OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

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: Neskey, David M, M.D. MSCR, FACS

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

POSITION TITLE: Assistant Professor of Otolaryngology and Cell and Molecular Pharmacology

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 DateMM/YYYY | FIELD OF STUDY |
| --- | --- | --- | --- |
| Colby College, Waterville, ME | B.A. | 06/1999 | Biology |
| Albany Medical College, Albany, NY | M.D. | 06/2006 | Medicine with Distinction in Research |
| University of Miami, Miami, FL | Residency | 06/2011 | Otolaryngology – Head and Neck Surgery |
| MD Anderson Cancer Center, Houston, TX | Fellowship | 06/2014 | Head and Neck Surgery |
| Medical University of South Carolina | M.S.C.R. | 05/2016 | Master of Science in Clinical Research |

1. **Personal Statement**

My ongoing research stems from my fellowship experience under the mentorship of Dr. Jeffrey Myers and has focused on the impact of mutations in the tumor suppressor, *TP53*, on tumor progression and metastases in head and neck squamous cell carcinoma (HNSCC). This work combines a translational component including the analysis of clinical and genomic data with preclinical modeling including *in vitro* assays of cell proliferation, migration, and invasionand *in vivo* experiments including orthotopic mouse models of oral cancer and tail vein metastatic models. I was recruited to the Medical University of South Carolina (MUSC) as one of three K12 Paul Calebresi Clinical and Translational Oncology scholars. Since joining the faculty at the Medical University of South Carolina, I have been investigating novel mechanisms associated with gain of function (GOF) or oncogenic characteristics of p53 mutations, specifically the role of the recently identified tumor suppressor, Non-Muscle Myosin IIA (NMIIA). These ongoing studies aim to correlate the tumor suppressive capability of p53 with a functional NMIIAthat is lost in the presence of oncogenic mutations in p53. The outcomes from this research will have an important impact in delineating the intertwined roles of NMIIA and mutp53 in HNSCC tumor progression and invasion, leading to novel treatment strategies for patients with head and neck cancer that target specific cytoskeletal changes observed only in NMIIA-depleted cells.

In addition to my lab-based studies, I have an ongoing investigator initiated clinical trial entitled “Phase II Trial of Nivolumab, an Anti-PD-1 Monoclonal Antibody, As a Novel Neoadjuvant Presurgical Therapy for Locally Advanced Oral Cavity Cancer”. As part of this work, I have developed a collaboration with my co-investigator Dr. Jessica Thaxton, Ph.D. (Department of Orthopedics), investigating the role of mTOR inhibition sustaining antitumor metabolism and protein translation which results in improved response to anti-PD-1 therapy in oral cancer. Preliminary data from this work has provided the foundation for the current IDEA award proposal. We anticipate the results from our ongoing clinical trial coupled with the support from IDEA award program announcement will be the foundation for externally funded research focused on overcoming PD-1 mediated immune dysfunction in head and neck squamous cell carcinoma.

**B. Positions and Honors
Postdoctoral Training and Employment:**

2006 - 2011 Otolaryngology - Head and Neck Surgery Residency
Jackson Memorial Hospital

