Focused Ultrasound Opening of the Blood-Brain Barrier for the Treatment of Parkinson's Disease

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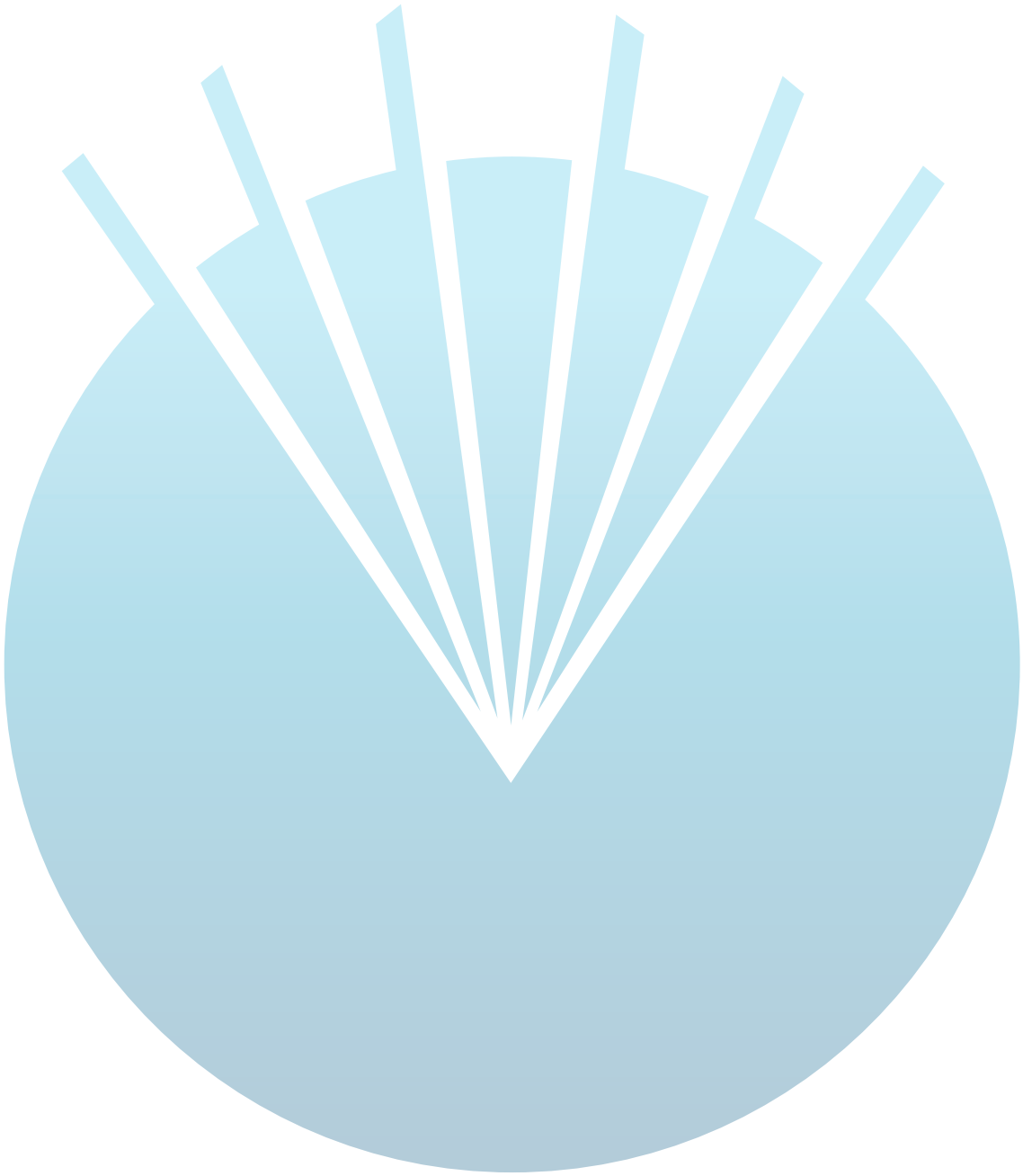

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October 21, 2018

Executive Summary

The Foundation is thankful for the work of Paul Fishman and Nir Lipsman, who organized and led this workshop. We look forward to articles in *Movement Disorders* that originated in this workshop and are being organized by Jose Obeso.

