Protective Effect from DEPRESSION by Polymer-Based Nanoantioxidant

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Introduction

Gut-Brain axis

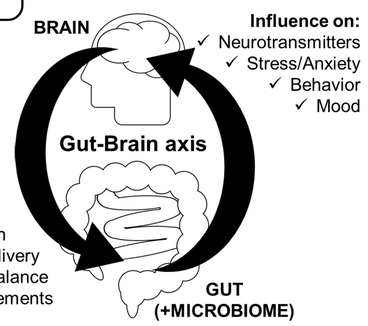
→ **The crosstalk between the gut (intestines) and brain through various pathways**

ex) Vagus nerve, Cytokines, Hormone and Bacterial metabolites, etc…

⇒ Disorders of the gut environments causes whole body disorder including mental illness.

Improvement of intestinal environment → **Treatment of various diseases**

Biomaterials



DEPRESSION

→ brain disorders caused by various stress

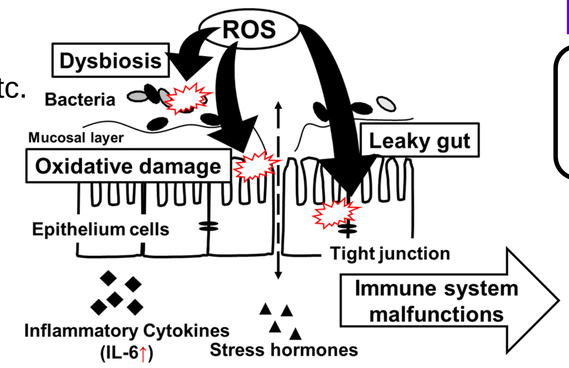
- ➢ Decrease of immune system activity
- ➢ Elevation of glucose level
- ➢ Increase of harmful bacteria

Reactive Oxygen Species (ROS)

→ highly reactive molecules derived from O_2

ex) Superoxide anion (O_2^-), Hydroxyl radial (OH ・), etc.

⇒ Overproduced ROS cause cellular damage and extra inflammation.



● Anticipated issues with ROS in the intestines

- Dysbiosis: disruption of the microbiota homeostasis
- Oxidative damage (→Leaky gut syndrome)
- Inflammation induced by stress

⇒ Immune system malfunctions

Strategy

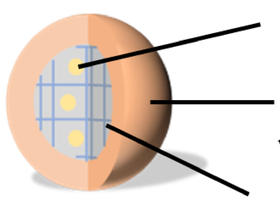
Aim of this study

To investigate the relation between intestinal oxidative damage and DEPRESSION

→ It is needed biomaterial which reduces oxidative stress only in the intestines selectively.

Material

Antioxidant nanoparticle (si-SMAPo^{TN})

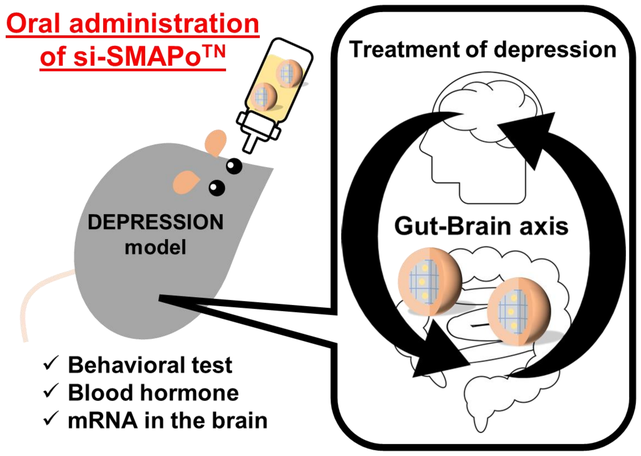


Antioxidant (TEMPO)
✓ Protection of the intestinal environment from ROS

Biocompatible polymer
✓ Long stay in the intestines
✓ No outflow into bloodstream

