BIOGRAPHICAL SKETCH

NAME: **Emanuele, Michael J**

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

POSITION TITLE: **Professor**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	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, Boston, MA	Postdoc	01/2013	Systems Biology

A. Personal Statement

My research centers on the role of ubiquitin signaling in regulating normal cell cycle progression and how dysregulated ubiquitination contributes to cancer development and therapy. As an independent investigator, my lab has identified key components of the ubiquitin pathway that control cell proliferation, uncovered their substrates, and elucidated mechanisms of ubiquitination and proteolytic regulation relevant to genome stability and tumorigenesis.

We approach these questions using a combination of cell, molecular, and systems biology techniques, providing a rigorous framework for addressing both fundamental and translational aspects of cancer biology. This environment also serves as a rich training ground for students and postdoctoral fellows. We work closely with collaborators in genomics, synthetic chemistry, enzymology, structural biology, and clinical research, enabling us to bridge mechanistic discoveries with translational insights.

I am also deeply committed to mentorship and training in biomedical sciences. I was honored with the Excellence in Mentorship Award by the UNC Biomedical Graduate Program and have completed many formal mentor training courses, including those offered through CIMER and the UNC Office of Graduate Education. Collectively, this experience will allow me to support Jose throughout his graduation training and to help him achieve his career goals. I also serve as the T32 Director of the UNC Pharmacological Sciences Training Program, the Associate Director for Shared Resources for the UNC Lineberger Comprehensive Cancer Center, and am a standing member of the NIH Biochemical and Cellular Oncogenesis study section.

<u>Relevant, currently funded projects include</u>:

R35-GM153250
Proteostasis signaling in cell cycle control
Emanuele (PI)
04/01/2024 – 03/31/2029
NIGMS, National Institute of Health

R01CA280482
Cell cycle paths as a framework for understanding drug resistance in tumor cell subpopulations
Emanuele (co-PI; other PIs include Purvis and Cook)
02/01/2024 -01/31/2029
NCI, National Institute of Health

R01CA305980-01
Hijacking FBXO22 for the development of novel cancer therapeutics
Emanuele (co-PI; other PIs include Brown and James)
07/01/2026 - 06/3/2031
NCI, National Institute of Health

Recent, corresponding author publications highlighting our work on cell cycle, ubiquitin signaling, and cancer:

1. Kim A, Gopalakrishnan P, Suárez-Pizarro M, Chen CC, Wang X, McCoy SM, Umesh N, Mordant A, Barker NK, Herring LE, Kakati RT, Spanheimer PM, **Emanuele MJ**, Benavente CA. USP7 inhibition perturbs proteostasis and tumorigenesis in triple-negative breast cancer. NPJ Breast Cancer. 2026 May 23. doi: 10.1038/s41523-026-00974-5. PMID: 42177192
2. Kavalipati A, Aponte A, Sullivan ME, Whittington SL, Martínez JC, Goda GA, Aleman MM, **Emanuele MJ**, Dominguez D. Charting the multilevel molecular response to palbociclib in ER-positive breast cancer. NAR Cancer. 2026 Feb 17;8(1):zcag003. doi: 10.1093/narcan/zcag003. eCollection 2026 Mar. PMID: 41710088
3. Bolhuis DL, Fleifel D, Bonacci T, Wang X, Mouery BL, Cook JG, Brown NG, **Emanuele MJ**. USP37 prevents unscheduled replisome unloading through MCM complex deubiquitination. Nat Communications. 2025 May 16;16(1):4575. doi: 10.1038/s41467-025-59770-7.
4. Mouery RD, Hsu C, Bonacci T, Bolhuis DL, Wang X, Mills CA, Toomer ED, Canterbury OG, Robertson KC, Branigan TB, Brown NG, Herring LE, **Emanuele MJ**. Proteomic Analysis Reveals a PLK1-Dependent G2/M Degradation Program and Links PKA-AKAP2 to Cell Cycle Control. *Cell Reports*. 2024 Aug 27;43(8):114510. doi: 10.1016/j.celrep.2024.114510. PMID: 39018246.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2026	Chair and organizer, FASEB Conference on Cell Cycle in Health and Disease
2025-present	UNC Lineberger Comprehensive Cancer Center, Associate Director of Shared Resources
2020-present	T32 Training Grant Director, Pharmacological Sciences Training Program, UNC-CH
2023-present	Biochemical and Cellular Oncogenesis (BCO) Study Section, NIH, Standing member
2023-2024	Ad hoc grant reviewer, American Cancer Society
2021-present	Editorial Board Member for *Journal of Biological Chemistry*
2021	Ad hoc reviewer, Molecular Oncology Study Section, NIH
2020-present	Editorial Board Member for *Cell Division*
2019-present	Associate Professor with tenure, UNC, Lineberger Cancer Center, Dept. of Pharmacology
2019	Ad hoc reviewer, HHMI Gilliam Program
2013-present	Member, Cancer Cell Biology Program, UNC Lineberger Comprehensive Cancer Center
2013-2019	Assistant Professor, UNC, Lineberger Cancer Center, Dept. of Pharmacology
2008-2013	Postdoctoral Fellow, Harvard Medical School (Stephen Elledge's Lab, HHMI, Lasker Award)
2002-2007	Graduate Student, University of Virginia (Todd Stukenberg's Lab)
2000-2002	Research Technician, University of Pennsylvania (Theresa Busch's Lab)

