Radionuclide Imaging for Neuroscience: Current Opinion and Future Directions

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Abstract
This meeting report summarizes a Consultants Meeting that was held at International Atomic Energy Agency headquarters in Vienna to provide an update on radionuclide imaging for neuroscience applications.

Keywords
advances in PET/SPECT Probes, clinical translational molecular imaging, imaging in neuroscience, neuroscience, PET, SPECT

Introduction
The International Atomic Energy Agency (IAEA) helps its Member States to benefit from a wide range of applications of nuclear science and technology for peaceful purposes. Use of nuclear technology for medicine constitutes a major application, and IAEA works with a focus on deploying technology and medical procedures using radiation and isotopes to improve global health. One such application is noninvasive nuclear diagnostic imaging, which is an indispensable tool in oncology, cardiology, and neurosciences.

The IAEA organizes Consultant Meetings (CMs), Technical Meetings (TMs), Training Courses, and Research Coordination meetings, per IAEA-approved procedures. For example, CMs are held with a limited number of experts in the field and are conducted for various purposes including IAEA document preparation, design of specific programs, obtaining recommendations for future IAEA activities, and so on. A CM was held at IAEA headquarters in Vienna, February 24-27, 2020, to obtain updates on radionuclide imaging for neuroscience applications, which is helpful for deciding future activities for IAEA Member States related to this topic. During the CM, different aspects of neuroimaging developments were discussed, which are summarized in this report for the interest of researchers in the field.

For the purposes of this report, the term neuroscience encompasses psychiatry, neurology, neuro-oncology, and brain-peripheral interactions (systems biology). The group of experts discussed the current state of the art of radionuclide imaging in neuroscience and its potential within the global imaging market. This report summarizes the discussions on key neuroimaging applications and considerations regarding radiotracer design and development, including target identification and validation, radionuclide selection, radiochemistry methods, preclinical evaluation (in vitro and in vivo), and clinical translation (regulatory considerations). The report also provides some recommendations for future priority areas, challenges, and opportunities for the field; how to capitalize on potentially disruptive technologies; and means for dissemination of these

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techniques across the globe. Detailed review of the radiotracers used in preclinical and clinical studies in neurosciences is not the scope of this report.

Radionuclides and Radiotracers: Application Areas for Neuroimaging

The group reflected on the current state of the art regarding radionuclides and radiopharmaceuticals used for imaging of the central nervous system (CNS). The most common positron emission tomography (PET) radionuclides are carbon-11 ($t_{1/2} \approx 20$ minutes) and fluorine-18 ($t_{1/2} \approx 110$ minutes), while single-photon emission computed tomography (SPECT) is still dominated by technetium-99m ($t_{1/2} \approx 6$ hours) and iodine-123 ($t_{1/2} \approx 13$ hours). More recently, there has been increasing interest in exploring the additional PET radionuclide gallium-68 ($t_{1/2} \approx 68$ minutes) and other radionuclides with relatively long half-lives such as iodine-124 ($t_{1/2} \approx 4$ days), copper-64 ($t_{1/2} \approx 13$ hours), and zirconium-89 ($t_{1/2} \approx 78$ hours) due to their compatibility with the biological half-lives of larger molecules of interest, including peptides, antibodies, engineered fragments, and cells.

In the context of radiopharmaceuticals, $2-[^{18}F]$fluoro-2-deoxy-D-glucose ($[^{18}F]$FDG) remains the mainstay of clinical neuroimaging using PET (Figure 1). [$^{99m}$Tc]HMPAO and [$^{123}$I]DaTsc can (Figure 1) are commonly used SPECT tracers to assess cerebral blood flow in various neurological diseases and for imaging transporters to distinguish Parkinson’s disease from essential tremor, respectively (Figure 1). Outside the clinical setting, new research radiotracers are being developed for numerous neuroimaging applications. Such radiotracers have the potential to provide noninvasive information on the molecular underpinnings of the CNS in health and disease, currently not possible using in vitro techniques or other imaging methodologies. Radionuclide imaging is now commonly used to study target engagement, dose response, pharmacokinetic (PK)/pharmacodynamic (PD), and disease/biology, in addition to diagnosis, patient stratification, monitoring treatment response, and follow-up to de-risk drug development decision-making. For example, these techniques are being used in the following diseases, behaviors, and conditions:

