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STATE-OF-THE ART REVIEW:

TOTAL-BODY PET: MAXIMIZING SENSITIVITY TO CREATE NEW OPPORTUNITIES FOR CLINICAL RESEARCH AND PATIENT CARE

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ABSTRACT

Positron emission tomography (PET) is widely considered as the most sensitive technique available for non-invasively studying physiology, metabolism and molecular pathways in the living human being. However, the utility of PET, being a photon deficient modality, remains constrained by factors including low signal-to-noise ratio (SNR), long imaging times and concerns regarding radiation dose. Two developments offer the potential to dramatically increase the effective sensitivity of PET. First by increasing the geometric coverage to encompass the entire body, sensitivity can be increased by a factor of ~40 for total-body imaging or a factor of ~4-5 for imaging a single organ such as the brain or heart. The world's first total-body PET/computerized tomography (CT) scanner is currently under construction to demonstrate how this step change in sensitivity impacts the way PET is utilized both in clinical research and patient care. Second, there is the future prospect of significant improvements in timing resolution that could lead to further effective sensitivity gains. When combined with total-body PET, this could produce overall sensitivity gains of more than two orders of magnitude compared to existing state-of-the-art systems. In this article we discuss the benefits of increasing body coverage, describe our efforts to develop a first-generation total-body PET/CT scanner, discuss selected application areas for total-body PET and project the impact of further improvements in time-of-flight (TOF) PET.

NOTEWORTHY

- The concept of total-body PET refers to a scanner which encompasses the entire body within the field of view and allows imaging of all the tissues and organs of the body simultaneously (page 4).
- The increase in geometric coverage of total-body PET produces a sensitivity increase of a factor of ~40 for imaging the entire body (page 4).
- Total-body PET images could be obtained with 6-fold better SNR, or in 1/40th the scanning time or with 1/40th of the injected activity while maintaining existing SNR (page 5).
- The world's first total-body PET scanner, called EXPLORER, is currently being constructed (page 12).

INTRODUCTION

All nuclear medicine studies in humans are limited by the trade-offs between the number of detected decay events, imaging time and absorbed dose. The number of detected events determines the SNR in the final image, but constraints on administered activity, as well as high random event rates and dead time that occur at high activities, currently prevent acquisition of high SNR images in very short times. This in turn limits the ability to perform high-resolution, dynamic imaging studies with tracer kinetic modeling, because short time frame datasets are always very noisy. A further limitation is that while the tracer injection is systemic and radiotracer is present in the entire body, current imaging systems only contain a small portion of the body within the field of view. For applications where the distribution of radiotracer in the entire body or multiple organ systems is of interest, this leads to further inefficiencies and makes it difficult to acquire dynamic data from all the tissues of interest. If one takes whole-body PET scanning with ^{18}F-fluorodeoxyglucose (FDG) as an example, the total efficiency with which pairs of coincidence photons that escape the body are detected is well under 1% even on today's best scanners. Simplistically, this number can be derived by considering that the average geometric sensitivity within the field of view of a typical clinical PET scanner is under 5% and that with an axial coverage of 20 cm, less than 1/8th of the body is in the field of view at any one time. In this article, we discuss how improving the geometric coverage directly increases sensitivity by over an order of magnitude for total-body PET scans. We describe progress to date on building the first prototype total-body scanner that will show a roughly 40-fold sensitivity gain over existing PET scanners for imaging the entire body. We also discuss how such a large increase in effective sensitivity has the potential to dramatically broaden the utility of PET in human medical research, potentially leading to new clinical applications, as well as how it can positively impact existing clinical applications. Finally, we describe how anticipated improvements in timing resolution can produce further increases in effective sensitivity, leading to the prospect of PET scanners that are ~200 times more sensitive than current commercial systems for total-body imaging.

FROM WHOLE-BODY PET TO TOTAL-BODY PET

There are two major factors corresponding to the extremely poor sensitivity of less than 1% for current whole-body PET scans (Fig. 1A). The first and most obvious is that at any one time, roughly 85 to 90% of the body is outside the field of view (FOV) of the scanner and no signal from these regions of the body are collected. Secondly, even for the tissues/organs within the scanner FOV, no more than ~3-5% of the available signal (photon pairs that escape the body without being attenuated or scattered) can be collected, because the radiation is emitted isotropically and the majority does not intercept the detector rings. Both of these factors are addressed by extending the detector rings so that they cover the entire body (Fig. 1B). This concept we call "total-body PET" and allows almost maximal detection of the radiation emitted from the body. Computer simulations of a cylindrical phantom approximating the dimensions of the adult human predict that extending a PET scanner from a typical 20 cm axial FOV of view to a 200 cm FOV leads to a ~40-fold increase in the effective sensitivity (as measured by the noise equivalent counting rate) for imaging the body from head-to-toe (*1,2*). The major application where the entire body is imaged by PET is in melanoma. More commonly in clinical scans, the coverage is from "eyes to thighs" where the predicted sensitivity gain is ~24-fold. The gains for imaging a single organ (e.g. brain or heart) are more modest, because these organs already fit within the FOV of existing scanners. However, even here, the second factor is important and leads to a 4-5-fold increase in effective sensitivity.

Impact

The predicted 40-fold gain in sensitivity of a total-body PET scanner has major implications for molecular imaging. For a given scanning situation, the SNR in reconstructed PET images is dominated by the Poisson statistics inherent in radionuclide decay detection and is proportional to the square root of the number of detected events N. This in turn depends on the injected activity, A, and the imaging time T. To first order, the signal-to-noise ratio in a reconstructed PET image can be approximated by:

$$SNR \approx k\sqrt{S \times A \times T} \qquad \text{(Equation 1)}$$

where *k* is a constant and *S* is the effective sensitivity of the scanner. If the scanner sensitivity, *S,* is increased by a factor of 40, then the following consequences are apparent:

1) The sensitivity gain can be used to increase the SNR in the reconstructed image by a factor of $\sqrt{40} = 6.3$ using the same protocols (injected activity, imaging time) that we currently use. This could support reconstructing images at higher spatial resolution and would presumably allow detection of smaller or lower contrast structures/lesions and improved quantification in both static and dynamic scans.

