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Nanoparticle Augmented Radiotherapy Using Titanium Oxide Nanoparticles

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Abstract

Cancer represents the second most important cause of death and morbidity in the EU, with an estimated 3.5 m cases and 1.9 m deaths per annum. Just over half of cancer patients receive radiotherapy as part of their treatment program [1]. Radiotherapy is second only to surgery in its cure rates, being the primary treatment used in 16% of patients who are cured of their cancer [2]. By comparison, chemotherapy is the principal modality in only 2% of curative treatments [3]. It is also highly cost effective, EU estimates that radiotherapy costs €3000 per patient compared with €7000 for surgery and, on average, €17000 for chemotherapy [4].

Radiotherapy targets a beam of high energy photons, typically 6 meV in energy, at the tumour site. Photons may interact with the tumour cell directly, by DNA absorption, or indirectly as the X-ray scatters off water molecules in the tumour. Indirect scattering results in>90% of the incident energy being transferred to an electron. This electron scatters off other nearby electrons causing a cascade effect where a field of progressively less energetic electrons is generated, finally resulting in an interaction with molecular oxygen and consequent generation of superoxide free radicals. Superoxide free radicals then induce cancer cell damage and apoptosis [5].

As molecular oxygen is required to form superoxide free radicals, radiotherapy is markedly less effective in hypoxic tumour regions. This has significant clinical repurcussions since hypoxia is associated with the most aggressive tumour phenotypes [6].

Titanium oxide is a well-known, non-toxic, photoactive material that generates hydroxyl free radicals by water splitting under ultraviolet light [7,8]. Doping rare earth ions into titanium oxide nanoparticles results in strong interactions with X-ray generated electrons and the consequent free radical production induces cell apoptosis. Nanoparticles of rare earth doped titanium oxide may be injected into a tumour prior to treatment to enhance interaction with radiotherapy in both normal and hypoxic tumour regions.

In vitro trials using radioresistant pancreatic tumour cell lines (PANC-1) are shown to increase the dose effectiveness of radiotherapy by X1.9 over the control line.

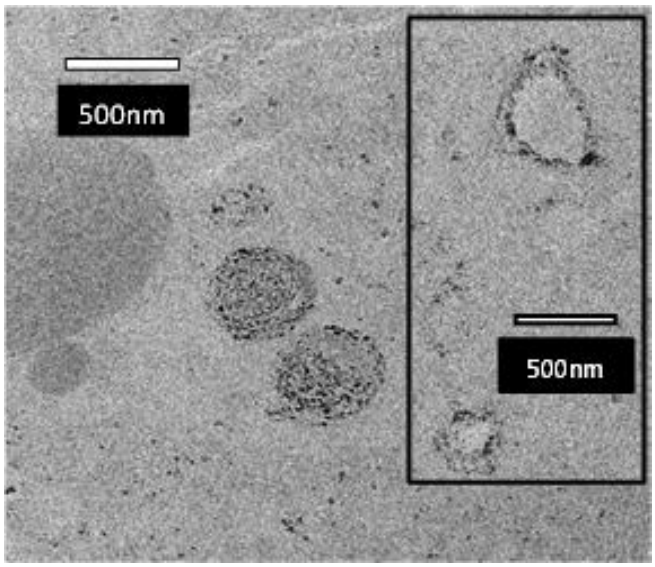

Figure 1: Accumulation of rare earth doped titanium oxide nanoparticles within the Golgi apparatus of a FaDu oropharyngeal cancer cell during radiotherapy treatment (Inset: Destroyed Golgi apparatus four weeks following end of treatment).

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In vivo studies using oropharyngeal (FaDu) mouse xenografts show nanoparticles disperseing throughout the tumour matrix and undergoing endocytosis into cancer cells, whereupon they concentrate in the Golgi apparatus. Nanoparticle induced free radicals then destroys the Golgi apparatus during radiotherapy inducing cell apoptosis.

