**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: CHARTOFF, ELENA

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

POSITION TITLE: Assistant Professor

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 |
|---|---|---|---|
| Carnegie Mellon University, Pittsburgh, PA | B.S. | 06/1992 | Biology |
| University of Washington, Seattle, WA | Ph.D. | 05/2001 | Neurobiology & Behavior |
| Harvard Medical School, Belmont, MA | Postdoctoral fellow | 08/2004 | Behavioral Genetics |

## A. Personal Statement

My research focuses on the neurobiological underpinnings of reward function and motivated behavior in the context of psychiatric disorders such as bipolar disorder, depression, and drug addiction. A major biological question in my laboratory is how neural circuits act under normal circumstances to regulate mood and how these circuits can be disrupted to produce mood disorders. In this context, we are investigating the role of kappa opioid receptor systems and AMPA glutamate receptors in limbic brain regions such as the nucleus accumbens, amygdala, and prefrontal cortex in reward function. To accomplish this, we are using pharmacological and molecular genetic approaches to selectively enhance or disrupt kappa opioid or AMPA receptor-related signaling pathways within these limbic circuits in order to determine causal relationships between these systems and affective states. We utilize several sophisticated behavioral assays, including intracranial self-stimulation (ICSS), intravenous drug self-administration, and place conditioning, which are sensitive to affective states and changes in motivated behavior. Collectively my laboratory has over 15 years of experience using molecular genetics (including viral vector-mediated gene delivery) and behavioral pharmacology to study how the brain regulates mood and motivated behavior in laboratory rodent models. In addition, McLean Hospital is one of the best environments in the world for conducting research on psychiatric illnesses.

The following papers are listed to highlight expertise in my lab:

1. Mavrikaki M, Pravetoni M, Page S, Potter D, **Chartoff E**. Oxycodone self-administration in male and female rats. *Psychopharmacology*. 2017. 234(6):977-987. PMID:28127624
2. Russell SE, Puttick DJ, Sawyer AM, Potter DN, Mague S, Carlezon WA Jr., **Chartoff EH**. Nucleus accumbens AMPA receptors are necessary for morphine withdrawal-induced negative affective states in rats. *J. Neurosci.* 2016. 36(21):5748-5762. PubMed PMID: 27225765.
3. **Chartoff EH** and **McHugh RL**. Translational studies of sex differences in sensitivity to opioid addiction. *Neuropsychopharmacology*. 2016. Jan;41(1):383-4. doi: 10.1038/npp.2015.272. *Hot Topic*
4. Russell SE, Rachlin AB, Smith KL, Muschamp J, Berry L, Zhao Z, **Chartoff EH**. Sex differences in sensitivity to the depressive-like effects of the kappa opioid receptor agonist U-50488 in rats. *Biol Psychiatry*. 2014 Aug 1;76(3):213-22. PubMed PMID: 24090794.

## B. Positions and Honors

## Positions and Employment

1992 - 1995 Research Assistant, Harvard University, Cambridge, MA
1998 - 1998 Teaching Assistant, Department of Pharmacology, University of Washington, Seattle, MA

| | |
|---|---|
| 2000 - 2000 | Teaching Assistant, Department of Pharmacology, University of Washington, Seattle, WA |
| 2004 - 2007 | Instructor, Department of Psychiatry, Harvard Medical School, Belmont, MA |
| 2007 - | Assistant Professor, Department of Psychiatry, Harvard Medical School, Belmont, MA |
| 2011 - | Faculty Affiliate, Graduate Program in Neuroscience, Harvard Medical School, Boston, MA |

