BIOGRAPHICAL SKETCH

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NAME: Taylor, Derek J

eRA COMMONS USER NAME (credential, e.g., agency login): WADS117

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
Fort Lewis College	B.S.	1993-1997	Biochemistry; Cell & Molecular Biology
University of California, San Diego	Ph.D.	1999-2003	Biochemistry; Virology; Structural Biology
The Wadsworth Center	Post-Doc	2004-2008	Computational Biology; Molecular Imaging
University of Colorado at Boulder	Visiting Scientist	2008-2009	Biochemistry; Structural Biology

A. Personal Statement

My lab relies on the accessibility of state-of-the-art cryo electron microscopy (cryoEM) and detection equipment in order to probe the three-dimensional structure of macromolecular complexes. My diverse training in electron microscopy, x-ray crystallography, biochemistry, and molecular biology places me in a unique position to engage in a multifaceted approach for investigating these structures. As a graduate student I was trained in molecular virology, x-ray crystallography, and macromolecular biophysics under Dr. Jack Johnson (The Scripps Research Institute). Later, during my postdoctoral tenure, my research concentrated on understanding ribosome dynamics and the independent steps required for protein synthesis. Using cryoEM and single particle reconstruction, I determined the three-dimensional structure of factors bound to the eukaryotic ribosome at subnanometer resolution. I was fortunate to learn cryoEM under the tutelage of Dr. Joachim Frank (now at Columbia Univ), a pioneer in the EM field and together we published specialized papers describing cryoEM related techniques. After my postdoctoral career, I spent one year working with Dr. Tom Cech (Univ. of Colorado), a leader in the RNA field and Nobel Laureate, investigating the structure and function of telomere and telomerase nucleoprotein complexes. I have continued to use electron microscopy as a primary tool in my independent lab, now at Case Western Reserve University. Specifically, my lab uses electron microscopy to probe the structures of assemblies that are important to mRNA 3' processing, telomere complexes, functional ribosome complexes, the ABCA4 transporter, and Protein Phosphatase 2A.

B. Positions and Honors

Positions and Employment

1995	Undergraduate Student Research Assistant, Fort Lewis College
1996	Undergraduate Student Research Assistant, University of Georgia
1997-1999	R&D Chemist, Rosemont Pharmaceutical Inc., Denver, CO
1999-2003	Graduate Student Research Assistant, University of California, San Diego with Dr. John E. Johnson
2004-2008	HHMI Postdoctoral Fellow, Health Research Inc., The Wadsworth Center with Dr. Joachim Frank
2008-2009	Visiting Scientist, University of Colorado at Boulder with Dr. Thomas R. Cech
2009 – 2017	Assistant Professor, Department of Pharmacology, Case Western Reserve University
2017 –	Associate Professor with tenure, Department of Pharmacology, Case Western Reserve University

Professional Memberships

2010 – American Association for the Advancement of Sciences
2010 – American Society for Pharmacology and Experimental Therapeutics
2007 – Microscopy Society of America
2005 – Biophysical Society

Honors and Awards

2013 National Institutes of Health Director's New Innovator Award
2013 American Cancer Society – Research Scholar Award
2011 Case Western Reserve University School of Medicine – Mt. Sinai Scholar
2011 American Heart Association – Young Investigator Award
2004-2008 Howard Hughes Medical Institute Postdoctoral Fellow
2002 The Scripps Research Institute Society of Fellows Poster Award
2000-2003 University of California, San Diego Excellence in Teaching Award
1997 Fort Lewis College Senior in Chemistry Award
1997 Magna Cum Laude, Fort Lewis College
1996-1997 Beta Beta Beta Biological Honor Society

C. Contributions to Science

1. Work from my lab has contributed toward an understanding of the interactions that occur between telomere end-binding proteins and telomere DNA. The POT1-TPP1 heterodimer binds selectively to single-stranded DNA exhibiting telomere sequence. In addition to preventing illicit induction of the DNA damage response, POT1-TPP1 interacts intimately with telomerase to localize it to the telomere and to enhance its ability to synthesize telomere DNA. Work from my lab has demonstrated that the binding of multiple POT1-TPP1 proteins unfolds DNA secondary structure and compacts the telomere DNA into globular structures, where the protein likely surrounds the DNA to provide more protection. Together, these data provide insight into how POT1-TPP1 proteins interact with telomere DNA to protect it from degradation and regulate telomerase-mediated extension.