2) One could choose to use the sensitivity gain to reduce imaging times by a factor of 40 while maintaining the SNR at its current level. Thus a 10-20 minute total-body protocol could be completed in just 15-30 seconds! One could argue under these circumstances that there could also be additional improvements in image quality, because there would be far less patient motion, and single-breath-hold PET imaging would be feasible.

3) Alternatively, the sensitivity gain could be used to reduce the injected activity by a factor of 40. Thus, total-body FDG scans could be performed injecting just 9.25 MBq (250 μCi) rather than 370 MBq (10 mCi) with the same SNR that is currently achieved (SNR may actually improve due to the reduced randoms fraction and dead time at lower activities). This would allow PET scanning at effective doses of <0.2 mSv, potentially opening up broader use of PET in sensitive populations (infants, children and adolescents), and also allowing up to 40 scans in a subject for the same effective dose they currently receive in a single scan.

A less obvious consequence is that the increase in SNR broadens the dynamic range of the scanner and allows radiotracers to be followed for longer in time before the signal decays to such an

extent that it is not detectable. A 40-fold increase in sensitivity means that a tracer could be followed for 5-6 additional half-lives (ignoring biological clearance) above the ~3 half-lives possible on existing scanners. For ^{18}F-labeled radiotracers this implies that imaging could be conducted as late as ~18 hours, ~3 hours for ^{11}C, ~18 minutes for ^{15}O, and for a long-lived radiotracer such as ^{89}Zr, sufficient signal might still be available for imaging ~30 days after injection. The wide dynamic range also improves the viability of multi-tracer studies, where a first tracer is injected at say 1/20th the activity of a second tracer introduced a few minutes later, such that the signal from the first tracer would only minimally interfere with that from the second tracer.

Last, but not least, a critical advantage of a total-body PET scanner is that the entire body is in the FOV at one time and every tissue and organ can be imaged simultaneously. This presents interesting opportunities for studying the body as a system and employing systems kinetic modeling approaches (*3*). Total-body dynamic imaging (*4,5*), which to date has been hampered by poor SNR and sparse temporal sampling due to the need for multiple bed positions, will be much more practical and the high SNR means that even very short frame data will carry high-quality information for kinetic analysis. Furthermore, the heart chambers and major blood vessels will always be in the field of view, enabling high-statistics image-derived input functions to be obtained for total-body parametric imaging.

TECHNOLOGICAL DEVELOPMENT AND CHALLENGES

History

The concept of long-axial FOV PET scanners is not new with a documented history of groups and individuals proposing and simulating such systems (*6-11*). There has been a slow, but inexorable, move to increase the axial length of commercial PET systems from the 10 cm common in the early 1990s to the 20-30 cm used in most systems today, however they still only cover a fraction of the body. The longest axial FOV scanner built to date was a 68.5 cm long research scanner developed by Hamamatsu (*12*). However, the slow and relatively low light-yield scintillator (bismuth germanate) necessitated the use of coarse axial septa to minimize scatter and count-rate problems, greatly reducing the possible sensitivity gain. There also have been a range of computer simulation studies

designed to examine the effects of longer axial FOVs and the impact on scatter and random coincidences, as well as to determine the most effective way to distribute a fixed volume of scintillator material given this is a key determinant in the overall cost of a PET system (*1,7,10,13-17*). The availability now of improved scintillation materials based on lutetium compounds, which have a more favorable combination of speed, light output and stopping power, have made it feasible to develop fully 3D systems that can handle the higher count rates and scatter fraction, and additionally also provide time-of-flight information to further improve performance.

Challenges

Developing a total-body PET scanner at this point is largely an engineering and economic challenge rather than a scientific challenge, although there are many difficult design choices that require optimized solutions. Existing time-of-flight PET detector technology used in current generation PET/CT and PET/magnetic resonance imaging (MRI) scanners can in principle be utilized. While it would be desirable to further improve timing resolution, and also incorporate depth-of-interaction encoding into the detectors to account for increased parallax errors caused by the long cylindrical geometry (*18*), the largest increment in sensitivity and utility comes immediately from the geometry of the total-body PET concept which covers the entire body and efficiently detects almost all the photons that leave the body, no matter which direction they are emitted in.

The first significant challenge relates to the event rates and system electronics. The rate at which single events are detected by each detector module is in fact no higher than in current systems for the same injected activity. The challenges therefore are at the coincidence electronics, which have to process data from many more detectors and will have to, in real time, handle far higher rates of singles and coincidence events. An alternative approach is to extract coincidences in software, after data has been collected. In this scenario, each detector module streams single events to disk with a precise and accurate time stamp, and coincidence events between modules are formed by sorting through all the singles data later. This removes the data collection bottlenecks, as data can be streamed onto multiple disks in parallel to support the event rate, as long as the data across all hard drives is properly synchronized in time. This singles-based acquisition approach also has the

advantage that timing and energy windows or weighting can be applied on an event by event basis during reconstruction, and can be varied after data is collected for optimal image quality for any given application. For example, applying a variable coincidence timing window, based on the known body contour (extracted from the CT scan) and length of a line of response through the body, will reduce the contribution of random events (*19*).

The second challenge relates to how large amounts of data (list mode datasets could easily contain tens or even a hundred billion events and reach > 1 TB in size) are moved around, processed and reconstructed in a timely fashion. This requires appropriate thought and investment in the computational infrastructure of the scanner to ensure that these steps do not limit the use and number of subjects per day that can be scanned. Ideally, the processing time for each study should be on the order of the acquisition time so that in the worst case, all data processing can happen overnight to process the previous day's acquisitions. With the need to reconstruct ~40-fold more events for a standard injected activity, and the large size of the image matrix given the large axial field of view, image reconstruction is likely to be the computational bottleneck. However, given the parallel nature of the problem, it is largely a question of providing sufficient computing power and memory, which is well within the capability of existing technology assuming that the computational infrastructure is properly resourced.

