Avant-garde of RNA therapeutics

BIORCHESTRA

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Introduction (Team & History)

Management	**Founder/CEO**	Branden JH (Jin-Hyeob) Ryu, PhD
	CMO	Louis St.L. O'Dea, MD moderna AKCEA Oxford Immunotec EMD SERONO
	CFO	Young-Gil Kim, CPA
Location	**Headquarter**	Daejeon, South Korea
	US affiliate	One Kendall Cambridge, MA
	Research center	Daejeon, JPOD@BOSTON, JLABS@NYC
	GMP site	Daejeon, South Korea
Employees	78 (PhD: 26)	
Investors	MIRAE ASSET, E&, SBI Investment, CKD venture capital, IMM In Manus Mundus, DAYLI Partners, LSK INVESTMENT, INVESTMENT	
Total fund raising	79 million USD	

Year	History
2022	• Series C (48 mil USD)
2021	• BDDS polymer-GMP site in South Korea • US affiliate registration (BOSTON) • Quick fire challenge award in Neuroscience (JJ) • Open US office @ JLAB in NYC
2020	• Open US office @ JPOD in Boston • Endless Frontier Labs program graduation (US) • Series B extension (10 mil USD)
2019	• Series B (17 mil USD)
2018	• Series A funding raised (3 mil USD for POC) • Elected as Market Related Future Biotechnology Development Business (South Korea)
2017	• Seed funding raised (0.5 mil USD), 5 employees • TIPS (South Korea)
2016	• BIORCHESTRA Co., Ltd. foundation

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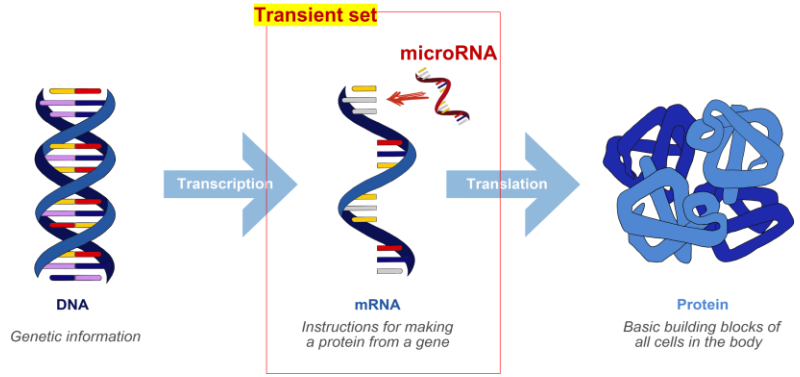
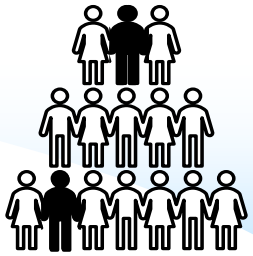
Introduction (Company technology)

RNA TARGET DISCOVERY & PATIENT SELECTION

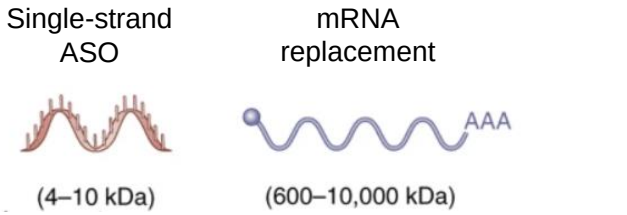


- Selection of individuals with upregulated expression of a target microRNA within clinically diagnosed population
- Selection of individuals with mutation of gene within clinically diagnosed population



RNA PLATFORM

▪ PROPRIETARY SEQUENCE

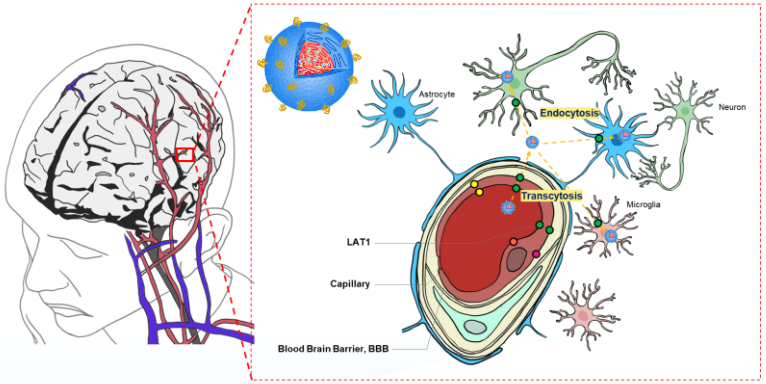


- microRNA-based epigenetic reprogramming
- mRNA-based genetic reprogramming

BRAIN DDS PLATFORM

▪ BDDS™-CNS

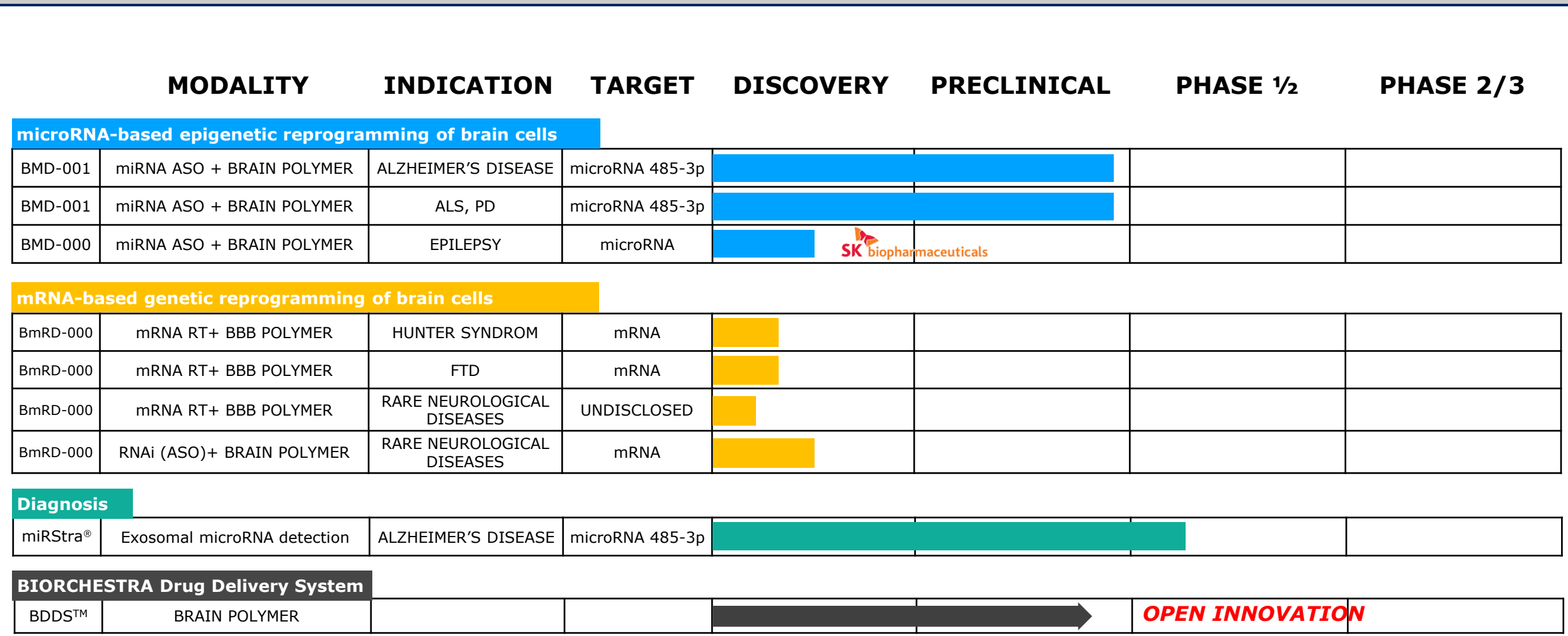
Brain-targeting polymer for nucleic acid delivery