University of Miami Miller School of Medicine, Miami, FL

2011 - 2014 Fellowship

 Advanced Training in Head and Neck Surgical Oncology

 University of Texas MD Anderson Cancer Center, Houston, TX

2014 - Assistant Professor

 Department of Otolaryngology - Head and Neck Surgery

 Department of Cell and Molecular Pharmacology

 Medical University of South Carolina, Charleston, SC

2019 - Interim Co-Program Leader

 Cancer Immunology

 Hollings Cancer Center

**Professional Societies and Committees:**

2007 - American Academy of Otolaryngology-Head and Neck Surgery

2013 - American Head and Neck Society

2015 - American Academy of Cancer Research

2016 - South Carolina Oncology Society

2016 - North Carolina South Carolina Otolaryngology Society

2016 - South Carolina Medical Association

2016 - American Head and Neck Society Research Committee

2016 - NRG Oncology Head and Neck Cancer General Committee

2019 - American Head and Neck Society Advanced Training Council

**Honors And Awards:**

2005 Alpha Omega Alpha, Albany Medical College

2006 Doctorate in Medicine with Distinction in Research, Albany Medical College

2009, 2010 Chandler Society Resident Research Award

University of Miami Miller School of Medicine, Otolaryngology

2012 Best Basic Science Poster 8th International Conference on Head & Neck Cancer

2015 Protocol selected for AACR/ASCO Methods in Clinical Cancer Research Workshop

2016 Best Oropharyngeal Poster 9th International Conference on Head & Neck Cancer

2016 Head and Neck Researcher of the Year, 31st F. Johnson Putney Lecture in Head and Neck Cancer

2017 Inducted as a Fellow of the American College of Surgeons

**C. Contributions to Science**
**Neoadjuvant PD-1 inhibition in Head and Neck Cancer.**

Squamous cell carcinoma of the head and neck (HNSCC) is the sixth most common neoplasm in the world and despite advances in treatment, the 5-year survival remains approximately 50%. Because of the need for new therapies, immunotherapeutic approaches for HNSCC patients has gained interest. Our ongoing clinical trial has revealed the majority our patients with oral squamous cell carcinoma (OCSCC) respond to neoadjuvant presurgical PD-1. Furthermore, our data suggests that response to PD-1 blockade is associated with an increase in the central memory phenotype within the TILs.

1. Kaczmar J, Kompelli A, Graboyes EM, Hornig J, Lentsch EJ, Day TA, Paulos CM, Young MR, **Neskey DM.** Phase II Trial of Nivolumab, an Anti-PD-1 Monoclonal Antibody, as a Novel Neoadjuvant Pre-surgical Therapy for Locally Advanced Oral Cavity Caner. International J of Radiation Oncology. 2018, Vol. 100(5):1315.
2. Horton JD, Knochelmann HM, Day TA, Paulos CM, **Neskey DM**. Immune Evasion by Head and Neck Cancer: Foundations for Combination Therapy Trends Cancer. 2019 Apr;5(4):208-232. doi: 10.1016/j.trecan.2019.02.007. Epub 2019 Mar 20. Review.

**The Tumor Suppressor Capability of p53 is Dependent in Myosin IIA Function.**

Currently, molecular biomarkers are not used in head and neck squamous cell carcinoma (HNSCC) but several genes have been identified including mutant *TP53* (mutp53)*,* where our recent work has identified an approach to stratify patients with tumors harboring high or low risk *TP53* mutations. More recently non-muscle Myosin IIA (NMIIA) has been identified as a tumor suppressor in HNSCC. In the study, I demonstrate low NMIIAexpression is associated with a decreased survival in patients with head and neck cancer harboring low-risk mutp53 but not high-risk mutp53. Furthermore, inhibition of NMIIA leads to an increased cellular invasion in cells harboring wildtype p53 (wtp53), which was not observed in high-risk mutp53 cells. This increased invasiveness of wtp53 following NMIIA inhibition was associated with reduction in p53 target gene expression in cells expressing wtp53 but not mutp53. This reduced expression may be due in part to a decrease in nuclear localization of wtp53 but not mutp53. Overall the implication of this work is the tumor suppressor capability of p53 is dependent upon a functional non-muscle Myosin IIA.

1. Coaxum C, Tiedeken J, Garrett-Mayer E, Myers JN, Rosenzweig SA, **Neskey DM**. The tumor suppressor capability of p53 is dependent on Non-muscle Myosin IIA function in Head and Neck Cancer. Oncotarget 8:22991-23007, 2017. PMID: 28160562.
2. Coaxum C, Tiedeken J, Garrett-Mayer E, Myers JN, Rosenzweig SA, **Neskey DM**. The tumor suppressor capability of p53 is dependent on Non-muscle Myosin IIA function in Head and Neck Cancer. American Society of Head and Neck Surgery 9th International Conference on Head and Neck Cancer. 2016 July 16-20. Oral Presentation.

***TP53* as a Prognostic and Predictive Biomarker in Head and Neck Squamous Cell Carcinoma**

*TP53* is the most frequently mutated gene in HNSCC and some mutations (mutp53) termed gain of function (GOF) are associated with increased cell invasion, decreased patient survival, and chemotherapy resistance. I have validated a novel method termed EAp53 that can identify high-risk *TP53* mutations associated with decreased survival and increased development of distant metastases in HNSCC patients which is corroborated in both *in vitro* and *in vivo* studies of invasion, tumorigenicity, and development distant metastases. Additionally, high-risk *TP53* mutations identified by EAp53 are associated with decreased sensitivity to cisplatin in pre-clinical studies and in an analysis of a neo-adjuvant chemotherapy clinical trial. Furthermore, the associated chemotherapy resistance observed in the GOF mutant p53 can be overcome through synthetic lethality by targeting cell cycle checkpoint kinases.

