Interview

Imaging in prognostic radiology in cancer

Ralph Mason speaks to Sarah Miller, Commissioning Editor.

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Dr Ralph Mason, an expert in prognostic radiology, currently serves as Director of the Cancer Imaging Program at UT Southwestern (TX, USA), putting his experience of over 20 years in cancer imaging, therapy and tumor pathophysiology to good use. He is also a Professor of radiology and member of the Simmons Comprehensive Cancer Center. For many years, the work of Dr Mason and his colleagues has been supported by the National Cancer Institute, Cancer Prevention and Research Institute of Texas, Department of Defense breast and prostate cancer initiatives and various foundations. His primary research interest is prognostic radiology and his current work focuses on oxygen-sensitive MRI in various human cancers. In addition, Dr Mason is an expert in the development of novel ^{19}F NMR reporter strategies. His ongoing projects concern the investigation of novel gene reporter molecules, novel vascular disrupting agents and novel drug efficacy and approaches for the assessment of pathophysiology of tumor response to therapy.

■ **You are well renowned for your work on prognostic radiology in cancer. How did you first get involved in this field?**

Following general scientific training in Natural Sciences, I had the good fortune to pursue a PhD in Cambridge with Jeremy Sanders. He was a pioneer in the biological applications of NMR and encouraged innovations and imagination. At that time, I focused on bacterial metabolism [1], but it prompted me to explore the many diverse applications of NMR. Laurie Hall, a luminary in early MRI, suggested I pursue a postdoc in Dallas, which was just establishing small animal and human MRI in 1986. I joined the laboratories of Ray Nunnally and Peter Antich who posed challenges with respect to MRI of tumor pathophysiology and allowed great latitude to explore new applications.

■ **What are your main areas of current research, and is there a particular area that you are most excited about?**

My primary areas of research have included the development of fluorine NMR with particular focus on novel reporter molecules and the development of non-invasive assays of tumor pathophysiology. Considering fluorine NMR, there are incredible opportunities to explore oxygen dynamics, pH and reporter molecules for enzyme activity and gene expression. Fluorine is incredibly sensitive to the local microenvironment, and both chemical shift and relaxation processes can be tuned to respond to specific parameters. Indeed, the fun lies in innovations in chemistry, physics and biology to develop reporter molecules for effective molecular imaging [2]. Sometimes, it feels like we are competing in the Olympics, where we are all continually seeking methods that are faster, more precise, more specific and more sensitive. We always have the goal of improving spatial and temporal resolution, but ultimately, our goal is to develop agents that are practical in terms of general application with an eye towards clinical translation.

One application of ^{19}F MRI is for the evaluation of tumor oxygenation: hypoxia remains one of the primary limiting factors in terms of radiation therapy. For many years, it has been widely believed that lack of oxygen influences radiation response, but even today, there is no practical method to assess tumor hypoxia in the clinic.

We developed *in vivo* applications of the reporter molecule hexafluorobenzene to assess tissue oxygen heterogeneity, and perhaps more importantly, examine the dynamics in response to interventions. We have been able to demonstrate correlations between tumor oxygenation, its modulation

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and response to radiation therapy [3]. However, I recognize that fluorine NMR currently remains esoteric in human systems and therefore, we are exploring totally noninvasive methods based on the intrinsic characteristics of tissues to avoid the need of reporter molecules.

■ One of your most recent publications explores the use of blood oxygenation level-dependent MRI for evaluating early tumor response to chemotherapy. Where do you think this technology is heading?

Blood oxygenation level-dependent (BOLD)-MRI has become a foundation of investigations of brain function and neural activation in the form of so-called functional MRI. We cannot stimulate tumors in the same way; however, we can gain insight into tumor hypoxia, perfusion and oxygen dynamics in response to a challenge, such as hyperoxic gas breathing. In terms of clinical applications, oxygen-sensitive MRI has the great advantage that no specific exogenous reporter molecule is required. BOLD-MRI is directly sensitive to deoxyhemoglobin and this provides an insight into tissue vascular oxygenation. Our initial translational work has focused on the ability to apply this method to diverse disease sites. Our first work was in breast cancer, and we were particularly excited to find that those tumors exhibiting a large BOLD signal response when patients breathed oxygen ultimately showed the most successful tumor response to chemotherapy [4]. At this stage, our study is largely proof of principle that we can make the measurements, but the results are incredibly exciting in terms of moving towards a larger study and validating the notion that vascular oxygenation correlates with clinical response. This should be relevant to many disease sites and we have recently received funding to initiate studies of human cervical cancer, prostate cancer and now lung cancer [5]. Each disease site introduces greater complexity in terms of technical challenges, such as motion artifacts, but our preliminary data are very encouraging. We also realized that vascular oxygenation alone may not always correlate with therapeutic response and, therefore, we are adding T_1-sensitive MRI, so-called TOLD, and initiating studies which we like to refer to as DOCENT or Dynamic Oxygen Challenge Evaluated by T_1- and T_2*-sensitive MRI.

