In Vivo Biodistribution and Impact Evaluation of Microplastic

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

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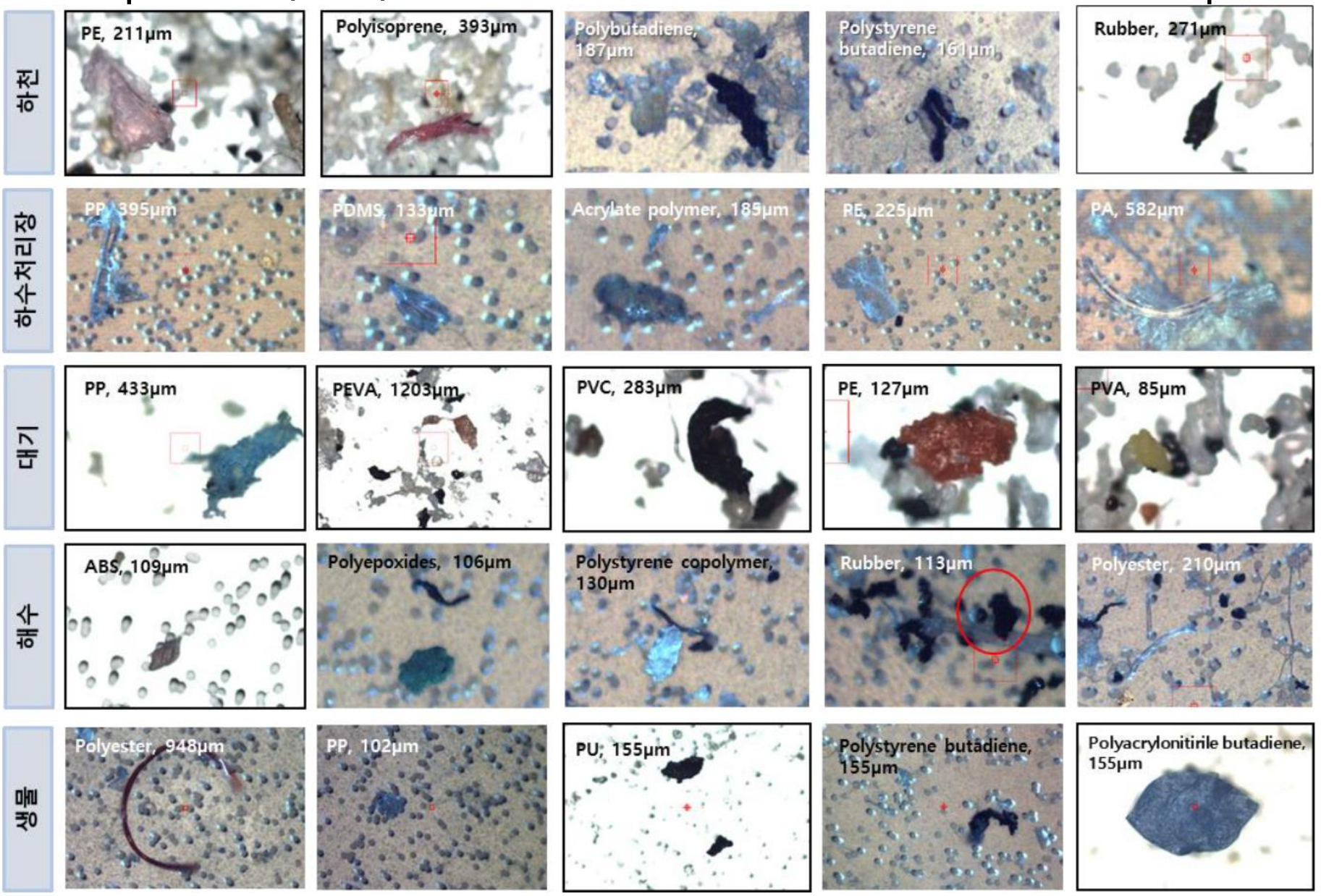
Korea Institute of Radiological & Medical Sciences, Research Department
University of Sciences & Technology, Radiological & Medico-Oncological Sciences

Microplastics (MPs) Detected In Various Environmental Samples



KIOST ("Research on food safety management for microplastics", 2017 Research Report)

Clam Chowder? Plastic Soup?

Clam Chowder

Plastic Soup

Questions about the Impact of MPs on the Human Body

- What pathways do MPs take to enter & exit the human body?
- What are the impacts of MPs on our brains?
  - Will it cause brain dysfunction?
  - Wouldn't it induce a brain disease?
- Any Impact on the Digestive Tract?
  - Stomach, large intestine

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 γ-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.

Key Words: microplastic; polystyrene; ^{64}Cu; [^{64}Cu]Cu-labeled polystyrene; PET

J Nucl Med 2022; 63:461–467
DOI: 10.2967/jnumed.120.256982

Microplastics with diameters of less than 5 mm are recognized as a new environmental threat and human health risk (*1*). Microplastics have been observed to accumulate in many different marine animals, including fish (*2–5*), copepods (*6,7*), mussels (*8–10*), European flat oysters (*11*), and others (*12–14*). Fiber-type 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 γ-rays emitted from the tissue originated from [^{64}Cu]Cu-DOTA-polystyrene or from ^{64}Cu.

MATERIALS AND METHODS

Synthesis and Radiolabeling

To 300 μL of 0.1 M sodium carbonate buffer (pH 9.0), 2.5 mg of amino-polystyrene (0.2–0.3 μm; Spherotech) were added. Then, 260 μg (471.70 nmol) of *S*-2-(4-isothiocyanatobenzyl)-1,4,7,10-tetraazacyclododecane tetraacetic acid (*p*-SCN-Bn-DOTA) in 50 μL of deionized water were added, and the mixture (pH 9.0) was shaken at 1,000 rpm and 25°C for 20 h. Unconjugated *p*-SCN-Bn-DOTA was removed using an Amicon centrifugal filter (30-kDa cutoff; Millipore). DOTA conjugation was confirmed using Fourier-transform infrared spectroscopy (Nicolet iS5; Thermo Fisher Scientific), and the resulting spectra were analyzed using Omnic software from Nicolet Instrument Corp. To determine moles of DOTA per milligram of plastic, 50 μL of filtrate were analyzed by high-performance liquid chromatography (Waters). The quantity of DOTA in the filtrate was calculated from a standard curve (prepared from an analysis of known concentrations of DOTA). The conjugated moles of DOTA to polystyrene were then calculated by subtracting the moles of DOTA in the filtrate from the total moles of DOTA for the reaction. Physicochemical characterization of DOTA-polystyrene was performed using a field-emission scanning electron microscopy and dynamic light scattering. Concentrated DOTA-polystyrene was subsequently buffer-exchanged to isotonic buffered saline for

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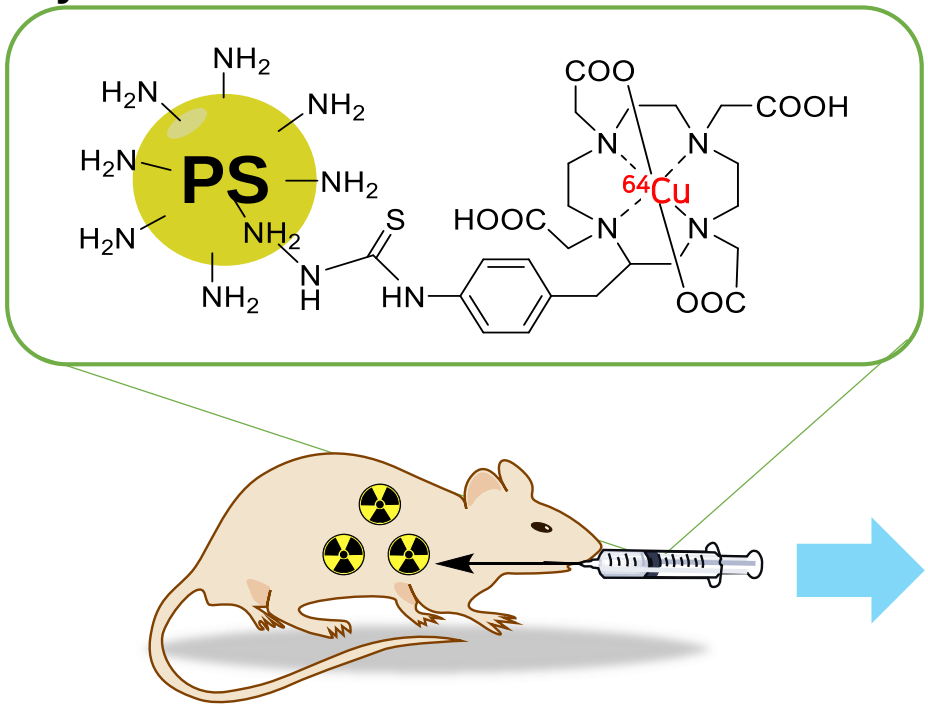
*Contributed equally to this work.
Published online Jul. 2, 2021.

