## 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 professional career has focused on understanding the molecular interactions that control fundamental and essential biological functions. A primary focus of my lab is on understanding the molecular architecture and functional interactions that regulate human telomeres and telomerase. We are particularly interested in understanding how the telomere is assembled and how it interacts with telomerase to regulate its function. Another primary area of research in my lab addresses how telomere end-binding proteins interact exclusively with telomere DNA to prevent illicit induction of the DNA damage response. An overarching goal is to use the detailed, mechanistic insight to design small molecules that can be used to manipulate processes related to telomeres and telomerase in cancer cells. An NIH Innovator Award (DP2) had provided the primary funding to initiate this latter objective.

An equally important emphasis within my research group lies in the structural determination of macromolecular complexes. Before starting my own lab in 2009, I benefited from diverse and specialized training in a range of techniques under the tutelage of highly successful mentors. 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 an HHMI sponsored postdoctoral fellowship, my research concentrated on understanding ribosome structure and dynamics to detail the independent steps required for protein synthesis. I was fortunate to work under the guidance of Dr. Joachim Frank (now at Columbia Univ), a pioneer in cryo-electron microscopy and single-particle reconstruction techniques, a National Academy member, and 2017 winner of the Nobel Prize in Chemistry. After my postdoctoral career, I spent one year working with Dr. Tom Cech (Univ. of Colorado), a leader in the RNA field, HHMI Investigator, National Academy member, and Nobel Laureate, investigating the structure and function of telomere and telomerase nucleoprotein complexes. The exceptional training opportunities have placed me in a unique position to continue to probe the molecular interactions and regulatory pathways of macromolecular and multi-component assemblies.

**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

## B. 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. We have additionally helped to uncover the role of SLX4IP, an understudied protein, in regulating telomere maintenance mechanisms.

    a. Robinson, N.J., Morrison-Smith, C.D., Gooding, A.J., Schiemann, B.J., Chang, J., Jackson, M.W., **Taylor, D.J.,** & Schiemann, W.P. (2020). SLX4IP regulates telomere maintenance and Wnt signaling to control breast cancer metastasis. *Life Sciences Alliance.* Feb. 18;3(4). PMID: 32071280
    b. Xu, M., Kiselar, J., Whited, T.L., Hernandez-Sanchez, W., & **Taylor, D.J.** (2019) POT1-TPP1 differentially regulates telomerase via POT1 His266 and as a function of single-stranded telomere DNA length. *PNAS.* Nov 19; 116(47):23527-23533. PMID: 31685617.
    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.

2. Beyond our interest in understanding the molecular interactions that govern fundamental cellular events, we use the generated structure and mechanistic insight to develop small-molecule drugs and strategies for manipulating the abrogated processes that are associated with human afflictions. My group has used the structural and molecular information related to telomeres and telomerase to develop small molecule compounds that inhibit or exploit telomerase activity to be used as putative chemotherapeutic agents. Additionally, the cryo-EM structure of a small molecule activator of PP2A (SMAP) bound to PP2A identifies a novel mode of action for a new class of chemotherapeutic compounds. Finally, as a potential antiviral

approach, we have identified small molecule compounds that block maturation and infectivity of the eukaryotic virus, NωV.

a. Leonard, D.*, Huang, W.*, Izadmehr, S., O'Connor, C.M., Wiredja, D., Wang, Z., Zaware, N., Chen, Y., Schlatzer, D., Kiselar, J., Vasireddi, N., Schuchner, S., Perl, A.L., Galsky, M., Xu, W., Brautigan, D., Ogris, E., **Taylor, D.J.**†, & Narla, G.† (2020). Small molecule selectively enhances phosphatase function through biased heterotrimer stabilization. *Cell.* In Press.
b. Hernandez-Sanchez, W., Huang, W., Plucinsky, B., Garcia-Vazquez, N., Robinson, N.J., Schiemann, W.P., Berdis, A.J., Skordalakes, E., & **Taylor, D.J.** (2019) A non-natural nucleotide uses a specific pocket to selectively inhibit telomerase activity. *PLOS Biology.* Apr 5; 17(4):e3000204. PMID: 30951520.
c. 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.
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.

3. 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). The ADPR modification completely inhibits protein synthesis in the infected host and results in cell death. Through my work, we were able to show how the ADPR moiety interferes with ribosome decoding of the messenger RNA during protein synthesis. Furthermore, we were able to use the ADPR as a novel density marker to better understand the GTP-induced conformational changes eEF2 undergoes to catalyze the movement of the mRNA-tRNA duplex from the A- and P-sites of the ribosome to the P- and E-sites, respectively. In separate studies, we used cryo-EM to understand how eukaryotic release factors 1 and 3 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. **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.
c. 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.
d. **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.

