DESIGAN KUMARAN PhD

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Summary

- 15 years of drug discovery experience as productive and motivated structural biologist in the infectious disease therapeutic area.
- Scientific expert in X-ray crystallography, protein biochemistry, and molecular biology with a record of 42 peer-reviewed publications and several press release coverages including BBC news.
- Innovative X-ray crystallographer that has solved more than 120 crystal structures including antigens and protein kinases using advanced crystallographic techniques.
- Extensive and proven experience with gene-to-structure pipeline, including construct design, expression, purification, crystallization screening, crystal optimization, acquisition of X-ray data, and structure determination.
- Experience with biochemical and biophysical characterization methods such as analytical ultracentrifugation, isothermal titration calorimetry, surface plasmon resonance, chromatographic techniques, dynamic light scattering, small-angle X-ray scattering, etc.
- Collaboratively led projects in CDC classified Tier I/select A pathogens utilizing, drug discovery, enzyme-substrate/inhibitor complexes, macromolecular crystallography, biochemistry, and molecular biology techniques.
- Experience with membrane protein expression, purification, and crystallization.
- Excellent communication skills (written, presentation, and oral), project management skills, and thrive on challenges to identify/develop new areas of scientific expertise in protein crystallography.

CORE CAPABILITIES

1. Structural Biology
2. Gene-to-Structure Pipeline
3. Structure-based Drug Discovery
4. Protein Crystallography
5. Neurotoxins and Select A Pathogens
6. Membrane Transporters

TECHNICAL SKILLS AND EXPERTISE

X-ray Crystallography: Crystallization using different vapor diffusion and batch techniques in conventional and high throughput environments. Design and implementation of automated robotic crystallization methodologies. Crystallization screening and optimization including seeding techniques. Crystal harvest and mounting tactics, synchrotron and in-house X-ray data collection, and data processing methodologies. Specialized in SAD and MAD data collection with tunable synchrotron beam lines at absorption edges of different heavy atoms.

Structure determination by MR, SAD, MAD, MIR, MIRAS, and SIRAS with crystallography packages such as CCP4i, PHENIX, SHARP, SHELX, CNS, and ARP/wARP. Graphics packages, including COOT, O, Pymol, Molscript, Raster3D, Grasp, and Rasmol.

Molecular Biology: Standard cloning techniques such as PCR, cloning into expression vectors, handling of bacterial and mammalian strains, transformation with plasmids, over expression of recombinant proteins using IPTG and auto induction procedures.

Biochemistry: Protein purification using affinity tags, ion exchange chromatography, and gel filtration. Protein biochemical and biophysical characterization techniques such as analytical ultracentrifugation, isothermal titration calorimetry (ITC), surface plasmon resonance (SPR), dynamic light scattering (DLS), small-angle X-ray scattering (SAXS), etc. Cell-based, HPLC and florescent-based enzyme assay methods and high throughput inhibitor screening. Membrane protein purification.

Enzymology: Enzyme kinetics, mechanism of enzymatic action, transition state intermediates, enzyme substrate/inhibitor interaction studies, site-directed mutagenesis, lead identification and optimization, pharmacophore and Structure Activity Relationship (SAR) studies.

Drug Design: Molecular modeling and drug design using the Insight II (BIOSYM), QUANTA, and MODELLAR. Docking programs such as AutoDock, AutoDock Vina, AutoDock Tools, and PyRx.

KEY ACCOMPLISHMENTS

- Discovered and developed effective inhibitors against bioterrorism agents such as botulinum neurotoxins (BoNTs).

- Cloned non-toxic catalytic domain or light chain (LC) of BoNTs, and performed expression, purification, biochemical/biophysical characterization, crystallization, and X-ray structure determination of native enzyme with and without inhibitors. Executed, docking studies for the inhibitor lead identification and optimization, high-throughput inhibitor assay screening, inhibition mechanism derivation, and structure activity relationship (SAR) studies.

- Discovered structure and substrate-based peptide inhibitors with Ki better than 15nM for Botulinum Neurotoxin serotype A (BoNT/A); project funded by the Defense Threat Reduction Agency (DTRA).

- Conducted structural studies on intact Clostridium botulinum neurotoxins with and without inhibitors; funded by the US Department of Defense (DOD).

- Participated as a member in the New York Structural Genomics Research Consortium (NYSGRC) and determined more than 120 protein structure initiative (PSI) target structures of different organisms,

including biomedically relevant pathogens, and deposited structural coordinates in the Protein Data Bank (PDB).

