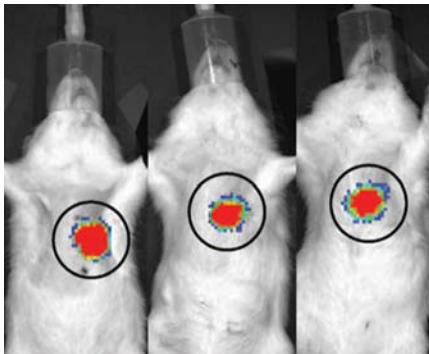


Monitoring cardiogenic differentiation of stem cells



Cell-based therapy is a potential new therapeutic option for regenerating the infarcted heart. Cardiosphere-derived resident cardiac stem cells (CDCs) are readily isolated and promote cardiac regeneration in the mammalian heart. Cardiomyocytes and their precursors can be enriched by transducing stem cells with vectors encoding selectable markers under the control of a cardiomyocyte-specific promoter. Barth *et al.* evaluated CDC transduction by viral vectors (adeno-associated virus vs. lentivirus) and compared the myocardial specificity of five commonly used cardiac promoters in the context of these vectors *in vitro* and *in vivo*. They also tested the utility of an optimized lentivector system to report the cardiogenic phenotype in CDCs. *See page 957.*

Adenovirus-mediated interleukin-2 gene therapy trial

Interleukin-2 (IL-2) induces regression of metastatic tumors. In this issue, Dummer *et al.* report findings of a phase I/II, multicenter, open-label, dose-escalating study to evaluate the safety, efficacy, and biological effects of repeated intratumoral injections of adenovirus-IL-2 (TG1024) in patients with advanced solid tumors and melanoma. Of the six local objective responses recorded, two were complete responses. Common side effects were injection-site reactions and flulike

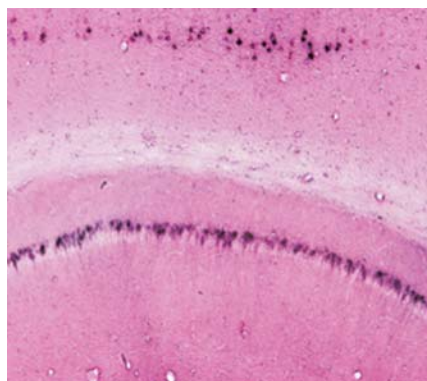
syndrome. TG1024 dose intensification resulted in increased serum IL-2 levels after the injection. Intratumoral TG1024 injection induced pronounced inflammation of the treated lesion and CD8 T-cell infiltration. The results show that intratumoral injections of TG1024 are safe and well tolerated. *See page 985.*

Therapeutic angiogenesis gains a leg to stand on

Nikol *et al.* report the evaluation of the efficacy and safety of intramuscular NV1FGF, a plasmid-based angiogenic gene delivery system for local expression of fibroblast growth factor 1 in patients with critical limb ischemia. In a double-blind, randomized, placebo-controlled, European multinational study, 125 patients unsuitable for revascularization and presenting with nonhealing ulcer(s) were randomized to receive eight intramuscular injections of placebo or NV1FGF. The primary end point was incidence of complete healing of at least one ulcer in the treated limb at week 25. Secondary end points included amputation and death. Although similar improvements in ulcer healing occurred with NV1FGF or placebo, NV1FGF significantly reduced the risk of all amputations. *See page 972 and Commentary on page 808.*

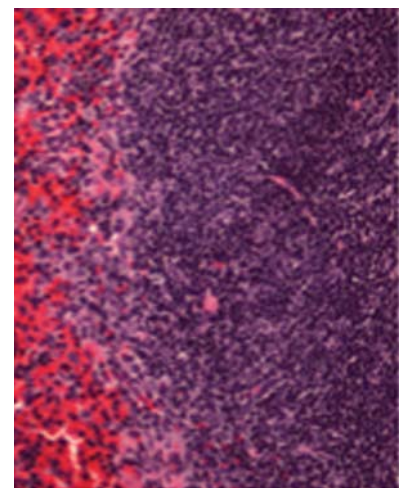
“Immunomodulating” immunotherapy for Alzheimer’s disease

Immunotherapies designed to dissolve existing amyloid plaques or to interrupt amyloid- β (A β) accumulation may be



feasible for treatment and/or prevention of Alzheimer’s disease (AD). Frazer *et al.* describe how they constructed a herpes simplex virus-based amplicon vector that co-delivers A β 1-42 along with interleukin-4, a cytokine that promotes the generation of Th2-like T-cell responses, which are favored in the setting of AD immunotherapy. An increase in Th2-related, A β -specific antibodies, improvement in learning and memory functioning, and prevention of AD-related amyloid and tau pathological progression were observed in AD mice vaccinated with the amplicon vector. *See page 845.*

Systemic siRNA delivery inhibits tumor growth



Leaf Huang and co-workers have previously published work characterizing a nanoparticle delivery system that includes protamine to condense nucleic acids, a cationic lipid element, PEGylation, and a ligand to target cell-surface sigma receptors. In this issue, Li *et al.* describe the use of this delivery system to dose an siRNA cocktail into mice by intravenous administration to reduce growth of pulmonary implants of a melanoma tumor. Reduction of target protein levels was demonstrated by immunohistochemistry, and reduced tumor growth was shown, resulting in improved survival. Elevated cytokine expression was seen only with doses of siRNA greater than that used in the tumor study. *See page 942.*