

**Assessing Prophylactic and Therapeutic Efficacy of
a Cellulose Ether Compound TC-5RW on CJD**

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Background

- Cellulose ethers (CE)**

Ingredients in foods and pharmaceuticals

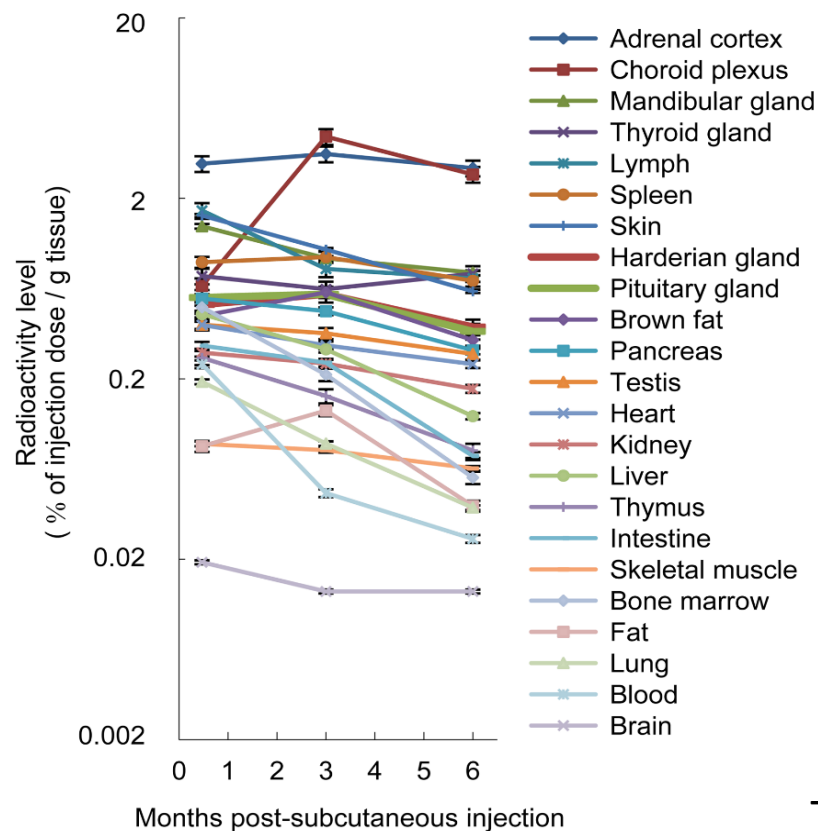
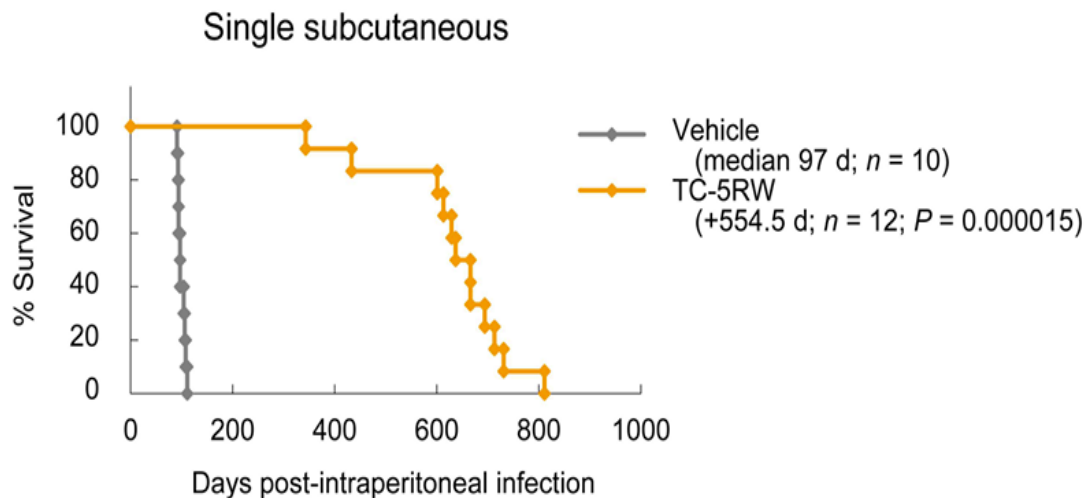
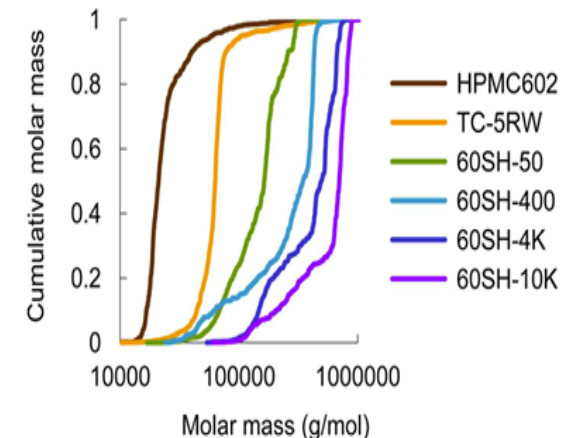
- Why TC-5RW?**

Small molecular weight (easy to penetrate BBB)

Long exiting time in tissue,

Improve survival rate for prion disease in rodents

	Content (mol/AGU)		Viscosity (2%, 20°C, mPa·s)	Molecular weight (Mn)
	O-CH ₃	O-CH ₂ CH(OH)CH ₃		
HPMC602	1.90	0.24	1.68	7,215
TC-5RW	1.91	0.24	5.8	10,695
60SH-50	1.88	0.24	50.4	21,257
60SH-400	1.92	0.24	390	40,720
60SH-4K	1.92	0.24	3860	84,351
60SH-10K	1.92	0.24	9730	113,150

