

## research highlights

# This work published in *PNAS* has been chosen as one of "Research Highlights" in *Nature Chemical Biology*

Although widespread resistance to antimalarials has created an urgent need for new drugs, progress in identifying new drug classes and targets has been slow. In large-scale efforts to increase the chemical and target diversity of potential antimalarials, two groups have reported high-throughput screens for compounds that inhibit the growth of asexual blood-stage *Plasmodium falciparum* at low micromolar concentrations. Gamo *et al.* screened nearly 2 million compounds, identified and confirmed over 13,000 hits and used previous bioactivity data to suggest modes of action for over 4,000 of these. Only 15% of the hits were toxic to a human liver cancer cell line, and about 60% inhibited a multi-drug-resistant *Plasmodium* strain. Guiguemde *et al.* screened a diverse chemical library of over 300,000 compounds, leading to approximately 1,100 confirmed hits. They subsequently evaluated nearly 230 structurally diverse compounds for synergies with known antimalarial drugs, *in vitro* inhibition of 66 potential malarial drug targets and growth inhibition across a range of drug-resistant *Plasmodium* strains and other protozoan parasites. *In vivo* pharmacokinetic and toxicity

### PHOTOSYNTHESIS

#### Transcriptional light switch

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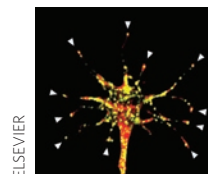
To survive in a fixed location, plants have evolved mechanisms to adapt to varying intensities and wavelengths of light. Alterations in light quality may perturb the balance of electron transport between the two photosystems (PSI and PSII), which leads to photosynthetic inefficiency. Plastoquinone (PQ), a mobile redox-active electron shuttle between PSI and PSII, is believed to sense these photosynthetic imbalances and initiate a transcriptional program response that resets the stoichiometry of the two photosystems in chloroplast membranes. Shimizu *et al.* now provide evidence in *Arabidopsis thaliana* that the redox state of PQ results in changes in the phosphorylation state of plastid sigma factors (SIGs), which directly regulate transcriptional levels of photosystem genes. The authors showed that phosphorylation of Thr170 of SIG1—the most abundant sigma factor in *Arabidopsis* leaves—selectively reduces the transcription of *psaA*, a gene coding a

component of PSI, but only weakly affects transcription of PSII genes such as *psbA*. Using small-molecule reagents to perturb the redox state of PQ, the authors concluded that in the oxidized state, SIG1 is phosphorylated in the RNA polymerase holoenzyme complex and reduces *psaA* transcription to adjust the balance. Though further work will be needed to identify the kinase that mediates SIG1 phosphorylation and to show how it is regulated by PQ redox state, this study provides a working model for how transcriptional changes are linked to electron transport-state sensing in plants. TLS

### TRANSLATION

#### DCC coupling

*Cell* **141**, 632–644 (2010)



Although it is well known that the translation of mRNAs into proteins occurs in the cytoplasm of the cell, less is known about how translation—for example, to produce proteins involved in cell motility, cellular adhesion and synaptic plasticity—is localized to particular subregions of a cell. Tcherkezian *et al.* now report that the Deleted in Colon Cancer (DCC) protein, a transmembrane receptor involved in axon growth and guidance, acts as a link between the translational machinery and the plasma membrane of neuronal axons and dendrites. The authors find that DCC directly interacts with several eukaryotic initiation factors (eIFs) as well as ribosomal subunits. DCC is a receptor for netrin-1, an extracellular protein that mediates axon guidance and cell migration, and the authors determine that the cytoplasmic domain of DCC is required for the netrin-1-dependent translation of a reporter gene. Truncations of the cytoplasmic region of DCC revealed that the P1 region—which is conserved from *C. elegans* to mammals—is required for the observed activity, and additional studies revealed that the P1 subdomain directly interacts with ribosomal protein L5. Further work is needed to determine exactly how DCC links the extracellular presence of netrin-1 to the intracellular translation of key mRNAs, but it seems likely that other transmembrane receptors use similar mechanisms to spatially localize translation to the plasma membrane in response to an extracellular signal. JMF

### GLYCOLIPIDS

#### Defensins on offense

*Science* **328**, 1168–1172 (2010)

Antimicrobial peptides such as the defensins are generally thought to act by forming amphipathic structures that interrupt the bacterial membrane, but recent reports suggest that these sequences may have additional or alternate targets. In exploring the function of plectasin, a 40-residue defensin, Schneider *et al.* observed that it did not act similarly to other agents that interrupt the membrane or those with intracellular targets; rather, plectasin showed kinetic behavior akin to that of compounds such as vancomycin that interfere with cell wall biosynthesis. Labeling studies confirmed that glucosamine—a precursor of Lipid II and other cell wall components—was not incorporated in plectasin-treated cells, whereas other biomolecular building blocks were used normally. Analysis of Lipid II and its biosynthetic precursors in plectasin-treated cells demonstrated the accumulation of an early intermediate; more direct tests showed that plectasin inhibited reactions using Lipid I or Lipid II by binding the substrates directly with low-micromolar affinity. In combination with NMR characterization of the complex, these data suggest a mode of action in which plectasin sits at the membrane interface and binds to the exposed peptidoglycan portion of these cell wall precursors. As this specific mode of action is distinct from that of vancomycin, plectasin and functionally related defensins identified in this study could provide an important complement to known therapies. CG

