Matthew D. Simon

Contact Information

Molecular Biophysics & Biochemistry
Institute of Biomolecular Design & Discovery
Yale University

West Campus Office: 1-203-737-3274
E-mail: matthew.simon@yale.edu
http://simonlab.yale.edu

Education

The University of California, Berkeley, CA — September 1999 - August 2006
Ph.D., Chemistry, Adviser: Professor Kevan M. Shokat

Tufts University, Medford, MA — September 1995 - May 1999
B.A., Biochemistry, Minor: Mathematics, *Summa Cum Laude*

Positions

Associate Professor with Tenure, Yale University — July 2021 - present
Department of Molecular Biophysics & Biochemistry
Member, Institute of Biomolecular Design and Discovery

Associate Professor, Yale University — July 2017 - July 2021
Department of Molecular Biophysics & Biochemistry
Member, Chemical Biology Institute

Assistant Professor, Yale University — January 2013 - July 2017
Department of Molecular Biophysics & Biochemistry
Member, Chemical Biology Institute

Research Scientist, Yale University — August 2012 - December 2012
Department of Molecular Biophysics & Biochemistry
Member, Chemical Biology Institute

Postdoctoral Fellow, Massachusetts General Hospital — September 2006 - July 2012
Department of Molecular Biology, MGH;
Department of Genetics, Harvard Medical School
Adviser: Professor Robert E. Kingston

Personal Statement

My lab studies chromatin and RNA biology. We specialize in the identification of important biological questions that are not adequately addressed by existing methods, and use the principles of organic chemistry and biochemistry to develop new technologies to address these needs.

Chromatin. As a graduate student in Kevan Shokat's lab, I developed methyl-lysine analogue histones to study direct biochemical consequences of histone lysine methylation. As a postdoctoral fellow with Bob Kingston, I developed Capture Hybridization Analysis of RNA Targets (CHART) to track the genomic localization of non-coding RNAs that regulate chromatin. My lab at Yale recently discovered acetyl-methyllysine (Kacme), a new post-translational modification that marks histone H4 at active transcription start sites. Our longer term goal is to understand the biological regulation imparted by modifications including Kacme in healthy and diseased contexts.

RNA. We are broadly interested in RNA biology. We developed technologies to understand functional RNAs including Xist that impact gene expression. We have developed nucleoside chemistry to track distinct populations of RNA to reveal principles of the kinetics of reguated gene expression. This work has led to new efficient chemistry to isolate RNAs that have been metabolically labeled with 4-thiouridine (s^4U) based on methane thiosulfonate (MTS) chemistry. In a complementary approach, we developed chemistry that is capable of re-coding the hydrogen bonding pattern of s^4U and s^6G nucleotides in metabolically labeled RNA, converting them into cytosine and adenosine analogues. This approach allows the identification of newly transcribed RNA directly in a sequencing experiment without the need for biochemical enrichment (TimeLapse). Further, we have been able to use the chemistry we developed to study nascent transcription (TT-TimeLapse-seq) and the kinetics of a highly regulated step in early transcription, promoter-proximal pausing using Start-TimeLapse-seq (STL-seq). Our longer term goal is to develop a unified platform to study the rates of the different regulated steps of RNA metabolism and to use this platform to identify which steps are altered by physiological stimulation and by disease.

Publications

Lu-Culligan, W.J., Connor, L.J., Xie, Y., Ekundayo, B.E., Rose, B.T., Machyna, M., Pintado-Urbanc, A.P., Zimmer, J.T., Vock, I.W., Bhanu, N.V., King, M.C., Garcia, B.A., Bleichert, F., Simon, M.D. Acetyl-methyllysine marks chromatin at active transcription start sites. *Nature.* **2023** 622(7981):173-179. PMID: 37731000.

Gao, Y., Zimmer, J.T., Vasic, R., Liu, C., Gbyli, R., Zheng, S.J., Patel, A., Liu, W., Qi, Z., Li, Y., Nelakanti, R., Song, Y., Biancon, G., Xiao, A.Z., Slavoff, S., Kibbey, R.G., Flavell, R.A., Simon, M.D., Tebaldi, T., Li, H.B., Halene, S. ALKBH5 modulates hematopoietic stem and progenitor cell energy metabolism through m6A modification-mediated RNA stability control. *Cell Rep.* **2023** 42(10):113163. PMID: 37742191.

