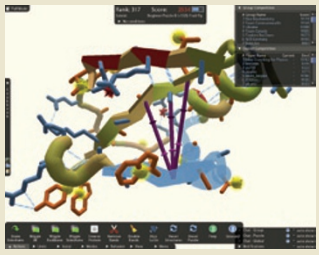
The structure-solving crowd



Take a very hard biophysics problem, turn it into a computer game, allow anyone on the internet to play—scientists and nonscientists alike—and a large network of people will reach better solutions than those produced by sophisticated supercomputers. This paradigm-rattling insight is described by Cooper *et al.* in a recent paper about 'Foldit', an online game in which players compete to fold proteins into their lowest-energy conformations. Foldit presents improperly folded proteins to be optimized and directs players to the incorrect parts of the structures by highlighting high-energy areas (such as exposed hydrophobic residues, steric clashes and cavities) in color. Players, working alone or in teams, can manually tug and tweak the proteins and run simplified energy-minimization programs. Out of ten blind puzzles, humans outscored the protein-folding software Rosetta in five and played to a draw in three. (Neither side did well on the remaining two.) Human players were especially good at finding solutions that involved substantial backbone rearrangements, whereas Rosetta remained trapped in local energy minima. The authors note the "complexity, variation and creativity" of the human protein-folding strategies and the intricate social strategies that emerged, via chat and a wiki, to support the players. (*Nature* **466**, 647–651, 2010) *KA*

Tau and Fyn conspire in Alzheimer's

The molecular mechanisms underlying the toxicity of amyloid-β oligomers in Alzheimer's disease are not well understood. A major player seems to be the microtubule-associated protein tau. Tau is normally localized to the axons of neurons, whereas toxic effects are mainly observed in the dendrites, making it difficult to explain tau's involvement. During the course of the disease, tau becomes abnormally phosphorylated, detaches from the microtubules and relocates to other neuronal compartments. Ittner *et al.* elucidate how this might be detrimental for neurons. Besides microtubules, tau also interacts with a number of nonreceptor tyrosine kinases. A prominent example is Fyn, which is involved in organizing the postsynaptic machinery by phosphorylating a subunit of the NMDA receptor (NMDAR), thereby increasing its affinity to the scaffolding protein PSD95. Increased binding of NMDAR to PSD95 has been shown to cause neurotoxicity in other diseases. Ittner *et al.* now find that access of Fyn to the dendrites is regulated by tau in mice. In *Tau*$^{-/-}$ cells, Fyn is excluded from the dendrites, and expression of a truncated tau mutant that is excluded from the dendrites leads to sequestration of Fyn in the soma. When tau detaches from the microtubules upon phosphorylation, it can access the dendritic compartment, thereby increasing the Fyn concentration and consequently NMDAR phosphorylation. The authors show that therapeutically targeting the PSD95-NMDAR interaction with a cell-permeable peptide improves survival and memory in a mouse model of Alzheimer's disease. (*Cell* **142**, 387–397, 2010) *ME*

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

Chemical inducers of HSC expansion

Hematopoietic stem cell (HSC) transplantation has been used for more than four decades to treat patients with life-threatening diseases of the blood and bone marrow. However, the challenge of identifying defined culture conditions to expand human HSCs *ex vivo* has limited full realization of the clinical potential of the approach. Boitano *et al.* address this issue by assaying CD34 and CD133 expression in cultured human HSCs screened with a library comprising 100,000 heterocyclic compounds. One of these, a purine derivative named SR1, expands CD34^{+} cells from humans, monkeys and dogs but not mice. Culturing human HSCs with SR1 increases by 17-fold the number of cells capable of hematopoietic reconstitution in immunodeficient mice. Mechanistic studies suggest that SR1 binds directly to and inhibits the aryl hydrocarbon receptor, which was not previously known to have a role in human HSC biology. (*Science*, published online 5 August 2010; doi:10.1126/science.1191536) *PH*

Higher resolution optical imaging

Conventional microscopes can resolve the position of individual fluorophores only to about half the imaging light's wavelength. Additional knowledge about the specimen can be used to increase the resolution. If, for example, well-separated individual fluorophores are imaged, the accuracy of the position measurement is theoretically limited only by the number of photons that can be collected for each light-emitting molecule. This principle lies at the heart of so-called super-resolution microscopy techniques, such as PALM or STORM. In practice, the achievable resolution has been limited to 5–10 times worse than the theoretical estimates. Pertsinidis *et al.* now show that using closed-loop feedback control to lock the signal of individual fluorescent molecules can correct for positional noise caused by thermal fluctuations. Moreover, addressing the CCD array at any desired subpixel location can minimize systematic localization errors caused by defects and dirt on the optics and especially irregularities in the charge-coupled device (CCD) arrays used for light detection. With their feedback control system, they can achieve accuracies of up to 0.5 nm, close to the theoretical limit for the number of photons collected. They use their new technology to investigate the intersubunit distances in E-cadherin dimers. Although the technology has only been applied to pairs of fluorophores, imaging applications with many molecules seem possible. (*Nature* **466**, 647–651, 2010). *ME*

Saving cone cells

In certain forms of retinitis pigmentosa (RP), cone cells persist for awhile after rod cells have died. This provides a window of opportunity to rescue cones, the loss of which results in total blindness. Busskamp *et al.* were able to do just that in mouse models of RP by delivering the gene for a well-studied bacterial halorhodopsin (light-activated chloride pump from *Natronomonas pharaonis*, cNpHR) via an adeno-associated vector (AAV). The opsin (or green fluorescent protein (GFP) in control animals), under the control of cell-specific promoters, was delivered into the subretinal space of 21-day-old mice, and isolated retinas were later tested for gene expression, light responses and the ability to relay information to ganglion cells. They found that opsin expression persisted until the mice were 110 days old and that the retinas responded to both light-on and light-off signals as well as directional signals. The transduced mice performed better than control mice on behavioral tests. Finally, in isolated human retinas transduced with a lentivirus vector, which expresses more rapidly than AAV (human retinas persist in culture for only 2–3 weeks), the researchers detected gene expression after 2–3 days, as well as light responses not seen in control retinas. (*Science* **329**, 413–417, 2010) *LD*