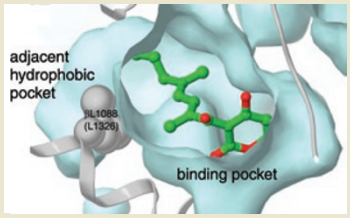
Antibiotics shackle bacterial claw



Bacterial RNA polymerase (RNAP) is the target of the rifamycins, the mainline antibiotic class used to control tuberculosis. However, clinical utility of the rifamycins is diminishing as resistant strains of mycobacteria emerge. Now three compounds isolated from *Myxococcus* bacteria have been found to inhibit bacterial RNAPs by a different mechanism from the rifamycins. These new compounds freeze the claw-like arms of the polymerase in a closed position, preventing the entry of DNA promoter regions into, and transcription initiation by, the protein. Using mutants selected for resistance to the α-pyrone antibiotic, myxopyronin (Myx), Mukhopadhyay *et al.* map the antibiotic-binding region of RNAP to the switch region. Functionally, the antibiotic prevents the production of abortive RNA products (indicative of initiation) and elongation products, as well as the formation of heparin-resistant RNAP-operon complexes. Structural studies confirmed that Myx binds at a site remote from the active site of the enzyme, buried in the folds of the protein. Myx-resistant mutants displayed cross-resistance to both structurally related (α-pyrone corallopyronin) and unrelated (macrocyclic-lactone ripostatin) antibiotics. The mechanism of action of this group of antibiotics resembles that of the nonnucleoside reverse transcription inhibitors of HIV/AIDS drugs. This, plus their broad spectrum of activity, leads the authors to suggest that these three myxobacterial antibiotics may provide a fruitful starting point for new antibiotic development. (*Cell* **135**, 295–307, 2008) *LD*

Flipping for apoptosis

Overexpression of the anti-apoptotic protein Bcl-2 is believed to contribute to tumor resistance to chemotherapy and radiation, which has made it a target for various drug development programs. Now, Kolluri *et al.* describe a peptide that causes the protein to flip from being anti-apoptotic to pro-apoptotic. Using the Bcl-2 binding domain of the pro-apoptotic nuclear receptor Nur77 as a guide, the researchers design a nine amino-acid peptide and conjugate it to a cell-penetrating peptide. This peptide and its enantiomer induce apoptosis in Bcl-2–expressing mouse fibroblast cells and mouse tumors. In fluorescence polarization assays, the researchers show that the peptide binds to an unstructured loop structure in the Bcl-2 protein, interfering with intramolecular interactions between the loop and a BH4 domain and exposing the BH3 domain, believed to be a purveyor of death through its interaction with other Bcl-2 family members, Bax and Bak. Structural studies with the peptide provide more insights into the functioning of unstructured loops, a feature shared among many signaling proteins that figure in important biological processes, including tumorigenesis. The enantiomer, which is protease resistant, could point the way toward possible therapeutic interventions in Bcl-2–overexpressing tumors. (*Cancer Cell* **14**, 285–298, 2008) *LD*

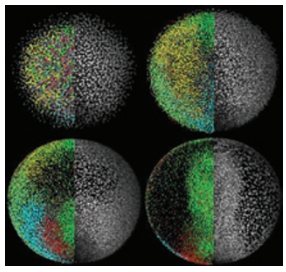
Dual-targeted kinase inhibitor

Bayer's (Leverkusen, Germany) Nexavar (sorafenib) and Pfizer's (New York) Sutent (sunitinib) were the first approved targeted therapies with dual mechanisms of action. The former primarily targets the serine/threonine kinase RAF/MEK/ERK pathway and tyrosine kinase receptors for vascular endothelial growth factor 2 (VEGFR2) and platelet-derived growth factor-β (PDGFR-β), whereas the latter inhibits c-KIT as well as VEGFR, PDGFR-α/β and FLT-3. Now Shokat and colleagues have systematically searched for a lead that targets both a tyrosine kinase and phosphatidylinositol kinase (PI(3)K) without affecting serine/threonine kinase activities. To achieve this, they screen 300 analogs of a pyrazolopyrimidine Src inhibitor for activity against PI(3)K but negligible effect on serine/threonine kinases, such as Raf or Alk4. By tweaking the structure of one of the resulting leads to enable it to occupy a binding pocket conserved between the two protein classes, they generate a compound that promiscuously targets both classes of oncogenic kinase. The findings not only reveal a new type of multitargeted kinase that targets PI(3)K—a protein providing a mechanism of resistance to tyrosine (protein) kinase inhibitors—but also suggest principles that may guide drug design to selectively broaden activity against structurally divergent protein families. (*Nat. Chem. Biol.* **4**, 691–699, 2008) *PH*

Malaria parasites sequenced

Research on anti-malarial drugs and vaccines has been given new impetus with the publication of the genome sequences of two malaria-causing parasites. The sequence of *Plasmodium falciparum*, the agent of the most severe and widespread form of malaria, was released in 2002. The newly sequenced parasites are *P. vivax*, responsible for 25–40% of worldwide malaria cases, and *P. knowlesi*, which primarily infects monkeys. *P. vivax* is little studied because of the difficulty of propagating it in the laboratory. Through comparative genomic analysis, Carleton *et al.* find that it possesses eight novel gene families and erythrocyte invasion mechanisms of similar complexity to those of *P. falciparum*. *P. vivax* and *P. falciparum* also show a high degree of conservation with respect to metabolic pathways, housekeeping genes and predicted membrane transporters. The sequence of *P. knowlesi*, reported by Pain *et al.*, reveals five novel gene families and an unprecedented organization of variant gene families involved in antigenic variation, which are distributed throughout the genome and colocalize with intrachromosomal telomere sequences. (*Nature* **455**, 757–763, 2008; *Nature* **455**, 799–804, 2008) *KA*

Google Earth meets zebrafish development



Scientists in Germany have tracked the movement of every cell in a zebrafish embryo as it develops from a single cell into ~20,000 cells over 24 hours. Using a new imaging technology, digital scanned laser light sheet microscopy (DSLM), Keller *et al.* collected ~400,000 images per embryo to reconstruct the first digital, three-dimensional representation of early vertebrate development. Similar to Google Earth, the digital embryo allows researchers to zoom in on select cellular details (http://www.embl-heidelberg.de/digitalembryo/). DSLM is an improved version of light-sheet microscopy, which illuminates the sample along a single plane, reducing phototoxicity. The new technique provides higher-quality, higher-speed imaging by generating a plane of light with a laser scanner that moves rapidly through the sample vertically and horizontally. Compared with DSLM, confocal and two-photon microscopy exposed the embryos to 5,600- and 1,000,000-fold more energy, respectively. The authors describe various novel insights into zebrafish development, including morphodynamic symmetry breaking at the 512-cell stage. (*Science*, published online 9 October 2008 (doi: 10.1126/science.1162493)) *KA*

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