## Other Experience and Professional Memberships

| | |
|---|---|
| 1995 - | Member, Society for Neuroscience |
| 2005 - | Ad Hoc Reviewer, *Journal of Neuroscience, Developmental Brain Research, Journal of Neurochemistry, Journal of Psychopharmacology, Molecular Brain Research, Neuroscience, Neuropsychopharmacology, Psychopharmacology, Biological Psychiatry, British Journal of Psychopharmacology, Neuroscience and Biobehavioral Reviews, International Journal of Neuropharmacology, EMBO* |
| 2011 - 2011 | Reviewer, National Institute on Drug Abuse, Special Emphasis Panels |
| 2011 - 2011 | New Investigator Temporary Member, National Institute on Drug Abuse, MNPS Study Section |
| 2012 - | Field Editor, *International Journal of Neuropsychopharmacology* |
| 2013 - 2013 | Reviewer, National Institute on Drug Abuse CEBRA Special Emphasis Panels |
| 2016 - | Judge, Cards Against Humanity Science Ambassador Scholarship |
| 2016 - 2016 | Reviewer, National Institute on Drug Abuse CEBRA Special Emphasis Panels |
| 2017 - 2017 | Reviewer, NIDA Centers of Excellence Grant Program |

## Honors

| | |
|---|---|
| 1991 | Undergraduate Research Grant, National Science Foundation |
| 1991 | Small Undergraduate Research Grant, Carnegie Mellon University |
| 1995 | Graduate School Fellowship, American Rewards for College Scientists |
| 1999 | Travel Award, International Behavioral Neuroscience Society |
| 2002 | Kaneb Fellowship in Psychiatry, McLean Hospital |
| 2003 | Travel Award, New York Academy of Sciences |
| 2007 | Travel Fellowship, Winter Conference on Brain Research |
| 2009 | Travel Award, International Narcotics Research Conference |
| 2010 | Travel Award, International Narcotics Research Conference |

## C. Contribution to Science

1. My overarching interest in how modulation of the mesocorticolimbic system impacts behavior began with my graduate thesis work, conducted jointly in the labs of Drs. Dan Dorsa and Richard Palmiter at University of Washington. There I studied how the neuropeptide neurotensin is regulated within the striatum and acts as a brake on hyperdopaminergic function, which is critical for normal control of movement but—under pathological conditions—can induce motor impairments. Specifically, my publications from this time showed that typical antipsychotic drugs such as haloperidol, which act primarily as dopamine D2 receptor antagonists, induce striatal neurotensin expression in a PKA-dependent manner through activation of adenosine 2a and NMDA receptors. Using dopamine-deficient mice (previously generated in the Palmiter lab), which display a profound supersensitivity to dopamine, I showed that the supersensitive behavioral responses to dopamine replacement are mediated by dopamine D1 receptors and attenuated by neurotensin. By providing mechanistic evidence for how neurotensin contributes to motor impairment, this work may lead to improvements in the side effect profiles of antipsychotic drugs and engender research on the use of neurotensin ligands to treat disorders involving dysregulated dopamine transmission.

    a. **Chartoff EH**, Marck BT, Matsumoto AM, Dorsa DM, Palmiter RD. Induction of stereotypy in dopamine-deficient mice requires striatal D1 receptor activation. Proc Natl Acad Sci U S A. 2001 Aug 28;98(18):10451-6. PubMed PMID: 11517332; PubMed Central PMCID: PMC56981.

    b. **Chartoff EH**, Ward RP, Dorsa DM. Role of adenosine and N-methyl-D-aspartate receptors in mediating haloperidol-induced gene expression and catalepsy. J Pharmacol Exp Ther. 1999 Nov;291(2):531-7. PubMed PMID: 10525068.

c. Adams MR, Brandon EP, **Chartoff EH**, Idzerda RL, Dorsa DM, McKnight GS. Loss of haloperidol induced gene expression and catalepsy in protein kinase A-deficient mice. Proc Natl Acad Sci U S A. 1997 Oct 28;94(22):12157-61. PubMed PMID: 9342379; PubMed Central PMCID: PMC23735.