HIGHLY-EFFICIENT RNA-BASED REPROGRAMMING OF HUMAN BRAIN CELLS

=> REPROGRAMMING OF BRAIN CELLS TO CORRECT ABNORMAL FUNCTION THAT LEADS TO DISEASE

Introduction (Pipeline & Technology)

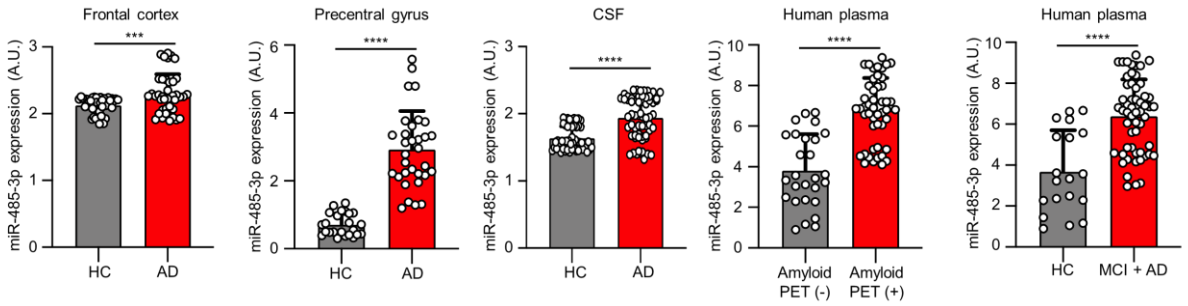


miRNA: microRNA / mRNA: messenger RNA / RT: Replacement Therapy

TARGET VALIDATION

miR-485-3p induced AD neuropathological hallmarks can be reversed by TAMI-0320 (miR-485-3p ASO)

1. miR-485-3p in clinical samples



2. Pathogenic role of miR-485-3p

miR-485-3p gain of function study

- Neuroinflammation
- Aβ production
- Tau production
- Synaptogenesis impairment

3. Molecular function of miR-485-3p

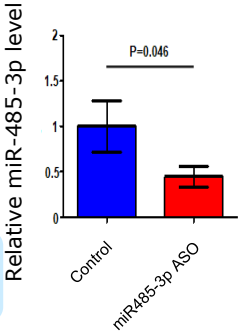
SIRT1 regulation
- Neuroinflammation
- NLRP3 inflammasome
- Autophagy
- ß-amyloidopathy & Tauopathy

PGC-1α regulation
- Neuro-restoration
- Mitochondrial biogenesis

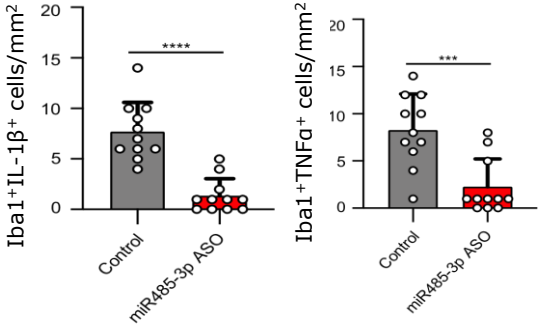
CD36 regulation
- Phagocytosis
- ß-amyloidopathy

4. ASO-mediated miR-485-3p inhibition reverses AD pathogenesis (PoC, ICV injection)

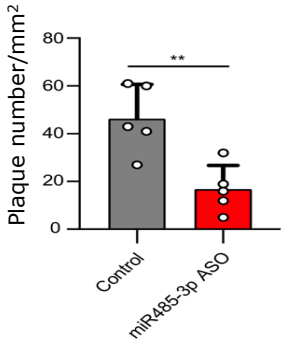
- ASO-mediated inhibition



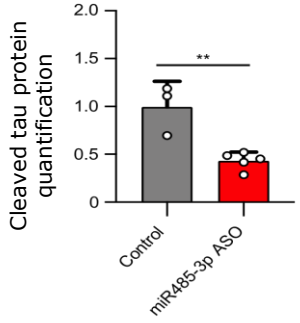
- Downregulation of neuroinflammation



- Aβ clearance



- Reduction of cleaved tau

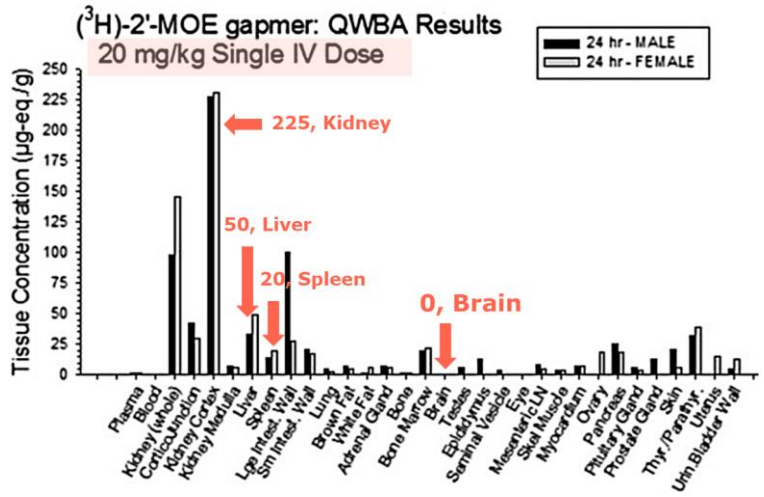


- Drug: TAMI-0320 (in vivo-jetPEI® formulation, commercial)
- RoA: ICV injection
- Animal model: 10~13 months **old 5XFAD mice**

doi: 10.3390/ijms222313136

Currently, Naked ASO shows No blood-brain barrier penetration through intravenous injection and only limited portion was delivered to brain and spinal cord through intrathecal injection.