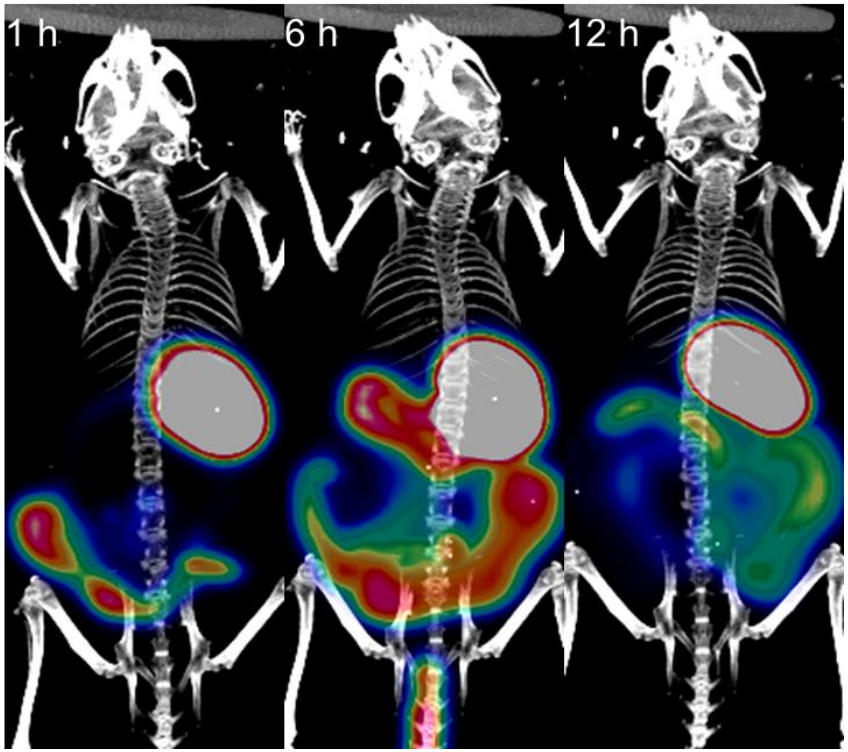
Evaluation of Absorption Pathways Using Positron Emission Tomography (PET) (Split-timed observation of the absorption process)

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



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

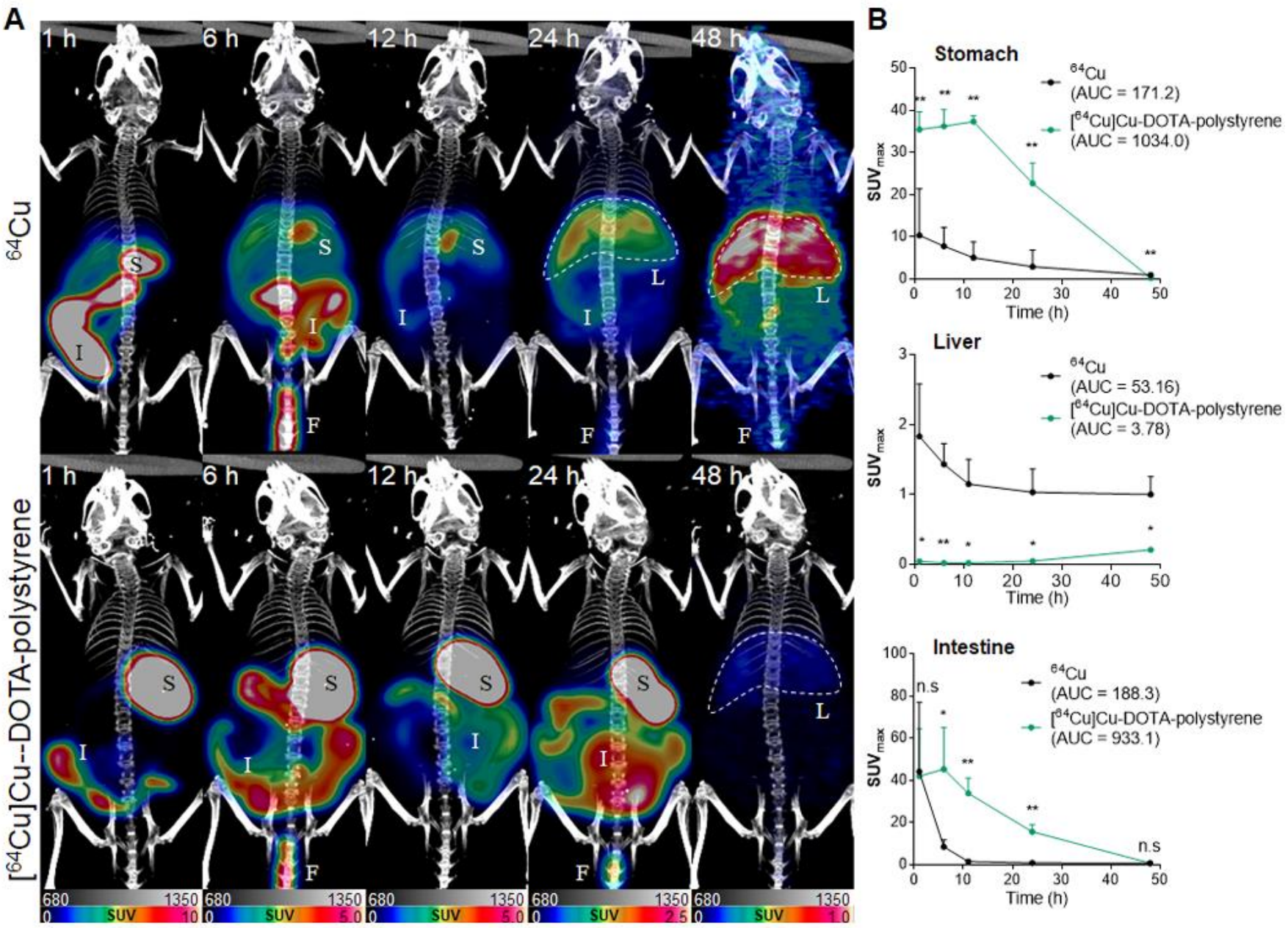
PET/CT imaging and Bio-distribution of ^{64}Cu-DOTA-PS



- amino-polystyrene (0.2–0.3 μm, Spherotech, Lake Forest, IL, USA)
- Label using Cu-64, a proton emitting isotope, by attaching DOTA chelator to MPs.
- [^{64}Cu]Cu-DOTA-polystyrene (4.81 MBq/57.8 μg/100 μL) 100 ppm / 100 uCi is orally administered to each mouse.
- Micrometre (μm): 1×10 ^{6} metre. A human hair has a thickness of about 80 μm.

Journal of Nuclear Medicine

Biodistribution Images of Radiolabeled Cu Plastics



Press Report

- **Microplastics rapidly spread throughout the body at all time?**
  Named “People Who Make Korea Shine” selected by BRIC /Interview by IOPscience, U.S.
  YTN, “Microplastics travel through the body fast”
  UST Class, a lecture at the Seoul Museum of Science, *Saturday Science Night*


BRIC 한빛사

한빛사논문 | 추천논문 | 상위피인용논문 | 인터뷰 | 그이후

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CV PDF 1.79 MB

조회 112

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PET tracing of biodistribution for orally administered 64Cu-labeled polystyrene in mice

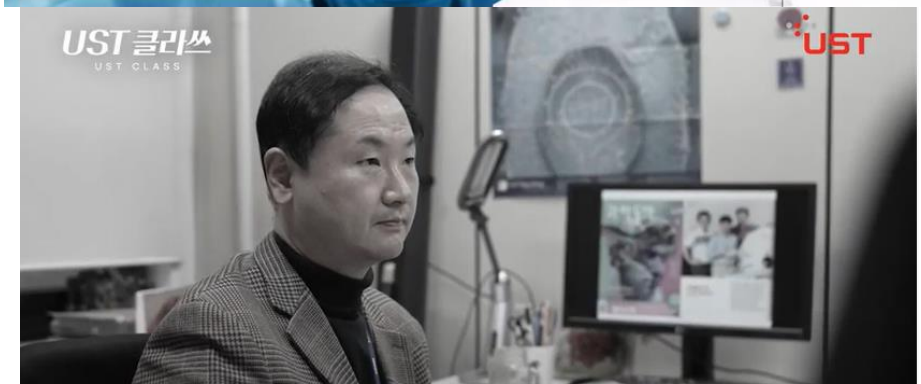
Authors and Affiliations

Abstract

Purpose: Plastics are used commonly in the world because of its 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, which cause environmental threat and human health risk. Therefore, real-time monitoring of orally administered microplastics is tremendously important to trace them in the body.

