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Citizenship

Naturalized US citizen (1990).

Education

1961	B.Sc. University of Mumbai, Mumbai, India. Chemistry
1963	M.S. California Institute of Technology, Pasadena, CA. Chemistry
1968	PhD. New York University, New York, NY. Chemistry

Postdoctoral Training

1967	New York Univ. Medical School New York, NY. Biochemistry.
1968 - 1969	AT&T Bell Laboratories, Murray Hill, NJ. Biophysics.

Appointments

1970 - 1984	Member of Technical Staff, Polymer Chemistry Department, AT&T Bell Laboratories, Murray Hill, NJ
1984 - 1992	Professor of Biochemistry & Molecular Biophysics, College of Physicians & Surgeons, Columbia University, New York, NY
1992 -	Member, Structural Biology Program Memorial Sloan-Kettering Cancer Center (MSKCC), New York, New York
1994 -	Professor, Graduate Program in Biochemistry & Structural Biology, Weill School of Medical Sciences, Cornell University, New York, NY

Honors and Awards

1961 - 1963	Jamshetjee N. Tata Fellow
1983	AT&T Bell Laboratories Distinguished Technical Staff Award
1992 -	Abby Rockefeller Mauzé Chair in Experimental Therapeutics (MSKCC)
1997	Distinguished Alumnus Award, New York University
1997 - 1999	Harvey Society (Vice-President 97-98; President 98-99)
2013	NIH Directors Transformative R01 Award (with Thomas Tuschl and Uwe Ohler)
2014	2014 FEZANA Jamshed and Shirin Guzdar Excellence in Profession Award
2015	Einstein Professorship of Chinese Academy of Sciences, China
2019	Lifetime Achievement Award, American Association of Indian Scientisits in Cancer Research
2019	Inaugural Tan Jiazhen International Life Science Collaboration Award

Academy Memberships

2009	Member, National Academy of Sciences, USA
2014	Member, American Academy of Arts and Sciences, USA

MSKCC Committees

1993 - 1997	SKI Committee of Appointments and Promotions
1997 - 2004	MSKCC Committee of Appointments and Promotions
2016 - 2021	SKI Committee of Appointments and Promotions

External Review Committees

1984 - 2005 National Institutes of Health, Bethesda, MD
• Member, Molecular and Cellular Biophysics Study Section (84-88)
• National Cancer Institute, Board of Scientific Counselors-B (00-05)
1989 - 1996 Howard Hughes Medical Institute, Chevy Chase, MD
• Member, Scientific Review Board - Structural Biology (89-92)
• Member, Medical Advisory Board (93-96)
2015 - Joint Center for Life Sciences, Tsinghua-Beijing Universities, Beijing, China
2017 - 2018 Watson-Cheerland Precision Medicine Institute, Shenzhen, China

Scientific Advisory Boards

2009 - 2018 European Institute of Chemistry & Biology, Bordeaux, France
2010 - 2011 Epinova, GlaxoSmithKline, Stevenage, United Kingdom
2011 - Institute for Research in Biomedicine, Barcelona, Spain
2016 - Beijing Advanced Innovation Center for Structural Biology, Beijing, China
2016 - Center for Life Sciences, Harbin Institute of Technology, Harbin, China
2019 Shenzhen Bay Area Committee, Shenzhen, China
2019 - Biology Department, Southern University of Science and Technology, Shenzhen, China

PERSONAL STATEMENT

I received my PhD in Chemistry from New York University (NYU) in 1968 for research in the photochemistry. I decided next to shift the emphasis of my research to the life sciences and hence completed postdoctoral training (one year) in Biochemistry at NYU School of Medicine followed by postdoctoral training (two years) in Biophysics at AT&T Bell Laboratories. I was next promoted to permanent Member of Technical Staff at Bell Labs and spent the next 15 years undertaking NMR-based studies of the structure and dynamics of cyclic peptides, proteins and nucleic acids. I moved to Columbia University Medical School in 2004 as a tenured Professor of Biochemistry and Molecular Biophysics where my group spent the next 8 years doing NMR-based research on DNA mismatches, bulges and junctions, on DNA triplexes and G-quadruplexes, and drug-DNA complexes. I was recruited in 1992 as a tenured Member to the Cellular Biochemistry and Biophysics Program at the Memorial Sloan-Kettering Cancer Center to set up a Structural Biology component to the program. My group's research during the 1990s focused on NMR-based studies of covalent chiral carcinogen-DNA adducts, and complexes of antibiotics and peptides with natural and *in vitro* selected RNA targets.

My laboratory began to increasingly use x-ray crystallography starting around 2000 with the emphasis initially on RNA-mediated gene regulation, with subsequent extension to histone-mark and DNA-mark mediated epigenetic regulation, to lipid transfer proteins, and more recently to nucleic acid pattern recognition receptors, CRISPR-Cas surveillance complexes, Structure Maintenance Complexes (SMCs) and complexes mediating meiotic recombination. We have complemented our structural efforts with functional studies undertaken by collaborators to deduce mechanistic insights into the biological systems of interest. Starting in 2019, my group has increasingly used cryoEM to study macromolecular structure, recognition and regulation.

Dr. Patel has published 570+ papers and reviews. His h-index (Google Scholar) is 138.

Web site: http://www.mskcc.org/mskcc/html/10829.cfm

Patel NAS induction profile is available in ***Proc. Natl. Acad. Scis. USA*** (2015). 112, 10570-19572. PMCID: PMC4553825.

CONTRIBUTIONS TO SCIENCE

1. CRISPR-Cas and cGAS-STING Surveillance Complexes

Efficient and site-specific genome engineering can be achieved based on programmable dsDNA cleavage using CRISPR-Cas systems. Our structural studies on single- and multi-component Cas complexes are shedding light on the principles underlying cleavage chemistry of dsDNA, ssDNA and ssRNA targets. Future challenges include an understanding of the diverse mechanisms adopted by distinct CRISPR-Cas systems in efforts to broaden and enhance their applicability as genome editing tools.

The Patel group has contributed to the field of pattern recognition receptors that sense double-stranded nucleic acids in the cytosol, defined aspects of the cGAS-STING pathway, thereby triggering a cascade of events that activate the innate immune response.

1a. Single-subunit CRISPR-Cas Systems

Current efforts in the Patel lab are focused on single subunit type V (Cas12) and type VI (Cas13) systems. These systems are unique since Cas12 has a single RuvC nuclease to cut both DNA target and non-target strands. Cas13 is unusual in that it uses target RNA to pair with crRNA and in turn cleave substrate RNA.

Gao, P., et al. & Patel, D. J. (2016). Type V CRISPR-Cas Cpf1 endonuclease employs a unique mechanism for crRNA-mediated target recognition. ***Cell Research*** 26, 901-913. PMCID: PMC4973337.

Yang, H., et al., & Patel, D. J. (2017). PAM-dependent target DNA recognition and cleavage by C2c1 CRISPR-Cas4 endonuclease. ***Cell*** 167,1814-1828. PMCID: PMC5278635.

Wang, B., et al., Patel, D. J. & Yang, H. (2021). Structural basis for self cleavage prevention by tag:anti-tag pairing complementarity in Type VI Cas13 CRISPR systems. ***Mol. Cell*** 81, 1100-1115. PMCID: PMC8274241.

1b. Multi-subunit CRISPR-Cas Systems

The structural studies in the Patel lab are also being extended to multi-component CRISPR-Cas systems with an emphasis on type III systems given their multiple activities associated with ssRNA cleavage, ssDNA cleavage and cyclic-oligoadenylate (cOA) formation.