Focused ultrasound (FUS) is an early-stage, disruptive, noninvasive therapeutic technology that has the potential to improve the lives of millions of patients with a variety of medical disorders by providing an alternative or complement to existing techniques. The Focused Ultrasound Foundation convened a multidisciplinary group of experts in Parkinson's disease (PD), including neurologists, neurosurgeons, neuroscientists, radiologists, biomedical engineers, and industry representatives with the goal of determining the best way to use FUS to temporarily open the blood-brain barrier (BBB) and treat PD.

FUS-induced thermal ablation has been used to lessen the movement disorders which can arise from PD or its treatment. The goal of this 1-day meeting was to identify the research projects needed to enable more comprehensive, and possibly curative, treatment options for PD. The group addressed the following key questions.

- Develop research roadmaps for the treatment of PD using BBB opening
- Prioritize, streamline and organize collaborations for future work
- Identify technology and/or knowledge gaps

The discussion began with a discussion of the latest preclinical progress, technical issues, current ablative approaches and BBB opening experiences. The group formulated a number of conclusions for future research, listed below. These items are listed in random order, as the group did not prioritize them.

- The group agreed that BBB opening in human patients can be done safely, repeatedly and reversibly.
- BBB Opening can be combined with the following therapeutic agents.
  - Glucocerebrosidase (GBA)-enhancing therapy
  - Agents targeting a reduction of α-synuclein
    - Several trials are underway.
    - Combination with FUS may add targeted delivery.
  - Neurotrophic factors such as neurturin
    - Initial trials have not succeeded, but poor BBB penetration is a likely cause
  - Adeno-associated viral (AAV) vectors
    - Changing the output of the STN from dopaminergic to glutaminergic using AAV vectors. This might serve a neuroprotective benefit.
    - Target other regions of the brain, such as the locus coeruleus.
- The participants agreed that mesenchymal stem cells were NOT a good candidate for FUS delivery, as preclinical data does not suggest safety and efficacy for the treatment of PD.

- Clinical Biomarkers
  - There is a need for outcome measures of efficacy in PD.
  - Consideration should be given to dopaminergic neuronal markers (such as TH and dopamine transporter [DAT]) as a predictor of clinical outcome.
    - There was some disagreement among participants on the utility of these markers and that they don't always correlate to clinical improvement.
- Patient Selection
  - Patients with early/mild disease (around 3 years post-diagnosis) without neurodegeneration
  - Participants agreed that patients with GBA mutations should be considered

The group was thoroughly engaged in discussion from the beginning of the workshop until departure. The attendees were asked to continue thinking and collaborating on these issues, and to share any additional thoughts with their colleagues and the FUSF.

Technical Approach and Mechanisms

Current and Emerging Understanding of FUS Mechanisms

Marilena Karakatsani from Columbia University spoke about FUS-induced BBB opening. Neurodegenerative diseases are difficult to group together. One way is to group them by the main brain structure that they affect.[1] For example the target for amyotrophic lateral sclerosis (ALS) is the spinal cord, Alzheimer's disease is the cerebral cortex, and both Parkinson's disease (PD) and Huntington's disease target the midbrain. Focused ultrasound (FUS) is appealing for neurodegenerative diseases because it is a noninvasive and targeted technology. Acoustic energy can be concentrated on the brain structure of interest. Effect sizes range from 1x1.5 to 10x16 mm. FUS can be used for different applications with varying underlying mechanisms. FUS is used for ablation (thermal effects), blood-brain barrier (BBB) opening (microbubble-induced cavitation), and neuromodulation (acoustic radiation force, cavitation, or thermal effects).

FUS-induced thermal ablation is a non-invasive technique that results in cell death of a targeted area through temperature elevation and causes minimal damage to the surrounding tissue.[2–5] FUS-induced thermal ablation can be monitored by magnetic resonance imaging (MRI) through temperature elevation estimation and ultrasound imaging through tissue characterization.[3–6] FUS-induced thermal ablation has been used to treat brain disorders such as essential tremor, neuropathic pain, and PD-related movement disorders.[7–9]

The BBB is formed by the cerebral vascular endothelium connected by tight junctions and is regulated by the inductive properties of the neighboring cells of the neurovascular unit.[10–12] BBB permeation occurs by free diffusion of small lipophilic molecules, specific membrane proteins for small hydrophilic compounds, metabolic routes, and receptor-mediated transport for large molecules.[12,13] There are several techniques that can circumvent the BBB, but they are either non-invasive yet not targeted or they are targeted but invasive. FUS is the only technique that can noninvasively open the BBB and target local brain regions.