Methods: In this study, to visualize their absorption path, we labeled polystyrene with [^{64}Cu]Cu-DOTA. We prepared radiolabeled polystyrene with ^{64}Cu after, [^{64}Cu]Cu-DOTA-polystyrene was then orally administered to mice and evaluate its transit and absorption in mice using PET imaging. The absorption path and distribution of [^{64}Cu]Cu-DOTA-polystyrene were determined using positron emission tomography (PET) over 48 h. Ex vivo tissue-radio thin-layer chromatography (Ex vivo-radioTLC) 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. [^{64}Cu]Cu-DOTA-polystyrene accumulation in the liver was also observed. Biodistribution of [^{64}Cu]Cu-DOTA-polystyrene confirmed the observed distribution of [^{64}Cu]Cu-DOTA-polystyrene from PET images. Ex vivo-radioTLC was used to demonstrate that the detected



Environment International 161 (2022) 107121

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journal homepage: www.elsevier.com/locate/envint

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,*]

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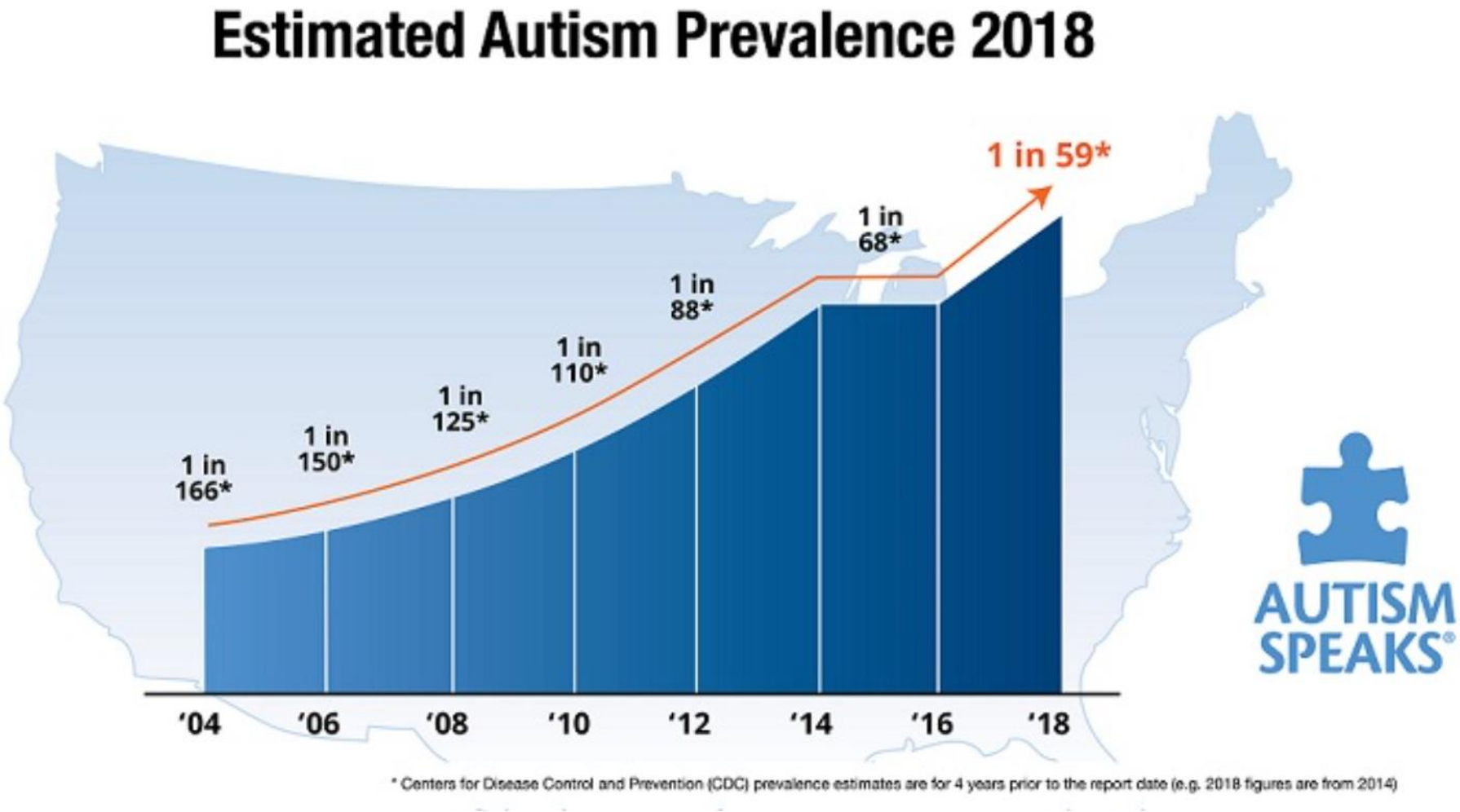
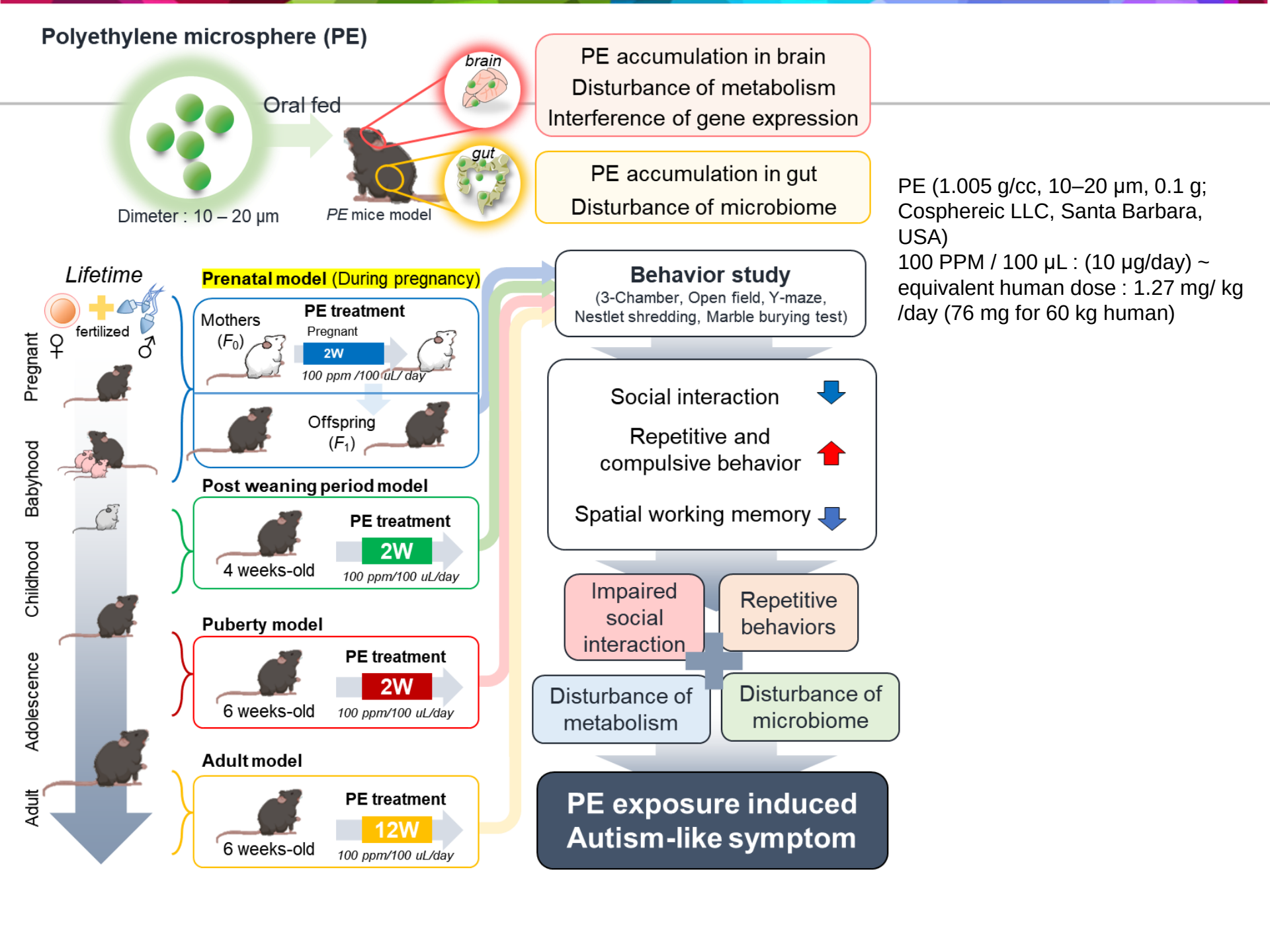
Autism Prevalence Reported by the CDC





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)

Press Report

- **MPs, a potential risk factor for Autism Spectrum Disorder (ASD)**
  Named as “People Who Make Korea Shine”
  SBS, “Autism revealed, ‘Microplastics reduce sociability’”
  YTN, “Microplastics cause ASD”
  TBS “The unexpected reason Autism rates are up”

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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.