- mood disorders (depression, bipolar disorder, etc) and suicide prevention,
- schizophrenia,
- autism spectrum disorder,
- addictions (opioids, cannabinoids, eating disorders, social media, etc),
- traumatic brain injuries and comorbidities,
- stroke,
- epilepsy,
- neurodegenerative diseases,
- neuroinflammatory diseases,
- peripheral brain connections (gut–brain, heart–brain axis),
- neuro-oncology,
- pain,
- behavior studies (eg, aggression), and
- gender studies (eg, postpartum depression).

Generally, the need for specific imaging biomarkers of neurodegenerative diseases coupled with expanding multisite clinical studies (eg, the Alzheimer’s Disease Neuroimaging Initiative) and therapeutic trials (eg, with aducanumab, solanezumab, and bapineuzumab [Figure 2] or BAN2401) has sparked the widespread use of PET for neuroimaging. Additionally, PET neuroimaging applications will likely further increase due to the growing aging population, improvements in access to health care, and the expanding awareness and recognition of mental health illnesses. This is reflected by the growing numbers of PET centers working in the neurosciences and highlights the need for training the next generation of radiopharmaceutical scientists.

Reimbursement from health care providers for neuroimaging applications is limited and geographically heterogeneous. Moreover, the acquisition of neuroimaging data is resource intensive due to complex and expensive
infrastructure, highly qualified personnel, increasing regulatory demands, and the dependency of the field on government, private foundations, or industry-sponsored research. Notably, partnerships between academia and the pharmaceutical sector have been mutually beneficial. While radiochemistry laboratories in hospital settings generally lack some key resources that are available to the pharmaceutical sector (eg, personnel, funding, and medicinal chemistry capabilities), they do have access to patient populations and expertise for conducting such studies.

In general, these discussions revealed multiple important regional and cultural differences in the neuroimaging community, including:

- access to radionuclide neuroimaging technology,
- different health-care systems,
- inconsistent regulatory frameworks,
- varying terminology and practices between brain health disciplines,
- cultural stigmas around mental health, and
- susceptibility, polymorphisms, and metabolism across different ethnicities (eg, translocator protein 18 kDa [TSPO] polymorphism is generally not considered among Asian populations).

**Important Strategies for CNS Radiotracer Development: Bench to Bedside**

Neuroimaging applications are intimately linked to the availability of radiotracers. The development of clinically useful radiotracers depends on unique selection of appropriate biological targets, design, and selection of promising candidate molecules and radiolabeling strategies, in vitro and in vivo preclinical evaluation of candidate radiotracers, and clinical applications (Figure 3). In the past few decades, important developments have taken place in all of these fields, and many new radiotracers are being evaluated for imaging neuroreceptors, neurotransmitter systems, misfolded proteins, and so on. Future challenges and opportunities in these areas are highlighted in this report.

While numerous radiotracers exist to probe different aspects of the CNS in health and disease, efforts toward the development of imaging agents for certain key targets are still needed (eg, TDP43 aggregates, α-synuclein, 3R- and 4R-tau protein, soluble β-amyloid, oxytocin, activated glia beyond TSPO). When designing such radiotracers, several important parameters have emerged that should be considered in order to maximize the chances of successful translation:

**Target Selection and Validation: Is the Target Appropriate and Accessible?**

Arguably, the most important and time-consuming step is to identify and validate an appropriate imaging target to answer a given biological question of interest. The major reasons for failure of CNS radiotracers include poor brain access/accumulation in regions of interest and high nondisplaceable binding. Early assessment of the tractability of a target or a radiotracer lead candidate (eg, appropriate target selectivity, abundance, and accessibility [membrane, intracellular, and nuclear]) is often guided by data obtained from techniques such as immunohistochemistry, binding assays, and autoradiography using

![Figure 2. [11C]PiB PET images from patients treated with bapineuzumab and those given placebo (reprinted from Rinne et al with permission from Elsevier).](image-url)
animal and human tissues. In general, the most successful CNS PET imaging targets (receptors, enzymes, and transporters) are expressed at a concentration ($B_{\text{max}}$) greater than $\sim 10$ nM. While imaging targets at lower concentrations are possible, achieving the required physicochemical and pharmacological parameters may make tracer design challenging.\(^7\)-\(^9\) Different considerations may apply to other classes of imaging targets (eg, highly abundant protein aggregates, ion channels and G-proteins that exist in multiple conformations, and so on).

