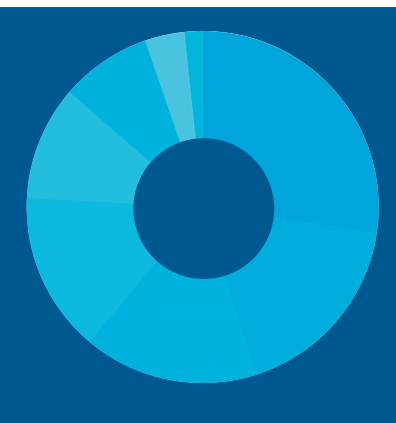
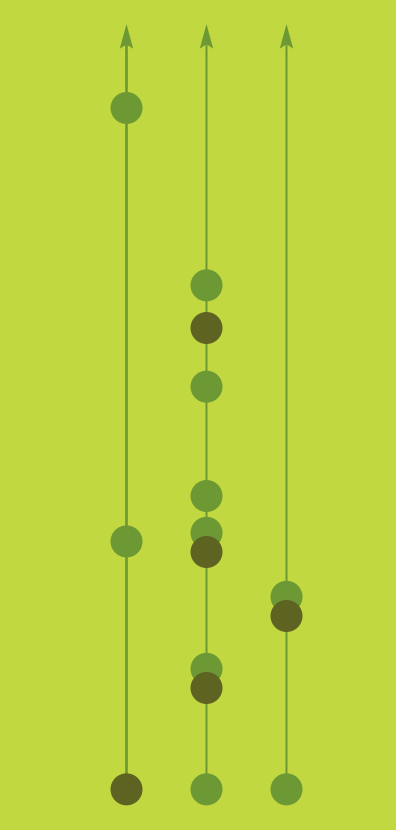


2024

Mechanisms of Action



FOCUSED
ULTRASOUND
FOUNDATION



Mechanisms of Action

Ultrasound Applications and Biological Effects

A mechanism of action occurs when an ultrasound application produces a biological effect.

Focused ultrasound is a medical technology that provides a uniquely flexible treatment platform, making it applicable to a wide range of diseases and conditions. It can produce treatments across the spectrum of thermal to mechanical effects, and these various treatments elicit a multitude of responses in biological tissues.

Varying ultrasound power, utilizing continuous versus pulsing modes, and changing the total treatment time create different ultrasound applications. These applications can be categorized based on the type of energy they deliver, thermal or mechanical, and whether treatment effects are permanent or transient. When focused ultrasound produces a high-power, continuous pressure wave, thermal energy accumulates rapidly at the focal point. This technique, termed thermal ablation, is used most frequently in the clinic and produces permanent effects. Still, additional ultrasound treatment regimens are under investigation in preclinical experiments and clinical trials. One of the most promising ultrasound applications assessed in clinical trials is a low-power, pulsed treatment that produces mild mechanical forces capable of enhancing drug delivery to the brain. This effect is transient; treated tissue reverts to normal within a few hours.

The effects induced by focused ultrasound can vary greatly depending on the ultrasound application and the type of tissue targeted. These biological effects are sometimes uniquely paired to ultrasound parameters, as with blood-brain barrier (BBB) disruption. Still, others may be induced by multiple ultrasound applications. One active area of research is immunomodulation—

III. Mechanisms of Action

III. 2 Mechanisms of Action

Ultrasound Applications and Biological Effects

Research

III. 4 Ultrasound Applications and Biological Effects

Table

III. 5 Ultrasound Applications and Biological Effects

Graphic

III. 6 Research Sites by Region

III. 8 Clinical Trials for Indications with New MOAs

Number of Sites for Biological Effects by Indications

III. 9 Histotripsy

III.12 Hyperthermia

III.16 Nonthermal

III.24 Nonthermal, BBB opening

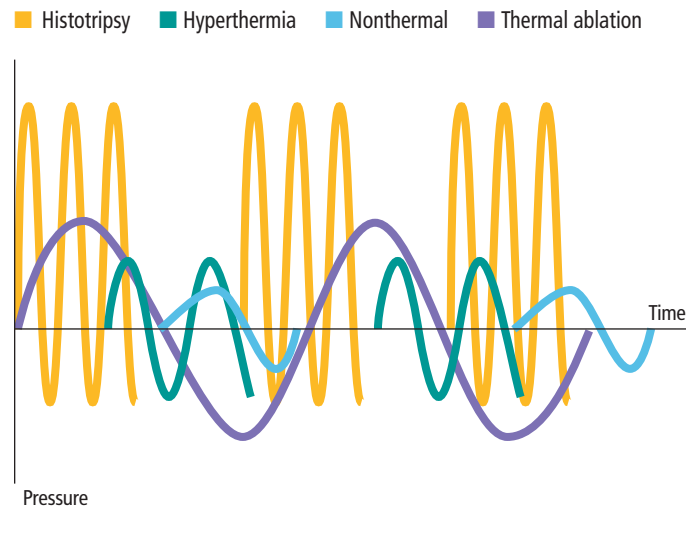
III.28 Thermal ablation

altering the immune response to treated tissue. The immune response to focused ultrasound depends on the nature of the treatment parameters, although most treatments do induce a response.

In this section, we describe several ultrasound applications and the various biological effects they are known to produce. Researchers are actively working on many of these combinations of ultrasound applications and biological effects, and more are discovered yearly.

The following pages include a detailed breakdown of each ultrasound application and the resulting biological effects under investigation. As will become apparent, most of this work is in the early stage—with very few indications reaching the commercial stage. As you read through the chapter, notice the overwhelming interest in nonthermal uses of focused ultrasound to treat disease. Before 2023, thermal ablation was the only mechanism of action with regulatory approval. In 2023, histotripsy for liver tumors was authorized by the FDA.

What do sound waves look like?



