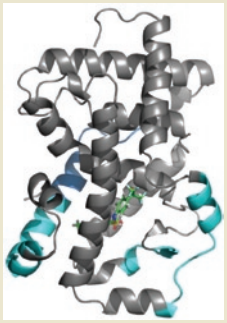
T_H17 cell differentiation inhibitors



T-helper lymphocytes expressing interleukin-17 (T_H17 cells) have been implicated in a range of autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, Crohn's disease, psoriasis and lupus. Therapies that target the retinoic acid receptor–related orphan receptors α and γt (RORα and RORγt), which are required for the differentiation of naive $CD4^+$ T cells to T_H17 cells, are an attractive alternative to current autoimmune disease treatments that work by general immunosuppression. Until recently, however, the absence of well-characterized ROR ligands has frustrated progress. Two groups now report the feasibility of selectively blocking ROR receptor activity to inhibit T_H17 cell differentiation and function. Huh *et al.* show that digoxin, long used to treat congestive heart failure, and two of its less toxic derivatives all suppress T_H17 cell development by antagonizing RORγt activity. Solt *et al.* derivatize a promiscuous modulator of several nuclear receptors to identify a synthetic suppressor (shown green in inset binding the RORγt ligand-binding domain) of both RORα and RORγt. Both studies use an animal model of multiple sclerosis to demonstrate the ability of the compounds tested to reduce the severity of autoimmune disease in mice. (*Nature* published online, doi:10.1038/nature09978, 27 March 2011; doi:10.1038/nature10074, 17 April 2011) *PH*

Silencing the silencers

Pinning down the functions of microRNA (miRNA) families is tricky because their members are often coexpressed, have redundant function and share a common seed region involved in target recognition. Obad *et al.* harness this last property to silence multiple family members using antisense oligonucleotides with a single sequence. The authors inhibit miRNAs by transfecting cells or intravenously injecting mice with tiny locked nucleic acids (LNAs), short 7- or 8-mer modified oligos that are complementary to the shared miRNA seed regions. These tiny LNAs are shown to be specific—working only when the seed region, and not other regions of the miRNA, is targeted—and active in cultured HeLa and Huh-7 cells as well as *in vivo* in many mouse tissues and a mouse model of breast cancer. Experiments using gene expression microarrays, proteomics and luciferase reporter assays suggest that off-target effects are minimal. The advantages of silencing miRNA family members with a single antisense oligo, rather than several oligos having different sequences, remain to be demonstrated. (*Nat. Genet.* **43**, 371–378, 2011) *CM*

Synthetic biology for antibacterials

Anticoumarins are a potent antibiotic class restricted to use only in Gram-positive bacteria because of their poor penetration through the outer membranes of Gram-negative strains. Alt *et al.* use synthetic biology to expand their spectrum by creating a codon-optimized biosynthetic pathway for the anticoumarin chlorobiocin, attaching to it an 'import handle' that allows entry through an iron transporter. The anticoumarins comprise three moieties, one of which is not essential for their activity as gyrase inhibitors. The redesign involved removing the nonessential moiety and replacing it with the catechol 3,4-dihydrozybenzoic acid (3,4-DBA), known from work with β-lactam antibiotics to engage with the iron transporter of *Escherichia coli*. The researchers first knocked out the *cloQ* gene from *Streptomyces roseochromogenes*, which inactivates the inessential moiety 3-dimethylallyl-4-hydroxygenzoyl. They then constructed a biosynthetic pathway for 3,4-DBA, borrowing enzymes from two bacteria (chorismate pyruvate lyase from *E. coli* and 4-hydroxybenzoate 3-hydrozylase from *Corynebacterium cyclohexanicum*). Finally, the two exogenous genes were codon-optimized for expression in streptomycetes. The new molecule, novoclobiocin 401, was produced copiously (9 mg/l) in chemically defined medium and showed activity against *E. coli* and *Staphylococcus aureus* gyrases *in vitro* and antibacterial activity against *E. coli* cells. (*Chem. Biol.* **18**, 304–313, 2011) *LD*

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MicroRNA shuttles

The direct exchange of RNAs between cells by membrane-derived vesicles is an important mechanism of intercellular communication. Two studies now describe new extracellular RNA carriers. Vickers *et al.* report that human high-density lipoprotein (HDL) binds both endogenous and exogenous miRNAs and can deliver them to cells *in vitro*. The miRNAs remain functional and downregulate their target mRNAs in the recipient cells. HDL derived from healthy volunteers and individuals with familial hypercholesterolemia contains different sets of miRNAs that suppress distinct target genes. Arroyo *et al.* demonstrate that only a minority of the miRNAs found in human serum are associated with vesicular carriers, whereas up to 90% are found in free ribonucleoprotein complexes. A significant portion of the latter are bound by complexes containing Argonaute2, an important mediator of RNA interference. Arroyo *et al.* did not investigate whether circulating miRNA-protein complexes are taken up by cells or have distinct biological functions. These RNA transport mechanisms suggest new approaches for delivering therapeutic RNAs. (*Nat. Cell Biol.* **13,** 423–433, 2011; *Proc. Natl. Acad. Sci. USA* **108**, 5003–5008, 2011) *ME*

Nanoparticles for circulating tumor cells

Monitoring circulating tumor cells (CTCs) in cancer patients could improve detection and treatment of metastatic disease. Current technologies for detecting CTCs are time-consuming and can have high false-positive rates. Wang *et al.* describe a method for detecting CTCs in blood through surface-enhanced Raman spectroscopy, using gold nanoparticles previously found to target tumors *in vivo* (*Nat. Biotechnol.* **26**, 83–90, 2008). In the current work, the particles are coated with polyethylene glycol, which prevents particle aggregation. Nanoparticles conjugated with a peptide of epidermal growth factor (EGF) give signals in proportion to the amount of EGF receptor on cell surfaces. Of 19 patients with squamous cell carcinomas of the head and neck, which overexpress EGFR in the majority of cases, all but one had detectable levels of CTCs. The identities of tumor cells were verified by performing Raman spectroscopy and immunohistochemistry on slides where tumor cells can be distinguished morphologically from leukocytes. Signals obtained from patient samples correlate with the stage of disease. One patient was tested when a distant metastasis was detected and then again after treatment. At recurrence, this patient had 11 CTCs per milliliter; after treatment, none were detectable. According to the authors, their method is both faster and more specific than previous technologies, although direct comparisons have yet to be made. (*Cancer Res.* **71**, 1526–1532, 2011) *LD*