**Design and Synthesis of New Tracers**

Once the target has been identified and validated, a set of pharmacological and physicochemical properties have to be fulfilled in the selection of radiotracer candidates (eg, lipophilicity, target affinity, selectivity, and molecular weight).\(^9\) Incorporating a radionuclide without negatively impacting any of these properties must be confirmed. For example, fluorinated isomers are known to have dramatically different biological behavior in drug molecules—commonly referred to in medicinal chemistry as the “fluorine effect”.\(^10\) For example, this has been observed for 2-, 5- and 6-[$^{18}$F]FDOPA; each derivative having distinct pharmacological and PD behaviors (Figure 4).\(^11\) Moreover, the position of the label needs to be considered to avoid troublesome radiolabeled metabolites, as these can confound image analysis and quantification.\(^12\) In carbon-11 radiochemistry, the position of the label may also be critical. A classic example is [$^{11}$C-O-methyl]WAY-100635, which resulted in a brain-penetrating radiometabolite. The generation of the confounding-labeled metabolite could be avoided by labeling the molecule in a different position, that is, [$^{11}$C-carbonyl]WAY-100635 (Figure 5).\(^12\),\(^13\)

A major challenge in radiochemistry is the limited choice of reagents (or labeled fragments) and synthetic approaches for the preparation of novel radiotracers. Robust, reliable, and automated methods for incorporation of short-lived radionuclides into small molecules are required for neuroimaging. To date, most small molecules cannot be labeled with PET radionuclides without derivatization of the lead compounds. In the field of fluorine-18 labeling, two examples that attempt to address this issue include copper-mediated radiofluorination and the use of iodonium ylides to label nonactivated aromatics (Figure 6). Both strategies have recently been translated for human PET imaging studies.\(^14\),\(^15\)

**Higher Throughput Syntheses and Evaluation**

Higher throughput development (eg, “library radio-synthesis”\(^13\)) is needed as PET tracer discovery still remains a long, arduous process that entails a degree of trial and error. One such strategy is [$^{11}$C]CO$_2$ fixation (Figure 7), which takes advantage of the same combinatorial chemistry strategies to synthesize limitless arrays of [$^{11}$C]-carbamates and [$^{11}$C]-ureas via reaction of amines and/or phenols. Another advantage of [$^{11}$C]-carbonylation (via [$^{11}$C]CO$_2$ fixation, [$^{11}$C]CO, [$^{11}$C]COCl$_2$, etc) is that $>70\%$ of pharma pipelines for CNS therapeutics can be accessed in contrast to $<20\%$ of compounds via [$^{11}$C]-methylation.\(^16\),\(^17\) [$^{11}$C]CO$_2$
fixation has also been applied to the preparation of fluorinated lead molecules, thereby obviating the need for time-consuming $^{18}$F-labeling of individual compounds. Radiolabeled building blocks and fragments can be used to generate a larger number of tracers and rapidly optimize the physicochemical and pharmacological profiles of prototype molecules, thereby increasing the chances for successful translation. For example, this strategy has been used with radiolabeled benzaldehydes for reductive amination.\textsuperscript{18} Increased throughput has also been achieved in preclinical PET scanning where multiple rodents can be imaged simultaneously to guide radiotracer development by quickly assessing brain penetration and PK data.\textsuperscript{19,20}

Prior to embarking on a new radiotracer development campaign, the following criteria\textsuperscript{9} should be considered:

**Design criteria**
1. Must have an appropriate target to investigate biological question of interest
2. High in vitro affinity and selectivity for target
3. Able to be radiolabeled reliably
4. Capable of accessing the target
5. Low nondisplaceable binding

