Editorial overview

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EDITORIAL OVERVIEW OF THE 2021 MOLECULAR IMAGING SECTION

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Molecular imaging arose as a novel discipline in the mid 1990's to study molecular and cellular events in a non- or minimally invasive manner in living subjects. It rapidly gained broader recognition and interest with the incorporation of 'Molecular Imaging' into the name of the Society of Nuclear Medicine (SNM) in 2007, and the foundation of dedicated molecular imaging societies such as the European Society of Molecular Imaging (ESMI) in 2005 and the World Molecular Imaging Society (WMIS) in 2011. Today, the numerous encouraging proof-of-concept studies in animals and humans have led to the approval of several targeted contrast agents for radio-isotope molecular imaging, now routinely used in clinical practice. Their application aims at personalized and precision patient care, warranting better characterization of disease in order to improve patient stratification towards the right treatment and treatment follow-up. Therefore, molecular diagnostic imaging strongly links with therapy, where, in certain cases, the same or an analogous targeted agent can be used both for imaging and therapy (theranostic imaging). Novel agents are continuously emerging, seeking to target novel biomarkers expressed in diseased tissue. Altmann *et al.* discuss in their review the recent advancements in biotechnology that can facilitate the discovery of novel targeting ligands and illustrate this with successful examples such as FAPI- and SFITGv6-radiotracers. Over the years it became clear that not only ligand engineering is important, but also that the label attached can dramatically affect the pharmacokinetics of the tracer, ultimately influencing its specificity and sensitivity. With a focus on radiometal-based radiochemistry, Sneddon *et al.* provide an extensive overview of the emerging chelators developed over the past 2-3 years. These chelators possess superior properties in terms of stability and radiolabeling conditions, resulting in the optimization of the chelation of commonly used isotopes as well as novel or repurposed diagnostic and therapeutic isotopes gaining popularity. Likewise, Usama *et al.* review how the structure of near-infrared fluorescent dyes has significantly evolved with the development of hydrophilic but net-neutral designs, resulting in fluorescent tracers with improved *in vivo* properties for image-guided surgery. Since many radiopharmaceuticals, and in particular those labeled with radiometals, are reabsorbed and retained in the kidneys, several strategies are investigated to either prevent the renal reuptake of radiotracers or promote the excretion of radiometabolites to avoid possible nephrotoxicity. In addition to the blocking of renal endocytic receptors, Chigoho *et al.* discuss how the modulation of physicochemical properties of tracers, the insertion of cleavable linkers or pretargeting approaches can overcome this limitation.

Originating in nuclear medicine, the principles of molecular imaging are more and more being embraced also by those clinical diagnostic imaging modalities that are mostly used to provide

anatomical and functional information towards diagnosis. Current advances in MRI, CT and US reviewed in this issue are aimed at pushing these modalities into the molecular imaging field. While the mainly anatomical imaging capabilities of proton-MRI are widely established in clinical and preclinical practice, the ability of NMR-techniques to provide spatially encoded information on function and metabolism based on molecular imaging of metabolites by MR Spectroscopy (MRS), hyperpolarized MRI, functional MRI and chemical exchange saturation transfer (CEST) are currently employed in a research context only. The field of MRI with heteronuclear contrast is still very young but nevertheless promising. The recent advances, reviewed by Van Zijl *et al.,* to improve the relevance and capabilities of CEST and especially MRS towards increased and fast non-invasive diagnostic power, may move these modalities towards being accepted in clinical routine practice in the foreseeable future. In CT, reviewed by Sawall *et al.*, earlier hardware and software innovations were mainly pushing the resolution boundary for visualizing anatomy with the highest possible image quality at the lowest possible radiation dose, both for clinical as for preclinical applications. Nowadays, we are at the doorstep of a major technological hardware advance by the implementation of spectral photon-counting detectors in CT scanners. Accompanied with the engineering of dedicated contrast agents sparked by the new opportunities that spectral CT brings about, the current innovations would greatly increase the capability of CT for molecular imaging, including multiplexing of signals, on top of its superb resolution for imaging of tissue context in both laboratory animals as in patients. The most recent advances for US molecular imaging lie in the development of novel strategies for the targeting of ultrasound contrast agents or microbubbles. As reviewed by Langeveld *et al.*, these include magnetic functionalization, triple targeting or the use of new ligands and conjugation methods, resulting in improved microbubble targeting capabilities. Furthermore, microbubbles have the unique advantage to be exploited for the enhancement of local drug delivery via a process called sonoporation. Thus, since targeted microbubbles improve drug delivery compared to non-targeted microbubbles, the new developments in targeted microbubble design also have implications for therapy (theranostic imaging).

