BIOGRAPHICAL SKETCH

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NAME: Gupta, Yogesh K.

eRA COMMONS USER NAME: YGUPTA

POSITION TITLE: Assistant Professor of Biochemistry and Structural Biology

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Dr. B. R. Ambedkar University, Agra, India	B.Sc.	12/1996	Chemistry and Biology
Dr. B. R. Ambedkar University, Agra, India	M.Sc.	10/2000	Biochemistry
Anna University, Chennai, India	M. Tech.	12/2001	Biotechnology (with distinction)
CERM, University of Florence, Florence, Italy	Ph.D.	01/2005	Structural Biology
Mount Sinai School of Medicine, New York, USA	Postdoctoral	06/2009	Structural and Chemical Biology

A. Personal Statement

My independent research program is directed at investigating the mechanisms by which different enzymes and accessory factors assemble on and alter the structures of DNA (chromatin remodelers) and RNA (2'-*O-ribose* and N^6-*adenosine* methyltransferases) in pediatric cancers and infectious diseases. My studies combine biochemistry and structural biology methods with cell-based assays to elucidate structures and mechanisms of nucleoprotein complexes with a final goal of developing novel therapeutic modalities. Recently, we uncovered a new RNA-mediated regulation of m6dA activity of human METTL3-METTL14 enzymes (**eLife 2022**). We also provided the structural basis of the 2'-*O* methylation of mRNA cap by SARS-CoV-2 (**Nature Communications**, **2020, 2021**). Our previous work on a newly discovered DNA repair enzyme, PrimPol, provides unprecedented mechanistic details regarding how a bifunctional enzyme couples DNA primase and DNA polymerase activities to maintain genome integrity in human cells (**Nature Communications 2021, Science Advances 2016**)**.** Solving the structures of RNA methyltransferase (SARS-CoV-2 nsp16/nsp10), DNA motor enzyme EcoP15I (a SWI/SNF SF2 family ATP motor), and DNA repair (PrimPol) enzyme complexes represent major milestones of my scientific career. The EcoP15I study provides the foundation of the idea of ATP-driven processes in long-range communication between distantly located sites on single DNA during viral invasion. This also represents the first structure of any dimeric DNA methyltransferase bound to the DNA substrate and a SF family DNA motor highlighting for the first time a 'division of labor' by the two methyltransferases for DNA recognition and methylation (**Nature Communications 2015**). Currently, we are investigating structures and functions of the human human RNA modification machinery with a final goal of developing novel therapeutic agents.

Ongoing projects that I would like to highlight include:

1R01AI161363
NIH/NIAID
Gupta (PI)
8/1/2021 – 7/31/2026
Mechanism based targeting of RNA processing machinery of SARS-CoV-2
This application received an exceptional impact/priority score of 14.

RP190534
CPRIT
Gupta (PI)
8/31/2019 – 2/28/2022 (NCE till 8/31/2022)

Mechanism-based targeting of core module of the BAF complex in Cancer

Citations:

1. **RNA binding to human METTL3-METTL14 restricts N^6-deoxyadenosine methylation of DNA *in vitro*.** Qi S., Mota J., Chan S.H., Villarreal J., Dai N., Arya S., Hromas R.A., Rao M.K., Corrêa I.R. Jr, Gupta Y.K.* (2022) *eLife*. 11:e67150. PMID: 35060905. *corresponding author
2. **A metal ion orients SARS-CoV-2 mRNA to ensure accurate 2'-*O* methylation of its first nucleotide.** Viswanathan T., Misra A., Chan S-H., Qi S., Dai N., Arya S., Martinez-Sobrido L., Gupta Y.K.* (2021) *Nature Commun.* 29;12 (1):4020. PMID: 34078893. *corresponding author
   [highlighted by > 20 international news & editorials]
3. **Structural basis of RNA cap modification by SARS-CoV-2.** Viswanathan T., Arya S., Chan S-H., Qi S., Dai N., Misra A., Park J.G., Oladunni F., Kovalaskyy D., Hromas R.A., Martinez-Sobrido L., Gupta Y.K.* (2020) *Nature Commun*. 11 (1): 3718. PMID: 32709886. *corresponding author.
   [highlighted by >40 international media outlets, received >40,000 articles access in the 1st week, Top 50 SARS-CoV-2 articles]
4. **Structure and mechanism of human PrimPol, a DNA polymerase with primase activity.** Rechkoblit O.,* Gupta Y.K.,* Malik R.,* Rajashankar K.R., Johnson R.E., Prakash L., Prakash S., Aggarwal A.K. (2016) *Science Advances.* 2: e1601317. PMID: 27819052. *Co-first author.
5. **Structural basis of asymmetric DNA methylation and ATP-triggered long-range diffusion by EcoP15I.** Gupta Y.K., Chan S.H., Xu S.Y., Aggarwal A.K. (2015) *Nature Commun.* 6:7363. PMID: 26067164

