Application of machine learning based artificial intelligence to search for substances that modulate the activity of RORγ/RORγT receptors.

Many low molecular weight compounds (e.g. steroid hormones, vitamin A derivatives, vitamin D, xenobiotics) exert their biological activity by binding to transcription factors called nuclear receptors. Nuclear receptors are a family of proteins that regulate the expression of their target genes in response to the binding of these chemical compounds (which are called ligands). Nuclear receptors are involved in the development, differentiation and maintenance of homeostasis of organism and any disturbances in their functions are associated with human diseases, including: atherosclerosis (liver X receptor - LXR), osteoporosis (vitamin D receptor - VDR and estrogen receptor - ER), diabetes (peroxysome-proliferator-activated receptor - PPAR), cancer (retinoid receptor - RAR, estrogen receptor - ER, androgen receptor - AR) and are molecular targets of drugs commonly used against these diseases, e.g.: Tamoxifen, Enzalutamide, Dexamethasone, Clofibrate.

RORγ and RORγT are receptors, which are an interesting molecular targets in the therapy of metabolic diseases, autoimmune diseases and cancer. Both are protein products of one gene - *RORC*. They are the result of the use of two promoters (the DNA sequences upstream of the gene, which contains the binding sites for polymerase II and transcription factors) and are expressed in different tissues. Longer version of protein - RORγ is expressed in many tissues where it regulates the level of expression of genes involved in the circadian cycle and the metabolism of glucose and lipids. The shorter version is present only in some types of lymphocytes - Th17 cells, where it regulates the differentiation of these cells and the expression of cytokines crucial for the function of Th17. Th17 lymphocytes, although they have a very important protective function (e.g. against *Staphylococcus aureus* or *Candidia albicans*) developed negative reputation for their role in maintaining inflammation in some autoimmune diseases (e.g. rheumatoid arthritis, multiple sclerosis, Crohn's disease). Due to the fact that RORγT is a protein essential for the development of Th17 cells, it has become a potential pharmacological target. Researchers started to search for chemicals inhibiting its activity and as consequence, development of Th17 cells. However, it was found that Th17 cells can also be useful in cell therapy against cancer. If we isolate these cells from the patient and then multiply them in laboratory and then inject them back into the bloodstream, these cells have extraordinary properties for activating the immune system and destroying cancer. Thus, the chemicals that activate RORγT and Th17 cells are also needed. So far, the search for such compounds (we also did it!) has been done with the use of chemical libraries and a tedious screening process. Now, with the development of technology, software and computers, we want to apply a different computer-based approach, which is gaining more and more recognition in drug design. Well, on the basis of known compounds, which are activators or inhibitors of RORγ/RORγT receptors, we want to teach the computer to determine the molecular features of compounds needed to maintain the desired activity towards RORs. In the next stage, we want to compel the computer (artificial intelligence) to propose structures of new compounds that we will be able to study with biological methods, and which in the future may become drugs.