MECHANISMS OF ACTION

Ultrasound Applications and Biological Effects*

Table

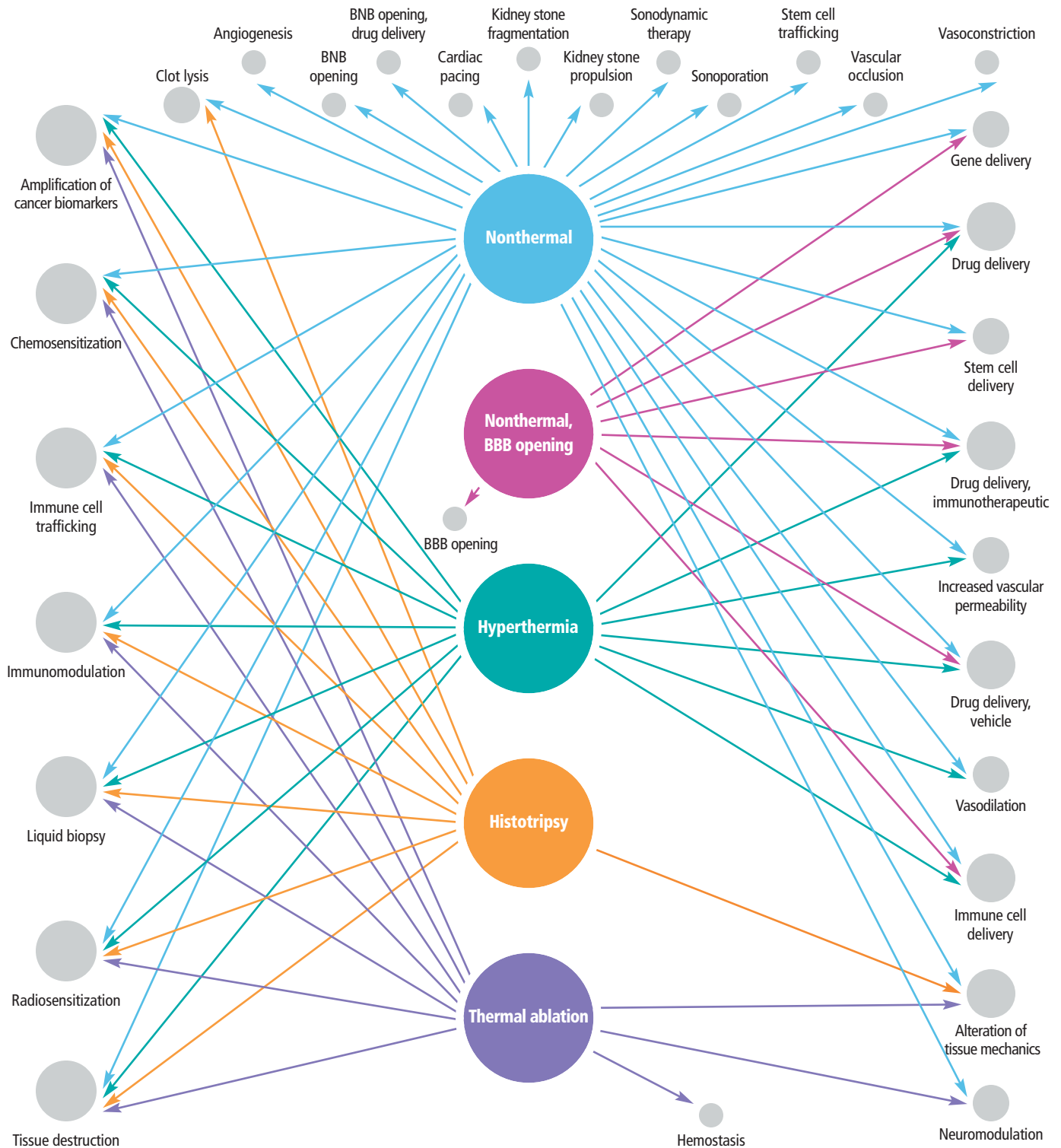
HISTOTRIPSY	HYPERTHERMIA	NONTHERMAL	NONTHERMAL, BBB OPENING	THERMAL ABLATION
9	13	29	7	10
biological effects	biological effects	biological effects	biological effects	biological effects
- Alteration of tissue mechanics - Amplification of cancer biomarkers - Chemosensitization - Clot lysis - Immune cell trafficking - Immunomodulation - Liquid biopsy - Radiosensitization - Tissue destruction	- Amplification of cancer biomarkers - Chemosensitization - Drug delivery - Drug delivery, immunotherapeutic - Drug delivery, vehicle - Immune cell delivery - Immune cell trafficking - Immunomodulation - Increased vascular permeability - Liquid biopsy - Radiosensitization - Tissue destruction - Vasodilation	- Alteration of tissue mechanics - Amplification of cancer biomarkers - Angiogenesis - BNB opening¹ - BNB opening¹, drug delivery - Cardiac pacing - Chemosensitization - Clot lysis - Drug delivery - Drug delivery, immunotherapeutic - Drug delivery, vehicle - Gene delivery - Immune cell delivery - Immune cell trafficking - Immunomodulation - Increased vascular permeability - Kidney stone fragmentation - Kidney stone propulsion - Liquid biopsy - Neuromodulation - Radiosensitization - Sonodynamic therapy - Sonoporation - Stem cell delivery - Stem cell trafficking - Tissue destruction - Vascular occlusion - Vasoconstriction - Vasodilation	- BBB opening - Drug delivery - Drug delivery, immunotherapeutic - Drug delivery, vehicle - Gene delivery - Immune cell delivery - Stem cell delivery	- Alteration of tissue mechanics - Amplification of cancer biomarkers - Chemosensitization - Hemostasis - Immune cell trafficking - Immunomodulation - Liquid biopsy - Neuromodulation - Radiosensitization - Tissue destruction

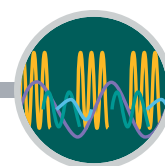
* This table lists all mechanisms of action utilized across all treatments and research types. Not all of these are being investigated specifically in mechanisms of action research projects and may not appear in other tables in this section. All other tables reflect self-reported data by research and treatment sites.

¹ BNB opening stands for blood-nerve barrier opening.

Ultrasound Applications and Biological Effects

Graphic

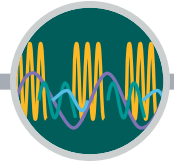




Mechanisms of Action Research Sites by Region

	Regions					Total
	N. America	Europe	Asia	Oceania	Mid East	
Histotripsy 53 sites						
Alteration of tissue mechanics	1	1	–	1	–	3
Amplification of cancer biomarkers	3	–	–	–	–	3
Chemosensitization	2	–	–	–	–	2
Immune cell trafficking	2	–	–	–	–	2
Immunomodulation	6	3	–	–	–	9
Liquid biopsy	3	–	–	–	–	3
Radiosensitization	–	1	–	–	–	1
Tissue destruction	21	6	2	1	–	30
Hyperthermia 53 sites						
Chemosensitization	1	–	–	–	–	1
Drug delivery	10	8	2	1	1	22
Drug delivery, immunotherapeutic	1	2	–	–	–	3
Drug delivery, vehicle	1	2	–	–	–	3
Immune cell trafficking	1	–	–	–	–	1
Immunomodulation	1	1	–	–	–	2
Increased vascular permeability	1	–	–	–	–	1
Radiosensitization	4	3	1	–	–	8
Tissue destruction	6	2	3	–	1	12
Nonthermal 337 sites						
Amplification of cancer biomarkers	6	–	1	–	–	7
Angiogenesis	3	1	2	–	–	6
BNB opening, drug delivery	1	–	–	–	–	1
Cardiac pacing	–	–	–	–	1	1
Chemosensitization	5	2	–	–	–	7
Clot lysis	13	2	2	–	–	17
Drug delivery	14	7	2	1	1	25
Drug delivery, immunotherapeutic	8	2	–	1	–	11
Drug delivery, vehicle	28	9	18	–	2	57
Gene delivery	5	–	–	–	–	5
Immune cell delivery	2	–	–	–	–	2

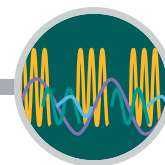
For more information about specific mechanisms of action research sites, please visit: www.fusfoundation.org/the-technology/research-sites.
Use the “search by biological effects research” dropdown menu.