Besides advances towards clinical applications, the use of molecular imaging evolved to become embedded as standard technology in life sciences to study more fundamental aspects of (patho)physiology. During the past few decades, in particular bioluminescence imaging (BLI) has become a widespread and indispensable research tool to report on live cell proliferation and location in small animal models of diseases such as cancer, metastasis, infection etc. Zambito *et al.* review the current developments that are oriented not only towards optimizing sensitivity and specificity to broaden cellular and intracellular imaging applications by creating brighter and red-shifted systems, but also towards multiplexing of signals by engineering enzyme-substrate pairs. Modulating color

emission or substrate-selectivity of different enzyme-substrate pairs brings dual- or even multicolor applications within the scope of BLI, where these were already within reach for fluorescent markers.

Optical imaging modalities span molecular imaging applications at multiple scales and multiple resolutions. On the microscopic end of the scale, reviewed by Giampetraglia & Weigelin *et al.*, intravital microscopy (IVM) has grown over the last decades into a mature technique that provides us with information on cell activity, cell signaling and much more at the single cell level in live tissues. Its development goes hand in hand with the development of multiple fluorescent tools such as targeted fluorescent probes, transgenic reporter animals, and hardware and software innovations for intensity as well as lifetime-based measurements of fluorescence, and label-free approaches. Overcoming challenges to improve penetration depth and image quality for IVM in scattering tissue involves both optimization of microscopy hardware as advances in computational approaches. Current innovations often involve the implementation of IVM in a correlative imaging approach, which aims at combining information from macroscopic imaging modalities with cellular information obtained by IVM in order to provide for better interpretation of signals within the larger tissue/organ/organism context. Moving along the resolution scale, between whole-body imaging and imaging at the cellular level lies a gap to be bridged by innovations in (optical) imaging at the mesoscopic scale, reviewed by Munck, *et al.* Mesoscopic imaging comprises those imaging approaches such as optical projection tomography and light sheet microscopy that visualize the organization of molecules and cells into tissues and organs at the submicron to centimeter scale. Their innovation has been levered by developments in tissue clearing protocols as well as hardware and computational advances. Currently mainly a preclinical research tool, it may well be envisaged to complement classical histopathology in clinical diagnosis.

Besides multiscale and multiresolution evolutions, also multimodality where the strengths from different imaging approaches are combined, has become a major focus in molecular imaging. This can be achieved either on the hardware level (such as PET-MR) or by constructing dual-modality contrast agents (such as nanoparticles). Ground-breaking insights driven by the power of correlative imaging, can tremendously increase our insights of cellular function in healthy and diseased tissues. At the same time, integration of multimodality imaging along the translational pipeline of therapeutics, can have a significant impact on their development. In their review, Bernal *et al.* exemplify how molecular (multimodality) imaging can help to improve nanomedicines' drug development by better understanding their *in vivo* biodistribution and targeting and better monitoring their therapeutic efficacy.

Taking together, current and future advances in single modalities, correlative approaches and supporting domains in an interdisciplinary context will push the molecular imaging field greatly

towards the ultimate goal of molecular imaging, which is to visualize *all* chemical and biological processes in the body i*n real time*. Such advances warrant parallel innovations in handling and storage of large data, and deep learning/artificial intelligence become particularly relevant in the context of extracting new information from vast imaging data. Finally, in view of wide technology acceptance, the need for standardization in both the clinical as basic research context becomes even more pronounced.