The goal of this Project is to verify the effectiveness of delivering at the tumor site **a therapeutic system** based in an **oncolytic virus** shielded by **mesenchymal stem** cells. Use of such therapeutic system made of oncolytic virus shielded by cellular carrier is a precondition to increasing efficacy of tumor destruction by means of the so-called oncolytic therapy.

Certain kinds of viruses have the ability to infect and multiply in various types of cancer cells. This propensity makes it possible to use these viruses for destroying cancerous cells and also makes feasible destruction of actual tumors *via* the so-called oncolysis. However, only in the case of efficient delivery of the oncolytic virus to the tumor site conditions are met to trigger oncolysis, whereas adjacent tumor site remain intact.

The preferred type of drug delivery in clinical oncology, intravenous administration, might however encounter serious obstacles in the case of oncolytic therapy because of a systemic reaction of the recipient immune system to the intravenous delivery of a virus. The therapeutic virus can be destroyed or removed from the body before it reaches its target. This is why we propose in the Project to deliver the oncolytic virus shielded by bone marrow-derived **mesenchymal stem cells (MSC)**. Such cells are weakly immunogenic and they possess distinct tropism (the propensity to move) towards a proinflammatory milieu such as the one formed in neoplastic focus.

In order to increase the effectiveness of the proposed therapeutic system the Project envisions the use of three novel recombinant viruses of **oncolytic-acting, improved** recombinant **myxoma viruses (MYXVs)**. Owing to the fact that the parent myxoma virus is not pathogenic to man or mice (it is contagious only to some Leporidae) and because it is selective towards cancer tissue, the genetically improved recombinant MYXV elicit great hopes in cancer therapy.

The first among the proposed recombinant MYXV encodes additionally interleukin 15 (IL-15), a cytokine that elicits T lymphocytes, induces proliferationon of natural killer (NK) cells and contributes to release of interferon gamma (IFNγ), which leads directly to strongly enhanced antitumor response. The second recombinant MYXV has a gene introduced that encodes tumor necrosis factor LIGHT/TNFSF14 which increases tumor infiltration by T lymphocytes. The third recombinant MYXV, by means of genetic manipulation, has been devoid of M011L gene encoding a Bcl-2 protein homologue, making it possible to try triggering apoptosis of MYXV-infected cancer cells.

Implementation of the Project envisions human or murine bone marrow-derived MSC cells to be isolated first. Such MSC cells will then be infected *in vitro* by recombinant MYXV. Next, the ability of infected MSC cells to pass the infection to co-cultured neoplastic cell lines will be evaluated. In other words, the so-called permissiveness of the examined cancer cells to the recombinant MYXV will be checked, at the same time demonstrating potential usefulness of the proposed therapeutic system for *in vivo* applications (if permissive, the cultured cancer cells should be eliminated).

The tested therapeutic systems will next be evaluated *in vivo* by injecting them intravenously into mice harboring experimental tumors (aggressive, hard-to-reach neoplasms such as melanoma, glioma and pancreatic cancer). Biological assessment will be carried out to check therapeutic systems' usefulness to destroy primary and metastatic lesions. The underlying research hypothesis assumes that the therapeutic recombinant virus will be protected from adverse reactions of the recipient immune system and that only after release from MSC cells in the vicinity of tumor site will it be possible for the virus to exert its destructive action leading to oncolysis. Additionally, as a result of oncolysis, release and increased presentation of cancer antigens will take place further enhancing the overall anticancer effect.

Parallel to the evaluation of the proposed therapeutic systems virus spread in the treated mice as well as the immune reaction directed against the therapeutic virus will be examined (virus neutralization tests and antiviral antibodies' level) Tumor tissues will be examined by an experienced pathologist and the level of T lymphocytes and NK cells (antitumor immune response) will be evaluated by immunohistochemistry.

The proposed way of raising the effectiveness of oncolytic therapy has not been so far fully reported and explored. The suggested therapy is thus an attempt to meet an urgent demand for more effective treatments for melanoma, gliomas and pancreatic cancers, the neoplasms being a great scientific and economic challenge in many developed countries. The anticipated results should help to better understand the therapeutic preconditions at the molecular level and should lead to less expensive methods of treatment.