BIOGRAPHICAL SKETCH

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NAME: Benjamin Creekmore

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

POSITION TITLE: M.D./Ph.D. Student

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
University of North Carolina at Chapel Hill, Chapel Hill, NC	B.S.	08/2014	05/2018	Chemistry (Biochemistry track)
University of North Carolina at Chapel Hill, Chapel Hill, NC	B.A.	08/2014	05/2018	Biophysics
University of Pennsylvania, Philadelphia, PA	M.D.	08/2018	Expected 05/2026	
University of Pennsylvania, Philadelphia, PA	Ph.D.	08/2018	Expected 05/2026	Biochemistry and Molecular Biophysics

A. Personal Statement

My long-term goal is to become a physician-scientist at an academic institution, leading an independent research laboratory while dedicating a minority of my time to providing clinical patient care. My previous research experiences have given me a variety of experiences including clinical research, structural biology, biochemistry, drug development, and computational analysis of metagenomic data. I have had varying roles in many projects, but through them all I grew as a researcher and became increasingly independent. Through my undergraduate experiences in research and clinical settings at the University of North Carolina at Chapel Hill, I was able to clarify my interest in pursuing an M.D./Ph.D. dual degree to give myself the best training to not only improve clinical care through research, but also to guide research based on clinical experiences. The University of Pennsylvania has many physician-scientists who have inspired me through their ability to leverage their combined training to identify clinically relevant hypotheses and use the results of their research to directly impact patient care. One example is the inspiration for the work I propose here. Prior to Dr. Lee's discovery, VCP mutations had mostly been associated with TDP-43 pathology. On an autopsy case, however, Dr. Lee discovered a patient who had dementia and tau pathology related to a VCP mutation. This guided the hypothesis that maybe VCP is important for disaggregation of tau not only in mutations, but in sporadic cases of Alzheimer's disease and other tauopathies too. As Alzheimer's disease is a devastating disease that affects many people, yet has almost no effective therapy options, discovering a potentially new therapeutic target is very exciting. Additionally, using clinical scenarios to guide bench research reminded me of why I wanted to pursue an M.D./Ph.D. in the first place. Ultimately, I hope to not only translate my research from the bench to the bedside but also to remain grounded in clinically relevant problems and questions that have potential to improve patient care.

My position as an M.D./Ph.D. student in Dr. Lee and Dr. Chang's labs at the University of Pennsylvania will provide me the resources and support to achieve my goals. I will develop crucial skills in critical thinking, experimental design, scientific communication, and more that will allow me to move towards my goal of becoming an independent investigator. Within the collaborative environment of Penn, I will be able to pursue scientific questions that are both interesting and clinically relevant. My prior research and my current environment at the University of Pennsylvania will give me the necessary training, support, and mentorship to take steps forward in my career as a physician-scientist.

B. Positions and Honors

Academic and Professional Honors

2021 Selected for Structural Biology and Molecular Biophysics Pre-Doctoral Training Program
2018 Graduated Honors Carolina with highest honors and highest distinction in Chemistry and Biophysics, University of North Carolina at Chapel Hill
2017 Phi Beta Kappa, University of North Carolina at Chapel Hill
2017 James S. Gold Faculty-Mentored Research Fellowship
2016 E. C. Markham Summer Research Fellowship
2015 ACC Academic Honor Roll
2014 UNC Student-Athlete 4.0 Club

C. Contributions to Science

1. Undergraduate Research Matthew R. Redinbo 10/2015-08/2018

The Redinbo laboratory studies the human microbiome to contextualize and understand human disease and metabolism. I had the opportunity to work on several projects during my multiple years spent in the Redinbo laboratory.

Bacterial β-Glucuronidase (GUS) is a bacterial enzyme that hydrolyzes a glucuronide moiety from compounds in the gastrointestinal (GI) tract. Glucuronidation is used as a metabolic pathway to mark compounds for release from the body. Bacterial GUS can reactivate compounds in the GI causing enterohepatic recirculation and, in the case of the chemotherapeutic irinotecan and non-steroidal anti-inflammatory drugs, dose-limiting GI toxicity. Additionally, some endogenous compounds, such as estrogen that plays a role in breast cancer, are glucuronidated, but may be able to be recirculated after hydrolysis by GUS enzymes. I used enzyme kinetics, crystal structures, and thermodynamic assays to determine the mechanism of action and structure activity relationship of novel inhibitors of bacterial GUS. I used similar techniques to characterize estrogen-glucuronide hydrolysis by bacterial GUS enzymes and how bacterial GUS inhibitors affect these reactions. We discovered a novel mechanism of action of an inhibitor and variable efficacy of that inhibitor on GUS from different bacterial species with different substrates.

The Human Microbiome Project (HMP) took stool samples from many individuals in the United States to characterize the human microbiome. The GUS enzymes from this data were characterized and purified. I helped characterize the kinetic activity and pH dependence of these enzymes *in vitro*. We found that GUS enzymes from different bacterial species had different pH preferences and kinetic activity that may correspond to location in the GI tract. Other metagenomic datasets sequenced stool samples from mice, healthy humans, or humans with either colon polyps or colorectal cancer. I used command line software and wrote code in MATLAB to analyze these datasets to identify potential proteins from this sequencing data. I then determined sequence identity and similar, assigned bacterial taxa, compared different groups within the datasets, and identified potentially novel or characteristic motifs. I identified new proteins to purify to determine if sequence clustering algorithms could predict functional clades of proteins. We found that mice and humans have different GUS enzymes in their GI and that the mouse GI is affected by many variables common to mouse experiments. Additionally, we found that humans from different parts of the world have vastly different GUS enzymes present, which may lead to functional differences. We found that there may be some functional clades of GUS enzymes that are enriched in individuals with colorectal cancer or healthy individuals.

Similar to glucuronidation, sulfation is another form of metabolism to mark a compound for release from the human body. Bacterial sulfatases can remove sulfate groups allowing free compounds to be recirculated. My role in the project was to create a rubric and write code to identify bacterial sulfatases from available human metagenomic data then use sequence similarity analyses to identify structural relationships that may correlate to function and choose proteins to be purified and further characterized. My role in the project identified predicted microbial sulfatases, predicted functional clades, and identified proteins to purify for *in vitro* testing with endogenous sulfated compounds.