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

09/01/2022 –	Associate Professor, with tenure, UT Health San Antonio
2017 – Present	Assistant Professor/Tenure track, UT Health at San Antonio, (UTHSA) Investigator, Greehey Children's Cancer Research Institute, UTHSA Faculty, UTSA-UTHSA Joint Graduate Program in Biomedical Engineering (BME)
2013 – 2017	Research Assistant Professor, Icahn School of Medicine at Mount Sinai, New York, NY
2009 – 2012	Instructor, Icahn School of Medicine at Mount Sinai, New York, NY
2005 – 2009	Postdoctoral fellowship, Mount Sinai School of Medicine, New York, NY (Advisor: Dr. Aneel Aggarwal)
2002 – 2005	Graduate Student, CERM, University of Florence, Florence, Italy (Advisors: Drs. C. Luchinat and I. Bertini)
7/2001 – 2/2001	Research Intern, National Institute of Immunology, New Delhi, India
5/2001 – 7/2001	VSRP Fellow, Tata Institute of Fundamental Research, Mumbai, India
1/2000 – 7/2000	Research Intern, JALMA Institute for Leprosy & Other Mycobacterial Diseases, Agra, India

Service to the University and Other Commitments

2021 – Present	Search Committee for Biochemistry faculty, UTHSA, Member
2020	MITACS program, Canada, Grant Reviewer
2019	Childhood Cancer Symposium, San Antonio (session: Epigenetic and pathways), co-Chair
2019 – Present	Seminar Series Planning Committee, Greehey Children's Cancer Institute, UTHSA, Chair
2019 – Present	Chemical safety committee, UT Health San Antonio, Member
2019 – Present	Discipline Executive Committee, Biochemical Mechanisms in Medicine, UTHSA, Member
2019	Search Committee for Junior and Senior Biochemistry faculty, UTHSA, Member
2018	Search Committee for Welch Chair (Senior) in Biochemistry, UTHSA, Member
2017– Present	American Association for Cancer Research, Member
2017– Present	Graduate Student Admission Committee, UTHSA, Member
2017– Present	Mays Cancer Center, UTHSA MD Anderson Cancer Center, Member
2017– Present	Structural biology advisory committee, UTHSA, Member
2016 – Present	*Ad-hoc* Reviewer: Nature Communications, Science Advances, eLife, J of Virology, RNA, Genes and Immunity, RNA Biology, Molecular Biology Reports, The Protein Journal

Honors

2022 Reviewing editor, eLife
2021 Rising Star Award for Basic & Translational Research, Long School of Medicine, UTHSA
2021 Guest Reviewing Editor, eLife
2020 Institutional Nominee, Mallinckrodt Foundation Scholar Award
2020 Clinical Translational Science Award, UTHSA
2020 San Antonio Partnership for Precision Therapeutics Award
2019 Co-chair, Epigenetics and Pathways session, Childhood Cancer Symposium, San Antonio, TX
2019 President's Translational and Entrepreneurial Funds Award
2019 Young Investigator Award by the Max and Minnie Tomerlin Voelcker Trust Fund
2017 Rising STARs Award by the University of Texas system
2017 Institutional Nominee, Pew-Stewart Scholar for Cancer Research
2012 Outstanding Poster Award, New York Structural Biology Discussion Group Meeting, New York
2008 Best Poster Award, Department retreat, Icahn School of Medicine at Mount Sinai, New York
2007 Institutional Nominee, Charles Revson Senior Fellowship in Biomedical Sciences
2004 Assegnista di Ricerca (Research fellowship), Ministry of Education, Italy
2003 CIRMMP Fellowship for International Ph.D. program in Structural Biology (joint program of University of Florence, Utrecht University, Goethe University Frankfurt)
2001 VSRP Fellow, Tata Institute of Fundamental Research, Mumbai, India
2000 Fellowship to pursue M. Tech program, Department of Biotechnology, Govt. of India
1991 National Scholarship, Department of Education, Govt. of India