This result of this is a significant reduction in tumour re-growth rates following treatment with no increase in systemic toxicity being observed.

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In silico Design of Degrading Nanomaterials as a Novel Form of Tumor Therapy

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Abstract

Nanomaterials for cancer therapy are generally used as delivery vehicles or mediators for external stimuli. Some preliminary data had shown that degrading NMs can elicit toxicity profiles that differn between cancerous and non-cancerous cells [1]. Here, our aim was to develop ZnO NMs with finely tuned degradation kientics in order to maximize cancer-cell specific cell death [2]. Through the process of flame spray pyrolysis, ZnO NMs could be made that were doped with different levels of Fe ions (up to 10% without any interference on the crystal structure). These NMs had been shown to display clear differences in their dissolution rates [3]. Based on the intrinsic physicochemical properties of the NMs, quantitative nanostructure-activity relationship models were generated to define the dissolution rate and cell death of the different Fe-doped ZnO NMs and to generate an optimal formulation for toxic-by-design NMs that could selectively kill cancer cells under conditions where non-cancerous cells remained unaffected.

A series of Fe-doped ZnO NMs (0, 1, 2, 4, 6, 8, or 10% Fe) were evaluated in terms of cytotoxicity on 2 cancerous (HeLa, and KLN 205) and 2 non-cancerous cell types (MSC, Beas-2B). A multiparametric high-content screening method was used for the analysis. The data clearly revealed that low Fe-doping caused higher overall toxicity that could be reduced as the Fe-doping level increased. *In silico* analysis then revealed that 2% Fe-doped ZnO NPs were the mosty selective towards the cancer cells, mainly through the generation of higher levels of oxidative stress and mitochondrial damage in cancer cells than in non-cancerous cells.

These data were then further confirmed in co-culture models, where cancer cells were cultured together with non-cancerous cells and exposed to the NPs, revealing that under the conditions used (2% Fe-doping, 25 μg/ml concentration, 8 h duration), only cancer cells were affected by the NMs, while the non-cancerous cells did not display any significant toxicity [2]. This was then further evaluated in a syngeneic mouse model (DBA/2 mice with subcutaneous KLN 205 cells) (Figure 1).

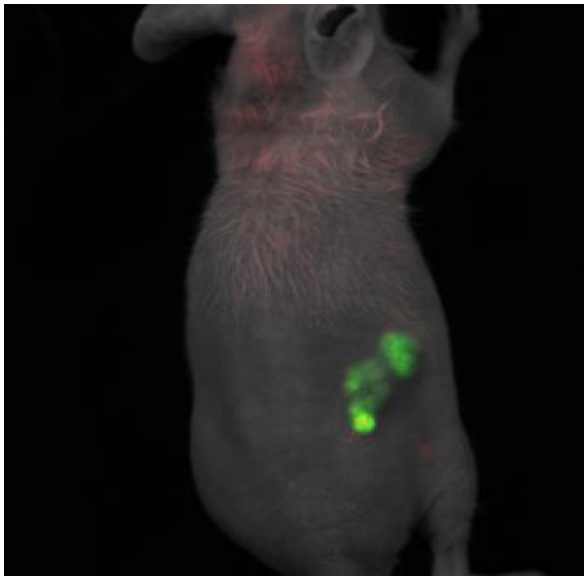

Figure 1: Representative fluorescence image of a DBA/2 mouse with GFP-fLuc expressing cells.

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Upon administration of pure ZnO NMs, 2 or 10% Fe-doped ZnO, the level of Zn^{2+} ions present in the tumor was shown to inversely correlate with the Fe-doping level of the NMs.

In terms of therapeutic activity, the pure ZnO NMs were found to be toxic to the mice, while 10% Fe-doped NMs did not cause any toxicity, nor caused any major therapeutic benefit. However, 2% Fe-doped NMs resulted in a clear reduction in tumor growth, without any negative effect on animal wellbeing. The clear induction of cell death in the mice could be observed via optical imaging by means of decrease in luciferase activity.

