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# Proton Therapy, Magnetic Nanoparticles and Hyperthermia as Combined Treatment for Pancreatic BxPC3 Tumor Cells

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**Abstract:** We present an investigation of the effects on BxPC3 pancreatic cancer cells of proton therapy combined with hyperthermia, assisted by magnetic fluid hyperthermia performed with the use of magnetic nanoparticles. The cells' response to the combined treatment has been evaluated by means of the clonogenic survival assay and the estimation of DNA Double Strand Breaks (DSBs). The Reactive Oxygen Species (ROS) production, the tumor cell invasion and the cell cycle variations have also been studied. The experimental results have shown that the combination of proton therapy, MNPs administration and hyperthermia gives a clonogenic survival that is much smaller than the single irradiation treatment at all doses, thus suggesting a new effective combined therapy for the pancreatic tumor. Importantly, the effect of the therapies used here is synergistic. Moreover, after proton irradiation, the hyperthermia treatment was able to increase the number of DSBs, even though just at 6 h after the treatment. Noticeably, the magnetic nanoparticles' presence induces radiosensitization effects, and hyperthermia increases the production of ROS, which contributes to cytotoxic cellular effects and to a wide variety of lesions including DNA damage. The present study indicates a new way for clinical translation of combined therapies, also in the vision of an increasing number of hospitals that will use the proton therapy technique in the near future for different kinds of radio-resistant cancers.

**Keywords:** magnetic nanoparticles; magnetic fluid hyperthermia; proton therapy; clonogenic survival; double strand breaks; pancreatic cancer

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## 1. Introduction

To fight cancer, medicine has multiple tools at its disposal including, e.g., surgery, X-ray radiation therapy, chemotherapy, hadron therapy, brachytherapy, and immunotherapy. Particularly, in recent years, research has introduced new strategies against cancer, especially in the field of precision medicine [1]. Scientists devoted strong effort towards the use of nanotechnology and nanomaterials, which, after reaching cancer cells, for instance, can