PROJECT SUMMARY FOR THE GENERAL PUBLIC

Structural and functional analysis of immune checkpoints

The immune system constantly monitors our body seeking and striving to eliminate the hazards. The basic role of distinguishing between "self" and "non-self" is implemented through a number of relatively well-understood mechanisms. However, the immune system is a powerful weapon which, when misused, can easily turn against its own host as observed in autoimmune disorders. That is why a strict, multi-level control of the activation of defense mechanisms is essential. One of the elements of this supervision are the immune checkpoints. The checkpoints provide additional signals, stimulating or mitigating the responses of the cells which had (most often) already recognized the primary signal. This project is focused on the immune checkpoints. This line of verification, which in adequate instances enhances and directs the immune response, prevents inadequate activation and helps silence the response after elimination of danger, is still poorly understood in many aspects. Therefore, **the aim of the project is to understand the mechanistic and structural basis of signal transduction in selected immune checkpoints.** The checkpoints consist of a protein receptor and its ligands exposed on the surface of immune cells and other cells interacting with the above. X-ray crystallography is the method of choice in uncovering the mechanistic principles of function of protein systems at atomic level. This methodology will be utilized in the project to visualize the interactions within selected immune checkpoints. Currently it is not known how these receptors and ligands "look" like, that is how the atoms building these molecules are arranged and how do the constituents of the system recognize each other. It is fascinating how the receptor and the ligand are able to identify each other with high confidence among hundreds of other proteins, and this question will be elucidated in the proposed study.

Apart from scientific curiosity, understanding the immune checkpoints has great therapeutic potential. It is currently known that tumor cells hide from the immune systems by displaying ligands for co-inhibitory immune checkpoint receptors. Therapeutic blocking of these interactions reactivates the ability of the immune cells to destroy cancer. Such therapies are successfully developed and used in clinics for the last decade. Similar role of other immune checkpoints has been demonstrated in experimental systems and first clinical trials based on these findings are being conducted. The research planned in the project will indirectly contribute to the development of the therapeutic aspect by providing the foundations for structure based low molecular weight inhibitor design. Such studies are not planned within the project, but rather constitute its broader perspective.

The second important avenue of planned research is in defining the mechanism of signal transduction within selected immune checkpoint transmembrane receptor. These questions are beyond the direct access of X-ray crystallography: how ligand binding at a location distant from the outer surface of the cell induces changes at the inner side of the cell membrane which are further propagated in a signal cascade. There are currently no direct methods of exploring such dynamic phenomena with atomic resolution, but one may create reliable models of such processes through well-planned indirect experiments. Using reporter systems to track signal transduction, by modifying the receptor and ligand surface, and through various other modifications known in protein engineering, we will strive for a coherent mechanistic model of signaling through the receptor. These studies, although demanding, will provide a pioneering insight into the analyzed phenomena, and their results are likely to enter into the canon of understanding of signal transduction within the immune checkpoints.

In conclusion, **the research envisioned within this project will deliver structural information on the interaction of immune checkpoint receptors and their ligands, and provide insights into the dynamic aspects of signal transduction within the receptor**. Apart from the fascination led exploratory aspect, in a broad perspective, these studies have the potential to contribute to the advancement of treatments for cancer and autoimmune disorders.