Non-invasive Neurosurgery using MR guided Focused Ultrasound
About InSightec

- Founded in 1999, headquarters Haifa, Israel
- US offices in Dallas, Texas
- Asian offices in Beijing, China, and Tokyo, Japan
- Develop Focused Ultrasound therapy for non invasive therapy under MR guidance and intraoperative feedback and control
- Over 30 ongoing clinical trials conducted in various applications - Uterine Fibroids, Breast Cancer, pain palliation of Bone metastases, Prostate, Liver, Brain
- Over $150M invested in technology and clinical R&D
- Over 35 patents and other intellectual property
What is MR guided Focused Ultrasound Surgery?
Key Enabling Technologies

MR guided Focused Ultrasound Surgery (MRgFUS) - breakthrough technology that combines:

- **High Intensity Focused Ultrasound treatment**
  Heats and ablates targeted tissue, non-invasively

- **Magnetic Resonance Imaging Guidance**
  Enables visualization of patient anatomy to define the target and guide a personalized ultrasound beam to intended target

- **MR Thermal Imaging monitoring and control**
  Enables real time temperature measurement in tissue to control progress of the treatment for safety and efficacy
Closed Loop Feedback and Control

Image Registration → Treatment Planning → Closed Loop Feedback

Patient Preparation → On-Table Outcome Assessment

Caution: Investigational Device. Limited by United States Law to Investigational Use.
InSightec Body System
ExAblate® OR

Uterine Fibroids:

- First and only FDA approved focused ultrasound therapeutic application
- More than 7000 treatments
- Up to 36 months follow-up

The body system incorporates FDA validated key concepts:

- **Targeting based on MR images of patient while in actual treatment position**
- **Embedded safety features**
- **Real-time temperature feedback**
- **Closed loop control of treatment outcome**

Ongoing clinical research in oncology applications:

- **Pain palliation of bone metastases and myeloma, prostate and breast cancer**
Applying Focused Ultrasound Surgery to the Brain?
Treating Brain Tissue with MRgFUS

Translate approved technology to bring potential benefit in Neuro-applications:
- Tumor Ablation
- CNS functional diseases for Neurological disorders treatment
- Neurovascular applications
- Localized & reversible BBB opening

Although the safety of this technology is demonstrated in other organs it should be proven in the brain:
- Non-invasive
- Highly localized damage
- No ionizing radiation effects
- No long term toxicity
- Immediate biophysical response
Research Programs and Partners
Functional Neurosurgery Program

Brain Tumors Program

Stroke Program

Targeted Drug Delivery Program
Non-invasive tissue ablation to replace resection or invasive ablation (RF/Laser)

**Reduce Risks**
- Minimize brain tissue damage caused by penetration
- Avoid local bleeding and infraction risks
- Benefits of non-invasive procedure [infection, open surgery, anesthesia]

**Improve outcome**
- Prevent intraoperative tissue displacement
- Targeting accuracy (closed loop feedback and control)
- Localize effect limited to target tissue.

**Better accessibility to targets**
- No trajectory constraints (tissue loss and planning limitations)
Non-invasive Thalamotomy - Clinical Results

- Using MRgFUS to perform Deep Brain Ablation
- Clinical feasibility study (12 patients) to evaluate safety and initial efficacy in patients with chronic, therapy-resistant neuropathic pain
- Maximum focal temperatures of 56° to 62°C are well reached to produce tissue coagulation
- Only small perifocal edema in the acute phase, not visible at 1 to 3 months control MR imaging
- The lesion size decreases over time and results at 1 year follow-up in ~10-20mm³ in size
- Mean pain relief:
  - 49.4% at 3 month follow up (12 patients)
  - 57.9% at 1 year follow up (7 patients)
High Intensity Focused Ultrasound for Non-Invasive Functional Neurosurgery
High Intensity Focused Ultrasound for Non-Invasive Functional Neurosurgery


Immediately after Treatment

48h Post Treatment

T2w

Diffusion

9.5mm

4M Post Treatment

1Y Post Treatment

T2w

5.5mm

5.6mm

6.6mm

ExAblate® Neuro
Brain Tumors

Safety study for non-invasive treatment of GBM and brain metastasis through intact skull

**Status**
- Treated 4 of 10 patients in FDA approved trial
- Thermal focus demonstrated
- Validated safety on skull heating
- No clinical or neurological deficit during or after procedure
- 4th patient developed a delayed hemorrhage resulting in intra-ventricular hemorrhage and eventual death at 6 days post treatment
- Case being analyzed clinically and technically
- Protocol modified to include patients with lower risk of bleeding; system safety tools enhanced

Ischemic Stroke – Preclinical Research

Non-invasive clot lysis to restore flow

**In Vitro Clot Model**
- Human blood clots
- Pulsating flow dynamics
- Ex-vivo human skull

**Initial Results**
- High power sonications → complete clot lysis in target focus
- Low power sonications → clot weight reduced providing recanalization

**Status**
- Undergoing pre-clinical research to optimize treatment parameters and collect data to start phase -1 study
Non-invasive clot lysis to enable clot evacuation

**In Vitro Model**
- Pig blood naturally clotted
- Lysis by FUS through ex-vivo human skull

**In Vivo Model**
- Pig model with clot implanted in brain
- Clot lysed in-vivo through ex-vivo human skull
- Apply FUS under MR monitoring to visualize liquefaction effect

**Research Status**
- Undergoing pre-clinical research to collect data to start phase-1

*Courtesy of Dr. S. Harnof, Sheba Medical Center, Israel*
Targeted Drug Delivery – Preclinical Research

- Extensive literature on BBB disruption with FUS in-vivo
- Localized, reversible, non-invasive
- Technically shown in preclinical studies
  - Successful delivery of MR contrast agents, Trypan blue, antibodies and chemotherapeutic agents into mouse brain
  - Transient BBB disruption possible – MR signal intensity near baseline at 2 to 5 hours post FUS treatment
  - Develop clinical hypothesis and select suitable drug
  - Perform basic research animal studies to show safety and potential efficacy

**MR signal intensity over time**
Hynynen, NeuroImage 2005
For more information, visit our website

www.insightec.com