The third challenge relates to mechanical design and engineering. Detector modules need to be packed tightly together in both axial and transaxial directions as any significant gaps quickly reduce sensitivity. At the same time, modules need to have excellent temperature stability, cooling to handle the heat generated by the electronics, and must be accessible for servicing/replacement. These are perhaps some of the most difficult engineering challenges in realizing a high-sensitivity, reliable and robust scanner. There also are additional mechanical design issues related to the long cantilever of the bed, and the need for internal bore covers that are strong, low-attenuation, liquid impermeable and easily cleaned/sterilized.

The economic challenge will be an obvious one to the reader. What is the cost of such a device going to be? With healthcare costs increasing, how can such an expensive device be justified? At the present time, this question can only be addressed in part, because what ultimately

matters is the cost to benefit ratio, and the benefit cannot begun to be quantified until the first scanners are built and operational. Although a total-body PET scanner is roughly equivalent to eight conventional PET scanners, because of the CT and other components that are common, and also some economies of scale, the cost of a total-body scanner is NOT expected to scale by a factor of 8. Rather, initial estimates from industry suggest that a price tag of around $10M for a total-body PET/CT scanner is feasible, compared to $1.5 to $2M for a standard PET/CT scanner. Given that the cost of the instrument is only one component of the cost of carrying out a clinical PET scan, and that a total-body PET/CT scanner could do the work load of several PET scanners without the corresponding increase in technical staff and expensive hospital real estate, it is not impossible, even at this price point, that an economic justification can be made. A further impact on the cost infrastructure of PET is that the increased sensitivity of total-body PET permits studies to be performed using much lower injected activity, thus allowing radiopharmaceutical distributors to deliver clinically-relevant doses, over much longer distances, or produce many more doses per synthesis.

In the research environment, where we envision the main initial uptake of such a scanner would be, the considerations regarding cost are quite different. The ability to acquire unique kinetic data with a total-body scanner system, and conduct research that directly converges with the growing focus on systems medicine is hard to put a price on. Perhaps a reasonable analogy is to look at the evolution of MRI systems. The cost for a human 7T MRI scanner, with building/installation costs, exceeds the estimated $10M for a total-body PET/CT scanner. Yet, there are ~50 such installations in the world already. And one can argue that the incremental performance advantage in moving from 3T to 7T, and its impact on applications, may turn out to be at best comparable, and perhaps inferior, to the potential step-change in both performance and total-body imaging coverage provided by the total-body PET concept. Time will tell.

Multimodal Integration with CT or MRI

Total-body PET will also need integration with an anatomic imaging modality. From a workflow and cost perspective, CT is the most attractive starting point. Total-body CT scans can be acquired rapidly (potentially as subject is being moved into the PET scanner), and a standard CT scanner can

be used in the conventional tandem PET/CT configuration. The one major limitation of CT in this context is the additional radiation dose, which will be a factor when utilizing the low dose capability of total-body PET. However, there has been significant progress in low-dose CT protocols with advanced reconstruction methodology (*20*), and for diagnostic use, and many research applications, the effective dose using these techniques is likely acceptable. In instances where the CT is only needed for attenuation correction, further reductions in radiation dose are possible, as the spatial resolution and signal-to-noise requirements on the CT are somewhat relaxed. For applications where only extremely low levels of absorbed dose can be tolerated, there are other opportunities for deriving attenuation correction factors using either the natural background radioactivity present in the lutetium-based scintillators used in most PET scanners (*21*), or the introduction of a small number of external line sources, as transmission sources (*22*). When combined with time-of-flight information that can aid in separating events that arise from the radiotracer within the body from events arising from transmission sources outside the body, and advanced joint estimation reconstruction methods, very low dose simultaneous emission/transmission imaging may be feasible.

While integration with total-body MRI may be technically feasible, the fact that rapid total-body MRI protocols (*23*) are not widely employed and require movement of the subject through the relatively small homogeneous field region used for imaging, not to mention the costs and engineering challenges that would be associated with such a development, suggest it is prudent to start total-body PET developments using CT as the anatomic imaging modality.

REALIZING TOTAL-BODY PET

After six years of preparatory work, in 2011 we were awarded a grant from the National Cancer Institute as part of their “Provocative Questions” program to undertake detailed feasibility studies of total-body PET. We formed the EXPLORER consortium (*24*), led by the University of California, Davis, in collaboration with research groups at the University of Pennsylvania and the Lawrence Berkeley National Laboratory, to tackle this project and over the course of the last several years also have greatly benefitted from the input of expert researchers and clinicians around the world. In late 2015 we were awarded a Transformative R01 grant from the National Institutes of

Health under their High-Risk, High-Reward program (*25*) to build the world's first total-body PET/CT scanner. Significant progress now has been made towards the first prototype, and critically, there is now engagement with industry and the growing interest from within the molecular imaging community that highly increases the likelihood that total-body PET/CT will become commercially available. In this section, we summarize progress to date and describe the design of the first prototype system.

EXPLORER Mock-up

In collaboration with United Imaging Healthcare America (Houston, TX) we have developed a mock-up of the human EXPLORER scanner (Fig. 2) that allows us to study a range of practical issues related to the geometry of the scanner. The system consists of the gantry and bore covers, as well as the patient handling system. With this mock-up we plan to study patient tolerance of different scanning protocols, especially whether claustrophobia is an issue, and evaluate methods to reduce anxiety and motion using images projected above the patients' face, air flow through the bore and other approaches. We will investigate motion tracking strategies using cameras (both to evaluate how to minimize motion and also ultimately to apply correction for motion during imaging), and bed deflection and correction. We also will study challenges associated with injecting tracers for dynamic imaging deep inside the bore, as well as access for arterial blood sampling. Finally, we will use the mock-up to examine work flow and personnel requirements for different protocols, especially long dynamic scans with blood sampling and metabolite analysis. Once the actual EXPLORER is built, we plan to retain this mock-up to use as a simulator for subject training. This will enable us to allow subjects to gain experience and be more comfortable with the scanning environment without impacting scheduling on the EXPLORER scanner itself. This is likely to improve patient enrollment and compliance with imaging protocols for critical studies.

