

Bridging the Gaps in ^{18}F PET Tracer Development

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The field of radiofluorination chemistry for ^{18}F positron emission tomography (PET) is distinctive in terms of the wide-reaching and interdisciplinary training required for its practice. Typically, the same scientists and/or research groups are responsible for all stages of progress, from fundamental method development, to translation, to clinical production of a useful PET tracer. This process is in sharp contrast to drug discovery and development in a pharmaceutical industry context, wherein a well-defined pipeline exists to bring a molecule from lead to (pre-)clinical candidate. We argue that the lack of a similarly well-defined pipeline creates gaps in ^{18}F PET tracer development, between innovation and clinical application. In recent years, a sharp rise in new method development for ^{18}F radiochemistry has illuminated these gaps and the need to create new bridges in order to make clinical advances. In this Perspective we examine, from the viewpoint of chemists, some of the problems in ^{18}F PET tracer development and implementation, and possible solutions that may help to accelerate progress.

Over the past decade, organic chemistry research has led to significant advances in fluorination chemistry.¹⁻⁵ While potential applications in positron emission tomography (PET) are often cited as a motivation for fluorination research in synthetic chemistry,⁶⁻⁹ many new reactions are never adapted to fluorination with the radioisotope ^{18}F , let alone translated to radiotracer development for PET. In this Perspective, we discuss the gaps that exist in the ^{18}F PET tracer pipeline, from fundamental method development through clinical implementation. For the majority of the fundamental advances in radiofluorination chemistry that have occurred in recent years, the path to clinical use or clinical research use is not clear; as an unfortunate consequence, it is difficult to measure the value of many new radiofluorination methods. However, this does not mean that fundamental advances in radiofluorination methodology lack value, and indeed we believe the recent proliferation of new methods is a positive development that, given sufficient time, will ultimately expand the chemical space available for clinical ^{18}F PET tracer production. We wish to provide a perspective here that appropriately distinguishes between fundamental innovation and practical use, and outlines a strategy to accelerate the process of bridging the gaps that exist in PET tracer development. A number of recent reviews have addressed the special concerns that are involved in translating a new fluorination reaction to a radiofluorination reaction, as well as current limitations in what types of substrates and functional groups can and cannot be labeled with ^{18}F .⁷⁻⁹ We support the analysis of these reviews and do not intend to rehash the information contained in them, but rather to address a different point that is only beginning to gain attention in the community:¹⁰ how to accelerate the connection between recent fundamental advances in radiofluorination and real clinical or clinical research needs.

At the outset, we would also like to clarify some terminology that is potentially confusing in a conversation between synthetic organic chemists and radiochemists. First, the term “target” is often used in organic chemistry parlance to refer to a particular molecule that one is trying to make, such as a synthetic target. When talking about radiochemistry and clinical imaging, however, “target” is used to refer to an imaging target, such as a particular protein or receptor. In this Perspective, we will use “target” in the clinical sense, and distinguish molecular synthetic targets using language such as “candidate tracer molecules.” Along these same lines, it is important to distinguish that the process of radiolabeling a small molecule, injecting it into a human or animal model, and performing a PET scan is not limited to only one purpose. For example, radiolabeling a known drug molecule and performing an imaging study will generally provide information about the molecule itself (pharmacokinetics, brain penetration, etc.). On the other hand, a radiotracer that is meant to engage a specific target will provide information about that target and potentially about other drug molecules binding to the same target. Finally, we want to make clear that the term “clinical” is often used to describe imaging in humans, but we note that “clinical” is not synonymous with “diagnostic.” Clinical research in humans is fueled by radiotracer development toward novel targets (see above); such clinical research is highly valuable, for example, to improve the success rate of central nervous system (CNS) drug development,¹¹ even though it does not necessarily lead to a new diagnostic or routinely prescribed clinical scan.

The ^{18}F PET “Pipeline”

Through our groups’ own work in developing ^{18}F radiochemistry over the past decade, we have begun to experience first-hand the hurdles and gaps that exist in the ^{18}F PET tracer development “pipeline.” One striking feature of most academic PET