IVYSPRING INTERNATIONAL PUBLISHER

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

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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 stomach. The 4-week daily repetitive dose of fluorescent conjugated PS was deposited in the gastric tissues of mice. When PS was exposed, a 2.9-fold increase in migration rate was observed for NCI-N87 cells. Immunocytochemistry results showed decreased E-cadherin and increased N-cadherin expression, and flow cytometry, qPCR, and western blot analysis indicated a 1.9-fold increase in N-cadherin expression after PS exposure. Further, PS-induced multidrug resistance to bortezomib, paclitaxel, gefitinib, lapatinib, and trastuzumab was observed in the NCI-N87 mouse model due to upregulated CD44 expression. RNA-seq results identified increased asialoglycoprotein receptor 2 (*ASGR2*) expression after PS exposure, and *ASGR2* knockdown decreased cell proliferation, migration, invasion, and drug resistance.

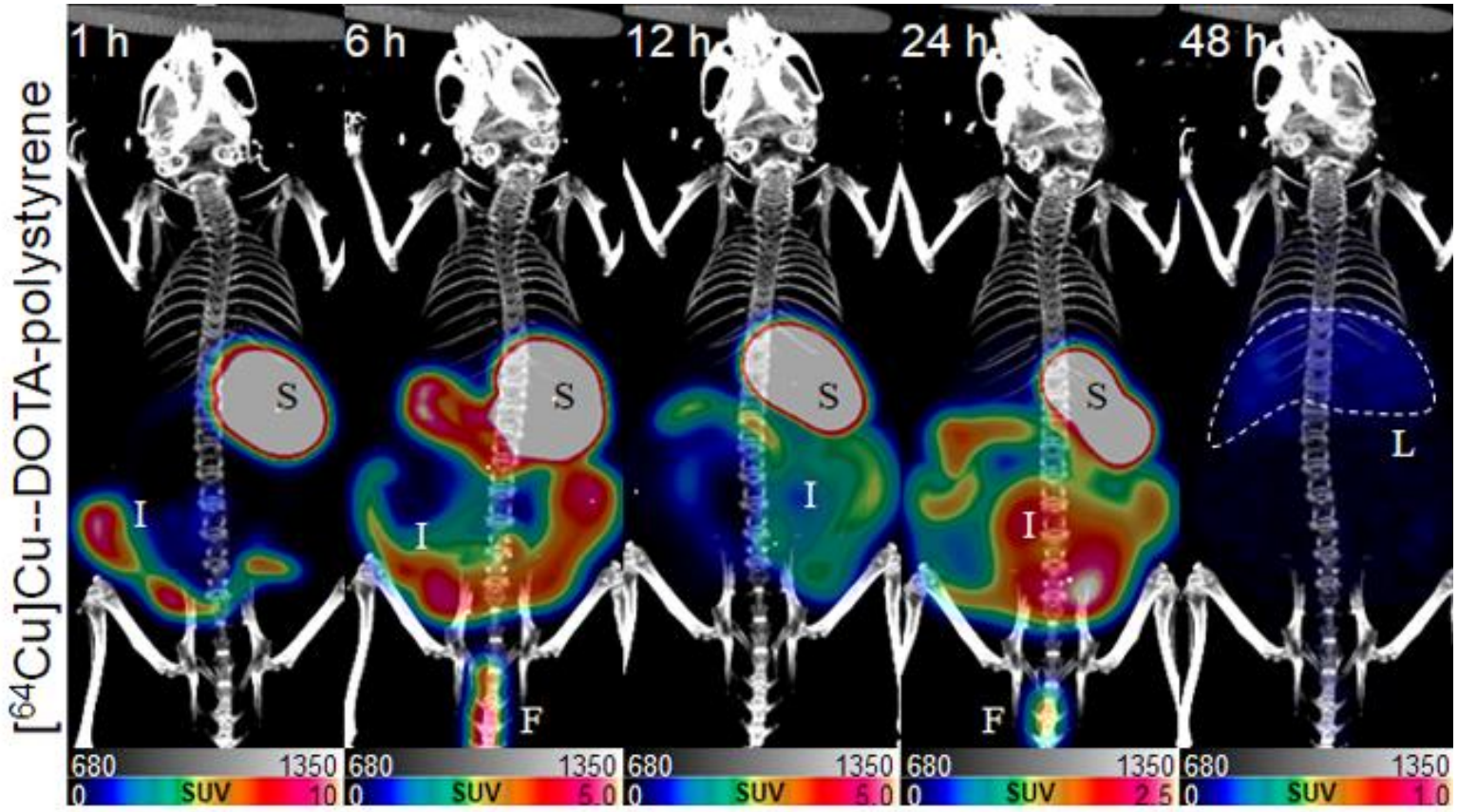
Conclusion: We demonstrated that *ASGR2* enhanced cancer hallmarks on PS exposure and induced resistance to chemo- and monoclonal antibody-therapy. Our preclinical findings may provide an incentive for further epidemiological studies on the role of MP exposure and its association with gastric cancer.

Key words: Microplastics, gastric cancer, cancer hallmarks, polystyrene, ASGR2

Introduction

Microplastics (MPs) with a diameter less than 5 mm are recognized as a new environmental threat and human health risk [1]. An analysis of tap water samples from around the world found that a high proportion of drinking water is contaminated with MPs (83% of samples collected worldwide, up to 94% in the USA) [2]. MP contamination of food can no longer be ignored [3, 4]. MP in food and contamination of MP and during food processing and cooking was reported [5, 6]. MP are a ubiquitous global contaminant, identified throughout the marine environment, including seawater, sediment and biota [7]. Pre/post-natal exposure to MP as a potential risk factor for autism spectrum disorder was reported [8]

Stomach Exposed to MPs



Observation: What would happen if MPs stayed in the stomach for a day?

Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

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[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
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DOI 10.1016/j.cell.2011.02.013

The hallmarks of cancer comprise six biological capabilities acquired during the multistep development of human tumors. The hallmarks constitute an organizing principle for rationalizing the complexities of neoplastic disease. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Underlying these hallmarks are genome instability, which generates the genetic diversity that expedites their acquisition, and inflammation, which fosters multiple hallmark functions. Conceptual progress in the last decade has added two emerging hallmarks of potential generality to this list—reprogramming of energy metabolism and evading immune destruction. In addition to cancer cells, tumors exhibit another dimension of complexity: they contain a repertoire of recruited, ostensibly normal cells that contribute to the acquisition of hallmark traits by creating the "tumor microenvironment." Recognition of the widespread applicability of these concepts will increasingly affect the development of new means to treat human cancer.

INTRODUCTION

We have proposed that six hallmarks of cancer together constitute an organizing principle that provides a logical framework for understanding the remarkable diversity of neoplastic diseases (Hanahan and Weinberg, 2000). Implicit in our discussion was the notion that as normal cells evolve progressively to a neoplastic state, they acquire a succession of these hallmark capabilities, and that the multistep process of human tumor pathogenesis could be rationalized by the need of incipient cancer cells to acquire the traits that enable them to become tumorigenic and ultimately malignant.

We noted as an ancillary proposition that tumors are more than insular masses of proliferating cancer cells. Instead, they are complex tissues composed of multiple distinct cell types that participate in heterotypic interactions with one another. We depicted the recruited normal cells, which form tumor-associated stroma, as active participants in tumorigenesis rather than passive bystanders; as such, these stromal cells contribute to the development and expression of certain hallmark capabilities. During the ensuing decade this notion has been solidified and extended, revealing that the biology of tumors can no longer be understood simply by enumerating the traits of the cancer cells but instead must encompass the contributions of the "tumor microenvironment" to tumorigenesis.

In the course of remarkable progress in cancer research subsequent to this publication, new observations have served both to clarify and to modify the original formulation of the hallmark capabilities. In addition, yet other observations have raised questions and highlighted mechanistic concepts that were not integral to our original elaboration of the hallmark traits. Motivated by these developments, we now revisit the original hallmarks, consider new ones that might be included in this roster, and expand upon the functional roles and contributions made by recruited stromal cells to tumor biology.

