Discussion on ‘(Molecular) Imaging: Developments Enabling Evidence-Based Medicine’

H. Hofstraat

Healthcare Strategic Partnerships, Philips Research Laboratories/CTMM, Eindhoven, The Netherlands

Discussion

Dr. Nassar: Is a magnetic resonance spectroscopy (MRS) very sensitive in detecting mild derangements in the metabolism of the cell or does the cell have to be rapidly growing, such as a malignant or tumor cell, to be detected?

Dr. Hofstraat: The problem with magnetic resonance imaging (MRI) is that it is not very sensitive. Typically with MRI a little bit less than millimolar quantities are measured; 7-Tesla is more sensitive. Of course this limits application to those constituents of a body with rather abundant cells. If you are looking for the first signs of a disease for instance, it is impossible to do so with MRI. There you need to apply nuclear imaging if you want to measure a surface marker which is present in very low quantities. It is impossible to do that with MRI, with the techniques I just discussed.

Dr. Nassar: We performed MRS on protein energy malnutrition patients and the actual curves of the metabolites were not sensitive so we calculated the ratios between the metabolites for more information, but the primary curves did not help us much.

Dr. Hofstraat: Perhaps what you were doing should be looked at in more detail. At present we are doing MRS on the brain and we have been able to measure a number of active substances in the brain at millimolar concentrations. This is relevant, but sensitivity is also a problem, as is quantification.

Dr. Bier: You brought up the issue of cost which we would like to pursue because at least the development of MRI was facilitated to some degree in that it was able to answer clinical questions that could not be answered in any other way, and one could actually charge quite a lot for the service. But we are talking about nutrition where a great fraction of the questions are never going to generate any revenue. How does one approach this and what is happening with the cost of instruments? Many people in this room would love to have the 7-Tesla instrument, but can’t afford.

Dr. Hofstraat: Indeed cost is an issue particularly for nutritional applications and this is a fundamental question. We are presently finishing some discussions with the Dutch government about healthcare, not about nutrition. The questions are about medical technology and imaging instruments costing EUR 2.5 million. The questions are what does it bring, what does it replace, how does healthcare become less costly?
Of course the answer is that in the short-term it does add to the cost, but one needs to have a long-term view and not look only at medical technology assessment in the sense of one method being replaced by another and what does that mean, but looking at the intergrowth of the cost of healthcare. It is not about cost but about investment and return on investment, and at the moment we are very slow in making the transition. People are presently investing more in taking their car to a garage every year so that nothing goes wrong somewhere along the road, than in their own healthcare.

**Dr. Bier:** One of the issues with regard to MRIs originally being applied clinically actually resulted in a neologism in English called the ‘incidentaloma’, that is what is found incidentally that turned out to raise the cost of medical care for a lot of very healthy people. So it is hard factoring in where money can actually be saved and gets to be a difficult issue in prevention.

**Dr. Hofstraat:** Absolutely, this is a fundamental question. It is not just a matter of introducing an instrument but also introducing a solution rather than an instrument. This is an essential question which can basically only be addressed by collaboration between a company, like Phillips or Siemens, and clinicians.

**Dr. Brandtzæg:** I like your imaging ideas for the future very much, but I wonder if your ultimate goal is to get rid of the pathologists. Since all these techniques are non-invasive, they are an attractive idea. However, also pathology as such is now using imaging more and more. How do you see the future of combining the noninvasive and invasive molecular imaging in the evaluation of biomarkers?

**Dr. Hofstraat:** That is very much the future. Let’s take the example of nodule detection. You can find extremely small nodules with CT imaging. But many of these nodules that are found need not actually be treated because there is no problem with them. So pathology is needed to get additional information perhaps from biomarkers, from in vitro diagnostics, to work jointly with imaging to provide the right answer. However, this is sometimes difficult because tumors can be heterogeneous for instance. It is important to get the biopsy from the right position which may not be so easy, and here again imaging can help pathology by locating the tumor for biopsy. When the tumor biopsy has been obtained, it is brought to the pathologist who diagnoses the disease, and here also imaging and pathology go hand in hand.

**Dr. Gluckman:** Our particular concern of course is neonates and children. The issue for us is that, certainly in the neonatal period, one can do a quantification of body fat by MRI and DEXA because the child can lie still. But between about 3 or 4 weeks of age and about 5 years of age without sedation, we have a problem because of the time of movement. Do you see any techniques on the horizon that are going to be so rapid that it may be possible to get better measures of the metabolic state in a child without sedation? I think the combination of the sedation issue and the radiology issue, particularly if one is using a radiation-based technique, is really limiting our ability to ask the questions we really need to ask.

