FOCUSED ULTRASOUND FOUNDATION

Brain Applications of Focused Ultrasound

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History of Ultrasound

1800 Piezoelectric effect: Pierre & Marie Curie

1881 Converse Effect: Gabriel Lippmann

- Mathematical derivation: Fundamental thermodynamic principles
- Pierre Curie & Paul Langevin: Ultrasound

1906 Pierre Currie dies

1911 Scandal: Paul Langevin & Marie Curie

- Nobel Prize x 2: French Royal Academy

1914 Paul Langevin

- Sonar
- Biological effect: Fish

University of Paris

Radioactivity

Ultrasound

Sonar

Medical imaging
- X Ray
- Ultrasound

Image guided surgery

Radiotherapy

Therapeutic ultrasound

Focused Ultrasound in Neurosurgery

1910s	*Langevin:* Fish
1926	*Wood & Loomis:* Biological effects unicellular organisms
1940s	*Lynn et al:* Liver
1940s	*Fry Bro's:* Animal Brain
1950s	*Leksell:* Lesions for pain through craniotomy
1950s	*Frey & Meyers:* Parkinson's disease through craniotomy
1959	*Nelson, Lindstrom, Haymaker:* Lobotemy
1980s	*Guth Kelch*: Hyperthermia for residual gliomas
1990s	*Ram:* MR guided ablation brain tumor through craniotomy
2000s	*Jolesz:* Brain tumors transcranial
2000s	*Jeanmonod & Martin:* Thalamotomy neuropathic pain transcranial
2010	*Elias:* Essential tremor
2011	*Jeanmonod:* Parkinson's disease
2012	*Martin:* Brain tumor

Minimally Invasive: Early Attempt

1950

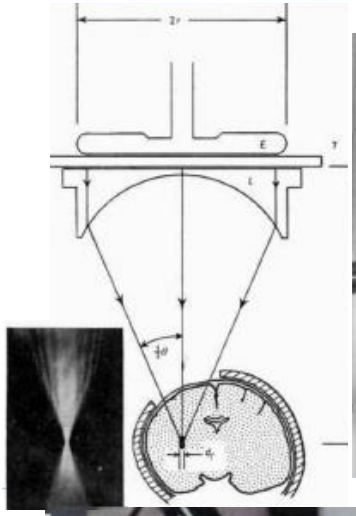
Leksell's approach

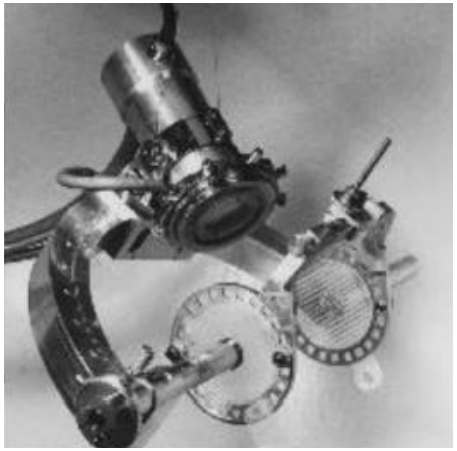
Minimally invasive

- Introduces intersecting beams of focused ultrasound
- Abandonment of technique
- Skull defect, imaging

Search for way through intact skull

- Ionizing radiation





Next Innovation: Gamma Knife

1967

Non-invasive solutions achieved with Gamma Knife

- Intersecting beams of radiation
- Stereotactic localization

Full Circle

MRgFUS

FUS

FUS Abandoned:
- Skull defocusing
- Lack of imaging

Gamma Knife

Advent of image guided interventions

MRI

Enabling technologies:
- Computer processing
- MRI imaging
- Transducer technology

Focused Ultrasound

Noninvasive, early stage, revolutionary therapeutic technology

Alternative or complement to surgery, radiation therapy, drug delivery

Potential to transform treatment

Improved outcomes, decreased cost

Early Stage

MR 30 years ago

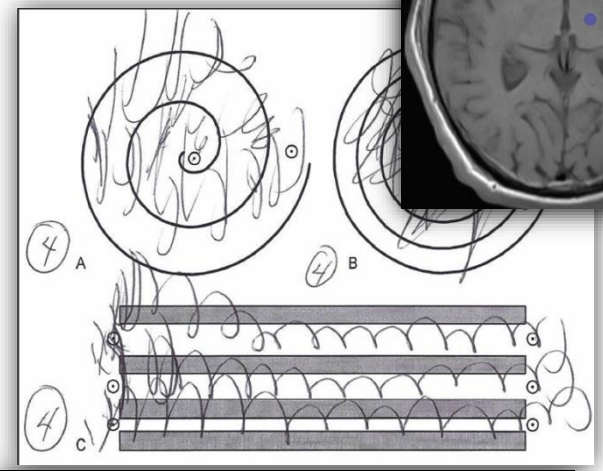
- Unknown
- Revolutionized diagnoses

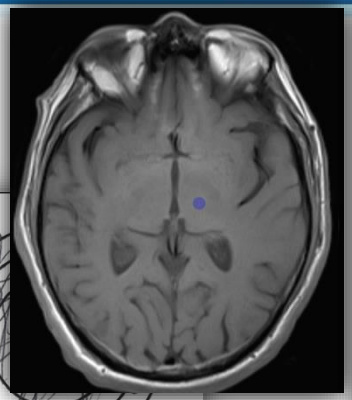
Focused Ultrasound today

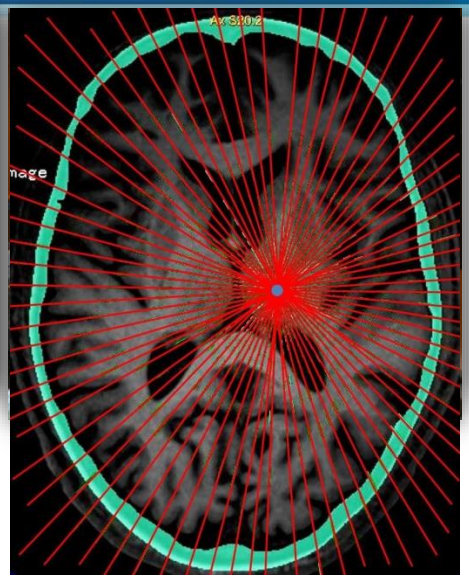
- Unknown; "Medicine's Best Kept Secret"
- Revolutionize therapy

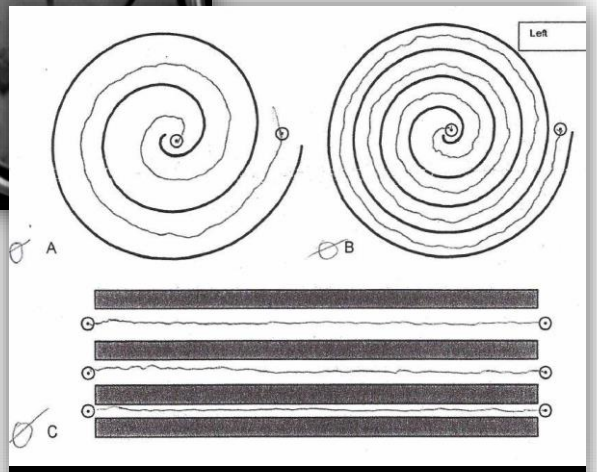
Infancy

Essential Tremor Treatment









No burr holes
No electrodes
No infection
No blood clots
No brain damage

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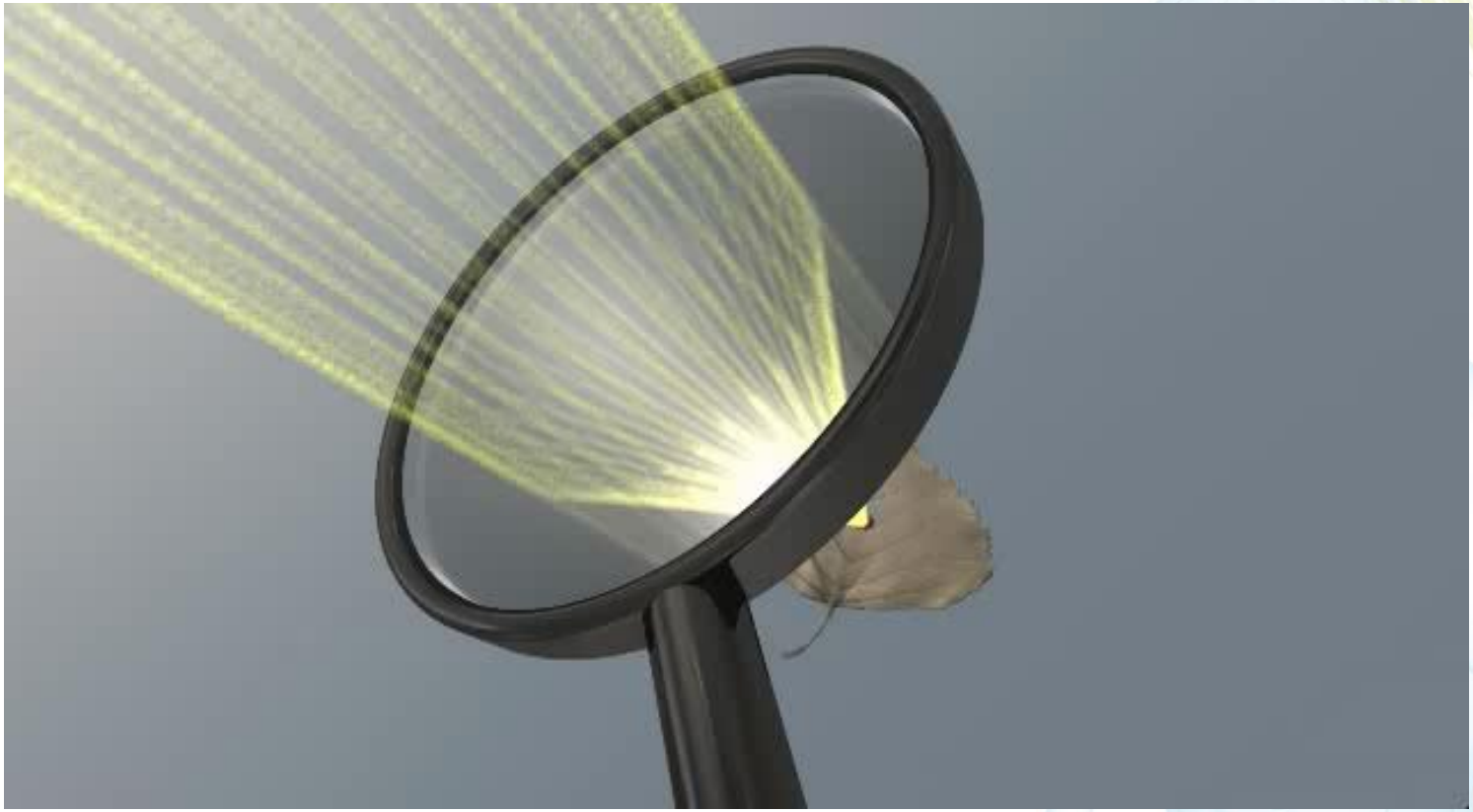
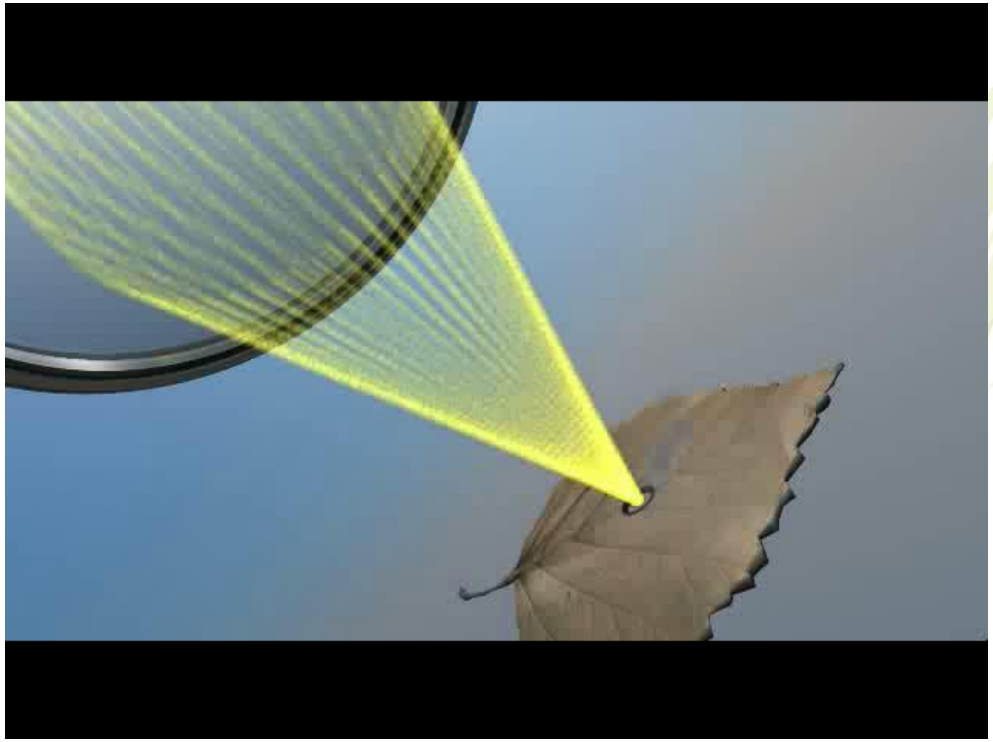
The Principle