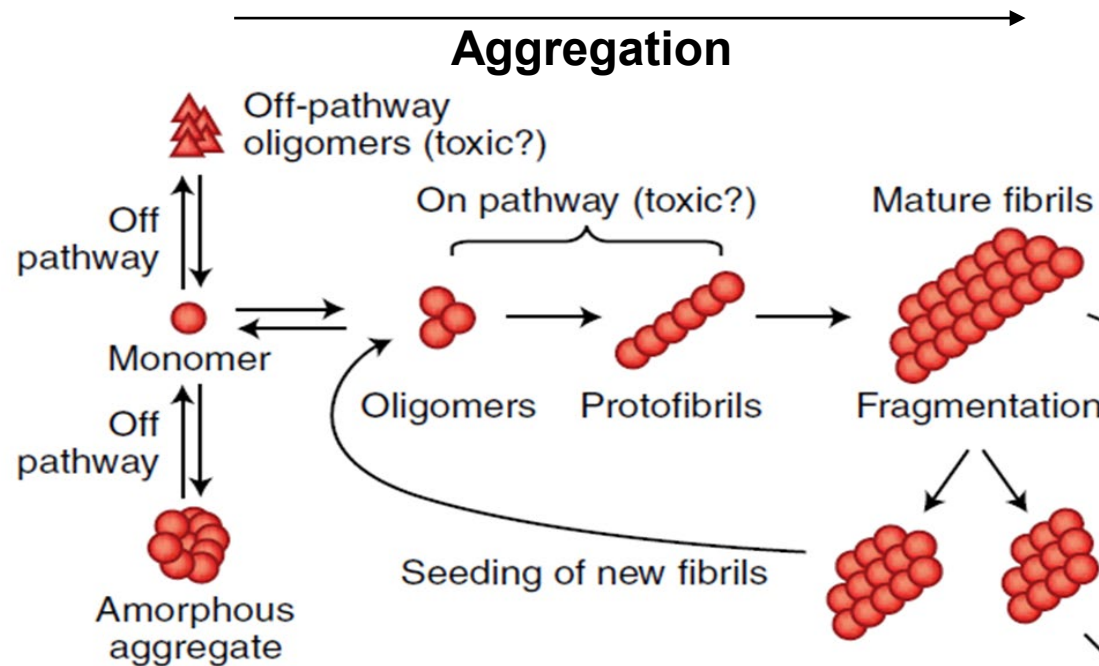


Background

Neurodegenerative diseases: AD, PD, PrD, HD, ALS...

Misfolded proteins: α -syn, tau, A β , PrP^{Sc}, TDP43

Seeding amplification assay (SAA): RT-QuIC



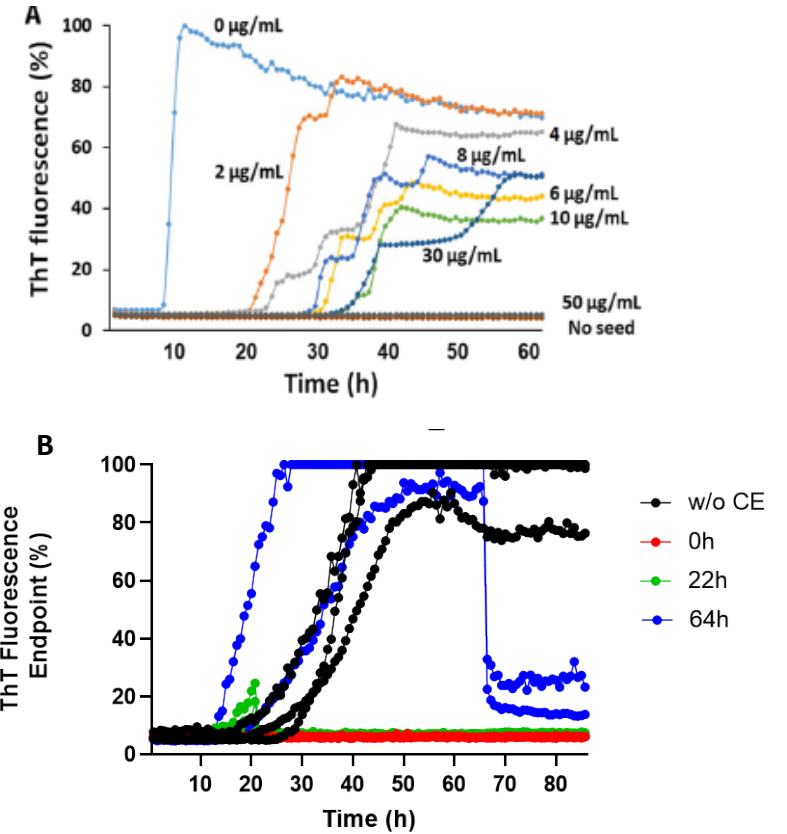
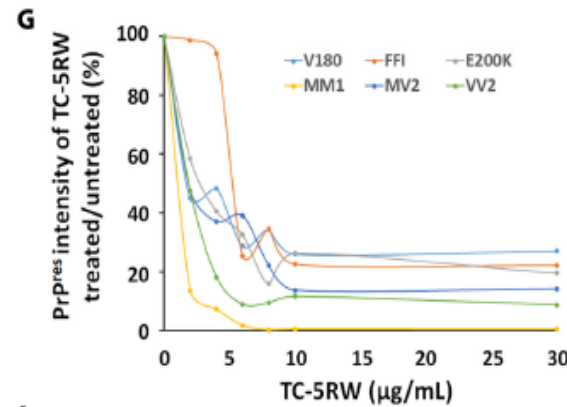
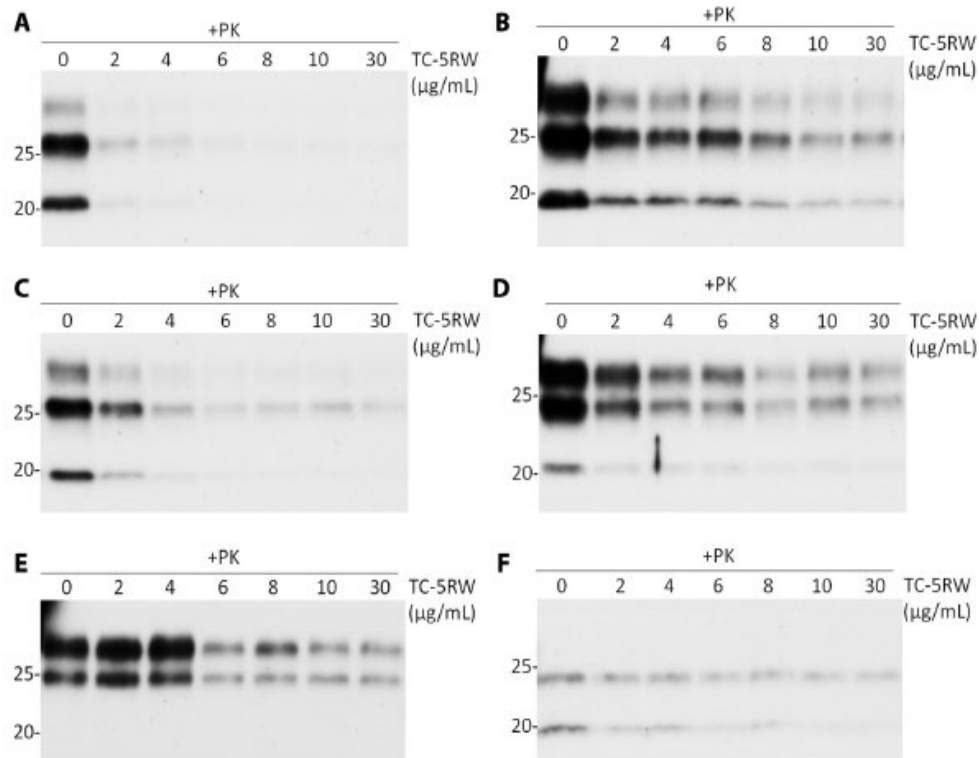
Hypothesis

