Brief Report

Molecular Imaging
Volume 23(1): 1–15

DOI: 10.1177/15353508241245265
journals.sagepub.com/home/mix

Combining Nuclear Medicine With Other Modalities: Future Prospect for Multimodality Imaging

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Abstract

This meeting report summarizes a consultants meeting that was held at International Atomic Energy Agency Headquarters, Vienna, in July 2022 to provide an update on the development of multimodality imaging by combining nuclear medicine imaging agents with other nonradioactive molecular probes and/or biomedical imaging techniques.

Keywords

molecular imaging, multimodality imaging, nuclear medicine, hybrid Imaging

Received December 21, 2023; Accepted for publication March 19, 2024

Introduction

The International Atomic Energy Agency (IAEA) works to ensure its member states can capitalize on a wide range of nuclear science and technology capabilities for peaceful purposes. Application of nuclear science to medical applications constitutes a major part of IAEA's mission, with a careful focus on deploying technology utilizing radioactivity and isotopes, along with ancillary technology, to improve global health and well-being. One such application is noninvasive nuclear diagnostic imaging, and related molecular imaging techniques, which have become indispensable tools in oncology, cardiology and neurology research as well as clinical care.

The IAEA organizes different types of meetings, the Consultancy Meeting (CM) held at IAEA headquarters in Vienna, 5-8 July 2022, took stock of the current state-of-the-art around the development of molecular probes for multimodality imaging, with the goal of distilling potential future activities for IAEA member states related to this topic. The purpose of the CM was to (i) obtain an overview of the status and trends of multimodal imaging applications involving nuclear techniques like single photon emission computed tomography (SPECT) and/or positron emission tomography (PET) modalities in both the preclinical and clinical setting, (ii) discuss future potential and trends in this area, including, but not limited to, development of molecular probes for multimodal imaging, and (iii) to obtain recommendations for agency activities in this area for the benefit of member states. During the CM, numerous different facets of multimodal imaging developments and their relation

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to nuclear science and applications at the IAEA were discussed and captured. The results are highlighted in this report for the benefit of researchers in the field.

For the purposes of this report, the following terms were employed:

1. *Multimodality (or multimodal) imaging*—encompasses the integration of two (or more) different types of imaging tools to provide complementary information (eg, PET-magnetic resonance imaging (MRI), PET-magnetic resonance spectroscopy (MRS), qualitative and quantitative, etc);
2. *Multiparametric imaging*—using the same modality, but in different ways (eg, chemical exchange saturation transfer (CEST) and T2 MRI; B and M mode ultrasound);
3. *Multiplex imaging*—resolving several channels (eg, discriminating energies) to interrogate more than one target using the same modality (eg, CEST over several chemical shifts; different fluorescent probes; mass cytometry).

The CM primarily focused on the combination of nuclear medicine imaging agents with other nonradioactive molecular probes and/or biomedical imaging techniques. A combination of multiple imaging modalities not involving PET or SPECT was not considered, although this is an active area of research.[1] The group of experts discussed the state-of-the-art in development of molecular probes for multimodality imaging, as well as challenges and opportunities for such hybrid imaging techniques in the global imaging community. This report summarizes the discussion, providing an overview of the field and summarizing the groups' thoughts about multimodal imaging, including access considerations, available instrumentation, design and development of multimodal imaging probes (including production methods, current good manufacturing practice (cGMP) considerations, and regulatory oversight), and potential applications that might particularly benefit from multimodal imaging, such as simultaneous interrogation of two or more biological systems. The report also provides some recommendations for priority areas in this field for future IAEA activities (and the greater imaging community), thoughts on challenges and opportunities for multimodal imaging, including how to capitalize on the benefits of the technology and means for disseminating practical information to imaging scientists all over the world.

A detailed review of the many preclinical and clinical applications of multimodality imaging is not the intent of this meeting report, and readers are instead pointed to reviews on the synthesis[2] and applications[1] of multimodality imaging agents.

General Considerations

The group of consultants considered the following imaging techniques for multimodality imaging:

Nuclear Medicine (PET and SPECT)

Nuclear medicine is a form of functional molecular imaging that employs radiopharmaceuticals labeled with PET-, SPECT-, or therapeutic (radiotherapy) radionuclides. Imaging of radiotherapeutics is a growing area and, while it has yet to be incorporated into multimodal imaging technology to the best of the group's knowledge, this application is anticipated in the future.

Magnetic Resonance Imaging

MRI is a collection of medical imaging techniques that employ a magnetic field and computer-generated radio waves to create anatomic images. The functional variant of MRI (fMRI) is primarily used for brain imaging, where the detection of changes associated with blood flow can be used to study brain activity. More recently it has also been employed in other organs such as the heart and pancreas. There are many developments that continue to expand the utility of MRI. For example, CEST is an MRI technique that enables the detection of imaging probes capable of exchanging protons with surrounding water molecules at concentrations that are too low to be detected using standard MR imaging.

Computed Tomography

Computerized tomography (CT) is a diagnostic imaging technique that utilizes *x*-ray technology to produce anatomical images. A series of *x*-ray images is taken from various angles and then assembled into a 3D image by computer (tomography).

Optical Imaging

Optical imaging is a group of imaging techniques that employ light to interrogate molecular function in the body. Optical imaging techniques have primarily been utilized in preclinical studies but are beginning to enter clinical trials. Optical techniques include:

- Near-infrared fluorescence imaging
- Bioluminescence imaging
- Photoacoustic imaging
- Optical microscopy
- Diffuse optical tomography
- Molecular endoscopic imaging

Ultrasound

Ultrasound imaging uses sound waves to either generate anatomical images (diagnostic ultrasound) or to interact with tissues in the body such that they are either modified or

destroyed (therapeutic ultrasound). Diagnostic ultrasound can be further classified as anatomical and functional. Anatomical ultrasound produces images of internal organs, while functional ultrasound combines anatomical images with information acquired during the scan (eg, blood velocity, tissue properties) to generate dynamic information maps.

Overview of Multimodal Imaging

During the initial discussions at the CM, it quickly became apparent that multimodal imaging is an expansive topic that includes numerous disparate disciplines. While many of the individual imaging modalities are quite advanced, combining them with one another with the intent of conducting multimodal imaging is comparatively in its infancy. Moreover, while a number of the emerging techniques are in various stages of preclinical evaluation, translation to clinical use is only just beginning for many combinations of modalities.

Laboratories conducting research in different imaging modalities are frequently housed within the same department, but may also be in different departments (eg, Radiology, Biomedical Engineering, Nuclear Engineering). In either instance, the different groups are often siloed from one another, potentially being housed in different buildings as well as attending different seminars and conferences, and there is a paucity of true multimodality research groups. Moreover, multimodality imaging groups that do exist (including those represented by some of the consultants attending this meeting) are diverse in nature and often have little in common with one another (eg, a group working on PET/ultrasound imaging requires different equipment and expertise as a group working on SPECT/MRI imaging).

With this big picture in mind, the group began by considering the state-of-the-art in multimodality imaging around the world, including access considerations, existing technology, multimodal imaging probes, their radiolabeling and pharmacokinetics, applications, regulatory and GMP considerations, challenges, future opportunities for the field. The meeting concluded with the formulation of some recommendations for future priority areas for IAEA consideration to coordinate efforts with the wider imaging community, potentially capitalize on disruptive technologies and disseminate to IAEA member states. The following key concepts emerged in the discussion, that permeates this meeting account:

- Different multimodal imaging modalities are capable of providing different information—thus the choice should be carefully made to ensure the most useful data is obtained for a given application;
- Availability of multimodal scanners varies considerably across institutions and geographical regions;
- Development of multimodal imaging probes requires a diverse skill set (eg, radiochemistry, stable labeling);
- The regulatory and cGMP considerations between modalities are heterogeneous.