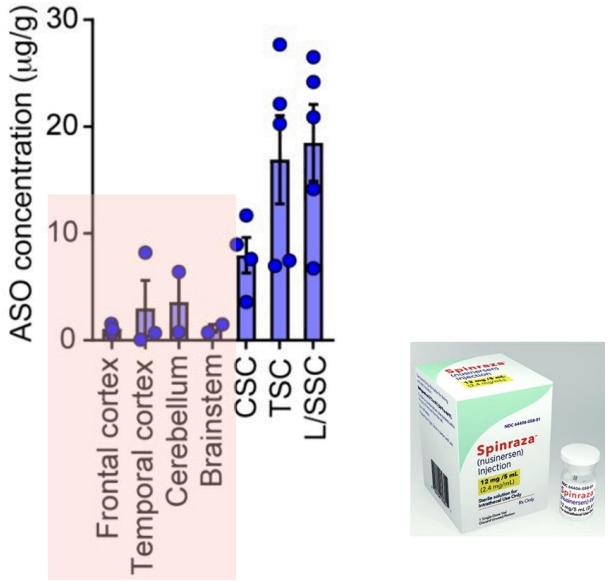
Naked ASO administration via Intravenous



Tissues	Target K_d (%)
Liver	−95
Kidney	−97
Adipose	−75
Heart	−65
Mes LN	−61
Diaphragm	−50
Brain	0
Duodenum	−64
Stomach	−55
Lung	−86
Adrenal	−90
Gall bladder	−95
Bladder	−51
Prostate	−79

Geary et al. Advanced drug delivery review, 2015

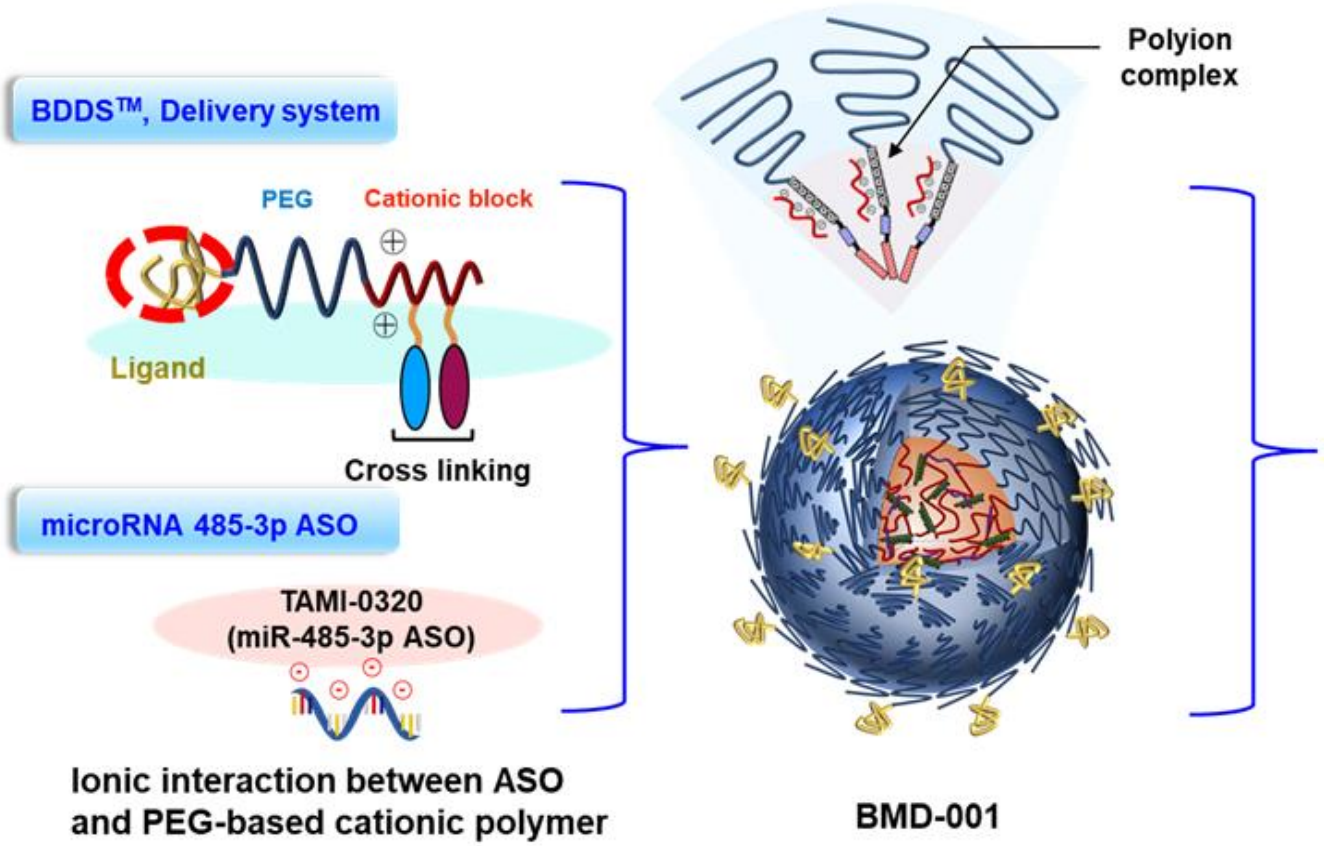
Naked ASO administration via Intrathecal

