## 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: Cram, Erin Jean

eRA COMMONS USER NAME (credential, e.g., agency login): ERINCRAM07

POSITION TITLE: Associate Professor of Biology

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 |
|---|---|---|---|
| University of North Carolina, Chapel Hill | B.S. | 05/1995 | Biology |
| University of California, Berkeley | Ph.D. | 12/2000 | Molecular Cell Biology |
| Princeton University – Postdoctoral Training | | 07/2006 | Molecular Biology |

### A. Personal Statement

Mechanotransduction, the sensation of and response to mechanical forces, is essential for cell fate determination, organ morphogenesis and tissue function. **Our research goals are to understand how cells in a living organism form a tube and valve system, and how the cells of this tube sense and produce a coordinated response to mechanical input.** The potential impact on human health is exemplified by the finding that metastatic behavior of breast cancer cells (derived from the epithelial ducts) are strongly influenced by the mechanical properties of the surrounding tissue and that proper sensation and response to pressure, stretch, and flow is essential for cardiovascular health. Despite deep insights from biophysics and from cell biology on engineered substrates, very little is known about how cells convert mechanical information, such as stretch, into the biochemical signals that control tissue function *in vivo*. Towards this goal, we are developing a novel and facile *in vivo* system for studying mechanotransduction: the stretch-sensitive and responsive cells of the *C. elegans* reproductive system.

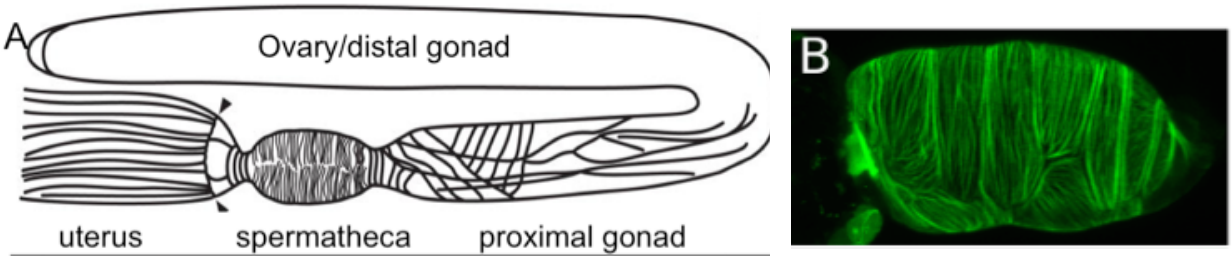


**Fig. 1 A) Diagram of the *C. elegans* reproductive system. B) Cells of the spermatheca with labeled actin.**

The reproductive system of the hermaphroditic nematode *C. elegans* is a tube comprised of an ovary containing germ cells and oocytes surrounded by smooth muscle-like sheath cells, the spermatheca, and the uterus (Fig. 1). The spermatheca consists of a single layer of 24 myoepithelial cells, and is the site of sperm storage and fertilization. Sheath cell contractions propel the oocyte into the spermatheca, dramatically stretching the cells and initiating waves of calcium that sweep across the tissue, culminating in spermathecal cell contraction, opening of the spermathecal-uterine valve and expulsion of the fertilized egg into the uterus. The cells of the spermatheca are clearly visible in the living animal and the ovulation cycle repeats every ~20 minutes to produce >300 progeny. Therefore, the *C. elegans* spermatheca provides an excellent system to study how tubes respond to cycles of stretch.

Why did I decide to become what my department chair refers to as a "worm gynecologist"? Towards the end of my graduate work, which focused on small molecule modulation of cancer cell cycles, I attended a talk by Dr. Mina Bissell describing the essential role of tissue structure in the control of metastatic breast cancer. Inspired by her vision, I decided to radically change what I was doing. I needed a system in which I could observe and manipulate the behavior of cells in a natural 3D environment. This desire led me to a postdoctoral fellowship in the laboratory of Dr. Jean Schwarzbauer at Princeton University, where I studied the network regulation of cell migration using the nematode, *C. elegans*. This work, with its focus on integrin and matrix control of cell behavior, laid the groundwork for my first (cell migration) and second (mechanotransduction) R01. Our work is enhanced by vibrant and productive collaborations with Bioengineering at Northeastern (I am an affiliate) and with Dr. Ronen Zaidel-Bar at the Singapore Mechanobiology Institute.

