Research News

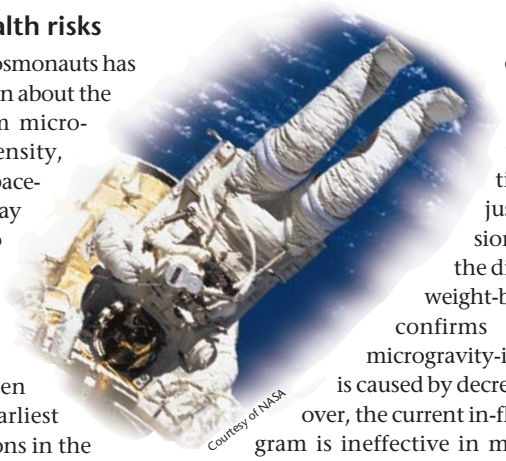
Gene therapy flexes its muscles

A study published in the June issue of *Nature Biotechnology* uses chimeric oligonucleotides to successfully repair a mutation that causes Duchenne muscular dystrophy in golden retrievers (GRMD). GRMD is caused by a splice site point mutation, leading to deletion of exon 7 from the dystrophin mRNA and termination of translation. Bartlett *et al*. designed a hairpin-shaped DNA–RNA chimeric oligonucleotide to induce host cell mismatch repair and correction of the chromosomal mutation. They report that direct skeletal muscle injection of the chimeric oligonucleotide into the cranial tibialis comparment of an affected dog restored inclusion of exon 7 into dystrophin mRNA. Normal-sized dystrophin could be detected in multiple regions of cranial tibialis muscle for up to 48 weeks after treatment. This gene therapy approach may be preferable to transgene expression approaches, as it actually modifies the endogenous mutant gene, allowing it to remain under the control of all its native regulatory elements. The authors are attempting to determine whether serial administration of chimeric oligonucleotides has an additive effect that will be measurable by determination of force-generation.

RAGE against cancer!

'Signal transduction therapy' may present a way forward for the treatment of cancer, according to a report in the 18 May issue of *Nature*. Taguchi *et al*. disrupted the receptor for advanced glycation end products (RAGE) and one of its ligands, amphoterin. They found that this reduced the growth, motility and invasiveness of a number of natural and implanted types of tumors in nude mice. On a molecular level, blocking RAGE/amphoterin led to suppression of several MAP-kinase-related signaling proteins (p44/p42, p38 and JNK). This in turn disrupted downstream cellular events, such as the expression of metalloproteinases, which are required to break up the extracellular matrix through which cells metastasize. The authors showed that many peptide, antibody and genetic methods of blocking RAGE/amphoterin were able to repress tumors, while on page 643, Yan *et al*. show that RAGE antagonists suppress amyloid deposition in mice. Thus, RAGE signaling blockade may have a wide range of clinical applications.

Space travel health risks


Courtesy of NASA

A study of Russian cosmonauts has provided information about the effects of long-term microgravity on bone density, and indicates that space-induced bone loss may be more difficult to combat than previously believed. The association between microgravity and osteoporosis has been known since the earliest human space missions in the 1970s, but it has been difficult to determine its precise nature and time course. In the 6 May issue of *The Lancet*, Vico *et al*. reported the effects of microgravity on bone mineral density (BMD) in 15 Russian cosmonauts who visited the MIR space station for different periods of time. The authors found that cosmonauts experienced a mean BMD loss of almost 22% in weight-bearing tibial bones after just a 1-month mission, but no losses in the distal radius, a less-weight-bearing bone. This confirms suspicions that microgravity-induced bone loss is caused by decreased force. Moreover, the current in-flight exercise program is ineffective in maintaining bone mass. Bone loss increased during longer space missions, and in some cases BMD did not return to pre-flight values after astronauts returned to Earth. The authors found substantial inter-individual differences in BMD loss, and plan to study environmental and genetic factors behind osteoporosis predisposition.

A function for trophic factors in drug addiction

A recent study indicates that the neurotrophic factor GDNF is involved in biochemical and behavioral adaptations to drugs of abuse. Neurotrophic factors have been studied for many years because of their function in nervous system development and in the plasticity of the adult nervous system. In the April issue of *Neuron*, Messer *et al*. reported that administration of GDNF, a neurotrophin known to be involved in dopaminergic neuronal development, prevented biochemical and behavioral adaptations to morphine and cocaine in rats. The authors suggested that endogenous GDNF may downregulate normal responses to drug exposure, as infusion of antibodies against GDNF increased the rats' responses to drugs. Mice lacking one copy of the GDNF gene showed a similar increase in drug sensitivity. The authors found a decrease in GDNF receptor signaling after chronic exposure to morphine or cocaine in dopaminergic regions of rat brain, and concluded that GDNF, and perhaps other neurotrophins, could be involved in the neuronal plasticity associated with addiction. Medications targeted to the GDNF signaling pathway may be a new approach to treating addictive disorders.

Outbreak alert

Four eclectic articles published in *The New England Journal of Medicine* have indicated that emerging infections are becoming more common and complex. Two studies in the 27 April issue suggested that the surge in livestock production and extensive use of antibiotics promote the spread of rare or new infectious agents. Goh *et al*. provided clinical details of cases of Nipah virus encephalitis among pig farmers in Malaysia, believed to be caused by direct viral transmission from pigs to humans. Additionally, Fey *et al*. reported that a child living on a farm in Nebraska contacted a ceftriaxone-resistant salmonella infection through contact with infected cattle. The studies also suggest that careless food preparation is a means to quickly spread pathogens, as Aureli *et al*. reported that cafeteria food contamination with *Listeria monocytogenes* caused febrile illness and gastroenteritis in 1,566 people in a school in Northern Italy. Finally, the worldwide increase in the numbers of immunocompromised people may also promote pathogen emergence; Petrillo *et al*. reported that a chronically ill 12-year-old boy contacted the rare and often fatal disease enteritis necroticans ('pigbel') from food. In an accompanying editorial, Michael Osterholm wrote that the public health infrastructure cannot keep up with the increasing number of factors supporting the emergence of infections, and quick government action should be taken to address this growing crisis.

Contributions by Kristine Novak & John MacFarlane