August 30, 2023

To,

The Selection Committee

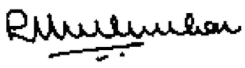
Sun Pharma Science Foundation Research Awards

Sub: Nomination of Prof. Sanjeev Galande for Sun Pharma Science Foundation Research Award in Medical Sciences- Basic Sciences

I am delighted to nominate Prof. Sanjeev Galande, Dean, School of Natural Sciences, Shiv Nadar Institution of Eminence (SNIoE) Delhi-NCR for the Sun Pharma Research Award in Medical Sciences- Basic Sciences in 2023. Dr Galande has made original contributions in the area of chromatin biology and epigenetics, in particular, the role of dynamic 3-dimensional chromatin organization and gene regulatory networks in health and disease. Dr. Galande is an extremely accomplished biologist as exemplified by his high quality publications in journals of high repute. Dr. Galande started his independent research career in 2001 at NCCS, Pune, then moved to IISER Pune in 2010. In 2021, he moved on lien to SNIoE. He has contributed significantly in building various programs and facilities at all these places and by virtue of these has contributed immensely to the scientific research and education ecosystem in India. The detailed justification for this nomination is appended on following pages. In my opinion, he eminently deserves the recognition through this award.

I sincerely hope the committee will positively consider his nomination.

Sincerely,



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Detailed Justification

Significance of research contributions

Dr. Galande began his independent career at National Centre for Cell Science (NCCS) Pune in 2001 by testing a hypothesis that SATB1 is a chromatin level functional end point for the PDZ-mediated signal transduction resulting in coordinated gene regulation by studying the PDZ-mediated interactions of SATB1. Since SATB1 is a T-lineage restricted regulator, Galande initially focused on regulation of cytokine genes and discovered that in HIV-1 infected cells, SATB1 is targeted by Tat, the viral transactivator, such that genes under the control of SATB1 such as IL-2 and its receptor are upregulated. The functional interaction between HIV-1 Tat and SATB1 requires its PDZ-like domain, and that the HDAC1 corepressor also binds through the same. Furthermore, Tat competitively displaces HDAC1 that is bound to SATB1, leading to increased acetylation of the promoters in vivo. These results suggest a novel mechanism by which HIV-1 Tat might overcome SATB1-mediated repression in T-cells (Kumar et al. 2005, Mol. Cell Biol.). This publication is regarded as one among the important contributions in the area of gene dysregulation upon HIV infection and Dr. Galande has received a number of invitations for delivering talks describing this work in national as well as international meetings. While studying the mechanism of regulation of global gene expression by SATB1, his group found that phosphorylation status of SATB1 governs its mutually exclusive association with HDAC1 and PCAF. Gene expression profiling studies using RNA from cells overexpressing point mutants of SATB1 defective in phosphorylation or acetylation unequivocally demonstrated the importance of these modifications towards the ability of SATB1 to act as a global regulator of gene expression (Kumar et al., 2006, Mol. Cell). This seminal study is one of the first reports revealing the molecular mechanism of action of a global transcription factor and chromatin organizer, and is therefore cited in number of reviews pertaining to T cell biology. Galande then set out to define more precisely the role of SATB1 in global gene regulation by identifying its novel partner proteins and identified the promyelocytic leukemia (PML) oncoprotein as a SATB1-interacting protein. Using modified in vivo chromatin conformation capture methodology (3C) combined with chromatin immunoprecipitation (ChIP), he and coworkers demonstrated PML and SATB1 form a novel type of regulatory complex that governs gene regulation in a global manner by establishing distinct chromatin loop architecture (Kumar et al. 2007, Nature Cell Biol.). **These findings have opened up many avenues to study the link between higher-order chromatin organization and coordinated gene expression**. Although SATB1 can act both as a repressor and activator of gene expression, the precise mechanism of how these contrasting activities are manifested at a global level was not clear. Galande's elegantly designed experimental strategy revealed that SATB1 and CtBP1 form a repressor complex by recruiting HDAC1 whereas β-catenin forms an activator complex with SATB1 by recruiting p300 in vivo (Purbey et al., 2009, *Mol. Cell Biol*.,). Analysis of occupancy of SATB1 at its genomic targets indicated specific recruitment of these factors and corresponding changes in histone modifications at SATB1 and Wnt targets (Notani et al. 2010, *PLoS Biol*. Notani et al., *J Biosci* 2011). These results unequivocally establish SATB1 as a mediator of Wnt/β-catenin signaling and provide mechanistic insights into how two factors with contrasting activities, namely CtBP1 and β-catenin, cooperate with the chromatin organizer SATB1 to regulate gene expression upon Wnt signaling. These findings have tremendous implications in development, differentiation and cancer. Findings from all

of these studies have made significant impact on the chromatin biology-gene regulation community.