4. In addition to the ribosome and telomere complexes described in detail above, my lab has used cryo-electron microscopy to solve the structures of cellular assemblies that are important for removing post-translational phosphorylation modifications, DNA packaging, mRNA 3' processing and membrane transport. Our contributions include the cryo-EM structures of the bacterial efflux pump that is partially responsible for antibiotic resistance, and a ligand gated ion channel. We have additionally combined structures from x-ray crystallography and electron microscopy to assemble 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. Su, C-C., Kambakam, S., Rajavel, M., Morgan, C.E., Scott, H., Huang, W., Emerson, C., **Taylor, D.J**, Stewart, P.L., Bonomo, R., & Yu, E.W. (2019). Cryo-EM structure of an *Acinetobacter baumanii* multidrug efflux pump. *mBio.* July 2;10(4). PMID: 31266873.
b. 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.
c. 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.
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

5. I have made key contributions to the structural biology field, specifically through training in cryo-EM and in structure determination of large, complex viruses using x-ray crystallography. My involvement in generating detailed protocols has benefited cryo-EM users throughout the world by providing them with technical training and documentation for doing so. In addition, I have contributed to understanding the structure, function, assembly and maturation of eukaryotic viruses. In addition to structural investigation, I have used genetic mutations and biophysical analysis to characterize viral assembly, maturation, and infectivity.

a. Grassucci, R. A., **Taylor, D.**, and Frank, J. (2008) Visualization of Macromolecular Complexes using Cryo-Electron Microscopy with FEI Tecnai Transmission Electron Microscopes. *Nat Protoc.,* 3:330-339. PMID: 18274535.
b. Grassucci, R. A., **Taylor, D. J.**, and Frank, J. (2007) Preparation of Macromolecular Complexes for Cryo-Electron Microscopy. *Nat Protoc.,* 2:3239-3246. PMID: 18079724.
c. **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.
d. **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.

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

**D. Research Support**

**Ongoing Research Support**

R01 GM133841 (PI: Taylor) 07/01/2019-06/30/2023
NIH/NIGMS
Molecular interactions and regulatory events of telomere proteins.

The major goal of this project is to determine the molecular and cellular interactions that govern telomere length homeostasis to maintain proper genomic stability. We will use cryo-electron microscopy to determine the structure of the POT1-TPP1-DNA nucleoprotein complexes that reside at the ends of telomeres and we will use a series of pathogenic mutations to define the diverse yet fundamental roles in telomere maintenance.
Role: PI
NO OVERLAP

R01 CA240993 (MPIs: Taylor, Narla-contact) 06/01/2019-05/31/2024
NIH/NCI
Structural and molecular determinants of protein phosphatase 2A function in lung cancer.

The major goal of this project is to develop small molecule activators of the phosphatase PP2A to be used in treating human cancers. The proposal combines expertise from two independent labs to probe the cellular and organismal changes in PP2A activity in the context of recurring cancer mutations. My role in the project is to solve the structure of the drug-bound PP2A complexes and interpret the molecular interactions with the intention of designing next generation compounds that are more potent and selective. The compounds are then used as a single agent or with other drugs in the Narla lab to determine anti-cancer effects in xenograft mouse models of lung cancer.
Role: MPI
NO OVERLAP

**Pending Research Support**

U.S. – Egypt Science and Technology Joint Fund, Cycle 20 09/01/2020-08/31/2023
USAID/STDF
Targets for anticancer and antiviral therapies: mechanistic and structural studies of cap-independent translation.

The primary goal of this proposal is to work with a team of investigators from Zewail City of Science and Technology in Cairo Egypt to understand how Hepatitis C Virus and certain cancer genes can bypass conventional cap-dependent protein synthesis in disease states. We will focus primarily on the use of Internal Ribosomal Entry Sites (IRESs) in the 5' untranslated region of genes to understand cap-independent translation applications. The study combines biophysical and structural analysis with functional, cellular assays to probe interactions between HCV and cellular IRESs with the small, ribosomal subunit to jump-start protein synthesis without a cap or the full cohort of initiation factors that are traditionally needed for eukaryotic protein synthesis.
Role: (MPIs: Aboul-Ela and Taylor)
NO OVERLAP

## BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Chris G, Dealwis

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

POSITION TITLE: Associate Professor of 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 Date MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| Kingston University, Kingston – upon – Thames | B.Sc. (Hons) | 1987 | Applied Science |
| University of London, London, England | Ph.D. | 1993 | Protein Crystallography |

### A. Personal Statement

My training and experience in crystallography and biophysical techniques has prepared me to conduct the research outlined. I have been investigating how ribonucleotide reductase (RR) is regulated for nineteen years. RR is a multi-subunit enzyme that is exquisitely controlled by allosteric regulation. Our lab determined the first eukaryotic RR1 structure and explained the molecular basis of substrate selection. We were able to determine the human RR1 structure to high resolution. Now we are focusing on determining how the allosteric activator ATP and the allosteric inhibitor dATP regulate RR by oligomerization. This is a new and exciting frontier that is changing the way we used to think about how RR maintains balanced dNTP pools in the cell. The old model of a RR hetero-tetramer that could not explain how ATP and dATP regulate RR activity has been challenged by the new paradigm that involves RR oligomerization in response to cellular ATP and dATP concentrations. My lab was the first to visualize a RR hexamer using x-ray crystallography and then the dATP – Å6 β2 hollow complex using medium resolution cryo- electron microscopy. Recently, we have discovered the first competitive none nucleoside small molecules binding at the catalytic site and noncompetitive small molecules binding at cryptic allosteric sites which are useful molecular probes for studying allosteric regulation.

