Chronic respiratory diseases are the most common medical conditions in the world and are the sixth cause of death worldwide. Millions of people suffer from asthma, chronic obstructive pulmonary disease, cystic fibrosis and lung cancer. In both industrialized and developing countries, respiratory diseases represent a challenge to public health because of their frequency, severity and economic impact. It is obvious that smoking, infections, and genetics are responsible for the majority of airways diseases, but the molecular background of these pathologies is still only partially elucidated.

The bronchial epithelium is of a pseudo-stratified structure, it lines most of the respiratory tract, consists of specialized cell types and plays an active role in airway defense by protecting the airways from infection and damage induced by environmental toxins. The maintenance of spatiotemporal differentiation of bronchial epithelial cells has a crucial role for proper lung function. However, knowledge of the molecular mechanisms regulating development and homeostasis of the airway epithelium remains limited. For this reason, there is an urgent need for comprehensive research that will lead us to better understand the biology of bronchial epithelial cells and potentially bring us closer to the ultimate goal of improved management of respiratory system diseases.

Heat shock proteins (HSPs), a large group of highly evolutionary conserved chaperone proteins, are considered as the main elements of the cellular protein quality control system and are involved in modulation of multiple cellular and physiological processes. In the context of bronchial epithelium, the data on HSPs roles are limited – so far their physiological roles were linked with the mucin secretion in airway epithelium and with the protection of bronchial cells against toxic pollutants. In our previous research, we showed that HSPA2, a testis-enriched protein and one of the least characterized HSPs, is present in selected populations of cell in the stratified/pseudostratified epithelia, like the epidermis, esophagus and bronchus. Taking into account the universal presence of HSPA2 in the epithelial cells it is tempting to think that HSPA2 can be a unique example of a differentiation-related chaperone in stratified/pseudostratified epithelia. Recently, for the first time, we have revealed that HSPA2 is involved in controlling basal cell differentiation in the epidermis. Therefore, we hypothesize that HSPA2 can play a role of a universal differentiation-related chaperone in epithelial cells, also in bronchial epithelium.

The goal of our project is to resolve the biological role of the HSPA2 protein in human bronchial epithelial cells. We also intent to examine whether HSPA2 in bronchial epithelial cells plays a specific role or its activity is redundant with other member of the HSPA family, namely a well-known cytoprotective HSPA1. This protein is constitutively produced in bronchial epithelial cells. Using tools of modern molecular biology, as well as cellular and tissue engineering technologies we will construct an in vitro model that allow us to analyze how and to what extend HSPA2 and HSPA1 impact on the phenotype of human bronchial epithelial cells. Using genetic modifications methods we will remove the genes of interest from bronchial epithelial cells. Than we will analyze the dependence between altered HSPAs expression and cell's potential to: 1) proliferate; 2) form colonies; 3) adhere to extracellular matrix components. Evaluation of the role of HSPAs in maintaining homeostasis of bronchial epithelium will be conducted using advanced air-liquid interface culture system *in vitro*. This system enables reconstitution of a spatial multicellular epithelium comprised of basal cells, ciliated cells, goblet cells with fully-developed impermeable barrier.

This project is fully original and pioneering because it focuses on a novel role of HSPA2 protein as a basal cell-specific chaperone that supports proper structure and/or function of cells in multilayered epithelia. A greater knowledge of human bronchial epithelial cells biology is of a high clinical relevance since disturbances of their proliferation and differentiation can lead to respiratory diseases, including asthma, chronic obstructive pulmonary disease, cystic fibrosis and lung cancer.