V. Richter: "The low toxicity and originality of the pharmaceutical agent are its major advantages"

There is no question that the government needs to provide vigorous financial support to Russian researchers looking to design new drugs. A different question is to what extent should the government participate in the financing and at what point should industrial investors join in?

Vladimir Richter

In the course of implementation of the initial stage of the strategy Development of Pharmaceutical and Medical Industries in the Russian Federation over the Period up to 2020 and Future Prospects, there are signs of the first active initiatives of the government focused on funding research-and-development in the field of new drugs. To be more exact, there are the results of competitions for government grants for a number of activities to be implemented within a particular Federal target programme (FTP). One of the goals consists in providing financial support in the development of products that could reach the market in the nearest future. This year, the Ministry of Education and Science of the Russian Federation announced that it was holding an open competition for the right to negotiate contracts for conducting preclinical studies for promising, cutting-edge drugs. We interviewed **Vladimir Richter**, the Deputy Director for Science at the Institute of Chemical Biology and Fundamental Medicine, Siberian Branch of the Russian Academy of Sciences, whose project, Preclinical Studies of a Pharmaceutical – Antitumour Agent Based on Human Milk-Derived Peptide Lactaptin, won the competition.

Vladimir Aleksandrovich, please tell us about this innovative pharmaceutical agent? Do you intend to carry out preclinical trials?

For many years, surgery, chemotherapy, and radiation therapy aimed at removing a primary tumor have been the major means for treating oncological diseases. Meanwhile, metastatic tumor growth has remained the main agent causing subsequent death of patients. Our novel oncotherapeutic agents are based on the principle of targeted therapy. Put in another way, agents suppressing the viability of tumor cells, without causing normal cell death, are being designed.

Several years ago we established that human milk contains the protein factor that induces apoptosis (i.e., programmed cell death) of cancer cells. We purified this factor to a homogeneous state and found out that it was a peptide, which is a fragment of kappa-casein present in milk. It consists of 74 amino acid residues and has a molecular weight of 8.6 kDa. The novel peptide became known as lactaptin (this name represents its peptide origin and apoptotic properties).

Then, we used genetic engineering techniques to obtain a number of producers of various analogues of this peptide in *E. coli* and compared the effect they have on cancer cells. The properties of the RL2 analogue were the most similar to those of the natural peptide. This analogue was used to test efficacy against various cell lines. Human breast adenocarcinoma cells MCF7 demonstrated the

highest levels of sensitivity to the agent. Therefore, all subsequent experiments aimed at elucidating the mechanism of *in vitro* apoptotic action of the RL2 analogue were carried out using this cell line.

Judging from the fact that you proceeded to preclinical trials, the agent showed good results on model animals. Is it true?

Yes, it is. We established that our peptide induces apoptosis of several murine oncotransformed cell lines. We attempted to develop a method to treat malignant neoformations in mice and obtained very encouraging results: after the intravenous introduction of RL2 to tumor-grafted mice, tumor growth was significantly held back. Moreover, RL2 therapy considerably increases the lifespan of mice with ascytic tumors. We compared the action of our peptide with that of the standard drug cyclophosphamide, which has been conventionally used for chemotherapy. The cytotoxic action of these agents is similar. Hence, we ascertained that our peptide specifically acts on a selected target and can thus be considered to be a potential antitumor agent.

What is the advantage of your pharmaceutical agent?

The low toxicity and originality of the pharmaceutical agent are its major advantages. The drug candidate is based on a nontoxic and non-immunogenic protein derived from human milk. The patent research has demonstrated that proteolytic fragments of kappa-casein (including lactaptin) had not previously been used for cancer therapy.

Speaking about the rivals: aren't you afraid that pharmaceutical giants may leave you behind, since they have much more resources?

For a start, let's just say that there have been few antitumor pharmaceuticals of peptide or protein nature on the market thus far. It is quite possible that some companies will do their best and leave us behind. However, such a course of events is not guaranteed. Even registered patents do not ensure 100% protection. We are positively aware of the fact that it will be very difficult for us to bring the new agent to registration as a drug even with preclinical trials being successful. At this stage, there is nothing we can do but work strenuously and hope that we will be able to strike a partnership with a large pharmaceutical company.

Are you going to conduct trials yourself or do you intend to share this work with partners?

Most of the work will be done by us. Since regulations for conducting preclinical studies suppose that certain work is done by authorized organizations, we are going to engage these organizations in conducting the individual stages of the trial.

Are off-budget funds required to conduct the preclinical trials under a Government Contract?

Our partner is a small commercial enterprise which has been participating in the research and investing funds into project implementation for a long time. Today, it is this small enterprise that equips the working area to produce pilot scale batches of the pharmaceutical agent.

Was it difficult to carry out the project expertise?

At the stage where the objective was formulated, we held long-lasting correspondence with the supervising expert. At first, we did not understand each other very well, since we knew nothing about the specific requirements imposed on medical products as we were used to dealing with fundamental science only. We gained valuable experience and are grateful for the patience of our expert during project preparation. ●

Interview by
Elena Novoselova