# pH in Cancer

RJ Gillies, H Lee Moffitt Cancer Center and Research Institute; Tampa, FL USA 33602
Robert.Gillies@moffitt.org

**Target audience:** – Clinical and Pre-clinical cancer researchers

**Objectives:** –

1. Understand the causes of tumor acidity
2. Be able to discuss some consequences of acidity that are relevant to carcinogenesis and therapy.
3. Discuss some of the approaches to measure Tumor pH with MRS, MRI, optical or PET methods.

## *Causes and Consequence of tumor acidity*

Two common characteristics of malignant solid tumors is a high rate of glucose metabolism, usually measured with FDG PET, and heterogeneous perfusion, usually measured with Contrast Enhanced MRI. The combination of these two characteristics leads to microenvironments that are hypoxic and acidic. It can also be shown that this characteristics are present early in carcinogenesis, and they are significant factors in guiding the somatic evolution of cancers. Conversion of a normal epithelium to metastatic carcinoma occurs through a series of steps along an evolutionary processes and hence represent the successful responses to sequential environmental selections. Commonly observed traits, or "hallmarks" (1), of cancer represent successful adaptation strategies to commonly experienced environmental selection pressures, including hypoxia and acidosis, which are not only highly selective, they can be shown to be genotoxic (2, 3). In addition to promoting evolutionary divergence in cancers, acid pH can also inhibit the activity of numerous chemotherapeutic agents(4).

## *Imaging tumor pH*

Interest in measuring tumor pH has a long history, and has been reviewed in (5, 6). Early measurements used radioactive weak acid tracers, and pH-sensitive microelectrodes. In the 1980's and 1990's, $^{31}$P MRS showed that the intracellular pHi of tumors was neutral-to-alkaline and that the extracellular pHe was acidic (7, 8). $^{31}$P MRS has limited spatial resolution and higher resolution can be obtained with $^{1}$H and $^{19}$F labeled agents which have been used to measure localized tumor pH using spectroscopic imaging (MRSI) with spatial resolution approaching 1x1x1 mm (9). These images show significant pH heterogeneity within tumors. Higher resolution pH measurements can be obtained with pH-dependent T1 relaxometry (10, 11). An issue with these measurements is the need for simultaneous pixel-by-pixel correction for concentration. An alternative method uses the rate of acid-catalyzed chemical exchange of hydrogens with bulk water to measure pH. This approach, chemical exchange saturation transfer (CEST), can be made more sensitive using pH-sensitive paramagnetic lanthanide chelates (ParaCEST) or through a large number of exchanging groups (DiaCEST) so that measurements can be made with clinically achievable doses. A related magnetization transfer approach interrogates the pH-dependent exchange of hydrogen with endogenous amides of peptide backbones. This technique, called Amide Proton Transfer, APT, has been successfully used in humans (12). In addition to MR approaches, optical approaches are well developed for pre-clinical models, and a number of SPECT and PET tracers are heading toward clinical use.

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