제주플러스 국제환경포럼 (2022년 8월 5일)

# 미세플라스틱 생체분포지도와 영향평가

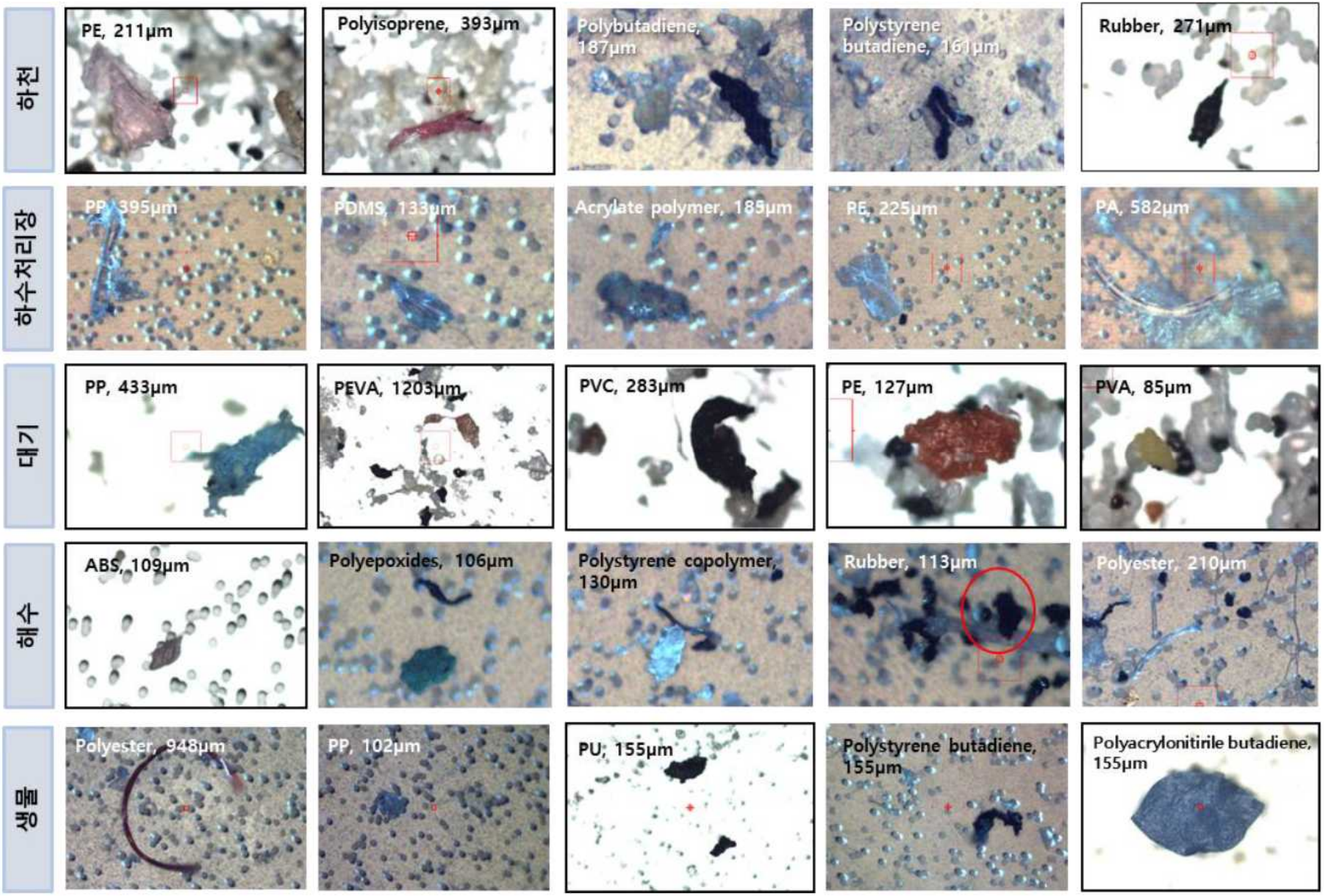
PET tracing of biodistribution
for orally administered $^{64}$Cu-labeled polystyrene in mice
(Journal of Nuclear Medicine 2022) IF =10.057
Pre/post-natal exposure to microplastic
as a potential risk factor for autism spectrum disorder
(Environment International 2022) IF=9.621
Enhanced ASGR2 by microplastic exposure leads
to resistance to therapy in gastric cancer (Theranostics 2022)
IF= 11.556


김 진수, PhD
한국원자력의학원 방사선의학연구소
과학기술연합대학원대학교 방사선종양의과학


UST 과학기술연합대학원대학교 UNIVERSITY OF SCIENCE & TECHNOLOGY

KIRAMS 한국원자력의학원 KOREA INSTITUTE OF RADIOLOGICAL & MEDICAL SCIENCES

# 다양한 환경 시료에서 검출된 미세 플라스틱




한국해양과학기술원 (2017년 연구보고서, 미세플라스틱 식품안전관리방안연구)

# 클램차우더 스프? 플라스틱 스프?

클램차우더 스프

플라스틱 스프

# 미세플라스틱에 생체에 미치는 영향에 대한 궁금증

- 미세플라스틱은 어떠한 경로로 몸에서 흡수되고 배출될까?
- 뇌에는 어떤 영향을 미칠까?
  - 뇌기능 장애를 일으키지 않을까?
  - 뇌질환을 유발하지 않을까?
- 소화기에 미치는 영향을 없을까?
  - 위, 대장

# PET Tracing of Biodistribution for Orally Administered $^{64}$Cu-Labeled Polystyrene in Mice

Changkeun Im*[1,2], Hyeongi Kim*[1], Javeria Zaheer[1,2], Jung Young Kim[1], Yong-Jin Lee[1], Choong Mo Kang[1,2], and Jin Su Kim[1,2]

[1]*Division of Applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, Korea; and* [2]*Radiological and Medico-Oncological Sciences, University of Science and Technology, Seoul, Korea*

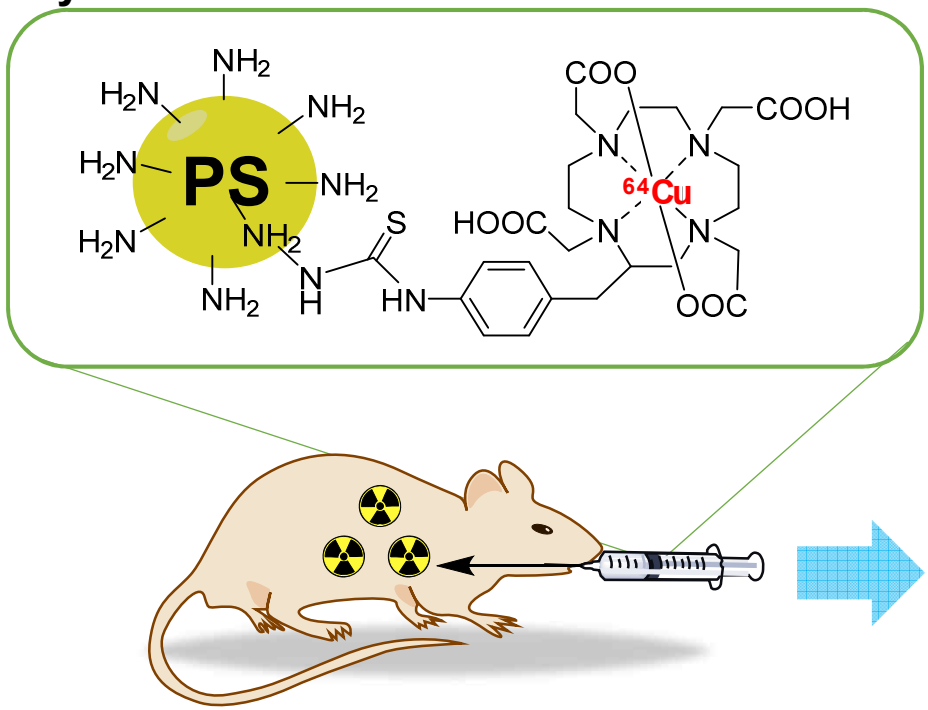
Plastics are used commonly in the world because of their convenience and cost effectiveness. Microplastics, an environmental threat and human health risk, are widely detected in food and consequently ingested. However, degraded plastics are found everywhere, creating an environmental threat and human health risk. Therefore, real-time monitoring of orally administered microplastics to trace them in the body is tremendously important. **Methods:** In this study, to visualize their absorption path, we labeled polystyrene with [$^{64}$Cu]Cu-DOTA. We prepared radiolabeled polystyrene with $^{64}$Cu. Afterward, [$^{64}$Cu]Cu-DOTA-polystyrene was orally administered to mice, and we evaluated its transit and absorption using PET imaging. The absorption path and distribution of [$^{64}$Cu]Cu-DOTA-polystyrene were determined using PET over 48 h. Ex vivo tissue radio–thin-layer chromatography (TLC) was used to demonstrate the existence of [$^{64}$Cu]Cu-DOTA-polystyrene in tissue. **Results:** PET images demonstrated that [$^{64}$Cu]Cu-DOTA-polystyrene began to transit to the intestine within 1 h. Accumulation of [$^{64}$Cu]Cu-DOTA-polystyrene in the liver was also observed. The biodistribution of [$^{64}$Cu]Cu-DOTA-polystyrene confirmed the distribution of [$^{64}$Cu]Cu-DOTA-polystyrene observed on the PET images. Ex vivo radio-TLC demonstrated that the detected $\gamma$-rays originated from [$^{64}$Cu]Cu-DOTA-polystyrene. **Conclusion:** This study provided PET evidence of the existence and accumulation of microplastics in tissue and cross-confirmed the PET findings by ex vivo radio-TLC. This information may be used as the basis for future studies on the toxicity of microplastics.

microplastics have been found in mussels purchased at markets in Belgium (*15*). Considering that microplastics are widely detected in food, we can assume that microplastics are ingested along with the contaminated food. Therefore, it is highly likely that human consumption of microplastics is widespread. To understand the full significance of microplastic ingestion, the absorption path for microplastics ingested with foods needs to be visualized.

PET imaging is a powerful tool for observing absorption, distribution, metabolism, and excretion (*16*). PET can also be used to visualize the in vivo distribution of toxic substances labeled with radioactive isotopes, including diesel exhaust (*17*), and inhaled aerosols of toxic household disinfectants (*18*). Figure 1 shows a schematic of the study. We first identified the absorption path and distribution of microplastics using PET. Microplastic polystyrene was labeled with $^{64}$Cu ([$^{64}$Cu]Cu, to yield [$^{64}$Cu]Cu-DOTA-polystyrene) and then was orally administered to mice. In a separate experiment, $^{64}$Cu was orally administered as a control to assess the effects of the harsh stomach conditions on dechelated $^{64}$Cu. PET was performed to monitor the absorption and distribution of [$^{64}$Cu]Cu-DOTA-polystyrene or $^{64}$Cu over 48 h. The ex vivo biodistributions of [$^{64}$Cu]Cu-DOTA-polystyrene or $^{64}$Cu was measured. Ex vivo tissue radio–thin-layer chromatography (TLC) was performed to identify whether $\gamma$-rays emitted from the tissue originated from [$^{64}$Cu]Cu-DOTA-polystyrene or from $^{64}$Cu.

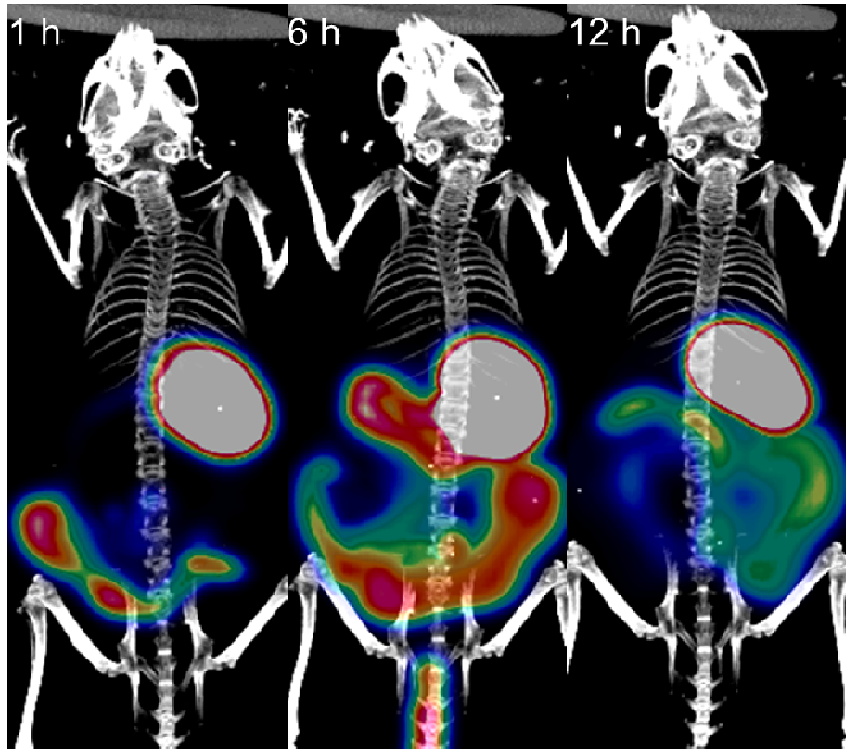
# 양성자방출단층 촬영 기법(PET) 이용 흡수 경로 평가 (시간 대 별로 흡수 과정 관찰)

