

## **The role of diet in the development of autoimmune diseases - new interleukin 15 inhibitors among dietary polyphenols and their gut microbiota metabolites**

In recent years there has been a substantial increase in the number of inflammatory and autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, type I diabetes, T leukaemias and many other conditions. The development of these disorders have been associated with the increased activity of a protein, interleukin 15 (IL-15). IL-15 is a pleiotropic cytokine responsible for the proper immune response. Nevertheless, its increased activity has been associated with the development of aforementioned diseases.

In our previous research we have identified 12 small-molecule inhibitors of IL-15 activity, seven of which share the same structural component – benzoic acid. Our further research have revealed 15 more benzoic acid derivatives inhibiting IL-15 activity.

Many benzoic acid derivatives are naturally present in plant and animal tissues and can be produced by microorganisms. Among them we can distinguish a wide group of dietary polyphenols and their gut microbiota metabolites. Polyphenols are produced in plant cells and are an important component of everyday diet, high concentrations can be found inter alia in small dark fruits and wine. They can reduce the risk of a number of diseases, including cardiovascular diseases, cancer, hypertension and neurodegenerative diseases. Polyphenols can be metabolised and absorbed in different parts of digestive tract. When not absorbed in the earlier parts of the gastrointestinal tract polyphenols reach colon where they may be degraded by gut microbiota into numerous phenolic and carboxylic acid products including benzoic acid derivatives.

In addition to the most common antioxidant activity, polyphenols display anti-inflammatory activity. However little is known about their impact on IL-15, which plays a pivotal role in autoimmune diseases development.

**The current proposal aims to provide scientific evidence on the inhibitory activity of dietary polyphenols and their gut microbiota metabolites, especially benzoic acid derivatives, towards IL-15.** Our preliminary studies uncovered two polyphenols metabolites which inhibit IL-15 activity. The basis for the selection of the compounds from a large group of dietary polyphenols and their gut microbiota metabolites will be the computer-assisted methods. They will allow the selection of compounds which can bind to the IL-15 receptor with high probability. The selected compounds will be tested for their activities in cell-based and animal models. This will enable us to uncover the active inhibitors of IL-15 activity among dietary polyphenols and their gut microbiota metabolites.

**The proposed project will develop the knowledge and give new information about the possible mechanisms of anti-inflammatory action, specifically the IL-15 activity inhibition, of polyphenols and their gut microbiota metabolites.** Searching for IL-15 inhibitors among dietary polyphenols and their gut microbiota metabolites is an innovative approach leading to more precise diet guidelines for patients suffering from autoimmune diseases or even a new immunosuppressive drug development. Based on the structure of active polyphenols and their gut microbiota metabolites the novel small-molecule inhibitors could be designed.