Project kick-off meeting

Efficacy and antitumor mechanisms of photodynamic therapy using photosensitizers based on bacteriochlorins with different molecular charges

COMPETITION FOR FINANCIAL SUPPORT FOR BILATERAL PROJECTS – BULGARIA – RUSSIA
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ИНСТИТУТ ПО ЕЛЕКТРОНИКА
БЪЛГ.АКАДЕМИЯ НА НАУКИТЕ

SECHENOV UNIVERSITY

Team members

Bulgaria	Russia
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Summary of the project - 1

- The actuality and relevance of the project is based on the need to expand the possibilities of using photodynamic therapy (PDT) in relation to tumor neoplasms, as well as in the treatment of viral and bacterial infections, both by increasing the effectiveness of the impact on the specific object and due to the reduction of the side effects of photodynamic treatment. The latter can be achieved by increasing the selectivity of the photodynamic action and reducing the residual phototoxicity by accelerating the elimination of photosensitizers (PS) from healthy tissues adjacent to the treated object (e.g., tumor) including the skin and blood of the patient. One of the ways to solve this problem is an PDT using PS with effective excitation in the spectral range (710-800 nm) within the "therapeutic window" of biological tissues. In line with current research in the field of PDTs, one of the most promising sensitizers in this range are the derivatives of synthetic bacteriochlorines, characterized by increased rate of excretion from the body, high quantum yield of singlet oxygen, as well as simpler procedures for their synthesis and wide availability of raw materials.
- The proposed project is mainly devoted to the physical investigation of the physicochemical, pharmacokinetic and photo-physical properties of PS - new synthesized electroneutral and polycationic derivatives of synthetic bacteriochlorins, capable of providing an effective photodynamic effect in the treatment of deeper-situated tumors.

Summary of the project - 2

- Particular attention will be paid to the relationship between the photodynamic properties of the newly synthesized PSs with the magnitude of the charge of their molecules. The scientific novelty of the study is that new PSs, based on bacteriochlorins, will be created and studied, with properties optimized to increase the efficiency of PDT, including through the charge of molecules. The synthesis strategy will include the creation of new PSs with optimal chemical structure and charge of the molecules, as well as adherence to proven practice methods for their solely and / or co-administration with other therapeutic drugs in tumor treatment procedures. It is planned for a first time to investigate the in-vitro phenomena that occur when the treated cells interact with the newly-synthetized PSs with different molecular charges. The mechanisms of interaction and destruction of cell fragments during sensitization and photodynamic treatment will be studied and analyzed.
- For a first time, in vitro levels and kinetics of accumulation and localization of the generated FSs with different molecular charges in the target cells will be investigated. At the same time, it is planned to evaluate the binding of new PS to immune cells involved in innate immune responses (macrophages, monocytes, neutrophils) and with the vascular endothelial cells. The scientific significance of the results of this type of studies is that new knowledge will be gained about the effects of photosensitizers based on electroneutral and polycationic derivatives of synthetic bacteriochlorins in eukaryotic cells, both from tumor and healthy tissues.

Summary of the project - 3

- The processes of sensitization and the efficacy of photodynamic therapy of tumors of experimental animals using bacteriochlorine FS with different charges will also be investigated to determine the pharmacokinetics, bio-distribution and elimination rate of PS from healthy tissues. These studies will also clarify the role of the charge of photosensitizer molecules in terms of antitumor efficacy and mechanisms of tumor tissue destruction. As a result, we expect to clarify new requirements regarding the optimal composition and structure of the investigated PS in the specific PDT procedures applied.
- The project envisages the investigation of the mechanisms and efficacy of photodynamic action on tumors of laboratory animals using the optimal from the point of view of efficiency synthesized PS, based on the results obtained in the frames of in vitro cell line studies. This will allow us to develop optimal PDT approaches for tumors with different genesis. The results of this strategy will be applicable in future technological developments with respect to preclinical and clinical trials of prospective PSs.
- The results of the project will enable an establishment of basic protocols for the strategy for photodynamic treatment in oncology, and its implementation will significantly contribute to the solving a wide range of problems in the treatment of tumors and clarifying the prospects for applications of photodynamic inactivation in pathogens microorganisms and viruses.