These projects resulted in several publications:

a. Ervin, S. M., Simpson, J. B., Gibbs, M. E., Lim, L. Walton, W. G., **Creekmore B. C.**, Gharaibeh, R. Z., Redinbo, M. R.: “Structural Insights into Endobiotic Reactivation by Human Gut Microbiome-Encoded Sulfatases.” *Biochemistry,* 2020, *59(40):*3939-3950.

b. Bhatt, A. P., Pellock, S. J., Biernat, K. A., Walton, W. G., Wallace, B. D., **Creekmore, B. C.**, Letertre, M. A., Swann, J. R., Wilson, I. D., Roques, J. R., Darr, D. B., Bailey, S. T., Montgomery, S. A., Roach, J. M., Azcarate-Peril, M. A., Sartor, R. B., Gharaibeh, R. Z., Bultman, S. J., Redinbo, M. R.: "Targeted Inhibtion of Gut Bacterial β-Glucuronidase Activity Enhances Anticancer Drug Efficacy." *Proc Natl Acad Sci*, 2020, *117(13)*: 7374-7381.
c. **Creekmore, B. C.**, Gray, J. H., Walton, W. G., Biernat, K. A., Little, M, S., Xu, Y., Liu, J., Gharaibeh, R. Z., Redinbo, M. R.: "Mouse Gut Microbiome-Encoded β-glucuronidases Identified Using Metagenome Analysis Guided by Protein Structure." *mSystems*, 2019, *4(4)*:e00452-19.
d. Pellock, S. J., Walton, W. G., Ervin, S. M., Torres-Rivera, D., **Creekmore, B. C.**, Bergan, G., Dunn, Z. D., Li, B., Tripathy, A. Redinbo, M. R. "Discovery and Characterization of FMN-Binding β-Glucuronidases in the Human Gut Microbiome." *J Mol Biol*, 2019, S002-2836(19)30011-7.
e. Pellock, S. J., Walton, W. G., Biernat, K. A., Torres-Rivera, D., **Creekmore, B. C.**, Xu, Y., Liu, J., Tripathy, A., Stewart, L. J., Redinbo, M. R. "Three Structurally and Functionally Distinct β-Glucuronidases from the Human Gut Microbe *Bacteroides uniformis*." *J Biol Chem*, 2018, *293(48)*: 18559-18573.
f. Pellock, S. J., **Creekmore, B. C**., Walton, W. G., Mehta, N., Biernat, K. A., Cesmat, A. P., Ariyarathna, Y., Dunn, Z. D., Li, B., Jin, J., James, L. I., Redinbo, M. R.: "Gut Microbial β-Glucuronidase Inhibition via Catalytic Cycle Interception." *ACS Cent. Sci.,* 2018, *4(7)*: 868-879.
g. Pollet, R. M., D'Agostino, E. H., Walton, W. G., Xu, Y., Little, M. S., Biernat, K. A., Pellock, S. J., Patterson, L. M., **Creekmore, B. C**., Isenberg, H. N., Bahethi, R. R., Bhatt, A. P., Liu, J., Gharaibeh, R. Z., Redinbo, M. R.: "An Atlas of β-glucuronidases in the Human Intestinal Microbiome." *Structure,* 2017, 25 (7): 967-977.e5.

2. Graduate Research Edward B. Lee/Yi-Wei Chang 05/2018-Present

A VCP mutation discovered by Dr. Lee presented clinically with dementia and showed tau pathology on autopsy. This mutation showed decreased VCP activity and impaired tau clearance by *in vitro*, cell, and mouse studies. As such, we hypothesized that increasing VCP activity may be beneficial for clearance of tau fibrils. From a publicly available high-throughput screen for VCP inhibitors we identified potential VCP activators based on increased VCP activity. We purchased over 100 compounds for screening. I am performing *in vitro* experiments to validate these potential hits and identify compounds that will increase VCP activity.

Additionally, with collaboration between my co-mentors Dr. Edward Lee and Dr. Yi-Wei Chang, I have been structurally studying the interaction of VCP with brain-derived tau fibrils. In my preliminary work, I have learned to purify tau fibrils from human brains, purified recombinant VCP, learned to use cryo-electron microscopes, and worked to optimize sample preparation and imaging conditions to image VCP with tau fibrils by cryo-electron tomography. I have also taken images of tau fibrils alone to learn the software necessary for computationally analyzing the data I will generate. During this time, I developed the background research for my project into 2 review articles.

a. **Creekmore, B. C.**, Chang, Y., Lee, E. B.: "The Cryo-EM Effect: Structural Biology of Neurodegenerative Disease Aggregates." *JNEN*, 2021, *80(6)*:514-529.
b. **Creekmore, B. C.**, Chang, Y., Lee, E. B.: "The Cryo-EM Effect: Structural Biology of Neurodegenerative Disease Proteostasis Factors." *JNEN*, 2021, *80(6)*:494-513.

D. Additional Information: Research Support and/or Scholastic Performance

YEAR	COURSE TITLE	GRADE
	UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL	
2014	General Descriptive Chemistry II	A
2014	Introduction to Economics	A
2014	Lifetime Fitness: Beginning Jogging	A
2014	Multivariable Calculus I	A
2014	Mechanics and Relativity	A
2015	Quantitative Chemistry Lab II	A-
2015	English Composition & Rhetoric	A
2015	Film & History in Europe and the United States	A-