**Synthesis and validation of $^{64}$Cu-DOTA-PS**




**Oral administration of $^{64}$Cu-DOTA-PS**

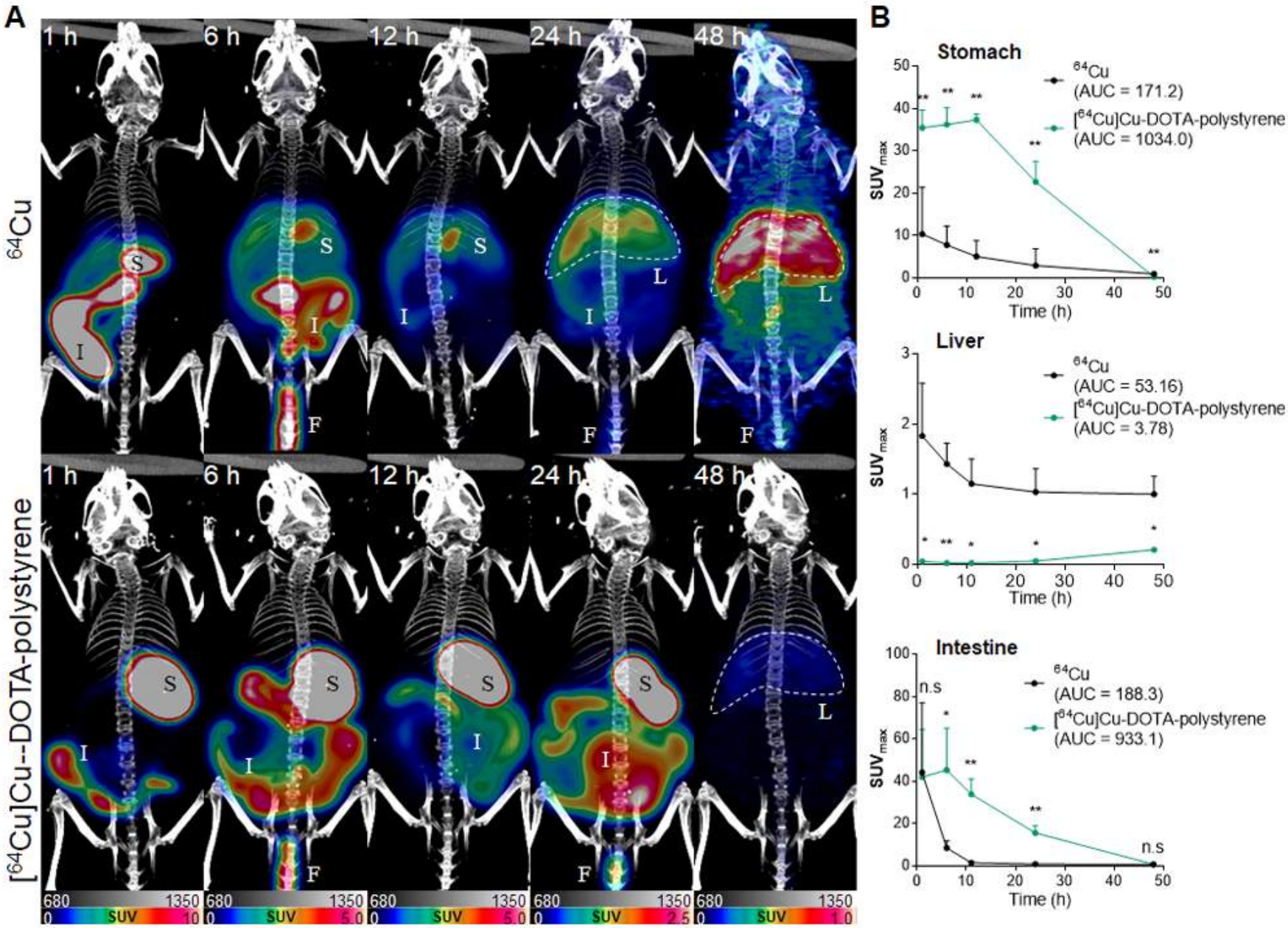
**PET/ CT imaging and Bio-distribution of $^{64}$Cu-DOTA-PS**



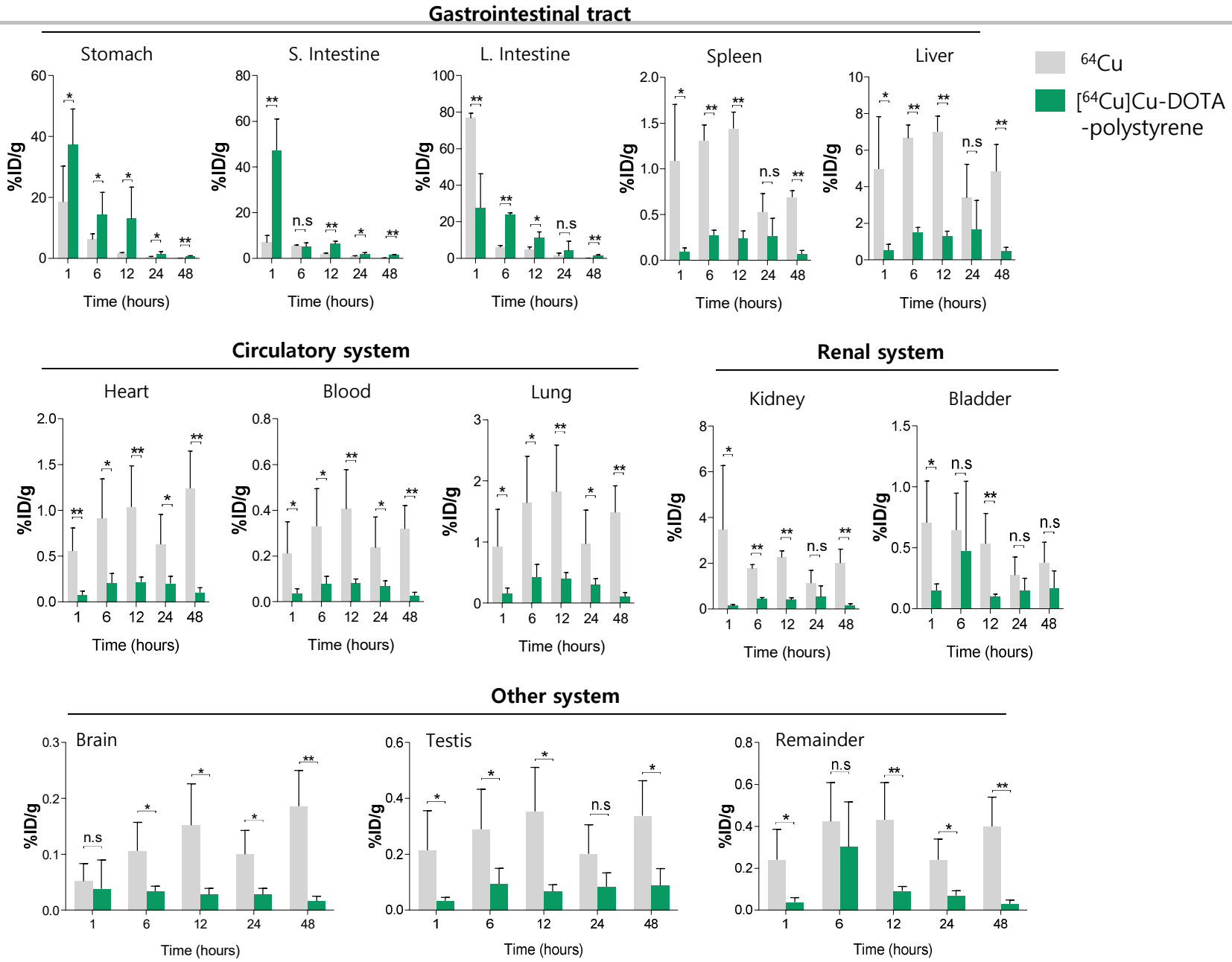

- amino-polystyrene (0.2-0.3 μm, Spherotech, Lake Forest, IL, USA)
- 미세플라스틱에 DOTA chelator를 부착하여 양성자 방출 동위원소인 Cu-64를 이용해 표지 함.
- 마우스당 [$^{64}$Cu]Cu-DOTA-polystyrene (4.81 MBq/57.8 μg/100 μL) 100 ppm / 100 uCi 의 미세플라스틱 경구 투여함.
- 마이크로미터(μm): 100만분의 1m. 보통 머리카락 굵기가 80 μm임

Journal of Nuclear Medicine

# 방사성 구리를 표지한 플라스틱의 생체분포 영상



# 생체 내 분포 (Bio-distribution)



# 언론보도

- 미세플라스틱 빠른시간내에 체내 모든 시간에 퍼져
  한국을 빛내는 사람들 선정 / 미국 과학잡지 인터뷰 IOP SCIENCE
  YTN 미세플라스틱, 빠른 시간에 체내 모든 기관에 퍼져
  UST 클라스, 서울시립과학관 토요과학강연



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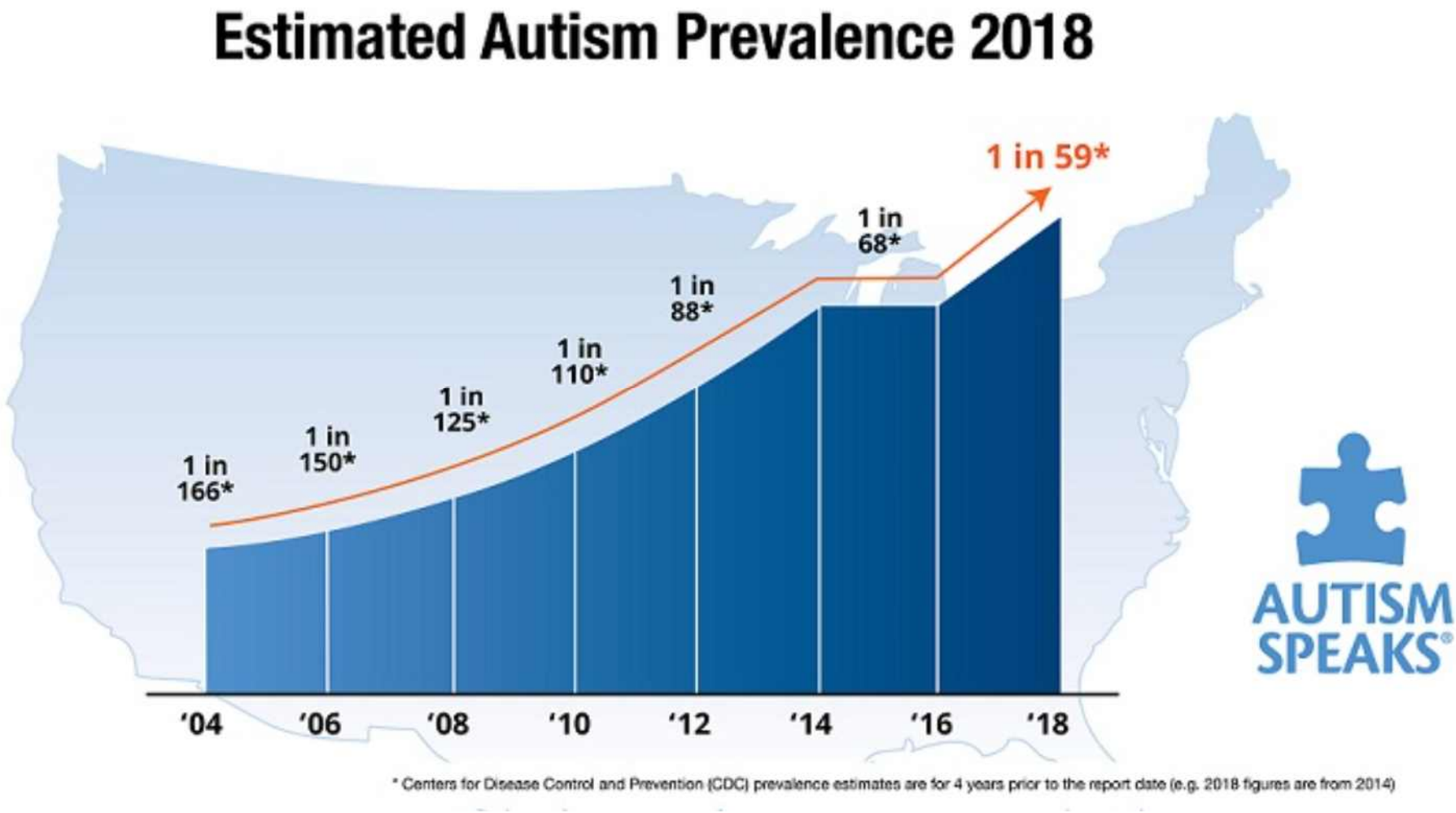
Full length article

# Pre/post-natal exposure to microplastic as a potential risk factor for autism spectrum disorder

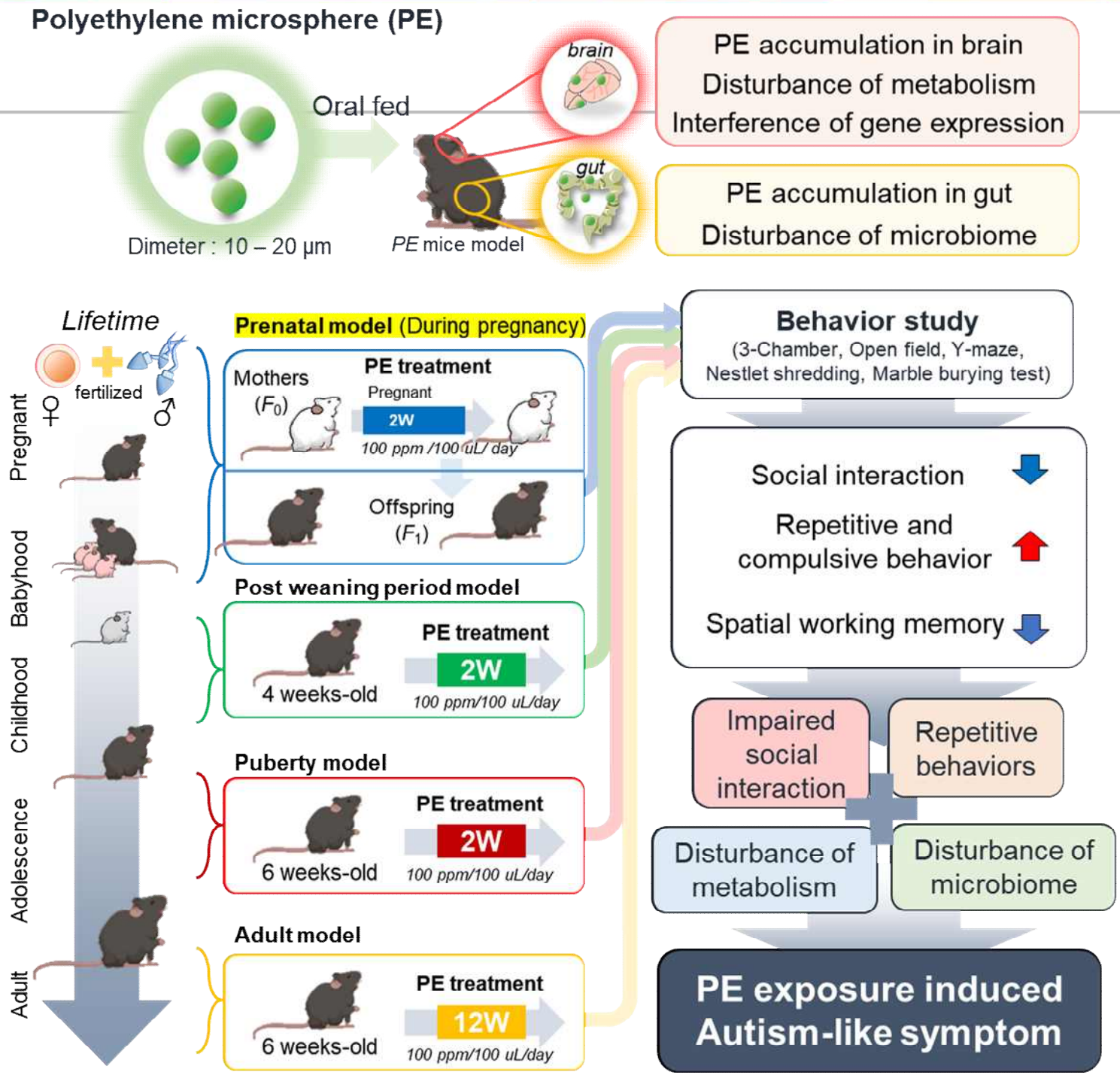
Javeria Zaheer [a,b,1], Hyeongi Kim [a,d,1], In Ok Ko [a], Eun-Kyeong Jo [c], Eui-Ju Choi [d], Hae-June Lee [e], Insop Shim [f], Hyun-jeong Woo [g], Jonghoon Choi [g], Gun-Ha Kim [h], Jin Su Kim [a,b,*]