---

**B. Positions and Honors**

**Positions and Employment**

| | |
|---|---|
| 1992-1995 | Undergraduate Research Assistant, University of North Carolina, Chapel Hill, NC |
| 1995-2000 | Graduate Research Assistant, University of California, Berkeley, CA |
| 2001-2006 | Postdoctoral Fellow, Princeton University, Princeton, NJ |
| 2006-2012 | Assistant Professor of Biology, Northeastern University, Boston, MA |
| 2012- | Associate Professor of Biology, Northeastern University, Boston, MA |

**Other Experience and Professional Memberships**

| | |
|---|---|
| 2000- | Member, American Society for Cell Biology |
| 2000- | Member, Genetics Society of America |
| 2011 | NSF Integrated Organismal Systems Pre-Proposal Peer Review |
| 2012 | NIH Early Career Reviewer for the Intracellular Interactions (ICI) Study Section |
| 2014, 2016 | NIH reviewer for Interactions (ICI) Study Section |

**Honors**

| | |
|---|---|
| 1991 | National Merit Scholar |
| 1995 | Departmental Honors in Biology |
| 1998-2000 | US Army Medical Research and Materiel Command Breast Cancer Research Program Predoctoral Fellowship #BC971062 |
| 2002-2004 | Robert Black Charitable Foundation Fellow of the Damon Runyon Cancer Research Fund |
| 2004 | Science Advisors Award - Princeton Chapter Sigma Xi |
| 2005 | Departmental Teaching Award – Princeton University Molecular Biology Department |
| 2012 | University Excellence in Teaching Award - Northeastern University |

---

**C. Contributions to Science**

1. My graduate work in Dr. Gary Firestone's laboratory at U.C. Berkeley helped to elucidate the mechanism of action of glucocorticoids and dietary indoles on the cell cycle of cancer cells. I discovered that the glucocorticoid receptor could directly and specifically activate the expression of the cell cycle inhibitor p21, despite the lack of a canonical GRE in the p21 promoter. I also cloned the human cyclin dependent kinase CDK6 promoter (pre-genome!) and identified CDK6 as a key target of the dietary indole, indole-3-carbinol.

    a. **E.J. Cram**, R.A. Ramos*, E. Wang, H.H. Cha, G.L. Firestone. (1998) The glucocorticoid stimulation of p21Waf1/Cip1 gene promoter activity in growth suppressible rat hepatoma cells is functionally dependent on expression of CCAAT/Enhancer Binding Protein-α. J. Biol. Chem. 273: 2008-2014. *co-first author

    b. H. Cha, **E.J. Cram***, E. Wang, A. Huang, H. Kasler, G.L. Firestone. (1998) Glucocorticoid induced growth suppression cascade in rat hepatoma cells stimulates p21Waf1/Cip1 gene expression and

targets multiple elements within a steroid responsive region of the p21 promoter. J. Biol. Chem. 273: 1998-2007. *co-first author

c. C.M. Cover, S. Jean Hsieh, **E.J. Cram**, C. Hong, J.E. Riby, L.F. Bjeldanes, G.L. Firestone. (1999) Indole-3-carbinol and tamoxifen cooperate to arrest the cell cycle of MCF-7 human breast cancer cells. Cancer Research 59: 1244-1251.

d. **E.J. Cram**, B.D. Liu, L.F. Bjeldanes, G.L. Firestone. (2001) Indole-3-carbinol inhibits CDK6 expression in human MCF-7 breast cancer cells by disrupting Sp1 transcription factor interactions with a composite element in the CDK6 gene promoter. J. Biol. Chem. 276: 22332-22340.