Guo, T. W., et al., Patel, D. J. & Subramaniam, S. (2017). Cryo-EM structures reveal mechanism and inhibition of DNA targeting by a CRISPR-Cas surveillance complex. ***Cell*** 171, 414-426. PMCID: PMC5683424.

Jia, N., et al., Marraffini, L. A. & Patel, D. J. (2019). Type III-A CRISPR Csm complexes: Assembly, target RNA recognition, periodic cleavage and autoimmunity. ***Mol. Cell*** 73, 264-267. PMCID: PMC6355164.

Jia, N., et al., & Patel, D. J. (2019). Second messenger cA_4 formation within the composite Csm1 Palm pocket of type III-A CRISPR-Cas Csm complex and its release path. ***Mol. Cell*** 75, 933-943. PMCID: PMC6731140.

More recently, the Patel group has focused on details of DNA integration by the CRISPR-Cas transposon complex.

Jia, N., et al. & Patel, D. J. (2020). Structure-function insights into the initial step of DNA integration by a CRISPR-Cas-Transposon complex. ***Cell Research*** 30, 182-84. PMCID: PMC7015049.

1c. Accessory Nucleases

We are also interested in how cOA second messengers activate and regulate CARF domain containing RNases and DNases [Collaborator: Luciano Marraffinin (Rockefeller)].

Jia, N., et al., & Patel, D. J. (2019). CRISPR-Cas III-A Csm6 CARF domain is a ring nuclease triggering stepwise cA_4 cleavage with ApA>p formation terminating RNase activity. ***Mol. Cell*** 75, 944-956. PMCID: PMC6731128.

Rostol, J.T., et al., Patel, D. J. & Marraffini, L. A. (2021). The Card1 nuclease provides bacterial defense during Type III CRISPR immunity. ***Nature*** 590, 624-629. PMCID: PMC7906951.

1d. Anti-CRISPR Proteins

Efforts in the Patel lab are underway to provide a structural understanding of recognition principles involving evolved bacteriophage suppressor proteins that inhibit the CRISPR-Cas pathway, thereby regulating the genome engineering activities of CRISPR-Cas systems [Collaborator: Sriram Subramanian (NCI)]. Additioal studies have been undertaken on anti-CRISPR proteins targeting type VI CRISPR system [Collaborator: Luciano Marraffini (Rockefeller)].

Yang, H. & Patel, D. J. (2017). Inhibition mechanism of an anti-CRISPR suppressor targeting SpyCas9. ***Mol. Cell*** 67, 117-127. PMCID: PMC5595222.

Guo, T. W., et al., Patel, D. J. & Subramaniam, S. (2017). Cryo-EM structures reveal mechanism and inhibition of DNA targeting by a CRISPR-Cas surveillance complex. ***Cell*** 171, 414-426. PMCID: PMC5683424.

Meeske, A. J., et al. Patel, D. J. & Marraffini, L. A. (2020). Phage-encoded anti-CRISPR enables full escape from type VIA CRISPR-Cas immunity. ***Science*** 369, 54-59. PMCID: PMC7975689.

Review

Jia, N. & Patel, D. J. (2021). Structure-based functional mechanisms and biotechnology applications of anti-CRISPR proteins. *Nat. Rev. Mol. Cell Biol.* 22, 563-579. PMCID:

1e. cGAS-STING Pathway

Our efforts have focused on cGAS, the metazoan sensor of cytosolic dsDNA, the second messenger cGAMP and the adaptor STING. Our structural studies identified cGAMP, produced by DNA-activated cGAS from GTP and ATP, to be c[G(2',5')pA(3',5')p], that contained an unanticipated 2',5' linkage at the GpA step. This research was next extended to STING activation by cGAMP and targeting by the anti-viral agent DMXAA [Collaborators: Thomas Tuschl (Rockefeller), Winfried Barchet (University Hospital-Bonn) and Roger Jones (Rutgers)].

Wang, Y., et al., Micura, R., Tuschl, T., Hartmann, G. & Patel, D. J. (2010). Structural and functional insights into 5'-ppp-dsRNA pattern recognition by the innate immune receptor RIG-I. ***Nat. Struct. Mol. Biol.*** 17, 781-787. PMCID: PMC3744876.

Gao, P., et al., Tuschl, T. & Patel, D. J. (2013). Cyclic [G(2',5')pA(3',5')p] is the metazoan second messenger produced by DNA-activated cyclic GMP-AMP synthase. ***Cell*** 153, 1094-1107. PMCID: PMC4382009.

Gao, P., et al., Tuschl, T. & Patel, D.J. (2013). Structure-function studies of STING activation by c[G(2',5')pA(3',5')p], its linkage isomers and DMXAA. ***Cell*** 154, 748-762. PMCD: PMC4386733.

Gao, P., et al., Hartmann, G., Tuschl, T., Deng, L., Barchet, W. & Patel, D. J. (2014). Binding pocket and lid region substituents render human STING sensitive to mouse-selective drug DMXAA. ***Cell Reports*** 8, 1668-1676. PMCID: PMC4381552.

Xie, W., et al., Tuschl, T. & Patel, D. J. (2018). Human cGAS catlytic domain has an additional DNA-binding interface that enhances enzymatic activity and liquid phase condensation. ***Proc. Natl. Acad. Scis. USA*** 116,11046-11955. PMCID: PMC6575157.

1f. Inhibitors Targeting cGAS

We are interested in identifying activators and inhibitors of human cGAS and STING given the importance of the cGAS-STING patway in innate immunity. To date, we have made progress in identifying inhibitors of human cGAS that exhibit distinct specificities for mouse versus human cGAS [Collaborators: Fraser Glickman and Thomas Tuschl (Rockefeller) and Roger Jones (Rutgers)].

Vincent, J.**,** et al., Tuschl, T., Patel, D. J., Glickman, J. F. & Ascano, M. (2017). Small molecule inhibition of cGAS reduces interferon expression in primary macrophages from autoimmune mice. ***Nat. Commun.*** 8:750. PMCID: PMC5622107.

Lama, L., et al., Glickman, J. F., Patel, D. J. & Tuschl, T. (2019). Development of human cGAS-specific small molecule inhibitors with biochemical and cell-based activity for repression of dsDNA-triggered interferon expression. ***Nat. Commun.*** 10: 2261. PMCID: PMC6529454.

2. DNA Double Strand Break Repair Pathways

Structure Maintenance of Chromosome (SMC) complexes are central to chromosome segregation, compaction and DNA repair, thereby impacting on gene expression and regulation. SMC family members that control chromosome topology during the cell cycle, range in eukaryotes from cohesion, condensin and Smc5/6 exhibiting ATPase-mediated hydrolysis activities, to the MRN/MRX complex with both ATPase and nuclease activities. Ongoing efforts in our lab have focused on Smc5/6, MRX and Spo11 complexes mediating DNA double strand break (DSB) repair.

2a. Smc5/6 Complex

Smc5/6 plays a critical role in mediating homologous recombination (HR)-mediated rescue of stalled or collapsed replication forks, thereby preventing DNA entanglements, breakages and translocations associated with DNA damage syndromes caused by Smc5/6 mutations. We are currently investigating distinct DNA-bound complexes of Smc5/6 and plan in the future to investigate the role of its Nse5 and Nse6 subunits, SUMOylation and ubiquitination, as well as the interaction with partner proteins, in mediating Smc5/6 function [Collaborator: Xiaolan Zhao (MSKCC)].

Yu, Y., et al., Patel, D. J. & Zhao, X. (2021). Integrative analysis reveals unique structure and functional features of the Smc5/6 complex. ***Proc. Natl. Acad. Scis. USA***. 118, e2026844118. PMCID: PMC8126833.

