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SPECIAL REPORT

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SUMMARY: The blood-brain barrier (BBB) presents a major obstacle to the treatment of malignant brain tumors and other central nervous system (CNS) diseases. The Eleventh Annual Blood-Brain Barrier Disruption Consortium Meeting was convened to discuss recent advances and future directions in imaging and nanomedicine. Two sessions, one on Cell and Molecular Imaging in the CNS and another on Nanotechnology, Nanobiology, and Nanomedicine, were held March 17–18, 2005, in Portland, Ore. CNS imaging presentations targeted differentiating tumor, neural lesions, and necrosis from healthy brain tissue; methods of delivery of imaging agents across the BBB; and new iron oxide–based nanoparticle contrast agents for MR imaging. Nanobiology presentations covered the development of new nanotechnology and its use in imaging, diagnosis, and therapy in the CNS. Discussions at this meeting stressed the role of biotechnology in the convergence of CNS imaging and nanomedicine and are summarized in this article.

Neuroimaging techniques have become increasingly important in assessing the biologic and physiologic properties of brain tumors and neurologic lesions. The priorities that were identified include the need to (1) determine tumor-specific imaging protocols; (2) improve assessment of tumor response, extent, and biology; and (3) evaluate new contrast media such as the iron oxide nanoparticle MR contrast or molecular agents based on therapeutic agents or tumor-specific antibodies or cells. Prospective clinical trials are necessary to assess the effectiveness of imaging techniques, including positron-emission tomography (PET), single-photon emission CT, and MR imaging (including T1 maps, T2 maps, MR spectroscopy, and perfusion- and diffusion-weighted imaging). Superparamagnetic iron oxide (SPIO) and ultrasmall superparamagnetic iron oxide (USPIO) nanoparticle MR contrast agents are being increasingly used in the CNS for characterizing particle delivery, monitoring trafficking of particles and cells, and visualizing intracerebral tumors. Newer molecular imaging techniques should be integrated into brain tumor management to providing critical information that may significantly improve the survival and care of patients with brain tumors.

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PET Imaging of Gliomas

PET imaging can be helpful in differentiating low-grade gliomas, high-grade tumors, and radiation necrosis and allows determination of important clinical parameters such as metabolism ([^{18}F]fluorodeoxyglucose [FDG]) and proliferative activity (2-[^{11}C]thymidine [TdR] and [^{18}F]3′-deoxy-3′-fluorothymidine [FLT]). The sensitivity of FDG PET for distinguishing recurrence of glioma from radiation necrosis is high (81%–86%), but specificity is suboptimal.[1] Since the mid-1980s, it has been established that high uptake of FDG signifies malignancy and poor prognosis, whereas low uptake signifies low-grade disease and better prognosis.[2] More recently it has been demonstrated that this observation pertains only to untreated and recurrent gliomas.[3] Increases in FDG metabolism immediately following radio- or chemotherapy correlate with longer, not shorter, survival rates. Also, quantitative measurements of FDG uptake within 2 weeks after radiation therapy do not correlate with length of survival.

Discussion at the meeting centered on new PET radiotracers under development. New agents allow measurement of membrane biosynthesis, alkyltransferase activity, epidermal growth factor receptors, apoptosis, and angiogenesis. [^{18}F]fluoromisonidazole uptake in gliomas is now being evaluated with PET as a marker of regional hypoxia, a well-established resistance mechanism to radiation therapy. DNA synthesis via uptake of exogenous nucleotide (the salvage pathway), but not de novo nucleotide synthesis, can be estimated with PET with TdR, which becomes incorporated into DNA, or with FLT, which does not. In regions of gliomas in which the blood brain barrier (BBB) is intact, these radiotracers may be limited in their capacity to estimate cellular proliferation. In regions in which the BBB is broken down, the uptake of either TdR or FLT is dominated by transport and not trapping of metabolites in DNA or along the salvage pathway. Further studies will be necessary to define the usefulness of these new agents in clinical practice.

