Novel ligands of the histamine H4 receptor as potential anti-allergic and anti-inflammatory drugs

More than 130 million people in Europe have symptoms of upper respiratory tract allergies, making antihistamines one of the most commonly used pharmacological agents.

In the case of allergies the most important element of pharmacotherapy is blocking histamine H1 receptors. In the human body, the histamine concentration in the serum is negligible, only under the influence of physical factors (cold, oppression) or chemicals such as pharmaceuticals it is released, which is manifested, inter alia, by allergic symptoms. Histamine secretion affects all types of histamine receptors: H1, H2, H3 and H4. Antyhistamines administered for allergic rhinitis and common cold are the antagonists of the human histamine H1 receptor. Unfortunately, the first generation of drugs (H1 blockers) have a number of side effects, including drowsiness, cholinergic effects and orientation disorders (difficulty in driving). In addition, the anti-histamines – H1 and/or H2 receptor blockers – used in medicine does not have a wide range of applications in the treatment of immune diseases e.g. for atopic dermatitis. Therefore, researchers focused their attention on the most recently recognized H4 receptor. It has been found that the H4 receptor plays an important role in immune and inflammatory responses, it is important in the pathophysiology of diseases such as asthma, enteritis, allergic gastroenteritis, arthritis, atopic dermatitis and other chronic inflammatory diseases, as well as in the development of certain cancers. Therefore, searching for new and active H4R ligands will improve the prognosis of these diseases, especially in the treatment of atopic dermatitis.

The aim of this interdisciplinary project is to search for the high activity and selectivity ligands of H4R with novel chemical scaffolds as potential anti-allergic and anti-inflammatory properties. The additional aim is to find double ligands of the H1R/H4R heterodimer. The Project is **interdisciplinary,** since it will be pursued by a broad range of specialists from **different fields of life, natural, and computational sciences** and include the following steps:

A) Modeling of the histamine receptor structures and their complexes with ligands

B) Synthesis of the selected compounds

C) In vitro pharmacological studies of the compounds obtained

Within the project, the ligands with proven activity and selectivity for H4R will be selected. The project is part of the current trend in pharmaceutical sciences that involves searching for a new drug, from the choice of a biological target to the selection of a compound ready for animal testing. A pioneering concept of the Project consists in the combination of molecular modeling with chemical synthesis and pharmacological screening which makes it easy to obtain ligands with desired properties and identify the mechanisms of action of the selected compounds of the H4 receptor and the H1/H4 heterodimer.

The Project will help to select compounds for subsequent studies *in vivo* and will significantly influence the development of histamine receptor science.