Kevin M. Hellman, Ph.D.

NorthShore University HealthSystem
Department of Obstetrics & Gynecology
Walgreen Building, Suite 1530
2650 Ridge Avenue
Evanston, IL 60201
Office: (872)-226-7214
Fax: (847)-926-6545
Email: khellman@northshore.org
Web page: www.painscientist.org

BRIEF BIOGRAPHY

I study mechanisms and treatments for dysmenorrhea, the leading cause of school/work absence and foremost risk factor for chronic pain in reproductive age women. Our NIH (*3 separate grants*) and institutionally funded laboratory has developed new animal models, investigated novel diagnostic methods, and conducted treatment studies. *Five* of our nine recent manuscripts on dysmenorrhea or related gynecological pain issues are published in the American Journal of Obstetrics & Gynecology, the most cited journal in gynecology. My goal is to advance understanding of the pathophysiology of dysmenorrhea and develop new treatments while simultaneously training a cadre of future investigators to revolutionize the science of visceral pain. **Our research is essential because there are few other laboratories dedicated to eradicating dysmenorrhea, one of the most frequent causes of suffering and gender disparity worldwide.**

ACADEMIC AFFILIATIONS

2009-2010	Research Associate (Assistant Professor), Department of Neurobiology, University of Chicago
2011-	Assistant Professor (part-time), Department of Obstetrics and Gynecology, University of Chicago

ACADEMIC TRAINING

1994-1998	B.S., Computer Science, University of Wisconsin-Madison
1998-2004	Ph.D., Neuroscience, The University of Pennsylvania
2004-2009	Postdoctoral Scholar, The University of Chicago

LICENSURE AND CERTIFICATIONS

2010-	CITI Certification in IRB compliance for Clinical Research
2012-	Federal and Illinois DEA licensure for research class drugs

SCHOLARSHIP

(a) Peer-reviewed publications in the primary literature, exclusive of abstracts (note trainees listed in italics):

1. Lytton WW, **Hellman KM**, Sutula TP. Computer models of hippocampal circuit changes of the kindling model of epilepsy. (1998) Artificial Intelligence in Medicine. 13(1-2):81-97 http://dx.doi.org/10.1016/S0933-3657(98)00005-0

2. Graves LA, **Hellman KM,** Veasey S, Blendy JA, Pack AI, Abel T. Genetic Evidence for a Role of CREB in Sustained Cortical Arousal. (2003) Journal of Neurophysiology 90(2):1152-9. http://jn.physiology.org/cgi/content/full/90/2/1152

3. Ouyang M, **Hellman KM**, Abel T, Thomas SA. Adrenergic Signaling Plays a Critical Role in the Maintenance of Waking and in the Regulation of REM Sleep. (2004) Journal of Neurophysiology. 92(4):2071-82 http://jn.physiology.org/cgi/content/full/92/4/2071

4. Keeley MB, Wood MA, Isiegas C, Stein J, **Hellman KM**, Hannenhalli S, and Abel T. (2006) Differential Transcriptional Response to Non-Associative and Associative Components of Classical Fear Conditioning in the Amygdala and Hippocampus. Learning and Memory 13(2):135-42. http://learnmem.cshlp.org/content/13/2/135.long

5. Brink TS, **Hellman KM**, Lambert AM, Mason, P. (2006) Raphe magnus neurons help protect reactions to visceral pain from interruption by cutaneous pain. Journal of Neurophysiology 96(6):3423-32. http://jn.physiology.org/cgi/content/full/96/6/3423

6. **Hellman KM**, Abel T. Fear Conditioning Increases NREM sleep. (2007) Behavioral Neuroscience 121(2):310-323. http://psycnet.apa.org/journals/bne/121/2/310.pdf

7. **Hellman KM**, Brink TS, Mason, P. Activity of murine raphe magnus cells predicts tachypnea and on-going nociceptive responsiveness. (2007) Journal of Neurophysiology 98(6):3121-33. http://jn.physiology.org/cgi/content/full/98/6/3121

8. **Hellman KM**, Mendelson SJ, Mendez-Duarte MA, Russell JL, Mason P. Opioid microinjection into raphe magnus modulates cardiorespiratory function in mice and rats. (2009) American Journal of Physiology 297(5): R1400-8 http://ajpregu.physiology.org/cgi/reprint/00140.2009v1.pdf

9. **Hellman KM**, Hernandez, P, Young A, Park A, Abel T. Genetic Evidence that Protein Kinase A Regulates Thalamocortical Oscillations during NREM Sleep. (2010) Sleep 33(1):19-28. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2802244/

10. Tu FF, **Hellman KM**, Backonja M. Gynecological Management of Neuropathic Pain. (2011) American Journal of Obstetrics & Gynecology 205(5):435-43. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3205239/

11**. Hellman KM**, Mason P, Opioids disrupt pro-nociceptive modulation mediated by raphe magnus. (2012) Journal of Neuroscience 40:13668-78. http://www.jneurosci.org/content/32/40/13668.long