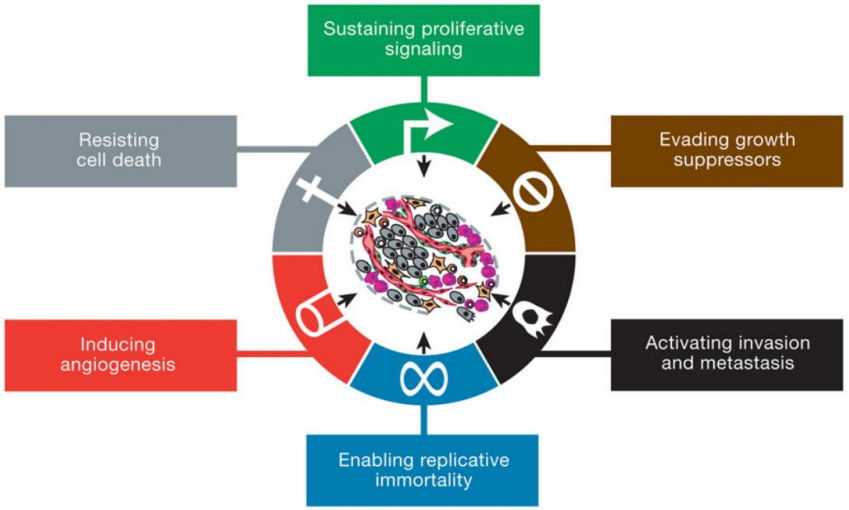
HALLMARK CAPABILITIES—CONCEPTUAL PROGRESS

The six hallmarks of cancer—distinctive and complementary capabilities that enable tumor growth and metastatic dissemination—continue to provide a solid foundation for understanding the biology of cancer (Figure 1; see the Supplemental Information for downloadable versions of the figures for presentations). In the first section of this Review, we summarize the essence of each hallmark as described in the original presentation in 2000, followed by selected illustrations (demarcated by subheadings in italics) of the conceptual progress made over the past decade in understanding their mechanistic underpinnings. In subsequent sections we address new developments that broaden the scope of the conceptualization, describing in turn two enabling characteristics crucial to the acquisition of the six hallmark capabilities, two new emerging hallmark capabilities, the constitution and signaling interactions of the tumor microenvironment crucial to cancer phenotypes, and we finally discuss the new frontier of therapeutic application of these concepts.

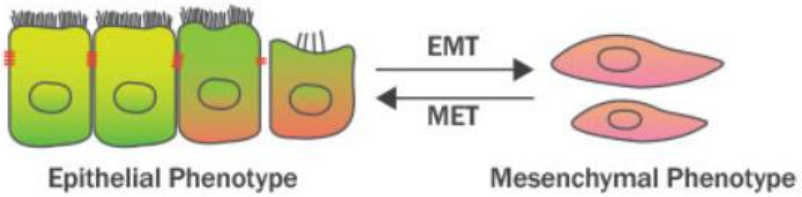
Sustaining Proliferative Signaling

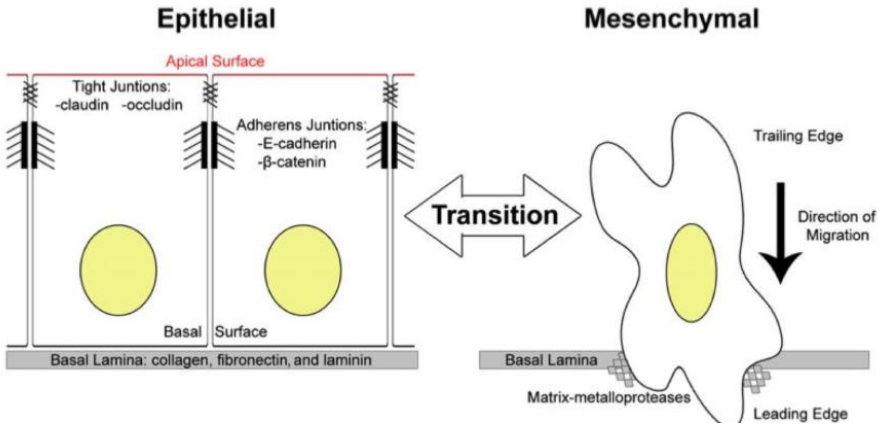
Arguably the most fundamental trait of cancer cells involves their ability to sustain chronic proliferation. Normal tissues carefully control the production and release of growth-promoting signals that instruct entry into and progression through the cell growth-and-division cycle, thereby ensuring a homeostasis of cell

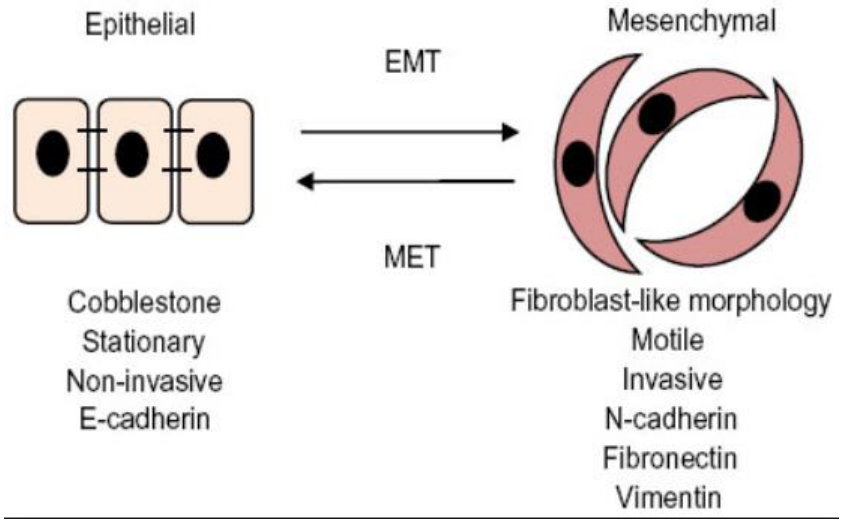
Hallmarks
What are the Hallmarks of Cancer?



