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RESEARCH SUMMARY

Autophagy is a cellular sorting and recycling mechanism that is highly conserved through evolution and occurs in all cell types. Because autophagy degrades proteins and organelles, studying what autophagy engulfs can shine a light into what defines the cell's function or is critical for the cell's health. For example, an immune cell presenting antigen, an adipocyte switching fates between white and beige, or a tumor cell that is addicted to a certain metabolite are all processes that depend on functional autophagy. While autophagy is important in all cell types, neurons uniquely require autophagy for homeostasis, and inhibition of autophagy leads to rapid neuron death. Furthermore, defects in autophagy are a pathological hallmark of neurodegenerative disease. The mutations associated with neurodegenerative diseases that pepper the many steps of the autophagy pathway each affect different functional aspects of autophagy. Therefore, understanding what autophagy degrades in neurons and how different neurodegenerative disease mutations disrupt the removal of particular cargo can help to identify the critical processes that support neuron function and resilience. I plan to study how neurodegenerative disease mutations affect autophagy in neurons and glia, and the interactions between these cells, with the goal of identifying new therapeutic angles to improve healthspan.

EDUCATION AND TRAINING

University of Pennsylvania, November 2018 – present
Healey Center ALS Scholar in Therapeutics Postdoctoral Fellow
Advisor: Dr. Erika Holzbaur

University of California, San Francisco, September 2012 - October 2018
Ph.D Biomedical Sciences (BMS) Program
Advisor: Dr. Jayanta Debnath

University of Oxford, St. Hugh's College October 2006 - June 2010
M.Biochem. undergraduate degree in Molecular and Cellular Biochemistry
Tutor (Advisor): Dr. Anthony Watts
Master's Research Advisor: Dr. Louis Mahadevan

RESEARCH EXPERIENCE AND ACCOMPLISHMENTS

Postdoctoral Researcher, November 2018 - Present
Holzbaur Lab
Department of Physiology
University of Pennsylvania

I am investigating the molecular mechanisms that define how autophagy maintains neuron homeostasis, and how it is deregulated in neurodegenerative disease. Using unbiased enrichment of autophagosomes from brain and cultured primary and iPSC-derived neurons and proteomics, immunoblotting, and live imaging on a spinning disk confocal microscope, I found that small mitochondria enriched for mitochondrial DNA are a basal cargo in neurons (Goldsmith et al., Neuron, 2022). Further, we used similar approaches to understand how autophagy is changed and compensated for in different mouse models of Parkinson's disease (Goldsmith et al., BioRxiv, 2022).

Graduate Student, July 2013 - October 2018
Debnath Lab
Department of Pathology
University of California, San Francisco

My PhD research focused on the consequences of impaired autophagy in regulating protein translation, with a focus on cancer initiation. Using ribosome profiling, RNA-Seq, and polysome profiling, I found that impaired autophagy prevents the efficient translation of cell cycle genes and DNA damage repair genes,

including *Brca2*, commonly disrupted in familial breast cancer (Goldsmith et al., Comm. Biol. 2020). During my training, mastered many different autophagy assays and various in vivo and in vitro breast cancer and metastasis models. I collaborated with many members of the Debnath lab to study how autophagy impacts different hallmarks of cancer, including tumor cell metastasis and migration, immune recognition, metabolism, and angiogenesis, contributing to 5 peer reviewed papers.

Research Assistant, October 2010 - August 2012
Ahmed Lab
Nuffield Department of Obs. and Gyn.
University of Oxford

My research contributed to the discovery of a novel combination therapy to enhance the chemotherapeutic treatment for ovarian cancer. I performed a high content imaging screen of a whole kinome knockdown in ovarian cancer cell lines and identified Fer kinase as a druggable modulator of microtubule stability. Working with chemists at the University of Oxford, I tested the newly designed inhibitor to Fer in a panel of ovarian cancer cell lines (Zheng et al., Nat. Comm., 2018).

Master's student, September 2009 - February 2010
Mahadevan Lab
Department of Biochemistry
University of Oxford

I studied histone variant H2AX acetylation and phosphorylation on the expression of immediate early genes by acid urea gel and SDS-PAGE analysis and immunoblotting following the activation of stress-induced signaling pathways in cell culture. My dissertation and oral examination were marked as firsts.

