Special issue on fluorine-19 magnetic resonance: technical solutions, research promises and frontier applications

Sonia Waiczies¹ · Mangala Srinivas² · Ulrich Flögel³ · Philipp Boehm-Sturm^{4,5} · Thoralf Niendorf¹

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Research on fluorine MR has been progressing at an impressive pace and yielding tangible results at the forefront of biomedical research. Several decades after its first documented application [1], the unprecedented opportunities of fluorine MRI in medical research remain intense and represent an area of increasing clinical interest. The challenges associated with fluorine MRI are also equally recognized, most notably the restrictively low detection limits and sensitivity boundaries. Nevertheless, fluorine MRI remains an extremely attractive method for following fluorinated labels that avoids the use of radioactive tracers. New developments from various research domains such as chemistry, physics, engineering and material sciences have joined forces to overcome these challenges and technical barriers. In fact, progress in fluorine MRI spans a very broad range of fields, from the chemistry of label and probe synthesis and production, through to biological and clinical applications, as well as physics, information technology and data science for image acquisition and processing [2].

The cutting-edge papers in this Special Issue illustrate new developments in the field of fluorine MRI from different research domains and demonstrate the versatility of these developments for clinical application.

One important focus of fluorine MRI research is the driving of technical developments surrounding MR signal acquisition and data processing, to lower the detection levels and boost sensitivity. Several innovative developments such as compressed sensing (CS) will ultimately be required to provide the high signal-to noise ratio (SNR) efficiency necessary for fluorine MRI. Controlling the fidelity of these methods will also be an essential task on the way to reaching the desired sensitivity for in vivo measurements. For instance, low SNR can lead to artifacts in CS reconstructions that reduce the image quality. This can be compensated by data resampling strategies that improve image quality and suppress background [3]. Quantification of the fluorine MR signal will also be essential for most of the conceivable applications [4–11]. Therefore, the necessary technologies such as B_1 mapping to correct for non-uniform radiofrequency fields [12] or development of new radio frequency coil technologies [13, 14] must be available to make quantification of the fluorine MR signal feasible and accurate.

The design and synthesis of novel fluorine-rich molecular labels and imaging probes is another important domain in fluorine MRI research. Fluorinated probes are commonly designed with the goal of improving signal strength by increasing the number of fluorine atoms per molecule [4,

✉ Sonia Waiczies
Sonia.Waiczies@mdc-berlin.de

Mangala Srinivas
Mangala.Srinivas@gmail.com

Ulrich Flögel
floegel@uni-duesseldorf.de

Philipp Boehm-Sturm
philipp.boehm-sturm@charite.de

Thoralf Niendorf
thoralf.niendorf@mdc-berlin.de

¹ Berlin Ultrahigh Field Facility (B.U.F.F.), Max-Delbrueck-Center for Molecular Medicine in the Helmholtz Association, Berlin, Germany

² Department of Tumor Immunology, Radboud Institute for Molecular Life Sciences (RIMLS), Radboud University Medical Center (RadboudUMC), Nijmegen, The Netherlands

³ Experimental Cardiovascular Imaging, Molecular Cardiology, Heinrich Heine University, Düsseldorf, Germany

⁴ Department of Experimental Neurology and Center for Stroke Research Berlin, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

⁵ Charité, Universitätsmedizin Berlin, NeuroCure Cluster of Excellence and Charité Core Facility 7T Experimental MRIs, Berlin, Germany

[15]. Such fluorinated probes have been particularly valuable for labeling cells to track them in vivo. In this special issue, a dissociation of the fluorescence and the fluorine label was shown signal over time, both in vitro and in vivo. This has a critical impact on the interpretation of long-term experiments validated by standard fluorescent techniques [6]. Fluorine-rich probes can also act as labels within microcapsules impregnated within cells for in vivo applications; e.g., microcapsules containing and protecting stem cells from immune rejection following transplantation [8].

One strategy in fluorine MR research is to manipulate the MR properties of the fluorinated probes to favor ideal conditions for MR signal acquisition. The complexation of fluorinated chelates with paramagnetic lanthanide ions leads to enhanced spin–lattice relaxation [16], thereby opening up the possibility for increasing SNR per unit time. Researchers have also designed and employed probes that prompt the desired MR signal following a trigger. The trigger is commonly a change in environmental conditions such as temperature [17], pH [18] or oxygenation state [7]. This has implications for several pathological situations. Perfluorocarbon nanoemulsions can determine changes in tissue oxygenation during vascular pathology, as shown in model of vascular cognitive impairment [7]. Functionally active crystal structures such as nickel complexes act as pH sensors [18], thereby positioning them as potential tumor markers for future in vivo studies. Investigating the relaxation properties of fluorinated drugs under different environmental conditions such as temperature [17] within the physiological range will also be an absolute requirement for studying drug distribution in vivo. Fluorination is a process in medicinal chemistry that is usually meant to improve pharmacological activity, but it does not preclude the use of fluorinated drugs as fluorine MRI probes. The MR activity of fluorinated drugs is an added benefit, above and beyond the expected enhancements in pharmacological activity, and will be an invaluable asset to study drug distribution and bioavailability [11].

The application of fluorine probes and fluorine MRI in (pre)clinical disease settings continues to expand, particularly in the area of diagnostics such as imaging of inflammation [5, 9], tissue oxygenation [7], and assessment of bile acid disorders [10]. This translational research is very encouraging en route to clinical applications and provides expanded knowledge into the distribution of the fluorinated probes in larger animals, particularly during pathology, and while using clinical scanners, thus advancing the opportunities of fluorine MRI for clinical application.

All research efforts and goals from these various domains are centered on the need for promoting fluorine MR signal to answer crucial questions in pathophysiology. Achieving this common goal will certainly require extra resources—and the will to go there. The endeavor to take advantage of

enabling technologies that go beyond standard tools, such as cutting-edge cryogenically cooled radio frequency coils and ultrahigh magnetic field strengths [19], will certainly require support from research institutions, funders and government bodies. Most of the efforts devoted to discovery and proof-of-principle research will benefit from an integration of these tools and technologies, to reach the maximum potential and realize the faraway visions and goals that will contribute to patient health care. The question as to whether the health system will eventually be able to adopt this state-of-the-art research into clinical settings will depend on the passion and motivation in our current research endeavors.

We hope that this issue will convey this dynamic vision and inspire you to also become pioneers in pushing the envelope of current technologies in fluorine MRI to be able to answer challenging and important biological questions in the future.

Guest Editors
Sonia Waiczies
Mangala Srinivas
Ulrich Flögel
Philipp Boehm-Sturm
Thoralf Niendorf
Editor
David G. Norris

Compliance with ethical standards

Conflict of interest The authors declare that they do not have a conflict of interest with the exception that Thoralf Niendorf is CEO and founder of MRI.TOOLS GmbH, Berlin, Germany.

Ethical standards This editorial does not contain any studies with human participants or animals performed by any of the authors with the exception of references to previously published work included in this editorial.

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