Development of Theranostic Silica Nanoparticles Combining Quantitative ^{19}F MRI and Boron Neutron Capture Therapy (BNCT)

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Introduction

Radiotherapy (RT) is used in 30% to 50% of cancer treatments, often in combination with chemotherapy or surgery. Unfortunately, RT is not applicable to all types of cancers, especially such as melanoma, due to the presence of melanin, which plays a protective role by capturing radiation and limiting its effects. Moreover, Melanoma is an aggressive type of skin cancer that is well known for not responding to conventional treatment as targeted therapy or immunotherapy.**[1]** Boron Neutron Capture Therapy (BNCT) could offer a promising solution for melanoma patients with a poor prognosis. It involves introducing ^{10}B containing compounds into tumors, followed by exposure to thermal neutrons. This exposure triggers a boron neutron capture reaction (^{10}B(n,α)^{7}Li) within the boron containing cells, generating high-linear energy transfer particles of an average path of 5-9 µm that effectively destroy the tumor cells.**[2,3]**

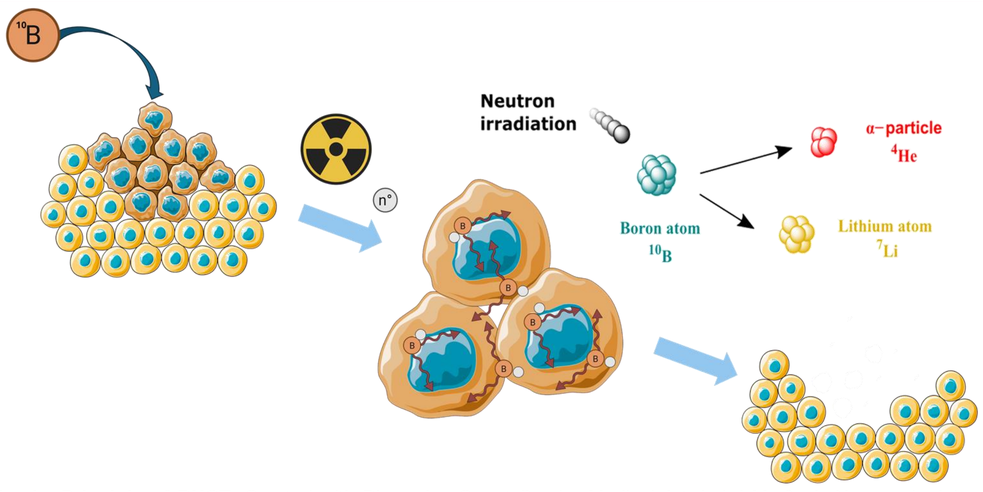


Fig. 1 : Principle of BNCT. Created with Biorender, Smart Servier Medical Art, Laird M. *&* *al.*, Nanoscale Adv., 5, 2537, 2023

Mesoporous silica nanoparticles

One of the strategies for advancing BNCT is to develop new agents enabling high boron accumulation in the tumor, with low toxicity and coupled with an imaging technique enabling the study of the compound biodistribution in tissue. **[4]** Among possible solutions, the use of **nanovectors** appears as an attractive option as they can promote the cellular uptake of therapeutic molecules. In our case, we chose to combine this nanoparticular approach with ^{19}F MRI through **core-shell** silica nanoparticles.

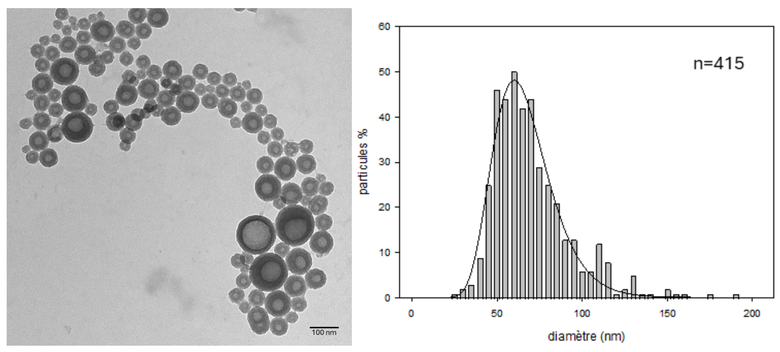
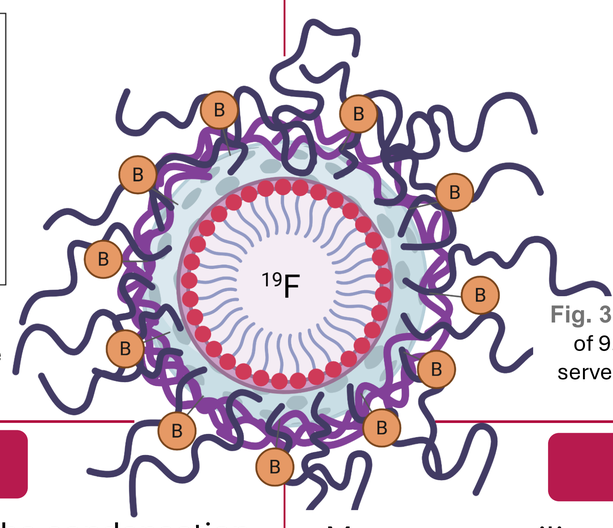


Fig. 2 : Transmission electron microscopy confirmed **core-shell** structure of Si@PEG_BSH, with an average diameter of 74 ± 24 nm (PDI: 1.42)



