Project title: A Groundbreaking Research Project aiming to Improve Cancer Diagnosis, Treatment, and Survival in Taiwan by National Cheng Kung University Hospital Program title: Development of a clinical diagnostic assay kit and new therapeutic agents to improve the survival rate of pancreatic cancer patients

IL-8/CXCR2 Pathway is a Possible Therapeutic Target in Pancreatic Cancer and Cachexia

Ya-Chin Hou[1], Ying-Jui Chao[1,3], Hao-Yun Chen[1], Chih-Jung Wang[1,3], Hao-Chen Wan[3], Hui-Ling Tung[5], Yan-Shen Shan[1,2,3]

侯雅琴，趙盈瑞，陳浩雲，王志榮，王昊宸，董慧玲，沈延盛

[1]Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [2]Department of Clinical Medical Research, [3]Division of General Surgery, Department of Surgery, National Cheng Kung University Hospital, Tainan, Taiwan

Background: Cancer cachexia (CC), characterized by body weight loss and sarcopenia, contributes to over 20% of all cancer-related death. Approximately 80% of pancreatic cancer (PC) patients develop CC during the disease course. Pro-inflammatory cytokines, including Interleukin-1β (IL-1β), Interleukin-6 (IL-6), Interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α), have been correlated with CC; however, its prognostic significance remains unclear and the molecular mechanisms responsible for the development of CC are poorly understood.

Material and Methods: IL-1β, IL-6, IL-8, and TNF-α levels were determined in serum from normal donors and PC patients with/ without CC. IL-8 expression was also assessed in PC tissue microarrays. The correlation of the concentrations of each cytokine from different groups with disease progression, weight loss, and sarcopenia was calculated. Functional screening of skeletal muscle cell differentiation and orthotopic cachexia mouse model were used to dissect the molecular mechanisms driving CC.

Results: Of these mentioned cytokines, only serum IL-8 level was positively correlated with CC status and sarcopenia in PC patients. IL-8 expression in tissue samples was also related to CC symptoms and disease progression in PC. Utilizing muscle cell differentiation and orthotopic cachexia mouse models we identified IL-8/CXCR2 pathway activation as a potent inducer of CC. IL-8 blockade by CXCR2 inhibitor SB225002 reversed body weight loss, restored muscle and fat tissue mass, inhibited tumor growth, and improve survival in vivo.

Conclusion: IL-8/CXCR2 acts a key driver of CC and as a potential therapeutic target for the treatment and/or prevention of PC and CC.