Frequency, pulse length, and characteristics of microbubbles contribute to the optimization of FUS-induced BBB opening.[14–19] The ultimate goal is dynamic control of cavitation. FUS-induced BBB opening was originally investigated for the delivery of therapeutic agents into the brain. Numerous experiments have studied this in preclinical studies using antibodies, chemotherapeutics, viruses, stem cells, and neurotrophic factors.[20–23] More recently, investigations into multisession delivery have been carried out. BBB opening results in an immune response. For example, Alzheimer's disease models suggest that microglia activation can clear extracellular aggregates.[24–27]

Preclinical Models of FUS-Induced BBB-Opening in Parkinson's Disease

The efficacy of FUS-induced BBB opening has been validated in the MPTP mouse model (which mimics early-stage PD by depletion of the dopaminergic pathway) using the following neurotrophic growth factors:

- Single and multiple delivery of neurturin, a glial-derived neurotrophic factor (GDNF) family member
- Gene delivery of glial-derived neurotrophic factor (GDNF)
- Intranasal delivery of brain-derived neurotrophic factor (BDNF)

Preliminary evidence suggests upregulation of tyrosine hydroxylase (TH), the rate limiting enzyme of dopamine production, in the substantia nigra region and caudate region with both single and triple treatments. Intranasal delivery of GDNF with viral vectors also results in upregulation of TH in the substantia nigra and caudate. In the α-synuclein model (A53T model) of PD in mice there is a loss of dopaminergic neurons in the substantia nigra pars compacta.[28,29] Passive immunization of a novel monoclonal alpha-syn antibody (9E4) with FUS-induced BBB opening resulted in a reduction of α-synuclein in the substantia nigra. Additionally, FUS-induced BBB opening reduced hyperphosphorylated tau levels in the rTg4510 Alzheimer's disease mouse model. This suggests that delivery of neurotrophic growth factors can be delivered across the BBB with FUS.

Overcoming Technical Challenges

Mor Dayan from Insightec discussed technical challenges of FUS-induced BBB opening. There is rapid growth in the annual rate of publications on BBB opening, but many of the related mechanisms are still unknown. FUS-induced BBB opening in human patients with the Exablate system requires head shaving and a stereotactic frame followed by MRI, treatment planning, microbubble injection, burst sonications, real-time acoustic control, and concurrent MRI to measure safety and efficacy during the procedure. Creating a procedure that does not require a frame or head shaving will likely be necessary for greater appeal to patients.[30] The ability to monitor cavitation throughout the procedure through real-time acoustic feedback is one of the key challenges. The specific location in the brain depends on the target region and determining the specific power needed to reach this target can be challenging. The power level required is related to the skull, target location, and tissue composition. The company is optimizing movement within brain regions for automatic control of acoustic parameters. Another future feature will be the ability to calculate the spatial cavitation dose per sub-spot.

Different microbubbles have varying characteristics and do not behave in the same way.[31] Future systems will allow continuous infusion of microbubbles instead of only bolus injections. Control of the pore size created during BBB opening is a future goal. The molecular weight, size, shape, and penetration depth of delivery agents influence BBB opening and effect the risk of micro bleeds.[17] Improvements in cavitation feedback are necessary to mitigate risk. Future systems will also tailor the BBB opening to the anatomical target shape. BBB opening closes within 24 hours, but the timing for optimal delivery of therapeutic agents or BBB opening in specific targets is unknown.

Quantitative imaging techniques to assess the clinical effect are necessary, but there is a lot of research needed to develop these.[32] There is a need to enhance the efficiency

of drug delivery into the targeted tissue. Translation to clinical applications is still in development.[33] It will be necessary to create larger volumes, not just focal effects. There is very little evidence regarding the repeatability of the procedure in human patients.[34,35] Dayan mentioned that an Exablate system specific for BBB opening is in development. The systems currently in use were designed for thermal ablation.

Dayan briefly described FUS for thermal ablation in PD. Targeting within the pallidum is a key component. It is necessary to use anatomical imaging to optimize the targeting or with fast gray matter acquisition T1 inversion recovery (FGATIR) tractography. The geometry of the skull influences the thermal spot in the target location. There are a few techniques that help target the correct location; one aims for an off-target effect that targets the region of interest. Another option is to create several smaller spots that will lead to a larger thermal spot. The endpoint for treatment still needs to be determined. For PD, there is limited patient feedback available and intraoperative endpoints will be necessary.