When considering the combination of two (or more) imaging modalities, the team homed in on important general guiding questions that should be considered, particularly before embarking on a multimodal research project:

- Are there applications where multimodal imaging makes sense and/or is essential?
- What is the (pre)clinical question and which modalities will provide the most relevant information to answer it?
- What special imaging requirements are needed (eg, Does imaging need to be qualitative or quantitative? What are the temporal and spatial requirements? Is high sensitivity needed?)
- Should multimodal imaging be conducted with one (eg, contrast-free MR and PET) or two molecules (eg, glucose spectroscopy and FDG, which has been done in canines[3]).
- If two probes are needed, does it make sense to make a multimodal probe, or employ two (or more) individual probes? There are practical (eg, one pharm-tox study vs two) and regulatory (PET drug vs pharmaceutical cGMP) considerations tied to each probe. Is there a big enough advantage to justify a multimodal probe?
- What is the workflow for developing the needed multimodality probes?

These concepts will be further addressed below.

Access Considerations

The team also gave consideration to access considerations in the context of multimodal imaging. According to nuclear medicine databases,[4,5] 134 of 195 countries have clinical nuclear medicine facilities. However, large discrepancies in SPECT and PET camera availability between upper- and lower-middle income countries (approximately 6-fold[6]) and heterogeneous geographical distribution of cameras across individual geographic regions still limit broad global access.[6,7] Similar global disparities impact access to MRI.[8] While not all multimodality molecular imaging approaches will require nuclear medicine or MRI, the acknowledgment of such disparities is key to outlining the pathway to the broad implementation of multimodality molecular imaging clinically.

Access to infrastructure for preclinical molecular imaging continues to increase, with a compound annual growth rate of 6.2% from 2016 to 2021[9] While data on global access to preclinical imaging infrastructure is lacking, we assume that a similar heterogeneity in the geographic distribution of preclinical infrastructure exists that parallels the clinical situation. Importantly, radiopharmaceutical access, whether preclinical or clinical, will be similar due to their reliance

upon both cyclotron facilities and/or generators and specialized equipment for radiotracer production.

Where multimodality molecular imaging access is present, clinical barriers to the uptake of multimodality imaging were identified, including questions of the reimbursement of multitracer and/or contrast agent procedures, who will be allowed to read scans (eg, nuclear medicine physicians vs radiologists) and the clinical value of multimodal molecular imaging over single molecular target scans. However, if the diagnostic or prognostic value of multimodal molecular imaging is established, clinical reimbursement will likely follow in due course. Meeting discussions surrounding the clinical value of multimodal molecular imaging evolved to evaluate whether such value was present at the preclinical stage. Several targeted areas of development for multimodality molecular imaging at the preclinical level were identified:

- There is a need to standardize/harmonize workflows in preclinical multimodality molecular imaging to allow for interindividual and interinstitution evaluations of imaging outcomes;
- A systematic approach to defining the value of multitarget molecular imaging across modalities should be developed to facilitate the accumulation of preclinical outcomes that build a case for clinical evaluation;
- Multimodality molecular imaging necessarily requires research teams comprised of multidisciplinary experts to ensure proper experimental design, execution, and analysis. The research team's expertise should extend beyond imaging modality experts and be inclusive of (radio) chemistry, biochemistry, clinical expertise, etc;
- An immediate consequence of requiring multidisciplinary teams to advance multimodality molecular imaging is the requirement to rethink the approach to training scientists and clinicians in this area. Consideration of the breadth and depth of knowledge to effectively integrate modalities while maintaining value in the data or diagnosis/prognosis is necessary;
- An outstanding question that can begin to be evaluated preclinically is whether multimodality molecular imaging necessarily requires scanners with multiple integrated modalities and, if so, what properties of tracers/contrast agents, targets of interest or modalities (eg, sensitivity differences, temporal resolution requirements, etc) justify the combination of two (or more) imaging modalities.

Ultimately, the question is whether preclinical work is already where it needs to be? By addressing the above points, the promise of multimodal molecular imaging can begin to be realistically defined, and potential clinical applications of multimodal (as well as multiparametric and multiplexed) molecular imaging can begin to be advanced. Certainly, multimodal molecular imaging bears promise both preclinically and clinically, but currently it remains at an early stage of development.

Multimodal Scanners

Key questions emerged in the group's discussions of multimodal imaging hardware and data analysis,[10] including whether multimodal imaging should be conducted on individual scanners (eg, separate PET and MRI scanners), or hybrid scanners (eg, a single PET-MRI scanner). The consultants considered the current state of multimodal scanners, which are in various stages of development for both preclinical and clinical applications, including:

Clinical Scanners

- SPECT/CT: Siemens Intevo, Philips Brightview XCT, GE Discovery NM/CT 670
- PET/CT: Siemens mCT Flow, Philips Vereos, United Imaging uMI 780, GE Discovery IQ, Toshiba Celesteion
- PET/MRI: Siemens mMR, Philips ingenuity, GE Signa
- PET/SPECT/CT: Mediso Anyscan
- PET/Linac and PET/CT/Linac: Reflexion IGRT and BGRT
- Photoacoustic imaging: iThera MSOT Acuity Echo and RSOM Explorer C50

The development of multimodal hybrid scanners is an active area of innovation, and new hybrid instrumentation is expected to be introduced in the foreseeable future. For example, the integration of MRI with ultrasound transducers has been demonstrated to provide real-time respiration correction without gating.[11] A second example is the introduction of magnetic particle imaging (MPI) into clinical use[12] for which a hybrid scanner has already been demonstrated for preclinical imaging (*vide infra*). Note that the hybrid scanners listed do not consider endoscopic, intraoperative, or interventional imaging, as this was considered out of the scope of the meeting.

Preclinical Scanners

Preclinical hybrid scanner technologies cover a broader range of modalities than clinical ones, providing ample opportunities for tracer/contrast agent development for multimodal molecular imaging. Existing commercialized scanner technologies currently include:

- PET/CT: Sofie biosciences GNEXT, Sedecal SuperArgus, Mediso Nanoscan, Bruker Albira Si, Bioemtech, MI Labs VECTor
- SPECT/PET/CT: MI Labs VETor, Mediso NanoScan, Bruker Albira Si, FLEX Triumph
- SPECT/MRI: Mediso Nanoscan, Bruker Albira Si
- PET/MRI: Bruker, MR Solutions MRS-PET, Mediso
- MPI/CT: Magnetic Insight Momentum CT
- Fluorescence/PET/SPECT/CT: MI Labs

- Fluorescence/X-ray and Fluorescence/CT: IVIS XRMS and SpectrumCT, Trifoil InSyTe, Spectral Instruments Imaging Lago X and AMI HTX
- Photoacoustic imaging: Fujifilm VisualSonics Vevo LAZR-X, iThera MSOT inVision and RSOM Explore P50

Additional multimodal hybrid technologies for preclinical use are expected to emerge as commercial products in the near future, including a PET/CT/Ultrasound (PETRUS) system,[13] as well as PET/SPECT hybrid systems for Compton imaging.[14]