    a. Hernandez-Sanchez, W., Huang, W., Plucinsky, B., Garcia-Vazquez, N., Robinson, N.J., Schiemann, W.P., Berdis, A.J., Skordalakes, E., & **Taylor, D.J.** (2018) A non-natural nucleotide uses a specific pocket to selectively inhibit telomerase activity. *PLOS Biology.* Epub: April 5, 2019. https://doi.org/10.1371/journal.pbio.3000204. PMID: 30951520.
    b. Zeng, X., Hernandez-Sanchez, W., Xu, M., Whited, T.L., Baus, D., Zhang, J., Berdis, A.J., & **Taylor, D.J.** (2018) Induction of cancer cell death by telomerase-mediated incorporation of a nucleoside analog into telomeric DNA. *Cell Reports.* 23: 3031-3041. PMID: 29874588.
    c. Rajavel, M., Orban, T., Xu, M., Hernandez-Sanchez, W., de la Fuente, M., Palczewski, K., & **Taylor, D.J.** (2016) Dynamic peptides of human TPP1 govern diverse functions in maintaining telomeres. *Nucl. Acids. Res*. 44(21): 10467-10479. PMID: 27655633.
    d. Mullins, M.R., Rajavel, M., Hernandez-Sanchez, W., de la Fuente, M., Biendarra, S., Harris, M.E., & **Taylor, D.J.** (2016) POT1-TPP1 binding to telomere DNA discriminates against G-quadruplex structural morphology. *J. Mol. Biol.* Epub: 428(13): 2695-2708. PMID: 27173378.
    e. Rajavel, M., Mullins, M.R., & **Taylor, D.J.** (2014) Multiple facets of TPP1 in telomere DNA maintenance. *Biochim Biophys Acta Proteins & Proteomics.* 1844:1550-1559. PMID: 24780581

2. My work has also focused on understanding the intricate details of ribosome-catalyzed, protein synthesis in eukaryotes. Years before being solved by x-ray crystallography, I was able to use cryo-EM to detail one of the first structures of a eukaryotic 80S ribosome at sub-nanometer resolution that included the full sequence of ribosomal RNA and many of the ribosomal proteins. My work also revealed, in molecular detail, how specific factors interact with the eukaryotic ribosome to perform distinct functions. Bacterial toxins, including exotoxin A and diphtheria toxin, exert cytotoxicity by adding an ADP-ribosylation (ADPR) moiety to a uniquely modified diphthamide residue residing at the tip of eukaryotic elongation factor 2 (eEF2). In separate studies, I used cryo-EM to understand how eukaryotic release factors coordinate to bind the mammalian ribosome when a STOP codon exists in its A-site. Finally, we have shown how stress conditions stall protein translation in eukaryotic cells by causing 80S ribosomes to enter a reversible state of hibernating dimeric structures.

a. **Taylor, D.**, Unbehaun, A., Li, W., Das, W., Lei, S., Lao, H., Grassucci, R.A., Pestova, T.V., & Frank, J. (2012) Cryo-EM structure of the mammalian eRF1-eRF3-associated termination complex. *Proc Natl Acad Sci U S A*, 109, 18413-8. PMID: 23091004.
b. Krokowski, D., Gaccioli, F., Majumder, M., Mullins, M.R., Yuan, C.L., Papadopoulou, B., Merrick, W.C., Komar, A.A., **Taylor, D.**, & Hatzoglou, M. (2011) Characterization of hibernating ribosomes in mammalian cells. *Cell Cycle.* 10(16):1-12. PMID: 21768774.
c. **Taylor, D. J.**, Devkota, B., Huang, A., Topf, M., Narayanan, E., Sali, A., Harvey, S., & Frank, J. (2009) Comprehensive Molecular Structure of the Eukaryotic Ribosome. *Structure.* 17, 11591-1604. PMID: 20004163.
d. Frank, J., Gao, H., Sengupta, J., Gao, N., & **Taylor, D.J.** (2007) The process of mRNA-tRNA Translocation. *Proc Natl Acad Sci U S A*, 104, 19671-8. PMID: 18003906.
e. **Taylor, D.J.**, Nilsson, J., Merrill, A.R., Andersen, G.R., Nissen, P., and Frank, J. (2007) Structures of modified eEF2•80S ribosome complexes reveals the role of GTP hydrolysis in translocation. *EMBO J.* 26, 2421-2431. PMID: 17446867.