Yu, Y., et al. & Patel, D. J. (2022). Cryo-EM structure of dsDNA-bound *S. cerevisiae* Smc5/6 complex reveals DNA clamping enabled by multi-subunit conformational changes. ***Proc. Natl. Acad. Scis. USA***. PMCID:

2b. MRX Complex

The MRN complex in humans (MRX in yeast) and ATM govern a major axis of the DNA damage respone and several lines of evidence implicate that axis in tumor suppression. We have initiated a program towards the structure determination of the dsDNA-bound *S. cerevisiae* MR complex (composed of a dimer of MRE11 and Rad50) that established DNA encapsulation within the Rad50 scaffold [Collaborator: John Petrini (MSKCC)].

Hohl, M., et al., Patel, D. J., Burgers, P. M., Cobb, J. A. & Petrini, J. H. (2020). Modeling cancer genomic data in yeast reveals selection against ATM function during tumorigenesis. ***PLOS Genetics*** 16:e1008422. PMCID: PMC7105138.

2c. DSB Formation and Repair During Meiosis

Meiotic recombination initiates with DNA double-strand breaks (DSBs) made by the Spo11 protein together with a suite of accessory factors. We are interested in the structural and functional characterization of the *Saccharomyces cerevisiae* DSB Spo11-Rec102-Rec104-Ski8 core complex, as well as the Rec114-Mei4-Mer2 complex that forms nucleoprotein condensates on DNA that are critical for regulating DSB timing, number and location [Collaborator: Scott Keeney (MSKCC)].

Boekhout, M., et al., Carmerini-Otero, R. D., Patel, D. J. & Keeney, S. (2019). ANKRD31 anchors meiotic double-strand break formation as a direct partner of REC114. ***Mol. Cell*** 74, 1053-1068. PMCID: PMC6555648.

Bouuaert, C. C., et al., Patel, D. J. & Keeney, S. (2021). DNA-driven condensation assembles the meiotic break machinery. ***Nature*** 592, 144-149. PMCID: PMC8016751.

3. Readout of Histone and DNA Epigenetic Marks

The Patel group initiated a comprehensive research program in epigenetic regulation focused on understanding the diversity of mechanisms for site- and state-specific readout of histone marks by writer, reader and eraser protein modules.

Methylation of cytosine in the CpG context has pronounced effects on gene expression with DNA methylation patterns established during embryonic development, faithfully maintained during subsequent somatic cell division.

3a. Histone Mark Readout

Much of the effort in the Patel lab has focused on a structrural understanding of the histone- and -site specific readout of histone methylation and acetylation by writers, readers and erasers of these marks [Collaborators: David Allis (Rockefeller), Or Gozani (Stanford) and Yang Shi (Harvard)].

Li, H., et al., Allis, C. D. & Patel, D. J. (2006). Molecular basis for site-specific readout of H3 lysine 4 trimethylation by the BPTF PHD finger. ***Nature*** 442, 91-95. PMCID: PMC4690523.

Ruthenberg, A. J., et al., Allis, C. D., Patel, D. J. & Verdine, G. L. (2006). Histone recognition and presentation by the WDR5 module of the MLL1 complex. ***Nat. Struct. Mol. Biol.*** 13, 704-712. PMCID: PMC4698793.

Li, H., et al., Allis, C. D. & Patel, D. J. (2007). Structural basis for lower lysine methylation state-specific readout by MBT repeats and an engineered PHD finger module. ***Mol. Cell*** 28, 677-691. PMCID: PMC4689580.

Wang, G. G., et al., Patel, D. J. & Allis, C. D. (2009). Haematopoietic malignancies initiated by dysregulation of a chromatin-binding PHD finger. ***Nature*** 459, 847-851. PMCID: PMC2697266.

Iwase, S., et al., Allis, C. D., Picketts, D. J., Patel, D. J., Li, H. & Shi, Y. (2011). ATRX ADD domain links an atypical histone methylation recognition mechanism to human mental retardation syndrome. ***Nat. Struct. Mol. Biol***. 18, 769-776. PMCID: PMC3130887.

Rajakumara, E., et al., Patel, D. J. & Shi, Y. (2011). PHD finger recognition of unmodified histone H3R2 links UHRF1 to regulation of euchromatic gene expression. ***Mol. Cell*** 43, 275-284. PMCID: PMC4691841.

Kuo, A. J., et al. Patel, D. J. & Gozani, O. (2012). ORC1 BAH domain links dimethylation of H4K20 to DNA replication licensing and Meier-Gorlin syndrome. ***Nature*** 484, 115-119. PMCID: PMC3321094.

Cai, L., et al., Patel, D. J., Allis, C. D., Strahl, B. D., Song, J. & Wang, G. (2013). An H3K36me3-containing Tudor motif of polycomb-like proteins mediates PRC2 complex targeting. ***Mol. Cell*** 49, 571-582. PMCID: PMC3570589.

Cheng, Z., et al., Gozani, O. & Patel, D. J. (2014). A molecular threading mechanism underlies jumonji lysine demethylase KDM2A regulation of methylated H3K36. *Genes Dev*. **28**, 1758-1771. PMCID: PMC4197961.

Chen, S., et al., Armstrong, S. A., Patel, D. J. & Gozani, O. (2015). The PZP domain of AF10 senses unmodified H3K27 to regulate DOT1L-methylation at H3K79. ***Mol. Cell*** 60, 319-327. PMCID: PMC4609290.

Noh, K. M., et al., Patel, D. J., Li, H. & Allis, C. D. (2015). Engineering of a histone recognition domain in Dnmt3a alters the epigenetic landscape and phenotypic features of mouse ESCs. ***Mol. Cell*** 59, 89-103. PMCID: PMC4491196.

Reviews

Taverna, S. D., et al., Allis, C. D. & Patel, D. J. (2007). How chromatin-binding modules interpret histone modifications: Lessons from professional pocket pickers. ***Nat. Struct. Mol. Biol.*** *14*, 1025-1040. PMCID: PMC4691843.

Patel, D. J. and Wang, Z. (2013). A structural perspective of readout of epigenetic posttranslational modifications. ***Ann. Rev. Biochem***. 82, 81-118. PMCID: PMC4696766.

3b. Mutlivalent Readout of Histone Marks

Initial efforts on readout by single effector modules was expanded over time by the Patel group to multivalent readout at the histone peptide and nucleosomal levels [Collaborators: David Allis (Rockefeller), Michelle Barton (M. D. Anderson Cancer Center) and Joan Massague (MSKCC)].

Wang, Z., et al., Allis, C. D. & Patel, D. J. (2010). Pro isomerization in MLL1 PHD3-Bromo cassette connects H3K4me3 readout to CyP33 and HDAC-mediated repression. ***Cell*** 141, 1183-1194. PMCID: PMC4690531.

Tsai, W-W., et al., Patel, D. J. & Barton, M. C. (2010). TRIM24 links recognition of a non-canonical histone signature to breast cancer. ***Nature*** 468, 927-932. PMCID: PMC3058826.

Xi, Q., et al., Patel, D. J. & Massague, J. (2011). A poised chromatin platform for Smad access to master regulators. ***Cell*** 147***,*** 1511-1524. PMCID: PMC3582033.

Ruthenburg, A., et al., Patel, D. J. & Allis, C. D. (2011). Recognition of a mononucleosomal histone modification pattern by BPTF via multivalent interactions. ***Cell*** 145, 692-706. PMCID: PMC3135172.

Reviews

Ruthenburg, A. J., et al., Patel, D. J. & Allis, C. D. (2007). Multivalent engagement of chromatin modifications by linked binding modules. ***Nat. Rev. Mol. Cell Biol****.* 8, 983-994. PMCID: PMC4690530.

