BIOGRAPHICAL SKETCH

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NAME: Heller, Elizabeth A

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

POSITION TITLE: Assistant Professor of Pharmacology; Founder, Rafias LLC

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)	END DATE MM/YYYY	FIELD OF STUDY
University of Pennsylvania, Philadelphia	AB	06/2002	Biology
The Rockefeller University, New York	PHD	06/2009	Molecular Biology
Icahn School of Medicine at Mount Sinai, New York	Postdoctoral Fellow	12/2015	

A. Personal Statement

I have the expertise, leadership, and motivation to successfully carry out the proposed research project. As a drug abuse researcher, I am motivated to identify and analyze novel drug targets in addiction. Because there are currently no medications for treating cocaine use disorder, our investigation into Nr4a1 will inform a major gap in the literature and the treatment space. Our preliminary investigations have determined that Nr4a1 activation after abstinence can successfully attenuate cocaine seeking, which is an essential attribute of our target product profile. The expertise of the team and approach described in this application are ideally suited to demonstrate the potential of small molecule activation of Nr4a1 in the treatment of cocaine use disorder.

Since starting my lab in 2016 I have successfully competed for several foundation- and NIH-funded grants. I successfully administered the projects, established meaningful collaborations, disseminated the work at meetings, and published peer-reviewed articles. As a member of the Institute for Translational Medicine and Therapeutics and the Penn Epigenetics Institute at the University of Pennsylvania, I have access to the resources and collaborative expertise to support the multifaceted approach described in this application.

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

UL1-TR001878
Fitzgerald (PI) Role: Pilot
1/01/21 – 1/01/23
Nanoparticle-based, Nr4a1 agonist delivery to combat cocaine addiction

DP1 DA044250
Heller (PI)
7/15/17 – 6/30/22
Chromatin-Mediated Alternative Splicing in Reward Pathophysiology

R01 DA052465-01A1
Heller (PI)
7/01/21 – 6/30/26
Epigenetic mechanisms of sustained transcription across cocaine abstinence.

STXBP1 Postdoc Fellowship
Heller (Mentor)
11/01/21 – 10/31/23
Editing the epigenome: Curing STXBP1/MUNC18-1 heterozygosity

Syngap Research postdoc fellowship Fund
Heller (Mentor)
1/01/21 – 12/31/22
SYNGAP1 Epigenetic Regulation

U18 DA052513
Heller (PI)
9/30/20 – 9/29/21
Pharmacological activators of Nr4a1 for the treatment of cocaine use disorders.

Citations:

1. Xu S, Lombroso SI, Fischer DK, Carpenter MD, Marchione DM, Hamilton PJ, Lim CJ, Neve RL, Garcia BA, Wimmer ME, Pierce R Christopher, Heller EA. Set2-mediated alternative splicing of Srsf11 regulates cocaine reward behavior. Neuron. 2021 Sep 15; 109(18):2943-2966. PMC8454057.
2. Hu Q, Greene CS, Heller EA. Specific histone modifications associate with alternative exon selection during mammalian development. Nucleic Acids Res. 2020 May 21;48(9):4709-4724. PMC7229819.
3. Carpenter MD, Hu Q, Bond AM, Lombroso SI, Czarnecki KS, Lim CJ, Song H, Wimmer ME, Pierce RC, Heller EA. Nr4a1 suppresses cocaine-induced behavior via epigenetic regulation of homeostatic target genes. Nat Commun. 2020 Jan 24;11(1):504. PMC6981219.
4. Sase AS, Lombroso SI, Santhumayor BA, Wood RR, Lim CJ, Neve RL, Heller EA. Sex-Specific Regulation of Fear Memory by Targeted Epigenetic Editing of Cdk5. Biol Psychiatry. 2019 Apr 15;85(8):623-634. PMC30661667.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2016 -	Assistant Professor, Perelman School of Medicine, University of Pennsylvania, Philadelphia
2011 - 2013	Adjunct Assistant Professor, Biology, Queens College, City University of New York, New York
2010 - 2010	Research Assistant, Center for Neural Science, New York University, New York
2009 - 2010	Visiting Assistant Professor, Bard/Rockefeller Semester in Science, New York

Honors

2002	Phi Beta Kappa, The University of Pennsylvania
2003	Women & Science Fellowship, The Rockefeller University
2012	Institutional Postdoctoral National Research Service Award, NIDA
2013	Postdoc Appreciation Award, Icahn School of Medicine at Mount Sinai