3. In addition to the ribosome and telomere complexes mentioned above, my lab has used electron microscopy to define the structural architecture of assemblies that are important for DNA packaging, mRNA 3' processing and membrane transport. Combining x-ray crystallography and electron microscopy, we assembled a complete model of the P22 bacteriophage tail needle and demonstrated a pH-induced dependence on its structural organization. The structural data of the human pre-mRNA 3' processing complex remains the most comprehensive analysis of the fully assembled complex. Similarly, the three-dimensional structure of the ABCA4 ATP transporter is the most complete structure of this receptor to-date. The structural analysis of the ABCA4 transporter combined with immunolabeling provided the precise localization of the individual domains of the transporter to fully define its molecular organization. The structure of ACBA4 in ATP-bound and ADP-bound states further identified conformational changes in the transporter that are responsible for its function.

    a. Basak, S., Gicheru, Y., Samanta, A., Molugu, S., Huang, W., de la Fuente, M., Hughes, T., **Taylor, D.J.**, Nieman, M., Moiseenkova-Bell, V., & Chakrapani, S. (2018) Cryo-EM structure of the full-length 5-HT3A receptor in its resting conformation. *Nat. Comm.* Epub: 2018 Feb 6;9(1):514. PMID: 29410406.
    b. Scott, H., Kim, J-K., Yu, C., Huang, L. Qiao, F., & **Taylor, D.J.** (2017) Spatial organization and molecular interactions of the *Schizosaccharomyces pombe* Ccq1-Tpz1-Poz1 shelterin complex. *J. Mol Biol.* 429:2863-2872. PMID: 28807855.
    c. Bhardwaj, A., Sankhala R.S., Olia, A.S., Brooke, D., Casjens, S.R., **Taylor, D.J.**, Prevelige Jr., P.E., & Cingolani, G. (2016) Structural plasticity of the protein plug that traps newly packaged genomes in *Podoviridae virions*. *J. Biol. Chem*. 291:215-226. PMID: 26574546.
    d. Tsybovsky, Y., Orban, T., Molday, R.S., **Taylor, D.**, & Palczewski, K. (2013) Molecular organization and ATP-induced conformational changes of ABCA4, the photoreceptor-specific ABC transporter. *Structure*, 854-860. PMID: 23562398
    e. Shi, Y., Di Giammartino, D.C., **Taylor, D.**, Sarkeshik, A., Rice, W.J., Yates III, J.R., Frank, J., & Manley, J.L. (2009) Molecular Architecture of the Human pre-mRNA 3' Processing Complex. *Mol. Cell.* 33, 365-376. PMID: 19217410.

4. My Ph.D. thesis focused on understanding the structure, function, assembly and maturation of small, non-enveloped eukaryotic viruses. I worked primarily on *Nudaurelia capensis* ω virus (NωV), a *T=4* icosahedral virus that shares structural homology with poliovirus and exhibits an auto-catalytic cleavage of its coat protein that is similar to that of reovirus. I used genetic mutations and biophysical analysis, which included cryo-EM, to characterize NωV maturation and autocatalytic cleavage. We discovered that the autocatalytic cleavage event "locks" the NωV capsid in its mature state. However, I showed that mutating the asparagine residue at the scissile bond made the pH-induced maturation of NωV reversible, while other mutations abrogated proper assembly of the virion. As a potential antiviral approach, we identified small molecule compounds that would block maturation of NωV. Finally, during my Ph.D. training, I was able to use x-ray crystallography to solve the structure of Providence virus that, like NωV, is a member of the *Tetraviridae* Family.

    a. Speir, J.A., **Taylor, D.J.**, Natarajan, P., Pringle, F.M., Ball, L.A. & Johnson J. E. (2010) Evolution in Action: N and C Termini of Related T=4 Viruses Exchange Roles as Molecular Switches. *Structure.* 18:700-709. PMID: 20541507.