12. Tu FF, Epstein AE, Pozolo KE, Sexton DL, Melnyk AI, **Hellman KM**. A Non-Invasive Bladder Sensory Test Supports a Role for Dysmenorrhea Increasing Bladder Noxious Mechanosensitivity. (2013) Clinical Journal of Pain 29(10):883-90. http://dx.doi.org/10.1097/AJP.0b013e31827a71a3

13. *Westling AM*, Tu F, Griffith JW, **Hellman KM**, The association of dysmenorrhea with noncyclic pelvic pain accounting for psychological factors. (2013) American Journal of Obstetrics & Gynecology 209(5): 422.e1-422.e10 http://dx.doi.org/10.1016/j.ajog.2013.08.020

14. **Hellman KM**, *Patanwala IY, Pozolo KE*, Tu FF, Multimodal nociceptive mechanisms underlying chronic pelvic pain. (2015) American Journal of Obstetrics & Gynecology 213(6):827.e1-9. http://dx.doi.org/10.1016/j.ajog.2015.08.038

15. Tu FF, *Kane J*, **Hellman KM**, Non-invasive experimental bladder pain assessment in painful bladder syndrome. (2016) British Journal of Obstetrics & Gynecology 124(2):283-291. http://dx.doi.org/10.1111/1471-0528.14433

16. **Hellman KM**, *Yu PY, Oladosu, FA Segel C, Han A*, Prasad PV, Jilling T, Tu FF. The Effects of Platelet-Activating Factor on Uterine Contractility, Perfusion, Hypoxia, and Pain in Mice. (2017) Reproductive Sciences 25(3):384-394 http://doi.org/10.1177/1933719117715122

17. *Oladosu FA*, Tu FF, **Hellman KM**. Nonsteroidal antiinflammatory drug resistance in dysmenorrhea: epidemiology, causes, and treatment. (2017) American Journal of Obstetrics & Gynecology S0002-9378(17)31095-5 http://doi.org/10.1016/j.ajog.2017.08.108

18. **Hellman KM**, *Kuhn CS*, Tu FF, *Dillane KE, Shlobin NA*, Senapati S, *Zhou X*, Li W, Prasad PV. CINE MRI During Spontaneous Cramps in Women with Menstrual Pain. (2018) American Journal of Obstetrics & Gynecology S0002-9378(18)30084-X http://doi.org/10.1016/j.ajog.2018.01.035

19. *Zuckerman R*, Silton RL, Tu FF, Eng JS, **Hellman KM**. Somatic Symptoms in Women with Dysmenorrhea and Noncyclic Pelvic Pain. Archives of Women's Mental Health. (2018) *in press*

(b) Non-peer-reviewed original articles

1. Mason P, **Hellman KM** review of Changes in expression of NMDA-NR1 receptor subunits in the rostral ventromedial medulla modulate pain behaviors. Faculty of 1000: http://f1000.com/prime/6657956

2. Mason P, **Hellman KM** review of Acetate causes alcohol hangover headache in rats. Faculty of 1000: http://f1000.com/prime/8249956

3. Mason P, **Hellman KM** review of Unmasking the tonic-aversive state in neuropathic pain. Faculty of 1000: http://f1000.com/prime/1168048

4. **Hellman KM**, Tu FF, Reply to Ruan et al. Multimodal nociceptive mechanisms underlying chronic pelvic pain. American Journal of Obstetrics & Gynecology, Volume 215, Issue 1, 132 – 133. http://dx.doi.org/10.1016/j.ajog.2016.02.051

5. **Hellman KM**, Summary of relevant findings at SFN 2016. Pelvic Pain Special Interest Group Newsletter (January 2016)

(c) Books:

As a reviewer of scientific content:
Mason P. Medical Neurobiology. (2011) 665 pp. Oxford University Press

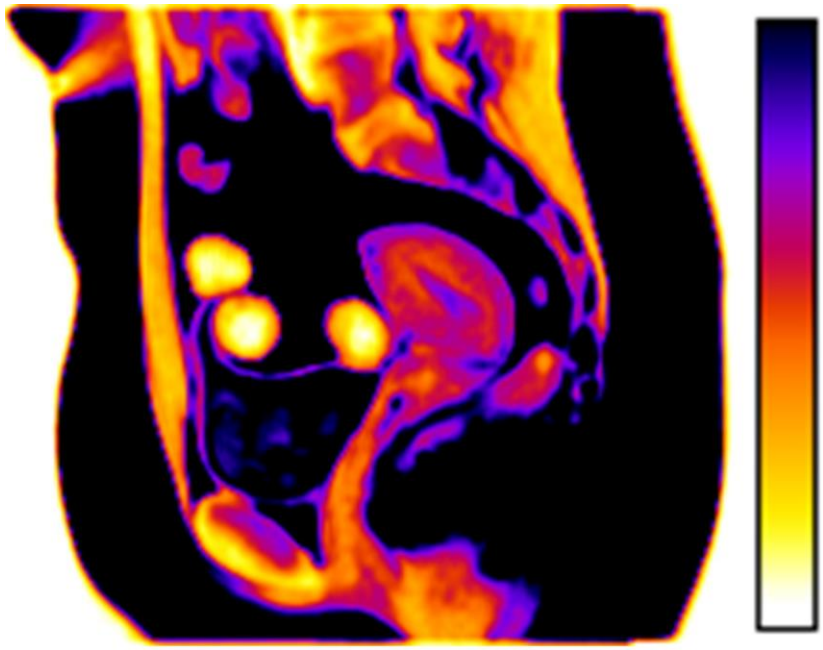
(d) Book chapters:
Hellman KM, Abel T. (2003) Chapter 15: Molecular Mechanisms of Memory Consolidation. Sleep and Brain Plasticity. Editors: Maquet P, Smith C, and Stickgold R. Oxford University Press.