Honors and Awards

2019	Excellence in Mentoring Award, UNC Office of Graduate Education (trainee nominated)
2019-2024	American Cancer Society, Research Scholar Grant Award
2013-2016	Susan G. Komen, Career Catalyst Award
2013-2015	Jimmy V Scholar Award
2013	UNC IBM Junior Faculty Development Award (UNC)
2008-2011	Damon Runyon Post-doctoral Fellowship Award
2007	Outstanding Graduate Student Award, University of Virginia

C. Contributions to Science

1) Cell cycle regulation by E3 ubiquitin ligases. Ubiquitin ligases are essential regulators of cell cycle progression. 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. To address this significant challenge, I have developed genomic, proteomic and in silico methodologies that enable E3 ligase substrate discovery and have leveraged these methods to identify numerous ligase substrates. I have also detailed mechanisms that modify and control specific E3s, and how these mechanisms contribute to cell cycle progression.

   a) Mouery RD, Hsu C, Bonacci T, Bolhuis DL, Wang X, Mills CA, Toomer ED, Canterbury OG, Robertson KC, Branigan TB, Brown NG, Herring LE, **Emanuele MJ**. Proteomic Analysis Reveals a PLK1-Dependent G2/M Degradation Program and Links PKA-AKAP2 to Cell Cycle Control. *Cell Reports*. 2024 Aug 27;43(8):114510. doi: 10.1016/j.celrep.2024.114510. PMID: 39018246.

   b) Enrico TP, Stallaert W, Wick ET, Ngoi P, Wang X Rubin SM, Brown NB, Purvis JE, **Emanuele MJ**. Cyclin F drives proliferation through SCF-dependent degradation of the retinoblastoma-like tumor suppressor p130/RBL2. Elife. 2021 Dec 1;10:e70691. doi: 10.7554/eLife.70691. PMID: 34851822.

   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 Reports. 2017 Sep 26;20(13):3212-3222. PMID: 28954236 PMCID: PMC5662023 (highlighted in F100)

   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 PMCID: PMC3226719.

2) Cell cycle regulation by deubiquitinases. Like other post-translational modifications, ubiquitination is reversible. Ubiquitin is removed from substrates by catalytic proteases termed deubiquitinases or DUBs. The human genome encodes ~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. In addition, we have extensively reviewed the role of DUBs in cancer proliferation.

   a) Bolhuis DL, Fleifel D, Bonacci T, Wang X, Mouery BL, Cook JG, Brown NG, **Emanuele MJ**. USP37 prevents unscheduled replisome unloading through MCM complex deubiquitination. Nat Commun. 2025 May 16;16(1):4575. doi: 10.1038/s41467-025-59770-7.

   b) Dissenting degradation: Deubiquitinases in cell cycle and cancer. Bonacci T, **Emanuele MJ**. *Seminars in Cancer Biology*. 2020 Dec;67(Pt 2):145-158. PMID: 32201366 PMCID: PMC7502435.

   c) 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*. 2019 Mar 12;26(11):3076-3086.e6. PMID: 30865895 PMCID: PMC6425951

   d) 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 PMCID: PMC6092620

3) Development and application of global technologies that interrogate the ubiquitin networks. Global proteome reorganization occurs through transcriptional changes in gene expression and altered protein degradation. While global strategies exist to map changes in gene expression, systematic methodologies that interrogate the ubiquitin system are still in their infancy. I developed genetic and proteomic technologies that globally examine ubiquitination. In addition, we developed and applied in silico approaches based on substrate features and synthetic genetic interactions in model organisms to uncover new connections between enzymes and substrates.

   a) Franks JL, Martinez-Chacin RC, Wang X, Tiedemann RL, Bonacci T, Choudhury R, Bolhuis D, Damrauer JS, Yan F, Harrison JS, Major MB, Hoadley K, Suzuki A, Rothbart SB, Brown NG, **Emanuele MJ.** In silico APC/C substrate discovery reveals cell cycle degradation of chromatin

regulators including UHRF1. PLoS Biology. 2020 Dec 11;18(12):e3000975. PMID: 33306668 PMCID: PMC7758050

b) Sirtuin 5 is Regulated by the SCF-Cyclin F Ubiquitin Ligase and is Involved in Cell Cycle Control. Mills CA, Wang X, Bhatt DP, Grimsrud PA, Matson JP, Lahiri D, Burke DJ, Cook JG, Hirschey MD, Emanuele MJ. Molecular and Cellular Biology. 2020 Nov 9;MCB.00269-20. PMID: 33168699

c) 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. PMID: 28559284 PMCID: PMC5535025

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 PMCID: PMC3226719

4) Synthetic lethal interactions with the Ras oncogene. The Ras oncogene is one of the most recurrently mutated genes in cancer. The challenge of targeting Ras using conventional therapeutic approaches implies a need to evaluate alternative strategies for killing Ras mutant cancer cells. A synthetic lethal screen identified Ras specific vulnerabilities. This identified many proteins in the mitotic apparatus, including several druggable candidates, such as Polo and Aurora kinases. Polo inhibitors recently received fast track FDA status for the treatment of Ras mutant colorectal cancers.

a) 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. PMID: 23236152 PMCID: PMC3535619.

b) 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. PMID: 19490893 PMCID: PMC2768667.

5) Mechanisms of cell division. Chromosome movement during cell division is controlled by microtubule-kinetochore interactions. I described mechanisms that control assembly of the kinetochore and identified and a protein that regulates microtubule binding at both kinetochores and. 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. In addition, we have described the regulation of cell division by defining substrates of mitotic ubiquitin ligases and DUBs.

a) 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 PMCID: PMC5655498

b) **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. PMID: 18426974 PMCID: PMC2315672

c) **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

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1n9YnI_4kxIkV/collections/62190243/public/