuses on a promising methicilin-resistant *Staphylococcus aureus* (MRSA, a critical pathogen in hospital environments) antibiotic, synthesized by a plurality of polyketide biosynthetic strategies. Analysis of this molecule and its analogs shows its potential and amenability towards engineering with improved activity.

Separate Nonribosomal Peptide Gene Clusters: Now on Speaking Terms

PAGE 160

One of the orphan biosynthetic gene clusters in the 8.2 Mbp genome of the erythromycin-producing bacterium *Saccharopolyspora erythraea* encodes a nonribosomal peptide synthetase (ErcD) for the production of erythrochelin, a novel iron-chelating diketopiperazine. Remarkably, Lazos et al. now show that the synthesis of erythrochelin also requires the action of a novel acetyltransferase encoded in a wholly separate gene cluster, in which the resident NRPS is inactivated by a frameshift mutation. Detection of two clusters collaborating to make a single molecule suggests a new factor to consider in future genome mining and sheds an intriguing light on the evolution of these bacterial pathways.

Redesigning Glycosylation



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Many therapeutic agents are based on glycosylated polyketide and peptide natural products. Alteration of sugar residues within these compounds can improve pharmacological properties. This has focused attention on enzymes that synthesise NDP-linked sugars and catalyze their transfer to aglycone acceptors. Here, Hutchinson et al. report in vivo glycosylation engineering of amphotericin B. A hybrid glycosyltransferase was shown to modify the aglycone core with perosamine rather than mycosamine. This represents the first rational redesign of a polyene glycosyltransferase and defines the GDP-sugar and aglycone-binding domains. This work will allow further glycorandomization to develop further the antifungal, antiparasitic, and antiviral activities of polyene macrolides.

Ganglioside GD2 Finds Its Small Molecule Ligand

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In this study, Tong et al. combined the use of NMR experiments and molecular modeling to furnish details on the molecular recognition of the ganglioside GD2 by anti-GD2 monoclonal antibody 3F8. Three small peptide ligands of GD2 were designed using the structural information. Peptide ligands were validated in binding and functional studies and in NMR experiments performed on GD2-peptide complexes. The work furthers the concept that it is possible to develop small molecule ligands of highly flexible targets such as carbohydrates and rationalizes that gangliosides may be druggable targets.

Targeting a Protein Kinases Inactive Form

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Several protein kinases have been characterized in a specific inactive form called the DFG-out conformation. This conformation has been targeted by selective type II inhibitors, including the cancer drugs imatinib and nilotinib. Despite this, the determinants that allow kinases to adopt this conformation are still unknown. Here, Ranjitkar et al. have identified a general pharmacophore that binds to this DFG-out conformation of kinases. Fluorophore-conjugated versions of this pharmacophore allow the determination of the thermodynamics and kinetics of ligand binding to the kinase catalytic domain. In addition, immobilized analogs of the general scaffold are effective reagents for enriching DFG-out-adopting kinases from cell lysates. (Figure credit: Ranjitkar et al.)