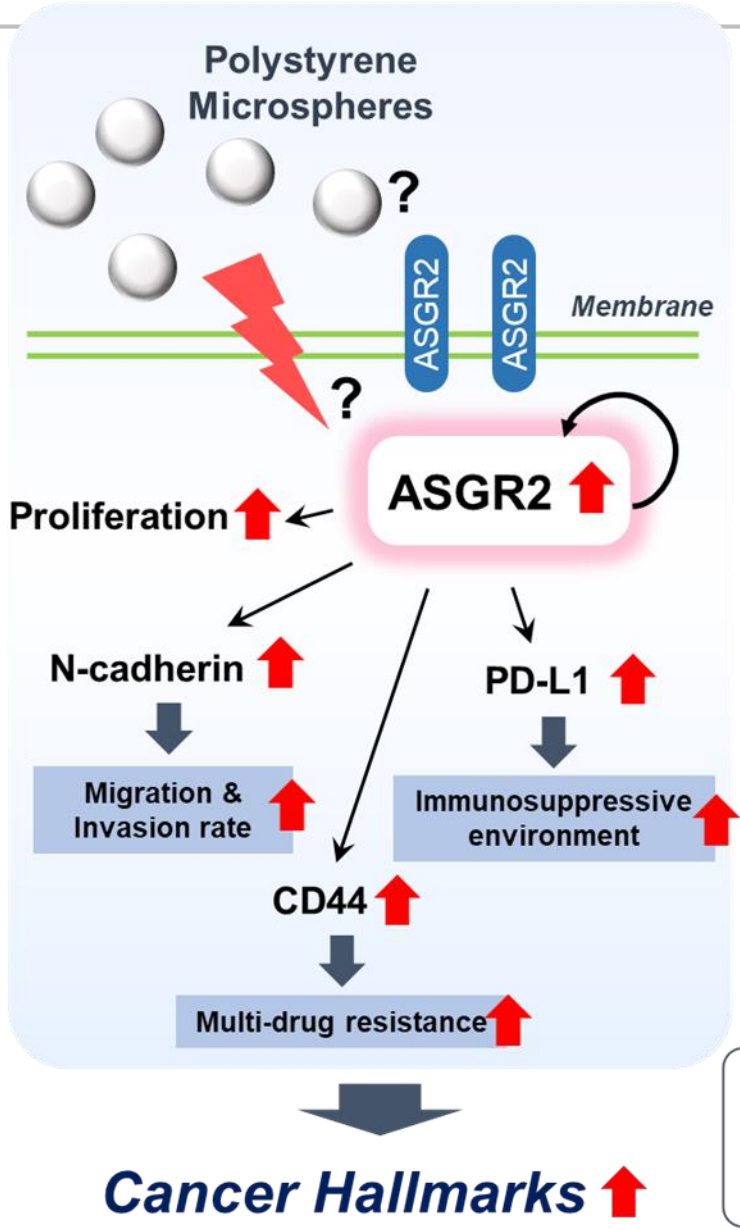
EMT

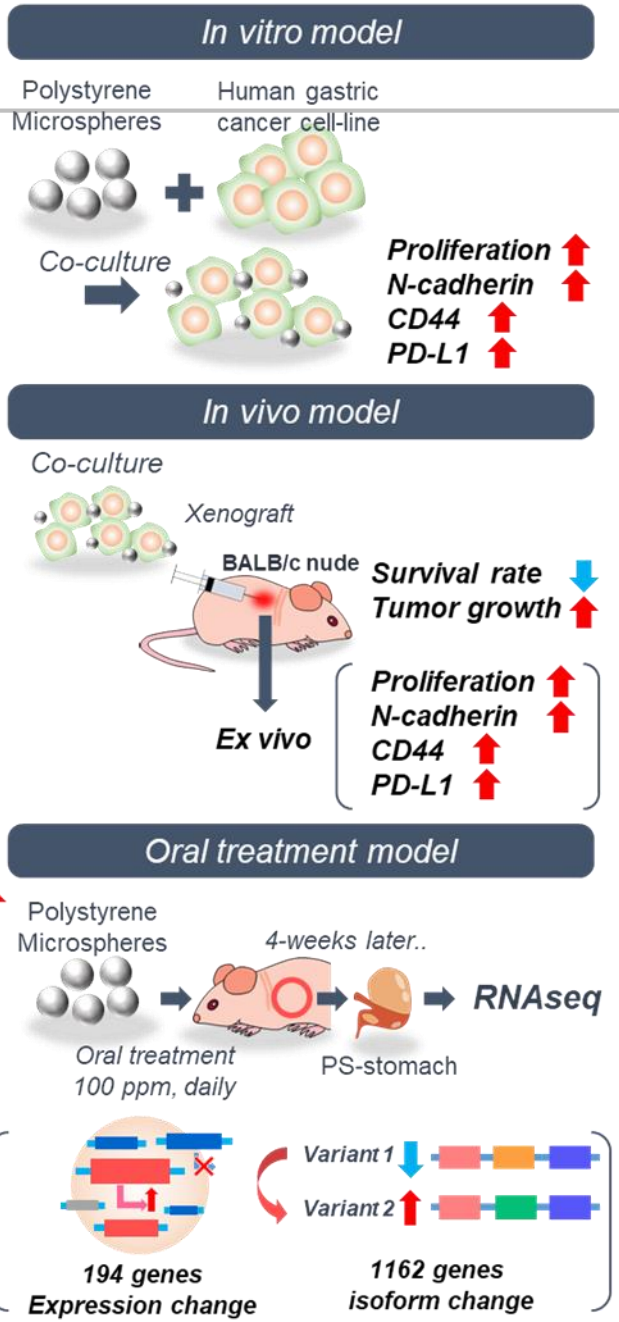

EMT
MET
Epithelial Phenotype
Mesenchymal Phenotype


Epithelial
Mesenchymal
Apical Surface
Tight Juntions:
-claudin -occludin
Adherens Juntions:
-E-cadherin
-β-catenin
Basal Surface
Basal Lamina: collagen, fibronectin, and laminin
Transition
Trailing Edge
Direction of Migration
Basal Lamina
Matrix-metalloproteases
Leading Edge


Epithelial
Mesenchymal
EMT
MET
Cobblestone
Stationary
Non-invasive
E-cadherin
Fibroblast-like morphology
Motile
Invasive
N-cadherin
Fibronectin
Vimentin

