

Blood-Brain Barrier disruption with focused ultrasound and microbubbles



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Blood-Brain Barrier disruption with focused ultrasound and microbubbles

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Focused Ultrasound

Ultrasound imaging

Focused Ultrasound (FUS)

transducer	frequency range (MHz)	acoustic pressure (MPa)	acoustic intensity (W/cm ²)
Diagnostic	0.5	<0.1	low
BBB	0.5-2	0.1	400-1000
Thermal ablation	0.5-1	0.5-1	1-10
Photocoagulation	1-3	<0.5	1
Brachytherapy	1-3	0.5-1	<0.5
Thermal therapy	1-3	<1	0.5-1

FUS+IV injected microbubble induced BBBD

Microbubbles
FDA-approved US contrast agent, gas-filled microbubbles (1-3 μm size)

BBBD with FUS+MB

Sound pressure can activate microbubbles dynamics in the targeted brain

Mechanical stress may induce BBBD

Video courtesy of Dr. Konofagou in Columbia University

Blood-brain barrier (BBB)

Whole-body autoradiogram of a mouse sacrificed after IV injection of a small molecule (histamine, 111 Da)

>98% of small molecule drugs do not cross the BBB	~100% of large molecule drugs do not cross the BBB	<1% of drug companies have a BBB drug targeting program	<1% of academic neuroscience programs emphasize BBB transport biology
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William M. Pardridge, "Blood-brain barrier delivery"
Drug Discovery Today Volume 12, Numbers 1/2 January 2007 p54-61

Non-invasive, temporary, targeted BBB disruption

- Delivery of therapeutic agents into targeted brain

579.0kDa

~50kDa

~100kDa

150kDa

Cells

- Anti-cancer agents: Doxorubicin / Doxil
Park et al. 2012 JCR, Treat et al. 2007 UC
- Parkinson's disease: dopamine D4 receptor antibody
Kinoshita et al. 2006
- Alzheimer's disease: Anti- β -amyloid antibody
Raymond et al. 2008 PLoS ONE
- Anti-cancer agents: Herceptin
Park et al. 2012 JCR, Kinoshita et al. 2006 PNAS
- Neural stem cells
Park et al. In preparation

DGMIF

Kinetics of Blood brain barrier disruption

DGMIF

MR-guided FUS for BBB disruption

Experiment set up

Animals

- Twenty male Sprague-Dawley rats (weighing: 250-350 g)

Experiment conditions

- 0.69 KHz frequency transducer (Diameter: 100 mm, Radius curvature: 80 mm)
- 10 ms bursts at 1Hz for 60 s with PRPA 0.68 and 0.72 MPa
- USCA (Definity) IV injection at dosage of 10 μ l/kg
- MRI contrast agent (Magnevist) IV injection at 0.125 mmol/kg
- Doxorubicin hydrochloride (M.W: 579.98) IV injection at a dose of 5.67mg/kg
- Trypan blue IV injection 0.1g/kg in 0.45% NaCl

DGMIF

Characterizing BBBD with dynamic contrast enhanced MRI

$t_{1/2} \sim 2h$

A

B

A

B

J. Park et al. "The kinetics of blood brain barrier permeability and targeted doxorubicin delivery into brain induced by focused ultrasound." J Control Release. 2012 Aug 20;162(1):134-42. 2012

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Blood tumor barrier disruption

