

**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: Aneel K. Aggarwal

eRA COMMONS USER NAME (credential, e.g., agency login): aggarwal1

POSITION TITLE: Professor

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
King College, University of London, England	B.Sc.	1981	Biology & Physics
Kings College, University of London, England	Ph.D.	1984	Biophysics
Harvard University, Cambridge, MA	Postdoc.	1984-89	Biochem. & Mol. Biol.

**A. Personal Statement**

My laboratory has made seminal contributions in the study of protein-ligand interactions and to the discovery of therapeutics. I have published more than 130 peer-reviewed papers (including 22 in *Nature*, *Science*, and *Cell*) and more than 15 reviews/book chapters. My laboratory employs a range of modern biophysical and structural methods, from X-ray crystallography and NMR to Cryo-EM to study protein-ligand interactions. I have also trained >30 pre- and post-doctorates who have gone onto successful careers in academia and industry. Overall, my research has had a powerful and sustained influence in the fields of protein-ligand interactions and structural biology for over 30 years.

1. A.K. Aggarwal, D.W. Rodgers, M. Drottar, M. Ptashne, and S.C. Harrison (1988). Recognition of DNA operator by the repressor of phage 434: A view at high resolution. **Science** 242, 899-907.
2. M. Newman, T. Strzelecka, L.F. Dorner, I. Schildkraut, and A.K. Aggarwal (1995). Structure of *Bam*HI endonuclease bound to DNA: Partial folding and unfolding on DNA binding. **Science** 269, 656-663.
3. J. Trincao, R.E. Johnson, C.R. Escalante, S. Prakash, L. Prakash, and A.K. Aggarwal (2001). Structure of the catalytic core of *S. cerevisiae* DNA polymerase  $\eta$ : implications for translesion DNA synthesis. **Mol. Cell** 8, 417-426
4. T. D. Silverstein, R.E. Johnson, R. Jain, L. Prakash, S. Parakash, and A.K. Aggarwal (2010). Structural basis for the suppression of skin cancers by DNA polymerase  $\eta$ . **Nature** 465, 1039-1043

**B. Positions and Honors****Positions and Employment**

1989-97	Assistant Professor, Department of Biochemistry and Molecular Biophysics, Columbia University
1997-02	Associate Professor, Department of Physiology and Biophysics, Mount Sinai School of Medicine
2002-16	Professor, Department of Structural and Chemical Biology, Mount Sinai School of Medicine
2003-present	Professor, Department of Oncological Sciences, Mount Sinai School of Medicine
2016-present	Professor and Vice Chair, Department of Pharmacological Sciences, Mount Sinai School of Medicine

## Honors and Awards

1981	B.Sc. with First Class Honors
1981	Flowers Memorial Prize in Physics, Kings College
1981	Layton Science Research Prize, Kings College
1981-84	Predoctoral Scholarship, Science and Engineering Research Council of Great Britain
1985-87	NATO Research Fellowship
1990-95	Irma T. Hirschl Career Scientist Award
1990-92	Basil O'Connor Starter Scholar Research Award
1995	The Doctor Harold and Golden Lamport Award for Excellence in Basic Science Research, Columbia University
2007	Endowed Chair, Mount Sinai Professor in Structural Biology
2010	Faculty Council Award for Academic Excellence, Mount Sinai
2012	Dean's Award for Excellence in Basic Science Research
2018-present	Elected Fellow, Royal Society of Biology (UK)

## Service

1997-98	Biology Panel, Brookhaven National Synchrotron Light Source
1999	Ad-Hoc Member, BBCA Study Section, NIH
1999	Guest Reviewer, Damon-Runyon Walter Winchell Cancer Research Fund
1999	Panel Member, National Cancer Institute Site Visit, Wistar Institute
2000-04	Charter Member, BBCA Study Section, NIH
2001	Member, Special Emphasis Panel, NIDCD, NIH
2002	Member, High End Instrumentation Panel, NRCC, NIH
2003, 2005	Section Editor, Current Opinions in Structural Biology
2008	Beamline Review Committee, Brookhaven National Synchrotron Light Source
2010	NIH Special Study Section, Member Conflicts in Biochemistry and Biophysics
2006-Present	Board of Directors, New York Structural Biology Center
2012	SMART (Students Modeling A Research Topic) Team Mentor for High School Students
2015	Ad-Hoc Member, MSFC Study Section, NIH
2016	NYX Beamline Advisory Team, Brookhaven National Laboratory