C. Contributions to Science

1. Structural and Mechanistic Insights into RNA/DNA Metabolism during Host-Pathogen Interaction

The elucidation of first structure of EcoP15I (Type III R-M enzyme) represents a milestone in the field of dimeric DNA methyltransferases (MTases) and SF2 type ATP motors. It provided a simple and compelling model of the coordinated action of DNA MTases and pseudo-helicase subunits in DNA recognition, asymmetric DNA methylation, and ATP-triggered long-range diffusion –activities that help bacteria evade viral infections. We have also provided mechanistic insights into human PrimPol, a novel DNA damage repair enzyme that couples DNA primase and polymerase activities to maintain genome integrity. PrimPol can bypass ultraviolet light-induced DNA lesions and/or skip them altogether to initiate *de novo* DNA synthesis downstream to a damage. More recently, we have elucidated the first structure of a ternary complex of SARS-CoV-2 nsp16/nsp10 2'-O methyltransferase with RNA cap and methyl donor SAM. This work revealed an induced fit model for RNA cap modification by SARS-CoV-2, and how the virally encoded mRNAs evade the innate immune response. We are expanding this work to further elucidate structure and mechanism of RNA processing machinery of SARS-CoV-2.

a. **Gupta Y.K.,** Yang L., Chan S.H., Samuelson J.C., Xu S.Y., Aggarwal A.K. Structural insights into the assembly and shape of Type III restriction-modification (R-M) EcoP15I complex by small-angle X-ray scattering. J Mol Biol. 2012 Jul 20;420(4-5):261-8.
b. **Gupta Y.K.,** Chan S.H., Xu S.Y., Aggarwal A.K. Structural basis of asymmetric DNA methylation and ATP-triggered long-range diffusion by EcoP15I. Nature Communications 2015 Jun 6:7363.
c. Rechkoblit O.,* **Gupta Y.K.,*** Malik R.,* Rajashankar K.R., Johnson R.E., Prakash L., Prakash S., Aggarwal A.K. Structure and mechanism of human PrimPol, a DNA polymerase with primase activity. Science Advances 2016 Oct 21;2: e1601317. * Co-first author
d. Viswanathan T., Arya S., Chan S.H., Qi S., Dai N., Misra A., Park J.G., Oladunni F., Kovalskyy D., Hromas R.A., Martinez-Sobrido L., **Gupta Y.K.***. Structural basis of RNA cap modification by SARS-CoV-2. Nature Communications 2020 July 24: 3718. *corresponding author

2. RNA binding proteins, and mRNA modifications in development and cancer progression

We are deeply interested in understanding the cross talk, mode of assembly, mRNA specificity, and architecture of human N^6-methyladenosine (m^6A) writing enzymes, METTL3/METTL14 in particular. With an aim to develop the m^6A human RNA methylome as a therapeutic regime, understanding the interplay of these factors in cancer cells becomes crucial. We recently uncovered the interplay of m^6A writer/eraser/reader components. We also studied structures of other RBPs such as human Pumilio/RNA complexes with an aim to understand the molecular promiscuity its Puf repeats. Pumilio is a modular and sequence specific RNA binding protein. This work sheds unprecedented details on alternate modes of RNA recognition by Puf repeats and furthers our understanding of the underlying complexity for engineering Puf specificities. More recently, using HTS approach, we identified a small molecule inhibitor against an RNA binding protein Musashi1 for glioblastoma therapy.

