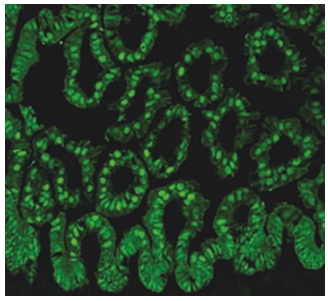
Off target in the colon

A class of compounds developed for Alzheimer disease could have a future in treating colorectal cancer, suggest two studies in the 16 June *Nature*.

γ-secretase inhibitors inhibit processing of APP, a protein implicated in Alzheimer disease—but the use of these drugs is plagued by side effects, including alterations in intestinal cells. γ-secretase inhibitors also inhibit signaling of Notch, a protein that regulates numerous cell-fate decisions.



Courtesy of Silvia Fre

Intracellular Notch (green) is expressed in all nuclei in the mouse intestinal epithelium.

The new studies (*Nature* **435**, 959–963, 964–968) investigate Notch signaling as cells in the intestine are born and differentiate in mice, a process that occurs in adulthood. Silvia Fre *et al.* examined cells with excess Notch signaling; they report reduced numbers of differentiated cells, such as mucous-secreting goblet cells, and increased numbers of proliferating, less differentiated cells. Johan van Es *et al.* report that knocking out the Notch pathway had an opposite effect, converting proliferative cells into differentiated cells. The new findings dovetail with studies in zebrafish, suggesting that Notch may regulate stem cells in the intestine.

van Es *et al.* also asked whether blocking Notch signaling with a γ-secretase inhibitor could shrink adenomas in mice with a mutation of the Apc tumor suppressor gene, commonly mutated in human colorectal cancer. They found that the drug could induce differentiation of proliferative cells in many of the tumors.

Previous work had shown that the Wnt-Apc pathway regulates intestinal development. But the Wnt pathway makes a tough drug target because—downstream of APC—it is regulated mainly by protein-protein interactions. γ-secretase inhibitors could present an alternative and are already in clinical trials for certain leukemias. —*CS*

Synergizing STDs

The risk of HIV infection increases in individuals afflicted with other sexually transmitted diseases such as herpes and chlamydia—presumably due to inflammation and lesions that provide a route for viral entry. Gonorrhea does not cause such symptoms, but it still increases the risk for HIV; a report in the 15 June *Journal of Immunology* examines why (174, 7995–8002).

In studies in mice and in human cells, Jizhong Zhang *et al.* showed that gonococci activated dendritic cells, antigen-presenting cells that can serve as a reservoir for HIV. Activation of dendritic cells in turn led to increased production of HIV virus by these cells. The experiments suggest that activation of dendritic cells occurred through recognition of Toll-like receptor 2 (TLR2) on the cells by an unidentified component of the gonococci.

The researchers propose that activation of TLR2 upregulates a transcription factor, NF-κB, that interacts with a component of the HIV genome—ultimately leading to the production of more virus by dendritic cells. Whether this mechanism operates in people remains to be seen. —*JB*

Written by Allison Alcivar, Jasmine Bhatia, Eva Chmielnicki, and Charlotte Schubert

Endocrine disruption

Environmental exposure to a common class of toxins, endocrine disrupters, leads to heritable genome changes, according to a report in the 3 June *Science* (**308**, 1466–1469) What's more, the changes—which appear to be epigenetic—can persist for four generations.

Endocrine disrupters interrupt normal hormone function by acting as hormone mimics or inhibitors. Matthew Anway *et al.* tested two of these disrupters, vinclozolin, a common vineyard fungicide that inhibits the androgen receptor, and methoxychlor, a pesticide that activates the estrogen receptor. Both of these compounds are known to induce sterility in progeny of treated rats. Indeed, the researchers found that a single injection of these compounds into gestating female rats—albeit at levels higher than typical human exposures—led to male progeny with reduced sperm motility, low sperm counts and high levels of apoptosis in sperm precursor cells.

The researchers bred the male rats for four generations, and showed that the decrease in fertility endured without waning in 90% of the males. Altered methylation patterns occurred in the testis and sperm DNA of male rats with diminished fertility, consistent with an epigenetic mechanism. —*AA*

Stress and addiction

Stressful events can drive former drug addicts to relapse—but what is really going on their brains? Previous work in rats had shown that the stress neurohormone corticotrophin-releasing factor (CRF) induces drug-seeking behavior. But beyond that not much was known.

In the 1 June *Journal of Neuroscience*, Bin Wang *et al.* (25, 5389–5396) report that stress increases CRF expression in a region of the brain associated with drug abuse—and that CRF seems to affect the brains of 'addicted' rats differently than control animals.

The investigators stressed rats by shocking their feet. In both cocaine-naive and cocaine-experienced rats, footshock induced CRF release into the ventral tegmental area (VTA), an addiction-associated brain region. The increase in CRF caused drug-seeking behavior only in the cocaine-experienced animals—through release of dopamine and glutamate into the VTA. These neurotransmitters drive the mesocorticolimbic dopamine system, which mediates many of the pleasurable effects of cocaine.

These results suggest that chronic drug use alters the response of the brain to stress, predisposing drug-experienced individuals to relapse into drug-seeking behavior. —*EC*

Cancer source

A long-term quest of cancer biologists is to find the cells that give rise to cancer. Although stem cells are prime candidates, it has been hard to pin them down, especially in solid tumors. In a study of the mouse lung, Carla Bender Kim *et al.* come close.

Previous work had hinted that stem cells exist in the lung, and in the 17 June *Cell* (**121**, 823–835), the investigators find them. These rare, specialized cells reside at the junction between the bronchus and the alveoli and have all the hallmarks of stem cells, including self-renewal capacity and the ability to give rise to different cell types. In addition, when these cells expressed oncogenic K-ras, they expanded in culture. In similar experiments in mice, these cells expanded in precursors of lung tumors when K-ras was expressed in lungs damaged by a chemical.

The investigators propose that the accumulation of mutations in these stem cells could drive tumorigenesis. —*CS*