(e) Other works that are publicly available:

2014 Interview on the Pelvic Messenger blogtalk RadioShow: The Holy Grail of Prevention of Pelvic Pain. http://www.blogtalkradio.com/pelvicmessenger/2014/02/21/the-holy-grail-of-prevention-of-pelvic-pain

(f) Cover Artwork:

May 2018 issue of American Journal of Obstetrics & Gynecology:



Single pseudocolor frame from a new method for studying causes of menstrual pain using cine MRI. The full sequence shows myometrial activity before the perception of a self-reported

menstrual cramp indicative of a potential cause of dysmenorrhea. [Image enhanced in ImageJ for cover artwork]

(g) Works in review, in preparation, etc. not yet publicly available

Hellman KM, Silton RL, Dillane KE, Polnazsek K, Harte SE, Tu FF. Cortical Mechanisms of sensory amplification in visceral pain sensitivity. [*under revision for Journal of Pain*]

Oladosu, FA, Tu FF, Farhan S, Garrison EF, Steiner ND, Roth GE, **Hellman KM.** Abdominal skeletal muscle activity precedes spontaneous menstrual cramping pain in primary dysmenorrhea. [*under review at American Journal of Obstetrics & Gynecology]*

Hellman KM*,* Datta A, Steiner ND, Kane J, Garrison EF, Clauw DJ, Tu FF. Identification of experimental bladder sensitivity among dysmenorrhea sufferers [*under review at American Journal of Obstetrics & Gynecology*]

FUNDING

(a) Past:

1. Epilepsy Foundation of America: Student Research Award. Title: Computational Model of Dentate Gyrus. 6/1/99-9/1/99 $5000.

2. NIH MH064329-02. Graduate Student National Research Service Award. Memory Consolidation and Sleep. 9/1/02- 8/31/03 $60,630.

3. NIH DA022429. PI: P. Mason. Role: Co-investigator. Opioid Analgesia in Awake Mice. $416,989.

4. American Academy of Sleep Medicine. Role: PI. “Neurophysiological Investigation of Pain Induced Arousal” 01/04/06 - 01/03/07. $60,000.

5. NorthShore Research Career Development Award. PI: KM Hellman. Modulation of Pain and Autonomic Function. 10/1/10-10/1/13. $225,000.

6. NIH HD081709. PI: KM Hellman. Neurophysiological Diagnostics for Menstrual Pain 8/01/2014-7/31/17. $414,996.

(b) Current:

1. NIH HD09150102. PI: KM Hellman “Noninvasive imaging of uterine physiology to improve dysmenorrhea” 08/2/17-06/31/19 $429,000.

2. NIH DK100368. PI: FF Tu. My role: Co-investigator. “Deciphering the hormonal and nociceptive mechanisms underlying bladder pain” 04/01/2014 – 03/31/2019 $2,408,178.

3. NIH DK100368-04S1. Fellowship. My role: Mentor. 04/01/2017 – 03/31/2019 $156,674.

(c) pending:

NIH HD096332-01 "Early Menstrual Pain Impact on Multisensory Hypersensitivity" [17th percentile on first submission—preparing for revision]

HONORS, PRIZES, AND AWARDS

1994 Frank Academic Scholar
1995 University of Wisconsin Honor Society
1997 Neuroscience Training Program award for Outstanding Research in Neurobiology
2000 National Institute of Health, National Research Service Award
2004 Elliot Stellar Scholar
2004 U.W. Madison Neuropsychology Travel Fellowship
2006 American Academy of Sleep Medicine Faculty Research Award
2012 Best abstract on pelvic pain, AAGL Global Congress
2012 Honorable mention poster award, International Pelvic Pain Society
2013 Best abstract on pelvic pain, AAGL Global Congress
2013 Best poster award, International Pelvic Pain Society
2014 New investigator of the year, NorthShore University HealthSystem
2016 Spotlighted abstract, Society for Affective Science
2017 Best paper award, Chicago Gynecological Society