DGMIF

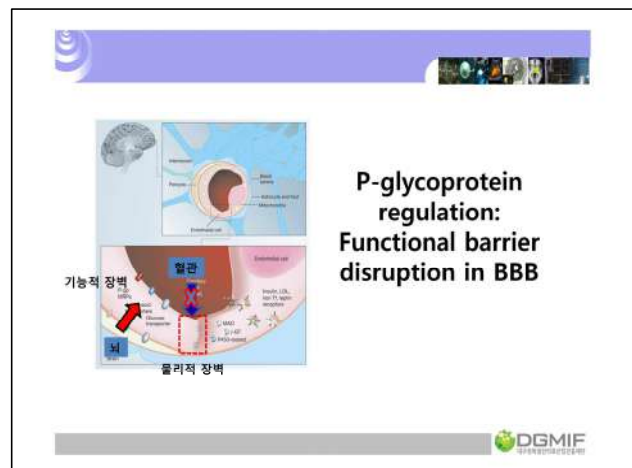
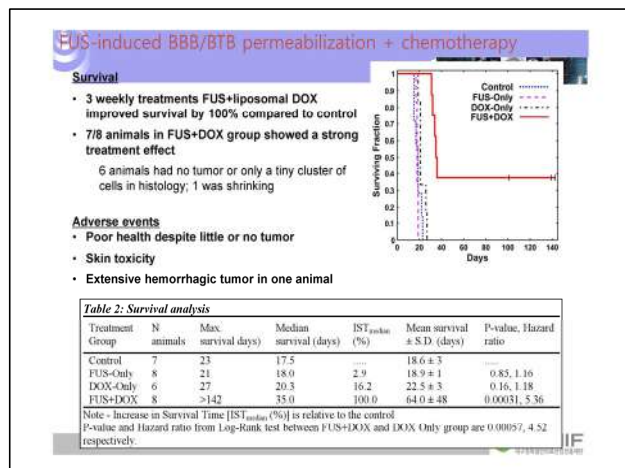
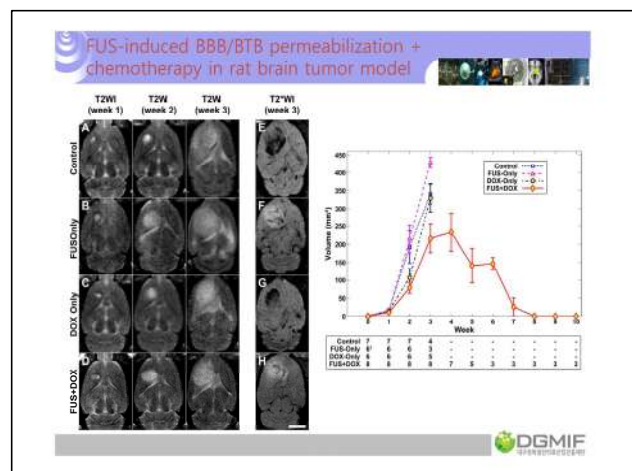
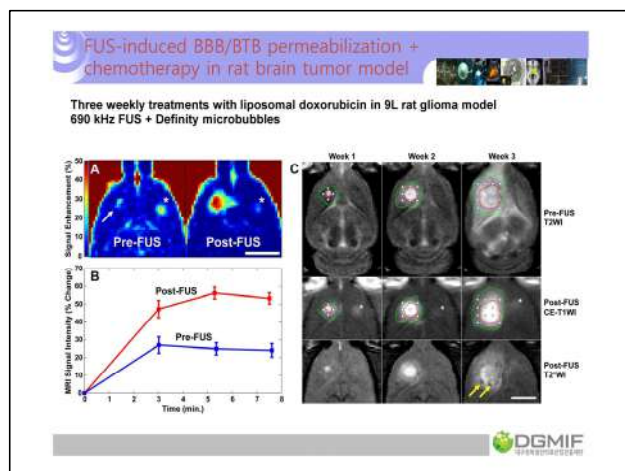
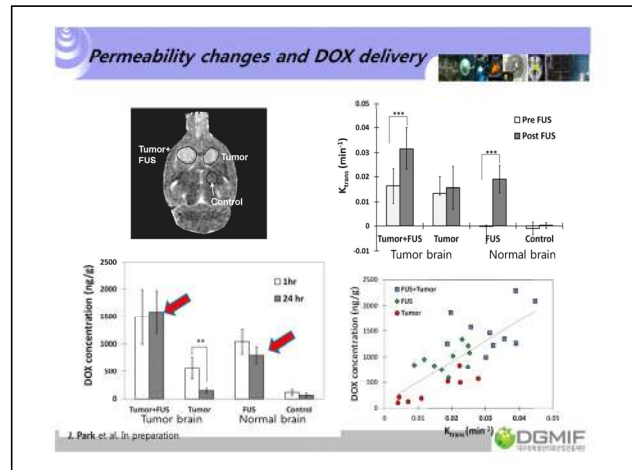
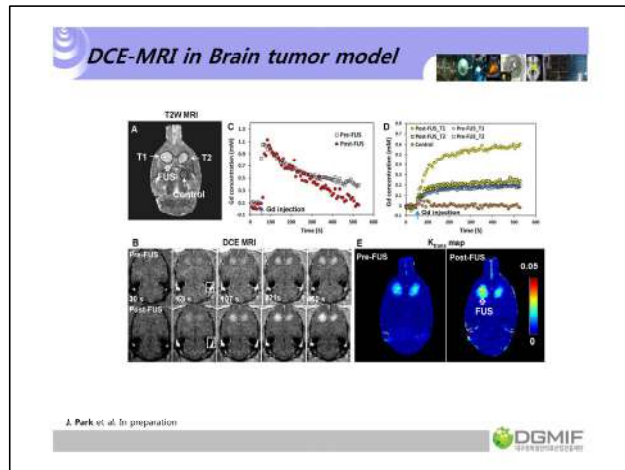
Brain tumor model: 9L cells