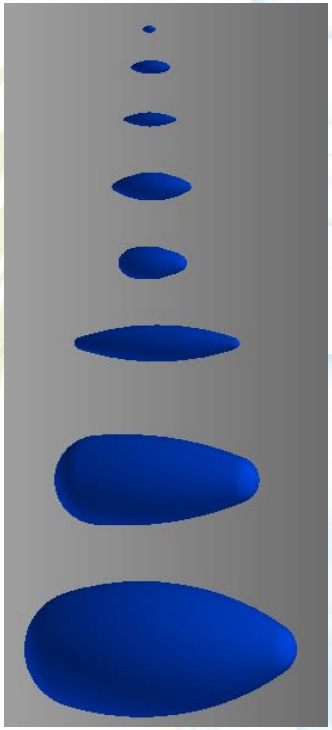


The Principle

Multiple intersecting beams of ultrasound

- Focused accurately (submillimeter)
- Target in body
- Individual beams pass harmlessly through adjacent tissue
- Profound effect at point of convergence

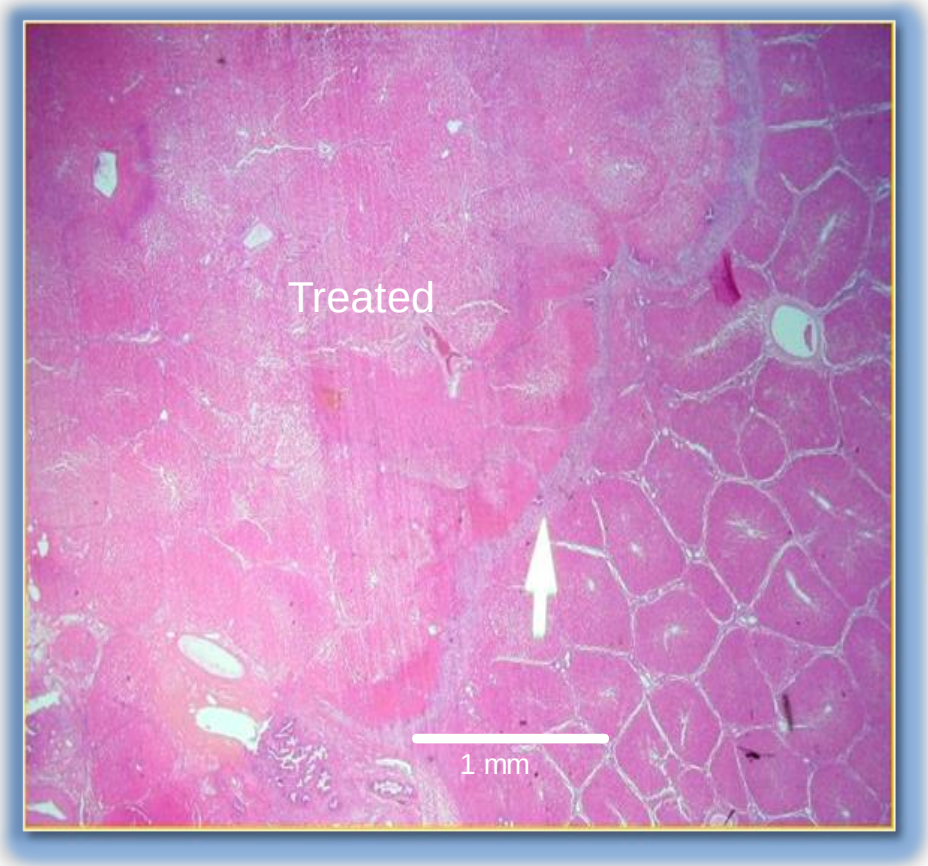




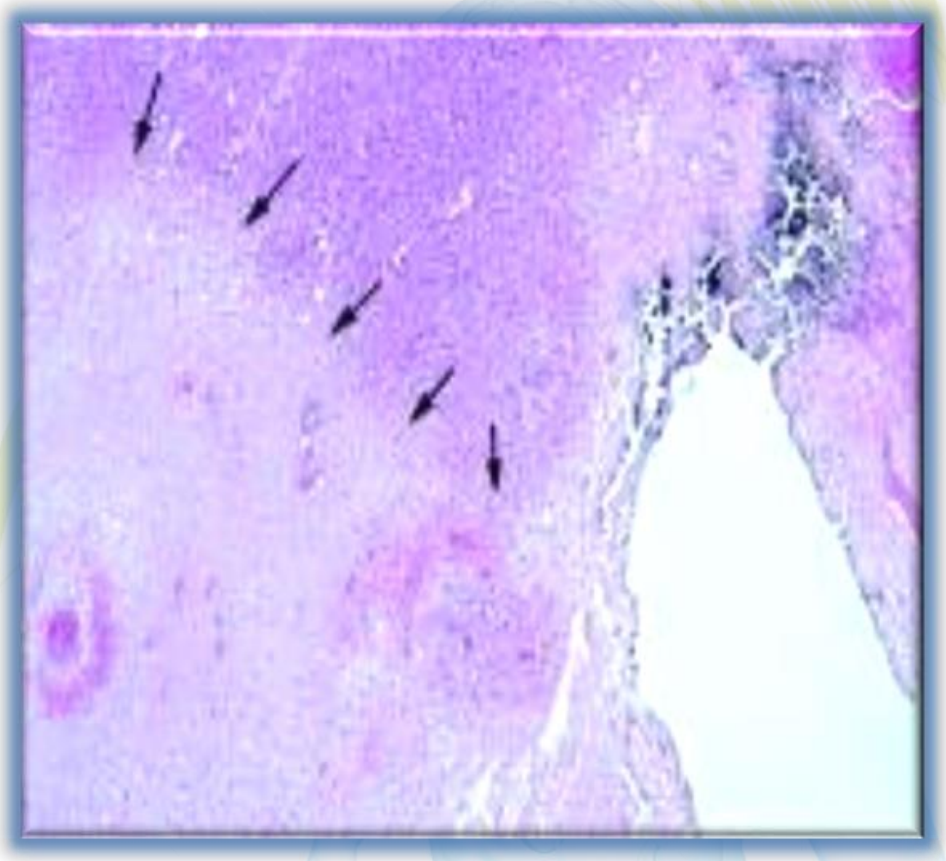
FOCUSED ULTRASOUND FOUNDATION

Adjacent Tissue Sparing

Liver



Brain



Effects at Focal Point

- **Thermal ablation**
- **Histotripsy**
- **Focal drug delivery**
- **Blood brain barrier opening**
- **Immunomodulation**
- **Neuromodulation**
- Radiation sensitization
- Drug activity enhancement

- Amplification of cancer biomarkers
- Dissolve clots: sonothrombolysis
- Coagulate blood vessels
- Vasodilation
- Vasoconstriction
- Stem cell delivery
- Sonodynamic therapy

