BIOGRAPHICAL SKETCH

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NAME: Martin S. Taylor

eRA COMMONS USER NAME (credential, e.g., agency login): mtaylo56

POSITION TITLE: Fellow, Pathology, and Visiting Postdoctoral Associate

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	Completion Date	FIELD OF STUDY
Princeton University, Princeton, NJ	B.S.E.	09/2001	05/2005	Chemical Engineering
Johns Hopkins University School of Medicine, Baltimore, MD	M.D.	08/2005	05/2015	Medicine
Johns Hopkins University School of Medicine, Baltimore, MD	Ph.D.	07/2007	05/2015	Pharmacology
Massachusetts General Hospital, Boston, MA	Resident	06/2015	08/2018	Anatomic Pathology
Massachusetts General Hospital, Boston, MA	Clinical Fellow	08/2018	06/2021	Gastrointestinal Pathology
Whitehead Institute for Biomedical Research, Cambridge, MA	Research Fellow	08/2018	08/2021	Cell Biology
Harvard Medical School and Massachusetts General Hospital	Instructor	07/2021		Pathology

A. Personal Statement

I am an independently-funded scientist and practicing gastrointestinal pathologist with significant training and research in pulmonary and molecular pathology. My mentored research focuses on understanding growth factor signaling through mTOR Complex 2 (mTORC2), a large macromolecular machine that integrates extracellular signals to control key growth pathways through predominantly unknown mechanisms. I also maintain active collaborative interests and translational research on the LINE-1 transposon, an area in which I have developed significant expertise and methodology over the last ~10 years, much of which was done in an active and ongoing collaboration with Drs. Kathy Burns, Jef Boeke, and John LaCava. These along with my pathology expertise and resources provide key support for the present proposal, which leverages my pathology training along with our collaborative expertise in the biochemistry and biophysical characterization of LINE-1, which continues to emerge as a contributor and potential target in human diseases including cancer, aging, and autoimmune diseases including systemic lupus erythematous.

My career as a physician scientist began the summer after my junior year in college, when I was inspired while working in Dr. Curt Civin's stem cell lab at Johns Hopkins. His basic discovery of the hematopoietic stem cell marker CD34 saved patients' lives and advanced research and diagnostics, and I was intrigued by the prospect of a career blending clinical practice and investigation. Returning to Princeton, I became fascinated with protein structure and function and my thesis in the lab of Professor C.A. Floudas added biological relevance to a mathematical *de novo* protein design framework and applied it to G-protein coupled receptors; this work was honored with an undergraduate research award and resulted in a number of publications and selection to the NIH Medical Scientist Training Program (MSTP) at Hopkins. I soon joined the labs of Dr. Phil Cole and Jef Boeke in a combined bench and bioinformatic project seeking to understand the mechanism and consequences of ghrelin signaling. At the time, ghrelin was widely called a "hunger hormone" but its exact effects on mammalian physiology remained obscure. I therefore co-developed and validated a mechanism-based inhibitor of the ghrelin-activating enzyme ghrelin-O-acyltransferase (GOAT). This work, recognized by publications in *Science*, *JBC*, and *Bioorganic Chemistry*, identified GOAT as a target for treatment of obesity and metabolic syndrome,

clarified the physiologic role of ghrelin as a fat sensor controlling lipid metabolism, and provided key structural and mechanistic insights into the function of the important membrane bound O-acyltransferases (mBOAT) family.

Rather than return to medical school at this point as is typical, I pursued a unique opportunity to move to the Boeke lab and start a multi-institution collaborative project; our initial work established robust protein-protein interaction (interactome) techniques in human cells and described the first detailed characterization of human LINE-1 (L1) retrotransposition intermediates and the L1-host interactome, which are emerging topics in cancer and developmental biology. This work also created tools and analytical system to study LINE-1 that are in broad use in the field and have provided novel insights into LINE-1 biology, evolution, and the evolutionary role of p53. This work was recognized by publications in *Cell*, *eLife, Mobile DNA,* and others*,* along with two graduate research awards.