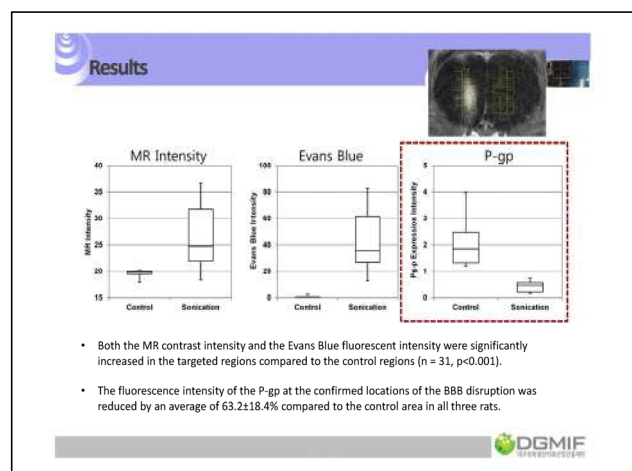
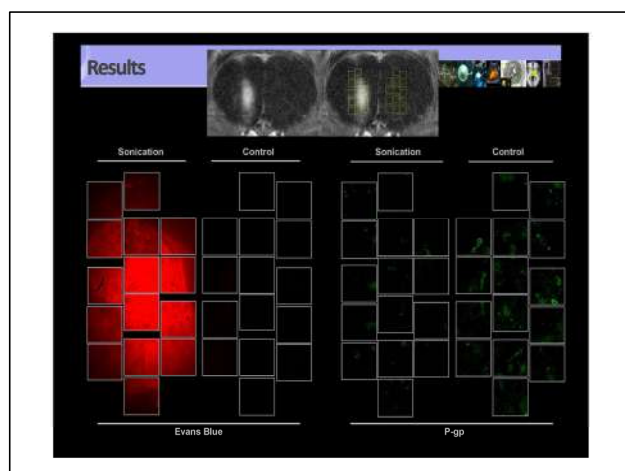
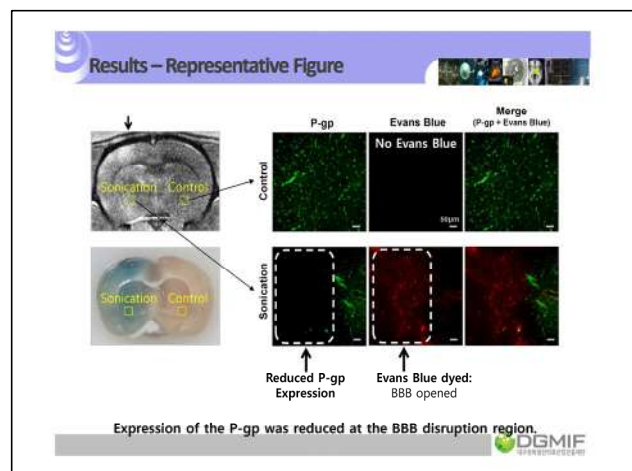
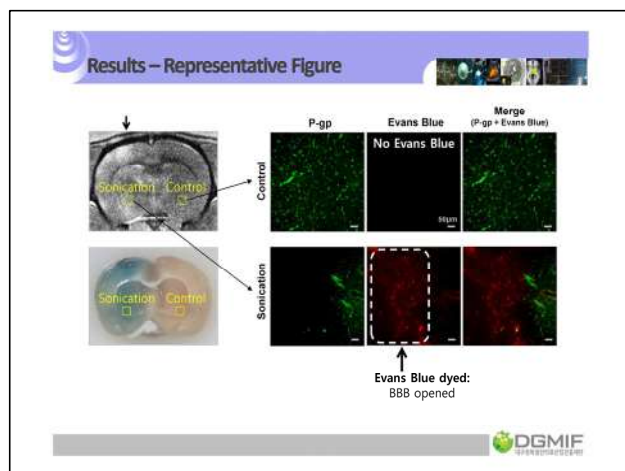
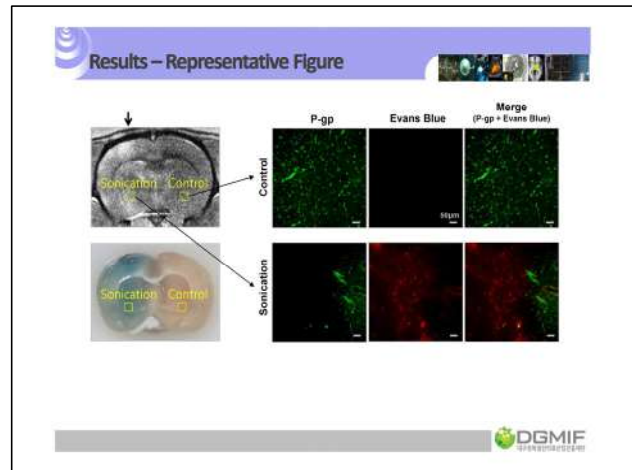
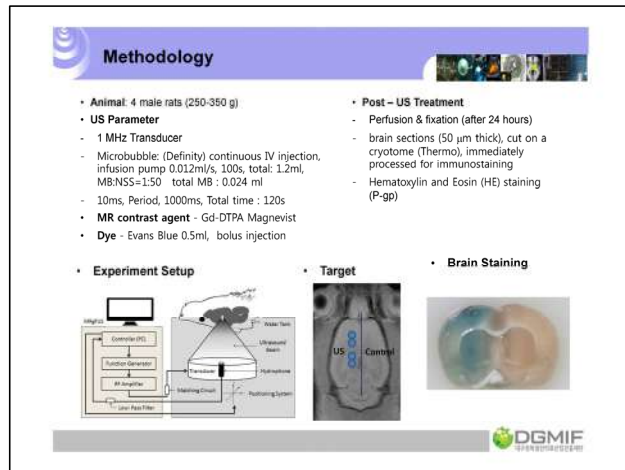