^{19}F MRI quantitative signal

^{19}F MRI is a promising technique that can be coupled with BNCT, as it is non-invasive, specific to the injected fluorinated compound, and quantitative. To generate a detectable signal, the core of the nanoparticles consists of a **perfluoro-15-crown-5 (PFCE)** emulsion. PFCE is chemically inert and contains 20 chemically equivalent fluorine atoms that enable a single, intense signal.**[5]**

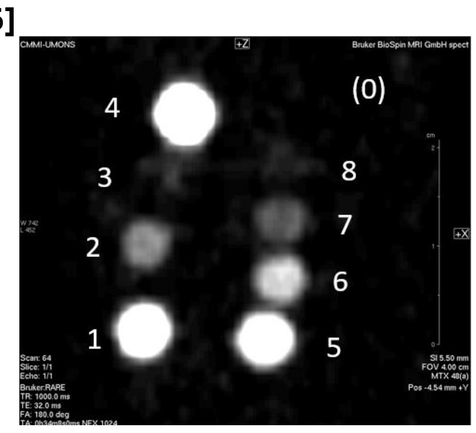


Fig. 3 : ^{19}F MRI phantoms of nanoparticles (samples 4 to 8) at concentrations of 9.9, 4.95, 2.48, 1.23, and 0.62 mM of PFCE, respectively. Samples 1 to 3 served as reference at concentrations of 65, 16, and 4.3 mM of trifluoroacetic acid. Sample 0 was water. (Bruker BioSpin 9.4T)

Chemical versatility

The silica shell enables surface functionalization through the condensation of silane compounds. Grafting of **PEG** chains improves the colloidal stability of nanoparticles and **BSH** (^{10}B-$Na_2B_{12}H_{11}SH$ Sodium mercaptododecaborate) provides boron for BNCT. The maximum concentration reached was 37.7 mg of boron per gram of particles.

Fig. 4 : Comparison of Infra-red spectra of BSH and Si@PEG_BSH, both showing the B-H absorption band at 2490 cm^{-1}

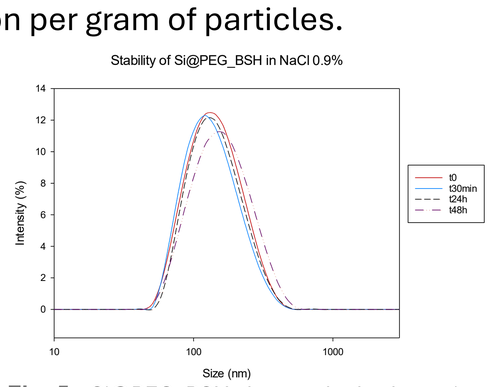


Fig. 5 : Si@PEG_BSH shown a hydrodynamic diameter of 169,46 nm (PDI : 23,3%) stable under physiological condition for at least 48 hours (determined by Dynamic Light Scattering)

Biocompatibility

Mesoporous silica nanoparticles are well-known for their biocompatibility. This was demonstrated with MTT assay on the **A375** (melanoma) and **NHDF** (Normal Human Dermal Fibroblast) cell lines after the removal of CTAB (CetylMethylAmmonium Bromide) surfactant.

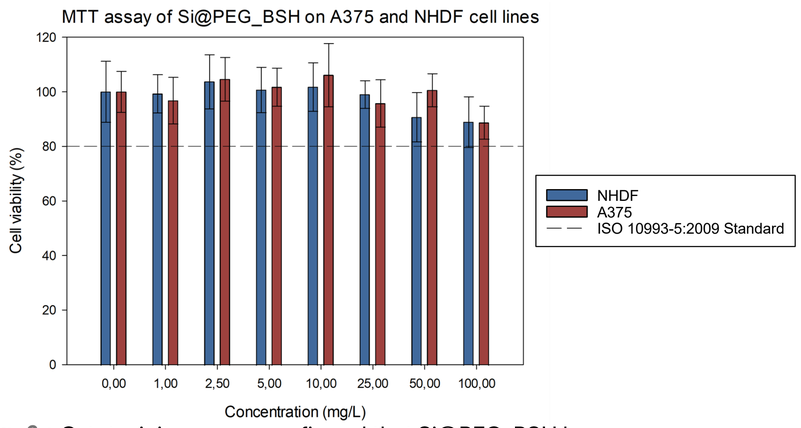


Fig. 6 : Cytotoxicity assays confirmed that Si@PEG_BSH have no toxicity on A375 and NHDF cell lines. (24h exposition)

Perspectives

- Functionalization of nanoparticles with RGD peptides to enhance specificity toward cancer cells.
- Evaluation of Si@PEG_BSH uptake in 2D and 3D spheroid models, including A375, drug-resistant A375-R, and A375/NHDF co-culture.
- Next steps will also include *in vivo* biodistribution study on murine models, as well as *in vitro* irradiation.

Conclusion

While BNCT holds significant promise, key challenges remain. Our nanoplatform addresses these through the development of core-shell nanoparticles, featuring a PFCE emulsion for ^{19}F MRI and mesoporous silica shell for biocompatibility and chemical versatility. Preliminary experiments have confirmed the successful synthesis of these nanoparticles showing a fluorinated content and a good colloidal stability. Further optimization and testing are ongoing to enhance their potential for BNCT applications.

References

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Acknowledgments

This work was performed with the financial support of the FNRS through a FRIA grant.

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