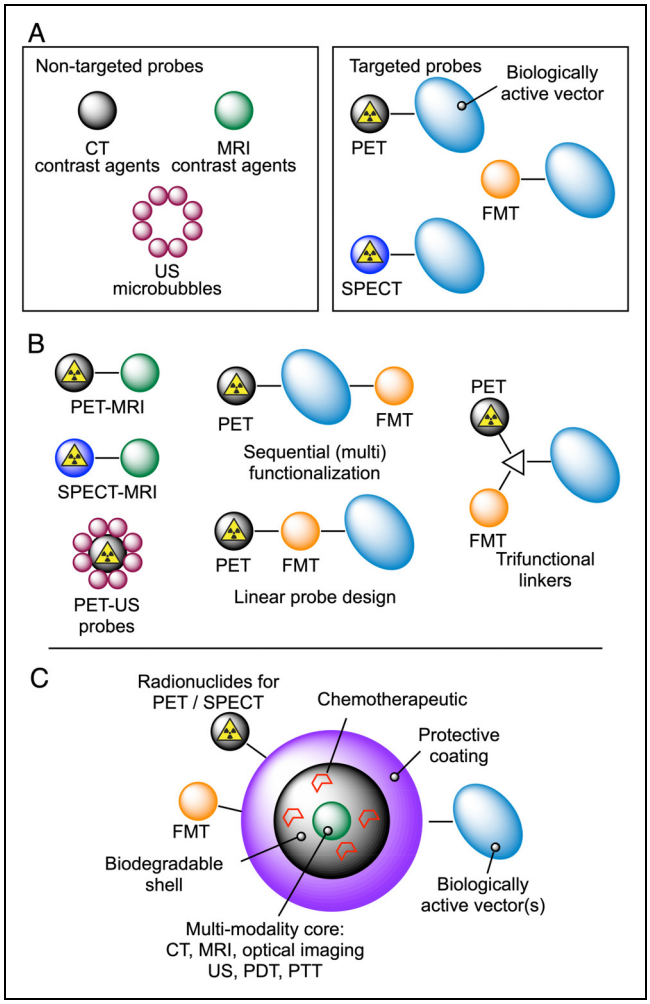

Figure 1. Schematic representation showing, (A) classic single-modality contrast agent or probe design for either nontargeted or molecularly targeted imaging. (B) Dual-modality probes which are frequently designed and tested in preclinical multimodal imaging studies. (C) Multimodality design with multifunctional nanoparticles, in this example with an extremely large number of functionalities (FMT, fluorescence molecular tomography; PDT, photodynamic therapy; PTT, photothermal therapy).

Multimodal Probes

With the development of multimodal imaging systems, including the commercial systems listed above, chemists have turned their attention toward the design and synthesis of multifunctional compounds to generate appropriate probes (Figure 1). Multimodal probes can be designed using many different types of imaging probes available today (Figure 1A). The simplest type of multimodal imaging probes are dual-modality probes consisting of moieties for imaging with two different techniques (Figure 1B), but more complex probes compatible with more than two imaging modalities are also possible. Nanoparticles (NPs), for example, provide a useful construct in terms of size and potential for modification to encapsulate or functionalize with a range of contrast agents, dyes and radioisotopes (Figure 1C). Specifically, radiolabeling of NPs is addressed in the following section.

Radiolabeling Methods

Several strategies have been used to radiolabel NPs.[15,16] An overview of the main approaches, including surface functionalization, coating modifications, and more recent intrinsic (or chelate-free) methods is presented in Figure 2. Radiometal isotopes for PET (or SPECT) can be attached to the NP surface using a chelator through either "final-step" or "two-step" protocols. An early example of final step chelator-based radiolabeling utilizes the combination of copper-64 and DOTA.[17,18] DOTA is commonly used due to the general applicability and commercial availability of precursors but is not optimal for all radiometals (Figure 2A).[19]

An alternative method for forming chelator-based radiolabeled NPs is the initial radiolabeling of a bifunctional chelator (chelating agent with a reactive group) followed by conjugation of the radiometal complex to the NP. The advantage of this method is that the radiometal is stably bound to the chelate before attachment to the NP, hence other, potentially weaker, surface coordination interactions are not possible. Louie et al developed one of the first radiolabeled magnetic NP systems using this methodology, which has been studied and advanced significantly in the past 15 years.[20]

To shield the nanoparticle from interactions with proteins and other components of blood in order to enhance circulation times, the majority of nanoparticles use a bioorthogonal chemical coating. This coating can take different forms but is often a derivative of n-polyethyleneglycol (PEGn) or a sugar-based polymer like carboxymethyldextran. Chemical modifications of the coatings can also be performed selectively to introduce different cargo molecules including radionuclides (Figure 2B).

More recently, pioneering work from the Cai group introduced a reliable and highly versatile way of labeling metal oxide NPs using only the intrinsic chemistry of the particle surface or core (Figure 2C). These methods, collectively,