EXPLORER Total-Body PET/CT Scanner Design

The design of the first prototype EXPLORER scanner in collaboration with United Imaging Healthcare has been completed (Fig. 3) and components are currently being fabricated and tested. The detector modules are based on 2.76 x 2.76 x 18.1 mm LYSO scintillator crystals read out by

silicon photomultipliers (SiPMs). Based on preliminary measurements, these detectors exhibit an energy resolution of ~12.5% and a timing resolution of ~400 psecs. These detector modules will be assembled to form a scanner with a diameter of 78.6 cm (clear bore 70 cm) and an axial length of 195 cm. There will be a total of 564,480 LYSO crystals and 53,760 SiPMs in the system. A 64-slice CT scanner will be mounted on the front of the system for anatomic imaging and to provide the necessary information for attenuation correction. The footprint of the system (not including bed) is expected to be 290 cm long by 191 cm wide, and when accounting for the required travel of the bed, and space needed to separate detector rings for servicing, can be accommodated in a room that is 4-5 meters wide by 8-9 meters long which is not significantly greater than the room sizes used in most current PET/CT and PET/MRI installations. Both real-time coincidence sorting (up to acceptance angles of +/- 57°), and the option to stream all single events to disk and form coincidences off line, will be available. The expected effective sensitivity gain of this first prototype for an adult subject, relative to a Siemens mCT PET/CT scanner (*26*) which was used for baseline computer modeling and simulations, is anticipated to be between 30-50, with the exact number depending on the timing resolution that is achieved at the system level. Construction of the system is expected to be completed in the third quarter of 2018 with first imaging studies commencing shortly thereafter.

Concurrently, the University of Pennsylvania is designing a second prototype total-body system based on digital SiPMs (*27,28*) to evaluate the benefits of even better timing resolution in the total-body geometry. The detectors, which are based on those in the Philips Vereos PET/CT scanner, use 8 x 8 arrays of 3.9 x 3.9 x 19 mm^3 LYSO scintillation crystals, coupled in a 1-to-1 configuration to the digital SiPM sensor. Compared to the commercial implementation with these detectors which achieves a timing resolution of 320 ps (*29*) the total-body prototype will operate at a lower temperature (5–10˚C) to achieve a timing resolution below 250 ps. A prototype detector ring with a transverse diameter of 76.4 cm and an axial extent of 22.9 cm has been constructed and will be expanded to a larger axial FOV by adding further rings.

Mini EXPLORER

We also have developed a small-scale mini EXPLORER scanner designed to recapitulate some of the large axial acceptance angles of a total-body scanner, but on a more manageable scale that is appropriate for total-body PET imaging in nonhuman primates (rhesus macaques). This system allows the effect of collecting axially oblique lines of response (e.g. trade-offs between sensitivity, resolution, scatter fraction, randoms fraction) to be determined, as well as providing a platform for developing data correction and image reconstruction strategies. However, it has a second more important purpose, and that is to provide a fully functional system that can be used to develop and evaluate some of the more speculative or early-stage applications ideas in nonhuman primates prior to use in human subjects. This takes advantage of the fact that UC Davis is home to one of the seven national NIH-funded primate centers, and that the mini EXPLORER will be housed alongside an existing clinical PET/CT scanner in that facility.

The mini EXPLORER system is based on the components from a Siemens mCT scanner (*26*) which have been reconfigured into a scanner that is roughly one half the diameter and twice the axial length. This results in a system with a bore diameter of 43.5 cm, a transaxial field of view of 30 cm and an axial field of view of 45.7 cm. Performance characterization shows a sensitivity gain of 5-fold over the standard mCT using the NEMA sensitivity protocol (*30*), a peak sensitivity at the center of the FOV of 15% and a reconstructed spatial resolution of ~3 mm. Importantly, only very modest degradation of spatial resolution due to the high solid angle coverage and acceptance angles were observed. The system, along with representative images from a low-activity total-body FDG scan in a nonhuman primate, are shown in Fig. 4.

A second mini EXPLORER system has recently been developed based on the exact components that will be used in the human EXPLORER scanner. In addition to being the test environment prior to scaling up to build the human EXPLORER, this PET/CT system has been designed with companion animal applications in mind and will be installed at the UC Davis School of Veterinary Medicine.

APPLICATIONS FOR TOTAL-BODY PET

Human Research

The major motivation for developing total-body PET is to expand current, and more importantly open up new, translational applications for PET in the study of human disease. In addition, the capability of acquiring acceptable images using very low administered activities affords opportunities to study normal physiology at radiation doses below those received from a month of natural background, allowing the considerable power of the tracer kinetic principle to be applied, for example, in studies of development, aging, nutrition and exercise. It is anticipated that some of the clinical research areas in which total-body PET methodology is developed and applied may also lead to new health care applications for PET as part of the developing vision of personalized, precision, systems-based medicine (*31*).

A number of significant applications for total-body PET have already been identified through engagement with experts worldwide. We take a moment to briefly expand on several of these below. Undoubtedly, however, there are other opportunities that have been overlooked, or not even conceived of at this point. This provides a major motivation for writing this article, as we encourage researchers and clinicians from all disciplines to consider areas where this sensitive total-body imaging device could help generate new knowledge, improve disease detection, staging, prognosis, or inform and monitor therapy.

Systemic Disease: Cancer and Beyond. Total-body PET offers several opportunities to change the methodological approach to cancer detection and staging, and this same methodology could also be applied to other systemic conditions, including inflammation (e.g. sarcoidosis), vascular disease, sepsis and infectious disease. The increased sensitivity and dynamic range of total-body PET will allow imaging at high SNR at much later times after tracer injection. Tumor contrast typically increases with time as tracers clear from other tissues (*32,33*), thus later imaging may reveal a different picture regarding the extent of disease and allow smaller or less tracer avid lesions to be picked up. A second approach is to use the kinetic information inherent in any total-body PET scan. Even a relatively short (20-30 min) scan will contain considerable kinetic information that might be used to identify small regions of infiltrating tumor cells that are below the resolution limit of the scanner and cannot be seen directly, but alter the kinetics within a voxel sufficiently so that their

presence can be inferred (*34*). Such a paradigm could allow low-grade disease (cancer, inflammation, infection) to be detected and quantified. Tracers exist and continue to be developed for cancer and inflammation (*35*), and while specific tracers for a range of infectious agents (HIV, tuberculosis, malaria, parasites) are sorely needed, some are already in the pipe line (*36*).

