BIOGRAPHICAL SKETCH

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NAME: Mark Miedel

eRA COMMONS USER NAME (credential, e.g., agency login): MMIEDEL

POSITION TITLE: Research Assistant Professor of Computational & Systems Biology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Pennsylvania State University, University Park, PA	B.S.	05/2002	Biology
University of Pittsburgh, Pittsburgh, PA	Ph.D.	08/2008	Cell Biology
University of Pittsburgh, Pittsburgh, PA	Postdoctoral	04/2013	Cell Biology

A. Personal Statement

My role in the Breast Cancer Alliance (BCA) Exceptional Project Grant proposal is as a co-investigator. I am a Research Assistant Professor at the University of Pittsburgh's Drug Discovery Institute and I am motivated to pursue an academic research career with translational focus. My primary interest as a researcher is in obtaining a better understanding of the cellular mechanisms that drive disease progression with the goal of turning mechanistic insight into new therapeutic treatments. This interest is of particular relevance with respect to metastatic breast cancer, as estrogen receptor (ESR1) ligand-binding domain (LBD) mutations have a significant role in driving the progression of breast cancer metastasis. Collaborating with Dr. Stern, the goal of our proposal is to examine the impact of the tumor microenvironment on distinct metastatic phenotypes that are conferred by clinically relevant ESR1 LBD mutations. Our most recent studies, published in *Oncology* (see reference below), identified key phenotypic differences between clinically relevant ESR1 LBD mutations. These observations serve as the foundation for the studies proposed in this application, which aims to examine the relationship between this class of ESR1 mutations and the tumor microenvironment employing a liver microphysiological system designed to recapitulate critical aspects of the breast cancer metastatic niche.

My background as a cell biologist has provided me with a diverse skill and I have a demonstrated record of accomplished and productive research projects in areas of high relevance. As a graduate student, I studied membrane trafficking defects associated with the pathogenesis of the lysosomal storage disorder Mucolipidosis Type IV (MLIV). At the time, little was known regarding the underlying mechanisms of pathogenesis for this rare storage disorder. My studies were among the first to establish that the mechanism of disease pathogenesis was linked to perturbations in the lysosomal ionic microenvironment and not due to defects in endocytic transport. These findings have led researches to focus on developing therapies designed to correct deficiencies in the lysosomal microenvironment as treatments for MLIV. During my postdoctoral fellowship, I investigated the role of serpin anti-protease function in the regulation of cellular protein homeostasis using the *C. elegans* model system. My findings linked serpin function to the regulation of misfolded protein turnover *via* the endoplasmic reticulum-associated degradation (ERAD) pathway. My work not only resulted in the creation of novel reagents for studying misfolded protein degradation in the *C. elegans* platform, but it also provided new insight into how the ERAD pathway is regulated. Numerous diseases result from the de-regulation of ERAD, and the ability to control this pathway through protease inhibition that is not directly related to proteasome function is a novel concept that will open new avenues for the discovery of pharmacological agents to modulate this pathway. Overall, I believe my broad experimental background and experience in mechanistic, disease-specific research will enable me to effectively contribute towards our efforts

to elucidate the mechanisms that regulate the relationship between ESR1 LBD mutations and the tumor microenvironment with the goal of providing new therapeutic avenues for the treatment of metastatic breast cancer.

a) Shanhang J*, Miedel MT*, Ngo M, Hessenius R, Wang P, Bahreini A, Li Z, Ding Z, Chen N Shun TY, Zuckerman DM, Taylor DL, Puhalla SL, Lee AV, Oesterreich S, Stern AM. Clinically observed Estrogen Receptor Alpha Mutations Within the Ligand-Binding Domain Confer Distinguishable Phenotypes. (2018) *Oncology*. Jan 6; 94(3): 176-189. PMID: 29306943. [* joint first author]

B. Positions and Honors

Positions and Employment

2013-2016 Research Associate, Department of Pediatrics, Division of Newborn Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA
2016-2017 Research Associate, Drug Discovery Institute, Department of Computational & Systems Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA
2017- Research Assistant Professor, Drug Discovery Institute, Department of Computational & Systems Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA

Other Experience and Professional Memberships

Honors

2003-2006 University of Pittsburgh School of Medicine Teaching Fellowship
2006- Travel award, Canadian Society for Cell & Molecular Biology, Membrane Proteins in Health and Disease conference
2007-2008 Training Award from University of Pittsburgh Clinical and Translational Science Institute
2010-2013 Individual NIDDK Ruth L. Kirschstein National Research Service Award

C. Contributions to Science

1. Identification of the molecular mechanisms responsible for pathogenesis of the lysosomal storage disease Mucolipidosis Type IV (MLIV). MLIV results from mutations in the transient receptor potential (TRP) cation channel family member, mucolipin-1 (TRP-ML1). TRP-ML1 is an intracellular cation channel, localized to both late endosomes and lysosomes. During my graduate training, my work characterized the sorting machinery and intracellular pathway involved in TRP-ML1 trafficking to lysosomes, showing that the trafficking of this protein is mediated by discrete motifs present within both its N- and C–terminal cytosolic domains. I also demonstrated that TRP-ML1 is subject to proteolysis along the biosynthetic pathway, and that this processing serves to negatively regulate channel activity. Furthermore, I provided insight into the cellular mechanisms that contribute to the pathogenesis of MLIV. I demonstrated that while the trafficking of lipids and proteins was unperturbed in cells lacking TRP-ML1 there was a selective defect in the hydrolysis of specific lipid species in these cells. This work is significant because it helped to distinguish between current models of MLIV pathogenesis and provides insight into how the normal physiological environment of the lysosome is maintained.