YEAR	COURSE TITLE	GRADE
2015	1st Course in Differential Equations	A
2015	Electromagnetism and Quantum Mechanics	A-
2015	Molecular Biology & Genetics	A
2015	Modern Analytical Methods for Characterization and Separation	A
2015	Laboratory in Separations and Analytical Characterization of Organic and Biologic Compounds	A-
2015	Introduction to Organic Chemistry I	A
2015	British Literature from Medieval to 18th Century	A-
2016	Introduction to Inorganic Chemistry	A
2016	Introduction to Organic Chemistry II	A
2016	Laboratory in Organic Chemistry	A
2016	Research in Chemistry for Undergraduates	A
2016	Honors Junior Colloquium: Global Migration	PS
2016	Numerical Techniques in Physics	A-
2016	Introduction to Biological Chemistry	A
2016	Fundamentals of Human Anatomy & Physiology	A-
2016	Fundamentals of Human Anatomy & Physiology Laboratory	A-
2016	Seminar on Academic Mentoring	PS
2016	Research in Chemistry for Undergraduates	A
2016	Macromolecular Structure & Metabolism	A-
2016	Intermediate Electricity & Magnetism	A-
2016	Experimental Techniques in Physics	A
2017	Seminar on Academic Mentoring	PS
2017	Metabolism and Cellular Regulatory Networks	B+
2017	Physical Chemistry I	B
2017	Laboratory Techniques for Biochemistry	A
2017	Honors Junior Colloquium: The Culture of Global Sports	PS
2017	Basic Mechanics	A
2017	Religion in Latin America	A
2017	Cellular & Developmental Biology	B+
2017	Physical Chemistry II	B
2017	Synthetic Chemistry Laboratory I	A
2017	Making Sense of Ourselves	A
2017	Biological Physics	A
2018	Physical Chemistry Laboratory I	A
2018	Senior Honors Thesis	A
2018	Seminar on Biological Chemistry	A
2018	Introduction to Rock Music	A
2018	Research with Faculty Mentor in Physics II	A
	UNIVERSITY OF PENNSYLVANIA	
2018	Genetics	P
2018	Biochemistry	P
2018	Cell and Tissue Biology	P
2018	Embryology	P
2018	Doctoring 1A- Introduction to Medicine And Society	P
2018	Introduction to Clinical Medicine: The Doctor-Patient Relationship	P
2018	Clinical Anatomy	P
2018	Introduction to Clinical Medicine: First Semester	P
2018	Immunology	P

YEAR	COURSE TITLE	GRADE
2018	Microbiology And Infectious Diseases I	P
2018	Cancer Biology	P
2018	Epidemiology	P
2018	Topics In Molecular Medicine	A
2019	Mechanisms Of Disease And Therapeutic Intervention	P
2019	Introduction To Ultrasound Diagnostics	P
2019	Doctoring 1B – Patient/Family Centered Care: Communicating With Patients/Families	P
2019	Brain and Behavior	P
2019	Health Care Systems	P
2019	Reproduction	P
2019	Endocrinology	P
2019	Gastroenterology	P
2019	Introduction to Clinical Medicine: History And Physical Exam	P
2019	Cardiology	P
2019	Introduction to Clinical Medicine: Pediatrics	P
2019	Dermatology	P
2019	Doctoring 1C – Personal/Professional Development: How To Maintain One's Well Being In Clinic	P
2019	Renal	P
2019	Pulmonary	P
2019	Microbiology And Infectious Diseases II	P
2019	Introduction to Clinical Medicine: Differential Diagnosis	P
2019	Independent Study: Dr. Edward B. Lee	A
2019	Lab Rotation	A
2019	Case Studies in Translational Research	A
2020	Clerkship in Psychiatry	SC
2020	Doctoring II	P
2020	Clerkship In Neurology	SC
2020	Clerkship In Emergency Medicine	SC
2020	Introduction to Ophthalmology	P
2020	Neurodegenerative Aggregation And Microscopy Imaging Techniques Research	P
2020	Macromolecular Biophysics: Principles And Methods	A+
2020	Lab Rotation	A
2020	Independent Study: Dr. Yi-Wei Chang	A
2021	Structural And Mechanistic Biochemistry	A
2021	Data Analysis: Data Analysis and Scientific Inference	A
2021	Candidacy Exam Course	A
2021	Pre-Dissertation Lab	A

At University of North Carolina at Chapel Hill courses are graded A-F, except for courses (seminars/colloquiums) that use Pass/Fail grading are graded PS/F. At University of Pennsylvania, graduate school courses are graded A-F and medical school courses in the first three semesters are graded P/F. Due to extraordinary circumstances surrounding the COVID-19 pandemic, clinical clerkships in Spring 2020 were graded Successful Completion/Unsuccessful Completion. Clinical electives (Ophthalmology) were graded P/F.

BIOGRAPHICAL SKETCH

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NAME: Chang, Yi-Wei

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

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Chung Hua University, Taiwan	B.S.	07/2004	Mechanical engineering
Academia Sinica & National Tsing Hua University, Taiwan	Ph.D.	07/2010	Structural biology and bioinformatics
California Institute of Technology, Pasadena, CA	Postdoctoral Fellow	08/2014	Cellular structural biology

A. Personal Statement

With a college major in mechanical engineering, I have always been deeply intrigued by the inseparable relationship between structure and function of an object. This passion has driven me to enter the amazing field of structural biology over 15 years ago as a graduate student, aiming to understand the principle and evolutionarily fine-tuned mechanisms of biological molecules through detailed structural inspections. Using X-ray crystallography, I have resolved more than 10 atomic structures of purified proteins and obtained my PhD degree. However, I have also come to realize that many macromolecular assemblies simply cannot be preserved for structural inspections in vitro. I then joined Grant Jensen's laboratory at Caltech to explore the powerful technique cryo-electron tomography (cryo-ET) for studying macromolecular structures directly in their native cellular context. In the 7 years at Caltech, I applied my engineering background to develop and master cutting-edge methods of (i) correlative super-resolution microscopy and cryo-ET to locate molecular structures in cells with high accuracy; (ii) high-throughput cryo-ET data collection to capture molecular structures in cells with high speed; and (iii) extensive subtomogram averaging and data analysis to resolve molecular structures in cells with high resolution. I have acquired and analyzed over 5,000 tomograms to study several pathogenesis-associated molecular assemblies in intact bacterial cells, including the type IV pilus machines and the type IV and type VI secretion systems. Because the intact structures of these molecular machines have been unable to resolve in vitro due to the loss of structural integrity after purification, visualizing them in situ by cryo-ET has uniquely provided a wealth of new mechanistic insights.