b. **Taylor, D.J.**, Speir, J.A., Reddy, V., Cingolani, G., Pringle, F.M., Ball, L.A., and Johnson, J.E. (2006) Preliminary x-ray characterization of authentic providence virus and attempts to express its coat protein gene in recombinant baculovirus. *Arch Virol*, 151, 155-165. PMID: 16211330.
c. **Taylor, D.J.**, and Johnson, J.E., (2005) Folding and Particle Assembly are Disrupted by Single Point Mutations near the Auto-catalytic Cleavage Site of *Nudaurelia capensis* ω *virus* Capsid Protein *Protein Sci.* 14, 401-408. PMID: 15659373.
d. Lee, K.K., Tang, J., **Taylor, D.**, Bothner, B., Johnson, J.E. (2004) Small compounds targeted to subunit interfaces arrest maturation in a nonenveloped, icosahedral animal virus. *J. Virol.*, 13, 7208-7216. PMID: 15194797.
e. **Taylor, D.J.**, Krishna, N.K., Canady, M.A., Schneemann, A., and Johnson, J.E. (2002) Large Scale, pH-Dependent, Quaternary Structure Changes in an RNA Virus Capsid are Reversible in the Absence of Subunit Autoproteolysis. *J. Virol.*, 76, 9972-9980. PMID: 12208973.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/16E_oA59hirQC/bibliography/46016877/public/?sort=date&direction=descending

APPLICANT BIOGRAPHICAL SKETCH

NAME: **Daniel Leonard**

eRA COMMONS USER NAME (credential, e.g., agency login): **DLEONARD03**

POSITION TITLE: **MD/PhD Candidate, Medical Scientist Training Program (MSTP)**

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
State University of New York at Albany, Albany, NY	B.S.	08/2006	05/2010	Biology
Cleveland Clinic Lerner College of Medicine, Cleveland, OH	MD Trainee	05/2012	Present	Medicine
Case Western Reserve University School of Medicine, Cleveland, OH	PhD Trainee	05/2016	Present	Pathology: Cancer Biology Training Program

A. PERSONAL STATEMENT

In my future career as a physician-scientist, I will work to advance pre-clinical therapeutics, designed by my research endeavors, for the clinical management of patients with cancer. My current interests involve creating innovative therapeutic approaches, such as re-activation of tumor suppressors, for the treatment of both hematologic and solid tumors. I believe the functional directionality coupled with broad regulatory scope of tumor suppressors prevents a therapeutic avenue only minimally explored.

Early in my pursuit of a career in medicine, I quite literally stumbled into a basic science laboratory. I had never really thought about how the information in the textbooks I had so vigorously studied was actually discovered until that day. Dr. Melinda Larsen, my soon to be Principal Investigator, sparked my curiosity with a simple question after some initial conversation, “Well how would you go about proving that?” she posed. I found that laboratory research had this unique ability to capture and intrigue, stimulating my curiosity, and leading to more questions than answers with each experiment. This passion for understanding the human body from organ systems down to intracellular mechanisms is, I believe, pertinent in becoming a great physician-scientist. I believe a Kirschstein-NRSA Fellowship would provide the necessary support and guidance to further cultivate this passion, building on the foundation of scientific pursuits and exploration I have been part of in my journey to become a successful physician-scientist.

My first lab experience, under the guidance of Dr. Melinda Larsen, could be best portrayed as a fish out of water. Studying the biology of submandibular salivary gland development, I quickly learned how little the scientific community actually “knew” about this process. I was overwhelmed with questions. Despite this flood of questions, my main goal at the time was to learn the tools of the trade; how to perform a western blot, how to perform imaging based localizations studies, what information could we gather from these techniques. These fundamental tools would lay the groundwork for my continued pursuit of a scientific career as I applied for the Post-Baccalaureate Intramural Research Training Award (IRTA) through the NIH.

Under the direction of Dr. Thomas Bugge at NIH, my role as a scientific investigator further evolved. The Bugge lab was focused on the cellular recognition mechanisms of tissue injury. In a somewhat serendipitous manner, we made an observation suggesting the receptor, uPARAP, had a role in binding and recycling collagen. I quickly realized that there were no established tools to directly visualize the process I had decided to study. My dedication pushed me to develop a new technique in which we could follow the assembly and subsequent degradation of exogenous collagen fibers through a novel two-photon/confocal hybrid imaging modality. This journey at NIH was both humbling and motivating, but I quickly realized that I was struggling with the lack of translational application of the project. I was struck with an internal dilemma, on the one hand I felt noncompetitive as an applicant to a dual degree program but I knew that I would never be fully satisfied by pursuing only one realm of science. This desire to pursue an education emphasizing research through a clinical lens directed me to the Cleveland Clinic Lerner College of Medicine.

