BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Gupta, Yogesh K.

eRA COMMONS USER NAME: YGUPTA

POSITION TITLE: Associate 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

As a graduate student, I was trained in the lab of Late Prof. Ivano Bertini, a pioneer in the field of paramagnetic NMR spectroscopy. As a postdoc, I was mentored by a renowned structural biologist, Dr. Aneel Aggarwal, at Mount Sinai School of Medicine. I started my independent research program at Greehey Children's Cancer Research Institute (GCCRI) of UT Health San Antonio in 2017. I determined the first structure of a Type III Restriction-Modification enzyme EcoP15I complex (~280 kDa) to 2.6Å by X-ray crystallography. This study provides the foundation of the idea of ATP-driven long-range communication on DNA and a remarkable 'division of labor' by the two methyltransferases (MTases) for DNA recognition and methylation (**Nature Commun 2015**). We postulated that all dimeric DNA/RNA MTases, including human METTL3/METTL14 may function akin to EcoP15I. Our work on a newly discovered enzyme, PrimPol provided unprecedented details regarding how a bifunctional enzyme couples DNA primase and polymerase activities to maintain genome integrity in human cells (**Nature Commun 2021, Science Adv 2016**)**.** My independent research laboratory investigates how different enzymes and accessory factors write and erase various chemical modifications (2'-*O-methyl ribose* and N^6-*methyladenosine*) in nucleic acids to affect cellular homeostasis and disease outcomes. I combine enzyme biochemistry and structural biology methods to elucidate the structures and mechanisms of nucleoprotein complexes relevant to cancer growth and infectious diseases. We recently uncovered a new RNA-mediated regulation of m^6dA activity of human METTL3-METTL14 enzymes (**eLife 2022**). We also revealed the structural basis for the 2'-*O* methylation of mRNA cap by SARS-CoV-2 (**Nature Commun 2021, 2020**). I also contributed to several studies on m^6A enzymes in the growth and progression of pediatric sarcomas and breast cancers (**Cancer Research, 2022; Science Advances 2018**). Currently, we are investigating the structures, specificity, and basic mechanisms underlying genome replication and integrity in human viruses.

Active research projects:

1R01AI161363 Gupta (PI) 8/1/21 – 7/31/26
NIH/NIAID
Mechanism based targeting of RNA processing machinery of SARS-CoV-2
This application received an exceptional impact/priority score.

AQ- 2101 Gupta (PI) 6/1/22 – 5/31/25
Welch Foundation
Covalent nucleic acid modification in DNA repair and innate immune response

U01AG073148 Zaidi (PI), Gupta (subaward PI) 9/30/21 – 8/31/26
NIH/NIA

A Humanized Monoclonal FSH Blocking Antibody for Alzheimer's Disease

RP200110 Rao and Gupta (MPI) 3/1/20 – 2/28/24
Cancer Prevention Research Institute of Texas (CPRIT)
ALKBH5 as a novel promoter of osteosarcoma growth and metastasis

Peer-reviewed publications that highlight my experience and qualifications are:

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 article at Nature Communications, Featured by Advanced Photon Source as significant discovery]
4. **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

Complete list of publications (a total of 28 peer-reviewed research articles) in my Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/52614760/?sort=date&direction=descending

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022 – present	Associate Professor (tenured), UT Health San Antonio, San Antonio (UTHSA), TX
2017 – 2022	Assistant Professor/Tenure track, UT Health San Antonio, San Antonio, TX 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
2009 – 2012	Instructor, Icahn School of Medicine at Mount Sinai, New York
2005 – 2009	Postdoctoral fellowship, Mount Sinai School of Medicine, New York (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

2023	NIH MSFC (Macromolecular Structure and Function C) study section
2023	NSF GFRP (Graduate Fellowship Research Program) review panel
2022	Search Committee for Biochemistry faculty, UTHSA, Member
2022	*Ad hoc* grant reviewer, Swiss National Science Foundation
2021	Search Committee for Biochemistry faculty, UTHSA, Member
2020	*Ad hoc* grant reviewer, MITACS program, Canada
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, Structure, J of Virology, RNA, Genes and Immunity, RNA Biology, Cancer Research Commun

Honors

2022 Reviewing editor, eLife
2021 Long School of Medicine Rising Star Award for Basic and Translational Research, 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
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 DNA motors and Repair enzymes

The elucidation of first structures of EcoP15I (Type III R-M enzyme), and human PrimPol enzymes represents milestones in the field of dimeric DNA methyltransferases (MTases), SF2 type DNA motors, and bifunctional DNA primase and polymerase enzymes. EcoP15I study 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 bacteriophage 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 presented several structures of PrimPol to show how this bifunctional enzyme accurately synthesize DNA opposite oxidatively damaged DNA in human cells.

a. Rechkoblit O., Johnson R.E., **Gupta Y.K.**, Prakash L., Prakash S., Aggarwal A.K. Structural basis of DNA synthesis opposite 8-oxoguanine by human PrimPol primase-polymerase. **Nature Communications**. 2021 Jun 29;12(1):4020. PMID: 34188055
b. 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. PMID: 27819052 * Co-first author
c. **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. PMID: 26067164
d. **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. PMID: 22560991

2. Nucleic acid binding and chemical modifications in human development and pediatric cancers

Many childhood cancers may be viewed as diseases of arrested differentiation. RNA binding proteins and RNA modification enzymes provide new opportunities of therapeutic targeting in pediatric cancers. We are taking an integrative structural biology approach to understand the cross talk, mode of assembly, substrate specificity, and architecture of human N^6-methyladenosine (m^6A) writer (METTL3/METTL14) and eraser (ALKBH5) enzymes in pediatric leukemias, sarcomas. Our work deciphered the substrate specificity and regulation of METTL3-14 by structured RNA elements. In another recent study, we uncovered a cancer specific interplay of m^6A components and epigenetic regulation by an ALKBH5 in osteosarcoma. I also led studies that elucidated the atomic level details of SARS-CoV-2 mRNA capping machinery. This work revealed an induced fit model for RNA cap modification, and mechanism by which the viral mRNAs evade the innate immune response. Our earlier work includes structural elucidation of 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.

a. Yadav P., Panneerdoss S., Rajamanickam S., Eedunuri V.K., Timilsina S., **Gupta Y.K.**, Huang Y., Hromas R., Meltzer P., Houghton P., Chen Y., Rao M.K. M6A RNA methylation regulates histone ubiquitination to support tumor growth and progression. **Cancer Research** 2022 May 16;82(10):1872-1889. PMID: 35303054

b. Viswanathan T., Misra A., Chan S-H., Qi S., Dai N., Arya S., Martinez-Sobrido L., **Gupta Y.K.*** A metal ion orients SARS-CoV-2 mRNA to ensure accurate 2'-*O* methylation of its first nucleotide. **Nature Communications***.* 2021 Jun 29;12 (1):4020. PMID: 34078893. *corresponding author

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. PMID: 30306128

d. **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.

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 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. 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. PMID: 32762776

b. 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.PMID: 27104980. * Highlighted by **Nature Reviews Drug Discovery** 2016 June 1 (15):381, **Cancer Discovery** 2016 June 2 (6):573.

c. 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. PMID: 25453078

d. 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. PMID: 25453081

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. 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.

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. 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.

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. 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. PMID: 17910448 ¶

b. 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. PMID: 16405996

c. 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. PMID: 15751103 ¶

d. 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. PMID: 15122922 ¶

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