I chose to pursue my residency and fellowship training in anatomic pathology at Massachusetts General Hospital because of the department's rigorous clinical training and commitment to molecular pathology and both basic and translational research. I was keen to develop an understanding of disease at the tissue level, and I believed a role in pathology would offer synergy in identifying and understanding human disease while providing for unique opportunities for clinical and basic science collaboration, translational work, and access to patient samples. I was also excited by the prospect of a rich scientific environment and large clinical referral base, and these expectations were exceeded by the many still-mysterious diseases I encountered, several of which led to publications themselves, and one on the tumor microenvironment in colorectal cancer with my mentor Dr. Deshpande (sub-award on the present proposal) was honored with the Stowell Orbison Award for best research work at the 2018 USCAP international meeting.

I pursued subspecialty fellowship training in gastrointestinal pathology, based on my continued interest in the pathology of gastrointestinal cancers and potential roles of LINE-1 in their pathologies, a number of excellent mentors, and the broad range of clinical samples and model systems. My interests in LINE-1, its role in carcinogenesis, and potential in diagnostics also led me to became particularly interested in molecular genetics of cancer and how rare Mendelian cancer syndromes, cancer-associated mutations, and gene fusion events inform our understanding of normal biology. I felt strongly that the best way to make truly novel contributions was to obtain additional rigorous basic science training that I could then apply to questions of my own interest. I was therefore thrilled to pursue a joint postdoctoral fellowship between Whitehead Institute and Harvard Medical School, where I am based primarily in the lab of Dr. Phil Cole, leveraging my experience in interactomics and receiving new training in cell biology, structural biology, and chemical biology as I pursue hypotheses about both mTORC2 and LINE-1. I am committed to launching an independently funded lab and plan to leverage understanding of signaling biology through protein structure, function, and cellular and organismal metabolism to elucidate mechanisms that can be targeted for treatment of diseases including diabetes, metabolic syndrome, lupus, and cancer.

B. Positions and Honors

Positions, Employment Experience

2015 – 2018	Resident physician in Anatomic Pathology, Massachusetts General Hospital
2017 – 2018	Clinical fellowship training in Gastrointestinal Pathology
2018 – 2021	Clinical fellow in Anatomic Pathology
2018 – 2021	Postdoctoral associate, Whitehead Institute for Biomedical Research
2021– present	Instructor, Harvard Medical School

Honors, Awards, and Certifications

2000	Cum Laude Society (first election)	Gilman School
2001	National Merit Scholarship Finalist	Gilman School
2001	Alexander Randall, Jr. Prize for Publications	Gilman School
2001	AP Scholar with distinction.	Gilman School
2004	Summer Medical Student Award	American Society of Hematology
2004	Elected to Tau Beta Pi (First Election)	Princeton University
2004	Elected to Sigma Xi (First Election)	Princeton University
2005	Merck Outstanding Senior Thesis Award	Princeton University
2005	Myers Award	Princeton University Track and Field
2005	Magna Cum Laude	Princeton University
2005-2015	Medical Scientist Training Program Award	National Institutes of Health
2011	Outstanding Presentation Prize	Johns Hopkins Molecular Biology and Genetics

2014	The Outstanding Abstract in Basic Research	Johns Hopkins University Pathology
2015	Paul Ehrlich Award	Johns Hopkins University School of Medicine
2015	Pathology Young Investigators' Day Award	Johns Hopkins University Pathology
2017-2018	Chief Resident	Massachusetts General Anatomic Pathology
2018	Stowell Orbison Award	US & Canadian Academy of Pathology
2018	Poster of Distinction	Harvard Medical School Pathology
2018	MA state medical license	MA Board of Registration in Medicine
2018	Diplomate, Anatomic Pathology	American Board of Pathology
2018-2021	T32 Awardee (CA009216)	National Institutes of Health
2021-	K08 Awardee (DK129824)	National Institutes of Health