research centers is that, in general, one group or team is responsible for all aspects of progress. This includes fundamental method development, automation and scale up to a clinically-relevant dose, and ultimately proof-of-concept and preclinical imaging studies, including the requisite *ex vivo* or biological experiments. In many ways this self-sufficiency is a strength, but there are consequences that emerge as a result. By comparison, this lack of sub-specialization is in sharp contrast to the classical pipeline of drug development in the pharmaceutical industry, in which many separate teams with different specializations are responsible for different stages of drug development, creating a smooth pathway all the way from medicinal chemistry and method development to commercial-scale production. While we recognize that academia and industry have somewhat distinct missions, and that a direct one-to-one comparison is not possible, examining the radiotracer development pipeline in contrast to the drug development pipeline in pharmaceuticals development is conceptually illuminating. One way to bridge the gaps in ^{18}F PET tracer development may be to recognize missing human roles: for example, the position of “process chemist” in drug development has the critical responsibility of making a given synthesis scalable and economically viable. Because process chemists exist, medicinal chemists have the freedom to synthesize molecules with fewer practical constraints, so a small amount of material can be evaluated to determine if the molecule has drug potential. This lack of constraints leads to greater molecular diversity, with the recognition that most of the molecules evaluated will not become drugs; thus, there is no reason to invest heavily in “practicality” for each molecule. We would propose that researchers with an analogous “process chemistry” expertise are needed in radiotracer development, but currently this role is ill defined and uncommon in the field. The solution to this problem will be multi-tiered, but must begin with changes to how radiochemistry

training is conducted. When appropriate, student or postdoctoral trainees in a method development program should be given the opportunity to apprentice in a routine production environment, in order to understand the technical aspects of radiotracer production. This type of training would then allow such researchers to contribute to the technical advances needed to connect method development and radiotracer production. In our opinion, there are currently too few mechanisms in place to facilitate the training of qualified researchers who are able to translate a new method from the fundamental stages through robust and scalable tracer production for clinical (research) use.

The Value of Fundamental Development

The existence of gaps in the ^{18}F radiotracer development pipeline has also resulted in somewhat lopsided progress in recent years. New synthetic method development has proliferated, without commensurate progress in clinical PET imaging. This, of course, raises questions in the community regarding the value of these method developments. If these methods are indeed valuable, how and when are we going to see and make use of that value? One honest answer is that it is simply too soon to tell, and that it is unfair to judge a newly developed method too soon, especially in comparison to older methods that are already established in the clinic. We argue, however, that the fundamental lack of diverse methods for ^{18}F labeling (and thus increased diversity in molecules evaluated as radiotracers) necessitates new method development in a way that is initially decoupled from eventual clinical use. The radiochemical space accessible for ^{18}F labeling is still quite restricted, and the clinically-relevant portion of this space is much smaller yet. New method development—even if not immediately connected to clinical use—not only expands the overall radiochemical space, but provides areas for the clinically relevant space to

expand into (Figure 1). Subsequent expansion of the clinically relevant radiochemical space must then be actively pursued, such as through adoption of new methods by PET practitioners and by technical advances that can make new methods compatible with scale up and automation needed for clinical dose production. We also suggest that method development targeting previously inaccessible ^{18}F -labeled functional groups can be used as a starting point to reevaluate what may be considered a potentially relevant tracer molecule. Just as the exploration of three dimensionality and degree of saturation has led to a reconsideration of what makes a molecule “drug-like,”^{12,13} increased diversity in ^{18}F -labeled molecules may expand the community’s perception of clinically relevant radiochemical space.

The primary goal of recent method development has been to expand the radiochemist’s toolbox. Currently an unproductive cycle exists, in which candidate tracer molecules are restricted to molecules that we can already label with existing ^{18}F radiochemistry. What this means is that method development cannot be driven by the desire to label a particular molecule, unless that molecule already has established value as a radiotracer. Of course the ability to more efficiently label a desired radiotracer is valuable, and recent method development has certainly made strides in this regard. But one key hurdle is the ability to rapidly label and evaluate new potential tracer candidates, and this is where fundamentally new method development is of value. In this regard, it is therefore important to recognize that substrate scope is not necessarily relevant, and a new method only needs to provide access to one useful tracer molecule to be of immense value. Furthermore, a substrate table in a radiochemistry method paper may not contain any relevant radiotracer molecules, and this is not an inherent problem. It may take a number of years and significant effort before a new method proves useful in enabling access to a valuable tracer candidate.

