Current status and future challenges for molecular imaging

Carolyn J. Anderson¹ and Jason S. Lewis²,3

¹Departments of Medicine, Radiology, Bioengineering, and Pharmacology & Chemical Biology, University of Pittsburgh, Pittsburgh, PA 15219, USA
²Department of Radiology and the Program in Molecular Pharmacology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
³Weill Cornell Medical College, New York, NY, USA

Molecular imaging (MI), used in its wider sense of biology at the molecular level, is a field that lies at the intersection of molecular biology and traditional medical imaging. As advances in medicine have exponentially expanded over the last few decades, so has our need to better understand the fundamental behaviour of living organisms in a non-invasive and timely manner. This commentary draws from topics the authors addressed in their presentations at the 2017 Royal Society Meeting 'Challenges for chemistry in molecular imaging', as well as a discussion of where MI is today and where it is heading in the future.

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1. History of imaging

Although the first image (or rather the earliest known surviving photograph) was taken by Joseph Nicéphore Niépce in 1826 (http://www.hrc.utexas.edu/exhibitions/permanent/firstphotograph/), it was not until 1838 that a human was captured in a photograph by Louis Daguerre in Paris (http://mashable.com/2014/11/05/first-photograph-of-a-human/#Q5v6ultiGgqC). The first produced compound light microscope has been attributed to the year 1590 when two Dutch eye glass makers, Zaccharias Janssen and son Hans Janssen, experimented with multiple lenses placed in a tube. The Janssens observed that objects in front of the tube appeared magnified. The foundations of modern light
microscopy were established by Ernst Abbe in the later 1800s, when he demonstrated that the
diffraction of light by the object being imaged and the objective lens determined image resolution
[1]. It was not until 1895 that the first ‘medical’ image was generated by Wilhelm Conrad Röntgen,
after his discovery of the X-ray [2]. This image, featuring the bones of his wife’s hand and showing
her wedding ring on her fourth finger, was the world’s first X-ray.

Over the following 120 years, medical imaging became a mainstay of clinical practice with
routine application of imaging modalities for the diagnosis and monitoring of disease. The broad
range of modalities now available for medical imaging, from nuclear imaging (positron emission
tomography (PET) and single photon emission computed tomography (SPECT) [3–5]) to magnetic
resonance imaging (MRI) [6–9], ultrasound (US) [10,11] to computed tomography (CT) [12,13],
and the newer emerging technologies (e.g. optical, hyperpolarized MRI, photoacoustic, optical
coherece tomography (OCT), multi-spectral optoacoustic tomography (MSOT) and Raman)
have provided a wealth of tools able to image from the cellular level to the whole body. The
wide array of tools available presents its own unique set of challenges with regards to choosing
the appropriate modality, answering the right question, at the right time, while minimizing costs
while ensuring accuracy and quality.

2. What is molecular imaging?

Molecular imaging (MI), as its name implies, is a field that lies at the intersection of molecular
biology and traditional medical imaging. As advances in medicine have exponentially expanded
over the last few decades, so has our need to better understand the fundamental behaviour of
organisms (from cells to human) in a non-invasive, timely and cost-efficient manner. Over the
past two decades, a number of factors have acted in concert to fuel the ascent of MI in both the
laboratory and the clinic: an increased understanding of the molecular mechanisms of disease,
development of clinically relevant mouse models and the continued development of in vivo
imaging technologies, ranging from improved detectors to efficient labelling methodologies. MI
also contributes to improving the treatment of disease by optimizing the pre-clinical and clinical
tests of new medications. The advent of MI has, in turn, prompted a paradigm shift in medical
imaging as a whole, from its foundations in purely anatomical imaging towards techniques
aimed at probing tissue phenotype and function. Taking cancer as an example, both the cellular
expression of disease biomarkers and fluctuations in tissue metabolism and microenvironment
have emerged as extremely promising targets for imaging. Indeed efforts have been focused on
the development of effective molecularly targeted agents applied with a wide variety of imaging
modalities, from fluorescence and luminescence to magnetic resonance.

3. Where does molecular imaging have a role?

The use of routine anatomical and functional imaging modalities used in standard medical
practice, e.g. for identifying a broken bone, diagnosing cancer (by its size and tissue density)
or looking at kidney function, will always have its place in hospitals and clinics worldwide.
Currently, MI, primarily at this point with PET, plays a major role for diagnosis, staging and
monitoring treatment efficacy for several diseases, including cancer and neurological diseases.
We now ask the question of what are the future roles of clinical MI?