3c. Epigenetic Drug Targets

These studies have been extended by the Patel group to the identification of small molecules that targeted effector pockets with high affinity and specificity [Collaborator: GlaxoSmithKline (UK)].

Kruidenier, L., et al., Patel, D. J., Lee, K., & Wilson, W. (2012). A selective H3K27 demethylase inhibitor modulates the proinflammatory macrophage response. ***Nature*** 488, 404-408. PMCID: PMC4691848.

Reviews

Wang, Z. & Patel, D. J. (2013). Small molecule epigenetic inhibitors targeted to histone lysine methyltransferases and demethylases. ***Q. Rev. Biophys***. 46, 349-373. PMCID: PMC4696758.

3d. DNA Methylation Mark Readout

The Patel group group initiated their research on DNA methylation mark-mediated epigenetic regulation by focusing our structural studies on DNMT1-DNA complexes, whereby they established how a combination of autoinhibitory and productive mechanisms ensured the high fidelity of DNMT1-mediated maintenance DNA methylation. This research has been extended to multiple readout of marks by DNMT1 [Jikui Song (UCal-Riverside and Greg Wang (UNC-Chapel Hill)], writers and readers of plant DNMTs [Collaborator: Steve

Jaconsen (UCal-Los Angeles)] and on ATPase-containing fungal DNMT5 [Hiten Madhani (UCal-San Francisco)].

Song, J., et al. & Patel, D. J. (2011). Structure of DNMT1-DNA complex reveals a role for autoinhibition in maintenance DNA methylation. ***Science*** 331, 1036-1040. PMCID: 4689315.

Rajakumara, E., et al., Patel, D. J. & Jacobsen, S. E. (2011). A dual flip out mechanism for 5mC recognition by the *Arabidopsis* SUVH5 SRA domain and its impact on DNA methylation and H3K9 dimethylation *in vivo.* ***Genes Dev.*** 25, 137-152. PMCID: PMC3022260.

Song, J., Teplova, M., Ishibe-Murakami, S. & Patel, D. J. (2012). Structural principles underlying DNMT1-mediated DNA methylation. ***Science*** 335. 709-712. PMCID: PMC4693633.

Zhong, X., et al., Patel, D. J. & Jacobsen, S. E. (2014). Molecular mechanism of action of plant DRM *de novo* DNA methyltransferases. ***Cell*** 157, 1050-1060. PMCID: PMC4123750.

Ren, W., et al., Patel, D. J., Wang, G. G. & Song, J. (2020). Direct readout of heterochromatic H3K9me3 and H4K20me3 regulate DNMT1-mediated maintenance DNA methylation. ***Proc. Natl. Acad. Scis. USA*** 117, 18439-18447. PMCID: PMC7414182.

Ren, W. et al., Patel, D. J., Wang, Y., Cui, Q., Strahl, B. D., Gozani, O., Miller, K. M., O'Leary, S. E., Wade, P. A., Wang, G. G. & Song, J. (2021). DNMT1 reads heterochromatic H4K20me3 to reinforce LINE-1 DNA methylation. ***Nat. Commun.*** 12: 2490. PMCID: PMC8093215.

Wang, J., Catania, S., Wang, C., de la Cruz, M. J., Rao, B., Madhani, H. & Patel, D. J. (2022). SNF2 ATPase remodels DNA methyltransferase to enable durable epigenetic memory. ***Mol. Cell*** in press. PMCID:

3e. Crosstalk Between Histone and DNA Methylation

More recently, structure-function studies have provided insights into the molecular basis underlying the process whereby CHG DNA methylation in *A. thaliana* is controlled by the H3K9 methylation mark through a self-reinforcing loop between DNA methyltransferase CMT3 and H3K9 histone methyltransferase Kryptonite [Collaborator: Steve Jacobsen (UCLA)].

Du, J., et al., Patel, D. J. & Jacobsen, S. E. (2012). Dual binding of chromomethylase BAH and chromo domains to H3K9me2-containing nucleosomes in the targeting of DNA methylation. ***Cell*** 151,167-180. PMCID: PMC3471781.

Du, J., et al., Patel, D. J. & Jacobsen, S. E. (2014). Mechanism of DNA methylation-directed histone methylation by KRYPTONITE. ***Mol. Cell*** 55, 495-504. PMCID: PMC4127122.

Li, H., et al. Patel, D. J., Bulyk, M., Shi, Y. and Wang, Z. (2017). Polycomb-like proteins link the PRC2 complex with CpG islands. ***Nature*** 549, 287-291. PMCID: PMC5937281.

Review

Du, J., et al., Jacobsen, S. E. and Patel, D. J. (2015). DNA methylation pathways and their crosstalk with histone methylation. ***Nat. Rev. Mol. Cell Biol***. 16, 519-532. PMCID: PMC4672940.

3f. RNA-directed DNA Methylation

The research on DNA methylation was next extended by the Patel group to studies of RNA-directed DNA methylation that provided mechanistic insights into plant proteins that mediate the role of RNA polymerases pol-IV and pol-V in RNA-directed DNA methylation [Collaborator: Steve Jacobsen (UCal-Los Angeles)].

Law, J. A., et al., Patel, D. J. & Jacobsen, S. E. (2013). SHH1 recruits RNA polymerase-IV to RNA-directed DNA methylation targets. ***Nature*** 498, 385-389. PMCID: PMC4119789.

Johnson, L. M., et al., Patel, D. J. & Jacobsen, S. E. (2014). SRA/SET domain proteins link RNA polymerase V binding to DNA methylation. ***Nature*** 507, 124-128. PMCID: PMC3963826.

Stroud, H., et al. Patel, D. J. & Jacobsen, S. E. (2014). Non-CG methylation patterns shape the epigenetic landscape in Arabidopsis. ***Nat. Struct. Mol. Biol***. 21, 64-72. PMCID: PMC4103798.

4. siRNA and siRNA Biogenesis and Silencing

The Patel labs studies on the molecular mechanisms underlying RNA-mediated gene regulation have focused primarily on the roles of Argonaute and Dicer nucleases in siRNA interference and their inhibition by viral suppressors, as well as piRNA mediated protection of genome integrity against transposons.

The PIWI-intercating RNA (piRNA) pathway protects genome integrity in part through establishing heterochromatin at transposon loci.

4a. Prokaryotic Argonaute Silencing Complexes

In the RNA silencing area, the Patel group has made fundamental discoveries related to the structural biology of prokaryotic Argonaute proteins and their complexes with guide and target strands, thereby providing mechanistic insights into the nucleation, propagation and cleavage steps of Ago-mediated cleavage of mRNA [Collaborators: Thomas Tuschl (Rockefeller) and David Bartel (MIT)].

Ma, J-B., Ye, K. & Patel, D. J. (2004). Structural basis for overhang-specific small interfering RNA recognition by the PAZ domain. ***Nature*** 429, 318-322. PMCID: PMC4700412.

Ma, J. B., et al., Tuschl, T. & Patel, D. J. (2005). Structural basis for 5'-end-specific recognition of the guide RNA strand by the *A. fugidus* PIWI protein. ***Nature*** 434, 666-670. PMCID: PMC4694588.

Yuan, Y. R., et al. Tuschl, T. & Patel, D. J. (2005). Crystal structure of *Aquifex aeolicus* Argonaute, a site-specific DNA-guided endoribonuclease, provides insights into RISC-mediated mRNA cleavage. ***Mol. Cell*** 19, 405-419. PMCID: PMC4689305.