C. Contributions to Science

1. As a resident, I became interested in molecular pathology of rare diseases and of rare genetic fusions in cancer. I co-identified a novel pattern of acute lung injury and a conserved pathway of distal airway regeneration, which we now believe is likely a rare adverse event from trimethoprim-sulfamethoxazole treatment (manuscript submitted). I also pursued unusual molecular features identified by our in-house sequencing assay in patients whose disease did not fit established classifications; some of these led to publication.
    a. Miller JO, Shih AR, Mino-Kenudson M, **Taylor MS***, Goldman JL*. "*Trimethoprim-Sulfamethoxazole Associated Fulminant Respiratory Failure in Children and Young Adults*". **Am J Respir Crit Care Med**. 2021 Apr 1;203(7):918-921. PMID: 33513317. PMCID: PMC8017575
    b. **Taylor MS***, Chivukula RR*, Myers LC, Jeck WR, Tata PR, O'Donnell WJ, Farver CF, Thompson BT, Rajagopal J, Kradin RL. "*Delayed Alveolar Epithelization: A Distinct Pathology in Diffuse Acute Lung Injury."* **Am J Respir Crit Care Med**. 2018 Feb 15; 197(4):522-524. PMCID: PMC5821904
    c. **Taylor MS***, Chivukula RR*, Myers LC, Jeck WR, Waghray A, Tata PR, Selig MK, O'Donnell WJ, Farver CF, Thompson BT, Rajagopal J, Kradin RL. "*A Conserved Distal Lung Regenerative Pathway in Acute Lung Injury.*" **Am J Pathol**. 2018 Feb 21. PMCID: PMC5906746
    d. Farago AF*, **Taylor MS***, Doebele RC, Zhu VW, Kummar S, Spira AI, Boyle TA, Haura EB, Arcila ME, Benayed R, Aisner DL, Horick NK, Lennerz JK, Le LP, Iafrate AJohn, Ou SI, Shaw AT, Mino-Kenudson M, Drilon A. "*Clinicopathologic Features of Non–Small-Cell Lung Cancer Harboring an NTRK Gene Fusion."* **JCO Precision Oncology** 2018:2, 1-12. PMCID: PMC6132056

2. Despite contributing more than half of the human genome, the mechanisms of the LINE-1 transposon were poorly understood. I co-developed methods to study the LINE-1 interactome in human cells, and insights and tools developed in this work led to an interest in the consequences of LINE-1 de-repression and retrotransposition in human cancers, especially those of the gastrointestinal tract. I continued this work at the Massachusetts General Hospital in collaboration with Drs. John LaCava, Vikram Deshpande, David Ting, Kathleen Burns, and Omer Yilmaz; my organoid work facilitated the development of the PDOOX model. Unpublished work on understanding the colon cancer microenvironment received the prestigious Stowell Orrbison award at the 2018 United States & Canadian Academy of Pathology Annual Meeting.
    a. **Taylor MS***, Altukhov I*, Molloy KR*, Mita P, Jiang H, Adney EM, Wudzinska A, Badri S, Ischenko D, Eng G, Burns KH, Fenyö D, Chait BT, Alexeev D, Rout MP, Boeke JD, LaCava J. *"Dissection of affinity captured LINE-1 macromolecular complexes."* Elife. 2018 Jan 8;7. PMCID: PMC5821459
    b. **Taylor MS*,** LaCava J*, Mita P, Molloy KR, Huang CRL, Li D, Adney EM, Jiang H, Burns KH, Chait BT, Rout MP, Boeke JD, Dai L*, "*Affinity proteomics reveals human host factors implicated in discrete stages of LINE-1 retrotransposition.*" **Cell.** 155(5):1034-1048 (2013). PMC3904357.
    c. Rodić N, Steranka JP, Makohon-Moore A, Moyer A, Shen P, Sharma R, Kohutek ZA, Huang CR, Ahn D, Mita P, **Taylor MS**, Barker NJ, Hruban RH, Iacobuzio-Donahue CA, Boeke JD, Burns KH. *"Retrotransposon insertions in the clonal evolution of pancreatic ductal adenocarcinoma."* **Nat Med.** 2015 Sep;21(9):1060-4. PMC4775273.

d. Ardeljan D, Steranka JP, Liu C, Li Z, **Taylor MS**, Payer LM, Gorbounov M, Sarnecki JS, Deshpande V, Hruban RH, Boeke JD, Fenyö D, Wu PH, Smogorzewska A, Holland AJ, Burns KH. "Cell fitness screens reveal a conflict between LINE-1 retrotransposition and DNA replication." Nat Struct Mol Biol. 2020 Feb;27(2):168-178. PMID: 32042151 PMCID: PMC7080318

