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Has molecular imaging delivered to drug development?

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Pharmaceutical research and development requires a systematic interrogation of a candidate molecule through clinical studies. To ensure resources are spent on only the most promising molecules, early clinical studies must understand fundamental attributes of the drug candidate, including exposure at the target site, target binding and pharmacological response in disease. Molecular imaging has the potential to quantitatively characterize these properties in small, efficient clinical studies. Specific benefits of molecular imaging in this setting (compared to blood and tissue sampling) include non-invasiveness and the ability to survey the whole body temporally. These methods have been adopted primarily for neuroscience drug development, catalysed by the inability to access the brain compartment by other means. If we believe molecular imaging is a technology platform able to underpin clinical drug development, why is it not adopted further to enable earlier decisions? This article considers current drug development needs, progress towards integration of molecular imaging into studies, current impediments and proposed models to broaden use and increase impact.

This article is part of the themed issue 'Challenges for chemistry in molecular imaging'.

1. Drug development challenges

The pace of scientific discovery and innovation has led to the development of numerous tools to enhance drug discovery, fuelling investment across the biopharmaceutical industry over the last 15 years. For example,

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biobanks have enabled a better understanding of the molecular basis of disease, ensuring that there is strong evidence that putative drug targets are related to human biology. Supported by these technology platforms, a flow of new molecules have emerged, able to bind to targets and modulate cellular features relevant to disease. Yet despite increased investment, advances in technology and many significant achievements, the industry productivity in delivering novel medicines to patients remains disappointingly low [1].

(a) What is driving the lack of productivity?

Analyses have been conducted to pinpoint the causes of failure and the stages at which drug development presents most risk [2–4]. Although failure can occur at any stage of development, the cost of failure increases as programmes progress to large, resource-intensive, late-stage studies to support regulatory decision-making. Therefore, the early stage of drug development is the point at which risk is best addressed. Simply put, there is a need to improve how we characterize our drug candidates in early clinical studies.

(b) Progress towards a more informed drug development paradigm

The initial demonstration of clinical benefit by a novel therapeutic entity in a patient population is termed *proof of concept*. Failure to demonstrate robust proof-of-concept readouts in early first-in-patient studies is likely to lead to termination of a programme. Reasons for such failure are multifaceted, including factors such as: an incorrect biological hypothesis; pre-clinical models of disease tested were not relevant to the clinical disease; clinical endpoints were not adequate to capture a clinically relevant response in the timescales of the trial; the candidate molecule did not reach the tissue at the required level to engage the target; and the wrong patient population was investigated. As a result, there is a risk of terminating a programme, without having the appropriate tools to fully understand the molecule, its mechanism or relevance to a given disease. Without robust endpoints, the alternative risk is that a molecule will pass through early development and fail later, in more costly phases of drug development.

To minimize such failures, an approach termed 'experimental medicine' is being promoted in drug development. It is defined by the Medical Research Council as 'Investigation undertaken in humans, relating where appropriate to model systems, to identify mechanisms of pathophysiology or disease or to demonstrate proof-of-concept evidence of the validity and importance of new discoveries or treatments' (https://www.mrc.ac.uk/research/initiatives/experimental-medicine/). This guiding philosophy applied to early clinical drug evaluation can deliver information-rich studies in small, short, well-controlled trials to provide a vital filter in the drug development process.

Focusing on potential specific knowledge gaps that experimental medicine approaches can address, Morgan *et al.* [3] described the concept of the *three pillars*, drug attributes that if characterized can decrease programme failure: drug access to tissue, target engagement and demonstration of downstream pharmacology. The three pillar framework promotes a disciplined translational approach, increasing preparation for more informed clinical studies early, for example, by ensuring robust and qualified biomarkers are prepared.

To facilitate experimental medicine, studies must maximally characterize the candidate early using optimized trial designs, integrating the best technology platforms available, the most informative pre-clinical experiments and patient stratification strategies.

