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14. ABSTRACT

Although SCLC patients respond to initial chemotherapies, most of them will inevitably relapse, resulting in early death. High incidence of metastasis and drug resistance are the major factors responsible for reduced survival observed in SCLC patients compared to other type of lung cancers. I this regard, we are analyzing the therapeutic utility of Umbralisib in transgenic and patient-derived xenograft mouse models of SCLC. Umbralisib is a dual Phosphatidylinositol-3-kinase δ (PI3Kδ) and casein kinase-1ε (CK1ε) inhibitor. PI3Kδ and CK1ε are dysregulated in SCLC and are known to drive translation of various oncogenes, including MYC, which is involved in SCLC progression and drug resistance. We hypothesize that a clinically approved Umbralisib may inhibit SCLC progressing and metastasis by suppressing various oncogenic activities. In this proposal, we will evaluate the ability of Umbralisib to prevent or delay the malignant transformation of the lungs and subsequent progression/metastasis in a transgenic and patient derived-xenograft mouse model of SCLC. We will further analyze if Umbralisib can inhibit MYC signaling and act synergistically with chemotherapy against aggressive and metastatic SCLC. These studies will establish the therapeutic potential of Umbralisib against SCLC progression, metastasis and drug resistance.

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NONE LISTED

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TABLE OF CONTENTS

1. Introduction

SCLC is a recalcitrant disease due to its disseminated stage at initial diagnosis and quick relapse after first-line chemotherapy with acquired cross-resistance to additional therapies. The very low survival rate in SCLC patients has not been changed much from last 4 decades. Therefore, there is a significant need to develop novel therapeutic strategies against highly metastatic and drug resistant SCLC.

Protein kinases are vital in the process of oncogenic signal transduction contributing to different hallmarks of cancers. Recently, CK1ε was identified as one of the enriched kinases in SCLC patients using weighted gene co-expression gene network analysis. However, the functional roles of CK1ε in SCLC pathogenesis are still unknown. CK1ε is a well-established positive regulator of Wnt/β-Catenin signaling pathway. Activation of Wnt/β-Catenin signaling pathway promotes tumor progression and CSCs activity in different cancers, including SCLC. A recent study has shown that CK1ε is specifically upregulated in intestinal stem cells and is required for the maintenance of these cells. Our preliminary data shows that expression of CK1ε is specifically upregulated in SCLC patient tumors compared to other type of lung cancers and normal lungs. As such, CK1ε represents an interesting therapeutic target against aggressive and drug resistant SCLC. In this proposal, we will define the role of CK1ε in SCLC progression. Recent studies have shown that Wnt signaling pathway is activated in relapsed SCLC tumors after chemotherapy. Wnt signaling promotes drug resistance by enhancing CSCs activity. Therefore, we will also evaluate the role of CK1ε in overcoming SCLC drug resistance by suppressing CSCs activity. Umbralisib; inhibitor of CK1ε, has recently been approved by FDA for the treatment of lymphoma. We will test the therapeutic utility of Umbralisib against SCLC initiation, progression, and drug-resistance using SCLC transgenic and patient-derived xenograft (PDX) mouse models.

The overall objective of this proposal is to define the role of CK1ε in SCLC progression, metastasis and drug-resistance. We will first evaluate if suppressing CK1ε can inhibit the growth, progression and metastasis of SCLC using in vitro and in vivo assays. Next, we will evaluate if inhibiting CK1ε can sensitize drug-resistant SCLC cells to cisplatin chemotherapy. Furthermore, we will evaluate the therapeutic potential of CK1ε inhibitor alone or in combination with cisplatin against SCLC progression and drug resistance using PDX mouse models.

2. Keywords

Small Cell Lung Cancer, Casein Kinase-1 epsilon, Metastasis, Cancer Stem Cells, Chemotherapy resistance, patient-derived xenograft

3. Accomplishments

None

4. Impact

The patient survival rate is very low in SCLC compared to other type of lung cancers, due to acquired resistance to chemotherapy and lack of effect therapies against drug-resistant SCLC. Our studies defining the novel roles of CK1ε in SCLC will have significant impact on the current understanding of molecular mechanisms involved in development of CSCs activities, tumor progression and drug resistance. The use of FDA approved and orally active inhibitor of CK1ε Umbralisib, drug-resistant cells lines and PDX models in the proposed pre-clinical studies will ensure the development of novel therapeutic options for aggressive and drug resistant SCLC. Overall, our studies will define novel role of CK1ε in SCLC initiation and progression and will establish its inhibitor as a novel therapeutic agent against aggressive and drug resistant SCLC.

5. **Changes/Problems:** We requested to transfer the project from The Ohio State University, Columbus, Ohio, USA to Indian Institute of Technology Jodhpur, India in March 2022. The extensive paperwork requirement for international transfer delayed the transfer of project significantly. Although the project has been transferred to Indian Institute of Technology Jodhpur on 10th January 2023, the fund has not been released to us yet, due to unavailability of SAM.GOV unique entity identifier for our collaboration institute (All India Institute of Medical Sciences Bhopal, Madhya Pradesh, India). Therefore, the proposed work has not been started yet. We have received NCAGE code for both the institutes and also obtained SAM unique entity identifier Indian Institute of Technology Jodhpur. We have submitted the request to obtain SAM unique entity identifier for All India Institute of Medical Sciences Bhopal and the unique entity identifier is awaited. Therefore, I request you to provide us an additional 1 year no cost extension.

6. **Products**

   None

7. **Participants & Other Collaborating Organizations**

   Collaborator: Ashok Kumar, Associate Professor, Department of Biochemistry, All India Institute of Medical Sciences Bhopal, Madhya Pradesh, India.

8. **Special Reporting Requirements**

   None

9. **Appendices**