- TC-5RW could potentially serve as a prophylactic and therapeutic agent for human prion diseases.
- TC-5RW could also have an inhibitive effect on other misfolded proteins such as α -syn and tau

Aim

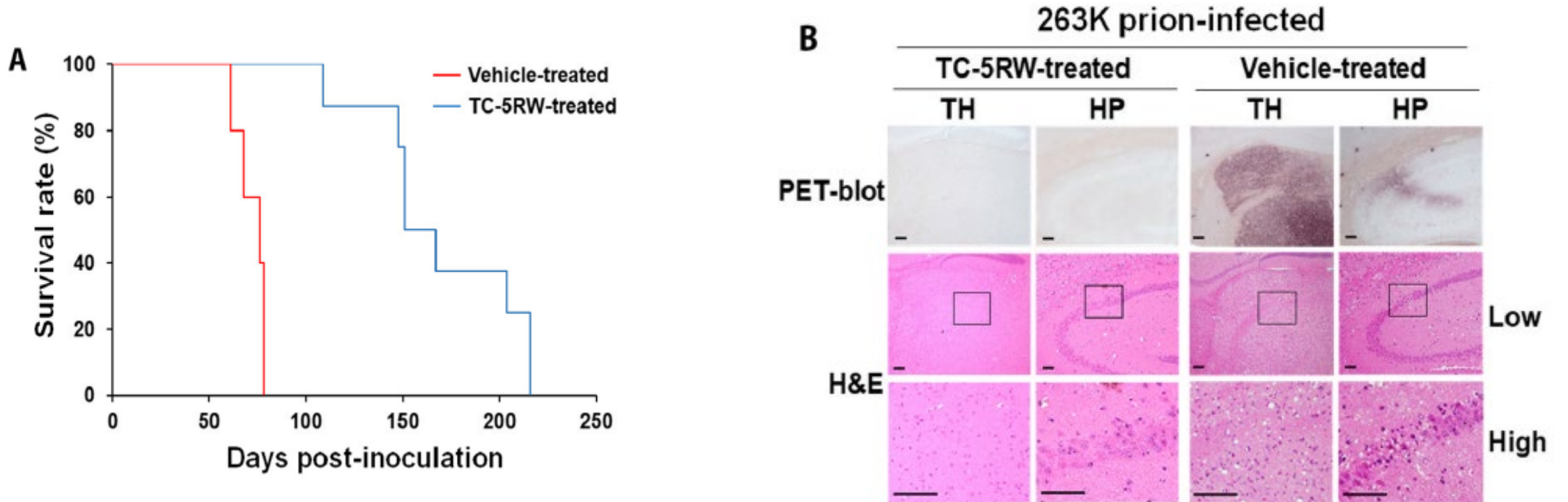
- Develop effective prevention and treatment of human prion diseases.

Inhibitive effect of TC-5RW on CJD in vitro



- TC-5RW is able to inhibit seeding activity of human PrPSc and to directly decrease PrPSc upon incubation of TC-5RW with brain homogenates of patients with different sporadic and genetic CJD *in vitro*

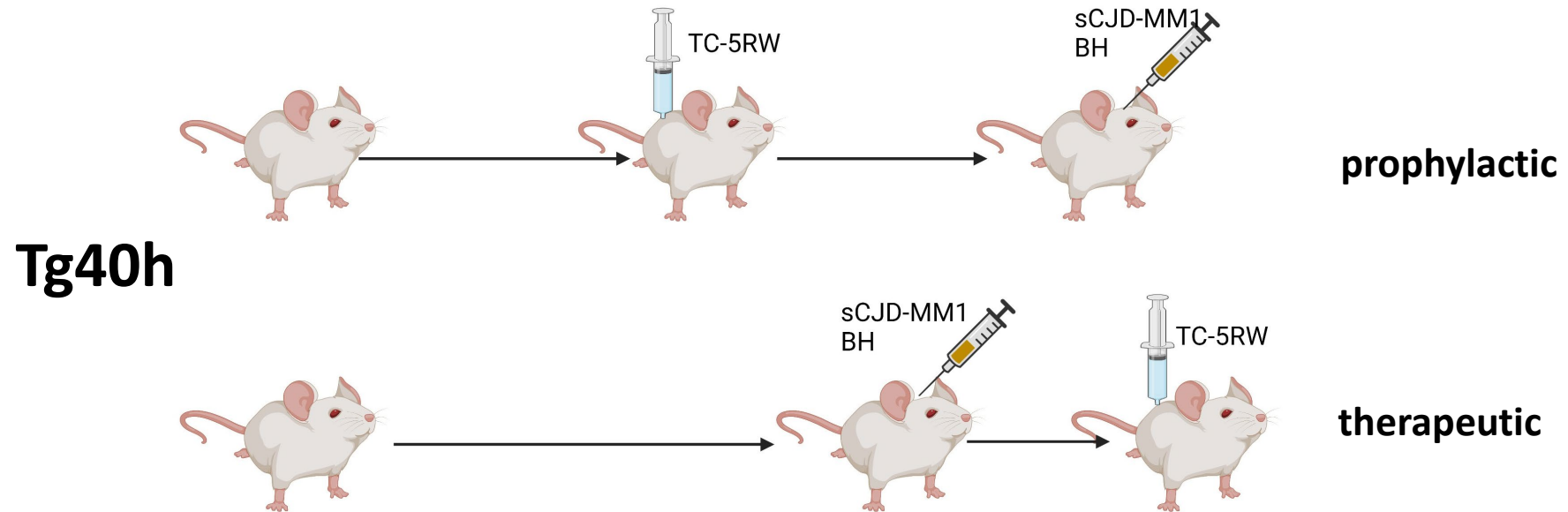
Protective effect of TC-5RW on PrP^{Sc} *in vivo*