a. **Gupta Y.K.,** Nair D.T., Wharton R.P., Aggarwal A.K. Structures of human pumilio with noncognate RNAs reveal molecular mechanisms for binding promiscuity. Structure 2008 Apr;16, 549-557.
b. **Gupta Y.K.,** Lee T.H., Edwards T.A., Escalante C.R., Kadyrova L.Y., Wharton R.P., Aggarwal A.K. Co-occupancy of two Pumilio molecules on a single hunchback NRE. RNA 2009 Jun;15:1029-35.*
   * One of the structures from this work was featured on Journal's cover (RNA 2009 Jun;15:1029-35)
c. Paneerdoss S., Eedunuri V., Timilsina S., Rajamanickam S., Suryavathi V., Yadav P., Abdelfattah N., Onyeagucha B., Cui X., Mohammad T., **Gupta Y.K.,** Huang T., Huang Y., Chen Y., Rao M.K. Cross-talk among writer, reader and eraser of m^6A regulates cancer growth and progression. Science Advances 2018 Oct 3;Vol. 4, no. 10, eaar8263
d. Yi C., Li G., Ivanov D.N., Wang Z., Velasco M., Hernandez G., Kaundal S., Villarreal J., **Gupta Y.K.,** Qiao M, Hubert CG, Hart MJ, Penalva LOF. Luteolin inhibits Musashi1 binding to RNA and disrupts cancer phenotypes in glioblastoma cells. RNA Biology 2018 Oct 26.

3. Structure-based approaches in drug discovery

In addition to solving structures related to basic biology described above, we also defined a novel way of targeting the human RAS oncogene by a small molecule that binds to the RAS binding domain (RBD) of RAF proteins, and thus may act as RAS-mimetic to block cancer signaling. This molecule is currently in phase III clinical trials for myelodysplastic syndrome. Repositioning FDA-approved drugs with known side effects has become a major focus of drug development. Bisphosphonates are the most commonly prescribed medicines for osteoporosis and skeletal metastases. They also reduce tumor burden and improve survival, but only in some patients. We have defined the mechanism of action of bisphosphonates and introduced the concept that they could be repurposed against HER-family driven lung and breast cancers. These studies emphasized the strength of structural biology in addressing the basic mechanisms and developing new therapeutic modalities. More recently, we have characterized a new role of an RNA binding protein SERBP1 in progression and development of glioblastoma.

a. Stachnik A, Yuen T, Iqbal J, Sgobba M, **Gupta YK,** Lu P, Colaianni G, Ji Y, Zhu LL, Kim SM, Li J, Liu P, Izadmehr S, Sangodkar J, Scherer T, Mujtaba S, Galsky M, Gomez J, Epstein S, Buettner C, Bian Z, Zallone A, Aggarwal AK, Haider S, New MI, Sun L, Narla G, Zaidi M. Repurposing of bisphosphonates for the prevention and therapy of nonsmall cell lung and breast cancer. **Proc Natl Acad Sci U S A** 2014 Dec 16;111(50):17995-8000
b. Yuen T, Stachnik A, Iqbal J, Sgobba M, **Gupta YK,** Lu P, Colaianni G, Ji Y, Zhu LL, Kim SM, Li J, Liu P, Izadmehr S, Sangodkar J, Bailey J, Latif Y, Mujtaba S, Epstein S, Davies TF, Bian Z, Zallone A, Aggarwal AK, Haider S, New MI, Sun L, Narla G, Zaidi M. Bisphosphonates inactivate human EGFRs to exert antitumor actions. **Proc Natl Acad Sci U S A** 2014 Dec 16;111(50):17989-94.
c. Divakar S., Vasquez R., Dutta K., Baker S.J., Cosenza S.C., Basu I., **Gupta Y.K.,** Reddy M.V., Ueno L., Hart J.R., Vogt P.K., Mullholland D., Guha C., Aggarwal A.K., Reddy E.P. A small molecule RAS-mimetic disrupts RAS association with effector proteins to block signaling. **Cell** 2016 Apr 21;165(3):643-655.*
   * Highlighted by **Nature Reviews Drug Discovery** 2016 June 1 (15):381, **Cancer Discovery** 2016 June 2 (6):573.
d. Kosti A, Rosa de Araujo P, Li W, Guardia GD, Chiou J, Yi C, Ray D, Meliso F, Li Y-M, Delambre T, Qiao M, Burns S, Lorbeer FK, Georgi F, Flosbach M, Klinnert S, Jenseit A, Lei X, Sandoval K, Kevin C. Ha, Zheng H, Pandey R, Gruslova A, **Gupta YK**, Brenner AJ, Kokovay E, Hughes TR, Morris Q,