Discussion from Presentations

- There was a question on the depth of penetration into the brain after BBB opening.
  - Most molecules diffuse within a few millimeters of the BBB as imaged with gadolinium-enhanced MRI.
- There was a question on the immunological consequences of BBB opening
  - Studies show that the immune response is a neutral mechanism. However, controlling the immune response so that it is beneficial, and not an ongoing sustained response, is necessary. When the BBB is opened, anything in the blood vessels will diffuse into the brain.
- There was a question on whether it is technically possible to steer the focal spot for thermal ablation?
  - It is possible to steer the beams independently as well as perform beam correction.
- Deep brain stimulation (DBS) can be modified by the neurosurgeon. The electrical field is created by modifying different electrodes. Can this method be applied to spot shaping for FUS?
  - In order to target the correct area, fewer elements are in use and therefore less heating and intensity.
- There was a question on a way to set up a detection system or exclusion zone for the internal capsule?
  - There is a tradeoff, by creating areas of low-energy density peak temperature is compromised. For BBB opening, this is not an issue because the power required for BBB opening in the presence of microbubbles is very small compared to thermal ablation.
- Spot shape is a major clinical problem, and will it be a limitation for FUS?
  - Dayan mentioned that his talk only focused on short term tools and strategies. There is a long-term plan in process to tailor the spot shape for a specific patient using

microbubbles. This is part of an auto focusing plan that is in preclinical trials and will move to human trials soon.

- The effect of skull shape on thermal heating is an active area of research. Skull shape can create misalignment. To move the target area, sonication parameters are changed, and skull overheating is a greater risk.
- The goal of treatment is to create the smallest focal spot possible while using the whole beam array. Some of the elongated spots that appear in lateral regions are already the smallest possible. Enlarging the spot will mean losing energy, which may not be sufficient for thermal ablation. To overcome this, both frequency and the number of elements could be increased to provide more flexibility in the shaping. There is no FUS system that can do this now, but this could be a potential solution over time.

- There was some discussion on the repeatability of BBB opening. Microbubbles release their contents within 2 seconds after the sonication pulse; therefore, it will be possible to get the procedure down to a few seconds for clinical use.
- A question was asked about the biological effect of the inflammatory response caused by FUS-induced BBB opening. Microglial activation can last for up to three days after BBB opening. Astrocytes may be activated for longer. Preclinical studies have shown that after BBB opening at 450 KPa, the BBB is closed within 2 days and microglia activation has returned to baseline.
- There was some concern because patients with PD already have neurodegeneration and potential BBB alterations. In human studies of FUS-induced BBB opening in patients with AD, there were no structural changes after BBB opening on gadolinium-enhanced MRI. However, the investigators did not check for BBB integrity.
- There was a question on whether patients with PD were more likely to have brain hemorrhage during BBB opening compared with patients with AD. There is some evidence from clinical studies that there may be leakiness of the BBB in patients with PD.
  - In a preclinical mouse study at 16 months of age, there were no observed differences in BBB opening (on contrast-enhanced MRI) size, or leakage, between control brains and the experimental mice. However, this experiment should be repeated in older mice. Cavitation monitoring versus fixed parameters could be a method to normalize the BBB opening if the BBB is compromised.
- There was some discussion on the differences between white and gray matter. With thermal ablation, heat is conducted across white matter tracts. White matter can be ablated at lower temperatures. Areas with greater white matter have less vascularization and may therefore be more difficult to treat with BBB opening combined with therapeutic agents.
- A participant asked about the intravascular dosing amounts in PD mouse experiments.
  - Dosing is done at a high level, around 1.5 mg for the GDNF experiments, to see results. Dosing has not been titrated to the minimum necessary to see effects.