In conclusion, we have demonstrated that through controlled dissolution and *in silico* modelling, NMs can be generated that cause selective cancer cell toxicity. This principle is likely generic and is easily applicable to other NM formulations. This novel type of therapy can further be exploited as an alternative means of NM anti-cancer therapy.

Acknowledgements

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Personalized Approaches for Nanomaterial Delivery to Tumors

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Abstract

The use of nanomaterials (NMs) for tumor therapy is gaining much interest, but more efforts need to be made in view of successful delivery and therapy of these NMs to solid tumors. Here, we aimed to correlate the NM dose to the size and metabolic activity of the tumor on the level of the single individual instead of relating this to animal weight (normal for pharmaceutical drugs). We observed a clear and significant improvement on the therapeutic efficacy and the reproducibility of the treatment compared to control animals where a general dose was administered based on the average tumor size and metabolism of the animals [1].

Most studies currently ongoing that include the use of NMs for cancer therapy will use a single particular amount of NMs that will be given to all animals of the same study group. However, tumor sizes and their respective metabolic activity can vary quite a bit between different individual animals. This hardens any straightforward analysis as it will lead to a large intragroup variation. To overcome this problem, we looked into the use of non-invasive optical imaging to determine the metabolic activity of the tumors of the different animals and then provided fluorescent CdTe NMs at toxic levels, either at a general average dose, or at a personalized level calculated on the metabolic activity of the tumor cells.

Initially, the cytotoxic effect of the CdTe NMs was calculated over a broad concentration range suing an in-house developed high content imaging approach for evaluating bio-nano interactions [2]. Based on these studies, it could be calculated that 20% acute (at 24 h) cell death could be reached upon exposure of the lung tumor cells (KLN 205) to $13.91*10^7$ NPs/cell, and 10% acute cell death was reached upon exposure to 10.43×10^7 NPs/cell.

Next, in a syngeneic model (DBA2 mice) a series of known numbers of luminescent KLN cells were used, after which the luminescence was measured using an IVIS Spectrum system. A standard curve was then made to calculate the approximate number of cells based on the luminescence signals obtained was then set up.

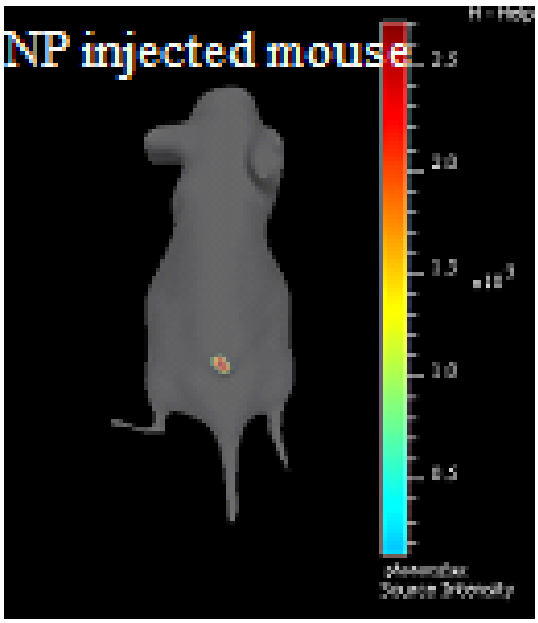

Figure 1: Representative fluorescence image of a DBA/2 mouse with CdTe NMs injected peritumorally.

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Based on these two data sets, a series of 5 groups of mice with subcutaneous KLN 205 tumors were generated. The animals were either given 100 µl of saline (control animals) or 100 µl saline containing 435 or 318 µg CdTe quantum dots (standard reference groups G_{Hequal} (20% cell death) and G_{Lequal}, (10% cell death) respectively), or 362-480 or 269-361 µg CdTe personalized medicine groups G_{HRel} (20% cell death) and G_{LRel}, (10% cell death), respectively) [1].