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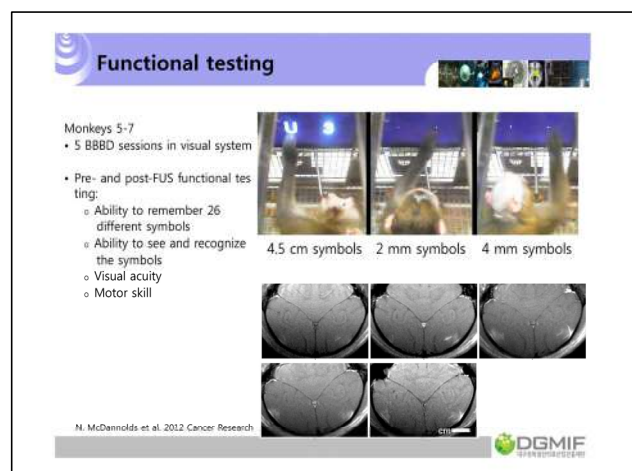
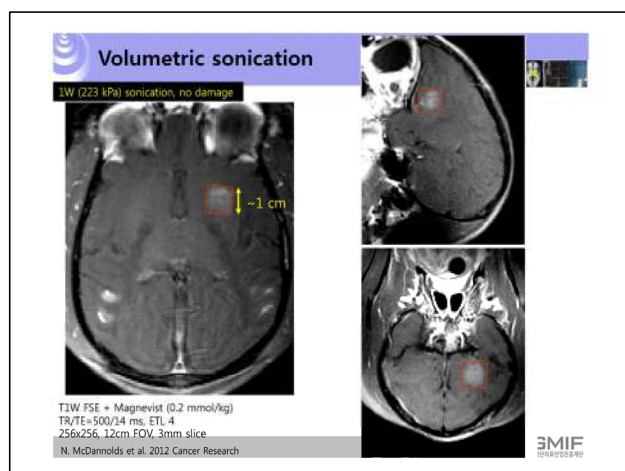
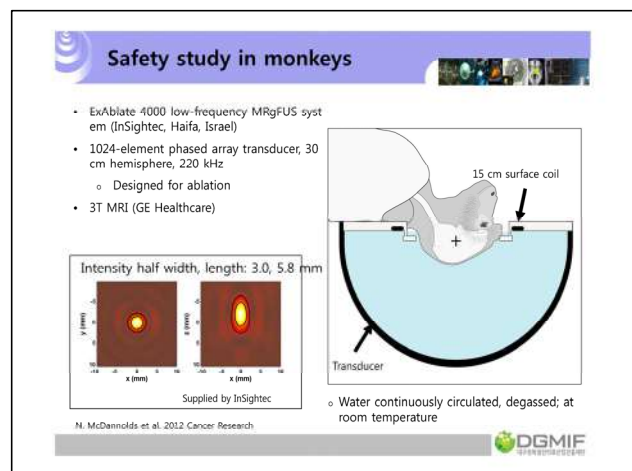
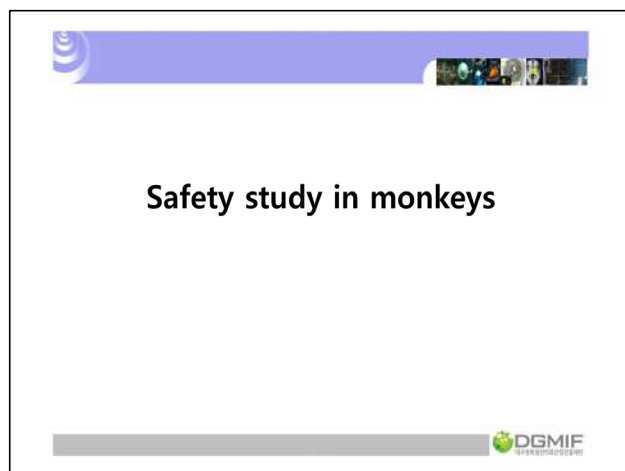
