

# Abstract

Although researchers have made great strides toward understanding the biological processes underlying cancer pathology, this has not led to major improvements in the management of the disease. Development of new treatments to combat cancer remains imperative. Nanosized therapies show promise to improve tumor treatment response by localizing therapy while reducing treatment-related toxicity. Understanding how nanotherapies are taken up and cause their effects at the intact tumor level *in vivo* will complement *ex vivo* histological and *in vitro* biochemical studies and facilitate the translation of nanotherapy treatments to the clinic. Currently, few *in vivo* methods exist to study nanotherapy uptake and response at the intact tumor scale. Magnetic resonance imaging (MRI) and positron emission tomography (PET) are imaging methods that provide different but complementary information about the tumor microenvironment and nanotherapy uptake/response. Direct spatiotemporal correlation of PET and MRI data via their simultaneous acquisition has the potential to be powerfully synergistic, especially for the study of physiological processes that are time sensitive or where good spatial coregistration of the multimodal data is important. As the field of hybrid PET/MRI is still in its infancy, with only a handful of active systems worldwide, it is vital that continued PET/MRI technology development be pursued to realize its full potential.

The objective of this thesis is to develop noninvasive, multimodal PET/MRI methods to study the uptake and response of cancer nanotherapies. Three studies were pursued toward this goal. First, we describe the development of a quantitative, small animal simultaneous PET/MRI system that is capable of dynamic, intratumoral imaging. The results show that the system provides quantitative images that are highly correlated with *ex vivo* autoradiography. The system was able to follow the uptake of a radiolabelled antibody inside the tumor over time, visualizing antibody movement from the vascular space to the tumor mass. Second, we adapted a functional MRI technique, diffusion MRI, to monitor treatment response of the cancer nanotherapy CRLX101. CRLX101-treated ani-

mals showed a significant diffusion MRI response within 2 days of treatment, before significant size changes were observed. Modeling of the diffusion MRI data was able to predict the potent antiproliferative effect of CRLX101, commensurate with histological data. Finally, we developed MRI and PET/MRI methods to study the tumor response to the tumor-penetrating peptide iRGD, which has shown good potential to improve cancer nanotherapy uptake. The results show that iRGD can have a variable tumor response, which may be dependent on the tumor microenvironment.

The primary contributions of this thesis work is the development of small animal hybrid PET/MRI technology to enable multimodal intratumoral studies and the development of clinically-applicable imaging methods to monitor the uptake and response of cancer nanotherapies.