Objective of the project

Lung cancer is the number one cause of cancer-related deaths in industrialized countries and is expected to cause yearly ~ 200,000 and 350,000 deaths in the European Union and United States alone. Growing evidence accumulates that pituitary sex hormones (SexH) play an important role in development and progression of several malignancies arising in gonads, urogenital track and breast. Interestingly, as we have recently demonstrated pituitary SexH are also involved in progression of malignancies originating in skeletal muscles and hemato/lymphohematpoietic tissues. To support this notion evidence indicates that pituitary SexH such as follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL) are potent mitogens. Furthermore, the level of FSH increases with age as result of age-related gradual dysfunction of gonads. This age-related increase as postulated could explain increase of some malignancies including lung cancer in aged population. To support this, in fact a level of pituitary SexH in circulating blood has been demonstrated to be enhanced in lung cancer patients. Moreover, our preliminary data indicate that LC cells express functional pituitary SexH receptors. Based on these observations the main hypothesis of this proposal is that pituitary SexH may play an important and still somehow underappreciated role in pathogenesis of lung cancer and to shed more light on a role of SexH in lung cancer we propose 3 interrelated specific aims to **study the role of pituitary SexH in regulating the metastatic behavior of LC, molecular pathways involved in pro-metastatic signaling of pituitary SexH in LC cells and finally to phenotype patient-derived LC samples for expression of pituitary SexH receptors and level of SexH in peripheral blood through collaboration** with dr hab. Marcin Moniuszko , Head of Department of Regenerative Medicine and Immune Regulation from Medical University of Bialystok. .

Innovativeness of this proposal

The pathogenesis of lung cancer and mechanisms that regulate metastasis of cancer cells are still not very well known. This application is highly innovative as we propose based on exciting preliminary data a hypothesis that pituitary SexH play an important role in pathogenesis of lung cancer. We will study a pro-metastatic role of pituitary SexH on human lung cancer cell lines in state of art in vitro and in vivo experimental models. We will study a prognostic value of expression of SexH receptors on different morphological types of lung cancer cells as well as level of SexH in peripheral blood of lung cancer patients. Finally based on our novel data on involvement of MAPKp38-HO-1 axis in migration of cells, we will employ molecular modifying agents of this axis to see if inhibition of MAPKp38 or upregulation of HO-1 in cancer cells will decrease pro-metastatic potential of lung cancer cells. This part of proposal is highly translational for future clinical applications.