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Correlating MALDI and MRI Biomarkers of Breast Cancer

PRINCIPAL INVESTIGATOR:
Amelie R. Gillman, M.S.

CONTRACTING ORGANIZATION:
Vanderbilt University
Nashville, TN 37232-2310

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Amelie R. Gillman
Email: amelie.r.gillman@vanderbilt.edu

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14. ABSTRACT
The processes of tumor growth and treatment response are associated with the up-regulation of numerous proteins, yet current clinical imaging methods of cancer characterization monitor only gross morphology. This study combines specialized in vivo magnetic resonance imaging (MRI) with matrix-assisted laser desorption ionization (MALDI) analysis of healthy and tumorous ex vivo specimens in order to examine the proteomic influences on contrast in MRI. During the current research period, protocols were developed to image and correlate data from breast cancer metastases to bone. MRI data acquisition was expanded from that of the previous research period to include gadolinium contrast-enhanced, diffusion-weighted, and relaxometric data in an intra-tibial mouse model of metastatic breast cancer. Multi-parametric MRI data were collected for eight mice at each of three time points. Acquisition of MALDI data for each mouse is currently underway. Coregistration of proteomic and MRI hind limb data will incorporate both rigid and non-rigid methods in order to fuse the two datasets based on fiducial markers in the absence of a non-deformable stereotactic frame. Data analysis will focus on identification of specific (groups of) proteins that most strongly correlate with variations in multi-parametric MRI data. This work represents a basic yet vital step towards the long-term objective of facilitating clinical assessment of tumor status via non-invasive imaging techniques.

15. SUBJECT TERMS
MRI, MALDI, breast cancer, metastases, proteins, correlation, mouse model, coregistration

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INTRODUCTION

THIS REPORT SUMMARIZES THE WORK AND RESULTS OF THE SECOND OF THREE YEARS OF TRAINING FUNDED BY THIS GRANT. THIS GRANT SUPPORTS THE PI'S PREPARATION FOR A CAR CANCER RESEARCH BY PROVIDING FOR TRAINING IN IMAGE PROCESSING, ANALYTICAL METHODS THE-ART LABORATORY TECHNIQUES USED IN CANCER RESEARCH. THE PURPOSE OF THE FUNDED ASSESS THE CORRELATION BETWEEN PHYSIOLOGICAL PARAMETERS REPORTED BY MAGNETIC RE IMAGING AND TUMOR PROTEIN DISTRIBUTION DETERMINED FROM MATRIX-ASSISTED LASER IONIZATION (MALDI) MASS SPECTROMETRY MEASUREMENTS. THE OVERARCHING GOAL OF THIS ELUCIDATE THE PROTEOMIC INFLUENCES OF CONTRAST IN MR CANCER IMAGING IN AN EFFOR CLINICAL BREAST CANCER CARE BY ENABLING CLINICIANS TO QUICKLY ESTABLISH OR MOD REGIMENS BASED ON NON-INVASIVE ASSESSMENT OF CELLULAR-LEVEL TUMOR STATUS.

BODY

THE TRAINING PLAN PROPOSED IN THE APPROVED STATEMENT OF WORK INCLUDES COURSEWORK, LABORATORY TRAINING, AND CULTIVATION OF A BROAD-BASED KNOWLEDGE OF BREAST CANCER AND IMAGING SCIENCE ISSUES VIA ATTENDANCE OF RELEVANT SEMIN CONFERENCES. DURING THE FIRST AWARD YEAR, THE SUPPORT PROVIDED BY THIS TRAINING GR PI TO EARN A M.S. DEGREE FROM THE VANDERBILT UNIVERSITY (VU) GRADUATE SCHOOL, C LABORATORY TRAINING AS OUTLINED IN THE STATEMENT OF WORK, AND TO REFINE AND V ACQUISITION AND ANALYSIS METHODS IN AN ANIMAL MODEL OF BRAIN CANCER. DURING THE SEC YEAR, THE PI CONTINUED TO WORK CLOSELY WITH VANDERBILT UNIVERSITY INSTITUTE OF IMA (VUIIS) FACULTY MENTORS TO DEVELOP COMPUTATIONAL TECHNIQUES FOR THREE-DI RECONSTRUCTION AND CO-REGISTRATION OF MR AND MALDI DATA VIA PROCESSES DESCRIBE ADDITION, THE PI BEGAN COLLABORATION WITH THE VU TUMOR MICROENVIRONMENT NET INTERDISCIPLINARY NETWORK OF SCIENTISTS FUNDED BY THE NATIONAL CANCER INSTITUTE ELUCIDATE MECHANISMS OF TUMOR-HOST INTERACTIONS IN CANCER, TO FURTHER REFINE ME FUSION OF MULTI-MODALITY IMAGING DATASETS.