Mechanisms of Action Research Sites by Region continued

	Regions					Total
	N. America	Europe	Asia	Oceania	Mid East	
Nonthermal continued						
Immune cell trafficking	4	–	–	–	–	4
Immunomodulation	14	4	3	–	–	21
Increased vascular permeability	1	–	–	–	–	1
Kidney stone fragmentation	2	–	–	–	–	2
Liquid biopsy	6	2	1	–	–	9
Neuromodulation	27	10	13	1	3	54
Radiosensitization	5	–	–	–	–	5
Sonodynamic therapy	6	6	7	1	–	20
Sonoporation	9	2	2	–	–	13
Stem cell delivery	6	–	–	–	1	7
Stem cell trafficking	3	–	–	–	–	3
Tissue destruction	21	12	11	1	–	45
Vascular occlusion	9	2	3	–	–	14
Nonthermal, BBB opening 114 sites						
Blood-brain barrier opening	20	13	4	–	–	37
Drug delivery	24	16	19	1	1	61
Drug delivery, immunotherapeutic	3	1	1	–	–	5
Drug delivery, vehicle	1	–	–	1	–	2
Gene delivery	2	1	1	–	–	4
Immune cell delivery	3	–	–	–	–	3
Stem cell delivery	1	–	1	–	–	2
Thermal ablation 89 sites						
Amplification of cancer biomarkers	3	1	–	–	–	4
Chemosensitization	2	1	–	–	–	3
Hemostasis	2	–	–	–	–	2
Immune cell trafficking	3	1	–	–	–	4
Immunomodulation	7	3	2	–	–	12
Neuromodulation	1	–	–	–	–	1
Radiosensitization	1	–	–	–	–	1
Tissue destruction	30	17	11	1	3	62

For more information about specific mechanisms of action research sites, please visit: www.fusfoundation.org/the-technology/research-sites.
Use the “search by biological effects research” dropdown menu.

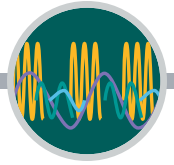


Clinical Trials for Indications with New MOAs

2023

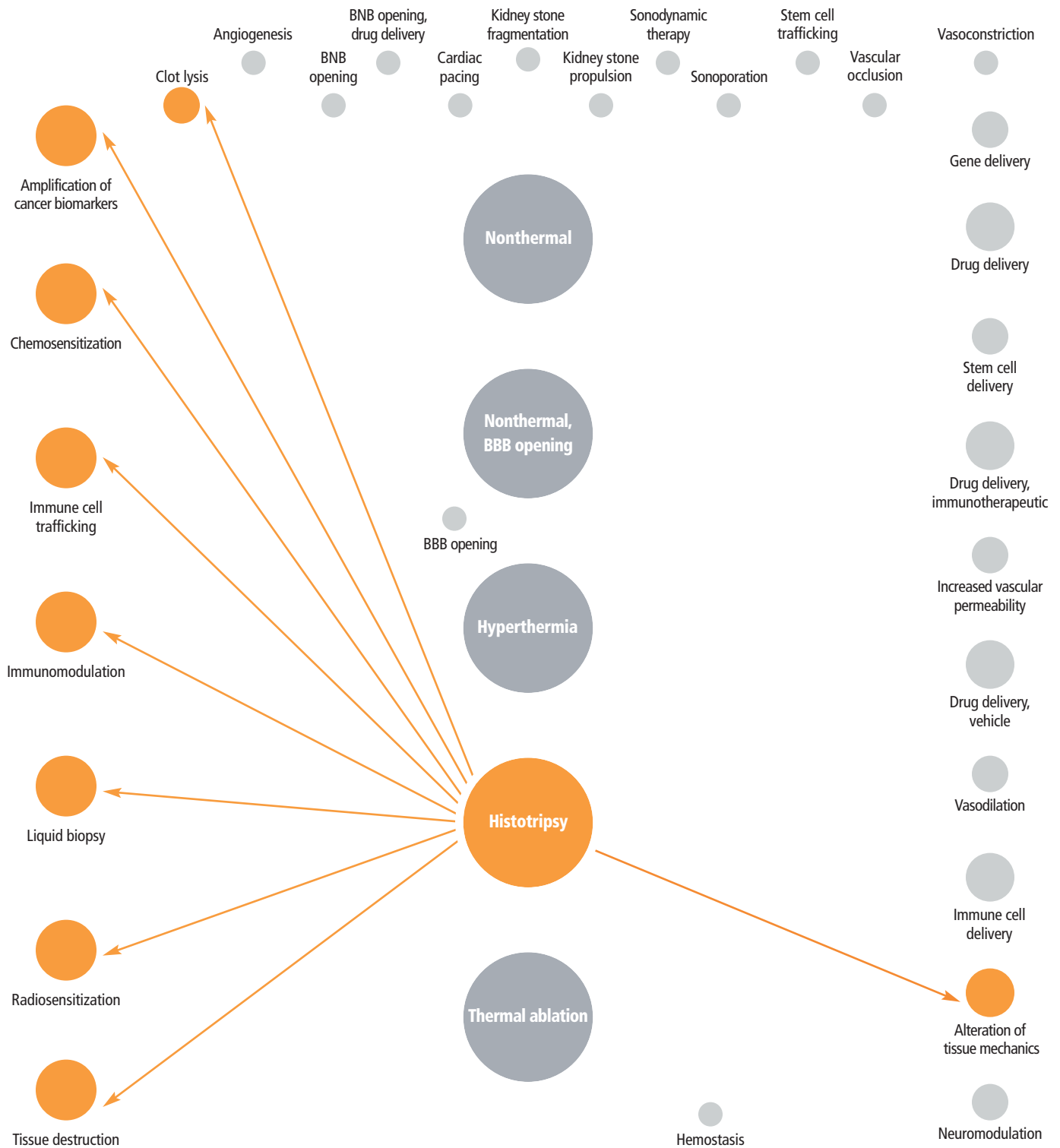
No. of Trials	MOA	Indication	Clinical Trial ID
1	Histotripsy		
	Tissue destruction	Kidney tumors	NCT05432232
5	Nonthermal		
	Neuromodulation	Addiction, other - cocaine	NCT05857852
		Addiction, other - impulsive behavior	NCT05875181
		Addiction, other - nicotine	—
		Dystonia	NCT05965960
		Parkinson's disease, underlying cause	IRAS322261
1	Nonthermal, BBB opening		
	Drug delivery, immunotherapeutic	Pontine glioma	NCT05615623

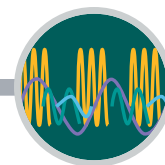
The 7 clinical trials listed above all began in 2023. These were first-in-human studies where a new mechanism of action was being utilized to treat a particular disease. As mentioned previously, until last year thermal ablation, tissue destruction was the only mechanism of action that had regulatory approval anywhere in the world. This table and last year's FDA approval of histotripsy to treat liver tumors indicate that the field as a whole and how we use ultrasound technology to treat diseases is changing rapidly.



Ultrasound Applications and Biological Effects

Graphic—*Histotripsy*

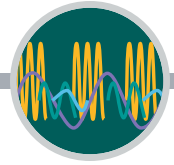




Histotripsy—Number of Sites for Biological Effects by Indications

Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Histotripsy Alteration of tissue mechanics			
Breast tumors, malignant	1	—	—
Deep vein thrombosis	1	—	—
Heart valve calcifications	1	11	—
Liver tumors	1	—	—
Presbyopia	1	—	—
Wound healing	1	—	—
Histotripsy Amplification of cancer biomarkers			
Glioblastoma	1	—	—
Soft tissue cancer	1	1	—
Histotripsy Immune cell trafficking			
Breast tumors, malignant	1	—	—
Histotripsy Immunomodulation			
Brain tumors, general	1	—	—
Breast tumors, malignant	1	—	—
Glioblastoma	1	—	—
Liver tumors	2	—	—
Melanoma	2	—	—
Neuroblastoma	2	—	—
Pancreatic tumors, malignant	4	—	—
Soft tissue cancer	2	—	—
Histotripsy Liquid biopsy			
Pontine glioma	1	—	—
Histotripsy Radiosensitization			
Breast tumors, malignant	—	—	1 ¹

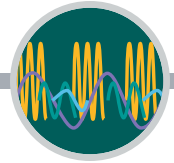
1 Indications being performed off label in a region are shown in bold.