2. The potential for molecular imaging

Biomarker application is now established as a prerequisite for successful drug development using experimental medicine strategies [5]. Imaging-derived biomarkers offer favourable attributes: non-invasiveness enables temporal sampling of the same tissue before and after treatment; imaging can interrogate specific organ systems where tissue cannot be accessed or blood-based

markers offer poor surrogates of tissue activity; and measuring systemic manifestations of complex diseases by surveying the whole body. Molecular imaging technologies specifically enable the evaluation of the drug, the target and biological response. So, what progress have we made to incorporate these methods?

(a) The current role of imaging in drug development

Historically the role of imaging in pharmaceutical research and development (R&D) has centred on basic structural evaluation of disease, for example, tumour size evaluation in oncology trials, brain volumetric measurements in neurology, or joint space width in osteoarthritis. Such assessments are considered to have clinical significance and the methods parallel routine clinical assessments, and therefore can be readily integrated into large, multi-centre trials. The robustness of some of these measures allows the endpoints they provide to be considered by regulatory bodies to judge drug efficacy.

While these morphological measurements can study elements of efficacy in large patient cohorts with long treatment durations, they lack sensitivity to evaluate subtle disease response characteristics in small, shorter, early phase clinical trials. In addition, most structural changes result from processes downstream from the initial drug–target interaction and therefore offer little insight into drug mechanism. Although structural assessments will remain important clinical trial tools, molecular and functional methods are increasingly being considered.

Molecular imaging in clinical drug development is largely dichotomized between early and late phase clinical trial application as summarized in table 1. Molecular imaging in early phase studies can be applied to interrogate mechanistic hypotheses in order to support earlier internal decision-making on whether to progress a candidate drug towards subsequent larger scale clinical trials. In such studies, due to their small size, more sophisticated and intensive methods can be employed, such as dynamic imaging, bespoke radioligands or imaging protocols incorporating multiple molecular and functional methods.

By contrast, application of molecular imaging in late phase drug development is impeded by a lack of data supporting the use of a method and the practicality and cost of implementing a technique across multiple study centres. Therefore, most uses of molecular imaging in these large trials will typically parallel routine clinical use. For these reasons, molecular imaging in late phase studies is limited mostly to using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and amyloid positron emission tomography (PET) imaging in oncology and Alzheimer's disease, respectively. In both of these examples, techniques are broadly available and some clinical relevance has been established.

(b) Progress towards adopting molecular imaging for early phase clinical drug development

As outlined, the three pillar concept provides a framework by which molecular imaging can be systematically incorporated into early drug development to study access to tissue, target engagement and downstream pharmacology. How can molecular imaging evaluate these parameters?

(i) Drug access to tissue

Radiolabelled (^{11}C or ^{18}F) small molecule drug candidates studied with PET can provide a direct measure of the *in vivo* distribution in a healthy volunteer or patient. Following intravenous administration of a low dose of radiopharmaceutical, the distribution and kinetics can be measured with PET. Beyond small molecule drug candidates, antibodies can be labelled with isotopes such as zirconium-89, with the longer radioactive decay half-life suitably matching the longer biological half-life of the drug to optimize tissue measurement [6]. One of the challenges with this approach is that quantifying radiotracer distribution at low concentrations may not fully reflect the distribution of the compound at *therapeutically* relevant levels, due to dose

Table 1. Contrasting how molecular imaging is applied in different stages of drug development. In early stage studies, methods can be highly complex and established at a single centre. In later-phase studies, techniques must be simplified to enable standardized implementation across many study centres.

