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FIRST REACTIONS

Building a Better Magnetic Resonance Imaging Contrast Agent Using Macromolecular Architecture

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Introducing a new class of exceptionally stable, biocompatible nitroxide magnetic resonance imaging contrast agents with unprecedented transverse relaxivity as a potential substitute to current metal-based contrast agents.

In vivo imaging enables us to peer deeply within living subjects and is producing tremendous opportunities both for the study of cancer biology and clinical diagnostics.[1] Rapid advances in fluorescent imaging, magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), and ultrasound imaging promise to translate the insights from basic science at the single-cell level to clinical application. Among these imaging modalities, MRI is among the most prominently used in medical diagnostics. Metal-based contrast materials have been widely adopted to clearly visualize the functional architecture of physiological structures. At present, Johnson and co-workers exploit a potential substitute in the form of nitroxide-based macromolecular contrast agents with unprecedented transverse relaxivity and stability for MRI of tumors.[2]

MRI is a noninvasive, nonionizing modality offering anatomical, physiological, and even molecular information within the bodies of living subjects.[1] Standard MRI inherently suffers from low sensitivity stemming from the mechanism of signal detection which typically measures the relaxation rates of water protons. Contrast agents are thus used to alter the water proton relaxation rates and highlight anatomical and pathological features in the imaged tissues by enhancing images contrast (Figure 1). On the basis of the physical MR mechanism that enables them to generate a signal, two primary classes of MR contrast agents are T_1 and T_2 contrast agents. T_1 contrast agents (e.g., Gd^{3+} or Mn^{2+} chelates, and analogous paramagnetic complexes) decrease protons' longitudinal relaxation time (spin−lattice, T_1) and result in a faster signal decay and a brighter region in the image (positive contrast).[3] T_2 contrast agents (e.g., superparamagnetic iron oxide nanoparticles) reduce the transverse relaxation time (spin−spin, T_2) and induce localized darker spots (negative contrast).[4−6] T_1 contrast agents generally contain metals with a large number of unpaired electrons (Gd^{3+} with seven unpaired electrons and Mn^{2+} with five unpaired electrons) and have significantly improved MRI performance. Despite their wide employment, key problems remain, particularly issues associated with the toxicity of metals coupled to their tendency to accumulate in biological tissues. Metal-free MRI contrast agents can overcome these disadvantages and enable to MRI be performed in people with high risk for the side effects of traditional contrast agents. Paramagnetic nitroxide-based organic radical contrast agents (ORCAs), chemical exchange saturation transfer (CEST) contrast agents, hyperpolarized ^{13}C and ^{19}F MRI probes, have become new innovative tools with critical applications in MRI. Among these metal-free MRI contrast agents, nitroxide ORCAs are in principle most likely to translate to the clinic since they acquire an MRI signal using standard water relaxation mechanisms. ^{19}F MRI and CEST agents have problems in their inherent insensitivity,[7,8] while hyperpolarized ^{13}C agents suffer from complex preparation processes and limited imaging times. For these reasons, an increasing number of studies have been devoted to developing nitroxide ORCAs, but until now their low relaxivity values compared to metals and their fast in vivo reduction to diamagnetic hydroxylamines with half-lives on the order of minutes have restricted their clinical application.

Modifying MRI contrast agents with a rigid macromolecular scaffold, such as the spirocyclohexyl nitroxide derivative "chex", is one of the most efficient ways to increase the relaxivity.[9] Johnson's group further stepped up the relaxivity values, by appending chex to the core of

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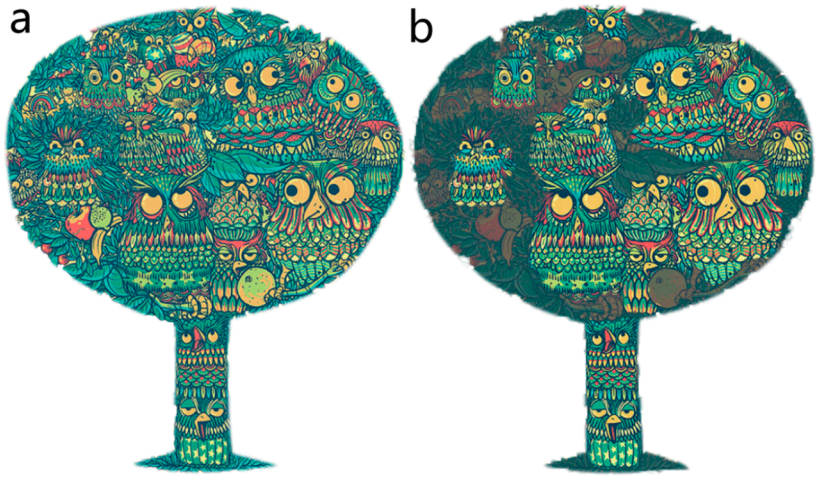