During my medical school training, I worked in Dr. Edward Plows’ lab, characterizing an alternative inside-out platelet activation signaling cascade through ADAP associated Integrins. This was an opportunity for me to further refine my scientific approach, focusing on generating cogent hypotheses and designing appropriate

questions. These skills were truly put to the test during my clinical research experience with Dr. Joseph Nally, a Cleveland Clinic Nephrologist. I posed the question, what serological alterations occurred prior to renal dysfunction that could act as a prognostic indicator while still leaving time for intervention before irreversible damage occurred? Retrospective patient analysis I performed, allowed me to identify a potential candidate marker. This preliminary work allowed us to secure funds to create an Acute and Chronic Kidney Disease Biorepository for which further analysis could be done.

My current research, mentored by Dr. Goutham Narla, is focused on characterizing the diverse functions of the phosphatase PP2A in the setting of cancer, while utilizing this knowledge to design screening platforms for novel cancer therapeutics. This opportunity began as a one year HHMI Medical Fellowship and has blossomed into the pursuit of a PhD. I believe this decision has been a culmination of the years of training and scientific evolution that I have been working towards, both consciously and sub-consciously, since stumbling into Dr. Larsen's lab those many years ago. My experiences have spanned many different fields of study utilizing different laboratory techniques and intellectual strategies to answer the question at hand. My role in each of these projects progressively evolved from technician-type tasks to that of an independent researcher, analyzing literature, understanding the clinical and basic science gap, and formulating a testable hypothesis to help close these gaps and advance patient care.

I have chosen a mentor and a lab that fit my career goal of intertwining laboratory research with clinical practice. This opportunity to train under a Kirschstein-NRSA Fellowship will allow me to further refine my abilities, striving to advance cancer therapeutics, and allow me to receive the guidance necessary to define myself as an independent investigator.

B. POSITIONS AND HONORS

ACTIVITY/OCCUPATION	Start Date	End Date	Institution/Company	Supervisor
HHMI Medical Fellow	06/2015	05/2016	Howard Hughes Medical Institute	Goutham Narla, M.D., Ph.D.
Post-baccalaureate IRTA	06/2010	05/2012	National Institute of Dental and Craniofacial Research	Thomas Bugge, Ph.D.

Academic and Professional Honors

2018	AAP/ASCI/APSA Joint Meeting Best Poster Award
2018	AAP/ASCI/APSA Joint Meeting Travel Award
2015-2016	Howard Hughes Medical Institute Medical Student Fellowship
2012-Present	Cleveland Clinic Lerner College of Medicine – 5-year student scholarship
2010-2012	National Institute of Health Post-Baccalaureate Training Award
2010	Graduated Summa Cum Laude – State University of New York at Albany
2010	National Society of Collegiate Scholars Delegate
2010	Presidential Scholars Scholarship
2009	Presidential Award for Excellence in Research
2009	International Scholar Laureate Program Delegate

Membership in Professional Societies

2015-Present	American Physician Scientist Association
2013-Present	American Medical Student Association

C. CONTRIBUTION TO SCIENCE

1. Undergraduate Graduation with Honors Thesis

The functional Submandibular Salivary Gland (SMG) develops through a complex process known as branching morphogenesis. This process involves the coordinated differentiation and 3-dimensional alignment of acinar and ductal cells, directed by the dynamic extracellular environment. The temporal and spatial expression of growth factors in determining cell fate od the developing SMG had never been addressed. To study this dynamic process, I utilized an ex vivo culture technique of day E13 SMG's where the ECM was surgically extracted under a dissection microscope and the remnant epithelial tissue was grown in a 3D matrigel matrix. This ex vivo system allowed us to experimentally investigate the extracellular cues directing SMG differentiation. I found that exposure to FGF10 resulted in terminal and exclusive ductal differentiation

that could not be overcome with FGF7 exposure, whereas FGF7 exposure followed by FGF10 induced complete differentiation of both acinar and ductal cells. This work marked the first characterization of a developmentally regulated step-wise induction of differentiation required by growth factors for the generation of a functional SMG. This work laid the foundation for expanded analysis of the temporal/spatial ECM composition on SMG bud differentiation and was granted as an Honors thesis with Distinction upon my graduation. Additional work leading to the characterization of an ECM dependent myoepithelial function governing the SMG bud differentiation through Rac1 signaling and respective intracellular Par1b localization directing cellular differentiation was subsequently published in Organogenesis.