a. Miedel MT, Rbaibi Y, Guerriero,CJ, Colletti G, Weixel KM, Weisz OA and Kiselyov, K. Membrane traffic and turnover in TRP-ML1 deficient cells: a revised model for mucolipidosis type IV pathogenesis. (2008) J Exp Med 205(6): 1477-1490, 2008. PMID: 18504305.

b. Miedel MT, Weixel KM, Bruns JR, Traub LM and Weisz OA. Posttranslational cleavage and adaptor protein complex-dependent trafficking of mucolipin-1. J Biol Chem (2006) 281(18): 12751-12759, 2006. PMID: 16517607.

2. Identification of serpin proteins as regulators of cellular protein homeostasis. Serpins are a large family of protease inhibitors whose function is a critical factor in the regulation of a core stress response pathway that protects cells from necrosis in response to numerous noxious stimuli. During my postdoctoral fellowship, my work explored whether serpin function was involved in the regulation of the cellular response to stress induced through disturbances in cellular protein homeostasis. Using the *C. elegans* model system, I showed that the ER-associated degradation (ERAD) pathway of misfolded protein clearance was impaired in animals lacking the serpin protein, SRP-6. Moreover, a model ERAD substrate had not yet been described in the *C. elegans* system; therefore, I was the first to design and characterized a fluorescently tagged luminal ERAD substrate that has been subsequently used by numerous research groups. Additionally, using both RNAi screening and proteomics based approaches, my work went on to demonstrate that 1) serpin regulation of ERAD is dependent on the cysteine protease inhibitory activity of SRP-6 and 2) to identify the specific interacting protease targets of SRP-6. This work is significant because numerous diseases result from the de-regulation of ERAD. The ability to control ERAD through protease inhibition will open new avenues for the discovery of pharmacological agents to modulate this pathway.

a. Miedel MT, Graf, NJ, Stephen, K, Pak, SCO, Perlmutter, DH, Silverman, GA, and Luke, CJ. A pro-cathepsin L mutant is a luminal substrate for endoplasmic-reticulum-associated degradation in *C. elegans*. PLoS ONE 7(7): e40145. (2012), July 2. PMID: 22768338.

b. Miedel MT, Zeng X, Yates NA, and Luke CJ. Isolation of serpin-interacting proteins in *C. elegans* using protein affinity purification. (2014). Methods, Aug 1;68(3):536-41 PMID: 24798811.

3. Identification of distinguishable phenotypes in clinically relevant estrogen receptor mutations. I am interested in studying the role of estrogen receptor (ESR1) ligand-binding domain (LBD) mutations in metastatic breast cancer as they are expressed in 20-50% of ER+ metastases and their clinical relevance as drivers of endocrine therapy resistance. As a Research Assistant Professor working with Dr. Stern, I wanted to understand the possible differences among the phenotypes conferred by ESR1 LBD mutations; therefore we performed a quantitative analysis to assess phenotypic differences engendered by clinically relevant ESR1 mutations. These studies described key phenotypic differences between the two most common ESR1 mutations. These findings have the potential to increase the impact of monitoring these mutations as markers of disease progression, enhance our ability to design next-generation ESR1 antagonists, and to adapt and optimize therapeutic strategies for patients harboring polyclonal mutations. Furthermore, these studies form the basis for our continuing efforts to understand the mechanistic relationship between this class of mutation and the metastatic microenvironment outlined in this proposal.

a) Shanhang J[*], Miedel MT[*], Ngo M, Hessenius R, Wang P, Bahreini A, Li Z, Ding Z, Chen N Shun TY, Zuckerman DM, Taylor DL, Puhalla SL, Lee AV, Oesterreich S, Stern AM. Clinically observed Estrogen Receptor Alpha Mutations Within the Ligand-Binding Domain Confer Distinguishable Phenotypes. (2018) *Oncology*. Jan 6; 94(3): 176-189. PMID: 29306943. [* joint first author]

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/sites/myncbi/1TcW1IMwU1Bs3m/bibliography/54637472/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

Completed Research Support

F32DK086112 Miedel (PI) 10/1-2010- 9/30-2013
The Role of Intracellular Serpins in the Regulation of Necrosis.

Independent National Research Service Award: to identify genetic modifiers and interacting proteins that are involved in serpin-mediated regulation of necrosis using the *C. elegans* model system.
Role: PI

TL1RR024155 Miedel (Predoctoral Trainee) 5/1/2007-4/30/2008
Function of Mucolipin-1 in Pathogenesis of Mucolipidosis Type IV.
T32 Predoctoral Training Award: to study the function of the TRP channel Mucolipin-1 in the regulation of endocytic membrane traffic and to examine its role in the pathogenesis of the lysosomal storage disease Mucolipidosis Type IV.
Role: Predoctoral Trainee