Figure 1. Nature likes mimicry; radiologists like to highlight lesions for medical diagnostics. With plain MRI (a), the object of the examination might be visible, but nor clearly delineated. Providing contrast with an extrinsic agent (b) may help to highlight specific pathologies.

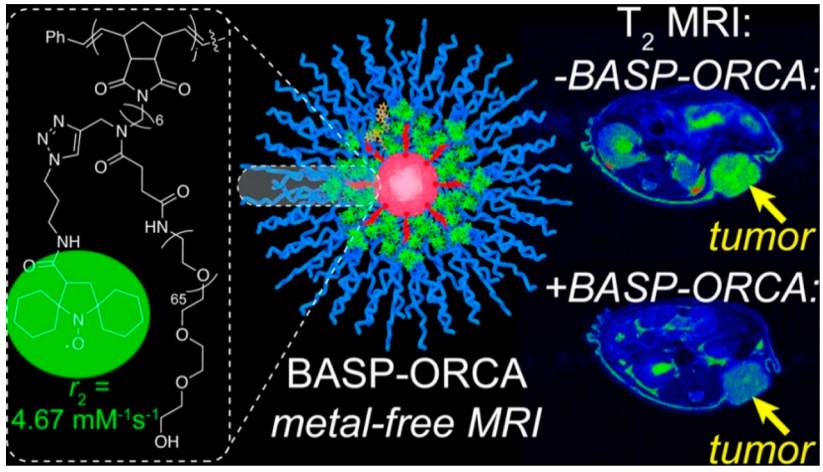

Figure 2. Nitroxide-based macromolecular contrast agents (BASP-ORCA) with unprecedented transverse relaxivity and stability for magnetic resonance imaging of tumors. Reproduced with permission from ref 2. Copyright 2017 American Chemical Society.

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PEGylated branched-bottlebrush polymers, demonstrating in 2014 that increasing the macromolecular size and chex density leads to increases in both r_1 and r_2.[10] But the problem of their poor in vivo stability has not been well resolved by now.

To address these problems, Johnson and co-workers have systematically investigated and uncovered a new class of nitroxide nanoparticles—brush-arm star polymer ORCAs (BASP-ORCAs) (Figure 2). These nanoparticles contain a dense layer of chex nitroxides bound in an interlayer between a hydrophilic poly(ethylene glycol) (PEG) shell and a rigid poly(acetal) core. The authors discovered that the distinct cross-linked multilayer nanostructure resulted in a shielded and dense nitroxide layer, providing dramatic increases in relaxivity values (44 times higher than common nitroxides). In addition, the average molecular r_1 and r_2 values for BASP-ORCAs are even greater than those for the commonly used FDA-approved Gd-based contrast agent Magnevist and iron-based nanoparticles such as Feraheme. The rigid chex environment in the BASP-ORCAs contributes to the low rate of chex reduction, which allows for tumor MRI in mice up to 20 h after tail-vein injection.

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These features combine to allow the BASP-ORCAs to perform with unprecedented transverse relaxivity, exceptional stability, and good in vivo biocompatibility. The advent of the BASP-ORCAs overcomes the challenges associated with previous nitroxide-based organic radical contrast agents for MRI, which should pave the way for organic radicals as viable alternatives to metal-based MRI contrast agents. The reported BASP-ORCAs are the first nitroxide MRI contrast agents to enable MRI imaging in vivo over time scales using clinical high-field ^{1}H MRI techniques. This technology will clear the path for the translation of nitroxide ORCAs from academic laboratories to current and future clinical high-field MRI instruments.

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