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Issue Highlights

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Expert interview: Exploring the past, present, and future of total-body PET with Dr. Simon R. Cherry[1]

E: Dr. Cherry, thank you for joining us today to talk about your experience with total-body PET. Before we continue, we'd like to first congratulate you for winning the 2022 Benedict Cassen Prize from the Society of Nuclear Medicine and Molecular Imaging (SNMMI). We especially enjoyed your lecture titled "A Matter of Time" which showcased the development of PET over the years.

S: Thank you very much!

E: You have mentioned in your lecture, as well as in many of your past presentations, that the idea of total-body PET for adult human imaging is not new and can be dated back to 1990 when Dr. Terry Jones proposed the concept using parallel large detector panels. Can you please speak a bit about your early involvement in total-body PET and why you and Dr. Ramsey Badawi decided to pursue this concept?

S: That is a good question – if my memory serves me correctly, this all started about 18 years ago. At the time, the Department of Radiology at UC Davis was looking to hire someone well-versed in nuclear medicine physics. At the time I had no real connection with Radiology as my appointment was in the Department of Biomedical Engineering. However, I had known Ramsey from the time he was a graduate student at the University of London, and I was very pleased when Radiology recruited him to UC Davis.

Naturally, Ramsey and I quickly began chatting about research projects that we could collaborate on. Ramsey had done a lot of simulation work on longer axial field of view (FOV) PET systems up to 60 cm and studied effects such as random and scatter coincidences because the general consensus at the time was that the longer axial FOV PET systems would be dominated with these types of coincidence events, and therefore the idea would not be worth pursuing.

Ramsey's simulations on longer axial FOV PET systems showed that the effects of scatter and random coincidences did not grow as quickly as one might expect. Given Ramsey's interests in this phenomenon and my experience in preclinical instrumentation which already had relatively large axial FOV capable of covering an entire mouse, the conversation quite naturally turned to building longer axial FOV PET systems for human imaging.

I recall having the conversation about how long the system should be. At the time, the state-of-the-art clinical PET system was about 20 cm long. I am not sure who said it first, but we decided if we were going to build a long axial FOV PET system, we should take it to the extreme because otherwise you would always be left wondering what would happen if you built a longer system. The ability to capture the entire human body and watch the radiotracer move across the human body with improved sensitivity struck us as an exciting challenge that had never been attempted before. I think both Ramsey and I like big ideas and we are not afraid to take on those challenges. Shortly after, the total-body PET idea was born.

Looking back now I think we had no idea what the journey was going to be like. I would not have predicted that it would have taken so long. At the same time, I do not think I would have predicted that it would have been so successful either. So far, I have been very happy with what has transpired.

E: As many people know, the EXPLORER total-body PET system (now known as the uEXPLORER® system) was born out of a collaboration with United Imaging Healthcare. Can you please talk a bit about why you and Dr. Badawi decided to collaborate with a medical imaging device manufacturer? What are some advantages you saw with such collaborations compared to developing the system entirely in-house at UC Davis?

S: After we were awarded the $15.5 M transformative R01 grant from the National Institutes of Health in 2015, we quickly recognized that even though we had the funding, from the academic side we had little expertise or experience in building a PET system on an industrial scale. At the same time, we also realized we were going to receive a lot of attention due to the amount of funding we were awarded for this project. As many have experienced, academic projects can sometimes take longer than expected; and while the prototypes can produce images, they may not be stable or robust enough for routine clinical use. Therefore, we wanted to use the funding in a way that would lead to a lasting change in the field.

From the beginning, we were aware of the massive responsibility and that it was essential to collaborate with an industry partner. In fact, we have discussed the total-body PET idea with multiple companies even before we received the award. However, the response from industry at the time was generally lukewarm as they did not see a clear market need and were heavily invested in PET/MR technology at that time.