Abini-Agbomson, S., Gretarsson, K., Shih, R.M., Hsieh, L., Lou, T., De Ioannes, P., Vasilyev, N., Lee, R., Wang, M., Simon, M.D., Armache, J.P., Nudler, E., Narlikar, G., Liu, S., Lu, C., Armache, K.J. Catalytic and non-catalytic mechanisms of histone H4 lysine 20 methyltransferase SUV420H1. *Mol Cell.* **2023** 83(16):2872-2883, PMID: 37595555.

Patel, S., Sexton, A.N., Strine, M.S., Wilen, C.B., Simon, M.D., Pyle, A.M. Systematic detection of tertiary structural modules in large RNAs and RNP interfaces by Tb-seq. *Nat Commun.* **2023** 14(1):3426. PMID: 37296103.

Zimmer J.T., Vock, I.W., Schofield, J.A., Kiefer, L., Moon, M.H., Simon, M.D. Improving the study of RNA dynamics through advances in RNA-seq with metabolic labeling and nucleotide-recoding chemistry. *bioRxiv* [Preprint]. **2023** PMID: 37292657

Vock, I.W. and Simon, M.D. STL-seq reveals pause-release and termination kinetics for promoter-proximal paused RNA polymerase II transcripts. *RNA*, **2023** 29(7):958-976. PMID: 37028916.

Courvan, M.C.S., Niederer, R.O., Vock, I.W., Kiefer, L., Gilbert, W.V., Simon, M.D. Internally controlled RNA sequencing comparisons using nucleoside recoding chemistry. *Nucleic Acids Res.*, **2022** 50(19):e110 PMID: 36018791

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Swartzel, J.C., Bond, M.J., Pintado-Urbanc, A.P., Daftary, M., Krone, M.W., Douglas, T., Carder, E.J., Zimmer, J.T., Maeda, T., Simon, M.D., Crews, C.M. Targeted Degradation of mRNA Decapping Enzyme DcpS by a VHL-Recruiting PROTAC. *ACS Chem Biol.* **2022** 17(7):1789-1798. PMID: 35749470

Biancon, G., Joshi, P., Zimmer, J.T., Hunck, T., Gao, Y., Lessard, M.D., Courchaine, E., Barentine, A.E.S., Machyna, M., Botti, V., Qin, A., Gbyli, R., Patel, A., Song, Y., Kiefer, L., Viero, G., Neuenkirchen, N., Lin, H., Bewersdorf, J., Simon, M.D., Neugebauer, K.M., Tebaldi, T., Halene, S. Precision analysis of mutant U2AF1 activity reveals deployment of stress granules in myeloid malignancies. *Mol Cell* **2022** 82(6):1107-1122.e7. PMID: 35303483

Zimmer, J.T., Rosa-Mercado, N.A., Canzio, D., Steitz, J.A. and Simon, M.D. STL-seq reveals pause-release and termination kinetics for promoter-proximal paused RNA polymerase II transcripts. *Mol Cell*, **2021** 81(21):4398-4412.e7. PMID: 34520723

Wei, J., Alfajaro, M.M., DeWeirdt, P.C., Hanna, R.E., Lu-Culligan, W.J., Cai. W.L., Strine, M.S., Zhang, S.M., Graziano, V.R., Schmitz, C.O., Chen, J.S., Mankowski, M.C., Filler, R.B., Ravindra, N.G., Gasque, V., de Miguel, F., Patil, A., Chen, H., Oguntuyo, K., Oguntuyo, K.Y., Abriola, L., Surovtseva, Y.V., Orchard, R.C., Lee, B., Lindenbach, B., Politi, K., van Dijk, D., Kadoch, C., Simon, M.D., Yan, Q., Doench, J.G., Wilen, C.B. Genome-wide CRISPR screen of multiple pathogenic coronaviruses reveal host factors critical for SARS-CoV-2 infection. *Cell* **2021** 184(1) PMID: 33147444

Rosa-Mercado, N.A., Zimmer, J.T., Apostolidi, M., Rinehart, J., Simon, M.D., Steitz, J.A. Hyperosmotic stress alters the RNA polymerase II interactome and induces readthrough transcription despite widespread transcriptional repression *Mol Cell*, **2021**, 21(3), sPMID: 33400923