Multi-Organ Disease. It has become increasingly apparent that many diseases and conditions thought originally to be confined within a single organ are much more complex and involve the interplay of that organ with other organs or systems (e.g. the endocrine system, immune system and the microbiome). An obvious example would be the emerging evidence of the role of the gut-brain axis (which includes the central nervous system, enteric nervous system, immune system and the gut microbiota) in diverse conditions such as anxiety, schizophrenia, autism and Parkinson's disease (*37*), which classically have been treated as purely the domain of the brain. This link is further reinforced by the fact that cognitive behavioral therapy has been shown to be effective for a range of gastrointestinal disorders most notably in irritable bowel syndrome (*38*). A second example of multi-organ disease would be the strong link between nonalcoholic fatty liver disease and heart disease, just one of several conditions where liver and cardiac disorders are intertwined (*39*). In a further example, a clear relationship between the availability of nicotinic acetylcholine receptors in the brain as determined by PET with hepatic nicotine metabolism, and its dependency on smoking, was demonstrated (*40*). While these findings lead to an increasing interest in studying and treating disease from a systems perspective, there are few tools and assays that can provide data to support such research. Total-body PET has the necessary capabilities (whole-body coverage, high sensitivity, non-invasive, low-risk) to permit human research in this area, although for many applications, new radiotracer development will be needed, for example, to support imaging of endocrine regulation or the mobilization and movement of immune cells to study immune-mediated inflammatory diseases.

Drug Development and Toxicology. The ability to determine the pharmacokinetics of new drugs in all the organs and tissues of the body at very low masses and radiation doses has the potential to accelerate translation of new therapeutic agents to humans (*41*). Early low-risk studies in humans circumvent the many limitations of using animal models to predict drug transport, metabolism and excretion, and could lead to better and earlier go/no-go decisions prior to launching expensive clinical

trials. The same holds true for new imaging radiotracers (or other imaging contrast agent) development, where pharmacokinetics and human dosimetry could be established using radiation doses that are well below the annual natural background. The ability to measure slower kinetics relative to the half-life of a given radionuclide across the entire body can be used to improve the precision with which the cumulated activity and thus the absorbed dose is estimated. Another area that whole-body pharmacokinetics capability would enable are toxicological studies. There are many unanswered questions regarding the fate and the biological effects of a range of elements, molecules and particulates found in foods, food packaging, consumer products and the environment that cannot readily be studied in humans using current techniques.

Monitoring Cellular and Nanoparticle-Based Therapies. Another paradigm where very high sensitivity is generally a prerequisite are imaging studies designed to track the fate of cells (*42*) or nanoparticles *in vivo*. With a growing number of clinical trials using therapeutic cells, and large numbers of preclinical studies showing the promise of nanoparticle-mediated therapies, many questions remain as to the distribution and fate of these cells and particles when they are introduced into the body. Radiolabeling these entities (*43-45*) renders them visible, but with current PET scanners, only large numbers can be detected, and they can only be followed for a relatively short period of time. Total-body PET has the potential to allow lower numbers of cells and particles to be detected, and following an injection of cells or particles labeled with a long-lived positron emitter such as ^{89}Zr (half-life 3.3 days), it may be possible to follow their fate *in vivo* for weeks or even a month. Total-body PET could thus be an important tool in measuring and optimizing the efficiency of cell-based therapies, as well as providing information on the delivery and retention of nanoparticles elsewhere in the body over extended timescales. A particular opportunity is to develop the necessary methodology to image the trafficking of immune cells to support the rapid clinical deployment and variable outcomes of cancer immunotherapy.

Maternal-Fetal Medicine. PET has seen virtually no use in human maternal-fetal medicine due to concerns over the effects of radiation on the unborn fetus. However, critical questions exist in maternal-fetal physiology, for example, brain oxygen utilization, which could be studied using $^{15}O_2$. Other opportunities include the transport of tracers of nutrients across the placenta, fetal inflammation

and infection. The risk due to radiation must be placed in the context of current diagnostic methods that are often invasive and themselves carry significant risk. Earlier work in nonhuman primates with PET (*46,47*) as well as recent clinical studies in humans with MRI (*48,49*) demonstrate the value of advanced imaging of the fetus. Total-body PET offers the possibility of conducting scans at extremely low radiation doses, indeed at doses that pregnant women are often exposed to from other sources such as intercontinental flights. Is there a case to be made for ultra-low dose diagnostic PET scanning in situations where the fetus and/or mother are at risk? (*50*) How far can the effective dose be reduced while still providing diagnostic information? Total-body PET opens the door to study these challenging questions, so that the risk/benefit trade-offs and related ethical considerations may be appropriately evaluated.

Normal Physiology and Metabolism. In its early days, PET was used as research tool (*51*), with a substantial number of studies being conducted in volunteers, especially to map out task-related activation sites in the brain prior to the advent of fMRI, as well as to study a range of physiological parameters in the brain and heart. It is our hope that with the low-dose capability of a total-body system, PET will once again become more widely utilized to study normal biology, metabolism and physiology, but this time addressing different sets of questions which are not amenable to study with existing tools. New metabolic tracers are becoming available, for example the recent introduction of ^{18}F-fluoroglutamine for imaging of glutamine metabolism(*52*). There are a broad range of studies that could be conducted to study the role of nutrition and exercise and their impact on metabolism, inflammation, the immune system, the cardiovascular system, the endocrine system and the microbiome. In addition to established tracers for metabolism and inflammation, new tracers will be needed to assess immune activation and hormonal regulation *in vivo*.

Clinical Care

While the primary driving motivation for developing total-body PET was originally clinical research, discussions within the community also have highlighted opportunities for improving current clinical care. Taking a standard “eyes-to-thighs” whole-body FDG cancer imaging protocol as a reference, we are anticipating that the first-generation EXPLORER scanner will be able to reduce

imaging times by approximately a factor of 24. Thus, a 12-minute multi-bed position study could be conducted on a total-body PET scanner in 30 seconds in a single bed position with the same image quality. The CT scan would be acquired as the patient moves into the PET scanner and thus the entire imaging examination can be completed in well under 5 minutes. Accounting for patient positioning, 40 patients per day (15-minute patient slots, similar to those used for CT examinations) seems entirely feasible for a 10-hour working day. Furthermore, images could be obtained, in a majority of patients, in a single breath-hold. That could reduce motion artifacts and significantly improve lesion detectability in some regions of the body (*53*).