Peer Reviewed Publications:

Gervais EM, Sequeira SJ, Wang W, Abraham S, Kim JH**, Leonard D,** DeSantis KA, Larsen M. Par-1b is required for morphogenesis and differentiation of myoepithelial cells during salivary gland development. *Organogenesis* 2016; 12(4):194-216. PMC5198941

Presentations:

Leonard D, Sequeira SJ, Larsen M. *Rac GTPase is required for the formation of cell-cell junctions and regulation of cell polarity during embryonic salivary gland development.* (2010) Oral and poster presentation. Albany Presidential Research Symposium. Albany, NY.

2. Post-Baccalaureate Research Training

The physiologic response to tissue injury is multifaceted. There has been a vast amount of research focused on understanding the initial stages of physiologic and cellular responses to tissue injury but the last stage, ECM remodeling, has long been attributed to the secretion of broad spectrum matrix enzymes known as matrix metalloproteinases (MMP). Unfortunately, this model does not adequately explain the clearance of degraded proteins nor does it account for the targeted remodeling of ECM proteins in MMP knockout mice. To investigate an alternative mechanism of targeted ECM degradation, cellular internalization, I generated ex vivo, fluorescently labeled, collagen fibrils that formed physiologic collagen fiber networks when injected subcutaneously in mice; allowing for visualization at the requisite depth and clarity with a confocal/two-photon hybrid approach. This novel design allowed me to track the formation and subsequent internalization of fluorescently labeled collagen. To test the role of receptor mediated endocytosis, I utilized two individual and crossed transgenic knockout mouse models of the cell surface receptors uPARAP and MR, both of which have been shown to bind major ECM proteins. This allowed me to identify a targeted mechanism of collagen internalization with about 10-20% regulated by uPARAP and the resulting 80% regulated by MR. Lastly, I crossed macrophage specific versus fibroblast specific tagged transgenic mice with the respective cell surface receptor knockout mice, concluding that MR dependent internalization was mediated by M2-type macrophages, whereas uPARAP mediated internalization was directed by activated fibroblasts. This story was subsequently published in the Journal of Cell Biology.

Peer Reviewed Publications:

Leonard D*, Madsen DH*, Masedunskas A, Moyer A, Jürgensen HJ, Peters DE, Amornphimoltham P, Selvaraj A, Yamada SS, Brenner DA, Burgdorf S, Engelholm LH, Behrendt N, Holmbeck K, Weigert R, Bugge TH. M2-like macrophages are responsible for collagen degradation through a mannose receptor-mediated pathway. *J Cell Biol* 2013; 202(6):951-66. PMC3776354

* Authors contributed equally to this manuscript

Presentations:

Leonard D, Bugge T. *The endocytic collagen degradation mechanism* (2012). Oral and poster presentation. National Institute for Dental and Craniofacial Research Fellows Meeting. Bethesda, MD

3. Graduate Research Training

Tumor suppressors have long been considered “undruggable” as many are subject to irreversible inactivating mutations. Alternatively, PP2A is unique in that it has a low mutational incidence, about 2% of all cancers, yet is inactivated through a multitude of other mechanisms in cancer. This makes re-activation of PP2A a plausible endeavor for the treatment of cancer, and as such, Dr. Narla’s Laboratory has engineered a novel class of small molecule activators of PP2A (SMAPs) that demonstrate pre-clinical efficacy in mouse models of lung, prostate, and endometrial cancers. My work during this year of research has focused on identifying the mechanisms of PP2A re-activation through SMAP therapy. Utilizing hydroxyl-radical footprinting has allowed us to identify a particular region of the scaffold subunit of PP2A that demonstrates a high degree of protection upon the addition of these SMAP molecules. My project focused on exploring the dependence of these protected sites in regulating the re-activation potential through SMAP therapy. To do this, I generated

cell lines overexpressing tagged PP2A scaffold protein, mutating key residues that were protected after the addition of SMAPs. We hypothesized that the protection observed was due to direct SMAP binding, thus mutation of these residues would disrupt SMAP binding, resulting in diminished tumor suppressive capabilities of these molecules. Indeed, *in vivo* xenograft models of tumor growth and response utilizing these mutant cell lines demonstrates a single point mutation at two of the three key residues demonstrated resistance to SMAP therapy. This work was part of a recent publication in the Journal of Clinical Investigation.