3. PhD thesis work (pharmacology): Ghrelin and Ghrelin-O-Acyltransferase (GOAT) Co-advised by Philip A. Cole and Jef D. Boeke. I co-developed and validated the first inhibitors of GOAT in vitro, in cells, and in mice. I demonstrated that our inhibitors targeted GOAT directly. Inhibition of GOAT in mice prevented weight gain on a high fat diet and improved glucose control, validating GOAT as an attractive target for the treatment of obesity and diabetes. Subsequent first-author publications established the topology and key structural features of GOAT and probed its enzymologic mechanism.
    a. Barnett BP*****, Hwang Y*****, **Taylor MS***, Kirchner H, Pfluger PT, Bernard V, Lin YY, Bowers EM, Mukherjee C, Song WJ, Longo PA, Leahy DJ, Hussain MA, Tschöp MH, Boeke JD, Cole PA. "*Glucose and weight control in mice with a designed ghrelin O-acyltransferase inhibitor*." **Science**. 330(6011):1689-92 (2010). PMC3068526.
    b. **Taylor MS**, Ruch TR, Hsiao PY, Hwang Y, Zhang P, Dai L, Huang CR, Berndsen CE, Kim MS, Pandey A, Wolberger C, Marmorstein R, Machamer C, Boeke JD, Cole PA. *"Architectural Organization of the Metabolic Regulatory Enzyme Ghrelin-O-Acyltransferase."* **J Biol Chem.** 288(45):32211-32228 (2013). PMC3820860.
    c. **Taylor MS**, Dempsey DR, Hwang Y, Chen Z, Chu N, Boeke JD, Cole PA, *"Mechanistic analysis of ghrelin-O-acyltransferase using substrate analogs."* **Bioorg Chem.** 2015 Oct;62:64-73. PMID: 26246082. PMC4567917.
    d. **Taylor MS**, Hwang Y, Hsiao PY, Boeke JD, Cole PA. *"Ghrelin O-acyltransferase assays and inhibition."* Methods Enzymol. 514:205-28. Review (2012). PMC3763810.

4. Early work (chemical engineering applied to medicine)
   Advised by Christodoulos A. Floudas; undergraduate thesis research and post-graduation collaboration. In this work on mathematical de novo protein design, I designed and implemented a new computational validation strategy and added biological relevance to the design method. This work lead to improved predictions of intra and inter-molecular interactions and the ability to study more difficult targets including HIV-1 and G protein-coupled receptors. I also built an online workbench to allow researchers to use our group's software.
    a. Bellows ML*****, **Taylor MS***, Cole PA, Shen L, Siliciano RF, Fung HK, Floudas CA. "*Discovery of entry inhibitors for HIV-1 via a new de novo protein design framework.*" **Biophysical Journal** No. 99(10):3445-53 (2010). PMC2980751.
    b. **Taylor MS**, Fung HK, Rajgaria R, Filizola M, Weinstein H, and Floudas CA. "*Mutations Affecting the Oligomerization Interface of G-Protein Coupled Receptors Revealed by a Novel De-novo Protein Design Framework.*" **Biophysical Journal** No. 94(7):2470-81 (2008). PMC2267121.
    c. Smadbeck J, Peterson MB, Khoury GA, **Taylor MS**, Floudas CA. "Protein WISDOM: A Workbench for In silico De novo Design of BioMolecules." **J. Vis. Exp**. (77), e50476, (2013). PMC3846368.

Authors marked with a * indicate equal contribution

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1f1dAsdofkukq/bibliography/public/

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

Ongoing

NIH K08DK129824 Taylor (PI) 2021 - present
Elucidating structural, mechanistic, and allosteric determinants of mTOR Complex 2 (mTORC2) signaling
The goals of this five-year training grant are to establish my independent career and improve our understanding of the structure and function of the key mTORC2 signaling node in growth factor signaling
Role: Principal Investigator

Completed

NIH T32CA009216 Langenau (PI) 08/2018 - present
Research Training in Molecular Immunology and Tumor Biology at Massachusetts General Hospital
The goal of this grant is to provide mentored research funding for physician-scientists in MGH Pathology
Role: Postdoctoral trainee, laboratory of David M. Sabatini, M.D., Ph.D.