Through the multi-year intensive cryo-ET work mentioned above, I have developed a comprehensive understanding of the strength and limitation of this powerful technology. After I started my own group at the University of Pennsylvania in 2019, I have quickly established state-of-the-art cryo-ET infrastructure and workflow in the school. I am further applying my expertise in engineering to optimize the cryo-ET technology for enhancing its power and reach to study biological systems that currently are too challenging to image, such as many host-pathogen interactions. My long-term goal is to marry biology and engineering to expand the boundary of understanding biology from a structural perspective.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments:

2020 - present	Editor, Applied Microscopy
2019 - present	Assistant Professor, Department of Biochemistry and Biophysics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
2019 - present	International Advisor, Academia Sinica Cryo-EM Center, Taiwan
2016 - 2018	Vice President, Southern California Society for Microscopy and Microanalysis
2014 - 2018	Research Scientist, California Institute of Technology, Pasadena, CA
2014 - 2016	Advisory Board Member, Southern California Society for Microscopy and Microanalysis
2014	Committee Member, the 7th International Electron Tomography Congress

Honors:

2019	Packard Fellowships for Science and Engineering, The David and Lucille Packard Foundation
2013	Caltech Center for Environmental Microbial Interactions Award, California Institute of Technology
2010	Honorary member, Phi Tau Phi Scholastic Honor Society of R.O.C.
2006	Presidential Scholarship, National Tsing Hua University, Taiwan

C. Contributions to Science

(out of 36: https://www.ncbi.nlm.nih.gov/myncbi/yi-wei.chang.1/bibliography/44704026/public/)

1. In situ structures of the rhoptry secretion system in apicomplexan parasites

Apicomplexa are a large phylum of unicellular eukaryotic parasites including several important human pathogens, such as *Plasmodium*, *Cryptosporidium*, and *Toxoplasma*. These intracellular parasites secrete the content of a specific organelle, the rhoptry, into their host for invasion. We discovered a molecular machine at the parasites' cell apex regulating rhoptry secretion, which we named the 'rhoptry secretory apparatus (RSA).' We found that RSA shares a common ancestry to a membrane fusion machine in Ciliata but is adapted with an additional enigmatic membrane vesicle for parasitism. Using extensive cryo-ET and subtomogram averaging analyses, we uncovered the extensive ultrastructure of the RSA and several new structural features associated to rhoptries in both *Cryptosporidium* and *Toxoplasma* cells. Together, our studies provided unique structural frameworks to dissect rhoptries' structure and mechanism.

a. Mageswaran S, Guérin A*, Theveny L*, Chen W*, Martinez M, Lebrun M, Striepen B, **Chang YW**. In situ ultrastructures of two evolutionarily distant apicomplexan rhoptry secretion systems. *Nat Commun.* 2021 Aug 17;12(1):4983. PubMed PMID: 34404783

b. Aquilini E, Cova M, Mageswaran S, Vargas D, Najm R, Graindorge A, Sparvoli D, Pacheco N, Suarez C, Maynadier M, Berry-Sterkers L, Urbach S, Fahy P, Guérin A, Striepen B, Dubremetz J, **Chang YW**, Turkewitz A, Lebrun M. An Alveolata secretory machinery adapted to parasite host-cell invasion. *Nat Microbiol*. 2021 Jan 25;6(4):425-434. PubMed PMID: 33495622

2. Architecture and mechanism of the bacterial type IV pilus (T4P) machines

Type IV pilus (T4P) machines are widespread filamentous appendages across bacteria. They have important functions in many stages of bacterial infection, from host cell contact to colonization, remodeling of the host cell surface, invasion, and dissemination to new sites of infection. Using cryo-ET and subtomogram averaging analysis, I resolved the overall structures of T4P machines from *Myxococcus xanthus* and human pathogen *Vibrio cholerae* with and without a pilus assembled. I then dissected the locations of each of the 10 protein components in the overall structures through imaging mutant cells with individual genes knocked out or fused with an additional tag for difference analysis against the wild-type structures. Combining the result with known biochemical information about component interactions, I was able to dock structures of components from X-ray crystallography or cryo-EM single particle reconstruction to obtain architectural models of the entire T4P machine in piliated and non-piliated states in these model organisms of T4P studies. These produced a burst of new mechanistic insights into pilus biogenesis and

surface recognition as well as the enigmatic switch between pilus extension and retraction activities. Comparing the T4P architectures between *M. xanthus* and *V. cholerae* further revealed convergent evolution of the remarkably similar structures, with non-homologous proteins serving similar roles.

a. **Chang YW**, Rettberg LA, Treuner-Lange A, Iwasa J, Søgaard-Andersen L, Jensen GJ. Architecture of the type IVa pilus machine. *Science*. 2016 Mar 11;351(6278):aad2001. PubMed PMID: 26965631
b. Treuner-Lange A, **Chang YW**, Glatter T, Herfurth M, Lindow S, Chreifi G, Jensen G, Søgaard-Andersen L. PilY1 and minor pilins form a complex priming the type IVa pilus in Myxococcus xanthus. *Nat Commun.* 2020 Oct 7;11(1):5054. PubMed PMID: 33028835
c. **Chang YW**, Kjær A, Ortega DR, Kovacikova G, Sutherland JA, Rettberg LA, Taylor RK, Jensen GJ. Architecture of the *Vibrio cholerae* toxin-coregulated pilus machine revealed by electron cryotomography. *Nat Microbiol*. 2017 Feb 6;2:16269. PubMed PMID: 28165453

