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: Sagar D. Khare

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

POSITION TITLE: Associate Professor, Department of Chemistry and Chemical Biology, Rutgers

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
Indian Institute of Technology Delhi	Int. M.Tech	05/2000	Biochemical Engineering and Biotechnology
The University of North Carolina at Chapel Hill	PhD	05/2006	Biochemistry and Biophysics
University of Washington	Postdoc	06/2012	Enzyme design and engineering

A. Personal Statement

I am pleased to participate in the Rutgers team for this as a faculty mentor for the RU-Prepared program. Education and training within the classroom, laboratory, university, and national scientific community are integral components of my activities as an academic researcher.

As a mentor, I have supervised 15 graduate students and 4 postdoctoral fellows over the last 10 years: 9 PhD students from my lab have graduated thus far, and 3 have gone on to postdoctoral fellowships at prestigious institutions, and all but one of the 19 graduate or postdoctoral trainees are currently in research-related careers. 2 graduate students received competitive graduate research fellowships (e.g. NSF GRFP) and 2 received honorable mentions in the NSF GFRP. Currently, I mentor 6 graduate trainees and 2 of my graduate student trainees are being supported by federally-funded T32 training grants. I have mentored 1 LatinX female graduate student, and more than 10 undergraduate students from under-represented backgrounds. I have been a reviewer for the NSF GFRP for several years, and a member of the Institute for Quantitative Biomedicine at Rutgers Diversity, Equity and Inclusion committee. I am the PI on a T32 application for Molecular Biophysics training at Rutgers (currently under review).

I am the Graduate Program Director for the graduate program in Quantitative Biomedicine at Rutgers and an active faculty mentor in the NIH T32 Biotechnology training grant at Rutgers. My research lab is very interdisciplinary and focuses on designing enzymes using a combined computational-experimental approach. We have developed tools, grounded in protein biophysics, to understand and predictively modulate from the bottom up, various enzyme properties including stability, specificity and supramolecular structure. I have lead Rutgers teams of undergraduates to participate in research competitions (iGEM, BIOMOD) where they have received Gold and Silver medals based on research they carried out in my lab, and directly supervised by graduate students in my group.

I have designed and developed a graduate course on Statistical Thermodynamics taken by students with backgrounds in chemistry and biosciences, and have given guest lectures in the Molecular Bioscience core curriculum as well as designed and run Quantitative Biomedicine Boot Camps at Rutgers. I have served as a poster judge for the NIH T32 Biotechnology program retreat. My pedagogical philosophy has been to emphasize the underlying chemical/physical principles to students with varied backgrounds using diverse examples from biology so that connections between seemingly disparate areas are highlighted. I am a keen [SACNAS etc.]. My involvement in these activities reflects my deep commitment to training the next generation of scientists, increasing diversity of the biomedical workforce and supporting career development at all levels. I have embraced the evolution of biomedical education toward use of active learning to master concept inventories and core competencies and the evolution of graduate and postdoctoral training toward development of both broad and specialized skills required for pursuit of diverse careers in the biomedical sciences.

Ongoing Research Support

National Institutes of Health R01GM132565 09/27/19-06/30/23
"Principles for Designing Stimulus-Responsive Enzymes"
The goal of this project is to develop a general bottom-up approach for developing spatial and temporal control over enzymes that are used in chemotherapy. These designed enzymes have the potential to make chemotherapy regimes safer and more potent.
Role: PI

National Science Foundation CBET1929237 09/15/19-08/31/23
"Collaborative Research: Engineering Hyperstable Enzymes via Computationally Guided Protein Stapling."
The goal of this project is to develop a new, effective, and potentially general strategy for dramatically enhancing the thermal and chemical stability of an enzyme without impacting its native function.
Role: PI

National Science Foundation CHE2226816 09/01/2022-08/31/2025
"MFB: Targeting the dark proteome by machine-learning-guided protein design."
The goal of this project is to develop AI/ML-guided pipeline for the design of in situ protein editing technology.
Role: PI