Luo, Y., Schofield, J.A., Na, Z., Hann, T., Simon, M.D., Slavoff, S.A. Discovery of cellular substrates of human RNA-decapping enzyme DCP2 using a stapled bicyclic peptide inhibitor. *Cell Chem Bio*, **2020** S2451-9456(20). PMID: 33357462

Na, Z., Luo, Y., Schofield, J.A., Smelyansky, S., Khitun, A., Muthukumar, S., Valkov, E., Simon, M.D., Slavoff, S.A. The NBDY Microprotein Regulates Cellular RNA Decapping. *Biochemistry*, **2020** 59(42), 4131-4142, PMID: 33059440

Luo, Y., Schofield, J.A., Simon, M.D., Slavoff, S.A. Global Profiling of Cellular Substrates of Human Dcp2. *Biochemistry*, **2020** doi: 10.1021/acs.biochem.0c00069. PMID: 32365300

Machyna, M., Kiefer, L., Simon, M. D.# Enhanced nucleotide chemistry and toehold nanotechnology reveals lncRNA spreading on chromatin. *Nat Struct Mol Bio*, **2020**, *27(3)*, PMID: 32157249 #corresponding author

Olivero, C.E., Martínez-Terroba, E., Zimmer, J., Liao, C., Tesfaye, E., Hooshdaran, N., Schofield, J.A., Bendor, J., Fang, D., Simon, M.D., Zamudio, J.R., Dimitrova, N. p53 activates the long noncoding RNA Pvt1b to inhibit Myc and suppress tumorigenesis. *Mol Cell*, **2020**. PMID: 31973890

Smith, T.S., Zoltek, M.A., Simon, M.D.# Reengineering a tRNA methyltransferase to covalently capture new RNA substrates. *J Am Chem Soc.* **2019**, *141(44)*, 17460-17465. PMID: 31626536 #corresponding author

Canzio, D., Nwakeze, C. L., Horta, A., Rajkumar, S. M., Coffey, E. L., Duffy, E. E., Duffié, R., Monahan, K., O'Keeffe, S., Simon, M. D., Lomvardas, S., and Maniatis, T. Antisense lncRNA transcription mediates DNA demethylation to drive stochastic protocadherin α promoter choice. *Cell*, **2019**, *177(3)*, 639-653. PMID: 30955885

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Wang, P. Y., Sexton, A. N., Culligan, W. J., and Simon, M. D.# Carbodiimide reagents for the chemical probing of RNA structure in cells. *RNA*, **2019**, *25(1)*, 135-146. PMID: 30389828 #corresponding author

Duffy, E. E., Schofield, J. A., and Simon, M. D.# Gaining insight into transcriptome-wide RNA population dynamics through the chemistry of 4-thiouridine. *Wiley Interdiscip Rev RNA*, **2019**, e1513. PMID: 30370679 #corresponding author

Kiefer, L., Schofield, J. A., and Simon, M. D.# Expanding the Nucleoside Recoding Toolkit: Revealing RNA population dynamics with 6-Thioguanosine. *J Am Chem Soc*, **2018**, *140(44)*, 14567-14570. PMID: 30353734 #corresponding author

Duffy, E.E., Canzio, D., Maniatis, T., and Simon, M.D.# Solid phase chemistry to covalently and reversibly capture thiolated RNA. *Nucleic Acids Research*, **2018**, *46(14)*, 6996-7005. PMID: 29986098 #corresponding author

Schofield, J.A., Duffy, E.E., Kiefer, L., Sullivan, M.C., and Simon, M.D.# TimeLapse-seq: adding a temporal dimension to RNA sequencing through nucleoside recoding. *Nature Methods*, **2018**, *15(3)*, 221-225. PMID: 29355846 #corresponding author

Machyna, M. and Simon, M.D.# Catching RNAs on chromatin using hybridization capture methods. *Brief Funct Genomics*, **2017**, *17(2)*, 96-103. PMID: 29126220. #corresponding author

Sexton, A.N., Wang, P.Y., Rutenberg-Schoenberg, M., and Simon, M.D.# Interpreting reverse transcriptase termination and mutation events for greater insight into the chemical probing of RNA. *Biochemistry*, **2017**, *56(35)*, 4713-4721. PMID: 28820243. #corresponding author ^{U} undergraduate author

Li, H., Tong, Y., Zhu, S., Batista, P.J., Duffy, E.E., Zhao, J., Bailis, W., Cao, G., Kroehling, L., Chen, Y., Wang, G., Chen, Y.G., Broughton, J.P., Kluger, Y., Simon, M.D., Chang, H.Y., Yin, Z. and Flavell, R. m6A mRNA methylation controls T cell homeostasis by targeting IL-7/STAT/SOCS pathway. *Nature*, **2017**, *548(7667)*, 338-342. PMID: 28792938.

