Research news

Designer immunosuppressants

Screening of combinatorial peptide libraries has revealed a new peptide that is able to block specific molecular events involved in organ graft rejection, which may lead to the development of better immunosuppressive drugs. The drugs now used for immunosuppression after organ transplantation, cyclosporin A and FK506, function by blocking the calcineurin, a phosphatase required to activate the transcription factor NFAT and initiate the immune response. These drugs are also believed to interfere with other cell signaling pathways, and these secondary effects have been associated with kidney failure, neurotoxicity and increased risk of malignancy. In the 24 September issue of *Science*, Aramburu and colleagues report the discovery of a peptide, VIVIT, which selectively inhibits NFAT activation by calcineurin. Expression of VIVIT in cultured T cells prevented NFAT nuclear translocation and NFAT-dependent cytokine expression, but did not affect expression of other genes that require calcineurin but not NFAT. Although the *in vivo* ability of this peptide to block immune activation has not yet been demonstrated, these results suggest new avenues to explore in designing more-selective, and thus potentially less-toxic, immunosuppressants.

Knocking out alcohol damage

After feeding knockout mice with a high-ethanol, high-calorie diet, researchers have identified tumor necrosis factor (TNF)-α as a molecular culprit in alcohol-induced liver damage. The discovery, reported in the October issue of *Gastroenterology*, opens up the possibility that anti-TNF-α drugs may be useful in the treatment of alcoholic cirrhosis. Ronald Thurman's team compared TNF-α knockout mice with wild-type mice and found that, after four weeks of chronic alcohol consumption, liver pathology—steatosis, inflammation and necrosis—was seven times more severe in wild-type mice than in mice lacking the receptor, TNF-R1. This phenomenon did not occur in TNF-R2-deficient mice. This finding is the first definitive proof that TNF-α, produced in Kupffer cells in the liver, mediates alcoholic liver injury. There is plenty of room for improvement in alcoholism therapy: current medications include the opiate antagonist naltrexone, which reduces craving, and disulfiram, which causes nausea and vomiting when taken with alcohol. Alcoholism affects around 14 million people in the US.

New York virus still a mystery

Sequence analysis of DNA taken from brains of victims of the deadly encephalitis outbreak in New York City suggests that the infectious agent may undergo yet another name change. When the first patients contacted the disease last August, the diagnosis, based on the symptoms, was St. Louis encephalitis. Then, preliminary genetic analysis led researchers to believe that the encephalitis was caused by West-Nile virus, a flavivirus only previously reported to occur in Africa, Asia, and Europe. The most recent sequence data, published in the 9 October issue of *The Lancet,* suggests that the virus has higher homology to an Australian flavivirus, the Kunjin virus. However, after sequencing 40% of the viral genome, the authors are still not sure exactly what this virus is. "The nomenclature for flavivirus is complicated," explains Ian Lipkin, senior author on the paper. "No one is quite sure how to assign it to a category. Some say these viruses should be categorized by amino-acid homology alone, while others say it should be determined by cross-protection studies". The Centers for Disease Control (CDC) is also sequencing the viral genome independently of the Lipkin group. Tom Skinner, spokesman for the CDC, says that their data are too premature to determine exactly what the virus is or where it came from. The virus has been associated with the death of six people in New York City, and dozens more are suspected of having contracted mild to serious cases of the illness.

Breast cancer therapy still questionable

In the US, up to 30,000 metastatic breast cancer patients have been treated with a costly therapeutic regimen of high-dose chemotherapy followed by hematopoietic stem cell transplantation, despite the fact that the efficacy of this procedure over conventional chemotherapy has yet to be established. A study published in the 13 October issue of *JAMA* attempts to provide information about what types of patients are most likely to respond to this controversial therapeutic approach. This study describes a multivariate analysis of 1,188 women with advanced breast cancer who received high dose chemotherapy and hematopoietic stem cell transplants at 63 hospitals. The paper reports that an increased risk of treatment failure (death, disease progression or cancer recurrence) is associated with several factors, including a patient age of over 45 years, a hormone-receptor-negative tumor, prior adjuvant chemotherapy, and number and location of metastases. An accompanying editorial points out that these factors also predict poor outcome in patients receiving standard-dose chemotherapy that does not include stem cell transplant. Thus, the determination of whether high-dose therapy followed by stem cell transplants improves the chances for survival of breast cancer patients still awaits a large randomized, well-controlled clinical trial in which the two procedures are directly compared. Meanwhile breast cancer victims who can afford it will understandably, but perhaps mistakenly, continue to turn to an unproven procedure.

PAG pain relief

A newly developed detection method has revealed the endogenous production of cannabinoids by neurons in a region of the brain known as the periaqueductal gray (PAG). Cannabinoid receptors were already known to be localized to the PAG, which is involved in pain modulation, and cannabinoid receptor agonists are well-established producers of analgesia. In the 12 October issue of *PNAS*, Walker *et al*. report that electrical stimulation of the PAG causes neurons to release the cannabinoid anandamide, inducing analgesia in rats. The existence of a cannabinergic pain modulatory system may have relevance for treatment of pain when opiates are ineffective.

CONTRIBUTIONS BY SARA MARIANI, KAREN BIRMINGHAM AND KRISTINE NOVAK