	molecular imaging for early phase drug development	molecular imaging for late phase drug development
applications	bio-distribution, target engagement, markers of pharmacology, patient stratification	patient stratification; response/progression evaluation
availability	complexity is acceptable, bespoke single centre study or if necessary standardized scanning across a small number of centres	a distribution network needs to be in place to access the tracer for the study in the required geographies. May need to be available in tens to hundreds of centres
image acquisition	can be highly specialized, e.g. dynamic scanning, blood sampling	close to clinical routine but standardization is important
cost	cost of the method development (e.g. radiolabelling) can be far higher than the total scanning cost	costs include scanning, standardization and central analysis efforts. When multiplied by the number of subjects and time points this can represent a significant percentage of the total trial cost
analysis	highly specialized analysis/modelling can be conducted	site-based assessments or images transferred for central, standard analysis
examples	radiolabelled drug, target engagement	^{18}F-FDG-PET supplementing structural response criteria in assessment of solid tumours; amyloid PET
impediments to broader use	cost and complexity of method development	availability of the method across clinical trial centres; evidence that a given method has clinical relevance

dependent on- and off-target binding at low concentrations; this has been a particular challenge in quantifying tumour penetration of antibody drug conjugates [7].

(ii) Target engagement

Target engagement can be interrogated using radiolabelled probe molecules in conjunction with PET using varying doses of the drug candidate. This has been a widely used strategy in recent years where demonstrating the level of target engagement can inform the subsequent therapeutic dose selected [8,9]. Most target engagement studies have been conducted in the central nervous system (CNS), where PET has been the only way to acquire such information [10,11]. Once radiochemistry methods have been established, these studies are operationally straightforward and the occupancy–exposure relationship can be measured using small numbers of healthy volunteers at a single centre. Extending these concepts to other tissues and in complex, heterogeneous diseases is required.

(iii) Expression of pharmacological activity

Assessing the downstream effects of drug–ligand interaction is a further setting in which molecular imaging can provide valuable information. In these cases, targeting a generic physiological process or disease characteristic rather than specific molecular expression can be useful. Examples of such processes include metabolism, inflammation, hypoxia, pH and angiogenesis. A wide range of molecular imaging agents have been developed to assess these processes; however, with the exception of FDG and glycolysis, none have gained clear acceptance as a standard assessment.

As such methods are generic to disease processes and not specific to any one drug, this is the arena in which the greatest potential for collaboration between pharmaceutical companies exists.

Such collaboration could help develop and standardize toolkits of molecular imaging to evaluate different physiological targets and promote widespread acceptance.

(c) Using molecular imaging to select the right patients in trials

Molecular imaging has not been widely adopted to confirm disease pathology within a clinical trial setting. Demonstration of the potential, however, comes from efforts to prove the amyloid hypothesis in Alzheimer's disease. Initial early phase clinical trials of beta-amyloid clearing therapeutic monoclonal antibodies were limited to the evaluation of [^{11}C] Pittsburgh compound B (PIB) PET to evaluate mechanism. More recently, the availability of multiple ^{18}F radiolabelled PET tracers has enabled incorporation of molecular imaging into large, late-stage development studies, allowing for both demonstration of amyloid presence (confirming diagnosis) in addition to measuring the extent of amyloid clearance [12,13].

3. Current barriers to using molecular imaging

Molecular imaging has tremendous potential to support an information-rich, rational drug development process. So why has integration of these methods been limited and relatively constrained to neuroscience applications?

(a) Logistical and financial challenges

There remains a perception in the industry that the incorporation of molecular imaging into clinical trials represents complexity, high cost and long set-up time. While these techniques provide valuable insight into the pharmacology and patient characterization, value will significantly increase if certain methods are able to predict clinical outcome in advance of standard endpoints. In order to simplify implementation and generate data to increase value, efforts should be directed at standardization of acquisition techniques, consensus on analysis methodologies and efforts to qualify and validate some of these tools as outcome biomarkers. Steps towards these goals have been made by the Radiological Society of North America in their efforts to lead the Quantitative Biomarker Imaging Alliance [14]. In addition, the Alzheimer's Disease Neuroimaging Initiative has made enormous inroads towards characterization of techniques and their direct application to map the progression of a complex neurological disease [15,16]. Furthermore, O'Connor *et al*. [17] analysed the current challenges in imaging biomarker development for cancer studies and proposed a systematic roadmap to support validation and qualification. These collaborative networks focused on specific disease areas will continue to be important in the delivery of new imaging methods for drug development.