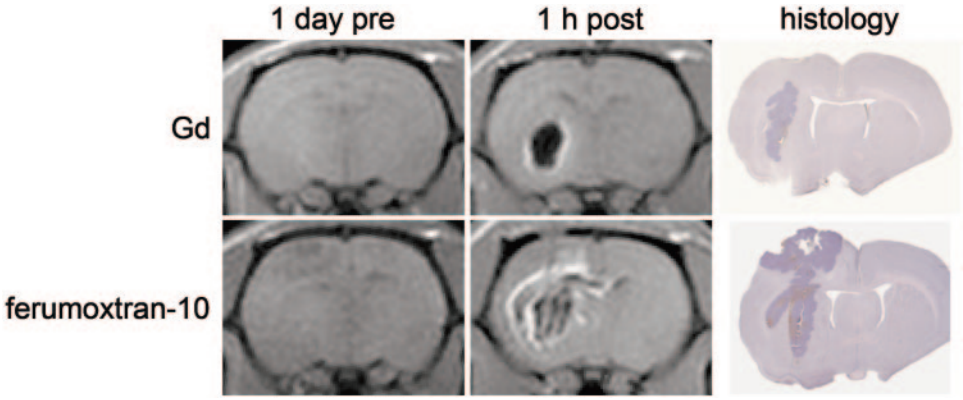


Fig 1. Imaging intratumor injection. Nude rats with 7-day intracerebral small cell lung carcinoma xenografts were scanned by MR imaging 1 day before and 1 hour after intratumor injection of either gadolinium (top) or ferumoxtran-10 (bottom) contrast agents. Axial T1-weighted MR images were obtained at 3T by using a custom rat head coil.[9] One day after contrast injection, coronal 100-μm rat brain sections were evaluated for histology by hematoxylin staining. Delivery of the USPIO is highly heterogeneous throughout the tumor and brain around the tumor, in contrast to the more homogeneous distribution of gadolinium.

Imaging Delivery to the Brain

Intracarotid or intravertebral infusion of hyperosmotic mannitol leads consistently to a reversible opening of the BBB. This successful mechanism to introduce therapeutic agents throughout a cerebral vascular distribution is used in the BBB Consortium to treat patients with brain tumors.

An alternative mechanism to obtain high local distribution of therapeutic agents in brain and tumor is focal inoculation with bulk flow, termed convection-enhanced delivery (CED).[4] Clinical trials have begun with CED of recombinant cytotoxins,[5] but there remains a need for an effective imaging technique for CED. Distribution of iopamidol (molecular weight, 777) can be determined by in vivo real-time and postinfusion CT scanning, which correlates with quantitative autoradiography.[6] This technique appears to be safe and suitable for monitoring convective delivery of relatively low-infusion volumes in the brain.

CED has also been evaluated for improving the brain distribution of the iron oxide nanoparticle MR contrast agents, ferumoxides, an SPIO, and ferumoxytol and ferumoxtran-10, both USPIOs.[7,8] In normal rat brain, signal-intensity changes were detected even 3 months after intracerebral CED injection of ferumoxides, ferumoxtran-10, or ferumoxytol. No pathologic brain cell or myelin changes were detected after either intracerebral inoculation or BBB disruption delivery of these agents, even 3 months after USPIO administration.[7] After CED inoculation of 25 μg of ferumoxtran-10 into rat intracerebral tumors, signal intensity changes were nonhomogeneous throughout the tumor and brain around tumor (Fig 1). In contrast, intratumor injection of an equal volume of gadolinium showed a small and homogeneous distribution (Fig 1).

Preclinical and Clinical Studies of CNS Imaging with Iron Oxide MR Imaging Agents

Studies have been performed to evaluate the potential of the USPIO MR imaging contrast agents for scanning tumor and lesions in the central nervous system (CNS). High-field-strength (8T) MR imaging in combination with USPIO allows high-resolution scanning of tumor microvasculature and delineation of areas of increased cellularity and vascular proliferation. In an animal brain tumor model, low concentration of USPIO at 8T markedly improved imaging of tumor microvasculature.[9,10]

After intravenous (IV) administration, ferumoxtran-10 enhanced one small cell lung carcinoma intracerebral tumor model (human LX-1 xenografts) within 30 minutes, with maximal enhancement observed at 6–24 hours. No enhancement was detected at 7 days after administration of the ferumoxtran-10. MR enhancement correlated with iron staining in nontumor cells, including cells with astrocytic morphology at the tumor margin and in cells with macrophage morphology in areas of hypoxia/necrosis. In contrast, no ferumoxtran-10 enhancement was seen in another small cell lung cancer xenograft, and there was poor enhancement in a glioblastoma model. Ferumoxytol was nearly equivalent to ferumoxtran-10 for imaging rat tumor models, whereas no enhancement was seen after IV administration of ferumoxides (Feridex IV).[7] The different patterns of enhancement may provide differential diagnostic information relative to both BBB integrity and to phagocytic activity in various types of CNS lesions.