Variety of effects, variety of disorders

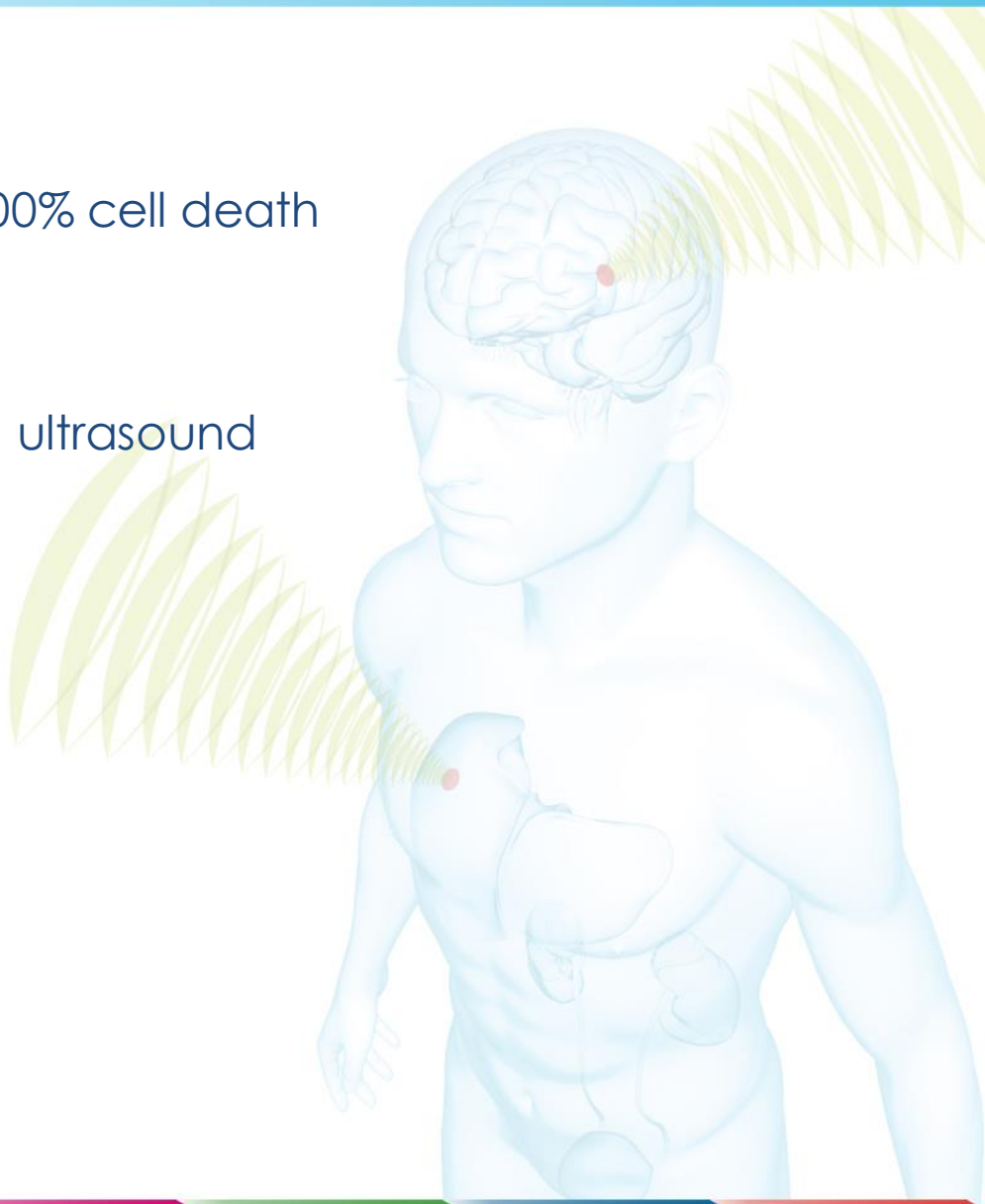
Destroy Tissue

Thermal Ablation

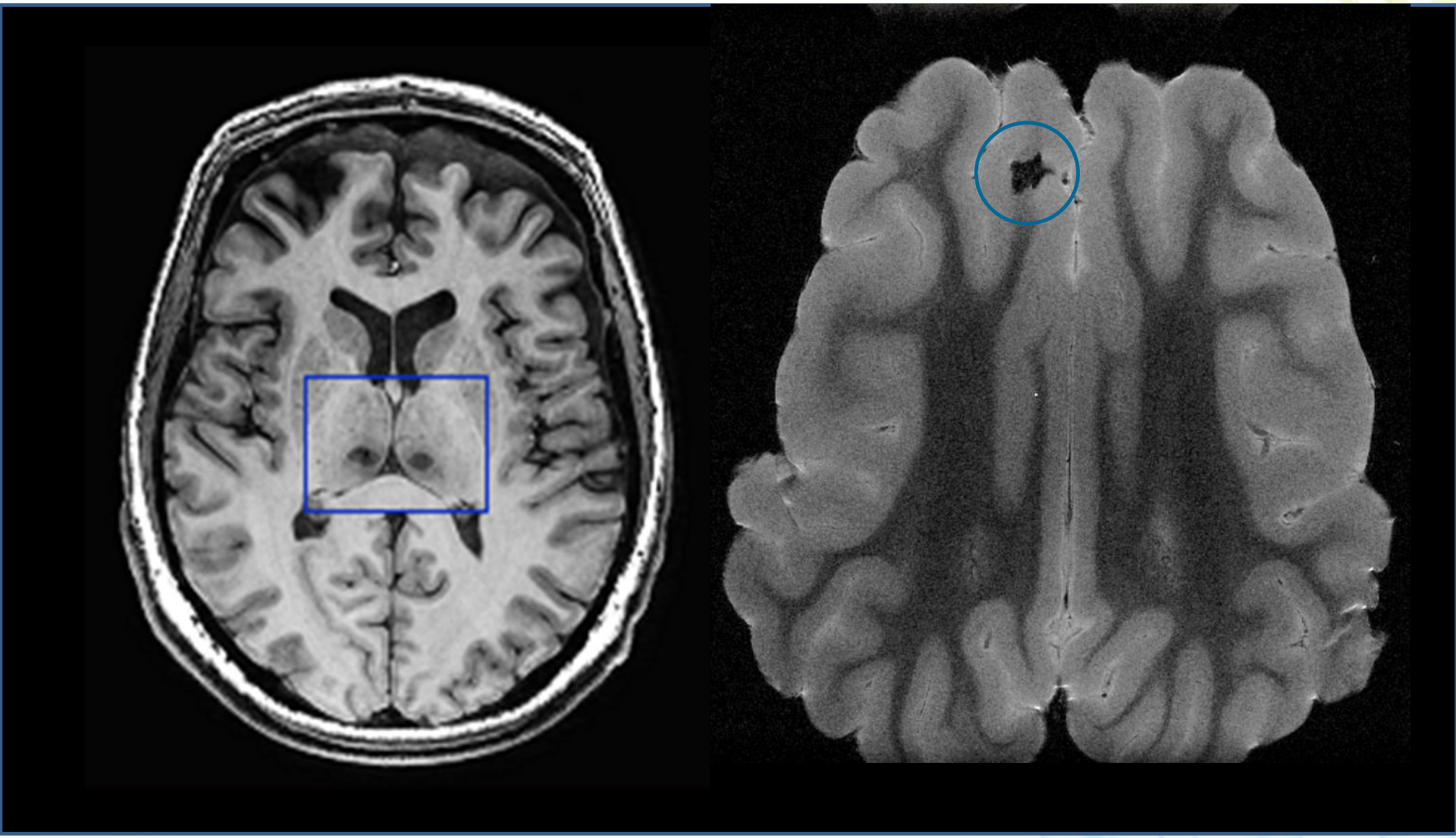
- 130°F (56°C) for 1 second = 100% cell death

Histotripsy

- Disruption of cell membranes, ultrasound



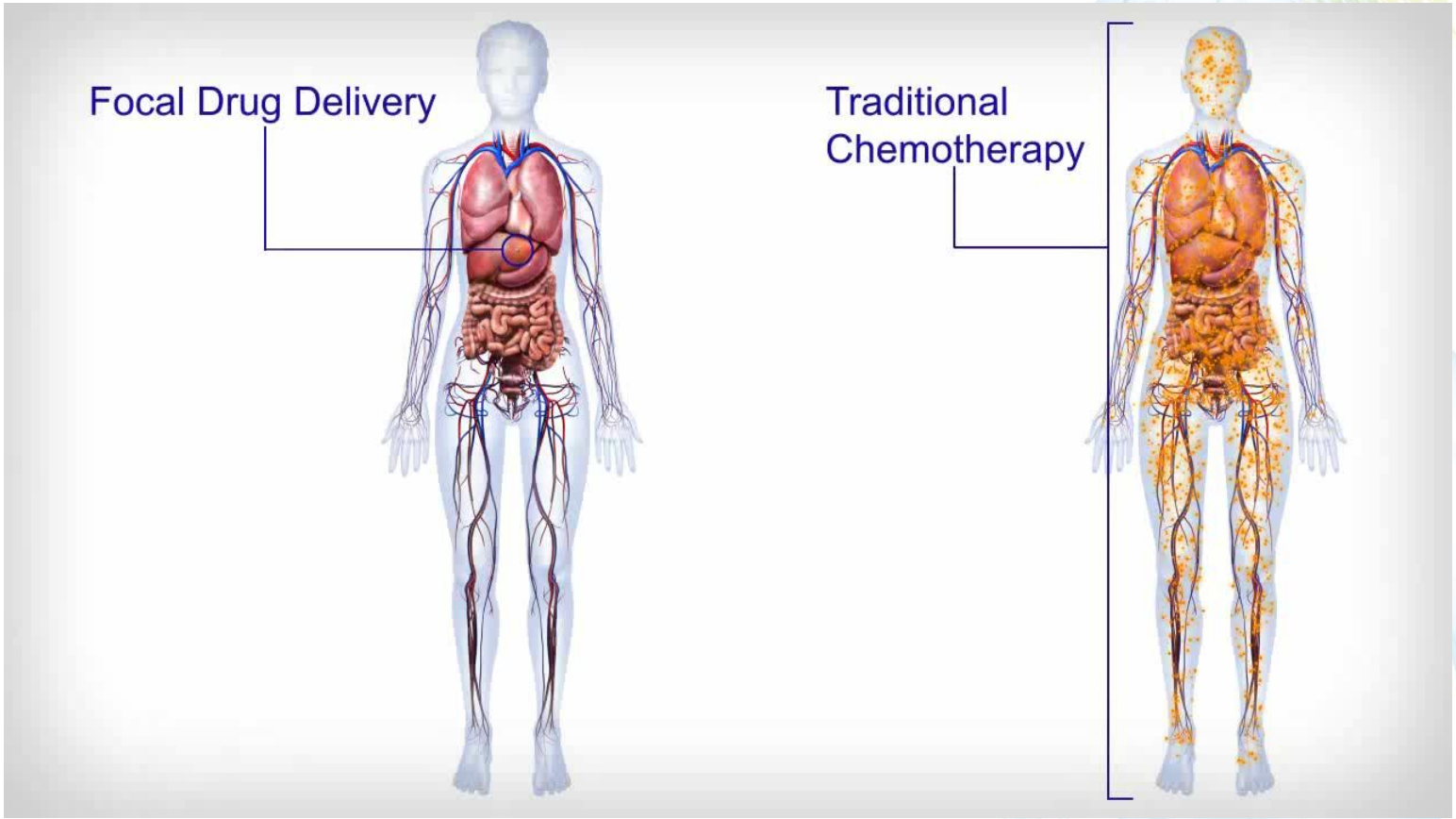
Thermal Ablation vs. Histotripsy



Focal Drug Delivery

Deliver drugs in high concentrations

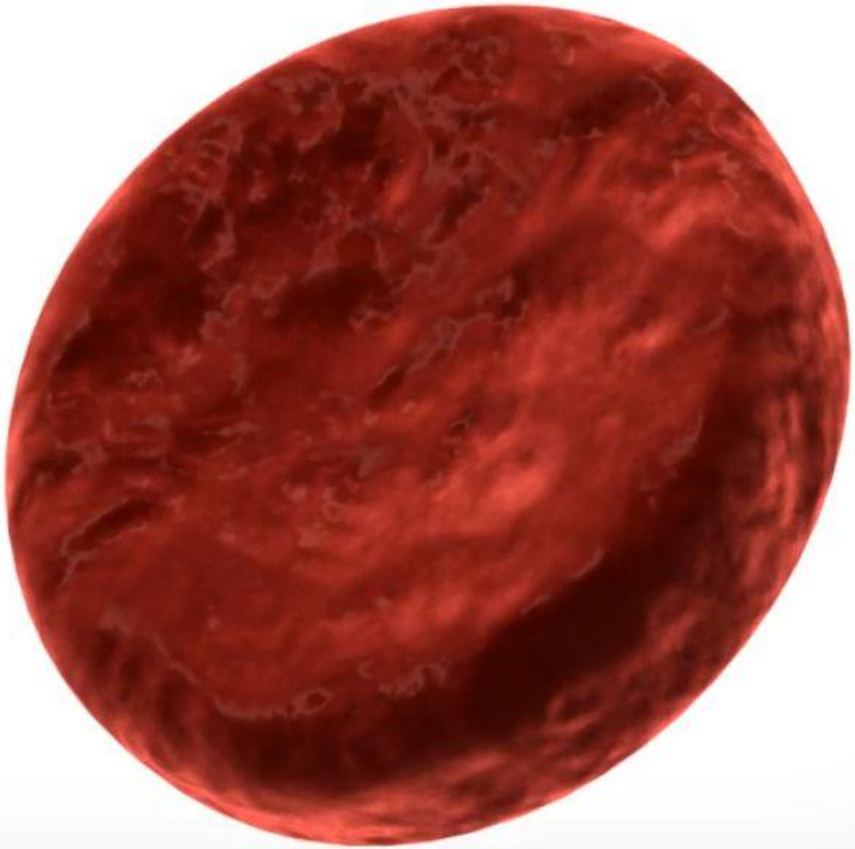
- Precisely where needed, minimizing systemic toxicity