[a] Division of RI Application, Korea Institute Radiological and Medical Sciences, Seoul 01812, Republic of Korea
[b] Radiological and Medico-Oncological Sciences, University of Science and Technology (UST), Seoul 01812, Republic of Korea
[c] School of Health & Environmental Science, College of Health Science, Korea University Seoul 02841, Republic of Korea
[d] Department of Life Sciences, School of Life Sciences and Biotechnology, Korea University, Seoul 02841, Republic of Korea
[e] Division of Radiation Biomedical Research, Korea Institute Radiological and Medical Sciences, Seoul 01812, Republic of Korea
[f] Department of Physiology, College of Medicine, Kyung Hee University, Seoul 02453, Republic of Korea
[g] Department of Biomedical Engineering, School of Integrative Engineering, College of ICT Engineering, Chung-Ang University, Seoul 06974, Republic of Korea
[h] Department of Pediatrics, Korea Cancer Center Hospital, Korea Institute Radiological and Medical Sciences, Seoul 01812, Republic of Korea

# 미국 질병통제예방센터에서 보고한 자폐 유병율



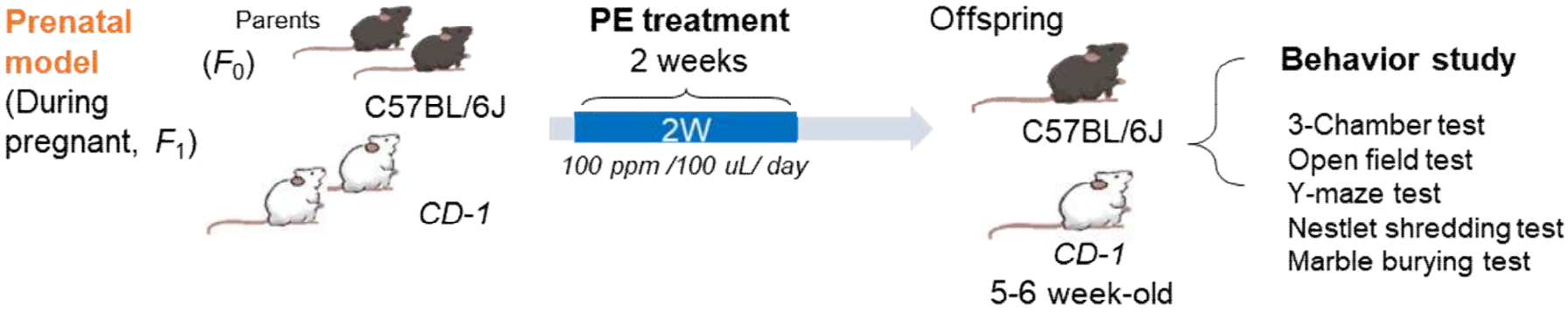

미국 CDC 자료 발췌

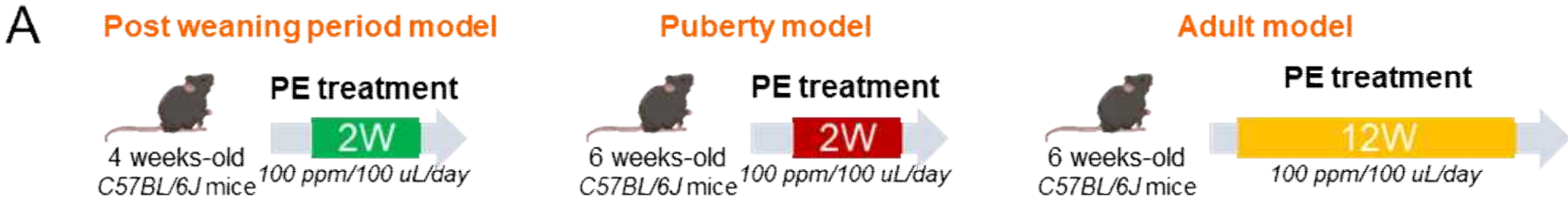

Polyethylene microsphere (PE)
Oral fed
Dimeter : 10 – 20 μm
PE mice model
brain
gut
PE accumulation in brain
Disturbance of metabolism
Interference of gene expression
PE accumulation in gut
Disturbance of microbiome
Lifetime
fertilized
♀
♂
Pregnant
Babyhood
Childhood
Adolescence
Adult
Prenatal model (During pregnancy)
Mothers ($F_0$)
PE treatment
Pregnant
2W
100 ppm /100 uL/ day
Offspring ($F_1$)
Post weaning period model
4 weeks-old
PE treatment
2W
100 ppm/100 uL/day
Puberty model
6 weeks-old
PE treatment
2W
100 ppm/100 uL/day
Adult model
6 weeks-old
PE treatment
12W
100 ppm/100 uL/day
Behavior study
(3-Chamber, Open field, Y-maze, Nestlet shredding, Marble burying test)
Social interaction
Repetitive and compulsive behavior
Spatial working memory
Impaired social interaction
Repetitive behaviors
Disturbance of metabolism
Disturbance of microbiome
PE exposure induced Autism-like symptom

# 연구에 사용된 방법

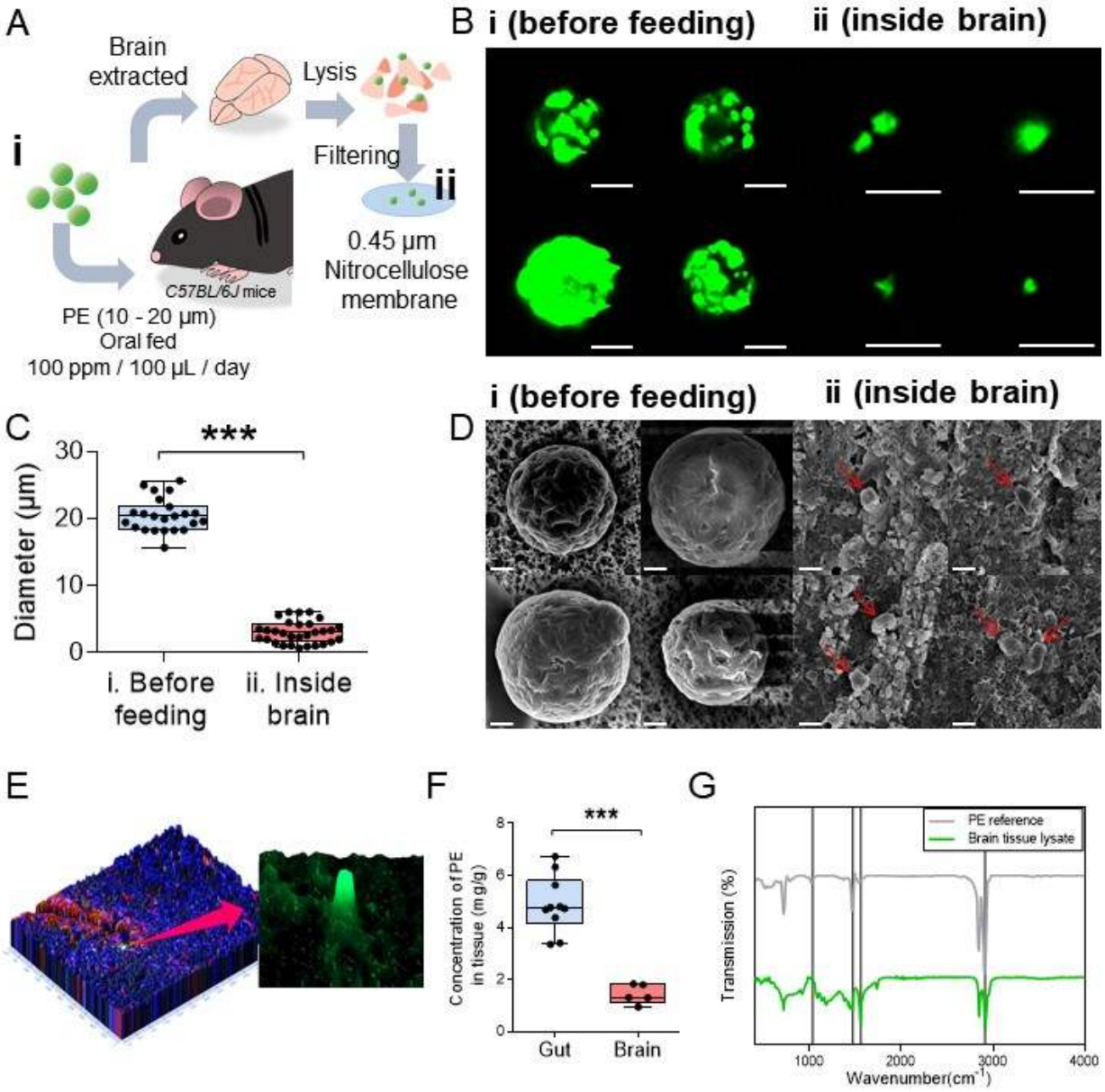
- PE (1.005 g/cc, 10–20 μm, 0.1 g; Cosphereic LLC, Santa Barbara, USA)
  100 PPM / 100 μL : (10 μg/day) ~ equivalent human dose : 1.27 mg/ kg /day (76 mg for 60 kg human)
- PE accumulation in tissue
- 16S Metagenomic sequencing
- Identification of relevant gene using microarray
- Gene confirmation using qPCR
- Molecular Imaging using FDG PET, MRS
- Behavior study (3 chamber, Y-maze (spatial working memory), Nestlet shredding, Marble burying, Adhesive Removal test (anxiety), Open Field test (anxiety)

# Animal model

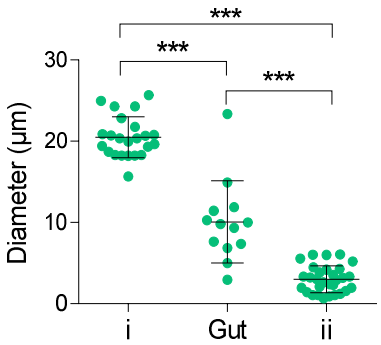


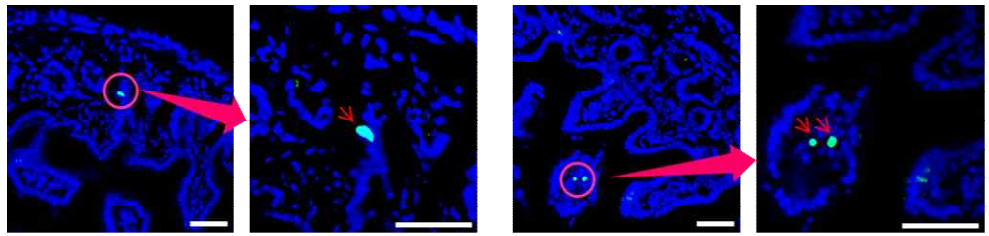



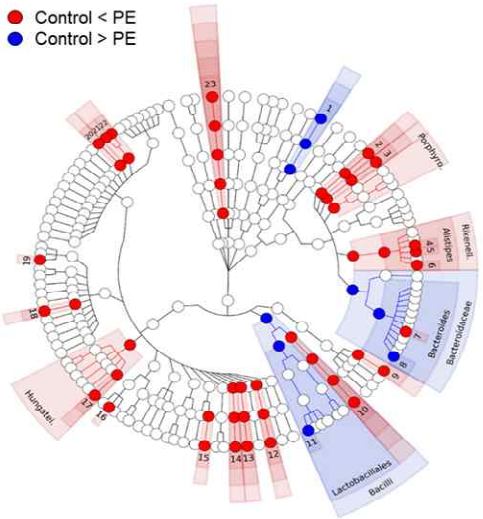
# PE was deposited in the brain

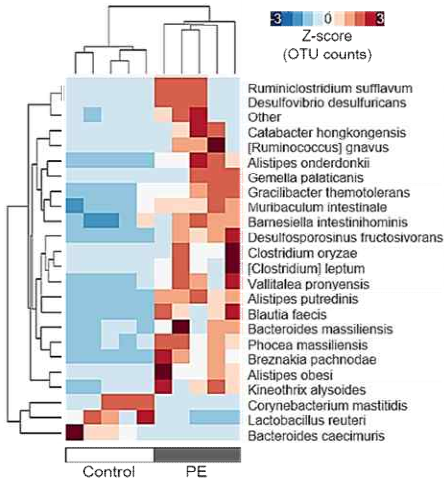


# ASD traits of gut microbiota after PE exposure





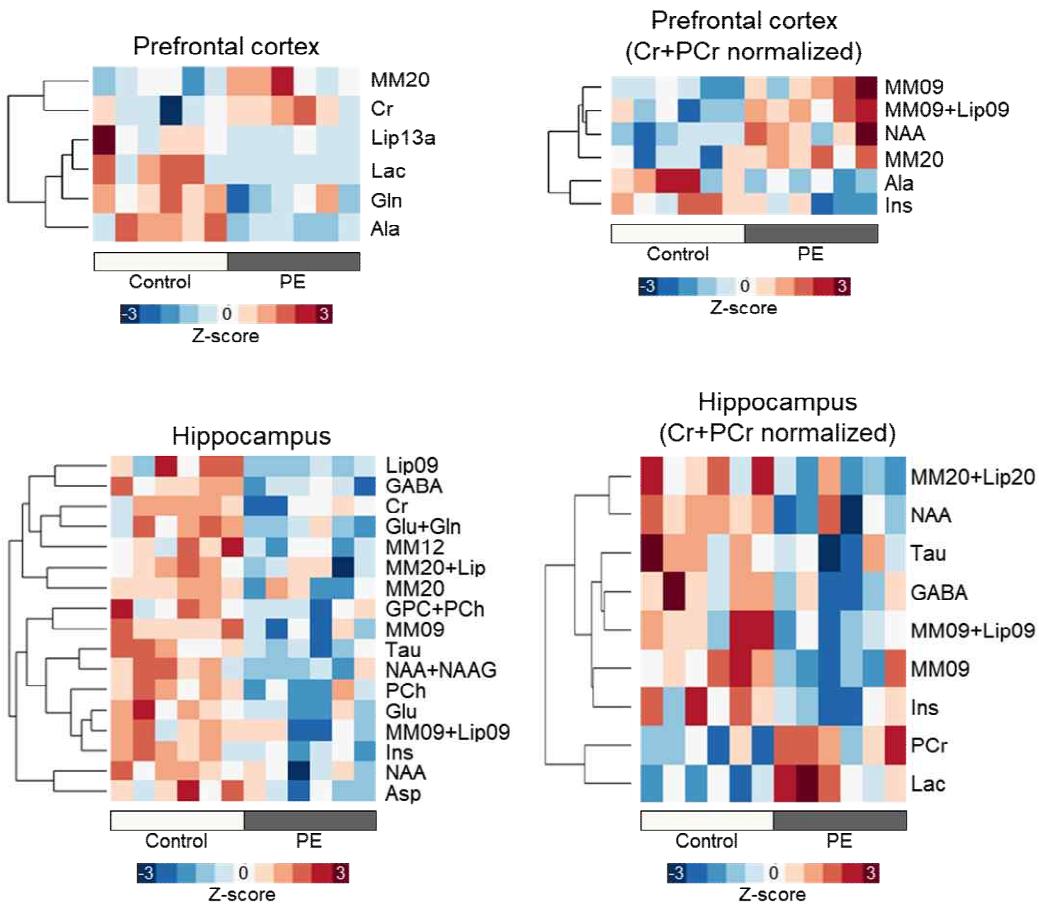




A total of 12 species (B. pachnodae, G. thermotolerans, B. faecis, D. fructosivorans, A. onderdonkii, A. obesi, C. leptum, C. oryzae, C. hongkongensis, G. palaticanis, R. sufflavum, D. desulfuricans, and R. gnavus) were not observed in control mouse fecal samples; however, these species have sprung after PE exposure in mice.