Genomic medicine is an exceptionally powerful tool, but as stated by O’Rourke, ‘As advances
in genomic medicine have captured the interest and enthusiasm of the public, an unintended
consequence has been the creation of unrealistic expectations’ [14]. In cancer, the ability to
image the whole tumour rather than relying on the genetic analysis of a selected biopsy of a
heterogeneous tumour [15–17] certainly has merits. Further, patients presenting with multiple
metastases are limited by the inability to biopsy all of the metastatic foci. Accurate, comprehensive
and quantitative MI could yield powerful diagnostic and staging information not possible by any
other means. Such an example was presented by Sorensen et al. [18], where they quantified the
expression of HER2 in breast cancer tumours and metastases using the radiolabelled affibody
68Ga-labelled ABY-025. They demonstrated that standard uptake values calculated from PET correlated with biopsy HER2 expression scores. This may be especially important for women who initially present with a HER2-negative primary tumour, but have HER2-positive metastases, which could respond to anti-HER2 drugs [19].

Alzheimer’s disease (AD) is another disease where MI, particularly PET and SPECT, has made major contributions to emerging drug therapies, although there is currently no gold standard drug that provides more than symptomatic treatment of this disease [20]. Definitive diagnosis of AD can only be made post-mortem, based on the presence of senile plaques and neurofibrillary tangles. However, the ability to image Aβ plaques and more recently tau proteins, provides a means to follow the progression of this disease in patients. Importantly, inclusion and exclusion criteria in AD drug trials can now be based upon tau and beta amyloid PET scans, which allow clinicians to objectively distinguish patients with AD versus those with other types of dementia. This same paradigm may also of course be used to guide novel drug discovery and for dose optimization. A recent series of trials with agents aimed at clearing amyloid plaque buildups from the brain in an effort to slow Alzheimer’s cognitive declines have showed encouraging results. However, one drug displayed consistently better results the longer patients took it (even with a disappointing Phase 3 result) [21,22], while another showed it yielded stronger efficacy the higher the dose [23]. Incorporation of a quantitative MI paradigms in these studies could lead to an optimized dosing regimen [24].

4. Imaging inflammation in multiple diseases

Inflammation is one of the oldest recognized medical ailments, having been documented by Sumerian cultures around 2700 BCE and described by a Roman academician in the first century CE [25]. A plethora of different stimuli and conditions can inflict inflammation in all organs and tissues in a subject, which is likely why our understanding of the underlying mechanisms responsible for the molecular and functional changes resulting in inflammation is incomplete. Research is ongoing to elucidate the downstream effects of inflammation, and how/whether inflammation can be partially or solely responsible for diseases that include cancer, neurological diseases, cardiovascular and pulmonary diseases among others [26,27].

The ability to quantitatively image specific immune cell types for a range of diseases is critical for further understanding the mechanisms of cause and downstream effects of inflammation, determining the progression or resolution of disease, and for monitoring therapeutic response [28]. 18F-FDG (2-deoxy-2-18F-fluoro-D-glucose; FDG) is approved by the US Food and Drug Administration and is primarily used clinically for tumour detection, staging and detecting recurrence, although indications for FDG also include non-oncologic applications such as evaluation of infection and atherosclerosis [29]. Because 18F-FDG is an analogue of glucose and is taken up into all metabolically active cells through glucose transporters, it is likely taken up in all activated immune cells and is not specific for any one type, although specificity has been suggested in the literature, in contradictory reports [30]. A review by Wu et al. [31] presents a thorough overview of many inflammation biomarkers and their correlative PET tracers for imaging various aspects of inflammation.

Of particular interest is a relatively new focus area in inflammation where systemic inflammation is being investigated as causal to a variety of diseases (e.g. [32–34]). Several serum biomarkers of inflammation, including C-reactive protein, fibrinogen, serum amyloid A, along with pro-inflammatory cytokines have been found in patients with chronic obstructive pulmonary disease, which has been linked to a risk of stroke [35]. Additionally, Libby et al. [36] posit that the ‘cardiovascular continuum’ which links the arteries and heart as formulated by Dzau & Braunwald [37], should now be expanded to encompass the nervous system, spleen and bone marrow. Libby et al. demonstrate that changes in FDG imaging in the spleen and bone marrow are found in patients with atherosclerosis, demonstrating that these systemic changes in inflammation, particularly leucocytes, can be non-invasively monitored. It can be argued that a pan-disease ‘systems biology’ approach should be applied more to imaging, as there are multiple shared imaging biomarkers (IBs) between diseases, with inflammation as a common factor.
5. Radiology and pathology

