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: **Emanuele, Michael J**

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

POSITION TITLE: **Associate 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
Bucknell University, Lewisburg, PA	B.S.	05/2000	Biochemistry & Cell Biology
University of Virginia, Charlottesville, VA	Ph.D.	01/2008	Biochemistry & Molecular Genetics
Harvard Medical School, Brigham & Women's Hospital, Boston, MA	Postdoc	01/2013	Systems Biology

A. Personal Statement

My research program examines signaling networks that promote cell cycle progression and genome stability and their role in the etiology and treatment of cancer. I am specifically focused on the ubiquitin proteasome system, which represents the major mechanism by which specific are targeted for degradation. Our long-term goal is to understand how dysfunction in ubiquitin signaling pathways contributes to cancer and to explore their therapeutic potential. To address these challenges my lab applies diverse experimental approaches in cell, molecular and systems biology. This represents a rigorous research environment for addressing these key questions, as well as an exceptional training environment for graduate students and postdoctoral fellows. These approaches build on my own former training. As a postdoctoral fellow in Stephen Elledge's lab (HHMI; Lasker Awardee, 2015), I developed global genetic and proteomic methodologies that interrogate the ubiquitin system at unprecedented depth. Prior to that, as a graduate student, I applied biochemical and cell biological methods to examine chromosome segregation. This background, and the diverse skillset it allowed me to build, enables the application of complementary experimental techniques, which are further supported by collaborations with experts in genomics, proteomics, synthetic chemistry, enzymology, structural biology, and translational and clinical research. Our expertise, combined with that of our collaborators, places us in a strong position to approach the complex challenge of determining mechanisms of proteome remodeling and their importance in cell cycle, genome instability and the proliferation and treatment of cancer.

My lab has made numerous contributions to the fields of ubiquitin signaling, cell cycle control and cancer. Recent corresponding author publications that highlight our productivity and ability to address these questions, include:

a. Arceci A, Bonacci T, Wang X, Stewart K, Damrauer JS, Hoadley KA, **Emanuele MJ**. FOXM1 Deubiquitination by USP21 Regulates Cell Cycle Progression and Paclitaxel Sensitivity in Basal-Like Breast Cancer. *Cell Reports*. 2019 Mar 12;26(11):3076-3086.e6. PMID: 30865895

b. Bonacci T, Suzuki A, Grant G, Cook JG, Brown NG, **Emanuele MJ**. Cezanne/OTUD7B is a cell cycle-regulated deubiquitinase that antagonizes the degradation of APC/C substrates. *EMBO Journal*. 2018 Aug 15;37(16). PMID: 29973362

c. Choudhury R, Truong A, Arceci A, Bonacci T, Mills CA, Kernan JL, **Emanuele MJ**. The E3 ubiquitin ligase SCF(Cyclin F) transmits AKT signaling to the cell cycle machinery. *Cell Rep*orts. 2017 Sep 26;20(13):3212-3222. PMID: 28954236

- *Highlighted in F1000 (recommended by Michele Pagano (HHMI, NYU)*

d. Choudhury C, Bonacci T, Arceci A, Lahiri D, Mills CA, Kernan JL, Branigan TB, DeCaprio JA, Burke D, **Emanuele MJ**. APC/C and SCF(cyclin F) constitute a reciprocal feedback circuit controlling S-phase entry. *Cell Reports*. 2016 Sep 20;16(12):3359-72. PMCID: PMC5111906.

B. Positions and Honors

Positions and Employment

2000-2002	Research Technician, University of Pennsylvania (Theresa Busch's Lab)
2002-2007	Graduate Student, University of Virginia (Todd Stukenberg's Lab)
2008-2013	Postdoctoral Fellow, Harvard Medical School (Stephen Elledge's Lab, HHMI, Lasker Award)
2013-present	Assistant Professor, UNC, Lineberger Cancer Center, Dept. of Pharmacology
2019-present	Associate Professor with tenure, UNC, Lineberger Cancer Center, Dept. of Pharmacology

Selected Honors and Awards

2007	Outstanding Graduate Student Award, University of Virginia
2008-2011	Damon Runyon Post-doctoral Fellowship Award
2013	UNC IBM Junior Faculty Development Award (UNC)
2013-2015	Jimmy V Scholar Award
2013-2016	Susan G. Komen, Career Catalyst Award
2019-present	American Cancer Society, Research Scholar Grant Award
2019	Excellence in Mentoring Award, UNC Office of Graduate Education (trainee nominated)