In the last five years the Dealwis, Taylor and Harris labs have joined forces to study the complex allosteric mechanisms regulated by oligomerization in RR. In the next stage of the project we will dwell deep into the allosteric regulation of this molecule by incorporating the study of EM to study oligomers structures, dynamics associated with all oligomerization incorporating MD simulations, site directed mutagenesis and multiple biophysical techniques. We have brought together a team of experts in molecular dynamics, ultracentrifugation, light scattering, electron microscopy, enzymology and structural biology to fulfill the goals outlined in this proposal.

1. F.M.Ahmed,Alam,I.,Huff,S.,Pink.J.,Flanagan.S.,Shewach.D.,Misko.T.A.,Oleinick>N.,Hatre.W.,Viswan athan.R.,Harris.M.,Dealwis.C.G.,, Potent competitive inhibition of human ribonucleotide reductase by a

non-nucleoside small molecule. PNAS (2017),114(31):8241-8246. Doi: 10.1073/pnas.1620220114. PMID 28716944

2. Fairman JW, Wijerathna SR, Ahmad MF, Xu H, Nakano R, Jha S, Prendergast J, Welin RM, Flodin S, Roos A, Nordlund P, Li Z, Walz T, **Dealwis CG.**
   Structural basis for allosteric regulation of human ribonucleotide reductase by nucleotide-induced oligomerization. ***Nat. Struct. Mol. Biol***. **2011** 18(3): 316-22. PMID: 21336276; PMCID: PMC3101628
3. Xu H, Faber C, Uchiki T, Fairman JW, Racca J, **Dealwis C**. Structures of eukaryotic ribonucleotide reductase I provide insights into dNTP regulation. ***Proc Natl Acad Sci U S A***. **2006** 14; 103(11):4022-7. PMID:16537479; PMCID: PMC1389704
4. Huff, S.E, Mohammed, F.A, Yang M, Pink J, Harris M.E, Dealwis CG**, Viswanathan R**. Structure-Guided Synthesis and Mechanistic Studies Reveal Sweetspots on Naphthyl Salicyl Hydrazone Scaffold as Non-Nucleosidic Competitive Inhibitors of Human Ribonucleotide Reductase.*Joint corresponding authors **J.Med.Chem 2017**. PMID: 29253340 DOI: 10.1021/acs.jmedcem.7b00530
5. Misko[a],T.A., Liu[b],Y., Harris[c],M.E., Oleinick[d],N.L., Pink[e],J., Lee[bf],H.Y., Dealwis[ag]*. C.G .Structure-guided design of anti-cancer ribonucleotide reductase inhibitors. **J Enzyme Inhib Med Chem**. 2019; 34(1):438-450. doi: 10.1080/14756366.2018.1545226.

## B. Positions and Honors

**Positions and Employment**

1993-1994 Research Associate, Department of Biochemistry and Molecular Biology, University of Chicago, IL
1994-1996 Research Scientist, Structural Biology, Abbott Laboratory, Abbott Park, IL
1996-1998 Research Fellow, Department of Pharmacology, Yale School of Medicine, New Haven, CT
1999-2005 Assistant Professor, Biochemistry & Cellular Molecular Biology, University of Tennessee, Knoxville, TN
2005-2007 Associate Professor, Biochemistry & Cellular Molecular Biology, University of Tennessee, Knoxville, TN
2007-till date Associate Professor, Pharmacology and Proteomics, Case Western Reserve University, Cleveland, Ohio

**Other Experience and Memberships**

2001 - Committee Biological Applications of Neutron Diffraction
2008- Case Comprehensive Cancer Centre; Developmental Therapeutics Program
2008 – Member of the Cleveland Center for Membrane & Structural Biology (CCMSB)

**Honors**

1985 Undergraduate Fellowship from the Science & Engineering Research Council (SERC), UK
1989 Postgraduate Scholarship from SERC, UK
1990 CASE Award from the Agriculture Research Council, UK
2000 Ralph. E. Powe Career Development Award

## C. Contributions to Science

**Graduate work.**

My graduate studies involved structure functions and drug discovery of the antihypertensive target renin of the renin-angiotensin cascade. Renin is a member of the aspartic acid protease and it's only known substrate is angiotensinogen. Inhibiting renin lowers hypertension with few side effects. Using x-ray crystallography, I was able to determine the high-resolution structure of mouse renin in complex with the angiotensin peptide. The structure provided molecular details of how this enzyme achieved its exquisite specificity and clues to inhibiting its activity using the rational drug design cycle. I also determined structures with non-hydrolysable surrogates such as hydroxy ethylene, glycol and phosphinates. This work was continued on by pharmaceutical companies eventually leading to the clinical approval of the drug Aliskiren that targets renin against hypertension.

