# In This Issue

## Selective NOD1 Inhibitors

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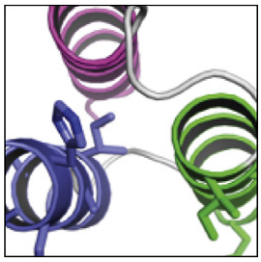
NLR proteins play seminal roles in innate immunity. In particular, NOD1 (NLRC1) activates various signaling pathways including NF-κB in response to bacterial ligands. *NOD1* polymorphisms are associated with several human inflammatory disorders including sarcoidosis, Crohn's disease, asthma, and autoimmune uveitis. Here, Correa et al. identify an inaugural class of 2-aminobenzimidazole compounds that selectively inhibit NOD1. Mechanistic studies of the prototypical compound Nodinitib-1 suggest that these molecules modulate NOD1 conformation and alter its subcellular localization. This inhibitor class constitutes chemical probes for interrogating mechanisms regulating NOD1 activity and tools for exploring the roles of NOD1 in various pathological conditions.

## Supercharged Human Proteins Take on the Delivery Job

PAGE 833

Macromolecules have become essential research tools and important human therapeutics but are limited by their general inability to cross cell membranes. Here, Cronican et al. searched for naturally supercharged human proteins (proteins with unusually high positive charge) and discovered a substantial class that potently deliver proteins in their functional form into mammalian cells both in vitro and also in murine retina, pancreas, and white adipose tissues in vivo. These proteins represent diverse macromolecule delivery agents for in vivo applications and also raise the possibility that they may possess native biological functions associated with their ability to penetrate cells.



## Peptide Tools for Angiogenesis

PAGE 839

In order to support on-going efforts in antiangiogenesis therapy and personalized medicine, Fedorova et al. used phage display to develop peptides that selectively recognizes vascular endothelial growth factor (VEGF) with nanomolar potency. The mode of VEGF recognition of the peptides was determined by high resolution X-ray crystal analysis. Using positron emission tomography, the show that radio-labeled peptides provided images of growing tumors in animal models 2 hr postinjection, which are comparable to images that were obtained 72 hr postinjection using a radio-labeled anti-VEGF antibody.

## Disrupting MAGL: Double Blow for Aggressive Cancers

PAGE 846

Characterizing the metabolic pathways that tumor cells use to support their malignant behavior is important for understanding and treating cancer. It has been shown that the lipolytic enzyme MAGL is elevated in aggressive breast, ovarian, and melanoma cancer cells, where it regulates a fatty acid network enriched in protumorigenic signaling lipids. Here, Nomura et al. show that MAGL is highly expressed in aggressive prostate cancer cells, in which it not only regulates protumorigenic fatty acid products, but also suppresses antitumorigenic endocannabinoid signals. Disrupting the MAGL pathway impairs tumor aggressiveness and offers a novel way to treat aggressive forms of cancer.

## Antimicrobial Peptide Biosynthesis

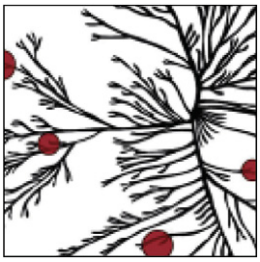
PAGE 857

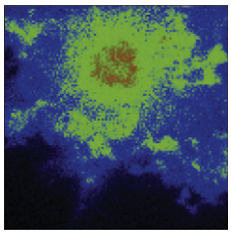
Lantibiotics are ribosomally synthesized and posttranslationally modified antimicrobial peptides. The recently discovered lantibiotic epilancin 15X produced by *Staphylococcus epidermidis* 15X154 contains an unusual N-terminal lactate group. In this study, Velásquez et al. elucidate the biosynthetic route towards epilancin 15X and demonstrate the activities of a serine-type leader peptide protease and a short-chain dehydrogenase/reductase involved in lactate formation in vitro. Furthermore, they show that the N-terminal lactate confers stability against proteolytic degradation by aminopeptidases, a feature that may be applied for the engineering of novel lantibiotics.

