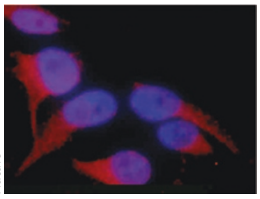
Stemming brain cancer



Nature

The BMP4 receptor (red) on stem cell–like cancer cells.

Research on stem cells uncovers a potential treatment for glioblastoma, one of the deadliest of cancers (*Nature* 444, 761–765).

Glioblastomas are thought to get much of their kick from a population of cancer cells with stem cell–like properties. Piccirillo *et al.* found that these cells expressed bone morphogenic proteins (BMPs) and their receptors, proteins that are involved in the differentiation of normal adult brain cells. They found that administering BMP4 could block tumor growth and prolong life in mice transplanted with human glioblastoma cells.

Other recent findings have identified a population of cells with stem cell–like properties in colon cancer (*Nature,* doi:10.1038/nature05384, doi:10.1038/nature05372). Whether BMP4 might counteract this and other cancers remains to be tested.—*CS*

Problem proteins in PD

Mutations associated with inherited forms of Parkinson disease have come to light recently—but it is still unclear how they lead to the death of dopaminergic neurons in the brain, a key event in this disease. Studies on two genes, α-synuclein and *LRRK2* (leucine-rich repeat kinase-2), address how such neuronal dysfunction may occur.

David Sulzer and colleagues found that cell lines overexpressing mutant α-synuclein had impaired dopamine release, a deficit linked to dysfunctional exocytosis of dopamine-containing vesicles (*J. Neurosci.* **26**, 11915–11922). Whether mutant α-synuclein interferes with dopamine release in neurons, and whether these problems contribute to dopaminergic neuron death, remains unclear.

A study in cells and rats (*Neuron* **52**, 587–593) suggests that mutant *LRRK2* reduces the formation of neurites, branch-like projections from a neuron's cell body that give rise to axons and dendrites. Asa Abeliovich and colleagues found that the kinase encoded by mutant *LRRK2* exhibited increased activity and seemed to prompt neuronal death and inhibit neurite outgrowth; conversely, knocking down *LRRK2* expression increased neurite length. Additionally, neurons that expressed mutant *LRRK2* contained tau aggregates, which are also present in the brains of some individuals with Parkinson disease caused by *LRRK2* mutations. The effect of mutant *LRRK2* on tau may shed light on other diseases that also exhibit tau aggregation, such as Alzheimer disease.—*EC*

Uncovering autism

Two studies have uncovered genes associated with autism.

Christelle Durand *et al.* found mutations in *SHANK3* in three families afflicted with the disease (*Nat. Genet.* 39, 25–27; 2006). Shank-3 binds multiple proteins that regulate functions at the neuronal synapse, including neuroligins. Since genes encoding neuroligins have been previously associated with autism, the findings suggest that these proteins and associated factors could be scrutinized in the search for a biological basis of autism.

Daniel Campbell *et al.* (*PNAS* 103, 16834–16839) report that mutations in the gene encoding the MET receptor tyrosine kinase raise the risk for autism. How *MET* may operate in the disease is unclear, although it is involved in neural development.—*CS*

Partners in drug crime

Behavioral responses to cocaine depend on the physical interaction between dopamine receptors and glutamate receptors, according to a study in *Neuron* (**52**, 897–909).

Interactions between dopamine and glutamate modulate the action of psychostimulant drugs, but the molecular mechanisms have been hard to pin down. Xian-Yu Liu *et al.* found that cocaine administration to rats triggered the formation of a complex between dopamine D2 receptors (D2R) and NR2B glutamate receptors in the striatum—a region of the brain highly susceptible to drugs of abuse. This interaction reduced NR2B phosphorylation and inhibited receptor function *in vitro*. Crucially, disrupting the D2R-NR2B interaction *in vivo* prevented the stereotyped behaviors, such as sniffing and biting, and the increase in locomotor activity seen after exposure to cocaine.

Future studies should test whether this interaction is relevant to the addictive properties of cocaine. —*JCL*

HIV-malaria linkage

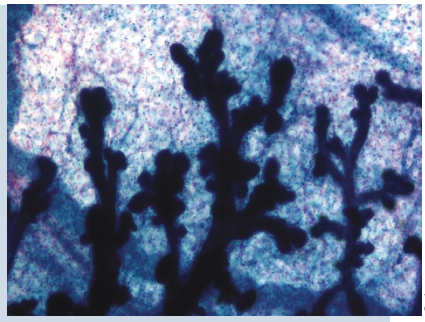
Episodes of malaria can cause levels of HIV virus to spike in the blood; conversely, HIV-infected patients have increased susceptibility to malaria. Laith Abu-Raddad *et al.* explore the public health implications of this dynamic (*Science* 314, 1603–1606).

The researchers created a mathematical model and applied it to a region in Kenya with an adult population of approximately 200,000. The researchers estimate that since 1980, the interaction between the two diseases may have been responsible for 8,500 more HIV infections than if malaria were not present, and 980,000 excess malaria episodes. Thus efforts to quell one disease could have a big impact on the other.—*CS*

Written by Eva Chmielnicki, Alison Farrell, Juan Carlos López and Charlotte Schubert.

Handle on hormones

BRCA1 is widely expressed, yet when mutations arise in this gene, it's the breast and ovarian tissue that are most susceptible to cancer. A report in *Science* (**314**, 1467–1470) examines this conundrum and suggests a new strategy against *BRCA1*-deficient tumors—administration of the progesterone receptor antagonist RU486 (mifepristone), perhaps best known as an abortion drug.



Science

Mammary glands branch out in *Brca1*-deficient mouse.

Previous research had found that BRCA1 interacts with both the estrogen and progesterone receptors, and Aleksandra Jovanovic Poole *et al.* considered whether this might underlie the specific effects of *BRCA1* mutations in hormone-responsive tissues. The investigators analyzed a mouse cancer model lacking Brca1 and the tumor suppressor p53. The mammary epithelial cells in these mice showed increased proliferation, an effect that could be amplified by estrogen or progesterone. What's more, treating the mice with RU486 prevented tumor development.

The absence of Brca1 resulted in stabilization of the progesterone receptor, which may account for the cells' enhanced proliferative response to progesterone. If these results hold up in human breast cancer cells, RU486 may be useful as a prophylactic treatment in carriers of *BRCA1* mutations. —*AF*

© 2007 Nature Publishing Group http://www.nature.com/naturemedicine