## **C. Contributions to Science**

1 **Transcription.** In the 1980s, a pressing question in transcription related to the existence of a protein-DNA recognition code. As such, many laboratories made an intense effort to derive the first high-resolution structure of a protein-DNA complex. As a postdoctoral fellow in Dr. Stephen Harrison's laboratory at Harvard, I solved one of the first high-resolution crystal structures of a protein-DNA complex, namely that of phage 434 repressor in complex with its regulatory OR1 DNA operator site (*Science*, 1988). The structure revealed an intricate network of interactions and laid the basis for direct and indirect readout of DNA sequence. I followed up this work when I established my independent laboratory at Columbia University - but with an increasing focus on eukaryotic transcription factors. This work was motivated by questions of how closely related transcription factors achieve specificity *in vivo*, as pertaining to homeodomain proteins; and, in understanding the innate cellular response to viral infection mediated by interferon regulatory factors (IRFs). In collaboration with many wonderful colleagues such as Drs. Michael G. Rosenfeld, Richard Mann and Dimitris Thanos, we established some of the first structural principles by which eukaryotic transcription factors come together to form cooperative, combinatorial complexes to specifically bind DNA enhancer sites *in vivo*. In collaboration with Dr. M.M Zhou (*Nature*, 1999), we also showed for the first time that the bromodomain, present in many chromatin modifiers, is an acetyl-lysine binding module. The implications of this finding extend to many transcriptional systems.

- a. C.R. Escalante, J. Yie, D. Thanos, and A.K. Aggarwal (1998). Structure of IRF-1 with bound DNA reveals determinants of interferon regulation. **Nature** 391, 103-106
- b. J. M. Passner, H.-D. Ryoo, L. Shen, R.S. Mann, and A.K. Aggarwal (1999). Structure of a DNA-bound Ultrabithorax-Extradenticle homeodomain complex. **Nature** 397, 714-719

- c. K. Scully, E.M. Jacobson, K. Jepsen, V. Lunyak, H. Viadiu, C. Carriere, D.W. Rose, F. Hooshmand, A.K. Aggarwal\*, M.G. Rosenfeld\* (2000). Allosteric effects of Pit-1 DNA sites on long-term repression in cell-type specification. **Science** 290, 1127-1132 (\* co-corresponding authors)
- d. C.R. Escalante, E. Nistal-Villán, L. Shen, A. García-Sastre, and A.K. Aggarwal (2007). Structure of IRF-3 bound to the PRDIII-I regulatory element of the human interferon-beta enhancer. **Mol. Cell** 26, 703-716

**2. Restriction Enzymes and DNA Diffusion.** The central problem faced by all DNA binding proteins is how to select the correct DNA sequence from the vast sea of non-specific sequences in a cell. The problem is particularly acute for restriction enzymes because cleavage at an incorrect DNA site can be lethal for the cell. To understand the stereochemical basis of the extraordinary specificity of restriction enzymes, in collaboration with many wonderful colleagues at New England Biolabs Inc, we determined structures of BamHI at almost every step of its catalytic pathway. These include structures of the “free”, “non-specific” and “specific” DNA bound forms of the enzyme, as well as structures of the metal bound pre- and post-reactive intermediates along the reaction pathway. Together, these structures provide one of the most complete pictures of the sequence of events underlying sequence specific recognition and DNA cleavage. In further collaborations, we sought to use the structural information on enzymes such as BamHI, FokI, BglII and others, to rationally engineer new restriction enzymes. However, this proved intractable and we showed that this is due their inherent “naturally selected” immutability. Our more recent effort is on a class of ATP-dependent restriction enzymes (Type III), which were discovered >40 years ago (by Dr. Matt Meselson, Dr. Werner Arber and others) but for which there is no structural information. Remarkably, these enzymes communicate over thousands of base pairs by consuming only a few ATPs. Through structural studies on multi-subunit EcoP15I, we have provided the bases by which these enzymes behave as ATP-dependent molecular switches for long-lived DNA sliding - rather than conventional DNA/RNA unwinding or step-wise translocation. Another new direction is a class of MmeI-like enzymes that provide a natural platform for engineering new DNA-binding specificities. These enzymes offer the exciting possibility of creating of hundreds of new enzymes with “true” restriction enzyme specificity.

