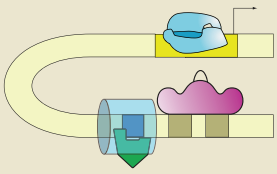
Synthetic enhancers



Although enhancers are found in most genomes, their utility for synthetic biology applications has been limited by the lack of a quantitative understanding of their regulatory behavior. Enhancers are genetic elements that influence gene expression at distances of anywhere from hundreds of bases to hundreds of kilobases from the gene promoter. Using extensive quantification of gene transcription from artificial bacterial enhancer constructs, Amit *et al.* now describe predictive mathematical models for simple enhancer elements. Their enhancers consist of a promoter that uses a sigma factor (σ^{54}) that is unable to initiate transcription without an additional activator (NRI~P), which binds upstream of the promoter. The authors introduce spacers of varying lengths, containing different binding sites for tetracycline-responsive TetR or TraR DNA-binding proteins, between promoter and activator sequences. Both the length of the spacer and the number of bound proteins influence the propensity of the DNA to form a loop that brings sigma factor and activator in contact to start transcription. The authors find that enhancers can be engineered to show stepwise dose-response curves and that quantitative behavior can be predicted by their models when correctly parameterized in experiments. (*Cell* **146**, 105–118, 2011) *ME*

Shotgun cancer vaccination

Until now, broad and effective use of cancer immunotherapy has been thwarted by two main challenges: the identification of one or two tumor-specific antigens that avoid the stimulation of immune response against normal cells; and countering the emergence of cancer cells resistant to the acquired antitumor immune response. Kottke *et al.* show that a less targeted strategy, which affords the immune system more comprehensive exposure to tumor-associated antigens, has the potential to address both challenges. In mice, intravenous delivery of highly immunogenic vesicular stomatitis viruses expressing a library of cDNAs derived from healthy human prostate tissue cures >80% of established prostate tumors without triggering autoimmunity. The key to their success apparently lies in the use of altered-self epitopes encoded by cDNA prepared from the same organ as that from which the tumor was derived. Although use of a virally delivered library avoided the need to individualize vaccines for particular patients, it remains to be established whether the results are generalizable to other tumor models and whether the vesicular stomatitis virus vector can be used safely in humans. (*Nat. Med.* **17**, 854–859, 2011) *PH*

Predicting seasonal influenza vaccine efficacy

Vaccine efficacy is traditionally evaluated using a handful of surrogate markers, such as antibody titers. In 2009, the Pulendran research group used gene expression profiling to study the systems-level responses in humans to a live attenuated vaccine against yellow fever. Nakaya *et al.*, working in the same group, extend this approach by analyzing responses to two seasonal influenza vaccines over three influenza seasons. They profile gene expression changes in peripheral blood mononuclear cells and flow cytometry–sorted cell populations at 0, 3 or 7 days after vaccinating 56 young adult human volunteers with either a live attenuated, or a trivalent inactivated, influenza vaccine. These data are analyzed to develop a 'classifier' algorithm that can predict antibody titers 28 days after vaccination with >90% accuracy. Further investigation of one gene, *CAMK4*, whose expression is negatively correlated with antibody titers, reveals a role for the gene in B-cell responses. This study, together with previous work from this group, suggests that gene expression analyses of vaccine responses may be useful in the development of both live attenuated and inactivated vaccines, as well as in offering new insights about the molecular mechanisms regulating vaccine immunity. (*Nat. Immunol.* advance online publication, doi:10.1038/ni.2067, 10 July 2011) *CM*

The mother of all HSC cells

Isolating hematopoietic stem cells (HSCs) from bone marrow or cord blood cell populations has long been a goal of stem cell researchers, and markers have been identified whose presence (e.g., CD34 or Thy1) or absence (lineage-specific markers) define HSCs. Notta *et al.* now show that the Thy1$^-$ niche appears to be heterogeneous, whereas cells bearing the surface integrin CD49f act like true HSCs. Among other things, they show that Thy1$^-$ cells engraft in a mouse xenograft model with the same distribution of cell lineages as Thy1$^+$ cells, only differing in their ability to serially transplant. Furthermore, when cultured with stromal cells, Thy1$^-$ cells can become functional Thy1$^+$ cells. To isolate true HCSs, the researchers turned to adhesion molecules, which occur on murine stem cells, and found that, when a particular integrin, CD49f$^+$, was present, cells were almost seven times more effective in engrafting than when the integrin was absent, with ten times the potential for long-term engraftment. Finally, they could isolate CD49f$^+$ cells from a population of Thy1$^-$ cells that had stem cell properties. Whereas CD49f$^-$ cells could give rise to all cell lineages, the xenograft was not durable, suggesting that CD49f$^-$cells represent an intermediate cell type, analogous to multipotent progenitor cells. (*Science* **333**, 218–221, 2011) *LD*

Making neurons with microRNAs

Transcription factors have the starring roles when it comes to techniques for altering cell fate, whether it be for turning differentiated cells into induced pluripotent stem cells or for converting one differentiated cell type into another. But recently, microRNAs seem to be stealing some of the limelight. Earlier this year, it was reported that somatic cells can be reprogrammed to a pluripotent state simply by expressing a small number of microRNAs. Now, a new study by Yoo *et al.* shows that microRNAs can convert human fibroblasts into neurons without the aid of exogenous transcription factors. Building on their earlier findings that miR-9* and miR-124 mediate chromatin remodeling as developing neurons become post-mitotic, the authors deliver miR-9/9* and miR-124 by lentiviral vectors to human neonatal fibroblasts. After four weeks, cells expressing both microRNAs (but not either alone) resemble neurons morphologically and express the neuronal marker MAP2. The efficiency of conversion to neurons can be increased by co-expressing the neurogenic transcription factors NEUROD2, ASCL1 and MYT1L, suggesting that these factors act synergistically with miR-9/9* and miR-124. (*Nature* advance online publication, doi:10.1038/nature10323, 13 July 2011) *KA*

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