

FINAL PROGRESS REPORT
**Blood-brain barrier opening for facilitating drug delivery
in neurodegenerative diseases in non-human primates
(PI: Konofagou)**

Summarize work to-date

Here is a summary of what was accomplished over the past 6 months:

- Over the past two years, 125 sonication procedures were performed in the striatum of 4 rhesus and 2 fascicularis macaques monkeys. 119/125 (95.2%) success in opening BBB. All animals are healthy.
- Bubble delivery and sonication could be monitored outside the MRI using cavitation response.
- BBB opening was confirmed with MRI within the first 24 hours after opening.
- Slight drop (10%) in heart rate and pressure was attributed to anesthesia, not FUS.
- No gross effects on behavior due to FUS alone - animal is seen by veterinarian after every procedure. No motor impairment or change in feeding behavior. Animals would return to normal locomotion, eating, drinking and in the case of N and O, regular paired behavior (grooming, playing). The weight for all animals stayed consistent across the study with the only decrease occurring with all animals due to a restriction of fruit rewards not being given on days when behavioral testing did not occur.
- Four animals were trained on behavioral tests of motor control, decision-making and motivation. FUS alone produced no impairment in any of the monkeys used (measured variables: number of trials initiated, accuracy, fluid consumption, response time).
- Drug effect with FUS: Two drugs were tested. As noted before, domperidone (a D2-antagonist) did cause hemilateral Parkinsonian effects, and the Haloperidol (also D2-antagonist) has shown subtle but significant changes with respect to the contralateral reaction times only in the case where the BBB was opened with FUS.
- The lack of impairment to the behavioral task on the days when the animals are not sonicated was further confirmed, so repeated BBB openings were not shown to have long-lasting physical effects outside the drug dosage window (up to 48 hours post sonication).
- Initial feasibility on awake monkeys mounted with a head plate for controlling their head movements was also shown with >95% success rate. This opens up a new opportunity for a clinical paradigm where BBB opening can be applied in awake humans.

Therefore, the safety of the BBB opening and initial drug delivery facilitated by the FUS-induced BBB opening in monkeys was established.

Presentations or publications associated with the project

Presentations

- Matthew E. Downs, Amanda M. Buch, Marilena E. Karakatsani, Vincent P. Ferrera, Elisa E. Konofagou, Non-invasive focused ultrasound blood-brain barrier opening in awake non-human primates, Cold Spring Harbor Laboratory Meeting: The Blood-Brain Barrier (Cold Spring Harbor, NY, USA), December 10 to 13, 2014.
- Matthew E. Downs, Amanda M. Buch, Marilena E. Karakatsani, Carlos J. Sierra Sánchez, Shangshang Chen, Vincent P. Ferrera, Elisa E. Konofagou, Behavioral effects of targeted drug delivery via non-invasive microbubble enhanced focused ultrasound blood brain barrier opening in non-human primates, 4th International Symposium on Focused Ultrasound (Washington, DC, USA), October 12 to 16, 2014
- Gesthimani Samiotaki, Marilena E. Karakatsani, Shih-Ying Wu, Amanda M. Buch, Matthew E. Downs, Vincent P. Ferrera, Sachin R. Jambawalikar, Elisa E. Konofagou,

Pharmacodynamic analysis for efficient drug delivery through the FUS-induced BBB opening in Non-Human Primates in vivo, IEEE International Ultrasonics Symposium (Chicago, IL, USA), September 3 to 6, 2014

- Shih-Ying Wu, Carlos J. Sierra Sánchez, Matthew E. Downs, Amanda M. Buch, Gesthimani Samiotaki, Vincent P. Ferrera, Elisa E. Konofagou, Focused Ultrasound-Induced Blood-Brain Barrier Opening in Non-Human Primates with Transcranial Cavitation Detection In Vivo, IEEE International Ultrasonics Symposium (Chicago, IL, USA), September 3 to 6, 2014
- Gesthimani Samiotaki, Sachin R. Jambawalikar, Elisa E. Konofagou, Pharmacodynamic analysis of gadodiamide's diffusion through the focused-ultrasound blood-brain barrier opening in non-human primates in vivo using Magnetic Resonance Imaging, Annual Meeting of the International Society for Magnetic Resonance in Medicine (Milan, Italy), May 10 to 16, 2014
- Shih-Ying Wu, Carlos J. Sierra Sánchez, Matthew E. Downs, Amanda M. Buch, Gesthimani Samiotaki, Vincent P. Ferrera, Elisa E. Konofagou, Focused Ultrasound-Induced Blood-Brain Barrier Opening in Non-Human Primates with Transcranial Cavitation Detection In Vivo, 14th International Symposium on Therapeutic Ultrasound (Las Vegas, NV, USA), April 2 to 5, 2014
- Matthew E. Downs, Amanda M. Buch, Carlos J. Sierra Sánchez, Marilena E. Karakatsani, Shangshang Chen, Elisa E. Konofagou, Vincent P. Ferrera, Behavioral Effects of Targeted Drug Delivery via Non-Invasive Focused Ultrasound Blood Brain Barrier Opening in Non-Human Primates, 14th International Symposium on Therapeutic Ultrasound (Las Vegas, NV, USA), April 2 to 5, 2014

Publications

- Marquet F., Teichert T., Wu S-Y, Tung Y-S, Downs M.E., Chen C.C., Ferrera V. P., Konofagou E. E. , Transcranial Monitoring of Safe Blood-Brain Barrier Opening in Non-Human Primates, PLoS One, Volume 9, Number 2, February 2014
- Wu S-Y, Marquet F., Tung Y-S, Teichert T., Downs M.E., Chen C.C., Ferrera V. P., Konofagou E. E. , Transcranial Cavitation Detection in Primates during Blood-Brain Barrier Opening - A Performance Assessment Study, IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control, 2014 Jun;61(6):966-78.
- Downs M, Wu S-Y, Marquet F, Tung Y-S, Teichert T, Chen C, Ferrera V, Konofagou EE, Safety of Blood-Brain Barrier Opening in Non-Human Primates In Vivo, PloS One (submitted).

Follow-on funding

National Institutes of Health: NIH R01 EB009041 (P.I.: Konofagou): Optimization of Ultrasound-Induced Blood-Brain Barrier Opening (renewal awarded: 04/01/14-03/31/18).