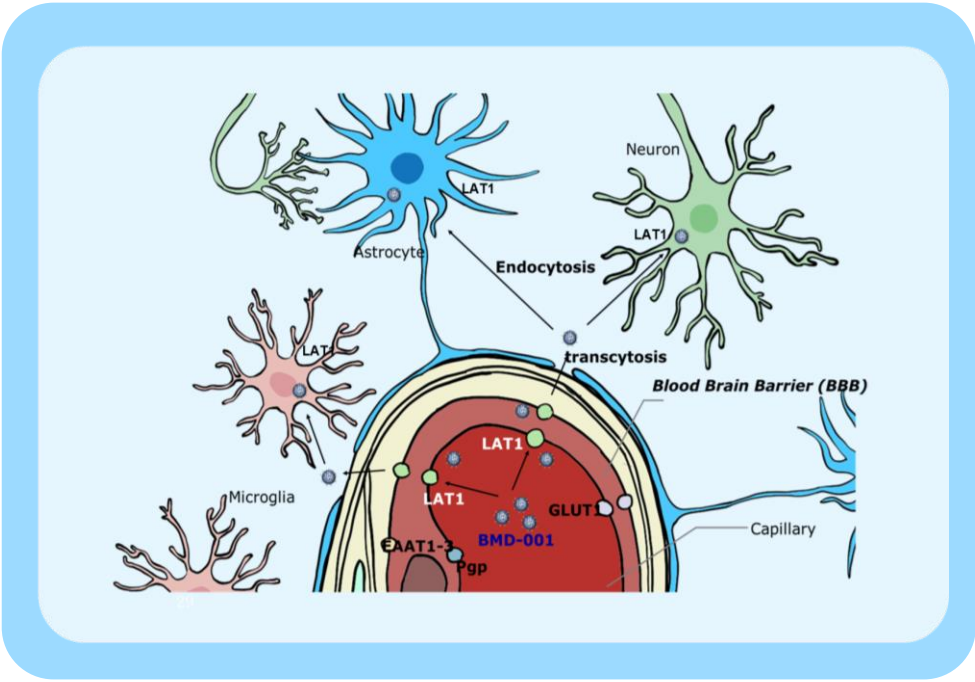


Ramos et al. The Journal of clinical investigation, 2019

DDS-BIORCHESTRA Solution

Innovative delivery technology for Nucleic Acid for CNS

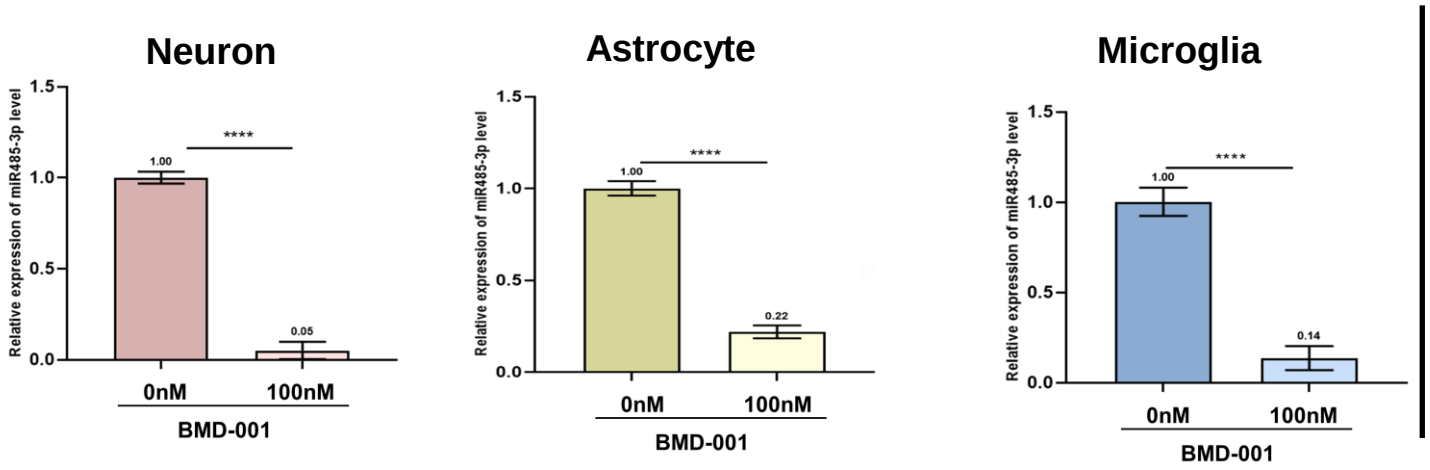


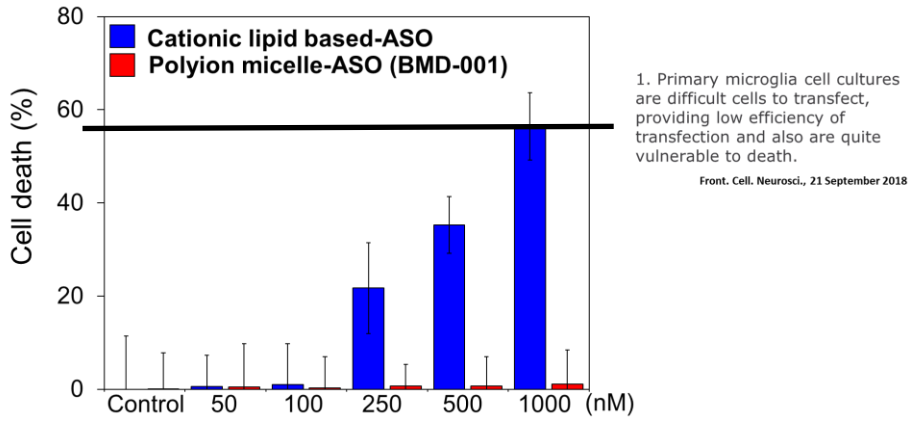


Large Amino acid Transporter targeting strategy to make our proprietary platform technologies cross the BBB and penetrate Brain cells through transporter-mediated transcytosis and endocytosis (TMT and TME).

DDS (PoC – In vitro test)

Successful delivery of ASO across brain cell membranes and into the cells





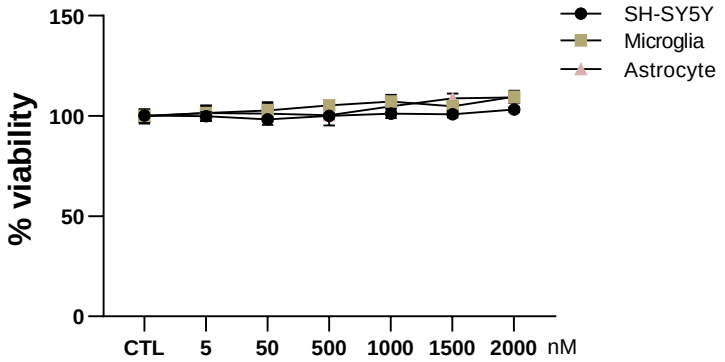
1. Primary microglia cell cultures are difficult cells to transfect, providing low efficiency of transfection and also are quite vulnerable to death.

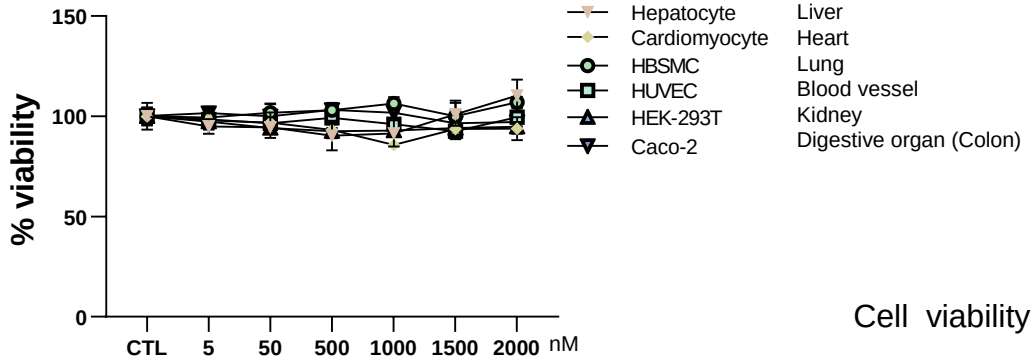
Front. Cell. Neurosci., 21 September 2018

- **Inhibition of target microRNA observed across the human-derived brain cells**
- **Noticeable safety for brain cells of BIORCHESTRA's drug delivery system compared to cationic lipid-based delivery, showing the potential of safe applications in humans.**

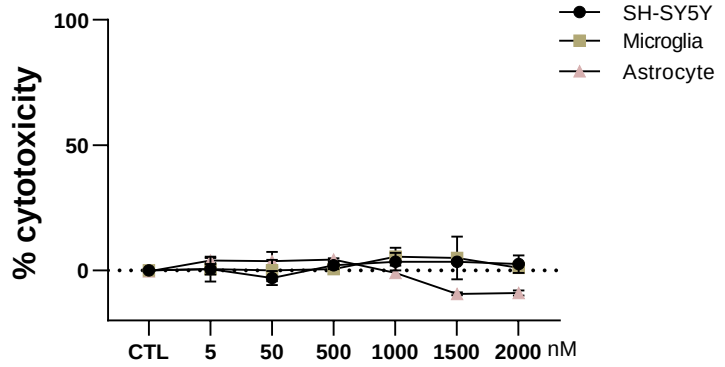
DDS (PoC – In vitro viability test)

