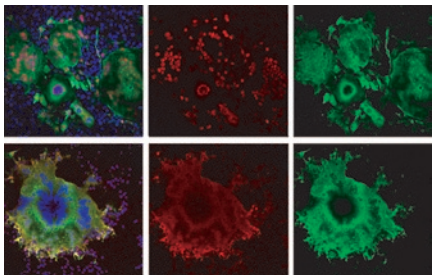
doi:10.1038/mt.2009.50

Oncolytic virotherapy 2.0



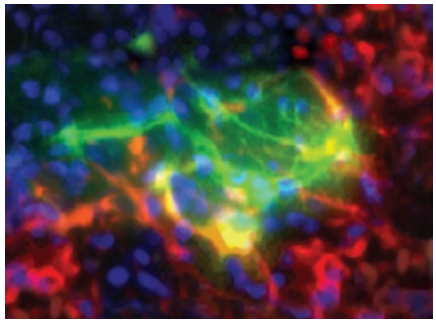
Many of the oncolytic viruses currently under laboratory development, including Newcastle disease virus (NDV), are too attenuated to be therapeutically effective in humans. The main impediment to their efficacy is the ability of some tumor cells to mount an antiviral response—probably mediated through interferon. In this issue, Zamarin *et al.* show that a recombinant NDV harboring and expressing an influenza virus NS1 protein, that is known to antagonize the interferon response, is a more broadly active antitumor virus in an animal model. The virus had increased oncolytic activity and promoted antitumor immunity, despite being no more virulent than the parental virus. ***See page 697.***

Efficient gene silencing with reduced nonspecific effects

Small interfering RNAs (siRNAs) are short, double-stranded RNAs that mediate gene silencing in a sequence-specific manner by utilizing the endogenous RNA interference (RNAi) pathway. The standard synthetic siRNA structure is a 19-bp duplex with 3′ overhangs of two nucleotides (the 19 + 2 form). However, this synthetic structure shows several sequence-independent, nonspecific effects. In this issue, Chang *et al.* report an asymmetric siRNA (asiRNA) backbone structure with duplex regions shorter than 19 bp that can efficiently trigger gene silencing in human cell lines. Importantly, this asiRNA structure reduces nonspecific effects triggered by conventional 19 + 2 siRNA scaffold, such as sense strand–mediated off-target gene silencing and saturation of the RNAi machinery. ***See page 725.***

DNA nanoparticles for long-term CNS expression

Nonviral vectors for gene delivery are being developed because of perceived benefits such as relatively low costs for large-scale manufacturing, lack of risk of vector replication, and lack of preexisting vector immunity, which may translate to potential safety advantages when compared with viral vectors. In this issue, Yurek *et al.* present proof of concept for delivery and expression of compacted plasmid DNA in the central nervous system. Proprietary techniques were used to compact DNA with polyethylene glycol–substituted lysine 30-mer peptides, forming nanoparticles (NPs) with diameters between 8 and 11 nm. They report long-term (11 weeks) expression with minimal toxicity in the rat brain following direct intracerebral injection of DNA NPs. ***See page 641.***



ERT treats CNS lesions in a lysosomal storage disease

Lysosomal storage diseases (LSDs) are characterized by a progressive multisystemic pathology and premature death. Repeated intravenous injection of the deficient enzyme, called enzyme replacement therapy (ERT), is a clinical option for several LSDs without central nervous system involvement. In this issue, Matzner *et al.* assess the efficacy of long-term ERT in metachromatic leukodystrophy (MLD), an LSD with prevailing nervous system disease. They treated immunotolerant arylsulfatase A (ASA) knockout mice with 52 doses of either 4 or 50 mg/kg recombinant human ASA. ERT was tolerated without side effects and improved disease manifestations in a dose-dependent manner, demonstrating prevention of nervous system dysfunctions that dominate early stages of MLD. ***See page 600.***

New animal model for frontotemporal lobar degeneration

Since the discovery of neuropathological lesions comprising TDP-43 and ubiquitin in frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis, there has been a burst of effort to develop an animal model for these diseases. In this issue, Tatom *et al.* describe an animal model for FTLD created by use of an adeno-associated viral vector to transduce neurons of the substantia nigra (SN) with human TDP-43. Gene transfer caused loss of dopaminergic neurons in the SN and their axons in the striatum. Behavioral motor dysfunction resulted after TDP-43 gene transfer that was vector dose–dependent and progressive over time. The cytoplasmic expression, ubiquitination, and neurodegeneration mimicked features of FTLD. ***See page 614.***