Shan, L. (2004). *Hyperpolarized (13)C-labeled bicarbonate (H(13)CO3(−)) for in vivo pH measurement with (13)C magnetic resonance spectroscopy. Molecular Imaging and Contrast Agent Database (MICAD).* Bethesda, MD: National Center for Biotechnology Information (US).

Magnetic resonance spectroscopy (MRS) is a technique that allows the noninvasive detection of multiple small metabolites within cells or extracellular spaces in vivo (1–4). Although MRS is theoretically applicable to any nucleus possessing spin, the more frequently investigated applications are in proton ((1)H) and carbon-13 ((13)C) (5–7). (13)C MRS is superior to (1)H MRS in many respects (3,7–9). (13)C MRS can provide specific information about the identity and structure of biologically important compounds. The chemical shift range for carbon (~250 ppm) is much larger than that for proton (~15 ppm), allowing for improved resolution of metabolites. However, (13)C MRS is limited by the low natural abundance of (13)C (1.1%) and its very low nuclear spin polarization ($2.5 \times 10(-6)$ polarization at 3 T and 37 masculineC) (2,3). Several techniques have been used to overcome these limitations, including dynamic nuclear polarization (DNP), which introduces one or more (13)C molecules into a metabolic substrate (2,3,9). Because the T1 relaxation time of (13)C in small molecules is much longer than that of (1)H (0.1–2.0 seconds in a magnetic field of 0.1–3.0 T), hyperpolarized (13)C-labeled tracers can be generated outside the subject and the magnetic resonance scanner (7). Nearly 100% nuclear polarization for (1)H and 50% for (13)C can be achieved in various organic molecules when DNP is performed in a strong magnetic field and at cryogenic temperatures. Replacing the (12)C isotope (98.9% natural abundance) with the (13)C isotope at a specific carbon or carbons in a metabolic substrate does not affect the substrate's biochemistry. Hyperpolarized (13)C-labeled substrates can provide >10,000-fold enhancement of the (13)C MRS signals from the substrate and its subsequent metabolic products, allowing the assessment of changes in metabolic fluxes in vivo and the imaging of blood vessels and tissue perfusion without background signal from surrounding tissues (1,3,4,10–14). (13)C MRS with DNP technique has also been investigated for measuring tissue pH in vivo (4,15). HCO3(−) is the primary extracellular buffer, and it resists changes in pH through interconversion with CO2 in the reaction catalyzed by carbonic anhydrase. In principal, tissue pH can be determined from (13)C MRS measurements of endogenous H(13)CO3(−) and (13)CO2 because their concentration ratio can be used to calculate pH from the Henderson–Hasselbalch equation with an acid dissociation constant (pKa) of 6.17 in vivo. On the basis of this principal, Schroeder et al. measured the pH in diseased and healthy cardiac myocytes with simultaneous detection of hyperpolarized [1−(13)C]pyruvate-derived H(13)CO3(−) and (13)CO2 (15). Their results suggest that hyperpolarized [1−(13)C]pyruvate with MRS detection of its derived H(13)CO3(−) and (13)CO2 can be used to measure the intracellular pH (pHi) of cardiomyocytes in vivo. Similarly, Gallagher et al. generated a nontoxic, pH-probe, hyperpolarized H(13)CO3(−) and exploited the pH in tumors with measurement of the H(13)CO3(−) and (13)CO2 concentration ratio after administration of hyperpolarized H(13)CO3(−) (4). The tumor microenvironment is characterized by low extracellular pH (pHe) and neutral-to-alkaline pHi (16,17). The average pHe could be as low as 6.0. A pH gradient (pHi > pHe) exists across the cell membrane in tumors. This gradient is contrary to that found in normal tissues, in which pHi (7.2–7.4) is lower than pHe. In addition, diffusion of the H(+) ions along concentration gradients from tumors into adjacent normal tissues creates a peritumoral acid gradient. Accurate measurement of