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Feasibility Study of shRNA Polyplex as a Multi-functional Drug for Alzheimer's Disease

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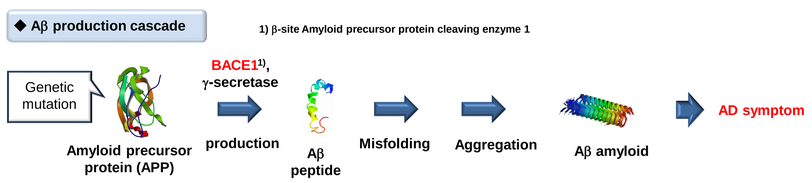
Alzheimer's disease (AD) 1

AD is characterized by the deposition of amyloid β (Aβ) amyloid in the brain.

◆ Aβ production cascade

1) β-site Amyloid precursor protein cleaving enzyme 1



◆ Development of new drug candidates

Approval and clinical phase of drug candidates (2020)

Candidates	Action mechanisms	Phase
Aducanumab	Anti Aβ antibody	Approval application
Lecanemab	Anti Aβ protofibril antibody	Ⅲ
Elenbecestat	BACE1 inhibitor	Wtihdraw (Ⅲ)
TRx0237	Tau aggregation inhibitor	Ⅲ
AVP-786	NMDAR/SNRI/σ1R inhibitor	Ⅲ

〈 Alzheimer Europe : HP 〉

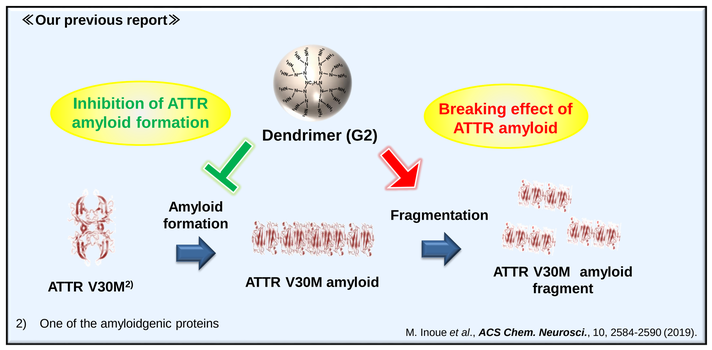
→ FDA approval (June, 2021)

A therapeutic drug for reduction of Aβ amount in the brain is expected !

Dendrimer (G2)[1)] as an amyloid inhibitor 2

1) Starburst® polyamidoamine dendrimer (generation 2; G2)

≪Our previous report≫



2) One of the amyloidgenic proteins

M. Inoue *et al.*, ***ACS Chem. Neurosci.***, 10, 2584-2590 (2019).

Dendrimer is expected as both the inhibitor and the breaker of amyloid !

Cyclodextrin[1)]/dendrimer conjugate (CDE) 3

1) 6-*O*-α-(4-*O*-α-D-Glucuronyl)-D-glucosyl-β-cyclodextrin

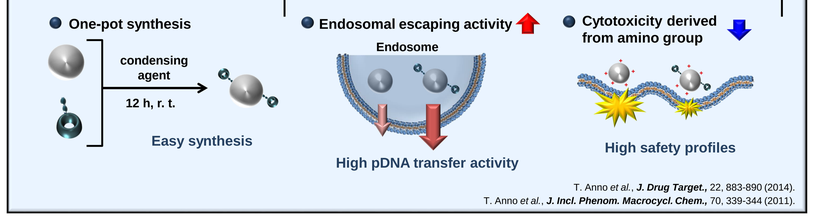
≪Our previous reports≫

CDE has a high gene transfer activity *in vitro* and *in vivo*.