Wang, Y., et al., Tuschl, T. & Patel, D. J. (2008). Structure of the guide-strand-containing argonaute silencing complex. ***Nature*** 456, 209-213. PMCID: PMC4689319.

Wang, Y., et al., Tuschl, T. & Patel, D. J. (2008). Structure of an argonaute silencing complex with a seed-containing guide DNA and target RNA duplex. ***Nature*** 456, 921-926. PMCID: PMC2765400.

Wang, Y., et al., Tuschl, T. & Patel, D. J. (2009). Nucleation, propagation and cleavage of target RNAs in Ago silencing complexes. ***Nature*** 461, 754-761. PMCID: PMC2880917.

Swarts, D. C., et al., Patel, D. J., Berenguer, J., Brouns, S. J. & van der Oost, J. (2014). DNA-guided DNA interference by prokaryotic Argonaute. ***Nature*** 507, 258-261. PMCID: PMC4697943.

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Swarts, D. C., et al., Koonin, E. V., Patel, D. J. and van der Oost, J. (2014). The evolutionary journey of Argonaute proteins. ***Nat. Struct. Mol. Biol***. **21**, 743-753. PMCID: PMC4691850.

4b. Eukaryotic Argonaute Silencing Complexes

The research on prokaryote Argonautes has been extended to their eukaryotic counterparts, thereby identifying a catalytic tetrad responsible for modulation of cleavage activity [Collaborators: David Bartel (MIT), Thomas Tuschl (Rockefeller) and Mien-Chie Hung (M. D. Anderson Cancer Center)]

Nakanishi, K., Weinberg, D. E., Bartel, D. P. & Patel, D. J. (2012). Structure of yeast Argonaute with guide RNA. ***Nature*** 486, 368-374. PMCID: PMC3853139.

Shen, J., et al., Patel, D. J. & Hung, M. C. (2013). EGFR modulates miRNA maturation in response to hypoxia through phosphorylation of Ago2. ***Nature*** 497, 383-387. PMCID: PMC3717558.

Nakanishi, K., et al., Tuschl, T. and Patel, D. J. (2013). Eukaryote-specific insertion elements control human ARGONAUTE slicer activity. ***Cell Reports*** 3, 1893-1900. PMCID: PMC3757560.

4c. Viral Inhibitors of RNA Silencing

Viruses generate small proein inhibitors that target distinct steps of the RNA silencing pathway. The Patel lab is interested in the principles underlying molecular recognition in the arms race between RNA silencing and its suppression [Collaborator: Nam Hai Chua (Rockefeller)].

Ye, K., Malinina, L. & Patel, D. J. (2003). Recognition of siRNA by a viral suppressor of RNA silencing. ***Nature*** 426, 874-878. PMCID: 4694583.

Zhang, X., et al. Tuschl, T., Patel, D. J. & Chua, N-H. (2006). Cucumber mosaic virus-encoded 2b suppressor inhibits *Arabidopsis* AGO1 cleavage activity to counter plant defense. ***Genes Dev*****.** 20, 3255-3268. PMCID: PMC1686603.

4d. Dicer Silencing Complexes

More recently, the Patel group group has extended our RNA silencing research to Dicer proteins where we identified a phosphate-binding pocket in human Dicer and its role in dsRNA cleavage chemistry [Collaborator:

Narry Kim (Seoul National University)], as well as identified an unanticipated inside-out non-canonical pathway of dsRNA cleavage by budding yeast Dicer, in contrast to an outside-in pathway for Dicer's cleavage activity in higher eukaryotes [Collaborator: David Bartel (MIT)].

Weinberg, D., Nakanishi, K., Patel, D. J. & Bartel, D. P. (2011). The inside-out mechanism of Dicers from budding yeasts. ***Cell*** 146, 262-276. PMCID: PMC3169304.

Park, J. E., et al., Patel, D. J. & Kim, V. N. (2011). Dicer recognizes the 5'-end of RNA for efficient and accurate cleavage. ***Nature*** 475, 201-205. PMCID: PMC4693635.

Tian, Y., et al., Kim, V. N. & Patel, D. J. (2014). A phosphate-binding pocket within the platform-PAZ-connector helix cassette of human Dicer. ***Mol. Cell*** 53, 606-616. PMCID: PMC4217634.

4e. piRNA-mediated Protection of Genome Integrity

The goal of the piRNA research is to decipher molecular events associated with silencing and the requirement of piRNA-guided targeting of nuclear PIWI proteins to nascent transposon transcripts [Collaborator: Project championed by Alexei Aravin (Caltech). To this end, the lab Patel recently contributed to the determination that nascent RNA binding complex SFiNX licenses piRNA-guided heterochromatin formation [Collaborator: Project championed by Julius Brennecke, IMBA- Austria}

Le Thomas, A., et al., Patel, D. J. & Aravin, A.A. (2014). Trans-generationally inherited piRNAs trigger piRNA biogenesis by changing the chromatin of piRNA clusters and inducing precursor processing. ***Genes Dev***. 28, 1667-1680. PMCID: PMC4980073.

Webster, A., et al., Patel, D. J. & Aravin, A. A. (2015). Aub and Ago3 are recruited to nuage through two mechanisms to form a ping-pong complex assembled by Krimper. ***Mol. Cell*** 59, 564-575. PMCID: PMC4545750.

Chen, A., et al., Patel, D. J., Smibert, C. A., Lipshitz, H. D., Toth, K. F. & Aravin, A. A. (2016). Cutoff suppresses RNA polymerase II termination to ensure expression of piRNA precursors. ***Mol. Cell*** 63, 97-109. PMCID: PMC4980073.

Batki, J., et al., Patel, D. J. & Brennecke, J. (2019). The SFINX complex licenses piRNA-guided heterochromatin formation. ***Nat. Struct. Mol. Biol.*** 26, 720-731. PMCID: PMC6828549.

Huang, X., et al., Patel, D. J., Sachidanandam, R., Toth, K. J., Aravin, A. A. & Li, S. (2021). Binding of guide piRNA triggers methylation of the unstructured N-terminal region of Aub leading to assembly of the piRNA amplification complex. ***Nat. Commun.*** 12: 4061. PMCID: PMC8249470.

Schnabl, J., et al., Patel, D. J. & Brennecke, J. (2021). Molecular principles of Piwi-mediated cotranscriptional silencing through the dimeric SFiNX complex. ***Genes Dev.*** 35, 392-409. PMCID: PMC7919418.

Andreev, V. I., et al., Patel, D. J. & Brennecke, J. (2022). Panaromix SUMOylation on chromatin connects the piRNA pathway to the cellular heterochromatin machinery. ***Nat. Struct. Mol. Biol***. in press. PMCID:

4f. RNA Tailing

RNA tailing (nontemplated nucleotide addition to the 3' end of RNA) is one of the most frequent types of RNA modification with a deep evolutionary root and diverse molecular functions. Studies have been undertaken to mechanistically understand the role TUTases in 3'-uridylation and WISPY in 3'-adenylation of microRNAs [Collaborator: Project championed by V. Narry Kim laboratory (Seoul National University)].

Lim, J., et al., Patel, D. J. & Kim, V. N. (2014). Uridylation by TUT4 and TUT7 marks mRNA for degradation. ***Cell*** 159, 1365-1376. PMCID: PMC4720960.

Lee, M., et al., Patel, D. J. & Kim, V. N. (2014). Adenylation of maternally inherited microRNAs by Wispy. ***Mol. Cell*** 56, 696-707. PMCID: PMC4378961.

Kim, B., et al., Patel, D. J., Joo, C. & Kim, V. N. (2015). TUT7 controls the fate of precursor miRNAs by using three different uridylation mechanisms. ***EMBO J.*** 34, 1801-1815. PMCID: PMC4516432.