- There was a question on whether it was possible to quantify and predict how much drug is delivered?
  - Currently, preclinical studies are measuring proof of concept and whether drug is getting into the brain. Multiple participants mentioned that work is ongoing to measure and predict dosing. Comparing cavitation dose is challenging. Inertial cavitation activity within the brain and the harmonic signals are filtered by the skull bone and must be calculated. The variability in humans is much higher than in mice or rats, and it is very difficult to compare between patients.
- A question was asked about plasticity effects of neuromodulation after FUS. There is ongoing research with repeated weekly stimulation in animal models to study this question. After a single sonication, effects can be seen for up to 2 hours, but long-term effects are still under investigation.
- Another participant asked if there were any post-mortem studies in humans. Primate studies suggest that there are no lesions formed after BBB opening, but this hasn't been done in human studies yet.
- There was a question on the anatomical boundaries of FUS and whether it would be possible to treat areas in the brainstem like the locus coeruleus, or pons, as targets for PD. There was some disagreement among experts on this question, although some felt that it was possible. It might be possible with off-target effects.

Workshop Presentations

Ablative Applications and Experiences

Several brief presentations provided an overview of FUS for essential tremor (ET), and the history of lesioning for patients with PD.

Vibhor Krishna from Ohio State University provided an update on the use of FUS for ET. Tremor suppression after magnetic resonance guided FUS (MRgFUS) thalamotomy for ET is stably maintained at 2 years and no adverse events occurred during the follow up period.[36,37] This data came from a multicenter randomized sham-controlled trial in 76 patients. About 40% of patients had less than 50% improvement over 2 years. The overall safety profile of MRgFUS thalamotomy for ET is promising.[38] Procedure-related serious adverse events were very infrequent (1.6%), without intracerebral hemorrhages or infections.[38] Adverse events were usually transient and commonly rated as mild (79%) and rarely severe (1%).[38] Preliminary data from an international cohort looking at predictors of outcome after MRgFUS for ET suggest that age (<70 years), shorter disease history, and operative factors (fewer sonications and higher maximum temperature) suggested better outcomes. To improve the safety of the procedure, tractography-based targeting of the ventral intermediate nucleus is being used to improve visualization of brain anatomy.[39,40] Currently, there is no intraoperative endpoint that defines success; and this is necessary to achieve increased rates of ET improvement. Krishna mentioned a few unknown factors for MRgFUS thalamotomy for ET such as variable lesion size and shape, and the optimal thermal dose for durable efficacy. Repeated sonications and skull heating issues need to be refined for better efficacy. He also recommended the following improvements in technology: better MRI (ideally with a head coil), 3D thermography, the ability to measure acoustic pressures at the target and treatment preplanning.

Raúl Martínez-Fernández from HM CINAC presented on MRgFUS subthalamotomy for the treatment of PD. Preclinical research suggested benefits for lesioning the subthalamic nucleus (STN) in patients with PD.[41] The STN is the preferred and most effective surgical target to treat PD cardinal motor features. There is no technical limitation for lesioning the STN with MRgFUS and it can be performed bilaterally. A pilot study of MRgFUS subthalamotomy in patients with asymmetrical PD demonstrated safety and efficacy.[42] After two years of follow up, efficacy remains.[43] A network assessment analysis showed that optimal treatment was obtained with lesions located within the dorsolateral motor region of the STN as compared with those centrally located within the dorsal border of the STN and the zona incerta. Data is currently being collected in a prospective, randomized, double-blind trial to evaluate safety and efficacy in patients with PD that have predominant motor features/disability on one side of the body. Patients will be evaluated at four months and followed for 12 months. Twenty-eight patients have already been treated with full results expected in sometime next year.

Paul Fishman from the University of Maryland School of Medicine discussed MRgFUS mediated pallidotomy for patients with PD. There is some controversy over whether unilateral pallidotomy is comparable to lesioning the STN. In general, lesioning the STN alleviates parkinsonian symptoms and pallidotomy is better for reducing dyskinesia associated with chronic L-DOPA treatment. Unilateral pallidotomy for patients with PD has shown comparable efficacy with other procedures, such as DBS and radiofrequency lesions.[44] Complications associated with pallidotomy include visual deficit, mild motor impairment, or interference with speech, but these are mostly transient. A small pilot trial for FUS pallidotomy for PD was conducted in Korea and reported improvements in UPDRS scores.[45] A pilot study has also been conducted in the US. Twenty patients with L-DOPA responsive PD with significant asymmetry and functionally interfering dose fluctuations including significant dyskinesias were treated and followed for one year. FGATIR sequences to target the internal globus pallidus (GPi) were used along with diffusion tensor imaging (DTI) superimposed to visualize the pyramidal tract. Adverse events were mild, 3% of patients had dysarthria and 2% had a visual field deficit. This side effect profile is better compared to radiofrequency lesioning. In conclusion, unilateral MRgFUS pallidotomy is a promising new procedure in the treatment of patients with PD with asymmetric motor signs and intrusive dose fluctuations dyskinesia. The next step is an in-progress multicenter placebo-controlled double-blind study in patients with significantly asymmetric motor signs and dose fluctuations.