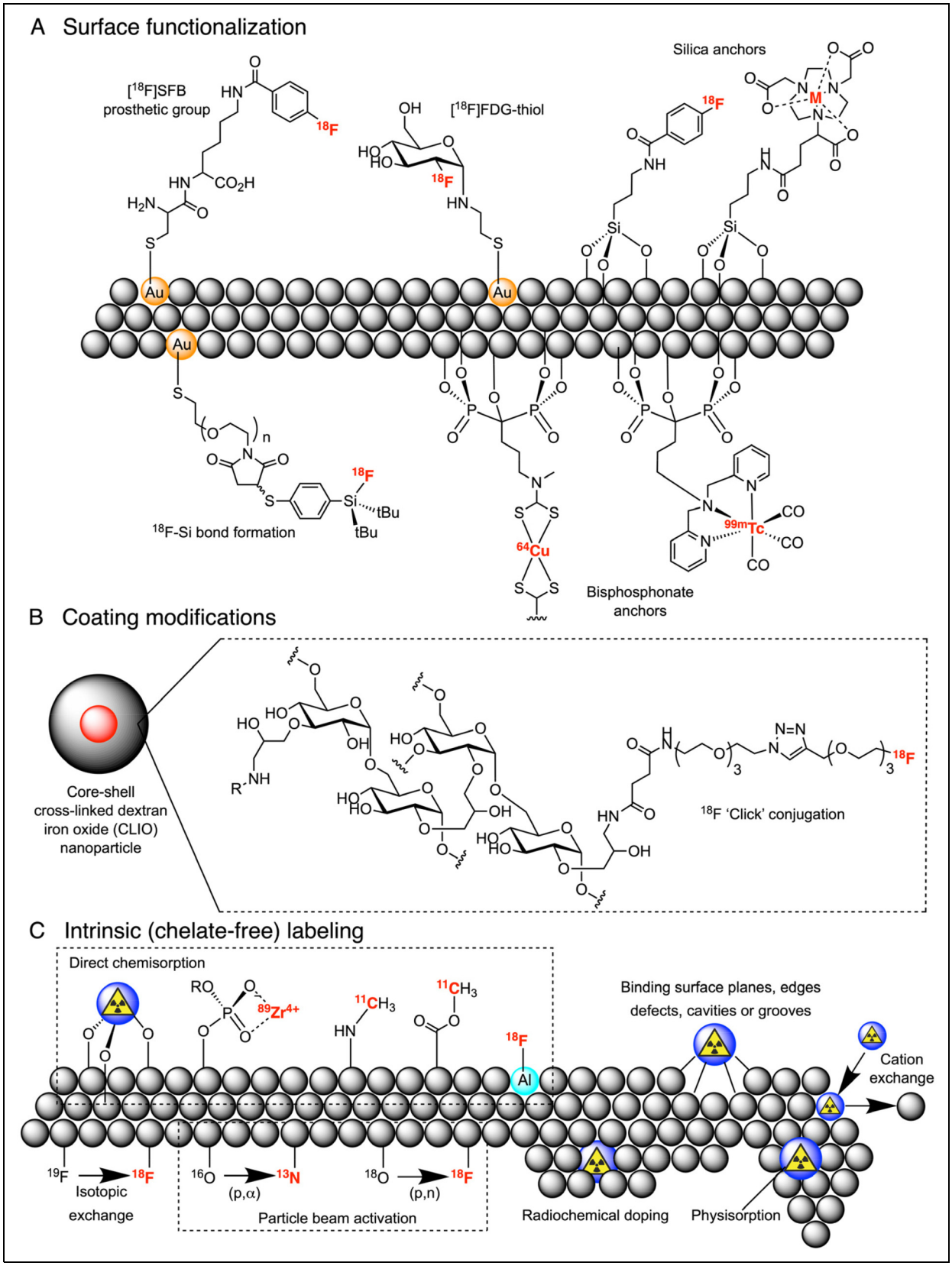

Figure 2. Schematic showing examples involving classical (A) surface functionalization or (B) chemistry to modify the NP coating, and (C) a summary of modern "chelate-free" methods that rely on the intrinsic chemistry of the NP surface or core. This figure is adapted from work originally published in Lamb and Holland[15] and is reused with permission. © Society of Nuclear Medicine and Molecular Imaging.

have been classified as "chelate-free" approaches. At least 7 different mechanisms can be identified that fall within the scope of "chelate-free" radiolabeling. These include:

1. Radiochemical doping
2. Direct chemisorption
3. Physisorption
4. Isotopic exchange
5. Particle beam activation
6. Cation exchange
7. Cavity encapsulation

Classification of the type of intrinsic labeling process depends on the nature of the interaction and the location of the radionuclide in the structure of the NP. Dose challenges exist for 1:1 agents combining, for example, a nuclear modality with an MR contrast agent, where required concentrations of radioisotope are 10^6 times lower than a standard T_1-shortening MR contrast agent.

The pool of chemical methods that can be used to radiolabel NPs continues to grow steadily. Intrinsic labeling methods offer several advantages:

1. Radiolabel is often found to be stably bound to the particle under relevant physiological challenge conditions.
2. Labeling methods work with a wide range of *p*-, *d*- and *f*-block radiometals. Known examples include: ^{64}Cu, ^{68}Ga, ^{89}Zr, ^{111}In, ^{177}Lu, ^{90}Y, among others.
3. Chelate-free methods with many radionuclides (though not all) can be used to label metal oxide (M_xO_y) NPs where the nature of the M can vary. Examples by Cheng et al have shown that at least 10 different metal oxide NPs can be labeled with ^{89}Zr (Figure 3),[21] and the work of Shaffer et al extended the concept to silica NPs.[22]

One point that the group noted is that irrespective of the chemical method chosen to label the NP, control over the precise stoichiometry of the product remains a major challenge. For instance, creating particles with a 1:1 combination of a drug with a radionuclide remains an imprecise science. In addition, there are still many issues that remain to be addressed over the reproducibility of NP synthesis. In this area, control over size and particle distribution are crucial factors. Some groups claim to have solved these issues for several types of NPs, notably the size and shape of Au NPs can be controlled in the nanometer scale (Figure 4),[23] but in general, there is no "one method fits all" approach that would work for different NP compositions.

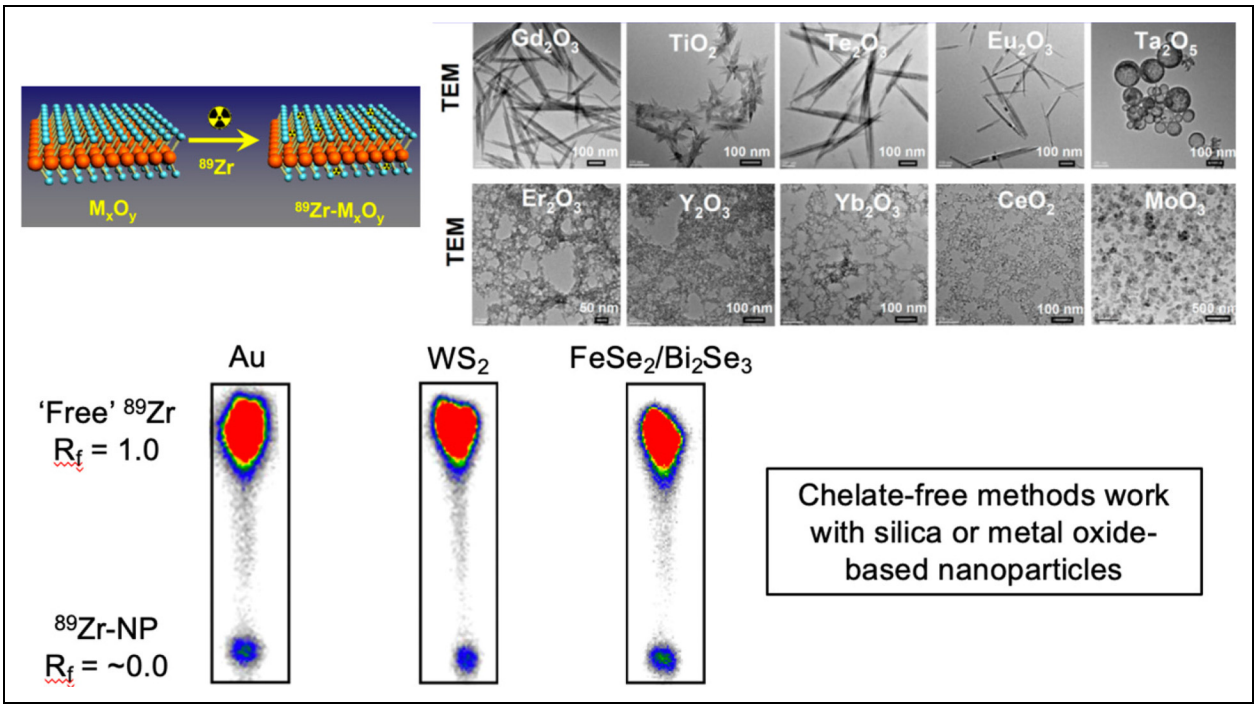

Figure 3. Chemical versatility in the chelate-free radiolabeling of metal oxide NPs with various radionuclides. Top row: Schematic illustration showing the chelator-free labeling of a metal oxide (MxOy) with ^{89}Zr (left); Transmission electron microscopy (TEM) and magnified TEM images of M_xO_y nanomaterials including Gd_2O_3 nanorods, TiO_2 nanorods, Te_2O_3 nanorods, Eu_2O_3 nanorods, Ta_2O_5 nanospheres, Er_2O_3 nanoparticles, Y_2O_3 nanoparticles, Yb_2O_3 nanoparticles, CeO_2 nanoparticles, and MoO_3 nanoparticles (right). Bottom row: TLC plates of various nanomaterials after mixing ^{89}Zr: Au nanoparticles (left); WS_2 nanosheets (center); $FeSe_2/Bi_2Se_3$nanocomposites (right). All figures reproduced from Cheng et al[21] with permission. © American Chemical Society.