C. Contributions to Science

1. Cell cycle regulation by E3 ubiquitin ligases. Substrate specificity in the ubiquitin system is imparted by E3 ubiquitin ligases. Despite the vital role of ubiquitin in all aspects of cellular physiology, it remains challenging to connect ligases with their cognate substrates, akin to mapping kinase or transcription factor targets. Using diverse experimental approaches, including global strategies, mass spectrometry-based proteomics, and in silico approaches, I have described numerous substrates in ubiquitin system, the E3 ubiquitin ligases that control them, and additional signaling inputs that control ligase activity and regulation.

    a. Choudhury C, Bonacci T, Arceci A, Lahiri D, Mills CA, Kernan JL, Branigan TB, DeCaprio JA, Burke D, **Emanuele MJ**. APC/C and SCF(cyclin F) constitute a reciprocal feedback circuit controlling S-phase entry. *Cell Reports*. 2016 Sep 20;16(12):3359-72. PMCID: PMC5111906.

    b. Choudhury R, Truong A, Arceci A, Bonacci T, Mills CA, Kernan JL, **Emanuele MJ**. The E3 ubiquitin ligase SCF(Cyclin F) transmits AKT signaling to the cell cycle machinery. *Cell Rep*orts. 2017 Sep 26;20(13):3212-3222. PMID: 28954236.

    c. Wang X, Arceci A, Bird K, Mills CA, Choudhury R, Kernan JL, Zhou C, Bae-Jump V, Bowers A, **Emanuele MJ**. VprBP/DCAF1 regulates the degradation and non-proteolytic activation of the cell cycle transcription factor FoxM1. *Mol Cell Biol*. 2017 Jun 15;37(13). PMID: 28416635.

    d. **Emanuele MJ**, Elia EH, Xu Q, Thoma CR, Izhar L, Guo A, Rush J, Hsu PW, Yen HS, Elledge SJ. Global Identification of Modular Cullin-Ring Ligase Substrates. *Cell*. 2011 Oct 14;147(2):459-74. PMID: 21963094.

2. Cell cycle regulation by deubiquitinases. Like other post-translational modification, ubiquitination is reversible, and ubiquitin is removed from substrates by catalytic proteases termed deubiquitinases or DUBs. The human genome encodes approximately 100 DUB enzymes. These enzymes exhibit strong in vivo specificity and are the most likely class of druggable enzymes in the ubiquitin pathway. We have described DUBs involved in normal cell cycles and shown how their dysregulation might contribute to cancer.

    a. Arceci A, Bonacci T, Wang X, Stewart K, Damrauer JS, Hoadley KA, **Emanuele MJ**. FOXM1 Deubiquitination by USP21 Regulates Cell Cycle Progression and Paclitaxel Sensitivity in Basal-Like Breast Cancer. In press at *Cell Reports*. Accepted January 2019.

    b. Bonacci T, Suzuki A, Grant G, Cook JG, Brown NG, **Emanuele MJ**. Cezanne/OTUD7B is a cell cycle-regulated deubiquitinase that antagonizes the degradation of APC/C substrates. *EMBO Journal*. 2018 Aug 15;37(16). PMID: 29973362

    c.

3. Development and application of global technologies that interrogate the ubiquitin system. Global proteome reorganization occurs through transcriptional changes in gene expression and altered protein degradation through the ubiquitin system. While global strategies exist to map changes in gene expression, systematic technologies that interrogate the ubiquitin system are still in their infancy. I developed genetic and proteomic technologies that globally examine ubiquitination. The proteomic strategy combines quantitative mass spectrometry with ubiquitinated peptide enrichment. This method is complemented by a genetic approach (Global Protein Stability Profiling, or GPS) that relies on florescent reporters coupled to ~15,000 human ORFs, cell sorting and genomic deconvolution methods. These methods enable a global analysis of ubiquitin dynamics at unprecedented depth.

    a. **Emanuele MJ**, Elia EH, Xu Q, Thoma CR, Izhar L, Guo A, Rush J, Hsu PW, Yen HS, Elledge SJ. Global Identification of Modular Cullin-Ring Ligase Substrates. *Cell*. 2011 Oct 14;147(2):459-74. PMID: 21963094.