Lipid Microbubbles

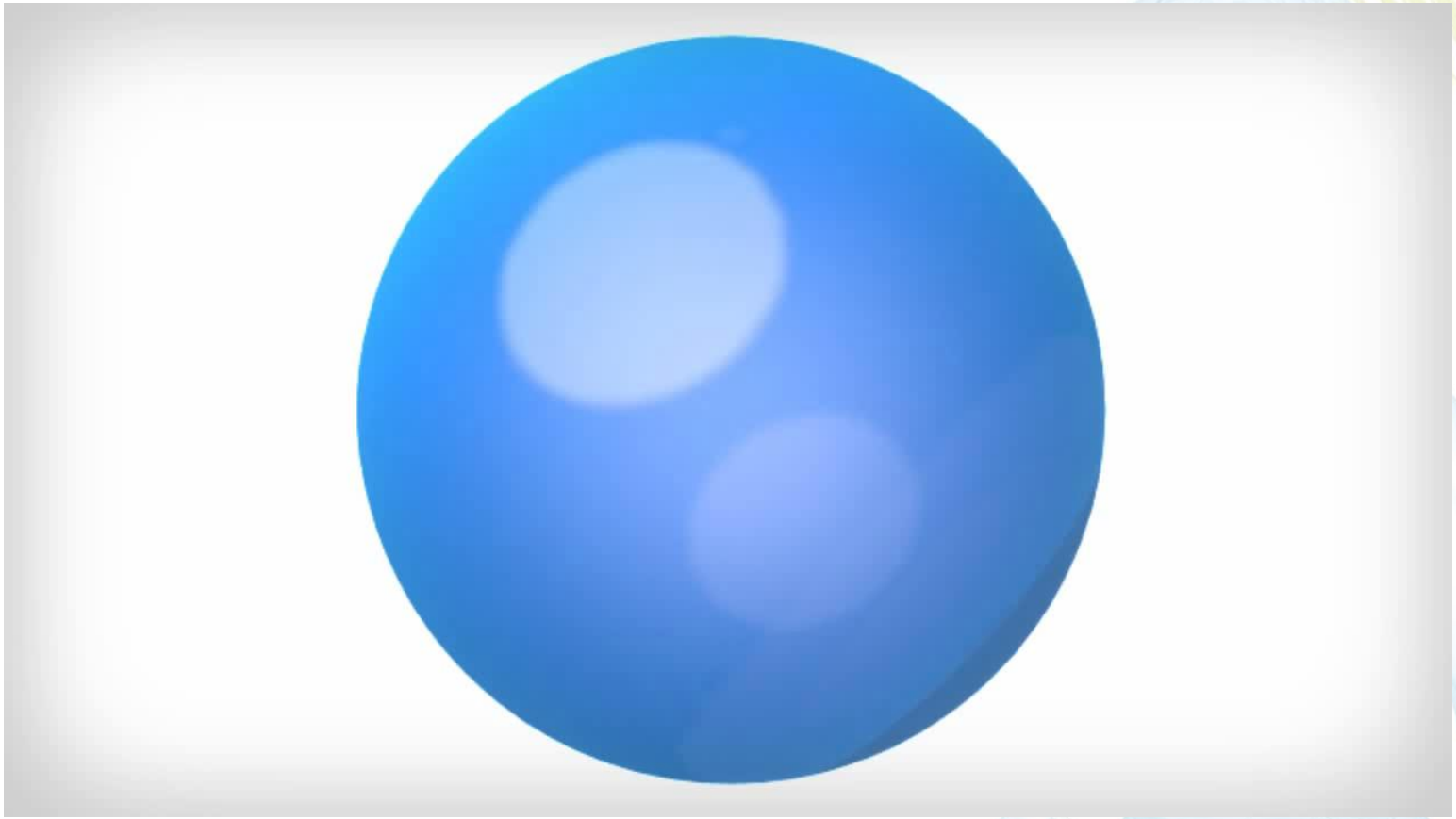
Microbubble

Red Blood Cell

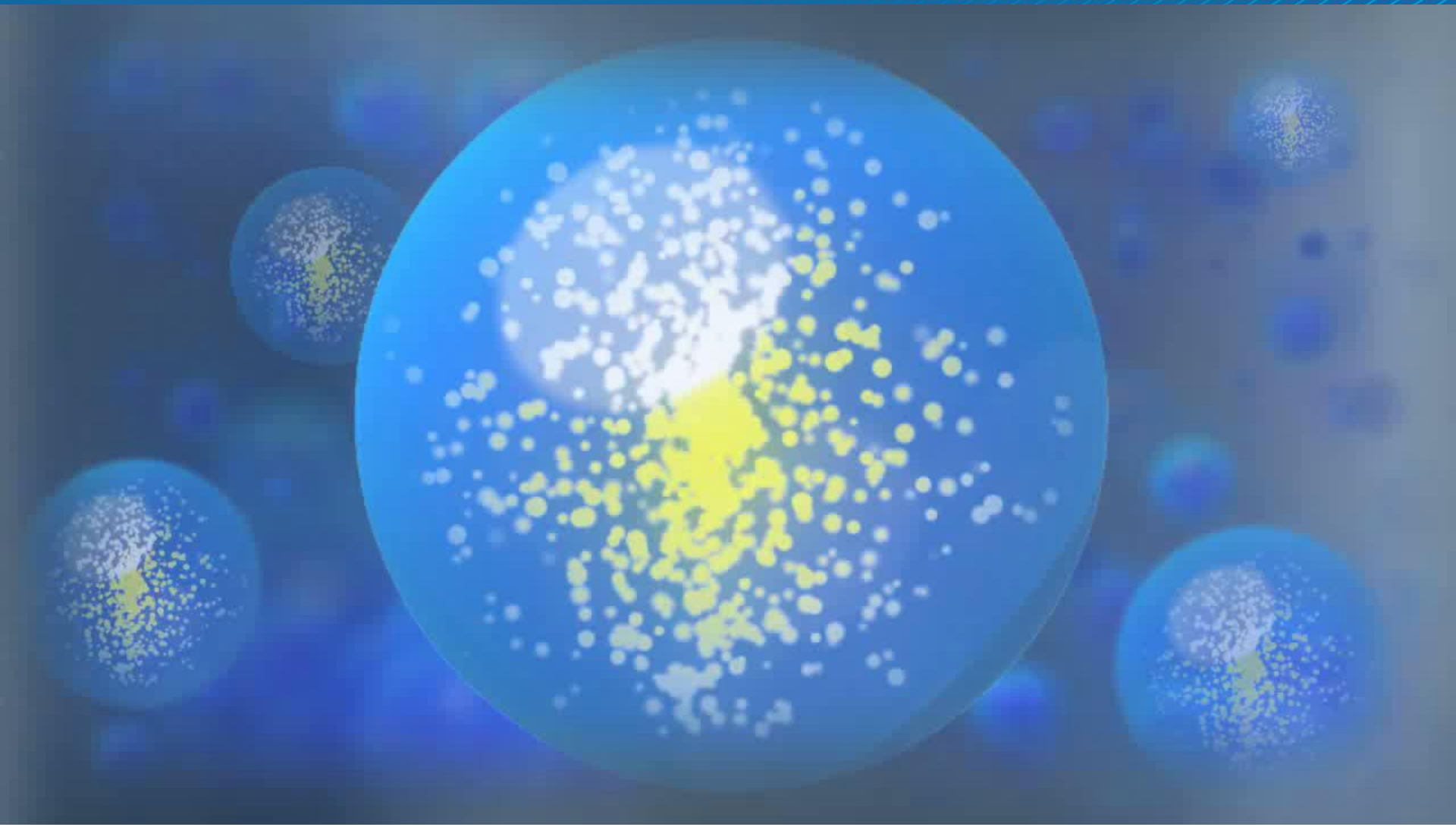


Lipid Microbubbles

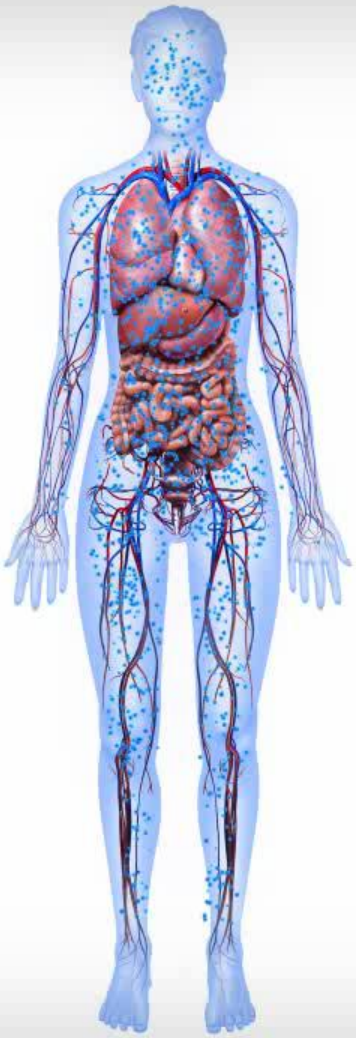
Chemotherapeutic agents, genes, growth factors