With that said, our first exposure to United Imaging Healthcare was at the IEEE Medical Imaging Conference in late 2015 where we met Dr. Hongdi Li (CTO of United Imaging Healthcare). I remember sitting down with him, and Hongdi was rapidly sketching ideas on the back of a napkin. He already had ideas about how to build a total-body PET scanner with United Imaging Healthcare technology and he offered to come to UC Davis to give a detailed presentation on how United Imaging Healthcare could help with the project within a couple of weeks, which he did. While we were impressed with his proposal, we did not know much about the company other than Hongdi. He then invited us to visit the United Imaging Healthcare headquarters in Shanghai several weeks later in January 2016. That was the pivotal point for us; in only 8 hours our perception of the company completely transformed despite its relatively young age. Although we had our doubts before visiting, after we toured the facilities and met the people we knew that we would move forward with United Imaging Healthcare, because we had found a team with *the same mindset* we had. I remember well that at the end of our visit, Min Xue, President of United Imaging Healthcare said "if you want to do this project with us, we will do it and we will do it well," and with those words and a handshake, the partnership was born. Total-body PET was an ambitious and difficult project, but it was worth doing. It was high risk, but United Imaging Healthcare leadership was willing to take the risk. They trusted and believed in us, and we trusted and believed in them, and it has worked out extremely well.

E: The term "total-body PET" has seen increased usage in the literature since the EXPLORER project was funded in 2015. Can you please talk about why you used the term "total-body PET" instead of the more common "whole-body" PET? What are the differences between the two?

S: The term "whole-body PET" has been in widespread use for a long time, and it typically refers to an eyes-to-thighs scan performed by stepping the patient through a conventional PET system in multiple bed positions. We needed a distinct terminology to denote the fact that we are not moving the bed and we are capturing the *entire human body at once*, and hence we created the term "total-body PET" to distinguish itself from "whole-body PET." The key distinction here is that "total-body PET" allows us to capture the kinetics across *all tissues in the body* by imaging the entire human *simultaneously* without moving the bed. Capturing kinetics across the entire human is very difficult and inefficient to achieve with "whole-body PET," especially when imaging radiotracers with faster kinetics.

E: Prior to the installation of the uEXPLORER system at UC Davis, you mentioned that total-body PET provides improved tradeoffs between scan time, radiation dose, and image quality. Having been the users of the first clinical total-body PET system in the world since 2019, what are some additional advantages of total-body PET that you and Dr. Badawi have realized?

S: Given the extensive amount of simulations we have previously performed, we had very high expectations for total-body PET and were not surprised by the image quality improvement achieved with the higher system sensitivity. However, after seeing the first images, we were amazed by the clarity and sharpness which were achieved with both high sensitivity *and* fine spatial resolution without the need to apply smoothing filters. In addition to the first dynamic total-body PET movie showing the radiotracer moving across the entire body, the ability to perform dynamic PET imaging of the entire body using 0.1 s time frames (which

has never been done before) and visualizing the cardiac cycle via PET was mind-blowing and eye opening.

E: What are some of the latest research projects you and Dr. Badawi are working on that were made possible using the uEXPLORER system?

S: One of the projects that we are involved in is the total-body imaging of CD8+ T cells for COVID-19 using ^{89}Zr-Df-Crefmirlimab-Berdoxam. This radiotracer has been used in cancer patients for immunotherapy, and the resulting radiation dose given to the patients, while justifiable, can be quite high. To use the same radiotracer to assess COVID-19 in recovering patients as well as in control groups (i.e., healthy volunteers), it is essential to utilize a PET system that can minimize the radiation dose administered to the patient.

To the best of my knowledge, we are currently the only people that have ^{89}Zr-radiolabled human imaging data with a control baseline from healthy human volunteers. This is because total-body PET is a necessity for imaging ^{89}Zr at greatly reduced injected radioactivity levels. The imaging of ^{89}Zr-radiolabled control groups would not have been possible without total-body PET systems. Also, with regards to the immune system, there are many chronic diseases where there may be value in scanning multiple time points (at 20 y/o, 30 y/o, 40 y/o, etc.) and performing interventional studies (e.g., before and after vaccination). These are new considerations that would not have previously been feasible without the large dose reduction enabled by total-body PET.