Trainee, July 2005 - September 2008
Buxbaum Lab
Department of Psychiatry
Mount Sinai School of Medicine

I worked part time during my senior year of high school and three summer internships in the Buxbaum lab. I assisted in the autism genome project, sequencing candidate genes from affected families, performing basic cell culture and learning general laboratory practices. This experience sparked my interest in studying human disease, and a dedication to mentorship.

ARTICLES

Goldsmith J, Ordureau A, Harper JW, Holzbaur ELF. Brain-derived autophagosome profiling reveals the engulfment of nucleoid-enriched mitochondrial fragments by basal autophagy in neurons. Neuron 2022 Jan 13 PMID:35051374

Goldsmith J, Ordureau A, Stavoe AKH, Boecker CA, Arany M, Harper JW, Holzbaur ELF. Distinct adaptations revealed by unbiased proteomic analysis of autophagy cargos in the brain of PINK1 and LRRK2 models of Parkinson's disease. Manuscript on BioRxiv. https://doi.org/10.1101/2022.10.03.510717

Goldsmith J, Marsh T, Asthana S, Leidal, AM, Suresh D, Olshen A, Debnath J. Ribosome profiling reveals a functional role for the autophagy pathway in mRNA translational control. Commun. Biol. 2020 Jul 17 PMID:32681145

Goldsmith J, Holzbaur ELF. Punctum: Proteomic profiling shows mitochondrial nucleotides are autophagy cargo in neurons: implications for neuron maintenance and neurodegenerative disease. Autophagy 2022 Mar 29 PMID:35343362

Goldsmith J, Holzbaur ELF. Presynaptic homeostatic plasticity staves off neurodegenerative pathophysiology up to a tipping point. Neuron 2020 Jul 8 PMID:3264530

Goldsmith J, Levine B and Debnath J. Autophagy and cancer metabolism. Methods in Enzymology, 542:25-57, 2014 PMID:24862259

Boecker CA, **Goldsmith J**, Dou D, Cajka GG, Holzbaur ELF. Increased LRRK2 kinase activity alters neuronal autophagy by disrupting the axonal transport of autophagosomes. Current Biology 2021 Mar 18

PMID:33765413

Cason S, Carman P, Van Duyne C, **Goldsmith J**, Dominguez R, Holzbaur ELF. Sequential dynein effectors regulate axonal autophagosome motility in a maturation-dependent pathway. Journal of Cell Biology 2021 Jul 5 PMID: 34014261.

Kaur J, **Goldsmith J**, Tankka A, Bustamante Eguiguren S, Gimenez AA, Vick L, Debnath J, Vlahakis A. Atg32-dependent mitophagy sustains spermidine and nitric oxide required for heat-stress tolerance in Saccharomyces cerevisiae. Journal of Cell Science 2021 Jun 1 PMID: 34096604

Rudnick J, Monkkonen T, Mar FA, Barnes JM, Starobinets H, **Goldsmith J**, Roy S, Bustamante Eguiguren S, Weaver VM, Debnath J. Autophagy in stromal fibroblasts promotes tumor desmoplasia and mammary tumorigenesis. Genes and Development 2021 Jul 1 PMID: 34168038

Leidal AM, Huang HH, Solvik T, Marsh T, Ye J, Zhang D, Kai F, **Goldsmith J**, Liu JY, Huang Y-H, Monkkonen T, Vlahakis A, Huang EJ, Yu L, Wiita AP and Debnath J. The LC3 Conjugation Machinery Specifies the Loading of RNA-Binding Proteins into Extracellular Vesicles. Nature Cell Biology 2020 Feb PMID: 31932738

Zheng Y, Sethi R, Mangala L, Taylor C, **Goldsmith J**, Wang M, Masuda K, Karami M, Ranjbar N, Mannion D, Miranda F, Herrero-Gonzalez S, Hellner K, Chen F, Alsaadi A, Albukhari A, Fosto DC, Yau C, Jiang D, Pradeep S, Rodriguez-Aguayo C, Lopez-Berestein G, Knapp S, Gray N, Campo L, Myers K, Dhar S, Ferguson DJP, Bast R, Sood A, Delft F, Ahmed A. Tuning microtubule dynamics to enhance cancer therapy by modulating FER-mediated CRMP2 phosphorylation. Nature Communications 2018 Feb 2 PMID: 29396402

Starobinets H, Ye J, Broz M, Barry K, **Goldsmith J**, Marsh T, Roster F, Krummel M, Debnath J. Antitumor adaptive immunity remains intact following inhibition of autophagy and antimalarial treatment. Journal of Clinical Investigation 2016 Dec1 PMID: 27775547