Bulgarian team activities – 1 year

1.Development of methods and studies of the photophysical properties of PS (shape and intensity of absorption, shape and intensity of the fluorescent band, quantum yield of singlet oxygen) to assess their relationship with the concentration of provided bacterichlorine PS, the degree of aggregation at high concentrations of the PS. To study the photodynamic efficiency against bacteria. normal and tumor cell lines.

2. Study of the photostability of the studied PS depending on their chemical structure and concentration.

3. Study of the accumulation of the studied PS in tumor cells, depending on their chemical structure, the charge of the molecules and the concentration of FS during the incubation, the time of incubation of the cells with P.

4. Study of the phototoxicity of the studied PS towards the tumor cells, depending on their chemical structure, the charge of the molecules and the concentration of the PS during the incubation, the incubation time of the cells with the PS and the light dose.

5. Subcellular spectral-fluorescence studies of tumor cells after accumulation of PS studies and photodynamic effects using laser confocal microscopy.

6. Preparation of scientific publications and preparation of scientific reports for participation in a specialized international conference.

7. Preparation of a report and preparation of the activities for the second year of the project

Russian team activities – 1 year

1. Creation of long-wave PS on the basis of electro-neutral and polycationic derivatives of bacteriochlorins. Development of methods and studies of the photophysical properties of the synthesized PS (shape and intensity of the strips of absorption and fluorescence, lifetime of excited states) and evaluation of their relationship with the concentration of PS, the degree of aggregation at high concentrations of PS and determination of levels of photodynamic efficiency.

2. In vitro study of the binding of the synthesized PS with tumor cells, normal cells, vascular endothelial cells and cells of the innate immune response (macrophages, monocytes, neutrophils) depending on the chemical structure of PS and the charge of the molecules and their concentration .. Evaluation of the sensitivity of these cells to photodynamic effects.

3. The study of the accumulation of PS in tumor cells and their phototoxicity depending on the chemical structure, molecular charge and concentration of PS, the incubation time of cells with PS and the dose of light.

4. Spectral fluorescence and immunohistochemical studies of cells after accumulation of the studied PS and photodynamic effects.

5. Preparation of scientific publications and participation in international conferences.

6. Preparation of a report for 1 year of the project

Bulgarian team activities – 2 year

1. The study of changes in tumor cells during incubation with PS and photodynamic treatment using the created PS depending on their structure, molecule charge, concentration of PFS and incubation time in cells. Study of the mechanisms of the photodynamic effects of the used PS on tumor cells.
2. Studies of the bio-distribution and pharmacokinetics of PS with different charge of molecules in the constituent parts of the cells of model tumors.
3. The study of the effectiveness of PDT in model tumors of laboratory animals depending on the charge of PS molecules, the amount of introduced PS and radiation parameters (the interval between the introduction of PS and the beginning of irradiation, power density and light radiation dose).
4. The study of the mechanisms of tumor damage in PDT, depending on the charge of the PS molecules and the radiation parameters.
5. Preparation of scientific publications and preparation of scientific reports for participation in international conferences.
6. Preparation of the final report on the performed research on the project.

Russian team activities – 2 year

1. The study of the mechanisms of the photodynamic effects of the synthesized FS on tumor cells depending on the structure and charge of their molecules.

2. In vivo studies of the bio-distribution and pharmacokinetics of PS with different charge of molecules, their content in model tumors, blood and skin of laboratory animals.

3. The study of the effectiveness of PDT in model tumors of laboratory animals depending on the charge of the PS molecules, the amounts of introduced PS, the radiation parameters (time interval between the introduction of PS and the beginning of exposure, power density and radiation dose) .

4. Patho-morphological and immunohistochemical study of the mechanisms of tumor damage in PDT depending on the charge of PS molecules and radiation parameters.

5. Preparation of scientific publications and participation in international conferences.

6. Preparation of the final project report.

WP/month	01-03	04-06	07-09	10-12	13-15	16-18	19-21	22-24
WP 1. Development of methods for photophysical properties evaluation								
WP2. Investigation of pharmacokinetic properties								
WP 3. In vitro phototoxicity studies								
WP 4. Biodistribution and pharmacokinetics in vivo								
WP 5. Efficiency and optimization - PDT in vivo								
Preparation of scientific publications and reports								
Preparation of a report								

Thank you for your attention

DISCUSSION QUESTIONS

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BULGARIAN SCIENCE FUND