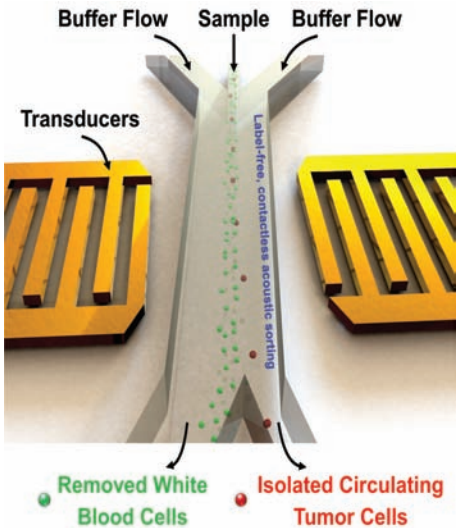
In This Issue

Isolating rare circulating tumor cells

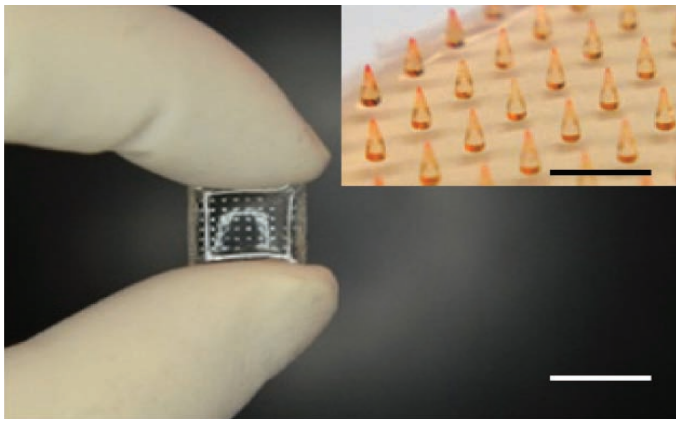
Isolating circulating tumor cells (CTCs) in the bloodstream represents a minimally invasive way to both clinically assess cancer and advance the study of metastasis. Previous studies have shown that acoustic waves can sort and separate cultured cancer cells from blood cells based on physical properties, such as size and density, as well as mechanical properties. However, isolating small numbers of rare cancer cells from other cells and blood components remains a significant challenge. Using parametric studies and simulations, Peng Li et al. (pp. 4970–4975) designed an optimized tilted-angle standing surface acoustic waves platform, dubbed acoustic tweezers, which increased the separation throughput of cancer cells by up to 20 times compared with previous designs. To test the device, the authors cultured a variety of cancer cells and successfully separated low concentrations of cancer cells from white blood cells with a recovery rate greater than 83%. The authors also demonstrate the platform's real-world applicability by isolating CTCs in blood samples obtained from patients with breast cancer. In practice, this label-free method based on acoustic tweezers might represent a supplemental tool in cancer research, diagnostics, drug efficacy assessment, and therapeutics, according to the authors. — T.J.



Acoustic tweezers separate rare circulating tumor cells.

Improving skin vaccination

The delivery of vaccines into skin rather than muscle is known to produce stronger immune protection against viruses. Yet skin immunization has not been broadly adopted, partly due to relatively high rates of pain and irritation and the difficulty of vaccine administration. Ji Wang et al. (pp. 5005–5010) developed a painless, efficient strategy for delivering vaccines into skin using arrays of microneedles, which are separated by sufficient distances to



Microneedle array held by two fingers. (*Inset*) A portion of loaded microneedles. (Scale bar, 1 cm or 1 mm in *Inset*).

constrain vaccine-induced inflammation and promote rapid healing. Whereas intradermal injection of the bacillus Calmette–Guérin vaccine caused skin irritation in mice, microneedle-array immunization produced mild skin reactions. Further, the authors incorporated an approved nonablative fractional laser (NAFL) treatment, which provokes a local, transient inflammatory response that augments vaccine-induced immune protection. Mice that received NAFL pretreatment at the inoculation site followed by microneedle-array immunization with an H1N1 influenza vaccine survived exposure to the H1N1 virus, whereas microneedle-array immunization alone protected only 30% of mice. Moreover, the combination therapy conferred a high level of cross-protection against other H1N1 viruses and the H3N2 virus, increasing survival rates, compared with microneedle-array immunization alone. Because mismatches often occur between vaccine and circulating strains of viruses, the cross-protection offered by NAFL might enhance vaccine efficacy and reduce death rates during the flu season, according to the authors. — J.W.

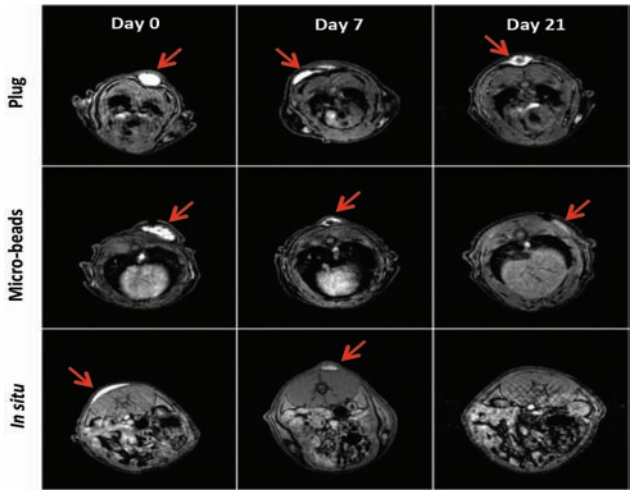
Protecting mice against hypervirulent *Mycobacterium tuberculosis*