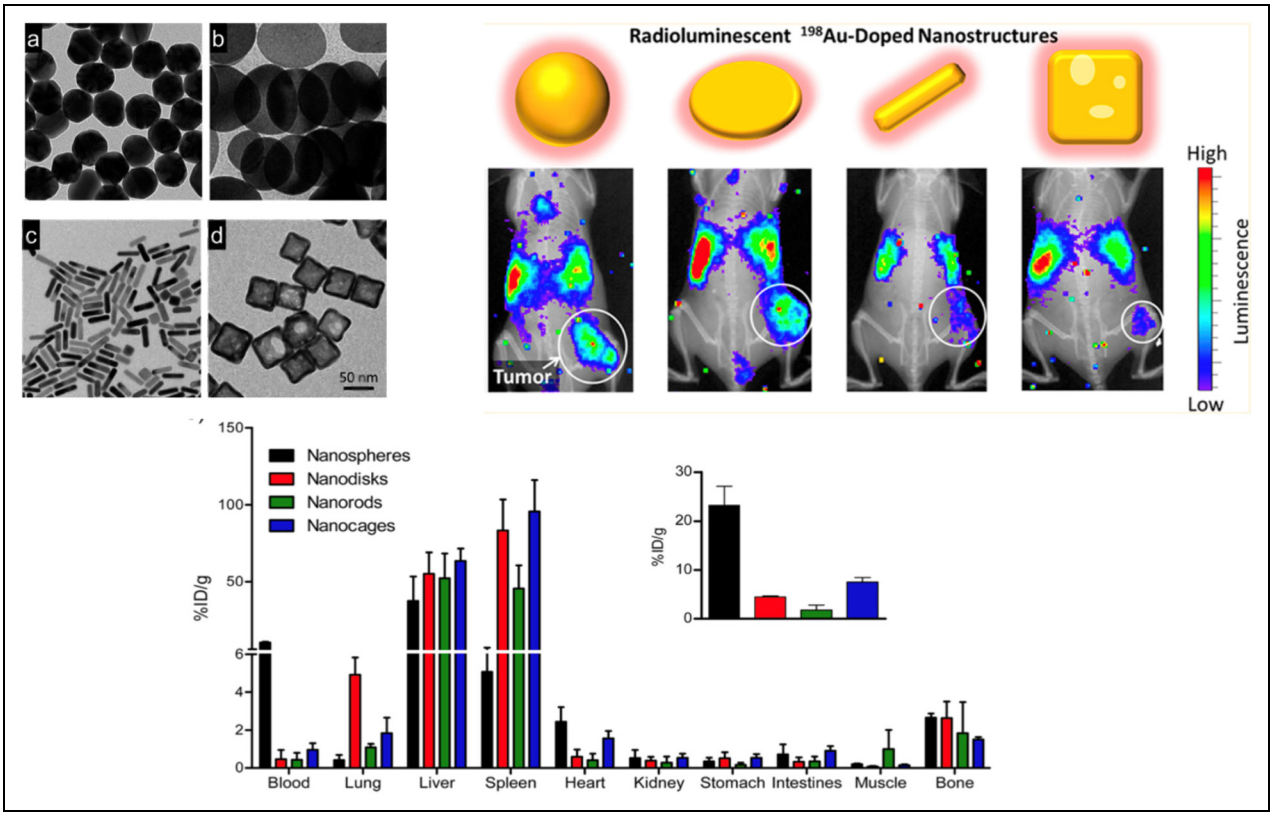

Figure 4. Overview of work by Black et al showing control over Au NP size and shape (spheres, disks, rods, and square cages) and the dependence of the pharmacokinetics and biodistribution of the ^{198}Au-radiolabeled particles in mice with NP shape. Top row: TEM images of four different types of Au nanostructures in the nonradioactive version: (a) nanospheres, (b) nanodisks, (c) nanorods, and (d) cubic nanocages. The scale bar applies to all images. (left); coregistered *in vivo* luminescence and X-ray images of the tumor-bearing mice at 24 h postinjection of the different types of ^{198}Au-incorporated nanostructures (right). Bottom row: Biodistribution of the different types of ^{198}Au-incorporated Au nanostructures at 24 h postinjection, together with tumor uptake data (inset). All figures reproduced from Black et al[23] with permission. © American Chemical Society.
TEM, Transmission electron microscopy.

Biodistribution and Pharmacokinetics: A Role for Nuclear Imaging in Validation

There is growing interest in applying the sensitivity and quantification of nuclear imaging to determine the biodistribution of multimodal probes and NPs in vivo because of the ability to perform absolute quantitation and there being no limit to the depth of imaging penetration.[24] Wang et al introduced multiple radioactive isotopes in the same construct at different positions to track the *in vivo* behavior and metabolism of their multicomponent nanoparticle system.[25] ^{59}Fe was used to label the iron oxide core, ^{111}In chelated to DTPA was added to the lipid (DMPE) coating along with ^{14}C-oleic acid as a stabilizer. *In vivo* biodistribution studies were used to determine how the different components were processed. As expected, the oleic acid used as a surfactant is rapidly disassociated *in vivo* after 10 min, whereas the biodistribution of ^{59}Fe and ^{111}In largely correlate, indicating that the DTPA-DMPE initially remains attached to the NP.[26] However, significant differences were noticed in the kidney and control experiments (administration of ^{111}In-DTPA-DMPE alone) showed a similar biodistribution potentially caused by micelle formation, suggesting instability of chelator attachment. This type of multiisotope study where different components can be separately tracked using high sensitivity and ideally quantitative nuclear imaging is complex but provides information on the stability and biodistribution of nanoparticles *in vivo* not achievable by nonnuclear modalities.

For human translational applications, the acquisition of suitable biodistribution data is only possible with nuclear imaging modalities. A comparison between nuclear and fluorescence imaging to examine the biodistribution of nanomaterials in mice showed clear superiority of nuclear imaging (Figure 5).[27] The translation into humans for biodistribution is only possible with nuclear imaging modalities. A comparison in mice was made between in vivo PET imaging, postsacrifice fluorescence imaging (whole animal), and both *ex vivo* gamma counting and fluorescence imaging of resected tissues. The conclusion that only tissues with low

