SURFACE MODIFIED NANOPARTICLES FOR TARGETED DRUG DELIVERY

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BACKGROUND

Efficient treatment of intracellular diseases (e.g genetic mutations and intracellular pathogens) is current limited to small molecule drugs as they can diffuse into the intracellular compartment through the cell membrane. One obstacle associated with these small molecule drugs is the difficulties related to the development of new types. As a result, there is an absence of coherence between the fast progression in the understanding of disease mechanisms and the development of new cures. This contrasts the development of biopharmaceuticals, including antibodies and oligonucleotides, which can be designed to target and inhibit function as well as expression of specific proteins thus enabling one to develop more specific and efficient therapeutics and is currently used for treatment of, among other diseases, cancer[1,2].

However, these types of treatments are limited[3,4]. One way to enhance treatments could be to combine biopharmaceuticals with nanoparticles (NPs), where especially solid lipid nanoparticle (SLN) based drug delivery systems (DDS) has gained interest due to properties like stability, biocompatibility and biodegradability, high drug loading, and ease of modification[5]. However, due to the hydrophobicity of these type of NPs they must be stabilized to prevent aggregation and to reduce the risk of clearance by the mononuclear phagocyte system. One method used is to stealth coat the NP surface with a highly hydrophilic corona composed of molecules such as polyethylenglycol (PEG) or proteins such as albumin[6]. Besides preventing aggregation and clearance, stealth coating limits non-specific interaction with and uptake in healthy cells reducing the side effects of the toxic cargo. However, stealth also reduces interaction with the disease target. An ideal DDS would, therefore, consist of NPs carrying and protecting the drug payload which is coated with a stealth corona improving circulation, and which is conjugated to antibodies enabling active targeting. Systems consisting of targeted, stealth drug NPs have been designed before but these have been translated poorly to clinical use[7] for several reasons: they have (i) been too difficult or too expensive to make reproducible up-scaling, (ii) been too unstable, (iii) included toxic or foreign components which could trigger systemic toxicity or immunogenic reactions. This PhD project will address these shortcomings.

The project will focus on further exploring, developing and testing a simple and inexpensive DDS design we have developed during my recently completed MSc thesis. The system consists of SLNs conjugated to both a stealth corona and antibodies which is capable of carrying a drug payload

AIM

Develop a generic drug delivery system consisting of stealth protein and antibody conjugated solid lipid nanoparticles to be used for targeted therapy aiming at treating cancer by enabling delivery of biopharmaceuticals to intracellular target sites within cancer cells

OBJECTIVES

1.Examine the encapsulation of different drug payloads
2. Study effect of different stealth and antibody proteins on target selectivity and cellular uptake
3.Verify of safety, selectivity and efficacy in vitro and in vivo

STAGES & METHODOLOGY

Stage I

Particle formulation
- Solvent injection method and emulsification (testing conditions such as: temperature, type of lipid, coupling conditions and chemistry, stealth and targeting moieties etc..)
- Encapsulation of small molecule drugs e.g. polyacetylenes as well as antibodies and antisense oligonucleotides -> targets intracellular proteins and mRNAs

Stage II

In vitro uptake studies
- Interaction between the particles and their target protein will be examined using time lapse fluorescence microscopy, Raman spectroscopy mapping, membrane protein silencing, antibody competition assays, and flow cytometry techniques
- Uptake routes and intracellular trafficking of different particles will be studies using e.g. live cell fluorescence microscopy, cell organelles fluorescence markers, super-resolution microscopy, and by blocking uptake routes using small molecule inhibitors

Stage III

In vitro function and toxicity
- Toxicity of the particles will be studies quantitatively and qualitatively using respectively using fluorimetric viability assays and fluorescence microscopy
- Particle selectivity will be examined by means of selectivity towards cancer cells binding, uptake and killing using fluorescence microscopy and flow cytometry e.g. by live/dead staining

Stage IV

Pre-clinical animal trial
- The best performing systems will be tested for effect *in vivo*, in a mouse model of a type of human cancer. This by examine (i) distribution using IVIS scanning and end-point histology, (ii) by monitoring tumor size using calipers, imaging and end-point histology and finally (iii) potential weight loss, behavior changes and toxicity in the mice will be studied.

REFRENCES

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