Decrease of Lactobacillus reuteri
: protects the intestinal barrier and controls permeability (Dicksvedet al. 2012)
: decreased in ASD mouse models

Increase of Alistipes putredinis and Barnesiella intestinih -> found in children with ASD

# Disturbed metabolites determined by proton magnetic resonance spectroscopy ($^1$H-MRS)




**Prefrontal lobe**

4 increased metabolites—MM09+Lip09, MM20, MM09, NAA

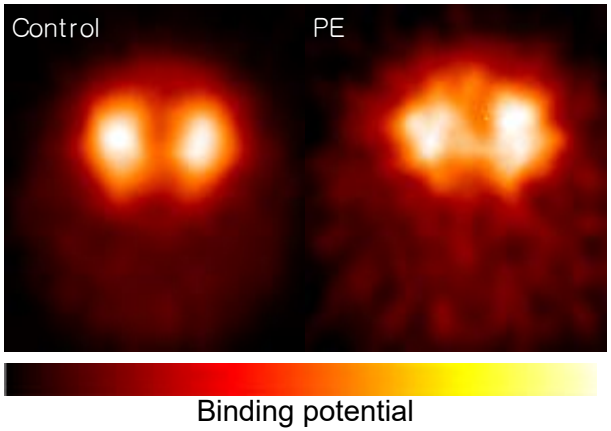
2 decreased metabolites—Ala, Ins

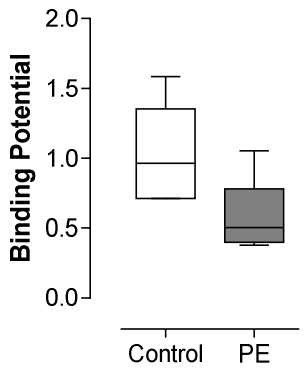
**Hippocampus**

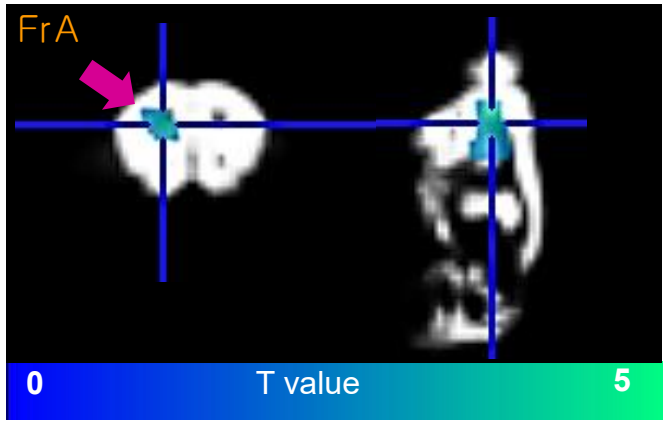
2 increased metabolites – Lac, PCr

6 decreased metabolites – Tau, MM20+Lip20, MM09, NAA, MM09+Lip09, and GABA

# Decreased binding potential and regional glucose metabolism in the prefrontal lobe



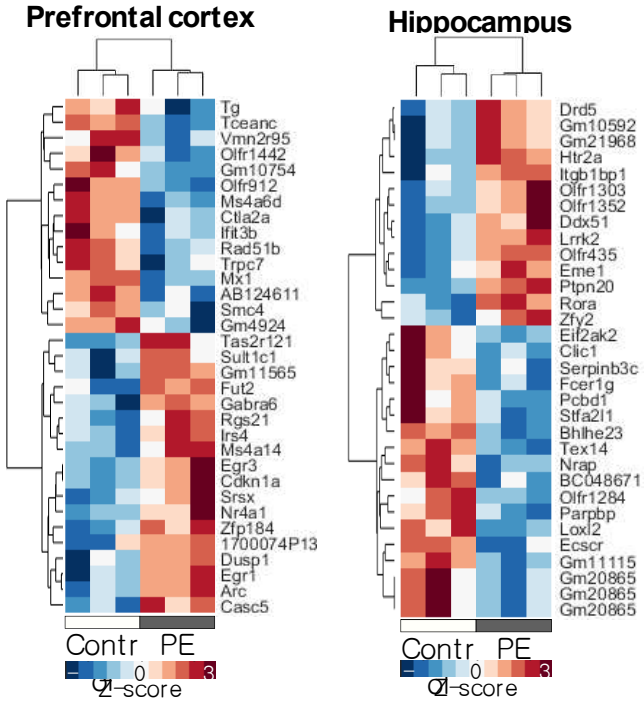




Defective dopamine transporter signaling has been linked to ASD (DiCarloet al. 2019).

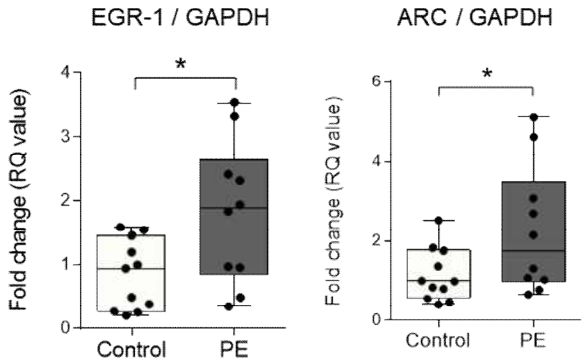
Decreased glucose metabolism in the left prefrontal lobe (FrA), which is consistent with the clinical PET findings of ASD (Hwanget al. 2017). Decreased glucose metabolism in the FrA has been correlated with working memory deficits (Antonio H. Lara 2015). A working memory deficit is a typical symptom of ASD (Evelien M Barendseet al. 2013).

# Disrupted gene expression in the brain




Prefrontal cortex : 18 genes increased / 15 genes decreased expression

Hippocampus region : 14 genes increased / 18 decreased expression

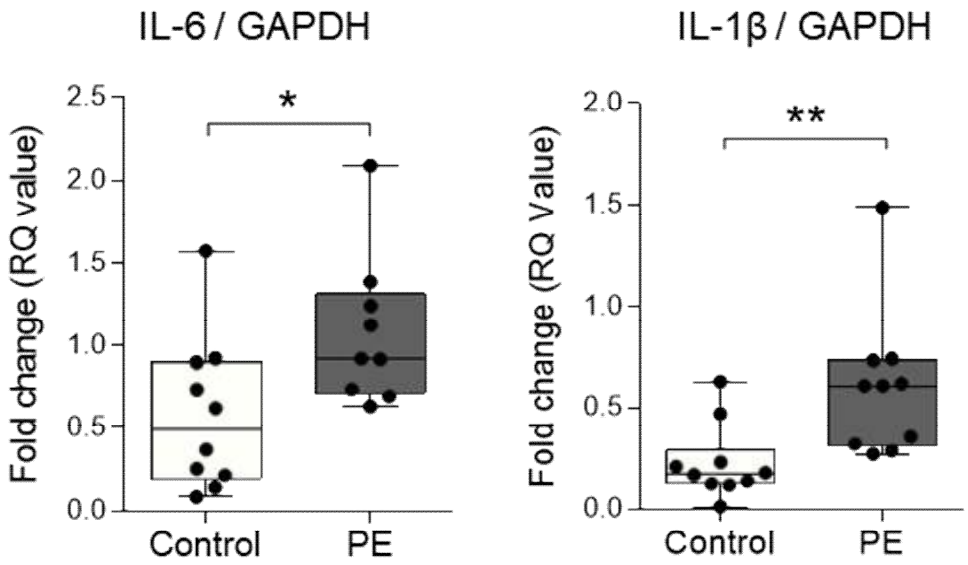



**Top 3 genes :** EGR-1, ARC, CDKN1A

EGR-1 : associated with neuropsychiatric disorders (Galloet al. 2018).
Excess mutations in EGR-1 have been linked to ASD (Liuet al. 2016).
ARC : associated with the pathogenesis of multiple neuropsychiatric disorders (Galloet al. 2018; Greeret al. 2010).
When ubiquitin processes are disrupted, ARC proteins accumulate in neurons, a phenomenon that has also been associated with ASD (Greeret al. 2010).
CDKN1A, upregulated gene expression in ASD (Jaume Forés-Martos 2019).

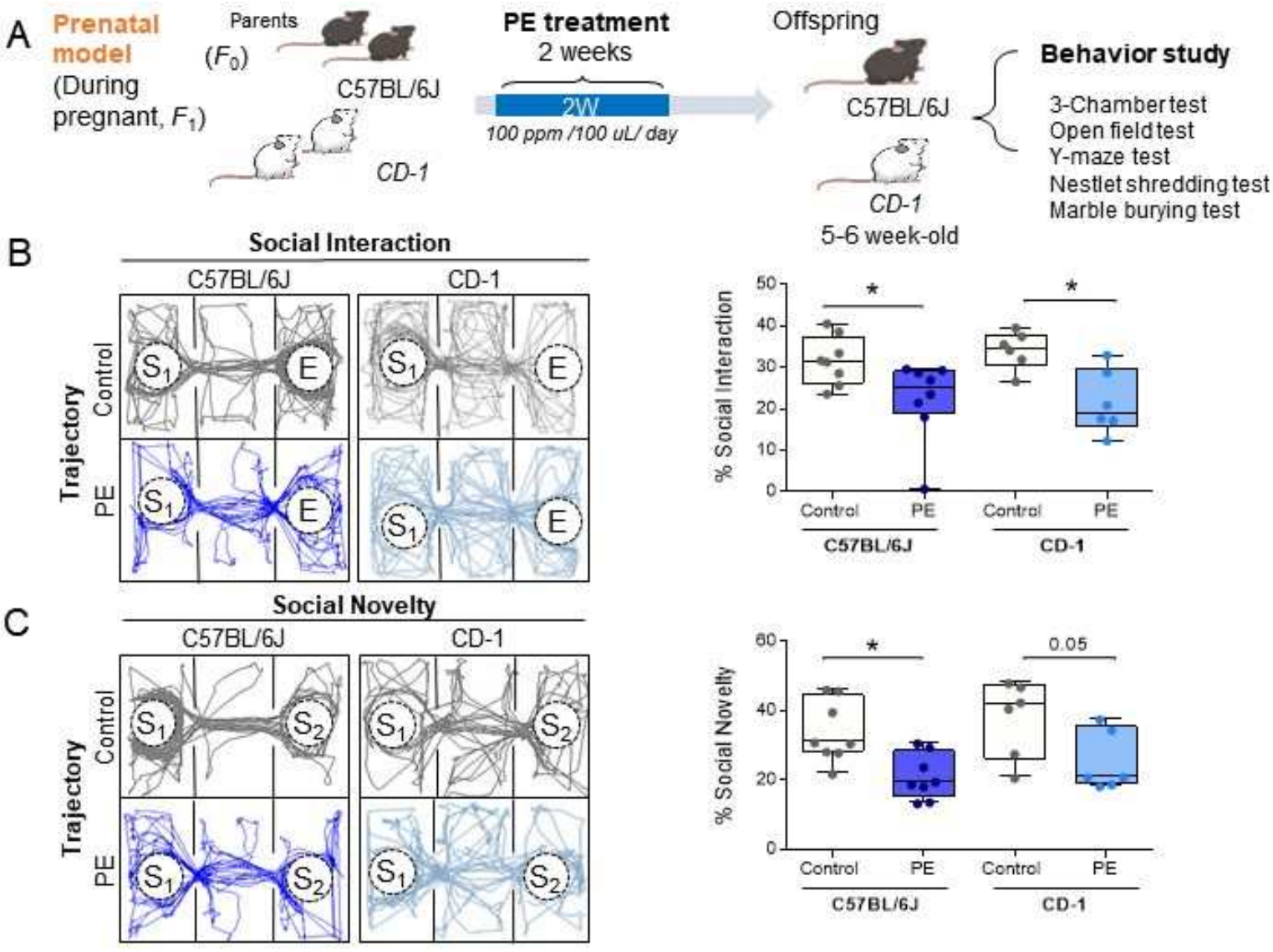
EGR-1 : early growth response protein 1
ARC : activity-regulated cytoskeleton-associated protein
CDKN1A : cyclin-dependent kinase inhibitor 1A

# Increase in cytokine

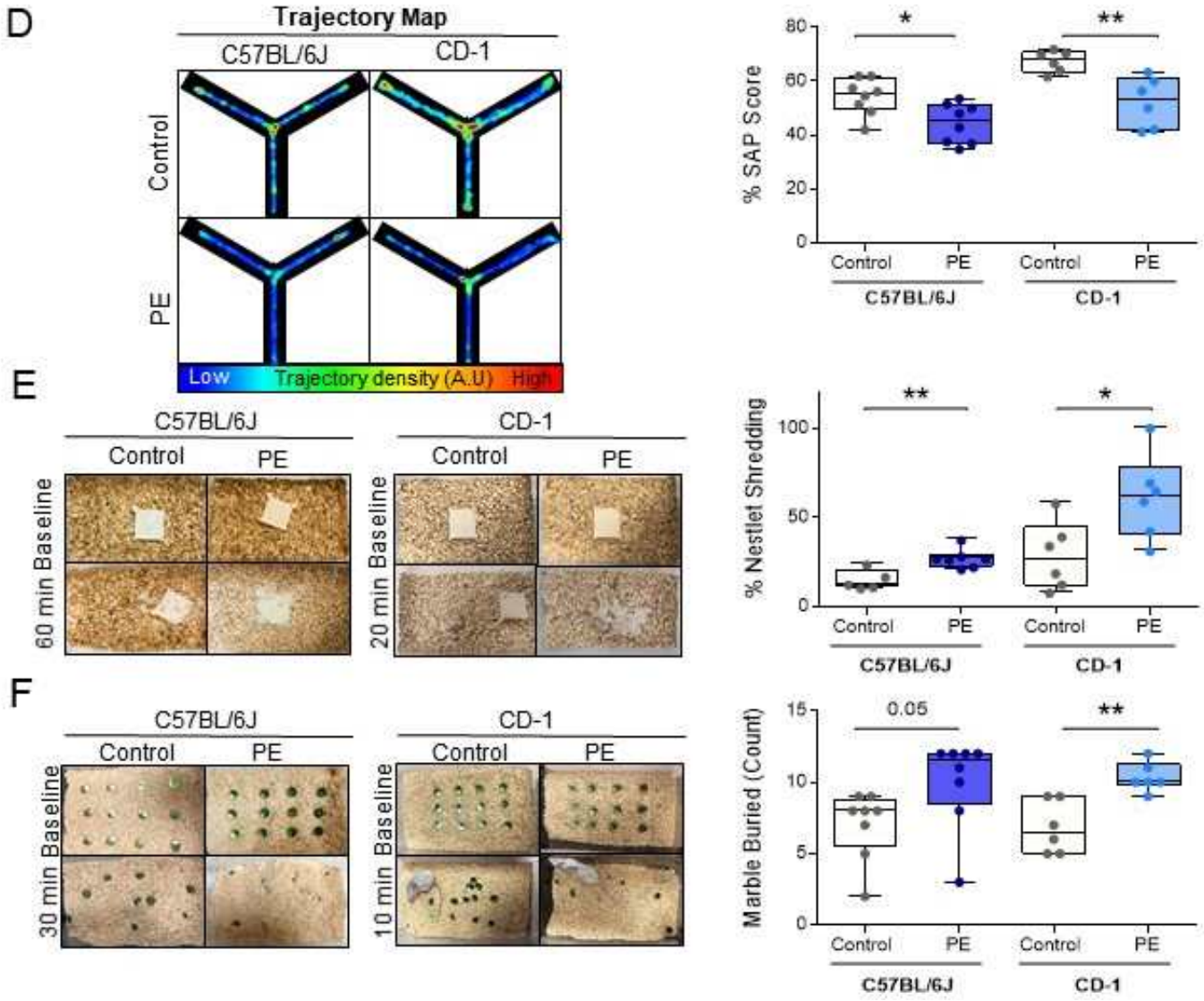



It is assumed that an increase in cytokine levels can induce inflammation in ASD (Masiet al. 2017).