THE RESEARCH PLAN PROPOSED IN THE APPROVED STATEMENT OF WORK DURING TH AWARD YEAR INCLUDES DEVELOPMENT OF PROTOCOLS FOR MR IMAGING OF BREAST CANCER M BONE IN AN INTRA-TIBIAL MOUSE MODEL OF METASTATIC BREAST CANCER. WORKING WITH THE V FOR SMALL ANIMAL IMAGING, MR PROTOCOLS WERE OPTIMIZED AND MULTI-PARAMETRIC MR D COLLECTED FOR EIGHT MICE, EACH WITH A SINGLE HIND LIMB TUMOR (SUCH THAT IMAGING D CONTRALATERAL HIND LIMB MAY SERVE AS CONTROL DATA), AT EACH OF THREE DIFFERENT TI MICE WERE THEN PREPARED FOR COLLECTION OF PROTEOMIC DATA, A PROCESS THAT IS CURRE IN CONTRAST TO COREGISTRATION TECHNIQUES EMPLOYED DURING THE FIRST AWARD YEAR US OF BRAIN CANCER AND FEATURING THE SKULL AS A NON-DEFORMABLE STEREOTACTIC FRAME, C PROTEOMIC AND MR HIND LIMB DATA IN THIS BREAST CANCER MODEL WILL INCORPORATE BOTH R RIGID METHODS DEVELOPED DURING THE SECOND AWARD YEAR IN ORDER TO FUSE THE TWO DA ON FIDUCIAL MARKERS IN THE ABSENCE OF A NON-DEFORMABLE STEREOTACTIC FRAME (FIGU APPENDIX). ANALYTICAL METHODS DEVELOPED DURING THE FIRST AWARD YEAR, DESCRIBED IN WILL BE APPLIED TO THE RESULTING HYBRID MULTI-MODAL DATA SETS. DATA ANALYSIS WI IDENTIFICATION OF SPECIFIC (GROUPS OF) PROTEINS THAT MOST STRONGLY CORRELATE WITH V PARAMETRIC MRI DATA.

KEY RESEARCH ACCOMPLISHMENTS

KEY RESEARCH ACCOMPLISHMENTS EMANATING FROM THIS TRAINING GRANT DURING THE FIRS
INCLUDE THE FOLLOWING:

- COMPLETION OF GRADUATE-LEVEL DIDACTIC COURSEWORK TO SUPPORT BREAST CAN
  RESEARCH (E.G., CANCER IMAGING, QUANTITATIVE MAGNETIC RESONANCE IMAGING, AND M
  IMAGE REGISTRATION CLASSES)

- COMPLETION OF LABORATORY TRAINING ON A 9.4 T VARIAN INOVA MR SCANNER

- COMPLETION OF LABORATORY TRAINING ON A LEICA CM3600 CRYOMACROTOME

- COMPLETION OF LABORATORY TRAINING ON AN AUTOFLEX III BRUKER DALTONICS LINEAR
  OF-FLIGHT MASS SPECTROMETER

- ADDITIONAL SUPPORTIVE TRAINING VIA ATTENDANCE OF REGULAR SEMINARS SPONSO
  VANDERBILT UNIVERSITY INSTITUTE OF IMAGING SCIENCE, THE VANDERBILT UNIVERSIT
  CENTER, AND MULTIPLE ACADEMIC DEPARTMENTS