National Institutes of Health R21AI174157 12/06/2022-11/30/2024
"Seeing the Unseen: High-Throughput Prospective Profiling and inhibition of SARS-CoV-2 receptor-binding domain variants"
The goal of this project is to use AI/ML methofs to identify the space of SARS-CoV-2 RBD variants that can bind receptor ACE2 and escape antibodies.
Role: PI

National Science Foundation DMR2118860 10/1/2021-09/30/2025
"Collaborative Research: DMREF: Machine Learning and Robotics for the Data-Driven Design of Protein-polymer Hybrid Materials"
The goal of this project is to develop hybrid protein-polymer materials that are stable and functional under extreme environments.
Role:Co-PI

Completed Research Support

Rutgers Center for COVID-19 Response and Pandemic Preparedness (CCRP2) SeedGrant 7/1/20-12/31/21
Role: co-PI (PI: Tumer)

To clone SARS-CoV-2 protease and determine the conditions for fragment screening.

National Science Foundation MCB1716623 08/01/17-07/31/20
"Design Principles of Molecular Computing Using Engineered Enzymes"
The goal of this project is to implement Boolean logic inside cells using engineered enzymes.
Role: PI

Defense Advanced Research Projects Agency FA8650-18-1-7800 12/27/17-08/31/19
"Self-modifying and fast analog molecular computing via designed enzymes"
The goal of this project is to develop a chemomathematical framework for *ex vivo* molecular computing via multicomponent enzymatic circuits.
Role: PI

Rosetta Commons RC8008 01/01/19-12/31/19
"Improving AmbRose: Extending the Amber-Rosetta consensus scoring and sampling approach"
The goal of the project is to further develop an Amber-Rosetta scoring approach for protein modeling.
Role: PI

B. Positions, Scientific Appointments, and Honors

07/2020-Present	Graduate Program Director, Quantitative Biomedicine, Rutgers
07/2018-Present	Associate Professor, Department of Chemistry and Chemical Biology, Rutgers
07/2015-Present	Full Member, Cancer Pharmacology Program, Rutgers Cancer Institute of New Jersey
09/2020-Presennt	Associate Editor, *Proteins: Structure, Function & Bioinformatics*
02/2021-Present	Editorial Advisory Board, *Protein Engineering, Design & Selection*

C. Contributions to Science

1. Design methods for predictively modulating enzyme properties: My lab has focused on establishing both computational and experimental aspects of a general, biophysical framework for predictively controlling from the bottom up various enzymatic properties including stability, activity, substrate specificity, spatio-temporal specificity and supramolecular structure including with unnatural amino acids and cofactors. The development of this methodology involves a close interplay of modeling, design simulations and biophysical characterization experiments.

a. K. M. Blacklock, G. A. Woolley, S. D. Khare "Computational design of a photocontrolled cytosine deaminase" (2018) *J. Am. Chem. Soc.* 140:14-17 (PMID: 29251923)

b. B. J. Yachnin and S. D. Khare "Designing a circularly permuted carboxypeptidase G2 enzyme for an autoinhibited enzyme drug" (2017) *Protein Eng. Des. Sel.* 30: 321-331(PMID: 28160000)

c. E. Moore, D. Zorine, W. A. Hansen, S. D. Khare[‡], R. Fasan[‡] "Enzyme stabilization *via* computationally-guided protein stapling" (2017) *Proc. Natl. Acad. Sci*. 114: 12472-12477 (PMID: 29109284, PMCID: PMC5703291)
([‡] = co-corresponding authors)

d. A. B. Rubenstein, M. A. Pethe and S. D. Khare "MFPred: Rapid and accurate prediction of multispecificity at protein-peptide interfaces using self-consistent mean-field theory" (2017) *PLOS Comp. Biol.* 13:e1005614 (PMID: 28650961)

2. Molecular mechanisms of protein aggregation. As a graduate student in Dr. Nikolay Dokholyan's laboratory at UNC Chapel Hill, I trained in computational biophysics and performed discrete molecular dynamics simulations of protein aggregation. I also trained with Dr. Michael Caplow, to perform detailed

experimental kinetic measurements of the aggregation process. My graduate work led to an understanding of the molecular mechanism of superoxide dismutase aggregation, and highlighted basic commonalities with other protein aggregation disorders. More recently, in collaboration with Dr. Jean Baum, I have applied molecular modeling tools to understand the mechanism of synuclein aggregation in Parkinson's disease and its macromolecular inhibition.