INVITED SPEAKING

2004 Research seminar, "Sleep and memory: Electrophysiological, genetic, and molecular studies", Elliot Stellar Lecture, University of Pennsylvania
2008 Research seminar, "Opioidergic Analgesia and Respiratory Depression", Postdoctoral Association, University of Chicago
2009 Research seminar, "Anti-lock descending modulation: a new model for pain control", Department of Pharmacology, Rosalind Franklin University Medical School
2010 Research seminar, "Anti-lock descending modulation: a new model for pain control", Department of Gastroenterology, Medical College of Wisconsin
2011 Research seminar, "Pathophysiology and Treatment of Pelvic Pain", Center for Neurosensory Disorders, University of North Carolina
2012 Research seminar, "Mechanisms of Visceral Pain and Therapeutics", International Pelvic Pain Society, Palmer Hilton Chicago
2012 Research seminar, "Anti-lock analgesia: Mechanisms underlying visceral pain", Department of Pharmacology, Sothern Illinois University Medical School
2012 Grand rounds, "Pathophysiology and Treatment of Pelvic Pain", Department of Obstetrics and Gynecology, St. Francis Hospital System.
2014 Research seminar, "Three myths about pain refuted", NorthShore Scientific Society
2014 Grand Rounds, "Mechanisms underlying Dysmenorrhea", University of Chicago, Department of Obstetrics and Gynecology
2014 Research seminar, "Novel ultrasonographic methods for investigating the mechanisms of menstrual pain", AAGL, Las Vegas
2016 Grand rounds, "Somatization: Is it all in your patient's head?", Department of Obstetrics and Gynecology, Northshore University HealthSystem
2016 Research seminar, "Somatization: Is it all in your patient's head?", NorthShore Research Institute
2016 Video presentation, "Functional Phenotyping of Menstrual Pain", AAGL, Washington DC

2017 Research seminar, “Electrophysiological investigation of the mechanisms responsible for sensory amplification in visceral pain”, Loyola University of Chicago
2017 Research seminar,” Somatization and Pain”, Department of Clinical Psychology, University of Illinois Chicago
2017 Research seminar, “Research tools for clarifying mechanisms of visceral pain”, Chronic Pain & Fatigue Research Center, University of Michigan
2017 Research seminar,” The influence of somatization in common female pain conditions and potential neurological mechanisms”, Department of Psychiatry, RUSH University Medical Center
2018 Research seminar,” Mechanisms of Visceral Pain,” International Pelvic Pain Society, Chicago IL
2018 Research symposium, “The role of dysmenorrhea in the transition from acute to chronic pain”, World Congress on Pain (pending), Boston MA

INVITED, ELECTED, OR APPOINTED EXTRAMURAL SERVICE

2004 Curriculum Committee, University of Pennsylvania
2009-2011 Councilor—Society for Neuroscience Chicago Chapter
2013 NorthShore IRB Committee on Informed Consent
2014- NorthShore Pilot Grant Review Committee
2015- NorthShore Institutional Animal Care and Use Committee
2016 Grant Reviewer, US-Israel Binational Science Foundation
2016 Grant Reviewer, Austrian Science Fund
Various ad hoc reviewer for American Journal of Obstetrics & Gynecology, American Journal of Physiology, Anesthesiology, Brain Research, Molecular Pain, Environmental Research, Journal of Neurophysiology, Journal of Neuroscience Methods, Journal of Visual Experiments, Neuroimage, Neuroscience, PAIN, Physiology & Behavior, PLoS ONE.

PROFESSIONAL SOCIETIES

Elected or invited membership:
Society for Reproductive Investigation (formerly SGI)
American Academy of Sleep Medicine
Society for Neuroscience
Faculty of 1000

Other:
International Pelvic Pain Society
International Association for the Study of Pain

EDUCATIONAL SERVICE

The University of Pennsylvania (B.A., B.S.):
2001-2002 Teaching Assistant, Biology, University of Pennsylvania
2003-2004 Teaching Assistant, Neurobiology, University of Pennsylvania

Courses at the University of Chicago
2013- Cluster group leader – Summer Research Program, Pritzker School of Medicine
2018- Neuroscience of Pain and Opioids, MS4 elective, Pritzker School of Medicine

Continuing medical education:

2010- Annual lecture on pelvic pain as part of the NorthShore Obstetrics and Gynecology departmental grand rounds.

*Research trainees: [note italics designate co-author of poster, * designates paper co-authorship]*

(a) High school students and teachers

2009-2010 Multiple students and high school teachers (20+)—Department of Anesthesiology, University of Chicago: Course on Neurobiology as part of an educational grant from the American Recovery and Reinvestment Act of 2009

2014- Stevenson High School, SPARK: Summer scientific Internship Program. I have had 3 high school students perform academic internships in my laboratory.

(b) Undergraduate (B.A., B.S.)

2005-2006 *Eric Ohlson*, Research project on pain. Currently medical student at University of Arizona

2006-2007 *Aaron Lambert**, Research project on pain. Currently Postdoctoral Science at Harvard.

2008-2009 *Nasya Mendoza-Elias*, research project on respiration, University of Chicago. Entering residency in neurosurgery

2008-2009 *Marco Mendez-Duarte**, research project on respiration, University of Chicago.