- Expressed, purified, enzymatically characterized and determined the crystal structures of beta-Hydroxyacyl-Acyl Carrier Protein Dehydratase (FabZ) from *Francisella tularenis* and *Yersenia pestis*.

- Utilized fragment-based and structure-based drug design approach and developed broad-spectrum antimicrobial drugs targeting *Francisella tularensis, Yersenia pestis* and *Burkholderia pseudomallei* pathogens; grant proposal was submitted to the National Institute of Health (NIH) as a team (Co-Investigator).

- Performed structure determination of outer surface protein C (OspC), a major antigen of *Borrelia burgdorferi*, causative agent of Lyme disease.

WORK EXPERIENCE

Employer: BROOKHAVEN NATIONAL LABORATORY

Upton, NY

04/1999 to 09/2015

Biophysicist (10/2009 – 09/2015)

Planned and executed structural biology research, including X-ray crystallography, biochemistry and molecular biology to develop an antidote against bioterrorism agents *viz* Botulinum Neurotoxins (BoNTs). Developed broad-spectrum antimicrobial drugs to target priority pathogens. Successfully completed PSI III phase, including structural and functional characterizations of PSI III targets.

Expressed, purified, and crystallized *Arabidopsis* Sucrose Transporters (ATSUC), which are membrane proteins.

Associate Biophysicist (10/2006 – 9/2009)

Contributed to drug discovery and developments of potential bio-war diseases such as BoNT using biochemistry molecular and structural biology. Performed enzymatic characterization and crystal structure determination of PSI II target proteins.

Developed different strategies for trapping substrate and inhibitors with a drug target, the light chain of BoNT serotype A.

Assistant Biophysicist (1/2004 – 9/2006)

Leveraged biochemistry and x-ray crystallography to investigate botulinum and tetanus neurotoxins in advance therapeutics. Continued high-throughput structure determinations of proteins from various pathogens during PSI I and PSI II phases.

Developed optimal strategies to set up crystallization trays using automated crystallization robotic systems like Phoenix from Art Robbins and TECAN liquid handling systems.

Research Associate/ Guest Research Associate (4/1999 – 12/2003)

Continued high-throughput structure determination of proteins as part of Structural Genomics PSI I research phase. Investigated BoNT and *Staphylococcus* enterotoxins (antigens) to advance vaccine and drug development. Performed structural analysis of Lyme disease antigens to help develop effective vaccine against multiple strains of Lyme disease.

Streamlined the high throughput crystal structure determination pipeline for Protein Structure Initiative (PSI) target proteins

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TRAINING/EDUCATION

Research Fellow/Associate, Dept. of Crystallography and Biophysics, University of Madras, Chennai, India, 1992 – 1999

PH.D.: CHEMISTRY (CRYSTALLOGRAPHY AND BIOPHYSICS) 1998
University of Madras, Chennai, India

MASTER OF SCIENCE: CHEMISTRY 1992
University of Madras, Chennai, India

BACHELOR OF SCIENCE: CHEMISTRY 1990
University of Madras, Chennai, India

AWARDS AND RECOGNITION

BNL Spotlight Award for Exceptional Job Performance, August 2007

Research Fellowship, Council of Scientific and Industrial Research, Government of India

Research Associate Award, Council of Scientific and Industrial Research, Government of India

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PROFESSIONAL AFFILIATIONS

American Crystallographic Association (ACA)

International Union of Crystallography (IUCr)

Indian Crystallographic Association (ICA)

Indian Biophysical Society (IBS)

News Media References (selective)

1. Press release regarding the Botulinum Neurotoxin entitled "**Scientists Reveal Structure of New Botulism Nerve Toxin Subtype**". The Brookhaven Bulletin December 2008. (http://www.bnl.gov/newsroom/news.php?a=1875).

2. Press release regarding the Botulinum Neurotoxin entitled **Antidote to lethal germ 'closer'.** BBC News, May 12, 2008. (http://news.bbc.co.uk/2/hi/science/nature/7395731.stm).

3. Press release regarding the Botulinum Neurotoxin entitled "**Scientists Determine Drug Target for the Most Potent Botulinum Neurotoxin**". The Brookhaven Bulletin April 29, 2008 (http://www.bnl.gov/newsroom/news.php?a=1780).

