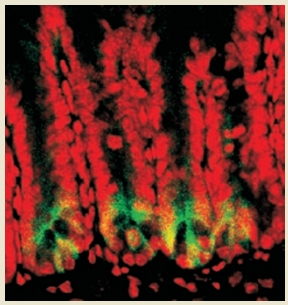
Intestinal stem-cell marker



The first molecular marker of stem cells in the small intestine and colon has been identified in a study published in *Nature*. Clevers and colleagues found that the *Wnt* target gene *Lgr5* (leucine-rich-repeat-containing G-protein-coupled receptor 5) is expressed in the stem cells of the adult mouse small intestine but not in other cell types of this tissue. The small-intestinal epithelium is organized into projections, called villi, and invaginated glandular structures, called crypts. Stem cells located near the base of the crypts give rise to transit-amplifying cells that generate fully differentiated cells as they migrate into the villi. Using lineage-tracing and radiation-sensitivity experiments, the authors determined that the transit-amplifying and specialized cells arise from *Lgr5*-expressing 'cycling crypt base columnar cells', located among the Paneth cells at the base of the crypt, rather than the '+4 position' cells previously proposed to be the crypt stem cell. They also found that *Lgr5*, a gene expressed in colon cancer cells, marks stem cells in the mouse colon and possibly in other adult tissues, such as the hair follicle and mammary gland. (*Nature* **449**, 1003–1007, 2007) *KA*

Back-scattering interferometry

Bornhop *et al.* describe a label-free optical approach to probe the interactions of biomolecules with zeptomolar sensitivity in as little as 350 pL. Their approach also eliminates the need for surface immobilization and characterization of at least one of the partners—both key limitations of the best broadly comparable alternatives. The interacting species are then mixed in a microfluidic channel that reflects a laser beam back and forth to generate an interference pattern that is imaged by a charge-coupled device camera. Back-scattering interferometry takes advantage of the fact that binding of molecular species in solution causes predictable shifts in this fringe pattern: the stronger the interaction, the larger is the shift. The authors exploit the change in refractive index that accompanies binding to determine dissociation constants for protein-protein interactions as well as binding of calmodulin to Ca^{2+}, a peptide and a small-molecule inhibitor. What's more, the approach should be equally feasible for carbohydrates and nucleic acids. (*Science* **317**, 1732–1736, 2007) *PH*

Handling massive MS data sets

Isotope labeling techniques for mass spectrometry enable sequence identification and quantification of proteins in complex mixtures. Because these isotope-based technologies cannot be used effectively for large numbers of samples, mathematical alignment algorithms have been developed for mass spectrometry on less than 20 samples. To overcome the mathematical hurdle that arises when analyzing more than 20 samples, Foss *et al.* develop an algorithm based on game theory with modest computational requirements that can be used to align mass spectrometry matrices in hundreds of samples. The authors aligned liquid chromatography tandem mass spectrometry data sets from hundreds of preparations of total cellular yeast proteins. They isolated proteins from eight independent cultures of two parent yeast strains and two independent cultures of each of 98 segregants to look at the genetic basis of variation in protein abundance. After identifying 137 proteins, whose abundance was different between the two parents, from data on 376 proteins, the authors looked at linkage between the levels of 221 proteins in the segregants and 2,951 genetic markers. Finally, the authors show that the loci that influence transcript levels differ from those that affect protein levels. Future experiments are required to determine whether this technology can be used to look at larger portions of the yeast proteome and to profile proteome variation in higher eukaryotes. (*Nat. Genet.* **39**, 1369–1375, 2007) *JWT*

Hepatitis C antiserum dragnet

Hepatitis C virus (HCV) remains an intractable public health problem, with only 50% of people responsive to therapy. Part of the problem lies in the variability of the virus, which, due to inherently error-prone replication, accumulates variants *in vivo* that can differ by as much as 30% of viral sequence. With the availability of genes for common variants of the two most variable viral proteins (the envelope proteins E1 and E2) as well as methods for preparing pseudo-viruses with different surface proteins, Johansson and colleagues set about fully characterizing the neutralizing activity of anti-HCV antibodies. They had previously isolated three antibodies that reacted against two E2 variants. From these antibodies, using a variety of assays—immunofluorescence, immunoprecipitation and western blotting, and an HCV pseudoparticle neutralizing assay—they isolated two antibodies that reacted broadly with variant E1E2 proteins. Finally, using a panel of E1E2 mutants with single amino acid substitutions, they mapped the epitope of both antibodies to overlapping regions of the protein. As anti-E2 antibodies have successfully protected chimpanzees against HCV infection, the presence of broadly reacting human antibodies suggests that such a prophylactic approach may be possible. (*Proc. Nat. Acad. Sci. USA Early Edition,* published online July 27, doi: 10.1073pnas0705522104) *LD*

Role for TRAIL in asthma

Tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) has been in the sights of cancer researchers for some time because of its ability to induce apoptosis in tumor cells. Now Weckmann and colleagues have shown that it is involved in the earliest stages of asthma. TRAIL was previously shown to be elevated in asthmatic lung, though its role was unexplored. Similarly, pathways involved with asthmatic response to allergens had been described, but the factors activating these pathways had not been discovered. This new work puts TRAIL in a central role in inducing airway hyperactivity (AHR, typified by enhanced lung resistance and decreased expiration) and inflammation. In TRAIL-deficient mice, there were fewer myeloid dendritic cells, which promote T-cell responses to allergens, and more plasmacytoid dendritic cells, which promote immune tolerance, than in control mice. In addition, TRAIL-deficient mice had fewer CCR6-expressing $CD4^+$ cells, which are recruited to the lungs during AHR. Similarly, reducing TRAIL only in the lung by applying siRNA to the airways abrogated AHR and inflammation. Finally, recombinant TRAIL given to mice intranasally induces AHR, upstream of the cytokine IL-13, an essential regulator of AHR. These results collectively suggest an important role for TRAIL in the early steps of asthma, and as such, provide a new target for asthma therapeutics. (*Nat. Med.* published online, October 14, doi: 10.1038/nm1660) *LD*

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