2009-2010 *Shaun Teo*, research project on itch, University of Chicago. Graduated with Research Honors. Presently graduate student at The Rockefeller University

2009 *Natalia Khosla*, Research project on itch. Currently medical student at University of Chicago

2011 Van Sandwick, Research project on pain. Currently consultant at Trinity Partners

2011 Jake Carrow. Research project on optics/pain. Currently Ph.D. candidate at Texas A&M

2010-2012 *Peter Yu**, research project on uterine pain. Presently medical student at Ohio State University

2011-2012 *Allyson Westling**, research project on uterine pain. Presently medical student at Tufts

2012-2013 *Alice Han**, research project on uterine pain. Presently medical student at University of Illinois

2011-2013 *Chaya Segel**, research project on uterine pain, presently graduate student at University of Maryland

2014- *Nathan Shlobin**, research project on MRI of uterine pain. Presently in combined undergraduate/ medical school program graduate student at Northwestern University

2015-2017 *Julia Kane**, Research project on bladder pain. Presently student in educational psychology.

2015-2017 *Katlyn Dillane**, Research project on MRI & EEG in dysmenorrhea. Presently student for master's program international epidemiology.

(c) Medical (M.D.)

2007-2008 *Scott Mendelson*,* University of Chicago. Currently a Fellow in Neurology at UCLA.

2013-2015 *Nita Padavil*, University of Chicago. Science & Discovery Track mentorship. Current Psychiatry Resident at Northwestern

2014- *Rebecca Zuckerman*,* University of Chicago. Summer Research Program mentorship.
2015- *Carrie Kuhn**, University of Chicago. Awarded Calvin Fentress Fellowship to study mechanisms of menstrual pain in my laboratory. Currently resident in Ob/Gyn at University of Chicago

(e) Postdoctoral
2012- *Adam Gafni-Kane*, Research Project on interstitial cystitis, Urogynecological Fellowship, University of Chicago.
2013- *Insiyyah Patanwala**, Research project on quantitative sensory testing in pelvic pain, Resident Physician, University of Chicago.
2013- *Sarah Conduit-Hulbert/Wilkinson*, Research project on hormonal transcriptional factors in pelvic pain, Resident Physician, University of Chicago
2014- *Jennifer Rosenbaum*, Research project on Ultrasound analysis of pelvic pain, Resident Physician, University of Chicago.
2015- *Diana X. Zhou**, Research project on MRI analysis of pelvic pain, Resident Physician, University of Chicago.
2016- *Folabomi A. Oladosu*,* Research project on mechanisms of NSAID resistance, Postdoctoral Scholar, University of Chicago.
2017- *Katharina Laus*, Research project on MRI analysis of pelvic pain, Resident Physician, University of Chicago.
2018- Richard Cockrum, Research Project on doppler ultrasound, Resident Physician, University of Chicago.

Other:
2012 Symposium Organizer and Moderator on “Translational Optogenetics” at The University of Chicago.
2015- Mentor for Evidence Based Medicine presentations – University of Chicago Resident Physician program

SCHOLARSHIP STATEMENT

(a) Prefatory background on women's visceral pain research and my prior research portfolio

Chronic visceral pelvic pain disorders (endometriosis-associated pelvic pain, irritable bowel syndrome, bladder pain syndrome) cause substantial morbidity, and cost upwards of 50 billion dollars in lost US wages and health care expenditures. **Our research[13a] and others has shown visceral pelvic pain is common (~25% prevalence in women), but predictable and may be preventable.** Two key overlapping constructs consistently convey vulnerability (odds ratio 13)[13] as shown in large prospective studies: dysmenorrhea and widespread sensory sensitivity (i.e., somatization). Neuroplasticity is present in young girls, permitting adverse early sensory experiences to amplify future pain sensitivity. Consequently, identifying and mitigating early pain experiences might reduce their predisposition to multisensory hypersensitivity. An obvious early opportunity to explore this is at menarche, when many girls first experience menstruation-associated pain (dysmenorrhea). Consistent with prior findings, our research in over 1000 adult women found that the severity of dysmenorrhea along with self-report of sensory sensitivity predict nearly 75% of the participants who experience high levels of overall pelvic pain.[13] Better understanding of the mechanisms responsible for dysmenorrhea and widespread sensitivity is needed to develop preventative strategies which could revolutionize current paradigms in pain management--including opioid use--the worst health epidemic of the decade.

I began studying visceral pain, widespread sensitivity, and opioid mechanisms during my postdoctoral training. I investigated the mechanisms of visceral pain and opioid analgesia. Most prior work studying descending modulation was conducted in anesthetized animals. Instead, by recording from brainstem neurons in awake animals,[11] I substantially reformed understanding of the mechanism responsible for opioid analgesia that explains the limited effects of opioids in visceral pain[5], and how opioids impair respiratory and cardiovascular function.[7,8]. Rather than producing tonic states of analgesia or hyperalgesia, brainstem neurons dynamically boost the reaction to painful stimulation in a context-dependent manner. We demonstrated that pauses in neuronal discharge produce synchrony that facilitates postsynaptic integration.[11] This finding has a broad impact in neuroscience, as it provides a new framework for understanding circuit function of neurons that pause in diverse brain areas. Finally, we demonstrated that opioids produce analgesia simply by disabling this pro-nociceptive circuit.[11] Thus, our results also refute the prevailing notion of how opioids produce central analgesia and provide mechanisms to explain opioid side effects (as described in Current Opinion in Neurobiology 22:640-5).

