TABLE OF CONTENTS

Dedication	iii
Acknowledgments	iv
List of Tables	vi
List of Figures	vi
Chapters:	
1: Introduction	1
Overview	1
Epidemiology and Molecular Biology of Breast Cancer	2
Breast Cancer Models	5
In Vivo Imaging of Breast Cancer	10
The Sodium Iodide Symporter and Breast Cancer	16
Goals of Project and Hypothesis	19
2: Materials and Methods	20
Animal Models	20
In Vivo Gamma Imaging and Data Acquisition	21
Image Analysis	22
Difference Plots	23
Specimen Fixation and Whole Mount Immunofluorescence	24

Immunohistochemistry	25
Apoptosis and Necrosis Staining	26
Statistics	26
3: Results	28
MMTV Tumor Distribution	28
Imaging Radioiodine Uptake In Vivo	29
In Vivo Screening for PyVT Mice	31
The Unique Biodistribution of Radioiodine in MMTV Tumors	32
Relationship Between Tumor Size, Uptake Patterns	32
Difference Plots	36
In Vivo Imaging of MMTV and PyVT Tumor	37
MMTV Tumorigenesis Influences ¹²⁵ I Accumulation	38
Comparisons of the Radioiodine Accumulation in Spontaneous	39
4: Discussion	63
Future Directions	70
Conclusion	72
APPENDIX	77
In Vivo Imaging of the Sodium Iodide Symporter	77
Dual Modality Application of the Gamma Camera	96
List of References	99
Vita	112

Dedicated to my parents Randall and Sylvia, to my brother Matthew, and to my grandmothers Dorothy and Arbiadella for all their love and support

ACKNOWLEDGEMENTS

I would like to thank my family for all their love, support and words of encouragement as I continued my education farther from home than they would have liked. I would like to acknowledge my advisor Dr. Eric Bradley for giving me the opportunity to work in his laboratory for the past three years on the breast cancer imaging project, and I appreciate the wealth of invaluable advice and training I have received from him in the laboratory. I appreciate all the support and opportunities I have received from Dr. Margaret Saha. It has been my pleasure to work alongside her in both the laboratory and in the classroom, and I find her acumen for teaching and science a treasure that I will always strive to attain. I also appreciate the anatomical training on mouse mammary gland biology, resection and implantation I received from Dr. Nicholas Kenney. I also greatly appreciate the assistance of my thesis committee member Dr. Patty Zwollo.

I greatly value the research training, support and companionship I received from former and current members of Dr. Bradley's laboratory and the biomedical imaging project team. I am grateful to Stephen Schworer for welcoming me into the lab and helping me during the beginning of my research. I also thank him for all the contributions he made to the biomedical imaging project and for being a true friend. I will forever be indebted to Dr. Jianguo Qian for all his initial work on the breast cancer imaging project and for teaching me how to use the gamma camera. I also thank Dr. Robert Welsh, Amir Yazdi and Jonathan Sutton for their contributions to the breast cancer imaging project and for developing the ROI program that has become invaluable to my research. I am truly appreciative of the support and companionship I have received from Alexandra Garafalo. I have been honored to work beside of her while striving to expand our breast cancer imaging project to ever new heights. I would finally like to thank Dr. Saha's laboratory member Matthew Wester for his perspicacity and technical assistance for the last three years.

This work was supported by the HHMI Undergraduate Science Education Program Grant to the College of William and Mary, the National Institutes of Health (National Institute of Biomedical Imaging and Bioengineering) (NIH/NIBIB) Grant (R15 EB000458), the College of William and Mary Arts and Sciences GSA Research Grant, and by the Department of Defense Breast Cancer Research Program (BC046053).

LIST OF TABLES

Table	Page
3.1. Prinicpal component scores for extracted MMTV variables	
3.2. Summary of the <i>in vivo</i> MMTV tumor development study	<u></u> 59
Appendix Table 1. Summary of imaging information for mice	

LIST OF FIGURES

<u>Figure</u> <u>Page</u>	
2.1. The second generation compact gamma camera22	
3.1. The distribution of MMTV mice used for the <i>in vivo</i> 41	
3.2. Nulliparous mouse shows no ¹²⁵ I uptake in the left42	
3.3. Gamma camera detects ¹²⁵ I uptake in a MMTV left43	
3.4. PyVT gamma image from a sixty minute imaging session44	
3.5. Gray scale three dimensional pixel luminescence 44	
3.6. NIS expression patterns in an early PyVT tumor45	
3.7. Example of gamma camera screening of the PyVT model46	

3.8. PyVT mammary gland ¹²⁵ I uptake	47
3.9. Contour plots of the three types of ¹²⁵ I distribution	48
3.10. Box plot analysis, comparing MMTV tumor	
3.11. MMTV tumor size positively correlates with tumor	50
3.12.1. Based on the correlation data, two trends of ¹²⁵ I uptake	51
3.12.2. Each cohort's dynamic ¹²⁵ I uptake was averaged based	52
3.13. Clustered variables based on the coefficient matrix	53
3.14. The first component extracted from the PCA test	54
3.15. The second component extracted from the PCA test	55
3.16. Box plot analysis, comparing PyVT tumor size	56
3.17. PyVT tumor size positively correlates with tumor	
3.18. Contour plots of the change in radioactive counts within the	58
3.19. Contour plots of a PyVT mouse imaged three times	60
3.20. The gamma image of a MMTV tumor bearing mouse	61
3.21. For the comparison study, the distribution of MMTV	62
4.1. Low power (10x) H&E stain of a cryosection	74
4.2. Low power (20x) immunhistochemical staining for AREG	
4.3. Gamma camera detects five tumors in an MMTV animal	
4.4. Gamma camera imaging of an MMTV animal 4 hours	76
Appendix Fig.1. A reconstructed coronal image from the 4 hour	<u>93</u>

Appendix Fig.2. Plot profiles of mphSPECT and NIS localization	<u></u> 94
Appendix Fig.3. ROI analysis of the individual mouse thyroid	
Appendix Fig.4. In vivo dual modality imaging of an MMTV mouse	
Appendix Fig.5. <i>Ex vivo</i> dual modality imaging analysis of a left	<u>98</u>