NIH 5T32GM007309 Siliciano (PI) 2005 – 2015
Medical Scientist Training Program at Johns Hopkins University School of Medicine
The Program seeks to train MD-PhD students for positions of leadership in academic medicine and medical research.
Role: M.D./Ph.D. trainee, laboratories of Philip A. Cole, M.D., Ph.D. and Jef. D. Boeke, Ph.D.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: van Eeuwen, Trevor

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

POSITION TITLE: Postdoctoral Associate

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	END DATE MM/YYYY	FIELD OF STUDY
Fairleigh Dickinson University, Madison, NJ	BS	01/2013	05/2015	Biochemistry
University of Pennsylvania, Philadelphia, PA	Ph.D.	09/2015	08/2021	Biochemistry and Molecular Biophysics
The Rockefeller University, New York, NY		05/2021	present	Structural Biology

A. Personal Statement

My long-term research plan is to investigate the role of RNA processing and nuclear transport in cancer. In addition to my previous experience in undergraduate research in cell biology and computational model, I have obtained strong expertise in structural biology (cryo-electron microscopy, cross-linking mass spectrometry), and protein biochemistry through my predoctoral training at the University of Pennsylvania. By leveraging these techniques and further training in *in situ* cryo-electron tomography, I aim to develop a comprehensive map of the nuclear pore interactome and characterize changes upon cellular stress and during oncogenesis. To date I have been involved in several research projects including my previous experience as an undergraduate researcher that have equipped me with the necessary technical skills and training to perform hypothesis driven research. During my undergraduate research training under the joint direction of Dr. Gloria Anderle and Dr. Patricia Melloy I studied checkpoints in mitosis, specifically the Mitotic Checkpoint Complex (MCC) in *Saccharomyces cerevisiae*. Using a combination of protein modeling, yeast genetics and fluorescence microscopy, I demonstrated how mutations in the MCC lead failures in faithful mitosis mutations through distinct mechanisms. This work culminated in presentations at society national meeting, a university award for outstanding Honors Thesis and an American Chemical Society sectional award. For my graduate training at the University of Pennsylvania, I shifted my focus to studying mechanisms of Nucleotide Excision Repair (NER), a subset of DNA repair using biochemical and structural techniques under the direction of Dr. Kenji Murakami. My predoctoral work on NER resulted in two publications on structures of the NER and transcription factor TFIIH. I have significantly contributed to structural studies on a diverse series of projects, and, through these collaborations, have obtained strong expertise in structural biology, in particular, single-particle analysis using cryo-electron microscopy, which can resolve atomic details of macromolecular complexes under physiological conditions.

To expand the scope of my training as I prepare for a career as an independent investigator, I began a postdoctoral research fellowship in the lab of Dr. Michael Rout, head of the National Center for Dynamic Interactome Research (NCDIR) at The Rockefeller University. My ongoing postdoctoral work looks to use combinatorial approaches in biochemistry, crosslinking mass-spectrometry, cryo-EM single particle analysis and *in situ* cryo-electron tomography to create integrative models of mRNA export from the nucleus via the nuclear pore complex (NPC). The nucleus, the quintessential eukaryotic organelle, is responsible for housing DNA, and is the site of gene expression. The NPC not only serves as a physical gate keeper to RNA leaving the nucleus but also plays significant roles in chromatin compaction, transcription activation and gene silencing. Malfunctions in the nuclear pore are frequently seen in aging, neurodegeneration and cancer so that integrative structure-function mapping of the NPC in transport will help determine its role in these diseases.

B. Positions and Honors

Positions and Employment

2014 - 2015 Laboratory Teaching Assistant, Fairleigh Dickinson University
2015 - 2021 Graduate Student Research Assistant, University of Pennsylvania
2021 - Postdoctoral Associate, Rockefeller University

Other Experience and Professional Memberships

2014 - 2015 Member, American Chemical Society
2014 - 2016 Member, American Society of Cell Biology
2016 - current Member, American Society of Biochemistry and Molecular Biology

Honors

2013 Honors Program, Fairleigh Dickinson University
2015 New Jersey Institute of Chemists Student Award in Biochemistry
2015 Jean Asell Duranna Award for Outstanding Research Presentation
67th Annual North Jersey Section ACS Undergraduate Research Conference
2015 FDU: University Honors Program Outstanding Research Student Award
2016 Chemistry Biology Interface (CBI) Scholar, The Wistar Institute
2016 - 2018 NIH T32 Structural and Molecular Biology Training Program, University of Pennsylvania
2017 National Science Foundation: Graduate Research Fellowship Honorable Mention
2020 Finalist for Penn Prize for Excellence in Teaching by Graduate Student, University of Pennsylvania