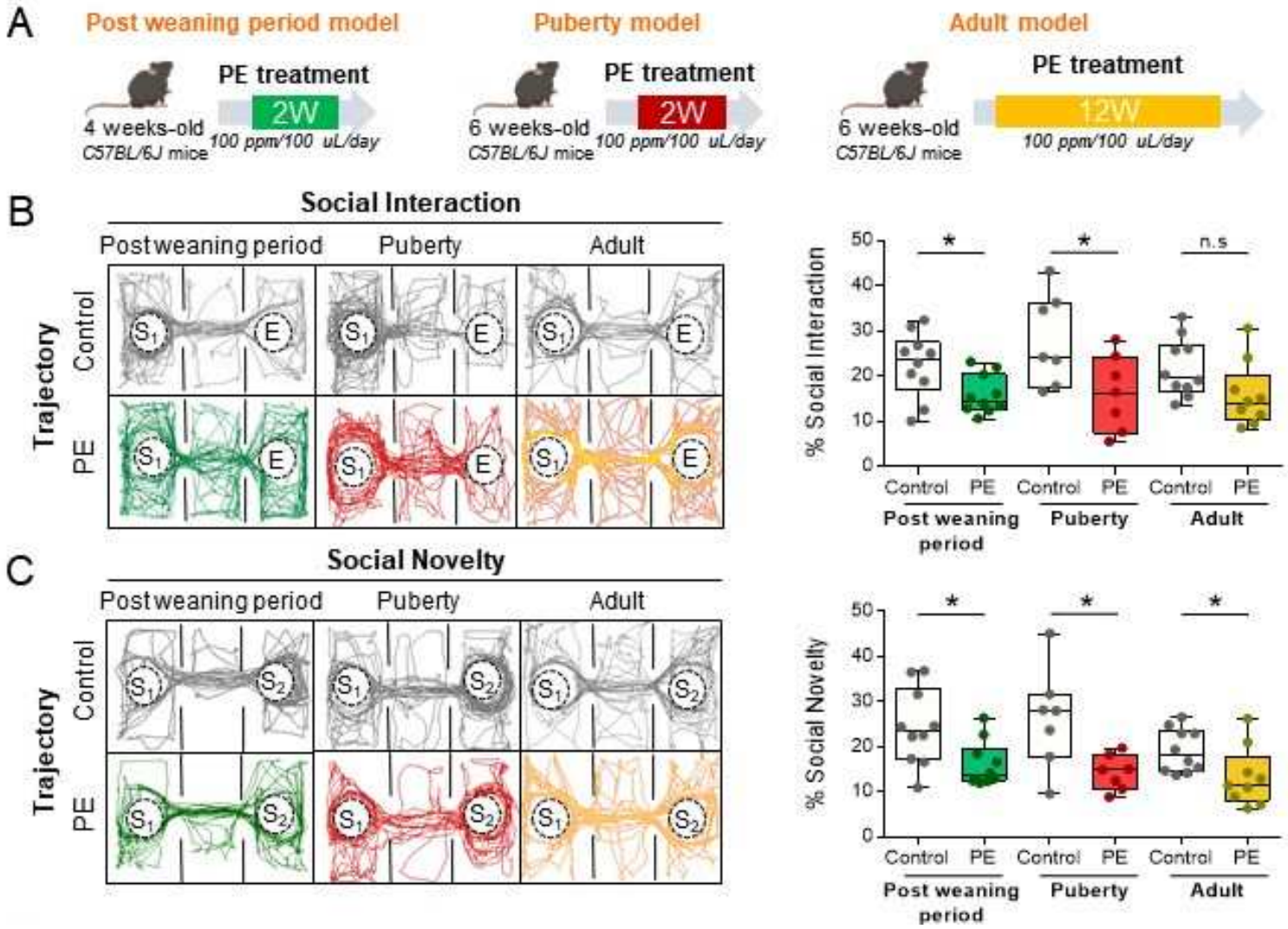
# ASD-like traits in the prenatal model



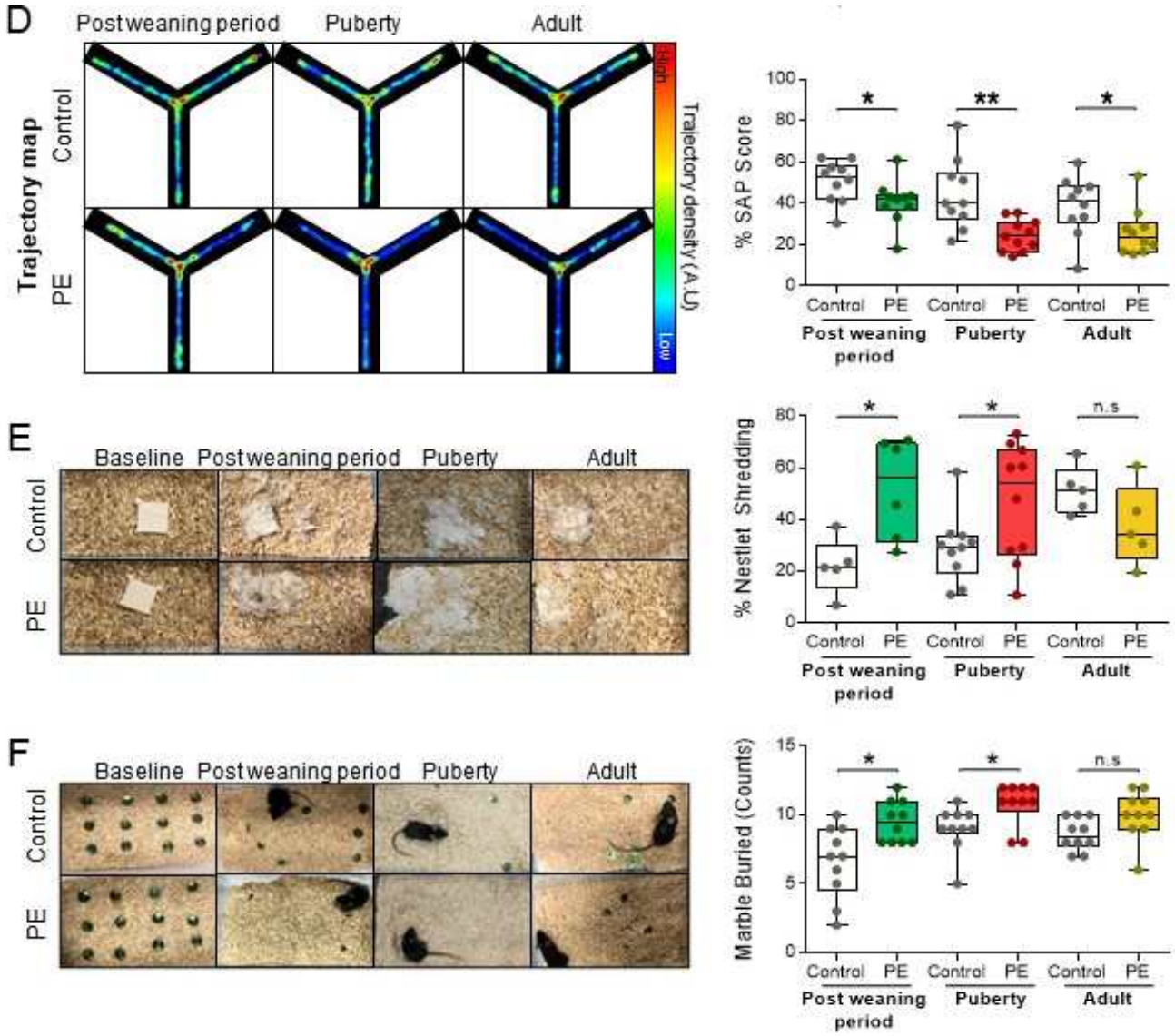
# ASD-like traits in the prenatal model



# ASD like traits in postweaning, puberty, and adult model



# ASD like traits in postweaning, puberty, and adult model



# 언론보도

- 미세플라스틱의 자폐스펙트럼장애
  한국을 빛내는 사람들 선정
  SBS “미세플라스틱 먹이나 사회성 감소 " 자폐유발규명
  YTN “미세플라스틱, 자폐 스펙트럼장애 유발”
  TBS “자폐 늘아나는 뜻밖의 이유 찾았다“

김진수 (Jin Su Kim)
한국원자력의학원, 과학기술연합대학원대학교 KIRAMS 캠퍼스(UST-KIRAMS)

CV PDF 1.79 MB

조회 62

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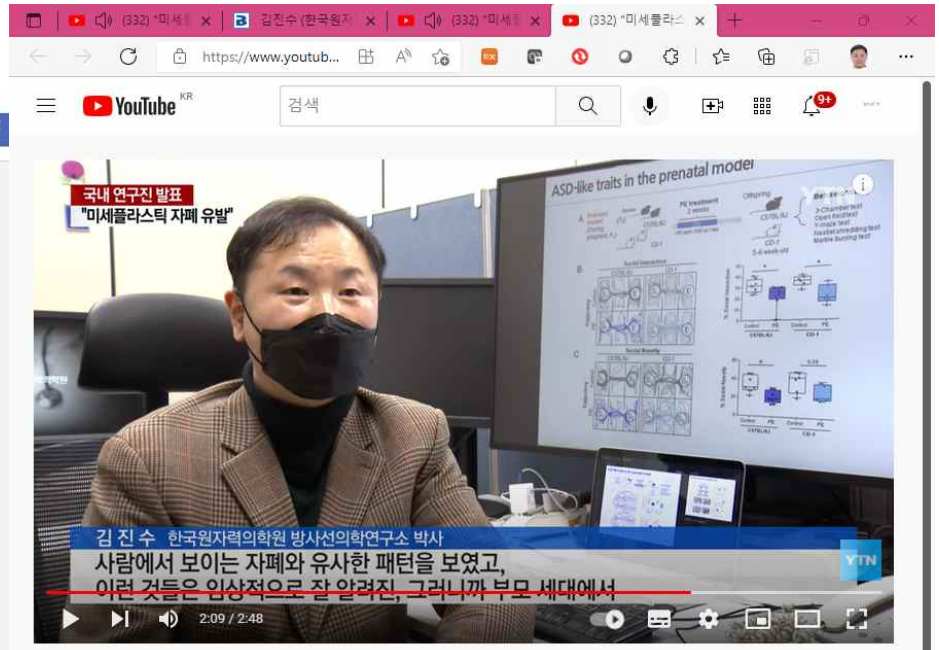
**Pre/post-natal exposure to microplastic as a potential risk factor for autism spectrum disorder**

⊞ Authors and Affiliations

Abstract

In common with the increase in environmental pollution in the past 10 years, there has also been a recent increase in the prevalence of autism spectrum disorder (ASD). In this regard, we hypothesized that exposure to microplastics is a potential risk factor for ASD. To evaluate the validity of this hypothesis, we initially examined the accumulation of polyethylene (PE) in the brains of mice and then assessed the behavioral effects using mouse models at different life stages, namely, prenatal, post-weaning, puberty, and adult models. Based on typical behavioral assessments of autistic traits in the model mice, we established that ASD-like traits were induced in mice after PE feeding. In addition, we examined the induction of ASD-like traits in response to microplastic exposure using positron emission tomography, magnetic resonance spectroscopy, quantitative real-time polymerase chain reaction, microarray, and microbiome analysis. We believe these findings provide evidence in microplastics as a potential risk factor for ASD.



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Theranostics

2022; 12(7): 3217-3236. doi: 10.7150/thno.73226

Research Paper

# Enhanced ASGR2 by microplastic exposure leads to resistance to therapy in gastric cancer

Hyeongi Kim[1,2], Javeria Zaheer[1,3], Eui-Ju Choi[2], and Jin Su Kim[1,3]✉

1. Division of RI Application, Korea Institute Radiological and Medical Sciences, Seoul 01812, Republic of Korea.
2. Department of Life Sciences, School of Life Sciences and Biotechnology, Korea University, Seoul 02841, Republic of Korea.
3. Radiological and Medico-Oncological Sciences, University of Science and Technology (UST), Seoul 01812, Republic of Korea.

✉ Corresponding author: Jin Su Kim, PhD, Division of RI Application, Korea Institute Radiological and Medical Sciences, 75 Nowon-Gil, Gongneung-Dong, Nowon-Gu, Seoul 01812, Korea. Radiological and Medico-Oncological Sciences, University of Science and Technology (UST), Seoul 01812, Republic of Korea. Tel: 82-2-970-1661, Fax: 82-2-970-2416, E-mail: kjs@kirams.re.kr.



