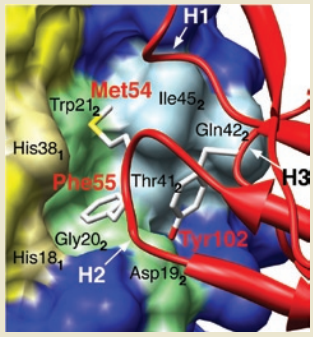
Influenza's Achilles' heel?



Two research teams use the co-crystal structures of broadly neutralizing antibodies complexed with influenza hemagglutinin (HA) to identify a highly conserved epitope that could be key to developing broad-spectrum prophylactic and therapeutic strategies that target influenza, including H5N1 strains. Both groups find that the antibodies bind a relatively concealed hydrophobic pocket in the conserved stem region of HA, which is normally shielded by the variable mushroom-shaped head of the protein but plays a critical role in viral entry by means of membrane fusion. Whereas the starting point for Sui *et al.* involved screening for single-chain Fv fragments with high cross-reactivity among Group 1 HA subtypes, Ekiert *et al.* worked with a Fab antibody fragment isolated from a human vaccinee. The antibodies studied by both groups protect mice against lethal infection with several H1 and H5 influenza viruses. The conservation of the epitope among multiple influenza subtypes and its critical role in membrane fusion suggests that it is a promising target for antiviral therapies and vaccines. (*Nat. Struct. Mol. Biol.* **16**, 265–273, 2009; *Science*, published online, doi:10.1126/science.1171491, 26 February 2009) *PH*

Before HIV gets a foothold

Creating a sustained immune response that can attack HIV at the mucosal viral entry sites at the earliest possible moment before the initial rapid viral replication is one of the most promising strategies for creating a protective AIDS vaccine. Normally, vaccines expose the immune system to viral antigens only for a limited time. After a primary peripheral T-cell response, central memory T cells (T_{CM}) reside mainly in the lymph nodes. To maintain extralymphoid effector memory T cells (T_{EM}) that can counter a viral challenge much more rapidly than T_{CM} cells, Hansen *et al.* use cytomegaloviruses (CMV) to create persistent infections that are largely benign for immunocompetent hosts. With rhesus monkeys as a model system, the authors create three rhesus CMVs that each carry part of the simian immunodeficiency virus (SIV) genome. Vaccination with the viruses gives rise to a sustained T_{EM} response in peripheral sites for more than three years and is able to protect monkeys from repeated challenges with SIV. This study underscores the importance of targeting HIV at the early replication sites and provides a viable strategy for the development of vaccines that generate mucosal immunity. (*Nat. Med.* **15**, 293–299, 2009) *ME*

New Alzheimer's targets

Two groups have identified new drug targets for Alzheimer's disease, a disease for which few targets exist beyond β- and γ-secretases, two endogenous proteases that cleave the amyloid precursor protein (APP) into toxic αβ peptides. In a *Science* paper, Thathiah *et al.* use a high-throughput screen to isolate proteins that enhance αβ production from among 1,200 potential drug targets, identifying an orphan G protein–coupled receptor 3 (GPR3). They verify that GPR3 expression modulates αβ production both in culture and in a transgenic mouse model of Alzheimer's disease, which overexpresses GPR3. They further show that GPR3 overexpression leads to increased formation within membranes of γ-secretase complexes that co-localize with GPR3, which is from a family of druggable targets and maps to a chromosomal location with a higher risk of Alzheimer's disease. In a *Nature* paper, a team of industrial and academic researchers reveal the potential role in Alzheimer's disease of a previously ignored N-terminal portion of APP (N-APP). They show that withdrawal of neuronal survival factors leads to accumulation of N-APP, which acts by binding a newly identified receptor DR6. They go on to identify intracellular protease caspase 6 apoptosis-related cysteine peptidase (CASP6) as the downstream effector of the DR6 signal. Taken together, these papers provide several new leads for Alzheimer's disease drug discovery. (*Science* **323**, 946–951, 2009; *Nature* **457**, 981–989, 2009) *LD*

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

Engineered phage foil antibiotic resistance

Antibiotic-resistant bacteria pose challenges in clinical, industrial, agricultural and food-processing settings. Phage have long been proposed as an alternative to antibiotics, but even here, bacteria can develop resistance to phage attachment. In a bid to combine phage and antibiotics, Lu and Collins harness the gene-delivery capabilities of the M13 bacteriophage, a viral pathogen of *Escherichia coli*, by engineering its genome to produce proteins that suppress the bacteria's natural defense mechanisms. The researchers deploy the engineered phage to enhance the efficacy of three diverse classes of antibiotics—ofloxacin (a quinolone), gentamicin (an aminoglycoside) and ampicillin (a β-lactam). The synthetic phage also enhance killing of antibiotic-resistant *E. coli* and reduce the development of resistance in bacteria exposed to subinhibitory concentrations of an antibiotic. These studies provide a flexible platform for developing libraries of phage that in the future could be applied with different antibiotic drugs against a range of bacterial infections. (*Proc. Natl. Acad. Sci. USA* **106**, 4629–4634 2009) *CM*

iPS cells by reversible integration

Clinical translation of induced pluripotent stem (iPS) cells is likely to require novel reprogramming methods that avoid the use of integrating viral vectors. In late 2008, two groups produced mouse iPS cells without genetic modification by delivering the reprogramming genes on adenoviral vectors or plasmids. Two new studies propose a different solution to the problem. Woltjen *et al.* use the piggyBac transposon to insert the reprogramming genes *Oct4*, *Sox2*, *Klf4* and *cMyc* into the genome of mouse embryonic fibroblasts and then excise the transgenes from the resulting iPS cells by expression of transposase. As shown in previous work, excision is seamless, leaving no trace in the genome. In a related approach, Soldner *et al.* generate iPS cells from the fibroblasts of five individuals with Parkinson's disease using doxycycline-inducible lentiviral vectors that can be excised by Cre recombinase. They find that continued low-level expression of largely silenced reprogramming genes in established iPS cells is not required to maintain the pluripotent state. Moreover, failure to remove the transgenes leads to subtle perturbations in global gene expression. (*Nature* advance online publication doi:10.1038/nature07863, 1 March 2009; *Cell* **136**, 964–977, 2009) *KA*