In clinical trials of ferumoxtran-10 and ferumoxytol in patients with brain tumor, enhancement was maximal at 24–48 hours after iron administration. The iron oxide agents will not replace conventional gadolinium-enhanced MR imaging but can add additional information regarding tumor type and extent and can be used in intraoperative and postoperative imaging of residual tumor (Fig 2). In approximately 10% of patients, investigators showed additional areas of enhancement with the use of iron oxide agents, compared with those in gadolinium imaging.[11,12]

The uptake of ferumoxtran-10 by reactive cells can provide visualization of the phagocytic components of CNS lesions. Ferumoxtran-10 was compared with standard gadolinium-enhanced MR images in an exploratory trial to assess its potential in the evaluation of CNS lesions with inflammatory aspects.[13] Twenty-three patients with different types of intracranial inflammatory lesions underwent brain MR imaging with and without gadolinium, then 24 hours after administration of ferumoxtran-10. In 5 cases (1 acute disseminated encephalomyelitis, 2 stroke, 1 cavernous venous vascular malformation, and 1 primary CNS lymphoma), the ferumoxtran-10 scan showed higher signal intensity, larger

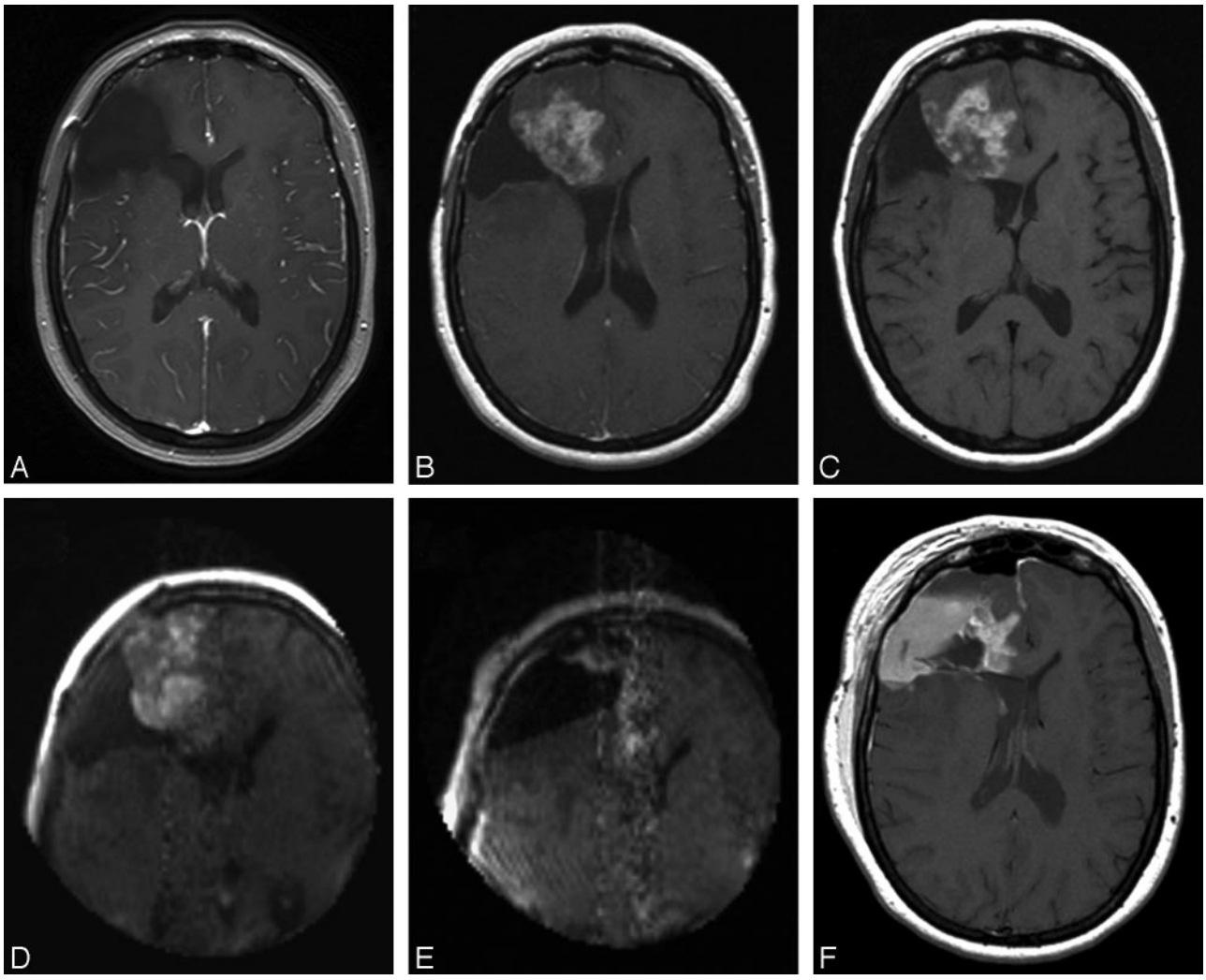


