## BIOGRAPHICAL SKETCH

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NAME: **Yogesh K. Gupta**

eRA COMMONS USER NAME: **YGUPTA**

POSITION TITLE: **Assistant Professor**

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 | 06/2012 | Structural and Chemical Biology |

### A. Personal Statement

My independent research program is directed at investigating the mechanisms by which different enzymes and accessory factors cross talk to modify RNA with 2'-O methyl, $N^6$-methyladenosine ($m^6A$), and 5-methylcytosine ($m^5C$) marks to regulate disease development and progression. I employ structural and biophysical methods together with cell-based assays, to elucidate structure and function of nucleoprotein complexes implicated in RNA/DNA metabolism. Recent work from my independent lab uncovered the structural basis of the 2'-O methylation of RNA cap by SARS-CoV-2 (**Nature Communications**, **2020**). 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 (**Science Advances 2016**)**.** Solving the structures of RNA methyltransferase (SARS-CoV-2 nsp16/nsp10), DNA motor (EcoP15I, a prototype of Type III Restriction-Modification enzymes), 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 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 RNA processing machinery of SARS-CoV-2 and its interplay with the host factors to better understand the biology of pathogenesis and develop more specific antivirals against COVID-19 and emerging coronaviral infections.


1. 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**
   [highlighted by >40 international media outlets, received >30,000 article accesses in 1 week]
2. 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**
3. **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.
4. **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.
   * One of the structures from this work was featured on Journal's cover (**RNA** 2009 Jun;15:1029-35)

## B. Positions and Honors

### Positions

| | |
|---|---|
| 01/2000-07/2000 | Project trainee, JALMA Institute for Leprosy & Other Mycobacterial Diseases, Agra, India |
| 05/2001-07/2001 | VSRP Fellow, Tata Institute of Fundamental Research, Mumbai, India |
| 07/2001-12/2001 | Research Project Trainee, National Institute of Immunology, New Delhi, India |
| 2002 – 2005 | Graduate Student, CERM, University of Florence, Florence, Italy<br>(Advisors: Drs. C. Luchinat and I. Bertini) |
| 2005 – 2009 | Postdoctoral fellowship, Mount Sinai School of Medicine, New York, NY<br>(Advisor: Dr. Aneel Aggarwal) |
| 2009 – 2012 | Instructor, Icahn School of Medicine at Mount Sinai, New York, NY |
| 2013 – 2017 | Research Assistant Professor, Icahn School of Medicine at Mount Sinai, New York, NY |
| 03/2017–present | Assistant Professor/Tenure track, UT Health at San Antonio (UTHSA), San Antonio, TX<br>Principal Investigator, Greehey Children's Cancer Research Institute, UTHSA<br>Faculty, UTSA-UTHSA Joint Graduate Program in Biomedical Engineering (BME) |

### Honors

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

## C. Contributions to Science

**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**

**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. High genomic amplification of METTL3 is linked to maintenance of tumorigenic state in AML and lung cancer cells. 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.*
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.

**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.

**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.

**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 23 peer-reviewed publications in my Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/52614760/?sort=date&direction=descending

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

**Research Support (Active)**

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|---|---|
| 165548-44096 (PI, Gupta)<br>Young Investigator Award by the Max and Minnie Tomerlin Voelcker Fund<br>Title: EEPD1 rescues oxidized replication forks<br>Goal: Explore the structure/function of a DNA repair enzyme EEPD1. | 07/01/2019 – 06/30/2022 |
| RP200110 (MPI, Gupta and Rao)<br>Cancer Prevention Research Institute of Texas (CPRIT)<br>Title: RNA Demethylase ALKBH5 as a Novel Therapeutic Target for Treating Osteosarcoma<br>Goal: Characterize pro-tumorigenic role and therapeutic potential of ALKBH5 in osteosarcoma. | 03/01/2020 – 02/28/2024 |
| RP190534 (PI, Gupta)<br>High Impact/High Risk Award by Cancer Prevention Research Institute of Texas (CPRIT)<br>Title: Mechanism-based targeting of core module of the BAF complex in Cancer<br>Goal: Develop strategies for targeting the BRG1/BRM enzyme in Ewing's sarcoma. | 08/31/2019 – 08/30/2021 |
| 165287 (PI, Gupta)<br>San Antonio Area Foundation<br>Title: Towards Understanding the Nature of Altered RNA Methylation Program in Cancer.<br>Goal: Develop a screening protocol for identification of an RNA methyltransferase antagonist for leukemia treatment. | 03/2019 – 09/2020 |
| 1R01CA239227 (co-I, Gupta; PI, Rao)<br>NIH/NCI<br>Title: FOXM1 inhibition: A novel therapeutic avenue to treat breast cancers.<br>Goal: Evaluate therapeutic potential of FoxM1 inhibition for treatment of triple negative breast cancers. | 12/01/2019 – 11/30/2024 |
| RP190012 (co-I, Gupta; PI, Kumar)<br>Cancer Prevention Research Institute of Texas<br>Title: *Berberine in prevention of biochemical recurrence*<br>Goal: Evaluate therapeutic potential of berberine in prostate cancer. | 03/01/2019– 02/28/2022 |

## Scholastic Performance

### Professional Activities and University Services

2010 Member, The New York Academy of Sciences
2015 Judge for poster awards, New York Structural Biology Discussion Group Meeting, New York
2016 – ***Ad-hoc* Reviewer: Nature Communications, Science Advances, eLife, RNA, Genes and Immunity, RNA Biology, Molecular Biology Reports, The Protein Journal**
2017 Judge for poster awards, San Antonio Postdoctoral Research Forum, BSB departmental retreat
2017– Member, X-ray core advisory committee, UTHSA
2017– Member, Mays Cancer Center, UTHSA MD Anderson Cancer Center
2017– Member, Graduate Student Admission Committee, UTHSA
2017– Member, American Association for Cancer Research
2018 **Member, Search Committee for Welch Chair (Senior) in Biochemistry, UTHSA**
2019 Member, Search Committee for Junior and Senior Biochemistry faculty, UTHSA
2019 Member, Discipline Executive Committee, Biochemical Mechanisms in Medicine of IBMS, UTHSA
2019 – Member, Chemical safety committee, UT Health San Antonio
2019 – **Chair, Seminar Series Planning Committee, Greehey Children's Cancer Institute, UTHSA**
2020 – Member, NMR core advisory committee, UTHSA

### Teaching Responsibilities at UTHSA

2018 – *"Molecules to Medicine"* course to 1st and 2nd year medical students (4 lectures)
2018 – *"BIOC6036"* course (Macromolecular Structure and Function) to graduate students (2 lectures)
2019 – "*BIOC6010*" course (Gene Expression and Omics) to graduate students (2 lectures)
2019 – *"Digestive Health and Nutrition"* course to 2nd year medical students (3 lectures)
2021 – "*Form and Function*" course to 2nd year medical students (1 lecture)
2021 – Course director: *BIOC6036 Macromolecular Structure and Mechanism (IBMS graduate school)*