Microbubbles Injected



Distribution of Microbubbles



Drugs Released at Focal Point

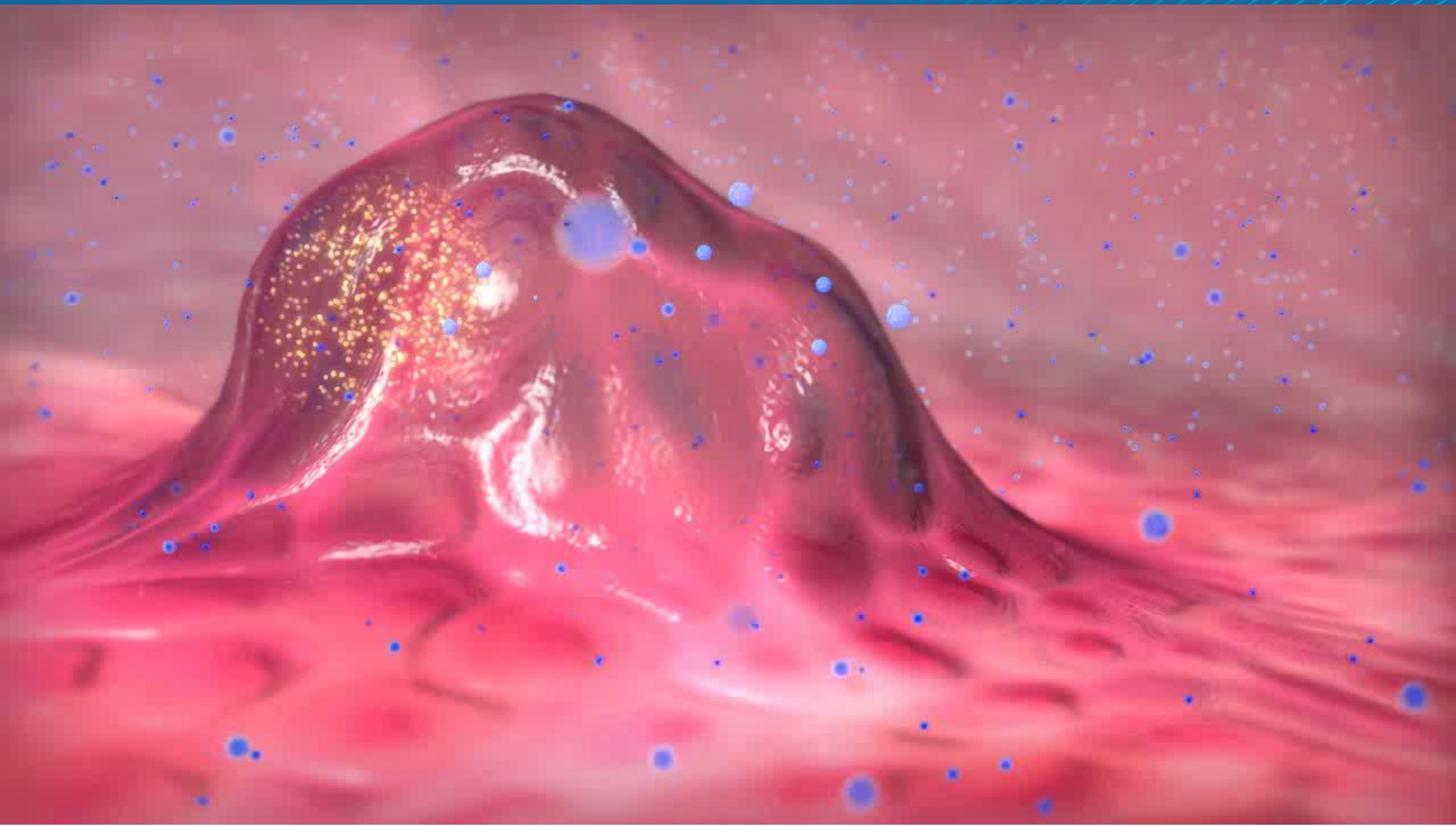
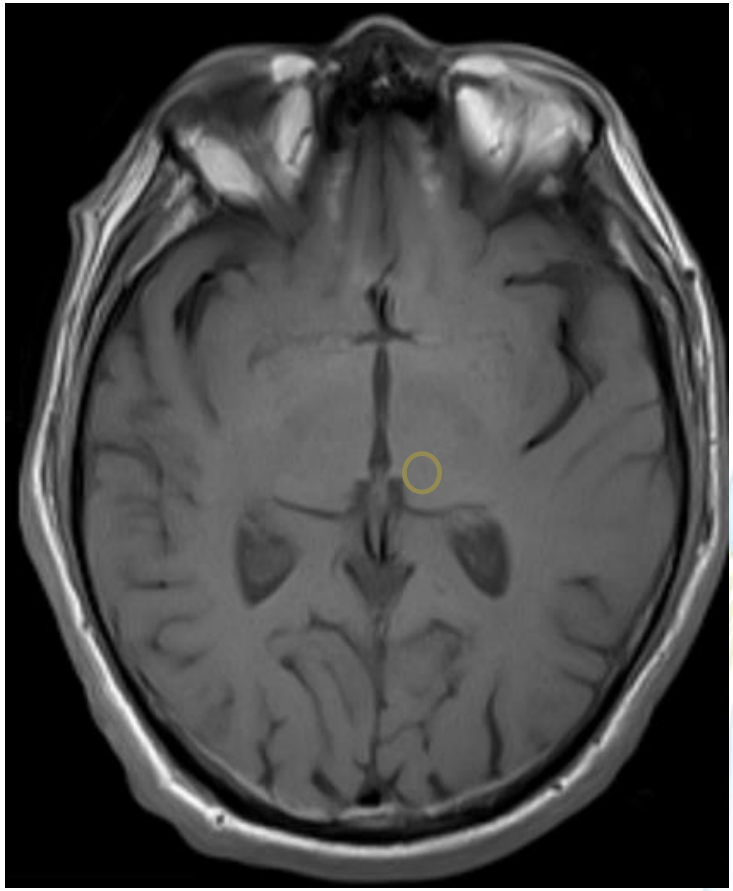
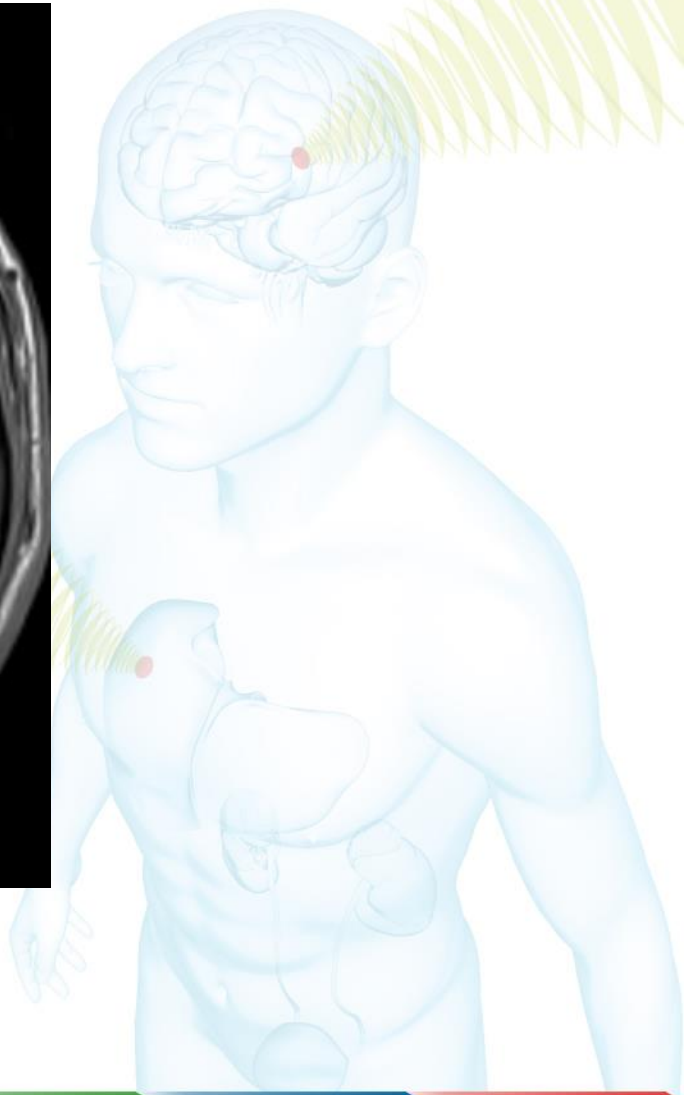


