Interview

Imaging in diabetes

Dr Anna Moore graduated from the Moscow State University (Moscow Russia) and holds a PhD in bioorganic chemistry from the Russian Academy of Sciences. She moved to the USA in 1990 and joined a Molecular Imaging Program at Massachusetts General Hospital/Harvard Medical School (MA, USA) in 1991, first as a postdoctoral fellow and then as a junior faculty member. Currently, she is an Associate Professor in Radiology and a Director of the Molecular Imaging Laboratory at the Martinos Center for Biomedical Imaging (MA, USA). Dr Moore is a member of the Affiliated Faculty of the Harvard-MIT Division of Health Sciences and Technology. Her research deals with noninvasive imaging of molecular targets in cancer, diabetes and neurological disorders. Dr Moore is a recipient of multiple grant awards from the NIH and other agencies, and her research has been published in high-impact journals including *Nature Medicine*, *Cancer Research*, *Diabetes*, *Radiology* and others.

Anna Moore
Molecular Imaging Laboratory, Athinoula A Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA
Tel.: +1 617 724 0540;
Fax: +1 617 643 4865;
amoore@helix.mgh.harvard.edu

■ **You gained your PhD in Bioorganic Chemistry from the Russian Academy of Sciences & came to MGH in 1991. What led you to research diabetes at MGH?**

This is a complicated question to answer as there was no imaging in diabetes back then. The reason I came to the MGH, or to the USA in general, was because there was no funding for science in the former Soviet Union, and I could not work there because there was simply no money. So in 1990 I moved to the USA to work as a scientist, and in 1991 I joined MGH.

■ **When did you carry out your first work on diabetes?**

The first work on diabetes was around 1998; before that I was studying imaging in cancer and it just so happened that the diabetes community was looking for new methods to assess diabetes and to find a tool for monitoring treatment of early diabetes, in which there were no tools at the time. We knew how to use imaging in cancer so we basically applied a similar concept to imaging in diabetes.

■ **Currently how many people are working on this at the Athinoula A Martinos Center for Biomedical Imaging, Harvard & MGH?**

In my lab there is approximately 15 people and we have several different projects. Imaging in diabetes is just one direction of my lab – we also continue to work on imaging in cancer. I collaborate with many people at the Martinos Center, Harvard and the broader Boston scientific community, and also within the USA and in other countries.

■ **What did you find from your early studies in animals?**

Taking into account that there were no studies on imaging in diabetes at the time, we were learning what the diabetes communities needed the most and what we could give them that they did not have. It emerged that there was a whole spectrum of different problems they had that could be answered by noninvasive imaging. One of the problems was noninvasive evaluation of functional β-cell mass. This was probably the most important thing for the diabetes researchers.

There were also other subjects that we could investigate and apply our tools to and see if we could resolve them, for example, imaging infiltration of immune cells in the pancreas. Infiltration of immune cells is the beginning of Type 1 diabetes, and by the time you start to see changes in blood sugar it is too late – the insulin-secreting β cells are already gone. β cells secrete insulin and in Type 1 diabetes these cells are under immune attack from the body's own T cells and, again, when changes occur in blood sugar it means that it is too late and the β cells are already under attack. What the diabetes communities wanted to see was whether we could detect this infiltration, this attack, ahead of time.

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There are also other manifestations of diabetes, for example, changes in pancreatic vasculature. This is something that could serve as a surrogate marker for early detection of diabetes. This was another opportunity for noninvasive imaging because there are many different ways to image vasculature. Imaging diabetic vasculature had not been done before. However, researchers gained a great deal of experience imaging tumors and the brain, so this knowledge and the acquired imaging tools could now be applied to diabetic vasculature. At present, people with diabetes receive drugs and can be monitored by blood biochemistry, but this does not always tell the whole story regarding the stage of the disease and does not provide an opportunity to look at what is going on in the pancreas.

■ What key technological advancements have enabled you to image β cells?

We are working in several areas, such as visualizing β cells, pancreatic vasculature, β-cell death and infiltration of lymphocytes. Another area is also the visualization of transplanted islets. Islet transplantation is really the only cure for Type 1 diabetes. Pancreatic islets are transplanted from donors; organs are donated and the cells are purified from these organs and then transplanted into Type 1 diabetes patients. The biggest problem that clinicians have with the procedure is that the islets were dying in massive amounts, for many different reasons. There is a great need to monitor these islets noninvasively, as biopsy should be avoided in these patients. We found that we could label the islets prior to transplantation with a contrast agent, then monitor those islets in the MR scanner, which worked quite well. We are currently carrying out studies in nonhuman primates, prior to bringing this method to the clinic. We are discovering many interesting things that the transplant teams were not aware of before.