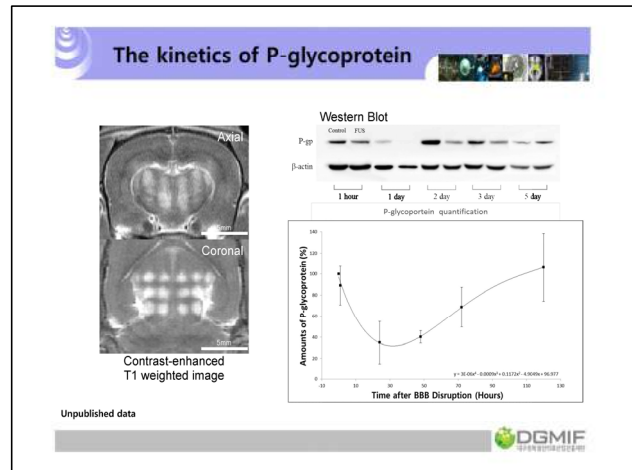
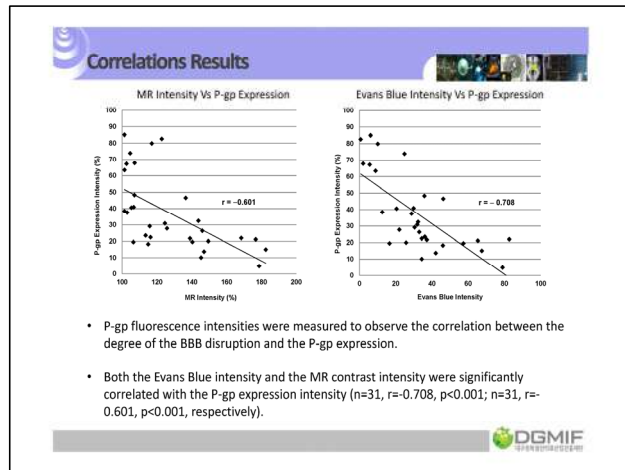
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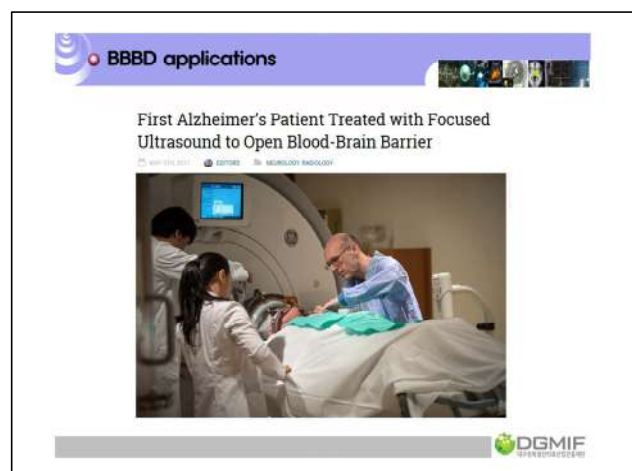
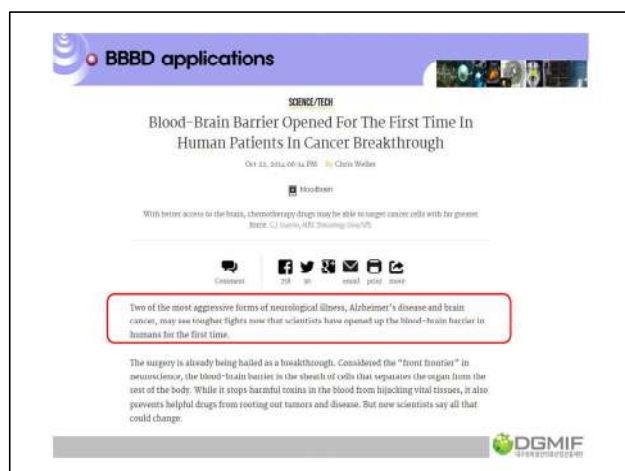