Furthermore, report from his laboratory has provided unequivocal evidence to establish that SATB1, a novel target of Wnt signaling, reprograms the expression of tumor growth and metastasis associated genes to promote tumorigenesis and functionally overlaps with Wnt signaling during colorectal cancer progression (Mir et al., 2015, *Oncogene*). SATB1 is now considered as an important determinant of prognostic value in multiple cancers and Galande's work has provided the molecular basis for the same (Naik & Galande, 2018, *Oncogene*). The immediate outcome of these studies has tremendous potential towards designing effective therapeutics. Recently, in series of seminal publications Dr. Galande has shown how signaling pathways regulate the alternative splicing of SATB1 in developing T cells, untimately regulating protein expression in an unprecedented manner- by regulating mRNA stability (Khare et al., 2019 *Front Immunol*; Patta et al., 2020 *Nucleic Acids Res*). These findings have added a new dimension to the studies on regulation of gene expression through integration of multiple signaling pathways. Recently, Dr. Galande published one of his finest scientific contributions on role of dynamic chromatin organization in early development. Galande focused on characterizing the function of lineage-restricted organizer protein Satb2 utilizing comprehensive genome wide occupancy and gene expression analysis upon transient loss of function revealing a novel Wnt-dependent role of Satb2 in dorsal organizer during gastrulation. **Temporal analysis of tractable loss of function and gain of function models made significant contributions to our understanding of pathological conditions associated with satb2 mutation.** This study systematically characterizes the role of Satb2 during neural crest specification and migration, failure of which leads to severe defects in craniofacial development. In a nutshell, an integrative analysis of the transcriptome, genome-wide occupancy and chromatin accessibility revealed molecular interplays by which gene regulatory networks are established throughout early embryogenesis and advocates the necessity to characterize the role of novel mechanisms by which dynamic chromatin architectural alterations orchestrate landmark developmental transitions (Pradhan et al., 2021, *Nature Communications*).

In another landmark study as part of his collaborations, Galande was instrumental in demonstrating age-dependent changes at the epigenetic and behavioral levels in mice challenged with early life stress (Suri et al. 2012, *Biol Psychiatry*). These results have important implications towards treatment of stress related disorders such as anxiety and depression. Further mechanistic studies in this direction are ongoing and the results will be published shortly. **Galande is also engaged in another multi-institutional collaborative project to study epigenetic regulation of diabetes and obesity**. The results of one of the first set of findings were published in *Cell Metabolism* (Hardikar et al., 2015) and Galande is now continuing the genome-wide analysis of epigenetic changes in the famous 'Thrifty Jerry' model. He is also involved in collaboration with group of clinician-researchers studying epigenetic alterations underlying type II diabetes by nutritional intervention in human cohort. The first set of results of this multi-institutional project are published early this year (Khare et al. DOHAD J 2023). Dr. Galande has also shown the effect of the activation of TCR signaling by phosphoantigens or anti-CD3 on the transcriptional status of Vγ9Vδ2 T cells along with IL2 stimulation. Further, he and coworkers demonstrated that the blockade of Notch signaling antagonistically affects this activation (Madhok et al., Front.

Immunol 2021). These findings have tremendous implications towards inmmunotherapy. The epigenomic profiling of the Vγ9Vδ2 T cells is currently ongoing in his lab. Prof. Galande is tenaciously working towards fulfilling these long-term projects whose outcomes have potential to become game-changers, albeit after many years. In summary, making best use of his early training in biochemistry, genetics and molecular biology and employing novel strategies, **Galande made an early mark in the field of epigenetics and rapidly established himself as a leading researcher. Galande has therefore been invited to large number of meetings and seminars all over the world. Outcome of research from Dr. Galande's group have been published in some of the best journals in the field and have attracted a lot of attention from the chromatin biology-gene regulation community**. **In 2020, he also co-edited (along with Prof. Geeta Narlikar, UCSF) a special issue of J Biosciences focused on Chromatin Biology and Epigenetics.** In collaboration with Prof. Narlikar (recipient of Vajra grant of DST), Prof. Galande is now working on deciphering the role of phase separation in chromatin biology via the disordered regions of chromatin organizer SATB1. This has tremendous implications towards the biology of autoimmune diseases (Madhok et al., Manuscript communicated). In collaboration with Tata Memorial Hospital, he is currently running a **phase 2/3 clinical trial for repurposing statins as antitumor agents**, especially in colorectal cancers by targeting chromatin organizer SATB1. The results of this study are highly promising and will be published shortly (Tripathi et al., Manuscript under preparation).

