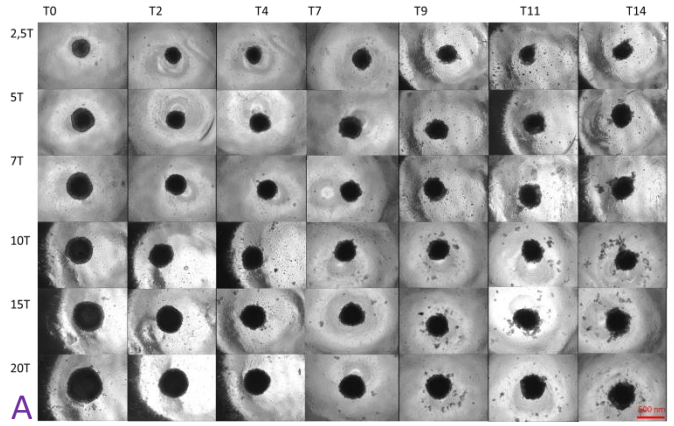
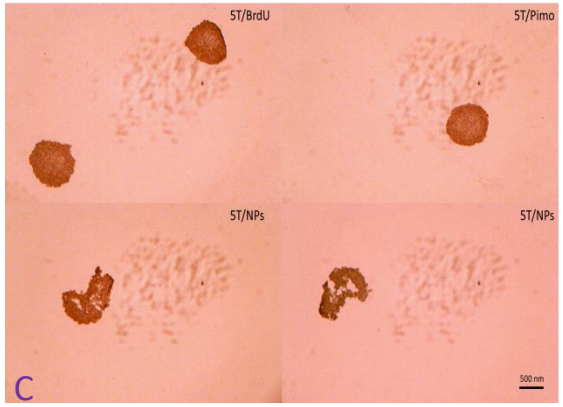
Radiosensitization effects of doxorubicin-iron oxide nanosystem in charged particle radiation therapy for human chondrosarcoma

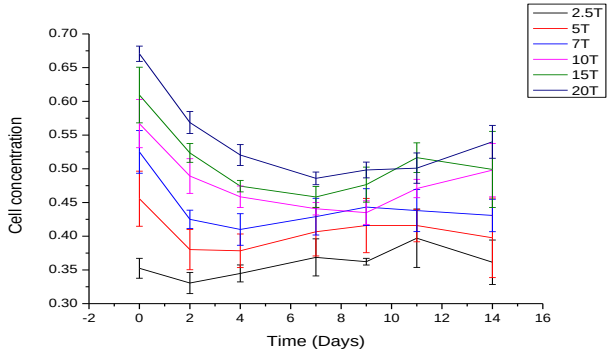
Mihaela Tudor[1,2], Roxana Cristina Popescu[1,3], Anna Rzjanina[4], Gennady Mytsin[4], Mihai Radu[1], François Chevalier[5,6], Diana Iulia Savu[1]

[1]Horia Hulubei National Institute for R&D in Physics and Nuclear Engineering (IFIN-HH); [2]University of Bucharest, Faculty of Biology; [3]Politehnica University of Bucharest (UPB) Department of Science and Engineering of Oxide Materials and Nanomaterials; [4]Laboratory of Nuclear Problems, Joint Institute for Nuclear Research; [5]UMR6252 CIMAP, CEA - CNRS - ENSICAEN - Université de Caen Normandie, Caen, France; [6]LARIA, iRCM, François Jacob Institute of Biology, DRF-CEA, Caen, France. Email: mihaela.tudor@nipne.ro

Objective: Charged particle radiotherapy (hadron therapy) shows better specificity and lower toxicity for the surrounding normal tissue compared to conventional photon therapy being a standard care for some chemo-/radio-resistant tumors such as chondrosarcoma. Still, the efficiency of the hadron therapy can be enhanced. For this, we proposed an intracellularly targeted method based on doxorubicin/polyethylene glycol-conjugated iron oxide nanosystem ($IONP_{DOX}$) to improve the cytotoxic effects of proton therapy.