Fig 2. T1-weighted MR imaging in a patient with recurrence of a low-grade astrocytoma. The patient had stable disease after previous craniotomy (*A*) but showed recurrence on gadolinium images in March 2005 (*B*). The patient received ferumoxtran-10, and 24 hours later underwent preoperative MR imaging (*C*) as well as MR imaging with the 0.15T intraoperative scanner before (*D*) and during (*E*) craniotomy. Postoperative MR imaging (*F*) correlated with the residual areas of enhancing tumor seen on intraoperative MR imaging. High signal intensity in the tumor cavity, not present on intraoperative MR imaging, demonstrates the problem of differentiating residual enhancing tumor from blood products. Because the ferumoxtran-10 persists for 4–7 days, the postoperative MR images were exactly the same with or without the addition of gadolinium.

area of enhancement, or new enhancing areas compared with the use of gadolinium. Most patients with multiple sclerosis showed less enhancement with ferumoxtran-10 than with gadolinium.[13]

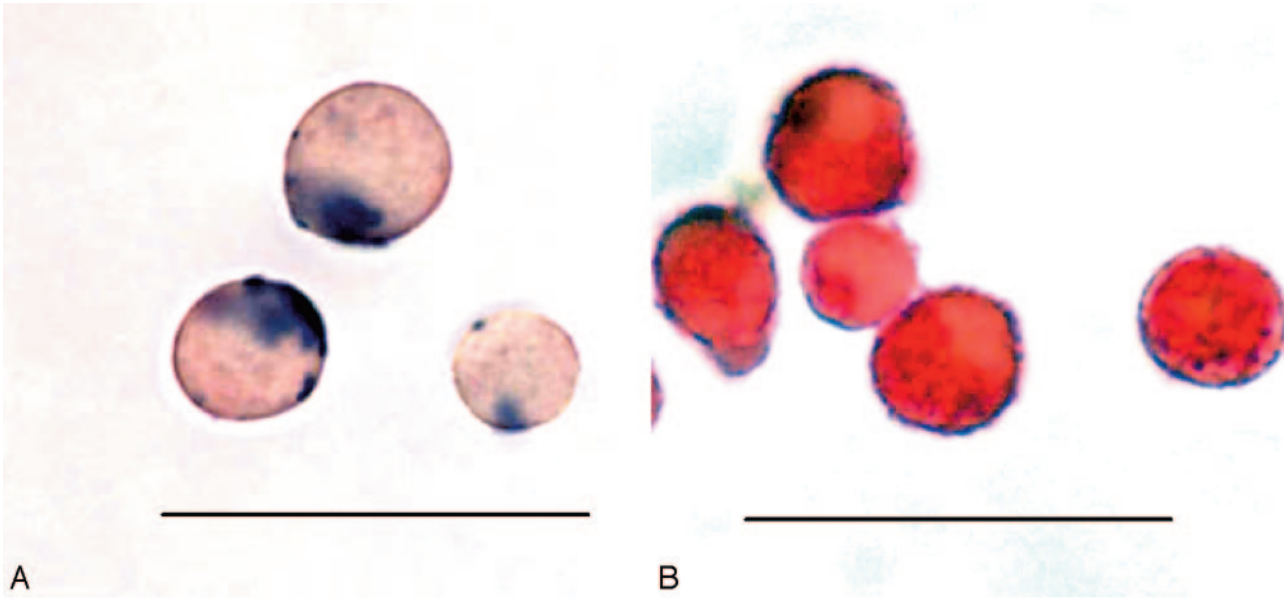
Tracking Magnetically Labeled Stem Cells

Various approaches have been developed using coated SPIO nanoparticles to magnetically label stem cells and other mammalian cells for cellular MR imaging.[14] Ferumoxides, a SPIO approved by the United States Food and Drug Administration (FDA), in combination with cationic transfection agents such as poly-L-lysine or the FDA-approved agent, protamine sulfate, can safely and effectively label cells (Fig 3).[15]