C. Contribution to Science

1. **Early Career:** My early career contributions focused on mitosis, the process by which cells faithfully divide their replicated chromosomes into two daughter cells. Progress through mitosis is governed by the Mitotic Checkpoint Complex (MCC). In a joint undergraduate research mentorship by Dr. Gloria Anderle and Dr. Patricia Melloy, I studied how I studied how temperature sensitive mutants affect the function of the MCC in *Saccharomyces cerevisiae.* In Dr. Melloy's lab, I used fluorescent microscopy and yeast genetics to characterize the interactions of temperature sensitive mutants of the MCC. In Dr. Anderle's lab, I used molecular dynamics and computational techniques to investigate the biophysical implications of mutations on a member of the MCC, Cdc20p. I could computationally demonstrate that some surface mutations destabilize Cdc20p at elevated temperatures, leading to mitotic arrest. I was able to support these conclusions by demonstrating that the destabilized proteins are trafficked away from the MCC for degradation *in vivo*. This work culminated in two poster presentations at society national meetings and a regional poster session award.

Posters and Citations:

   a. **van Eeuwen T**, Luginsland J, Melloy P, Anderle, G. (2014) Homology modeling and functional analysis of the mitotic checkpoint complex in budding yeast. *Mol Biol Cell* 25, 25 (abstract P1067). Poster. American Society of Cell Biology National Meeting; 2014 December; Philadelphia, PA. PMCID: PMC4263442.
   b. **van Eeuwen T**, Luginsland J, Melloy P, Anderle, G. (2015) Studying the structure of the mitotic checkpoint complex using computational analysis and temperature-sensitive yeast mutants. *Abstracts of Papers, 250th ACS National Meeting & Exposition, Boston, MA.* Poster. Sci Ed Section 2015:1324386 CAPLUS.

2. **Graduate Career**: My contributions to science in my graduate work centered on the DNA damage response and mechanisms of DNA repair by the transcription and repair factor TFIIH. The DNA damage response, the set of transcriptional and translational events resulting from lesions or breaks in DNA, and the resulting repair of this damage are essential processes for the survival of living cells.

Transcription of some stress responsive genes as part of the DNA damage response is regulated by Elongin. Early in my graduate work in the lab of Dr. Kenji Murakami, we were able to demonstrate a link between the *Saccharomyces cerevisiae* Elongin (Ela1-Elc1) complex and a RNA polymerase II degradation factor Def1 in transcription after DNA damage. Furthermore, we could demonstrate that Def1 not only enhanced transcription initiation and restart *in vitro* but also was required for proper regulation of stress responsive genes *in vivo*. I generated deletion mutants of the degradation factor, Δdef1 strains, and used these to demonstrate misregulation of stress responsive genes after DNA damage and heat shock by Real-Time Quantitative Reverse Transcription PCR (qRT-PCR). Def1 also binds tightly to TFIIH and may be responsible for recruiting TFIIH to sites of damaged DNA. These findings extended our understanding of the cellular response to stress with regards to gene regulation and transcription.

Citation:

a. Damodaren N, **van Eeuwen T**, Zamel J, Lin-Shiao E, Kalisman N, Murakami K. Def1 interacts with TFIIH and modulates RNA polymerase II transcription. *Proc Natl Acad Sci U S A*. 2017 Dec 12;114(50):13230-13235. doi:10.1073/pnas.1707955114. Epub 2017 Nov 27.