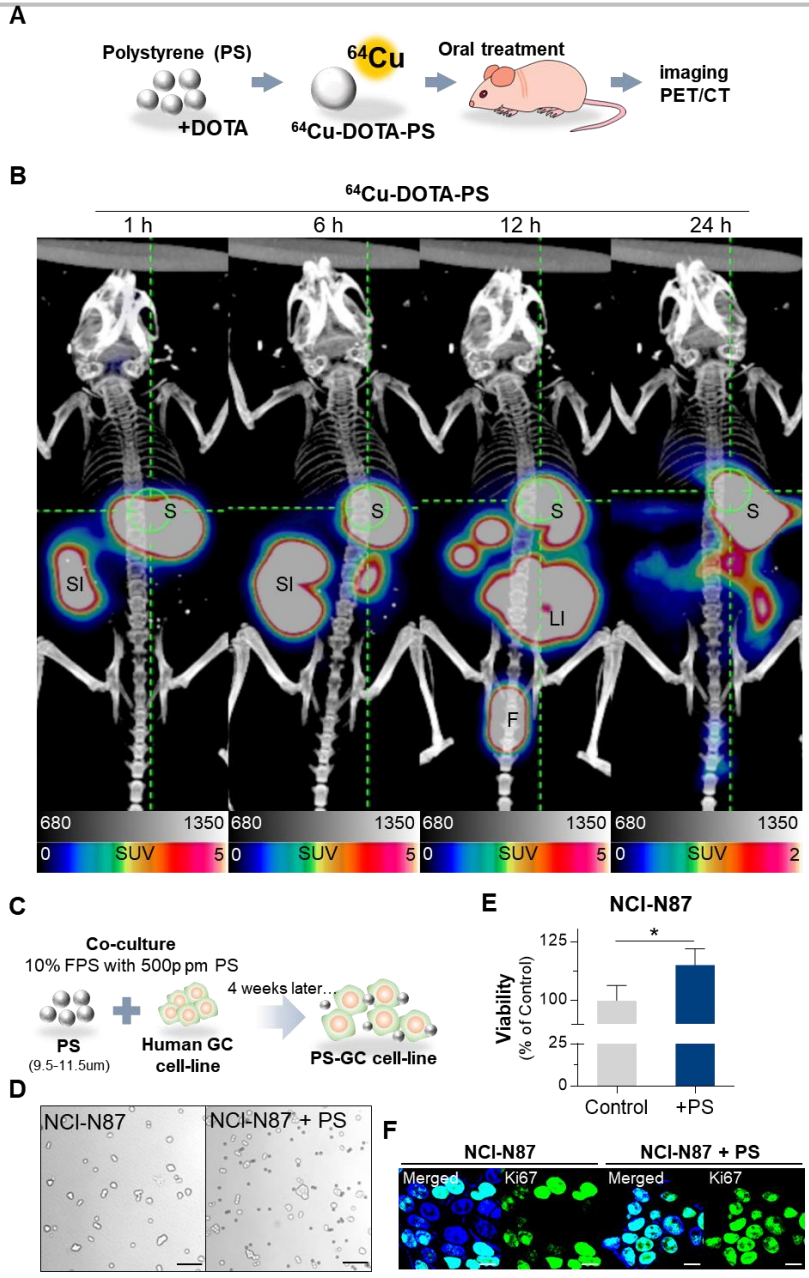
Research Summary

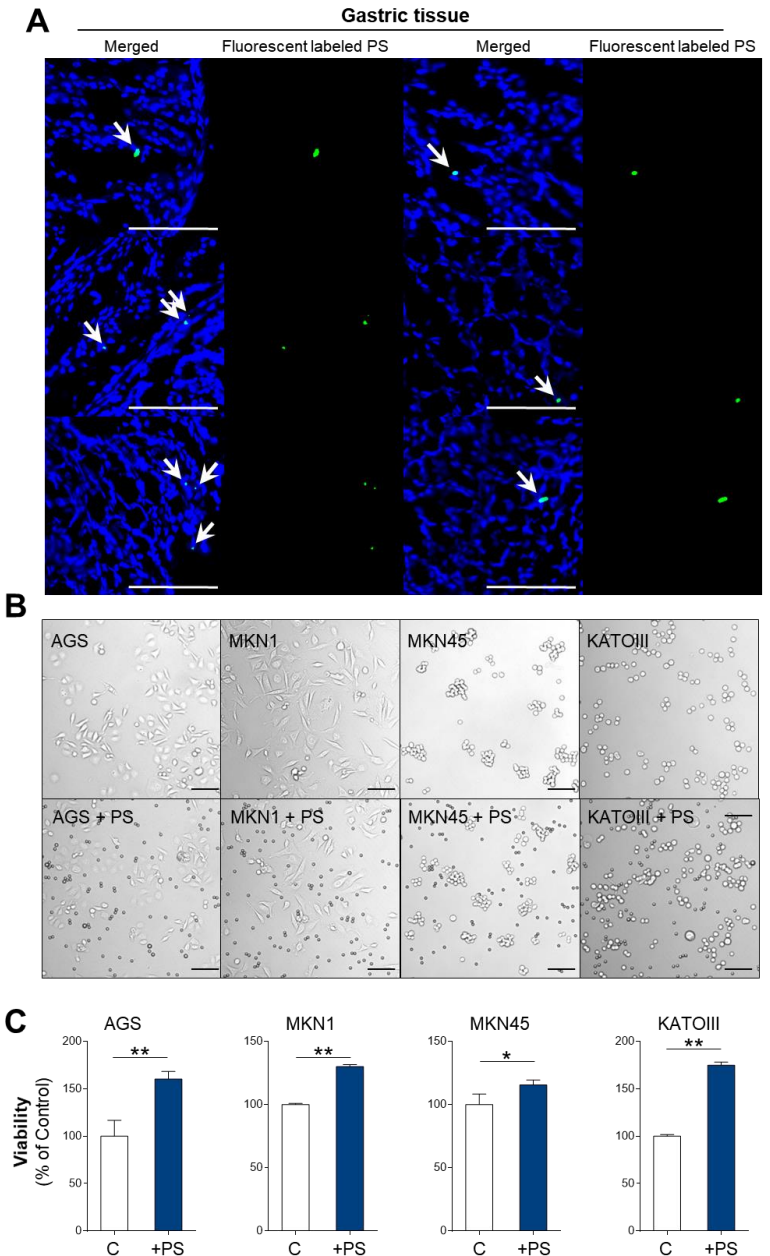




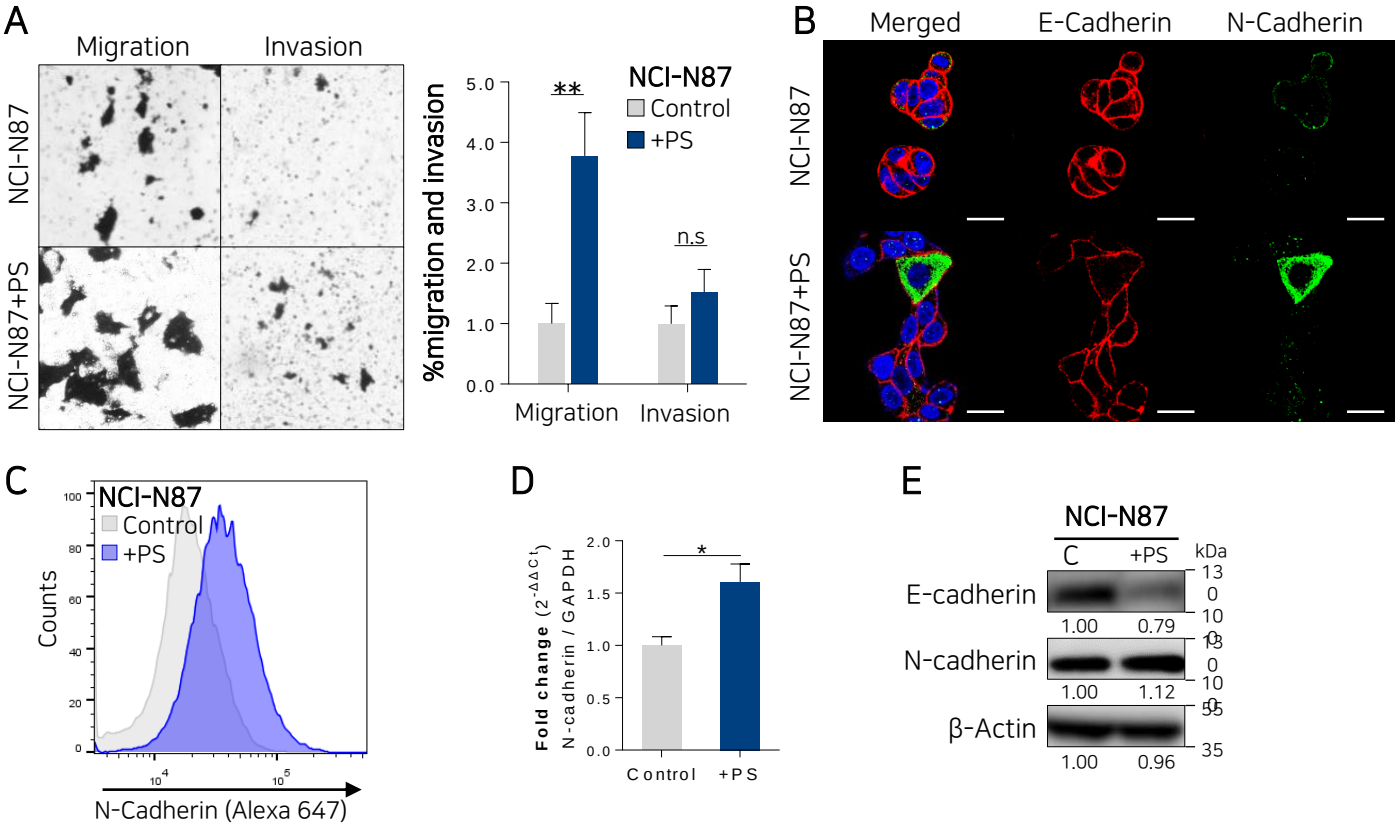
Same genes, but different amino acid sequences