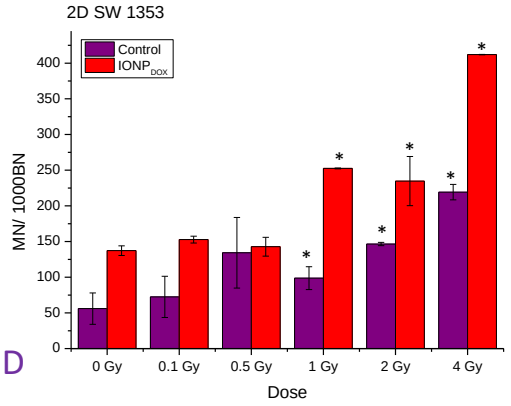


Core-shell IONP for the encapsulation of doxorubicin were previously synthesized and characterized. The 3D cell cultures were obtained using the liquid overlay technique.

A. Optical visualization of chondrosarcoma (SW1353) spheroids over 14 days. Scale bar 500 nm.

B. Spheroid growth was measured during the nurturing phase.

C. Morphological characterization of SW spheroids after $IONP_{DOX}$ treatment. Cell proliferation and hypoxia were evaluated for both treated and non-treated spheroids.



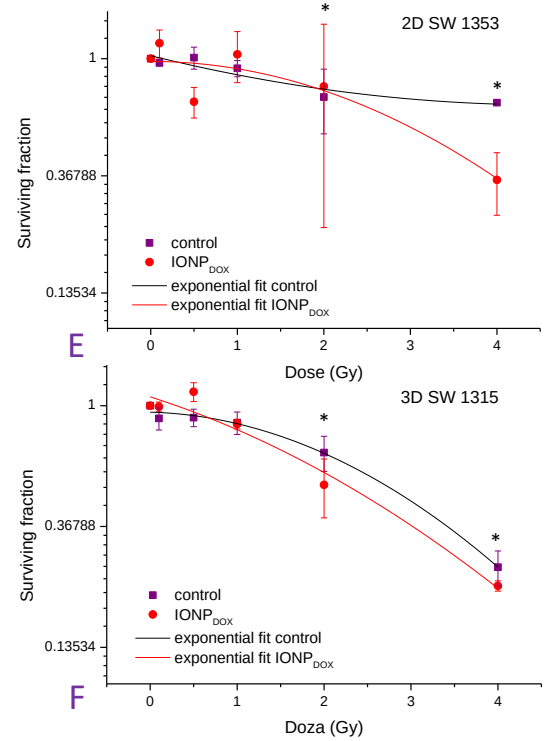
The long term cytotoxicity of $IONP_{DOX}$ and proton irradiation (0-4 Gy, 155 MeV) were assessed using the colony formation assay, while for the genotoxicity determination was employed the cytokinesis block micronucleus assay.

D. Micronuclei in chondrosarcoma cells. NP-Dox induced a statistically significant increased effect in comparison to non-treated irradiated cells.

E. Clonogenic cell death measurements for cells exposed to $IONP_{DOX}$ presented a statistically significant reduction in survival at doses of 2 Gy and 4 Gy.

F. NP-DOX for long term cytotoxicity measurements emphasized a radiosensitization effect of $IONP_{DOX}$ at 2 and 4 Gy ($P<0.05$).

Data is presented as mean ± SEM; $*0.01<P<0.05$.



Conclusion: The $IONP_{DOX}$ showed a potentiated cytotoxic effect of proton irradiated 2D and 3D chondrosarcoma cell models, proving the applicability of the nanosystem for radiosensitization purposes in charged particle radiation therapy of highly chemo-/radio-resistant chondrosarcoma.

Acknowledgments: We acknowledge the Romanian Ministry of Research and Innovation: 20 JINR-IFIN-HH/2019, PN 19060203/2019, 36 PFE/2018, 18PCCDI/2018, 64PCCDI/2018