



INTERNATIONAL CENTRE FOR GENETIC ENGINEERING AND BIOTECHNOLOGY

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Letter of Justification

Sun Pharma Science Foundation Research Awards 2023

To,

Office of Sun Pharma Science Foundation
8C, 8 Floor, Hansalaya Building
15-Barakhamba Road, Connaught Place
New Delhi-110001(India)

I am delighted to nominate Ruchi Anand for consideration for the Sun Pharma Science Foundation Research Award in **Pharmaceutical Sciences 2023** for her significant research contributions in arena of new therapies to combat drug resistance. Her exceptional research contributions in the realm of innovative therapies aimed at tackling drug resistance have positioned her as an outstanding candidate for this prestigious accolade. Her structural biology skills, complemented by her adept utilization of biochemical and biophysical methodologies, have yielded transformative insights into critical challenges that hold significance not only within India but also on a global scale. In her pursuit of combatting drug resistance, she has ingeniously adopted the approach of "**reversing resistance**." Her objective is to sensitize drug-resistant bacteria to existing antibiotics, thus revitalizing their effectiveness. For this purpose, she delved into understanding mechanisms that render normal bacteria resistant to antibiotics and focused on two such adopted mechanisms by multi drug (MDR) bacteria. First, target were efflux pump regulators, TetRs that assist in expelling antibiotics out of the cells thereby, lowering their concentration below effective limits. These regulators are pivotal in transporting antibiotics out of cells, leading to decreased antibiotic concentrations below therapeutic thresholds. Through the elucidation of the crystal structure of a series of TetRs complexed with DNA, she unveiled the intricate allosteric interplay between antibiotic and DNA binding sites, revealing invaluable insights for the development of efflux pump inhibitors (*NAR*, 2014). The second mode of drug resistance she undertook was wherein modifications within drug binding sites confer resistance. She directed her attention to ribosomal methyltransferases, enzymes that post-translationally modify ribosomes and are implicated in drug resistance among diverse pathogens. Methylation in the ribosomal exit tunnel renders bacteria resistant to more than 50 different antibiotics belonging to the macrolide, lincomamide and streptogramin class. By solving crystal structures and utilizing chimeric constructs of these enzymes, she discerned allosteric sites exclusive to these methyltransferases, found exclusively in drug resistant bacteria for targeted drug design against pathogenic methyltransferases (*JACS* 2019). Advancing from RNA constructs to the ribosome itself, she achieved a significant feat by unveiling the cryo-EM structure of a methyltransferase with the 30S ribosome thereby, unravelling specificity at the ribosomal level (*ACS Chem Bio*, 2022). Her recent work has furthered the understanding of allosteric binding sites and general molecular recognition mechanisms of methyltransferases (*JBC* 2022) that has now allowed her to design molecules that can assisting in reversing resistance and re-sensitizing the old antibiotics.

In parallel, Dr. Anand's explorations led her to the discovery of a novel enzyme, exclusive to pathogenic bacteria such as *Mycobacterium tuberculosis*, capable of selectively detecting and deaminating mutagenic bases. This finding suggests innovative avenues for drug repurposing (*JACS* 2017). Her insights into allosteric mechanisms within essential pathway enzymes, including the discovery of potential allosteric switches, bear promising implications for future drug development (*Sci Adv*, 2020, *ACS Catal.* 2022, *Curr. Opin. Chem. Biol.* 2023). Dr. Anand's remarkable achievements have garnered numerous accolades, including the **Women's BioScientist award by DBT in 2018**, and she is a fellow of both, *National Academy of Science and Indian Academy of Science*. She is also the recipient of the **Senior DBT-Welcome Trust Fellowship** and received the **Impactful Research Award 2020** by IIT Bombay. Her leadership led to the establishment of a state-of-the-art **Cryo-EM Center at IIT Bombay via a SERB grant** that she heads, further propelling the field of structural biology. She is also a member of advisory board of several journals.

Overall, her pioneering contributions to unraveling the molecular mechanisms that underlie drug resistance are seminal as they lead the way towards the development of effective drug development strategies towards 'reversing resistance'. Thus, I believe she is truly a deserving nomination for this prestigious award.

Sincerely,

Dr. Amit Sharma
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