Discussion from Presentations

- There was some discussion on how MRgFUS results compare to DBS and other standard techniques.
  - There is improvement in tremor with FUS, but no head-to-head experience yet. However, the scales used to measure tremor are not linear, they are exponential. It's hard to show a reduction in tremor. MRgFUS relies on lessons learned from other older techniques, such as radiofrequency. Additionally, the combination with MR allows visualization that is not possible with radiofrequency.
- The FDA is concerned with off-target effects, particularly as FUS moves away from MR monitoring in the future.
  - Some of the biggest risks are paralysis, transient weakness, and transient sensory loss. These risks are well-reported in the literature. However, these have not occurred in the pilot clinical trials. There are off-target effects, but they have been moderate to mild so far. DBS is an invasive procedure that leads to additional risks for bleeding and infection that don't exist with FUS. Several participants mentioned that the tradeoffs are more favorable to patients, particularly the shortened length of hospital stay required after FUS.
  - Clarification on bleeding and infection with DBS was given. Most bleeds require extended hospitalization and are transient and have very little neurological effects. Many bleeds may be clinically symptomatic. Patients may also have neurological effects

after DBS treatment even in the absence of bleeds such as seizures. Serious neurological deficits occur even with the most experienced physicians after DBS. So far, MRgFUS pallidotomy has fewer of these risks.

- An audience member asked about what treatment options are available to patients treated with MRgFUS if their tremor returns
  - Over the years, the optimal candidate for treatment with DBS has emerged and the same will likely happen with additional experience with MRgFUS. The treatment population most likely to benefit has yet to be defined.
- There was discussion on how FUS compares to Gamma Knife, based on current knowledge.
  - The level of evidence for safety and efficacy for Gamma Knife treatments for movement disorders is not at the same level as FUS at this time. FUS treatment has been carried out in a multicenter, randomized, placebo-controlled study, which has not been done with Gamma Knife. Another advantage for FUS is the real-time monitoring that is not possible with Gamma Knife procedures. It can take months to see any benefit or side effects, including radiation necrosis, with Gamma Knife procedures. There was disagreement among participants on whether Gamma Knife procedures are a viable option for movement disorders.
- Attendees discussed how to incorporate FUS into their practices with both colleagues and patients.
  - It can be difficult to advocate for FUS in a center where there is a great deal of experience with DBS. In those that have treated a few patients with FUS, some of the patients didn't respond and ended up getting DBS. The durability of FUS for treatment of PD is unknown. It is also technically difficult to perform pallidotomy compared to thalamus. Most patients are bilateral, so the opposite side will need treatment at some point.
  - Currently it is important to select ideal candidates such as those that are asymmetrical. Younger patients are more interested in FUS because they are not ready to commit to DBS. Patients are attracted to less invasive options, so using terms like 'less predictable' and 'wider variability' can lessen expectations with FUS. DBS has been refined over decades and results are more predictable.
  - It is reasonable to consider bilateral treatment at some point in the future for MRgFUS after safety and efficacy of unilateral treatment has been demonstrated.

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BBB Applications and Experiences

There were presentation on BBB opening with FUS in human patients and the potential for the use of this technique in patients with PD.

Nir Lipsman from Sunnybrook Health System discussed BBB opening with MRgFUS in human patients. FUS is a disruptive technology:

- Clinical Care
  - For example, a new 'standard-of-care' for patients with medically refractory tremor
- Patient Experience
  - Less invasive, well tolerated, patients are inquiring about this
- Resource Utilization and Cost
  - Single night stay, small team, image-based treatment, potential for 'same-day' surgery
  - No implant or programming, recurring costs or resources

For FUS-based treatment of ET, the first research application was submitted, and the device received regulatory approval from both Health Canada and the FDA within 5 years. This process usually takes 15 years. Along with this success, research into FUS for brain applications has increased exponentially over this same time frame. At Sunnybrook Research Institute at the University of Toronto, FUS is being explored for a variety of brain applications including neurodegenerative diseases, movement disorders, cancer, and mental health. Lipsman described the FUS clinical trial pipeline at Sunnybrook. There is a specific process that goes from multi-disciplinary discussion and working groups to protocol development, Health Canada submission, and finally to patient treatment in about 9 to 12 months. One advantage of this process is that institutional review board (IRB) members become more familiar with FUS as the number of protocol submissions increases.

