Development of an NK1 receptor homology model based on the data concerning interspecies differences in ligand binding

The development of medicinal chemistry in the XX century equipped the modern medicine with plenty of effective and safe drugs used for treatment of various diseases. Unfortunately, many disorders still exist whose treatment is highly inconvenient for the patients or difficult in general. Thus we still need to look for novel – more potent and safer – active compounds.

The drugs act by turning on or off various 'switches' inside our bodies. These "switches" are receptor proteins, enzymes, nucleic acids or other element, named *molecular targets*. A drug is active only if it fits (like a key fits a lock) a binding site of a molecular target. Rational and effective design of novel drugs requires that we know how exactly this fitting (called 'binding') does occur. Researchers can peep this by protein crystallography. Unfortunately, such experiments are rather difficult and in some cases even impossible to be performed. In such a situation, theoretical research and in particular: homology modelling, may help. Homology modelling tries to predict the shape of proteins and their binding sites by analogy to other similar proteins for which the structure is known.

The 'switch' that we want to analyse in our project – the tachykinin receptor NK1 – is just a case of a receptor lacking an experimental crystal structure. On the other hand, it is a potentially important molecular target for novel drugs. Targeting this 'switch' may enable us to control or treat problems such as chemotherapy-induced vomiting, mental disorders, chronic pain or cancer progression. This is why, in the course of the project, we want to develop homology models of the NK1 receptor. They will be of significant help for future drug discovery and design in the field of molecules acting via this protein.

An innovative element of our proposal is the fact of using not only computer-generated models. We want to assess the models by using diverse experimental data, including data on interspecies differences in activity of particular chemical compounds. It turned out that for example human and rat NK1 receptors differ as to their structure and activity. The data of this kind will help us to develop correct models of NK1 receptor structure.

In the project, we shall also synthesize and test a series of novel chemical compounds. They will serve us for development of the models. Potentially though, some of them may become tools for further research and even active drug susbtances.