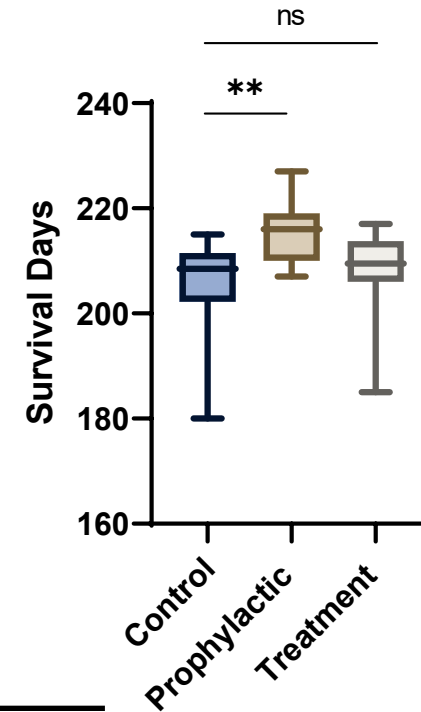
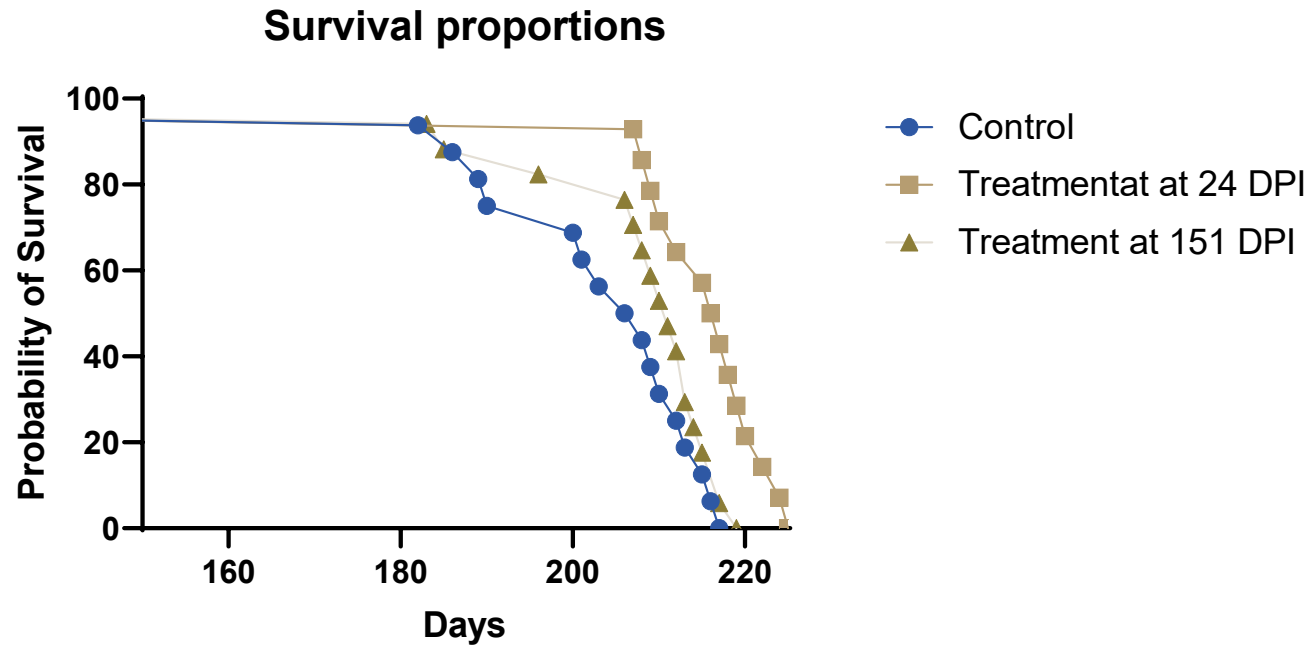
- 1) Reduce PK-resistant PrP^{Sc} upon incubation with the compound *in vitro*
- 2) Can inhibit human PrP^{Sc}- aggregation seeding activity
- 3) A single subcutaneous administration of cellulose ethers had a remarkable protective effects on hamsters

Current study 1:

Determine the **prophylactic** and **therapeutic** effects of TC-5RW on **humanized transgenic (Tg) mice** expressing **human wild-type PrP (Tg40h)** before or after inoculation with human prions



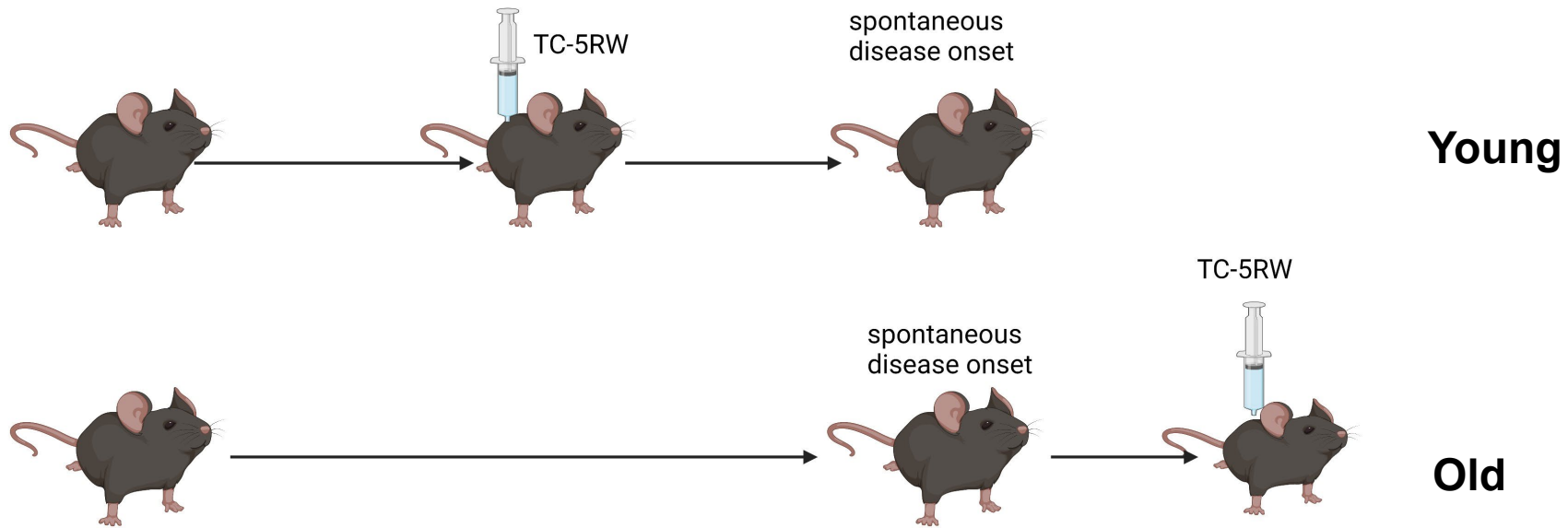
TC-5RW on humanized Tg40h mice before or after inoculation with human PrP^{Sc}