- REFINEMENT AND VALIDATION OF THREE-DIMENSIONAL RECONSTRUCTION AND INTER-SLIC
  OF SPECIMEN VOLUMES FROM MALDI DATA ON MULTIPLE TWO-DIMENSIONAL SPECIMEN SLI

- REFINEMENT AND VALIDATION OF METHODS FOR CO-REGISTRATION OF MR AND MALDI DATA

- APPLICATION OF PRINCIPAL COMPONENT ANALYSIS TO HYBRID MALDI/MRI DATA SETS TO ID
  MULTI-SPECTRAL BASIS SETS

- APPLICATION OF LINEAR REGRESSIVE AND CORRELATION ANALYSIS TECHNIQUES TO DE
  RELATIONSHIP BETWEEN PROTEOMIC AND DIFFUSION METRICS

KEY RESEARCH ACCOMPLISHMENTS EMANATING FROM THIS TRAINING GRANT DURING THE SECON
INCLUDE THE FOLLOWING:

- COMPLETION OF LABORATORY TRAINING ON A 7 T 16-CM BORE VARIAN SCANNER

- COMPLETION OF TRAINING IN THE CARE OF MICE USED IN SERIAL IMAGING STUDIES

- OPTIMIZATION OF PROTOCOLS FOR GADOLINIUM CONTRAST-ENHANCED AND T1-, T2-, AND
  WEIGHTED MR IMAGING OF HIND LIMB TUMORS IN A MOUSE MODEL OF METASTATIC BREAST

- ACQUISITION OF 24 MULTI-PARAMETRIC MOUSE HIND LIMB TUMOR MR DATASETS

- DEVELOPMENT OF METHODS FOR RIGID AND NON-RIGID CO-REGISTRATION OF IN VIVO MRI,
  MALDI VOLUME DATA IN A MOUSE MODEL OF METASTATIC BREAST CANCER

- ADDITIONAL SUPPORTIVE TRAINING VIA ATTENDANCE OF REGULAR SEMINARS SPONSO
  VANDERBILT UNIVERSITY INSTITUTE OF IMAGING SCIENCE, THE VANDERBILT UNIVERSIT
  CENTER, AND MULTIPLE ACADEMIC DEPARTMENTS

- ONGOING PREPARATION FOR DOCTORAL DISSERTATION PROPOSAL AND DEFENSE

REPORTABLE OUTCOMES

THE REPORTABLE OUTCOMES THAT HAVE RESULTED FROM THIS TRAINING GRANT IN THE FIR
INCLUDE THE FOLLOWING:

- ATTAINMENT OF THE DEGREE OF MASTER OF SCIENCE IN THE FIELD OF BIOMEDICAL ENGINE
  THE VANDERBILT UNIVERSITY GRADUATE SCHOOL

- PRESENTATION OF RESEARCH METHODS AND RESULTS TO THE VUIIS FACULTY, STAFF, AN
  THE 2009 ANNUAL VUIIS RESEARCH RETREAT [4]

THE REPORTABLE OUTCOMES THAT HAVE RESULTED FROM THIS TRAINING GRANT IN THE SECO
INCLUDE THE FOLLOWING:

- PRESENTATION OF RESEARCH METHODS AND RESULTS TO THE VUIIS FACULTY, STAFF, AN
  THE 2010 ANNUAL VUIIS RESEARCH RETREAT [5]

- CO-INVESTIGATION OF ORIGINAL RESEARCH PRESENTED BY ERIN SEELEY, PH.D., VU
  SPECTROMETRY RESEARCH CENTER, TO THE 58TH ASMS CONFERENCE ON MASS SPECT
  AND ALLIED TOPICS [6]

