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Spotlight

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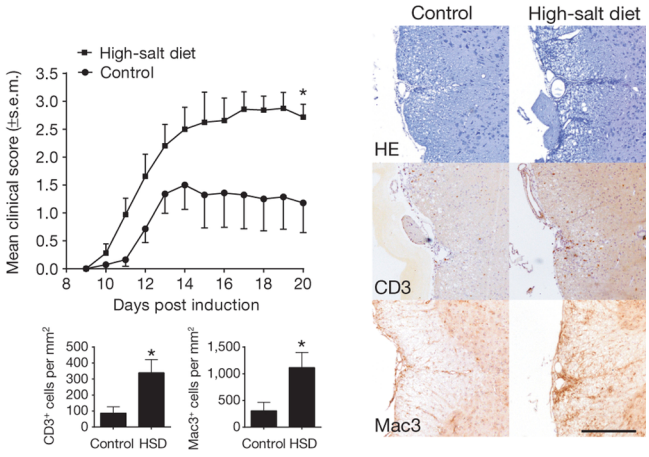
A SALTY PILL TO SWALLOW



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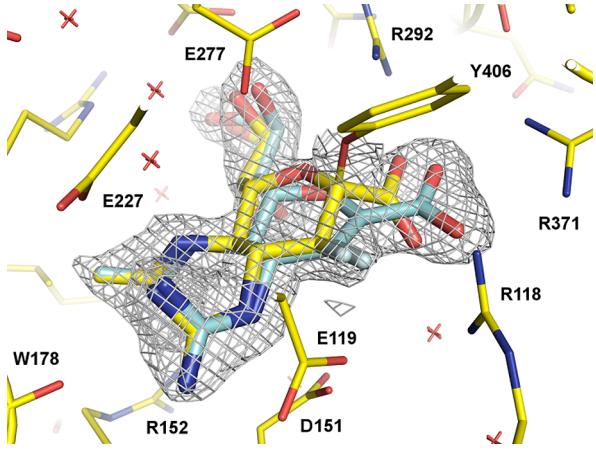
Autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, and type-1 diabetes afflict an estimated 24 million Americans. Perhaps even more alarming, the incidence of autoimmune disease has *tripled* over just the past few decades. Environmental factors such as diet are key suspects in this increase, and growing evidence is linking excess salt, or sodium chloride (NaCl), to adverse affects on the immune system. Kleinewietfeld *et al.* (*Nature* Epub ahead of print March 6, 2013; DOI: 10.1038/nature11868) now strengthen this link by finding that high levels of NaCl promote the development of T_H17 cells, a type of T cell implicated in autoimmunity.

The authors first asked whether salt intake affected human T_H17 cells in culture. They found that high concentrations of salt increased expression of IL-17A, the inflammatory protein that distinguishes T_H17 cells from other types of T cells. Next, gene expression microarray analysis demonstrated that exposure to high salt conditions resulted in upregulation of numerous pro-inflammatory cytokines, chemokines, and other proteins linked to autoimmune diseases. In addition, certain inflammatory and hypertonic pathways were stimulated under excess salt, including the p38/MAPK pathway that leads to activation of the transcription factor NFAT5. Blocking this pathway by chemical or gene silencing methods resulted in decreased production of IL-17A, as did inhibition of either NFAT5 or its downstream target kinase SGK1. Notably, similar gene expression and T_H17 differentiation effects of high salt were seen in mouse models of autoimmune disease. Moreover, mice on a high-salt diet experienced severe worsening of autoimmune disease symptoms. The authors propose that high-salt concentrations may promote an inflammatory response or cell migration into tissue, processes that characterize autoimmune disorders. Though they caution that more research is needed before salt can be held as the ultimate culprit for the increasing the prevalence of autoimmune disorders, this study illuminates the p38/MAPK pathway as a potential target for autoimmunity. **Eva J. Gordon, Ph.D.**

NEW DRUGS FOR NEURAMINIDASE



From Kim, J.-H., *et al.*, *Science*, February 21, 2013; DOI: 10.1126/science1232552. Reprinted with permission from AAAS.

The nasty, somewhat unpredictable infectious disease known as "the flu" afflicts anywhere from 5% to 20% of the U.S. population each year. While vaccines are incredibly important in reducing the spread and severity of influenza, antiviral drugs such as zanamivir and oseltamivir are also important contributors to controlling viral activity. Unfortunately, viral strains that are resistant to these drugs are rapidly emerging, creating an urgent need for different classes of compounds that can target these strains. To this end, Kim *et al.* (*Science* Epub ahead of print February 21, 2013; DOI: 10.1126/science1232552) now report the synthesis and biological activity of several new inhibitors of viral neuraminidase, an enzyme that plays a key role in the spread of influenza, as leads for new antiviral agents.