T. Anno *et al.*, ***J. Incl. Phenom. Macrocycl. Chem.***, 70, 339-344 (2011).

◆ Advantages of CDE

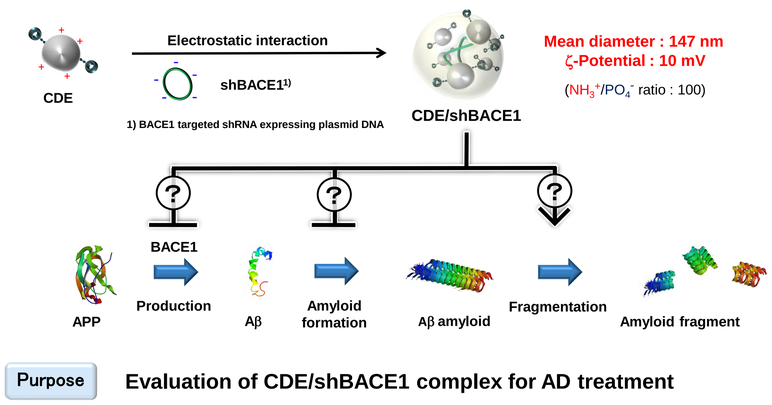
Advantages of cyclodextrin modification



T. Anno *et al.*, ***J. Drug Target.***, 22, 883-890 (2014).
T. Anno *et al.*, ***J. Incl. Phenom. Macrocycl. Chem.***, 70, 339-344 (2011).

CDE/pDNA complex may have the potential to suppress an amyloidogenic protein production !

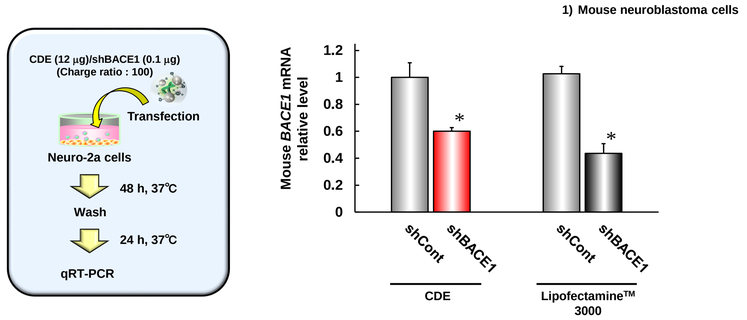
Strategy of therapeutic approach for AD 4



Purpose **Evaluation of CDE/shBACE1 complex for AD treatment**

CDE/shBACE1 suppressed BACE1 production in Neuro-2a[1)] cells. 5

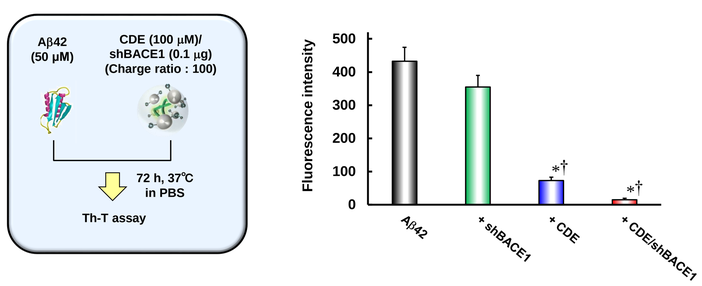
1) Mouse neuroblastoma cells



Inhibitory Effects of Various shBACE1 Complexes on Mouse *BACE1* mRNA Expression in Neuro-2a Cells

The level of mouse *BACE1* mRNA expression in CDE/shCont complex was set at 1.0. Each value represents the mean ± S.E. of 6 experiments. *$p < 0.05$, compared with shCont complex.

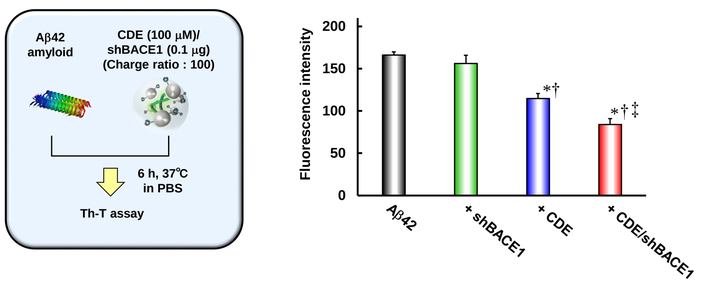
CDE/shBACE1 inhibited Aβ42 amyloid formation. 6



Inhibitory Effect of CDE/shBACE1 Complex on Amyloid Formation of Human Aβ42

Each value represents the mean ±S.E. of 6 experiments. *$p < 0.05$, compared with Aβ42. †$p < 0.05$, compared with + shBACE1.

