Pharmacokinetic Profiling and Tissue Distribution Studies of Liposome Encapsulated SN38 Therapeutic Microbubbles using ^{89}Zr Positron Emission Tomography (PET).

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Introduction

The method by which a drug is delivered can have a significant effect on its efficacy. All drugs have an optimum concentration range in which maximum benefit is achieved and there is a real need for multidisciplinary approaches to optimise the delivery of a therapeutic to its target tissue.

The Medicines Discovery Catapult have partnered with the University of Leeds to develop a therapeutic microbubble Platform (ThMb) as an innovative drug delivery System

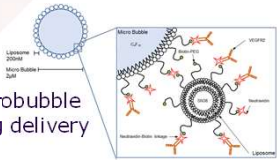


Figure 1: Therapeutic Microbubble Drug Loaded Complex

Micron sized gas filled phospholipid bubbles form the core of a therapeutic microbubble. Targeting molecules and drug payload are attached to the complex and injected into the body (Figure 1)

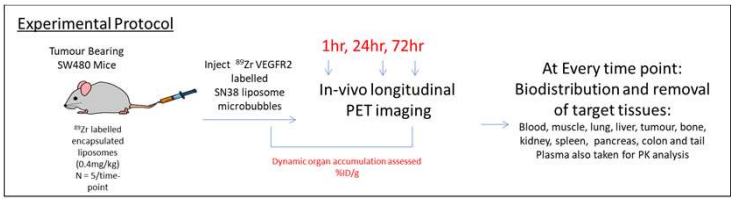
An ultrasound trigger causes the therapeutic drug complex to release its drug payload and cause localised release of drug.

MDC are working to differentiate the delivery platform as a superior method to conventional formulation using the therapeutic intervention for colorectal carcinoma liposome encapsulated SN38.

Study Aim & Methods

-Study Aim: To understand the pharmacokinetic distribution of LE-SN38 and the benefit of using targeted microbubbles as a carrier with ultrasound to demonstrate therapeutic delivery and controlled drug release

-Methods: Nude mice were subcutaneously injected with SW480 colorectal cancer cells.
Radiolabelling was performed by attachment of a chelator (df-Bz-NCS) to the liposome shell by an amine bond allowing attachment of ^{89}Zr (Seo *et al,* 2015).
Mice were injected with ^{89}Zr labelled liposomes, ^{89}Zr ThMb's with and without ultrasound destruction



Mice were imaged at 1, 24 and 72 hour post administration
Terminal tissues and satellite groups (n=5) at each imaging time point were taken for biodistribution analysis.

Results

Pharmacokinetics and distribution of liposome encapsulated SN38

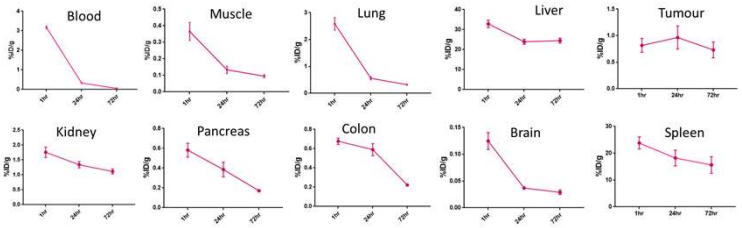


Figure 2: %ID/g and biodistribution of ^{89}Zr LE-SN38 at 1, 24 and 72 hours post administration of ^{89}Zr-SN38 liposomes

Distribution and degradation of LE-SN38 is through the reticuloendothelial system (RES). Greatest accumulation was observed in the liver and spleen. %ID/g tumour: 1hr - 0.83% ± 0.13; 24hr - 0.96% ± 0.21; 72hr - 0.73% ± 0.14

The benefit of using targeted microbubbles as a carrier

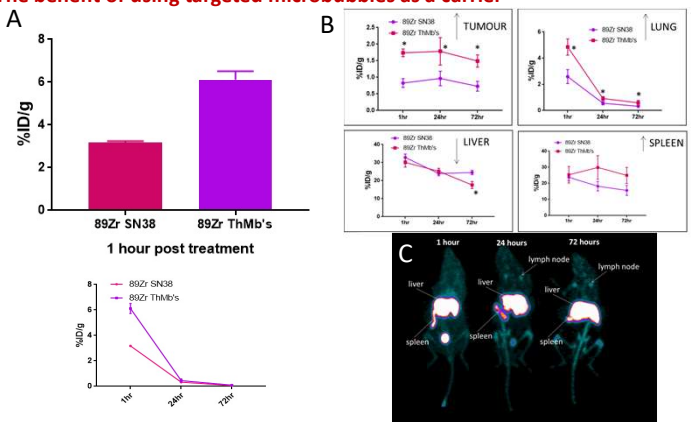
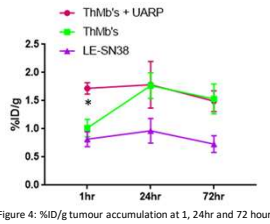


Figure 3: A: Circulating ^{89}Zr blood concentration ± ThMb's complex. B: %ID/g organ accumulation. C: Representative PET image distribution

Significantly increased ^{89}Zr LE-SN38 was observed in the blood 1 hour post administration with ThMb's. A 2 –fold increase in tumour accumulation was also observed at all time points post ThMb administration. Significantly increased accumulation in the lung (at all time points) and decreased uptake in the liver at 72 hours shows diversion of the RES at the final imaging time point

Targeted and controlled ultrasound release of drug



Ultrasound destruction and addition of UARP shows greater accumulation in tumour at 1 hour post administration showing transient and increased permeability changes to tumour tissue

Figure 4: %ID/g tumour accumulation at 1, 24hr and 72 hour post ^{89}Zr LE-SN38 administration , ^{89}Zr ThMb's with and without ultrasound destruction

Conclusions

- ^{89}Zr labelled LE-SN38 can be reproducibly tracked in a series of body organs
- Distribution and degradation of LE-SN38 is through the reticuloendothelial system
- ThMb's demonstrate greater accumulation in the tumour target organ enhancing efficacious effects compared to LE-SN38 alone
- Our understanding of the mechanism of controlled drug delivery and release and the potential as a drug delivery platform means we can now exploit this as a platform technology for use with multiple drugs across disease areas

References

Seo JW, Mahakian LM, Tam S, Qin S, Ingham ES, Meares CF, Ferrara KW. The pharmacokinetics of Zr-89 labeled liposomes over extended periods in a murine tumor model. **Nucl Med Biol.** 2015 Feb;42(2):155-63. doi: 10.1016/j.nucmedbio.2014.09.001

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