ISTU On-Air Webinar Series: June 25,2020 Q & A

Hong Chen, Ph.D. presenting "Focused Ultrasound-Enabled Liquid Biopsy for Noninvasive Diagnosis of Brain Cancer"

#	Question	Answer
1	For the pig studies, while the biomarkes increase for all pigs, it seems that there were 2 groups, sometimes a smaller increase and some with a larger technique. Did that correlate between the two biomarkers across pigs? Any idea for why some pigs had a much greater increase?	We observed large variations in our results. We think this is due to that the BBB opening volumes were not consistent in these pigs. We are working on improving the design of our FUS transducer and optimizing the parameters to see whether we can improve the consistency.
2	In your mouse sudy, did you examine any pressure levels between 0.59 and 1.29 MPa to fine tune the threshold between maximizing biomarker release and minmizing hemorrhage in the mouse brain?	Future work is needed to fine tune the parameters.
3	Have you looked at cavitation activity as a mechanism to predict the effectiveness of biomarker release during sonication? As well as a mechanism for safety to reduce the likelihood of hemorrhage?	We performed cavitation detection. But we haven't find correlation between cavitation and biomarker release yet. We did find in our previous study that cavitaiton can be used to predict tissue damage.
4	the mouse model showed multiple magnitude enhancement of biomarkers. The porcine model only a factor of 2-3. Do you think this is enough to make it a clinical reality.	Great question. The large blood volume of pigs is expected to dilute the concentrations of circulating biomarkers compared with mouse. However, we're expecting that there would be a higher concentration of tumor-specific biomarkers in a tumor environment due to apoptosis and necrosis and tumor-specific DNA and RNA could be smaller in size and have higher release efficiency.
5	Working with FUS and injection of Microbubles with a medicament, you are able to break BBB. Does it also create brain hemorrage at other areas which are not the one selected to break BBB?	FUS combined with microbubbles have been used in several clinical studies and found to be a safe technique. But you raised a valid concern. Hemorrage can happen in non-targeted area when the transducer design or parameters are not optimal.
6	How long does the disruption of the BBB last? Is it long enough to allow pathogens into the brain?	The BBB opening can last several hours to several days. We can tune the ultrasound parameters to control this duration. Once BBB is opened, pathogens can get into the brain. We need to consider the risk-benefit ratio.
7	The mouse model showed an increase of several orders of magnitude, while the pig model showed about a factor of 2-3. Do you think this difference is only due to the blood volume difference, or are there other variables?	First, we're expecting that there would be a higher concentration of tumor-specific biomarkers in a tumor environment due to apoptosis and necrosis. Second, tumor-specific DNA and RNA could be smaller in size than the protein markers and have higher release efficiency.
8	I wonder if there are other diseases with specific biomarkers that can apply this technology.	The technique could be applied to other brain diseases that need noninvaisve detection of gentic and molecular information.
9	Great talk, thank you. Can you comment on limits detection for this technique in large animals/humans? GFAP is expressed at very high levels, but tumour markers may be expressed at low levels	This is a wonderful quesiton. We need to perform studies in large aniamls/humans with brain tumors to address this question.
10	Haoli Liu: Wonderful talks! How do you think the potential for detecting AD related biomarkers ?	AD is an attractive application of this technique.
11	How to choose an appropriate contrast agent depending on the FUSF frequency and pressure or vice versa? What is the relation between them?	We haven't. It would be interesting to explore.
12	Hello. Very nice work! What about the clinical feasibility of this approach which requires expensive and poorly available devices at the moment?	I agree with your concern. For therapeutic drug delivery, FUS sonication needs to cover the whole tumor to distribute drugs throughout the tumor and kill every diseased cell. FUS sonication for LBx does not need to cover the entire tumor. Instead, FUS-LBx can pinpoint specific tumor locations for spatially targeted biomarker release. We would expect that the clinical device for LBx could be designed to be more affordable than those used in brain drug delivery.
13	Did you check how the process affects healthy brains? Did you note any changes in those markers in control pigs?	Great question. We performed histological staining of the pig brain tissue after our procedure. We did not note changes in GFAP level when comparing before and after FUS. But we need to perform molecular level analysis to verify it.
14	Very interesting technique! What would be the effect of the distance between the brain tumor and blood vessels?	I'm sorry that my cartoon illustration was a little misleading. The blood vessels are inside the tumors. The BBB should be more precisely called the blood-tumor barrier in the presence of tumor.

Meaghan O'Reilly, Ph.D. presenting "Ultrasound-Mediated Drug Delivery to the Spinal Cord"

#	Question	Answer
1	Does the bone heat up with the US parameters and what is the physiologic effect on the bone—is it weakened?	Great question. Due to the low time average intensity in these exposures we are not as concerned about bone heating as we are about potential mechanical damage. The soft tissue in the pre-laminar space could see high pressures due to reflection from the lamina, which can act as a parabolic reflector (see Xu and O'Reilly, Phys Med Biol 2018). We have seen bruising in the overlying muscle in our pig model in some locations, reflecting what we had already reported from bench and numerical studies. Fortunately, our numerical models predict that these prefocal pressure spikes will be reduced when moving to a larger aperture array that distributes the sound over more of the bone and also utilizes the paralaminar transmission pathways (Xu and O'Reilly IEEE TBME 2020).