Obesity is a major risk factor for asthma, but the mechanisms underlying obesity-driven airway inflammation and asthma development are not known. Obesity causes chronic low-grade inflammation that influences other organs and tissues and previous studies showed that obese phenotype enhances the secretion of pro-inflammatory adipokines that may influence also inflammation in the airway. However, as **not all obese patients develop asthma,** we assumed that another biological mechanism exist that link the inflammation of adipose tissue with the lungs and activates airway inflammation. One of the possibilities that would enable communication between distant organs or tissues such as adipose tissue and lungs are extracellular vesicles secreted by almost each cells types upon different stimuli such as stress or inflammation. Previous studies showed that up to 80% of exosome-derived miRNAs, small regulatory molecules, originate from adipose tissue, thus this tissue seems a potent regulator of systemic inflammation.

We hypothesized that diet-induced obesity alters the inflammatory phenotype of asthma via adipose-derived circulating miRNAs and that communication between adipose tissue and the airways is possible via exosomes. Despite the extensively studied role of adipokines secreted by adipose tissue in the systemic inflammation, the exact molecular mechanisms underlying change of inflammatory phenotype in the airways of obese asthma patients are not known. **The novelty of this project is an assumption that adipose tissue-derived exosomal miRNAs influence the airway inflammation phenotype**. We plan to investigate this hypothesis in animal model of asthma with diet induced obesity as well as in pediatric patients with "obese asthma" phenotype.

First, we plan to identify adipose-derived exosomal miRNAs that expression changes significantly upon high-fat high-carbohydrate diet (i.e. Western diet) in a rat model of asthma and obesity. We will also analyze the influence of diet-induced alteration in miRNA expression on the type of airway inflammation in sensitized and non-sensitized rats.

In the next step we plan to identify the miRNA expression profile specific for obese asthma phenotype in exosomes extracted from plasma of paediatric patients. This step will enable to select miRNAs for functional *in vitro* experiments in adipocytes and bronchial epithelial cells. In cell culture model we will investigate the effect of modulating of expression of selected miRNAs by transfecting them with miRNA mimics, monitor exosome uptake and identify target genes of overabundant miRNAs. The potential targets will be then validated by luciferase that will be further verified on protein level.

Then the effect of miRNA silencing will be verified *in vivo* in sensitized rats that will receive construct that will block the expression of selected miRNAs in adipose tissue to monitor the effect of silencing on protein targets and inflammatory phenotype in the lungs.

An innovative aspect of this project is the use of targeted silencing miRNA in adipose tissue to analyze its potential as a modifier of inflammation in the airways. Based on the potential of exosomes as nanocarriers for exogenous siRNA to control gene expression in the recipient cells, we aim to elucidate if targeted intereference of selected miRNAs to white adipose tissue may have beneficial effect on airway inflammation phenotype and asthma severity.

The project will identify miRNAs that mediate inflammatory signals from adipose tissue to the airways. **Identification of molecular predictors of obese asthma phenotype would facilitate diagnosis and predict response to the existing treatment.** The results may be also applied to develop **novel targeted therapeutics for obese asthma phenotype in children that are not responding to current asthma medications**. So far, therapies using miRNA mimics or inhibitors to reverse pathological phenotype were described in several diseases. Trials are also made in respiratory medicine, with the most successful solutions tested in a clinical setting for lung cancer. The administration of exogenous miRNAs (either mimic or inhibitors) could be, in the near future, a promising therapeutic strategy in the treatment of inflammation-related diseases. Moreover, for the pulmonary disease, **miRNA-based drugs could be delivered via inhalation thus reducing off-target effects and toxicity.**

Uncovering the mechanisms underlying exosomal communication between adipose tissue and the airways may be applied to identify the molecular mechanism underlying obesity-derived inflammatory profile change. Taking into account dynamic increase in the prevalence of obesity and obesity-related phenotypes, this project may also elucidate if the interventions into the adipose tissue could be beneficial to treat common obesity-related diseases such as insulin insensitivity, type 2 diabetes or metabolic syndrome.