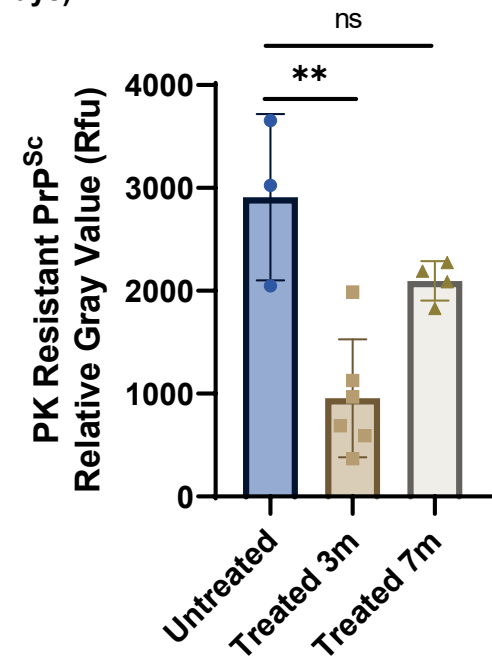
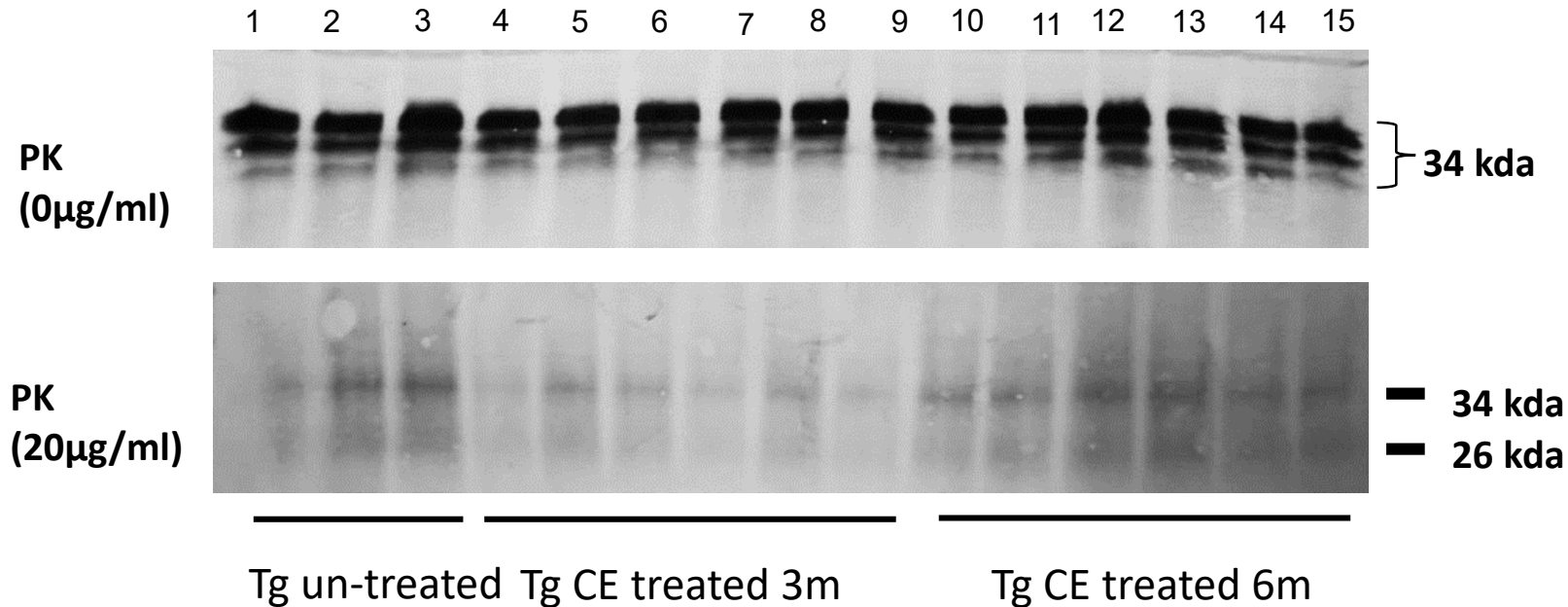
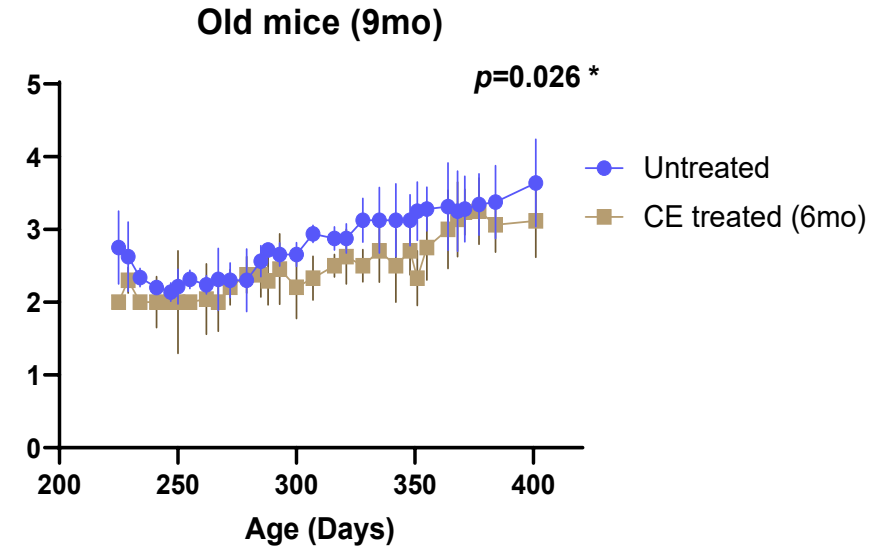
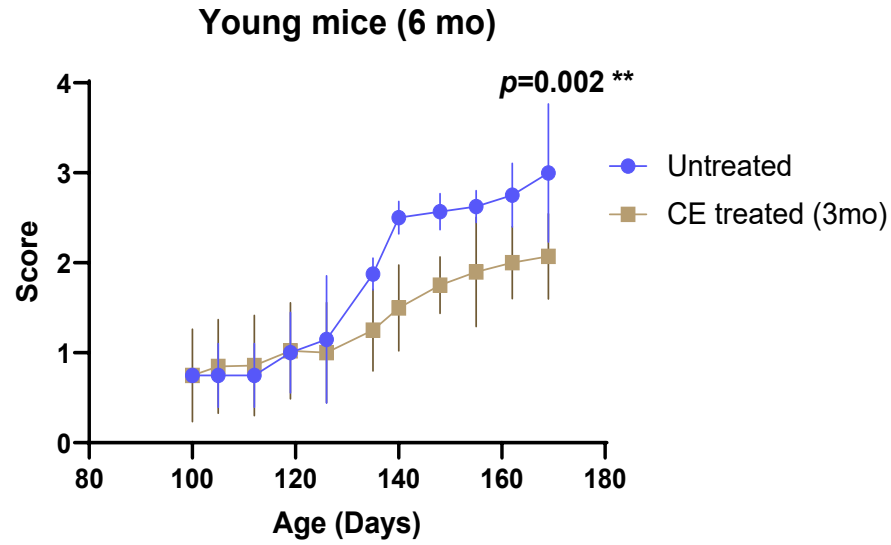
	Control	Prophylactic	Treatment
Number of values	16	15	16
Minimum	180	207	185
Maximum	215	227	217
Range	35	20	32
Mean	205.6	215.7	207.4
Std. Deviation	9.688	5.824	9.536
Std. Error of Mean	2.422	1.504	2.384

