IN THIS ISSUE

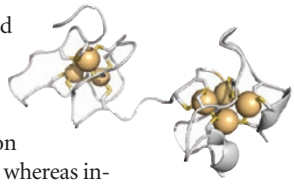
Cdc7 on the firing range

Many anticancer therapeutics target the elongation step of DNA replication. However, cancer cells can become resistant to these drugs, and so new therapeutics that operate via different mechanisms of action are therefore needed. MCM proteins and the Cdc7 kinase are known to be involved in assembling complexes critical for replication initiation, but the details of the process are still unclear. Through compound screening and biochemical analysis, Montagnoli *et al.* have identified the small molecule PHA-767491 as an inhibitor of Cdc7. They used the compound to show that Cdc7 inhibition decreases origin firing, thereby blocking initiation of DNA synthesis. Cell-based assays showed that PHA-767491 inhibits proliferation in many human cancer cell lines, and studies in rodents demonstrated that the compound has *in vivo* antitumor activity. [**Articles, p. 357; News & Views, p. 331**] *KS*

Methyltransferases on the loose

Methyltransferases are known to play an important role in epigenetics, and the histone target of G9a, a lysine methyltransferase, has been identified. However, a few reports also suggest that methylation occurs in a regulated fashion on non-histone targets, such as important biomolecules like p53. Rathert *et al.* surmised that these methyl modifications might be occurring on an even larger scale. The authors used peptide arrays to confirm the substrate specificity of G9a, then used this preferred peptide sequence to search a protein database for potential additional substrates. *In vitro* and *in vivo* characterization of G9a activity verifies that these protein substrates are modified and further suggests that introduction of the methyl groups can alter function or recognition. These results suggest that methylation may be occurring more broadly than previously appreciated, and they also highlight the utility of peptide arrays as a starting point for methyltransferase characterization. [Brief Communications, p. 344; News & Views, p. 332] *CG*

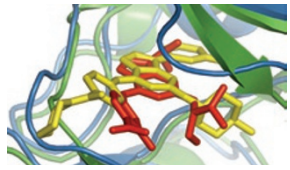
Attenuating Aβ toxicity



Alzheimer's disease (AD) is characterized in part by amyloid-β (Aβ) plaques and increased generation of toxic reactive oxygen species (ROS). Cu(II) binding to Aβ promotes both aggregation of Aβ into plaques and ROS generation, whereas interaction of Aβ with Zn(II) is thought to be neuroprotective. The Zn(II)-containing metallothionein Zn_7MT-3 has been shown to rescue the neuronal toxicity of Aβ, but the mechanism of this effect has remained unclear. Meloni *et al.* have now used spectroscopic analyses and cell culture studies to provide evidence that a metal swap between Zn_7MT-3 and Aβ–Cu(II) involving zinc and copper is likely to be responsible for the quenching of ROS production and the resultant protection against cellular toxicity. This mechanistic insight confirms the reported neuroprotective effect of Zn_7MT-3 and suggests potential new approaches to AD therapy. [**Articles, p. 366**] *KS*

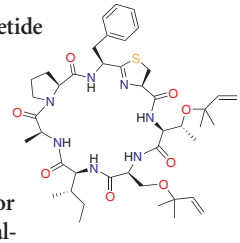
Written by Mirella Bucci, Catherine Goodman & Kenneth Sercy

Taking out malaria



Ca^{2+} is essential for malarial invasion of erythrocytes, but the exact mechanisms behind this requirement are unknown. Because of their conservation in parasites, Kato *et al.* hypothesized that the EF hand–containing calcium-dependent protein kinases (CDPKs) could be playing a role. The authors used a knowledge-based data-mining algorithm called ontology-based pattern identification that analyzes transcriptome profiles to cluster CDPKs with known biological processes, cellular components or molecular functions. This analysis placed *Plasmodium falciparum* CDPK1 (PfCDPK1) in a cluster of genes related to parasite motility. By screening a kinase-directed heterocyclic library of compounds, they found several derived from 2,6,9-trisubstituted purine kinase inhibitors, including purfalcamine, that could be computationally docked onto PfCDPK1. Transcriptome analysis of treated parasites suggested that purfalcamine affects the late schizogony or the merozoite life cycle stages. Purfalcamine could delay the onset of parasitemia in a mouse malaria model, which suggests a key role for PfCDPK1 as a potential druggable target in malarial infection. [Articles, p. 347; News & Views, p. 334] *MB*

Cyanobactins get it together



Nonribosomal peptide synthetases and polyketide synthases represent well-known biological machinery for assembling natural products. Some naturally occurring cyclic peptides, such as the patellamides, have been shown to use an alternate biosynthetic pathway of ribosomal synthesis of a hypervariable precursor followed by cyclization and tailoring by specialized enzymes. A genetic and small-molecule search now shows that this pathway is a ubiquitous assembly line in cyanobacteria. Comparison of a larger group of bacterial genomes demonstrates that the gene clusters contain a hypervariable region that encodes for precursor peptides; the remaining genes encode for enzymes that determine the oxidation state of the molecule or whether the product will be prenylated, as in the newly discovered trunkamide. Further biochemical investigations will shed light on how these enzymes work in tandem to create the final product. [Brief Communications, p. 341] *CG*

Comfortably numb

Δ^9-Tetrahydrocannabinol (THC), the main psychoactive component of marijuana, is attractive as an analgesic but also leads to undesirable side effects. CB_1, the brain receptor for THC, is also activated by the endogenous cannabinoids anandamide and 2-AG. These endocannabinoids are broken down by the enzymes FAAH and MAGL, respectively, and inhibition of FAAH activity has been shown to promote pain relief without the usual side effects associated with THC. Nomura *et al.* now provide biochemical and genetic evidence that some organophosphorus nerve agents mimic the effects of direct CB_1 agonists by inhibiting FAAH and MAGL, thereby raising brain levels of anandamide and 2-AG and lowering levels of arachidonic acid, a precursor to prostaglandins and other eicosanoids. These results will be useful in the search for new ways to relieve pain, and they also suggest a new role for endocannabinoids in brain eicosanoid pathways. [**Articles, p. 373**] *KS*