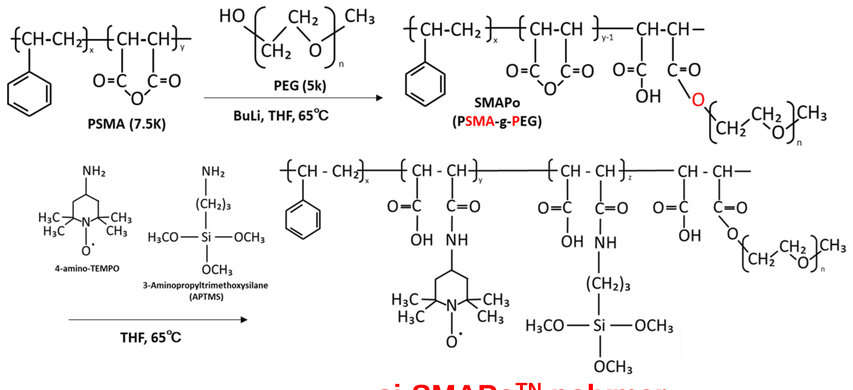
Silica Cross-linker
✓ Prevention from NPs collapse

Oral administration of si-SMAPo^{TN}



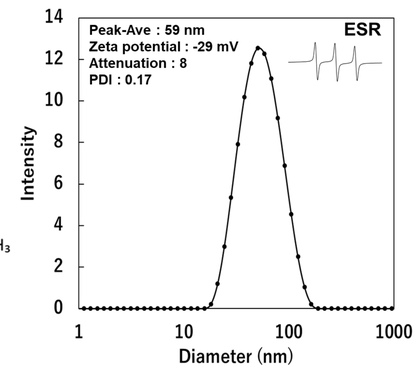
Preparation of si-SMAPo^{TN}

Reaction scheme of the polymer



si-SMAPo^{TN} polymer

NPs features

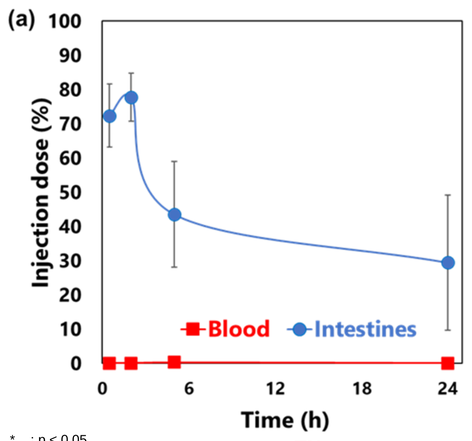


⇒ **Uniform si-SMAPo^{TN} NPs have been obtained.**

NPs : si-SMAPo^{TN} nanoparticles solution (TEMPO concentration: 5.0mM)

Characters of si-SMAPo^{TN}

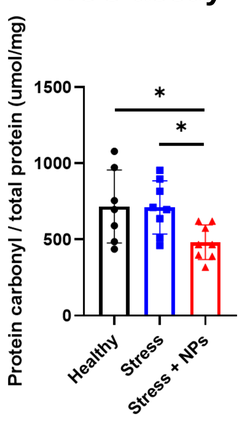
Pharmacokinetics of si-SMAPo^{TN}



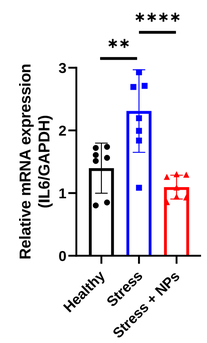
* : p < 0.05
** : p < 0.01
*** : p < 0.005
****: p < 0.001

⇒ **si-SMAPo^{TN} stayed at the intestines selectively without leak into blood.**

ROS assay



Inflammatory cytokines



⇒ **Oral administration of si-SMAPo^{TN} decreased the oxidative stress in the intestines.**

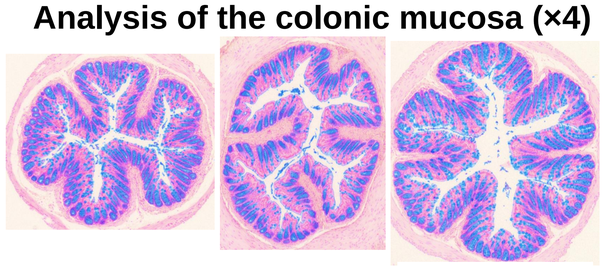
Effect of si-SMAPo^{TN} on the intestines