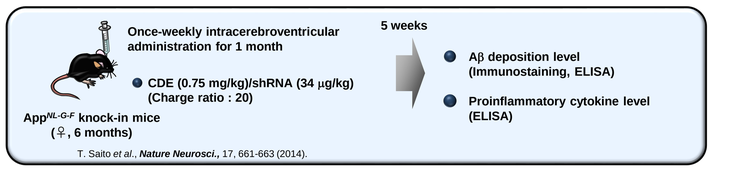
CDE/shBACE1 disrupted Aβ42 amyloid. 7



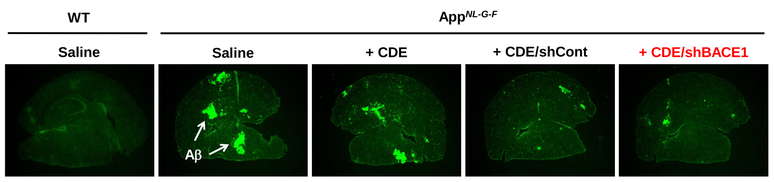
Breaking Effect of CDE/shBACE1 Complex on Human Aβ42 Amyloid

Each value represents the mean ±S.E. of 6 experiments. *$p < 0.05$, compared with Aβ42. †$p < 0.05$, compared with + shBACE1. ‡$p < 0.05$, compared with + CDE.

CDE/shBACE1 inhibited Aβ deposition in AD model mice. 8



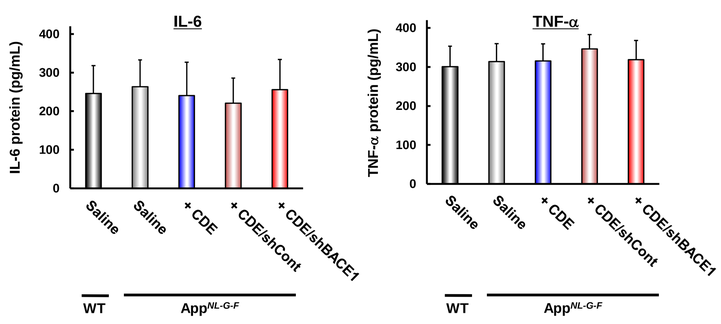
T. Saito *et al.*, ***Nature Neurosci.***, 17, 661-663 (2014).



Aβ Accumulation in Brain after Intracerebroventricular Administration of CDE and CDE/shRNA in App^{NL-G-F} Mice

These figures show the representative image for 4 experiments.

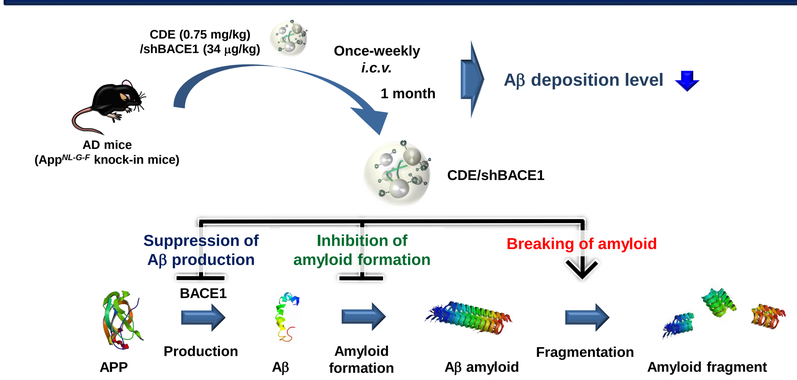
CDE/shBACE1 did not show any significant change in proinflammatory cytokine levels. 9



Quantitation of IL-6 and TNF-α Cytokine Levels after Intracerebroventricular Administration of CDE and CDE/shRNA Complexes to App^{NL-G-F} Mice

Each value represents the mean±S.E. of 4 experiments.

Summary 10



CDE/shBACE1 may have the potential as a multi-targeting amyloid inhibitor for AD treatment.

Acknowledgments 11

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