A phase I study for safety and feasibility of BBB opening for chemotherapy delivery in patients with glioblastoma was carried out at Sunnybrook with 6 patients. Multiple sonications were performed in 3x3 grids within the tumor and at margins. A 4 µl/kg dose of Definity microbubbles were injected prior to sonication and patients were treated with temozolomide about 30 minutes prior to FUS. This study provided sufficient safety data to proceed to a phase II study that will recruit 10 patients that are undergoing maintenance temozolomide. FUS BBB opening with temozolomide targeting the tumor rim and resection cavity and will occur on day 1 of each cycle for 6 cycles. Primary outcome measure is safety.

Sunnybrook is also actively involved in clinical research for FUS and AD. A phase I study of BBB opening in AD for safety and feasibility with a two-stage design (single sonication followed by repeated openings). Preclinical data suggested that FUS BBB opening alone could clear beta-amyloid,[24] so the phase I trial did not include the addition of any therapeutic agents. The target was a 5x5 mm (stage 1) and a 5x10 mm (stage 2) area in the white matter of the dorsolateral prefrontal cortex. There are still a lot of technical aspects of the procedure that need refining based on preliminary results. The procedure was well tolerated with no

serious adverse events.[34] One of the biggest issues was the requirement for head shaving, particularly in women. This led to an ongoing phase IIa study in 30 patients with mild-to-moderate AD. There will be three treatments, separated by 2 weeks. Primary outcome measure is safety. A phase 1 study for BBB opening in ALS is also ongoing to evaluate safety. In conclusion, BBB opening in human patients can be done safely, repeatedly, and reversibly. Technical challenges exist for both high- and low-frequency applications. Designing trials for efficacy will not be straight-forward. It is also key to have good working relationships with oversight bodies (federal and local). FUS for BBB opening is of great interest to patients to deliver less risk without sacrificing benefit.

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Jose Obeso from HM CINAC discussed the potential for FUS treatment of PD. PD can be modified by drug treatment (L-DOPA) and surgical options (DBS in the STN and GPi). There are certain kinds of symptoms that can be treated with GPi surgical lesioning, i.e. certain gait disturbances. When considering FUS treatment for PD, there remains the question of the best therapeutic option. The hallmark of PD is damage to the dopaminergic neurons of substantia nigra (SN), and α-synuclein containing inclusion bodies (Lewy pathology) in the surviving neurons, resulting in characteristic motor impairment. Younger patients (< 55 years of age) are preferred for pilot studies due to the complexity of disease in older patients. Additionally, the idea of functional restoration in the PD brain was considered. There is enhanced cortico-striatal activity, and enhanced glutamatergic release throughout the brain. Preclinical research suggests that DBS in the STN can reduce neuronal loss in the SN. However, in humans this is not the case because they have usually had PD for over 15 years and the disease has progressed too far. The focality at the beginning of PD is likely cortico-putamen activity that impinges on the dopamine synapse. This results in presynaptic release of αsynuclein and calcium, and may lead to degeneration. Lesions in the STN might act on this pathway. Obeso mentioned that a trial will be conducted for BBB opening with FUS in patients with PD dementia. However, there remains a lot of unknowns for other FUS applications. Younger patients have many options, and before BBB opening is conducted in that population, some demonstration of efficacy will be required. Non-human primate (NHP) models will be useful for answering questions of potential brain areas that might respond to lesions.

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Discussion from Presentations

- There was a question on whether FUS alone could treat AD.
  - It is important to also look at nontraditional ideas to create new therapeutic options for patients. It is also important to work in a step-wise fashion. Future studies could also deliver therapeutics with FUS and BBB opening, but demonstrating safety and working out the technical challenges is the current state of the field.
- There was some discussion on microglial activation. Preclinical work suggests that microglial activation peaks around day 4, and returns to baseline within 15 days. This research supports the 2-week treatment regimen planned for AD.