## High-Throughput Kinase Profiling for Inhibitor Discovery

PAGE 868

Selective protein kinase inhibitors have only been developed against a small number of kinase targets. Here, Miduturu et al. demonstrate that "high-throughput kinase profiling" of a library of 118 compounds constituting two distinct scaffolds is an efficient method for the discovery of lead compounds, both for established as well as unexplored kinase targets. They identified selective inhibitors with submicromolar cellular activity against various kinases. This inhibitor-centric approach permits a comprehensive assessment of a scaffold of interest and represents an efficient and general strategy for identifying new selective kinase inhibitors.





## Precise Control over $Ca^{2+}$ Signaling

PAGE 880

Many cellular processes rely on $Ca^{2+}$ signals to maintain healthy function. The ability to controllably generate local and global $Ca^{2+}$ signals thus facilitates the investigation of underlying $Ca^{2+}$ signaling that regulates cellular processes in healthy versus pathogenic cells. Here, Pham et al. developed LOVS1K, a genetically encoded and photoactivated synthetic protein that generates local or global $Ca^{2+}$ signals through binding to Orai1, a $Ca^{2+}$-specific membrane channel. This photoactivated system can be used to generate spatially and temporally precise $Ca^{2+}$ signals and to engineer synthetic proteins that respond to specific $Ca^{2+}$ signals.

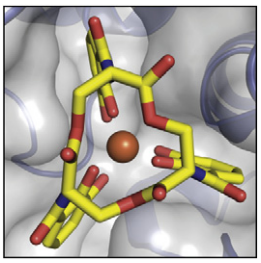
## Role of AAK1 in Neurotrophic Factor Signaling

PAGE 891

Identifying small molecules that target neurotrophic factor signaling may lead to novel therapeutics for a variety of nervous system disorders that involve altered brain plasticity. Here, Kuai et al. use an integrative quantitative proteomic and RNAi-mediated gene silencing strategy to identify adaptor-associated kinase 1 (AAK1) as a target of the indolocarbazole natural product K252a, which plays a critical role in the regulation of Nrg1/ErbB4-dependent neurotrophic factor signaling. These studies provide new insight into the molecular mechanisms that regulate neurotrophic factor signaling and may lead to novel approaches to regulate Nrg1/ErbB4 signaling in the brain.

## Siderophore Promiscuity

PAGE 907



Iron acquisition is crucial for survival and virulence of almost all microorganisms. Therefore, they secrete low molecular weight iron chelators, called siderophores, to mobilize iron from the environment. Iron-loaded siderophores are reimported into the cell by ATP-binding cassette transporters. The elucidation of the capture mechanism for different siderophores by the cognate transporter binding proteins is crucial for the potential development of new transporter-targeted antibiotics. Here, Peuckert et al. investigate the structural and stereochemical requirements for import of the prominent siderophore enterobactin and its synthetic analog mecam by X-ray crystallography and supporting iron uptake and mutational studies in vivo.

## p53 Inactivation with Lipidic Aldehydes

PAGE 920

Cancer and inflammation are known to be intrinsically linked pathologies in vivo; however, the chemical processes that underpin this linkage are largely unknown. Here, Nieva et al. show that direct modification of p53 by certain endogenous lipidic aldehydes, which are generated during inflammation, is sufficient to cause structural changes in p53 that may contribute to epigenetic silencing. This direct inactivation of p53 by cholesterol-derived aldehydes may therefore constitute a hitherto unknown chemical link between inflammation and cancer and may contribute in part to the cancers in which inactivation of wild-type p53 is a key component.

## tRNA Folding: Cooperative Effects of Nucleotide Modifications

PAGE 928

Using advanced RNA synthesis techniques and single molecule spectroscopy, Kobitski et al. describe the deconvolution of the individual contributions of posttranscriptional modifications to the overall folding and stabilization of tRNA. They find that the presence of $m^2G10$ alone does not facilitate the folding of $tRNA^{Lys}$, but that a stabilization of the biologically functional cloverleaf shape in conjunction with the principal stabilizing component $m^1A9$ exceeds the contribution of $m^1A$. This constitutes an unprecedented cooperative effect of nucleotide modifications in a naturally occurring RNA, which may be important for tRNA structure and for understanding the decay pathways of hypomodified tRNAs.