Histotripsy—Number of Sites for Biological Effects by Indications continued

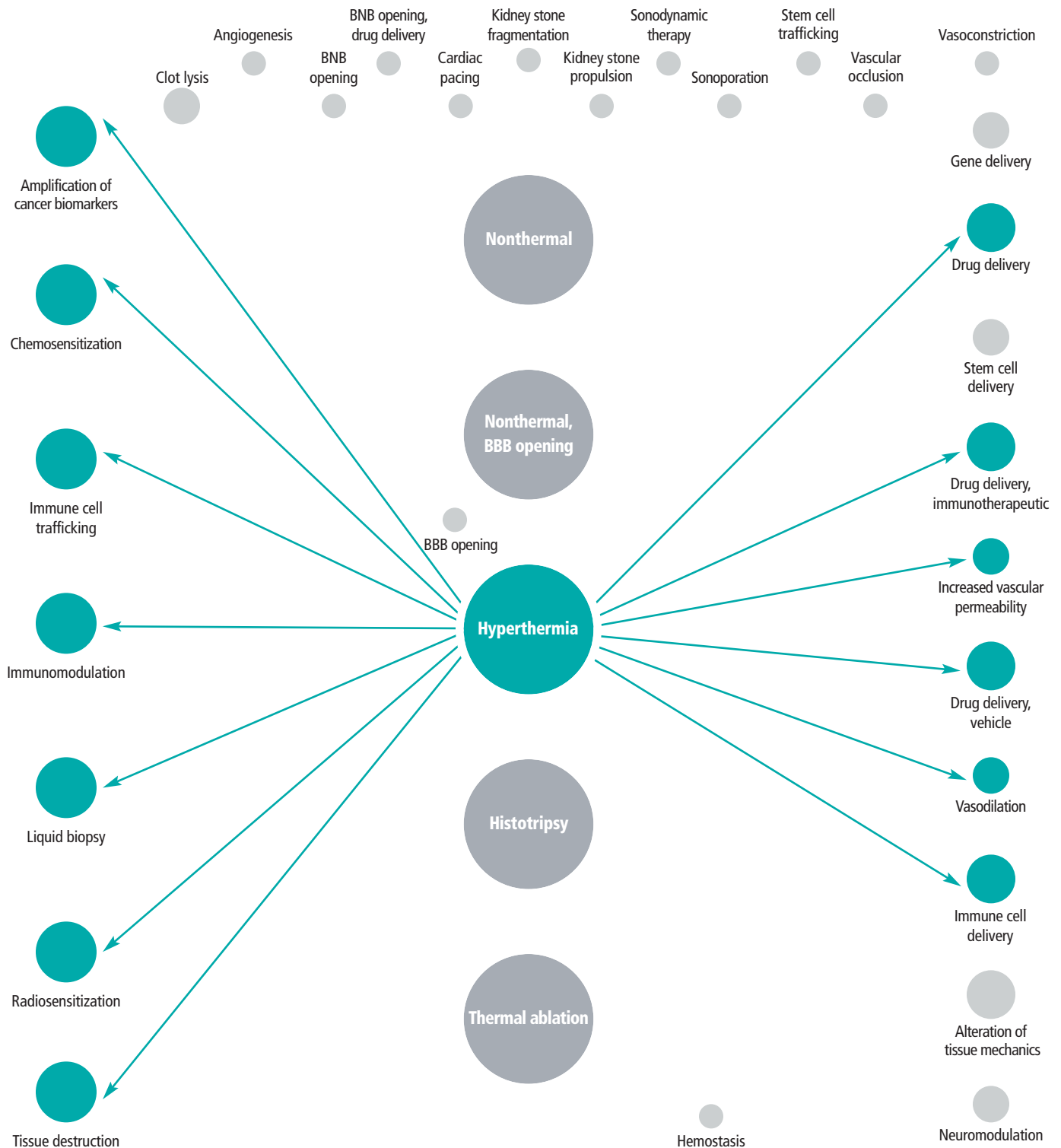
Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Histotripsy Tissue destruction			
Benign prostatic hyperplasia	1	—	—
Brain metastases, breast cancer	1	—	—
Breast tumors, malignant	1	—	—
Deep vein thrombosis	4	—	—
Dental infections	—	1	—
Epilepsy	2	—	—
Fetal heart anomalies	1	—	—
Glioblastoma	2	—	—
Hematoma	1	—	—
Heterotopic ossification	1	—	—
Infection	1	—	—
Kidney tumors	2	4	—
Liver metastases	1	—	1
Liver tumors	5	13	1
Lung cancer	1	—	—
Mitral regurgitation	1	—	—
Multiple tumors ²	1	—	—
Pancreatic tumors, malignant	3	—	—
Periodontal disease	1	—	—
Prostate cancer	1	—	—
Rotator cuff injury	1	—	—
Soft tissue cancer	2	—	—
Stroke, intracerebral hemorrhage	1	—	—
Tendon contracture	1	—	—
Thyroid cancer	1	—	—
Uterine fibroids	1	—	—

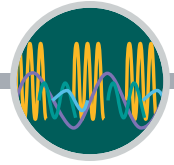
² Protocols inclusive of more than one indication



Ultrasound Applications and Biological Effects

Graphic—Hyperthermia

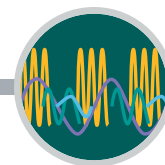




Hyperthermia—Number of Sites for Biological Effects by Indications

Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Hyperthermia Amplification of cancer biomarkers			
Breast tumors, malignant	1	–	–
Hyperthermia Chemosensitization			
Multiple tumors ²	–	1	–
Prostate cancer	1	–	–
Hyperthermia Drug delivery			
Breast tumors, malignant	–	1	–
Head & neck tumors	1	–	–
Multiple tumors ²	2	1	–
Osteopenia	1	–	–
Pancreatic tumors, malignant	1	2	–
Soft tissue cancer	1	–	–
Wound healing	2	–	–
Hyperthermia Drug delivery, immunotherapeutic			
Breast tumors, malignant	1	–	–
Glioblastoma	1	–	–
Pancreatic tumors, malignant	1	–	–
Soft tissue cancer	1	–	–
Hyperthermia Drug delivery, vehicle			
Bone metastases	–	1	–
Disc degeneration	1	–	–
Liver tumors	–	1	–
Soft tissue cancer	–	1	–
Hyperthermia Immune cell trafficking			
Brain tumors, general	1	–	–

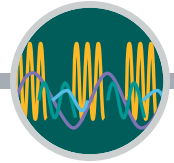
² Protocols inclusive of more than one indication