2013	Travel Award, American College of Neuropsychopharmacology
2013	Individual Postdoctoral National Research Service Award, NIDA
2014	NIDA Director's Travel Award, College on Problems of Drug Dependence
2015	Robin Chemers Neustein Postdoctoral Fellowship, Icahn School of Medicine at Mount Sinai
2015	Scholarship, Keystone Symposia
2017	National Academy of Sciences Kavli Scholar, Korean-American Frontiers of Science Symposium
2019	National Academy of Sciences Kavli Scholar, Japanese-American-German Frontiers of Science Symposium

C. Contribution to Science

1. Defined the mechanism of chromatin-mediated alternative splicing in vivo, using CRISPR-mediated epigenetic editing. There is an abundance of data on drug-regulated gene transcription, yet little is known about other gene regulatory mechanisms in this context. My recent publications demonstrate the prevalence of alternative splicing following drug exposure. We have elucidated the role of epigenetic modifications to alternative splicing. We take a multifaceted approach, including bioinformatic analyses, machine learning and CRISPR-mediated epigenetic editing. These publications report that specific histone modifications, H3K36me3 and H3K4me1, are enriched at splice junctions and predict alternative isoform expression in brain reward regions. This body of work is the first to establish direct causal evidence that histone modifications regulate alternative splicing in vivo.

    a. Xu S, Lombroso SI, Fischer DK, Carpenter MD, Marchione DM, Hamilton PJ, Lim CJ, Neve RL, Garcia BA, Wimmer ME, Pierce R Christopher, Heller EA. Set2-mediated alternative splicing of Srsf11 regulates cocaine reward behavior. Neuron. 2021 Sep 15; 109(18):2943-2966. PMC8454057.

    b. Hu Q, Greene CS, Heller EA. Specific histone modifications associate with alternative exon selection during mammalian development. Nucleic Acids Res. 2020 May 21;48(9):4709-4724. PMC7229819.

    c. Lopez Soto EJ, Gandal MJ, Gonatopoulos-Pournatzis T, Heller EA, Luo D, Zheng S. Mechanisms of Neuronal Alternative Splicing and Strategies for Therapeutic Interventions. J Neurosci. 2019 Oct 16;39(42):8193-8199. PMC6794923.

    d. Hu Q, Kim EJ, Feng J, Grant GR, Heller EA. Histone posttranslational modifications predict specific alternative exon subtypes in mammalian brain. PLoS Comput Biol. 2017 Jun;13(6):e1005602. PMC5487056.

2. Defined the direct causal relevance of neuronal histone methylation by pioneering epigenetic editing in vivo. My early contributions in drug abuse research elucidated the epigenetic regulation of Fosb, a key immediate early gene underlying drug pathophysiology in both rodents and humans. These publications include the first application of locus-specific epigenetic editing in vivo and reveal key roles for histone methylation and acetylation at the Fosb gene in mediating aggression, drug memory formation, and depression. Importantly, I was the first to apply cell-type specific epigenetic editing, revealing that the behavioral effects of histone modifications vary by neuronal subtype.

    a. Gajewski PA, Eagle AL, Williams ES, Manning CE, Lynch H, McCornack C, Maze I, Heller EA, Robison AJ. Epigenetic Regulation of Hippocampal *Fosb* Expression Controls Behavioral Responses to Cocaine. J Neurosci. 2019 Oct 16;39(42):8305-8314. PubMed Central PMCID: PMC6794929.

    b. Aleyasin H, Flanigan ME, Golden SA, Takahashi A, Menard C, Pfau ML, Multer J, Pina J, McCabe KA, Bhatti N, Hodes GE, Heshmati M, Neve RL, Nestler EJ, Heller EA, Russo SJ. Cell-Type-Specific Role of ΔFosB in Nucleus Accumbens In Modulating Intermale Aggression. J Neurosci. 2018 Jun 27;38(26):5913-5924. PubMed Central PMCID: PMC6021989.

    c. Hamilton PJ, Burek DJ, Lombroso SI, Neve RL, Robison AJ, Nestler EJ, Heller EA. Cell-Type-Specific Epigenetic Editing at the Fosb Gene Controls Susceptibility to Social Defeat Stress. Neuropsychopharmacology. 2018 Jan;43(2):272-284. PubMed Central PMCID: PMC5729576.

    d. Heller EA, Cates HM, Peña CJ, Sun H, Shao N, Feng J, Golden SA, Herman JP, Walsh JJ, Mazei-Robison M, Ferguson D, Knight S, Gerber MA, Nievera C, Han MH, Russo SJ, Tamminga CS, Neve

RL, Shen L, Zhang HS, Zhang F, Nestler EJ. Locus-specific epigenetic remodeling controls addiction- and depression-related behaviors. Nat Neurosci. 2014 Dec;17(12):1720-7. PubMed Central PMCID: PMC4241193.

