SYNTHESIS AND CHARACTERIZATION OF COMPOSITE NANOMATERIALS FOR BNCT

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INTRODUCTION

Boron Neutron Capture Therapy (BNCT) is a binary modality of radiotherapy based on the nuclear capture reactions that occur once the stable ^{10}B isotope is irradiated with thermal neutrons. The products of this reaction (α-particles) have high linear energy transfer characteristics. Their path lengths are in the range 4-10 μm, hence their energy deposition is limited to the diameter of a single cell. As a result, the decay products can selectively kill tumor cells while sparing healthy, neighboring tissues. Traditionally BNCT relies on the use of borated compounds (BPA, BSH) that must be selectively accumulated in tumors. The development of new, more selective boron delivery agents is one of the greatest needs for the future progress of BNCT. The use of nanoparticles as boron carriers offer the opportunity to deliver amounts of boron considerably higher than borated compounds with longer retention times[1].

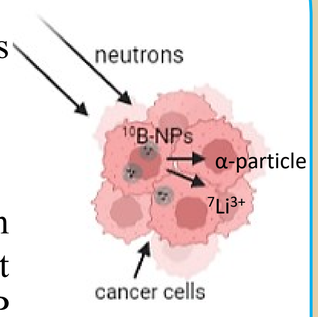
FACTS

1. For BNCT to be a successful therapy, over 25μg ^{10}B/g of tumor are needed. Moreover, the tumor/normal tissue uptake has to be > 3/1. B_4C and *BN* present a high boron content, enough to avoid the use of ^{10}B enriched compounds[1].
2. Both B_4C and *BN* are biocompatible, chemically inert materials, presenting very low toxicity levels.
3. The use of NPs allows the co-localization of ^{10}B carriers with MRI contrast agents.

EXPERIMENTAL

Two boron-rich nanomaterials have been investigated:

B_4C is a highly inert and hydrophobic material that needs stabilization in aqueous suspension.



B_4C based composite nanomaterials were obtained through:

- Heterogeneous nucleation of Fe_3O_4 on B_4C core in presence of polyacrylic acid (PAA) as capping agent (**FeBNP**). Magnetite increase stability in water of B_4C NP and make them visible in MRI imaging[2].
- Chitosan-polyacrylic acid Interpolyelectrolyte complex NPs[3] (**IPEC**). PAA forms a shell around B_4C and Fe_3O_4 NPs and is itself surrounded by CS through the IPEC layer.

BN NPs present excellent fluorescence properties and good dispersibility. Their unique properties arise from the synergic effect of surface effects, quantum confinement and defect centres[4].

BN NPs were obtained through:

- Solvothermal synthesis from different boron and nitrogen precursors
- Solid-state mechanochemical exfoliation of *BN* powders followed by sonication and hydrothermal treatment

  - NPs were characterized through DLS, XRD, TEM, SEM, spectrofluorimetry.
  - Fe and B content were quantified through a UV-Vis protocol, ICP and neutronic autoradiography.
  - *In vitro* tests were carried out on HeLa and Jurkat cells. The interaction between the produced NPs and biological systems was characterized via CLEM (Confocal Light and Electron Microscopy).