Peer Reviewed Publications:

Taylor SE, O'Connor CM, Wang Z, Shen G, Song H, **Leonard D**, Sangodkar J, LaVasseur C, Avril S, Waggoner S, Zanotti K, Armstrong AJ, Nagel C, Resnick K, Singh S, Jackson MW, Xu W, Haider S, Difeo A, Narla G. *The highly recurrent PP2A-Aα subunit mutation P179R alters protein structure and impairs PP2A enzyme function to promote endometrial tumorigenesis. Cancer Res.* 2019 (epub ahead of print)

Leonard D, O'Connor CM, Perl A, Sangodkar J, Narla G. *Therapeutic targeting of PP2A*. *Int J Biochem Cell Biol.* 2018;96:182-193. PMC5927617

Sangodkar J, Tohme R, Perl A, Kiselar J, Katrinsky D, Zaware N, Izadmehr S, Mazhar S, Wiredja D, O'Connor CM, Hoon D, Dhawan N, Schlatzer D, Yao S, **Leonard D**, Borczuk A, Gokultangan G, Wang L, Svenson E, Farrington C, Yuan E, Avelar R, Stachnik A, Smith B, Gidwani V, Giannini H, McQuaid D, McClinch K, Wang Z, Levine A, Sears R, Chen E, Duan Q, Datt M, Haider S, Ma'ayan A, Difeo A, Sharma N, Galsky M, Brautigan D, Ioannou Y, Xu W, Chance M, Ohlmeyer M, Narla G. A new cancer therapy based on activation of a tumor suppressor protein. *JCI* 2017;127(6):2081-2090. PMC5451217

Presentations:

Leonard D, Huang W, O'Connor CM, Wiredja D, Kiselar J, Haider S, Schlatzer D, Brautigan D, Taylor D, Narla G. *Small molecule regulation of Protein Phosphatase 2A through targeting of the disordered c-terminal tail of the catalytic subunit*. (2018) Poster Presentation. AAP/ASCI/APSA Joint Meeting. Chicago, IL

Leonard D, O'Connor CM, Schlatzer D, Brautigan D, Narla G. *Cancer associated PP2A-Aα mutations predict response to small molecule reactivation* (2016) Poster Presentation. Federation of American Societies for Experimental Biology – Phosphatase Conference. Steamboat Springs, CO

Leonard D, Tohme R, O'Connor C, Narla G. *Cancer associated PP2A-Aα mutations govern small molecule reactivation potential* (2016). Poster Presentation. The American Society for Clinical Investigation Joint Meeting. Chicago, IL

D. SCHOLASTIC PERFORMANCE

USMLE Step 1 Score: 240 — USMLE Step 2 CS: Pass
MCAT Score: 33 — Undergraduate GPA: 3.78
Degree Honors: Summa Cum Laude

YEAR	SCIENCE COURSE TITLE	GRADE	YEAR	OTHER COURSE TITLE	GRADE
	CCLCM/CWRU Graduate Courses				
	***denotes clinical rotations**				
2017	Experiment Pathology Sem II	*IP*	2015	Pediatrics Core at UH/VA*	AE
2017	Special Topic in Cancer Biology	*IP*	2014	Family Medicine Core at CCF*	AE
2017	Being a Professional Scientist	*IP*	2014	Internal Medicine Core at CCF*	AE
2017	Intro to Cancer Biology	*IP*	2014	Aging Core at CCF*	AE
2017	Thesis Research	P	2014	Neuroscience Core at CCF*	AE
2016	Contemp Approach to Drug Disc	A	2014	Psychiatry Core at CCF*	AE
2016	Thesis Research	P	2014	Hematology/Med Oncology*	AE
2016	Current Topics in Cancer	A	2014	Infectious Disease*	AE

