Development of Hyperthermia Treatments for Malignant Melanoma using Superparamagnetic Iron Oxide Nanoparticles in a Novel Transgenic In Vivo Model

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Introduction

Despite several breakthroughs in the treatment of melanoma, therapeutic resistance remains a significant clinical problem and there is a need for novel therapeutic approaches. Hyperthermia is one promising treatment modality where tissue is exposed to elevated temperatures to induce cell stress, apoptosis and/or necrosis. However, traditional hyperthermia treatments in both in vivo models and patients cause non-specific tissue damage. We hypothesise that Superparamagnetic Iron Oxide Nanoparticles (SPIONs) can provide an elegant solution to improving this therapeutic specificity; when they are placed into an alternating magnetic field, SPIONs they generate heat at a localised site.

This poster describes the development of system for in vivo hyperthermia using SPIONs in a novel transgenic murine model.

What are SPIONs?

Super-Paramagnetic Iron Oxide Nanoparticles (SPIONs) are a class of nanomaterial that can be induced to generate heat when placed in an alternating magnetic field. This process is called magnetic alternating current hyperthermia (MACH).

Murine Models of Melanoma

Mouse models of melanoma originate from the early twentieth century when melanocytic tumours arose spontaneously in inbred mouse strains. Of these, the syngeneic C57BL/6 B16 model is probably best known and widely investigated. However, in recent years, novel inducible melanoma models have been developed which closely resemble human disease.

In the genetically modified BrafV600E/Cre;Er/EPr1oss1+1 mouse, anatomically restricted metastatic melanoma can be formed with 100% penetrance and a minimal latency period. In this inducible Cre model, the Cre-recombinase:estrogen receptor (CreER) fusion protein is constitutively expressed in melanocytes by Tyrinosmine transgenic promoter elements, and after exposure to 4-hydroxytamoxifen, CreER in the cytoplasm translocates to the nucleus, activating mutant BrafV600E and inducing loss of EPr1. This results in melanogenesis.

Given the BrafV600E/Cre;Er/EPr1oss1+1 tumour model histologically and pathologically mimics human melanoma growth and metastasis, it was chosen for use in our study.

Intratumoural Biodistribution of SPIONs

Having defined our model of melanoma, it was necessary to assess whether the SPIONs Ferucarbotran could be effectively delivered into tumours using an intradermal technique.

Biodistribution within Reticulo-Endothelial System

Having shown that SPIONs can be effectively delivered intratumourally, it was important to assess their wider biodistribution within the wider reticulo-endothelial system (RES).

In Vivo Hyperthermia

Having investigated the biodistribution of SPIONs within the RES following intratumoural injection, we decided to test our hypothesis that SPIONs can be used to generate a controlled, localised hyperthermia. A bespoke MACH system was developed with our collaborators at the Royal Institution of Great Britain in order to facilitate in vivo testing.

Conclusions & Future Work

In this proof of concept study we have investigated and developed a model that shows that the SPION Ferucarbotran can be used to generate therapeutic hyperthermia in vivo in both a localised and controllable manner using a novel transgenic murine model.

Using this model of hyperthermia, we now plan to investigate the effect of hyperthermia treatment not only on the tumour, but also the effect of this hyperthermia on the host’s immune system. We believe that SPION-mediated hyperthermia may facilitate the generation of novel tumour antigens which could form the basis of a ‘self-vaccination’ therapy.

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