After studying brainstem mechanisms of visceral pain modulation, I was invited to move NorthShore University HealthSystem to develop a translational research program with Dr. Frank Tu. I was inspired by Dr. Tu's successful clinical research program studying bladder pain to expand our focus on dysmenorrhea. Together, Dr. Tu and I and co-founded the Gynecological Research Laboratory (**GyRL**). **The goal of the GyRL research program is to identify the mechanisms that cause visceral pain, including dysmenorrhea, and develop effective interventions to prevent the development of chronic pelvic pain.** The causes of visceral pain are poorly understood because diagnostic tests do not exist to distinguish pain due to primary nociceptor activation, referred abdominal muscular activity, organ perfusion, or oxygenation issues. Development of effective treatments for disruptive chronic pelvic pain conditions like dysmenorrhea and painful bladder syndrome are hindered by this lack of mechanistic understanding. **The GyRL research program has addressed this gap and began work towards developing superior treatments based on our novel diagnostic research methods, as described in the next section**. Additionally, the GyRL research program has provided intramural and extramural opportunities for dozens of trainees as described in the Educational and Institutional sections.

[a] Citations refer to peer reviewed publication number, starting from page 1

(b) Peer-reviewed work, published or accepted, since emergence from postdoctoral training

1. BETTER UNDERSTANDING OF PHYSIOLOGICAL MECHANISMS OF DYSMENORRHEA. *"Why are girls still missing so many days because of their menstrual cycle?"-Michelle Obama tweeting on barriers to girl's education in 2016.* A hidden, personal, and painful reality of many women is severe, gut-wrenching menstrual cramps occurring every 3-5 minutes for several days each month resulting in the leading cause of missed school and work. These cramps are hallmarks of dysmenorrhea, and are not relieved by nonsteroidal anti-inflammatories (NSAIDs) in ~15% of reproductive age women.[17] Although the field has commonly accepted that prostaglandin release causes uterine hypercontractility and ischemia resulting in pain, there are significant limitations regarding all prior studies. Most prior work either utilized *in vitro* methods, or characterized molecules with limited relevance to dysmenorrhea, or did not use precise methods to assess contractility, perfusion, oxygenation, and pain. Therefore, to address this limitation, we have developed novel methods for clarifying the mechanisms responsible for menstrual cramps.

a. We developed an *in vivo* mouse model to clarify the pathophysiological mechanisms responsible for dysmenorrhea and allow for the testing of new therapeutics. Our model allowed us to characterize the effects of multiple candidate molecules while simultaneously using novel optical methods to monitor uterine perfusion and oxygenation.[16] Our model demonstrated that prostaglandin and Platelet Activating Factor (PAF) could directly elicit visceral pain and pelvic hyperalgesia via uterine hypercontractility and uterine ischemia. These results challenge the dogma that uterine ischemia never occurs (as contended by others: FASEB 2013, doi: 10.1096/fj.13-232074). Furthermore, since PAF is not inhibited by NSAIDS[17] it represents a new potential druggable target for NSAID-resistant dysmenorrhea. This animal model was fundamental for providing the conceptual foundation for the mechanisms (inflammation, contractility and ischemic pain) underlying menstrual pain that we subsequently tested in humans as described below.

b. We have developed novel MRI and pain testing methods for clarifying pathophysiological mechanisms responsible for dysmenorrhea in humans. The use of invasive methods to study dysmenorrhea (e.g., intrauterine catheters and tissue biopsy) has resulted in confounded understanding of the mechanisms underlying pain, an insufficient array of predictive diagnostic tests, and limited treatment options. An additional limitation of all prior research was that the temporal relationship between myometrial activity and pain was not characterized. Overcoming this limitation in study design was one of our foci so that we could develop mechanistic understanding of uterine pain, as spontaneous cramps are the primary complaint of women who experience dysmenorrhea. The evaluation of the temporal relationship between the perception of pain and uterine physiological changes is also essential for establishing causality. To clarify whether contractile induced ischemia is responsible for menstrual cramps in humans, we developed a heretofore undescribed real-time method for monitoring spontaneous pain with fMRI.[18] In this paradigm, participants were instructed to squeeze a bulb every time they felt a severe menstrual cramp. Simultaneously, acquired MRI signals demonstrate that decreases in myometrial T2 signal occurred either coincident with pain report or 30-70 seconds afterwards. The location and directionality of signal change and temporal relationship to pain onset are consistent with cramping pain caused by a combination of uterine pressure and hemodynamic dysfunction. **Our study is unique in that it is the first demonstration of what occurs in an internal organ time-locked to the report of spontaneous pain. Thus, as a new technical method, it holds promise as a technique for identifying the cause of pelvic and abdominal pain and other visceral pain that is amenable to fMRI interrogation.**