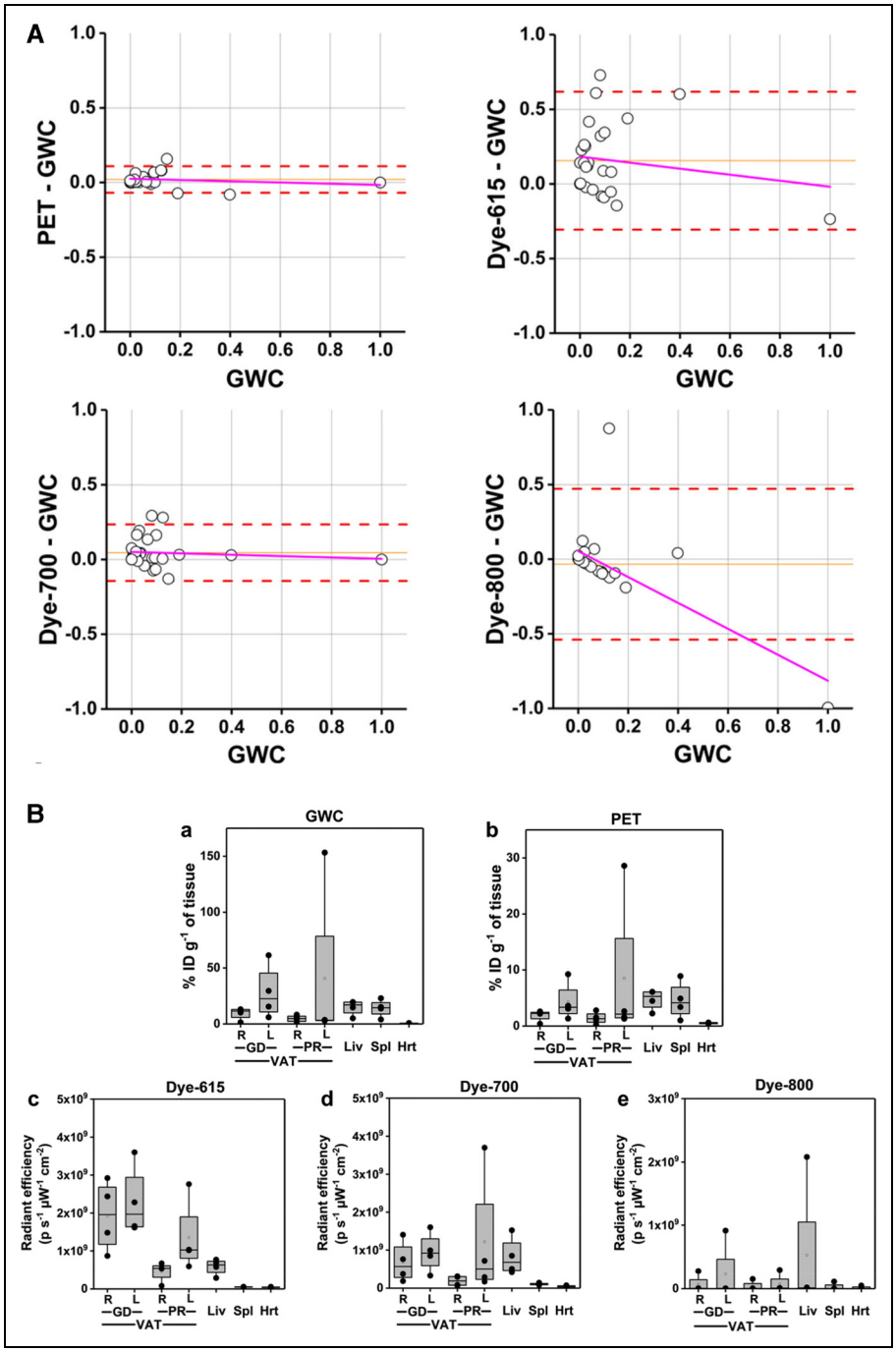

Figure 5. A comparison of biodistribution properties in mice of a dual PET/optical imaging agent showing the superior precision of PET imaging (determined in comparison to ex vivo resected tissue measurements from gamma counting). (A) Bland-Altman difference plots show normalized biodistribution values relative to gamma well counting (GWC) for PET, Dye-615, Dye-700, or Dye-800. Differences are plotted against GWC values for all tissues (white and red tissues). Orange horizontal lines are median values, dashed red lines are 95% confidence intervals, and pink lines are linear regressions. (B) Tissue biodistribution of D500-Rad-Fluor measured by gamma GWC, PET imaging, and fluorescence imaging for resected tissues. Plots show individual tissue biodistribution values calculated using (a) GWC, (b) PET images quantified using manually defined regions of interest, and deconvolved IVIS fluorescence for channels corresponding to (c) Dye-615, (d) Dye-700, and (e) Dye-800. Tissues shown are left (L) and right (R) gonadal (GD) and perirenal (PR) visceral adipose tissues (VAT), liver (Liv), spleen (Spl), and heart (Hrt). All figures reproduced from Deng et al[27] with permission. © American Chemical Society.
PET, positron emission tomography.

levels of light absorbance offer accurate quantification by fluorescence imaging after resection demonstrates the high value of combining *in vivo* PET imaging with other modalities. Further advances in NIR imaging and extended fluorescence lifetimes may reduce background and increase sensitivity but significant fundamental research is required for optical imaging to be an optimal tool in this application. The ongoing first-in-human trial of the fluorescent C'Dots (formerly Cornell dots) in glioma patients (NCT03465618) is the first clinical example of the use of zirconium-89 radiolabeling to validate the uptake of targeted silica nanoparticles. PET scans can be used at multiple timepoints and histological analysis carried out on patients undergoing surgical intervention. A further study in rats and macaques was carried out using PET/MRI with zirconium-89 radiolabeled AGuIX polymer NPs developed for MR contrast and radiosensitization. These particles, that are already in phase 2 clinical trials, showed tumor accumulation using a glioblastoma model and could still be detected in the tumor using PET after 1 week.[28]

Iodinated CT contrast agents with regulatory approval include Iopamidol from Bracco, which has been utilized clinically to develop a range of applications, from multimodality approaches to surgical interventions. CT mapping presurgery and fusion with biplane fluoroscopy have been demonstrated to be effective in endovascular procedures for aortic aneurysm repair, reducing radiation and contrast exposure for the patient. Iopamidol has also been used experimentally for CEST pH measurements.

Applications of Multimodality Imaging

It was unanimous among the group at the CM meeting that the possible applications for multimodal molecular imaging largely remain to be explored, which offers a wealth of opportunity for innovation and discovery for molecular imaging scientists in the future. Possible applications could include:

- Combinations of reporter genes (eg, OATP Gd transporters and sodium iodide symporter (NIS)) for multimodal synthetic biology;
- Tracking of multiple cell populations by combining *in vivo* cell radiolabeling with iron-oxide labeling for MRI or MPI;[29]
- Integrating Cerenkov radioluminescence imaging with ultrasound molecular imaging;[30]
- Interrogating molecular drivers of concussion and/or traumatic brain injury by PET simultaneously with MR tractography to better elucidate injury pathogenesis;
- Combining [^{18}F]FDG-PET with MR spectroscopy to differentiate immune infiltration from tumor growth and treatment failure;
- Interrogating two or more interacting signaling pathways simultaneously, providing a systems-level approach to the interrogation of pathology.

The overall consensus of the group was that the development of multimodal imaging approaches integrating molecular imaging biomarkers has the potential to significantly impact both clinical and preclinical imaging. The following examples were some of those discussed that supported this overall consensus:

- The identification of extensive neuroinflammation in noninfarcted regions of the brains of human chronic stroke patients by PET/MRI, with glial activation colocalizing with regions of structural integrity loss (see, eg, Schaechter et al[31]);
- The tracking of chimeric antigen receptor T-cell therapy in glioblastoma patients through the engineered expression of herpes simplex virus thymidine kinase as a reporter gene, and colocalization of [^{18}F]FHBG retention with tumor anatomical features by PET/MRI;[32]
- The simultaneous preclinical evaluation of both glucose uptake and retention ([^{18}F]FDG), and glucose utilization (lactate:pyruvate by MR Spectroscopy) to further characterize the heterogeneous metabolic phenotype of a tumor.[33] While yet to be demonstrated, the group discussed the extensive value of PET/MR spectroscopy imaging to map tumor hypoxia in the near future;
- The combination of preoperative SPECT and intraoperative fluorescence imaging using a bimodal [^{111}In]In-DOTA-labetuzumab-IRDye800CW anticarcinoembryonic antigen antibody conjugate resulted in altered clinical decision-making to improve the resection of previously undetected peritoneal metastases of colorectal cancer.[34]

While the aforementioned opportunities and examples of multimodality molecular imaging appear specific in scope, a multimodal approach could generally enhance imaging agent development by enabling quantitative evaluation of agent distribution and metabolism. In this application, effectively one modality is used to validate the other, taking advantage of the properties of one modality not present in the other. For example, the tissue residence of gadolinium-based contrast agents was evaluated using an isosteric [^{86}Y]Y-DTPA radiotracer surrogate of Gd-DTPA.[35] In this case, the high sensitivity and quantitative nature of PET afforded a more precise and quantitative determination of contrast agent clearance not possible by MRI alone. This particular application of multimodal molecular imaging will likely be valuable for the validation/evaluation of a broad range of imaging agents in the future, including small molecule, nanoparticulate, and synthetic biology approaches.