5. Molecular Chaperones and Transfer Proteins

Histone chaperones represent a structurally and functionally diverse family of histone-binding proteins that prevent promiscuous interactions of histones before their assembly into chromatin. Our understanding of the mechanisms of histone shuttling between different chaperone systems, and histone transfer onto and off DNA, has been hampered due to the availability of only a limited number of histone-chaperone complexes.

The Patel group initiated a structural biology program on lipid transfer proteins that acquire and release neutral glycosphingolpids and charged phosphosphingolipids during lipid intermembrane transfer and presentation processes.

5a. Histone Chaperones

Our studies have focused on the H3.3-specific chaperone DAXX [Collaborator: David Allis (Rockefeller)], chaperones Spt2 [Collaborator: Amine Nourani (Quebec)] and MCM2 and DNAJC9 [Collaborators: Anja Groth (BRIC-Copenhagen) and Hongda Huang (SUSTech)] that target H3-H4 tetramers.

Elsasser, S. J., et al., Allis, C. D. & Patel, D. J. (2012). DAXX histone chaperone envelops an H3.3/H4 dimer for H3.3-specific recognition. ***Nature*** 491, 560-565. PMCID: PMC4056191.

Chen, S., et al., Nourani, A. & Patel, D. J. (2015). Structural basis of histone H3/H4 tetramer maintenance during transcription by chaperone Spt2. ***Genes Dev.*** 29, 1326-1340. PMCID: PMC4495402.

Huang, H., et al., Groth, A. & Patel, D. J. (2015). A unique binding mode enables MCM2 to chaperone histones H3-H4 at replication forks. ***Nat. Struct. Mol. Biol***. 22, 618-626. PMCID: PMC4685956.

Saredi, G. et al., Patel, D. J. & Groth, A. (2016). H4K20me0 marks post-replicative chromatin and recruits the TONSL-MMS22L DNA repair complex. ***Nature*** 534, 714-718. PMCID: PMC4939875.

Huang, H. et al., Lieberman, P. M. & Patel, D. J. (2016). Structural basis underlying viral hijacking of a histone chaperone complex. ***Nat. Commun.*** 7:12707. PMCID: PMC5025803.

Prendergast, L., et al., Patel, D. J., Sullivan, K. F. & Almouzni, G. (2016). The CENP-T-CENP-W complex is a binding partner of the histone chaperone FACT. ***Genes Dev***. 30, 1313-1326. PMCID: PMC4911930.

Hoelper, D., et al., Patel, D. J. & Lewis, P.W. (2016). Structural and functional insights into ATRX-dependent and -independent functions of the histone chaperone DAXX. ***Nat. Commun.*** 8: 1193. PMCID: PMC5662737.

Hammond, et al., Patel, D. J., Huang, H. & Groth, A. (2021). DNAJC9 integrates heat shock molecular chaperones into the histone chaperone network. ***Mol. Cell*** 81, 2533-2548. PMCID: PMC8221569.

Bao, H., et al., Patel, D. J., Groth, A. & Huang, H. (2022). NASP maintains histone H3-H4 homeostasis through two distinct H3 binding modes. ***Nucleic Acids Res***. under revision. PMCID:

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Hammond, C. M. et al., Patel, D. J. & Groth, A. (2017). Histone logistics: the artistry of histone chaperones. ***Nat. Rev. Mol. Cell Biol.*** 18, 141-158. PMCID: PMC5319910.

5b. Lipid Transfer Proteins

Studies on lipid transfer proteins have established the molecular basis underlying differentiation of neutral from charged lipids by their respective head group recognition centers and defined the alignment of one or both lipid chains within a molded-to-fit hydrophobic tunnel, thereby supporting a cleft-like gating mechanism, whereby lipid chains sequentially entered and departed the tunnel in the membrane-associated state [Collaborators: Rhoderick Brown (Hormel Institute); Charles Chalfant (Florida)].

Malinina, L., et al., Brown, R. E. & Patel, D. J. (2004). Structural basis for glycosphingolipid transfer specificity. ***Nature*** 430, 1048-1053. PMCID: PMC2640488.

Malinina, L., et al., Brown, R. E. & Patel, D. J. (2006). The liganding mode of glycolipid transfer protein is controlled by glycolipid acyl structure. ***PLoS Biol.*** 4, 1996-2011. PMCID: PMC1618416.

Simanshu, D. K., et al., Chalfant, C. E., Brown, R. E. & Patel, D. J. (2013). Nonvesicular trafficking by ceramide-1-phosphate transfer protein regulates eicosanoid production. ***Nature*** 500, 463-467. PMCID: PMC3951269.

Hirano, Y., et al., Chalfant, C. E., Patel, D. J. & Brown, R. (2019). Structural basis of phosphatidylcholine recognition by the C2-domain of cytosolic phospholipase A2□. ***eLife***. 8:e44760. PMCID: PMC6550875.

Gao, Y-G., McDonald, J., Malinina, L., Patel, D. J. & Brown, R. E. (2022). Ceramide-1-phosphate transfer protein promotes sphingolipid reorientation needed for binding during membrane interaction. ***J. Lipid Res.*** 63, 100151. PMCID:

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Malinina, L., et al., Patel, D. J. & Brown, R. E. (2015). Sphingolipid transfer proteins defined by the GLTP-fold. ***Q. Rev. Biophys.*** 48, 281-322. PMCID: PMC4691851.

Malinina, L., Patel, D. J. and Brown, R. E. (2017). How □-helical motifs form functionally diverse lipid-binding compartments. ***Ann. Rev. Biochem.*** 86, 609-636.

6. Gene Regulation by Riboswitches and Ribozymes

One component of the Patel group's contributions towards understanding the mechanistic principles underlying small RNA recognition and catalysis have focused on riboswitches and ribozymes.

6a. Riboswitches

The role of RNA in information transfer and catalysis highlights its dual functionalities. The Patel group has determined the higher order architectures of compact riboswitch sensing domains bound to amino acids, metabolites, cofactors and ions, thereby defining the principles associated with intermolecular renucleosides, cognition, as well as elucidated how RNA containing only four nucleotides could generate pockets capable of recognizing specific ligands and discriminating against closely-related analogs [Collaborator: Ronald Micura (University of Innsbruck)].

Serganov, A., et al., Micura, R., Breaker, R. R. & Patel, D. J. (2004). Structural basis for discriminative regulation of gene expression by adenine- and guanine-sensing mRNAs. ***Chem. Biol.*** 11, 1729-1741. PMCID: PMC4692365.

Serganov, A., et al. & Patel, D. J. (2006). Structural basis for gene regulation by a thiamine pyrophosphate-binding riboswitch. ***Nature*** 441, 1167-1171. PMCID: PMC4689313.

Serganov, A., Huang, L. & Patel, D. J. (2008). Structural insights into amino acid binding and gene control by a lysine riboswitch. ***Nature*** 455, 1263-1267. PMCID: PMC3726722.

Serganov, A., Huang, L. & Patel, D. J. (2009). Coenzyme recognition and gene regulation by a FMN riboswitch. ***Nature*** 458, 233-237. PMCID: PMC3726715.

Huang, L. et al. & Patel, D. J. (2010). Structural insights into ligand recognition by a sensing domain of the cooperative glycine riboswitch. ***Mol Cell*** 40, 774-786. PMCID: PMC3726718.

Ren, A., Rajashankar, K. & Patel, D. J. (2012). Fluoride ion encapsulation by Mg^{2+} and phosphates in a fluoride riboswitch. ***Nature*** 486, 85-89. PMCID: PMC3744881.