We are going in many directions with imaging in diabetes, and are trying to cover the most important needs of clinicians. Of course, it will still be a long time before all of the research can be used in clinics as most of the studies are still at the level of small animals. In these studies, researchers bear a tremendous responsibility because you do not want to make sick people even sicker. Furthermore, you want to make sure that whatever you do with the islets, whether you label prior to transplantation or label them directly, you want the β cells to preserve their capacity for insulin secretion. That is the major problem that people have when they try to label cells – their function must be preserved.

■ With regard to the clinical aspect, at this stage, where do you think noninvasive imaging has the biggest potential: in the diagnosis or monitoring of diabetes?

I would say there is great potential in both. If you look at cancer research over the past 20 years you can see the tremendous improvement in the way people are treated. There is now an individualized approach to the patient, where the doctor can look at changes at the molecular and cellular level, and devise a unique protocol for that patient. That is what we ultimately want to see with diabetes – we want to be able to monitor every change that happens during treatment and to see whether these changes are positive or negative or ineffective and, depending on that, to provide better treatment.

Another important aspect is that pharmaceutical companies that are making drugs for diabetes patients are very interested in our research. At present, they are testing their drugs in mice, and the only way for them to see whether the drug is working is to sacrifice the animal after treatment, carry out histology on the pancreas and see whether the β cells are improving or not. If imaging tools were available it would not be necessary to sacrifice these mice, they could be followed over time, resulting in the use of fewer animals. In addition, you do not necessarily need to use very expensive clinical equipment as there are markets for systems for small animal imaging dedicated to rodents that can be translated to higher animals and then, eventually, humans. In drug discovery, imaging has an extraordinary role.

■ In terms of imaging in β cells, how early can diabetes be detected?

This is a very difficult question. Despite working on this for almost a decade we do not have a tool we can easily translate into

the clinic in terms of β-cell mass – it is still under development. We are looking for new markers responsible for early changes in β cells, prior to any changes in blood sugar. The changes in those markers could be imaged but it is hard to know how early.

I truly believe that at some point, we will be able to see all of those early changes and early markers of the disease. For example, in Type 1 diabetes, we can image the infiltration of immune cells. For Type II diabetes, which is more prevalent, there could also be an earlier marker. We need to keep in mind, however, that imaging β-cell mass *per se* does not really guarantee you early diagnosis. A patient can still have a full complete set of β-cells but something could be going on that you can only catch at the molecular and cellular level, and that is when noninvasive imaging could be useful.

So, it is hard to say how early diabetes could be detected at the moment, but the potential for early diagnosis is getting closer all the time.

■ What do you think about imaging screening programs, perhaps in high-risk groups to catch people before they develop full-blown diabetes?

I think this is definitely a good idea, especially in families were there is a history of the disease. This is something that could be done because there are certain markers of the disease that have been discovered to be responsible for diabetes and thus something we could screen for.

A moving factor for me personally was that my mom was diagnosed with Type II diabetes several years ago, although she is not obese and she exercises. With obese individuals, there is a 90% chance that they will experience trouble with their pancreas, but there is still 10% unaccounted for.

■ Going forward what obstacles do you think you will face? What are your challenges at the moment?

There are two types of obstacles: one is scientific and the other financial. Any research requires funding and with imaging research this does not come cheap. We hope that in the long run, despite using expensive techniques, which are actually getting cheaper and cheaper, our studies will bring the cost of diabetes down. Currently, the cost of diabetes is around US$200 billion a year in the USA. This is not diabetes itself; it is a systemic disease that affects the whole system – the kidneys, liver, then vasculature, limbs, vision, heart and so on. In the future, if we were able to provide early diagnosis through imaging, then this would bring the overall cost down. But the obstacle is that we need to finance this research right now. At present, we receive grants from the agencies that support us – the NIH and the Juvenile Diabetes Research Foundation – which is great, but more funding is definitely needed.

Regarding scientific obstacles, the pancreas is a very difficult object to image, as the pancreatic islets are of such a small size (150–400 μm). In addition, pancreatic islets represent only 1–2% of the whole pancreas mass and are scattered along the blood vessels of the pancreas. We have to find these small structures and somehow visualize them. These are the challenges.

■ Your research began in the visualization of cancer vasculature. Is this imaging technology applicable to other clinical areas?

Yes, the overall approach to imaging in diabetes is very similar to imaging in any other disease because it is necessary to find a certain marker of the disease. Once you have identified the marker, you then need to find a way to image that marker, whether through synthesizing a specific ligand that would target this marker or finding some other way to target it. It is a general approach that allows for imaging of certain events during disease progression, such as gene expression or a protein–protein interaction. In every case there are different markers/events going on, so of course you looking at very different things, but the overall approach is very similar.

Financial & competing interests disclosure

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