An alternative approach, recognizing that with a 30-second acquisition time the throughput is no longer limited by the length of the PET/CT scan but by other factors, would be to use the 24-fold effective sensitivity gain for a more balanced three-way benefit. One could, for example, reduce absorbed dose by a factor of 2, reduce imaging time by a factor of 3 and increase the signal-to-noise ratio of the images by a factor of $\sqrt{4}=2$. The product of these 3 benefits is still consistent with the 24-fold sensitivity gain. How best to use the sensitivity gain for clinical studies is not clear and will need studies that interrogate not only the diagnostic quality of the resulting images, but also the workflow in the hospital and the weighting of radiation dose versus medical benefit. The low dose procedures point to the opportunity for using PET for selected screening applications, for example as a secondary screen for lung cancer following a suspicious low-dose CT scan.

A rapidly developing area of clinical application is the use of PET for monitoring radionuclide therapy (*54,55*), especially for neuroendocrine tumors and prostate cancer. Total-body PET should be an ideal tool for longitudinally evaluating the results of these therapies in multiple metastasis spread through the body.

The economics for employing a total-body PET/CT scanner in the clinic may at first glance seem daunting, yet a combination of much higher throughput, lower radiation dose and perhaps improved diagnostic performance (though improved SNR and/or reduced motion as a consequence of shorter scan times) might, in busy centers that currently operate multiple scanners, lead to an acceptable cost/benefit ratio. One must also account for the fact that that while the capital cost of a total-body PET/CT scanner will be high, there are other significant factors that determine the ultimate

cost of providing a clinical PET/CT service. A further consideration is that distribution of radiotracers becomes more cost-effective if lower injected activities can still yield high-quality images. It may even be possible to distribute tracers based on shorter-lived radionuclides, particularly ^{11}C, which could lead to new clinical applications. Overall, there are many forces that ultimately will determine clinical feasibility of total-body PET, including how the cost of the technology evolves, whether multiple vendors compete in offering FDA-approved systems, and an analysis of the benefit versus cost for specific clinical applications as the axial FOV is increased to 200 cm. Early total-body PET/CT systems will provide a platform for acquiring data that can start to address the latter question and time will tell how the other, less predictable, factors will impact the adoption of total-body PET.

TOWARDS FURTHER GAINS IN EFFECTIVE SENSITIVITY

While the dramatic increase in geometric efficiency of the EXPLORER scanner will provide a step-change in sensitivity, further significant gains are possible, specifically through improvements in detector efficiency and timing resolution.

Detector Efficiency

Current PET detectors do not capture 100% of the radiation incident upon them, indeed the 20-mm thick Lu-based scintillators used in many systems can theoretically detect no more than 68% of the available events, and the number is lower than this due to gaps and dead areas within and between detector modules, as well as by rejection of events that deposit only part of their energy in the detectors and fall outside the energy window. However, at best only an ~1.5-fold improvement in sensitivity can be achieved by using a combination of detector materials with better photoelectric cross-sections, further reductions in gaps and dead space, and thicker detectors (which will also require good levels of depth-encoding so that timing resolution does not deteriorate).

Timing Resolution

` Measuring the difference in arrival time of the two annihilation photons, defines, within the uncertainty caused by the finite timing resolution of the detectors and electronics, the location of the

decaying nuclide along the line joining the two detectors (Fig. 5). This "time-of-flight" information spatially constrains the location of the event, leading to improved SNR in the reconstructed image. The relationship is given approximately by:

$$SNR \propto \frac{1}{\sqrt{\Delta t}} \qquad \text{(Equation 2)}$$

where Δt is the timing resolution. Thus improving timing resolution from typical values of ~400 psecs available today to, for example, 100 psecs, would lead to a further ~2-fold increase in SNR. Since SNR is proportional to the square root of the sensitivity, this is equivalent to a ~4-fold increase in sensitivity. Laboratory results already have demonstrated sub 100-ps timing under idealized conditions (*56*), and as sensors, scintillators and detector designs continue to improve, we can anticipate that the timing performance of scanners will continue to get better. Looking even further into the future, it may be possible to exploit prompt mechanisms, instead of relying on the relatively slow production of scintillation light, to generate signals in detectors that could obviate the need for image reconstruction and provide event coordinates directly (*57,58*). This, however, would require a timing resolution on the order of 20 picoseconds to achieve 3 mm spatial resolution.

If future work enables these two additional gains to be combined with the expected 40-fold gain in geometric efficiency of the EXPLORER prototype, then effective gains of over 200 hundred-fold with respect to current whole-body PET scanners for total-body imaging are entirely possible. Improvements in timing resolution appear the most promising avenue for further improving the effective sensitivity of PET beyond the geometric gains that will be realized in the EXPLORER prototype. Of course, any gains from improvements in timing resolution will also be beneficial for conventional shorter axial FOV scanners.

SUMMARY

We are hopeful that the large gain in sensitivity of the first EXPLORER total-body PET/CT prototype will open up a new chapter in the history of PET development and applications. However, it is a beginning not an end. Many questions and opportunities need to be addressed. Concerns inevitably focus on the ultimate cost to benefit ratio for total-body PET imaging. Careful clinical

studies and demonstration of the ability of EXPLORER to generate new knowledge through research will be required to define the benefits. Prospects for cost reduction will focus on decreasing component costs (especially the scintillation crystals that are a dominant component), and defining the axial extent needed for specific applications. For example, recent demonstrations that BGO scintillator may be able to support time-of-flight PET (*59,60*) offer one pathway to lower-cost systems without sacrificing sensitivity. As indicated above, opportunities also exist to further improve the effective sensitivity, primarily through better timing resolution. Commercial PET/CT systems have already broken the 400 picoseconds barrier, prototype clinical scanners are closing in on 200 ps timing resolution and benchtop measurements with latest generation photodetectors are below 100 picoseconds. For now, the success or otherwise of this endeavor will depend on demonstrating clear-cut benefits in biomedical research and clinical care using the first total-body systems. Some of the possibilities enabled by the large leap in sensitivity and total-body coverage have been outlined in this article, however we suspect many impactful applications remain to be uncovered and developed. We look forward to working with the PET methodology, clinical research and health care communities, as well as industry, to write this next chapter in the history of PET.

