# Nanoscale radiotherapy: NBTXR3 hafnium oxide nanoparticles as promising cancer therapy

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**Background :** There is considerable interest in approaches that could improve the therapeutic window of radiotherapy, which represents a crucial modality of treatment in oncology. We present the rationale for designing NBTXR3 nanoparticles activated by radiotherapy and validate the concept. We performed the Monte Carlo calculations for the first time based on the "local model" simulation that showed a dose enhancement of radiation to tumor cells of approximately nine-fold. NBTXR3 was shown to deposit high energy when the ionizing radiation source is "on" and to have chemically inert behavior in cellular and subcellular systems demonstrated by very good systemic tolerance, thus decreasing potential health hazards.

**Material and methods:** We used conventional methods, implemented in different ways, to explore interactions of high Z matter and ionizing radiation with biological systems. In addition, microtomography was performed to explore the nanoparticle volume occupancy inside the tumor and its persistence overtime in mouse tumor models. The antitumor activity of NBTXR3 and tolerance were evaluated in Ewing tumor (A673) and fibrosarcoma (HT1080) using high energy source.

**Results & Conclusion:** We created and developed NBTXR3 nanoparticles with a crystalline hafnium oxide core which provide high electron density structure and inert behavior in biological media. NBTXR3 nanoparticles' characteristics, size, charge and shape, allow for efficient interaction with biological entities, cell membrane binding and cellular uptake. The nanoparticles were shown to form clusters at the subcellular level in tumor models. Of most importance, we show NBTXR3 intratumor bioavailability with dispersion of nanoparticles in the three dimensions and persistence within the tumor structure, supporting the use of

NBTXR3 as effective antitumor therapeutic agent. Antitumor activity of NBTXR3 showed marked advantage in terms of survival, tumor specific growth delay and local control in A673 and HT1080 human tumor models. Changing radiotherapy benefit-risk ratio is challenging. These data are supportive for the first clinical development of hafnium oxide nanoparticles, with an on/off mode of action through successive fractions of radiation therapy using current equipment available in hospitals.