Current study 2:

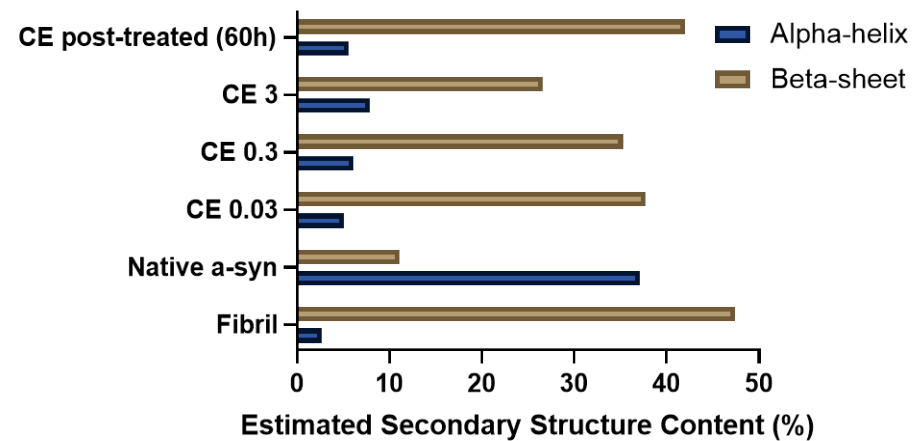
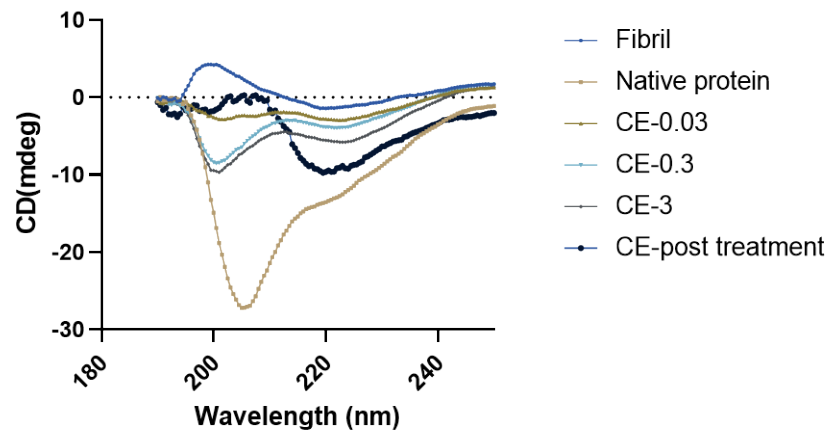
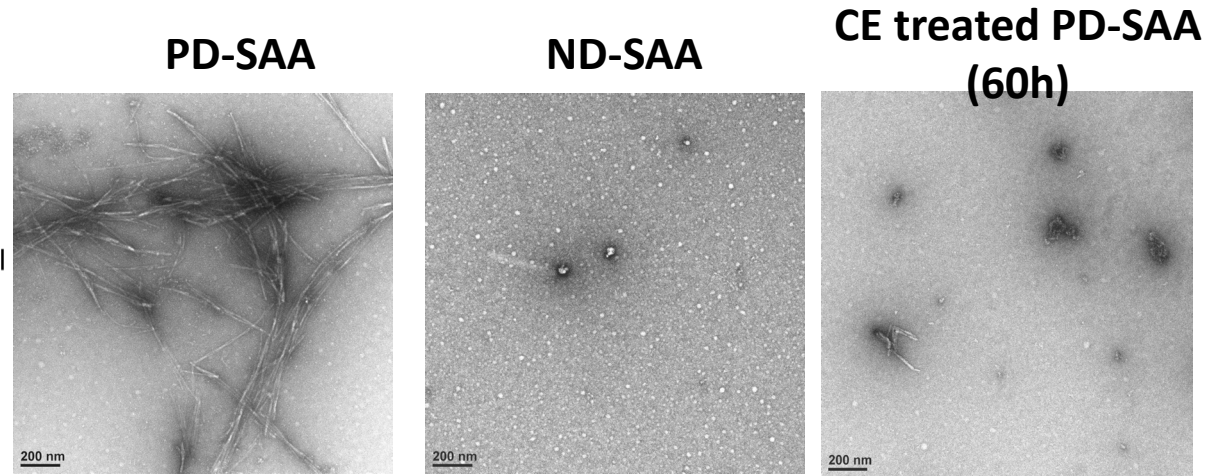
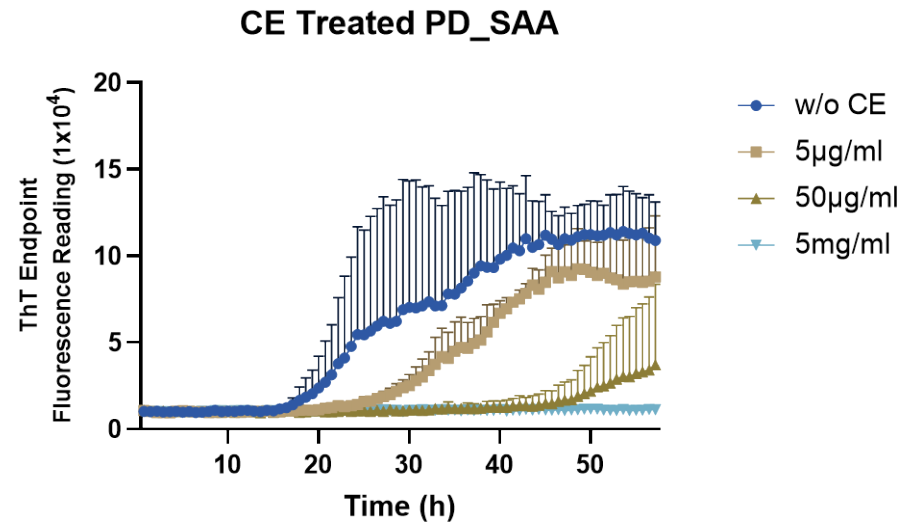
- Determine the prophylactic and therapeutic effects of TC-5RW on a **spontaneous prion mouse model (TgMHu2ME199K)** that expresses human PrP carrying a mutation equivalent to **human PrP-E200K** linked to genetic **CJDE200K**.



