PhD project

Research area: **Biomedical Engineering / Medical Imaging**

Required skills: 1) Initial training in physics with a specialization in medical imaging (MRI, magnetic resonance imaging)
2) Knowledge of image processing
3) Interest for physics-biology-biochemistry interfaces

Starting date: January - February 2024
Laboratory: CEA / DRF / JOLIOT / NeuroSpin / BAOBAB (CEA Saclay)
Address: CEA-Saclay, Bâtiment 145, 91191 Gif-sur-Yvette Cedex
PhD supervisor: Sébastien Mériaux
Phone: +33 1 69 08 94 23
Email: sebastien.meriaux@cea.fr
Collaborators: Sandra Prévéral & Damien Faivre (BIAM / MEM, CEA Cadarache)

Title

Active biological magnetic nanodevices as theranostic cancer agents against glioblastoma

Abstract

Overcoming resistance to chemoradiotherapy in glioblastoma is a critical unmet clinical need. Various nanotechnology-based strategies have been proposed to improve antitumor responses while minimizing side effects. Although chemically synthesized magnetic nanoparticles have attracted great attention as cancer theranostics, they lack antitumor efficacy due to toxicity, low targeting and internalization abilities. In previous dedicated studies, the MEM (BIAM, CEA Cadarache) and CIEL (NeuroSpin, CEA Saclay) laboratories have shown that magnetosomes, biogenic magnetic nanoparticles produced by magnetotactic bacteria, are biocompatible theranostic agents surpassing synthetic nanoparticles in terms of ultrasensitive T_2 contrast agents for Magnetic Resonance Imaging (MRI), sensitizers for photothermia and proton therapy, tumor targeting tools after genetic tailoring and capacities to respond to magnetic guidance. However, several limitations to their clinical translation remain to date, among which their inability to invade hardly penetrable tumors and to homogeneously distribute within cancer tissues.

Based on the multidisciplinary consortium in microbiology, genetic engineering, biology and physics originating from the MEM-CIEL collaboration, this PhD project aims in generating and testing with MRI unprecedented formulated magnetosomes, enabling a faster, prolonged and more homogeneous biodistribution within cerebral tumor tissues through magnetic guidance and nanoswimming properties. Thanks to the development of innovative MR-based molecular imaging protocols, one main outcome of the project will consist in identifying the most promising magnetosome designs for achieving therapeutic efficacy, and therefore strengthen the case for developing biogenic magnetoparticles for multimodal nanomedicine in cancer therapy.

Description of PhD project

SCIENTIFIC BACKGROUND

Various nanotechnologies have been proposed to overcome the resistance to chemoradiotherapy of certain brain tumors such as glioblastoma, while minimizing side effects. Although synthetic nanoparticles are well studied theranostic tools for cancer, limitations to their translation into the clinic remain (targeting, retention, functionalization). In the framework of the MEFISTO project, funded by the ANR P2N program in 2012, two CEA teams, one from BIAM in Cadarache (MEM laboratory) and one from NeuroSpin in Saclay (CIEL laboratory), have proposed a new class of magnetic nanoparticles, called magnetosomes, for molecular MR-based imaging of glioblastoma [1]. Magnetosomes are nanomagnets produced by magnetotactic bacteria that have very interesting characteristics for biomedical applications: *i)* a perfectly crystalline and regular magnetite nanocrystal, allowing to outperform the efficiency of synthetic nanoparticles in terms of ultrasensitive T_2 contrast agents for MRI [2], sensitizing agents for photothermia [3] and radiotherapy [4]; *ii)* magnetic properties that allow easy separation and guidance; *iii)* a natural lipid bilayer surrounding the nanoparticles that ensures their colloidal stability and biocompatibility [5]; *iv)* the possibility of functionalizing this lipid bilayer with biological functions to target biomarkers of interest; *v)* an absence of specific toxicity in rodents, even at very high injected doses, as shown by data in the literature [6,7,8,9] and those collected during the MEFISTO project.

In the context of the development of new therapeutic strategies for glioblastoma, the main objective of the project is to generate and identify new magnetosomes with optimal tumor targeting and anticancer efficacy. The main scientific and technical challenges are to optimize the delivery of magnetosomes in the tumor zone, in order to maximize their photothermal or radiosensitizing effect, while ensuring the necessary biocompatibility to consider a potential transfer to clinical applications.

PROPOSED WORK

The optimization of magnetosomes dose delivered into glioblastoma will start with the development and characterization of new magnetosomes, whose specific delivery to the tumor area as well as retention will be accelerated and prolonged by the combination of several approaches: functionalization of the lipid bilayer with peptides exhibiting a high affinity for tumor biomarkers (such as $\alpha_v\beta_3$ integrins overexpressed by tumor vessels), magnetic guidance through external magnetic fields and the addition of an original self-propulsion system based on enzyme grafting [10]. In a second step, new molecular imaging protocols implemented in ultra-high field MRI scanners will be developed to study the biodistribution of these new magnetosomes in models of glioblastoma and to confirm their accumulation in the tumor area. These developments will focus on the optimization of the injection protocol and the use of new tools for *in vivo* quantification of the magnetosomes concentration (QSM approach for Quantitative Susceptibility Mapping, [11]). Finally, the therapeutic effect induced by the delivery of these new magnetosomes in the tumor area will be evaluated by a photothermal approach under MRI guidance, allowing to directly link the magnetosomes concentration to the generated hyperthermia effects.

