Nuclear receptors is a class of ligand (compound that binds and forms complex with protein) activated transcription factors. When bound to specific sequences of DNA, they serve as on-off switches for gene expression. Nuclear receptors are involved in the regulation of variety of physiological functions via binding to respective sites in the DNA called response elements (RE). Nuclear receptors participate in the response to many internal and external stimuli and integrate multiple signaling pathways. This is why they are involved in pathogenesis of several diseases and are attractive therapeutic targets for treatment of many inflammatory and oncologic disorders.

RORγ and RORγT receptors are so called orphan receptors because they do not have identified physiological ligands yet. Both isoforms are generated by the alternative promoters within RORC gene and have completely different tissue distribution: RORγ is more widely expressed e.g. in liver, kidney, muscles while RORγT is almost exclusively expressed in specific populations of lymphocytes namely Th17. Both proteins regulate important functions of metabolic (RORγ) and immunological processes (RORγT). RORγ and RORγT as other nuclear receptors exhibit a modular structure with different regions corresponding to functional domains, and both differ by 23 amino acids in their N-terminal domain (A/B region of the receptor). Their other domains are identical.

Results observed by the other groups suggesting that these isoforms have different response to some compounds e.g. ligand for RORγ, was not able to upregulate transactivation properties of RORγT. We performed screening of two chemical libraries (more than 2000 compounds tested) and identified several other molecules showing similar effects. Because the ligand binding domains in both RORC isoforms are identical, we propose that the different ligand specificity depends on 23 aminoacids sequence in N-terminal domain. This domain modulates conformation and ligand binding properties of receptor possibly by mediating interaction with other proteins. This hypothesis is supported by our bioinformatic approaches identifying two sites for serine phosphorylation specific for RORγ and not for RORγT isoform. The aim of the proposed research is identification of novel isoform specific agonists of RORγ receptor, and delineation of molecular mechanisms involved in recognition different ligands by this isoform. Proposed research will provide novel data on the mechanism of the action of RORγ and RORγT isoforms and interactions of these receptors with different chemicals, including drugs. This may allow for development of more selective pharmacologic tools to modulate these receptors' function in many clinical conditions. For example: specific activator of RORγ could be a potential drug in sleep disorders, without side effects arising from the activation of Th17 cells and risk of autoimmune disease. Specific antagonist of RORγT will not cause a side effects from the side of circadian cycle, lipid and glucose metabolism.