In designing novel neuraminidase inhibitors, the authors exploited the mechanism of the enzyme, which utilizes a transient covalent intermediate to cleave sialic acid residues from the viral and host cell surface. Several inhibitor candidates capable of forming a stabilized covalent intermediate were synthesized. The inhibitors were quite specific for viral neuraminidase over its human counterpart, were potent inhibitors of viral replication in a human cell line, and were also active against several resistant strains *in vitro*. In mouse models, the compounds exhibited favorable pharmacokinetics for both intravenous and intranasal administration. Indeed, mice treated with the inhibitors were protected from infection, and assessment of viral RNA levels in the lungs confirmed that viral replication had been attenuated. This new class of neuraminidase inhibitors is a promising jumping off point for the development of novel influenza drugs capable of taking down resistant strains of influenza. **Eva J Gordon, Ph.D.**

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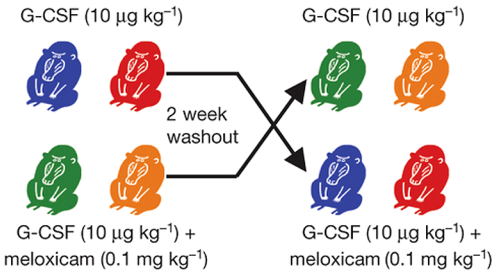
A NEW APPLICATION FOR NSAIDS



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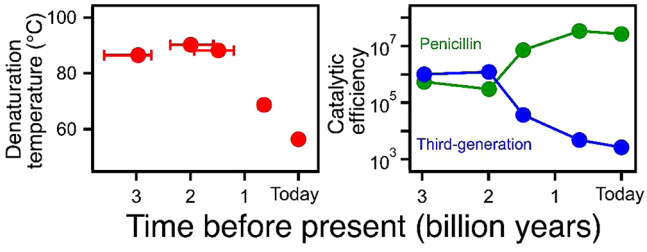
Nonsteroidal anti-inflammatory drugs have been used since the time of Hippocrates, who prescribed an extract from willow bark and leaves (later identified as a relative of aspirin) to reduce fevers and pain. While the effects of NSAIDs on the activity of mature white blood cells have been extensively studied for many years, less attention has been paid to their influence on various white blood cell precursors, called hematopoietic stem and progenitor cells (HSCs and HPCs, respectively). Building on recent data demonstrating a role for prostaglandin E2 (PGE2), a lipid involved in inflammation and whose biosynthesis is inhibited by certain NSAIDs, in HSC function, Hoggatt *et al.* (*Nature* 2013, *495*, 365−369; DOI: 10.1038/nature11929) now report that NSAID treatment results in the egress of HSCs and HPCs from the bone marrow to the peripheral blood.

The authors showed that in mice, primates, and humans treatment with the NSAID meloxicam results in increased levels of HSCs and HPCs, but not mature white blood cells, in the peripheral blood. Interestingly, however, the specific effects on HSCs were distinct from those on HPCs. For example, NSAID-induced HSC, but not HPC, egress was dependent on a reduction of the extracellular matrix protein osteopontin, and NSAID treatment enhanced expansion of certain populations of HPCs but had no effect on HSC phenotype or function. Experiments in PGE2 receptor knockout mice implicated a reduction of E-prostanoid 4 receptor signaling in these effects. Together, the data indicate that PGE2 signaling differentially regulates HPC and HSC retention in the bone marrow. These findings suggest a potential new therapeutic application of NSAIDs in bone marrow transplantations, and indeed HSC grafts mobilized with NSAIDs were more successful in restoring white blood cell populations in irradiated mice than grafts not treated with NSAIDs. **Eva J. Gordon, Ph.D.**