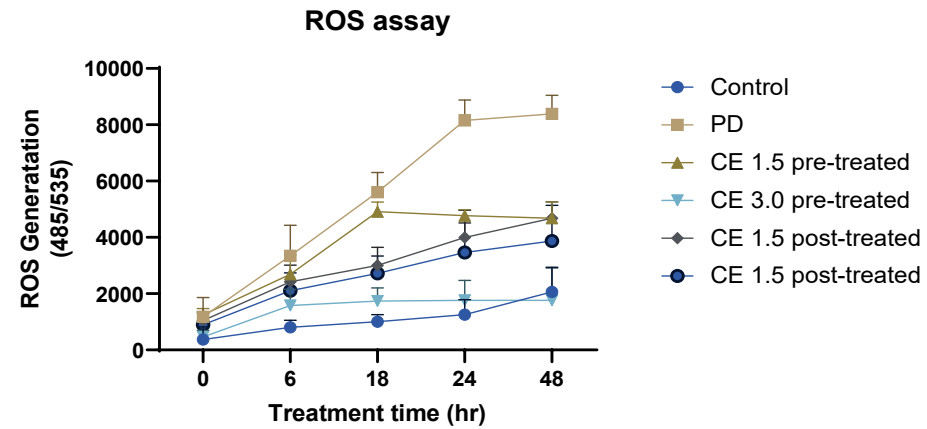
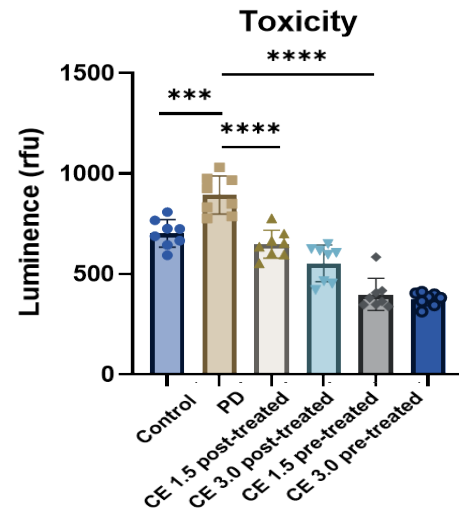
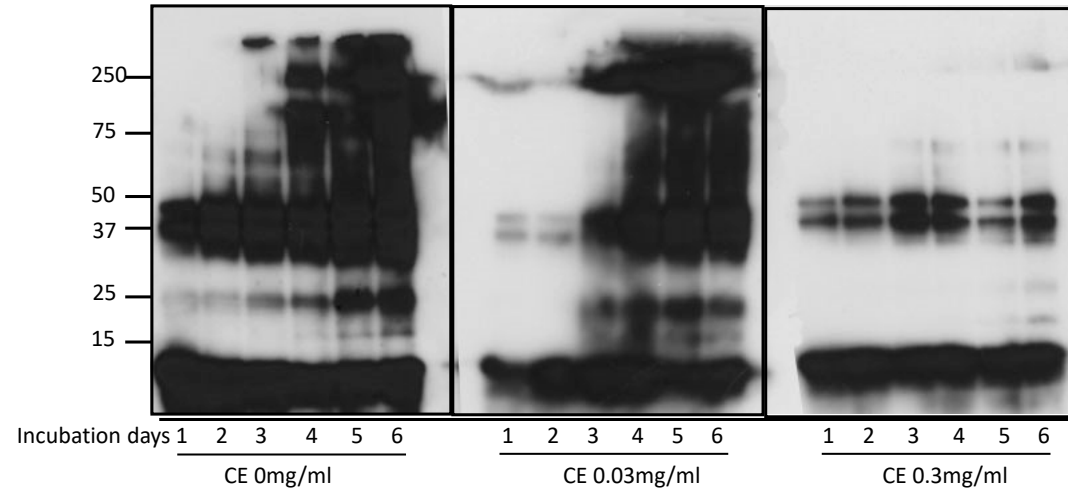
TC-5RW has prophylactic and therapeutic effects on TgMHu2ME199K mice