Galante PA, Tiziani S, Penalva L. The RNA binding protein SERBP1 functions as a novel oncogenic factor in glioblastoma by bridging "cancer metabolism" and epigenetic regulation. **Genome Biology** 2020 August 06; 21 (195): 1-32.

4. Structure-based enzyme engineering to develop novel DNA scissors.

Bi-functional R-M enzymes such as MmeI family members provide a natural platform for engineering new DNA-binding specificities to produce designer DNA scissors, but these efforts were hampered due to lack of structural information. Our studies on the MmeI/DNA complex provided a framework to produce hundreds of derivatives of MmeI that could potentially be used as new tools for biotechnology. We have also made successful strides in understanding and designing of novel nicking endonucleases (NEases) for DNA manipulation and their potential for molecular diagnostics. This work was done in collaboration with Dr. Richard Roberts's team at New England Biolabs.

a. Xu SY, **Gupta YK.** Natural zinc ribbon HNH endonucleases and engineered zinc finger nicking endonuclease. Nucleic Acids Res. 2013 Jan 1;41(1):378-90.
b. Thompson R., Shah R.B., Liu P.H., **Gupta Y.K.,** Ando K., Aggarwal A.K., Sidi S. (2015) An inhibitor of PIDDosome formation. Mol Cell 2015 Jun 4;58(5): 767-79.
c. Callahan S.J., Luyten Y.A., **Gupta Y.K.,** Wilson G.G., Roberts R.J., Morgan R.D., Aggarwal A.K. Structure of Type IIL Restriction-Modification Enzyme MmeI in Complex with DNA Has Implications for Engineering New Specificities. PLoS Biology 2016 Apr 15;14(4):e1002442.

5. NMR characterization of metal and RNA binding proteins, and development of NMR methods

My graduate and early postdoc work describe extensive characterization of metallo and RNA binding proteins by NMR spectroscopy. In my PhD, I developed new NMR spectroscopy methods and studied conformational freedom in flexible domains in a single protein by NMR. This approach is widely used for investigating the weak protein-protein interactions by NMR. We also applied this method to characterize the mode of calmodulin interaction to human α-synuclein, a protein associated with neurological disorders.

a. Baig, I., Bertini, I., Del Bianco, C., **Gupta, Y.K.,** Lee, Y.M., Luchinat, C., Quattrone, A. Paramagnetism-based refinement strategy for the solution structure of human α-Parvalbumin. **Biochemistry** 2004 May 11;43 (18), 5562 –5573. ¶
b. Bertini, I., **Gupta Y.K.,** Luchinat, C., Parigi, G., Schlörb C., Schwalbe H. NMR Spectroscopic detection of protein protons and longitudinal relaxation rates between 0.01 and 50 MHz. **Angew. Chem. Int. Ed.**, 2005 Apr 8;44 (15), 2223-5. ¶
c. Edwards, T.A., Butterwick, J.A., Zeng, L., **Gupta, Y.K.,** Wang, X., Wharton, R.P., Palmer III, A.G., Aggarwal, A.K. Solution structure of the Vts1 SAM domain in the presence of RNA. **J. Mol. Biol.** 2006 Mar 10;356(5):1065-72.
d. Bertini, I., **Gupta, Y.K.,** Luchinat, C, Parigi, G., Peana, M., Sgheri L., Yuan J. Paramagnetism-based NMR restraints provide maximum allowed probabilities for the different conformations of partially independent protein domains. **J. Am. Chem. Soc.** 2007 Oct 24;129(42):12786-12794. ¶

Note: ¶ I am the primary author in 3 publications of this section, but authors were alphabetically ordered by their surnames as per institutional (CERM, Univ. of Florence, Italy) rule in these three (3) publications.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/52614760/?sort=date&direction=descending