3. Development of cryogenic super-resolution fluorescence microscopy and its correlation with cryo-ET

A major challenge in cellular tomography is precisely imaging the right region of a cell and identifying structures of interest in the crowded cellular environment. To that end, I developed a technique to conduct, for the first time, super-resolution fluorescence microscopy under cryogenic temperature (named cryogenic photoactivated localization microscopy; cryo-PALM) and used it on frozen cryo-EM grid in correlation with cryo-ET. I designed and constructed a laser system into a commercially available cryo-stage on an inverted light microscope to host frozen grids for such imaging. I examined many photoactivatable or photoswitchable fluorescence proteins available at the time and found that, under a laser intensity low enough to avoid melting of the frozen samples, only the photoactivatable green fluorescence protein reacted and allowed such cryo-PALM imaging. The result has then stimulated several follow-up studies in the field to engineer cryo-compatible super-resolution fluorophores and/or design better imaging platforms to allow the use of higher laser intensity for triggering the signal from more types of fluorescence proteins under cryogenic condition. Using correlated cryo-PALM and cryo-ET, I was able to locate the type VI secretion system (T6SS) sheaths (11-14 nm wide and few tens to hundreds of nm long) inside frozen-hydrated *M. xanthus* cells and distinguish them from other similar tubular structures in the vicinity. I have captured both extended (pre-firing) and contracted (post-firing) conformations of the secretion system and found that the T6SS of *M. xanthus* is structurally conserved to that of other species. In addition, this technique allowed me to identify, for the first time, structures of assembly and disassembly intermediates that, given the highly dynamic nature of the system, could not be visualized by other structural biology techniques. I learned that the inner rod and outer sheath of the T6SS assemble concomitantly rather than sequentially. Intriguingly, I observed a sheet-like density in the disassembly intermediate that is likely ClpV, the AAA-ATPase responsible for sheath disassembly. This study demonstrates that this correlative approach can pinpoint structures as small as individual T6SS in whole-cell cryo-ET.

a. **Chang YW**, Chen S, Tocheva EI, Treuner-Lange A, Löbach S, Søgaard-Andersen L, Jensen GJ. Correlated cryogenic photoactivated localization microscopy and cryo-electron tomography. *Nat Methods*. 2014 Jul;11(7):737-9. PubMed PMID: 24813625

4. In situ structures of the bacterial type VI secretion system (T6SS)

After I captured T6SS inside intact *M. xanthus* cells by correlated cryo-PALM and cryo-ET, I used subtomogram averaging to further study its structures at higher-resolution in situ. I was able to generate the pseudo-atomic models of the sheath in both extended and contracted conformations. Excitingly, the extended sheath structure was revealed for the first time, since when I (and several other groups) tried to purify the T6SS sheath for cryo-EM single particle-based helical processing, every T6SS fired upon purification, and I could only solve the atomic structure of contracted sheaths. Comparing the atomic models of sheath before and after firing reveal mechanistic details, including how does the sheath contract to push the inner rod forward, and how is the recycling domain of sheath subunits concealed in the extended conformation to prevent the access by the sheath disassembly ATPase ClpV before contraction. In addition, I visualized for the first time the structure of the membrane-associated apparatus that anchors the sheath to cell envelope. Intriguingly, I also identified novel extracellular fibers resembling bacteriophage tail fibers associated with the T6SS, likely used for recognizing target cells.

a. **Chang YW**, Rettberg LA, Ortega DR, Jensen GJ. In vivo structures of an intact type VI secretion system revealed by electron cryotomography. *EMBO Rep*. 2017 Jul;18(7):1090-1099. PubMed PMID: 28487352

5. In situ structures of the bacterial type IV secretion systems (T4SS)

In *Helicobacter pylori*, one of the most successful pathogens, colonizing more than half of the world's population, the *cag* T4SS induces a raft of physiological changes in target cells resulting in gastritis, ulcers, or even cancer. To date, the interaction of *cag* T4SS effector-translocation channel with host cell surfaces has not been characterized in detail. By culturing human gastric epithelial cells on EM grids, infecting them with *H. pylori*, plunge-freezing the samples, and imaging them by cryo-ET, I have successfully captured the in situ *cag* T4SS structures on the host-pathogen interface. Moreover, the data also revealed an amazing and unexpected structure: a double-layered tube extending out from the surface of the bacterial cell with pipe-like portals along its length, which may represent a later stage of the *cag* T4SS action. Together these discoveries have provided many new hypotheses and a road map toward understanding the detail structural mechanism of *H. pylori* infection. I have also contributed these imaging and data analysis techniques to study another model T4SS system, the Dot/Icm system, in the human pathogen *Legionella pneumonia* to shed light on the relationship among its structure, positioning and function.

a. **Chang YW***, Shaffer CL*, Rettberg LA, Ghosal D, Jensen GJ. In vivo structures of the *Helicobacter pylori cag* Type IV Secretion System. *Cell Rep*. 2018 Apr 17;23(3):673-681. PubMed PMID: 29669273 (*equal contribution)

b. Ghosal D, **Chang YW**, Jeong KC, Vogel JP, Jensen GJ. In situ structure of the *Legionella* Dot/Icm type IV secretion system by electron cryotomography. *EMBO Rep*. 2017 May 1;18(5):726-732. PubMed PMID: 28336774

c. Jeong KC, Ghosal D, **Chang YW**, Jensen GJ, Vogel JP. Polar delivery of *Legionella* type IV secretion system substrates is essential for virulence. *Proc Natl Acad Sci U S A*. 2017 Jul 25;114(30):8077-8082. PubMed PMID: 28696299

d. Ghosal D, Kaplan M, **Chang YW**, Jensen GJ. In situ imaging and structure determination of bacterial toxin delivery systems using electron cryotomography. *Methods Mol Biol*. 2019 Jan 30;1921:249-265. PubMed PMID: 30694497

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Edward B. Lee, M.D., Ph.D.

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

POSITION TITLE: Associate Professor of Pathology and Laboratory Medicine

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
Stanford University	B.S.	06/1997	Biological Sciences
University of Pennsylvania School of Medicine	Ph.D.	05/2004	Neuroscience
University of Pennsylvania School of Medicine	M.D.	05/2005	
Hospital of the University of Pennsylvania	Residency	06/2007	Anatomic Pathology
Hospital of the University of Pennsylvania	Fellowship	06/2009	Neuropathology
University of Pennsylvania School of Medicine	Postdoc	06/2011	Neurodegeneration

A. Personal Statement

I am an Associate Professor of Pathology and Laboratory Medicine with tenure and the Associate Director of the Penn Alzheimer's Disease Research Center (ADRC), with an independent scientific research program which includes basic and translational studies on neurodegenerative diseases including Alzheimer's disease (AD), frontotemporal degeneration (FTD), amyotrophic lateral sclerosis (ALS), and chronic traumatic encephalopathy. I have contributed to over 130 publications including 26 first/last author manuscripts since starting my independent laboratory with an h-index of 53. I am an attending physician (neuropathologist) at the Hospital of the University of Pennsylvania and Neuropathology Core leader of the Penn ADRC, Penn Frontotemporal Degeneration Center, and CONNECT-TBI (a multi-institutional consortium to study the neuropathology of traumatic brain injury). Thus, I can provide training in pathology, biochemistry, molecular biology, RCR, and neurodegenerative diseases as highlighted in the references listed in this section and the Contributions to Science sections below.