The field of radiomics ‘aims to extract large amount of quantitative features from medical images using data-characterization algorithms’ [38–42] and radiogenomics is the study of correlations between cancer imaging features and gene expression (also known as imaging genomics) [43–47]. As tools in MI, and technologies in pathology advance exponentially, it is inevitable that these two fields are going to have to merge. This merger may be a painful process for some and may be met with resistance, but with the advent of machine learning and complex algorithms, it will have to happen.

6. Regulatory approvals and validation of imaging biomarkers (IBs)

IBs are fundamental to the successful management of cancer patients. Gaining approval and reimbursement for new imaging tests is a burdensome task that is not for the fainthearted [48–50]. This has been a recurring issue across the globe and a movement for consensus is required if the MI field is to continue to move forward. We have to step out of our silos to make this happen—and those in academic centres, driven by the need for new grants and papers need to be given equal credit for generating a drug to the final stages of approval. The recently published Imaging Biomarker Roadmap for Cancer Studies lays a foundation [51]. This report presents ‘14 key recommendations concerning the design, performance, governance and publication of IB studies, with the aim of accelerating IB translation into the clinic. These recommendations highlight: (1) the role of parallel (rather than sequential) tracks of technical validation, biological validation and cost effectiveness; (2) the need to develop IB standardization and accreditation systems; (3) the need to continually revisit IB precision; (4) an alternative framework for biological validation of IBs; and (5) the essential requirements for multicentre studies that will qualify IBs for clinical use’. Only if the MI field adopts such recommendations and pathways are we likely to overcome many of the challenges that have tempered our progress to date.

The amount of investment being put towards identifying serum biomarkers and other biological biomarkers (e.g. in urine or sputum) is vast. However, even if a biomarker was discovered and shown to have 100% specificity, it will still be imperative to find the source of the biomarker and to locate the site(s) of disease. This is of particular importance in the realm of cancer, where one needs to accurately locate neoplasms prior to resection and/or location targeted therapies, such as external-beam radiation or photodynamic therapy. Therefore, MI could potentially ‘rescue’ biomarkers by overcoming their existing limitations (e.g. [52]).

7. Musings on the future

As previously mentioned, traditional/conventional anatomic imaging will always play an important role in the management of human health. Of course, one of the most rapidly expanding and critical areas for MI is the ‘imaging of immunotherapy’—but this topic has been extensively covered by others [53–61]. There are other ‘new’ areas of MI, which also continue to expand, and the authors wish to highlight just a few areas that will advance MI in the future.

(a) Intraoperative imaging/image-guided surgery

There is an abundance of applications and platforms (small molecules to nanoparticles) that can be exploited in the surgical setting, and an imaging agent capable of identifying small volume macroscopic or microscopic disease will allow for more accurate assessment of residual disease, facilitating more complete resection of the disease while sparing healthy tissue, which ultimately will improve patient outcomes. In current surgical practice, ‘complete resection with no visible residual disease’ is the goal; however, these new technologies will ensure that patients are left with even less tumour burden.
Optical imaging is particularly powerful and well suited for surgical applications [62–66]. For example, fluorescent imaging probes can assist surgeons in delineating malignant from benign tissue [62]. This is done with the deployment of navigation systems that can both activate the imaging probe and then process the emitted light generating a real-time image [67]. Van Dam et al. used this approach as a first-in-human studies by developing a fluorescein-conjugated folate probe for imaging the over-expression of folate receptor alpha in ovarian cancer [65,68]. More recently, the field has shifted to agents that emit in the near infrared fluorescence range. Tummers et al., for example, conducted a trial in ovarian cancer patients who were administered with indocyanine green prior to image-guided cytoreductive surgery. Although all of the metastatic deposits in these patients exhibited near-infrared fluorescence, 13 non-malignant lesions also exhibited fluorescence, leading to a high false-positive rate of 62% [69].