S. D. Khare, M. Caplow, and N. V. Dokholyan, "The rate and equilibrium constants for a multi-step reaction sequence for the aggregation of superoxide dismutase in ALS" (2004) *Proc. Natl. Acad. Sci. USA,* 101: 15094-15099 (PMCID: PMC524068)

S. D. Khare, F. Ding, K. N. Gwanmesia, and N. V. Dokholyan, "Molecular origin of polyglutamine-mediated aggregation in neurodegenerative diseases" (2005) *PLoS Comp. Biol.,* 1: e30 PMCID: PMC1193989

S. D. Khare, and N. V. Dokholyan, "Common dynamical signatures of FALS-associated structurally-diverse Cu, Zn superoxide dismutase mutants" (2006) *Proc. Natl. Acad. Sci. USA,* 103: 3147-3152 PMCID: PMC1413921

G. M. Moriarty, M. P. Olson, T. Atieh, M. Janowska, S. D. Khare‡, J. Baum‡ "Formation of fibrils by beta-synuclein at mildly acidic pH mediated by charged interaction clusters" (2017) *J. Biol. Chem.* 292:16368-16379 (‡ = co-corresponding authors)

3. Computational *de novo* design of enzymes and protein-small molecule interfaces: As a postdoctoral fellow in Dr. David Baker's laboratory at the University of Washington, I worked on several aspects of protein-small molecule interface design, including *de novo* enzyme design, metalloenzyme redesign, designing with unnatural amino acids and, the design of selective ligand-binding proteins. In my approach we integrated ideas and techniques from fields as diverse as computer science, mechanistic enzymology, molecular biology and structural biophysics. I have been a co-developer of the Rosetta software for macromolecular design for the last decade, and my laboratory continues to develop and use new design methods in this framework. These studies have established new and powerful methods with which to exploit the large and ever increasing database of protein structures for developing functions that Nature has not (yet) explored. These methods are already assisting and enabling many molecular engineering and design efforts and will likely continue to be useful.

C. E. Tinberg*, S. D. Khare*, J. Dou, L. Doyle, J. Nelson, A. Schena, W. Jankowski, C. G. Kalodimos, K. Johnsson, B. L. Stoddard, and D. Baker, "Computational design of ligand binding proteins with high affinity and selectivity." *Nature* 501: 212-216 (2013). PMCID: PMC3898436

S. D. Khare*, Y. Kipnis*, P. J. Greisen*, R. Takeuchi, Y. Ashani, M. Goldsmith, Y. Song, J. L. Gallaher, I. Silman, H. Leader, J. L. Sussman, B. L. Stoddard, D. S. Tawfik, and D. Baker, "Redesign of a mononuclear zinc metalloenzyme for organophosphate hydrolysis." *Nature Chem. Biol*. 8: 294–300 (2012). PMCID: PMC3957331

J. H. Mills, S. D. Khare, J. M. Bolduc, F. Forouhar, V. K. Mulligan, S. Lew, J. Seetharaman, L. Tong, B. L. Stoddard, and D. Baker "Computational design of an unnatural amino acid-dependent metalloprotein with atomic level accuracy." *J. Am. Chem. Soc.* 135: 13393-13399 (2013).

S. D. Khare*‡ and S. J. Fleishman*‡ "Emerging themes in the computational design of novel enzymes and protein-protein interfaces" *FEBS Lett*., 587: 1147-54 (2013).
‡ = corresponding author

Complete List of Published Work:
http://www.ncbi.nlm.nih.gov/pubmed?term=Khare%2C%20Sagar%20D%5BAuthor%5D