IN THIS ISSUE

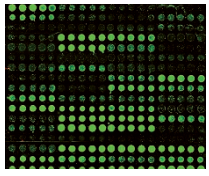
Paving a pancreatic road

Generation of pancreatic insulin-secreting beta cells from human embryonic stem cells (hESCs) holds great promise for treatment of metabolic diseases such as diabetes and for understanding the mechanisms of beta-cell formation. Chen *et al.* isolated (–)-indolactam V (ILV) from a high-content screen; when added to definitive endoderm that had been derived from hESCs, ILV increased the number of cells that express the pancreatic marker Pdx1. Using immunocytochemistry, the authors showed that these cells also expressed other pancreatic lineage markers. ILV acted synergistically with FGF10, a known contributor to pancreatic development, and its effects were mediated through protein kinase C. Transplantation of the cells into mice kidney capsules generated a population of insulin-positive cells *in vivo*, which suggests that the cells are on a path towards formation of mature insulin-secreting beta cells. [**Articles, p. 258; News & Views, p. 195**] *MB*

Quieting quorums

5′-Methylthioadenosine/*S*-adenosylhomocysteine nucleosidase (MTAN) is indirectly involved in the biosynthesis of quorum-sensing autoinducers (AIs), synthesizing a precursor of AI-2 and degrading feedback inhibitors of the enzymes that produce AI-1. Transition state analog inhibitors have been developed for MTANs, but they had not been tested in cells, thus making their applicability unclear. Gutierrez *et al.* now report that these Immucillin-A derivatives are effective against MTAN from *Vibrio cholerae*. The compounds persistently inhibit quorum sensing and biofilm formation but have no effect on cell growth overall. These results further support the inhibition of quorum sensing as an antibacterial strategy, and in particular validate MTAN as a relevant antibiotic target. [**Articles, p. 251**] *CG*

Host exosome meets HIV glycome



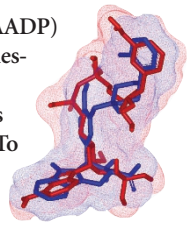
The mechanism of HIV exit is not well understood. One hypothesis suggests that HIV hijacks the microvesicle pathway to reach the cell surface. A lectin microarray analysis by Krishnamoorthy *et al.* now provides important support for this hypothesis. The authors observed that HIV and microvesicles from the same cell line were more alike than two HIV samples from different cells. The authors further pinpointed particular parts of the cell surface where the microvesicles and virus are likely to emerge, and particular glycans that are significantly enriched in the assemblies. These findings provide new insights into HIV trafficking and may help explain the lack of immunogenicity of HIV. [Articles, p. 244; News & Views, p. 198] *CG*

Prenylome probes

During protein prenylation, an isoprenoid tail is attached to the end of a substrate protein to promote its association with membranes and to modulate protein-protein interactions. Characterizing the prenylome of various cells, which has so far been laborious and lacking in sensitivity, will aid in understanding the impact that prenylation has on protein function. Nguyen *et al.* developed a functionalized isoprenoid called biotin-geranylpyrophosphate (BGPP) and, using structure-guided protein engineering, variants of the three mammalian prenyltransferases that are capable of conjugating BGPP to prenylation substrates. Each of the prenyltransferases exhibited a specific pattern of prenylation, including the modification of both known and new protein targets. The authors were also able to study the specificity of inhibitors of each of the prenyltransferases, offering a major advance over existing methods of prenylation analysis. [**Articles, p. 227; News & Views, p. 197**] *MB*

Written by Mirella Bucci, Catherine Goodman & Joanne Kotz

Mimic the messenger

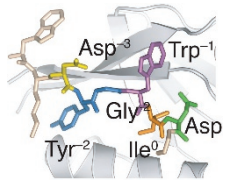


Nicotinic acid adenine dinucleotide phosphate (NAADP) has relatively recently been shown to be a second messenger involved in mediating Ca^{2+} signaling. Many of the roles of NAADP, along with the identity of its receptor, remain either unknown or controversial. To develop a chemical probe for NAADP-mediated processes, Naylor *et al.* conducted a virtual search for molecules with a similar three-dimensional shape and electrostatic distribution as NAADP. One of the hits, Ned-19, potently inhibited NAADP-mediated Ca^{2+} release in sea urchin eggs and mammalian cells. Further, Ned-19 revealed a role for NAADP in glucose-induced Ca^{2+} increases in mouse pancreatic beta cells. This work provides an important chemical tool for investigating the biology of NAADP. [Articles, p. 220] *JK*

Fishing for leukemia leads

Many leukemic oncogenes are transcription factors that regulate hematopoietic stem cell (HSC) differentiation. However, because HSCs are not highly prolific, they may be refractory to the cytotoxic agents typically used for treatment. Yeh *et al.* carried out a high-throughput screen of bioactive compounds to identify small molecules that could reverse the transcriptional effects of the leukemic oncogene AML1-ETO in zebrafish. The identification of nimeslide, a known COX-2 inhibitor, as a screening hit revealed an unexpected role for COX-dependent prostaglandin synthesis in mediating the effects of AML1-ETO on hematopoietic dysregulation. These results highlight the potential of zebrafish as a model for identifying chemical probes targeting oncogene function. [**Articles, p. 236**] *JK*

Dvl-oping Wnt inhibitors



Dishevelled (Dvl) proteins, which are key regulators of Wnt signaling pathways, contain a PDZ domain that mediates protein-protein interactions. Unlike most PDZ domains, which exclusively bind C-terminal peptides, the Dvl PDZ domain can also bind internal peptides. Zhang *et al.* used phage display to define an internal peptide consensus binding sequence that contained an invariant aspartate. Crystal structures of the Dvl PDZ domain with a C-terminal ligand and three internal peptide ligands revealed that aspartate can interact with the canonical C-terminal carboxylate contacts, and that the unusually flexible Dvl PDZ domain can accommodate a range of binding modes. A peptide ligand of Dvl PDZ inhibited Wnt signaling in a cell-based assay, which suggests the potential of this domain as a drug target. [**Brief Communication, p. 217**] *JK*