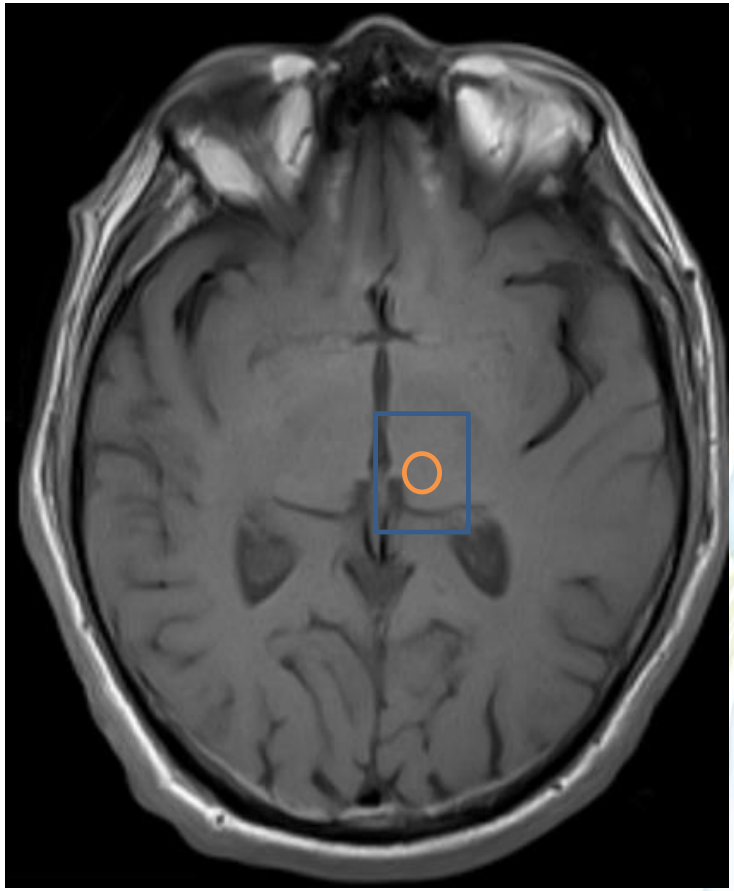
Image Guidance

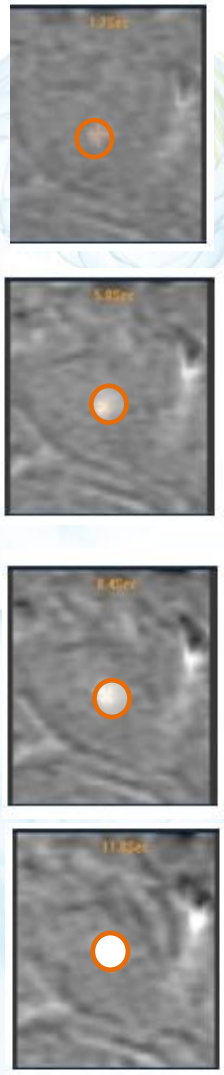




Focused Ultrasound Foundation

Control





Benefits

Single treatment, can be repeated

Immediate and verifiable effect

High precision and accuracy

Real time localization

Higher lesion drug dose, lower systemic effects

No cumulative dose

Benefits

No limitations on lesion size

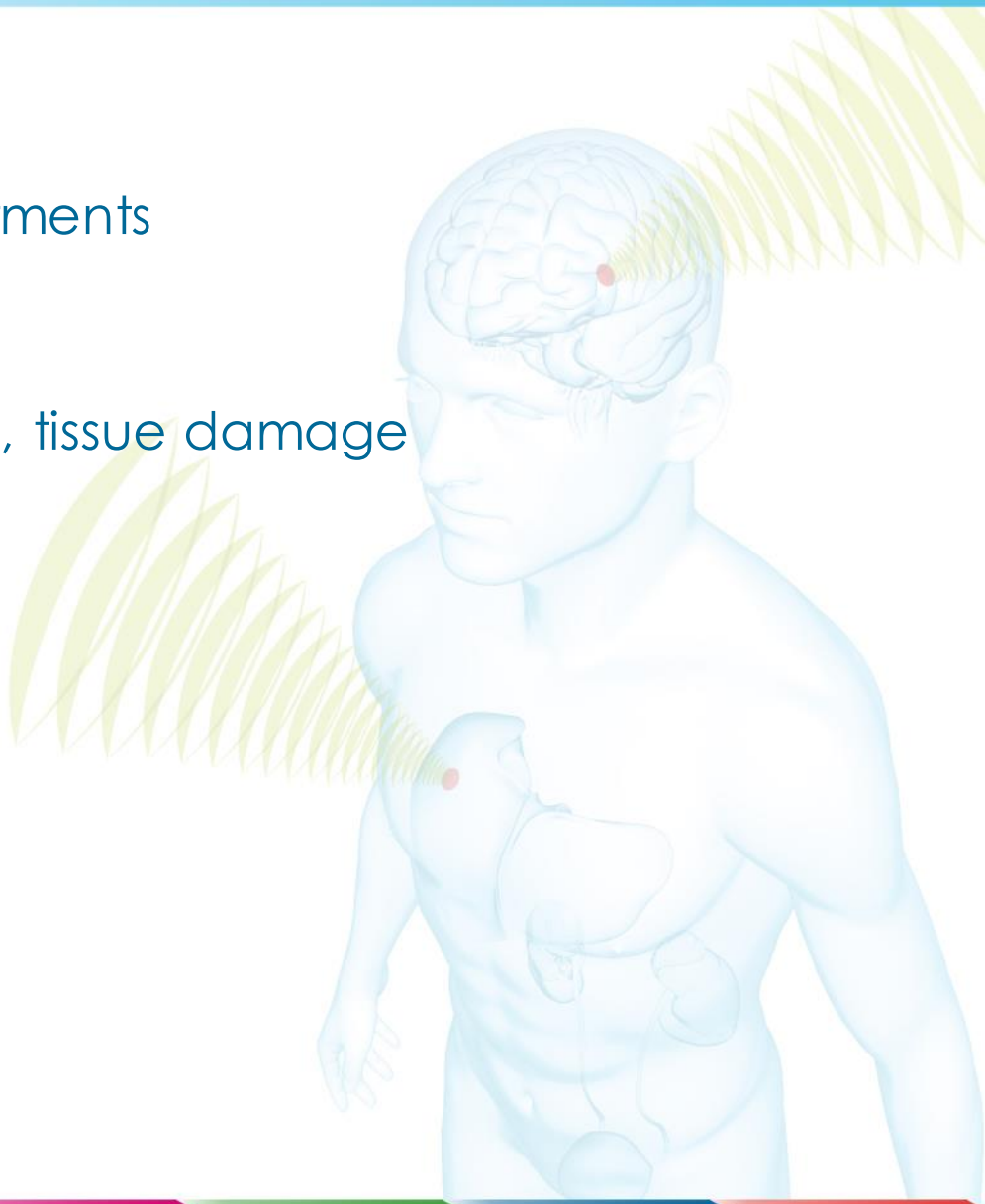
No limitations on number of treatments

No secondary malignancies

Decrease hemorrhage, infection, tissue damage

100% cell death

Sharp margins



Global Development Landscape

Neurological

- Essential Tremor
- Neuropathic Pain
- Parkinson's Disease
- Brain Tumors
- Depression
- OCD
- Alzheimer's Disease
- Epilepsy
- Hydrocephalus
- Multiple Sclerosis
- Stroke
- Traumatic Brain Injury
- Trigeminal Neuralgia
- AVM's
- Cancer Pain

Musculoskeletal

- Back Pain
- Osteoid Osteoma
- Osteoarthritis
- Disc Degeneration
- Muscle Atrophy
- Sacroiliitis
- Spinal Cord Injury
- Spinal Tumors

Oncological

- Bone Metastases
- Prostate Cancer
- Breast Cancer
- Kidney Cancer
- Liver Cancer
- Pancreatic Cancer
- Soft Tissue Tumors
- Brain Tumors
- Pediatric Neuroblastoma
- Head & Neck Cancer
- Lung Cancer
- Ovarian Cancer Bladder Cancer
- Colon Cancer
- Esophageal Cancer

Women's Health

- Uterine Fibroids
- Breast Fibroadenomas
- Uterine Adenomyosis
- Tubal Pregnancy
- Fetal Surgery
- Ovarian Cancer
- Polycystic Ovarian Syndrome

Cardiovascular

- Hypertension
- Atherosclerosis
- Atrial Fibrillation
- Deep Vein Thrombosis
- Heart Block
- HLHS
- Peripheral Artery Disease
- Septal Perforation

Urological

- Prostate Cancer
- Kidney Cancer
- Benign Prostatic Hyperplasia
- Acute Kidney Injury
- Acute Tubular Necrosis
- Ureterocele
- Bladder Cancer

Endocrine Disorders

- Thyroid Nodules
- Diabetes
- Obesity

Miscellaneous

- Hypersplenism

Global Development Landscape

Conceptual

AVM's
Bladder Cancer
Cancer Pain
Colon Cancer
Depression
Esophageal Cancer

Preclinical

Acute Kidney Injury
Acute Tubular Necrosis
Alzheimer's Disease
Atherosclerosis
Atrial Fibrillation
DVT
Diabetes
Disc Degeneration
Epilepsy
Head & Neck Cancer
Heart Block
Hydrocephalus
HLHS
Lung Cancer
Multiple Sclerosis
Muscle Atrophy
Obesity
Ovarian Cancer
Peripherial Artery Disease
PCOS
Sacroilitis
Septal Perforation
Spinal Cord Injury
Spinal Tumors
Stroke
Traumatic Brain Injury
Trigeminal Neuralgia
Ureterocele

Anecdotal

Fetal Surgery
Osteoarthritis

Clinical Trials

Brain Tumors
Breast Cancer
Breast Fibroadenomas
Essential Tremor
Hypersplenism
Hypertension
Kidney Cancer
Liver Cancer
Neuropathic Pain
OCD
Pancreatic Cancer
Parkinson's Disease
Pediatric Neuroblasto-ma
Soft Tissue Tumors
Thyroid Cancer
Tubal Pregnancy
Uterine Adenomyosis

Approved

FDA

BPH
Pain from Bone Mets
Prostate Cancer
Uterine Fibroids

Outside US

Back Pain
Breast Cancer
Breast Fibroadeno-mas
Essential Tremor
Kidney Cancer
Liver Cancer
Neuropathic Pain
Osteoid Osteoma
Pain from Bone Mets
Pancreatic Cancer
Parkinson's Disease