Kenific CM, Stehbens SJ, **Goldsmith J**, Leidal AM, Faure N, Ye J, Wittmann T, Debnath J. NBR1 enables autophagy-dependent focal adhesion turnover. Journal of Cell Biology 2016 Feb 22 PMID:26903539

Townley HE, Zheng Y, **Goldsmith J**, Zheng YY, Stratford MR, Dobson PJ, Ahmed AA. A novel biosensor for quantitative monitoring of on-target activity of paclitaxel. Nanoscale 2015 Jan 21. PMID: 25483994

Ahmed AA, Wang X, **Goldsmith J**, Lu Z, Le XF, Grandjean G, Bartholomeusz G, Broom B, Bast RC Jr. Modulating microtubule stability enhances the cytotoxic response of cancer cells to Paclitaxel. Cancer Res. 2011 Sept 1. PMID: 21775522

Ahmed AA, **Goldsmith J**, Fokt I, Le XF, Krzysko KA, Lesyng B, Bast RC Jr, Priebe W. A genistein derivative, ITB-301, induces microtubule depolymerization and mitotic arrest in multidrug-resistant ovarian cancer. Cancer Chemother. Pharmacol. 2011 Feb 22 PMID: 21340606

Cai G, Edelmann L, **Goldsmith JE**, Cohen N, Nakamine A, Reichert JG, Hoffman EJ, Zurawiecki DM, Silverman JM, Hollander E, Soorya L, Anagnostou E, Betancur C, and Buxbaum JD. Multiplex ligation-dependent probe amplification for genetic screening in autism spectrum disorders: Efficient identification of known microduplications and identification of a novel microduplication in ASMT BMC Medical Genomics 1:50, 2008 PMID: 18925931

Buxbaum JD, Cai G, Nygren G, Chaste P, Delorme R, **Goldsmith J**, Råstam M, Silverman JM, Hollander E, Gillberg C, Leboyer M and Betancur C. Mutation analysis of the NSD1 gene in patients with autism spectrum disorders and macrocephaly BMC Medical Genetics 8:68, 2007 PMID: 18001468

Buxbaum JD, Cai G, Chaste P, Nygren G, **Goldsmith J**, Reichert J, Anckarsäter H, Råstam M, Smith CJ, Silverman JM, Hollander E, Leboyer M, Gillberg C, Verloes A, and Betancur C. Mutation Screening of the PTEN gene in patients with autism spectrum disorders and macrocephaly, American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, Vol 144B, Issue 4 pp 484-491, 2007 PMID: 17427195

FELLOWSHIPS

ALS Scholar in Therapeutics, MGH Healey Center for ALS, Jul. 2021 - Jun. 2023
NIAMS Pennsylvania Muscle Institute T32 Training in Muscle Biology and Disease, March 2021, Declined for Healey Center Award
National Science Foundation Graduate Research Fellowship Program, Sept. 2014 - Aug. 2017
Moritz-Heyman Discovery Fellow, UCSF, Sept. 2014 - Aug. 2017
ARCS Scholarship, ARCS Foundation, Sept. 2013 - May 2014

AWARDS AND HONORS

Kavli Neuroscience Institute SYNAPSES seminar series, March 2023
Women in Autophagy Best Poster Prize, WIA 3rd Annual Symposium, Nov. 2022
EMBO Autophagy meeting travel award, Sept. 2017
Mary Lunt Prize in Practical Biochemistry, St. Hugh's College, University of Oxford, Oct. 2010

TEACHING AND MENTORING EXPERIENCE

Lab Mentor to students

Supporting early exposure to research environments is important to me, as my early experience working in a lab in high school was formative. I have mentored undergraduate summer students Albert Xu, a University of California, Berkeley student (2016) who is completing the MD/PhD program at UCSF after working as a laboratory technician, and Madeleine Arany, a University of Colorado, Boulder student (2021), who is currently completing her undergraduate degree, and applying for competitive summer internship programs in medicine. I designed and supervised my trainees' independent research projects that culminated in formal presentations to the lab and department. Madeleine's summer contributions earned her authorship in my most recent first author paper. Additionally, I have formally mentored rotation PhD and MD/PhD students and informally advised peers both scientifically and on career advancement during my postdoctoral fellowship and graduate research.