Regulatory Considerations

In terms of regulatory aspects for the translation of multimodal probes, Europe follows the same recommendations and directives for food products [European Commission. Directive 2002/178/EC laying down the general principles and requirements of food law, establishing the European

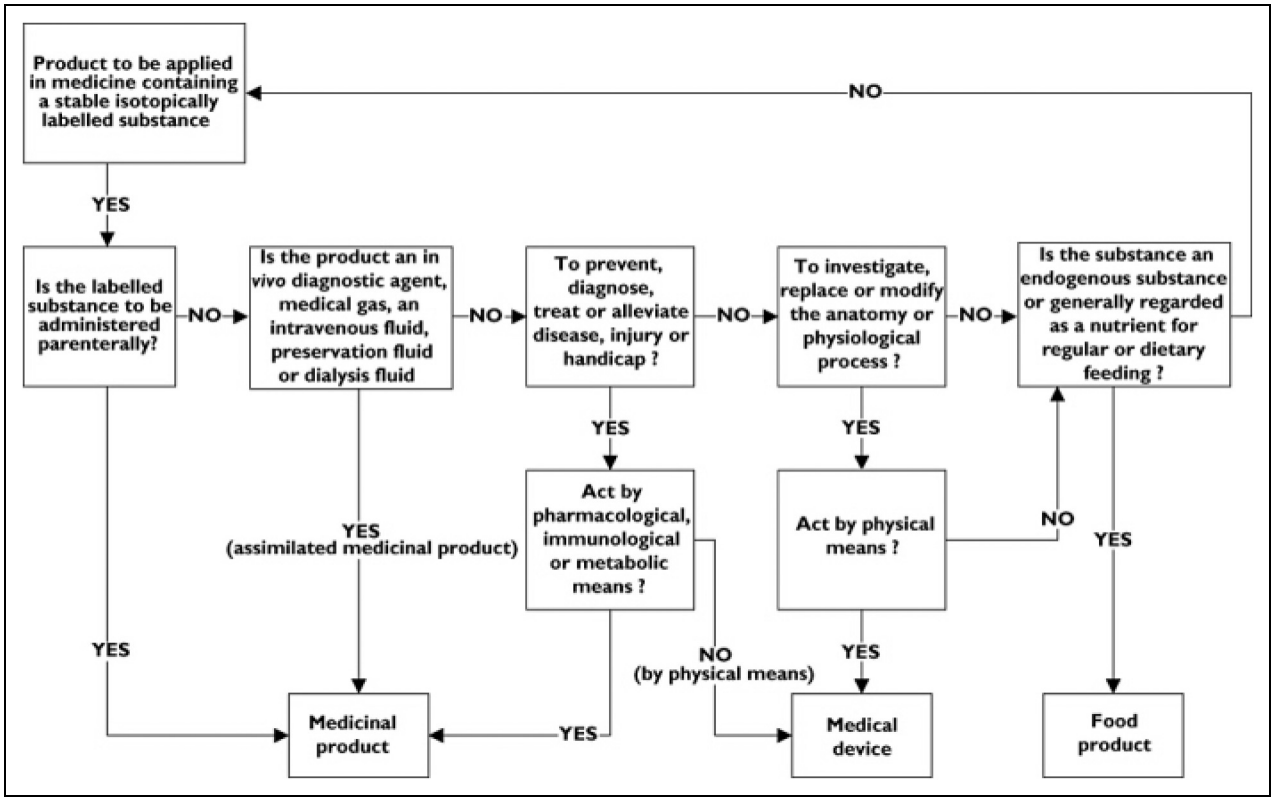

Figure 6. Pathway for determining the regulatory status of a new molecule. Reproduced from Schellekens et al[36] with permission. © John Wiley and Sons.

Food Safety Authority and laying down procedures in matters of food safety. 2002.] (2002/178/EC), medicinal products [European Commission. Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products. 1965.] (65/65/EEC), and medical devices [European Commission. Directive 93/42/EEC concerning medical devices. 1993.] (93/42/EEC). The diagram represented in Figure 6 shows the pathway for determining to which of the groups a new molecule labeled isotopically, radiolabeled, or including a fluorescent dye belongs.[36] Most newly developed probes fall into the medicinal product category. This makes clinical translation more challenging because it requires extensive testing, cGMP compliance, and high-quality control grades for the production of the materials (*vide infra*). In general, any product that is administered parenterally or applied to restore, correct, or modify physiological functions by exerting a pharmacological, immunological, or metabolic action, or to enable a medical diagnosis, is considered a medicinal product. The appropriate classification of multimodal agents is still being debated, because:

1. there is a lack of suitable probes/drugs for multimodal use;
2. the justification for translation is still unsure;
3. the directives regulating a food drug might not apply to a similar molecule with multimodal capabilities.

For example, most isotopically labeled metabolites can be considered food drugs. However, if it contains a radioactive label (eg, fluorine-18), it is automatically classified as a medicinal product because of its radioactive nature. The reasoning behind the reclassification is based on the fact that the pharmacokinetic and pharmacodynamic properties are altered, making the administration different, meaning the anatomy and physiology might be altered. We can stipulate that more straightforward multimodal probes could be those using the same type of labeling for assessing a different range of modalities. For example, metal-based radiometals like ^{68}Ga/^{67}Ga for PET/SPECT and optically active paramagnetic lanthanides for optical/MRI.

cGMP Considerations

When producing imaging probes, there are cGMP regulations that need to be considered. The degree of cGMP required for a given probe synthesis depends upon the application; preclinical studies require less cGMP compliance than clinical studies, and cGMP requirements also increase throughout the clinical trial process. cGMP requirements

differ between jurisdictions, although there are continuing efforts to harmonize regulations around the world, at least for radiopharmaceuticals.[37,38]

Regulations can also vary considerably for different classes of imaging agents. Because radiopharmaceuticals are typically administered as microdoses (defined as at least 100 times below the no observable adverse event level (NOAEL)), there are some regulatory nuances exclusive to this class of agent that do not apply to other imaging probes. For example, in the United States, PET drugs prepared according to cGMP have to meet the requirements outlined in the U.S. Pharmacopeia or 21CFR212 that have provisions stemming from the short half-lives of such agents. Conversely, stable imaging probes like MRI, CT, and optical agents are considered drugs and have to be prepared according to pharmaceutical cGMP (eg, 21CFR210 and 211). There are other differences in regulatory requirements for radiopharmaceuticals and stable imaging probes. The most significant difference is that for translation to humans. There are reduced pharmacology/toxicology (pharm/tox) testing requirements for radiopharmaceuticals because they are administered as microdoses. Single species testing ($\leq$\$150k) is acceptable for radiopharmaceuticals, while two species pharm/tox + genotoxicity testing (combined cost ~\$500k) is likely required for other imaging probes like molecular MRI agents or optical imaging probes. In addition to the testing costs, two-species pharm/tox + genotoxicity testing also requires substantially more test compounds which can often be costly. This inevitably makes the development and translation of such imaging agents more challenging than radiopharmaceuticals, and the same will be true of multimodal imaging agents.