The resulting damage from small insults to DNA like UV exposure can be disastrous for RNA or DNA polymerases, leading to mutagenesis or cell death. To remove these roadblocks, a series of proteins will recognize damage, open a small single stranded bubble, excise the damaged strand and then synthesize the proper complement, a process collectively called Nucleotide Excision Repair (NER). Failure to due this results in the diseases *xeroderma pigmentosum,* Cockayne syndrome and Trichothiodystrophy. My thesis work focused on the central player in NER, TFIIH, and its activity and structure in the repair context. By reconstituting the stepwise process of NER using purified proteins from *S. cerevisiae* and obtaining structures of these steps using cryo-EM single particle analysis. I successfully assembled the the damage recognition complex (Rad4-23) with TFIIH on a damaged DNA template and obtained a high-resolution reconstruction that demonstrated how TFIIH begins to unwind DNA in NER. Furthermore, TFIIH is regulated by a dissociable kinase subunit (TFIIK) that has an essential activity in transcription. Using cryo-EM single particle analysis, I determined the structure of the catalytic core of TFIIK. Using this structure and a combination of modeling methods, we propose a mechanism by which TFIIK recognizes its substrate RNA pol II. Combining our computational methods with using crosslinking mass spectrometry, I also devise a model of TFIIK in the pol II Preinitiation Complex. This work in total has contributed significantly to understanding the function of TFIIH in NER and transcription.

Citation:

a. **van Eeuwen T,** Shim Y, Kim HJ, Zhao T, Basu S, Garcia BA, Kaplan CD, Min JH, Murakami K. Cryo-EM structure of TFIIH/Rad4-Rad23-Rad33 in damaged DNA opening in nucleotide excision repair. *Nat Commun.* 2021 Jun 7;12(1):3338.

b. **van Eeuwen T,** Li T, Kim HJ, Gorbea Colón JJ, Parker MI, Dunbrack RL, Garcia BA, Tsai KL, Murakami K. Structure of TFIIK for phosphorylation of CTD of RNA polymerase II. *Sci Adv*. 2021 Apr;7(15). doi:10.1126/sciadv.abd4420. Print 2021 Apr.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/trevor.vaneeuwen.1/bibliography/public/

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

Scholastic Performance

YEAR	COURSE TITLE	GRADE
	FAIRLEIGH DICKINSON UNIVERSITY	
2013	Calculus II	A
2013	College Writing Workshop	A
2013	Introduction to Molecules, Cell & Genes Lab	A
2013	Introduction to Molecules, Cell & Genes	A
2013	Organic Chemistry I	A
2013	Organic Chemistry I Lab	A
2013	Research in Biology	A
2013	Microbiology	A-
2013	Microbiology Lab*	
2014	Latin American Culture & Civilization	A
2014	Applied Statistics	A
2014	Organic Chemistry II	A
2014	Organic Chemistry II Lab	A
2014	Inorganic Chemistry	A
2014	Inorganic Chemistry Lab*	
2014	Cell Biology	A
2014	Cell Biology Lab*	
2014	Research in Biology II	A
2014	Research Writing Workshop: Travel	A
2014	History of Film	A
2014	American Dreams, American Tragedies	A
2014	Instrumental Analysis	A
2014	Instrumental Analysis Lab	B
2014	Biochemistry I	A
2014	Mentored Research in Biology§	
2015	Multimedia	A
2015	Global Issues	A
2015	Perspectives on the Individual	A
2015	Honors Thesis Chemistry	A
2015	Chemistry Capstone Research Experience	A
2015	Biochemistry II	A
2015	Physical Chemistry II	A
2015	Physical Chemistry II Lab	A
2015	Analytical Chemistry	A
2015	Analytical Chemistry Lab*	
	UNIVERSITY OF PENNSYLVANIA	
2015	Cell Biology	B+
2015	Macromolecular Biophysics: Principles and Methods	A
2015	Macromolecular Crystallography: Methods and Application	A
2015	Lab Rotation	A
2016	Regulation of the Genome	B+
2016	Biological Data Analysis	A
2016	Structural and Mechanistic Biochemistry	A+
2016	Physical Principles of Mechano-Enzymes	A
2016	Computation Programming in Biochemistry and Biophysics	A

YEAR	COURSE TITLE	GRADE
2016	Lab Rotation	A
2016	Lab Rotation	A
2017	Candidacy Exam Course	A
2017	Passed Doctoral Preliminary Exam: 04-26-17	
2021	Defended Doctoral Thesis: 05-12-21	
2014	GRE GENERAL TEST	
	Verbal Reasoning: 164/170	(94%)
	Quantitative Reasoning: 160/170	(74%)
	Analytical Writing: 4.5/6.0	(82%)

*Lab grade incorporated into course grade. §Taken for no credit due to credit restriction.