Ren, A. and Patel, D. J. (2014). c-di-AMP binds the *ydaO* riboswitch in two pseudo-symmetry-related pockets. ***Nat. Chem. Biol.*** 10, 780-786. PMCID: PMC4217635.

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Serganov, A. & Patel, D. J. (2007). Ribozymes, riboswitches and beyond: regulation of gene expression without proteins. ***Nat. Rev. Genetics*** 8, 776-790. PMCID: PMC4696762.

Serganov, A. & Patel, D. J. (2012). Metabolite recognition principles and molecular mechanisms underlying riboswitch function. ***Ann. Rev. Biophys***. 4**1**, 343-370. PMCID: PMC4696762.

6b. Ribozymes

Small self-cleaving ribozymes contain catalytic domains that accelerate site-specific cleavage/ligation of phosphodiester backbones. Our research on ribozymes has elucidated the role of geometric constraints, nucleophilic activation, stabilization of the transition state and protonation of the leaving group, together with in-line alignment and divalent cation coordination, to cleavage chemistry [Collaborators: Ronald Micura (University of Innsbruck), Aiming Ren (Zhejiang University) and Andres Jaschke (Heidelberg}].

Serganov, A., et al., Jaschke, A. & Patel, D. J. (2005). Structural basis for Diels-Alder ribozyme catalyzed carbon-carbon bond formation. ***Nat. Struct. Mol. Biol.*** 12, 218-224. PMCID: PMC4692364.

Ren, A., et al. &, Micura, R. & Patel, D. J. (2015). In-line alignment and Mg^{2+} coordination at the cleavage site of the twister ribozyme. ***Nat. Commun***. 5: 5534. PMCID: 4373348.

Kosutic, M. et al., Patel, D. J., Kreitz, C. and Micure, R. (2015). A mini-twister variant and impact of residues/cations on the phosphodiester cleavage chemistry of this ribozyme class. ***Angew. Chemie Int. Edn.*** 54, 15128-15133. PMCID: PMC4715771.

Ren, A., et al. &, Micura, R. & Patel, D. J. (2016). Pistol ribozyme adopts an embedded pseudoknot fold facilitating site-specific in-line cleavage. ***Nat. Chem. Biol.*** 12, 702-708. PMCID: PMC4990474.

Zheng, L., et al., Patel, D. J., Micura, R. & Ren, A. (2017). Structure-based insights into self-cleavage by a four-way junctional twister-sister ribozyme. ***Nat. Commun.*** 8:1180. PMCID: PMC5660989.

Zheng, L., et al., Patel, D. J., Micura, R. & Ren, A. (2019). Hatchet ribozyme structure and implications for the precatalytic fold and cleavage mechanism. ***Proc. Natl. Acad. Scis. USA*** 116, 10783-10791. PMCID: PMC6561176.

Teplova, M., et al., Ren, A., Patel, D. J. & Micura R. (2020). On crucial roles of two hydrated Mg^{2+} ions in reaction catalysis of the pistol ribozyme. ***Angew. Chemie***. 59, 2837-2843. PMCID: PMC7027511.

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Ren, A., Micura, R. & Patel, D. J. (2017). Structure-based mechanistic insights into catalysis by small self-cleaving ribozymes. ***Curr. Opin. Chem. Biol.*** 41, 71-83. PMCID: PMC7955703.

7. Molecular Recognition Impacting on Disease

7a. Protein-RNA complexes

The Patel group has undertaken structural studies on complexes of peptides and proteins bound to their RNA targets to decipher principles associated with complex formation, as part of an effort towards the eventual formulation of a recognition code mediating protein-RNA complex formation. Our studies provide insights into the requirement for the structural integrity of both RNA-binding and dimerization domains of disease-related proteins, as well as their relative orientations, for their post-transcriptional regulatory functions. [Collaborators: Thomas Tuschl (Rockefeller); Elisa Izauralde (Max-Planck-Tubingen); Matsuo Inouye (Rutgers); Yang Shi (Harvard); Andres Jaschke (Heidelberg); Stefan Ameres (IMBA-Vienna); Michael Kharas (MSKCC)].

Teplova, M., et al., & Patel, D. J. (2006). Structural basis for recognition and sequestration of UUU_{OH} 3'-terminii of nascent mRNA polymerase III transcripts by La autoantigen. ***Mol. Cell*** 21, 75-85. PMCID: PMC4689297.

Teplova, M. & Patel, D. J. (2008). Structural insights into RNA recognition by the alternate splicing regulator muscleblind-like MBNL1. ***Nat. Struct. Mol. Biol.*** 15, 1343-1351. PMCID: PMC4689322.

Tian, Y., et al., Robinson, C. C., Tuschl, T. & Patel, D. J. (2011). Multimeric assembly and biochemical characterization of the Trax-translin endonuclease complex. ***Nat. Struct. Mol. Biol.*** 18, 658-664. PMCID: PMC3109869.

Teplova, M., Song, J., Gaw, H. Y., Teplov, V. & Patel, D. J. (2010). Structural insights into RNA recognition by the CUG binding protein 1. ***Structure*** 18, 1364-1367. PMCID: PMC3381513.

Phan, A. T. et al., Darnell, R. B. & Patel, D. J. (2011). Structure-function studies of FMRP RGG peptide recognition of an RNA duplex-quadruplex junction. ***Nat. Struct. Mol. Biol.*** 18, 796-804. PMCID: PMC3130835.

Teplova, M., et al., Izaurralde, E. & Patel, D. J. (2011). Structure-function studies of nucleocytoplasmic transport of retroviral genomic RNA by mRNA export factor TAP. ***Nat. Struct. Mol. Biol.*** 18, 990-998. PMCID: PMC3167930.

Teplova, M., et al., Tuschl, T. & Patel, D. J. (2013). Structure-function studies of STAR family Quaking proteins bound to their *in vivo* RNA target sites. ***Genes Dev.*** 27, 928-940. PMCID: PMC3650229.

Simanshu, D. K., et al. Inouye, M. & Patel, D. J. (2013b). Structural insights into mRNA recognition by toxin MazF and its regulation by antitoxin MazE in B. subtilis. ***Mol. Cell*** 52, 447-458. PMCID: PMC4691852.

Vasilyev, N., et al., Darnell, R. B., Patel, D. J. and Serganov, A. (2015). Crystal structure reveals specific recognition of a G-quadruplex RNA by a □-turn in the RGG motif of FMRP. ***Proc. Natl. Acad. Scis. USA***. 112, E5391-E5400. PMCID: PMC4593078.

Murn, J. et al., Patel D. J., Ule, J., Luscombe, N. M., Tsai, L. H., Walsh, C. A. & Shi, Y. (2015). Control of a neural morphology program by an RNA-binding zinc finger protein, Unkempt. ***Genes Dev.*** 29, 501-512. PMCID: 4358043.

Murn, J., et al., Shi, Y. & Patel, D. J. (2016). Recognition of distinct RNA motifs by the clustered CCCH zinc fingers of neuronal protein Unkempt. ***Nat. Struct. Mol. Biol.*** 23, 16-23. PMCID: PMC4703518.

Hofer, K., et al., Patel, D. J. & Jaschke, A. (2016). Structure and function of the bacterial decapping enzyme NudC. ***Nat. Chem. Biol.*** 12, 730-734. PMCID: PMC5003112.

Minuesa, G. et al. & Patel, D. J., Goldgur, Y., Chodera, J. D. & Kharas, M. G. (2019). Small-molecule targeting of MUSASHI RNA-binding activity in acute myeloid leukemia. ***Nat. Commun.*** 10:2691. PMCID: PMC6584500.

