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Prof. G. Mugesh

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Division of Chemical Sciences

August 23, 2024

Research Awards -2024 Committee
Sun Pharma Science Foundation

Justification letter for the nomination of Prof. Aravind Penmatsa

It is with great pleasure I nominate Prof. Aravind Penmatsa for the Sun Pharma Research Award for 2024 in the category of Pharmaceutical Sciences. Prof. Aravind Penmatsa had his undergraduate training in pharmaceutical sciences and his doctoral and postdoctoral training in structural biology and biophysics and runs a successful research group studying vital pharmacological targets involved in neurophysiology and multi-drug efflux.

A major part of Aravind's work is focused on understanding the role of integral membrane transporters and their pharmacology in neurons. Neurotransmitter transporters in the neural synapses control the levels of diverse neurotransmitters like noradrenaline, dopamine, serotonin and GABA and thereby their activation of postsynaptic receptors. An improper control of levels leads to neurological disorders like, depression, anxiety, pain, schizophrenia and seizures. These transporters have therefore been the prime targets of antidepressants, psychostimulants, antiepileptics and chronic pain medication. Aravind's group has done extensive studies on the noradrenaline block by chronic pain medications like duloxetine, milnacipran and tramadol using a neurotransmitter transporter from fruitflies (*Pidathala et al., 2021, Nat. Commun.*). His group has also delved into the pharmacology and mechanism of GABA uptake and inhibition that is a vital factor in the development of epilepsy and is a target of some antiepileptics like tiagabine used for partial seizures (*Joseph et al., 2022, EMBO J; Nayak et al., 2023, Nat. Struct. Mol. Biol.*).

His group has recently studied an important class of large-pore ion-channels Pannexins that are an important target for inflammatory pain medication and cellular ATP release. His group characterized the pore lining residues of Pannexin isoforms and studied the ability of carbenoxolone an anti-gout medication to interact with variations in the pore. The pore diameters are altered in each of the isoforms thereby influencing the electrical properties of the pannexins. They also characterized a germline mutant of Pannexin1 in a transmembrane helix of the channel that closes the pore of the channel through an allosteric effect signifying the importance of such mutants in disease physiology (*Hussain et al., 2024, Nat Commun.*).



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His lab has also studied the transporters in superbug membranes that have a surprising structural and mechanistic similarity to vesicular neurotransmitter transporters. These molecules are proton-coupled antiporters that are involved in multi-drug efflux of numerous antibacterial compounds in the drug-resistant strains of *Staphylococcus aureus*. His group studied the promiscuity of antibacterial interactions and subsequently determined the structure of a major efflux pump QacA (*Majumder et al., 2019, J. Mol. Biol.*; *Majumder et al., 2023, EMBO J.*). These insights would be vital for developing efflux pump inhibitors to block these transporters.

He has further pioneered the use of single domain Indian camelid antibodies as tools against these efflux pumps and used them as chaperones to successfully resolve the structures of multiple transporters like NorC and QacA. These could be used for diagnostic tools to identify strains of superbugs that carry these efflux pumps (*Kumar et al., 2020, J. Biol. Chem.*; *Kumar et al., 2021, Commun. Biol.*). In lieu of his cutting-edge research in structural biology and biophysics he has been recognised by numerous national and international awards and fellowships like the DBT-Wellcome Trust fellowships, Global investigator for EMBO, fellow of National Academy of Science, India, DBT-Innovative Biotechnologist award and more recently the inaugural Vigyan-Yuva Shanti Swarup Bhatnagar award.

It is therefore well justified for me to nominate Prof. Aravind Penmatsa for the prestigious Sun Pharma Research Award for 2024 and I strongly believe that his application is well suited for the award category of Pharmaceutical sciences. I fully support his application. Please do not hesitate to contact me with any further queries.

Thanks and best regards,

G. Mugesh
Dean, Division of Chemical Sciences