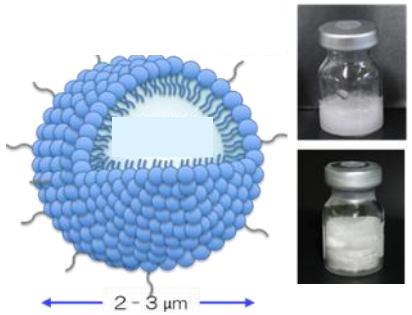
WellThera - Transforming Drug Delivery

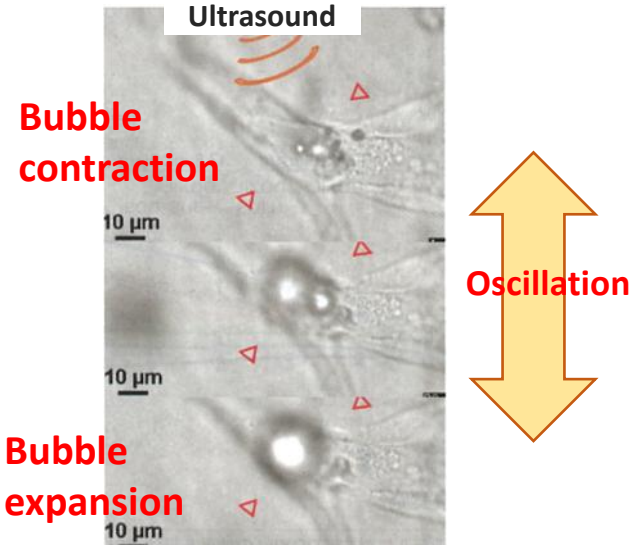
BUS-DDS (Bubble Ultrasound mediated Durg Delivery System): Ultrasound-Activated Microbubble Platform

An innovative drug delivery platform combining lipid-coated microbubbles filled with perfluoropropane gas (Theranostic Bubbles, TB) with low-intensity ultrasound to transiently open biological barriers (Tumor Vessels and BBB) and enable highly efficient, targeted drug delivery.

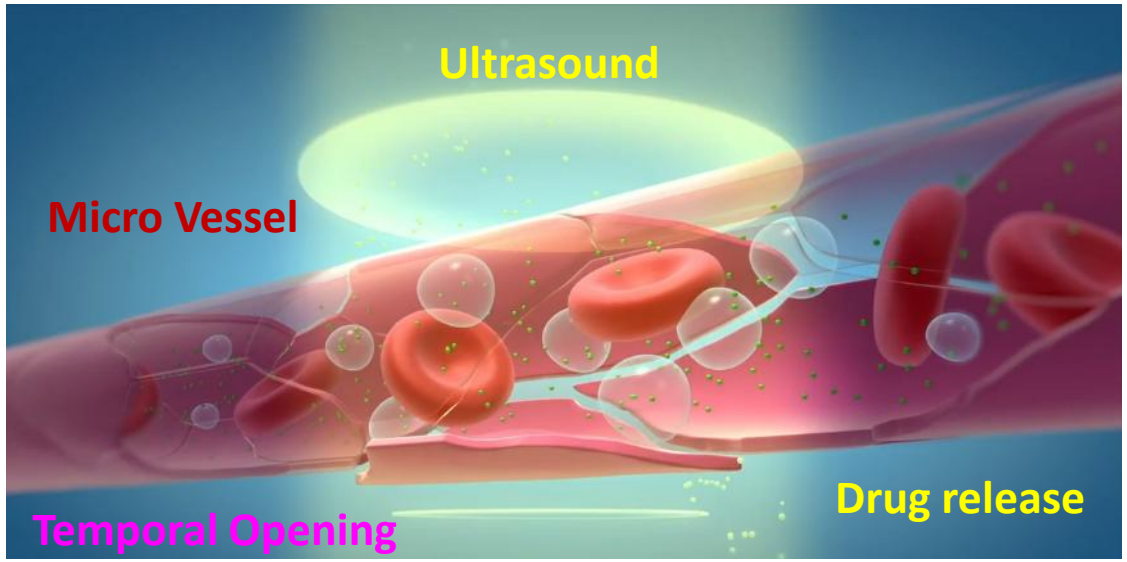
IV Administration of TB (Theranostic Bubbles) → **Low power Ultrasound Irradiation and Microbubble Oscillation** → **Transient Opening of Tumor Vessels /BBB** → **IV Administration of Drugs** → **Efficient Drug Delivery**