Reimbursed

Sparse

Brain Research Sites

Brigham & Women's Hospital, Boston

Columbia University, New York

Institut Langevin; Laboratoire Ondes et Acoustique, Paris

Pitie Salpetriere Hospital, neurosurgery department, Paris

Sheba Hospital, Tel Aviv

Stanford University

University of Toronto, Sunnybrook Health Sciences Centre

University of Virginia

University of Zurich

University of Utah

Yonsei University, Seoul

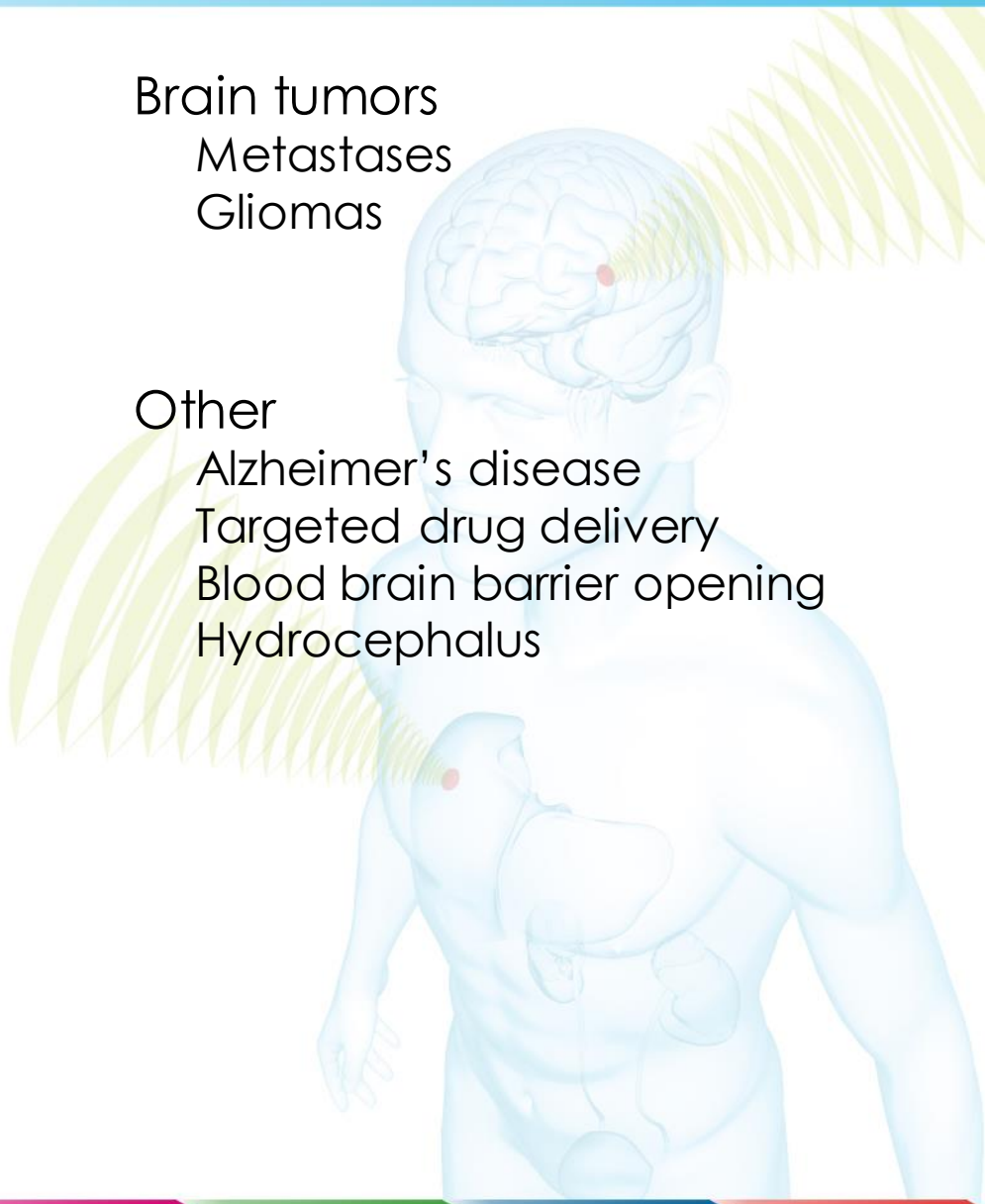
University of Maryland

University of Queensland

Manufacturers

Brain Indications

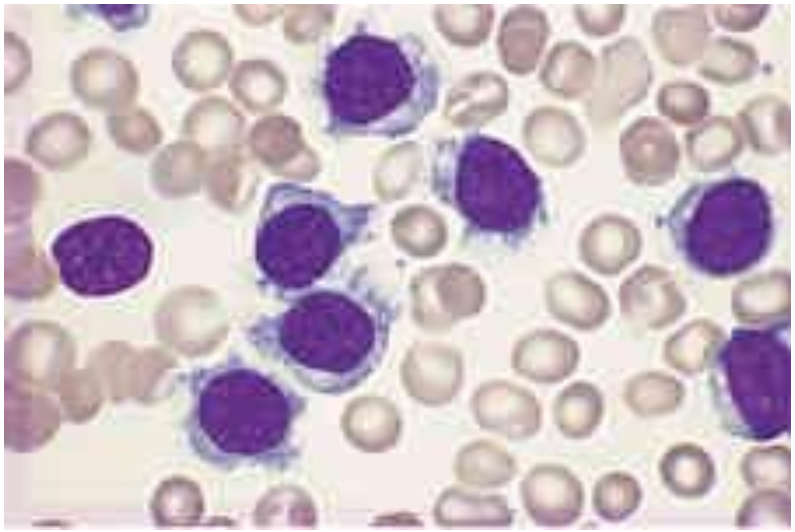
- Functional
  - Movement disorders
    - Essential tremor
    - Parkinson's disease: tremor
    - Parkinson's disease: dyskinesia
    - Dystonia
    - MS tremor
  - Epilepsy
  - Trigeminal neuralgia
  - OCD
  - Depression
  - Neuropathic pain
  - Neuromodulation
- Stroke
  - Intracerebral hemorrhage
  - Acute ischemic stroke
  - Arteriovenous malformations
- Brain tumors
  - Metastases
  - Gliomas
- Other
  - Alzheimer's disease
  - Targeted drug delivery
  - Blood brain barrier opening
  - Hydrocephalus



Snake Oil: Cure-all

Limitations

Leukemia



Scoliosis

Traumatic Injuries

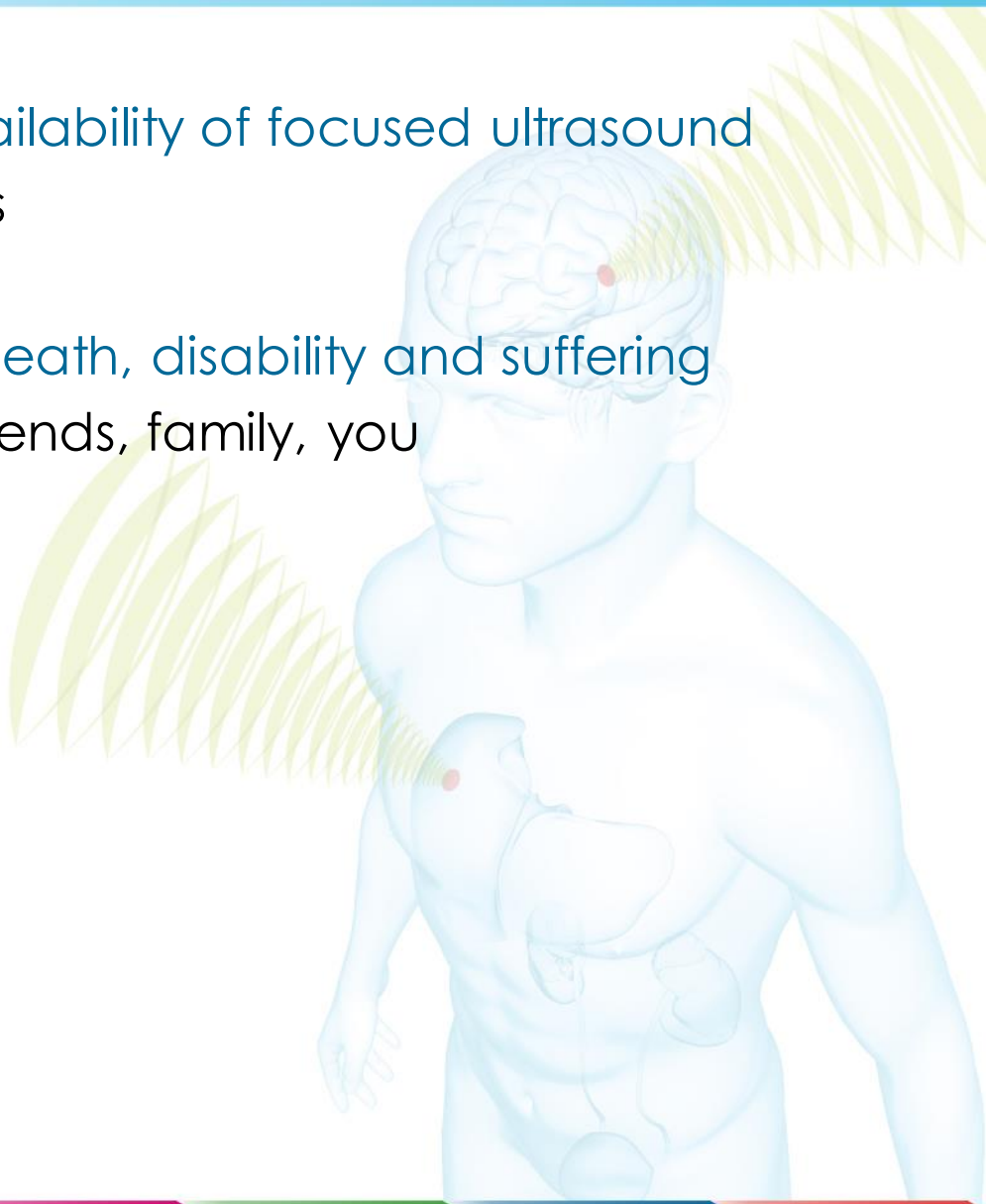
Potential Impact

Urgent need: widespread availability of focused ultrasound

- Saving time, saving lives

Delay results in unnecessary death, disability and suffering

- Countless individuals: friends, family, you

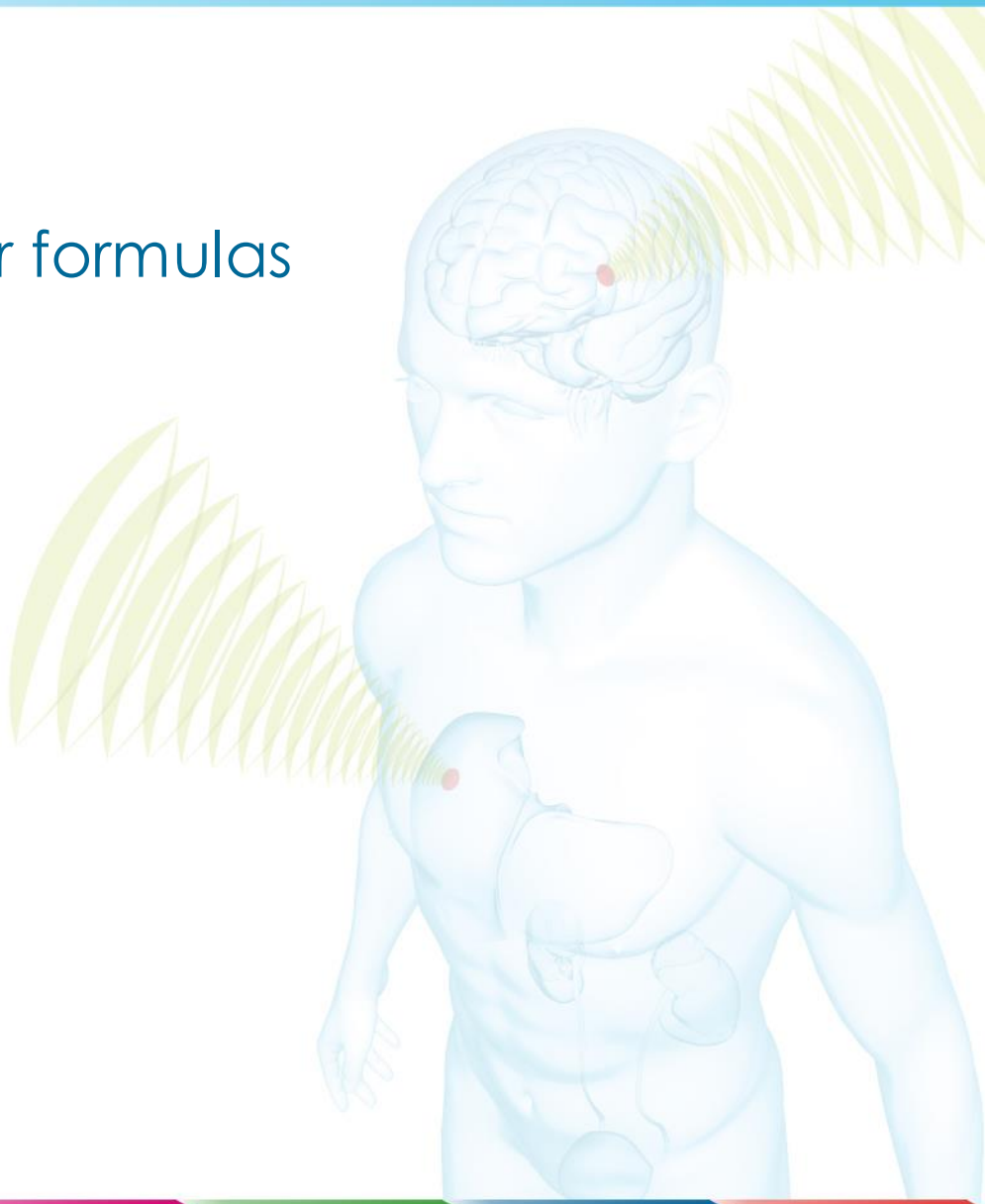


The Solution

Obscure

No roadmap, examples or formulas

Obligated to invent



The Challenge

"There is nothing more difficult to take in hand, more perilous to conduct, or more uncertain in its success, than to take the lead in the introduction of a new order of things."