I am passionate about training the next generation of physician-scientists as an active member of the Penn Medical Scientist Training Program, as I was once a student in the program. I serve as a faculty trainer, an MSTP mentor, an MSTP RCR section leader, and a member of the MSTP Core Admissions Committee. I lecture annually to medical and graduate students on neuropathology, and serve as a section leader for neuropathology small group sessions. I am a member of multiple graduate groups (Cell & Molecular Biology, Neuroscience, Biochemistry and Biophysics, Pharmacology) and have served on 29 thesis committees (not including graduate students in my lab) over the last 10 years. I have mentored 7 graduate students (including 3 MSTP students), four postdoctoral fellows, 14 undergraduate/high school students, and 12 neuropathology fellows. I have served on the Epidemiology and Biostatistics Graduate Group Review Committee. I chair our neuropathology Clinical Competency Committee, and I also lead an R13-funded national career development workshop for neuropathology trainees.

As an MSTP faculty trainer and principal investigator, I am fully committed to the responsible conduct of research, thoughtful mentorship for my trainees, and the promotion of a safe, inclusive and supportive research training environment. This commitment includes my willingness to 1) provide all of my mentees with training in rigorous and unbiased experimental design, methodology, analysis, interpretation, and reporting of results, 2) participate in mentorship and unconscious bias training programs whenever required, and 3) ensure that my trainees meet the MSTP requirement that thesis committee meetings are no more than 6 months apart. Finally, I recognize that an important part of my role as a mentor is to help all of my trainees complete their degrees in a timely fashion with the skills, credentials, and experiences needed to sustain careers in the biomedical research workforce as successful research physicians and veterinarians.

Ongoing and recently completed projects that I would like to highlight include:

Darwich NF, Phan JM, Kim B, … Lee EB (2020). Autosomal dominant *VCP* hypomorph mutation impairs disaggregation of PHF-tau. Science, 2020 Nov, 370(6519): eeay8826, PMCID: PMC7818661.

Nguyen AT, Wang K, Hu G, … Li M and Lee EB (2020). *APOE* and *TREM2* regulate amyloid-responsive microglia in Alzheimer's disease. Acta Neuropathologica, 2020 Oct, 140(4): 477-493, PMCID: PMC7520051.

Lee EB. Integrated neurodegenerative disease autopsy diagnosis. Acta Neuropathologica 2018 April, 135(4): 643-646, PMCID: PMC6186396

R01NS095793, Edward B. Lee, *Epigenetic editing of mutant C9orf72*; Role: PI Goal: Develop novel methods for targeted epigenetic editing.	02/16-1/22
U56NS115322, Douglas H. Smith, *CONNECT-TBI*; Role: Leader of Brain Bank Core. Goal: Elucidate the diverse neuropathologies associated with TBI.	9/19-05/24
P30AG072979, David Wolk, *Penn Alzheimer's Disease Research Center*; Role: Associate Director and Leader of Neuropathology Core. Goal: Perform comprehensive brain autopsy and bank AD/ADRD tissues.	07/21-06/26
P01AG066597, Murray Grossman, *Using networks to understand heterogeneity in TDP-43 related frontotemporal degeneration and aging*, Role: Leader NP Core and project. Goal: Perform comprehensive brain autopsy and bank FTD tissues, and perform single cell transcriptome analyses of human tissues.	09/20-05/25
R13AG059336, Edward B. Lee, *A longitudinal workshop to promote neurodegenerative disease neuropathology research*; Role: PI Goal: Lead a national career development workshop for neuropathology trainees.	07/18-07/22

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2004-present	American Society for Investigative Pathology, Membership Committee 2010-2012
2010-present	American Association of Neuropathologists, Executive Council, 2017-present, Assistant Secretary Treasurer 2017-present, Financial & Investment Committee 2020-present, Education Committee Chair 2017-present, Education Committee Member 2015-2017, Website Committee 2015-present, Program Committee Chair 2013-2015, Awards Committee Member 2013-2015
2011-present	Assistant Professor of Pathology and Laboratory Medicine, University of Pennsylvania
2014-present	Journal of Neuropathology and Experimental Neurology, Editorial board member
2014-present	Acta Neuropathologica, Editorial board member
2018-present	Neuropathology and Applied Neurobiology, Editorial board member
2020-present	Free Neuropathology, Associate Editor
2015-present	Ad hoc study section member, CMND, ZRG1 MDCN, NIA-N, NST-2, CDMRP (DoD)
2014-2017	Alzheimer's Disease Center Neuropathology Steering Committee (Chair 2016-2017)
2017-present	American Board of Pathology, Neuropathology Test Development Advisory Committee
2017-present	Scientific Program Committee, Alzheimer's Association International Conference
2021-present	Associate Professor of Pathology and Laboratory Medicine, University of Pennsylvania
2021-present	Associate Director, Penn Alzheimer's Disease Research Center

Honors

1997	Departmental Honors in Biological Sciences, Stanford University
1997	Phi Beta Kappa, Stanford University
2005	O.H. Perry Pepper Award for investigative work of exceptional merit and noteworthy competence as a clinician, University of Pennsylvania
2005	Experimental Pathologist-In-Training Award, American Society for Investigative Pathology
2005	Jesse H. Frank M.D. Prize in Pathology for excellence in research in Pathology and Laboratory Medicine, University of Pennsylvania

2009	Leonard Jarett Symposium Award, University of Pennsylvania
2010	Center for Neurodegenerative Disease Annual Retreat Award, University of Pennsylvania
2011	Thomas B. and Jeannette E. Laws McCabe Fund Fellow Award, University of Pennsylvania
2012	Excellence in Science Award, American Society for Investigative Pathology
2013	New Investigator Recognition at the Alzheimer Association's 2013 Rita Hayworth Gala
2016	Young Physician-Scientist Award, American Society for Clinical Investigation
2014…2020	Robert Terry Award for best paper in neurodegenerative diseases, American Association of Neuropathologists (awarded in 2014, 2018, 2019; honorable mention in 2020).
2021	Weil Award for best paper in experiment neuropathology, American Association of Neuropathologists