Magnetic labeling allows MR imaging monitoring of cell trafficking into the CNS across a disrupted or intact BBB and temporal and spatial analysis of cell migration in the brain.[16,17] MR imaging can detect labeled cells, including embryonic, mesenchymal, hematopoietic, and neural stem cells migrating toward areas of cerebral infarction or tumors.[14,17,18] Following IV injection of ferumoxides/poly-L-lysine–labeled endothelial progenitor cells, in vivo MR imaging showed cells incorporating into the developing vasculature in an implanted glioma mouse model (Fig 4).[17] Labeled stem cells may thus be followed in therapeutic applications such as stroke or treatment of CNS tumors. Labeled T cells sensitized to myelin antigens cross the BBB in SJL mice and induce experimental allergic encephalomyelitis, which can be detected as demyelinated lesions in the spinal cord.[16] Magnetic cell labeling has not been useful in spinal cord trauma models because it is difficult to distinguish hemorrhage and migration of labeled cells into areas of damage. MR imaging cannot, as yet, determine the functional status and differentiation of magnetically labeled stem cells into neuronal cells. This shortcoming supports the concept of a multitechnique imaging approach to monitor cellular therapies. MR imaging monitoring of the temporal spatial migration of SPIO-labeled cells has the potential for developing innovative experimental and clinical trials that allow the evaluation of stem cells or other genetically engineered cells that could be used for repair, replacement, or treatment of CNS diseases.

Nanotechnology, Nanobiology, and Nanomedicine

The National Institutes of Health Nanomedicine Vision aims to "characterize quantitatively the molecular scale compo-



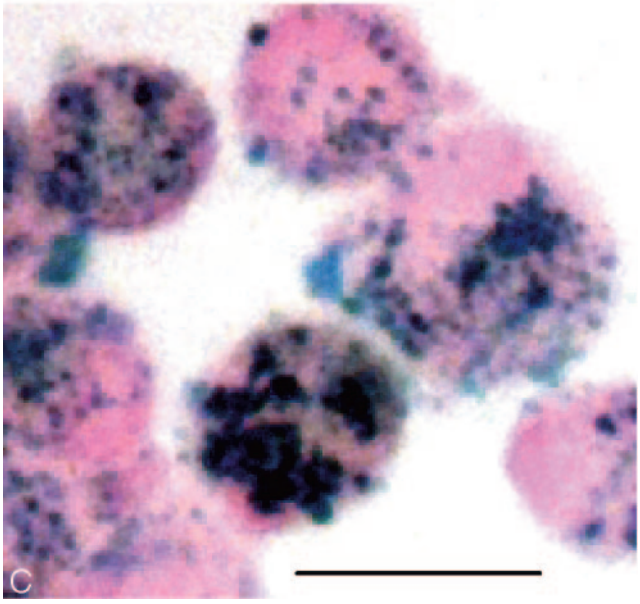


Fig 3. Examples of Prussian blue–stained histopathology of mouse Sca1+ hematopoietic stem cells labeled with ferumoxides/poly-L-lysine (*A*), human CD 34 AC 133 hematopoietic stem cells labeled with ferumoxides/protamine sulfate (*B*), and human mesenchymal stem cells labeled with ferumoxides/protamine sulfate (*C*). Both mouse and human hematopoietic stem cells have been used as endothelial precursor cells (Bar = 20 μm).

nents or nanomachinery of the cell and to precisely control and manipulate these molecules and supramolecular assemblies in living cells to improve human health." Nanotechnology offers exciting new opportunities for a number of biomedical applications. Superparamagnetic nanoparticles can serve as contrast agents in MR imaging to scan tumors, even micrometastases, as well as in tumor angiogenesis, cell tracking, and gene expression.[12,16,19] The magnetic nanoparticles can be coupled with diagnostic and therapeutic agents to provide cellular targeting. Stealth nanoparticles can act as pharmaceutical drug delivery devices to penetrate the BBB.[20]

Magnetic Nanoparticles for Biomedical Applications

Biocompatible magnetic nanoparticles are promising in several biomedical applications for tagging, imaging, sensing, and separation. Most magnetic particles or beads currently used in biomedical applications are based on ferromagnetic iron oxides with very low specific magnetic moments of approximately 20–30 emu/g or their polydispersive properties. The use of high magnetic moment and monodispersive nanoparticles may significantly enhance the contrast for MR imaging, reduce the concentration of magnetic particles needed for cell separation, or make drug delivery possible with much lower magnetic field gradients.