- a. C.M. Lukacs, R. Kucera, I. Schildkraut, and A.K. Aggarwal (2000). Understanding the immutability of restriction enzymes: crystal structure of BglII and its DNA substrate at 1.5Å resolution. **Nature Struct. Biol.** 7, 134-140
- b. Y.K. Gupta, L. Yang, S.H. Chan, J. Samuelson, S.Y. Xu, and A.K. Aggarwal (2012). 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.** 420, 261-268
- c. Y. K. Gupta, S.H. Chan, S.Y. Xu, and A.K. Aggarwal (2015). Structural basis of asymmetric DNA methylation and ATP-triggered long-range diffusion by EcoP15I. **Nature Comm.** 6, 7363
- d. S.J. Callahan, Y.A. Luyten, Y.K. Gupta, G.G. Wilson, R.J. Roberts, R.D. Morgan, and A.K. Aggarwal (2016). Structure of Type IIL restriction enzyme MmeI in complex with DNA has implications for engineering new specificities. **PLOS Biol** 14, e1002442

**3. Translesion DNA Synthesis and Repair.** The discovery of translesion synthesis (TLS) DNA polymerases about 15 years ago has changed our view of how cells cope with unrepaired DNA damage during replication. My laboratory has pioneered the structural studies of eukaryotic TLS DNA polymerases. In 2001, we reported the first crystal structure of a TLS DNA polymerase, namely yeast Pol $\eta$  (Mol. Cell, 2001). Mutations in human Pol $\eta$  are responsible for the inherited disorder, the variant form of xeroderma pigmentosum (XP-V). XP-V patients are sensitive to UV radiation and they suffer from a high incidence of sunlight induced skin cancers. In collaboration with Drs. Louise and Satya Prakash at UTMB, we followed this up with a number of other structures, which have revealed the remarkable differences in the active site shapes of these TLS polymerases and how these differences in shape manifest in TLS in specific ways. For example, we have discovered that human Pol $\iota$  uses Hoogsteen base pairing to bypass DNA lesions, whereas Rev1 uses itself as a “protein template” to bypass other lesions. Pol $\kappa$  is again different in that it encircles the DNA to maintain a grip on the template-primer for the extension step of the TLS reaction. Our more recent effort has focused on human PrimPol, a newly discovered TLS DNA polymerase that possesses both DNA polymerase and primase activities.

- a. D.T. Nair, R.E. Johnson, S. Prakash, L. Prakash, and A.K. Aggarwal (2004). Replication by human

DNA polymerase- $\epsilon$  occurs by Hoogsteen base-pairing. **Nature** 430, 377-380

- b. D.T. Nair, R.E. Johnson, S. Prakash, L. Prakash, and A.K. Aggarwal (2005). Rev1 employs a novel mechanism of DNA synthesis using a protein template. **Science** 309, 2219-2222
- c. S. Lone, S.A. Townson, S.N. Uljon, R.E. Johnson, A. Brahama, D.T. Nair, S. Prakash, L. Prakash, and A.K. Aggarwal (2007). Human DNA polymerase- $\kappa$  encircles DNA: Implications for mismatch extension and lesion bypass. **Mol. Cell** 25, 601-614
- d. O. Rechkoblit, Y.K. Gupta, R. Malik, K.R. Rajashankar, R.E. Johnson, L. Prakash, S. Prakash, and A.K. Aggarwal (2016). Structure and mechanism of human PrimPol, a DNA polymerase with primase activity **Science Adv.** 2, e1601317

**4. Translational Repression.** Transcription is only one mechanism for regulating gene expression. Translational regulation plays an equally important role, but an understanding of the underlying mechanisms has been hindered by the lack of structural data. Over a period of 10 years, in collaboration with Dr. Robin Wharton, we uncovered the structures of several key proteins that control mRNA translation during early fly development. This included Pumilio, which mediates the repression of *hunchback* mRNA at the posterior end of the fertilized egg, and Smaug, which represses *Nanos* mRNA translation in the bulk cytoplasm. We uncovered for the first time the structural features that allow these translational repressors to bind specific RNA sequences in the 3'UTRs of mRNAs and to form complexes with other components of the translational machinery.