1. **\*Neskey DM,** \*Osman AO, Ow TJ, Katsonis P, McDonald T, Hicks SC, Hsu TK, Pickering CR, Ward A, Patel A, Yordy JS, Skinner HD, Giri U, Sano D, Story MD, Beadle BM, El-Naggar AK, Kies MS, William WN, Caulin C, Frederick M, Kimmel M, Myers JN, Lichtarge O. Evolutionary Action score of TP53 (EAp53) identifies high risk mutations associated with decreased survival and increased distant metastases in head and neck cancer. Cancer Research 2015. PMID: 25634208. \* Denotes shared first author
2. \*[Osman AA](http://www.ncbi.nlm.nih.gov/pubmed/?term=Osman%20AA%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), **\*Neskey DM,** [Katsonis P](http://www.ncbi.nlm.nih.gov/pubmed/?term=Katsonis%20P%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Patel AA](http://www.ncbi.nlm.nih.gov/pubmed/?term=Patel%20AA%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Ward AM](http://www.ncbi.nlm.nih.gov/pubmed/?term=Ward%20AM%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Hsu TK](http://www.ncbi.nlm.nih.gov/pubmed/?term=Hsu%20TK%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Hicks SC](http://www.ncbi.nlm.nih.gov/pubmed/?term=Hicks%20SC%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [McDonald TO](http://www.ncbi.nlm.nih.gov/pubmed/?term=McDonald%20TO%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Ow TJ](http://www.ncbi.nlm.nih.gov/pubmed/?term=Ow%20TJ%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Ortega Alves M](http://www.ncbi.nlm.nih.gov/pubmed/?term=Ortega%20Alves%20M%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Pickering CR](http://www.ncbi.nlm.nih.gov/pubmed/?term=Pickering%20CR%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), Skinner HD, [Zhao M](http://www.ncbi.nlm.nih.gov/pubmed/?term=Zhao%20M%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Sturgis EM](http://www.ncbi.nlm.nih.gov/pubmed/?term=Sturgis%20EM%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Kies MS](http://www.ncbi.nlm.nih.gov/pubmed/?term=Kies%20MS%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [El-Naggar A](http://www.ncbi.nlm.nih.gov/pubmed/?term=El-Naggar%20A%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Perrone F](http://www.ncbi.nlm.nih.gov/pubmed/?term=Perrone%20F%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Licitra L](http://www.ncbi.nlm.nih.gov/pubmed/?term=Licitra%20L%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Bossi P](http://www.ncbi.nlm.nih.gov/pubmed/?term=Bossi%20P%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), Kimmel M, [Frederick MJ](http://www.ncbi.nlm.nih.gov/pubmed/?term=Frederick%20MJ%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Lichtarge O](http://www.ncbi.nlm.nih.gov/pubmed/?term=Lichtarge%20O%5BAuthor%5D&cauthor=true&cauthor_uid=25691460), [Myers JN](http://www.ncbi.nlm.nih.gov/pubmed/?term=Myers%20JN%5BAuthor%5D&cauthor=true&cauthor_uid=25691460). Evolutionary Action Score of TP53 Coding Variants (EAp53) is Predictive of Platinum Response in Head and Neck Cancer Patients. Cancer Res. 2015. PMID: 25691460. \* Denotes shared first author
3. Osman AA, Monroe MM, Ortega Alves MV, Patel AA, Katsonis P, Fitzgerald AL, **Neskey DM**, Frederick MJ, Woo SH, Caulin C, Hsu TK, McDonald TO, Kimmel M, Meyn RE, Lichtarge O, Myers JN. Wee-1 Kinase Inhibition Overcomes Cisplatin Resistance Associated with High Risk TP53 Mutations in Head and Neck Cancer through Mitotic Arrest Followed by Senescence. Mol Cancer Ther. 2014. PMID:25504633.
4. Gadhikar MA, Sciuto MR, Ortega Alves MV, Pickering CR, Osman AA, **Neskey DM**, Zhao M, Fitzgerald AL, Myers JN, Frederick MJ. Chk1/2 inhibition overcomes the cisplatin resistance of head and neck cancer cells secondary to the loss of functional p53. Mol Cancer Ther. Mol Cancer Ther. 2013 Sep;12(9):1860-73. PMID: 23839309.

**Genomic characterization of oral squamous cell carcinoma**

Oral squamous cell carcinoma (OCSCC) is a subset of head and neck cancer that until recently had limited investigations into the landscape of genomic alterations. Therefore, few molecular alterations have been identified that could be exploited clinically as biomarkers for treatment selection or clinical outcomes. Through this work I have helped develop genomic studies where well-defined patient populations with OCSCC of similar stage who have also received similar treatments were studied with the goal of improving the correlation between specific genomic alterations and patient outcomes.