DISCLOSURE

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FIGURE LEGENDS

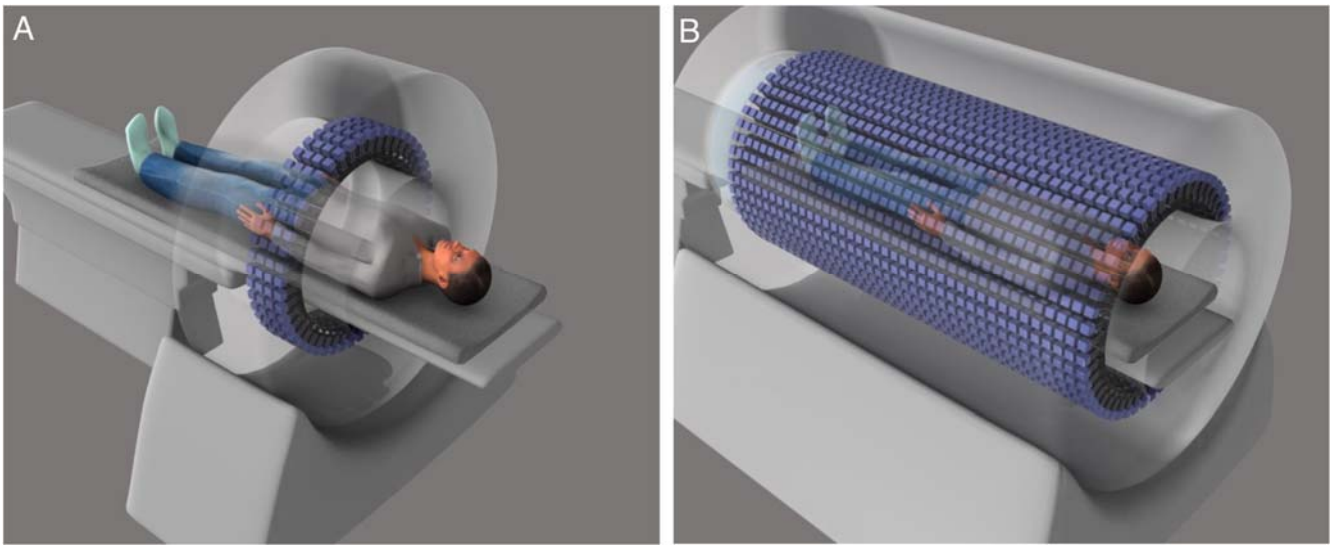

Fig. 1. Whole-body PET (A) versus total-body PET (B). Reprinted with permission from (*31*).

Fig. 2. Photograph of EXPLORER simulator installed at UC Davis Medical Center.

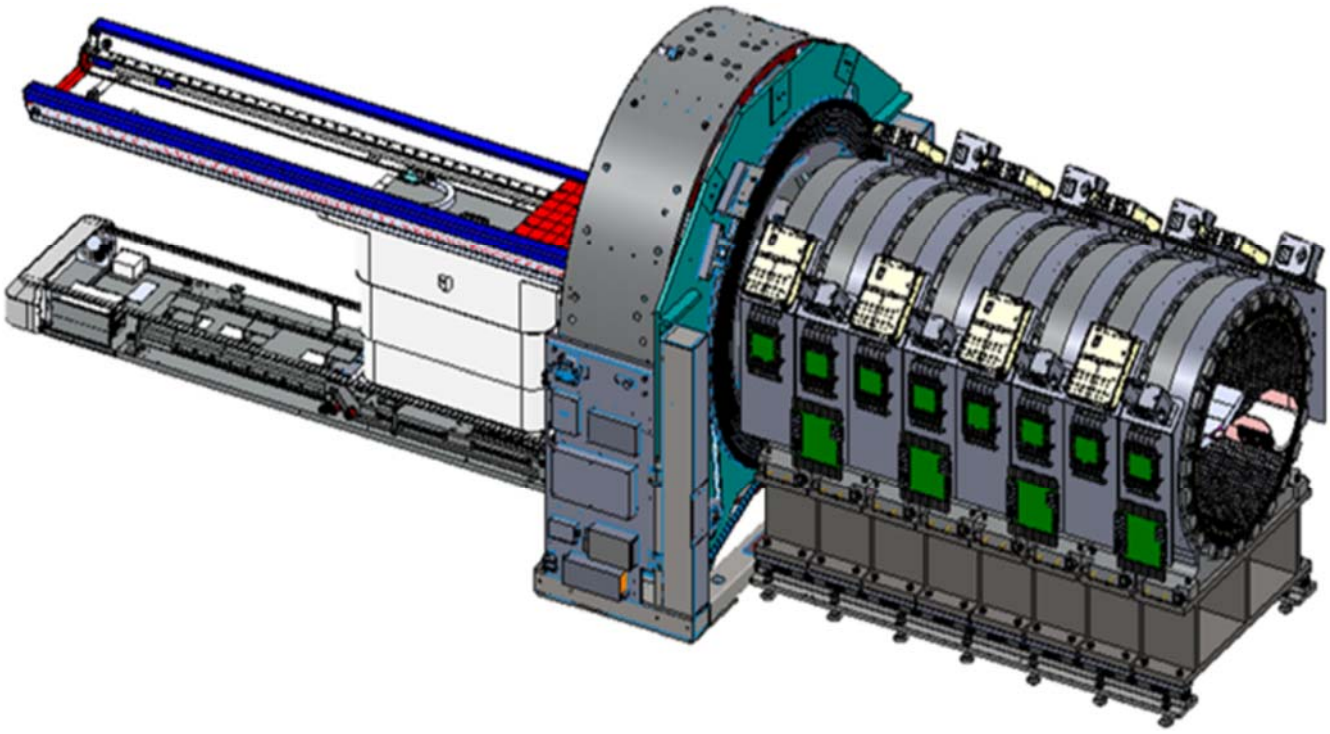

Fig. 3. Design drawing for the EXPLORER PET/CT scanner (courtesy United Imaging Healthcare).

