Development of a gene therapy vector by modifying bacteriophage M13 for targeting cancer cells

Project title: Development of a gene therapy vector by modifying bacteriophage M13 for targeting cancer cells

Acronym: ONCOPHAGE

Competition: Program P1 – Development of the National CD System, Subprogram 1.1 – Research projects for the stimulation of young teams (TE)

Project code: PN-III-P1-1.1-TE-2021-0939

Project duration: 24 months (16/05/2022 – 15/05/2024)

Budget: 450,000 RON

Coordinating Institution: "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, Research Center for Functional Genomics, Biomedicine and Translational Medicine

Project Director: Scientific Researcher III, Dr. Sergiu Chira

Summary:

Even though up to now, many tumor-cell targeting strategies based on non-viral and viral vectors have been developed, they have encountered numerous limitations related to specificity and efficiency, cytotoxic and genotoxic side effects. Additionally, these therapeutic vector systems are most often restricted to local administration to avoid inducing a systemic immune response when administered intravenously.
The project has as its general objective the development of a new hybrid vector system derived from M13 bacteriophage and adapted through genetic engineering and biotechnology techniques to target tumor cells with a higher efficiency than other systems based on synthetic non-viral or viral vectors. The inclusion of human genetic elements in its construction gives this gene transfer vector system the ability to persist as an episome in malignant cells, allowing it to be perpetuated in successive cell generations to exert its therapeutic effect over an extended time frame. Due to its non-pathogenic nature, potential cytotoxic and immune side effects are significantly reduced compared to synthetic non-viral or viral vectors derived from human pathogens, an aspect with relevance for clinical applications. Another advantage of the proposed vector is the low cost and simplified production method compared to vectors derived from human viruses, or synthetic non-viral vectors.

Specific objectives:

- Design and construction of the bacteriophage M13-derived hybrid vector expressing a ligand with high tumor selectivity on the viral capsid
- Optimizing high-titer vector production in the laboratory
- Functional and structural characterization of the hybrid phage vector
- Validation of the in vitro tumor transduction capacity of the hybrid vector system on a panel of human malignant lines using reporter genes

Results:

- A peptide library with amino acid variations at the N-terminus of the tumor-specific ligand iRGD was obtained
- A binary vector system was implemented, consisting of a construct containing the M13 phage genome, from which the origin of replication and the virion packaging signal were deleted, and an expression cassette of the recombinant iRGD peptide library was inserted. This design allows selective packaging of the second construct, containing the fluorescent reporter gene, into tumor-targeting phage particles.
- Through its objectives, the project opens the possibility of developing new anti-tumor gene therapies, providing a non-pathogenic vector system with selectivity for malignant cells.