As always, we want to develop better and better next-generation PET systems to enable more novel clinical and research imaging applications. I hope this is just the beginning for these kinds of high-end PET systems, and I hope the field continues to push towards developing better systems in the future because we still have some ways to go.

E: When it comes to PET scanner performance, often the most discussed performance parameters are 1) sensitivity, 2) spatial resolution, 3) count rate performance, and 4) time of flight (TOF) performance. How would you rank the importance of each of these parameters to ensure the future success of total-body PET?

S: This is a difficult question – there needs to be a balance to a certain extent, because otherwise the PET system would be limited by its weakest link. Care must be taken to not overemphasize one performance metric over the other. There is no point in having spatial resolution if there are insufficient counts to support the spatial resolution, for example. The other way around is also sub-optimal – if there are tons of counts but the detectors have coarser spatial resolution, the annihilation photons are not being fully utilized. If there is excessive deadtime, there can be a problem with count rate performance. So, these metrics are all linked to each other.

Therefore, I am going to answer the question a bit differently and ask "Where would I put my efforts in going beyond the current total-body PET systems? Where can we improve further?" Obviously, TOF performance is an area where we can do better, and so I think in the next few years it is not unreasonable for current PET detector technology to reach 100 – 150 ps TOF resolution. Challenging for sure – but I am confident that there is a way to get there. Of course, we would like to go down to well below 100 ps, but that is going to require some technological advancements which will take a bit longer.

I think another area to emphasize is "How do we deal with Compton scattering within the detector?" When comparing the measured sensitivity of a detector versus the predicted sensitivity based on the stopping power and thickness of the scintillator, the measured sensitivity is often much lower. The reason is that a lot of those Compton scattered photons are rejected since they are captured outside the photopeak energy window, and the detector efficiency is much lower as a result. We need to have detectors that are thick enough so that all of the energy gets absorbed; however at the same time there needs to be a way to determine the energy and the location of each interaction to best determine the first interaction among multiple interactions. So, I think this is another area to improve – perhaps one that is not mentioned very much because it is a little bit more of a subtle effect.

One thing of note is that we are not going to be able to make much more improvements in geometric coverage. The uEXPLORER system is the epitome of ultra-high geometric efficiency, so little sensitivity improvement can be gained from extending the system beyond 2 m.

Finally, I think we need to continue searching for new

scintillator materials. If we can get materials with better photoelectric cross sections, then we can get fewer events where inter-crystal scattering occurs. While BGO is better than LYSO in terms of photoelectric cross section, we do not yet have a robust way to obtain timing resolution down to below 100 ps. However, there are other materials that are in the early stages of development that have very good photoelectric cross sections and can be very fast, so we need to see effort and funding going into these materials. It took a good decade of development for LSO and LYSO to get to a point where it is usable for a PET system, and it will likely take a similar number of years for some of these new materials.

E: One of the advantages of PET systems with increasing axial FOV is the increasing axial coverage with uniform sensitivity. With the uEXPLORER system the axial length with uniform sensitivity is about 1 m. Can you speak a bit about the advantage of having uniform sensitivity axially? Are there any advantages to further extending the PET axial FOV beyond 2 m so that the axial length with uniform sensitivity covers the entire adult human?

S: Good question – of course, there is a lot of debate about the optimal axial length of a total-body PET system. Proponents for the shorter axial length total-body PET systems suggest that only the major vital organs (e.g., from the brain to the pelvis) must be covered and not the lower limbs. If that is the goal, then a system that is slightly over 1 m should suffice for most adult humans. However, to have ultra-high and uniform sensitivity across that entire 1 m region, the system needs to be considerably longer than 1 m due to its geometric response. Otherwise, the sensitivity at the first few cm of either end of the system (where the brain and pelvic regions are located at) is no better than that of a conventional PET system. So, I think a total-body PET system needs to be least 1.4 – 1.5 m to have ultra-high and uniform sensitivity across all the major organs of the body.