(b) Target engagement imaging

There has been a growing movement in this area to truly understand the biological behaviour of targeted therapies. The proof of concept for this was perhaps first demonstrated in studies using \(^{18}\)F-FDHT (e.g. [70–72]) and \(^{18}\)F-FES (e.g. [73–77]) for observing the tumour binding and receptor occupancy of androgen- and estrogen-receptor targeting agents. Other examples are now appearing; for example, the use of radiolabelled PARP imaging agents [78,79] could address several unmet clinical needs surrounding the early detection and management of cancer. Before treatment, PARP imaging could be used for determining PARP expression levels—which were shown to correlate with treatment prognosis [80,81]. Therefore, the level of radiolabelled PARP imaging tracer uptake (e.g. \(^{18}\)F-FTT or \(^{18}\)F-PARPi [82–85]) may correlate with the likelihood for response to PARP1/2 inhibitor mono- or combination therapy. This is fundamentally different from diagnostic imaging and tumour staging, and the inherent value and unmet clinical need of PARP tracers could lie in visualizing, monitoring and predicting how PARP1 inhibitors distribute throughout the human body—and if they reach their intended targets in individual patients. This paradigm for the use of radiotracers would therefore be an exceptionally powerful tool to help deliver personalized precision dosing regimen.

(c) Precision prevention

To provide all examples in this area would mean an exhaustive review in its own right. However, just using PARP agents as an example, radiolabelled PARP tracers will likely unfold their potential in well-equipped cancer centres due to the infrastructure demands required for PET imaging, but fluorescently labelled PARP tracers [86] could be used in an entirely different, yet in an equally important way. Many cancers have their underlying cause in hereditary germline mutations, but stochastic effects associated with DNA replication contribute in a substantial way to human cancer incidence [87]. While genomic analyses can help to identify and monitor risk groups, a large fraction of all cancers are due to environmental factors. Intuitively, malignant growths of stochastic origin need to be addressed through both primary and secondary prevention (primary: vaccines, avoidance of exposure to carcinogens or change in lifestyle; secondary: early detection and screening). Fluorescently labelled PARP tracers could play a significant role in secondary prevention of some epithelial malignancies, including cervical cancer [88] and oral squamous cell carcinoma [86] both of which have elevated PARP expression. These cancers originate at the tissue surface, which could not only allow non-invasive detection of a fluorescent marker (e.g. with a laparoscope, similar to what is being used intraoperatively [65]), but also topical application of the tracer [86]. This is attractive for several risk groups, including head and neck oral squamous cell carcinoma (HNSCC) patients who survive initial presentation and definitive treatment beyond 3 years (and who have a more than 10% HNSCC associated mortality within a median follow-up of 7.7 years [89]). Combined with the low cost and infrastructure requirements needed for optical imaging, regular follow-ups could be performed using topically applied PARP tracers, and even folded into a simple routine dental check-up. Similar screening scenarios are conceivable also.
for cervical cancer patients. Decentralized and low-cost precision prevention with PARP tracers could, therefore, increase the fraction of patients diagnosed at an early stage, when their disease is still local and more manageable.

(d) Hyperpolarized magnetic resonance imaging

Multi-modality biomedical imaging has become an important tool to non-invasively assess the metabolic status of a specific biological system [90]. One such example is the clinical application of PET/MRI [91–94]. In addition, hyperpolarized MRI is an emerging technique in the field of MI that allows for a dramatic increase of the signal available for magnetic resonance spectroscopy experiments in order to overcome the sensitivity limitation of conventional MRI [95–99]. Through a combination of low-temperature biophysical chemistry methods and conventional solution state NMR, hyperpolarization enables the observation of the NMR signal of a molecule nearly 100 000-fold stronger than its equilibrium state. This provides the signal to noise necessary to follow the molecule through enzymatic reactions in seconds [26]. The increased signal also enables rapid imaging of other nuclei ($^{13}$C and $^{15}$N) rather than only protons, expanding the range of MR active nuclei which can be readily used for efficient metabolic imaging. A drawback is the short polarization life times of the hyperpolarized nuclides, which are of the order of 30 s or less. Nonetheless, it is possible to design and use many contrast agents enabling the ability to probe metabolic pathways and to detect metabolic aberrations non-invasively and in vivo [100].

8. Conclusion

This short commentary touches very briefly on several important topics. It is by no means exhaustive and many of the exciting and interesting movements in MI have not been discussed (e.g. photoacoustic, OCT, MSOT and Raman). However, it is clear that MI has a place in every aspect of medicine—from basic research to clinical application, from determining target engagement to disease monitoring, from pre-clinical study to approved diagnostic tools.

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