Theranostic Bubbles (TB)



Microbubble oscillated in micro vessel (in vitro)



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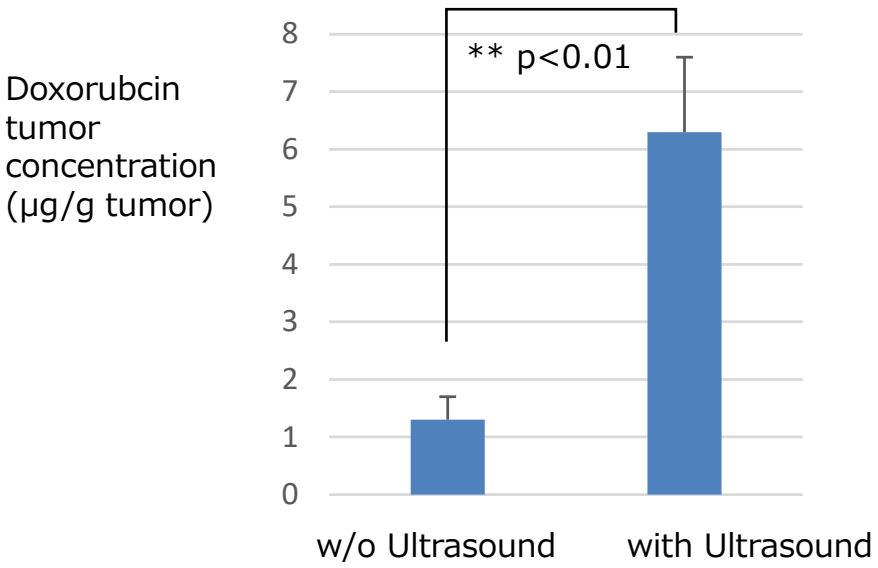
- Broad therapeutic applicability: small molecules, liposomes, nucleic acids, antibodies, ADCs
- Clinically feasible: uses existing ultrasound diagnostic workflows
- Strong IP & partnerships: international patents secured; LOI signed with ultrasound device manufacturer
- Large market potential: Oncology + CNS diseases

Indication	Combined Drug Type	Stage	Status
Pancreatic cancer	Established 1st-line anticancer drugs	Pre-clinical POC achieved	Manufacturing established Animal efficacy confirmed
Brain diseases (e.g. Parkinson's)	Nucleic acid drugs / Liposomes	POA achieved	BBB opening validation confirmed
Other cancers	Small Molecules/ Liposomes/ Antibody drugs / ADCs / ICIs	Discovery	Drug combination screening

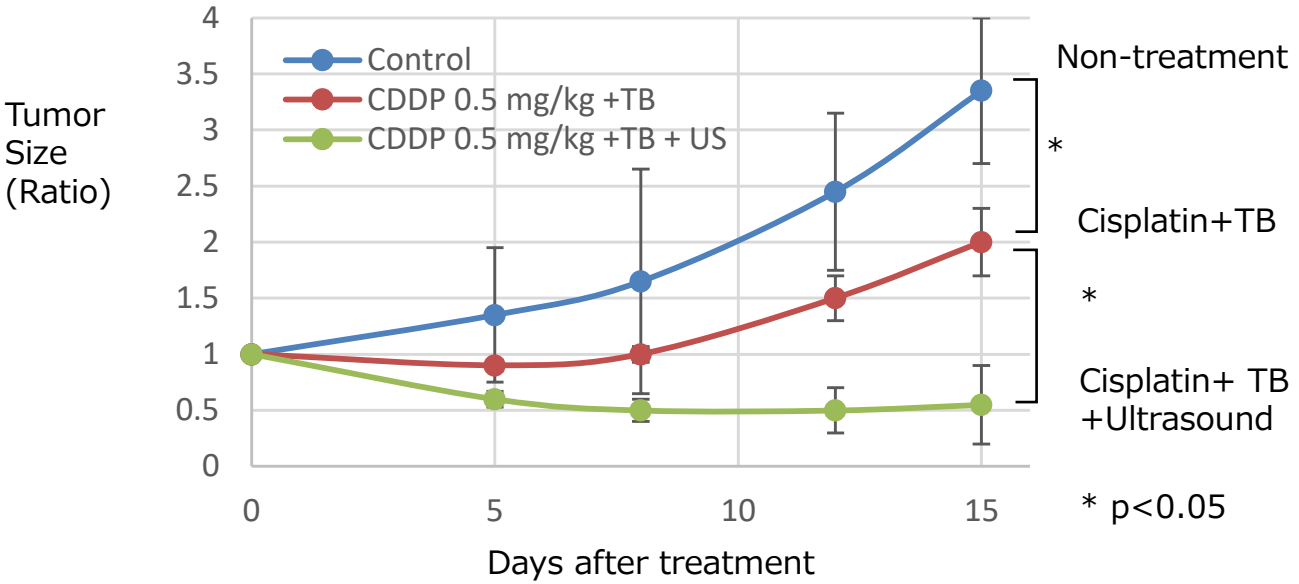
Oncology - Enhanced Drug Delivery and Anti-Tumor Efficacy