Of course, it is a bit more complicated than that – as you accept more oblique lines of response, then those lines get more heavily attenuated. This leads to more scattered photons because they travel a much longer path length through the body. So, while for point sources one can continue to benefit from sensitivity gains as the axial length increases, the gain is not as dramatic when imaging adult humans. So, while the minimum length required I would suggest is 1.4 – 1.5 m, the optimal length beyond that depends on the intended application, because there are applications where there is a need to image beyond the 1 m "high sensitivity" region. Some examples of our own research projects requiring high sensitivity information outside the 1 m region include the assessment of rheumatoid arthritis where there is a need to survey all the joints in the body simultaneously, and where disease is present in the wrists, ankles, and the feet as well. So, if the goal is to survey all of that, and knowing the radiotracer uptake is not very high in these small structures, having a system with ultra-high sensitivity is essential. In such scenarios, a 2 m system will really help.

Another example is our T cell study in COVID-19 subjects. As many people know, one of the production sites of T cells is the bone marrow. There is lots of bone marrow in the long bones of the leg, and we have seen quite some differences in radiotracer uptake between human subjects in our studies. This is another case where there is a need to extend the axial coverage beyond the pelvis and into the legs while minimizing the radiation dose given to the human subjects by taking advantage of the ultra-high sensitivity of total-body PET.

So, if I want to have a high-end PET system that is also a high-end research instrument to support all types of research related to systems medicine, the human connectome, and the immune system, then I want to have a scanner that can see the entire body with ultra-high sensitivity, and that pushes me much closer to having a 2 m system. The optimal length may very well turn out to be a different number if the intended application of the PET system is only for routine clinical use, such as FDG clinical oncology. On the other hand, if the goal is to develop new clinical indications by understanding the processes and treatment effects using systems such as the uEXPLORER, I think we want the best instrument we can get.

It is a long answer – it is not a question that has a single correct answer, but I am very glad we are able to get the uEXPLORER system built to the length that it is because it shows us what is possible and allows us to do things that we could not do otherwise.

E: The current NEMA NU 2-2018 standard for evaluating the performance of clinical PET systems using phantoms with lengths of 70 cm or less is not designed to evaluate PET systems with axial FOV greater than 65 cm. As a result, longer phantoms have been used at UC Davis to better reflect the actual performance of total-body PET systems when imaging adult humans. Do you think that the next NEMA NU 2 standard should include tests appropriate for evaluating total-body PET systems? Is there a need to revise the standard so that the tests are suitable for clinical PET systems of all lengths?

S: I think the next NEMA NU 2 standard needs to account for total-body PET systems since the current measurements do not fully reflect the real-world performance of these systems. Although one of the approaches to address this concern is to image longer phantoms, the process is not a simple undertaking – long phantoms can be heavy and difficult to fill, which is a resource intensive process.

Therefore, the challenge for the NEMA committee and for those who are trying to contribute is "How do we come up with a meaningful set of measurement that is also practical to do?" I do not think there is an easy answer for that currently, but certainly the standard needs to be revised to account for the new class of systems so one can fairly assess their performance in comparison to shorter systems. Ideally, rather than developing a new NEMA standard for long axial FOV systems, there would be an integrated standard that works for any length of scanner. It will be interesting to see where that discussion goes and what ideas people come up with.

The other thing that is not properly captured with the current NEMA measurement is the impact of different TOF performance on the resulting reconstructed images, and that also needs to be considered in the new NEMA standard now that we have scanners with considerably better TOF. One could assume that TOF is going to get better and better in the coming generations of scanners, so we need to be ready for that.

E: Where are we going with total-body PET in the next 5 to 10 years? How can a medical device manufacturer help facilitate this process with academic researchers from both a scientific and logistical standpoint?

