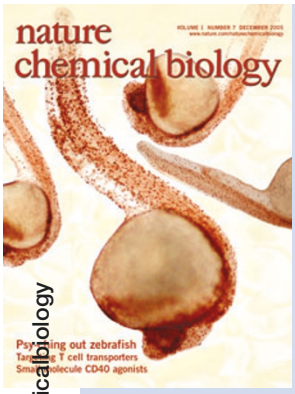


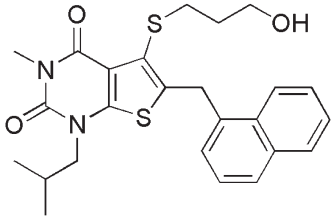
Cover story

The zebrafish has emerged as an important model system in which a variety of genetic and chemical techniques can be readily combined with *in vivo* analysis. Zon and colleagues have previously reported a zebrafish mutation called *crash&burn* (*crb*) that causes cell-cycle defects. In a paper in the current issue, the authors have now identified a chemical suppressor of the *crb* mutation. By screening a large library of compounds, the authors found a small molecule, persynthamide, that reversed many of the effects of the *crb* mutation. Mechanistic investigations showed that persynthamide functions by delaying S-phase; however, the precise molecular target remains to be identified. This study demonstrates that zebrafish will be a powerful model system for *in vivo* analysis of chemical cell-cycle inhibitors. **[Letters, p. 366; News & Views, p. 351]** *JK*

Rounding up CD40

Tumor necrosis factor (TNF) proteins are a superfamily of cytokines that regulate immune cell function. TNF proteins, which assemble into homotrimers, exert their effects by binding to TNF receptors on immune cells. Guichard and colleagues designed small molecules that mimicked the cytokine properties of CD40L (CD40 ligand), which binds to CD40 receptors on the surface of dendritic cells, macrophages and B cells. The authors synthesized a circular 'core' peptide with three lysine side chains spaced equally around the ring and attached to each appendage a short peptide, derived from CD40L, that had been shown to interact with CD40. They demonstrated that these compounds were effective CD40 agonists that activated downstream signaling pathways in several immune cell types. The molecules also activated CD40-bearing cells but did not cross-react with other TNF receptor proteins. The observed binding and activation specificity suggests that differential decoration of these molecular 'cores' may offer a general approach for small-molecule targeting of TNF receptors. [Letters, p. 377; News & Views, p. 353] *TLS*

Targeting T cell transporters



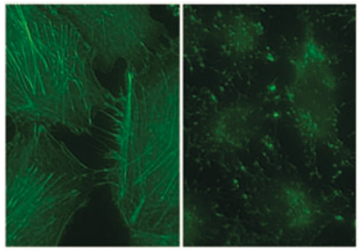
Studying a new class of immunosuppressive compounds whose mode of action was previously unknown, Murray and coworkers have now identified monocarboxylate transporter 1 (MCT1) as the molecular target of this class of drugs, using radiolabeled small molecules and proteomic analysis. During the rapid proliferation that follows activation, T cells are known to rely on energy from aerobic glycolysis, a process that generates ATP through the conversion of glucose to lactate. MCT1 is a lactate transporter that pumps out the excess intracellular lactate that is generated during this rapid cellular growth. The authors found that MCT1 inhibition led to an increase in intracellular lactate, which translated into a direct reduction of T cell proliferation. Besides characterizing the mode of action of a new immunosuppressive drug lead, this study demonstrates an unsuspected role for MCT1 in T cell proliferation. **[Letters, p. 371; News & Views, p. 356]** *JK*

In This Issue written by Mirella Bucci, Joanne Kotz, and Terry L. Sheppard.

Understanding side effects

Unexpected side effects are a frequent cause of the failure of drugs during clinical trials. The ability to predict these side effects at an earlier stage of drug research and development would be of clear value. Volkmann and colleagues have taken a step in this direction by doing a large-scale analysis of the connection between the biochemical activities and the side effects of more than 1,000 known drugs. The authors first generated a biochemical spectrum that described the activity of a drug against a large panel of proteins. Using the same drug, the authors generated a side-effect spectrum using the side effects reported during clinical trials. Comparison of the two spectra for a wide range of known drugs revealed a correlation between an individual drug's biochemical activity and the side effects it produced. This result provides a foundation for one day using biochemical activity information to predict side effects. [Articles, p. 389] *JK*

Invertebrate metabolite targets actin



Sea squirts form metabolites called bistramides that are highly toxic to mammalian cells, including various cancer cell lines. Their toxicity has been attributed to an effect on cell-cycle regulation, differentiation and apoptosis. Kozmin and coworkers found that bistramide A inhibited cytokinesis, so they suspected that bistramide A could work by inhibiting the contractile ring that is responsible for pinching mitotic cells into two. Indeed, they then found that bistramide A could bind stoichiometrically to actin, the major structural component of the contractile ring. These results fit well with the previous observations that bistramide A alters the mechanical activity of muscle, which uses an actin-based mechanism for contraction that is analogous to that of the contractile ring. Using cell-based and *in vitro* techniques, they showed that bistramide A disrupts the actin cytoskeleton in intact cells, inhibits cell proliferation and depolymerizes preformed actin filaments. **[Letters, p. 383]** *MB*

Receptors see the light

Light activation provides a way to temporally and spatially control activation of biological processes. However, naturally occurring mammalian ion channels cannot be directly activated by light. A number of chemical strategies have now been developed for creating photosensitive ion channels. In a Perspective in this issue, Kramer and colleagues review the progress and challenges of different approaches to regulating channel activity with light. These approaches offer the potential for a powerful system with which to investigate neuronal function. [Perspective, p. 360] *JK*