BIOGRAPHICAL SKETCH

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NAME: Aneel K. Aggarwal

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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 140 peer-reviewed papers (including 23 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.

Ongoing projects that I would like to highlight include:

R01-GM124047 (MPI)
Aggarwal (Contact PI)
09/15/2018 - 08/31/2022
Structure and mechanism of multisubunit complexes of DNA polymerase zeta

R35-GM131780
Aggarwal (PI)
09/01/2019 - 08/31/2024
Structure and specificity of restriction-modification (R-M) systems

Citations:

1. 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
2. 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 η . **Nature** *465*, 1039-1043
3. R. Jain, W.J. Rice, R. Malik, R.E. Johnson, L. Prakash, S. Prakash, I. Ubarretxena-Belandia, and A.K. Aggarwal (2019). Cryo-EM structure and dynamics of eukaryotic DNA polymerase δ holoenzyme. **Nat. Struct. Mol. Biol.** *26,* 955-963
4. R. Malik, M. Kopylov, Y. Gomez-Llorente, R. Jain, R.E. Johnson, L. Prakash, S. Prakash, I. Ubarretxena-Belandia, and A.K. Aggarwal (2020). Structure and mechanism of B-family DNA polymerase ζ specialized for translesion DNA synthesis. **Nat. Struct. Mol. Biol.** *27,* 913-924

B. Positions, Scientific Appointments, and Honors

Positions

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

Scientific Appointments

2021	Brookhaven National Laboratory Pandemic Discussion Group
2016	NYX Beamline Advisory Team, Brookhaven National Laboratory
2012	SMART (Students Modeling A Research Topic) Team Mentor for High School Students
2010	NIH Special Study Section, Member Conflicts in Biochemistry and Biophysics
2008	Beamline Review Committee, Brookhaven National Synchrotron Light Source
2006-Present	Board of Directors, New York Structural Biology Center, NY
2003, 2005	Guest Editor, Current Opinions in Structural Biology
2002	Member, High End Instrumentation Panel, NRCC, NIH
2000-04	Charter Member, BBCA Study Section, NIH
1999	Guest Reviewer, Damon-Runyon Walter Winchell Cancer Research Fund
1999	Ad-Hoc Member, BBCA Study Section, NIH
1999	Panel Member, National Cancer Institute Site Visit, Wistar Institute
1997-98	Biology Panel, Brookhaven National Synchrotron Light Source

Honors

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

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 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. 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.

b. 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

c. 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

d. 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)

2. **Restriction-Modification.** 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**.** 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. M. Newman, T. Strzelecka, L.F. Dorner, I. Schildkraut, and A.K. Aggarwal (1994). The structure of restriction endonuclease *Bam*HI and its relationship to *Eco*RI. **Nature** *368*, 660-664

b. D.A. Wah, J.A. Hirsch, L.F. Dorner, I. Schildkraut, and A.K. Aggarwal (1997). Structure of the multimodular endonuclease *Fok*I bound to DNA. **Nature** *388*, 97-100

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**. 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 Polη (Mol. Cell, 2001). Mutations in human Polη 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 Polι uses Hoogsteen base pairing to bypass DNA lesions, whereas Rev1 uses itself as a "protein template" to bypass other lesions. Polκ 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. 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 η: implications for translesion DNA synthesis. **Mol. Cell** *8***,** 417-426

b. D.T. Nair, R.E. Johnson, S. Prakash, L. Prakash, and A.K. Aggarwal (2004). Replication by human DNA polymerase-ι occurs by Hoogsteen base-pairing. **Nature** 430, 377-380

c. 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

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 Pumilo, 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. Pfleger, 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:
http://www.ncbi.nlm.nih.gov/sites/myncbi/15gUD6BtY5An/bibliography/40432071/public/?sort=date&direction=descending