Together, our animal and human methods provide a synergistic strategy for evaluating mechanisms, targets, and treatments for dysmenorrhea. We have published a comprehensive review describing the potential causes for refractory dysmenorrhea and a scientific plan to eliminate menstrual pain in AJOG.[17]

2. THE SCIENCE OF PREVENTING THE TRANSITION TO CHRONIC PELVIC PAIN:

a. We have developed a noninvasive bladder task that can identify participants with enhanced visceral sensitivity prior to the development of chronic pelvic pain. Since treatments for chronic pelvic pain have low efficacy, it is critical to develop prevention methods. A first step would be to identify at-risk women for prevention trials. The prior use of invasive visceral tasks (such as colorectal distension) greatly limited research because it deterred participation and was vulnerable to fear-related factors. Therefore, we have developed a noninvasive visceral pain task in which women are asked to drink water and characterize their level of bladder pain as their bladder fills and monitor this process with ultrasonography.[12] We have confirmed that a subset of women with severe dysmenorrhea (~25%) have significant bladder pain (even off menses) without having yet developed the clinical course characterized by chronic pelvic pain.[12] We have also validated our task and shown that it is less vulnerable to psychological factors than even questionnaire methods.[15] **The development and validation of this bladder task has led to its use as a tool for identifying preventable factors responsible for the transition from episodic menstrual pain to chronic pelvic pain. This task serves as the foundation for our NIH funded chronic pelvic pain prevention program and a variation has been adapted for the 10+ site program, "Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain."**

b. We have demonstrated that multisensory hypersensitivity, independent of anxiety and depression, is a key predictor of visceral pain, but not dysmenorrhea. Multisensory hypersensitivity (also known as somatization) has been associated with pelvic pain in several of our studies. [3,15,19] The role of somatization in pain is an important problem and has generated a great deal of interest from clinicians with requests for grand rounds presentations from all of the major psychology/psychiatry programs in Chicago (see invited talks page 6). Conversely, the role of somatization in dysmenorrhea has been overemphasized— we have confirmed this by demonstrating a clear peripheral mechanism[18] that overshadows limited psychosomatic mechanisms.[13,19] Furthermore, the implication that psychosomatic factors primarily underlie pain is often regarded as offensive by patients (Merskey, 2000). This sustained misattribution that we have effectively challenged has caused unnecessary stigma resulting in suboptimal medical treatment (Wong et al., 2015; Omidvar et al., 2016).

c. We have also established another important diagnostic indicator associated with pelvic pain risk detectable during routine gynecological care. [14] Women with pelvic pain have a combination of lower mechanical stimulation thresholds and increased duration of afterpain.[14] Our results imply that if clinicians could consistently document pelvic floor tenderness ratings, along with recording the presence of prolonged pain following pelvic exam (>5 minutes), patients could be documented as at-risk for chronic pain conversion. The response threshold and afterpain differences imply that two different alterations may occur in chronic pelvic pain. The decrease in mechanical thresholds likely reflects increased excitability (i.e., sensitization) in peripheral A-mechanically-sensitive nerve fibers (which respond on a rapid time scale) responsible for perception of "first pain". In contrast, our observed aftersensation differences point to aberrant C nerve fiber activity, which typically relays information about pain and temperature sensation. These C fibers are primarily implicated in sustained perception of pain, labeled "second pain." As

each class of fibers are differentially modulated by given treatment modalities (A-fibers are preferentially blocked by compression/ischemia, while C-fiber activity is reduced in animal models by DMSO or anticonvulsants), this points to the need to test our identified mechanistic classifications to determine if certain subtypes of pelvic pain selectively respond to physical therapy (A-fiber predominant) vs. oral neuromodulating drugs (C-fiber predominant). Thus, our research characterizing pelvic mechanical sensitivity provides a strategy to identify at-risk-women in clinical settings for development of specific interventional strategies.

EDUCATION STATEMENT

Physicians (and especially physician-scientists) necessarily require the skills to evaluate scientific evidence and apply the scientific method to expand the horizons of current limitations in clinical practice. I use modern education methods (Inquiry-based and skill-based learning using *the flipped classroom*- reversing the traditional learning environment by delivering instruction via alternative methods). However, the bedrock of this education method is mentorship. The success of my mentorship can be gauged by the number of successful research projects. Most have matured to posters at national scientific meetings; some are published and others are progressing towards final publication. The large number of trainees that have performed significant scholarship and resulted in authorship is shown by the italicized names in the publication list or asterisks on the list of trainees [page 7-8]. My commitment to diversity is reflected by increased involvement of ethnic/racial minorities and women (*admittedly our research program has more appeal to those whom we are dedicated to helping).*

Since funding is a necessary ingredient for successful long-term scholarship, I have assisted my trainees in this process. For example, I helped write a grant for Dr. Adam Gafni-Kane that resulted in $40,000 of research funding. Carrie Kuhn's project led to the funding of a Carl Fentress Fellowship. I also assisted the postdoctoral scientist in my lab to obtain an NIH minority fellowship. Thus, my mentorship has provided an experience that will allow medical students to achieve better residencies and medical postgraduates optimal fellowships through demonstration of independent scholarship.