Duffy, E.E., and Simon M.D.# Enriching s^4U-RNA using methane thiosulfonate (MTS) chemistry. *Curr Protoc Chem Bio*, **2016**, *8(4)*, 234-250. PMID: 27925666. #corresponding author

Rutenberg-Schoenberg, M., Sexton, A.N., Simon, M.D.# The properties of long noncoding RNAs that regulate chromatin. *Annu Rev Genom Hum Genet*, **2016**, *17*, 69-94. PMID: 27147088 #corresponding author

Simon, M.D.# Insight into lncRNA biology using hybridization capture analyses. *Biochim Biophys Acta* **2015**, S1874-9399(15)00190-X. PMID: 26381323. #corresponding author

Sexton, A., Machyna, M., and Simon, M.D.# Capture hybridization analysis of RNA targets (CHART-seq). *Methods Molecular Biology*, **2016**, *1480*, 87-97. PMID: 27659977 #corresponding author

Fang, R.⋆, Moss, W.N.⋆, Rutenberg-Schoenberg, M. and Simon, M.D.# Probing Xist RNA structure in cells using Targeted Structure-Seq. *PLoS Genetics*, **2015**, *11(12)*:e1005668. PMID: 26646615 ⋆equal contributions, #corresponding author

Duffy, E.E., Rutenberg-Schoenberg, M., Stark, C.D., Kitchen, R.R., Gerstein, M.B., and Simon M.D.# Tracking distinct RNA populations using efficient and reversible covalent chemistry. *Mol Cell*, **2015**, *59(5)*, 858-66. PMID: 26340425. #corresponding author

Simon, M.D.#,⋆, Pinter, S.F.⋆, Fang, R.⋆, Sarma, K., Rutenberg Schoenberg, M., Bowman, S.K., Kesner, B.A., Kingston R.E.#, and Lee, J.T.# High-resolution chromosomal maps of Xist RNA reveal a two-step spreading mechanism during X-inactivation. *Nature*, **2013** *504*, 465-469. PMID: 24162848. ⋆equal contributions, #corresponding authors.

Simon, M.D.#, and Shokat, K.M. A method to site-specifically incorporate methyl-lysine analogues into recombinant proteins, *Methods Enzymol*, **2013**, *512*, 57-69. PMID:22910202. #corresponding author

Simon, M.D.# Capture hybridization analysis of RNA targets (CHART), *Curr Protoc Mol Biol* **2013**, Chapter 21, Unit 21 21.25. PMID:23288463. #corresponding author

West, J.A., Davis, C.P., Sunwoo, H., Simon, M.D., Sadreyev, R.I., Wang, P.I., Tolstorukov, M.Y., and Kingston, R.E. The long noncoding RNAs NEAT1 and MALAT1 bind active chromatin sites. *Mol Cell*, **2014**, *55(5)*, 791-802. PMID: 25155612.

Alpatov, R., Lesch, B.J., Nakamoto-Kinoshita, M., Blanco, A., Chen, S., StÃ¼tzer, A., Armache, K.J., Simon, M.D., Xu, C., Ali, M., Murn, J., Prisic, S., Kutateladze, T.G., Vakoc, C.R., Min, J., Kingston, R.E., Fischle, W., Warren, S.T., Page, D.C., and Shi, Y. A chromatin-dependent role of the fragile X mental retardation protein FMRP in the DNA damage response. *Cell*, **2014**, *157*, 869-81. PMID: 24813610.

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Canzio, D., Chang, E.Y., Shankar, S., Kuchenbecker, K.M., Simon, M.D., Madhani, H.D., Narlikar, G.J., and Al-Sady, B. Chromodomain-mediated oligomerization of HP1 suggests a nucleosome-bridging mechanism for heterochromatin assembly. *Mol Cell*, **2011**, *41*, 67-81. PMID:21211724.