Inhibitory effect of TC-5RW on alpha-synuclein seeding aggregation

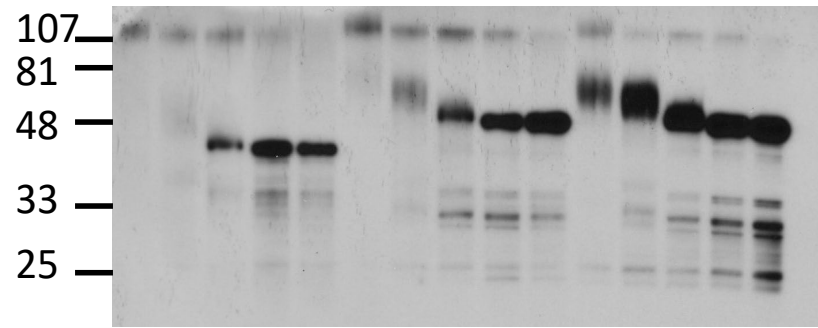


Inhibitory effect of TC-5RW on alpha-synuclein in vitro and in cell



Inhibitory effect of CE on tau aggregation

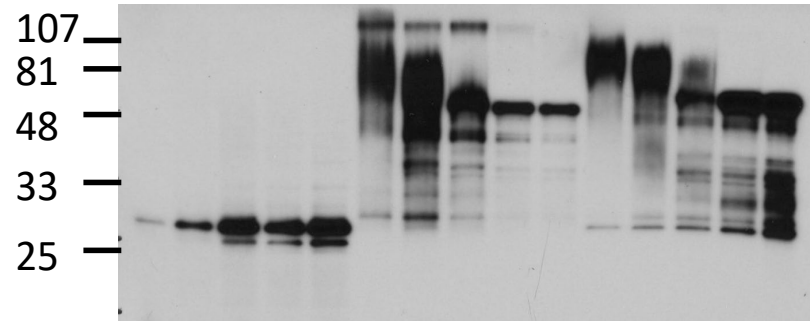
A



0N3R

1N3R

2N3R



CE(μ g/ml) 0 3 6 12 24

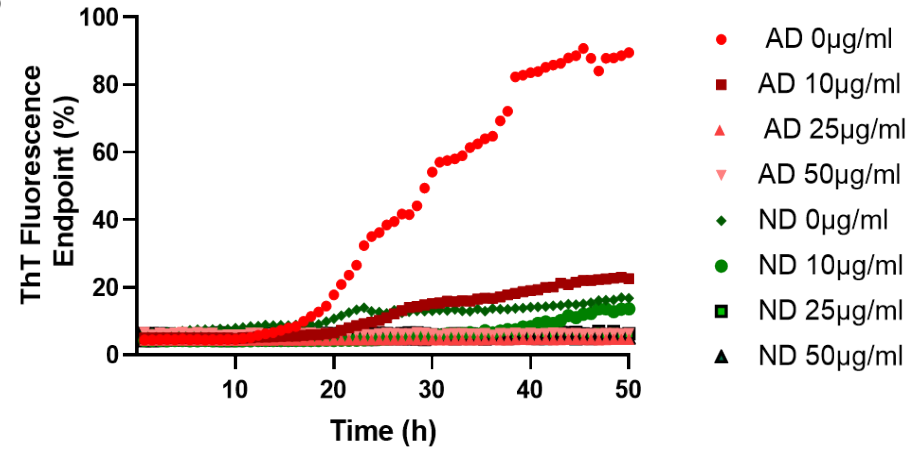
0N4R

1N4R

2N4R

B

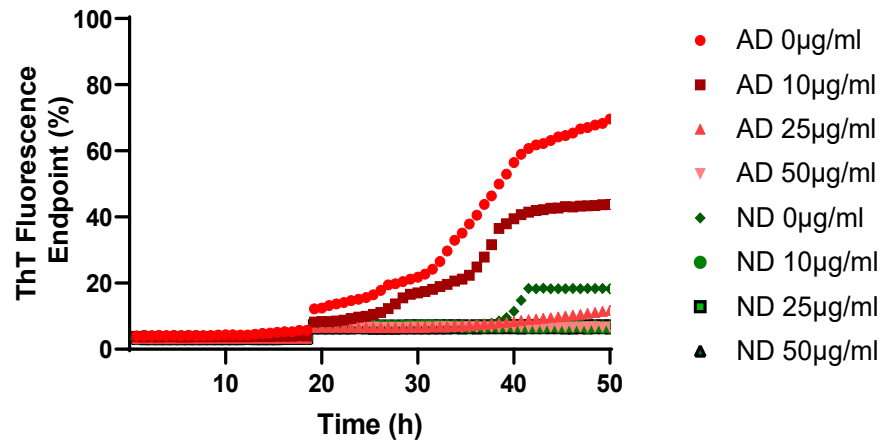
Average of AD&ND brain_3RCF



- AD 0 μ g/ml
- AD 10 μ g/ml
- ▲ AD 25 μ g/ml
- ▼ AD 50 μ g/ml
- ◆ ND 0 μ g/ml
- ND 10 μ g/ml
- ND 25 μ g/ml
- ▲ ND 50 μ g/ml

C

Average of AD&ND brain_4RCF



- AD 0 μ g/ml
- AD 10 μ g/ml
- ▲ AD 25 μ g/ml
- ▼ AD 50 μ g/ml
- ◆ ND 0 μ g/ml
- ND 10 μ g/ml
- ND 25 μ g/ml
- ▲ ND 50 μ g/ml

1. CE can inhibit tau aggregation in vitro
 2. CE can truncate tau protein into fragments with low MW
- ?Intracerebrally for further in vivo study

Summary of current findings

- Prion Disease Model: Inhibitive effect on in vitro aggregation, in cell (Abdulrahman et al., 2020), treatment effect in vivo (rodents) and show protective effect in **prophylactic group**.
- PD Model: Inhibitive effect on in vitro aggregation, in cell
- AD Model: Inhibitive effect on in vitro aggregation

TC-5RW, might function as a broad-spectrum inhibitor of protein aggregation. The implication of TC-5RW's potential to disaggregate a wide array of misfolded proteins suggests it could be a universal therapeutic strategy for various neurodegenerative diseases.

Plans

- Enhance the efficiency of the prophylactic approach through modification of injection routes.

Consider subcutaneous implantation or intracerebral injection.

- Explore the possible binding target of TC-5RW during the aggregation process, and identify potential small molecules that could synergistically boost the protective effect of CE.

Title: Assessing Prophylactic and Therapeutic Efficacy of a Cellulose Ether Compound TC-5RW on CJD

Name: Zerui Wang/Katsumi Doh-ura

Conclusions

- We found that one kind of cellulose ether called TC-5RW show therapeutic effect on prion disease of hamsters, in both prevention and post-treatment groups by single subcutaneous injection
- We found that TC-5RW can inhibit the PrP^{Sc} aggregation of CJD and other associated misfolded protein *in vitro*
- We are now testing the treatment effect of TC-5RW in humanized PrP mouse model and found that the extension of survival of prevention treatment group, but not as effective if given afterward by subcutaneous injection.
- We are exploring different injection routes of humanized PrP mouse model treatment, which might improve the treatment effect, and provide the possibility to develop efficient therapeutic compounds for CJD