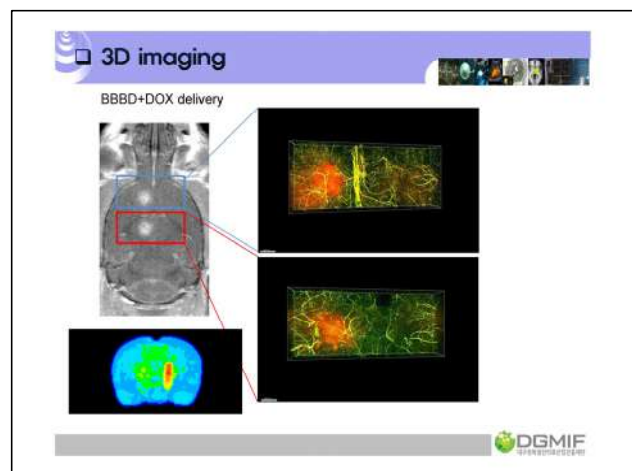
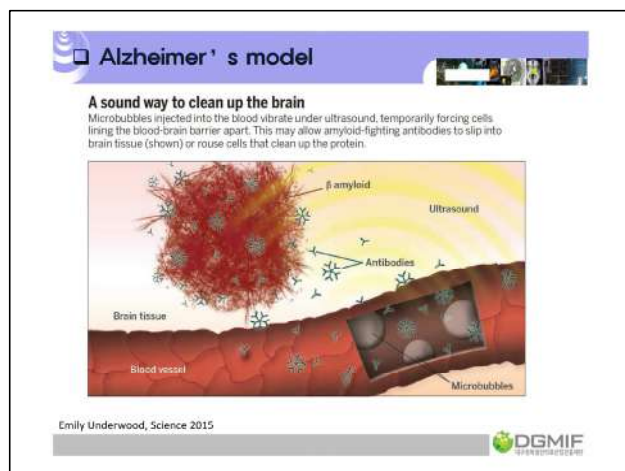
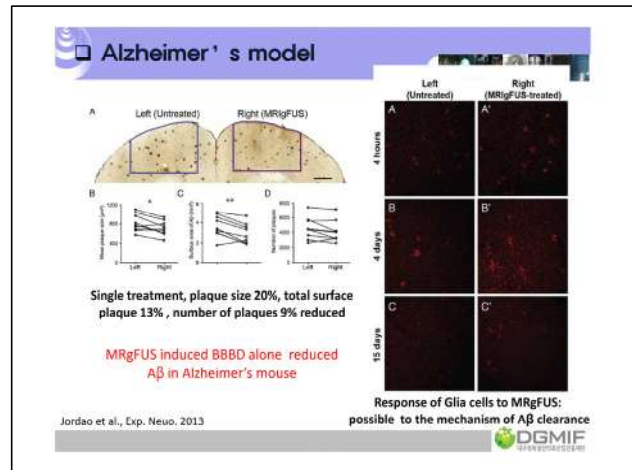
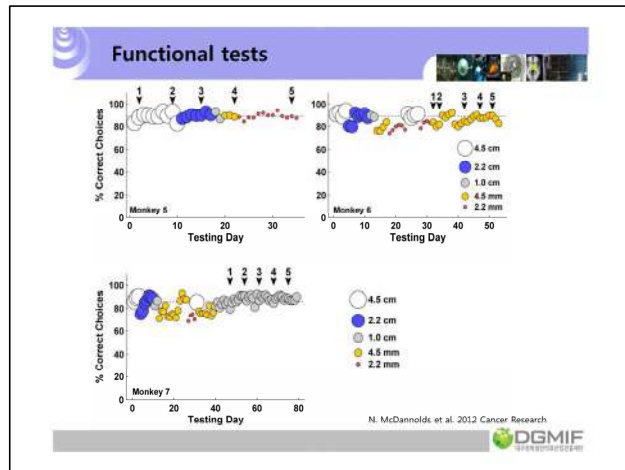
Unpublished data


DGMIF












□ Conclusions

- MR-guided FUS
 - induced non-invasive, temporary, targeted, repeated BBB/BRB/BTB disruption associated with drug delivery
 - can be used for treatment of most CNS disorders



Thank you

Questions?

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