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Simon, M.D.# Installation of site-specific methylation into histones using methyl lysine analogs. *Curr Protoc Mol Biol*, **2010**, Unit 21.18.21-10. PMID:20373501. #corresponding author

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Li, B., Jackson, J., Simon, M.D., Fleharty, B., Gogol, M., Seidel, C., Workman, J.L., and Shilatifard, A. Histone H3 Lysine 36 Dimethylation (H3K36me2) is sufficient to recruit the Rpd3s histone deacetylase complex and to repress spurious transcription. *J Bio Chem*, **2009**, *284*, 7970-7976. PMID:19155214.

Hung, T., Binda, O., Champagne, K.S., Kuo, A.J., Johnson, K., Chang, H.Y., Simon, M.D., Kutateladze, T.G., and Gozani, O. ING4 mediates crosstalk between histone H3 K4 trimethylation and H3 acetylation to attenuate cellular transformation. *Mol Cell*, **2009**, *33*, 248-256. PMID:19187765.

Francis, N.J., Follmer, N.E., Simon, M.D., Aghia, G., and Butler, J.D. Polycomb proteins remain bound to chromatin and DNA during DNA replication in vitro. *Cell*, **2009**, *137*, 110-122. PMID:19187765.

Lu, X., Simon, M.D., Chodaparambil, J.V., Hansen, J.C., Shokat, K.M., and Luger, K. The effect of H3K79 dimethylation and H4K20 trimethylation on nucleosome and chromatin structure. *Nat Struct Mol Biol*, **2008**, *15*, 1122-1124. PMID:18794842.

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Simon, M.D. and Shokat, K.M. Revealing biological specificity by engineering protein-ligand interactions. *Chemical Biology: From Small Molecules to System Biology and Drug Discovery*, Wiley, **2006**.

Simon, M.D., and Shokat, K.M. Adaptability at a protein-DNA interface: re-engineering the engrailed homeodomain to recognize an unnatural nucleotide. *J Am Chem Soc*, **2004**, *126*, 8078-8079. PMID:15225024.

Simon, M.D., Sato, K., Weiss, G.A., and Shokat, K.M. A phage display selection of engrailed homeodomain mutants and the importance of residue Q50. *Nucleic Acids Research*, **2004**, *32*, 3623-3631. PMID:15247345.

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Berlin, K., Jain, K.R., Simon, M.D., and Richert, C. A porphyrin embedded in DNA. *J Org Chem*, **1998** *63*, 1527-1535.

Patents & Patent Applications

Martin Machyna, Matthew D. Simon. Compositions and methods for improved RNA capture. App. No. US 16/412,527, Filed May 15, 2019

Jeremy Schofield, Matthew D. Simon. Time Lapse Sequencing: A convertible-nucleoside approach to enrichment-free analysis of RNA dynamics. App. No. US 15/941,323, Filed Mar 30, 2018

Robert E. Kingston, Matthew D. Simon, Jason A. West. Isolation of factors that associate directly or indirectly with ncRNAs. App. No. PCT/US2012/051565, Filed Aug 20, 2012

Robert E. Kingston, Jerome Dejardin and Matthew D. Simon. Isolation of factors that associate directly or indirectly with chromatin. App. No. PCT/US2010/024009, Filed Feb 12, 2010

Kevan M. Shokat and Matthew D. Simon. Site-specific installation of methyl-lysine analogues into recombinant histones. U.S. Patent 11961956, Filed Dec 20, 2007