For clinical trials, some type of regulatory approval (Federal or Institutional) is needed. For first-in-human studies, this is usually Federal approval (eg, an Investigational New Drug (IND) application[39,40]). In the case that imaging probes that are isotopologs of approved drugs (eg, prepared by isotopic labeling with $^{11}C/^{13}C/^{2}H$, etc) then additional pharm-tox testing may not be needed in order to obtain such approval, depending upon local regulations. There are also other special provisions in certain jurisdictions. For example, in Germany, PET radiopharmaceuticals are permitted to be manufactured according to the requirements set in Article 13(2b) of the Medicinal Products Act (Arzneimittelgesetz, AMG). This rule provides the provision that "*a person who is a doctor or dentist or who is otherwise authorized to practice medicine on humans does not require a license […] insofar as the medicinal products are manufactured under his direct professional responsibility for the purpose of personal use on a specific patient.*" This has historically enabled more straightforward translation to first-in-human studies in Germany compared to other nations. In the United States, PET radiopharmaceuticals can be used for basic clinical research under the approval of an institutional radioactive drug research committee as long as they meet certain provisions (eg, prior use in humans, known not to cause any pharmacological effects in humans at the proposed dose, and meeting certain dosimetry requirements).[41]

Overall, the regulatory environment is complex, highly heterogeneous around the world, and continues to evolve. Careful consideration should be given to cGMP and regulatory oversight as new multimodal imaging agents are developed and translated in the future.

Challenges and Future Opportunities

Challenges

- The cost of translation for multimodal agents is much higher than traditional microdosed radiopharmaceuticals and, with no clear funding sources in place to cover the cost, this is possibly the largest roadblock for academic groups to enter the space and drive to clinical implementation;
- There is a mismatch in sensitivity and concentrations for some modalities (eg, PET vs MRI);
- The need to show value added from a multimodal imaging probe compared to existing single modality techniques adds complexity and cost to development;
- There is no clearly defined roadmap/decision tree for development of multimodal imaging probes;
- Imaging scientists with expertise in multiple imaging modalities are not common. Training programs providing such expertise today are typically lab-based and heterogeneous;
- Barrier to entry is high for multimodality imaging since it requires additional capital investment (eg, purchasing multiple types of scanners or more costly hybrid scanners; hiring people with different types of expertise);
- The field of multimodality imaging has limited standardization at this point. There is often no consensus on how to analyze single modality data, let alone imaging data from multiple coregistered imaging modalities. Similar questions remain about how to power imaging studies employing multiple imaging modalities;
- Software for processing diverse types of multimodal imaging data is in its infancy;
- Production of different types of imaging probes requires different synthesis resources and capabilities. Nuclear medicine facilities frequently have synthesis facilities and personnel onsite because of the need for daily radiochemistry, while other groups (MRI, optical) frequently don't have synthesis capabilities. Indeed, today most MRI research is contrast-free. While there are a number of reasons for this, one challenge is certainly the synthetic accessibility of new MRI agents.

Future Opportunities

- Develop specific multimodal training programs (eg, Masters or PhD programs, training programs with support from

IAEA or Professional Societies) to create a workforce pipeline that has the necessary breadth of multimodal expertise;
- There is an opportunity for imaging researchers to build research (sub)groups focused on developing new chemistry (eg, biocatalysis) to produce different imaging probes (eg, labeled with ^{2}H, ^{13}C, ^{19}F, ^{31}P), similar to what has happened for late-stage radiolabeling in recent years. Radiochemistry groups are well positioned to help fill this gap because they have existing synthesis and cGMP knowhow and could undertake such projects without tying up radiochemistry equipment;
- Development of specific multimodal imaging societies, dedicated interest groups, and conferences. Existing organizations (eg, SNMMI, WMIS, ISMRM) have some activities, but different types of imaging groups appear siloed within these large societies;
- To date, multimodality work has focused primarily on diagnostic applications. However, with the increasing emergence of theranostics, modalities such as MRI can potentially also be combined with therapeutic radionuclides, as well as with biosensors;[42]
- With the advent of artificial intelligence and machine learning transforming radiology, multimodal imaging offers advantages for collecting "big data" since it is easier to collect data if it is all obtained from one scanner and stored in one place. There are already studies progressing utilizing PET data alongside other modalities to characterize tumors, in an attempt to predict disease progression and select treatment.[43] In order to fully exploit this potential, large consistent data sets with harmonized standards are needed, utilizing a wider range of radiotracers in multimodality imaging protocols;
- The combination of big data and multimodality imaging offers exciting opportunities in areas like radiomics and precision health;[44,45]
- New imaging modalities being developed will offer new combinations of multimodality imaging in the future, enabling access to new information. For example, electron resonance imaging has yet to be combined with other modalities and could potentially be combined with, for example, MRI or PET.

Recommendations

During the discussions at the consultancy meeting, it was apparent to the group that multimodal imaging is a growing field, that includes numerous disparate disciplines and is still more or less in its infancy. As such, the group did not have recommendations for specific technical documents or books at this time. Of the range of technologies identified, PET/MRI is likely the most well-known and developed multimodal imaging technology and it could be the focus of an IAEA Research Project, but even this might be premature. Nevertheless, given that PET and SPECT represent obvious modalities to combine with others like MRI, ultrasound and optical, it does make sense for the IAEA to further explore the area of multimodality imaging in its future activities as it pertains to its member states. The group thus recommended that the IAEA conduct a technical meeting on multimodality imaging with up to 20 experts across all of the technologies discussed in this meeting report, so as to better understand the state-of-the-art and prioritize multimodal imaging areas that should be the focus of future agency activities. Such activities could include, but are not limited to:

1. Development of a short-course curriculum suitable for educating imaging scientists and graduate-level trainees in key concepts of multimodality (and related) molecular imaging.
2. Develop a decision tree to assist in choosing appropriate multimodal imaging approaches for a given research question;
3. Identify priority topics that could be the subject of future IAEA publications covering multimodality imaging;
4. Identify additional multimodal imaging topics for future coordinated research projects/workshops;
5. Provision of support for developing world attendance at relevant multimodal imaging conferences and/or workshops.

Conclusions

Imaging modalities for multimodal imaging, including the development of probes, hardware and methods for data analysis, have steadily developed in recent years. Since there are differences between imaging techniques (eg, in sensitivity, information obtained), the field of multimodality imaging has emerged and continues to grow in recent years. With the additional advent of hybrid scanners, there is considerable interest in developing multimodality imaging agents that enable the use of different types of imaging tools to obtain complimentary information around a given preclinical or clinical question.

The field is quite diverse. The development of probes spans small molecule hybrid probes to nano constructs capable of being functionalized for use in conjunction with numerous imaging modalities. The field is also still quite young, and there are some challenges (eg, lack of standardization, high barrier to entry, complex regulatory environment), but also considerable opportunities (eg, new scanners continue to be developed that provide opportunities for future innovation; synthesis opportunities, potential applications in new areas like radiomics and precision health). Overall, multimodality imaging holds potential for the imaging field to combine forces, in order to better understand mechanisms of disease and support drug developers' search for new treatments.

Acknowledgments

Financial support from the IAEA is gratefully acknowledged. P.J.H.S. also thanks the University of Michigan (Department of Radiology and Support for Outstanding Research) for support. A.J.S. thanks the Canada Research Chair Program (950-230754) and the Natural Sciences and Engineering Research Council of Canada Discovery Grant Program (RGPIN-2021-03387) for their support.

Data Availability

The data supporting this review are from previously reported studies and datasets, which have been cited.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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