Focused Ultrasound Foundation

Research, education, advocacy organization

- High impact, entrepreneurial, market driven, and results oriented
- Tax exempt

Catalyst to accelerate the development and adoption

Model

- Private funding bridges gap between research & treatment
- Other new therapeutic devices

Activities

Foster Collaboration

Provide Resources

Overcome Obstacles

Influence Direction

Stimulate Innovation

Accelerate Development & Adoption

Centers of Excellence

Awareness Events

Aggregate & Share Information

Media Coverage

Reimbursement

Generate Evidence

Convene Community

Cultivate Next Generation

Regulatory

Create Evidence: Research

Organize, conduct and fund research

- Feasibility, safety, efficacy, cost

Niche: Translational: application > discovery

Focus: Brain, cancer, immunotherapy

Funding

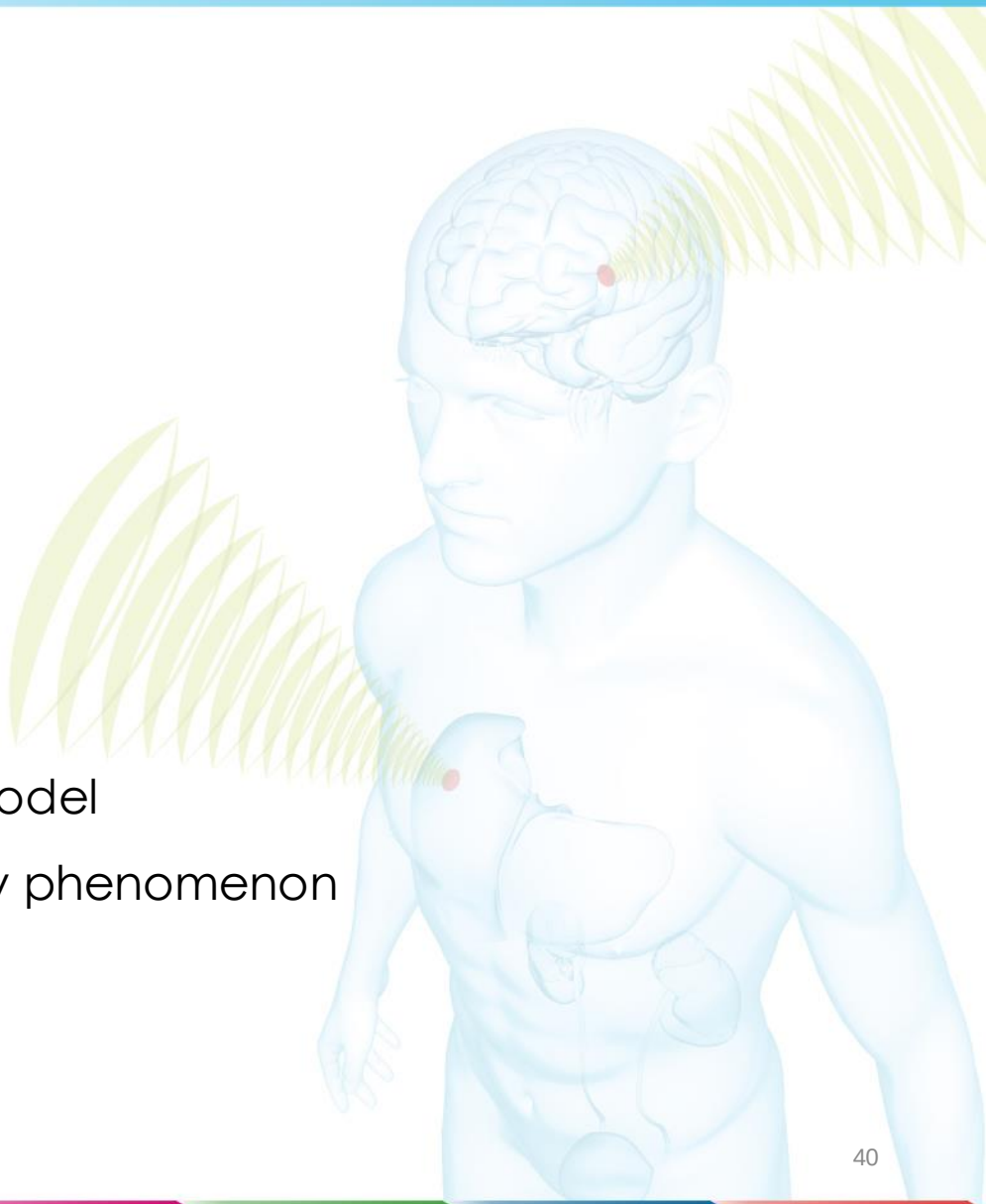
- Largest non-governmental source
- Co-funding, follow-on funding, alternative sources

Body of Knowledge

- Projects: technical (27), preclinical (31), clinical (30)

Technical Research Projects

- Real-time treatment imaging
- Volumetric thermometry
- Bone thermometry
- Non-thermal focusing
- Cavitation localization
- 3T head coil
- Volumetric treatment
- Thermal dose
- Treatment planning: simulation model
- Sonication guidelines: nonlinearity phenomenon



Preclinical Research Projects

- Histotripsy
- Sonodynamic therapy
- Focal tumor chemotherapy delivery
- Focal tumor immunotherapy delivery
- Alzheimer's amyloid beta clearance
- Parkinson's alpha synuclein

Clinical Research Projects

- Parkinson's tremor
- Parkinson's dyskinesia
- Dystonia
- Essential Tremor
- MS tremor
- Depression
- OCD
- Epilepsy: hamartoma
- Epilepsy: temporal lobe
- Alzheimer's disease
- Brain tumors

Brain Workshops

Blood brain barrier

Glioblastoma: enhanced immunotherapy

Immunotherapy

Alzheimer's disease

Neuromodulation

Sonication simulation

Brain Steering Committees

Movement disorders

Brain tumors

Epilepsy

Alzheimer's disease

Depression and OCD

Brain Working Groups

Blood brain barrier

Cancer Immunotherapy

Glioblastoma: chemotherapy delivery

Glioblastoma: immunotherapy delivery

Neuromodulation

Histotripsy

Brain Technical

Thermal imaging

Board of Directors...*active, engaged, passionate*

Neal F. Kassell, M.D.
Chairman, Focused Ultrasound Foundation
Professor of Neurosurgery, University of Virginia

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Founder, iThrive Initiative
Former Director, Landmark Communications

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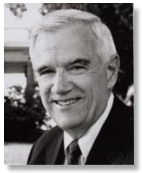
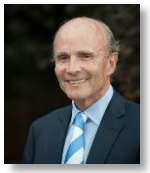


Daniel P. Jordan, Ph.D.
President Emeritus, Thomas Jefferson Foundation, Inc.



Edward J. "Ned" Kelly, III
Former Chairman, Institutional Clients Group, Citigroup

Edward D. Miller, M.D.
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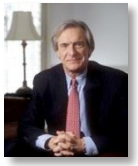
Frederic H. Moll, M.D.
Co-founder, Intuitive Surgical
Chairman & CEO, Auris Surgical Robotics, Inc.

Steve H. Rusckowski
President & CEO, Quest Diagnostics Inc.
Former CEO, Philips Healthcare

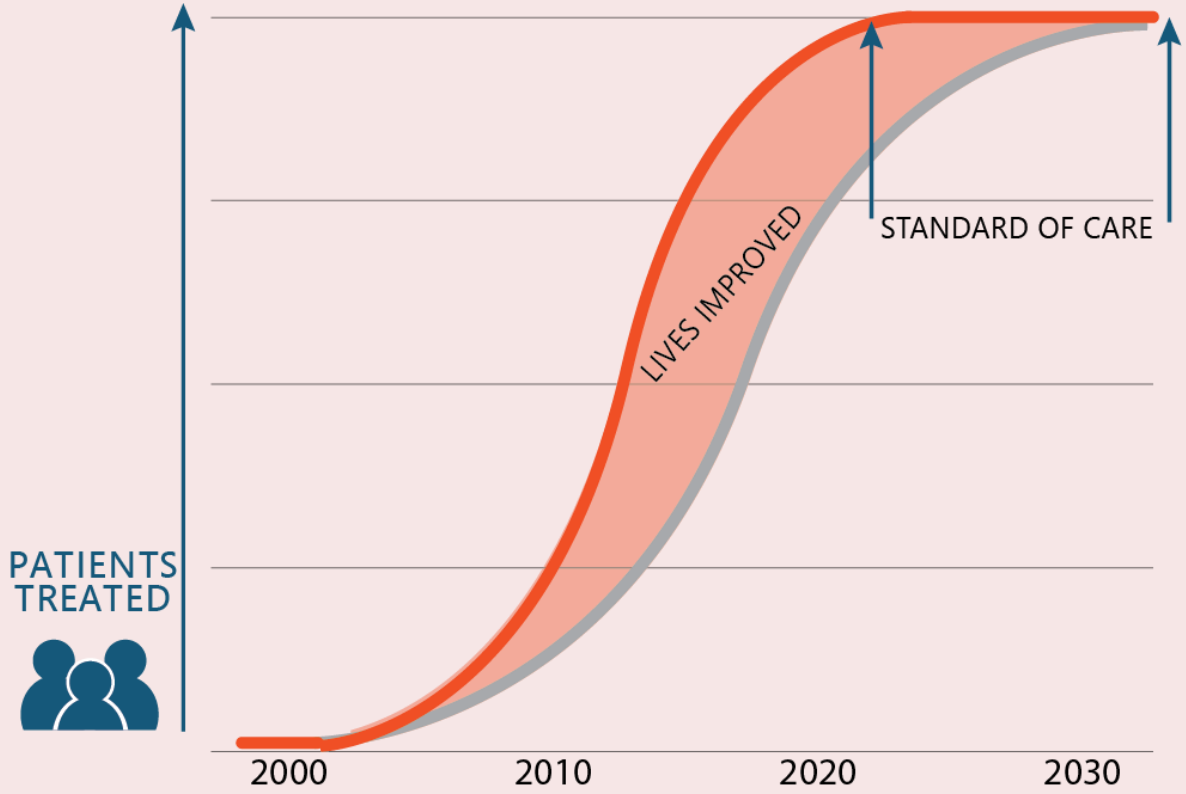
Andrew C. von Eschenbach, M.D.
Former Commissioner, Food and Drug Administration
Former Director, National Cancer Institute



Carl P. Zeithaml, Ph.D.
Dean, UVA McIntire School of Commerce

FOCUSED ULTRASOUND FOUNDATION

MAINSTREAM UTILIZATION



FOCUSED ULTRASOUND FOUNDATION

It’s all about the patients

saving time, saving lives