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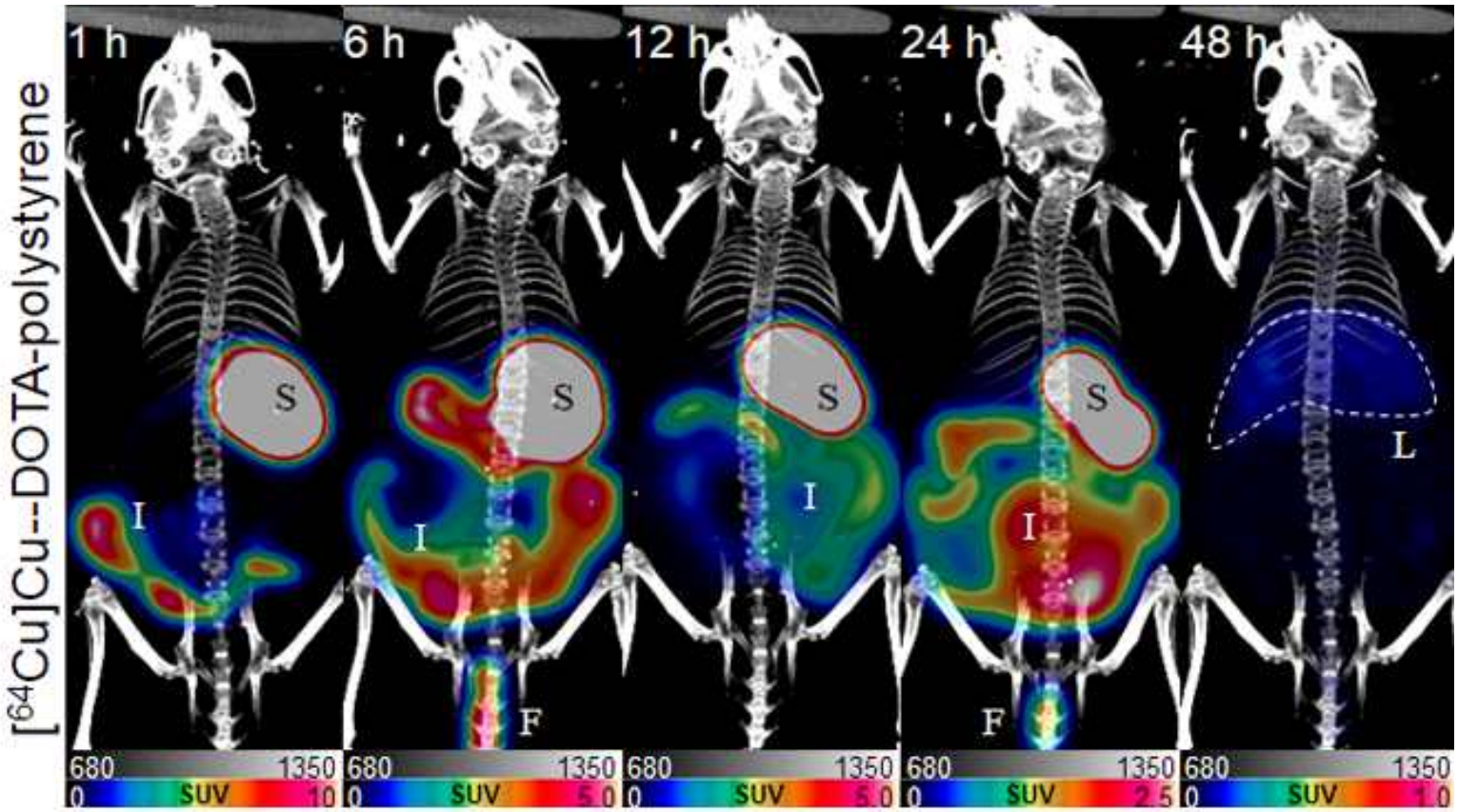
## Abstract

**Background:** Microplastics (MPs) are a new global environmental threat. Previously, we showed the biodistribution of MPs using [$^{64}$Cu] polystyrene (PS) and PET in mice. Here, we aimed to identify whether PS exposure has malignant effects on the stomach and induces resistance to therapy.

**Methods:** BALB/c nude mice were fed 1.72 × $10^4$ particles/mL of MP. We investigated PS accumulation in the stomach using radioisotope-labeled and fluorescent-conjugated PS. Further, we evaluated whether PS exposure induced cancer stemness and multidrug resistance, and whether it affected tumor development, tumor growth, and survival rate *in vivo* using a 4-week PS-exposed NCI-N87 mouse model. Using RNA-Seq analysis, we analyzed whether PS exposure induced gene expression changes in gastric tissues of mice.

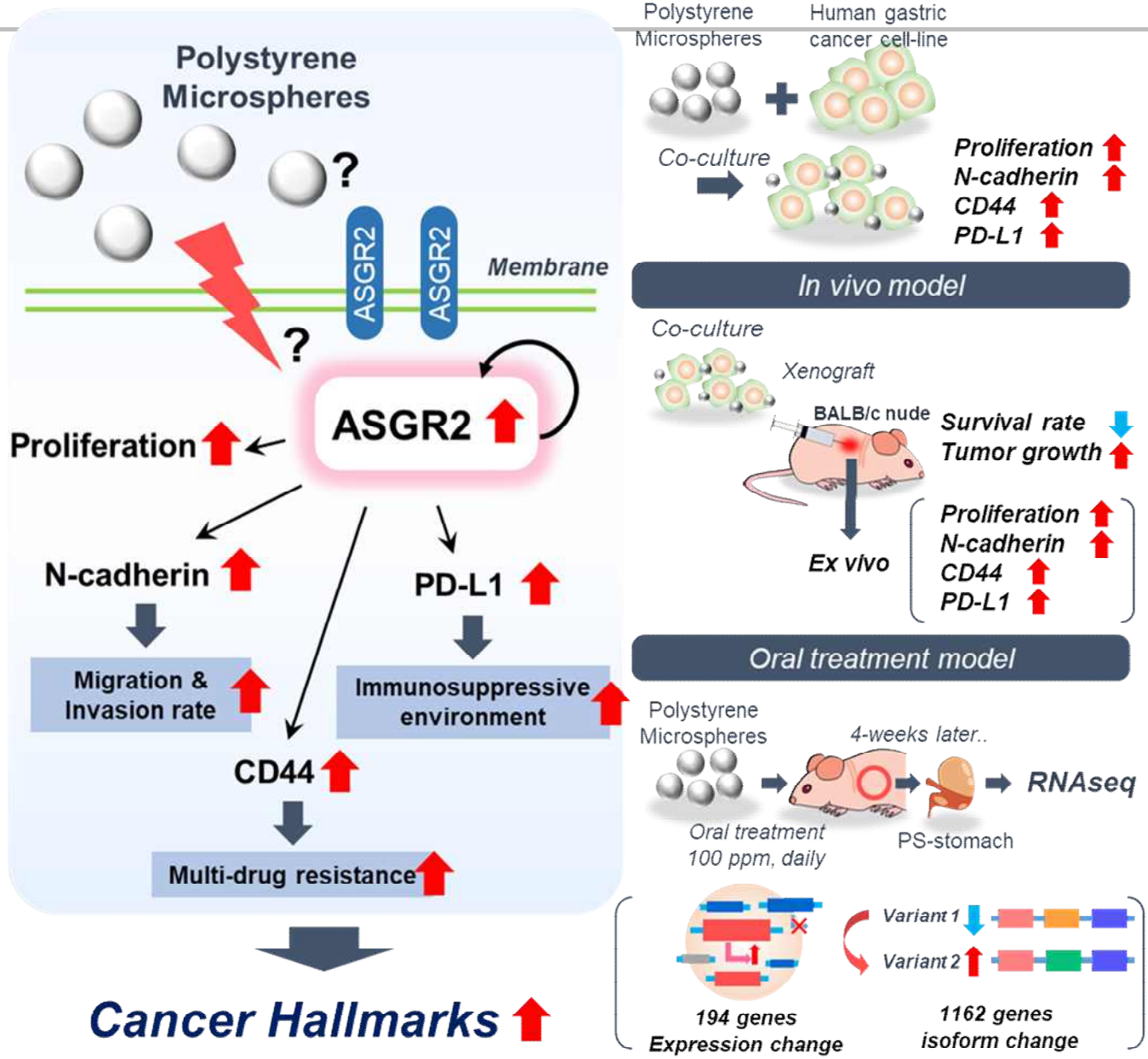
**Results:** PET imaging results showed that a single dose of [$^{64}$Cu]-PS remained for 24 h in the mice

# 미세플라스틱의 위 노출



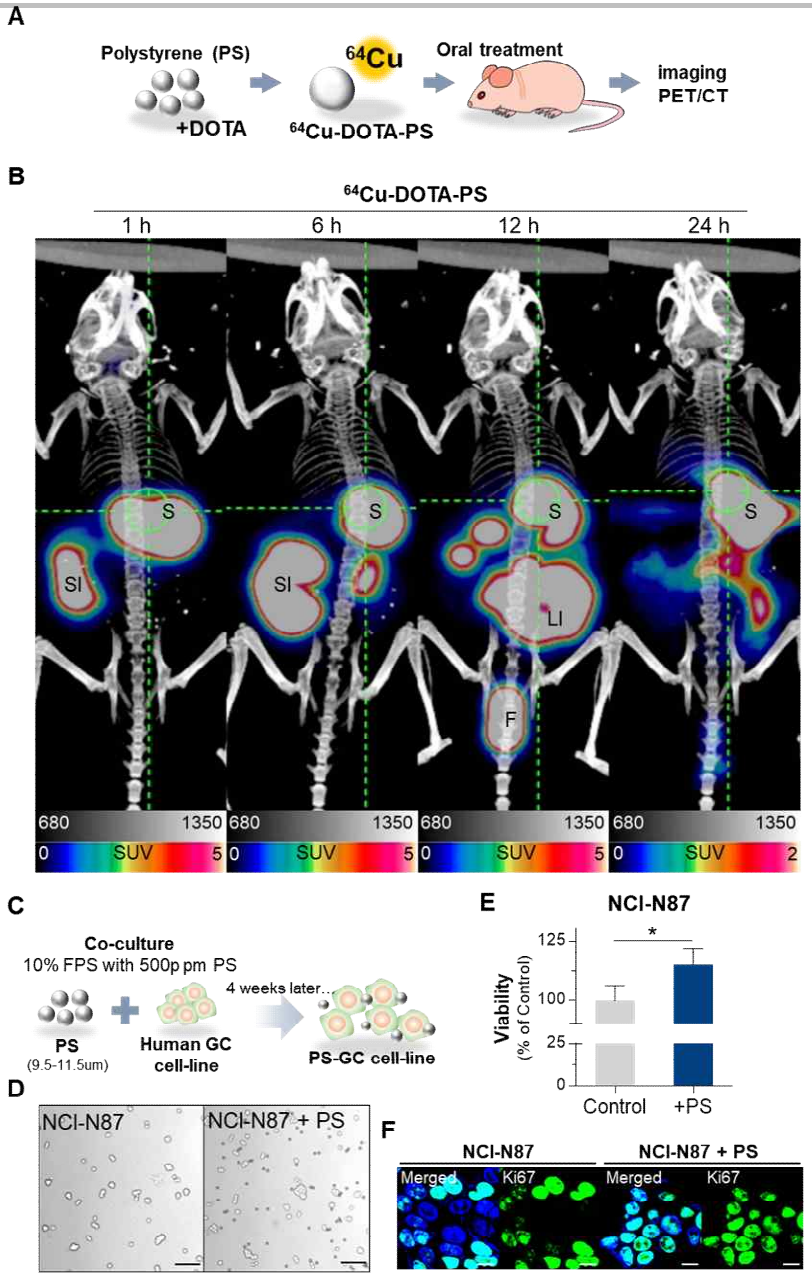

관찰 : 미세플라스틱이 위에 하루 동안 머무른다
위에 어떤 영향을 줄까?