1. Pickering CR, Zhang J, **Neskey DM**,Zhao M, Jasser SA, Wang J, Ward A, Tsai CJ, Ortega Alves MV, Zhou JH, Drummond JA, El-Naggar AK, Gibbs RA, Weinstein JN, Wheeler DA, Wang J, Frederick MJ, Myers JN. Squamous cell carcinoma of the oral tongue in young non-smokers is genomically similar to tumors in older smokers. Clin Cancer Res. 2014 Jul 15;20(14):3842-8. doi: 10.1158/1078-0432.CCR-14-0565. Epub 2014 May 29. PMID: 24874835
2. Pickering CR, Zhang J Suk, Yoo SY, **Neskey DM**, Xie TX,El-Naggar AK, Weinstein JN, Wang J, Gibbs RA, Wheeler DA, Myers JN, Frederick MJ. Integrated genomic characterization of oral cavity squamous cell carcinoma identifies frequent genomic drivers. Cancer Discov. 2013 Jul;3(7):770-81. doi: 10.1158/2159-8290.CD-12-0537. Epub 2013 Apr 25. PMID: 23619168

**CD44 promotes tumorigenesis and modifies EGFR signaling in head and neck squamous cell carcinoma**

Soluble CD44, a breakdown product of CD44, is overexpressed in oral rinses from HNSCC patients and can distinguish HNSCC patients from normal controls. CD44 has also been identified as a tumor-initiating marker in HNSCC. I have demonstrated with a xenograft model that introduction of CD44 into tumor cells induces aggressive tumor morphology and appears to enhance tumor initiation. Furthermore, cells overexpressing CD44 show increased proliferation, migration and resistance to cisplatin and apoptosis. Since CD44 is abundant in most HNSCC, these findings provide evidence that CD44 may be an excellent therapeutic target.

1. Perez A, **Neskey DM**, Wen J, Pereira L, Reategui EP, Goodwin WJ, Carraway KL, Franzmann EJ. [CD44 interacts with EGFR and promotes head and neck squamous cell carcinoma initiation and progression.](http://www.ncbi.nlm.nih.gov/pubmed/23265944) Oral Oncol. 2013 Apr;49(4):306-13. PMID: 23265944.
2. Perez A, **Neskey DM,** Pereira L, Goodwin WJ, Slingerland J, Franzmann EJ. CD44, CD29, and CD133 as potential markers for Cancer Stem Cells in Head and Neck Squamous Cell Carcinoma. American Association of Cancer Research Conference; 2009 April 18-22; Denver,CO. Poster # 4902

**D. Additional Information: Research Support and/or Scholastic Performance**

**Ongoing Research Support**

CA209-831

Bristol Myers Squibb Investigator Initiated Clinical Trial Neskey (PI) 05/03/2017 – 05/02/2022

Phase II Trial of Nivolumab, a Anti-PD-1 Monoclonal Antibody, As a Novel Neoadjuvant Pre-surgical Therapy for Locally Advanced Oral Cavity Cancer

The goal of this project is to look at the effectiveness of nivolumab in patients with oral cavity cancer (OCC) who are about to undergo surgery.

Role: PI

K08-DE026542-01

NIH/NIDCR Neskey (PI) 09/01/2016 - 08/31/2020

Mentored Clinical Scientist Research Career Development Award

The tumor suppressor capability of p53 is dependent on Non-muscle Myosin IIA function in Head and Neck Cancer.

The goal of this project was to validate the role of a key protein, non-muscle Myosin IIA, in the increased invasiveness of head and neck cancers harboring high-risk TP53 mutations, which ultimately could lead to precise therapies targeting these aggressive tumors and subsequently improving the survival of patients with head and neck cancer.

Role: PI

Team Science Award

Hollings Cancer Center Ogretmen (PI) 07/01/2019 – 06/30/2021

Overcoming immune lethergy following PD-1 blockade therapy

The goal of this project is to interrogate the impact of PD-1 blockade on the immune phenotype within the tumor and overcome immune lethargy with inhibition of inhibition of PI3Kδ.

Role: PI

**Pending Support**

R21 DE029592-01

NIH/NIDCR Neskey (MPI) 04/01/2020 - 03/31/2022

Achieving Tissue Robustness Through Harnessing Immune System Plasticity (PAR19-173)

Defining the role of CD26 in checkpoint blockaded induced tumor immunity

The goal of this project in conjunction with Chrystal Paulos, Ph.D (MPI) is to evaluate the role of CD26 expression in tumor infiltrating lymphocytes following PD-1 blockade in both patients with oral cancer and syngenic mouse models of oral cancer.

**Completed Research Support**

UL1TR001450

NIH/NCATS SCTR Pilot Discovery Grant Halushka (PI) 01/01/2017-06/30/2019

The Impact of PD-1 Inhibition on T Cell Memory Phenotype in Patients with Oral Cancer

The goal of this study is to assemble an interdisciplinary team comprised on Dr. Paulos and I and to subsequently evaluate the memory phenotype of TILs and determine the epigenetic changes of periphery T cells and TILs following PD-1 blockade.

Role: PI