YEAR	SCIENCE COURSE TITLE	GRADE
2016	Experimental Pathology Sem I	P
2015	Internal Medicine A.I.*	AE
2015	Surgery Core at MHMC*	AE
2015	Emergent Care Core at MHMC*	AE
2015	OB/GYN Core at UH/VA*	AE
2014	Foundations of Clinical Medicine II	AE
2014	Advanced Research in Medicine II	AE
2013	Clinical Research	AE
2013	Clinical Epidemiology	AE
2013	Medical Biostatistics	AE
2013	Clinical Research Journal Club	AE
2013	Endocrinology/Reproductive Biol. II	AE
2013	Longitudinal Clinic I	AE
2013	Endocrinology/Reproductive Bio. I	AE
2013	Renal Biology I	AE
2013	Musculoskeletal Sciences I	AE
2013	Neuro. and Behavioral Sciences I	AE
2013	Heme/Immunology/Microbiology	AE
2013	Advanced Research in Medicine I	AE
2013	Comm. and Physical Diag. Skills I	AE
2013	Longitudinal Clinic I	AE
2012	Fundamentals of Molecular Medicine	AE
2012	Research Journal Club	AE
2012	Cardiovasc/Respiratory Sciences I	AE
2012	Gastrointestinal Sciences I	AE
2012	Advanced Research in Medicine I	AE
2012	Foundations of Clinical Medicine I	AE
2012	Comm. and Physical Diag. Skills I	AE
2012	Longitudinal Clinic I	AE
2012	Fundamentals of Molecular Medicine	AE
2012	Basic/Translational Research Journal Club	AE
	SUNY at Albany (Undergraduate)	
2010	Topics in Stem Cell Biology	A
2010	Supervised Research	A
2010	Concepts of Race and culture in the Modern World	A
2009	Parasitic Diseases and Humans	B+
2009	Topics in Biology /Lab	A
2009	Supervised Research	A
2009	Cell Biology II	A
2009	Financial Accounting	A
2009	Introductory Cell Biology	A

YEAR	OTHER COURSE TITLE	GRADE
2014	EKG Interpretation	AE
2014	Cardiovascular and Respiratory II	AE
2014	Hematology II	AE
2014	Gastrointestinal System II	AE
2014	Foundations of Clinical Medicine II	AE
2012	Cardiovasc/Respiratory Sciences I	AE
2012	Gastrointestinal Sciences I	AE
2012	Advanced Research in Medicine I	AE
2012	Foundations of Clinical Medicine I	AE
2013	Neuro.l and Behavioral Sciences II	AE
2013	Musculoskeletal Sciences II	AE
2013	Comm. and Physical Diag. Skills II	AE
2013	Foundations of Medicine Seminar	AE
2009	Immunology	A
2009	Supervised Research	A
2009	Evolution	A
2008	Biological Chemistry I	B+
2008	Supervised Research	A
2008	Americna Literary Traditions	A
2008	General Physics I	B
2008	Organic Chemistry II	A
2008	Organic Chemistry II Lab	A
2008	Representations of the human body	A
2008	General Physics II	A
2008	General Physics Lab	A-
2008	Principles in Career/Life Planning	A
2007	Organic Chemistry I	A
2007	Organic Chemistry Lab I	A-
2007	General Physics I	W
2007	General Physics Lab	A-
2007	Methods in Peer Helping II	A
2007	Survey of Art in the Western World II	B
2007	General Biology II	A
2007	General Chemistry Lab II	A-
2007	Introductory Genetics	A
2007	Advanced General Chemistry	C+
2007	Introduction to Sociology	A-
2007	Methods in Peer Helping I	A
2006	General Biology I	A
2006	General Chemistry Lab I	A
2006	Advanced General Chemistry I	B

YEAR	SCIENCE COURSE TITLE	GRADE	YEAR	OTHER COURSE TITLE	GRADE
2009	Immunology II	A	2006	Elementary Statistics	A
2009	Supervised Research	A	2006	Introduction to Philosphical Problems	B+

Medical School Grading System: All medical school classes are assessed through a competency/portfolio based system with assignments similar to a pass/fail system. Assignments include, Achieves Expectations (AE), Achieves Expectation with Remediation (AER), and Does Not Achieve Expectations (F)

Graduate School Grading System: All graduate school classes were graded on an A to F scale (4.0-0.0) without subdivisions. Classes marked “P” were pass/fail.