Direct imaging of gemcitabine delivery in pancreatic ductal adenocarcinoma (PDAC) using CEST MRI

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Target audience: Physicians interested in predicting tumor response and improving drug delivery in pancreatic cancer.

Purpose: To test the feasibility of using the inherent Chemical Exchange Saturation Transfer (CEST) signal of gemcitabine (Fig.1), a chemotherapeutic drug for treating pancreatic cancer, to assess its uptake and biodistribution, without the need for additional MRI contrast agents. This would be useful to predict the tumor response.

Methods: The in vitro CEST properties of gemcitabine (dFdC) and its natural analog deoxycytidine (dC) were measured on a 9.4 T vertical bore Bruker MRI scanner using a previously reported procedure[1]. In vivo CEST MRI was performed on a Biospec11.7 T MRI scanner equipped with a 23 mm mouse brain volume coil[1]. Subcutaneous pancreatic ductal adenocarcinoma PDAC xenografts were inoculated on female Athymic Nude-*Foxn1*^{nu}/Foxn1^{+} mice (six weeks old, Harlan) by injecting 5x10^6 human Capan-1 cells into the lower flank of the mice. After tumors reached 100-200 mm^3 (3–4 weeks), ten sets of CEST weighted images (B_1=3.6 μT, 3 sec) were acquired before and within the first 50 minutes after the gemcitabine injection (i.v.) using a six-offset approach[2], i.e., at frequencies of ±2.0, ±2.3, and ±2.6 ppm, which allows compensating the B_0 inhomogeneity (measured by WASSR) in the data processing. The temporal resolution (per MTR_{asym} map) is ~ 2.5 or 5 minutes, for a single average or two averages, respectively, with an in-plane resolution of 0.3x0.6 mm^2. Data were processed using custom-written MATLAB scripts. CEST contrast at 2.3 ppm was calculated by $MTR_{asym}=(S^{\Delta\omega} - S^{+\Delta\omega})/ S_0$. The ΔMTR_{asym} at different time points were first calculated by $\Delta MTR_{asym}(t)=MTR_{asym}(t) - MTR_{asym}$ (pre). Based on the dynamic CEST signal, the following metrics were calculated pixel-by-pixel[3]: the area under curve (AUC); the maximal CEST enhancement in the tumor (Cmax); and the time to maximal contrast enhancement (Tmax).

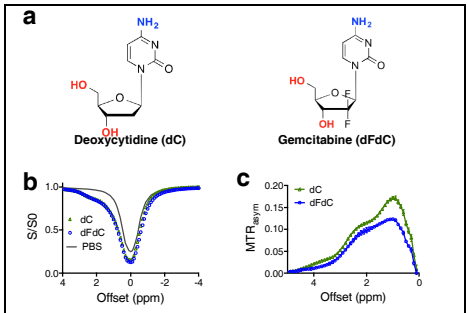

Figure 1. (**a**) The chemical structure of gemcitabine and its natural analog deoxycytidine. The CEST MRI contrast of dFdC and dC, as shown by z-spectra (**b**) and MTR_{asym} plots (**c**)

Results: As shown in Figure 1, our in vitro study confirmed that gemcitabine and its natural analog dC can be readily detected by CEST MRI via their inherently carried exchangeable amino (blue, ~2.3 ppm) and hydroxyl (red, ~ 1ppm) protons. We then used the CEST MRI to monitor the tumor uptake and intra-tumoral distribution of the injected gemcitabine in the human PDAC xenografts (Figs. 2a and 2b). In addition, we also calculated the quantitative pharmacokinetic parameters, AUC, Tmax and Cmax. The results clearly showed a heterogeneous distribution of the drug in the tumor (Figs. 2c-d).

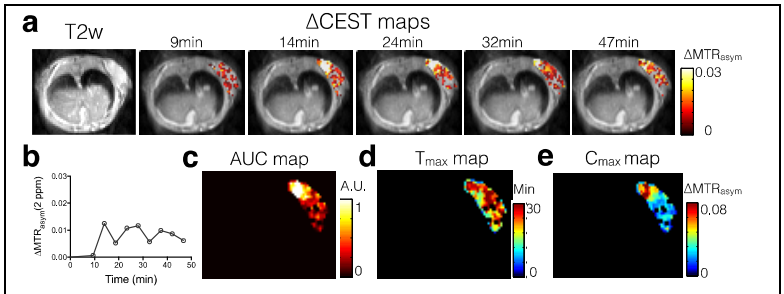

Figure 2. *In vivo* detection of gemcitabine using the proposed cytCEST MRI technology in a Capan-1 human pancreatic caner xenograft. (a) The ΔCEST (i.e. change in CEST) MRI contrast maps at 2.3 ppm over a period of 50 minutes after i.v. injection of 500 mg/kg gemictabine into the tail vein of the mouse. Note that only the CEST contrast within the tumor region is shown. (b) The dynamic change in CEST contrast for the whole tumor. (c)-(d) The calculated pharmacokentic parameteric maps: Area Under Curve (AUC), the time to maximal contrast enhancement (Tmax); and the maximal CEST enhancement (Cmax);

Discussion: This is the first preliminary study showing the feasibility of using the inherent CEST signal carried by a drug (gemcitabine) to directly detect its pharmacokinetics in PDAC. Such an approach requires no imaging tags or probes, making it possible to be directly translated to the clinic Moreover, this CEST MRI approach can be easily tailored to detect other cytidine analog anticancer drugs.

Conclusion: In the present study, we demonstrated that gemcitabine could be directly detected using CEST MRI in a murine PDAC model, which allowed us to monitor the drug delivery and quantify the pharmacokinetic parameters without the use of extra imaging agents. One potential applications of this MRI approach may be its use as a predictor of therapeutic outcome, with a great clinical translation potential as not additional agents are needed.

Reference: (1) Liu, G.; Moake, M.; Har-el, Y. E.*, et al. Magn. Reson. Med.* **2012**, *67*, 1106-13. (2) Zhou, J.; Blakeley, J. O.; Hua, J.*, et al. Magn. Reson. Med.* **2008**, *60*, 842-9. (3) Alic, L.; van Vliet, M.; van Dijke, C. F.*, et al. Phys. Med. Biol.* **2011**, *56*, 1601-16. (4) Frese, K. K.; Neesse, A.; Cook, N.*, et al. Cancer Discov* **2012**, *2*, 260-9. **This work is supported by NIH grants R21EB015609, R01EB015032 and R01EB012590.**