Peer mentor for Biomedical Postdoctoral Programs, University of Pennsylvania

I participated in 10 hours of structured training for peer support for other postdocs, including how engage in active listening, identify signs of mental illness, distress and crisis, and navigating the specialist resources available.

Teaching Assistant, Genetics, January 2014 - April 2014, UCSF

I was a TA of approximately 30 students and tutor for up to 5 students per year from 2015-2018 for the graduate intro to genetics class run by the BMS program at UCSF. I organized and distributed class materials, coordinated with lecturers, ran a weekly review session for 30+ students, held office hours once per week for the semester, and graded exams.

NSF writing workshop course, September 2015, UCSF

I co-organized and led a writing workshop for 30 graduate students and assisted 5 applicants personally in preparing their materials for the NSF GFRP application.

Inclusive STEM Teaching Project March 6- April 28 2023

16+ hrs of training to learn how to better teach and support URMs, focused on curriculum design and teaching tools based on quantitative and qualitative social science research to make courses inclusive and equitable in order to promote the successful learning of all students.

DIVERSITY-RELATED ACTIVITIES, LEADERSHIP AND SERVICE

Founding Member of the Committee for Diversity, Equity and Inclusion
Physiology Department, University of Pennsylvania

We have organized diversity trainings engaging over 80% of the department members, initiated a well-received seminar series bringing diverse speakers with remarkable research to Penn to meet with faculty and trainees (8 to date, 4 scheduled for 2023 spring semester and 2 for the 2023 fall semester), and

launched mentorship events, support networks and community building events that are held weekly and quarterly. I am spearheading a more targeted support program that will discuss specific topics monthly.

Volunteer teacher, September 2013 - May 2014
STAT program, UCSF Science and Education Partnership
I attended a teacher training pedagogy course (20h) and developed a week-long lesson plan teaching the scientific method including hand-on experiments and incorporating different types of learning styles, which we then taught to two fourth grade classes.

Community Service, 2013-2017

- Volunteer at **Lowell High School** after school program in San Francisco, where I led discussions and presentations ranging over a wide variety of topics including careers in science, applying to university, basic cancer biology and an introduction to genetics by discussing model organisms.
- Volunteer e-mentor for the **Alameda County Science Fair,** helping middle school and high school students to refine and develop their science projects.
- Volunteer judge for the **Bay Area Science Fair**
- Volunteer at the **Bay Area Science Festival**, running a booth with hands on experiments for children ages 5-12.
- I was involved for multiple years in the **UCSF Biomedical Sciences graduate student recruitment** and both organized hosting events, including dinners and day trips, and interviewed applicants.

SELECT PRESENTATIONS AT MEETINGS AND CONFERENCES

Poster Jefferson Synaptic Biology Symposium	13 April 2023, Philadelphia USA
Short talk and Poster at Keystone meeting on Autophagy and Neurodegeneration: Mechanisms to Therapies	26-29 March 2023, Snowbird, Utah, USA
SYNAPSES (Seminars at Yale Neuroscience: Advanced Postdoc Extramural Series) program	2 March 2023 Kavli Institute for Neuroscience, Yale, New Haven, USA
Talk in “Mitochondrial Organization and Inter-organelle Contacts” minisyposium, American Society of Cell Biology	4 December 2022 Washington DC, USA
Poster, recipient of Best Poster Prize, Women in Autophagy Annual Meeting	14-15 November 2022 Virtual meeting
Poster Pennsylvania Muscle Institute Annual Symposium	1 November 2022 University of Pennsylvania, USA
Poster UPenn Physiology Department Retreat	16 September 2022 Merion Tribute House, Phila. USA
Talk in “Neuronal Cell Dynamics” minisymposium American Society of Cell Biology	1-10 December 2021 Virtual meeting
Talk in “Vesicle Trafficking and Pathways to Neurodegeneration” Wellcome Trust Symposium	17-19 May 2021 Virtual meeting
Talk in “Autophagy” minisymposium and poster American Society of Cell Biology	2-6 December 2017 Philadelphia, USA
Talk, travel grant European Molecular Biology Organization: Autophagy meeting	24-29 September 2017 Cavtat, Croatia
Talk and poster Bay Area Meeting on Organelle Biology	6 June 2017 UC Berkeley, Berkeley, USA
Talk Discovery Fellows Michael Page PhD symposium	17 April 2017 UCSF, San Francisco, USA
Talk and Poster USCF Biomedical Sciences retreat,	14-16 October 2016 Granlibakken, Lake Tahoe, USA