Hyperthermia—Number of Sites for Biological Effects by Indications continued

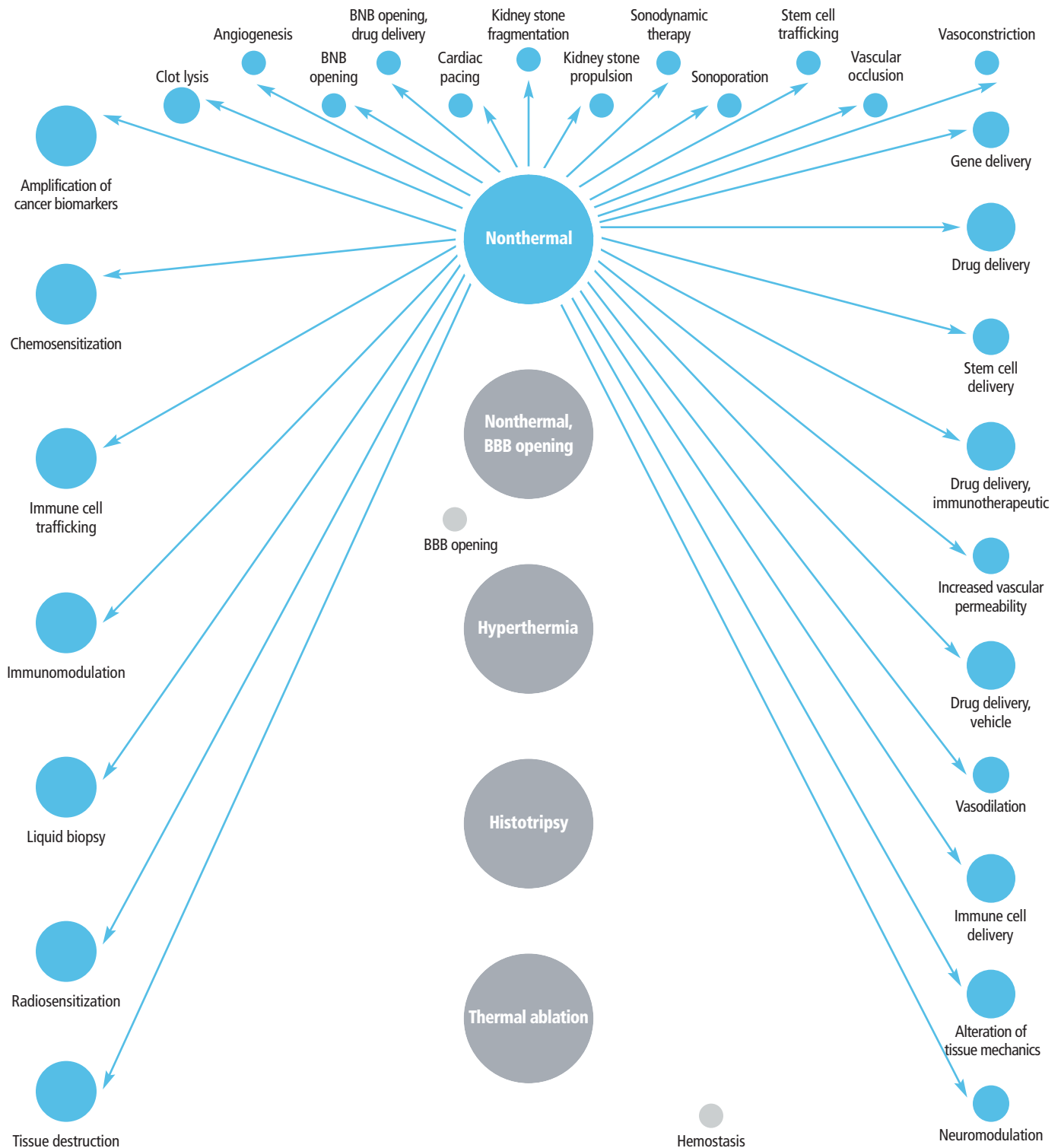
Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Hyperthermia Immunomodulation			
Breast tumors, malignant	1	–	–
Glioblastoma	1	–	–
Liver tumors	1	–	–
Pancreatic tumors, malignant	1	–	–
Prostate cancer	1	–	–
Hyperthermia Radiosensitization			
Bone metastases	–	1	–
Brain tumors, general	1	–	–
Breast tumors, malignant	–	1	–
Head & neck tumors	1	1	–
Liver tumors	1	–	–
Prostate cancer	1	–	–
Hyperthermia Tissue destruction			
Brain tumors, general	1	–	–
Endometriosis	–	1	–
Liver tumors	1	–	–
Lung cancer	1	–	–
Prostate cancer	1	2	–
Uterine adenomyosis	–	1	–
Hyperthermia Vasodilation			
Breast tumors, malignant	1	–	–

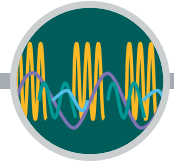
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Ultrasound Applications and Biological Effects

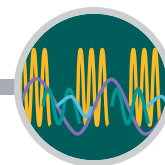
Graphic—Nonthermal





Nonthermal—Number of Sites for Biological Effects by Indications

Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Nonthermal Alteration of tissue mechanics			
Alzheimer's disease	2	—	—
Glioblastoma	1	—	—
Neuropathic pain	1	—	—
Osteopenia	1	—	—
Periodontal disease	—	3	—
Wound healing	1	—	—
Nonthermal Amplification of cancer biomarker			
Brain metastases, breast cancer	1	—	—
Brain tumors, general	1	—	—
Glioblastoma	1	1	—
Nonthermal Angiogenesis			
Muscle atrophy	1	—	—
Stroke, thromboembolic	—	1	—
Nonthermal BNB opening, drug delivery			
Glioblastoma	1	—	—
Nonthermal Cardiac pacing			
Cardiac pacing	1	—	—
Nonthermal Clot lysis			
Deep vein thrombosis	1	—	—
Hydrocephalus	1	—	—
Nonthermal Drug delivery			
Alzheimer's disease	1	—	—
Atherosclerosis	3	—	—
Bladder tumors	2	—	—
Bone tumors, benign	1	—	—
Brain tumors, general	1	—	—
Breast tumors, malignant	2	—	—
Colorectal tumors	1	4	—
Hemophilia	1	—	—

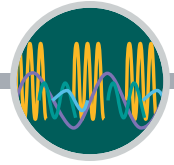


Nonthermal—Number of Sites for Biological Effects by Indications continued

Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Nonthermal Drug delivery continued			
Inflammatory bowel disease	1	—	—
Liver metastases	—	4	—
Pancreatic tumors, malignant	1	3	1¹
Pontine glioma	1	—	—
Stroke, intracerebral hemorrhage	1	—	—
Stroke, thromboembolic	2	—	—
Wound healing	1	—	—
Nonthermal Drug delivery, immunotherapeutic			
Multiple tumors ²	1	—	—
Pancreatic tumors, malignant	2	—	—
Nonthermal Drug delivery, vehicle			
Breast tumors, malignant	3	—	—
Cardiac hypertrophy	1	—	—
Colorectal tumors	1	—	—
Deep vein thrombosis	1	—	—
Glioblastoma	1	—	—
Kidney tumors	1	—	—
Liver tumors	—	1	—
Neuropathic pain	1	—	—
Pancreatic tumors	1	—	—
Pancreatic tumors, malignant	3	—	—
Parkinson's disease, underlying cause	1	—	—
Periodontal disease	1	—	—
Peripheral artery disease	1	—	—
Prostate cancer	1	—	—
Stroke, intracerebral hemorrhage	2	—	—
Stroke, thromboembolic	1	—	—
Urinary tract infection	1	—	—

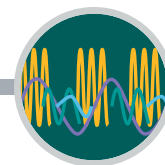
¹ Indications being performed off label in a region are shown in bold.