1. Dhanaraj V[1], **Dealwis CG[1]**, Frazao C, Badasso M, Sibanda BL, Tickle IJ, Cooper JB, Driessen HP, Newman M, Aguilar C, et al. X-ray analyses of peptide-inhibitor complexes define the structural basis of specificity for

human and mouse renins. ***Nature***. **1992** Jun 11;357(6378):466-72. PMID: 1608447 ₁V.D. and **C.G.D.** are joint first authors

2. Dhanaraj, V., **Dealwis, C. G.,** Frazao, C., Badasso, M., Sibanda, B. L., Tickle, I. J., Cooper, J. B., Driessen, H. P. C., Newman, M., Aguilar, C., Wood, S. P., Blundell, T. L., Hobart, P., Geoghegan, K. F., Ammirati, M. J., Danley, D. E., O'Connor, B. A. and Hoover, D. J. **(1992)** ***Royal Society of Chemistry*****, Molecular recognition, No. 111.** Molecular Recognition and Drug Design: The Structural Basis of Specificity of Human and Mouse Renin Defined by X-ray Analysis of Peptide Inhibitor Complexes.

3. **Dealwis, C. G.,** Frazao, C., Badasso, M., Cooper, J. B., Tickle, I. J., Driessen, H. P., Blundell, T. L. and Murakami, K. **(1993)** ***J. Mol. Biol.*** **236**, 342-360 The investigation of the three-dimensional structure of mouse submaxillary renin complexed with an inhibitor, CH66, based on the 4-16 fragment of rat angiotensinogen.

4. Lunney, E. A., Hamilton, H. W., Hodges, J. C., Kaltenbronn, J. S., Repine, J. T., Badasso, M., Cooper, J. B., **Dealwis, C. G.,** Wallace, B. A., Todd Lowther, W., Dunn, B. and Humblet, C. **(1993)** ***J. Med. Chem.*** **36**, 3809-3820. The analysis of ligand binding in five endothiapepsin crystal complexes and their use in the design and evaluation of novel renin inhibitors.

**The anticancer target ribonucleotide reductase.**

Ribonucleotide reductase is the rate limiting enzyme in *de novo* dNTP synthesis. It is a multi-subunit enzyme consisting of a large subunit called RR1, containing the catalytic side and two allosteric sites, and a small subunit called RR2 that houses a free radical essential for catalysis. In rapidly proliferating cells such as in cancer, RR is an established drug target. I have studied both the yeast ribonucleotide reductase and the human ribonucleotide reductase which belong to class I RR enzymes. In yeast I have focused on a small protein inhibitor called Sml1 that inhibits the large subunit RR1 and is heavily regulated by the RAD signaling cascade Mec1-Rad53. We were able to map out the phosphorylation sites of Sml1 by Dun1 kinase within the Mec1-Rad53 cascade. We have also determined that Sml1 inhibits RNR1 via uncompetitive mode of inhibition. Sml1 was also shown to be a two domain protein that is loosely folded, where the N-terminal domain is required for dimerization while the C-terminal domain contains the phosphorylation sites and a region required for binding to RR1. In 2006 we solved the first eukaryotic RR1 structure from yeast and provided the molecular details for substrate recognition. Ribonucleotide reductase catalyzes four substrates (CDP, UDP, GDP and ADP) to their deoxy diphosphate forms. The selection occurs when nucleotide effectors bind at the allosteric site called the specificity site and selects for substrates at the catalytic site through the phenomena known as specificity crosstalk. Our structures revealed how specificity is achieved by exquisite conformational changes adopted by a single loop called loop 2 that act as molecular signatures for each cognate effector substrate pair. In 2011 we reported the first human RR1 structure at high resolution. The structure provided details of how the allosteric activator ATP binds at the activity site as well as how the allosteric inhibitor dATP binds at the same site. Comparison of the structures enabled us to propose how the ATP achieves 100 fold higher affinity for binding at the activity site which is essential for maintaining a balanced nucleotide pool in the cell. We were the first to determine the hexameric structure of RR1 induced by dATP, providing clues to how the enzyme is regulated by change of oligomeric states. Based on the structure, the hexamer was shown to consist of a trimer of dimers where the oligomerization domain consisted of the first 16 N-terminal residues which are part of the dATP binding domain. Currently our major focus in the lab is to discover novel non-nucleoside drugs that inhibit ribonucleotide reductase to use as a therapeutic agent against cancer. The rationale is to use non-nucleoside drugs that are more specific against the enzyme and hence have less toxic side effects compared to clinically use drugs such as gemcitabine and clofarabine, which are nucleoside analogues. We have discovered a set of novel RR modulators binding at a newly discovered modulation site called the m-site (the pending patent number is **(PCT/US2013/033271)**

1. Xu H, Faber C, Uchiki T, Fairman JW, Racca J, **Dealwis C**. Structures of eukaryotic ribonucleotide reductase I provide insights into dNTP regulation. ***Proc Natl Acad Sci U S A***. **2006** Mar 14;103(11):4022-7. PMID:16537479; PMCID: PMC1389704Xu H, Faber C, Uchiki T, Racca J, **Dealwis C**.

Structures of eukaryotic ribonucleotide reductase I define gemcitabine diphosphate binding and subunit assembly. ***Proc. Natl. Acad. Sci. U S A***. **2006** Mar 14;103(11):4028-33. PMID: 16537480; PMCID: PMC1389703.

