To:

The Selection Committee,

2021 Sun Pharma Science Scholars Award.

Brief Summary of the Research

Neurodegenerative diseases are one of the most debilitating and devastating disorders affecting millions of people worldwide. It is caused by untimely death of a few parts of the brain though the scientific reasons behind this remain an enigma. Lack of sufficient understanding about it is also reflected by the unavailability of robust diagnosis tools and/or cure of these diseases. The research worked submitted for the consideration of Sun Pharma Science Scholars Awards-2021 was aimed at deciphering molecular details of a human neurodegenerative disorder called PHARC. PHARC is characterized by progressive loss of motor coordination (ataxia), hearing and visual disability, and demyelinating neuropathy. Prior studies have suggested that PHARC can be caused by accumulation of lysophosphatidylserine (lyso-PS) lipids in the brain. Lyso-PSs are metabolized by two enzymes – ABHD16A (biosynthetic) and ABHD12 (degradative) in the mammalian brain, and human PHARC subjects have mutations in abhd12 gene that encodes ABHD12. The principal question of Shubham's research work was to figure out how deregulated lyso-PS causes PHARC and if we alleviate PHARC by regulating lyso-PS levels or lyso-PS signaling. To develop an understanding of this, he characterized and mapped lyso-PS metabolism spatially and identified its crucial signaling effects in the brain. Further, he demonstrated how defective lyso-PS signaling causes aberrant microglial activation and hence neuroinflammation through Toll like receptor 2 and defective neural communications in the cerebellum. He also found that ABHD12 metabolizes oxidised PS – a toxic pro-apoptotic lipid metabolite known to cause nerve death (neurodegeneration). Next, he demonstrated in mice models that the PHARC pathophysiology can be alleviated by inhibition of TLR2 receptor, ABHD16A enzyme and/or administration of minocycline.

Overall, the submitted work demonstrates a rigorous characterization of lyso-PS lipid metabolism, provides molecular insights into PHARC pathophysiology and explores the therapeutic intervention possibilities to manage PHARC Syndrome.

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Nominee   Doctoral Supervisor

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