In addition, I direct educational activities at NorthShore by organizing a 2-3 hour journal club pertinent to pain research every Wednesday. These are often attended and presented by other University of Chicago students and resident physicians being mentored in nearby laboratories. Dr. Katharina Laus declared during her research rotation that this journal club was one of the best educational experiences during her residency. Beyond the educational value of the science being conveyed in these meetings, I have provided a safe and comfortable venue for other University of Chicago students and resident physicians to practice speaking about their research experience. This speaking experience is vital because it is one of the few venues where they can practice scientific speaking skills necessary for launching their own academic careers.

"*Education is a central part of the necessary cultural transformation of the approach to pain and recommended improvement in the curriculum and education for healthcare professionals.*" - National Pain Strategy 2017 Guidelines (https://iprcc.nih.gov/). As a long-term pain researcher, I fully endorse the recommendations of the National Pain Strategy guidelines that include 4 core competencies: the multidimensionality of pain, pain assessment, pain management, and clinical context. These core competencies overlap with our research interests (we dissect the multidimensionality of pain by assessing spontaneous pain and somatization, our diagnostic tests are cutting-edge methods for pain assessment, our trials address both management/clinical

context). As a result, every trainee that I mentor and every participant of every research seminar presentation I deliver is exposed to these 4 aspects.

I have recently expanded opportunities for educational opportunities by developing a fourth-year medical student elective entitled Neuroscience of Pain and Opioids as described in the adjacent institutional statement.

INSTITUTIONAL CITIZENSHIP STATEMENT *[1-page limit]:*

Past and current: My commitment to the University of Chicago began as a postdoctoral scientist with Dr. Peggy Mason. Beyond our success in NIH funding and publications, my support of Dr. Mason's laboratory while she was on sabbatical writing her textbook (as documented the textbooks acknowledgments) kept a vital piece of U of C alive. During that period, a graduate student performed ground-breaking research on empathy that was published in *Science (334:6061,1427-30)*. I was an active member of the postdoctoral association and councilor that represented the University of Chicago for the local Society for Neuroscience Chapter that won national awards for its programming and involvement. My prior experience with the University of Chicago has been useful when establishing productive cross-institutional collaborations. For example, I initiated the collaboration between Dr. Leslie Kay (U of C) and Dr. Sid Tan (NorthShore). This partnership has brought new insight into mechanisms of odor recognition and development while simultaneously providing data for grant applications. Similarly, to increase collaborative efforts on a larger scale, I organized a symposium on "Translational Optogenetics" for both members of NorthShore and University of Chicago on the University of Chicago campus.

Despite the fact that my primary appointment at NorthShore, which provides 90% of my support, is an hour-plus drive away I have been active in University of Chicago educational endeavors. My main contribution has been towards mentorship of undergraduate, graduate, and postdoctoral research projects—both within my laboratory and other laboratories.
Since 2013, I have been very active in the Pritzker Scholarship & Discovery and Summer Research Program, serving as a mentor, a cluster group leader, and paper judge. Although multiple group leaders are assigned to each section, clinical responsibility of the other leaders has often resulted in me being a sole facilitator at weekly sessions. Between these weekly sessions, I have helped the students with their statistical analyses and manuscript writing. This has resulted in a burden of 2-4 hours per week in addition to commute time from Evanston and participation in the weekly group meeting itself. Most importantly, I have provided strong encouragement for them to continue their projects which has led to their own publications. Cumulatively, I have read and commented on over 100 papers written by students in the Summer Research Program. The Summer Research Program is a critical transformative experience for medical students and it requires significant time commitment among many faculty members to insure its success.

I have also designed a new MS4 elective, Neuroscience of Pain and Opioids that was offered in January 2018. The high demand for this class resulted in maximal enrollment. I developed a website for a "*flipped classroom*" resulting in significant student dialogue (more than 50% of course time). Even off-line students were active with an average of 8 blog entries of more than 6 lines per student. Over a 4-week period, I provided a guided tour through the primary opioid and pain literature and taught how to critically evaluate scientific papers while simultaneously learning about the scientific basis for opioids in modern pain medicine. The experience of going through the primary literature provided a foundation for students that wish to educate their patients on the frontiers of pain research. We also discussed case studies relevant to selected articles. We went through 13 of the most clinically relevant scientific articles, review articles, and policy statements on the mechanisms of pain and opioid analgesia/addiction. At the end of the course, students developed a basic foundation of some of the most important scientific literature on pain to allow them to accelerate their own research. Student questionnaires confirmed, half of the students "strongly agreed" the course was successful on every evaluated course metric.

Proposed and future: I propose to maintain my track record of providing valuable mentorship by continuing current activities and improving options by expanding opportunities and pain education for University of Chicago students/residents. In particular, through further development of my MS4

elective *Neuroscience of Pain and Opioids,* I hope to provide an important component of medical education in an era where there is significant societal concern regarding these issues. I am investigating options for expanding outreach via MOOCS. With the increased size audience and contemporary civic interest in pain/opioids I hope to garner external funding support through the NIH, CDC, IASP and APS.