

BIOGRAPHICAL SKETCH

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NAME: Michael J Emanuele, PhD

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

POSITION TITLE: Assistant 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 laboratory is integrating genetic and proteomic technologies, with bioinformatics discovery approaches, to systematically define changes in cellular ubiquitylation during cell cycle progression. Since the regulatory circuits controlling cell cycle progression are disrupted in nearly all cancers, leading to unbridled proliferation and genome instability, we are interested in decoding the signaling events that control these processes. Mapping these pathways has begun to reveal unforeseen vulnerabilities in triple-negative breast cancer. Moving forward, we seek to understand the pathological rearrangements in these pathways and networks that contribute phenotypic hallmarks of disease. Our research efforts are buttressed by those of our collaborators, working in areas of bioinformatics, genomics, and proteomics. My topical expertise is in cell cycle control, which I have worked on various aspects of since graduate school, and the ubiquitin system. In addition, I have a strong and complementary experimental background in biochemistry, cell and systems biology. As a postdoc I developed and applied global methods to interrogate the ubiquitin system and have followed these studies by providing mechanistic insight into the point of regulation and physiological significance of ubiquitin signaling events. My topical and experimental expertise, in combination with that of my collaborators, place my lab in a strong position to deconstruct signaling events that contribute to cancer and evaluate their therapeutic potential in cell models of disease.

- 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-
- b. **Emanuele MJ**, Ciccia A, Elia AE, Elledge SJ. Proliferating cell nuclear antigen (PCNA)-associated KIAA0101/PAF15 protein is a cell cycle-regulated anaphase-promoting complex/cyclosome substrate. *PNAS* 2011. 108 (24) 9845-9850.
- c. 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.
- 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.

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, Brigham & Women's Hospital (Stephen Elledge's Lab)
2013-present Assistant Professor, University of North Carolina, Lineberger Cancer Center, Dept. of Pharmacology

Selected Honors and Awards

2007 Outstanding Graduate Student Award, University of Virginia, Biochemistry & Molecular Genetics
2008-2011 Damon Runyon Post-doctoral Fellowship Award
2013-2015 Jimmy V Scholar Award
2013 UNC IBM Junior Faculty Development Award
2014-2017 Susan G Komen Career Catalyst Research Award

C. Contribution to Science

1. Development 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 proteasome system (UPS). While global strategies exist to map changes in gene expression (microarray and sequencing), systematic technologies that interrogate the ubiquitin system are still in their infancy. I developed genetic and proteomic technologies that globally examine ubiquitylation. The proteomic strategy combines quantitative mass spectrometry with ubiquitylated peptide enrichment. This method is complemented by a genetic approach (Global Protein Stability Profiling, or GPS) that relies on fluorescent reporters coupled to ~15,000 human ORFs, cell sorting and microarray deconvolution. The application of these unparalleled discovery platforms provides a deep snapshot into the dynamics of the ubiquitin modified proteome at unprecedented depth. Ubiquitylated peptide enrichment in combination with SILAC mass spectrometry was first developed by myself, and fellow postdoc (Andy Elia). The GPS method was developed in the Elledge lab, and I was involved in further developing its capacity and 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.
2. Global Identification of E3 ubiquitin ligase substrates. Substrate specificity in the ubiquitin system is imparted by E3 ubiquitin ligases. The Cullin Ring ubiquitin ligases (CRLs) represent the largest E3 ubiquitin ligase family in humans. Through a modular assembly mechanism the CRLs assemble several hundred unique E3 ubiquitin ligases. Despite the immense importance of the CRLs in virtually all aspects of cellular physiology, a lack of global methods has precluded a systematic understanding of their substrates. Using a combination of genetic and proteomic methods (above), I examined the roles of CRLs in cellular physiology by globally identifying their substrates. These studies revealed hundreds of proteins regulated by the CRLs, and represents the largest single substrate identification study performed to date. These studies gave way to the characterization of two novel CRL substrates, Nusap1, a spindle protein involved in mitotic progression and chromosome stability, and PAF15, a cell cycle regulated PCNA binding protein. Nusap1 is a unique cell cycle protein, controlled by several E3 ubiquitin ligases at different points in the cell cycle and in response to cross-linking DNA damage. This suggests a potential role for Nusap1 in DNA damage response signaling in response to acute damage that activates the ATR signaling cascade. In addition, PAF15 plays a role in DNA damage repair choice and cell cycle progression. I was involved in conception, design and carrying out these experiments.
 - 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.