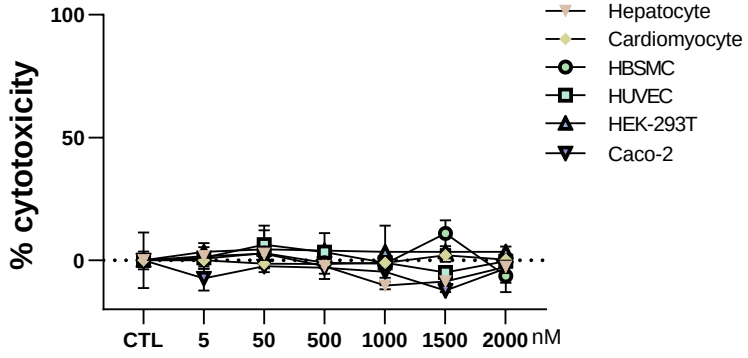
In vitro viability test





Cell viability assay: WST-8 assay





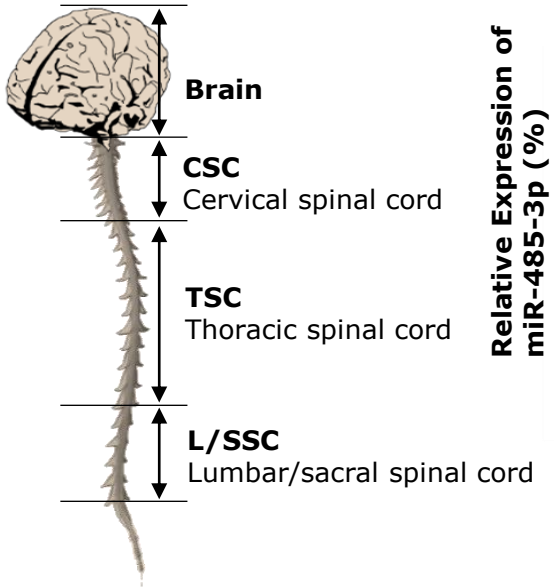
Cytotoxicity assay: LDH assay

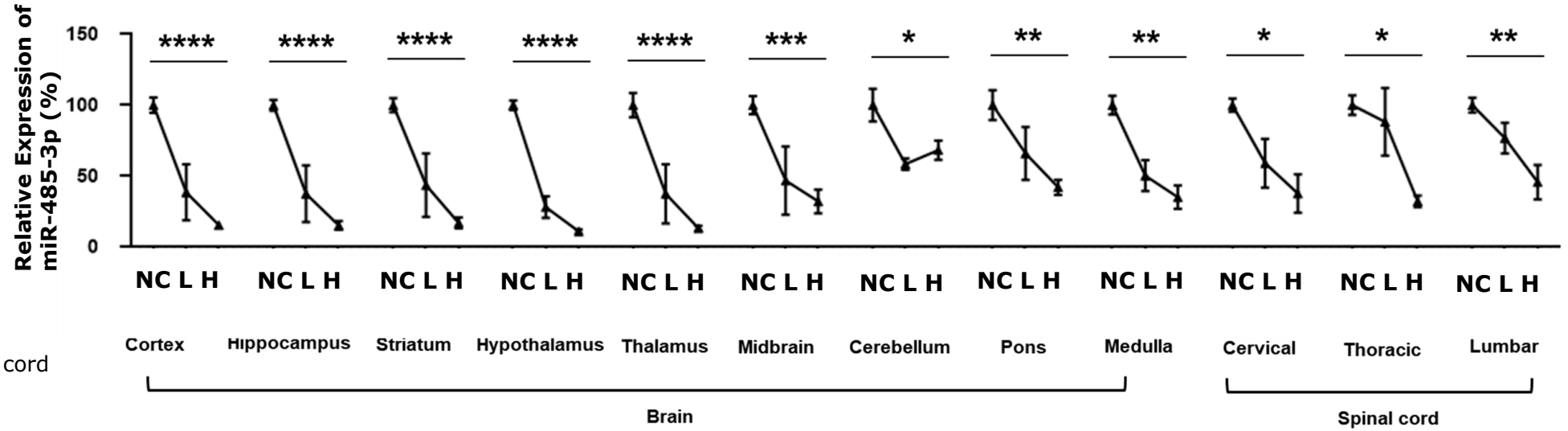
Remarkable cell viability of our formulation in various cell types derived from major human organs, showing the potential of safe applications in humans.

DDS (PoC – ICV injection)

Successful delivery of ASO across CNS

Intracerebroventricular (ICV) administration



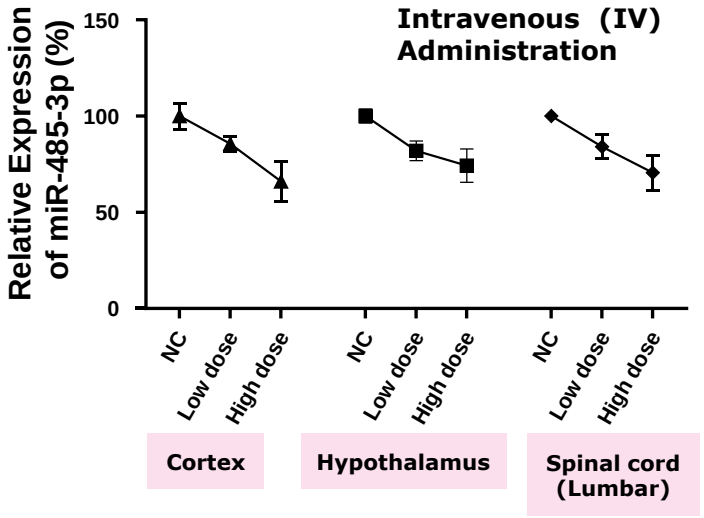


NC : Negative Control
L : Low dose
H : High dose

- **Inhibition of target microRNA observed across the CNS of mice following ICV administration**

DDS (PoC – IV injection)

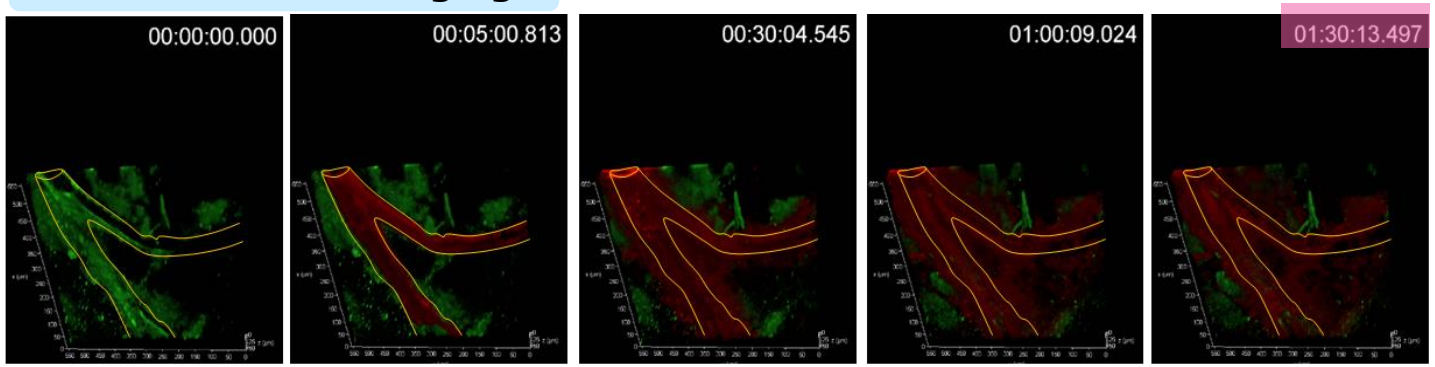
Successful delivery of ASO across CNS



Inhibition of target microRNA observed across the CNS of mice following IV administration