4. Press release regarding the Lyme disease entitled "**Lyme disease protein structure determined at BNL**". The Bulletin Vol 55(6), March 2001
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5. Press release regarding the Lyme disease entitled "**Structuring a Solution**". Newsday, March 13, 2001

PUBLICATIONS

1. **Kumaran D**, Adler M, Levit M, Krebs M, Sweeney, R, Moreira, T and Swaminathan S. Interactions of a potent cyclic peptide inhibitor with the light chain of botulinum neurotoxin A: Insights from X-ray crystallography. Bioorganic and Medicinal Chemistry, 2015, S0968-0896(15)30102-4.
2. Xiang DF, **Kumaran D**, Swaminathan S, Raushel FM. Structural characterization and function determination of a nonspecific carboxylate esterase from the amidohydrolase superfamily with a promiscuous ability to hydrolyze methylphosphonate esters. Biochemistry. 2014, 53(21):3476-85.
3. Ornelas A, Korczynska M, Ragumani S, **Kumaran D**, Narindoshvili T, Shoichet BK, Swaminathan S, Raushel FM. Functional annotation and three-dimensional structure of an incorrectly annotated dihydroorotase from cog3964 in the amidohydrolase superfamily. Biochemistry. 2013, 52(1):228-38.
4. Palani K, **Kumaran D**, Burley SK, Swaminathan S. Structure of a periplasmic glucose-binding protein from Thermotoga maritima. Acta Crystallogr Sect F Struct Biol Cryst Commun. 2012, 68(12):1460-4.
5. Yao Q, So ng CX, He C**, Kumaran D**, Dunn JJ. Heterologous expression and purification of Arabidopsis thaliana VIM protein: in vitro evidence for its inability to recognize hydroxymethylcytosine, a rare base in Arabidopsis DNA. Protein Expr Purif. 2012, 83(1):104-11.
6. Kumar G, **Kumaran D**, Ahmed SA, Swaminathan S. Peptide inhibitors of botulinum neurotoxin serotype A: design, inhibition, cocrystal structures, structure-activity relationship and pharmacophore modeling. Acta Crystallogr D Biol Crystallogr. 2012, 68(5):511-20.
7. Lakshminarasimhan D, **Kumaran D**, Agarwal R, Singh BR, Swaminathan S. Cloning, expression and purification of botulinum neurotoxin type A heavy chain -crystallographic evidence for a putative tetrameric pore. The botulinum journal. 2012, 2(2):135-149.
8. Kamat SS, Holmes-Hampton GP, Bagaria A, **Kumaran D**, Tichy SE, Gheyi T, Zheng X, Bain K, Groshong C, Emtage S, Sauder JM, Burley SK, Swaminathan S, Lindahl PA, Raushel FM. The catalase activity of diiron adenine deaminase. Protein Sci. 2011, 20(12):2080-94.
9. Bagaria A, **Kumaran D**, Burley SK, Swaminathan S. Structural basis for a ribofuranosyl binding protein: insights into the furanose specific transport. Proteins. 2011, 79(4):1352-7.
10. Kamat SS, Bagaria A, **Kumaran D**, Holmes-Hampton GP, Fan H, Sali A, Sauder JM, Burley SK, Lindahl PA, Swaminathan S, Raushel FM. Catalytic mechanism and three-dimensional structure of adenine deaminase. Biochemistry. 2011, 50(11):1917-27.
11. Xiang DF, Xu C, **Kumaran D**, Brown AC, Sauder JM, Burley SK, Swaminathan S, Raushel FM. Functional annotation of two new carboxypeptidases from the amidohydrolase superfamily of enzymes. Biochemistry. 2009, 48(21):4567-76.
12. **Kumaran D**, Eswaramoorthy S, Furey W, Navaza J, Sax M, Swaminathan S. Domain organization in Clostridium botulinum neurotoxin type E is unique: its implication in faster translocation. J Mol Biol. 2009, 386(1):233-45.
13. **Kumaran D**, Rawat R, Ahmed SA, Swaminathan S. Substrate binding mode and its implication on drug design for botulinum neurotoxin A. PLoS Pathog. 2008, 4(9): e1000165
14. Legler PM, **Kumaran D**, Swaminathan S, Studier FW, Millard CB. Structural characterization and reversal of the natural organophosphate resistance of a D-type esterase, Saccharomyces cerevisiae S-formylglutathione hydrolase. Biochemistry. 2008, 47(36):9592-601.
15. Ragumani S, **Kumaran D**, Burley SK, Swaminathan S. Crystal structure of a putative lysostaphin peptidase from Vibrio cholerae. Proteins. 2008, 72(3):1096-103.
16. **Kumaran D**, Rawat R, Ludivico ML, Ahmed SA, Swaminathan S. Structure- and substrate-based inhibitor design for Clostridium botulinum neurotoxin serotype A. J Biol Chem. 2008, 283(27):18883-91.
17. Mazumdar PA, **Kumaran D**, Swaminathan S, Das AK. A novel acetate-bound complex of human carbonic anhydrase II. Acta Crystallogr Sect F Struct Biol Cryst Commun. 2008, 64(3):163-6.
18. Tyagi R, **Kumaran D**, Burley SK, Swaminathan S. X-ray structure of imidazolonepropionase from Agrobacterium tumefaciens at 1.87 A resolution. Proteins. 2007, 69(3):652-8.
19. Almo SC, Bonanno JB, Sauder JM, Emtage S, Dilorenzo TP, Malashkevich V, Wasserman, SR, Swaminathan S, Eswaramoorthy S, Agarwal R, **Kumaran D**, Madegowda M, Ragumani S, Patskovsky Y, Alvarado J, Ramagopal UA, Faber-Barata J, Chance MR, Sali A, Fiser A, Zhang ZY, Lawrence DS, et al. Structural genomics of protein phosphatases. J Struct Funct Genomics. 2007, 8(2-3):121-40.
20. Guy JE, Whittle E, **Kumaran D**, Lindqvist Y, Shanklin J. The crystal structure of the ivy Delta4-16:0-ACP desaturase reveals structural details of the oxidized active site and potential determinants of regioselectivity. J Biol Chem. 2007, 282(27):19863-71.

