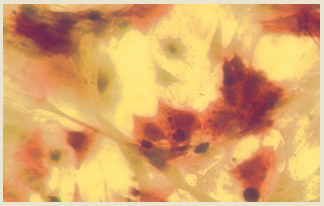
## 'Reversin' development



Stem cell research has been stymied by the difficulty of isolating truly pluripotent cells in useful quantities. One way around this dilemma would be to dedifferentiate readily available adult cells into pluri- or multipotent progenitors. Schultz and colleagues report on a molecule they term reversin that does just that. From a screen of 50,000 compounds designed to interact with protein kinases, likely central in differentiation, they isolated a compound that returns a mouse muscle (myogenic) cell line (C2C12) to a progenitor state. Cells treated with reversin lose myotube-specific proteins, and a substantial fraction can be induced to differentiate into two other specialized cell types, osteoblasts (35%) and adipocytes (40%). Transdifferentiation did not appear to account for changes as C2C12 cells not treated with reversin were not inducible, and differentiation of treated cells did not occur in the absence of inducers. An analysis of the structure-activity relationship of reversin, a 2,4-disubstituted purine, shows that the N9 hydrogen and the NH substitution at the C2 position on the purine ring are essential for activity. (*J. Am. Chem. Soc.* **126**, 410–411, 2004) *LD*

## Promiscuous antibiotics enzyme

The purification and characterization of a remarkable enzyme involved in the biosynthesis of lacticin 481 may open new avenues in antibiotic engineering. Lacticin 481 is produced by *Lactococcus lactis* and belongs to the bacteriocin class of antimicrobial peptides, the activity of which is determined by dehydration and cyclization modifications introduced into propeptides during post-translational maturation. Now, Xien *et al.* have purified a lantibiotic synthetase (LctM) and demonstrated that incubation of the enzyme with its substrate, the propeptide LctA, leads to the synthesis of lacticin 481. Remarkably, despite the complexity of the dehydration and cyclization reactions, LctM catalyzes all the biosynthetic steps, breaking eight bonds and forming six new ones with the requirement of only ATP and $Mg^{2+}$. As the enzyme appears capable of performing the same series of post-translational modifications on propeptides related to LctA, *in vitro* engineering of a range of lacticin analogs from semisynthetic substrates may now be possible. Given the spurious development of resistance to bacteriocins, this class of molecules represents an attractive alternative to existing antibiotics. (*Science* **303**, 679–681, 2004) *GTO*

## Drugs from signatures

Myeloid cells in patients with acute myelogenous leukemia (AML) are incapable of terminal differentiation. A new study by Golub and colleagues uses gene expression profiling by microarray to identify the genetic signature of AML cells, describes a cell screen for identifying chemicals that induce differentiation signature genes and identifies several novel compounds capable of triggering AML cell differentiation. Using extensive profiling of AML cells and of fully differentiated peripheral blood neutrophils and monocytes from unaffected individuals, the authors found four genes (*SPP, IL1RN, NCF1, ORM1*) that together are a consistent and robust marker of the differentiated state (though these genes do not appear directly involved in the myeloid differentiation *per se*). The researchers then screened a library of 1,739 chemicals against a human leukemia (HL-60) cell line and used mass spectrometry to identify when PCR products of the four signature genes were present. Using this approach, they identified eight lead compounds that induce the differentiation signature and validated their activity in biochemical and morphological tests. (*Nat. Gen.* **36**, 257–263, 2004) *GTO*

## Wounds and cancer

New work suggests that gene expression patterns associated with wound healing may in cancer cells be predictive of invasiveness and metastasis. Wound healing involves cell proliferation, invasion, remodeling of connective tissues/extracellular matrix and blood vessel formation—a process similar to tumor formation, invasion and metastasis. To test whether cancer cells share patterns of gene expression with fibroblasts in a wound model, Brown and coworkers first used microarrays to define a set of core serum response (CSR) genes in fibroblasts incubated in the presence of serum. They next analyzed expression of CSR genes in numerous tumors, using publicly available data sets. Whereas prostate and liver tumors all had the CSR signature, only certain lung, breast and gastric tumors expressed it. In the latter tumor types, two classes emerged with respect to CSR phenotype: in a set of 51 breast cancer tumors for which clinical data were available, those expressing CSR had significantly poorer prognoses (more metastases and poorer survival). The CSR signature thus appears an intrinsic property of invasive tumors, suggesting it might be useful in diagnosis. (*PLoS Biol.* published online Jan 13, 2004; DOI: 10.1371/journal.pbio.0020007) *LD*

## Improved TAT

**One of the best-known peptides for delivering macromolecules and other cargo into cells is the protein transduction domain (PTD) from the HIV-1 TAT protein. Little is known about the transduction mechanism, although it has been suggested that fusions with the TAT PTD directly cross the plasma membrane or are taken up through caveolae. Dowdy and colleagues have elucidated the mechanism of TAT PTD transduction and used that information to design more efficient TAT peptides. To assay transduction, they incubated cells bearing a genomic *lox*-stop-*lox*–enhanced green fluorescent protein (EGFP) reporter gene with a TAT-Cre fusion; in this system, expression of EGFP requires transport of TAT-Cre into the cytosol and nucleus, excision of the stop segment by recombination, and continued cell viability. The authors determined that TAT-Cre transduction proceeds by binding of the construct to the cell surface and lipid raft–dependent endocytosis. More specifically, it occurs by macropinocytosis rather than by caveolae-, clathrin- or IL2R-mediated endocytosis. The finding that much of the internalized TAT-Cre was trapped in macropinosomes led the authors to design an improved transduction peptide comprising the TAT PTD and an influenza virus hemagglutinin peptide known to disrupt lipid membranes at low pH.** (*Nat. Med.* **10**, 310–315, 2004) *KA*

*Research Notes written by Kathy Aschheim, Laura DeFrancesco, and Gaspar Taroncher-Oldenburg.*