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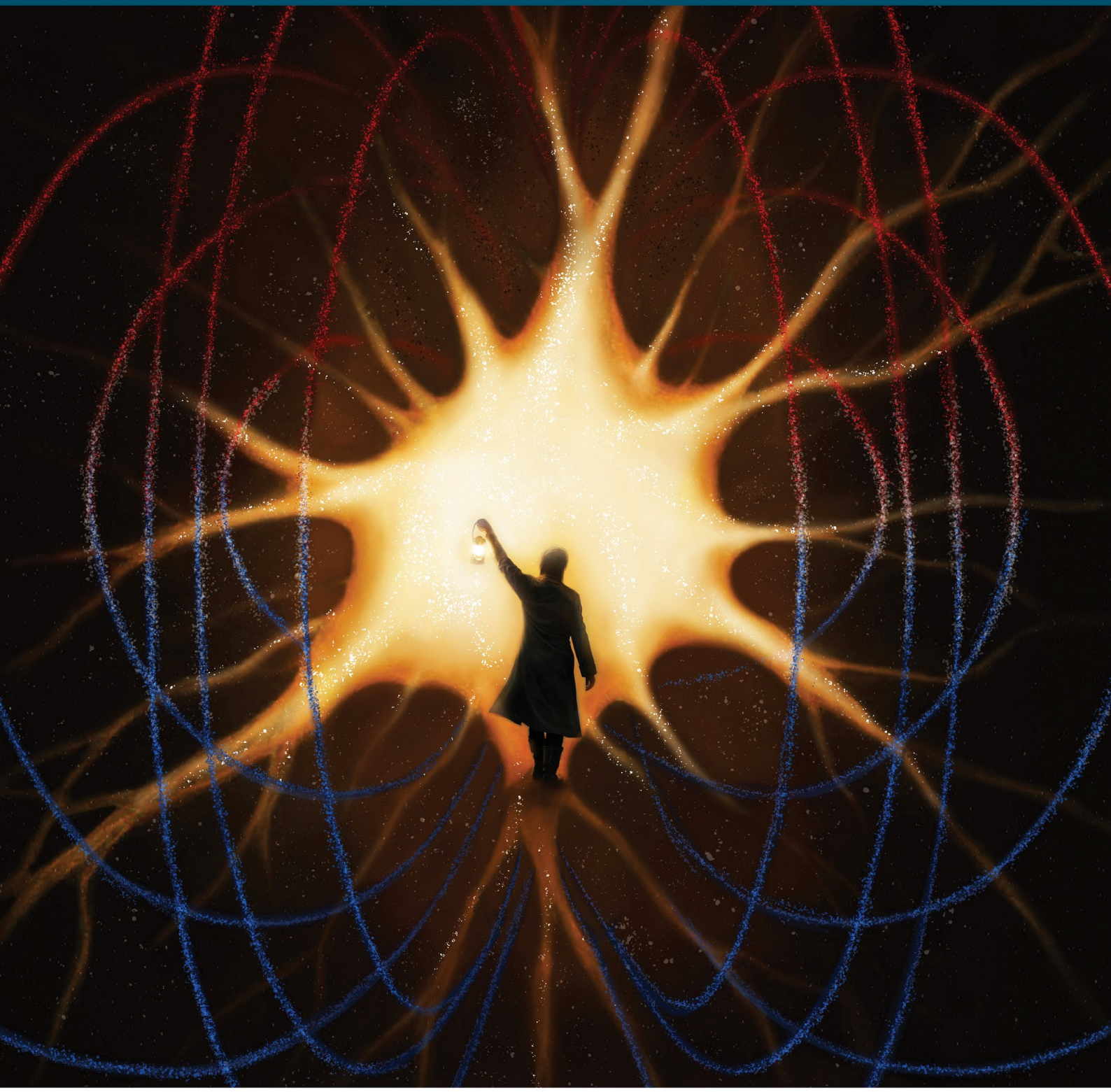

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Article

Cell Labeling with Responsive MRI Contrast Agents is Enabled through Solid-Phase Synthesis

