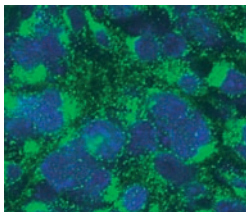
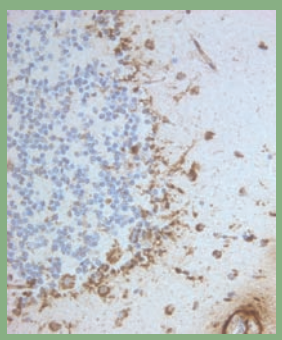
Biofilm formation controlled by neuraminidase

Therapeutics targeting a surface-bound enzyme encoded by the influenza virus neuraminidase are highly effective antiviral treatments. Many bacterial pathogens, including the opportunistic pathogen *Pseudomonas aeruginosa*, also encode neuraminidases. However, whether these enzymes are important for bacterial pathogenesis such that they would be appropriate antibacterial targets has not been clear until now (pages 2297–2305). In this issue, Soong and colleagues report that mice rapidly clear bacteria from the respiratory tract following intranasal infection with mutant *P. aeruginosa* lacking neuraminidase whereas they cannot clear wild-type *P. aeruginosa*. In contrast, mice were equally susceptible to intraperitoneal infection with wild-type and mutant *P. aeruginosa*, indicating a role for neuraminidase in the initial stages of respiratory infection. Further analysis showed that biofilm formation by mutant *P. aeruginosa* lacking neuraminidase was markedly impaired and that biofilm formation by wild-type *P. aeruginosa* could be abrogated in a dose-dependent manner by influenza virus neuraminidase inhibitors. These data indicate that the *P. aeruginosa* neuraminidase is crucial for the initial colonization of the respiratory tract and lead the authors to suggest that it could provide a new target to prevent infection with this bacterium.

Tackling tumor-associated macrophages

As tumor-associated macrophages (TAMs) can promote tumor cell proliferation and metastasis, Luo and colleagues have designed a cancer vaccine to specifically target these cells (pages 2132–2141). TAMs, but not tumor cells or other macrophage populations, were found to express high levels of the asparaginyl endopeptidase legumain, so the authors generated a DNA vaccine encoding legumain. When administered to mice, this vaccine inhibited tumor growth and metastasis in mouse models of breast, colon, and non–small cell lung cancer. These effects were associated with a legumain-specific cytotoxic $CD8^+$ T cell response that targeted TAMs in the tumor tissue. Consistent with the marked decrease in the number of TAMs in the tumor tissue of vaccinated mice, tumors contained decreased amounts of the tumor cell growth factor TNF and the proangiogenic factor VEGF. As a result, tumor cell migration, metastasis, and angiogenesis were markedly inhibited. The authors suggest that this demonstration that targeting TAMs can suppress tumor growth and metastasis could lead to the development of new therapies for cancer.

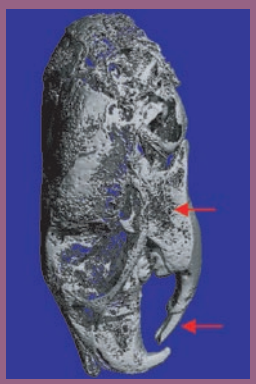




Antisense oligonucleotides hitch a ride through the CSF

The aggregation of toxic proteins in the CNS underlies many neurodegenerative diseases. Several strategies for removing excess proteins from the brain have been tried, but few have been successful due to the tight regulation of the blood-brain barrier. Smith and colleagues have now delivered effective doses of antisense oligonucleotides throughout all brain regions affected in the major neurodegenerative diseases and to all levels of the spinal cord through the cerebrospinal fluid (CSF) (pages 2290–2296). Once produced, CSF circulates from the ventricles to all regions of the CNS, yielding complete replacement 3 times a day. Exploiting this process and using second-generation oligonucleotides with enhanced tolerability and potency, the authors were able to modulate and deliver effective doses of antisense oligonucleotides. Antisense oligonucleotides to superoxide dismutase reduced protein and mRNA in the CNS. Delivery of antisense therapy initiated after the onset of symptoms slowed disease progression in a rat model of amyotrophic lateral sclerosis. This establishes that direct delivery of antisense oligonucleotides through the CSF can be an effective means of treating neurodegenerative diseases when the appropriate aberrant protein is known.

A potential treatment for progeria?



Hutchinson-Gilford progeria syndrome (HGPS) is a rare pediatric syndrome characterized by slow growth, sclerodermatous changes of the skin, alopecia, micrognathia, osteoporosis, osteolytic lesions in bone, and occlusive atherosclerotic vascular disease. HGPS is caused by an LMNA mutation that results in the synthesis of a mutant prelamin A (also called progerin). Progerin undergoes farnesylation but cannot be further processed to mature lamin A, a key structural component of the cell nucleus. In HGPS cells, progerin accumulates at the rim of the nucleus, causing misshapen nuclei. Yang and colleagues, authors of a study in this issue of the *JCI*, suspected that protein farnesylation might be crucial for the aberrant targeting of progerin to the inner nuclear membrane and were able to show that blocking farnesylation with an inhibitor would prove therapeutic (pages 2115–2121). Treatment of a new gene-targeted mouse model of HGPS with an inhibitor of farnesyltransferase (FTI) increased adipose tissue, improved body weight curves, reduced the number of rib fractures, and improved bone mineralization and bone cortical thickness. These studies suggest that FTIs may be useful for treating humans with HGPS.