Summary – popular version

Application of gene therapy and targeted drug delivery are two significant challenges in contemporary medical sciences with great significance for cancer therapy. Both require reliable delivery systems fulfilling high pharmacodynamic standards. Therefore, biomedical research involves numerous studies on design of new carrier molecules, including branched polymers like dendrimers and dendrons, and their application as new non-viral gene delivery vectors. Most often they are policationic macromolecules forming supramolecular complexes with RNA fragments that after introduction into the nuclei will "correct" cellular functions. Recently this research focusses on various organic mostly policationic molecules. However, for various reasons until now none of these systems was advanced into the clinical trials.

The main objective of the present project is design and synthesis of multivalent dimeric amphiphilic peptide dendrons (BIDEND), separated with biodegradable organic linker of the length promoting complexation of siRNA *via* two consecutive minor groves and their application as nanocarriers of siRNA or drugs in glioblastoma therapy. Chemical structure of BIDEND contains cationic, amphiphilic branched peptides and is a combination of the best characteristics of various macromolecular gene carriers appealing recently in biomedical literature: multivalent, branched architecture, cationic and amphiphilic character, biodegradability. We hope that additive value gathered in these compounds will allow to obtain better, less toxic, intelligent nanocarriers for gene therapy and targeted drug delivery useful in glioma therapy.

Dendrons are peptidic compounds with branched structure, that during well-controlled synthesis can be assembled with several types of residues with different biological functions allowing for design molecules with variable properties. BIDEND will be synthesized from the dendrons of the same or different structure and will undergo biodegradation due to involvement of pH (hydrazones) or redox-active (S-S bridge) chemical bonds. Single amphiphilic membrane-active dendrons will destroy endosome (cellular carrier system) and allow for more efficient siRNA release. Additional advantage of this design concept is opportunity of adjustment of length and structure of a linker part yielding better complexing properties of BIDEND carriers.

Polish group will focus on design and synthesis of amphiphilic peptide dendrons of 1-st and 2-nd generation and linkers containing biodegradable bonds as well as strategy of their arrangement into dimeric objects. The most important is development of efficient methodology for solid state synthesis yielding dendrons on gram-scale, design of biodegradable linker and strategy of their coupling into BIDEND structures. Preliminary evaluation of the complexing properties with siRNA and its biodegrability will be done with application of high performance liquid chromatography (HPLC) mass spectrometry (MS) and UV spectroscopy.

Performance of the BIDEND compounds will be verified in cooperating group of Valentin Ceña, professor of medical sciences at University of Castilla-La Mancha, Spain. Professor Ceña is working on therapy against cancer specific for nervous system cells, with particular emphasis put on application of dendrimrs and dendrons as biocarriers in gene therapy. Various tests, i.e. interaction of BIDEND with siRNA, their protective properties against cellular RNA-ses, siRNA entry ability into different cell types and specific toxicity will be performed. Finally, transfection yield and transfection mechanism will be evaluated. Moreover, additional goal of this project is strengthening cooperation between two groups that are part of international consortium established in 2014. Its mission was to formulate principles and to obtain preliminary data for setting up future application for EC grant in EURONANOMED panel.