Monodispersive core-shell nanostructured clusters have been synthesized for MR imaging.[21] Iron oxide nanoclusters with size ranges from 1 to 100 nm and small size distribution ($\pm$ 3%–10%) were formed with uniform iron oxide shells covering the iron clusters (Fig 5*A-D*). The specific magnetic moment of these core-shell nanoclusters is size-dependent and increases from 80 emu/g at the cluster size of 3 nm to $>$200 emu/g at sizes $<$80 nm (Fig 5*E*). Proteins, including antibodies, can be attached to these magnetic nanoparticles. Investigation of these and other derivatization procedures is underway.

Functionalized Nanoparticles for Brain Tumor Imaging and Treatment

A multifunctional nanoparticle polyethyleneglycol-chlorotoxin-fluorophore (NPC-Cy5.5) is capable of targeting glioma cells and is detectable by both MR imaging and fluorescence microscopy.[22,23] To synthesize this nanoprobe, we functionalized iron oxide nanoparticles coated with covalently bound bifunctional polyethyleneglycol (PEG) with chlorotoxin and the near-infrared fluorescing molecule Cy5.5. The chlorotoxin peptide binds with high affinity to the membrane-bound matrix metalloproteinase-two endopeptidase, which is preferentially upregulated in gliomas, medulloblastomas, and other tumors of neuroectodermal origin.[24] Use of near-infrared fluorescence minimizes autofluorescence interference from

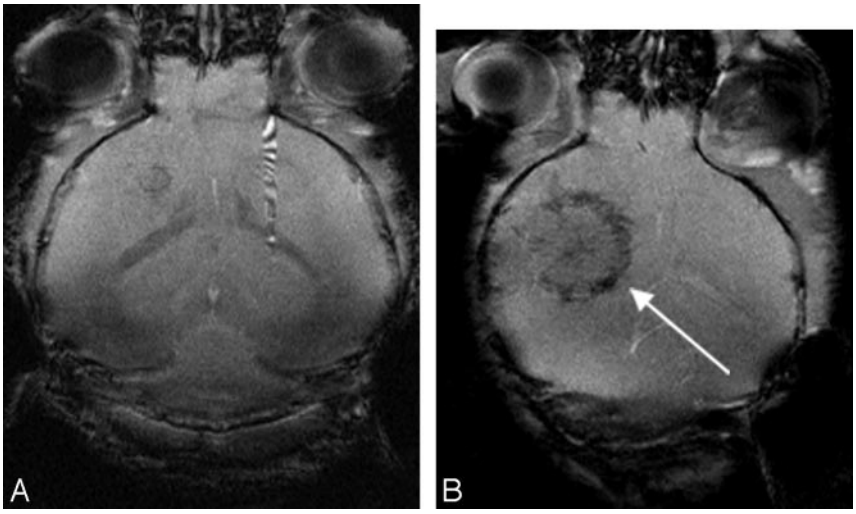


Fig 4. Axial T2*-weighted gradient-echo MR imaging (TR/TE, 450/4.2 ms, with resolution at 500 × 80 x 70 μm) at 7T performed 10 days after implantation of RT2 rat glioma into the brain of a mouse that received a tail vein infusion of 500,000 killed ferumoxides/poly-L-lysine–labeled Sca1+ endothelial precursor cells (*A*) or live 500,000 ferumoxides/poly-L-lysine–labeled Sca1+ endothelial precursor cells (*B*) 2 days before implantation of tumor. The hypointense ring (*arrow*) surrounding the tumor is clearly visible on the animal receiving magnetically labeled endothelial precursor cells and represents the incorporation of these cells into ongoing vasculogenesis and neovasculature of the growing tumor. Killed labeled cells served as a control and did not migrate to the tumor.[17] MR imaging courtesy of Stasia A. Anderson, MD.

healthy brain tissue and allows visualization of tissues millimeters in depth because of the efficient penetration of photons in the near-infrared range.[25] The PEG coating was used to prevent nanoparticle agglomeration and protein adsorption to increase particle blood circulation time and internalization efficiency.