UNLOCKING ANCIENT β-LACTAMASES



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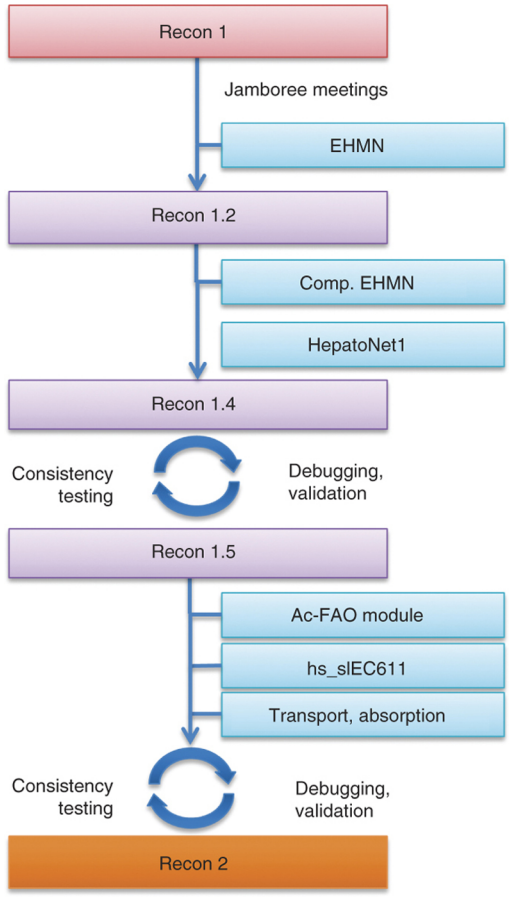
Antibiotic resistance remains a challenge of modern medicine, but antibiotic resistance genes also show up in samples found in soil, permafrost, and even on the ocean floor. In addition, β-lactamases, the enzymes that form the basis for resistance to penicillin and related antibiotics, exist throughout bacteria and are believed to be billions of years old. Now Risso *et al.* (*J. Am. Chem. Soc.* 2013, *135*, 2899−2902) have used genomic data to reconstruct these enzymes as a way to understand their evolution and piece together the mystery of resistance mechanisms.

Risso *et al.* constructed a phylogenetic tree of β-lactamases from Gram-positive and Gram-negative bacteria. Then they used computational tools to estimate when these genes diverged and to reconstruct the sequences of the ancestor proteins of those found in enterobacteria, proteobacteria and Gram-negative and Gram-postive bacteria. They put the DNA sequences of these enzymes into plasmids and expressed them in *E. coli*. They crystallized the enzymes, determined their structures, performed biophysical tests and assayed their activity against penicillin and other β-lactam antibiotics.

Though the amino acid sequences differ by up to 100 amino acids from modern β-lactamases, the 3D structure is similar across these proteins. The ancient enzymes are far more stable to heat than their modern counterparts: denaturation temperatures of the ancient enzymes are approximately 35 degrees higher. Although modern β-lactamase enzymes are far more active against penicillin, the ancient enzymes acted against a variety of β-lactam antibiotics including third generation, broad spectrum antibiotics.

The results support the working hypothesis that Precambrian life was thermophilic, and that evolution has moved enzymes from catalysts that were more promiscuous catalysts to more specialized ones. The ability to regenerate these ancient precursors and set up laboratory experiments for directed evolution may help researchers better understand these evolutionary processes and offer clues to antibiotic resistance mechanisms. **Sarah A. Webb, Ph.D.**

RECONSTRUCTING HUMAN METABOLISM



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Over ten years ago, the human genome project uncovered the human parts list in the form of genes. Today, a central challenge remains in understanding how these genes can lead to such a wide variety of cell fates and physiology. Understanding cellular metabolism involves building a biochemical picture of the reactants, the products and the diverse enzyme systems that catalyze and orchestrate the reactions. Several human metabolism models have previously been compiled by using biochemical knowledge, functional predictions, genomic and proteomic data. Now, in an impressive show of scientific partnership, a community of previously competing groups (Thiele *et al. Nat. Biotechnol*. Epub ahead of print March 3, 2013; DOI: 10.1038/nbt.2488) took the most widely used database, Recon 1, and expanded it with the information contained in other metabolism models to generate Recon 2.

The expanded Recon 2 computational model contains almost two times more biochemical reactions than Recon 1, published in 2007. It also vastly expands the catalog of metabolites produced in all cellular compartments. To check the model, 49 human disease states termed inborn errors of metabolism were used since there are experimental metabolite data for each disease. The model correctly predicted 77% of the metabolite biomarkers known from the biochemical data. In addition, Recon 2 predicts many extracellular metabolites that have been experimentally observed in biofluids or cell culture medium, plus it adds hundreds of new ones as likely candidates. The Recon 2 model was also combined with the Human Protein Atlas to generate metabolic reconstructions of 65 different cell types. The DrugBank database, which catalogs direct drug-enzyme relationships, was also integrated into this cell-type analysis. This allows Recon2 to model the effects of a particular drug not only in a global manner, but also peer into how that drug might alter one specific cell type's metabolism. Thanks to the strong sense of community among its builders, this immense reconstruction model and its future iterations are freely available at http://humanmetabolism.org. **Jason G. Underwood, Ph.D.**

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