2. As a postdoctoral fellow at McLean Hospital, Harvard Medical School, I focused my interest to studying how morphine regulates cAMP-mediated signal transduction pathways in the nucleus accumbens (NAc). The effects of chronic morphine in the NAc are thought to play an important role in morphine withdrawal-induced negative affective states. I set up an in vitro model—primary striatal neuron cultures—with which to examine the effects of acute and chronic morphine on dopamine D1 and glutamate receptor signaling. These studies led to two first-author publications and provided the preliminary data necessary for successful funding of my NRSA application to NIDA. With this funding, I took what we learned in cell culture to a rat model of morphine dependence and showed that morphine dependence upregulates cAMP signaling in the NAc and subsequently sensitizes D1 receptors. In a 2006 Journal of Neuroscience paper, I show that morphine dependence profoundly alters signaling in the NAc such that activation of D1 receptors completely blocks affective and somatic signs of morphine withdrawal. In a subsequent publication I show that these effects are modulated by ventral tegmental area projections to the NAc. More recently I have expanded the study of how signaling in the NAc regulates opiate withdrawal by examining the regulation and role of AMPA receptors. In a recent, 2016 publication in the Journal of Neuroscience, we demonstrate that activation of AMPA receptor GluA1 subunits in the NAc shell is necessary for morphine withdrawal-induced negative states. These publications are important because they connect drug-induced molecular plasticity with behavior and identify drug-able targets for treatment of opiate withdrawal syndrome.

   a. Russell SE, Puttick DJ, Sawyer AM, Potter DN, Mague S, Carlezon WA Jr, **Chartoff EH**. Nucleus Accumbens AMPA Receptors Are Necessary for Morphine-Withdrawal-Induced Negative-Affective States in Rats. J Neurosci. 2016 May 25;36(21):5748-62. PubMed PMID: 27225765; PubMed Central PMCID: PMC4879196.
   b. **Chartoff EH**, Barhight MF, Mague SD, Sawyer AM, Carlezon WA Jr. Anatomically dissociable effects of dopamine D1 receptor agonists on reward and relief of withdrawal in morphine-dependent rats. Psychopharmacology (Berl). 2009 Jun;204(2):227-39. PubMed PMID: 19148621; PubMed Central PMCID: PMC2921644.
   c. **Chartoff EH**, Mague SD, Barhight MF, Smith AM, Carlezon WA Jr. Behavioral and molecular effects of dopamine D1 receptor stimulation during naloxone-precipitated morphine withdrawal. J Neurosci. 2006 Jun 14;26(24):6450-7. PubMed PMID: 16775132.
   d. **Chartoff EH**, Papadopoulou M, Konradi C, Carlezon WA Jr. Dopamine-dependent increases in phosphorylation of cAMP response element binding protein (CREB) during precipitated morphine withdrawal in primary cultures of rat striatum. J Neurochem. 2003 Oct;87(1):107-18. PubMed PMID: 12969258; PubMed Central PMCID: PMC4205588.

3. In the vein of studying how modulation of dopaminergic transmission in the mesocorticolimbic system impacts behavior, a large portion of my contributions to science have focused on the role of the kappa opioid receptor (KOR) and its endogenous ligand dynorphin in motivated behavior. This work was initiated during my postdoctoral training and has continued in my laboratory with funding from NIDA. Like neurotensin, dynorphin is a negative regulator of dopaminergic transmission and dynorphin is thought to contribute to stress- and drug-induced depressive-like states. The focus of my publications in this area is understanding the molecular mechanism by which KORs produce depressive-like states and potentiate addictive behaviors. In an early paper, I showed that the selective KOR agonist salvinorin A activates neurons within the NAc and can potentiate the locomotor stimulant effects of cocaine. Importantly, selective activation of KORs triggers biphasic effects on reward-related behavior, which has a profound impact on cocaine reward. These publications contribute to a growing body of literature that support development of KOR ligands for therapeutic treatment of stress-related disorders and drug addiction. In fact, I demonstrate in a recent publication that KOR antagonist blocks the development of binge cocaine-induced anhedonia in male rats.

   a. **Chartoff EH**, Ebner SR, Sparrow A, Potter D, Baker PM, Ragozzino ME, Roitman MF. Relative Timing Between Kappa Opioid Receptor Activation and Cocaine Determines the Impact on Reward and

Dopamine Release. Neuropsychopharmacology. 2016 Mar;41(4):989-1002. PubMed PMID: 26239494; PubMed Central PMCID: PMC4748424.

b. Van't Veer A, Bechtholt AJ, Onvani S, Potter D, Wang Y, Liu-Chen LY, Schütz G, **Chartoff EH**, Rudolph U, Cohen BM, Carlezon WA Jr. Ablation of kappa-opioid receptors from brain dopamine neurons has anxiolytic-like effects and enhances cocaine-induced plasticity. Neuropsychopharmacology. 2013 Jul;38(8):1585-97. PubMed PMID: 23446450; PubMed Central PMCID: PMC3682153.

