Radioprotection of Normal Lung with SB415286, a GSK3-β Inhibitor

Xuan Ren, Ph.D,1 Shearwood McClelland III, M.D.1, Dinesh Thotala, Ph.D.1, Jerry Jaboin, M.D., Ph.D.1,2
1 Mallinckrodt, Washington University; 2 Radiation Medicine, OHSU

Problem / Question
Radiation is very effective for the treatment of lung cancers, however is limited by radiation’s impact on normal lung. The enhancement of radiation’s therapeutic ratio can be achieved by selectively increasing the radiosensitivity of tumors or decreasing the sensitivity of normal tissues to radiation.

Hypothesis
We hypothesize that the GSK3β inhibitor, SB415286, was capable of protecting normal lung tissues from radiation damage in mice.

Materials & Methods
C57BL/6 mice were evenly divided into two groups, 16 Gy plus DMSO and 16 Gy plus 1mg/kg SB415286. In addition, four mice in the control group and four mice in the SB415286 group were maintained for body weight monitor, and sacriﬁced at the end of experiment. One mg/kg SB415286 was subcutaneously injected into the mice at 24 hours and 30 minutes before irradiation. Mice received single-dose irradiation of 16 Gy to the thoracic area with the remainder of the body shielded. Body weight monitoring, BAL fluid analysis, histopathology and immunohistochemistry were performed at day 1, week 1, week 4 and week 8.

Impact on Weight Loss

Impact on lung inflammation

Impact on lung injury

Impact on cell damage

Results
• BAL fluid analysis, histopathology and immunohistochemistry revealed that radiation-induced lung inﬂammation reached maximum at week 4 after radiation and lasted until week 8. One mg/kg SB415286 pretreatment decreased the total cell number and the percentage of differentiated cells including neutrophils and lymphocytes in the BAL fluid;

• Lung histological examination revealed alveolar wall thickening, fewer neutrophils in the alveolar space as well as the interstitial space, and less proteinaceous debris ﬁlled the air space in the SB415286 plus IR treatment group compared to the group exposed to IR alone;

• immunohistochemistry demonstrated a significant decrease of TGFß expression in the lung tissue after pretreatment with 1mg/kg SB451286.

Conclusion
SB415286 is a radioprotector for normal lung cells in this murine model. Potential application for use in humans.