Moving the Field Forward

Looking forward, it is clear that recent fundamental research in radiofluorination methodology is starting to have a positive impact on ^{18}F PET. Iterative improvements in both conceptual and practical developments are beginning to provide improved access to a wider variety of ^{18}F -labeled small molecules. But, the recent wave of progress in method development has revealed serious gaps along the path to clinical implementation. As an outlook, we suggest here a few ways to potentially accelerate progress for ^{18}F PET imaging. First, it is essential to recognize that development in radiofluorination for PET has distinct stages, and that not all fundamental method developments need to have an immediate clinical connection in order to be valuable. Furthermore, even research programs focused on imaging have different stages or goals, including “biology-focused” imaging to learn about a target or the pharmacokinetics of a compound in development, versus diagnostic imaging in the clinic. Another significant problem in method development for ^{18}F PET is that many potentially useful new methods lack a suitable radiotracer candidate molecule to demonstrate value, which relates to the problem of our existing library of “useful” radiotracers being limited to things that we can already label. There is a shortage of good and readily-available information about biological imaging targets that lack a suitable radiotracer, which makes “target-driven” method development for radiofluorination inherently difficult. The development of a repository or database for imaging targets (and potential radiotracer candidates) would be immensely useful in bridging the gap between method development and radiotracer development. Such a development would also help bridge the disconnect between ^{18}F -labeled molecules that chemists think may be useful to make and radiotracers that end users in a clinical setting wish to have available. Along these lines, the establishment of strong

collaborations between radiochemists and nuclear medicine physicians can help to accelerate progress.

Many of the current gaps represent missing human roles, and changes in the infrastructure of ^{18}F PET research—beginning with how radiochemists are trained—will be important in the future. For example, in an academic setting, most research is performed by graduate students or postdoctoral researchers, with significant pressure to produce results in a limited amount of time. Most of these trainees do not spend the time learning clinical dose-scale radiotracer production, simply because this use of time does not typically result in “publishable” work as compared to time spent on new method development on a proof-of-concept scale. Concerted efforts to develop the technical aspects of production that need to accompany a new method are much less common.¹⁴ An unanswered question that results from this situation is: who is supposed to help end users in a clinical PET context? Pushing a new method from an academic lab to a robust, automated method for routine use is time- and labor-intensive, and this is currently not a well-defined role. Training (and then employing) researchers with appropriate expertise will be necessary in order for the field to progress. We recognize that reorganization of infrastructure and resources in ^{18}F PET research facilities may be needed, but fundamentally the solution must begin with a change to how radiochemists are trained in the early stages of their careers. A practical development in this regard is the recent improvement in radiochemistry capabilities of academic research groups, which is beginning to help reshape early-career training. Postdoctoral positions that focus on production-scale radiofluorination (after graduate training in method development, for instance) are one potential opportunity to produce valuable Ph.D.-level scientists with the specialized training necessary to facilitate the translation of new methods. A postdoctoral researcher in

such a role would also be well-positioned to focus on expanding the technology available for radiotracer production, for example through collaboration with groups that develop new technology for synthesis (flow chemistry, etc.). A variety of research groups focus on reaction automation for organic synthesis, and collaborative efforts involving radiofluorination could be a fertile testing ground for new automated reaction systems. Increased interaction between academia and industry (such as through direct collaborations, consortia, etc.) may also be beneficial to accelerate progress, for example to ensure that new methods are applied to relevant drug-like molecules being used in medicinal programs.¹⁵ Finally, such interdisciplinary efforts could be facilitated by focused workshops at conferences, to build bridges between technological development and radiochemistry method development. Future collaborative efforts towards ^{18}F PET tracer development will need to include a wide range of expertise, including a new generation of skilled radiochemists (as discussed herein), medicinal chemists, modelers capable of detailed analysis of PET scan data including kinetic analysis, and doctors involved in nuclear medicine. These suggestions are only intended as a starting point for further discussion, not a set of directives or a comprehensive plan; but, we feel that opening such a discussion in the field is important, and will hopefully lead to changes in the overall paradigm for research in ^{18}F PET tracer development.

Conclusions

We have attempted here to address some of the broad, unmet challenges that we perceive in the field of ^{18}F fluorination for PET. The development of new radiofluorination methodology by academic research groups has paved the way for major advances in ^{18}F PET tracer synthesis, but more work is needed. In our opinion, a major key to advancing PET through modern fluorination chemistry is recognizing

and bridging that gaps that exist in the radiotracer development “pipeline.” While it is beneficial in many ways for method development to be independent of technical concerns, there is a lack of suitable research infrastructure to connect new methods to radiotracer production for clinical or clinical research use. Making changes to how radiofluorination research is conducted will be necessary to accelerate progress, beginning with how chemists in the field are trained. More time will be needed, but we feel that—with the right focus— ^{18}F fluorination research is poised to make a real impact on PET imaging in the near future.

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Figure 1. Visual depiction of chemical space for ^{18}F radiochemistry. New developments are needed that simultaneously expand the accessible chemical space overall, and expand the clinically relevant chemical space through both fundamental and technical advances. We feel that a well-defined pathway bridging new method development to practical development for routine clinical use does not currently exist, and that this is a key bottleneck preventing new ^{18}F radiochemistry methods from having a meaningful impact in the PET clinic.