Ultimately, I envisage an oxygen-sensitive MRI screening exam to predict how patients will respond to standard therapy and using this as a basis to select patients for more aggressive therapy if they are predicted not to do well.

■ As Director of the Cancer Imaging Program at UT Southwestern, how does this particular program contribute to the wider aims of the National Cancer Institute Cancer Imaging Program?

Our Cancer Imaging Program was established through the National Cancer Institute pre-*In Vivo* Cellular and Molecular Imaging Center and the Small Animal Imaging Research Program grants providing impetus to develop infrastructure and interdisciplinary teams. It is now embraced by the Department of Radiology and the Advanced Imaging Research Center and forms a core resource of our Cancer Center. As envisaged by the National Cancer Institute, it has stimulated multidisciplinary collaborations including cancer biologists, chemists, physicists and imaging scientists. An early hurdle was persuading scientists from diverse disciplines to interact and, more specifically, establish common understanding of each other's capabilities and needs. The Cancer Imaging Program now serves as an effective catalyst to acquire new instruments, implement new techniques and technologies, and generate effective collaborations between diverse scientists.

From my point of view, some of the most successful and exciting current collaborations involve evaluation and application of novel vascular targeting therapeutics. Colleagues at Baylor University have been developing novel vascular disrupting agents and are interested in pharmacokinetics and pharmacodynamics to evaluate their efficiency [6]. Considering traditional dynamic contrast-enhanced MRI for examining tumor perfusion, we developed dynamic bioluminescent imaging. Recognizing that the emission of light from tumors is predicated on vascular

delivery of luciferin substrate, we explored and validated potential applications and now this has become a routine high throughput screen examining drug–dose activity relationships and time course of response. The dynamic bioluminescent imaging is particularly simple and effective for preliminary evaluation, but then we apply more sophisticated techniques, such as small animal ultrasound microscopy and MRI, to provide follow-up and deeper insights.

We also have the good fortune to work with colleagues developing engineered enhanced therapeutic antibodies, particularly targeting exposed vascular phosphatidylserine [7]. Here, bioluminescent imaging, fluorescent imaging, ultrasound, PET, SPECT and MRI are all playing a role.

Through the Cancer Imaging Program, we can rapidly assemble teams of investigators to tackle new challenges and point new investigators at the most efficient and effective methods.

■ How do you feel the field has progressed since you started out – has it been as you would have expected?

I think the greatest progress has been the commercial development and availability of robust instruments, reporter molecules and transfection vectors. In the past, every laboratory had to generate its own resources and early instruments were built in-house by teams of engineers. The new availability of diverse instrumentation, which is user friendly and provides data in convenient formats, has really transformed our ability to use small animal imaging as a routine rapid research tool.

■ What is the greatest advance that you have witnessed during your time in the field?

The incredible progress in the physics of image capture and reconstruction providing exquisite anatomical and pathophysiological details available through routine clinical MRI has clearly transformed clinical practice. In the laboratory, preclinical studies have probably been advanced most through the routine availability of bioluminescence imaging. The concept of moving the biology of the firefly to allowing routine assays of tumor growth, metastasis and vascular disruption is truly astounding. Indeed, it is quite exciting now to consider synthetic analogs of the luciferin/luciferase reaction to generate chemiluminescence, and this has become one of our recent interests.

■ What has been the highlight of your career so far?

Probably the most satisfying part of academic science is training new investigators to develop skills and build independent careers. Personally, my most exciting results have been the development of oxygen-sensitive MRI. In the preclinical situation, the ability to quantify tissue oxygenation and look at dynamic changes at multiple individual locations of a tumor using fluorine MR and then demonstrating its relevance to predicting response to radiation therapy has been my most satisfying outcome. Of course this is just a foundation and now moving this concept into the clinic is an impetus to continue research.

■ Looking to the future, what imaging developments would you like to see that could be game changers for improving cancer therapy? What challenges need to be overcome?

Multiple parameters are associated with tumor aggressiveness and potential response to therapy. Clearly, proteomics and genomics provide important insights, but currently there are no effective noninvasive tests for such characterization. In the long term, being able to effectively probe tumor heterogeneity for genetic aberrations will be crucial. In the immediate term, I strongly believe that tumor pathophysiology can provide crucial insights into tumor characteristics. Most significantly, we are already in a position to make such measurements and therefore, we need to develop a culture whereby patients are routinely screened for hypoxia and the ability to modulate hypoxia: we must then have the courage to use that information to choose the optimal therapy for a given patient. I believe we could rapidly make improvements to cancer therapeutic outcome by adopting oxygen-sensitive MRI as a crucial prognostic biomarker of tumor response to therapy.

■ Do you have any concluding comments or anything else you would like to discuss?

It is a pleasure to discuss research goals, needs and opportunities, so that a broader audience may appreciate the importance of current and future developments.

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