    b. Yi JJ, Paranjape SR, Walker MP, Choudhury R, Wolter JM, Fragola G, **Emanuele MJ**, Major MB, Zylka MJ. The autism-linked UBE3A T485A mutant E3 ubiquitin ligase activates the Wnt/β-catenin pathway by inhibiting the proteasome. The Journal of biological chemistry. 2017; 292(30):12503-12515.

    c. Olive AJ, Haff MG, **Emanuele MJ**, Sack LM, Barker JR, Elledge SJ, Starnbach MN. Chlamydia trachomatis-induced alterations in the host cell proteome are required for intracellular growth. Cell host & microbe. 2014; 15(1):113-24.

4. Synthetic lethal interactions with the Ras oncogene. The Ras oncogene represents one of the most recurrently mutated genes in all cancers. The inability to target Ras using conventional therapeutic approaches implies a need to evaluate alternative strategies for killing Ras mutant cancer cells. A pooled, shRNA based synthetic lethal screen was used to identify Ras specific vulnerabilities. This screen identified many proteins in the mitotic apparatus, including several druggable candidates, such as Polo and Aurora kinases. Through detailed cell biology and genetics, we found that Ras mutant cells were selectively sensitive to mitotic stress. These studies shed light on the Ras synesthetic lethal interaction network and suggested possible avenues for the treatment of Ras mutant tumors.

    a. Luo J, **Emanuele MJ**, Li D, Creighton CJ, Schlabach MR, Westbrook TF, Wong K, Elledge SJ. A genome-wide RNAi screen identifies multiple synthetic lethal interactions with the Ras oncogene. *Cell*. 2009 May 29; 137(5). 835-48. PMCID: PMC2768667.

    b. Weng MT, Lee JH, Wei SC, Li Q, Shahamatdar S, Hsu D, Schetter AJ, Swatkoski S, Mannan P, Garfield S, Gucek M, Kim MK, Annunziata CM, Creighton CJ, **Emanuele MJ**, Harris CC, Sheu JC, Giaccone G, Luo J. Evolutionarily conserved protein ERH controls CENP-E mRNA splicing and is required for the survival of KRAS mutant cancer cells. *Proc Natl Acad Sci U S A*. 2012 Dec 26; 109(52):E3659-67. PMCID: PMC3535619.

5. Regulation of mitotic progression. Chromosome movement during cell division is controlled by microtubule-kinetochore interactions. I have described key mechanisms that control assembly of the kinetochore, a macro-molecular protein complex assembled onto centromeric DNA during mitosis. I identified and described a protein regulating microtubule dynamics at both kinetochores and centrosomes, shedding light on the mechanisms by which kinetochore proteins assemble into a functional microtubule binding entity, and conservation of microtubule binding at their plus and minus ends in the spindle. More recently, my lab identified an interaction between a spindle proteins NUSAP1, and a mitotic SUMO ligase complex, suggesting a new link between ubiquitin and SUMO signaling in mitosis.

    a. Bonacci T, Suzuki A, Grant G, Cook JG, Brown NG, **Emanuele MJ**. Cezanne/OTUD7B is a cell cycle-regulated deubiquitinase that antagonizes the degradation of APC/C substrates. *EMBO Journal*. 2018 Aug 15;37(16). PMID: 29973362

    b. Mills CA, Suzuki A, Arceci A, Mo JM, Duncan A, Salmon ED, **Emanuele MJ**. Nucleolar and spindle-associated protein 1 (NUSAP1) interacts with a SUMO E3 ligase complex during chromosome segregation. *J Biol Chem*. 2017 Sep 12. PMID: 28900032

    c. **Emanuele MJ**, Lan W, Jwa M, Miller SA, Chan, CSM, Stukenberg PT. Aurora B kinase and Protein Phosphatase 1 have opposing roles in modulating kinetochore assembly. *J Cell Biol*. 2008 Apr 21;181(2):241-54. PMCID: PMC2315672.

    d. **Emanuele MJ** and Stukenberg PT. Xenopus Cep57 is a novel kinetochore component involved in microtubule attachment. *Cell*. 2007 Sep 7;130(5):893-905. PMID: 17803911

Full list of published work (link):
Emanuele Publication List: CLICK HERE