CONCLUSION

IN THE FIRST YEAR OF THIS STUDY, MALDI AND DIFFUSION-WEIGHTED (DW) MRI DATA WERE EXAM
C6 RAT BRAIN TUMOR MODEL (FIGURE 2 OF APPENDIX). SEVERAL HUNDRED REGIONS OF INTERES
IN COREGISTERED MALDI/MR DATASETS OBTAINED FROM MULTIPLE ANIMALS WERE FOUND
STATISTICALLY SIGNIFICANT LINEAR CORRELATIONS BETWEEN PROTEIN SIGNATURE INTENSI
DIFFUSION COEFFICIENT (FIGURE 3 OF APPENDIX) IN BOTH HEALTHY AND TUMOROUS TISSUES,
THAT PROTEIN CONTENT MAY SIGNIFICANTLY AFFECT CONTRAST IN DIFFUSION-WEIGHTED MR I
THE SECOND AWARD YEAR, MORE COMPLEX COREGISTRATION TECHNIQUES WERE DEVELOPE
ACHIEVE FUSION OF MR AND PROTEIN DATA IN A MOUSE MODEL OF BREAST CANCER METASTASIS
THIS ANIMAL MODEL, COREGISTRATION OF DATA FROM THE TWO DIFFERENT IMAGING MODALITI
THE USE OF THE TIBIA AND OTHER FIDUCIAL MARKERS WITHIN DEFORMABLE HIND LIMB DATA,
COMPUTATIONAL BENEFIT OF A NON-DEFORMABLE STEREOTACTIC FRAME SUCH AS THE SKUL
ANALYSIS MORE CLOSELY MIMICS THE COMPUTATIONAL CHALLENGES OF APPLICATION OF THESE
HUMAN BREAST CANCER DATA, WITH RESPECT TO THE CONFOUNDING NATURE OF CORE
DEFORMABLE HUMAN BREAST TISSUE. SERIAL MULTI-PARAMETRIC MR DATA WERE OBTAINED FO
WITH HIND LIMB TUMORS ORIGINATING FROM BREAST CANCER CELLS. ACQUISITION OF PROTE
THESE MICE IS UNDERWAY. UPON COMPLETION OF COLLECTION OF PROTEIN DATA, THE MR AND
WILL BE COREGISTERED AND SUBJECTED TO ANALYTICAL TECHNIQUES DEVELOPED DURING T
YEAR. DATA ANALYSIS WILL FOCUS ON IDENTIFICATION OF SPECIFIC (GROUPS OF) PROTEINS THA
CORRELATE WITH VARIATIONS IN MULTI-PARAMETRIC MRI DATA. THIS WORK REPRESENTS A BASIC
TOWARDS THE LONG-TERM OBJECTIVE OF FACILITATING CLINICAL ASSESSMENT OF TUMOR S
INVASIVE IMAGING TECHNIQUES.

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APPENDIX: SUPPLEMENTARY FIGURES

