Tata Institute of Fundamental Research
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To whomsoever it may concern,

I hereby sponsor the application of Ms. Namrata Shukla for the Sun Pharma Science Foundation Science Scholar Award 2021. Ms. Shukla is a senior Ph.D. student at the Tata Institute of Fundamental Research. The work she has pursued and her findings are outstanding and rather unique. This is because they not only provide fundamental insights into insulin signaling and nutrient-dependent effects on physiology, but also are relevant in a clinical setting. One part of thesis reveals the importance of insulin dose and kinetics in dictating downstream effects brought about by the signaling cascade. The other part of her thesis has illustrated the impact of nutritional inputs during development in shaping physiological fitness, stress resistance and lifespan in adults.

While both aspects of the study are extremely novel and the translational potential to improve human health especially in the context of metabolic diseases and aging, I will highlight the scientific discovery vis-à-vis action of insulin. This has been recently accepted for publication in PNAS (2021, In Press). Specifically, her work highlights novel regulatory mechanisms that control insulin signaling dynamics and also raises several questions about the efficacy of dose regimes for clinically administered insulin.

Diabetes and metabolic diseases are on the rise and India has emerged as country with very hurden incidence of metabolic syndromes (MetS). Insulin signaling is central to regulating physiology and maintain glycemic control. However, most of our understanding of insulin efficacy, moreso in the context of insulin administration in treating diabetes, is largely restricted to maintenance of glycemia.

Despite several decades of work (2021 being the 100th year of the discovery of insulin), there has been a paucity of information on the extent to which the signaling cascade is tuned as a function of insulin inputs across concentrations and time. In this regard, Ms. Shukla's work stands out since it has led to new discovery of kinetic control and has been either ignored or taken for granted in the field thus far.

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While the merits of the study will become apparent from her application, it is important to note that she has used a multi-disciplinary approach to understand the kinetics of insulin signalling and information flow through different arms downstream of signalling. These include the arm, which drives its metabolic functions (glucose uptake, protein and fat synthesis etc.) as well as cellular growth and proliferation promoting arm (consisting of the MAPK pathway and ERK activation). This has huge implications in the clinics since current understanding of actions of insulin do not take into account the impact on cellular/tissue physiology beyond glycemic control.

Ms. Shukla's efforts and findings are commendable for several reasons and can be summarized as below: (a) extremely well designed experimental paradigms that closely mimic in vivo context (b) meticulous planning of complex experiments and the rigor of science which is amply clear from the quality of her results (c) identify key questions, in an otherwise crowded field where most people would assume that we know everything about insulin signaling (d) use of multidisciplinary approaches to tackle this complex problem and integrate systems level methods.

The power of her findings will enable clinicians to re-evaluate the effects of normo-insulinemic and hyper-insulinemic stimulation in healthy individuals and in patients on therapy. Importantly, this will lead to a deeper understanding of the effects of insulin dosing/signaling that might continue to cause tissue damage even though they might show tight glycemic control.

It is important to emphasize that Namrata worked independently, without the help from any other member in the lab and her nuanced understanding of the field was key to nurture the collaboration with Dr. Ranjith Padinhateeri and Dr. Shantanu Kadam from IIT Bombay, which was used to develop mathematical models. Here again it should be noted that most of the questions that were realized using models couldn't have been possible without Namrata's deep insights.

Through her grit, planning and, thorough hard work, she was able to overcome these challenges, while also independently working on another completely different

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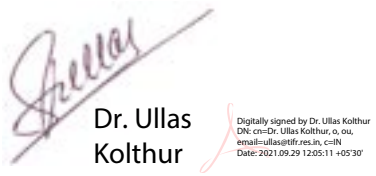
project in the lab (with a different model system, Drosophila melanogaster. The manuscript corresponding to this is also under revision, currently).

In conclusion, I strongly recommend the application for favorable consideration. In my view her application stands out based not only the relevance of her work but also because of her skills, which were vital to complete these, projects successfully

Sincerely



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