Two-way ANOVA	P value	P value summary
Interaction	0.9333	ns
Drug	**0.0001**	***
Brain region	0.9602	ns

In vivo confocal imaging



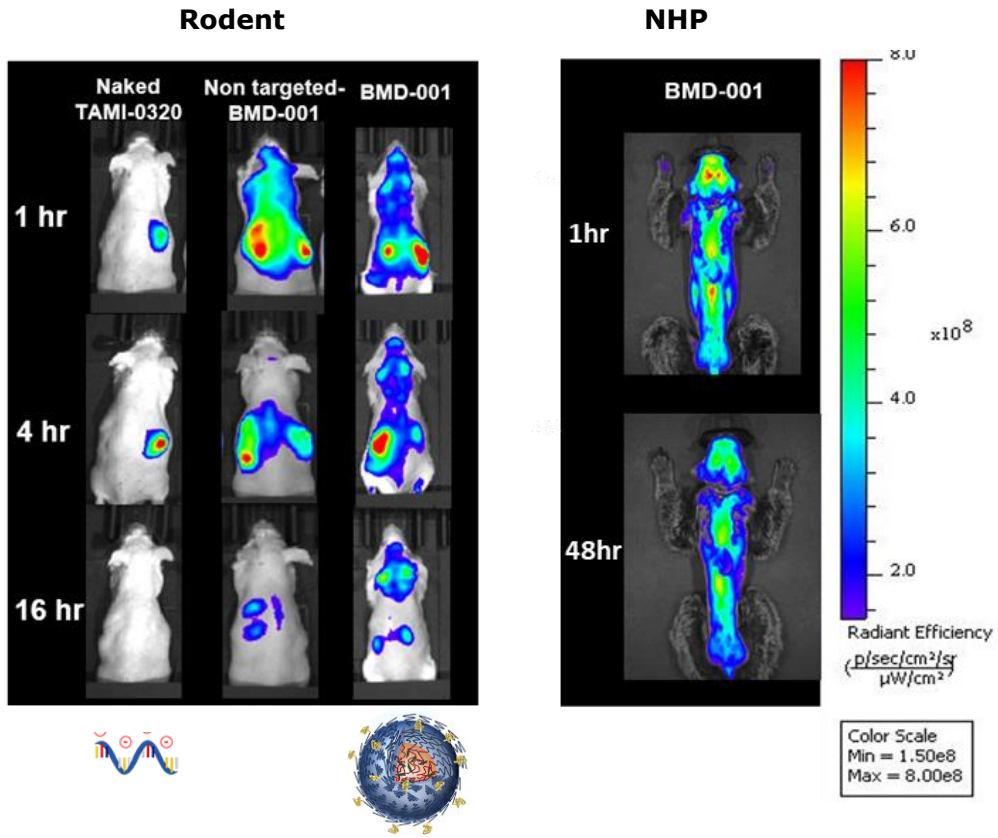
* Opening the skull
* Cy5.5 labeled RNA loaded micelle
* ***Stellaris s-5, Leica***
* Micelle administration by I.V. injection (tail vein) using catheter
* Imaging time: up to 90 min

EGFP signal (Ex/Em = 489/511): Brain parenchyma (Auto fluorescence)

Cy5.5 signal (Ex/Em = 672/690): Cy5.5 labeled ASO loaded micelle (BMD-001-Cy5.5)

Blood brain barrier

IVIS imaging

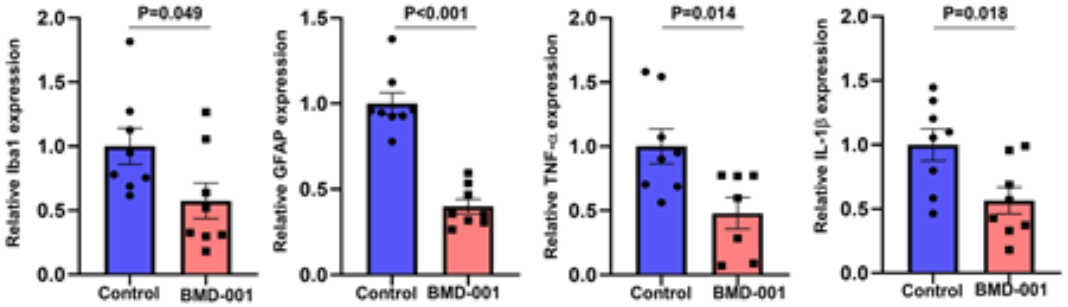


BMD-001 (BIORCHESTRA's ASO formulated with BDDS-CNS) delivery across the BBB following IV injection. BBB penetration of BMD-001 is superior to the non-targeted BMD-001.

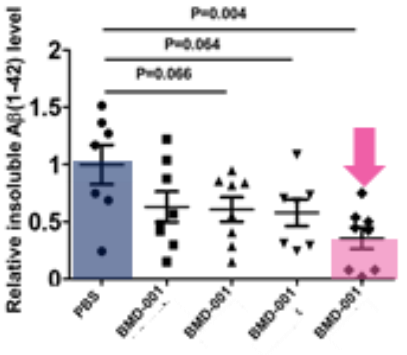
In-vivo preclinical efficacy data (AD animal model) – IV injection

BMD-001 treatment once a week for 4 weeks (5XFAD) / Single injection (3xTg)

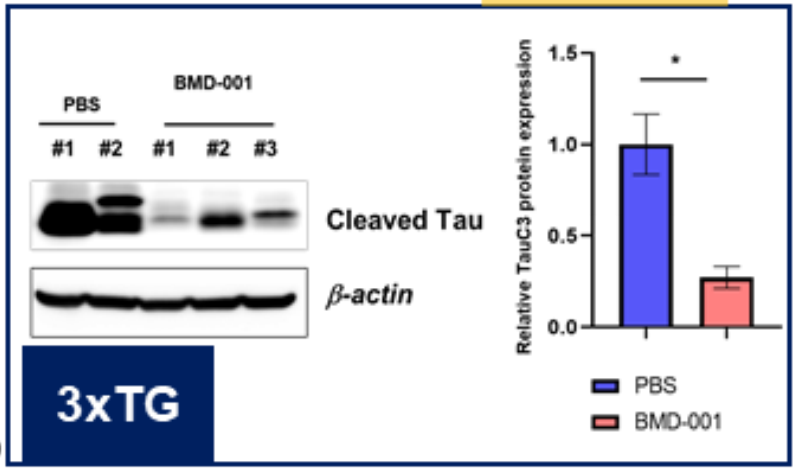
1. Downregulation of neuroinflammation (Hippocampus)