The results showed an impeded growth for all CdTe-treated tumors compared to control animals [1]. Interestingly, only those animals with personalized dosages displayed significant effects even at low NP concentrations, while at average dosages, these results were obscured due to the high level of variability. Additionally, the therapeutic activity could be monitored *in vivo*, as anticancer efficacy correlated with loss in fluorescence intensity (Figure 1).

In conclusion, this work demonstrates the advantages of noninvasive imaging for monitoring therapeutic delivery and to optimize NM-mediated cancer treatment via personalized medicine.

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An Alternative Test Concept for the Preclinical Toxicology Testing of Nanomedicines

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Introduction and Motivation

Nanotechnology is one of the key technologies of the 21st century that developed from a basic research to a worldwide important discipline in the last years with an enormous importance in life sciences and medicine. Whereas the toxicological effects of acute nanoparticle expositions were widely described in the last years, long-term risks depending on the structure and biodegradability of the nanomaterials as well as the disease state of the patients have not been systematically investigated. Furthermore, prediction models for degradation and toxicity of nanomaterials as well as the influence of the environment such as protein corona and the dynamic blood flow on particle behavior are often not in the focus of the nanotoxicological research. Many nanosafety studies did not systematically consider the role of the characterization of the life-cycle of nanomaterials and the changes of particle properties in the body.

Materials and Methods

Magnetic nanoparticles (MNP) with iron oxide cores, biodegradable and biopersistent shell materials (dextran, glucuronic acid, poly (ethylene glycol), poly (ethylene imine), silica, starch) with different surface charges were used. The MNP were characterized regarding their physicochemical properties using photon correlation spectroscopy (PCS), laser Doppler anemometry, electron microscopy, spectroscopic iron quantification, vibrating sample magnetometry and infrared spectroscopy during the overall life-cycle. The biodegradation of MNP was assessed (IR spectroscopy, differential scanning calorimetry, iron quantification, PCS) using complex artificial body fluids mimicking the plasma (simulated body fluid, SBF, pH 7.4) and the lysosomal compartment (artificial lysosomal fluid, ALF, pH 4.5 and 5.5) as well as simulated protein coronas. The experimental data were analyzed using different mathematical approaches. Furthermore, *in vitro* cyto- and hemocomaptibility [2] in endothelial cell cultures and sheep erythrocytes were correlated with particle effects in a shell-less ex ovo hen's egg model [1].

Results and Discussion

The importance of an extensive physicochemical characterization during the overall life-cycle of nanoparticles and particularly the changes in the biological environment were highlighted. The degradation of MNP was found to be pH, surface, temperature and protein corona dependent. Whereas in SBF all MNP were stable over 28 days, the core degradation in ALF was dependent on the biodegradability, water permeability, surface charge and acid/base character of the shell material. MNP degradation was correlated with a loss or degradation of the surface coating. However, in short-term applications cyto- and hemocompatibility tests showed that the properties of the core material itself were not relevant. Toxicity increased with higher polymer mass, neutral=anionic<cationic surface charge and charge density. Based on mathematical approaches it was possible to categorize the MNP in three groups, to establish structure-activity relationships and to predict nanosafety.

Furthermore, the development of new alternatives to animal-based methods (hen's egg model), to be applied in an integrated safety assessment of nanoparticles for *in vitro/in vivo* correlations, were established and integrated in a categorization model. Local and systemic toxicology, structure-flow profiles, and the interaction with blood cells and proteins could be visualized under flow conditions in the ex ovo hen´s egg model. The influence of a magnetic field on nanoparticle characteristics could be visualized.

Conclusion

The investigation not only of acute toxicity events but of the overall life-cycle of nanoparticles is of major importance for the nanosafety assessment. The shell-less *in vivo* hen's egg model favors the advantage to predict toxicity in a complex system under blood flow conditions as a prediction model in the preclinical development of nanomaterials.

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