Thus, the main methodological contributions of this 36-months PhD project will focus on the optimization of:

- the magnetosomes, including their MRI contrasting properties (iron core doping, use of magnetotactic bacteria forming magnetosomes of different sizes and/or morphologies), their tumor biomarker targeting properties (peptide ligand modifications, expression of multiple

ligands for multi-specificity), and their accumulation in the tumor area (propulsion, magnetic guidance/retention);

- the MR-based molecular imaging protocols, including injection/infusion protocols, imaging sequences and QSM quantification tools.

This optimization work will allow for biodistribution studies in models of glioblastoma, in order to estimate magnetosome doses delivered to the brain tumor, as well as accumulation in other organs (biocompatibility). Then, characterization studies of the antitumoral effects will be conducted using a photothermal approach under MRI guidance (collaboration with Claire Wilhelm's team).
The role of the PhD student will be to integrate all these developments into a coherent framework, in coordination with the PhD supervisor at NeuroSpin and the MEM collaborators, with a strong involvement in the production of new functionalized magnetosomes and in the implementation of molecular MRI protocols, in particular regarding the acquisition, processing and analysis of MRI data.

EXPECTED RESULTS

This PhD project proposes a transversal approach combining the expertise of both CEA teams (MEM of BIAM at Cadarache and CIEL of NeuroSpin at Saclay). The expected results mainly concern the design of new functionalized magnetosomes for theranostic applications in oncology, the evaluation of their biocompatibility and their molecular actions in models of glioblastoma, as well as the characterization by molecular MR-based imaging of their biodistribution, their retention and their therapeutic efficacy by photothermia. Ultimately, this PhD project should reinforce the interest of biogenic magnetic nanoparticles for multimodal nanomedicine in cancer therapy.

CONDITIONS OF THE THESIS

The PhD project will be conducted mainly at NeuroSpin (DRF/JOLIOT), the ultra-high field MRI research center of CEA located in Saclay, for a period of 3 years. The PhD student will have at his disposal three MRI preclinical scanners (7 T, 11.7 T and 17.2 T), and will work within a multidisciplinary team including specialists in cell culture, tumor models, histology, radiofrequency electronics, MRI methodology and data processing. The preparation of the functionalized magnetosomes and their characterization will take place at the CEA Cadarache site, in the MEM laboratory (DRF/BIAM), under the supervision of Sandra Prévéral and Damien Faivre.

BIBLIOGRAPHY

[1] **Boucher et al**, *Genetically tailored magnetosomes used as MRI probe for molecular imaging of brain tumor*, Biomaterials 2017, 121:167-178, doi: 10.1016/j.biomaterials.2016.12.013

[2] **Mériaux et al**, *Magnetosomes, biogenic magnetic nanomaterials for brain molecular imaging with 17.2 T MRI scanner*, Adv Healthc Mater 2015, 4(7):1076-1083, doi: 10.1002/adhm.201400756

[3] **Plan Sangnier et al**, *Targeted thermal therapy with genetically engineered magnetite magnetosomes@RGD: Photothermia is far more efficient than magnetic hyperthermia*, J Control Release 2018, 279:271-281, doi: 10.1016/j.jconrel.2018.04.036

[4] **Hafsi et al**, *RGD-functionalized magnetosomes are efficient tumor radioenhancers for X-rays and protons*, Nanomedicine 2020, 23:102084, doi: 10.1016/j.nano.2019.102084

[5] **Nan et al**, *A comprehensive assessment of the biocompatibility of Magnetospirillum gryphiswaldense MSR-1 bacterial magnetosomes* in vitro *and* in vivo, Toxicology 2021, 462:152949, doi: 10.1016/j.tox.2021.152949

[6] **Han et al**, *Research on the structure and performance of bacterial magnetic nanoparticles*, J Biomater Appl 2008, 22(5):433-448, doi: 10.1177/0885328207079064

[7] **Sun et al**, *Biocompatibility of bacterial magnetosomes: acute toxicity, immunotoxicity and cytotoxicity*, Nanotoxicology 2010, 4(3):271-283, doi: 10.3109/17435391003690531

[8] **Liu et al**, *Heating effect and biocompatibility of bacterial magnetosomes as potential materials used in magnetic fluid hyperthermia*, Prog Nat Sci Mater Int 2012, 22(1):31-39, doi: 10.1016/j.pnsc.2011.12.006

[9] **Xiang et al**, *Tumor detection using magnetosome nanoparticles functionalized with a newly screened EGFR/HER2 targeting peptide*, Biomaterials 2017, 115:53-64, doi: 10.1016/j.biomaterials.2016.11.022

[10] **Patiño et al**, *Fundamental Aspects of Enzyme-Powered Micro- and Nanoswimmers*, Acc Chem Res 2018, 51(11):2662-2671, doi: 10.1021/acs.accounts.8b00288

[11] **de Rochefort et al**, *Quantitative susceptibility map reconstruction from MR phase data using Bayesian regularization: validation and application to brain imaging*, Magn Reson Med 2010, 63(1):194-206, doi: 10.1002/mrm.22187