Enhanced Drug Delivery to Tumor Tissues



In colorectal tumor-bearing mice, the concentration of Doxil® in tumor tissues **increased approximately 5-fold** 6 hours after +TB administration when combined with ultrasound irradiation (**p<0.01**).

Enhanced Anti-Tumor Efficacy



In endometrial tumor-bearing mice, **cisplatin + TB + ultrasound** significantly **suppressed tumor volume growth** compared to cisplatin + TB alone (**p<0.05**).

Yamaguchi et.al, Cancer Science 2021; 00:1-11

- **Validated in various mouse tumor models: Pancreatic Cancer, Colorectal Cancer, Endometrial Cancer, Osteosarcoma, and Brain Tumors**
- **BUS-DDS maximizes the therapeutic potential of existing drugs**

(Detailed data available in partnering sessions)

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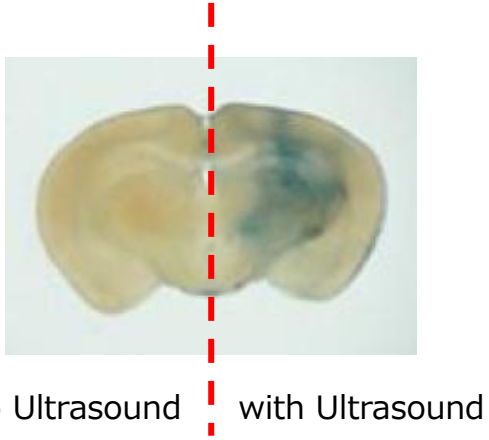
CNS Therapeutics - Crossing the Blood-Brain Barrier (BBB)

Enhanced Penetration into Brain Tissues

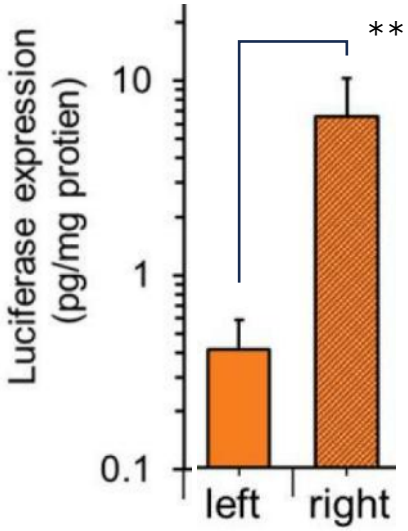


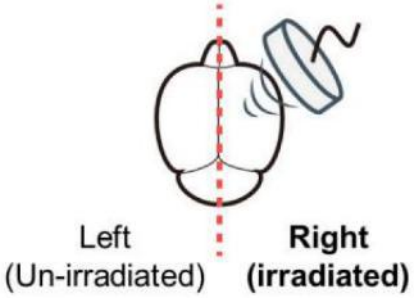
** p<0.01

In mice injected intravenously with **Evans Blue dye** and TB, **ultrasound irradiation applied to the right hemisphere** led to **over a 3-fold increase in dye accumulation** (**p<0.01**).

Omata et.al, J Control Release 311-312 2019, 65-73

Increased Gene Expression in Brain





In mice IV administered **mRNA-LNP encoding luciferase** and TB, **ultrasound irradiation applied to the right hemisphere** resulted in **over a 10-fold increase in luciferase expression** (**p<0.01**).

Ogawa et.al, J Control Release 348 2022, 34-41

In addition, in mouse brain tumor models, BUS-DDS combined with Cisplatin showed improved drug delivery and prolonged survival (Hagiwara et al., Pharmaceuticals 2023, 16, 1599)

(Additional case studies available in partnering sessions)

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