12th August 2024

To Whom It May Concern

I am writing to certify that the research work submitted by Mr. Sayak Ghosh for the Sun Pharma Science Foundation Scholar Fellowship has been conducted by him under my supervision. As an Assistant Professor at Amity University Kolkata, I have closely monitored Sayak's research activities over the course of four years.

The Research Project Titled **"Assessing Mitochondrial Dynamics, Metabolism, and Mitophagy Regulatory Proteins as Therapeutic Targets in Key Signalling Pathways Altering Mitochondrial Function in Cancer"** focuses on "Despite Warburg's hypothesis, mitochondria play diverse roles in cancer progression by influencing the cell cycle, gene expression, metabolism, immune response, proliferation, and survival. Elevated intra-mitochondrial reactive oxygen species (ROS) contribute significantly to the cancer microenvironment. Mitochondria, dynamic organelles undergoing fission and fusion, are crucial for mtDNA distribution, cristae remodeling, bioenergetic balance, and turnover maintenance. GTPases like Mitofusin 1 (Mfn1), Mfn2, and optic atrophy 1 (Opa1) mediate fusion, while dynamin-related protein 1 (Drp1) drives fission. Tumor suppressor p53 regulates Opa1, promoting mitochondrial fragmentation and cancer cell proliferation in ovarian and cervical cancers. Drp1, on the other hand, is linked to increased glycolytic metabolism in lung cancer and active oxidative metabolism and fusion in metastatic models. The effects of Drp1 expression vary by cancer type. Autophagy and mitophagy play dual roles in cancer, acting as either oncogenic or tumor-suppressive. PINK1, a mitophagy regulator, is elevated in squamous cell carcinoma but reduced in ovarian cancer. The roles of proteins like Drp1, PINK1, and Opa1 in cancer make them critical targets for therapeutic investigation. This study aims to explore the roles of Drp1, Opa1, and PINK1 as potential therapeutic targets in signalling pathways regulating mitochondrial metabolism and their links to cell proliferation in digestive tract cancers (e.g., gastric adenocarcinoma, hepatocellular carcinoma). The interplay between mitochondrial dynamics, mitophagy, and cell proliferation will be studied using chemical inducers/inhibitors and siRNA-mediated knockdown under normal conditions and in the presence of traditional (e.g., Cisplatin, Doxorubicin) and unconventional (e.g., NSAIDs) anti-cancer drugs. Previous research suggests NSAIDs induce mitochondrial dysfunction with potential anti-cancer effects, though the precise mechanisms remain unclear. This study will investigate the molecular pathways through which NSAIDs exert anti-neoplastic effects in gastrointestinal carcinomas". Throughout this period, Sayak has demonstrated exceptional skills in experimental setup and problem-solving skills, and his contributions have been integral to the progress of the project.

I can confirm that all aspects of the research, including data collection, analysis, and interpretation, have been carried out by him. And also, I confirm that the research work submitted for Sun Pharma Science Scholar Fellowship has actually been done by Mr. Sayak Ghosh. His commitment to maintain high standards of scientific integrity and ethical research practices has been commendable.

In conclusion, I fully endorse Mr. Sayak Ghosh's application for the Sun Pharma Science Foundation Science Scholarship and affirm that the work submitted is indeed his own.

Thank you for your consideration

Sincerely

Dr. Rudranil De, PhD

Assistant Professor (II)

Amity Institute of Biotechnology

Amity University Kolkata

Major Arterial Road, Action Area II, Kadampukur, West Bengal 700135

Email: drudranil@kol.amity.edu