S: People may disagree with me on this – I think that it is not so challenging to operate total-body PET systems in the current clinical environment. At the same time, I feel that we are not using PET in the most quantitative way possible in the clinic – we are still largely using semi-quantitative metrics such as SUV_{max}! Therefore, my hope for the manufacturers is that they will recognize the opportunities and potential for PET to be an accurate measurement device for biomedical research, which means that the system must be precise and accurate over a massive dynamic range. Of course, while it is essential to achieve accurate quantification, it is not a trivial task.

Tomorrow's research will lead to future clinical applications. Once we can prove that we can accurately measure small changes in the human body, then perhaps later the semi-quantitative metrics can eventually be utilized in the clinic. If we consider the history of 2-Deoxy-D-glucose research, which began as a quantitative research tool in animals and certainly long before anyone considered its clinical role – I think we are going to need to do the same kind of deep investigation on new radiotracers to better quantify them and unveil their potential for future clinical applications. Total-body PET is going to be the measurement tool that I believe we are going to need; however, we must view it also as a scientific instrument, not simply a producer of pretty pictures. Too many people are only talking about its clinical role – about "Let's make it a little bit cheaper" or "Let's get the dose down" or "Let's make it a bit quicker." That is not changing the field, and we will never change the world that way.

E: Finally, what do you think the ultimate PET scanner would look like and when will it be developed?

S: As I have mentioned in the Cassen Lecture at the 2022 SNMMI meeting, I think the ultimate scanner will not require image reconstruction once the TOF resolution reaches 20 – 30 ps. This will create new possibilities for all kinds of novel system geometries and correspondingly detector usage because we will not be restricted by the traditional radial and angular sampling framework anymore. The systems may also be more patient friendly as well.

While we are on our way to developing the ultimate scanner, there are still a few things we need to first solve. One of the problems that stands out to me is motion. Even if we can make our scanner extremely quantitatively

accurate and get the best quality information possible from our data, the data is no good if the patient moves and we do not know where the motion comes from. Therefore, we need to find a robust way to measure and correct for motion of all types. I think motion correction is one of the greatest methodological challenges that will also take a long time to solve, but ultimately, I think motion artifacts can be drastically reduced. Thus, while developing the next generation of PET scanners, the software piece is critical as well.

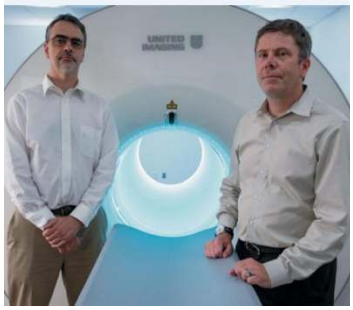
As we approach the limit where every count is carrying the maximum information possible, if we keep the detector efficiency high and detect *as many photons as possible*, we will be close to doing as well as we can. The technology that will enable us to do this is not available yet – there are several ideas for how to get there, and I think the answer to "When will we get there?" is:

"It's just a matter of time."

E: With that, Dr. Cherry, thank you very much again for your time and I hope you enjoyed exploring the past, present, and future of total-body PET with us!

S: My pleasure.

Expert's Biography



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Dr. Simon R. Cherry (right) is a distinguished professor in the Department of Biomedical Engineering and in the Department of Radiology at University of California, Davis (UC Davis). His work focused on various aspects of molecular imaging research, with an emphasis on position emission tomography (PET) instrumentation. As the co-director of the EXPLORER Molecular Imaging Center (with Dr. Ramsey D. Badawi, left), one of his most well-known research projects in the past several years includes the EXPLORER PET program, a $15.5 M transformative R01 project funded by the National Institutes of Health in 2015 to develop the first total-body PET system in the world. The program has led to the commercialization of the world's first and only total-body PET system capable of imaging the entire adult human in a single bed position (uEXPLORER) and has created new opportunities to study the human body using PET in ways that were previously not feasible due to the limited PET axial field of view.

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