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Translational studies of the effects of pulsed HIFU using a modified clinical MR guided focused ultrasound device

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In the past few months, we have further pursued pulsed HIFU drug delivery translation using a rabbit model and the InSightec ExAblate MRgFUS system. A further set of 3 animals were treated, for additional 30 treatments beyond the 43 we had previously reported. In these treatments, we abandoned the earlier parameters based on mouse studies and sought instead to find a regimen where heating could be well controlled. In particular, we increased the duty cycle from 5% (the standard in mouse treatments) to 25 and 50%. This significantly reduces the required treatment time. This decision was based upon the earlier studies, outlined in my previous report and the accompanying extended abstract (IEEE Ultrasonics, 2009), which seem to indicate that an enhanced delivery of MR contrast is best correlated to heat. With these duty cycles, we sought to achieve local temperatures between 46 and 48 °C for up 2-5 minutes. This way, we were able to more consistently achieve enhanced MR contrast delivery. Unfortunately, the safety of the procedure is much harder to control, and a number of the treatments contained central regions of thermal injury. As previously, enhanced contrast uptake was correlated with fluid build-up as measured by increased T2 signal from these regions. Following treatments, the animals were sacrificed and the treated muscle removed for sectioning and histology. Histology demonstrated that the enhanced contrast and T2 signal are related to edema and inflammation of the tissue in the treated region (Fig. 1).

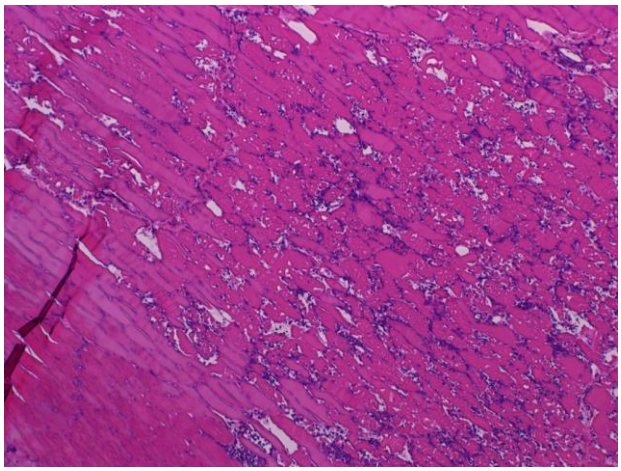

Figure 1. Histology from region of enhanced MR contrast uptake following pulsed HIFU. The bottom left corner is normal muscle. The upper right region shows significant edema and inflammation, and corresponds to bright regions on the T2 images.

In conclusion, after one year of study using the InSightec system for drug delivery with pulsed HIFU in a large animal model, it is clear that translation from the mouse model is not so simple. The ultrasonic parameters that yielded good results in the mouse model do not work well in larger animals. It appears that the mouse results were due in large part to the narrowness of the mouse geometry and the unavoidable proximity of skin and bone tissues to the treatment zone. Once these surfaces are removed, achieving measurable effects requires greater intensity and heating. Currently, we have some success in achieving our goal of improved delivery by relying on controlled heating, however, more study is

required to show treatment consistency and safety.

Progress towards Goals:

Phase 1 – Completed. We have developed a reliable system for pulsed HIFU treatment with the InSightec ExAblate system.

Phase 2 – Mostly completed. Some analysis of data remains. This phase became the focus of the project after the parameters used in the earlier studies did not elicit the same response in the rabbit muscle. Also, problems with morbidity in the test animals and, to a lesser extent, problems with InSightec RND system stability following upgrades led to difficulties in completing the studies planned beyond this point.

Phase 3 – Incomplete. Because the standard pHIFU parameters did not yield the expected results, a systematic study as envisioned in the original proposal for Phase 3 was not achievable in the first year.

Phase 4 – Partially complete. With fewer animals, more time was spent on system optimization. The result, as partially explained in Progress Report 1, is a method for treating at higher speed using the available electronic and mechanical steering of the device. This technique partially treats the local region using high speed electronic steering, to the point at which it begins to heat up significantly, then used mechanical steering to move and treat at another location some distance away. By the time the second treatment zone has begun to heat up, the first has cooled down, and treatment there can be completed. Thus the local duty cycle is low enough to avoid overheating, but the global duty cycle is much higher, and the treatment of large areas becomes much more efficient.