21. **Kumaran D**, Bonanno JB, Burley SK, Swaminathan S. Crystal structure of phosphatidylglycerophosphatase (PGPase), a putative membrane-bound lipid phosphatase, reveals a novel binuclear metal binding site and two "proton wires". Proteins. 2006, 64(4):851-62.
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23. Seetharaman J, **Kumaran D**, Bonanno JB, Burley SK, Swaminathan S. Crystal structure of a putative HTH-type transcriptional regulator yxaF from Bacillus subtilis. Proteins. 2006, 63(4):1087-91.
24. Jayaraman S, Eswaramoorthy S, **Kumaran D**, Swaminathan S. Common binding site for disialyllactose and tri-peptide in C-fragment of tetanus neurotoxin. Proteins. 2005, 61(2):288-95.
25. Rao KN, **Kumaran D**, Binz T, Swaminathan S. Structural analysis of the catalytic domain of tetanus neurotoxin. Toxicon. 2005, 45(7):929-39.
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33. Eswaramoorthy S, **Kumaran D**, Swaminathan S. A novel mechanism for Clostridium botulinum neurotoxin inhibition. Biochemistry. 2002, 41(31):9795-802.
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36. **Kumaran D**, Eswaramoorthy S, Luft BJ, Koide S, Dunn JJ, Lawson CL, Swaminathan S. Crystal structure of outer surface protein C (OspC) from the Lyme disease spirochete, Borrelia burgdorferi. EMBO J. 2001, 20(5):971-8.
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38. **Kumaran D**, Ponnuswamy MN, Jayanthi G, Ramakrishnan VT, Panneerselvam K, et al. Crystal structure of 4-(2-chlorophenyl)-3-(4-methoxyphenyl)-1,2,4- triazole-5-thione J. Cryst. Res. & Tech. 2000; 35(239).
39. **Kumaran D**, Ponnuswamy MN, Shanmugam G, Ponnuswamy S, Jeyaraman R, Shivakumar K, Fun HK. Molecular structures and conformations of three 3-azabicyclononanes. Acta Crystallogr B. 1999, 55(5):793-798.
40. Kuppayee M, **Kumaran D**, Ponnuswamy MN, Kandaswamy M, Violet MJ, et al. 1,4-Bis(2-hydroxy-5-methylbenzyl)piperazine Acta Cryst. . 1999, C55:2147.
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Manuscript under revision:

1. McGillick BE, **Kumaran D**, Vieni C, and Swaminathan, S. β-Hydroxyacyl-Acyl Carrier Protein Dehydratase (FabZ) from *Francisella tularensis* and *Yersinia pestis*: Structure Determination, Enzymatic Characterization, and Cross Inhibition Studies. Biochemistry, 2015.