THE FOLLOWING FIGURES ILLUSTRATE REPRESENTATIVE DATA AND RESULTS AS DESCRIBED IN TH

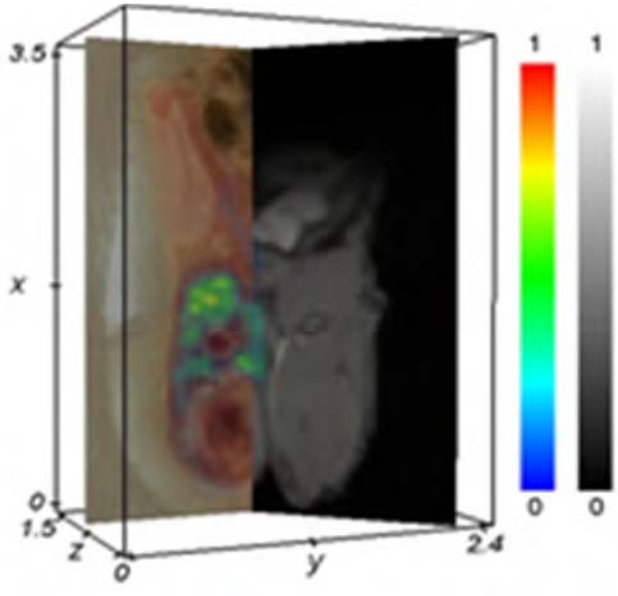

Figure 1: COREGISTERED OPTICAL IMAGE OF MOUSE TISSUE (RBG), MRI (GRAYSCALE), AND MA
(FALSE COLOR) DATA FOR PROTEIN OF MOLECULAR MASS 11838 DA. LEFT COLORBAR: RELA
CONCENTRATION. RIGHT COLOR-BAR: RELATIVE MR (GRAY) INTENSITY. *(AXES in cm)*

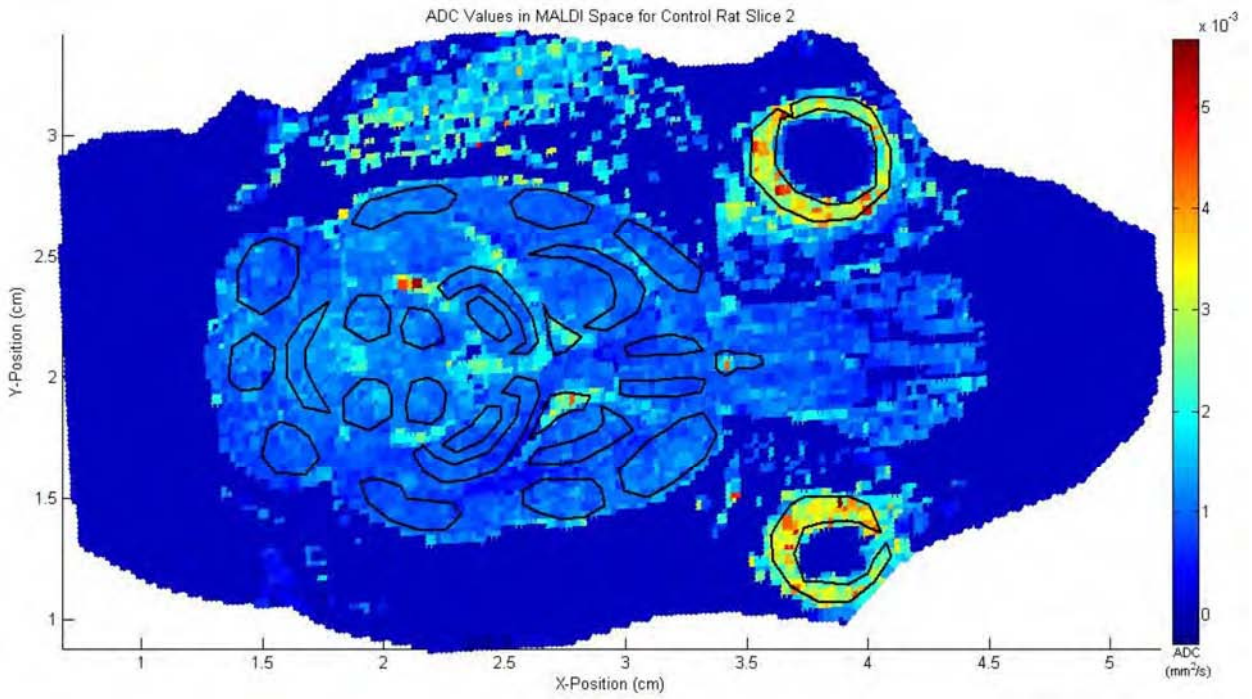

FIGURE 2: REPRESENTATIVE REGIONS OF INTEREST IN ADC DATA CO-REGISTERED TO MALDI SPAC
REGIONS OF INTEREST WERE MANUALLY DELINEATED TO DEFINE SELECTED ANATOMICAL STRUCT
IN [7].