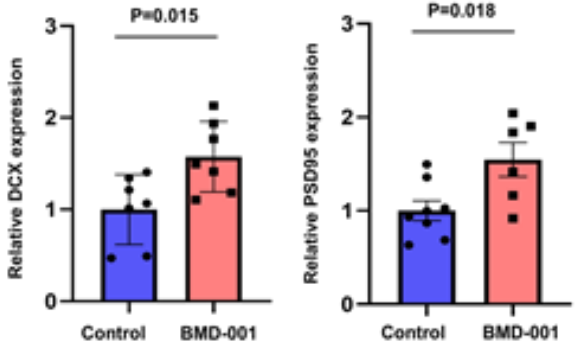
2. Enhanced Aβ clearance & Cleaved tau (Cortex)



* Western blot assay of insoluble Aβ (1-42)

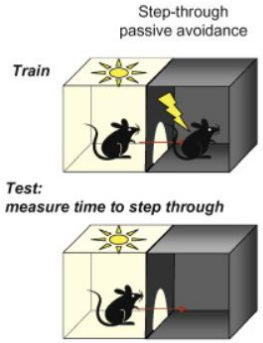


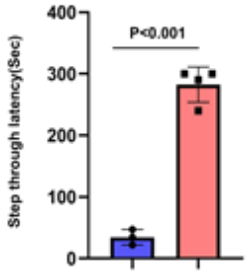
3. Neurorestoration (Hippocampus)



10, 13 months old 5XFAD mice and 3xTg

4. Improved cognitive function





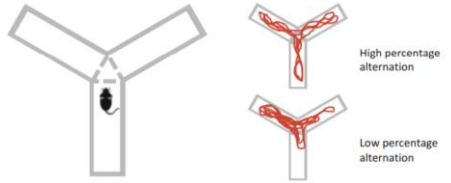
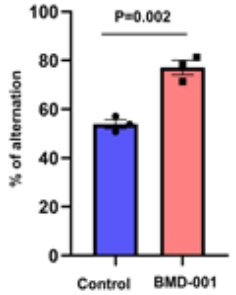


Fig. 1 Measurement of spontaneous alternation in the Y-maze. A high percentage alternation is seen as a high proportion of entries into consecutive arms. A low percentage alternation (e.g., poor working memory) is seen as a higher proportion of repeated entries into the same arm

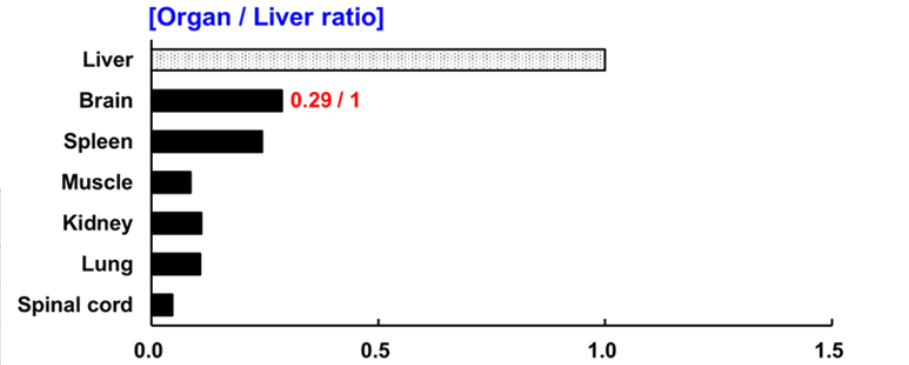


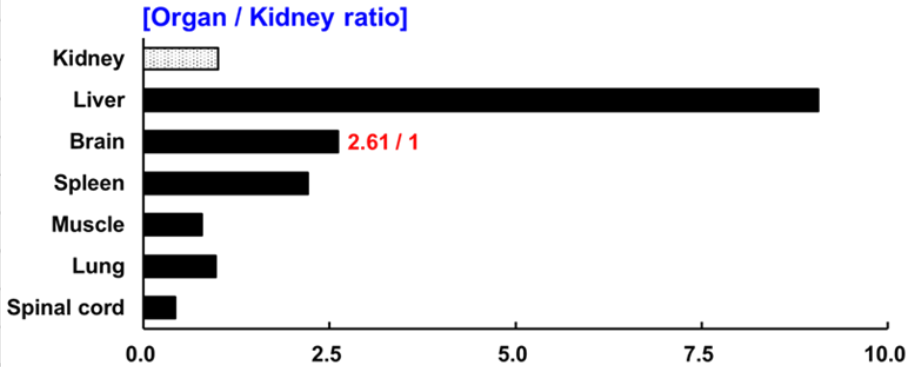
In-vivo Biodistribution of BMD-001

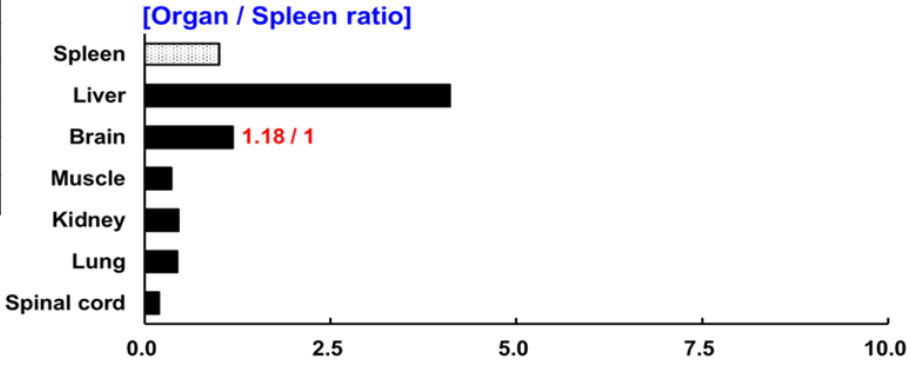
- Mice
- C57BL6/J

Region	
Brain	Cortex
	Hippocampus
	Cerebellum
	Striatum
	Olfactory bulb
	Hypothalamus
	Thalamus
	Medulla
	Midbrain
	Pons
Spinal cord	Cervical
	Thoracic
	Lumbar
Muscle	Cardiac
	Skeletal
Other organs	Lung
	Spleen
	Liver
	Kidney

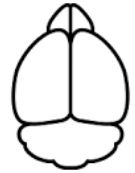
TAMI-0320=ASO



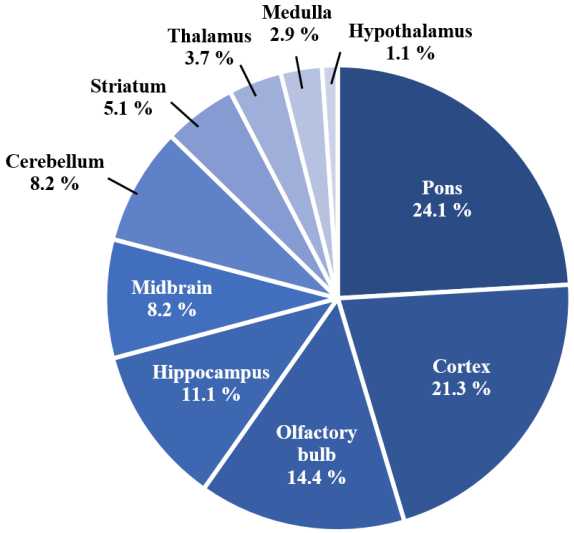




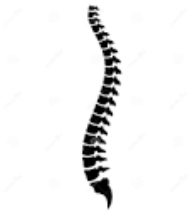
Distribution of TAMI-0320 in brain subregions