- b. **Emanuele MJ**, Ciccia A, Elia AE, Elledge SJ. Proliferating cell nuclear antigen (PCNA)-associated KIAA0101/PAF15 protein is a cell cycle-regulated anaphase-promoting complex/cyclosome substrate. *PNAS* 2011. 108 (24) 9845-9850.
3. 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 in paired, isogenic Ras mutant and WT cell lines. 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 suggest possible avenues for the treatment of Ras mutant tumors. The initial screen was performed entirely by fellow postdoc Ji Luo (now at NCI). I joined the Elledge lab shortly after completion and validation of the screen, and I was directly involved in evaluating the mitotic phenotypes of Ras mutant cells.
 - 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.
 - 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.
4. Delineate the proteins, sub-assemblies and signaling requirements in the vertebrate kinetochore. Chromosome movement during cell division is controlled by microtubule-kinetochore interactions. The kinetochore is a macro-molecular protein complex assembled onto centromeric DNA during mitosis. Key, unresolved questions at the time I was in graduate school were, what proteins assemble into the kinetochore, and how are they assembled on centromeres during mitosis. Using biochemical assays I identified preassembled sub-complexes of kinetochore proteins, and measured precise numbers of molecules for individual proteins at each kinetochore. This provided key molecular insight into the kinetochore-microtubule binding interface. I also showed that distinct populations of kinetochore proteins rely on a balance between the kinase Aurora B, and PP1 phosphatase, to stably associate the centromeres. Finally, I identified the protein Cep57 as a novel component of the vertebrate kinetochore that also localizes to the centrosome. Using in vitro biochemical and cell biological assays I found that Cep57 activity is required for microtubule binding at both points in the spindle. This work shed light on the mechanisms by which kinetochore proteins assemble into a functional microtubule binding entity, and conservation of in microtubule binding at the plus and minus ends of microtubules. I was directly involved in experimental design and execution. These studies were carried out during graduate training in Todd Stukenberg's lab at The University of Virginia.
 - a. **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.
 - b. Vorozko VV, **Emanuele MJ**, Kallio MJ, Stukenberg PT, Gorbsky GJ. Multiple mechanisms of chromosome movement mediated through the Ndc80 complex and Dynein/Dynactin. *Chromosoma*. 2008 Apr;117(2):169-79.
 - 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.
 - d. **Emanuele MJ**, McClelland ML, Satinover DL, Stukenberg PT. Measuring the stoichiometry and physical interactions between components elucidates the architecture of the vertebrate kinetochore. *Mol Biol Cell*. 2005 Oct;16(10):4882-92.
5. Analysis of hypoxic induction in mouse models treated with photodynamic therapy. Photodynamic therapy (PDT) is a unique treatment modality for solid tumors. PDT involves administration of a light sensitive drug that semi-selectively accumulates in tumor, following by drug activation with laser light.

PDT is used to treat a subset of solid tumors, including lung and prostate cancer. PDT requires the presence of sufficient oxygen in the light activated tissues to induce cell killing. To better understand the dynamics of PDT efficacy and oxygen consumption, mouse tumors treated with a PDT regime were excised, frozen, sectioned and stained for blood vessel perfusion and hypoxic induction using the nitroimidazole EF3. We identified gradients of hypoxia relative to blood vessel perfused regions that were dependent on the PDT dose. In addition, treatment induced hypoxia could be used to predict outcome in mice. These studies examined the effect of PDT dose on hypoxic induction, how these effects could be mitigated, and the predictive power of measuring hypoxia in translational studies. I directly carried out many of these experiments as a technician at the University of Pennsylvania in Theresa Busch's lab.

- a. Wang HW, Putt ME, **Emanuele MJ**, Shin DB, Glatstein E, Yodh AG, Busch TM. Treatment-induced changes in tumor oxygenation predict photodynamic therapy outcome. *Cancer Res.* 2004 Oct 15;64(20):7553-61.
- b. Busch TM, Hahn SM, Wileyto EP, Koch CJ, Fraker DL, Zhang P, Putt M, Gleason K, Shin DB, **Emanuele MJ**, Jenkins K, Glatstein E, Evans SM. Hypoxia and Photofrin uptake in the intraperitoneal carcinomatosis and sarcomatosis of photodynamic therapy patients. *Clin Cancer Res.* 2004 Jul 15;10(14):4630-8.
- c. Busch TM, Wileyto EP, **Emanuele MJ**, Del Piero F, Marconato L, Glatstein E, Koch CJ. Photodynamic therapy creates fluence rate-dependent gradients in the intratumoral spatial distribution of oxygen. *Cancer Res.* 2002 Dec 15;62(24):7273-9.

Full list of published work (link):

[Emanuele Publication List: CLICK HERE](#)

D. Research Support

Current Research Support

Title: Identify ubiquitin signaling networks that serve as targets for the treatment of cancer

Dates: 10/1/13 – 9/30/15

PI: Michael J Emanuele, PhD (Design, experimental implementation and data analysis)

Goals: Identify the relevance of Nusap1 destruction in mediating the interaction between DNA and spindle damaging agents.

Grant No: N/A

Award Name: V-Scholar Award

Funding Agency: Jimmy V Foundation

Title: Altered ubiquitin signaling networks regulating breast cancer proliferation.

Dates: 10/14/14 – 10/23/17

PI: Michael J Emanuele, PhD (Design, experimental implementation and data analysis)

Goals: Map deregulated ubiquitin signaling networks in triple-negative, basal-like breast cancer and identify the deubiquitylating enzyme controlling the FoxM1 transcription factor.

Grant No: CCR14298820

Award Name: Susan G Komen Career Catalyst Research Award

Funding Agency: Susan G Komen for the Cure

Title: Start-up package.

Dates: 01/2013 – 01/2018

PI: Michael J Emanuele, PhD

Grant No: N/A

Goals: N/A

Funding Agency: University Cancer Research Fund, University of North Carolina, Chapel Hill

Selected Completed Support

Title: Therapeutic targeting of the E2F transcription factor.

Dates: 01/2014 – 01/2015

PI: Michael J Emanuele, PhD (Design, experimental implementation and data analysis)

Grant No: N/A

Goals: Identify upstream regulators of the cell cycle E2F transcription factor.

Award Name: UNC IBM faculty Development Award

Funding Agency: University of North Carolina, Chapel Hill

Title: Identification and Characterization of Proteins Stabilized in Response to DNA Damage

Dates: 06/2008 – 06/2011

PI: Michael J Emanuele, PhD

Grant No: N/A

Goals: Identify and characterize proteins whose stability is controlled by DNA damage

Award: Damon Runyon, Dale Frey Postdoctoral Fellowship

Funding: Damon Runyon Cancer Research Foundation