2. Ahmad MF, Wan Q, Jha S, Motea E, Berdis A, **Dealwis C**. Evaluating the therapeutic potential of a non-natural nucleotide that inhibits human ribonucleotide reductase. ***Mol Cancer Ther.*** 2012 Oct;11(10):2077-86. PMID: 22933704; PMCID: PMC3569060

3. Fairman JW, Wijerathna SR, Ahmad MF, Xu H, Nakano R, Jha S, Prendergast J, Welin RM, Flodin S, Roos A, Nordlund P, Li Z, Walz T, **Dealwis CG**.

Structural basis for allosteric regulation of human ribonucleotide reductase by nucleotide-induced oligomerization. ***Nat. Struct. Mol. Biol***. **2011** Mar;18(3):316-22. PMID: 21336276; PMCID: PMC3101628.

**Neutron diffraction studies.**

Neutrons have the ability to visualize hydrogen atoms that are involved in catalysis, signaling, and solvent-mediated interactions. We were involved in the early stages of using spallation neutron sources for the structure determination of proteins. We have used neutrons to study how enzymes function by specifically focusing on dihydrofolate reductase (DHFR). Initially, the structure of DHFR with the drug methotrexate was determined and the ionization state of the drug and the catalytic aspartic acid residue in the active site was determined. The structure enabled us to do global comparisons of how hydrogen-deuterium exchange occurs with respect to several biophysical parameters, where the atomic depth was shown to have the greatest influence. Recently, we determined the structure of the Michaelis complex of the enzyme that enabled us to visualize the key water molecule involved in hydride transfer and the identification of the keto tautomer as the only tautomer in the pre-transition state.

1. Bennett BC, Meilleur F, Myles DA, Howell EE, **Dealwis CG**.

Preliminary neutron diffraction studies of Escherichia coli dihydrofolate reductase bound to the anticancer drug methotrexate. ***Acta Crystallogr D Biol Crystallogr***. **2005** May;61(Pt5):574-9. PMID: 15858267

2. Bennett B, Langan P, Coates L, Mustyakimov M, Schoenborn B, Howell EE, **Dealwis C**. Neutron diffraction studies of Escherichia coli dihydrofolate reductase complexed with methotrexate. ***Proc Natl Acad Sci U S A***. **2006** Dec5;103(49):18493-8. PMID: 17130456; PMCID: PMC1664550

3. Bennett BC, Gardberg AS, Blair MD, **Dealwis CG**.

On the determinants of amide backbone exchange in proteins: a neutron crystallographic comparative study. ***Acta Crystallogr D Biol Crystallogr***. **2008** Jul;D64 (Pt 7):764-83. PMID: 18566512.

4. Wan Q, Bennett BC, Wilson MA, Kovalevsky A, Langan P, Howell EE, **Dealwis C**.

Toward resolving the catalytic mechanism of dihydrofolate reductase using neutron and ultrahigh-resolution X-ray crystallography. ***Proc. Natl. Acad. Sci. USA (PNAS).*** **2014** Dec 23;111(51):18225-30. PMID: 25453083; PMCID: PMC4280638.

**Drug discovery on major diseases**

Using a multidisciplinary approach that are structure-based, modeling, biophysics and protein design I have contributed to the drug development against several diseases such as (HIV, hepatitis B, cancer and anthrax). Here the structural insights were used to develop diagnostic assays against HIV, validate drug targets, and develop small molecule drugs.

1 Chen YC, Delbrook K, **Dealwis C**, Mimms L, Mushahwar IK, Mandecki W. Discontinuous epitopes of hepatitis B surface antigen derived from a filamentous phage peptide library. ***Proc Natl Acad Sci U S A***. **1996** Mar 5;93(5):1997-2001. PMID: 8700874; PMCID: PMC39898.

2 **Dealwis, C.,** Fernandez, E. J., Thompson, D. A., Siani, M., and Lolis, E. **(1998)** ***PNAS*****, 95**,12,6941-6 Crystal Structure of Chemically Synthesized [N33A] SDF-1α a Potent Ligand for the HIV-1 "Fusin" Co-Receptor

3 Brad C. Bennett, Hai Xu, Richard F. Simmerman, Richard E. Lee and **Chris G. Dealwis**, (2007), ***J. Med Chem*** 50, 4374-81. Crystal structure of the anthrax drug target, Bacillus anthracis dihydrofolate reductase.

4 Zhang Y,[1†] Desai A, [1†] Yang S Y, [1†‡] Bae Ki Beom, [1†§] Monika I. Antczak,[2†] Stephen P. Fink,[1†] Shruti Tiwari,[1,10†]Joseph E. Willis,[3,4,10] Noelle S. Williams,[2] Dawn M. Dawson,[3,4] David Wald,[3,4,10] Wei-Dong Chen,[1++] Zhenghe Wang,[5,3] Lakshmi Kasturi,[1] Gretchen A. Larusch,[1] Lucy He,[1‡‡] Fabio Cominelli,[1,10] Luca Di Martino,[1] Zora Djuric, [11] Ginger L. Milne,[6] Mark Chance,[7] Juan Sanabria,[8,10] **Chris Dealwis**,[9] Debra Mikkola,[1] Jacinth Naidoo,[2] Shuguang Wei,[2] Hsin-Hsiung Tai,[12¶] Stanton L. Gerson,[1,3,10¶*] Joseph Ready,[2,13¶*] Bruce Posner,[2,13¶*] James K. V. Willson,[13¶*] Sanford D. Markowitz[1]**(2015)** ***Science*** **aaa2340-1**. Inhibition of the Prostaglandin Degrading Enzyme 15-PGDH Potentiates Tissue Regeneration.

