**Carbon allotropes as mesenchymal-epithelial transition activators of the phenotype of liver cancer cells via cytokine-dependent pathways**

Hepatocellular cancer is a malignant tumour with a high rate of recurrence after liver resection and transplantation. Currently, the 5-year survival rate of patients is not satisfactory due to the metastasis of tumour cells to distant sites. The influence of growth factors on cell changes its phenotype from epithelial (dormancy) to mesenchymal (invasive). Thus, a method is sought to "force" the cell to return to the phenotype of a sedentary cancer cell that is more susceptible to anti-cancer therapies. The project assumes inhibition of metastasis by induction of the epithelial cell phenotype.

Carbon nanomaterials, including fullerenes and graphene oxide, are characterised by low toxicity and immunogenicity and they are an attractive substrate for the growth of eukaryotic cells. These nanomaterials, by interacting with a cancer cell, and in particular, signal transduction could alter the expression of proteins involved in promoting tumorigenesis. It can be expected that the incorporation of fullerenes and graphene oxide into the extracellular matrix of liver cancer cells can reduce cell malignancy and improve cancer treatment.

In physiological conditions, growth factors secreted by tumour cells, tumour-associated cells and inflammatory cells promote and direct the migration of cancer cells. The recent research has shown that the overexpression of proteins, such as N-cadherin, vimentin and claudin is mainly observed in invasive cells. Furthermore, transcription factors Snail, Slug, Twist and Zeb are responsible for the reduction of protein expression associated with the epithelial phenotype, *i.e.* E-cadherin. The project chose the TGF-β1 / Smads pathway as the basic pathway for regulating the phenotype of cells. Our preliminary studies demonstrated the beneficial effects of fullerenes, used in the form of a nanofilm, on the expression of proteins involved in epithelial phenotype.

The goal of the project is the restoration of epithelial phenotype of liver cancer cells using fullerenes, fullerenol and graphene oxide as factors emitting a signal of mechanotransduction, and consequently restoring the proper interaction with the surrounding cell environment.

Planned experiments will be conducted on three hepatic cell lines, including one non-cancerous (HepaRG) and two cancerous lines (HepG2 and SNU-387). The tests will be carried out in *in vitro* conditions using traditional cell culture methods. The research will be organised in five merit panels: 1. Obtaining mesenchymal (invasive) phenotype, 2. Characterisation of nanomaterials and nanofilms, 3. Epithelial phenotype induction using nanofilms / nanocolloids, 4. TGF-β1 / Smads pathway signalling, 5. Metastasis in co-cultures with fibroblasts, monocytes and endothelial cells.

The novel approach is the application of nanomaterials as a system for optimising the signal of mechanotransduction against liver cancer cells.

The results of the planned project will allow to deepen the knowledge about phenotypic transformation of cancer cells, cell adhesion disorders and expand the possibilities of using carbon nanomaterials in the fight against hepatocellular carcinoma. In the future, these studies will form the basis for the development of a new therapeutic system in oncology.