सीएसआईआर-केन्द्रीय औषधि अनुसंधान संस्थान
CSIR-CENTRAL DRUG RESEARCH INSTITUTE

वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद्
COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH

प्रोफ़ेसर तपस कुमार कुंडू
पीएचडी, डीएससी, एफ्एनएएससी, एफ्एएससी, एफ्एनए, सर जेसी बोस नेशनल फेलो
निदेशक

Professor Tapas K. Kundu
PhD, DSc, FNASc, FASc, FNA, Sir J C Bose National Fellow
Director

Nomination- Sun Pharma Science Foundation Research Awards 2021

Dear Sir/ Madam

It gives me great pleasure to nominate Prof. Ravishankar Ramachandran, Chief Scientist & Chairperson, Biochemistry & Structural Biology Division, CSIR-Central Drug Research Institute, Lucknow, for the *Sun Pharma Science Foundation Research Awards 2021 in the category of Pharmaceutical Sciences*. I have had the privilege to interact with him and his work closely after taking over charge as the Director, CSIR-CDRI. Ravishankar secured Ph.D from Indian Institute of Science, Bangalore and subsequently carried out excellent work at Max-Planck Institute for Biochemistry as a Humboldt Fellow with Prof. Robert Huber, a Nobel laureate. He returned to India in 2002 to start an independent research group at CSIR-Central Drug Research Institute, Lucknow.

Ravishankar has made outstanding contributions in the areas of disease biology of TB infection and designing of therapeutic molecules, especially to understand the molecular basis of 'Feast/ famine regulation' and 'DNA Base-Excision-Repair (BER)' that are critical for the pathogen. He has elegantly used Structural biology, Rational drug-discovery and Drug-target based approaches to identify novel inhibitors with therapeutic potential that target these pathways and to overcome Anti-microbial drug-resistance. His contributions have brought International recognition and National awards like the *National Bioscience Award for Career Development*, 2010, by the Department of Biotechnology, Ministry of Science & Technology, Govt. of India & *NASI-SCOPUS Young Scientist Award*, 2010, by the National Academy of Sciences, Allahabad, India & M/s Elsevier.

Very recently, Ravishankar led a team that successfully completed "*Phase III, Randomized, Double-blind, Placebo controlled trial of Efficacy, Safety and Tolerability of Antiviral drug Umifenovir vs Standard care of therapy in non-severe COVID-19 patients*" conducted by CSIR-CDRI in association with three renowned medical university/ hospitals located in Lucknow, India, involving a total of 123 patients. Commercialization of the same is in advanced stages and a patent to protect the dosage used in the study is being filed internationally.

Some of his major contributions are detailed below:

(a) Characterization of BERoSomes in Mycobacteria and novel therapeutic strategies: BERoSomes are large multi-molecular complexes that function in the DNA Base Excision repair (BER) pathway. Ravishankar's group has pioneered the study of several such BERoSomes from Mtb and has identified multiple scaffolds that disrupt BERoSomes and/or target novel target sites. These include his studies on DnaN (sliding β-clamp)- class II apurinic/apyrimidinic-endonuclease/3'-5' exonuclease (XthA) in the presence and absence of DNA substrate, XthA-NAD$^+$-dependent DNA Ligase A, Nei2-DnaN, and others.

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He has dissected the molecular mechanisms of the individual components and the respective BERoSomes to identify novel therapeutic strategies that involve either disrupting the multimeric assemblies or by strengthening them to block the pathway. His studies have led to the identification of new classes of compounds that exhibit anti-bacterial specificity and distinguish the human enzyme several fold, both *in vitro* and in LigA-deficient strains. More recently he showed that XthA engages with LigA to form a BERoSome whose function is to counter futile cleavage and ligation cycles in Base Excision Repair. The latter represents a fundamental Base Excision Repair interaction that is necessary for effective and critical repair of damaged DNA. Disrupting this process can lead to new therapeutics for drug resistant bacteria/mycobacteria that have less toxic side-effects.

