Transfer and Validation of a Targeted Microbubble Drug Delivery Platform for Treatment of Colorectal Cancer

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Medicines Discovery Catapult (MDC)

MDC is a not-for-profit research company specialising in collaborative R&D exploring and developing new approaches to stimulate success in the UK drug discovery sector across Discovery Science & Technology, Informatics, Virtual R&D, Discovery Syndicates, and Samples & Data themes.

One of the challenges is to reduce the high rate of attrition in the delivery of new medicines to patients[1]. Innovative drug delivery technologies have the potential to address this by overcoming, for example, cell permeability limitations or by 'rescuing' drugs with a low therapeutic index.

Microbubbles for therapeutic delivery

Microbubbles (MBs) are micron-sized, gas-filled, lipid shells which have been used routinely in the clinic as contrast agents for ultrasound mediated imaging[2].

MB technology can enable therapeutic delivery by:

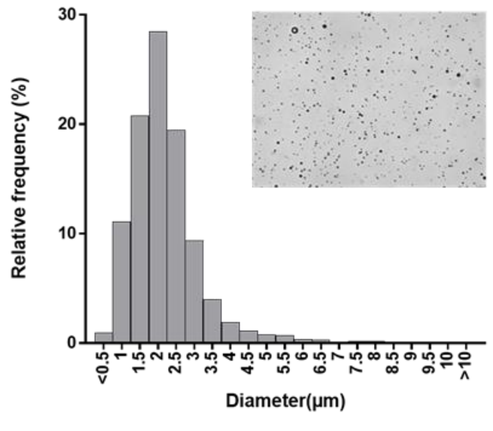
- carrying a drug payload
- attaching biological markers to target them to a specific tissue
- with controlled and directed bursting via ultrasound
- allowing an increase in localised therapeutic drug concentration
- reducing off target systemic effects.

This may help to restore a useful therapeutic profile to drugs that are stalled in development or previously failed to make it into the clinic.

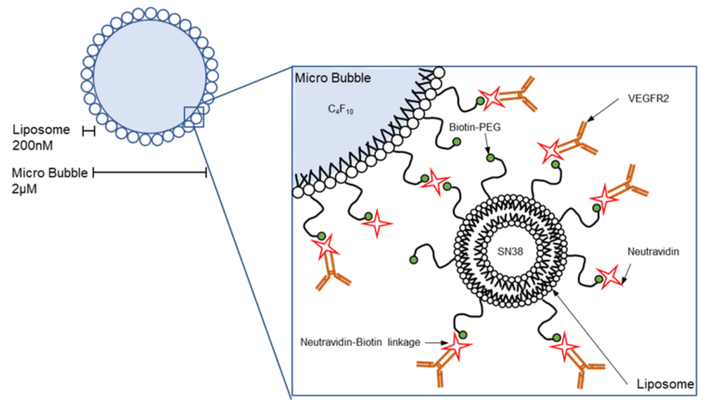
Microbubble & Liposome characterisation

MBs produced at the MDC are equivalent to those from Leeds for concentration (4.54E+08 ± 1.21E+08 ml^{-1}) and size distribution (2.1 ± 1.3µm). Importantly less than 1% of MBs are greater than 8µm which is superior to most commercial MBs used for diagnostics.

Liposomes were evaluated on the NS300 (Nanosight) and were found to have a concentration of 1.52E+09 ± 4.98E+08 ml^{-1} with an average size of 193 ± 71 nm (data not shown).



Working in collaboration with Leeds University, the MDC has accessed MB technology and is working to validate this approach and carry out preclinical studies to enter phase I clinical trials.
The Therapeutic MB complex (ThMB) here consists of liposomes containing SN38 attached to VEGFR2 targeted MBs.

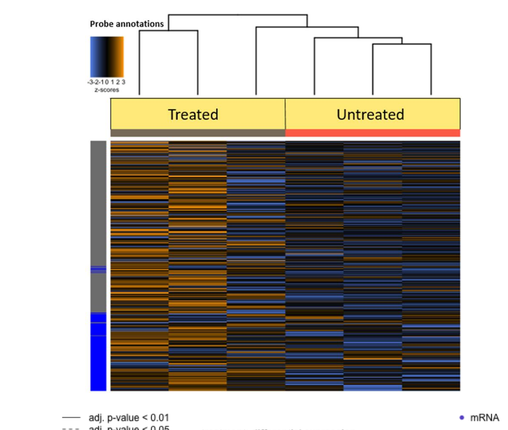


Gene expression analysis

Tissue samples from MB treated and non-treated xenograft mice were analysed using the (Human) PanCancer Pathways Panel code set (Nanostring) for quantitative analysis of RNA expression.