² Protocols inclusive of more than one indication



Nonthermal—Number of Sites for Biological Effects by Indications continued

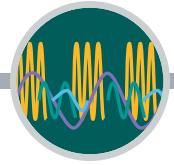
Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Nonthermal Gene delivery			
Brain tumors, general	1	–	–
Breast tumors, malignant	2	–	–
Cardiac hypertrophy	1	–	–
Epilepsy	1	–	–
Melanoma	1	–	–
Muscle atrophy	1	–	–
Parkinson's disease, underlying cause	1	–	–
Retinal injury	1	–	–
Nonthermal Immune cell trafficking			
Breast tumors, malignant	1	–	–
Glioblastoma	1	–	–
Melanoma	1	–	–
Nonthermal Immunomodulation			
Brain metastases, breast cancer	1	–	–
Brain metastases, melanoma	1	–	–
Brain tumors, general	1	–	–
Breast tumors, malignant	2	–	–
Colorectal tumors	1	–	–
Epilepsy	1	–	–
Glaucoma	–	1	–
Glioblastoma	2	–	–
Pancreatic tumors, malignant	2	1	–
Prostate cancer	2	1	–
Soft tissue cancer	–	1	–
Nonthermal Increased vascular permeability			
Breast tumors, malignant	1	–	–
Deep vein thrombosis	1	–	–
Periodontal disease	–	1	–



Nonthermal—Number of Sites for Biological Effects by Indications continued

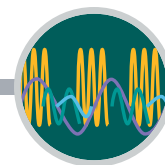
Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Nonthermal Kidney stone fragmentation			
Kidney stones	2	1	—
Nonthermal Kidney stone propulsion			
Kidney stones	1	1	—
Nonthermal Liquid biopsy			
Brain tumors, general	2	1	—
Glioblastoma	—	14	—
Parkinson's disease, underlying cause	1	1	—
Pontine glioma	1	—	—
Nonthermal Neuromodulation			
ADHD	—	1	—
Alzheimer's disease	2	16	1¹
Anxiety	2	6	—
Bipolar disorder	—	1	—
Brain tumor, general	1	—	—
Cancer pain	1	—	—
Dementia	—	1	—
Depression	6	10	—
Diabetes	2	—	—
Dystonia	—	2	—
Epilepsy	9	6	1¹
Essential tremor	—	2	—
Headache	1	—	—
Mood disorder	—	1	—
Neuropathic pain	3	4	—
Neuropathy	—	3	—
Obsessive-compulsive disorder	1	2	—
Opioid and other addictions	6	5	—

¹ Indications being performed off label in a region are shown in bold.



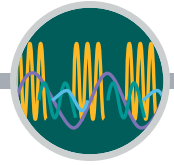
Nonthermal—Number of Sites for Biological Effects by Indications continued

Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Nonthermal Neuromodulation continued			
Parkinson's disease, dyskinesia	–	2	–
Parkinson's disease, tremor	1	4	–
Parkinson's disease, underlying cause	3	1	–
PTSD	–	1	–
Schizophrenia	–	2	–
Stroke, intracerebral hemorrhage	1	2	–
Stroke, thromboembolic	–	2	–
Traumatic brain injury	–	2	–
Tremor, orthostatic	–	1	–
Nonthermal Radiosensitization			
Brain tumors, general	2	–	–
Breast tumors, malignant	–	1	–
Glioblastoma	2	1	–
Head & neck tumors	–	1	–
Melanoma	–	1	–
Nonthermal Sonodynamic therapy			
Atherosclerosis	1	–	–
Brain metastases, melanoma	1	–	–
Brain tumors, general	4	–	–
Cavernomas	1	–	–
Deep vein thrombosis	1	–	–
Glioblastoma	3	10	–
Infection	1	–	–
Pancreatic tumors, malignant	2	–	–
Pontine glioma	1	4	–



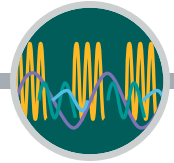
Nonthermal—Number of Sites for Biological Effects by Indications continued

Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Nonthermal Sonoporation			
Atherosclerosis	1	–	–
Head & neck tumors	1	–	–
Liver metastases	–	1	–
Liver tumors	–	1	–
Pancreatic tumors, malignant	1	1	–
Stroke, thromboembolic	1	–	–
Nonthermal Stem cell delivery			
Acute tubular necrosis	1	–	–
Atherosclerosis	1	–	–
Kidney disease, acute	1	–	–
Muscle atrophy	1	–	–
Nonthermal Tissue destruction			
Arteriovenous malformations	1	–	–
Arthritis, facetogenic	1	–	–
Benign prostatic hyperplasia	1	–	–
Brain tumors, general	1	–	–
Breast tumors, malignant	2	–	–
Glioblastoma	1	–	–
Head & neck tumors	1	–	–
Infection	1	–	–
Liver metastases	1	–	–
Liver tumors	2	–	–
Pancreatic tumors, malignant	3	–	–
Presbyopia	1	–	–
Prostate cancer	2	–	–
Soft tissue cancer	1	–	–
Uterine fibroids	1	–	–



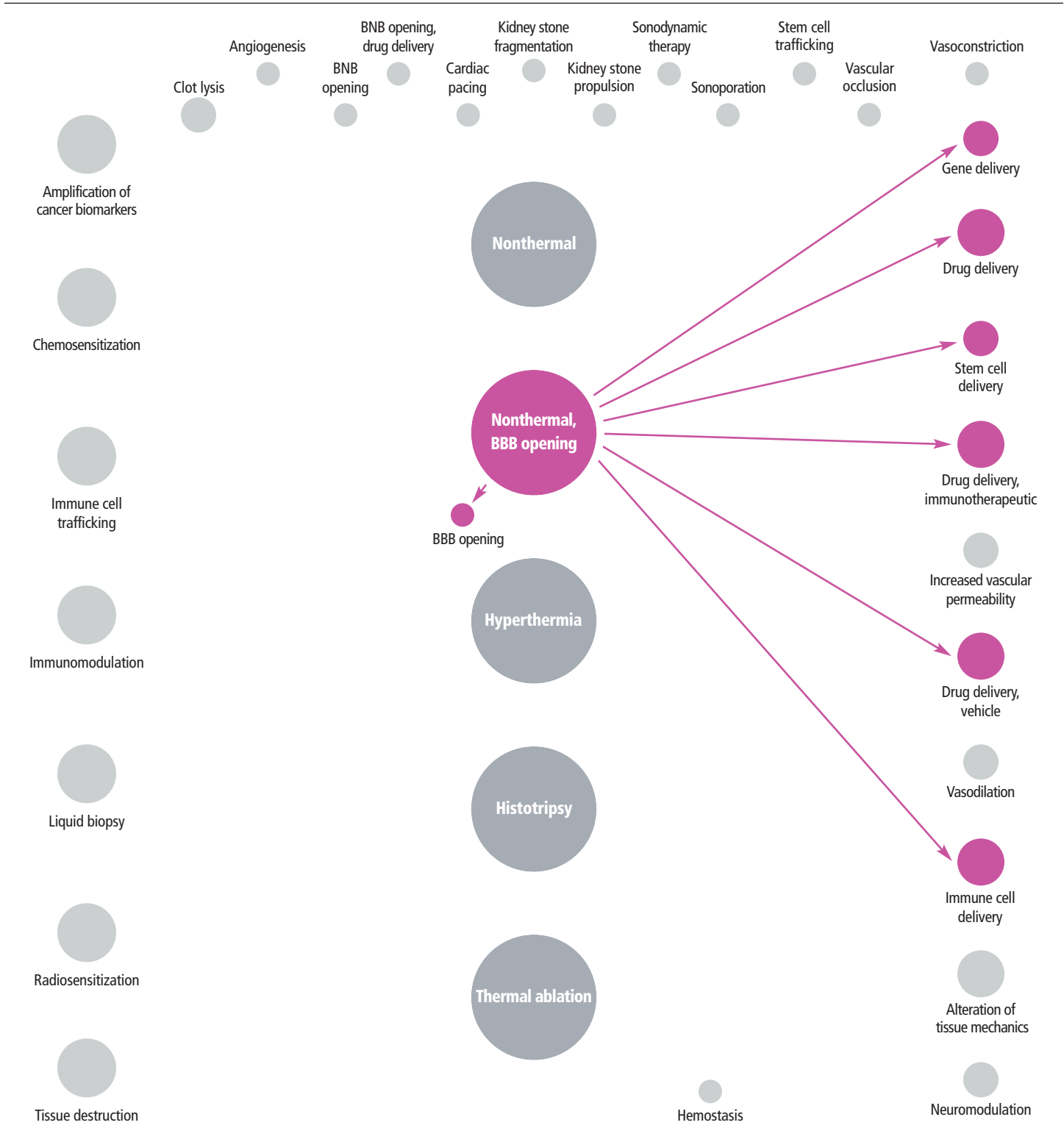
Nonthermal—Number of Sites for Biological Effects by Indications continued

