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
Radioactivity

Ultrasound

Sonar

Medical imaging
  - X Ray
  - Ultrasound

Image guided surgery

Radiotherapy

Therapeutic ultrasound
<table>
<thead>
<tr>
<th>Decade</th>
<th>Contribution</th>
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<tbody>
<tr>
<td>1910s</td>
<td><em>Langevin</em>: Fish</td>
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<td>1926</td>
<td><em>Wood &amp; Loomis</em>: Biological effects unicellular organisms</td>
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<tr>
<td>1940s</td>
<td><em>Lynn et al</em>: Liver</td>
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<td>1940s</td>
<td><em>Fry Bro’s</em>: Animal Brain</td>
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<td>1950s</td>
<td><em>Leksell</em>: Lesions for pain through craniotomy</td>
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<td>1950s</td>
<td><em>Frey &amp; Meyers</em>: Parkinson’s disease through craniotomy</td>
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<tr>
<td>1959</td>
<td><em>Nelson, Lindstrom, Haymaker</em>: Lobotemy</td>
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<td>1980s</td>
<td><em>Guth Kelch</em>: Hyperthermia for residual gliomas</td>
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<td>1990s</td>
<td><em>Ram</em>: MR guided ablation brain tumor through craniotomy</td>
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<tr>
<td>2000s</td>
<td><em>Jolesz</em>: Brain tumors transcranial</td>
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<tr>
<td>2000s</td>
<td><em>Jeanmonod &amp; Martin</em>: Thalamotomy neuropathic pain transcranial</td>
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<tr>
<td>2010</td>
<td><em>Elias</em>: Essential tremor</td>
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<td>2011</td>
<td><em>Jeanmonod</em>: Parkinson’s disease</td>
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<tr>
<td>2012</td>
<td><em>Martin</em>: Brain tumor</td>
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</table>
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

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

FUS Abandoned:
- Skull defocusing
- Lack of imaging

Advent of image guided interventions

MRgFUS

MRI

FUS

Gamma Knife
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 anesthesia
- No incisions
- No burr holes
- No electrodes
- No infection
- No blood clots
- No brain damage

Before Procedure

After Procedure
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
Adjacent Tissue Sparing

Liver

Brain

Treated

1 mm
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
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

**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

**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

**Women’s Health**
- Uterine Fibroids
- Breast Fibroadenomas
- Uterine Adenomyosis
- Tubal Pregnancy
- Fetal Surgery
- Ovarian Cancer
- Polycystic Ovarian Syndrome

**Miscellaneous**
- Hypersplenism
# Global Development Landscape

<table>
<thead>
<tr>
<th>Conceptual</th>
<th>Preclinical</th>
<th>Anecdotal</th>
<th>Clinical Trials</th>
<th>Approved</th>
<th>Reimbursed</th>
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<td>Fetal Surgery Osteoarthritis</td>
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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

Supersonic Imagine

Navifus

Insightec

EpiSonica

HistoSonics
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

**Brain tumors**
- Metastases
- Gliomas

**Other**
- Alzheimer's disease
- Targeted drug delivery
- Blood brain barrier opening
- Hydrocephalus

**Stroke**
- Intracerebral hemorrhage
- Acute ischemic stroke
- Arteriovenous malformations
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
"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

Centers of Excellence

Generate Evidence

Awareness Events

Convene Community

Aggregate & Share Information

Cultivate Next Generation

Media Coverage

Regulatory

Reimbursement

Accelerate Development & Adoption
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
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

Dorothy N. Batten
Founder, iThrive Initiative
Former Director, Landmark Communications

Lodewijk J.R. de Vink
Founding Partner, Blackstone Health Care Partners
Former Chairman & CEO, Warner-Lambert

Eugene V. Fife
Founding Principal, Vawter Capital
Former Chairman, Goldman Sachs International

John R. Grisham
Author

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

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Chairman & CEO, Auris Surgical Robotics, Inc.

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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

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

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

- Patients Treated
- Lives Improved
- Standard of Care

Year:
- 2000
- 2010
- 2020
- 2030
It’s all about the patients

saving time, saving lives