3. Contributed knowledge on the epigenetic regulation of genes involved in neuropsychiatric disease, including Cdk5, Nr4a1 and ACSS2. These publications highlight discoveries in brain reward areas, including ventral striatum, hippocampus, and ventral tegmental area, as well as many types of exposure, including cocaine, morphine, alcohol and stress. We have discovered the epigenetic regulation of cyclin-dependent kinase 5 during cocaine and stress exposure, and include findings on sex-differences in this context. Recently, we have uncovered a key role for neuronal Acyl-coenzyme A synthetase in neuronal histone acetylation and reward behavior, following both alcohol and cocaine exposure. Finally, we have recently uncovered a role for Nr4a1 activation in NAc in the repression of cocaine reward behavior as well as long-term gene regulation across abstinence.

    a. Carpenter MD, Hu Q, Bond AM, Lombroso SI, Czarnecki KS, Lim CJ, Song H, Wimmer ME, Pierce RC, Heller EA. Nr4a1 suppresses cocaine-induced behavior via epigenetic regulation of homeostatic target genes. Nat Commun. 2020 Jan 24;11(1):504. PubMed Central PMCID: PMC6981219.
    b. Mews P, Egervari G, Nativio R, Sidoli S, Donahue G, Lombroso SI, Alexander DC, Riesche SL, Heller EA, Nestler EJ, Garcia BA, Berger SL. Alcohol metabolism contributes to brain histone acetylation. Nature. 2019 Oct;574(7780):717-721. PubMed Central PMCID: PMC6907081.
    c. Sase AS, Lombroso SI, Santhumayor BA, Wood RR, Lim CJ, Neve RL, Heller EA. Sex-Specific Regulation of Fear Memory by Targeted Epigenetic Editing of Cdk5. Biol Psychiatry. 2019 Apr 15;85(8):623-634. PubMed PMID: 30661667.
    d. Heller EA, Hamilton PJ, Burek DD, Lombroso SI, Peña CJ, Neve RL, Nestler EJ. Targeted Epigenetic Remodeling of the Cdk5 Gene in Nucleus Accumbens Regulates Cocaine- and Stress-Evoked Behavior. J Neurosci. 2016 Apr 27;36(17):4690-7. PubMed Central PMCID: PMC4846670.

4. Cell-type specific proteomic characterization of inhibitory synapses. During my dissertation research at The Rockefeller University, under the mentorship of Dr. Nathaniel Heintz, I developed the first protocol for the specific biochemical isolation and characterization of the elusive inhibitory synapse. Unlike similar approaches, we were able to biochemically separate synaptic proteins from those contained in non-synaptic, membranous fractions. Overall, we made the remarkable discovery that inhibitory synapses consist of structural proteins and ion channels, yet are completely lacking in the signaling molecules that comprise the major component of excitatory synapses. We were the first to identify Lipoma HMGIC Fusion Partner-Like 4 (Lhfpl) as a member of the GABAA Receptor protein complex. This factor, which is necessary for GABA receptor function, was rediscovered in 2017 as GABAAR regulatory Lhfpl (GARLH). This aspect of my training experience makes me particularly well suited to carry out the proposed experiments in affinity purification of specific cell types, as well as to continue to develop novel methods to answer longstanding research questions.

    a. Heller EA, Zhang W, Selimi F, Earnheart JC, Ślimak MA, Santos-Torres J, Ibañez-Tallon I, Aoki C, Chait BT, Heintz N. The biochemical anatomy of cortical inhibitory synapses. PLoS One. 2012;7(6):e39572. PubMed Central PMCID: PMC3387162.
    b. Selimi F, Cristea IM, Heller E, Chait BT, Heintz N. Proteomic studies of a single CNS synapse type: the parallel fiber/purkinje cell synapse. PLoS Biol. 2009 Apr 14;7(4):e83. PubMed Central PMCID: PMC2672601.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/elizabeth.heller.1/bibliography/public/