2. During my post-doctoral work in Dr. Jean Schwarzbauer's laboratory at Princeton University, I characterized the role of integrin signaling in migration of the distal tip cells (DTC) in *C. elegans* and conducted a genome wide RNAi screen for genes required for cell migration. This was the first comprehensive RNAi screen for genes that regulate cell migration *in vivo*, and identified a network of ~100 genes required for migration of the DTC. I discovered key hubs necessary for the mechanics of cell migration and for coordinating cell migration with developmental stages. One of the novel regulators discovered in this screen, CACN-1/cactin is discussed below.

   a. M. Lee, **E.J. Cram**, B. Shen, J.E. Schwarzbauer. (2001) Roles for βpat-3 integrins in development and function of *Caenorhabditis elegans* muscles and gonads. J. Biol. Chem. 276: 36404-10.

   b. **E.J. Cram**, S.G. Clark, J.E. Schwarzbauer. (2003) Talin loss-of-function uncovers roles in cell contractility and migration in *C. elegans*. J. Cell Science 116: 3871-3878.

   c. **E.J. Cram**, H. Shang, J.E. Schwarzbauer. (2006) A systematic RNA interference screen reveals a cell migration gene network in *C. elegans*. J. Cell Science 119:4811-4818.

   d. **E.J. Cram**, K.M. Fontanez, J.E. Schwarzbauer. (2008) Functional characterization of KIN-32, *C. elegans* homolog of focal adhesion kinase. Developmental Dynamics Mar; 237(3):837-46.

3. A new paradigm to arise from our cell migration work is the importance of splicing and translational regulation in cell migration and developmental transitions. Our results suggest specific splice forms of signaling proteins may be required in conserved pathways to control cell migration and organ morphogenesis. Because CACN-1/cactin and the signaling pathways it impacts control cell migration and/or organogenesis in many organisms, and because so little is known about how alternative splicing is developmentally regulated, these studies have the potential to make a very important contribution to our fundamental understanding of how cells make decisions about when and where to migrate.

   a. H. Tannoury, V. Rodriguez, I. Kovacevic, M. Ibourk, M. Lee, and **E.J. Cram**. (2010) CACN-1/Cactin interacts genetically with MIG-2 GTPase signaling to control distal tip cell migration in *C. elegans*. Developmental Biology May 1;341(1):176-185.

   b. M. LaBonty, C. Szmygiel, L. E. Byrnes, S. Hughes, A. Woollard, **E.J. Cram**. (2014) CACN-1/Cactin plays a role in Wnt signaling in *C. elegans*. PLoS One. 2014 Jul 7;9(7):e101945. doi: 10.1371/journal.pone.0101945.

   c. M.F. Doherty, G. Adelmant, A.D. Cecchetelli, J.A. Marto, **E.J. Cram**. (2014) Proteomic analysis reveals CACN-1 is a component of the spliceosome in *C. elegans.* G3. 2014 Jun 19. pii: g3.114.012013. doi: 10.1534/g3.114.012013.

   d. A.D. Cecchetelli, J. Hugunin, H. Tannoury, **E.J. Cram**. (2016) CACN-1 is required in the C. elegans somatic gonad for proper oocyte development. Developmental Biology 2016 Apr 1. pii: S0012-1606(15)30282-7. doi: 10.1016/j.ydbio.2016.03.028.

4. Recently, we have moved from the cell migration world into the related and rapidly developing field of mechanotransduction. We are developing the stretch-responsive cells of the *C. elegans* spermatheca as a powerful genetic and imaging system for discovery of the mechanisms by which cells coordinately respond to mechanical input. We have discovered that the molecular strain gauge and actin-coordinating protein filamin is required for proper coordination of multicellular lipid and calcium signaling. We are using quantitative imaging, modeling, and molecular genetics approaches to build a mechano-chemical model of tissue function. Through this multidimensional, interdisciplinary work we plan to determine how intact tissues experience and respond to mechanical forces and to apply these ideas in tissue engineering contexts.

    a. I. Kovacevic and **E.J. Cram**. (2010) FLN-1/Filamin is required for maintenance of actin and exit of fertilized oocytes from the spermatheca in C. elegans. Developmental Biology, Nov 15;347(2):247-257.

    b. C. DeMaso, I. Kovacevic, A. Uzun and **E.J. Cram**. (2011) Structural and functional evaluation of C. elegans filamins FLN-1 and FLN-2. PLoS One, 6(7):e22428. Epub Jul 25.

    c. I. Kovacevic, J.M. Orozco, **E.J. Cram**. (2013) Filamin and Phospholipase C-ε are required for calcium signaling in the *C. elegans* spermatheca. PLoS Genetics. 10.1371/journal.pgen.1003510

    d. **E. J. Cram**. (2015) Mechanotransduction: feeling the squeeze in the *C. elegans* reproductive system. Current Biology 2015 Jan 19;25(2):R74-5. doi: 10.1016/j.cub.2014.12.007.