**Test criteria**
1. Suitable signal to noise ratio (S/N) in vivo
2. Appropriate in vivo pharmacokinetics
3. Appropriate in vivo distribution, specificity, and selectivity
4. Negligible labeled metabolites in regions of interest
5. High sensitivity toward target
6. Does not perturb the system under investigation
7. Suitable toxicology and dosimetry
8. Appropriate controls

**Translation**

The translation of radiotracers for human use is resource and time intensive. Requirements for translation of a new radiotracer include toxicity testing; dosimetry; a validated synthesis according to current Good Manufacturing Practice (cGMP) that includes product specifications, control of starting materials, preparation and testing procedures; and lastly, ethics committee and regulatory approvals. Legislation for radiopharmaceuticals intended for human use lists the requirements for production, quality assurance, and distribution. GMP regulations are intended to ensure that materials used in the manufacture of radiopharmaceuticals are appropriately tracked and controlled and that formulated products have appropriate identity, quality, and purity characteristics and are suitable for human use.

When translating novel neuroradiotracers to humans, it is important to keep in mind the following potential issues stemming from species differences:

1. Metabolism
2. Drug efflux pumps
3. Plasma protein binding
4. Polymorphisms
5. Tissue kinetics
6. Limitations of animal models
7. Target expression levels
8. Sequence homology
9. Anesthesia

**Future Possibilities**

The group speculated how the field of neuroimaging may change in the coming years and how disruptive technologies (eg, artificial intelligence [AI], radiochemistry, scanner innovations, etc) may cause us to reexamine how CNS imaging studies will be performed in the future. We envision that such technologies are likely to make neuroimaging and precision health more accessible to a larger subset of the general population across the globe.

By way of example, a new generation of total body PET (TBP) scanners have recently been developed that are a potentially disruptive technology. Total body PET scanners were initially built for whole-body nonhuman primate imaging, but further development of the technology has led to recent
introduction of the first TBP scanners for human imaging (Figure 8). The clinical scanners have up to 2-m fields of view, compared with approximately a 20-cm field of view for the current generation of scanners. The increase in solid angle provided by TBP scanners is providing 4- to 5-fold gains in scanner sensitivity, and with further improvements, TBP scanners are projected to provide a 40-fold gain in sensitivity and 6-fold increases in S/N ratio. The new opportunities arising from this development are multi-fold; for example, TBP may enable practitioners to scan patients:

- in shorter time periods (using the current standard radiotracer dose),
- at the same time—that is, simultaneous multipatient imaging studies whereby patients could be positioned, for example, head to head,
- for extended time periods (using the current standard radiotracer dose),
- with several-fold lower radiation and mass doses,
- dynamically, enabling the acquisition of whole-body pharmacokinetics, and
  - allow the study of different body system interactions (eg, gut–brain or spleen–brain dynamics in the context of neuroinflammatory diseases, and so on),
  - enable image-derived input function, and
  - test new mathematical models for possible noninvasive metabolite correction by acquiring liver, bladder, kidney, and blood pool kinetics.

In addition to the impact on clinical scanning, TBP may also have implications for the traditional satellite distribution model for radiotracers. Specifically, the increased sensitivity of scanner technology such as TBP could allow a wider distribution range for established radionuclides such as fluorine-18. The use of smaller amounts of injected activity also potentially enables routine distribution of shorter-lived radionuclides such as carbon-11. These developments may expand access to a greater range of tracers and radionuclides worldwide; however, widespread adoption of TBP is contingent upon affordability and clinically unprecedented neuroimaging applications.

Other Opportunities and Challenges

Radiochemistry

- Education and training: shortage of people with expertise in carbon-11 and fluorine-18 neuroradiotracer development.
- Fluorine-18 chemistry: universal methods to label nonaromatics with [18F]fluoride, labeling of polyfluorinated groups (eg, −CF₃) in high molar activities, robust C-H and C-OH radiofluorination, will continue to intrigue chemists.
- Carbon-11 chemistry: Specialized apparatus, niche methodologies, complex and costly infrastructure are still required for carbon-11 labeling of basic functional groups including ¹¹C-labeled amines.
- Chelation chemistry: Using [18F]AIF, gallium-68, technetium-99 m, and so on, for neuroimaging and achieving reasonable brain penetration of radiometal-based tracers (small and large molecules) is yet to be fully exploited.
- Solid-phase chemistry: These methods remain in their infancy for radiopharmaceutical production.
- Purifications: Rapid and efficient alternatives to HPLC are required, which may include optimized solid-phase extraction regimens.