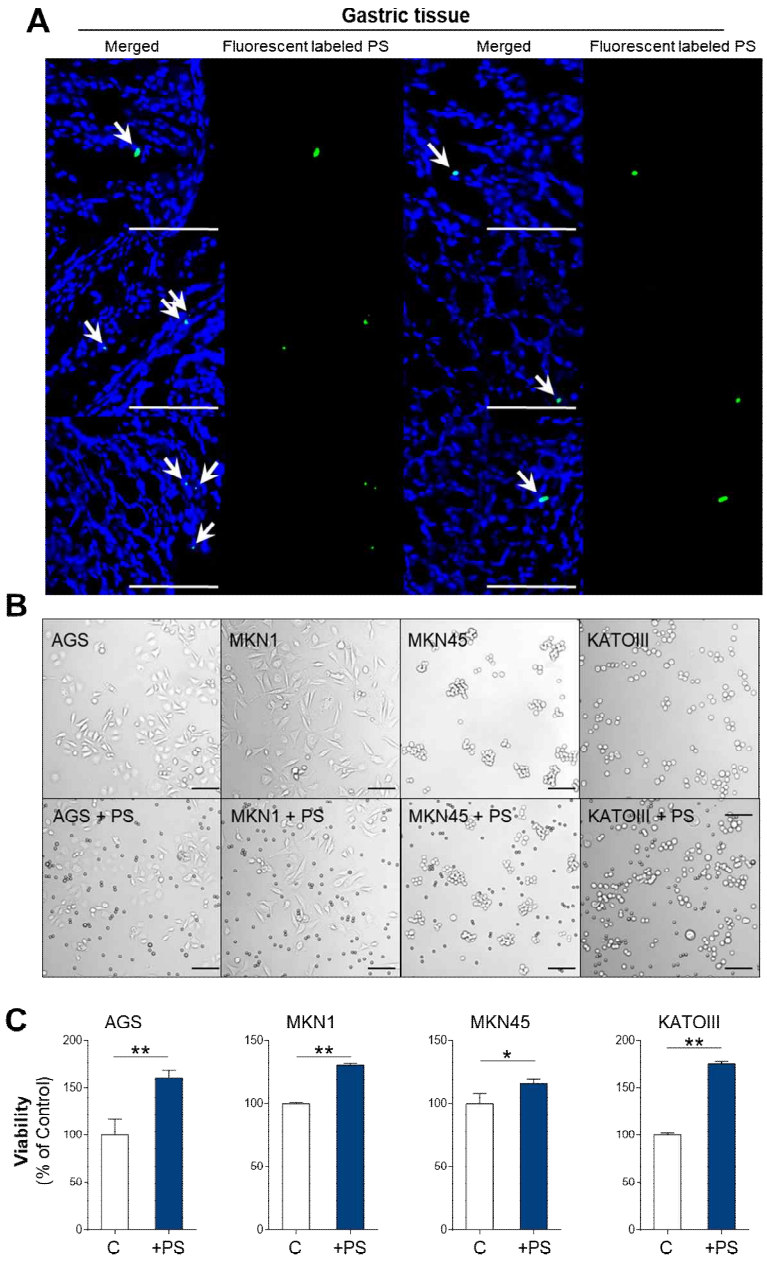
# 연구 결과 요약



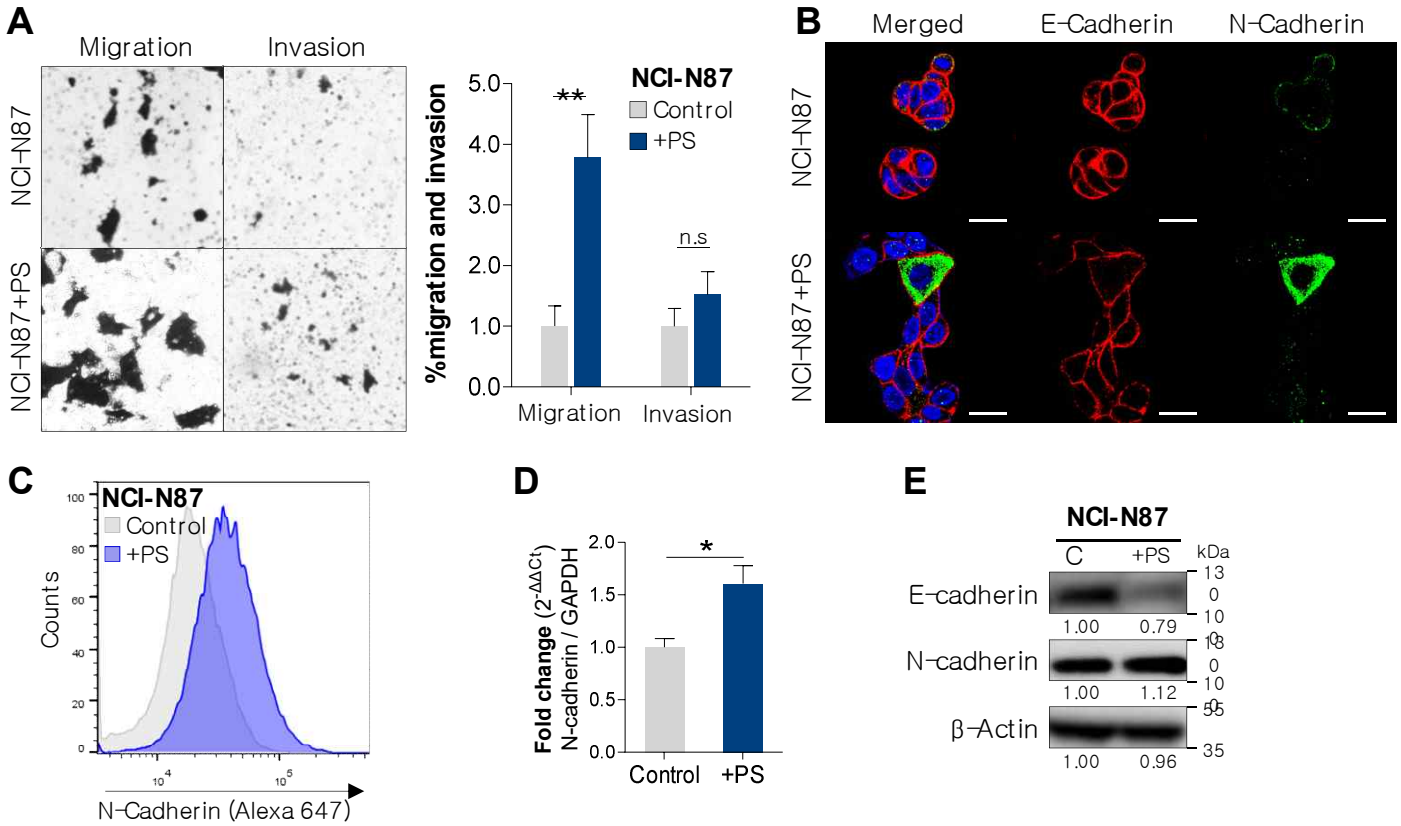

같은 유전자, but 다른 아미노산 서열

# 플라스틱이 위벽에 박혀 있음. 암세포 성장 촉진

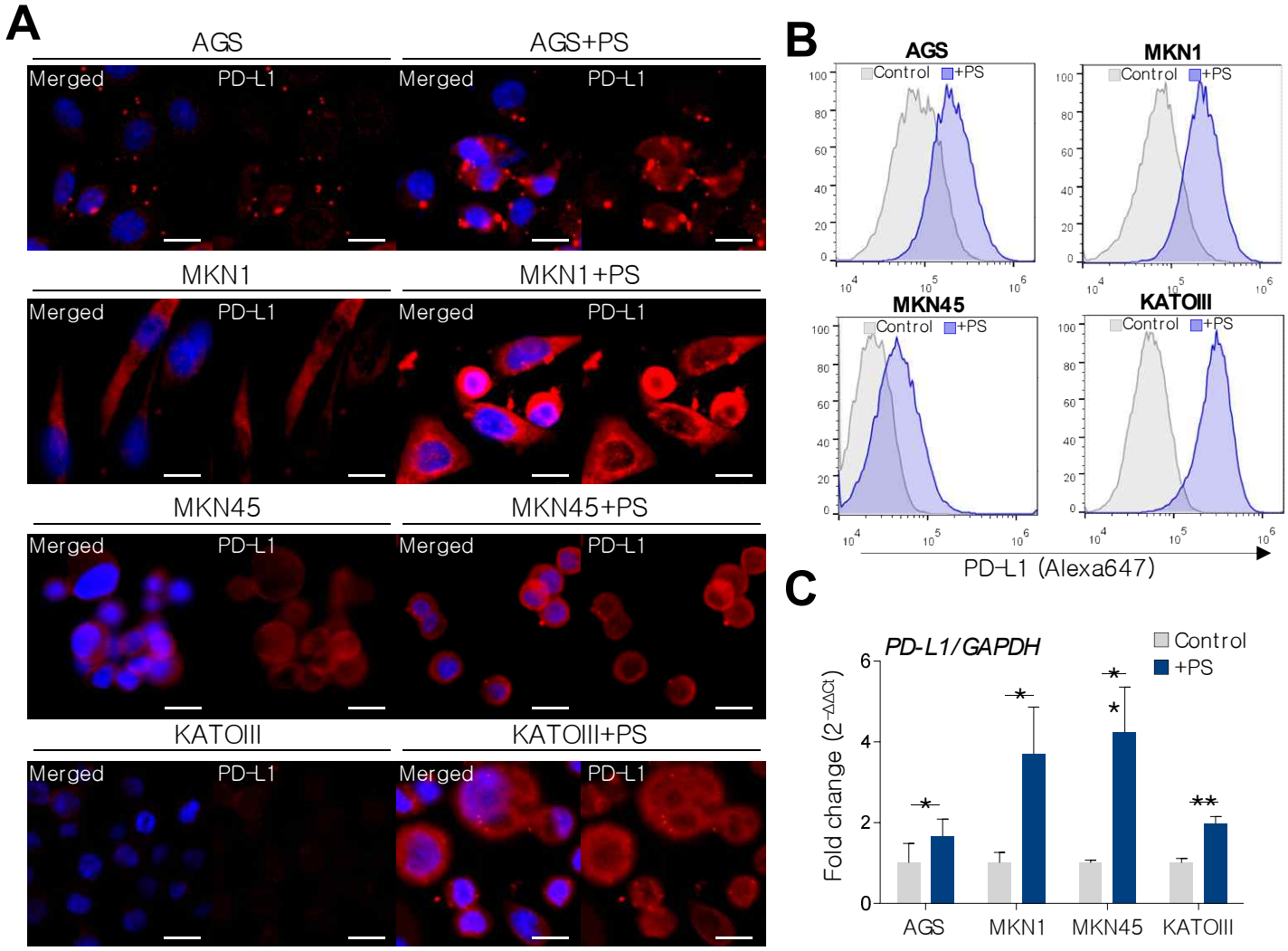


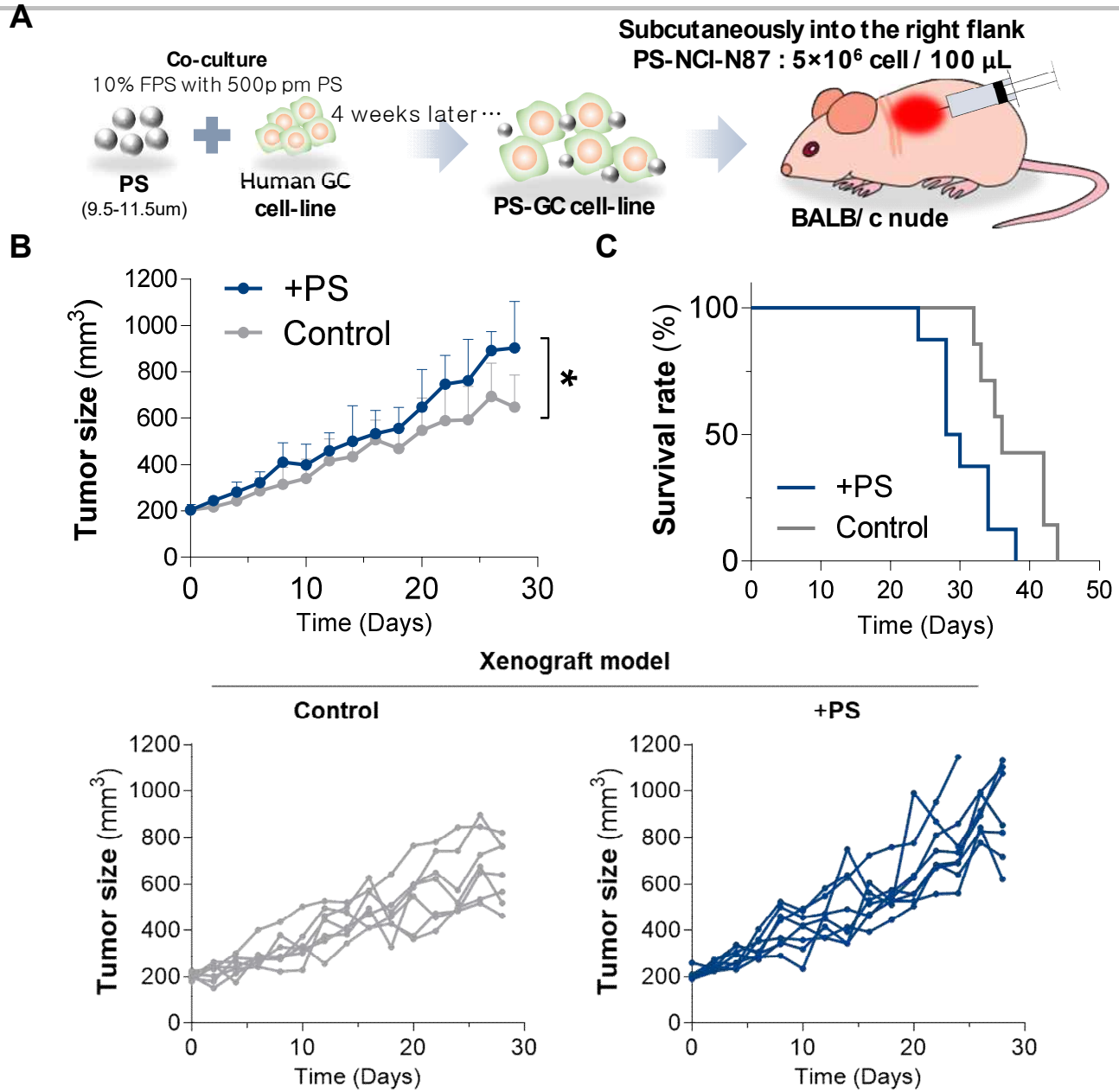
# 플라스틱 암 전이 촉진


A
Migration
Invasion
NCI-N87
NCI-N87+PS
%migration and invasion
NCI-N87
Control
+PS
**
n.s
Migration
Invasion
B
Merged
E-Cadherin
N-Cadherin
NCI-N87
NCI-N87+PS
C
NCI-N87
Control
+PS
Counts
N-Cadherin (Alexa 647)
D
Fold change (2-ΔΔCt)
N-cadherin / GAPDH
*
Control
+PS
E
NCI-N87
C
+PS
kDa
E-cadherin
1.00
0.79
N-cadherin
1.00
1.12
β-Actin
1.00
0.96

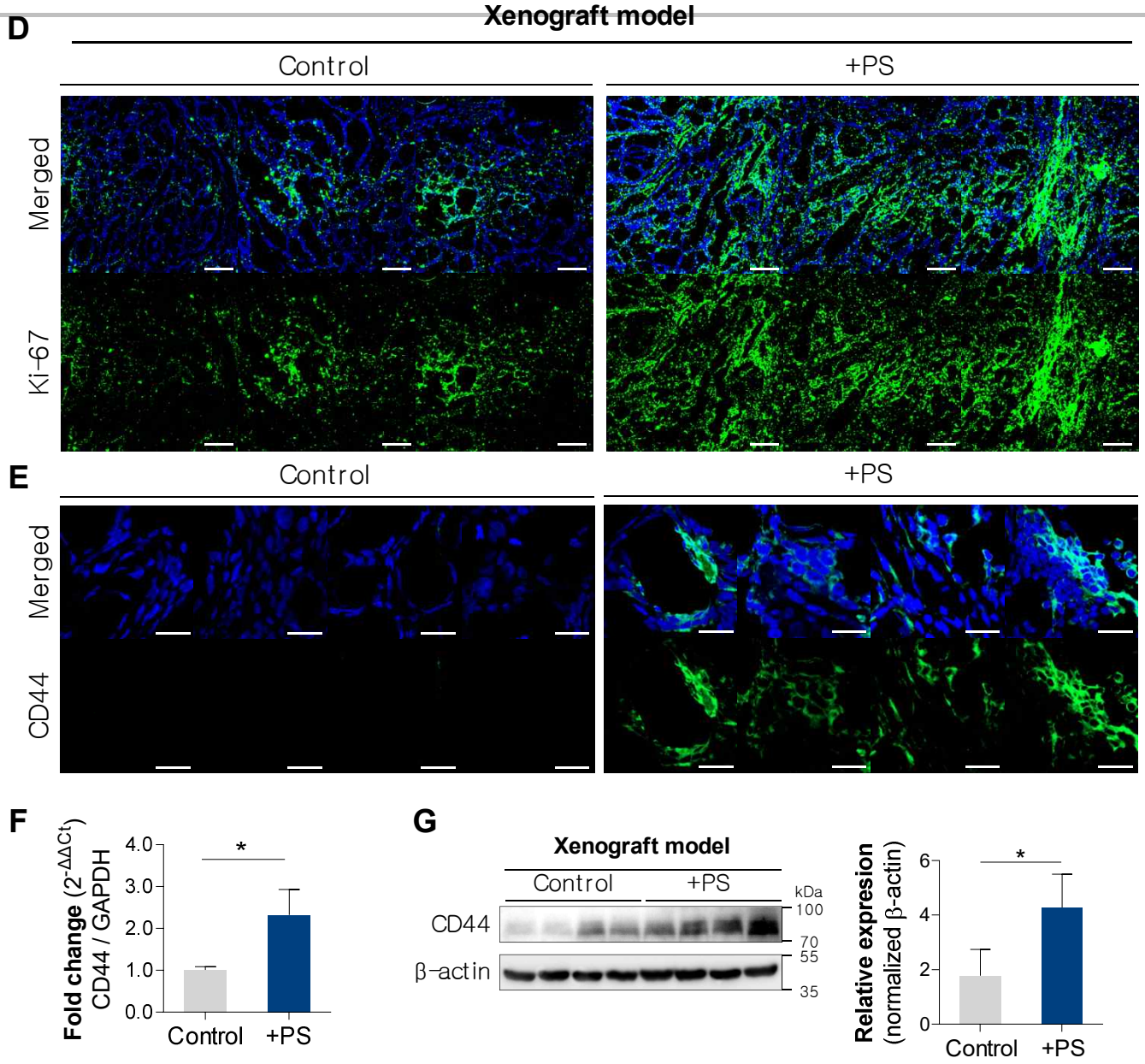
# 플라스틱 치료 저항성 유발 (PD-L1)