(b) Discovered that Mtb SerB2 is a target for Clofazimine against MDR and XDR-TB: Ravishankar has identified new functions for an essential mycobacterial HAD phosphatase (SerB2). Using Broncho Alveolar Lavage (BAL) samples from TB patients, he showed that it is secreted and mediates host-pathogen interactions. He subsequently identified several small-molecule inhibitors for it, including Clofazimine that is being evaluated in clinical trials against drug resistant TB by the Global TB alliance. The results excitingly demonstrate that SerB2 is a target for riminophenazines being evaluated clinically. A translational output in this context is that an agreement with the 'Global TB Alliance' was signed by his group/ CDRI for evaluating such compounds.

(c) Molecular mechanisms underlying Feast-Famine regulation in mycobacteria: Feast/ famine regulatory proteins (FFRPs) are global regulators that apparently help mycobacteria to switch/ adapt from 'Feast' to 'Famine' state. Ravishankar's studies importantly suggest how mycobacterial FFRPs can form nucleosome-like particles, and how effector-binding events can trigger specific regulatory outcomes. First-in-class small-molecule inhibitors have been identified by his group against an FFRP. He has also demonstrated that the rarely observed 'open' quaternary association is an operating principle in these regulators, that otherwise adopt closed oligomeric symmetry. The 'open' quaternary structure is important for the protein to bind to non-symmetric target DNA sites, and can be triggered in response to changes to the effector binding site; eg. those that occur upon ligand binding for regulatory activities.

(d) Direct evidence for a glutamate 'switch' mechanism has been identified to operate in a sub-class of aminotransferases, and carried out associated structure-function studies on mycobacterial factors like Lysine ε-aminotansferase (MtbLAT) and L-Alanine dehydrogenase (MtbALD) that are thought to be important for adaptation/maintenance of tuberculosis persistence/latency. The latter have incidentally been ranked among the top-3 targets against tuberculosis persistence by the TB-Structural-Genomics Consortium. The results were exploited to identify the very first inhibitors of MtbLAT using structure-based approaches that promise to be useful against persistent TB-infection.

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(e) Drug Repurposing of Umifenovir against Sars-Cov2. Ravishankar led a team that conducted the first "*Phase III, Randomized, Double-blind, Placebo controlled trial of Efficacy, Safety and Tolerability of Antiviral drug Umifenovir vs Standard care of therapy in non-severe COVID-19 patients*" in association with three renowned medical university/ hospitals located in Lucknow, India, involving a total of 123 patients. The Phase III trial represents the first double-blind placebo controlled trial to evaluate Umifenovir against COVID-19. The drug Umifenovir was identified and shortlisted based on the efficacy, toxicity, patent status and other favourable parameters. The interactions with COVID19 target was evaluated in vitro and computationally. Since it is not available in India, the process was implemented and transferred to a company (M/s Medizest, Goa) for manufacture under GMP conditions. Careful analysis of the dosage needed for COVID19 patients was carried out based on the reported pharmacokinetics. The results of the Phase III trial support the use of Umifenovir in Mild-asymptomatic COVID-19 patients. Commercialization is at an advanced stage. PCT and Indian patents to protect the dosage used is being filed.

As the Nodal scientist, Ravishankar spearheaded a CSIR-wide antiviral project on drug target discovery, assay development and repurposing against SARS-Cov2. The results have now been incorporated into a larger pan-CSIR antiviral mission program. During the pandemic, Ravishankar played a major role in COVID19 management and vaccination in CDRI as the Nodal officer. He liaised with the state government extensively for surveillance and sequencing of Sars-Cov2 viral strains. Over 3 lakh patient samples have been screened at the diagnostic facility setup at CSIR-CDRI. He is a member of the Task Force on Repurposing of Drugs for COVID19, that has been set up by the Principal Scientific Advisor to the Government of India.

Considering his significant contributions in the areas of fundamental biomedical research and drug development, I strongly recommend the candidature of Dr. R. Ravishankar for the *Sun Pharma Science Foundation Research Awards 2021.*

Thank you for the kind consideration,

(Tapas Kumar Kundu)