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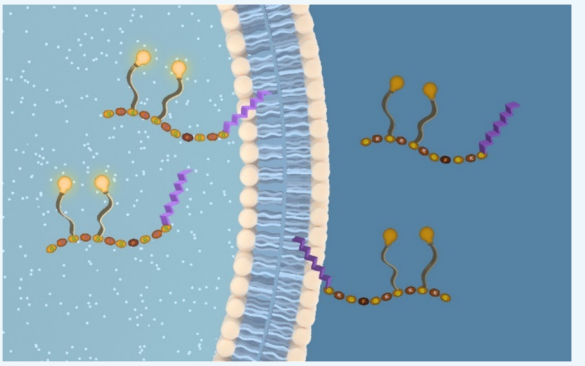
ABSTRACT: Bioresponsive or smart contrast agents (SCAs) for magnetic resonance imaging (MRI) can facilitate functional molecular imaging of numerous biological processes. These are MRI probes that alter the MRI signal along with the concentration changes of different biomarkers in their microenvironment, thus enabling the assessment of tissue physiology with high spatiotemporal resolution. One of the common shortcomings of SCA is their structural and functional insufficiency for accumulation in the targeted region, i.e., most frequently internalization into the cells to study the intracellular processes. Here, we report a strategy to prepare a multifunctional SCA that can be successfully incorporated into the cell membrane and internalized. We used the solid-phase synthesis methodology to obtain a trimeric SCA responsive to calcium ions, which bears a hydrophobic tetradecanoyl group to facilitate interaction with primary rat astrocytes. The developed MRI probe maintained high activity, exhibiting high calcium-triggered longitudinal and transverse relaxivity changes. Concurrently, it showed the ability to label the cell membranes and internalize into the astroglial cells while not causing cytotoxicity or affecting the electrophysiology of the cells.



INTRODUCTION

Visualization of biological processes is a critical step in their better understanding and control. To achieve this goal, molecular imaging techniques have played an essential role. Among different imaging methodologies used for this purpose, magnetic resonance imaging (MRI) is one of the most regarded choices due to the capability to deeply penetrate through the soft tissue noninvasively and produce high-resolution images. Consequently, it ensures obtaining very valuable information on the physical, chemical, or biological state of the tissue, aiding key conclusions on the occurrence of physiological processes or better diagnosis and treatment of the diseases.

The specificity of the obtained information can be significantly enhanced by using MRI probes. These are molecules that increase the MR signal, and, in most cases, for ^{1}H MRI, this is due to their paramagnetic nature.[1] For instance, typical T_1-weighted MRI probes are paramagnetic metal complexes of Gd^{3+} and Mn^{2+}, which greatly influence the longitudinal relaxation time of the surrounding water molecules. To reduce their toxicity, metal ions are encapsulated with polyamino polycarboxylic chelators that form multidentate coordinations;[2] the latter also allow various structural modifications to improve the MRI performance of the probes, their biocompatibility, or delivery features. One of the emerging classes of such probes, called bioresponsive or smart contrast agents (SCAs), are designed to respond to the alterations in their environment by changing their paramagnetic effect and thereby influencing the MRI contrast. These can be the change in concentration of ions and molecules involved in various biological processes (e.g., Ca^{2+}, Zn^{2+}, neurotransmitters) or changes in their activity (enzymes).[3−5]

Different types of SCAs have been developed to date as potential functional markers of a specific physiological process or a disease. Particularly, SCAs sensitive to Ca^{2+} have experienced significant progress, due to the essential role of this cation in cellular physiology and signaling.[6] Moreover, several examples of these SCAs were demonstrated to be active under in vivo conditions, showing enormous potential for performing functional MRI studies to provide important insights on biological processes on a molecular level.[7−10]

Irrespective of the chemical nature of the SCA (complexes of Gd^{3+} and Mn^{2+} or superparamagnetic iron nanoparticles suitable for T_1-, or T_2-weighted MRI, respectively), the delivery

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