Beyond standardization of scanning, adopting nascent molecular imaging techniques represents a step increase in the implementation challenge. Previously developed syntheses need to be established at the selected trial centre (s) necessitating considerable set-up time to ensure good manufacturing practice (GMP) grade production. If a bespoke probe molecule is required (e.g. a radiolabelled drug), even with tractable radiochemistry, extensive work-up can take years to prepare for a clinical study [18]. These long timelines can lead to asynchrony with drug development times, where delivering an imaging method late can result in zero value to programme decision-making. This can be overcome with careful planning and strategic investments early in the project life cycle. This begins by engaging with internal medicinal chemistry teams who have key knowledge around pharmacophores, coupled with an understanding of key design parameters for PET radiopharmaceuticals [19].

For bespoke radiotracer development, extensive chemistry work-up may not be successful or, if successful, the methods only ever applied in small studies. Such endeavours may be of limited academic interest and few commercial contract research organizations have the capabilities or expertise to support these activities. New organizational models are undoubtedly required to

enable and streamline the next generation of bespoke radiolabelled drug molecules and probes towards clinical application.

(b) The molecular imaging 'toolset' remains limited to support drug development

Access to a wide variety of molecular imaging tools is limited by several factors. At the centre of this problem is a lack of access to molecular libraries that can be used for the initial screening of leads, prior to optimization of the ideal properties associated with a molecular probe. This problem manifests in academia, in which most groups are forced to access lead molecules for a given target based on structures that are published by pharmaceutical companies. These molecules may not have the ideal profile and without knowledge of the pharmacophore, this may be challenging and time consuming for chemists. One consequence of a limited substrate/target pool is that academic groups may congregate around a promising target and develop several competing molecules, with inadequate characterization and uncertainty on which is the best agent to use. Mechanisms are required to enable industry to share libraries of compounds with suitable properties to develop novel molecular imaging agents and for stakeholders (funding agencies, both public and private) to develop mechanisms for data sharing and optimization around techniques to benefit the community at large.

(c) Qualification and validation of methods are not sufficiently studied

Application of novel probes is further impeded by the lack of qualification devoted to a given technique. The advent of relatively affordable pre-clinical PET imaging has allowed the application of molecular imaging broadly in model systems of disease. For well-characterized molecular probes, the data can be confidently interpreted. However, for new probes lacking biological validation and without comprehensive consideration given to acquisition and data modelling it may not be possible to sufficiently interpret the ability of a novel molecular probe to quantify a given target or process. One example is that of ^{64}Cu-ATSM, a PET tracer applied in several clinical studies in order to study hypoxia in tumours. Recent studies, however, raise questions regarding its mechanism and suggest that tumour uptake is similar to ^{64}Cu-chloride and ^{64}Cu-acetate and may relate, at least in part, to uptake of the dissociated ^{64}Cu ion [20,21]. This highlights the need for a systematic selection of the right probe and detailed biological characterization through rigorous data modelling.

Furthermore, datasets generated from disease settings with emerging probes remain typically limited in number and are sometimes confounded by the use of more than one radiotracer for a given target (take the amyloid tracers as an example). As such there is scope to collaborate through data-sharing exercises that enable more robust evaluation of individual radiotracers for given disease pathologies, understanding tracer performance across centres and development of advanced analysis methodologies including machine learning for supporting diagnosis, patient stratification and response assessments. Such advanced methods can only be developed through access to large datasets typically generated from multiple centres.