The rise in drug-resistant strains of *Mycobacterium tuberculosis* (*MTB*) has necessitated new approaches to treating tuberculosis (TB). A previous study found that silencing the cytokine IL-32 impaired the killing of *MTB*, suggesting that IL-32 has host-protective effects. To study the effects of IL-32 in vivo, Xiyuan Bai et al. (pp. 5111–5116) developed transgenic mice that expressed human IL-32γ in the lungs. When the authors infected these mice with a hypervirulent clinical strain of *MTB*, they found that at both 30 days and 60 days after infection, the transgenic mice had less *MTB* in their lungs and spleens than mice that did not express IL-32γ. The transgenic mice also survived longer and had increased numbers of host-protective innate and adaptive immune cells, compared with the nontransgenic mice. IL-32 expression was significantly

higher in the lungs of patients with active TB, compared with patients without TB, particularly in macrophages, airway epithelial cells, B cells, and T cells. Expression of human IL-32 in the lungs of mice is protective against *MTB*, and this protection is likely due to an increase in host-protective innate and adaptive immune cells, according to the authors. The authors suggest that IL-32 may represent a target for immunotherapy to treat TB. — S.R.

Tracking the performance of clinical implants

Regenerative medicine relies on approaches that deliver cells or molecules to help restore or establish normal function in tissues and organs. However, experimental tools for continuously and noninvasively monitoring the fate of implants in living animals are lacking. To overcome this hurdle, Alexandra Berdichevski et al. (pp. 5147–5152) combined fluorescent labeling with MRI to noninvasively track the precise fate of three biodegradable delivery platforms carrying VEGF, which promotes the formation of new



MR images of plugs, microbeads, and polymerized hydrogels. Arrows indicate labeled implants.

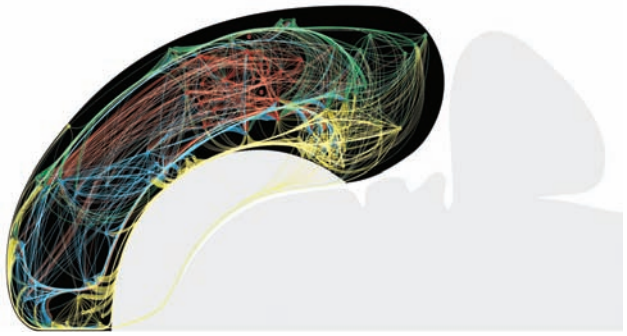
blood vessels. Rats were implanted with cylindrical plugs, injectable microbeads, or an injectable hydrogel solution, all of which released VEGF when degraded by enzymes or ingested by immune cells. Both the implant geometry and implantation method drastically affected the degradation and resorption of the biomaterials and may play an important role in the subsequent tissue repair process. In addition, the microbeads resulted in up to 16-fold more capillaries in the implanted tissue, compared with the plugs and injectable hydrogels. The findings suggest that microbeads may be a suitable platform for biomaterial applications such as tissue engineering and controlled drug delivery systems. According to the authors, bimodal MRI/fluorescence imaging might represent a powerful research tool in regenerative medicine. — J.W.

Early detection of chronic traumatic encephalopathy

Chronic traumatic encephalopathy (CTE) is a severe neurodegenerative disease characterized by a variety of cognitive and behavioral symptoms linked to traumatic brain injury. One major hallmark of CTE is the abnormal accumulation of tau protein aggregates in brain areas implicated in mood, emotions, and cognition. However, there is currently no definitive approach for diagnosing this condition in living humans. Jorge Barrio et al. (pp. E2039–E2047) used PET to detect abnormal protein aggregates in 14 retired professional American football players with an increased risk of developing CTE due to repetitive concussions and subconcussions, as well as persistent cognitive, behavioral, and psychiatric problems. By injecting a tau-sensitive brain imaging agent into the participants during PET scanning, the authors detected greater tau accumulation in the dorsal midbrain and amygdala—regions involved in regulating pain and negative emotions—in football players compared with control participants with normal cognitive abilities and patients with Alzheimer's disease, which may be misdiagnosed as CTE. According to the authors, this sensitive approach could enable early detection of the disease, potentially improving the likelihood of success of medical interventions, and provide a valuable baseline to develop methods to monitor disease progression and treatment response. — J.W.

Brain network analysis reveals hubs and rich clubs

Efforts to describe the organization of the rodent cerebral cortex are often based on connections derived from functional studies and on references to overlying cranial bones. To obtain a topographical map of associations crucial to cognition, Mihail Bota et al. (pp. E2093–E2101) performed a network analysis of more than 16,000 reports of axonal connections in the rat brain cortex. The authors report that 73 cortical regions could be clustered into one of four histologically distinct units in a core–shell configuration, with two units, which include the visual, auditory, and gustatory areas, comprising the core and two other units, which include the anterior cingulate, olfactory areas, and parts of the hippocampus, comprising the shell. Among regions of strong connectivity, a continuous cortical patch composed of the ectorhinal, perirhinal, and lateral entorhinal areas—implicated in Alzheimer's disease and epilepsy—emerged as a network hub. The authors also identified densely interconnected hubs, representing so-called "rich clubs." The lateral entorhinal area, for example, was found to belong to one such rich club, harboring the most cortical associations. Further, statistical analysis raised the intriguing possibility that some routes of information flow in the cortex may be partly genetically preordained. According to the authors, the findings might serve as a fulcrum for mapping cognition-related cortical associations at the neuron-type and single-neuron levels in mammals. — P.N.



Connections among gray matter regions in rat cerebral cortex.