C. Contributions to Science

1. Epigenetic modulation of mutant *C9orf72* in FTD and ALS. My laboratory was the first to suggest that epigenetic silencing of mutant *C9orf72* may be neuroprotective. A repeat expansion in *C9orf72* is the most common genetic cause of FTD and ALS. Prior to the three studies from my laboratory listed here, mutant C9orf72 was proposed to cause neurodegeneration through three potential pathways: (1) toxic RNA, (2) dipeptide repeat proteins, or (3) haploinsufficiency linked to epigenetic silencing of mutant *C9orf72*. Rather than causing disease, I reasoned that transcriptional silencing of mutant *C9orf72* may actually protect against disease progression. Indeed, my studies show that *C9orf72* silencing protects against toxicity in cell culture assays, neuropathologic inclusion formation in human brains, disease progression in humans, and grey matter degeneration and cognitive decline in living patients. Based on these findings, we developed a novel method of epigenetic editing whereby DNA methylation can be specifically and stably introduced into the endogenous genome in a template manner via homology direct repair.

1. Liu EY, Russ J, Wu K, Neal D, Suh E, McNally AG, Irwin DJ, Van Deerlin VM, Lee EB (2014). *C9orf72* hypermethylation protects against repeat expansion-associated pathology in ALS/FTD. Acta Neuropathologica, 128(4): 525-41. PMCID: PMC4161616

2. Russ J, Liu EY, Wu K, Neal D, Suh E, Irwin DJ, McMillan CT, Harms MB, Cairns NJ, Wood EM, Xie SX, Elman L, McCLuskey L, Grossman M, Van Deerlin VM, Lee EB (2015). Hypermethylation of repeat expanded *C9orf72* is a clinical and molecular disease modifier. Acta Neuropathologica, 129(1): 39-52. PMCID: PMC4282973

3. McMillan CT, Russ J, Wood EM, Irwin DJ, Grossman M, McCluskey L, Elman L, Van Deerlin V, Lee EB (2015). *C9orf72* promoter hypermethylation is neuroprotective: Neuroimaging and neuropathologic evidence. Neurology, 84(16): 1622-30. PMCID: PMC4409587

4. Cali CP, Park DS, Lee EB (2019). Targeted DNA methylation of neurodegenerative disease genes via homology directed repair. Nucleic Acids Res 47(22): 11609-11622. PMCID: PMC7145628

2. Mechanisms of neurodegeneration in TDP-43 proteinopathies. I have used a combination of molecular, biochemical, and histologic methods to study transgenic mice and human tissues to investigate molecular mechanisms of TDP-43 proteinopathies. We demonstrated that neurodegeneration in mice overexpressing cytoplasmic TDP-43 protein was not linked to TDP-43 aggregate formation. Rather, neuron loss was more tightly linked to the downregulation of endogenous TDP-43 protein, highlighting the role of TDP-43 autoregulation in disease pathophysiology. Our results, together with a growing literature on TDP-43 protein, raised the question as to whether the driving factor leading to neurodegeneration stems from a gain-of-toxic function due to cytoplasmic TDP-43, or a loss of function due to a downregulation of endogenous nuclear TDP-43 protein. I helped formulate and coalesce these concepts into a scientific review highlighting the known mechanisms linking TDP-43 dysfunction with neurodegeneration. We extended our analysis of TDP-43 transgenic mice using deep RNA sequencing to demonstrate that TDP-43 affects histone transcripts and nuclear chromatin supporting a link between abnormal chromatin structure and neurodegeneration. Based on these findings, we developed a novel method to isolate and sequence pathologic neuronal nuclei from human brain tissues. This led to the discovery that the loss of nuclear TDP-43 results in relaxation of chromatin of LINE retrotransposons in human neurons and enhanced retrotransposition in experimental models.

1. Igaz LM*, Kwong LK*, Lee EB*, Chen-Plotkin A, Swanson E, Unger T, Malunda J, Xu Y, Winton MJ, Trojanowski JQ, Lee VM. Dysregulation of the ALS-associated gene TDP-43 leads to neuronal death and degeneration in mice (2011). J Clin Invest 121(2): 726-38. PMCID: PMC3026736
*Co-lead authors

2. Lee EB, Lee VM, Trojanowski JQ. Gains or losses: molecular mechanisms of TDP43-mediated neurodegeneration (2011). Nat Rev Neurosci 13(1): 38-50. PMCID: PMC3285250

3. Amlie-Wolf A, Ryvkin P, Tong R, Dragomir I, Suh E, Xu Y, Van Deerlin VM, Gregory BD, Kwong LK, Trojanowski JQ, Lee VM, Wang LS, Lee EB. Transcriptomic changes due to cytoplasmic TDP-43 expression reveal dysregulation of histone transcripts and nuclear chromatin (2015). PLoS One 10(10): e0141836. PMCID: PMC4624943

4. Liu EY, Russ J, Cali CP, Phan JM, Amlie-Wolf A, Lee EB. Loss of nuclear TDP-43 is associated with decondensation of LINE retrotransposons (2019). Cell Reports. 27(5): 1409-1421. PMCID: PMC6508629

3. Integration of clinical, molecular and neuropathologic features in neurodegenerative diseases.
I am Core Leader of the Penn ADRC NP Core, having studied hundreds of brain autopsies. A driving principle of my work is to integrate data across diverse modalities to better achieve proper classification of disease and to provide insights into disease mechanisms. For example, I co-lead a study which demonstrated that *C9orf72* repeat exapansion mutation size was associated with disease duration in frontotemporal dementia, supporting a gain-of-toxic function mechanism. I also led a study which identified a unique subtype of FTLD-TDP using neuropathologic, biochemical and genetic methods. FTLD-TDP subtype E is associated rapid clinical progression, raising the prospect of a particularly virulent “strain” of neurodegenerative disease proteinopathy. I also led a study that involved over 15 institutions that identified intermediate *C9orf72* repeat expansions as a risk factor for corticobasal degeneration. We highlighted a mechanism based on increased expression of the *C9orf72* gene leading to abnormal proteostasis due to disruption in autophagy in experimental models. Finally, I have described the first neuropathologic description of the sequelae of anti-tau passive immunotherapy where a series of cases revealed accumulation of tau within perivascular astrocytic lysosomes which we speculate represents an attempt to degrade tau.

