Monitoring Treatment Response

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Highlights:

- MR biomarkers can quantify non-invasively changes in tumor microenvironment in response to therapeutic intervention.
- They include, 31P and 1H MRS, anatomical MRI, diffusion and perfusion MRI.
- These MR biomarkers are a subset of molecular imaging biomarkers that can be used to improve the quality, efficiency and cost effectiveness of preclinical investigations of novel cancer therapies.

Title: Quantitative magnetic resonance of therapeutic response in animal models of cancer

Target audience: cancer imaging scientists, clinician scientists, drug discovery scientists, biologists and pharmacologists.

Objectives: It is anticipated that the audience will leave with a greater understanding of the history, and knowledge of current and future preclinical imaging technologies such that they will be able to either successfully:

- Incorporate MR into a multimodal imaging investigation of novel therapies,
- Develop novel MR biomarker technology,
- Undertake important validation experiments of MR biomarkers.

Purpose: This session will explore three main purposes of using MRI to quantify therapeutic efficacy in preclinical models of cancer:

1) Provide non-invasive tools for exploring the micro-environment in animal models of cancer

In this section the different MR technologies and what they can measure will be discussed. More specifically how and why MRI should be used to quantify tumor metabolism, burden, cell-density and vascular status using MRS, anatomical MRI, diffusion and perfusion imaging. Also to be discussed is how advanced image processing algorithms can be used to produce images of biomarker change. An example of which is functional diffusion mapping[5].

2) Provide validation of MRI biomarkers for translation as biomarkers for human clinical trials and patient management

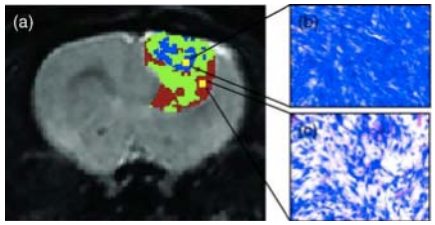
The field of MR is on the verge of providing several validated imaging biomarkers for use in clinical trials and patient management. The translation of these requires much validation. Preclinical investigations of these biomarkers

have and will continue to provide important information as to their validity, sensitivity and specificity.

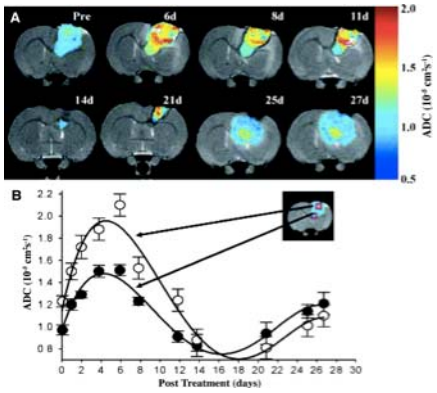
3) Improve the quality, accuracy, and efficiency of quantifying therapeutic efficacy in rodent models whilst reducing animal numbers.

Before novel therapies can be trialed in humans it is important that comprehensive preclinical data is acquired detailing the efficacy and mechanism of action.

The diversity of biological mechanisms that can be quantitatively imaged by MR means that quite a complete picture of the tumor microenvironment can be accomplished in one experimental session. The non-invasive nature of MR means that individual animals can be used as their own controls. In addition, the three dimensional nature of the spatial resolution allows for the heterogeneity of therapeutic response to be also quantified. These attributes allow for improved efficiency and reduced cost of these investigations without compromising quality and/or statistical power.

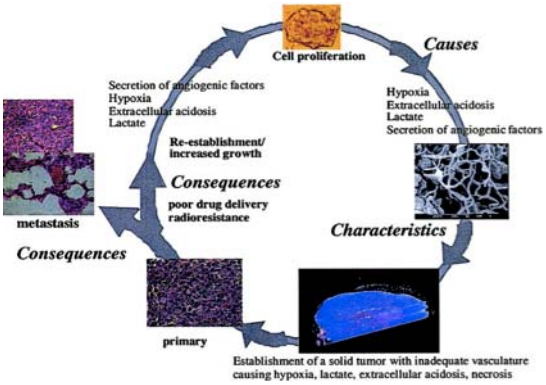


Functional diffusion mapping showing areas of increased b, blue voxels) and decreased (c, red voxels) cell density following chemotherapeutic intervention. [4]



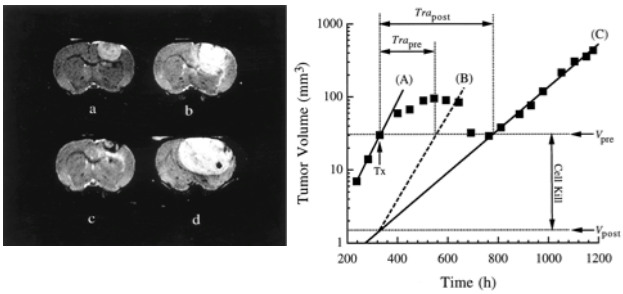
Imaging heterogeneous response using diffusion MRI. [7]

Methods/Results: Preclinical magnetic resonance (MR) technology is now part of a mature suite of molecular imaging technologies that can provide quantitative *in vivo* and non-invasive information regarding the changes within the tumor microenvironment[1] caused by therapeutic intervention.



Imaging the tumor micro-environment[1]

The use of *in vivo* MR to evaluate therapeutic response in cancer models dates back to the early 1980s when ^{31}P NMR was used to evaluate metabolic changes in mammary adenocarcinomas induced by therapeutic intervention [2]. Since then the use of quantitative MR has risen dramatically as cancer imaging scientists have exploited the significant advances in MR technology to quantify a rich array of MR based tumor biomarkers including, anatomical MRI[3], diffusion MRI[4-7], perfusion MRI[8], and MRS[2] to explore the biology of the tumor micro-environments response to therapeutic intervention (Figure 1).



Imaging changes in tumor burden allows for accurate calculations of tumor log cell kill. [3]

Conclusion: Multimodality preclinical core imaging facilities are becoming widespread within academic cancer research centers, pharmaceutical and contract research drug discovery programs, for which MR technology is a key component[9]. This has allowed preclinical imaging technology to mature to a level where its application is driven by pharmacologists, biologists and clinician scientists. As such there is now a strong move away from a modality-centric application due to a particular imaging expertise, to an "endpoint driven" application of imaging. Within this environment MR biomarkers should only be used if they are validated and provide tangible improvements over traditional methods.

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