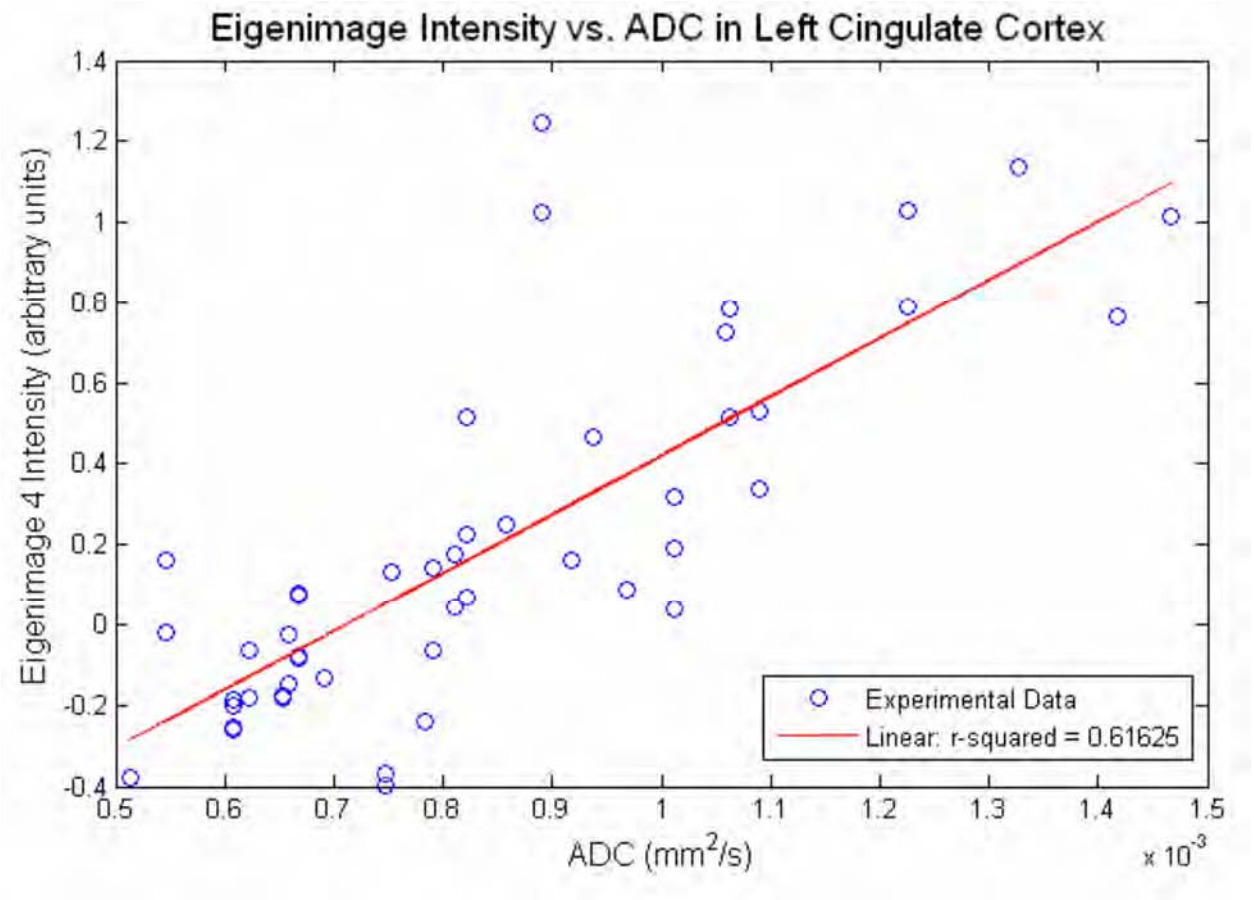

FIGURE 3: SCATTER PLOT CHARACTERIZING THE RELATIONSHIP BETWEEN THE ADC AND EIGENIMA
IN A REGION OF INTEREST DELINEATING THE LEFT CINGULATE CORTEX. THE DATA SHARE AN APPR
LINEAR RELATIONSHIP WITH A PEARSON CORRELATION COEFFICIENT OF 0.7850 AT A CONFIDENCE
(TO FIVE SIGNIFICANT DIGITS).