BIOGRAPHICAL SKETCH

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NAME: D'Souza, Areetha

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

POSITION TITLE: Research Instructor, Department of Biochemistry, Vanderbilt University

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
National Institute of Technology Karnataka (NITK), India	B.Tech	05/2012	Chemical Engineering
Nanyang Technological University (NTU), Singapore	PhD	02/2018	Biological Sciences
Syracuse University, NY	Postdoctoral	04/2021	Biochemistry
Vanderbilt University, TN	Postdoctoral	08/2023	Biochemistry
IBS Center for Genome Integrity (IBS-CGI), Korea	Visiting Senior Scientist	08/2024	Chemical and Cancer Biology Branch

A. Personal Statement

I am a Research Instructor in the laboratory of Dr. Walter J. Chazin at Vanderbilt University. My research interests center on structural and functional analysis of multiprotein machines in DNA repair pathways, and my research experience spans across biochemistry and structural biology of proteins, peptides, and interactions with ligands. My graduate studies and first postdoctoral work were focused on the design of peptides and proteins, and I used NMR spectroscopy as my major structural tool for characterizing the 3D structures and functions of proteins and peptides. Since joining the Chazin lab in Vanderbilt, I have gained experience in other structural biology techniques such as x-ray crystallography, small angle x-ray scattering, computational modeling, preparation of multi-protein/DNA complexes using gradient centrifugation and cryo-electron microscopy. My postdoctoral work focuses on the protein scaffold XPA-RPA and its role in nucleotide excision repair. I used the integrated structural biology approach to determine the structure of XPA and RPA in collaboration with Schärer lab. During my one-year as a visiting scientist in the Schärer lab, I used AlphaFold and molecular modeling to show that STK19, a core TC-NER factor stimulates and positions TFIIH into the TC-NER complex. My current project includes the use of the fragment-based drug discovery approach to develop inhibitors of XPA. This work will lay the foundation for future studies investigating the effect of XPA inhibition on NER activity and sensitivity to Pt-based agents. Collectively, these diverse projects and research experiences have provided me with a unique, multidisciplinary background particularly suited to the proposed research on structures and function of the nucleotide excision repair (NER) protein machinery.

1. S M. Kim, H.S. Kim, **A. D'Souza**, K. Gallagher, E. Jung, A. Topolska-Wos, K. Ogorodnik Le Meur, C.-L. Tsai, M.-S. Tsai, M. Kee, J.A. Tainer, J.-E. Yeo, W.J. Chazin, O.D. Scharer. "Two Interaction Surfaces between XPA and RPA Organize the Preincision Complex in Nucleotide Excision Repair." Proc. Natl. Acad. Sci., USA **119**, e2207408119 (2022).
2. **A. D'Souza**, A.M. Blee, and W.J. Chazin. "Mechanism of action of nucleotide excision repair machinery". Biochemical Society Transactions, 50(1): p. 375-386 (2022).
3. **A. D'Souza**, M. Kim, W.J. Chazin and O.D. Scharer. "Protein-protein and protein-DNA interactions in nucleotide excision repair. DNA Repair **141**, e103728 (2024).

4. van den Heuvel, D., M. Rodríguez-Martínez, P. J. van der Meer, N. N. Moreno, J. Park, H.-S. Kim, J. J. van Schie, A. P. Wondergem, **A. D'Souza,** G. Yakoub, O.D. Scharer*.. "STK19 facilitates the clearance of lesion-stalled RNAPII during transcription-coupled DNA repair." Cell 187(25): 7107-7125. e7125 (2024).

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023-pres Research Instructor, Vanderbilt University, Nashville, TN
2021-2023 Post-Doctoral Fellow, Vanderbilt University, Nashville, TN
2018-2022 Post-Doctoral Fellow, Syracuse University, Syracuse, NY

Honors

2018 NTU School of Biological Sciences, International PhD Research Fellowship

C. Contributions to Science

1. *De novo* design of β-sheet heme binding mini proteins

During my graduate school, I used the *de novo* design approach to design a series of multi-stranded β-sheet heme binding peptides that are well folded in aqueous and membrane-like environments. These studies highlight substantial progress made towards the design of functional β-sheets. The designed peptides or mini proteins adopt well-folded structures, bind single or multiple heme cofactors with high affinity, and perform peroxidase activity in aqueous and membrane environments. These mini proteins could be used as nano materials or could serve as a platform for creating novel protein mimics within the field of Synthetic Biology.

1. **D'Souza, A**., M. Mahajan and S. Bhattacharjya "Designed multi-stranded heme binding β-sheet peptides in membrane." Chemical science 7(4): 2563-2571 (2016).
2. **D'Souza A.**, Wu X, Yeow EKL, Bhattacharjya S. "Designed heme-cage β-sheet miniproteins". Angewandte Chemie;129(21):5998-6002 (2017).
3. **D'Souza, A**., Torres, J. and Bhattacharjya, S. "Expanding heme-protein folding space using designed multi-heme β-sheet mini-proteins." Communications Chemistry, *1*(1), p.78 (2018).

2. Design of peptide-based hydrogels for wound healing applications

During my first postdoctoral work in Syracuse University, I designed antimicrobial peptide-based hydrogels for wound healing applications. I initially designed a nine-residue peptide L9 that self-assembles in the presence of silver ions to produce a hydrogel L9–Ag with excellent rheological parameters. The resulting gel is self-healing and therefore potentially suited for practical applications including syringe delivery into wounds. I used a similar approach to design, prepare and characterize redox and pH responsive peptide-based hydrogels with wound healing and antimicrobial properties.

1. **D'Souza, A**., Yoon, J.H., Beaman, H., Gosavi, P., Lengyel-Zhand, Z., Sternisha, A., Centola, G., Marshall, L.R., Wehrman, M.D., Schultz, K.M. and Monroe, M.B. "Nine-residue peptide self-assembles in the presence of silver to produce a self-healing, cytocompatible, antimicrobial hydrogel". ACS applied materials & interfaces, 12(14), pp.17091-17099 (2020).
2. **D'Souza, A**., Marshall, L.R., Yoon, J., Kulesha, A., Edirisinghe, D.I., Chandrasekaran, S., Rathee, P., Prabhakar, R. and Makhlynets, O.V. "Peptide hydrogel with self-healing and redox-responsive properties". Nano convergence, 9(1), p.18. (2021)
3. Edirisinghe, D.I.U., **D'Souza, A**., Ramezani, M., Carroll, R.J., Chicón, Q., Muenzel, C.L., Soule, J., Monroe, M.B.B., Patteson, A.E. and Makhlynets, O.V. "Antibacterial and cytocompatible pH-responsive peptide hydrogel". Molecules, 28(11), p.4390 (2023).

3. Design of enzymes using NMR directed evolution approach

Directed evolution is a powerful tool for improving existing properties and imparting novel functions to proteins. In a proof-of-concept study, myoglobin, a non-enzymatic oxygen storage heme protein, was converted into a highly efficient Kemp eliminase using only three mutations. The mutagenic hot spots were identified using NMR spectroscopy making this a simplified approach for enzyme evolution.

1. Bhattacharya, S., Margheritis, E.G., Takahashi, K., Kulesha, A., **D'Souza, A**., Kim, I., Yoon, J.H., Tame, J.R., Volkov, A.N., Makhlynets, O.V. and Korendovych, I.V. "NMR-guided directed evolution". Nature, 610(7931), pp.389-393 (2022).

Complete List of Published Work on MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/areetha.d%20souza.1/bibliography/public/