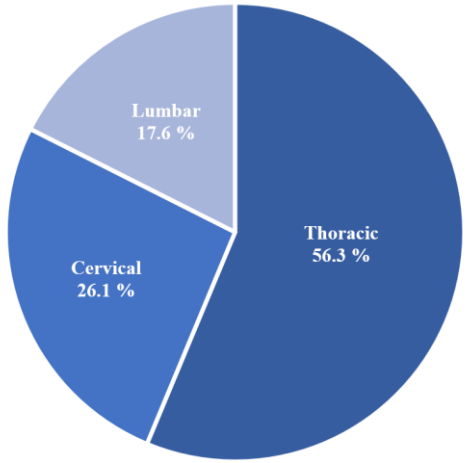
[Brain]



Distribution of TAMI-0320 in spinal cord



[Spinal cord]



Summary of BMD-001 in vivo safety data

No test article-related changes in Single dose and Repeat dose Toxicology studies

Non-GLP Tox studies in Rodents

- **Single IV infusion dose (systemic Tox)**
- no test article-related adverse effect
- No mortality, abnormal clinical signs, no changes in body weight, hematology and serum chemistry

Non-GLP Repeat Tox studies in Rodents

- **Multi-IV bolus injection dose (low & high dose / 5 times / once every week)**
- No test article-related adverse effects
- (no mortality, abnormal clinical signs and gross findings, no changes in body weight, hematology and serum chemistry)

Non-GLP Tox study in NHP

- **Single IV infusion dose (systemic Tox)**
- No test article-related adverse effects
- (no morality and abnormal clinical signs, no changes in hematology and serum chemistry)

GLP Tox study in Rat and NHP (On-going)

- **Multi-IV infusion dose study design for 7 weeks and 13 weeks**

Biomarker strategy

To increase the success rate of BMD-001 clinical trial through a precision medicine approach

miRStra® can be used as a companion diagnostic for patient selection and treatment monitoring for BMD-001 trials in AD
Patients will be selected and monitored by measuring miR-485-3p expression level

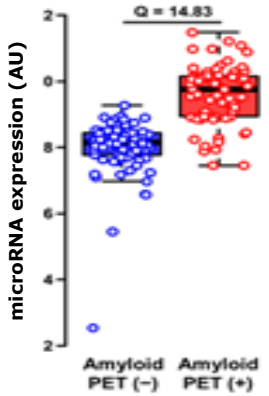
Patient Selection

Clinical AD diagnosis

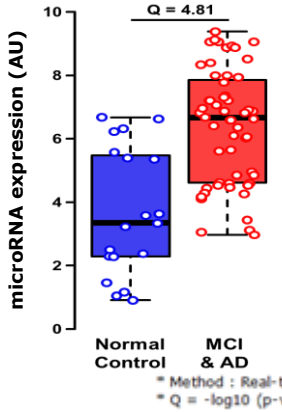
miRStra®:
microRNA 485-3p
detection kit

miR-485-3p expression

Saliva exosome



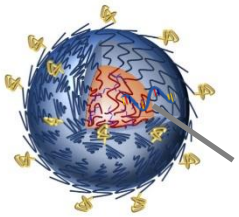
Plasma exosome



AD therapy

BMD-001
: Polyion complex micelle containing TAMI-0320

TAMI-0320 : Antisense-oligonucleotide of miR-485-3p

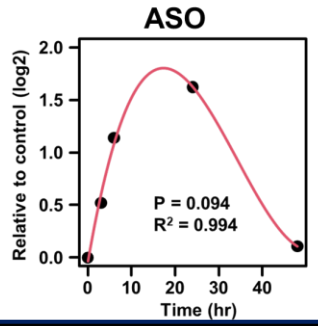


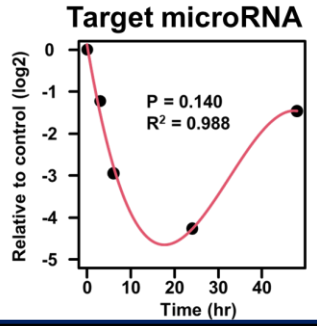
TAMI-0320 inhibits specific microRNA

In vivo long-term blood circulation
High BBB penetration ratio

Monitoring treatment effects

: We will monitor the effectiveness of BMD-001 throughout the clinical trials.





SUMMARY

Novel science (BMD-001)

- microRNA 485-3p inhibition induces disease modifying therapeutic effect in Alzheimer's disease

Novel RNA delivery system (BDDS™-CNS)

Table 1 Challenges erected by evolutionary barriers to RNA therapeutic delivery

Feature	Challenge for delivery
Oligonucleotide size and charge	Too large or too charged to passively diffuse across the lipid bilayer
RNase susceptibility	Rapid degradation by blood and tissue RNases.
Reticuloendothelial system	Rapid clearance from the blood by the kidneys and liver scavenger receptors
Immunogenicity	Oligonucleotides activate extracellular and intracellular innate immune responses
Endocytosis	Oligonucleotides are taken up, but trapped inside endosomes

Nature Biotechnology (*Nat Biotechnol*) ISSN 1546-1696 (online)

BIORCHESTRA Innovative RNA delivery system

- Small-sized and minimized charged formulation enables efficient delivery of RNA into the cells
- Formulation structure avoids rapid degradation by blood and tissue RNases
- Formulation dramatically reduces rapid clearance from kidneys and liver accumulation
- Formulation avoids endosomal TLR-RNA sensing pathway (Innate immune responses)
- Proprietary formulation enables efficient endosomal escape of RNA

Biomarker strategy (miRStra®)

- miRStra® is a tool for identifying patients earlier and tracking neurodegenerative diseases with BMD-001 as a precision medicine approach

FUTURE DIRECTION OF BIORCHESTRA

	PROGRAM	TARGET	MODALITY	STRATEGY	ROA	
BRAIN CELLS 	microRNA-based epigenetic reprogramming	Overexpressed microRNA	ASO	• Transient inhibition of target microRNA • Controllable manner	IV	• Internal program • Collaboration
	mRNA-based genetic reprogramming	Mutant mRNA	ASO	Durable silencing of target mRNA	IV or IT	• Internal program
			siRNA	Durable silencing of target mRNA	IV or IT	• Collaboration
		Mutant DNA	Gene editing complex	• Transient expression of target Cas mRNA & Guide RNA	IT	• Collaboration
		Normal mRNA	mRNA	• Transient expression of target mRNA • Controllable manner	IV or IT	• Internal program

- **Internal Brain cell reprogramming program expansion**
- **Open collaboration (Indication collaboration)**
- **Cellular reprogramming in other organ systems is ongoing (Muscle, lung, ocular, joint, cancer and immune cells)**

We strive to provide solutions to incurable diseases through innovation in RNA therapeutics

Despite the triumphs in scientific research, numerous people still suffer from incurable diseases.
In particular, there are no disease-modifying therapies for neurodegenerative diseases.

This is not someone else's problem. Incurable disease affect ourselves, our children, our families and our friends.
We develop novel drugs for in incurable diseases for all of humanity and the people dearest to us.

Thank you

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