BIOGRAPHICAL SKETCH

NAME: **Emanuele, Michael J**

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

POSITION TITLE: **Associate 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

The goal of my research program is to define signaling pathways and networks that control proliferation, cell cycle progression, and genome stability and to determine their role in the etiology and treatment of cancer. During cell cycle progression, the cellular landscape is dynamically remodeled by protein degradation. The ubiquitin system is the major regulator of protein degradation in eukaryotes, and an essential regulator of cell cycle progression. Like kinase-based signaling cascades, dysfunctional ubiquitin signaling is causative in cancer (e.g., MDM2-p53) and contributes to pathological phenotypes. My lab applies diverse experimental approaches in cell, molecular and systems biology, providing a rigorous environment for addressing these fundamental questions in human health and disease, and a rich training environment for graduate students and postdoctoral fellows. Our application of diverse experimental methods is supported by collaborators in genomics, synthetic chemistry, enzymology, structural biology, and translational and clinical research. Together, this places us in a strong position to approach the complex challenge of determining mechanisms of proteome remodeling and their importance in cell cycle and disease. My lab has made numerous contributions to these fields, highlighted by our current research support and recent corresponding author publications, which speak to our productivity and ability to address these challenges.

I am deeply committed to mentorship, training, and improving diversity in biomedical science. I was recognized for these efforts with an excellence in mentorship award given by the biomedical graduate program at UNC. I have received formal training in scientific mentoring (Entering Mentoring), Unconscious Bias Awareness, Culturally Aware Mentorship (HHMI Gilliam Program), Safe Zone (LGBTQ Awareness), and participate in ongoing workshops through the Racial Equity Institute (The Groundwater Approach: Building a practical understanding of structural racism). Through other additional trainings, I am continuing to work towards DEI certification from the UNC Office of Inclusive Excellence. I am the T32 director for my departments Pharmacological Sciences Training Program.

Relevant, currently funded projects include:

R01-GM120309
SCF ubiquitin ligases in cell cycle control and chromosome stability
Emanuele (PI)
04/01/2022 – 03/31/2026
NIGMS, National Institute of Health

R01- GM134231
Deubiquitinases in Cell Cycle Control
Emanuele (PI)
3/01/2020 -02/28/2024
NIGMS, National Institute of Health

RSG-18-220-01-TBG
Ubiquitin Ligases in Breast Cancer Proliferation and Therapeutic Resistance

Emanuele (PI)
01/01/2019 – 12/31/2022
American Cancer Society, Research Scholar Grant

Relevant, recent corresponding author publications include:

1. 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.
2. 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
3. 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 PMCID: PMC6425951
4. 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

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2021	Ad hoc reviewer, Molecular Oncology Study Section, NIH, NCI
2020-present	Editorial Board Member for *Cell Division*
2019-present	Associate Professor with tenure, UNC, Lineberger Cancer Center, Dept. of Pharmacology
2019	Peer review committee for 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-present	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) 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.
b) 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
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) 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
b) 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
c) 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.

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

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/1n9Ynl_4kxlkV/bibliography/43141487/public/?sort=date&direction=descending