Key Needs to Streamline Tracer Development/Success

- Methods to make radiotracer discovery more efficient: higher throughput radiotracer development and preclinical evaluations, reduced cost and burden for toxicity studies, and faster and facilitated regulatory filings.
- Better models to predict successful radiotracer candidates and understand the molecular basis of nondisplaceable binding.
- Optimal animal models to predict disease.
Facilitating blood–brain barrier transport of radiotracers (blocking of efflux pumps, focused ultrasound-mediated transport, intrathecal injections, and so on).

- Simplifying quantification, including kinetic modeling, automating radiometabolite analyses, and so on.
- Realizing the promise of pretargeting methodologies.
- Increased access to human CNS tissues.

**Technology**

- Positron emission tomography-MR for neuroimaging has not yet fulfilled its potential (e.g., applications beyond pediatric and pain imaging, and so on).
- Miniaturization of radiochemistry apparatus (including microfluidics, microwave, electrochemical, photochemical, ultrasound assisted reactions, etc) and cyclotrons/generators could enable widespread production and distribution of neuroradiotracers.
- Fully automated QC systems are needed to save space, reduce operator errors, and streamline the pre-release testing of radiopharmaceuticals.
- Harnessing the potential of neuroinformatics; big data and AI is in its infancy.
- New radiotracers and high-resolution brain-SPECT scanners that allow for quantitative imaging are being proposed.

**Other Observations**

- Shifting priorities and cyclical changes of several big pharmaceutical companies from neurosciences to other therapeutic areas are observed which make it necessary to regularly appraise the suitability of available labeling paradigms and strategies.
- Increased costs associated with GMP, acute toxicity, and regulatory compliance have slowed first-in-human translation.
- Careful management of the cost models of radionuclide-based imaging is required (including regulatory, infrastructure, staffing, etc) to guarantee widespread use and accelerated use of neuroradiotracers.
- Limited reimbursement of CNS radiotracers restricts their clinical application.

**Conclusion**

Concurrent with technology developments, there has been a steady growth in the number of novel radiotracers for neuroimaging applications over the past few decades. New radiotracers for established targets such as receptors, transporters, enzymes, and protein aggregates continue to be reported, typically with the goal of further improving imaging properties over existing radiotracers. While these radiotracers have provided unprecedented insights into the pathophysiology of CNS diseases and disorders, first-in-class radiotracers for currently elusive imaging targets (e.g., TDP43 aggregates, α-synuclein, 3R- and 4R-tau protein, soluble β-amyloid, oxytocin, activated glia beyond TSPO) are eagerly awaited.

Historically, brain imaging agents have been small molecules, while macromolecules and biologics have been confined to peripheral (non-CNS) applications. However, recent efforts demonstrating brain penetrating radiolabeled antibody fragments for amyloid imaging suggest an emerging role for biologics in functional neuroimaging. Realizing CNS delivery of macromolecules, biologics (e.g., peptides, proteins, antibodies), and cells will open new avenues for inquiry in the future—potentially improving the specificity and sensitivity of neuroimaging.

Building on the growing arsenal of radiotracers for brain PET and SPECT imaging, the last decade has seen the application of neuroimaging to precision medicine. Specifically, PET imaging has been utilized for patient stratification in clinical trials, predicting response to experimental therapies and subsequent monitoring to confirm expected response to therapy. This is particularly valuable in neuroscience where tissue sampling within the CNS is extremely difficult compared to, for example, the routine biopsies performed in oncology. Reflecting this, pharmaceutical companies are utilizing imaging technologies to support therapeutic clinical trials in neuroscience, such as the use of amyloid and tau PET in clinical trials of experimental therapies in Alzheimer disease and related dementias. We expect these applications and aforementioned disruptive technologies to continue to shape the future of neuroimaging.

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