Objectives of the project

The main goal of the proposal is to find novel anticancer drugs of enhanced clinical potential and reduced toxicity. These drugs block the activity of some enzymes, called USP proteins, which regulate cells division and mechanisms responsible for DNA repair.

Cancer is different than most of diseases, because it can start at any place in the body thus it should be treated rather as a collection of related diseases. In all types of cancer, some cells begin to divide without stopping and then they spread into the surrounding tissues. Normally, when cells grow old or become damaged, they die allowing new cells to take their place and this process is precisely regulated. When cancer develops, however, this natural order starts to break down. Some cells become more and more aberrant, old or damaged cells are not subjected to apoptosis (process of programmed cell death), and new cells form when they are not required. These extra cells can divide without stopping, which results in formation of abnormal structures called tumours, which are masses of tissue. Cancerous tumours are malignant as they can spread around and invade, nearby tissues. Mechanisms of cancer formation are now better understood. For example, it is known that aberrant activity of some proteins regulating of cell division and related processes may be a reason of cancer progression. In this proposal we plan to study a specific class of enzymes called USP proteins to find chemical compounds able to reduce their activity. The major function of USPs is to remove a small protein called ubiquitin, which is attached to other protein molecules thereby regulating their stability. The process of adding ubiquitin is called ubiquitination. Because this process is precisely regulated, even small changes may have disastrous consequences leading to cancer formation.

Why this research topic is important?

Cancer is a major public health problem in the most countries in the world. For example, in 2012 there were 14 million new cases and 8.2 million cancer-related deaths worldwide. Since our society is getting older and the expected lifespan is constantly growing the number of cancer-related deaths is also about to increase. Chemotherapy is so far one of the most efficient ways to treat cancer. Nonetheless, it has a number of side effects which may be quite harmful for the patient. Most of anticancer drugs are toxic for the fast dividing cells of the body such as blood cells and epithelial cells. More worryingly, some cancer cells are resistant to commonly used anticancer drugs. Due to this fact scientist are in pursuit of better anticancer therapies and targeted anticancer therapy is believed to be a promising strategy. Such a therapy is one of the major modalities of cancer pharmacotherapy. The general idea is to block cancer cells growth by interfering with specific proteins. Such a therapy can greatly reduce cellular toxicity, which is the major disadvantage of traditional chemotherapy. Selective increase in activity of USP proteins in observed in many cancers, thus drugs able to counteract that activity would be very less toxic than most of existing chemotherapeutics. Currently only a few inhibitors (compounds able to reduce the activity of a given enzyme) of these protein are available. We need to understand how these compounds work, which allow us to design stronger and more selective inhibitors having better clinical potential.

Research to be carried out

In order to understand the mechanism of action of a given protein it is necessary to reveal its structure on the atomic level. Nowadays, this seemingly impossible goal, can be achieved relatively easy using several methods. The most reliable and widespread of them is X-ray crystallography. In this method a crystal of protein is irradiated by a beam of X-rays, which are subsequently diffracted by the crystal. It allows to obtain a diffraction pattern providing information about the internal structure of the crystal. After mathematical processing of these data it is possible to determine the atomic structure of the protein molecules which form that crystal.

In the first stage of the project we use methods of molecular biology to produce USP proteins using bacteria or eukaryotic cells. The second step is to test whether some chemical compounds that we have are able to reduce the activity of USP proteins. These compounds are expected to form stable complexes with proteins whose structures can be studied further to reveal the molecular mechanism of inhibition. That knowledge allows us develop better inhibitors having more clinical significance, which is the ultimate goal of our research.