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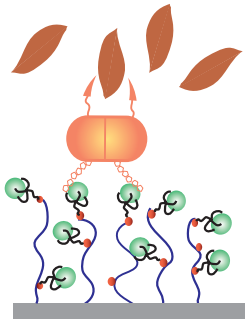
Decoding Docking Domains

Bacterial polyketide synthases (PKSs) generate an impressive collection of diverse, often therapeutically valuable natural products. Type I modular PKSs assemble their products by shuttling metabolic building blocks along a linear, multiprotein complex. Though many fascinating details about the catalytic properties of the PKS components have been elucidated, less is known about the process by which the intermediates are transferred from one module to the next. Buchholz *et al.* (DOI: 10.1021/cb8002607) now present a comprehensive analysis of this process in two PKS systems.

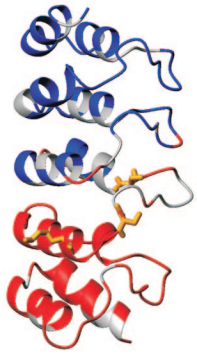
Surface plasmon resonance, fluorescence polarization, and X-ray crystallography were used to investigate the nature of the interactions between specific PKS modules, which occur at areas referred to as docking domains. The studies provide evidence of the significance of the binding specificity encoded in the docking domains for the proper linear arrangement of the PKS modules.



Phosphorylation: Regulating the Regulators

Cyclins, cyclin-dependent kinases, and cyclin-dependent kinase inhibitors (CKIs) are key players among the many enzymes and regulatory proteins that orchestrate the cell cycle. One CKI, $p19^{INK4d}$, has distinguished itself from other members of its CKI family by exhibiting distinct phosphorylation and degradation patterns, suggesting that unique mechanisms control its function. Using an elegant combination of experimental and computational methods, Löw *et al.* (DOI: 10.1021/cb800219m)and Point of View (DOI: 10.1021/cb900003f) explore the stability and structure of this important cell cycle regulatory protein.

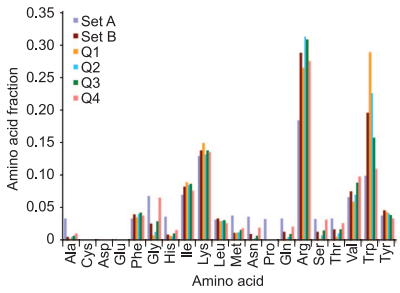
Stability, kinetic, and high-resolution nuclear magnetic spectroscopy studies of a $p19^{INK4d}$ variant that mimics its phosphorylated state revealed intriguing insights into how phosphorylation of $p19^{INK4d}$ affects its stability and function. In addition, molecular dynamics simulations provided further evidence that the phosphorylated state of $p19^{INK4d}$ may have increased susceptibility to degradation.



Cationic Peptides Combat Resistance

Given the rapid emergence of antibiotic resistant bacteria, it is particularly alarming that only two structurally novel antibiotics have been discovered in the past 40 years. Cationic antimicrobial peptides are a promising source of new antibiotics given their activity against a broad range of microorganisms and the low tendency of bacteria to become resistant to them. Now, Cherkasov *et al.* (DOI: 10.1021/cb800240j) combine computational approaches with experimental data to create novel antimicrobial peptide antibiotics.

Array technology was used to iteratively create two antimicrobial peptide-based libraries. The antibacterial activity of the peptides guided the use of quantitative structure–activity relationship modeling and a nonlinear modeling technique called artificial neural net approach to predict the biological activity of 100,000 virtual peptides. This led to the identification of several peptides with activity against various resistant bacterial strains.



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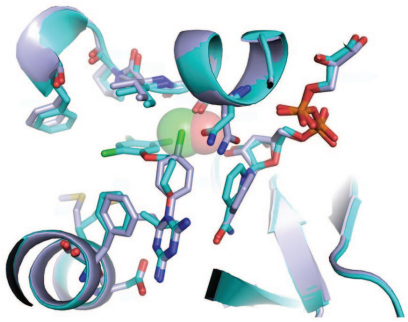
In Silico, Structure, and Serendipity

Malaria, caused by parasites of the *Plasmodium* genus, is a devastating global epidemic responsible for an astounding 350 million infections and up to 3 million deaths annually. Though several antimalaria drugs exist, the rapid emergence of resistant parasites signifies the urgent need for new treatments. Dasgupta *et al.* (DOI: 10.1021/cb8002804) report their partly serendipitous discovery of structurally novel inhibitors of the key malarial drug target thymidylate synthase-dihydrofolate reductase (TS-DHFR).

An *in silico* screen targeting a unique linker region in TS-DHFR identified several compounds to test in enzymatic and cellular assays. Three compounds containing a novel biguanide scaffold were discovered as parasite-specific TS-DHFR inhibitors, but surprisingly, computational and structural studies revealed that the compounds actually bound to the active site of DHFR. Nonetheless, the compounds represent an exciting new class of potential antimalaria drugs.



Good as Gold

The field of metagenomics strives to harness the genetic diversity harbored in the many unculturable bacteria found in the environment by extracting their DNA and expressing their genes in bacteria that can be cultured in the laboratory. Typically, *Escherichia coli* and *Streptomyces* are used as the expression hosts, limiting the findings to the capabilities inherent in these species. Craig *et al.* (DOI: 10.1021/cb8002754) explore the use of the bacteria *Ralstonia metallidurans*, known for its ability to thrive in high concentrations of heavy metals such as gold, as a potential new host for expression of environmental DNA (eDNA) libraries.

The eDNA libraries were expressed in *R. metallidurans* and screened for the production of both colored substances and antibiotic activity. Characterization of several isolated metabolites revealed some known compounds and two novel structures, validating the utility of *R. metallidurans* and enabling access to its unique characteristics as an eDNA expression host.