Teaching

Course (enrollment)	**Course Name**	**Lectures** (contributions)	**Term**
MB&B 300 (80)	Principles of Biochemistry	8	Fall 2023 *in charge*
MB&B 730 (16)	Methods & Logic in Molecular Biology	6	Fall 2023
CBB 752 (ca. 51)	Biomedical Data Science: Mining and Modeling	2 (guest)	Spring 2023
MB&B 743b (ca. 20)	Advanced Eukaryotic Molecular Biology	2	Spring 2023
MB&B 300 (113)	Principles of Biochemistry	8	Fall 2022 *in charge*
MB&B 730 (25)	Methods & Logic in Molecular Biology	6	Fall 2022
CBB 752 (41)	Biomedical Data Science: Mining and Modeling	2 (guest)	Spring 2022
MB&B 743 (10)	Advanced Eukaryotic Molecular Biology	2 (guest)	Spring 2022
MB&B 300 (72)	Principles of Biochemistry	12	Fall 2021 *in charge*
CBB 752 (36)	Biomedical Data Science: Mining and Modeling	2 (guest)	Spring 2021
MB&B 743b (29)	Advanced Eukaryotic Molecular Biology	2 (guest)	Spring 2021
MB&B 300 (113)	Principles of Biochemistry	8	Fall 2020 *in charge*
MB&B 730 (25)	Methods & Logic in Molecular Biology	8	Fall 2020
CBB 752 (31)	Biomedical Data Science: Mining and Modeling	2 (guest)	Spring 2020
MB&B 300 (82)	Principles of Biochemistry	8	Fall 2019 *in charge*
MB&B 730 (24)	Methods & Logic in Molecular Biology	8	Fall 2019
MB&B 743b (28)	Advanced Eukaryotic Molecular Biology	2 (guest)	Spring 2019 *on leave*
CBB 752	Biomedical Data Science: Mining and Modeling	1 (guest)	Spring 2019 *on leave*
MB&B 300 (138)	Principles of Biochemistry	3	Fall 2018 *on leave*
MB&B 490b (24)	Senior projects	6 students	Spring 2018
MB&B 743b (23)	Advanced Eukaryotic Molecular Biology	2 (guest)	Spring 2018
MB&B 300 (134)	Principles of Biochemistry	12	Fall 2017 *in charge*
MB&B 730 (23)	Methods & Logic in Molecular Biology	8	Fall 2017
CBB 752	Biomedical Data Science: Mining and Modeling	2 (guest)	Spring 2017
MB&B 743b (18)	Advanced Eukaryotic Molecular Biology	2 (guest)	Spring 2017
MB&B 300a (110)	Principles of Biochemistry	9	Fall 2016 *on JFF 2016-2017*

Course (enrollment)	**Course Name**	**Lectures** (contributions)	**Term**
CBB 752	Bioinformatics: Practical Application of Data Mining and Simulation	2 (guest)	Spring 2016
MB&B 743b (25)	Advanced Eukaryotic Molecular Biology	1 (guest)	Spring 2016
MB&B 300a (199)	Principles of Biochemistry	13	Fall 2015
MB&B 730 (21)	Methods & Logic in Molecular Biology	12	Fall 2015
MB&B 743b	Advanced Eukaryotic Molecular Biology	1 (guest)	Spring 2015
MB&B 670b	Responsible Conduct of Research	1	Spring 2015
CBB 752	Bioinformatics: Practical Application of Data Mining and Simulation	2 (guest)	Spring 2015
MB&B 300a (214)	Principles of Biochemistry	13	Fall 2014
MB&B 730 (21)	Methods & Logic in Molecular Biology	8	Fall 2014
MB&B 490b (40)	Senior projects	ca. 20 students	Spring 2014
MB&B 670b	Responsible Conduct of Research	1	Spring 2014
MB&B 743b	Advanced Eukaryotic Molecular Biology	2 (guest)	Spring 2014
MB&B 300a (191)	Principles of Biochemistry	14	Fall 2013
MB&B 730 (21)	Methods & Logic in Molecular Biology	4	Fall 2013
MB&B 730 (28)	Methods & Logic in Molecular Biology	5	Fall 2012

Distinctions

- ONO Breakthrough Science Initiative Awardee, **2018**
- NIH New Innovator Award, **2014-2018**
- Searle Scholar Award, **2014-2017**
- Helen Hay Whitney Foundation Postdoctoral Fellowship, **2007-2010**
- American Chemical Society Fellowship, Organic Division, **2003**
- National Science Foundation Graduate Fellowship **2001, 2002, 2004**
- Phi Beta Kappa, Tufts University, **1999**
- Norris and Richard Scholar, Tufts University, **1999**
- Victor Prather Scholarship, Tufts University, **1999**
- The Durkee Scholarship, Tufts University, **1999**
- James F. Norris & Theodore W. Richards Undergraduate Research Scholarship, **1998**
- Max Tishler Prize Scholarship, Tufts University, **1998**
- CRC Tufts Freshman Achievement in Chemistry Award, **1996**