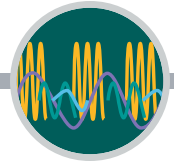
Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Nonthermal Vascular occlusion			
Arteriovenous malformations	–	1	–
Brain tumors, general	1	–	–
Glioblastoma	1	–	–
Macular degeneration	1	–	–
Twin-twin transfusion syndrome	3	–	–
Varicose veins	–	1	–
Nonthermal Vasodilation			
Neuropathy	1	–	–
Stroke, thromboembolic	1	–	–



Ultrasound Applications and Biological Effects

Graphic—Nonthermal, BBB opening

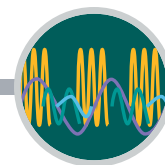




Nonthermal, BBB opening— Number of Sites for Biological Effects by Indications

Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Nonthermal, BBB opening BBB opening			
Alzheimer's disease	7	12	1¹
Amyotrophic lateral sclerosis	1	—	—
Brain metastases, breast cancer	1	—	—
Brain tumors, general	4	1	—
Dementia	1	—	—
Epilepsy	1	—	—
Glioblastoma	1	4	—
Parkinson's disease, underlying cause	—	1	—
Nonthermal, BBB opening Drug delivery			
Alzheimer's disease	8	3	—
Amyotrophic lateral sclerosis	1	1	—
Anxiety	1	—	—
Autism	1	—	—
Brain metastases, breast cancer	1	2	—
Brain metastases, melanoma	—	1	—
Brain tumors, general	5	3	—
Depression	1	—	—
Epilepsy	3	—	—
Glioblastoma	15	15	—
Infection	1	—	—
Neurofibromatosis	1	—	—
Parkinson's disease, tremor	1	—	—
Parkinson's disease, underlying cause	2	1	—
Pontine glioma	3	3	—
Spinal cord injury	2	—	—
Stroke, intracerebral hemorrhage	1	—	—
Stroke, thromboembolic	1	—	—
Traumatic brain injury	1	—	—

¹ Indications being performed off label in a region are shown in bold.

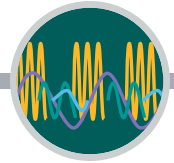


Nonthermal, BBB opening—

Number of Sites for Biological Effects by Indications continued

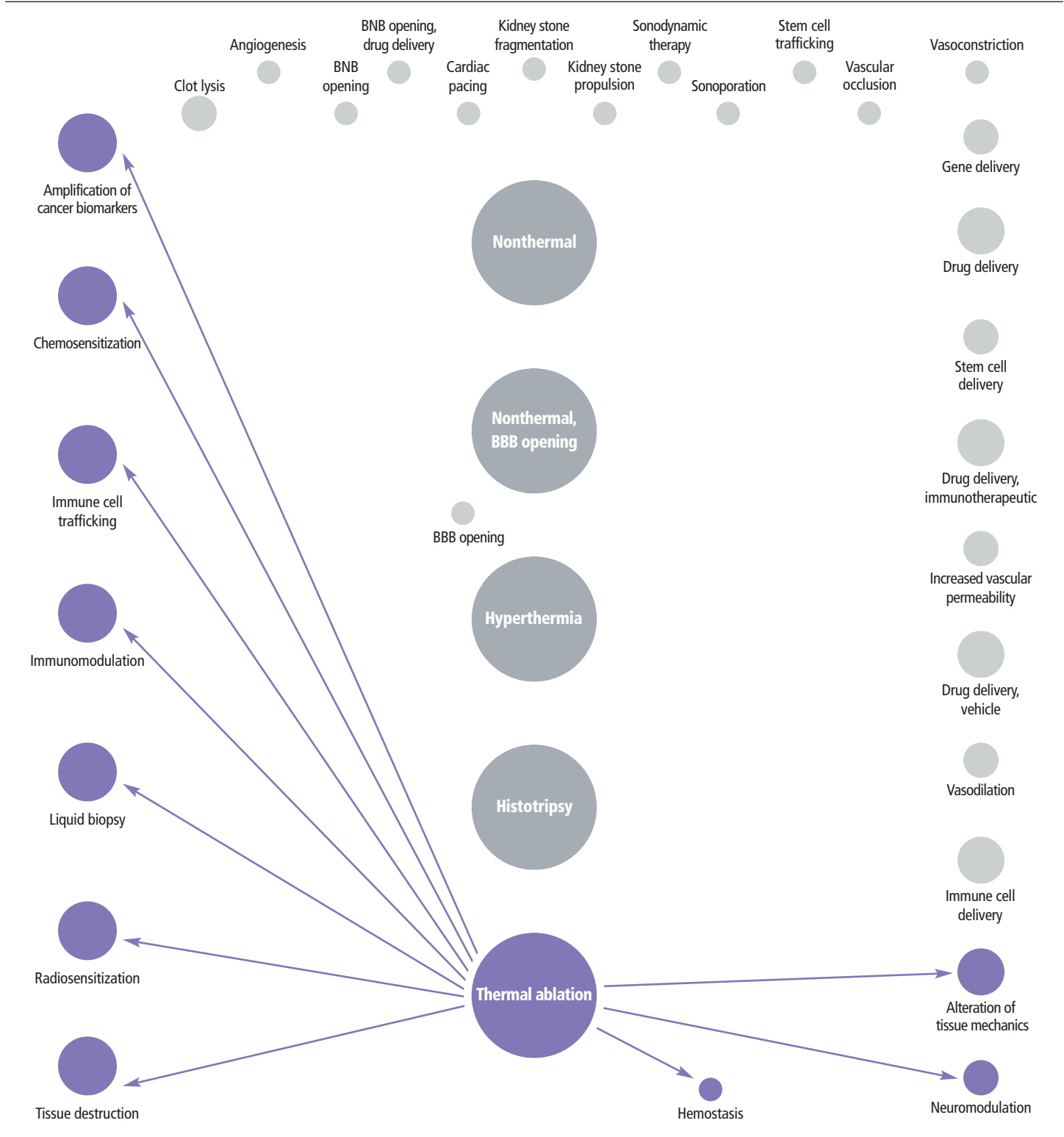
Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Nonthermal, BBB opening Drug delivery, immunotherapeutic			
Alzheimer's disease	2	1	—
Brain metastases, breast cancer	2	—	—
Brain metastases, lung cancer	—	5	—
Brain metastases, melanoma	1	—	—
Brain tumors, general	1	—	—
Glioblastoma	2	—	—
Pontine glioma	—	1	—
Nonthermal, BBB opening Drug delivery, vehicle			
Brain tumors, general	1	—	—
Glioblastoma	2	—	—
Nonthermal, BBB opening Gene delivery			
Alzheimer's disease	1	—	—
Brain tumors, general	2	—	—
Epilepsy	2	—	—
Glioblastoma	1	—	—
Huntington's disease	1	—	—
Niemann-Pick disease	1	—	—
Parkinson's disease, dyskinesia	1	—	—
Parkinson's disease, underlying cause	7	—	—
Rett syndrome	1	—	—
Nonthermal, BBB opening Immune cell delivery			
Brain metastases, breast cancer	1	—	—
Brain tumors, general	1	—	—
Glioblastoma	1	—	—
Nonthermal, BBB opening Stem cell delivery			
Alzheimer's disease	1	—	—