A subset of tumour samples dosed with SN38 showed increased expression (orange) in: apoptosis, chromatin modification and DNA damage genes.

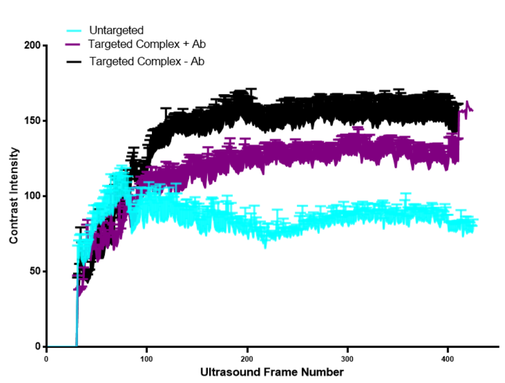
The xenograft samples showed consistent but limited effects compared to control treated SW480 cells. Additional gene expression analysis will be used as a measure of MB exposure for future studies.



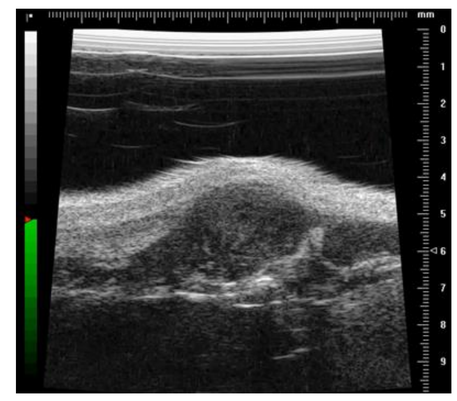
MB reproducibility *in vivo*

Time intensity curves visualised on the Vevo 770 *in vivo* (n=8) across three individual MB preparations showed similar wash-in slopes and AUC.

Accumulation changes were assessed for targeted/untargeted MBs, with targeted complexes preferentially observed more than untargeted MBs.

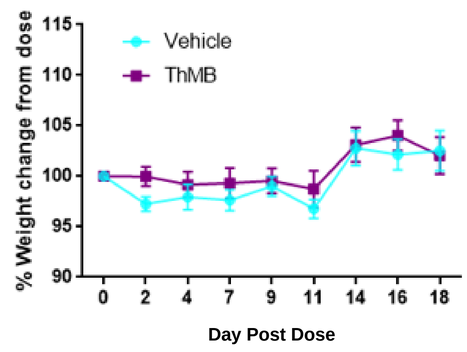


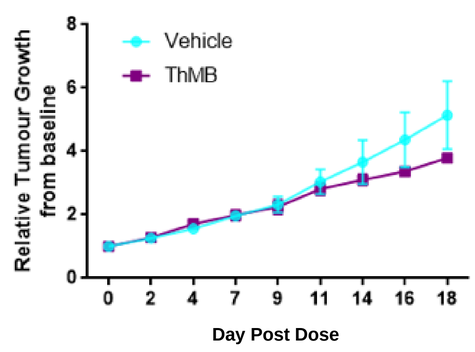
Group	Initial Slope	CoV
Untargeted	771.38 ± 43.43	15.9%
Targeted complex + VEGFR2 Ab	1214.42 ± 97.96	22.8%
Targeted complex - VEGFR2 Ab	1413.25 ± 164.87	32.9%



MB treatment reduces tumour volume

To test the efficacy of ThMBs, CD1 nude mice were dosed 5 times every 3 days with 100µL of freshly prepared ThMBs (0.17mg/kg). Data showed tumour volume inhibition of 26%, with no observable toxicity issues, reproducible tumour accumulation and pharmacokinetic behaviour. Although there is some separation between the treated and non-treated groups, further work is under way to explore maximise therapeutic effect.





Conclusion

A successful transfer of MB production technology and encouraging initial *in vivo* studies for SN38 mediated MB therapy for colorectal cancer.

[1]: Kola I, Landis J (2004) 'Can the pharmaceutical industry reduce attrition rates?' Nature Reviews Drug Discovery 3:711-716
[2]: Lindner J (2004) 'Microbubbles in medical imaging: current applications and future directions' Nature Reviews Drug Discovery 3(6):527-532

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