- A participant asked about metabolic imaging in the clinical trials. There was no metabolic imaging performed due to limitations on radiation dose, but it would be interesting to study.
- The patient tolerance of the overall experience was discussed. So far, patients have tolerated treatment well. There is a very involved patient consent processes so that they know what to expect at each step of the process.

Overall Discussion and Evidence Gaps

Open Discussion

The participants discussed how to move forward with FUS for the treatment of PD.

Regions of Interest for Lesions

- Striatum
- SN
- STN
  - There is a planned trial to lesion this area in patients with PD.

BBB Opening and Therapeutic Agents

- BBB opening combined with a therapeutic targeting the accumulation of α-synuclein.
  - There was discussion on this option. It would be hard to measure how much was entering the brain because there is no good marker for deposition in the brain that could be used post-mortem.
- BBB opening combined with glucocerebrosidase (GBA)-enhancing therapy.
- BBB opening combined with neurotrophic factors such as neurturin.
  - Clinical trials of neurotrophic factors, such as neurturin, did not show efficacy in clinical trials.
  - These trials likely failed because therapeutic amounts of neurotrophic factors were not delivered to the brain. Current work is underway using convection enhanced delivery, and it would be interesting to determine if FUS could also increase delivery to regions of interest in the brain.
- BBB opening combined with adeno-associated viral (AAV) vectors.
  - Changing the output of the STN from dopaminergic to glutaminergic using AAV vectors and suggested similar outcomes to DBS. This might serve a neuroprotective benefit in patients.
  - Other regions of the brain might of interest for AAV vectors such as the locus coeruleus.
- BBB opening combined with experimental antibodies (anti-amyloid or anti-α-synuclein).
  - Several trials are already underway with antibody treatment for patients with PD; these could potentially be combined with FUS for targeted delivery.
- Combining FUS with already approved agents may face fewer regulatory hurdles, and consideration should be given to therapeutics that are already FDA approved.
  - A participant mentioned that one approach is to first obtain regulatory approval for the device, and the path forward to testing experimental therapeutics will be easier.
- The participants agreed that mesenchymal stem cells were NOT good a good candidate for FUS delivery. There is little known about them and the preclinical data does not suggest safety and efficacy for the treatment of PD.

- An attendee mentioned that researchers should give some consideration to overall costs of the agents combined with the technology. Procedures with high initial costs will be difficult to implement in the real world.

Clinical Biomarkers

- There is a need for outcome measures of efficacy in PD.
- Consideration should be given to dopaminergic neuronal markers (such as TH and dopamine transporter (DAT)) as a predictor of clinical outcome
  - There was some disagreement among participants on the utility of these markers and that they don't always correlate to clinical improvement.
- Markers of inflammation were also mentioned as interesting possibilities, but the direct correlation to clinical outcomes is unknown.

Clinical Outcome Measures

- Participants discussed the utility of assessing motor function (UPDRS) and/or other measures such as mood and cognition as outcome measures for FUS interventions

Patient Selection

- Good candidates for FUS may not reflect the entire spectrum of the PD population, such as those older than 70 years of age.
- Patients with early and/or mild disease (around 3 years post-diagnosis) without neurodegeneration are good candidates as measure of neuronal repair could be used as clinical endpoints for improvement.
  - FUS may have a role for treatment of symptoms that don't respond to L-DOPA treatment such as retropulsion.
  - High-risk patients that have more aggressive disease might be more willing to participate in clinical trials.
- Participants agreed that patients with GBA mutations should be considered

Outcomes and Next Steps

Participants were encouraged to reach out to the Foundation with any research ideas or project proposals in this area. The FUS Foundation will continue engagement with this community to move the research forward.

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Abbreviations

AAV	Adeno-associated virus
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
BBB	Blood-brain barrier
CUSE	Comb-push ultrasound shear elastography
DAT	Dopamine transporter
DBS	Deep brain stimulation
DTI	Diffusion tensor imaging
ET	Essential tremor
FDA	Food and Drug Administration
FGATIR	Fast gray matter acquisition T1 inversion recovery
FUS	Focused ultrasound
GMA	Glucocerebrosidase
GDNF	Glial-derived neurotrophic factor
GPi	Internal globus pallidus
IRB	Institutional review board
MRgFUS	Magnetic resonance guided focused ultrasound
MRI	Magnetic resonance imaging
NHP	Non-human primate
PD	Parkinson's disease
STN	Subthalamic Nucleus
TH	Tyrosine hydroxylase

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