RESULTS

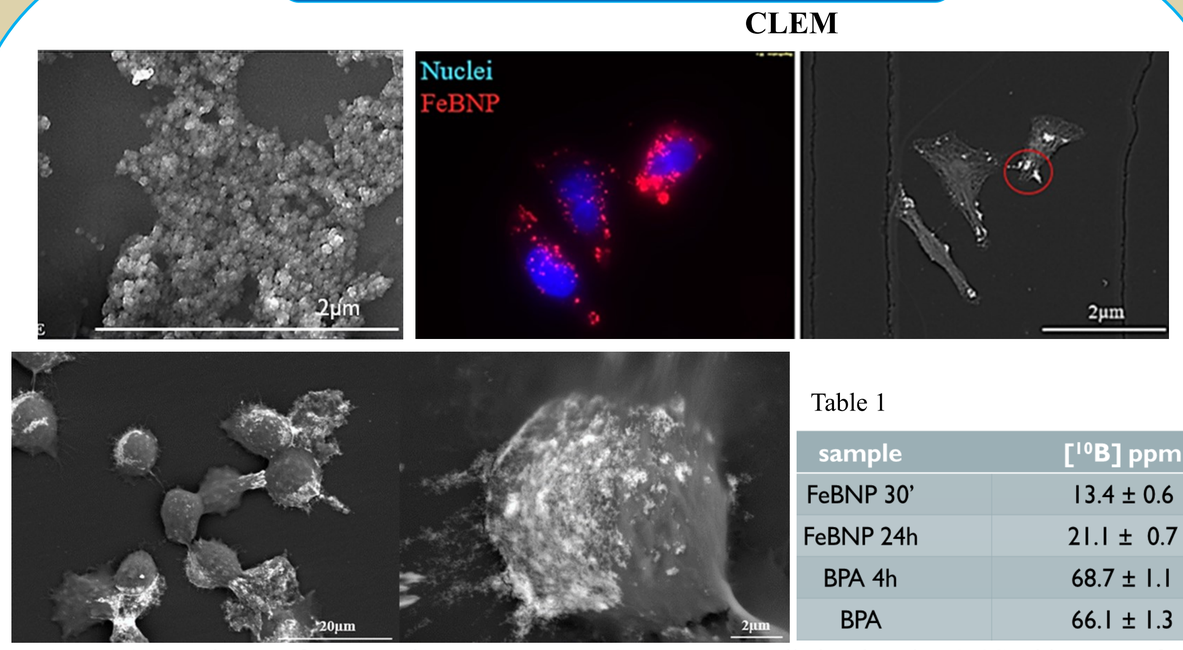


Table 1

sample	[^{10}B] ppm
FeBNP 30'	13.4 ± 0.6
FeBNP 24h	21.1 ± 0.7
BPA 4h	68.7 ± 1.1
BPA	66.1 ± 1.3

Fig. 1 (**A**) SEM image of FeBNP, size: 50-70nm. (**B**) CLEM, HeLa cells incubated at 37°C with FeBNP for 1h; [^{10}B]: 23.1 μg/mL; [Fe_3O_4]: 192 μg/mL (**C**) Jurkat cells incubated at 37°C with DiI-functionalized FeBNP for 24h, ^{10}B quantification via neutronic autoradiography was carried out: results shown in table 1. BPA is enriched in ^{10}B, the produced NPs have a natural abundance of ^{10}B (20% of total Boron)