(d) Expertise in molecular imaging is limited in pharmaceutical R&D

Pharmaceutical R&D has minimal resources to support molecular imaging method development. Imaging expertise is typically assigned to support a range of standard and non-standard methods, therapeutic areas and multiple phases of clinical development. Accessing specialized expertise and resource will only be achieved with strong external links to academic expert centres and commercial organizations. These relationships have been developed by numerous companies over the years and underline the need for long-term commitment that allows for two-way education and understanding of how each organization functions. Collaborating in this way will

increase the pool of trained imaging scientists who understand the use of biomarkers in drug development and can work either as internal industry experts, or as independent researchers in academia.

(e) Specialized methods are not always available where the patients are

Subject recruitment into clinical trials is difficult in certain patient populations, necessitating a broad consideration of the trial centres able to support a study. Few centres worldwide have the advanced molecular imaging capabilities required for certain methods: a cyclotron, specialized radiochemistry expertise, GMP-qualified facilities, blood sampling and analysis and advanced scanning facilities. The inability to efficiently recruit and scan patients at centres with the required methods at best results in slow study conduct. However, more generally, it limits how novel molecular imaging methods can be evaluated in patient populations of interest.

(f) Imaging in trials needs to be patient-focused

Fully quantitative analysis can necessitate long and intensive scans for patients. For example, for some radiotracers, the best quantification could involve a complex dynamic scanning protocol including arterial blood sampling and metabolite analysis [22]. Such methods can be taxing for patients and likely challenge patient recruitment. In addition, for some studies, the imaging method would need to be repeated several times to assess changes over time. In practice, this may not be achievable due to factors such as radiation dose limitations and increasing patient hospital visits, leading to fatigue. While some intensity of investigation is required to maximize data quality, imaging must be rationalized into pragmatic, patient-friendly protocols, as early as possible.

(g) Molecular imaging is unlikely to offer a flow of companion diagnostics

Given the challenge to access non-standard methods beyond highly specialized centres it seems unlikely that molecular imaging probes will be commonly developed in tandem with a drug treatment and then deployed across multiple geographies in time for pivotal (Phase 3) clinical trials. Feasibility would significantly increase if methods could be deployed across many more centres, for example, with longer-lived radioisotopes or simplified local production (e.g. with radioisotope generators).

While there is merit to consider this, particularly where blood/tissue companion diagnostic markers may not be useful (e.g. neuroscience), the practical constraints of deploying molecular imaging across many centres remain a significant barrier. It is reasonable to expect, however, that molecular imaging can play an increasingly important role to validate blood-based companion diagnostics.

4. New models are needed to establish molecular imaging as a drug development platform

Academic centres continue to apply highly innovative chemistry creating a flow of new *in vivo* molecular probes. There has never been a greater need to access these tools to support the drug development process. So how can these probes translate towards impactful clinical trial use?

(a) A pre-competitive approach is required

If a new molecular imaging probe has the potential for commercial clinical use, diagnostic companies will be incentivized to invest in validation activities and establish a distribution network to enable use in a trial setting (e.g. ^{18}F-flutemetamol). More commonly, there are many

probes that do not have a clear diagnostic role but may be valuable for drug development. A single pharmaceutical R&D company will not have the resources to develop and validate a range of molecular imaging probes. Rather a coordination of efforts across the industry would provide the scale needed to fully qualify high priority probe molecules. To reduce competitive sensitivities and evolving disease priorities, efforts could be focused on generic patho-physiological attributes, e.g. molecular markers of fibrosis and inflammation would be relevant to many diseases and programmes across the industry.

Efforts to promote pre-competitive collaboration, or sharing of novel biomarker data have met with limited success over the years. However, the advent of patient advocacy and focused non-profit investments in specific diseases may change this; for example, the Michael J Fox Foundation is sponsoring a $2 million prize for the first team to develop a viable selective alpha-synuclein PET tracer with a commitment to make that tracer available broadly (https://www.michaeljfox.org/research/imaging-prize.html).

