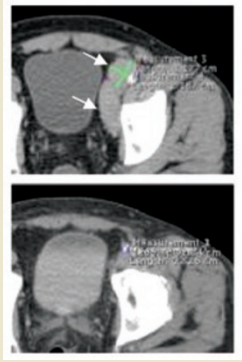
Lymphoma therapy with a BiTE



Bargou *et al*. have provided the first clinical evidence for the cytotoxic potential of very low doses of a bispecific T-cell 'engager' (BiTE) single-chain antibody to stimulate an individual's T cells against non-Hodgkin's B-cell lymphoma. Previous studies involving mouse models demonstrated that blinatumomab, a BiTE with dual specificity for CD19 (a differentiation antigen expressed on almost all B cell lymphomas and leukemias) and CD3 (an invariant T-cell receptor), activates resting T cells to serially lyse cancer cells. The authors now report that at serum levels five orders of magnitude below those required by the anti-CD20 antibody rituximab (Rituxan), blinatumomab can specifically eradicate cancer cells in humans (see inset computer tomography images of two lymph node tumors before (top) and after (bottom) eight weeks of treatment). The trial involved 38 patients who relapsed after multiple conventional therapies. All of the seven patients taking the highest dose of blinatumomab responded, with two complete and five partial regressions. (*Science* **321**, 974–977, 2008) *PH*

Myc targeted for cancer therapy?

The transcription factor Myc regulates multiple genes involved in cellular proliferation and is overexpressed in many types of cancer. Yet Myc is not generally considered a promising target for cancer drug discovery. Systemic inhibition of a protein that is critical to the proper functioning of stem cells in regenerating tissues, such as the gastrointestinal tract, skin and bone marrow, is expected to produce severe side effects. Moreover, Myc may not be a good target because its dysregulation is often caused by mutations in upstream proteins. Soucek *et al*. have now tested the safety and efficacy of Myc inhibition in a mouse model of Kras-induced lung adenocarcinoma. Using an inducible, interfering dimerization domain to block normal Myc heterodimerization, the authors find that Myc inhibition leads to a dramatic regression of lung tumors. Although it also results in profound attrition of highly proliferative tissues, these deleterious effects are fully reversible. (*Nature*, advance online publication, doi:10.1038/nature07260, 17 August 2008) *KA*

Enzyme target in Alzheimer's

The brains of Alzheimer's disease patients accumulate amyloid β (Aβ) peptide fragments that aggregate and become neurotoxic. Truncated peptides with pyroglutamate (pE) at certain positions are believed to resist proteolysis and provide a site for aggregation. Schilling and colleagues tested this hypothesis by looking at levels of glutaminyl cyclase mRNA and protein in the brains of individuals with Alzheimer's disease. Not only did they find this mRNA and protein elevated in patients, but they also observed higher concentrations of a particular pE-Aβ fragment, Aβ 3(pE)-42, in Alzheimer's disease brains. Aβ 3(pE)-42 was also shown to accumulate in a cell line transfected to co-express glutaminyl cyclase and amyloid precursor protein; and when an enzyme inhibitor (PBD150) was present, this accumulation was blocked, implicating glutaminyl cyclase in the production of the fragment observed *in vivo*. When the inhibitor was then given to two different transgenic mouse models of Alzheimer's disease, a dose-dependent reduction in Aβ 3(pE)-42 formation was observed, accompanied by less plaque deposition and better performance in memory and learning tests. To test inhibitor specificity, the researchers created a transgenic fly with neuron-specific expression of two amyloid fragments, one with pE and one without. When these flies were given PBD150, expression of the pE fragment, but not the other fragment, decreased. The results suggest glutaminyl cyclase may be a new therapeutic target for Alzheimer's disease and other dementias. (*Nat. Med.* **14**, 1106–1111, 2008) *LD*

MicroRNA markers in serum

A raft of studies extend the promise of microRNAs (miRNAs) in tissue-based diagnostic and prognostic applications by demonstrating their utility as minimally invasive serum biomarkers of clinical conditions. In two related reports, Gilad *et al*. identify three blood-based placental miRNAs as reliable indicators of pregnancy, expanding on the demonstration by Chim *et al*. of placental miRNAs in maternal plasma. Turning to serum as the sample, Lawrie *et al*. suggest the diagnostic potential of miR-21 for diffuse large B-cell lymphoma, whereas Mitchell *et al*. augment this finding by demonstrating that serum levels of miR-141 can distinguish patients with prostate cancer from healthy controls. Finally, Chen *et al*. report miR-25 and miR-223 as reliable blood-based markers of non-small cell lung cancer. Although the unusually high stability of miRNAs in formalin-fixed tissues is widely appreciated, the exceptional resistance of these serum miRNAs to RNase remains enigmatic. These unusual properties of miRNAs, together with their exquisite biological potency, suggests they could prove excellent surrogates for detecting altered physiology. (*PLoS ONE* **3**, e3148, 2008; *Clin. Chem.* **54**, 482–490, 2008; *Br. J. Haematol.* **141**, 672–675, 2008; *Proc. Natl. Acad. Sci. USA* **105**, 10513–10518, 2008; *Cell Res.*, published online 2 September 2008, doi: 10.1038/cr.2008.282) *PH*

Octaarginine counters drug resistance

Cancer chemotherapies often fail because tumor cells increase the expression of membrane pumps that expel hydrophobic small-molecule drugs such as Taxol (paclitaxel), camptothecin, doxorubicin and etoposide. To date, the most common approach to circumvent increases in P-glycoprotein–mediated efflux in drug-resistant cancer cells has involved switching treatment to an unrelated cytotoxic drug. Dubikovskaya *et al*. extend prior demonstrations that octaarginine enhances cellular uptake by attaching the peptide to Taxol to change how the drug is taken up by cells. Fortuitously, conjugation to octaarginine also increases the solubility of the drug, thus avoiding complications caused by formulation with a delivery agent. They further enhance drug release by incorporating a disulfide linker into the construct to ensure that the activity of the paclitaxel is restricted to the reducing environment inside the cell. The conjugates overcome paclitaxel resistance both in malignant cultured cells and in mouse models of ovarian cancer. Application of the approach to coelenterazine, another P-glycoprotein substrate, suggests that the approach may be applied more generally. (*Proc. Natl. Acad. Sci. USA* **105**, 1218–12133, 2008) *PH*

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