**Dr. Hofstraat:** That is certainly an issue. I showed the typical speed at which we can now take an MRI. For an adult of 2m height, it takes 40 s, but for a child it means a period of 10 s in which no movement should be made. We can correct for some movements, but it is very difficult to correct for erratic movements and that is really a problem. At the moment we are experimenting with an approach in which a scanner is introduced in what we call an ambient experience environment. Children, starting at 3 or 4 years of age, are guided by a dolphin and that helps to keep the children lying extremely still, even during a relatively long procedure. At the moment there is a tremendous improvement in the number of children who need to be sedated. It only helps, of course, as soon as the children are able to interact with their environment. It works, but it is not the solution for the whole problem.

**Dr. Gluckman:** Can you comment about the measurement of intrahepatic fat given the particular interest in hepatic fat as a measure in relation to the metabolic
syndrome and the new non-invasive technology for the measurement of hepatic fat?

Dr. Hofstraat: In principle it is also possible to measure hepatic fat. I am not a nutritionist so I am not able to comment on the importance of hepatic or other fats. There is also some literature on blood-borne markers, proteins in particular, that also may give some information. I am also interested in in vitro diagnosis and recently a group in Tubingen [1] published an article on that. So imaging is not necessarily the answer to all problems; in vitro diagnosis can also be of help.

Dr. Simell: In addition to the exposure time in small children, another big problem is the organ size. For instance the pancreatic islets have turned out to be tremendously difficult to visualize by any means. The other one is the gut which, from our point of view, is a very important organ. Do you have any ideas about how to do that?

Dr. Hofstraat: It is a matter of optimizing the instrumentation for the right application. For instance with CT or MRI, a rather high special resolution can be obtained, but generally that is at the expense of increasing the exposure time. For example, the rapidly moving bed scan gives sufficient data for adults, but I doubt whether the resolution would be enough for a small infant. We need to investigate that. We have developed a special MRI tool to measure small animals, rodents, where we can go down to a resolution of below 100 \( \mu m^2 \), I think it is 70–80 \( \mu m^2 \). It is a matter of optimizing for the right application, and the question of course remains whether somebody is willing to invest the money to do it. CT has the disadvantage that X-ray is needed, and to get a volumetric measurement you have to scan around. Even though we now have a 20-slice CT instrument it still takes some time and I am not sure whether one would want to do that repeatedly in small infants. With MRIs it is not as much a problem.

Dr. Walker: Along the same line of thinking there is a lot of interest in metabolomics and proteomics as a screening tool for biomarkers. Can you combine a less expensive technique such as that with your own more expensive techniques to define an early biomarker? Let’s say, for example, for a cardiovascular lesion because that is what we are looking for. We need to diagnose diseases much earlier so we can begin to prevent them.

Dr. Hofstraat: That is our ambition in this high risk initiative. It is based on 6,000 patient samples that are screened particularly for metabolites and proteins by BG Medicine. At the same time we do CT and MRI measurements on a subset of the same patients. The idea is that at some point you come to a screening approach in which the in vitro and in vivo diagnoses are combined, in vitro for early warning and in vivo for confirmation and to aid treatment. So that is exactly what is happening.

Dr. German: Since you are developing contrast agents as nanoparticles, could you actually use bacteria that would simultaneously be contrast agents and imaging metabolic markers? Further, since basically they go right through, they could be used in more of a surveillance mode and potentially even look at cross-talk with other bacteria in the intestinal mucus?

Dr. Hofstraat: Yes, very feasible. At the moment we are also developing tools to follow stem cells in the body and there will be no problem at all to follow bacteria as well. The question of course is under what circumstances you would be able to use these bacteria for diagnostic purposes. So there might be some requirements in order to do that.

Dr. German: We know little about that initial colonization of infants and how, for example, milk causes stimulation of appropriate bacteria. So if you could actually image using molecular contrast you could determine that particular bacteria are interacting?

Dr. Hofstraat: In principle that is very feasible. Indeed we followed stem cells which were labeled with nanoparticles or with very small iron oxide particles that can easily be followed with MRI. Then you can even see a concentration of cells, even
counting the individual cells, because in that case relatively large particles can be imaged.

**Dr. Polberger:** Do you think there is a future for imaging techniques of the brain as an evaluation of protein and/or nutrition?

**Dr. Hofstraat:** At the moment we are doing functional MRI of the brain. It enables us to see processes in the brain; you can actually see somebody think in principle. We have done some tests at the John Hopkins in Baltimore where children are doing things, such as looking at cartoons or they have a display with which they interact, and different spaces in the brain can be seen to become active. It is not on the average MR machine; some changes must be made to do that. It has been used for instance to identify children with attention deficit/hyperactive disorder. So in principle there are a lot of things that can be done with MRI to see the impact of chemistry or directly measure chemistry. The question though is what is the effect; is it a measurable signal or does it involve a material concentration that is sufficient for direct measurement in the case of MRI, or is it appropriate to use a radioactive analogon, so you can give a drug but at the same time have the radioactive analogon at a concentration of a few nanomolars present to enable detection? That is the question.

**References**