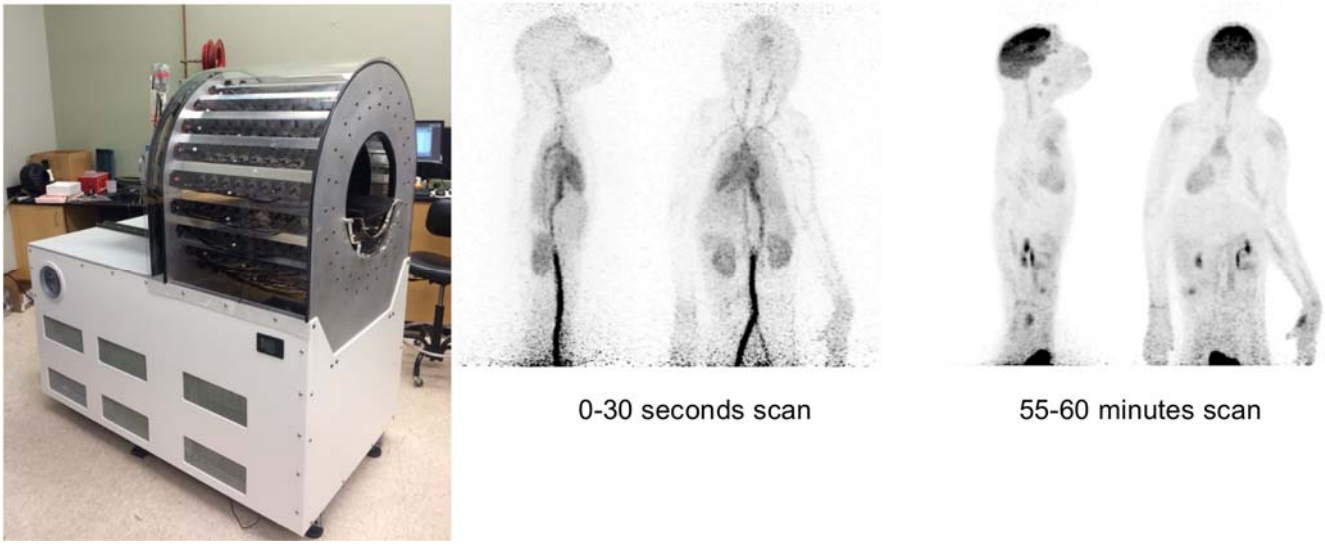

Fig. 4. Photograph of mini EXPLORER scanner (left) and maximum intensity projection images of two frames from a dynamic total-body imaging study following injection of 8.5 MBq ^{18}F-FDG (1/10th standard activity) in a 4.6 kg rhesus macaque (right).

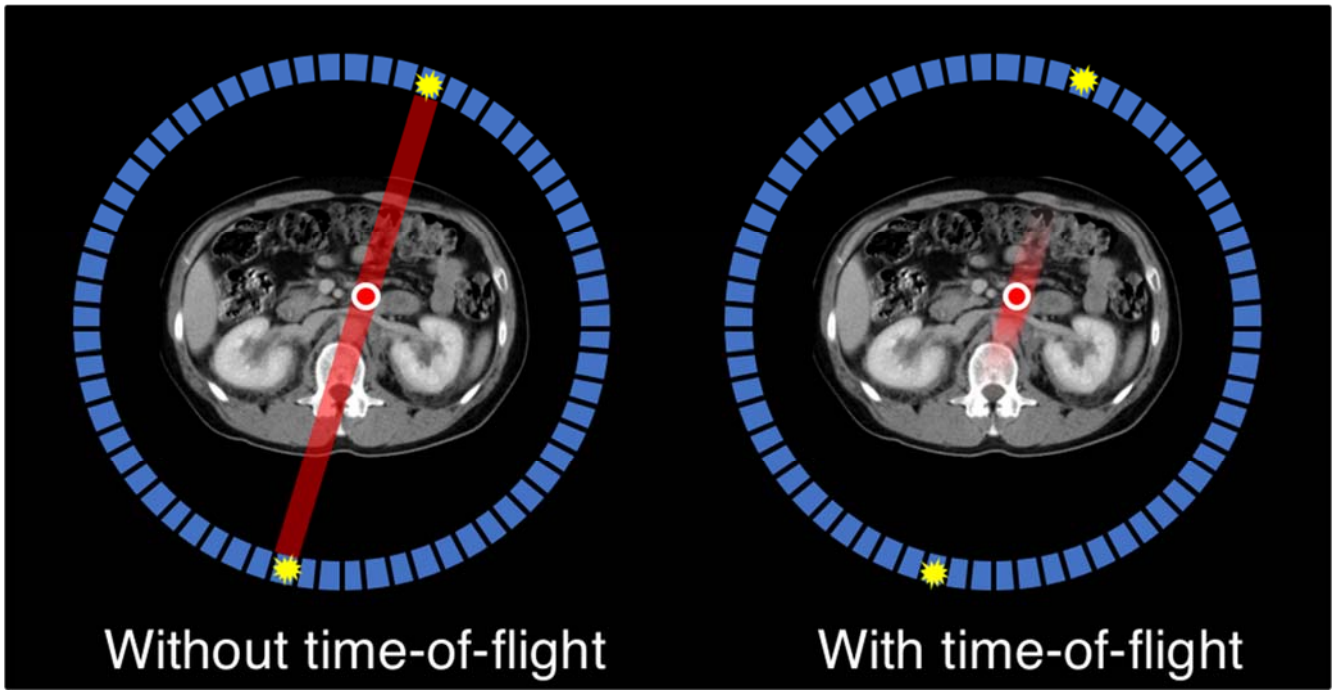

Fig. 5. Localization through time-of-flight PET showing effect of improving timing resolution. Better timing resolution translates into higher effective sensitivity due to the improved localization of each event.