(b) The potential of molecular imaging tools needs to be promoted

Neuroscience drug development has relied upon PET to study drug and targets in the CNS for many years. The dependence, driven by inaccessibility to tissue, means use will continue in this field, evidenced by the use of amyloid PET in multi-centre studies and active efforts to develop tau imaging agents. In diseases of other organ systems installment of new methods has been slow and remains limited—for example, development of specific markers of tissue inflammation. The molecular imaging community has an opportunity to promote by example how new tools can be used in areas that do not typically consider molecular imaging (for example, imaging virus for HIV research [23]).

(c) Molecular imaging needs to be integrated into a multi-modality framework

Molecular imaging cannot be considered in isolation from complementary structural and functional imaging, blood biomarkers, tissue analyses and physiological monitoring. Early in the drug development planning, teams should review all options available to decide on the most informative, tractable and cost effective technologies to inform the programme. This will likely include multiple technologies applied in an integrated fashion. How data integration from multiple sources is managed will be important with consideration given to applying the best analytical data tools. It is also very important to remain focused on the underlying scientific question that needs to be answered and the three pillar framework introduced earlier provides an important template to provide this focus.

Clinical molecular imaging in drug development is predominantly conducted using nuclear methodologies. It is imperative that we learn from the successes and challenges of nuclear molecular imaging as we look for opportunities to expand the molecular imaging toolset into magnetic resonance, optical and other technologies. While nuclear techniques will continue to deliver important methods, other techniques should be considered too. For example, optical imaging approaches can provide a high-sensitivity and high-specificity measurement technology with and without labelled probes and are showing promise in applications such as image-based surgical guidance [24,25]. In addition, magnetic resonance methods particularly through functionalized gadolinium chelates or ^{13}C dynamic nuclear polarization offer methods that are complementary to existing clinical molecular imaging techniques. Drug development organizations should explore the most relevant techniques for a given setting, asking practical questions such as: does the methodology need to be available across multiple centres? What cost is acceptable? Could radiation dose be a limiting factor in the given setting? It is likely that drug development will shift to access a broader range of methodologies, improving upon existing methods but also making method selection and implementation more complex.

(d) Establish a coordinated approach to develop and deploy new molecular imaging tools

To facilitate a flow of methods towards deployment in impactful clinical settings new organizational models should be considered. A coordinated, multi-disciplinary, academic and commercial network would ensure academic innovation in probe chemistry is channelled towards an operational framework to allow clinical application.

Developing and applying molecular imaging tools in single centres results in slow progress towards qualification and limits impact on drug development needs. Tools developed need to be applied efficiently in the right patients and therefore, usually, many centres. A network of centres could enable the development of a radiotracer in one centre with a plan to establish methods (or ship tracer if feasible) in other centres to study the required patient population.

New organizational models could include: agreed priorities for new clinical tools; cost-sharing of probe development; pre-competitive sharing of compound libraries; strengthened ties between chemistry and radiochemistry expertise; engagement between imaging scientists and disease biology and clinical expertise; multimodality programmes to ensure different imaging platforms (nuclear, magnetic resonance, optical) are considered and optimized for each application and greater consideration given to simultaneous diagnostic and therapeutic targeting agents. Coordination of such activities could be promoted by funding bodies.

5. Conclusion

In summary, it is clear that imaging has an integral role in drug development, but its application is dominated by limited therapeutic applications and structural-based endpoints that lack molecular specificity to optimally support early drug development. The increased use of molecular imaging methods able to provide the best support adds complexity and cost that in some cases may impede progress. There is a need to better define the value proposition that molecular imaging brings to drug development (across multiple therapeutic areas) in order that the appropriate level of investment can be accessed. It is clear that no one institution can implement all the molecular imaging strategies required for drug development; rather a networked, collaborative approach that is nimble and able to rapidly respond to new challenges will be required in the future to help provide the infrastructure and facilitate the widespread use of molecular imaging in drug development.

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