

10th ANNUAL DEPARTMENT OF PATHOLOGY YOUNG INVESTIGATORS' DAY
POSTER SESSION

POSTER #

32

(for Admin. use)

Thursday, April 17th, 2008
TURNER CONCOURSE
REGISTRATION FORM

Applicant's Name: Jinong_Li Degree: Ph.D.

Applicant's Division: Clinical Chemistry

Faculty Preceptor: Daniel W. Chan
(Must hold a primary appointment in Pathology)

Appointment Category: _____House Staff x Clin Fellow _____Research Fellow
_____Medical Student _____Graduate Student (Program:_____)

Register for: _____Clinical Research ___x___Translational Research _____Basic Research

Full Poster Title * **Targeted proteomics: Biomarker discovery and validation for the early detection of breast cancer**

Where has the work been presented?

Meeting Name Partial data presented at HUPO, Oct 6-10, 2007

Meeting Date _____

Not Previously Presented _____

Where is this work being published? _____

Journal Name, Volume, Page, Date _____

In Preparation (Y/N) - Where? Y Cancer Res/Clinical Cancer Res.

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***INCLUDE A ONE-PAGE ABSTRACT (including title and all authors) OF THE WORK YOU WILL BE PRESENTING**

**E-mail COMPLETED Registration form and abstract to:
Stacey Morgan (smorgan9@jhmi.edu) on or before
Friday, March 14th, 2008**

If you have questions or problems regarding your submission, please contact Stacey Morgan via e-mail (smorgan9@jhmi.edu)

Targeted proteomics: Biomarker discovery and validation for the early detection of breast cancer

Jinong Li, Junma Zhou, and Daniel W. Chan

Objective/Relevance: Our goal is to develop a multi-biomarker panel for the early detection of breast cancer. Nipple aspiration fluid (NAF) is chosen as the starting material since biomarkers discovered in proximal fluid have the desired tissue specificity and the likelihood to be released into serum.

Strategy: To achieve this goal, we will follow a four-step study plan: biomarker screening in NAF, validation in tissue, development of multiplexed immunoassays and quantitative evaluation in NAF and serum.

Methodology: NAF has limited sample volume and protein content. One of the proteomics technology we have used successfully is SELDI-MS (requires 1 µg of protein). By comparison of mass spectra from a small cohort of NAF, we have discovered a panel of three candidate biomarkers among them an unidentified 4.7 kD peptide BF5 (Clinical Cancer Research, 2005). To validate BF5, and to screen for additional biomarkers using a different proteomic platform, we have prospectively collected additional samples, and adopted a novel technology (Antibody Microarrays, Clontech). In combination with nano-scale two-color labeling, we were able to compare on the same array the relative abundance of 512 antigens in matched NAF (left-and-right) from 18 cancer cases, using 1 µg of protein.

Specimens: Bilateral aspiration was performed on 42 women with unilateral breast cancer/disease (locally invasive, 31; DCIS, 6; ADH, 5) and 31 controls. This collection yielded 123 NAF samples. The tissue microarray used for immunohistochemistry study consists of 180 cases of infiltrating breast cancer, representing the spectrum of clinical stages and histologic variants. For future validation, we have a multi-center serum collection consisting 480 specimens from 4 diagnostic groups (healthy, benign, DCIS and locally invasive breast cancer).

Results: 1) We have validated the cancer associated expression of BF5 in NAF on SELDI-MS, and determined its protein identity as 41/42-aa C-terminal peptide of alpha-1-antitrypsin (AAT). We demonstrated that C-41/42 can be generated in vitro by action of MMP-7 from the full length AAT which is elevated along with C-41/42. Therefore, elevated C-41/42 is likely the combined effect of elevated AAT synthesis and the activity of specific MMPs present in the tumor. The C-terminal fragments of AAT are functionally active. A C-36 fragment has been shown to serve as a tumor-derived suppressor to the host immune-system, a significant and distinct biological activity not exhibited by the full length protein. 2) We have identified by antibody array analysis 17 additional biomarkers. These proteins were elevated in at least 4 cancer cases out of 18 studied. 3) We have performed validation on one of the additional marker P116Rip. This protein has not previously been associated with breast cancer. We showed that P116Rip is selectively expressed in highly invasive "stromal like" breast cancer cell lines, and we observed positive cytoplasmic staining in breast cancer tissues.

Conclusions: We have completed biomarker screening in NAF using both SELDI-MS and antibody microarrays. We validated our result using an independent cohort and independent methods. Further tissue validations and development of multiplexed immunoassays will allow us to evaluate the potential clinical utility of these markers in NAF/serum.