MR imaging and confocal fluorescence analyses showed strong preferential uptake of chlorotoxin-bound nanoparticles compared with unconjugated nanoparticles. Significantly higher internalization of NPC-Cy5.5 conjugates was observed in glioma cells than in control cells. Signal intensity was retained for at least 24 hours, which may be advantageous in intraoperative imaging applications, and the cellular-level resolution may help accurate delineation of poorly defined glioma interfaces. The NPC-Cy5.5 nanoprobe inhibited cell migration, as demonstrated by the Matrigel invasion test, at even lower doses than unconjugated chlorotoxin. This finding indicates that chlorotoxin retained its bioactivity after conjugation to the nanoparticle and that the nanoparticles enhanced the cellular uptake and retention of chlorotoxin in the target cells. The application of this nanoprobe for preoperative and postoperative diagnostic imaging with MR imaging and real-time intraoperative visualization of tumor margins with optical devices is a novel approach to improve the effectiveness of diagnostic techniques and therapeutic modalities available for brain tumor patients.

Stealth Nanoparticle Delivery Across the BBB

Two novel biocompatible stealth nanoparticles were designed by using microemulsion methodology to optimize BBB circumvention and encapsulate drugs for brain delivery. A toxicologic study showed that the presence of the stealth nanoparticles in the neurovasculature had no significant effect on cerebral perfusion flow in vivo. Further, in vitro and in vivo data showed that the formulations lacked effect on barrier integrity, membrane permeability, or alteration of expression of the BBB tight-junction proteins, occludin, and claudin-1.[26] The in situ brain perfusion technique showed that uptake of the stealth nanoparticles across the BBB was significant and comparable to other neuropharmaceutical agents (eg, caffeine, theophylline, etc). Electron microscopy demonstrated that the nanoparticles remained intact after penetrating the brain extracellular space from the neurovasculature.[27]

The technology was applied to increase brain distribution of paclitaxel. This chemotherapeutic agent is active in various brain metastases in vitro but appears limited in actual efficacy because of p-glycoprotein–mediated brain efflux. Encapsulation of paclitaxel significantly increased brain drug uptake and increased toxicity toward p-glycoprotein–expressing tumor cells. On the basis of these data, it was hypothesized that incorporation into stealth nanoparticles effectively masked the characteristics of paclitaxel that interact with p-glycoprotein.[28]

The Impact of the Nanobiotechnology Center at Cornell University: The Study of Synaptic Transmission

The first Nanobiotechnology Center was formed at Cornell University in Ithaca, NY, in 2000. It assists interdisciplinary collaborative teams from several member institutions in applying the tools and techniques of nano- and microfabrication to develop new devices and approaches for the study of biologic systems. As an example, approaches to reveal the mechanisms of synaptic transmission on the nanoscale were described at the meeting. Using an approach named "patch amperometry," one can detect fusion of single vesicles with the plasma membrane in chromaffin cells by cell-attached patch clamp capacitance measurement while a carbon fiber microelectrode inside the pipette measures amperometrically the flux of catecholamine released from the vesicle.[29] The measurements provide direct information on vesicle and quantal size and reveal that regulation of quantal size by drugs like L-Dopa or reserpine involves a modulation of vesicle size and vesicle membrane area.[30] The measurements also reveal the details on the fusion pore that connects the vesicular lumen to the extracellular space. The initial pore is of molecular dimensions, and the modulation of fusion pore properties by mutations in proteins implicated in fusion will reveal further details on the precise function of these proteins.[29] Further information is anticipated by measuring conformational changes in these proteins by fluorescence resonance energy transfer[31] while opening of single fusion pores is imaged simultaneously by microfabricated electrochemical detector arrays.[32] Using optical tweezers, one can measure molecular forces of vesicle tethering and can reveal intracellular trafficking of neurotransmitter receptors directly by using fluorescent nanoparticles.

