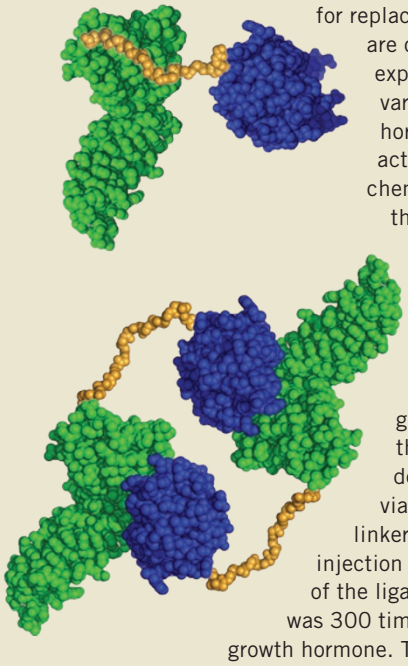
Fusing hormones to receptors



Daily injections of growth hormone for replacement therapy are cumbersome and expensive. Although variants such as pegylated hormones are longer acting, they require chemical modifications that reduce receptor affinity. Ross and colleagues have come up with an ingenious solution by fusing recombinant human growth hormone with the extracellular domain of its receptor via a flexible $(Gly_4Ser)_4$ linker. After intravenous injection into rats, clearance of the ligand-receptor fusion was 300 times slower than that of growth hormone. The authors also show that a single injection of the ligand-receptor fusion in growth hormone–deficient rats results in a weight increase over 10 days that was equivalent to that obtained with an equimolar dose of growth hormone injected daily in the same time period. The authors indicate that this technology might also increase the circulating half-life of other therapeutic cytokine hormones. (*Nat. Med.* **13**, 1108–1113, 2007) *JWT*

Natural product slows bone loss

Black cohosh (*Actaea/Cimicifuga racemosa L.*), a plant native to the eastern United States, has long been a remedy for menopausal symptoms among Native Americans and more recently has seen wide use in Europe. Up until now, little was known about the active ingredient, although it was assumed that a phytoestrogen was involved. Now Qiu and colleagues have put that assumption to rest. Among 46 compounds extracted from the rhizome of the plant, they found a triterpenoid glycoside (25-acetylcimigenol xylopyranoside (ACCX)) that was effective in blocking osteoclastogenesis—which leads to bone resorption when out of balance with osteoblastogenesis or bone formation. Osteoclasts derive from bone marrow precursors, a process that can be recapitulated *in vitro* by treating bone marrow cell–derived macrophages with macrophage-colony stimulating factor or RANKL (receptor activator of nuclear factor κB (NFκB) ligand). Using this system, the researchers identified ACCX and defined its mode of action by looking at the downstream events of activation by RANKL and tumor necrosis factor-α, which upregulates osteoclastogenesis; in each case, ACCX blocked phosphorylation by NF-κB of its downstream targets in a dose- and time-dependent fashion. What's more, in an animal model for osteoporosis, ACCX reduced, though did not inhibit completely, osteoclastogenesis. The race is on to find alternatives to hormone replacement therapy; this study may help put herbal remedies on the map. (*Chem. Biol.* **14**, 860–869, 2007) *LD*

Mopping up microRNAs

Sharp and colleagues describe an alternative to antisense oligonucleotides in derepressing microRNA (miRNA) targets. Their decoy mRNAs, called 'miRNA sponges', encode a reporter protein with a 3′ untranslated region bearing multiple copies of a sequence specific to the miRNA seed region. Inclusion of a bulge at the site of cleavage by Argonaute 2 prevents degradation of the sponge to enable its stable association with members of a miRNA seed family. In contrast, antisense oligonucleotides contain single binding sites, target single miRNAs and lack reporter functions useful to assess transfection efficiency and monitor miRNA activity. Although the authors do not test the efficacy of the approach *in vivo*, another difference is that whereas antisense oligonucletide–based approaches have only been shown to work after transient infection, miRNA sponges can be stably expressed from multiple chromosomal insertions. This approach should be invaluable in validating miRNA-target predictions and assaying miRNA loss-of-function phenotypes. (*Nat. Meth.* published online 12 August 2007, doi: 10.1038/nmeth1079) *PH*

Preempting avian flu

Insights into mutations that enable transmission of avian H5N1 influenza virus between humans and the effectiveness of mammalian immune responses to such variants are key to preparing for the possibility of a pandemic. As a shift in the specificity of the receptor-binding domain of hemagglutinin from avian α-2,3 sialic acid to human α-2,6 sialic acid may be sufficient to confer transmissibility of H5N1 between humans, Yang *et al.* focus their efforts on changing influenza hemagglutinin residues specifically implicated in binding specific sialic acid receptors in the respiratory tract. Not only can certain modifications in the hemagglutinin gene alter host-receptor binding, but vaccination of mice with these variants elicits production of mutant-specific neutralizing antibodies. These findings could be valuable in designing vaccines or antibody-based therapies that preempt modifications capable of transforming H5N1 into a human-adapted form with pandemic potential. (*Science* **317**, 825–828, 2007) *PH*

Signaling networks and cell type

Different cell types often rely on the same fundamental signaling pathways with different outputs. Miller-Jensen *et al.* sought to understand this paradox by developing a system-level description of how cellular information is processed by downstream 'effector' proteins. The authors focused on the overlapping pathways activated by tumor necrosis factor and adenoviral vectors in HeLa cells and HT-29 colon adenocarcinoma cells. They found that a common signaling network can give rise to cell type–specific outputs simply through integration of signals from upstream, differentially activated transducers by downstream effectors. The authors then asked whether the common-effector model could predict the responses of different cell types to treatment with an antitumor drug that targets the phosphatidylinositol-3-OH kinase pathway. As confirmed experimentally, the model correctly indicated the differential sensitivity of apoptosis to this pathway in HeLa and HT-29 cells. (*Nature* **448**, 604–609, 2007) *KA*

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