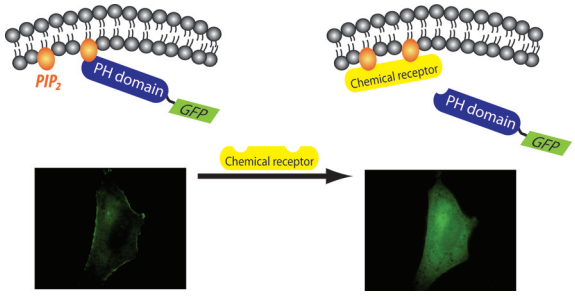
ACS chemical biology

In This Issue

pubs.acs.org/acschemicalbiology

KILLING THE MESSENGER

Second messengers are molecules that transmit messages from the cell surface to other parts of the cell. Tight regulation of the second messenger phosphatidylinositol (4,5)-bisphosphate ($PI(4,5)P_2$), which is also a precursor for other second messengers, is important for maintaining proper functioning of numerous cellular activities including actin polymerization and molecular transport processes. Pleckstrin-homology domains in lipid-binding proteins are the natural binding partners for $PI(4,5)P_2$ in the cell; Mak *et al.* (DOI: 10.1021/cb2003187) now present the design, synthesis, and biological activity of a small molecule mimic of a pleckstrin-homology domain.

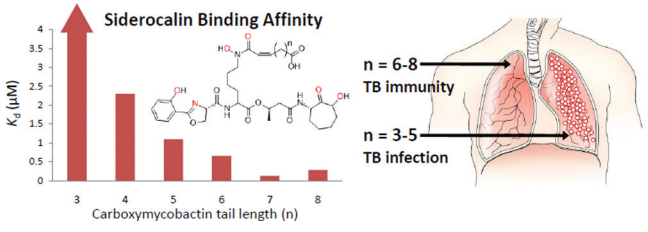


The small molecule pleckstrin-homology domain mimic, called PHDM, exploits the phosphate-binding properties of urea moieties and the diol-binding propensity of boronic acid groups to target $PI(4,5)P_2$ *in vitro* and in a cellular environment, as indicated by its ability to alter protein transport and actin fiber formation in cells. This "chemical receptor" is a clever molecular tool for exploring $PI(4,5)P_2$ biology and provides a launching pad for the development of drugs that target $PI(4,5)P_2$-dependent disorders.

IRON PIRACY

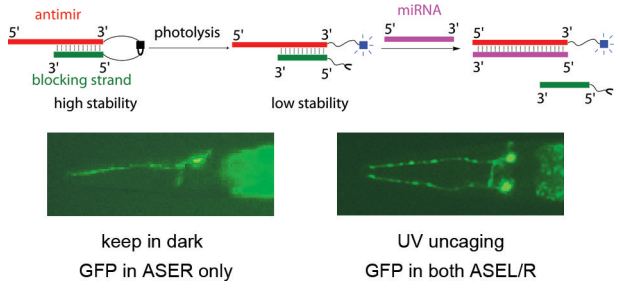
Many pathogenic bacteria, such as the causative agent of tuberculosis *Mycobacterium tuberculosis*, shrewdly pillage iron from their host organisms using small molecule iron chelators called siderophores. Human macrophages, white blood cells whose job it is to devour bacterial invaders, use a protein called siderocalin to bind siderophores and prevent iron transport to the bacteria. *M. tuberculosis* produces a family of siderophores called carboxymycobactins, but their interactions with siderocalin are not well characterized. Hoette *et al.* (DOI: 10.1021/cb200331g) now explore these interactions, offering insight into the mechanism by which these elusive iron-chelating agents contribute to *M. tuberculosis* pathogenicity.

Carboxymycobactins are hexadentate iron chelators that vary in the length of their fatty acid tail. Fluorescence binding assays and protein crystallography demonstrated that siderocalin uses distinct binding modes when interacting with carboxymycobactins with differing fatty acid tails, which contributes to the wide range of binding affinities observed among the interactions. This range of affinity suggests that at least some carboxymycobactins are able to elude siderocalin binding, perhaps aiding in the ability of the pathogen to escape innate immune detection.



SHINING A LITTLE LIGHT ON DEVELOPMENT

MicroRNAs (miRNAs) are small, noncoding RNAs that regulate gene expression by targeting mRNAs, and they have been implicated in numerous biological processes and human diseases. A single miRNA can target multiple mRNAs and have different roles in different cell types and at different stages of development, leading to extraordinarily complex biology that is difficult to disentangle using conventional experimental methods. In an effort to probe miRNA activity in a spatially and temporally controlled fashion, Zheng *et al.* (DOI: 10.1021/cb200290e) create photoactivatable antisense reagents.



The photoactivatable reagents, called cantimirs, are composed of two complementary strands of 2′-*O*-methyl oligoribonucleotides designed to target the miRNA *lsy-6*, which is involved in neuronal development in the nematode *C. elegans*. The cantimirs are inactive until exposure to 365 nm light, which triggers the release of a potent antisense inhibitor of *lsy-6*. Use of these innovative reagents in living worms led to the finding that transient expression of *lsy-6* at a specific stage of embryonic development is critical for determining neuronal cell fate.

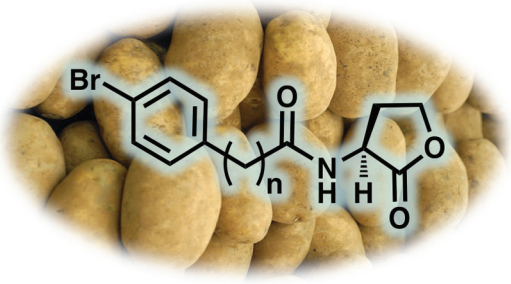
SYNTHETIC SENSORS

Bacteria talk to each other using a method called quorum sensing, where small molecules are used to communicate information about the bacterial population. This information lets the bacteria know whether particular activities important for bacterial growth and survival, such as biofilm formation, virulence factor production, or sporulation, are called for. Synthetic quorum sensing modulators are valuable tools for exploring these processes and have been used extensively in

Published: December 16, 2011

   dx.doi.org/10.1021/cb200462p | *ACS Chem. Biol.* 2011, 6, 1301–1302

bacterial culture-based systems, but the relevance of these systems to native bacterial behavior is unclear. Palmer *et al.* (DOI: 10.1021/cb200298g) now explore the activity of synthetic quorum sensing modulators in native host-pathogen environments.



Several synthetic quorum sensing compounds were first confirmed to be active in native interactions between the plant bacterial pathogen *Pectobacterium carotovora* and two of its hosts, the potato and the green bean. Interestingly however, it was observed that the timing of compound dosing was a critically important factor for inhibiting virulence in wild-type infections. This innovative study is the first showing that synthetic quorum sensing modulators are active in native host-pathogen interactions, and points to their potential in exploring other systems as well.