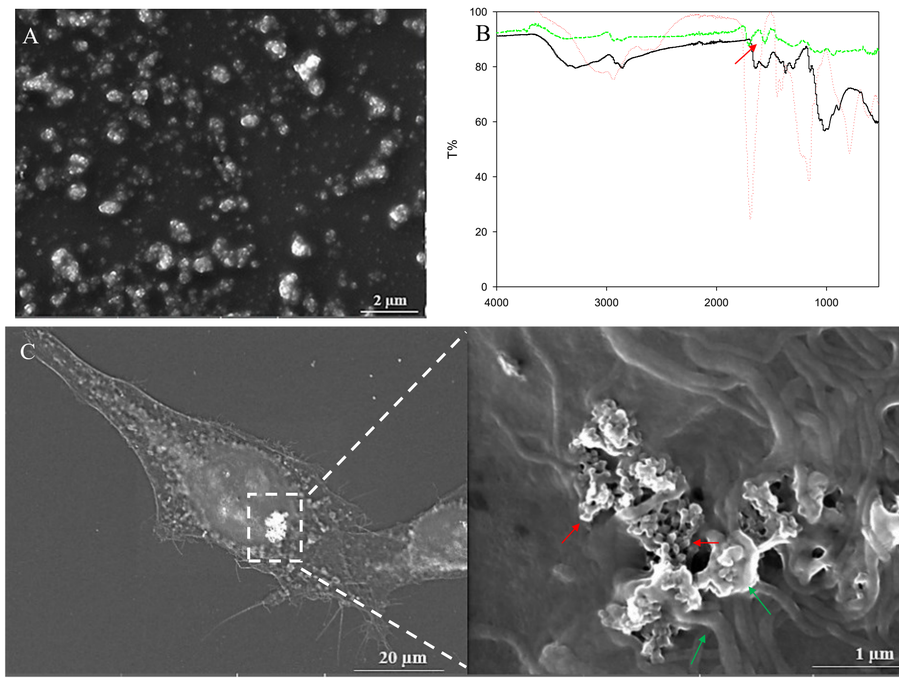


Fig. 2 (**A**) SEM image (SE) of IPEC NPs (**B**) μFTIR spectra of chitosan (black), PAA (red) and IPEC NPs (green). The spectra shows the presence of an amide bond (red arrow) between CS and PAA (**C**) HeLa cells incubated at 37°C with CSPAA FeBNP for 2h [^{10}B]: 3.6 μg/mL; [Fe_3O_4]: 15.7 μg/mL . NPs (red arrows) seem to adhere to the cells' microvillis (green arrows).

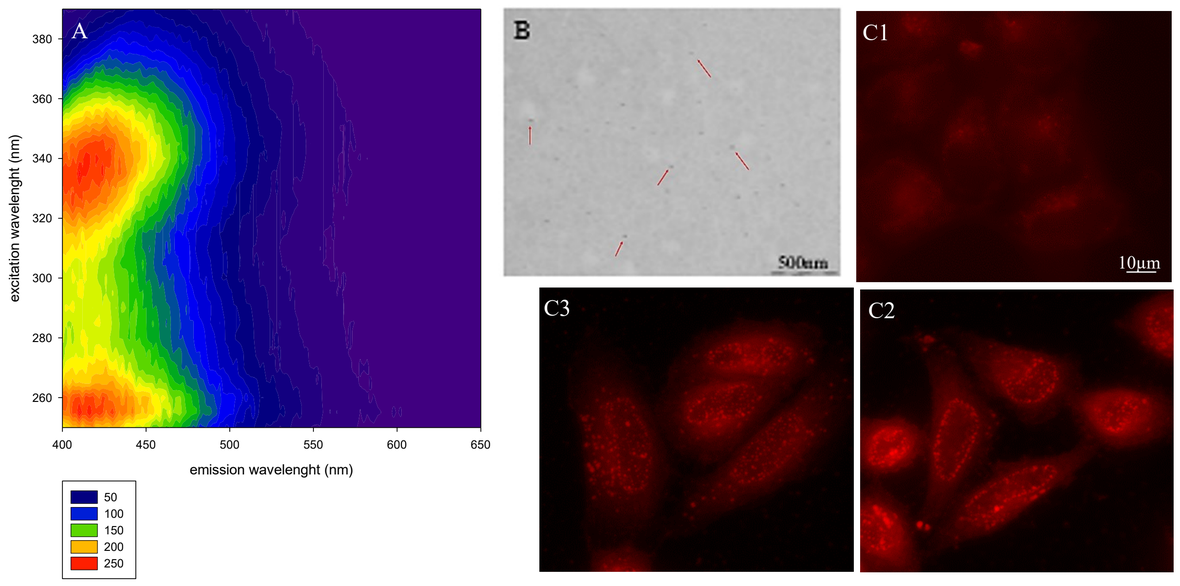


Fig. 3 (**A**) Emission plot of BN NPs excited at different wavelenghts, λ_{max}= 420nm (**B**) TEM picture of BN NPs (red arrows); (**C**) HeLa cells incubated with BN NPs. (**C1**) HeLa cells without BN NPs, (**C2**) HeLa cells incubated with BN NPs at 37°C for 16h, (**C3**) HeLa cells incubated with BN NPs at 37°C for 6h

CONCLUSIONS

The obtained composite NPs represent promising ^{10}B carriers for BNCT. They allow for a high B uptake by tumour cells and might avoid the use of isotopic enriched compounds, as neutronic autoradiography results show.
They also allow imaging of their distribution by MRI and confocal microscopy.
The development of such NPs aims to improve BNCT's therapeutic efficacy[1].

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