c. **Chartoff E**, Sawyer A, Rachlin A, Potter D, Pliakas A, Carlezon WA. Blockade of kappa opioid receptors attenuates the development of depressive-like behaviors induced by cocaine withdrawal in rats. Neuropharmacology. 2012 Jan;62(1):167-76. PubMed PMID: 21736885; PubMed Central PMCID: PMC3195851.

d. Potter DN, Damez-Werno D, Carlezon WA Jr, Cohen BM, **Chartoff EH**. Repeated exposure to the κ-opioid receptor agonist salvinorin A modulates extracellular signal-regulated kinase and reward sensitivity. Biol Psychiatry. 2011 Oct 15;70(8):744-53. PubMed PMID: 21757186; PubMed Central PMCID: PMC3186866.

4. In an exciting line of research for my laboratory, we are studying sex differences in motivated behavior and drug addiction. Men and women have strikingly different prevalence rates of psychiatric disorders including depression and drug addiction, and we hypothesized that sex differences in KOR and/or MOR function underlie at least some of these clinical differences.

a. Mavrikaki M, Pravetoni M, Page S, Potter D, **Chartoff E**. Oxycodone self-administration in male and female rats. Psychopharmacology (Berl). 2017 Mar;234(6):977-987. PubMed PMID: 28127624.

b. **Chartoff EH**, McHugh RK. Translational Studies of Sex Differences in Sensitivity to Opioid Addiction. Neuropsychopharmacology. 2016 Jan;41(1):383-4. PubMed PMID: 26657961; PubMed Central PMCID: PMC4677149.

c. **Chartoff EH**, Mavrikaki M. Sex Differences in Kappa Opioid Receptor Function and Their Potential Impact on Addiction. Front Neurosci. 2015 Dec 16;9:466. PubMed PMID: 26733781; PubMed Central PMCID: PMC4679873.

d. Russell SE, Rachlin AB, Smith KL, Muschamp J, Berry L, Zhao Z, **Chartoff EH**. Sex differences in sensitivity to the depressive-like effects of the kappa opioid receptor agonist U-50488 in rats. Biol Psychiatry. 2014 Aug 1;76(3):213-22. PubMed PMID: 24090794; PubMed Central PMCID: PMC4476271.

**Complete List of Published Work in My Bibliography:**
https://www.ncbi.nlm.nih.gov/pubmed/?term=chartoff+e*

## D. Research Support

### Active Research Support

*Performance period*: 07/01/2016-06/31/2018
*Title*: Use of kappa opioid receptor antagonists to prevent opiate abuse after use of prescription opioid painkillers
*Principal Investigator*: Chartoff, Elena H.
*Supporting Agency:* ITN Consortium: USAMRMC proposal 13057002.03, Award Number W81XWH-13-2-0075
*Project goals*: The major goal of these studies is to use a rodent model of opioid dependence and withdrawal in male and female rats to determine whether the KOR antagonist JDTic administered during opioid withdrawal blocks withdrawal-induced negative affective states and likelihood to self-administer oxycodone.

*Performance period*: 11/01/2016-10/31/2019
*Title*: Sex differences in the ability to predict and treat opiate abuse
*Principal Investigator*: Chartoff, Elena H.
*Supporting Agency:* USAMRMC proposal BA150026, Award Number W81XWH-17-1-0004

*Project goals*: The goal of this project is to determine whether measures of Distress Intolerance can predict the severity of the opiate withdrawal syndrome in male and female rats and to determine whether corticotropin releasing factor blockade can prevent addictive behavior in opiate withdrawn male and female rats.

**Completed Research Support (last 3 years)**

*Performance period*: 5/1/2010 – 4/30/2014
*Title*: Role of dopamine signaling in the mood-related effects of salvinorin A
*Principal Investigator*: Chartoff, Elena H.
*Supporting Agency:* NIH/NIDA; R01 DA026552
*Project goals*: The goal of this project is to study how the kappa opioid receptor agonist salvinorin A modulates behavioral, neurochemical, and molecular aspects of dopamine signaling in rats.