1. Suh E*, Lee EB*, Neal D, Wood EM, Toledo JB, Rennert L, Irwin DJ, McMillan CT, Krock B, Elman LB, McCluskey LF, Grossman M, Xie SC, Trojanowski JQ, Van Deerlin VM (2015). Semi-automated quantification of C9orf72 expansion size reveals inverse correlation between hexanucleotide repeat number and disease duration in frontotemporal degeneration. Acta Neuropathologica, 130(3): 363-72. PMCID: PMC4545720
*Co-lead authors

2. Lee EB, Porta S, Michael Baer G, Xu Y, Suh E, Kwong LK, Elman L, Grossman M, Lee VM, Irwin DJ, Van Deerlin VM, Trojanowski JQ (2017). Expansion of the classification of FTLD-TDP: Distinct pathology associated with rapidly progressive frontotemporal degeneration. Acta Neuropathologica 134(1): 65-78. PMCID: PMC5521959

3. Cali CP, Patino M, Tai YK, et al., Lee EB. C9orf72 intermediate repeats are associated with corticobasal degeneration, increased C9orf72 expression and disruption of autophagy (2019). Acta Neuropathologica 138(5): 795-811. PMCID: PMC6802287

4. Kim B, Mikytuck B, Suh E, et al., Lee EB. Tau immunotherapy is associated with glial responses in FTLD-tau. (2020) Acta Neuropathologica *online ahead of print.* NIHMSID: 1706127, PMCID pending

4. Neuropathology of diverse neurodegenerative disease conditions.
I have led or contributed in many studies describing the neuropathology of various types of neurodegeneration. I led one study demonstrated that TDP-43 aggregates are specific to neurodegenerative diseases and absent in other neoplastic, inflammatory or reactive conditions. I contributed to an influential ALS study based on immunohistochemical staining of tissues from our brain bank which elucidated four stages of ALS. I also authored additional studies on the distribution and spread of FUS pathology in atypical frontotemporal lobar degeneration and basophilic inclusion body disease, and the contribution of chronic traumatic encephalopathy

(tauopathy) to dementia in former rugby and soccer players.

1. Lee EB, Lee VM, Trojanowski JQ, Neumann M. TDP-43 immunoreactivity in anoxic, ischemic and neoplastic lesions of the central nervous system (2008). Acta Neuropathologica 115(3): 305-11.

2. Brettschneider J, Del Tredici K, Toledo JB, Robinson JL, Irwin DJ, Grossman M, Suh E, Van Deerlin VM, Wood EM, Baek Y, Kwong L, Lee EB, Elman L, McCluskey L, Fang L, Feldengut S, Ludolph AC, Lee VM, Braak H, Trojanowski JQ (2013). Stages of pTDP-43 pathology in amyotrophic lateral sclerosis. Ann Neurol. 74(1): 20-38. PMCID: PMC3785076

3. Lee EB, Russ J, Jung H, Elman LB, Chahine LM, Kremens D, Miller BL, Branch Coslett H, Trojanowski JQ, Van Deerlin VM, McCluskey LF (2013). Topography of FUS pathology distinguishes late-onset BIBD from aFTLD-U. Acta Neuropathologica Commun 1(9): 1-11. PMCID: PMC3767453

4. Lee EB, Kinch K, Johnson VE, Trojanowski JQ, Smith DH, Stewart W. Chronic traumatic encephalopathy is a common co-morbidity, but less frequent primary dementia in former soccer and rugby players (2019). Acta Neuropathologica 138(3): 389-399. PMCID: PMC6689293

5. Amyloid β peptides in Alzheimer's disease. My earliest scientific contributions relate to the role of diverse pools of Aβ peptide in the pathogenesis of Alzheimer's disease. Using human neuronal cell cultures, I found that BACE expression regulated the intracellular generation and secretion of truncated Aβ peptides. At this time, very little attention was paid towards truncated Aβ peptides, although understanding the mechanistic role of these truncated peptides is now investigated by several laboratories. I also found that the BACE expression regulated the subcellular site of Aβ peptide production. I generated novel BACE transgenic mice which revealed that depletion of synaptic Aβ due to BACE overexpression inhibited amyloid plaque deposition. The role of synaptic Aβ in the pathogenesis of Alzheimer's disease was not extensively studied prior to this publication, but has been shown since to play an important role in the pathogenesis of Alzheimer's disease. Finally, I was the first to demonstrate in a transgenic mouse model that targeting Aβ oligomers restores cognitive function. I developed a novel conformation-selective monoclonal antibody, NAB61, which recognizes oligomeric Aβ. Passive immunization of APP transgenic mice with this antibody improved learning and memory function. This antibody has been validated by other laboratories and continues to be used by multiple investigators to understand the role of oligomeric Aβ species in Alzheimer's disease.

1. Lee EB, Leng LZ, Zhang B, Kwong L, Trojanowski JQ, Abel T, Lee VM. Targeting amyloid-beta peptide (Abeta) oligomers by passive immunization with a conformation-selective monoclonal antibody improves learning and memory in Abeta precursor protein (APP) transgenic mice (2006). J Biol Chem 281(7): 4292-9.

2. Lee EB, Zhang B, Liu K, Greenbaum EA, Doms RW, Trojanowski JQ, Lee VM. BACE overexpression alters the subcellular processing of APP and inhibits Abeta deposition in vivo (2005). J Cell Biol 168(2): 291-302. PMCID: PMC2171598

3. Lee EB, Skovronsky DM, Abtahian F, Doms RW, Lee VM. Secretion and intracellular generation of truncated Abeta in beta-site amyloid-beta precursor protein-cleaving enzyme expressing human neurons (2002). J Biol Chem 278(7): 4458-66.

4. Lee EB, Leng LZ, Lee VM, Trojanowski JQ. Meningoencephalitis associated with passive immunization of a transgenic murine model of Alzheimer's amyloidosis (2005). FEBS Lett 579(12): 2564-8.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/edward.lee.1/bibliography/43218916/public/?sort=date&direction=ascending