Chronic Restraint Stress (CRS) model

c57BL/6J
8-week old

Restraint stress for 6h × 3 weeks

Analysis of the colonic mucosa (×4)

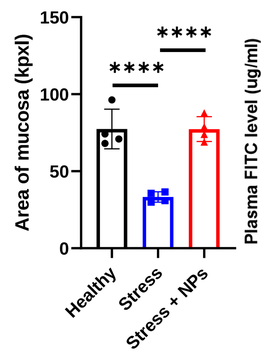


Healthy **Stress** **Stress + NPs**

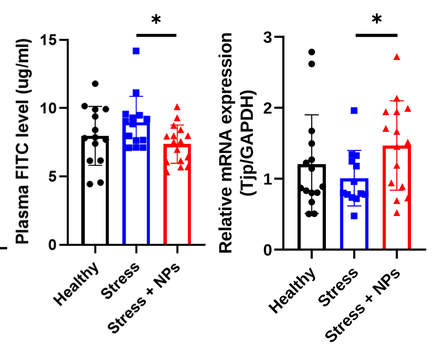
Alcian Blue (AB) staining

→ Blue part are the mucosal area and goblet cells (secreted source of mucin)

Quantification by software



Leaky gut analysis



⇒ **si-SMAPo^{TN} suppressed the decrease of mucosal area induced by CRS and prevented from the leaky gut condition.**

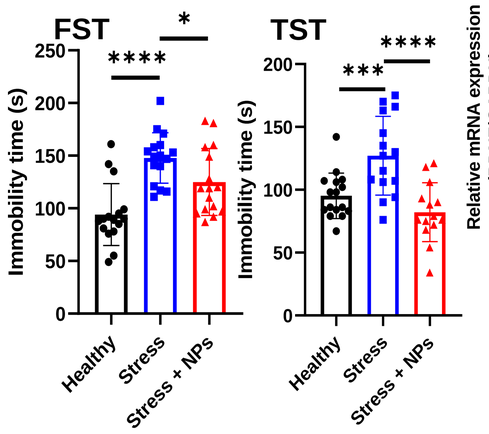
Evaluation of DEPRESSION markers in CRS mice model

Behavioral tests

(a) Forced Swimming Test

(b) Tail Suspension Test

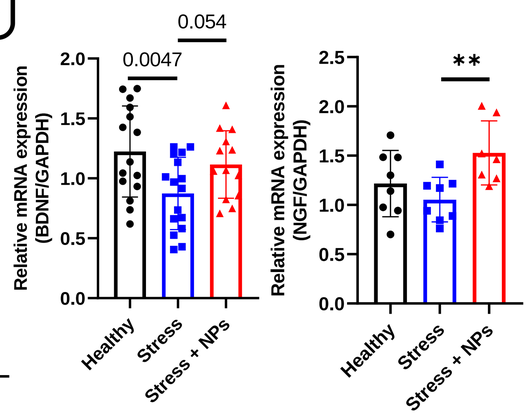
Depression → **Increase of immobility time**



Relative mRNA level of neurotrophic factors

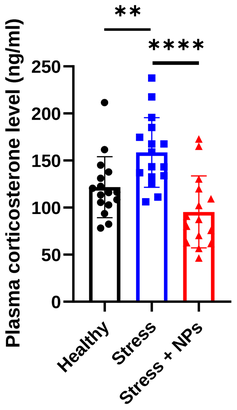
BDNF: Brain-derived neurotrophic factor

NGF: Neuro growth factor



Corticosterone Level of plamsa

→ a stress response hormone



⇒ **Oral administration of si-SMAPo^{TN} suppressed depression symptoms via gut-brain axis.**

Conclusion

- ✓ **Development of designed materials (si-SMAPo^{TN}) that have the characteristic of selectively staying in the intestines without leak into bloodstream**
- ✓ **Oral administration of si-SMAPo^{TN} nanoparticles protected from decrease of the intestinal barrier and depressive symptoms induced by CRS.**

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