Cancer Imaging with Hyperpolarized $^{13}$C

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Routine clinical imaging in oncology utilizes cross-sectional techniques such as Computed Tomography and Magnetic Resonance Imaging for the anatomical localization of the primary tumor and its metastases. Functional imaging is increasingly being employed in addition to anatomical imaging to detect processes such as tumor blood flow and movement of extracellular water. Newer techniques are enabling specific molecules and molecular interactions to be imaged at the tissue and cellular levels; dissolution Dynamic Nuclear Polarization (DNP) is an example of these techniques which has been applied to molecular imaging in oncology (1). In combination with anatomical imaging, these functional and molecular approaches may increase the sensitivity and specificity of tumor detection, and determine whether cancer therapies have been effective at an early stage.

Nearly a century ago it was observed that many cancers demonstrate high glucose consumption and lactate production compared to normal tissue, even in the presence of oxygen. This phenomenon of aerobic glycolysis was an early example of how tumor metabolism differs from normal tissue. More recent research has revealed more about the role of metabolism in cancer showing that some rare cancers are directly linked to specific mutations in metabolic enzymes (e.g. succinate dehydrogenase), oncogenes and tumor suppressors can directly increase nutrient uptake and alter metabolism, and tumor growth can be modified by altering metabolic activity (e.g. with L-asparaginase). Positron Emission Tomography (PET) has been used for many years to image altered metabolism in patients with cancer, and the most frequently used tracer in PET is a radiolabelled glucose analog, $^{18}$F-labelled fluorodeoxyglucose (FDG); although PET is very sensitivity as a molecular imaging technique, it cannot differentiate individual products of metabolism and exposes the patient to a significant radiation dose. DNP may complement PET (2) by allowing the in vivo detection of injected hyperpolarized $^{13}$C-labelled molecules and the products formed from them, therefore allowing metabolism to be probed non-invasively in real time. Furthermore, although MRI is less sensitive as an imaging tool than PET (even when used with DNP), it is free of ionizing radiation.

To date, a number of $^{13}$C-labelled probes have been used in conjunction with DNP to detect tumor metabolism. $[1-^{13}]$Cpyruvate has several chemical properties which makes it suitable for the process of hyperpolarization and, when coupled with its rapid cellular uptake and exchange into lactate, pyruvate has become the leading hyperpolarized molecule pre-clinically and clinically. Changes in the exchange of hyperpolarized $[1-^{13}]$Cpyruvate to $[1-^{13}]$C lactate have been used to detect and grade tumors pre-clinically (3,4). A reduction in the measured hyperpolarized lactate following the injection of pyruvate has been used as a very early marker of response to chemotherapy (5); metabolic responses to therapy are likely to occur more rapidly then the changes in tumor size which are traditionally used to measure response to treatment. Furthermore, targeted therapies are increasingly being used in oncology which may not produce significant changes in tumor size despite a clinical response to therapy; therefore imaging methods to detect changes in metabolism may be clinically important. For example, inhibition of the phosphatidylinositol 3-kinase pathway has been shown to correlate with a drop in hyperpolarized $[1-^{13}]$C lactate levels in a number of tumor models (6). Therefore, the early clinical trials of DNP will assess whether hyperpolarized pyruvate can be used as an early treatment response marker for patients receiving radiotherapy and chemotherapy, particularly targeted therapeutics.

Hyperpolarized molecules other than pyruvate also offer promise for imaging in oncology; examples include hyperpolarized $[1,4-^{13}]$C fumarate for detecting necrosis, $^{13}$C-labelled bicarbonate for imaging tumor pH, $[1-^{13}]$C dehydroascorbate for measuring tumor redox status, $[1-^{13}]$Clactate as an alternative method for measuring lactate dehydrogenase, and hyperpolarized amino acids to detect changes in uptake and metabolism that occur in cancer (1,7). Although the translation of DNP to the clinic faces many challenges, it has the potential to aid diagnosis, identify disease heterogeneity, predict disease outcome, help target biopsies and determine treatment response non-invasively. The first human trial of DNP is being undertaken in prostate cancer using hyperpolarized $[1-^{13}]$Cpyruvate.