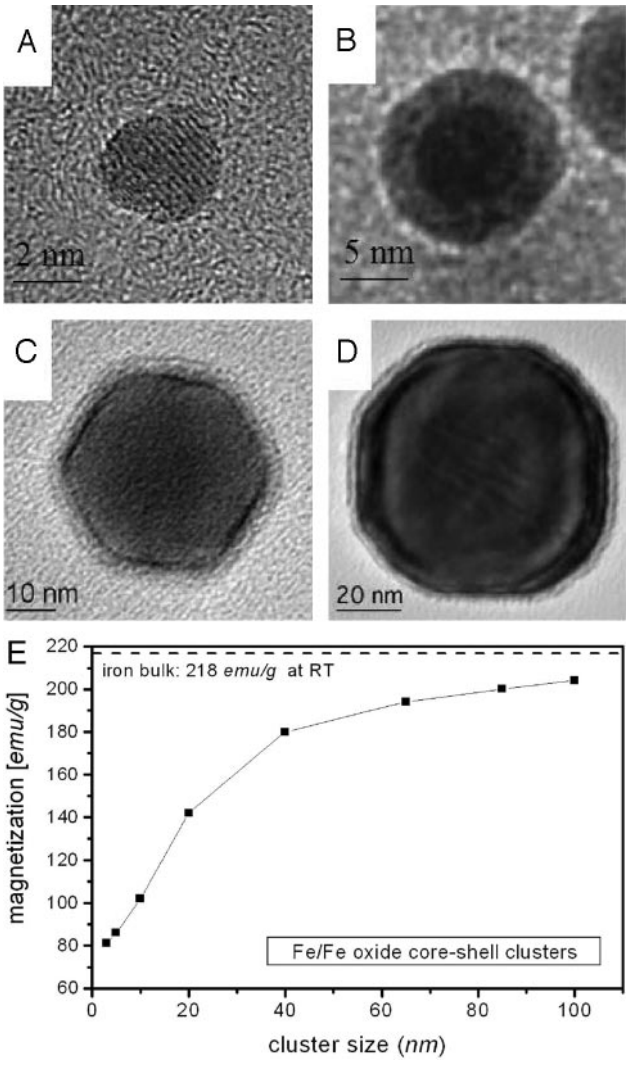


Fig 5. High-resolution transmission electron micrographs of the oxide-coated iron clusters with the diameters approximately 3–85 nm, prepared on carbon microgrids (*A-D*). The size-dependent-specific magnetic moments of iron oxide–coated iron nanoclusters are shown in panel *E*.

A Future Direction: Nanotechnology for CNS Regeneration

Molecular design of artificial environments to interact with cells will lead to great advances in biology and regenerative medicine. This opportunity is exciting, given the prospect of using chemistry to regenerate parts of the human body lost to trauma, disease, or genomic defects. The targets may include the brain and the heart or a cure for diabetes and the rapid regrowth of cartilage, skeleton, and teeth. Complex supramolecular polymers that deliver signals for cell survival, migration, proliferation, and differentiation of stem cells into defined lineages could be key players in achieving the goals of regenerative medicine. One of the fundamental chemical questions is what synthetic nanostructures are best to interact effectively with membrane receptors or to program the delivery of proteins that trigger signal intensity transduction pathways. Peptide amphiphile monomers were intended to polymerize through self-assembly to create bioactive nanofibers designed for cell signaling.[33-36] These nanostructures can present high densities of epitopes and proteins to cells with interesting biologic consequences. Self-assembling nanostructures have enormous potential in targets such as the repair of the CNS, bone regeneration, the growth of blood vessels, and the formation of insulin-producing organs to cure diabetes.

Conclusion

With regard to the nervous system, studies of cell and molecular imaging are rapidly converging with the emerging impact of nanotechnology on CNS imaging and therapy. Although currently PET imaging agents appear to be more biochemically specific (ie, FDG-PET) and high-field MR imaging provides spatial resolution to <100 μm, nanotechnology was clearly shown at the meeting to have already impacted preclinical and clinical CNS imaging. For instance, one form of iron oxide nanoparticle (ferumoxtran-10 USPIO) given intravascularly can target phagocytic cells (macrophages and astrocytes) in both neoplastic and nonneoplastic CNS lesions in both animal models and patients.[9,11,12] Another type of iron oxide nanoparticle (ferumoxides SPIO), which is ineffective for brain tumor imaging when given IV because of rapid adsorption, can be used in combination with protamine sulfate to label mononuclear white blood cells and stem cells.[15] Such novel cellular contrast agents labeled with inert nanoparticles can enable visualization by MR imaging in vivo of as few as 100 lymphocytes trafficking to mouse spinal cord experimental allergic encephalitis lesions.[16] Similarly SPIO-labeled stem cells can be imaged differentiating into endothelial cells vascularizing a glioma in vivo.[17] Indeed, the initial clinical trials of cellular contrast agents using SPIO visualized on MR imaging have now been reported.[37] Nanoparticle size and magnetic moment can be modulated depending on biologic requirements. Nanoparticles can be conjugated to targeting agents such as chlorotoxin to specifically bind glioma cells.[22,23] Stealth nanoparticles can ferry drugs or imaging agents across the BBB; these nanoparticles are normally substrates for endothelial efflux pathways (ie, p-glycoprotein) and thereby excluded from the CNS.[26,28] Indeed, even self-assembling high-epitope-attenuation nanofiber technology was reported to selectively guide differentiation of neural progenitor cells and to have impact in vivo on spinal cord injury[36]; therefore, biotechnology is active in the merging areas of CNS imaging and nanomedicine.

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