Xie, W. et al., Brennecke, J., Ameres, S. L. & Patel, D. J. (2020). Structural and functional analysis of miRNA 3'-end trimming by Nibbler. ***Proc. Natl. Acad. Scis. USA.*** 117, 30370-30379. PMCID: PMC7720153.

Cheng, Y. et al. Patel, D. J., Jaffrey, S. R. & Kharas, M. G. (2021). m^6A mRNA catalyzes a phase-separated nuclear body that suppresses myeloid leukemic differentiation. ***Cancer Cell*** 39, 958-972. PMCID: PMC8282764.

7b. Inhibitors Targeting Protein Scaffolds

Our group is interested in the design and structural characterization of inhibitors that target proteins mediating SARS-CoV-2 viral infection, and those involved in leukemic transformation [Collaborators: Jingyue Ju (Columbia) and Michael Kharas (MSKCC)].

Wang, X. et al. Patel, D. J. et al. & Ju, J. (2022). Combination of antiviral drugs to inhibit polymerase and exonuclease of SARS-C0V-2 as potential covid-19 therapeutics. ***Commun. Biol.*** in press.

Sacramento, C. Q. et al. Patel, D. J. et al. & Souza, T. M. (2021). The *in vitro* anti-viral activity of the anti-hepatitis C virus (HCV) drugs daclatasvir and sofosbuvir against SARS-CoV-2. ***J. Antimicrobial Chemotherapy*** 76, 1874-1885.

Minuesa, G. et al. & Patel, D. J., Goldgur, Y., Chodera, J. D. & Kharas, M. G. (2019). Small-molecule targeting of MUSASHI RNA-binding activity in acute myeloid leukemia. *Nat. Commun*. 10:2691

7c. Protein-DNA Complexes

Our group has undertaken structure-functional investigation of helicases, motor-nucleases, DSB repair proteins and transcriptional repressors that function at DNA complex level. These include structural studies on mycobacterial helicases and motor nucleases [Collaborator: Stewart Shuman (MSKCC)], the Shieldin complex involved in DNA repair and BEN domais transcriptional repressors [Collaborator: Eric Lai (MSKCC)].

Dai, Q., Ren, A., Westholm, J. O., Serganov, A., Patel, D. J. & Lai, E. C. (2013). The BEN domain is a novel sequence-specific DNA binding domain conserved in neural transcriptional repressors**.** ***Genes Dev.*** **27**, 602-614. PMCID: PMC3613608.

Dai, Q., Ren, A., Westholm J. O., Patel, D. J. and Lai, E. (2015). Common and distinct DNA-binding and regulatory activities of the BEN-solo transcription factor family. ***Genes Dev.*** 29, 48-62. PMCID: PMC4281564.

Jia, N., Unciuleac, M. C., Xue, C., Greene, E. C., Patel, D. J. & Shuman, S. (2019). Structure and single-molecule kinetic analysis of the mycobacterial motor-nuclease AdnAB illuminate the mechanism of DNA double-strand break resection. ***Proc. Natl. Acad. Scis. USA*****.** 116, 24507-24516. PMCID: PMC6900545.

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Xie, W., et al., & Patel, D. J. (2021). Molecular mechanisms of assembly and remodeling of human Shieldin complex. ***Proc. Natl. Acad. Scis. USA.*** 118, e2024512118. PMCID: PMC7923543.

Warren, G. M., Meier, A., Wang, J., Patel, D. J., Greene, E. C. & Shuman, S. (2022). Structure-activity relations at a nucleobase-stacking tryptophan required for chemomechanical coupling in the DNA resecting motor-nuclease AdnAB. ***Nucleic Acids Res.,*** in press. PMCID:

Zheng, L. et al., Patel, D. J., Zhang, L., Prasanth, S., Yu, Y, Ren, A. & Lai, E. C. (2022). Distinct structural bases for sequence-specific DNA binding by mammalian BEN domains. ***Genes Dev***. in press. PMCID:

Campello-Morillo, R. A. et al. Patel, D. J., Nobel, W. S., Llinas, M., Le Roch, K. G. & Kafsack, B. F. (2022). The transcriptional regulator HDP1 controls expansion of the inner membrane complex during early sexual differentiation of malaria parasites. ***Nat. Microbiol.*** 7, 288-299. PMCID:

7d. Peptide/Protein-Protein Recognition

Our group has collaborated with colleagues to solve peptide-protein and protein-protein structures, which when combined with functional studies, provide mechanistic insights into the biological systems of interest. The Patel lab has assisted our Rockefeller and MSKCC colleagues with structural biology projects impacting on biological recognition and regulation [Collaborators: David Allis (Rockefeller); Robert Roeder (Rockefeller); Paul Greengard (Roclefeller); Titia de Lange (Rockefeller); Stewart Shuman (MSKCC); Zhanxin Wang (Beijing Normal)].

Xiao, A., et al., Patel, D. J., Elledge, S. J. & Allis, C. D. (2009). WSTF regulates the DNA damage response of H2A.X via a novel tyrosine kinase activity. ***Nature*** 457, 57-62. PMCID: PMC2854499.

Oh, Y-S., et al., Patel, D. J., Kim, Y. & Greengard, P. (2013). SMARCA3, a chromatin remodeling factor, is required for p11-dependent antidepressant action. ***Cell*** 152, 841-843. PMCID: PMC3633087.

Sun, X-J. et al., Patel, D. J., Nimer, S. D. & Roeder, R. G. (2013). A stable transcription factor complex nucleated by dimeric AML1-ETO controls leukemogenesis. ***Nature*** 500, 93-97. PMCID: PMC3732535.

Schmutz, I., Timashev, L., Xie, W., Patel, D.J. & de Lange, T. (2017). TRF2 binds branched DNA to safeguard telomere integrity. ***Nat. Struct. Mol. Biol.*** 24, 714-742. PMCID:

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7e. Inhibitors Targeting RNA Scaffolds

Our group is interested in the molecular basis for site-specific aminoglycoside recognition both on natural and *in vitro* selected RNA targets.

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ONGOING RESEARCH SUPPORT

NIGMS-NIH (Patel) 1 R01 GM129430 04-08-19 to 03-31-23 1.2 cal. mths
Title: Class I and III multi-subunit CRISPR-Cas surveillance complexes: recognition, cleavage, autoimmunity and inhibition.
Determine cryo-EM structures of Csy and Csm complexes to deduce mechanistic insights into target cleavage and its regulation, as well as principles underlying anti-CRISPR recognition and inhibition.
Role: PI

NIAID-NIH (Tuschl) 1 R01 AI141507 06-10-19 to 05-31-23 1.2 cal. mths
Title: Development of small molecule cGAS inhibitors for repression of dsDNA-triggered interferon expression.
Design and structural characterization of small molecule inhibitors of cytoplasmic dsDNA sensor cGAS and their optimization.
Role: co-PI

Leukemia Lymphoma SCOR 10-01-19 to 09-30-24 1.2 cal mth
Title: Consortium for the study of epigenetic targeting in hematological malignancy.
Apply cryo-EM approaches to structurally characterize large complexes involved in writing, reading and erasing epigenetic marks.
Role: co-PI

ETC-MSKCC (Patel) 01-01-20 to 3-31-22 1.2 cal mths
Title: Development of small molecule inhibitors of METTL3-METTL14 m6A RNA merthyltransferase as drugs against acute myeloid leukemia.
Identify small molecules from high-throughput screens for targeting human METTL3-METTL14 and then optimize them through a combination of structure- and computational-guidance of medicinal chemists.
Role: PI; co-PI (Kharas)