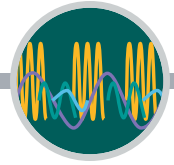
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Ultrasound Applications and Biological Effects

Graphic—Thermal ablation



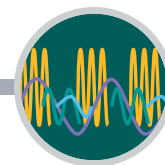


Thermal ablation—Number of Sites for Biological Effects by Indications

Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Thermal ablation Alteration of tissue mechanics			
Urinary incontinence, stress	–	–	1¹
Thermal ablation Chemosensitization			
Bone metastases	–	1	–
Breast tumors, malignant	1	–	–
Thermal ablation Hemostasis			
Hematoma	1	–	–
Twin-twin transfusion syndrome	–	2	–
Thermal ablation Immunomodulation			
Breast tumors, malignant	5	–	–
Cervical tumors	–	1	–
Esophageal tumors	–	1	–
Gastric tumors	–	1	–
Liver tumors	1	–	–
Lung cancer	–	1	–
Melanoma	2	1	–
Multiple tumors ²	1	2	–
Ovarian tumors	1	1	–
Pancreatic tumors, malignant	5	1	–
Soft tissue cancer	2	1	–
Thermal ablation Liquid biopsy			
Brain tumors, general	–	1	–
Thermal ablation Neuromodulation			
Epilepsy	1	–	–

¹ Indications being performed off label in a region are shown in bold.

² Protocols inclusive of more than one indication

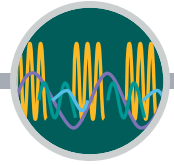


Thermal ablation—Number of Sites for Biological Effects by Indications continued

Thermal ablation, tissue destruction is the most mature of the focused ultrasound MOAs. This is evidenced by the few bench research sites working in this area or, conversely, by the number of sites in clinical and commercial stages.

Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Thermal ablation Tissue destruction			
Cardiovascular			
Arteriovenous malformations	–	1	1¹
Atrial fibrillation	2	–	–
Hypertension	–	3	–
Peripheral artery disease	–	1	–
Twin-twin transfusion syndrome	1	–	–
Varicose veins	–	6	10
Ventricular tachycardia	2	–	–
Endocrine disorders			
Thyroid nodules	–	–	14
Gastrointestinal			
Colorectal tumors	1	4	–
Gastric tumors	1	–	1¹
Liver fibrosis	–	–	2¹
Liver metastases	3	–	3¹
Liver tumors	14	20	125
Pancreatic tumors	2	4	41
Pancreatic tumors, malignant	6	12	34

¹ Indications being performed off label in a region are shown in bold.

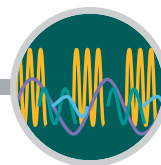


Thermal ablation—Number of Sites for Biological Effects by Indications continued

Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Thermal ablation Tissue destruction continued			
Miscellaneous			
Actinic keratosis	—	2	—
Basal cell carcinoma	—	3	—
Dercum's disease	—	1	—
Head & neck tumors	—	1	—
Hypersplenism	—	1	3¹
Infection	1	—	—
Kaposi's sarcoma	—	1	—
Lipoma	—	1	—
Multiple tumors ²	1	—	—
Sinonasal disease	1	—	—
Musculoskeletal			
Arthritis, facetogenic	3	14	3
Arthritis, knee	—	1	—
Arthritis, sacroiliac	—	3	1¹
Bone cancer	—	6	5
Bone metastases	5	21	23
Bone tumors, benign	1	3	2
Desmoid tumors	—	5	12
Osteoid osteoma	4	22	67
Plantar fasciitis	—	1	—
Sacral chordoma	—	1	—
Soft tissue cancer	2	5	3
Soft tissue tumors, benign	3	21	58
Tendon contracture	1	—	—

1 Indications being performed off label in a region are shown in bold.

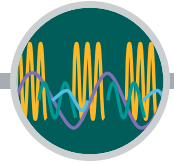
2 Protocols inclusive of more than one indication



Thermal ablation—Number of Sites for Biological Effects by Indications continued

Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Thermal ablation Tissue destruction continued			
Neurological			
Astrocytoma	—	2	—
Brain tumors, general	1	1	—
Cancer pain	—	1	—
Cerebral palsy	—	1	—
Depression	1	2	—
Dystonia	—	4	1¹
Dystonia, hand	—	1	2¹
Epilepsy	2	8	2¹
Essential tremor	—	17	136
Glioblastoma	1	3	—
Neurofibromatosis	—	2	—
Neuropathic pain	1	2	3
Neuropathy	—	—	1¹
Obsessive-compulsive disorder	—	2	—
Opioid and other addictions	—	—	1¹
Painful amputation neuromas	—	1	—
Parkinson's disease, dyskinesia	—	8	7
Parkinson's disease, tremor	—	12	88
Parkinson's disease, underlying cause	1	—	—
Tremor, orthostatic	—	1	—
Trigeminal neuralgia	—	1	1¹
Ophthalmological			
Glaucoma	3	2	14
Presbyopia	1	—	—

¹ Indications being performed off label in a region are shown in bold.



Thermal ablation—Number of Sites for Biological Effects by Indications continued

Ultrasound application Biological effects	Stages		
	Preclinical	Clinical	Commercial
Thermal ablation Tissue destruction continued			
Pulmonary			
Lung cancer	1	—	—
Tuberculosis	1	—	—
Urological			
Benign prostatic hyperplasia	—	2	46
Chyluria	—	1	—
Fetal bladder obstruction	1	—	—
Kidney tumors	2	15	58
Prostate cancer	6	68	487
Women's health			
Breast tumors, benign	2	4	23
Breast tumors, malignant	9	20	60
Cervical tumors	1	2	1¹
Cervicitis	—	—	1
Ectopic pregnancy	—	1	95¹
Endometrial tumors	2	1	1¹
Endometriosis	1	1	48¹
Endometriosis, colorectal	—	9	—
Lichen sclerosis	—	1	1
Ovarian tumors	2	1	—
Retained placenta	—	—	48¹
Urinary incontinence, stress	—	—	11¹
Uterine adenomyosis	3	27	332
Uterine fibroids	11	62	500
Vaginal tumors	—	2	—

¹ Indications being performed off label in a region are shown in bold.