My Biography Link:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Dealwis+

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

## Active

CTSC co-utilization grant PI Chris Dealwis. Developing second-generation pancreatic cancer drugs. $10,000 (2020 –).
PI Chris Dealwis in silico screen for FATP2 inhibitors sponsor Metro hospital, 2018-

**Completed**

PI Chris Dealwis RR modulation for the treatment of cancer CTSC case comprehensive Cancer Center dates December 2017–
PI Chris Dealwis development of RR modulators for the treatment of cancer funded by Taipei medical school – CWRU dates Feb 2016 – March 2017
Project Number: 1R01GM100887-01 (completed) (Principal Investigator): Chris Dealwis
Source: NIH RO1

Title of Project (*and/or Subproject*): Investigating the structural assembly of ribonucleotide reductase. Date: May 2012 to May 2017

Dealwis (PI) Development of RR modulators. Council to Advance Human Health

PI Chris Dealwis development of RR modulators for the treatment of cancer funded by Taipei medical school – CWRU December 2015 – December 2016

PI Chris Dealwis: RR modulation for the treatment of cancer CTSC Case Comprehensive Cancer Center dates November 2015 – November 2016 CAHH 2015-2016 / year

Project Number: R01CA100827-04A1 (Principal Investigator): Chris Dealwis Source: NIH RO1
Title of Project (*and/or Subproject*): Structure-function and inhibition of ribonucleotide reductase.
Overlap (summarized for each individual): None Dates of Approved/Proposed Project: 8-13-07 to 9-2012.

Title of Project (*and/or Subproject*): Structure-function and inhibition of ribonucleotide reductase. Dates of Approved/Proposed Project: 8-13-07 to 9-2012
Overlap (summarized for each individual): None
Principle Investigator Chris Dealwis
Source: NIH RO1 Supplement

Title of Project (*and/or Subproject*): Structure-function and inhibition of RNR Dates of Approved/Proposed Project: 8-1-09 to 7-21-2011
Overlap (*summarized for each individual*): None Project Number: DOE LDRD 20070131ER (Principal Investigator): Chris Dealwis Source: Source: DOE

## 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: Michael E. Harris

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

POSITION TITLE: 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 |
|---|---|---|---|
| Florida State University, FL | BS | 05/1986 | Chemistry |
| University of Alabama at Birmingham, AL | PhD | 06/1992 | Biochemistry |
| Indiana University, IN | Postdoc | 06/1996 | Chemistry |

### A. Personal Statement

With respect to our current NCCAT Block Allocation Group application, my relevant research accomplishments include the following: 1. My lab adapted powerful quantitative thiophilic metal ion rescue of site-specific phosphorothioate modifications to pinpoint active site divalent metal ions in the active site of the RNase P ribozyme and study the ligands and structures involved in stabilizing their binding. 2. Our research group developed in collaboration with Dr. Eckhard Jankowsky a generally applicable method for high throughput biochemical analyses of RNA processing and binding reactions, High Throughput Sequencing Kinetics and Equilibrium binding (HiTS-KIN/EQ). 3. Our lab pioneered the use of tandem mass spectrometry to measure isotope ratios in RNA with sufficient precision to measure kinetic isotope effects on RNA strand cleavage reactions. 4. In collaboration with Dr. Chris Dealwis our lab identified multiple novel inhibitors of the chemotherapeutic target ribonucleotide reductase and for the first time targeted the oligomerization interface for this protein. In addition, we identified long range allosteric communication between the two different allosteric regulation networks in human ribonucleotide reductase that provides additional inroads into inhibitor development. 5. In collaboration with Dr. Derek Taylor we determined the cooperative assembly mechanism for binding of POT1-TPP1 to telomere DNA and are now engaged in long term studies of RNase P structure and inhibition. Our work with RNase P enzymology and ribonucleotide reductase inhibition employ a range of methods to reveal mechanistic detail including NMR. Thus, the new instrumentation will have an important impact by increasing both the pace and scope of these two projects.

### B. Positions and Honors

**Positions and Employment**

1996 – 2003 Assistant Professor, Department of Molecular Biology and Microbiology, Case Western Reserve University School of Medicine
2003 – 2015 Associate Professor, Department of Biochemistry, Case Western Reserve University School of Medicine
2015 – 2016 Professor, Department of Biochemistry, Case Western Reserve University School of Medicine
2017 – Professor, Department of Chemistry, University of Florida

