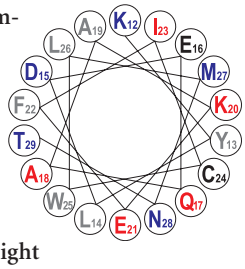
Bioorthogonal synthesis

The introduction of non-natural amino acids to proteins via ribosomal engineering typically requires the removal of amino acids that would compete with the desired non-natural amino acid, which limits the utility of the technique in mixed cell cultures. Ngo *et al.* now report the use of azidonorleucine, an amino acid completely excluded by normal protein synthesis procedures, in combination with a new mutant methionyl-tRNA synthetase that can effectively utilize azidonorleucine, to selectively label proteins in the presence of methionine. This approach should significantly expand the ways in which non-natural amino acids can be used to label and track biomolecules of interest. [**Brief Communication, p. 715**] *CG*

Entry denied

HIV entry begins when the glycoprotein gp120 binds to the host cell receptor CD4, undergoes a significant conformational change and binds to a second coreceptor. Entry inhibitors have primarily targeted the CD4 binding site, and the few inhibitors that bind to both sites are not highly effective. Baleux *et al.* now describe a bivalent strategy that employs heparan sulfate, which is known to bind gp120 in part via the rearranged coreceptor site. The authors created a synthetic glycopeptide containing a CD4 motif and a dodecasaccharide heparin sulfate fragment to recreate the normal interaction between gp120 and the host cell. This glycoconjugate showed a significant synergistic effect compared to the individual peptide and carbohydrate components, with affinities for gp120 in the low nanomolar range and antiviral activity against three HIV strains. [**Article, p. 743**] *CG*

A hormone hybrid

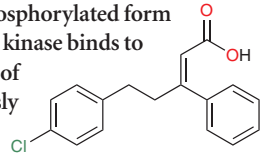


Glucagon and glucagon-like peptide play important roles in controlling blood glucose, and agonism of the glucagon-like peptide receptor is currently the most effective means of treating metabolic syndrome. Day *et al.* hypothesized that combining the lipolytic, glucose-elevating effects of glucagon with the compensating, glucose-lowering effects of glucagon-like peptide might help to burn fat while maintaining glucose levels. Analysis of the shared helical structure of the peptides led to a hybrid sequence capable of activating both systems. Treatment of mice and rats with stabilized peptides caused significant loss of body fat, demonstrating the success of the new approach. [Article, p. 749] *CG*

Tunnel vision

1,2,3-Trichloropropane can be detoxified by conversion to 2,3-dichloropropane-1-ol by haloalkane dehalogenases, but this process is not efficient enough for industrial purposes. Previous studies showed that a mutation in an access tunnel to the active site improved enzyme activity, but the basis for this effect was not known. Pavlova *et al.* now report the mutation of multiple residues in the tunnel, generating faster enzyme variants. This rate enhancement was due to a faster cleavage of the carbon-halogen bond, which was a direct outcome of placing larger residues in the tunnel and obstructing the access of disruptive water molecules to the active site. This result highlights the potential importance of engineering mutations distal to the active site. [Article, p. 727] *CG*

Chemical mimicry

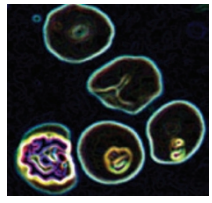


The kinase PDK1 is activated when the phosphorylated form of the hydrophobic motif (HM) of a target kinase binds to the substrate docking site, the 'PIF pocket', of PDK1. Biondi and colleagues had previously identified small molecules that bind to the PIF pocket of PDK1 and induce activation of the kinase in the absence of a phosphorylated HM binding partner. Hindie *et al.* now use a combination of approaches to define the conformational changes induced by small-molecule binding. In addition to local conformational changes at the site of binding, the activating compound induced more distant structural changes in the ATP binding site and activation loop. These conformational changes mirror those induced by docking of a phosphorylated HM, providing new insights into how small molecules can mimic phosphorylation-dependent conformational changes. [Article, p. 758] *JK*

Borrowing for T cells

The immunosuppressive drug cyclosporin A (CsA) binds the prolyl isomerase cyclophilin 18, and this complex is required for inhibition of the IL-2–mediated immune response involving the phosphatase calcineurin (CaN). Zhang *et al.* have now generated three photo-activated CsA derivatives to modulate immune signaling. These azobenzene (AB) derivatives could be reversibly converted from *trans* to *cis* forms with IR irradiation, with a biotin-bound "borrowed" protein cargo able to augment the structural difference between the photoswitchable conformers. The resulting bifunctional molecule was active in inhibiting CaN *in vitro* and *in vivo*. The *cis* and *trans* derivatives had distinct effects on CaN signaling patterns in activated T cells, thereby demonstrating their utility in modulating signaling in a non-invasive and selective manner. [**Brief Communication, p. 724**] *MB*

Mapping malarial responses



Development of new antimalarial drugs and an increased understanding of resistance mechanisms to current drugs are urgently needed. However, identifying the functionally relevant target of a small molecule is particularly challenging in the malarial parasite. Yuan *et al.* conducted quantitative high-throughput screening to determine the antiproliferative activity of 1,279 bioactive molecules across 7 parasite lines. For 3 of 149 compounds that produced differential chemical phenotypes between distinct parasite lines, the authors used genetic mapping to identify the determinants of the differential response. In one example, differential sensitivity to a serotonin receptor agonist mapped to *pfmdr1*, a gene encoding an ABC transporter involved in drug resistance. This study provides a method for investigating the mechanism of action and resistance of antimalarial drug leads. [Article, p. 765] *JK*

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