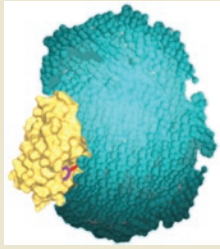
Imprinted microgel inhibitors



Molecularly imprinted polymers (MIPs) have been reported to specifically recognize proteins of interest and even exhibit low catalytic activity, but never to exhibit drug-like properties. Taking advantage of the known ability of benzamidine (red) to inhibit trypsin (yellow), Haupt and coworkers couple methacrylic acid to 4-aminobenzamidine to provide an anchoring monomer that initiates growth of cross-linked water-soluble microgel polymers (blue) close to the substrate-binding site of the protease. After removing trypsin from the polymers by electromigration, they demonstrate that the microgels bearing a specific recognition site not only bind selectively to trypsin, but also competitively inhibit its activity with ~1,000-fold greater potency than free benzamidine. The authors show that the position of the benzamidine is important; MIPs do not bind trypsin simply by virtue of carrying benzamidine. Especially as MIPs have better chemical and physical stability than antibodies, this proof-of-principle study suggests potential roles for synthetic polymers in drug development.
(*J. Am Chem. Soc.* **131**, 14699–14702, 2009) *PH*

Wnt knocked out of cancer's sails

The Wnt pathway is one of the most prominent oncogenic signaling cascades. The activity of the pathway is controlled by the relative stability of two proteins: β-catenin, the main transcription factor that enters the nucleus after Wnt activation, and axin, a scaffold protein required for the formation of the β-catenin destruction complex. Upon Wnt activation axin is degraded, which in turn stabilizes β-catenin. Drugs targeting the Wnt pathway have been hard to come by and specific inhibitors of Wnt production and of axin degradation have been found only recently. Huang *et al.* now use a cell-based high-throughput screen to identify new compounds targeting the Wnt pathway. Their lead molecule, XAV939, is an inhibitor of the poly-ADP-ribosylation (PARsyaltion) enzymes tankyrase 1 and 2, which had not been previously implicated in the Wnt pathway. XAV939 reduces PARsyaltion of axin and its degradation by the ubiquitin-proteasome pathway. It also inhibits the growth of colon cancer cells *in vitro*, suggesting that PARsyaltion inhibitors have potential as cancer therapeutics. Tankyrases are involved in several cellular processes, many of which favor cancer development. Thus, further testing of the inhibitor in animal models is warranted.
(*Nature* **461**, 614–620, 2009) *ME*

Gene therapy tackles Parkinson's

The cause of Parkinson's disease has been known for decades (loss of dopaminergic neurons in the midbrain), and since the 1960s, patients have gotten relief from symptoms with the dopamine precursor L-dopa. Yet long-term treatment with L-dopa frequently leads to involuntary movements (dyskinesis), likely caused by intermittent dopamine production. Partially restoring the dopaminergic pathway in animal models of Parkinson's disease has shown promise. Now Jarraya *et al.* show in a monkey model of the disorder that introducing genes for the entire biosynthetic pathway by means of a single lentivirus vector has long-lasting effects on symptoms without the animal developing dyskinesis. Using equine infectious anemia virus, which accommodates the three biosynthetic genes required—tyrosine hydroxylase, L-amino acid decarboxylase and GTP cyclohydrolase 1—genes were delivered bilaterally to the midbrain of macaque monkeys suffering from Parkinson's-like symptoms after receiving a potent neurotoxin (1-methyl, 4-phenyl 1,2,3,6 tetrahydropyridine). Treated monkeys showed improvements in movement and posture that lasted up to 44 months (the duration of the experiment). Only modest amounts of dopamine could be measured despite symptomatic relief. However, even when as many as 40% of dopaminergic neurons are still intact, Parkinson's disease symptoms are known to arise. Phase 1/2 clinical trials of the vector are underway in collaboration with UK-based Oxford Biomedica. (*Science Translational Medicine*, published online October 14, 2009; doi:10.1126/scitranslmed.3000130) *LD*

Written by Laura DeFrancesco, Markus Elsner, Peter Hare & Craig Mak

Mapping copy number variation

People have two copies of every gene, for the most part. It has become increasingly clear that having more or fewer copies of a gene accounts for genetic variation that results in differences in appearance, physiology and disease susceptibility. A collaborative effort between researchers at the Hospital for Sick Children in Toronto, Harvard Medical School in Cambridge, Massachusetts, and the Wellcome Trust Sanger Institute in London, has comprehensively identified and validated gene copy number variation (CNV) at the highest resolution to date. The researchers discovered 11,700 instances of copy number variation (more than ~500 bp long) across 40 individuals of European and African descent using a panel of 20 NimbleGen (Roche; Basel) arrays that tiled the nonrepeat regions of the human genome. Then, Agilent (Santa Clara, CA, USA) and Illumina (San Diego) arrays were designed to genotype 450 individuals for ~10,000 of the copy number variants. The wealth of resulting data shed light on the molecular mechanisms that generate copy number variation, the amount of variation between any two individuals and disease-associated copy number changes. Raw data are publicly available as an online resource, enabling in-depth examination of specific variants. (*Nature*, published online October 7, 2009; doi:10.1038/nature08516) *CM*

Human genome in 3D

The contributions of dynamic changes in chromosomal conformation to biotechnologically relevant phenomena such as pathology or stem-cell differentiation are poorly understood. Variations of an approach known as chromosome conformation capture (3C) have used spatially constrained ligation to characterize chromosomal folding at a limited number of loci, but are not capable of unbiased genome-wide analysis. Lieberman-Aiden *et al.* introduce Hi-C, an adaption of the 3C method that couples proximity-based ligation with massively parallel sequencing, to provide a spatial proximity map of the human genome at 1 Mb resolution. As in 3C, physically adjacent chromatin segments are cross-linked by formaldehyde and digested by restriction enzymes. But then the DNA ends are labeled with biotin and ligated to create chimeric molecules that can be purified for paired-end sequencing. Alignment of 8.4 million read-pairs from a Hi-C library prepared from a lymphoblastoid cell line with the human reference sequence provides two key insights into the three-dimensional architecture of the genome. First, the nucleus is organized into two discrete compartments, keeping active genes separate and accessible and unused DNA sequestered in a denser storage compartment. Second, chromatin conformation at the megabase scale is consistent with a fractal globule: a knot-free, polymer conformation that enables maximally dense packing while preserving the ability to easily fold and unfold a locus. Using Hi-C with more sequencing reads may define the interactions of distal enhancers, silencers and insulators with the genes they affect.
(*Science* **326**, 289–293, 2009) *PH*