**Other Experience** (selected activities that are most relevant to the proposal)

| | |
|---|---|
| 2004 | NIH, Biochemistry Study Section, *ad hoc* panel member |
| 2004 – 2005 | NIH, NRSA ZGR-1 Genes and Genomes Study Section, panel member |
| 2004 – 2006 | NIH, Fogarty International Grant Program Study Section, panel member |
| 2006 – | NSF, Chemistry and Molecular and Cellular Biosciences Divisions, reviewer |
| 2009 – 2010 | NIH, Challenge Grants in Health and Science Research, reviewer |
| 2006 – 2011 | NIH, ICP-1 International and Collaborative Projects Study Section, panel member |
| 2005 – 2012 | Biotechnology and Biological Sciences Research Council, UK, reviewer |
| 2012 | NIH, MSFB Macromolec Structure and Function-B Study Section, panel member |
| 2013 | NSF, Chemistry of Life Processes, panel member |
| 2014 | NIH, ZRG1 BCMB-S Biochem and Macromolecular Biophysics, panel member |
| 2014 – 2020 | NIH, TWD-B, Training and Workforce Development Study Section, panel member |
| 2017 | ISF, Israel Science Foundation, reviewer |
| 2017 | NSF, Chemistry of Life Processes, panel member |

## C. Contribution to Science

1. **RNA catalysis**. To understand basic principles of RNA specificity and mechanism my lab engaged in a long term investigation of the essential tRNA processing enzyme ribonuclease P. We adapted thiophilic metal ion rescue experiments to identify metal ligands in the active site of RNase P RNA. Quantitative analysis of the thiophilic metal ion rescue allowed us to identify the number and interactions of active site divalent metal ions. In a series of structure-function studies employing this method we showed how the shape and orientation of conserved helices in the catalytic core of RNase P stabilize active site metal ion binding. We demonstrated that the essential protein subunit of RNase P contributes to catalysis by indirectly stabilizing active site metal ion binding. Importantly, we further showed that many ptRNAs that lack optimal consensus motifs for RNase P recognition rely on additional contacts with the protein subunit in order to assemble a functional active site. Thus, our results illustrate general mechanisms of active site metal binding in catalytic RNAs, and show how indirect effects of RNA structure contribute to RNase P catalysis relevant to processing of tRNAs *in vivo*.

a. Harris ME, Pace NR. (1995). Identification of phosphates involved in catalysis by the ribozyme RNase P RNA. **RNA.** 1(2):210-8. PMID: 7585250
b. Christian EL, Kaye NM and Harris ME. (2002). Evidence for a polynuclear metal ion binding site in the catalytic domain of ribonuclease P RNA. **EMBO J**. 21, 2253-2262. PMID: 11980722
c. Christian EL, Johnson K, Perrera N and Harris ME. (2006). Evidence for a role for the P4 metal binding site in enhancing catalytic metal ion affinity by substrate positioning. **RNA.** 12(8):1463-7. PMID: 16822954
d. Sun L and Harris ME. (2007). Binding of C5 protein to the P RNA ribozyme increases catalytic rate by influencing active site metal ion affinity. **RNA.** 34:1-11. PMID: 17652407

2. **Specificity in RNA Molecular Recognition**. In parallel with studies of RNase P catalysis we investigated how the enzyme accommodates variation in the structure of genomically encoded ptRNAs encountered *in vivo*. We discovered cleavage at non-consensus sites within genomically encoded tRNA precursors, and observed remarkably fast $k_{cat}/K_m$ for tRNAs that nonetheless deviate from optimal sequence motifs at their RNase P processing. To discover the basis for these effects we measured functional binding to all possible sequence variants in the RNase P protein binding site in the 5' leader of ptRNAs. Comparison of the results with genomically encoded tRNA leaders showed that most have affinities near the median of the distribution. The findings showed that apparently nonspecific and specific RNA-binding modes do not differ fundamentally, but represent distinct parts of common affinity distributions. Our analysis of RNase P specificity further revealed how discrimination arises due to favorable interactions that stabilize the transition state for association, and unfavorable substrate RNA structure in the ground state. Expanding our studies of RNA specificity we collaborated with Dr. Blanton Tolbert to globally analyze hnRNP A1 specificity, and identified consensus motifs and showed how structural effects exert a large influence on relative affinities for alternative RNA targets.

a. Yandek LE, Lin H-C and Harris ME. (2013). Alternative substrate kinetics of Escherichia coli ribonuclease P: Determination of relative rate constants by internal competition. **J. Biol. Chem**. 288(12):8342-54. PMID: 23362254

b. Guenther U-P, Yandek LY, Niland CN, Campbell FE, Anderson D, Anderson VE, Harris ME and Jankowsky E. (2013). Hidden specificity in an apparently non-specific RNA-binding protein. **Nature** 502(7471):385-8. PMCID: PMC3800043
c. Jankowsky E and Harris ME. (2015). Specificity and non-specificity in RNA-protein interactions. **Nat Rev Molec Cell Biol.** 16(9):533-44. PMCID: PMC4744649
d. Lin H-C, Zhao J, Niland CN, Tran B, Jankowsky E and Harris ME. (2016). Comprehensive analysis of the C5 protein specificity landscape reveals RNA structure and sequence preferences that direct ribonuclease P substrate specificity. **Cell Chem Biol**. 23(10):1271-1281. PMID: 27693057