5. I am also involved in a collaborative project designed to improve production of anti-cancer compounds by the Madagascar periwinkle, *Catharanthus roseus*. *C. roseus* produces several highly valued pharmaceuticals, including the anti-cancer drugs vincristine and vinblastine, but the slow growth rate of the plant and the low concentration of product are significant barriers to efficient drug production. The high cost and need for these pharmaceuticals motivate our research to better understand their biosynthesis and ultimately overproduce these compounds using *C. roseus* cultures. The role of my laboratory in the project is to dissect the transcriptional network that controls the expression of the enzymes required to produce the drug compounds (terpenoid indole alkaloid (TIA) biosynthetic enzymes) and to provide molecular biology support and expertise for the transgenic engineering effort. We seek to better understand the transcriptional regulation of enzymes involved in the production of these medicinal alkaloids and to use a novel strategy based on gene silencing to enhance the production of these critical pharmaceutical compounds. Development of silencing protocols for medicinal plants will also strongly impact the natural products and pharmaceutical fields.

    a. S. Goklany, N.F. Rizvi, R.H. Loring, **E.J. Cram**, C.W.T. Lee-Parsons. (2013) Jasmonate-dependent alkaloid biosynthesis in *Catharanthus roseus* is mediated at the transcriptional level by the relative expression of *Orca* and *Zct* transcription factors. Biotechnology Progress. Aug. 22 doi:10.1002/btpr.1801.

    b. J. D. Weaver, S. Goklany, N.F. Rizvi, **E.J. Cram**, C.W.T. Lee-Parsons. (2014) Optimizing the transient Fast Agro-mediated Seedling Transformation (FAST) method in *Catharanthus roseus* seedlings. Plant Cell Rep. 2014 Jan;33(1):89-97. doi: 10.1007/s00299-013-1514-2.

    c. N. Rizvi, M. Cornejo, K. Stein, J. Weaver, **E.J. Cram**, C.W.T. Lee-Parsons. (2015) An efficient transformation method for estrogen-inducible transgene expression in *Catharanthus roseus* hairy roots. Plant Cell, Tissue and Organ Culture. Feb. 2015, Volume 120(2), pp 475-487.

**Complete List of Published Work in MyBibliography:**

http://www.ncbi.nlm.nih.gov/sites/myncbi/erin.cram.1/bibliography/40848160/public/?sort=date&direction=ascending.

---

**D. Research Support**

**Ongoing Research Support**

NIH R01 Grant # GM110268-01 Cram (PI) (Aug. 2014-Jul. 2018)
Title: *In vivo* analysis of mechanotransduction
Purpose: The major goal of this study is to characterize the molecular mechanisms by which the cells of a contractile tube in the *C. elegans* reproductive system coordinately respond to and exert mechanical forces.
Role: PI

NSF MCB Grant #1516371 Lee-Parsons (PI) (Aug 2015- July 2018)
Title: Zinc Finger Transcription Factors: Regulators of Growth, Development, and Alkaloid Biosynthesis
Purpose: To dissect the role ZCT family transcription factors play in the decision to switch from growth and reproduction to defense in the medicinal plant *Catharanthus roseus.*
Role: Co-PI (with Dr. Carolyn Lee-Parsons, Chemical Engineering)

**Recently Completed Research Support**

NIH R01 Grant # GM085077-01 Cram (PI) (Aug. 2008-Jul. 2013)
Title: Characterization of a novel regulator of cell migration
Purpose: The major goal of this study is to characterize the molecular mechanism by which *cacn-1*, a novel conserved regulator of cell migration functions during development in *C. elegans.*
Role: PI

NSF CBET Grant # 1033889 Lee-Parsons (PI) (Aug. 2010- Jul. 2013)
Title: Transcriptional control of alkaloid biosynthesis in *Catharanthus roseus* cultures
Purpose: The major goal of this study is to improve production of anti-cancer compounds by the Madagascar periwinkle, *Catharanthus roseus,* and to understanding the transcriptional control of biosynthetic enzymes.
Role: Co-PI (with Dr. Carolyn Lee-Parsons, Chemical Engineering)

---