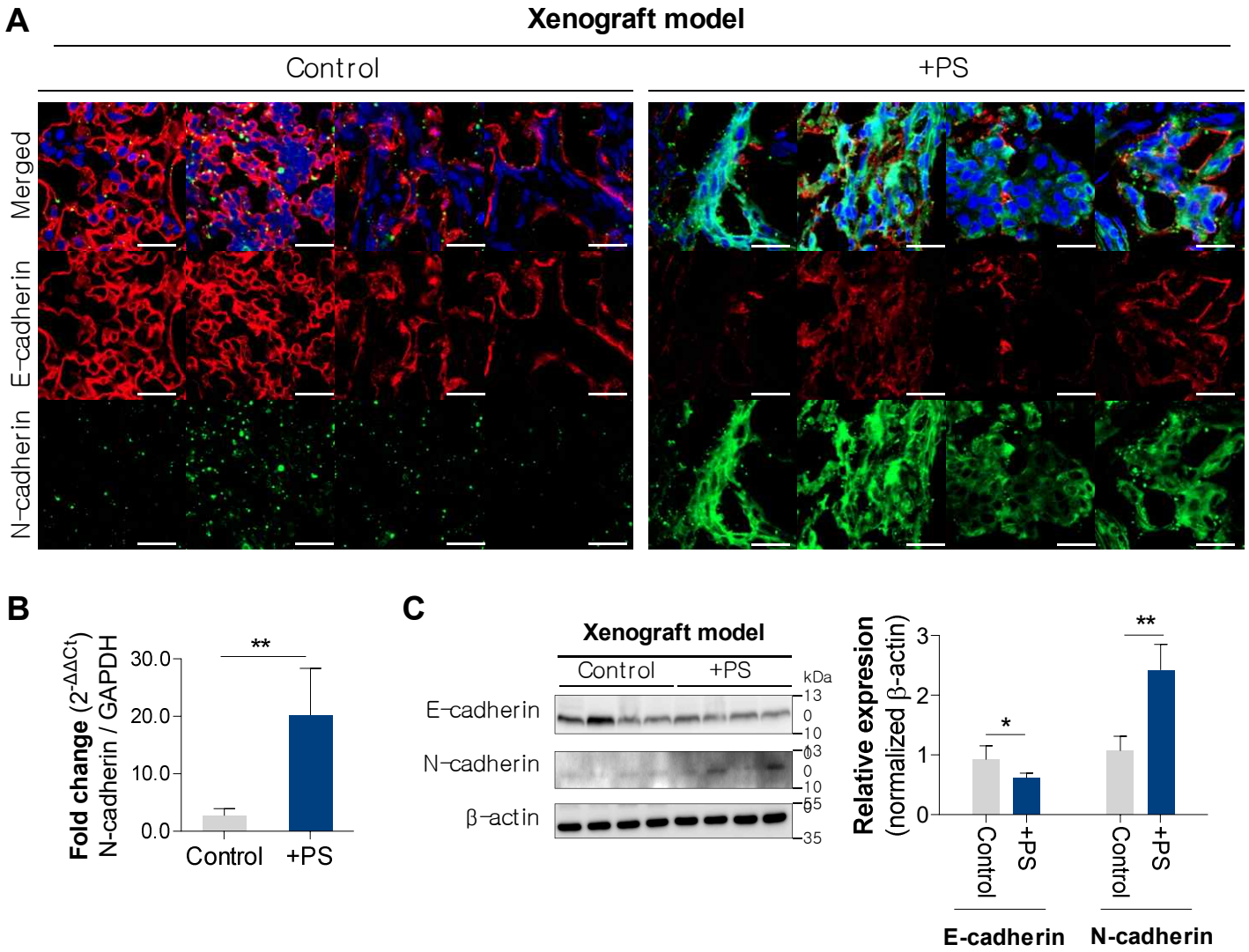
# xenograft model에서 생존율 악화



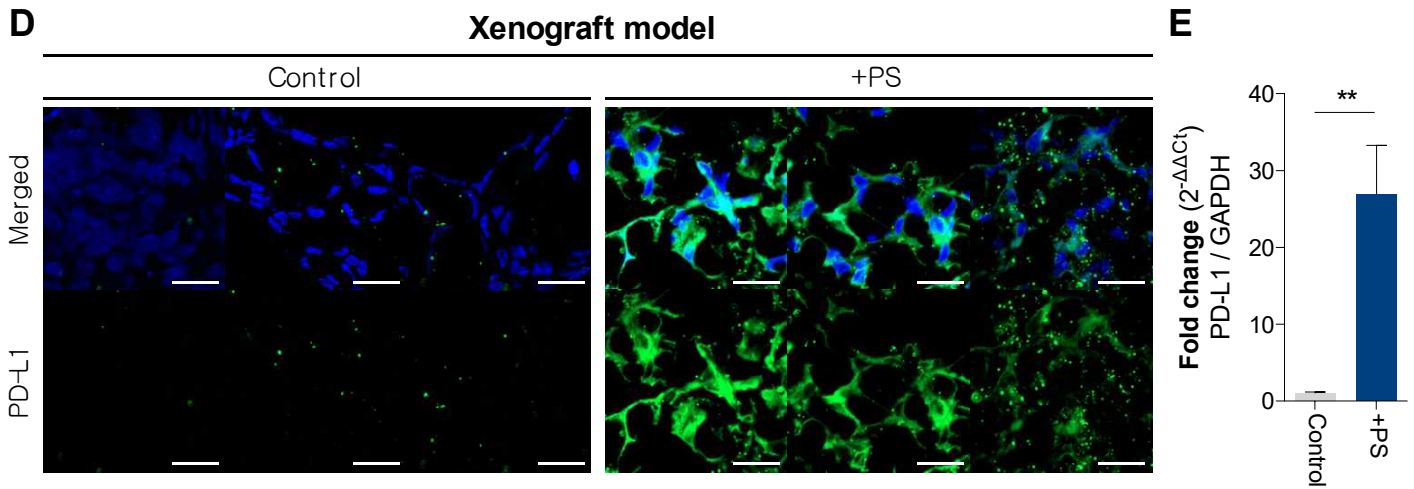
# Ex vivo (CD44 증가)



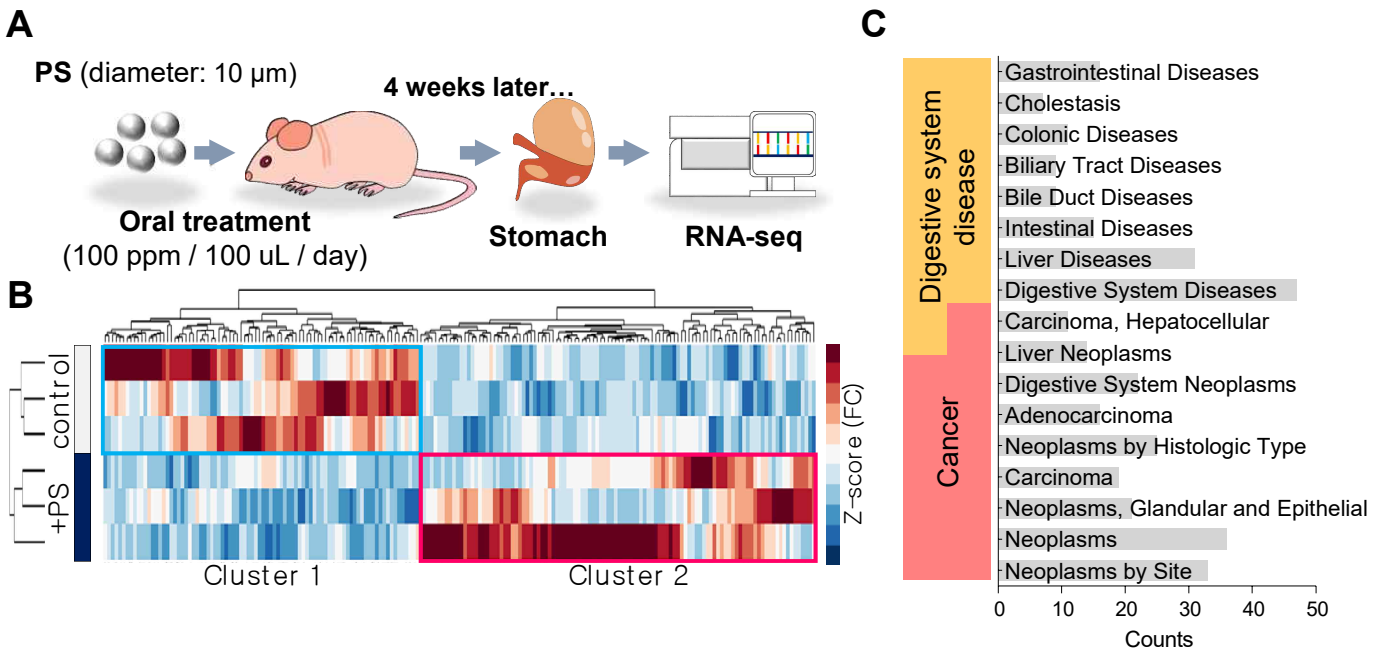
# xenograft data에서 전이 marker 확인



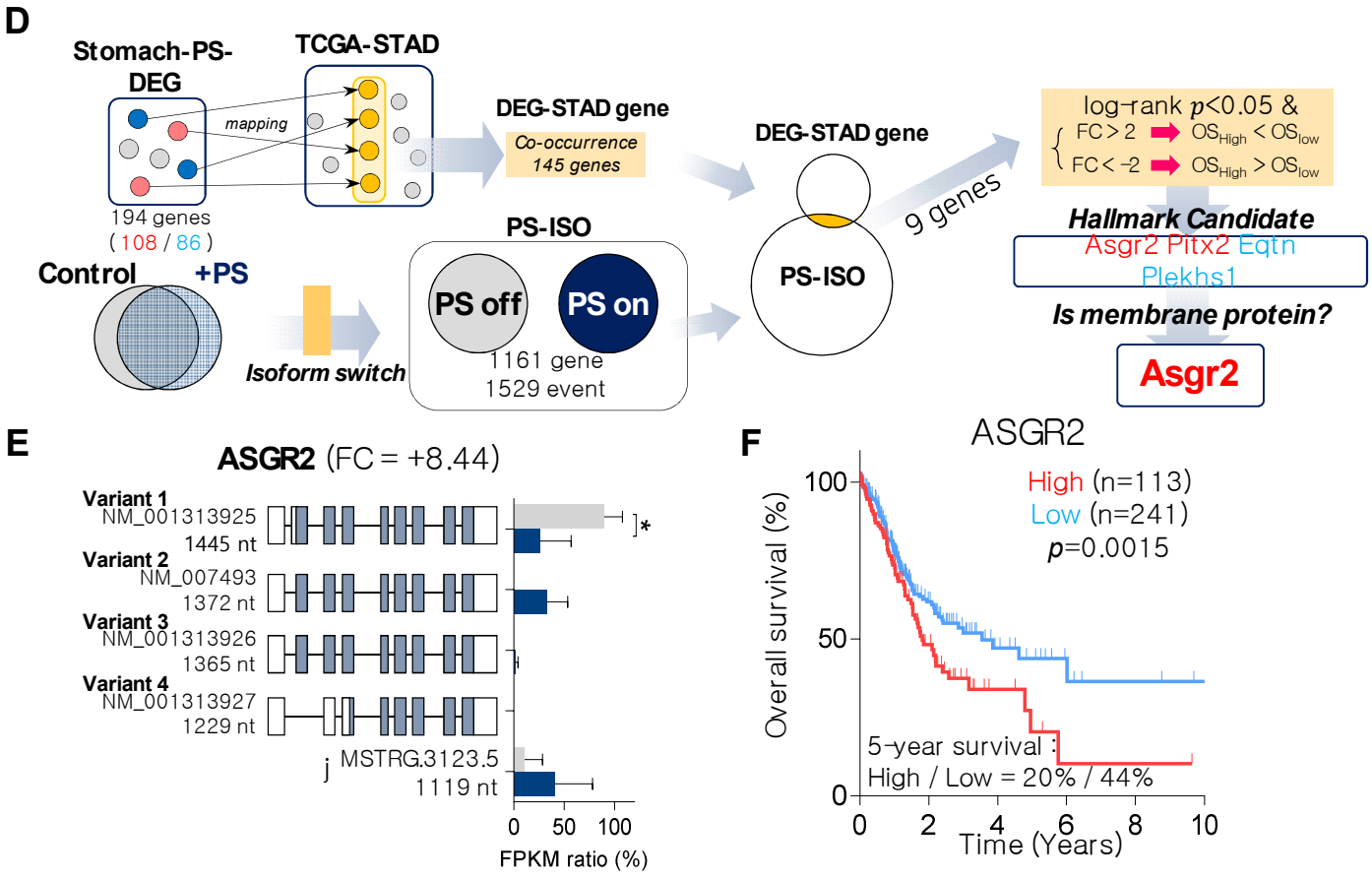
# xenograft model (ex vivo data)



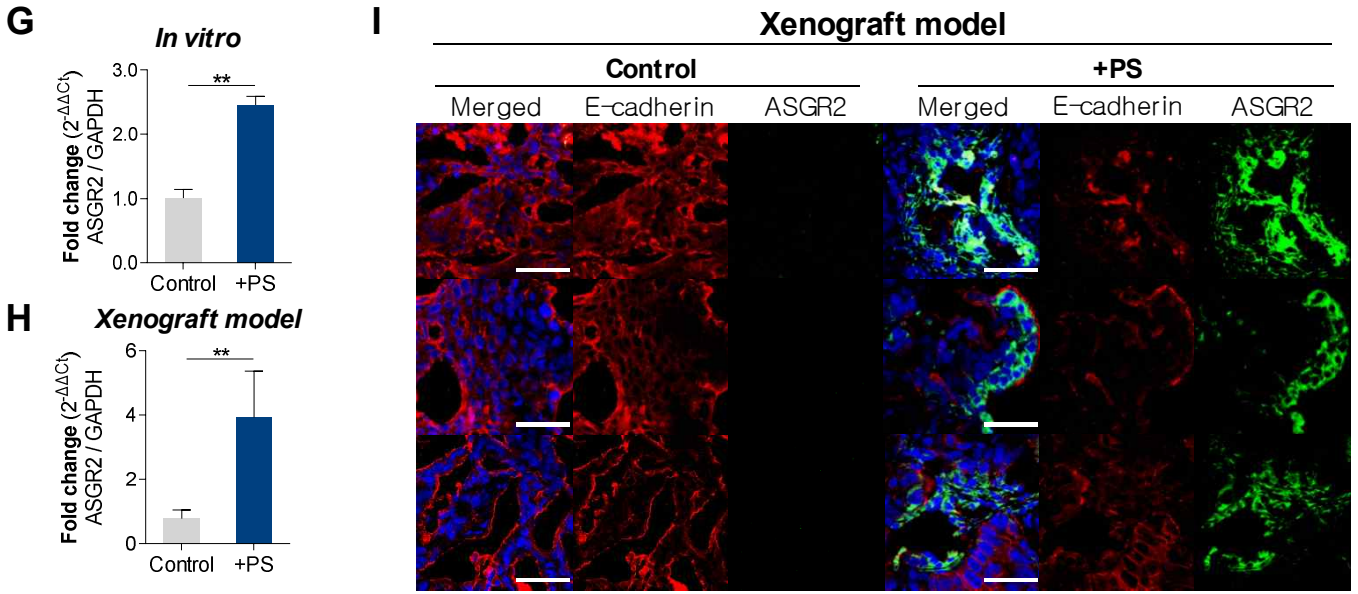
# RNA seq


A
PS (diameter: 10 μm)
4 weeks later…
Oral treatment
(100 ppm / 100 uL / day)
Stomach
RNA-seq
B
control
+PS
Cluster 1
Cluster 2
Z-score (FC)
C
Digestive system disease
Cancer
Gastrointestinal Diseases
Cholestasis
Colonic Diseases
Biliary Tract Diseases
Bile Duct Diseases
Intestinal Diseases
Liver Diseases
Digestive System Diseases
Carcinoma, Hepatocellular
Liver Neoplasms
Digestive System Neoplasms
Adenocarcinoma
Neoplasms by Histologic Type
Carcinoma
Neoplasms, Glandular and Epithelial
Neoplasms
Neoplasms by Site
0
10
20
30
40
50
Counts

# DEG & ISOFORM Change → ASGR2 발굴



# in vitro & ex vivo confirmation (ASGR2)



# Confirmation of ASGR2