3. **Transition state analyses of phosphoryl transfer.** Experimentally determining the structure of reaction transition states and identifying the interactions that stabilize them is enormously challenging. We tackled this problem by developing tandem mass spectrometry methods to measure precise isotope ratios in RNA. We teamed with Dr. Darrin York to use our mass spectrometry approaches to measuring kinetic isotope effects and use this data to guide and benchmark computational simulations in order to model transition states. We determined a late, highly charged transition state for base catalysis and the neutral stepwise mechanism for acid catalysis of RNA strand cleavage by 2'-*O*-transphosphorylation. We used KIE measurements to analyze the effects of metal ion catalysts on RNA strand cleavage transition states, and documented profound changes due to catalytic interactions with the reactive phosphoryl. Comparison of the primary and secondary $^{18}O$ KIEs for RNase A to values we observed for solution reactions revealed a late anionic transition state and showed that that expulsion of the 5′O remains an integral feature of the rate-limiting step both on and off the enzyme. Our ability to obtain chemically detailed descriptions of RNA transition states gives us the opportunity to determine how the catalytic modes and active site environments of RNases and ribozymes influence transition state structure.

a. Harris ME, Dai Q, Gu H, Kellerman DE, Piccirilli JA and Anderson VE (2010). Kinetic isotope effects for RNA cleavage by 2'-*O*-transphosphorylation: Nucleophilic activation by specific base. **J. Am. Chem. Soc.** 132(33):11613-21. PMID: 20669950
b. Wong K-U, Gu H, Zhang S, Piccirilli JA, Harris ME and York D (2012). Characterization of the reaction path and transition states for RNA transphosphorylation from theory and experiment. **Angew. Chem. Intl. Ed.** 51(3):823. PMID: 22076983
c. Gu H, Zhang S, Wong K-Y, Radak BK, Dissanayake T, Kellerman D, Dai Q, Miyagi M, Anderson VE, York DM, Piccirilli JA and Harris ME. (2013). Experimental and computational analysis of the transition state for ribonuclease A catalyzed RNA 2'-*O*-transphosphorylaiton. **Proc Natl Acad Sci USA**. 110(32):13002-13007. PMCID: PMC3740856
d. Chen H, Giese TJ, Huang M, Wong K-Y, Harris ME and York DM. (2014). Mechanistic insights into RNA transphosphorylation from kinetic isotope effects and linear free energy relationships of model reactions. **Chem Eur J.** 20(44):14336-43 PMID: 25812974

4. **Allosteric regulation and inhibition of human ribonucleotide reductase.** Ribonucleotide reductase generated deoxynucleotides for DNA synthesis and regulates nucleotide pools. RR is a widespread and conserved enzyme that is a key experimental system for exploration of protein allostery, and an important chemotherapeutic target. Development of small molecule allosteric regulators and inhibitors of human RR is an important goal. In collaboration with the laboratory of Dr. Chris Dealwis we developed a protocol for identifying inhibitors of RR that combines in silico docking, biochemical assays of binding and activity, and cell toxicity studies. We successfully identified multiple compounds that target the different nucleotide binding sites and oligomerization interface on RR. In parallel, we have pursued studies to understand the structure and molecular dynamics that underlie allosteric communication. We identified the key functional groups on nucleotide effectors that drive communication of chemical information essential for allosteric regulation of substrate specificity as well as uncovering long range communication between the two different allosteric binding sites on RR. These results identified important structural and biochemical features of RR allosteric regulation and have identified multiple useful scaffolds for optimization using medicinal chemistry.

a. Ahmad M, Huff S, Pink J, Alam I, Zhang A, Perry K, Harris ME, Misko T, Porwal SK, Oleinick NL, Viswanathan R, Miyagi M, Dealwis CG. (2015). Identification of non-nucleoside human ribonucleotide reductase inhibitors. **J Med Chem**. 58(24):9498-509. PMID: 26488902

b. Knappenberger AJ, Ahmad FM, Dealwis CG and Harris ME. (2016). Nucleotide effector analogs allosterically regulate human ribonucleotide reductase and identify chemical determinants of substrate specificity. **Biochemistry**. 55(41):5884–5896. PMID: 27634056
c. Ahmad MF, Alam I, Huff SE, Pink J, Flanagan SA, Shewach D, Misko TA, Oleinick NL, Harte WE, Viswanathan R, Harris ME, and Dealwis CG. (2017). Potent competitive inhibition of human ribonucleotide reductase by a non-nucleoside small molecule. **Proc Natl Acad Sci** 114(31):8241-8246. PMID: 28716944
d. Knappenberger AJ, Grandhi S, Sheth R, Ahmad MD, Viswanathan R, and Harris ME (2017). Phylogenetic sequence analysis and functional studies reveal compensatory amino acid substitutions in loop 2 of human ribonucleotide reductase. **J Biol Chem**. 292(40):16463-16476. PMID: 28808063

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**Research Support**

ACTIVE

R35 GM127100 (PI Harris) 03/01/2018 – 2/28/2023 2.5 calendar
NIH/NIGMS
**Specificity in Substrate Recognition and Catalysis by RNA Processing Enzymes**
This research aims to understand at a chemical level the two defining features of biological catalysis: exquisite substrate specificity and enormous rate enhancement. The experiments center on enzymes essential for biosynthesis and regulation of RNA. The results provide basic information for designing novel catalysts and enzyme inhibitors as potential therapeutics to treat human diseases.