- a. T.A. Edwards, S. Pyle, R.P. Wharton, and A.K. Aggarwal (2001). Structure of Pumilio reveals similarity in RNA and peptide binding motifs **Cell** 105, 281-289
- b. J.B. Green, C.D. Gardner, R.P. Wharton, and A.K. Aggarwal (2003). RNA-recognition via the SAM domain of Smaug. **Mol. Cell** 11, 1537-1548
- c. T.A. Edwards, B.D. Wilkinson, R.P. Wharton, and A.K. Aggarwal (2003). Model of the Brain Tumor Pumilio translation repressor complex. **Genes & Dev.** 17, 2508-2513
- d. Y.K. Gupta, T.H. Lee, T.A. Edwards, R.P. Wharton and A.K. Aggarwal (2009). Co-occupancy of two Pumilio molecules on a single hunchback NRE. **RNA** 15, 1029-1035

**5. Therapeutics.** We are dedicated to developing new chemical therapeutics for the treatment of cancer and viral infections. In collaboration with Dr. E. Premkumar Reddy, we have helped to define the action mechanism of several new drugs undergoing preclinical and clinical cancer trials. An exciting discovery is that rigosertib, which is in phase III clinical trials for myelodysplastic syndrome (MDS), acts as a RAS-mimetic to block the RAS-RAF-MEK signaling pathway. In collaboration with Drs. Adolfo Garcia-Sastre and Jian Jin, we are committed to developing antivirals against the Zika virus (ZIKV) by targeting enzymatic activities central to the life cycle of the virus. Much of our structure-based effort is directed towards the development of small molecule inhibitors against the ZIKV NS5 methyltransferase.

- a. S.K. Athuluri-Divakar, R. Vasquez-Del Carpio, K. Dutta, S. J. Baker, S.C. Cosenza, I. Basu, Y.K. Gupta, M.V. Reddy, C. M. Pflieger, L. Ueno, J.R. Hart, P.K. Vogt, C. Guha, A.K. Aggarwal, and E.P. Reddy (2016). Targeting RAS signaling with a small molecule RAS-mimetic that disrupts RAS interactions with effector proteins. **Cell** 165, 643-655
- b. R. Jain, J. Coloma, A. Garcia-Sastre, and A.K. Aggarwal (2016). Structure of the NS3 helicase from Zika virus. **Nature Struct. Mol. Biol.** 23, 752-754
- c. J. Coloma, R. Jain, K.R. Rajashankar, A. Garcia-Sastre, and A.K. Aggarwal (2016). Structure of NS5 methyltransferase from Zika virus. **Cell Rep.** 16, 3097-3102
- d. R. Jain, K.V. Butler, J. Coloma, J. Jin, and A.K. Aggarwal (2017). Development of a S-adenosylmethionine analog that intrudes the RNA-cap binding site of Zika methyltransferase. **Sci Rep.** 7, 1632

Complete List of Published Work in MyBibliography:

#### **D. Research Support**

R35-GM131780 (Aggarwal) 09/01/2019 - 08/31/2024

Structure and specificity of restriction-modification (R-M) systems

The goal of this project is to understand the structure and mechanism of DNA restriction and modification enzymes.

Role: PI

R01-GM124047 (Aggarwal, Prakash) MPI 09/15/2018 - 08/31/2022

Structure and mechanism of multisubunit complexes of DNA polymerase zeta

The goal is to understand the structure and function of DNA polymerase zeta using cryo-electron microscopy, kinetics and yeast genetics.

Role: Contact PI;

R21-AI142337-01 (PI: Aggarwal; Co-Is: Garcia-Sastre, Jin)

11/12/2018 - 11/30/2020

NIH/NIAID

Structure guided discovery of chemical probes for targeting Zika methyltransferase The goal of the project is to use the structure of Zika NS5 methyltransferase to derive small molecule inhibitors of the virus.

Role: PI

R01-CA200575 (Prakash, S.) 12/1/15 – 11/30/20

Genetic and Molecular Mechanisms of Replication of AraC Damaged DNA

The goals of this project are delineate the mechanisms by which the chemotherapeutic AraC is tolerated in human cells.

Role: Co-I.