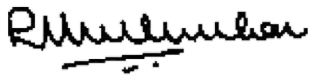
Collaborations and team-work

Galande has several ongoing projects involving collaborations with other groups within and outside of his institutions using genomic and proteomic technologies. He has also initiated interdisciplinary research with his chemist and physicist colleagues at IISER. His collaborations also include a large number of international centres. He is recipient of competitive funding for bilateral programs such as the Indo-US, Indo-Finnish, and Indo-Austrian collaborative research programs. Prof. Galande has pioneered the use of next generation sequencing technology for epigenetic studies in India. At the heart of next generation sequencing is data analysis and towards this, Prof. Galande has built a team of highly skilled bioinformaticians and computer scientists at IISER Pune. His team has also conducted workshops to disseminate the know-how of Epigenetics and NGS data analysis to large number of biologists. Prof Galande's vision has led to the setting up of a **Centre of Excellence in Epigenetics** (CoEE) at IISER Pune in 2010, which has resulted in a network of diverse biologists making use of knowledge and techniques of epigenetics. The CoEE then continued into its second phase (2016—21) after undergoing a competitive renewal. In particular, the centre is focused on epigenetic modifications underlying variety of biologically important phenomena and their role in gene expression, regeneration, cancer, and behavior. The holistic and multi-pronged approach of this team led by Prof. Galande necessitated more close and effective collaborations that were facilitated by trained manpower and by creation of state-of-the-art facilities. While each group was engaged in contemporary and competitive areas, this Centre of Excellence acted as a catalyst to bring these groups in active interaction – an effort of this kind was unprecedented in modern biology labs in India. The grand scheme of projects proposed by this team of scientists lead by Prof. Galande aimed to achieve the understanding of complex mechanisms of epigenetic regulation in various biological processes. This is accomplished using number of different eukaryotic model systems of increasing complexity from Hydra to mouse, so as to gain insights into the

evolution of epigenetic regulation. Using these model systems, Galande has dared to tackle important long-standing questions addressing fundamental phenomena in biology. The Drosophila and mouse model systems were used to understand epigenetic control of development and diseases. Prof. Galande took a very bold step to establish *Hydra* as a model system to understand epigenetic control of regeneration. Galande is undoubtedly the first researcher to initiate epigenetic and chromatin biology studies in *Hydra* – an early metazoan. He also introduced the *Hydra* model system as an educational tool for teaching cell and developmental biology to undergraduates. Galande has also used Zebra fish as a model system to understand mechanistic differences in the role of epigenetic regulation in the development of invertebrate and vertebrate organisms. Based on his early findings, two leading Zebrafish researchers namely Prof. Heisenberg from IST, Austria and Prof. Giraldez from Yale University have initiated collaborations with him. **The list of Prof. Galande's international collaborators and bi-lateral grants is indicative of his reputation as an international leader in his field.** Interestingly, using all these model systems Prof. Galande and coworkers focused on a common signaling pathway - the Wnt pathway. From education point of view, this is a **good example of unity (underlying common mechanism) in diversity (phenotypes) in biology**. By exploiting unique features of each model system his team was able to demonstrate multiple aspects of the fundamental link between this signaling pathway and epigenetic regulation of patterns of gene expression and resulting phenotypes. At the apex of all such studies is the ongoing Phase2/3 clinical trial for repurposing statins for cancer therapy. In collaboration with the clinicians at Tata Memorial Hospital, Mumbai, Galande's group has shown that the tumor regression by statins occurs by targeting the Wnt pathway. This work is funded by **DBT's Accelerated Translation Grants (ATG) scheme**. The Centre of Excellence in Epigenetics program continues at Shiv Nadar IoE and **a new centre focused towards translational biology** has been launched with Prof Galande as the team leader.

Two of the technologies developed by Dr. Galande's group are patented and he has also filed one more patent in cancer prognostics. Thus, Dr. Galande's research has not only paved way towards understanding fundamental mechanisms of gene regulation at a global level, but also pioneered development of innovative technologies for research in Life Sciences and Biotechnology.

Prof. Galande has been a good mentor in all the three institutions he has worked. At IISER Pune and Shiv Nadar University, Dr Galande has taken up senior leadership positions and nurtured the growth of these institutions by creation of new facilities and research programs and has also mentored large number of young faculty members at both these institutions.



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