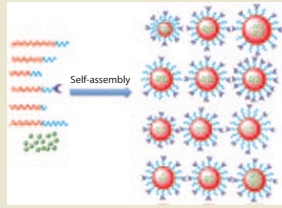


Docetaxel-loaded nanoparticles shrink human tumors

Using nanomedicine to treat cancer just got a step closer to the clinic, according to interim results from a phase 1 trial of targeted nanoparticle-mediated docetaxel (DTXL) delivery to treat various solid tumors. Hrkach *et al.* restricted nanoparticle components to already clinically approved materials to expedite the translation of the nanoparticle from mouse to man. A library of 100 nanoparticle variants was generated by combining varying proportions of the key components of the nanoparticle, namely polymers that form a core, the anticancer drug DTXL encapsulated inside the core and a surface ligand that binds prostate-specific membrane antigen, which is present in nearly all solid tumors. Comparing pharmacokinetics of nanoparticle-library variants in rats enabled identification of the best-performing DTXL-NP. Importantly, the authors found that the plasma concentrations of DTXL delivered by this nanoparticle were three orders of magnitude higher than those of commercial DTXL (Taxotere) injected intravenously in different preclinical animal models, suggesting that drug doses can be reduced through nanoparticle delivery. In an ongoing phase 1 trial, patients with various solid tumors were dosed every 3 weeks with increasing amounts of DTXL-NP. The pharmacokinetics of DTXL-NP in humans mirrored those obtained in preclinical studies, and tumors (lung and tonsillar cancer) shrank in 2 of 17 patients. (*Sci. Transl. Med.* **4**, 128ra39, 2012) *SJ*



Zinc-finger nucleases hone tumor cell therapy

Engineering a patient's own T cells to express tumor-targeting heterodimeric T-cell receptors (TCRs) is a promising therapeutic strategy. Even so, development of this method has been undermined by unintended dimerization of endogenous and exogenous TCR chains, resulting in hybrid receptors that lead to off-target effects and autoimmunity, and by suboptimal expression of the introduced tumor-specific TCR. Provasi *et al.* overcome these obstacles by first disrupting the endogenous TCR α and β chains using zinc-finger nucleases. Subsequent expression of tumor-targeting TCR chains delivered by lentiviral vectors produced high levels of expression of the expected antigen-specific TCRs. Tested in a series of experimental mouse models, the engineered cells did not set off an auto-immune response and protected the mice against leukemia. (*Nat. Med.* advance online publication, doi:10.1038/nm.2700, 1 April 2012) *JK*

Drug lead for osteoarthritis

Osteoarthritis occurs when synovial joints fail. Drugs that alter the course of this disease, rather than simply alleviate symptoms, are in clinical trials, but none have been approved yet in the United States or the European Union. Johnson *et al.* describe the discovery and characterization of a small molecule, kartogenin, that improves joint function and promotes the regeneration of cartilage *in vivo* in two rodent models of chronic and acute joint injury. *In vitro* experiments indicated that kartogenin induces the differentiation of mesenchymal stem cells into cartilage cells (chondrocytes) and protects existing chondrocytes under pathological conditions. The authors found that kartogenin binds filamin A, a protein that crosslinks actin filaments, through which it regulates the nuclear localization of a transcription factor complex of CBF β and RUNX2. Knockdown of either CBF β or RUNX2 with short-hairpin RNAs blocked the effect of kartogenin on cellular differentiation. Kartogenin is the first drug reported to target filamin A and as such may complement other osteoarthritis drugs under development. (*Science* published online, doi:10.1126/science.1215157, 5 April 2012) *CM*

Engineering a thymus

Understanding the complex relationships among cells and signaling molecules that underlie tissue organization is challenging, and developmental niches have been difficult to define concretely. Now Calderón and Boehm have capitalized on the fact that a single transcription factor (forkhead transcription factor, Foxn1) directs the differentiation of the thymus to create an experimental system for unraveling differentiation states. Using nude mice (homozygous deleted for *Foxn1*), which have a rudimentary thymus, the researchers engineer the thymus *in vivo* by adding back four factors previously identified as important to T-cell development—chemokines *Ccl25* and *Cxcl12*, the cytokine *Scf* (stem cell factor) and the Notch ligand *DLL4*. In animals, expressing each separately or together in various combinations, thymus glands are populated with different members of the hematopoietic family: *Ccl25* alone draws lymphoid cells to an otherwise empty thymus, *Cxcl12* brings in B-cell progenitors, *Scf* increases myeloid progenitor cells and *DLL4* alone does nothing but in combination over-rides the other factors in inducing T-cell differentiation. The researchers found that the factors acted synergistically—two factors together increased the numbers of progenitor cells—and in a context-dependent fashion—alone, *Cxcl12* supports B-cell progenitors, but with *DLL4*, T-cell progenitors predominate. Synthetic environments may prove useful in unraveling the complex relationships within microenvironments that determine cell fate. (*Cell* **149**, 159–172, 2012) *LD*

Pharmacogenomic profiling of cancer drugs

Most cancer drugs are effective in only a fraction of the patients who take them. If this responsive subset could be identified in advance, patients would be spared useless, cytotoxic treatments, and the regulatory pathway for new agents would be simplified. For a handful of drugs, efficacy is known to track closely with the presence of particular mutations, but, overall, the use of tumor genotype data to predict optimal drug regimens is still at an early stage. Two new reports have addressed this problem by pharmacological screening on human cancer cell lines at a larger scale than has been carried out previously. Garnett *et al.* tested 130 drugs on 639 cell lines, whereas Barretina *et al.* collected sequence, chromosomal copy number and transcriptional data on 947 cell lines and measured the activity of 24 drugs on 479 of these lines. Both studies uncovered known markers of drug sensitivity as well as novel candidate markers. Moreover, established correlations between drug efficacy and genotype were found to be invalid in some cases. (*Nature* **483**, 570–575 and 603–607, 2012) *KA*

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