Targeting the Sodium Iodide Symporter for *In Vivo* Detection and Characterization of Mammary Tumors in the Murine Model Using a Novel Gamma Camera

Randall Eric Blue

Pembroke, North Carolina

B.S., University of North Carolina at Chapel Hill, 2005

A Thesis presented to the Graduate Faculty of the College of William and Mary in Candidacy for the Degree of Master of Science

Department of Biology

The College of William and Mary

August, 2009

APPROVAL PAGE

This Thesis is submitted in partial fulfillment of
the requirements for the degree of

Master of Science

Randall Eric Blue

Randall Eric Blue

Approved by the Committee, July, 2009

Committee Chair
Professor Eric L. Bradley, Biology and Applied Science
The College of William and Mary

Professor Margaret S. Saha, Biology
The College of William and Mary

Associate Professor Patty Zwollo, Biology
The College of William and Mary

COMPLIANCE PAGE

Research approved by

W&M Institutional Animal Care and Use Committee

W&M Institutional Biosafety Committee

W&M Institutional Radiation Safety Committee

Protocol number(s): IACUC-5504-elbrad

IACUC-5872-elbrad

IBC-5913-mssaha

IRS-09-02-elbrad

Date(s) of approval: 2009-06-22

2009-03-17

2009-03-24

2009-01-01

ABSTRACT PAGE

Effective diagnosis and treatment of breast cancer rely on a precise and detailed understanding of the cellular-molecular alterations that give rise to an oncogenic phenotype. With the advent of new imaging technologies investigators have begun to follow mammary tumor development in vivo and noninvasively with high resolution and sensitivity. Continued progress requires combining molecular biology and imaging with the goal of imaging the metabolism of specific tumor-related molecules. As a result, we have developed a novel small animal gamma camera that is capable of detecting low levels (0.52 MBq, 14 uCi) of radioiodine (^{125}I). The dynamic uptake of ^{125}I through the sodium iodide symporter (NIS) was used to detect the progression of spontaneous mammary tumors in the mouse mammary tumor virus (MMTV) model as well as the transgenic animal model expressing the polyoma middle T oncoprotein (PyVT). Based on whole mount immunohistochemistry, NIS protein expression correlates with the gamma camera images of ^{125}I, which is also a promising radiotracer for detecting small, non-palpable tumors (3 mm). Additionally, gamma imaging was capable of identifying PyVT mice from their wild type littermates based upon their ability to accumulate ^{125}I in nulliparous mammary glands as early as 5 weeks of age. MMTV tumors are classified into three groups based on their unique ^{125}I distribution that is correlated with tumor size, but not propagation rate. Differences in ^{125}I uptake gain (or loss) are dynamic especially during early dose administration. Finally, mammary glands show differences in uptake pattern when a tumor is present.

Taken together, these results suggest that radioiodide imaging is a promising in vivo method for monitoring the changes associated with tumor development such as changes of tumor size, pattern, and aspects of gene-specific metabolism over both short and long durations. Our results also indicate that the classifiable heterogeneity present in dynamic gamma camera images may correlate with specific patterns or signatures of gene expression that, in turn, indicate tumor subtype and progression. These data may allow investigators to develop an effective and sensitive system of in vivo imaging of molecules and metabolism that reflect the molecular signature of a tumor in real time. Our system may provide a means for early detection, ideally even a precancerous state before malignancy develops, and a method to assess the overall state of a tumor with the goal of predicting the best therapeutic regime and following the efficacy of the therapy in real time by examining specific molecular targets.