Plastics Lodged in the Stomach Walls Stimulate Cancer Cell Growth

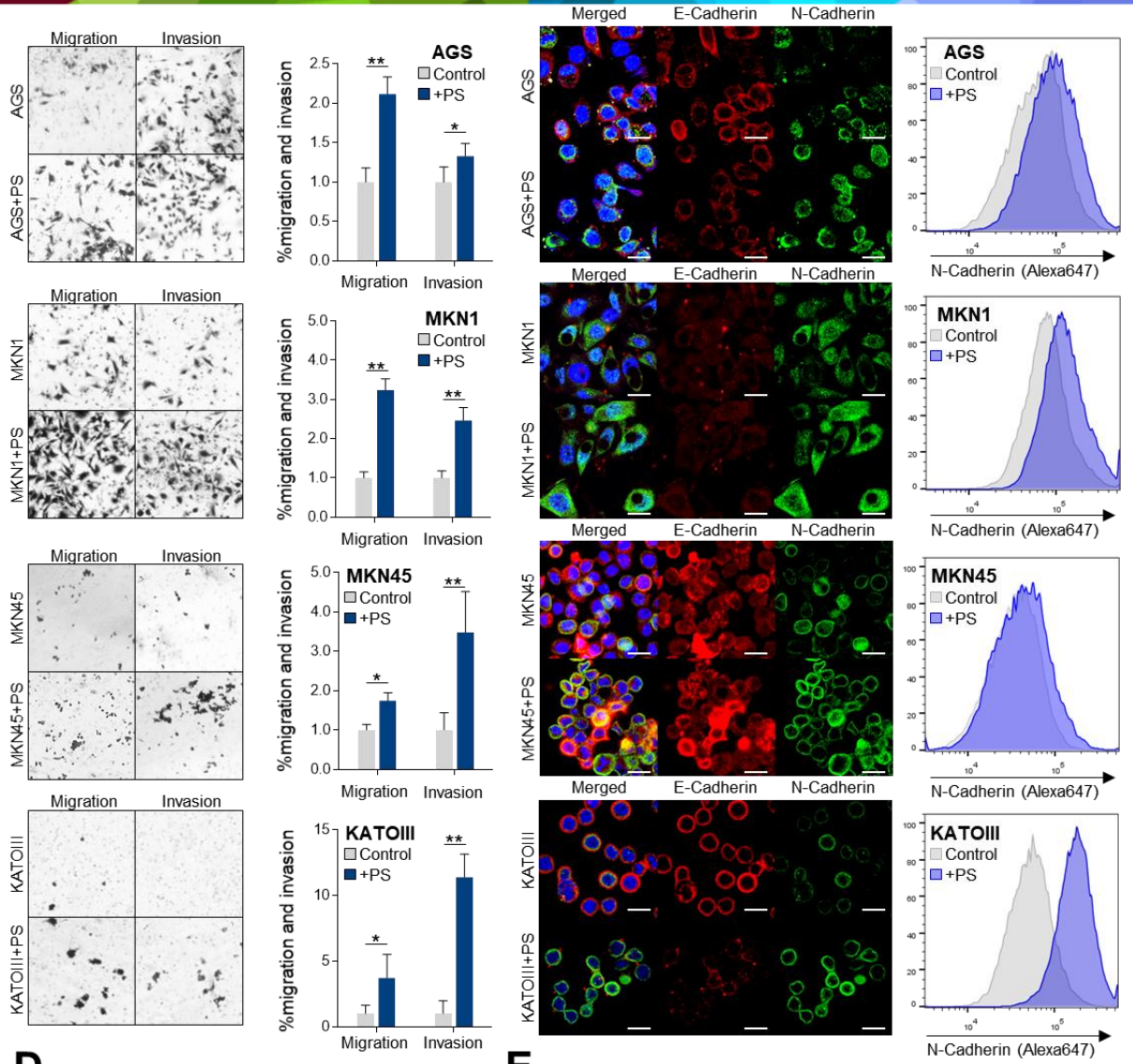


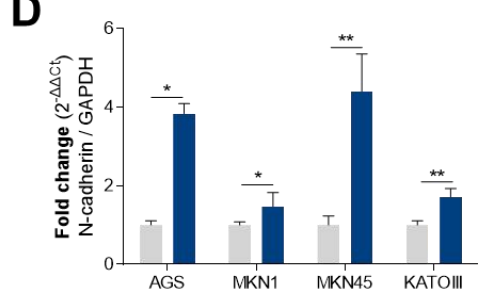


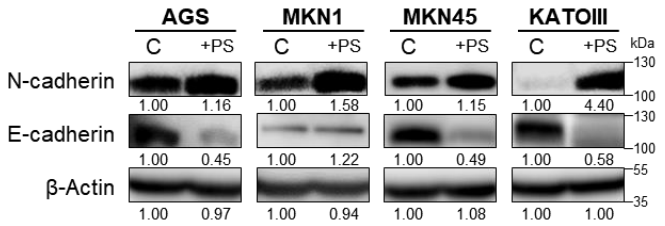
Plastics Promote Metastasis of Cancer



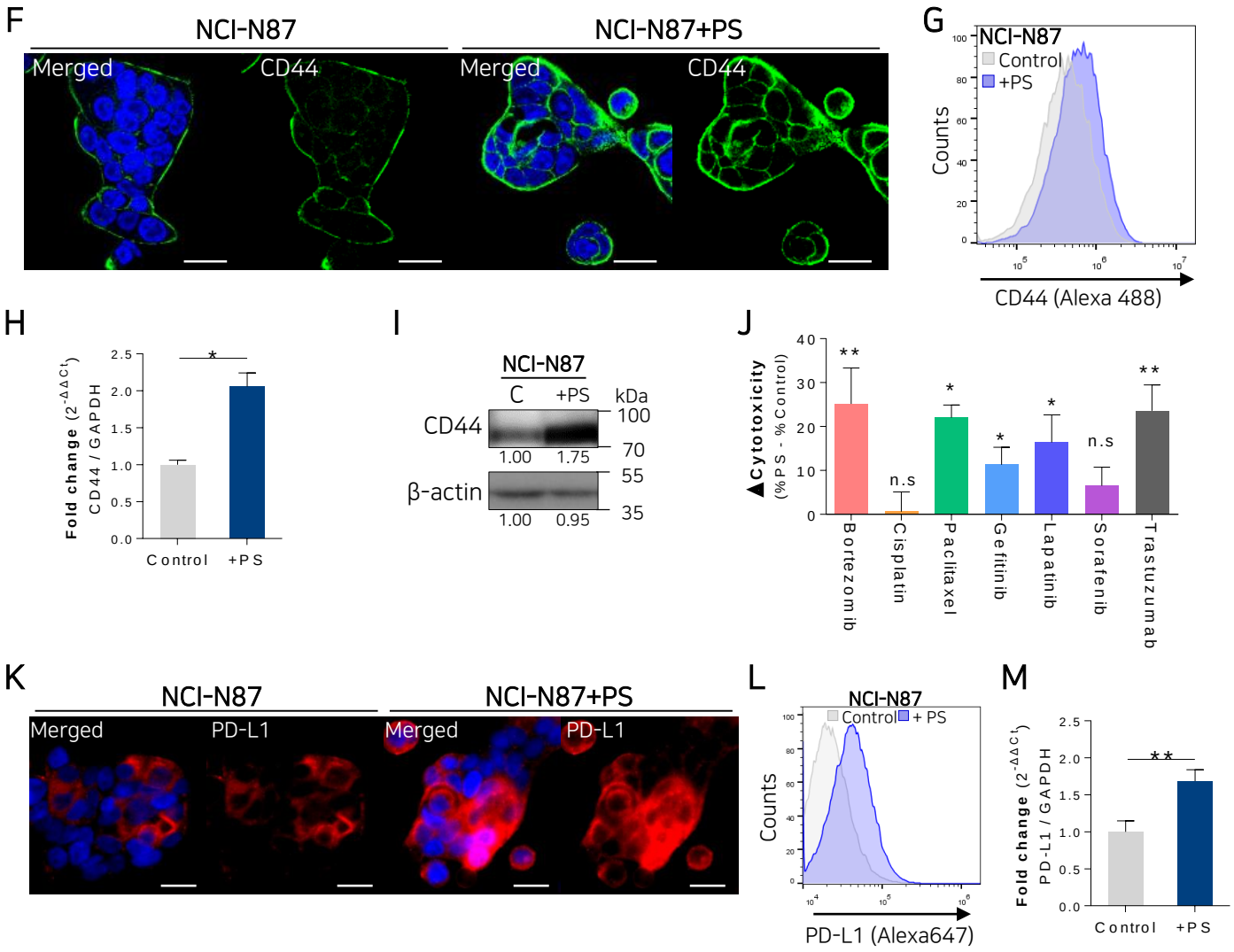
Plastics Promote Metastasis of Cancer



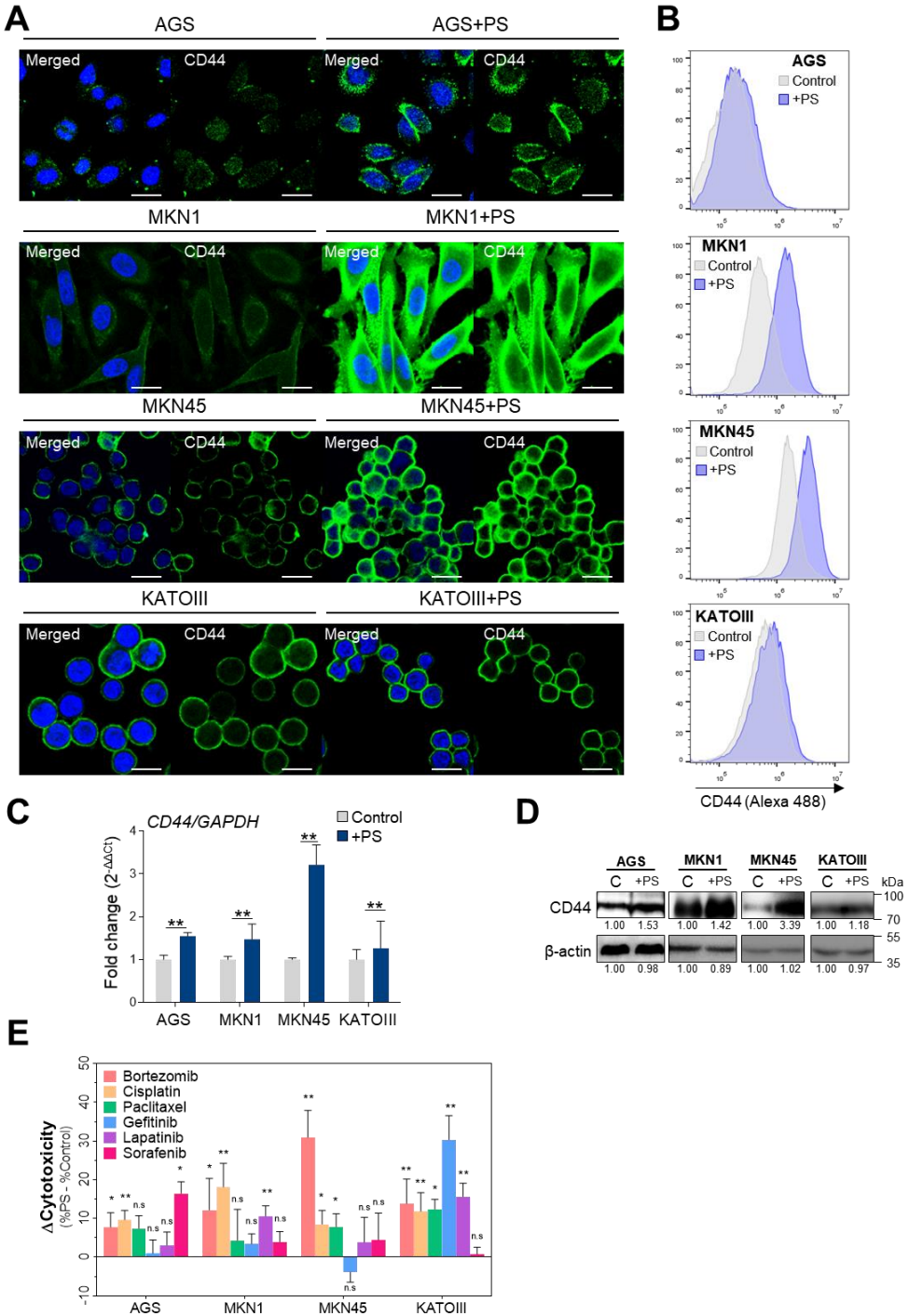




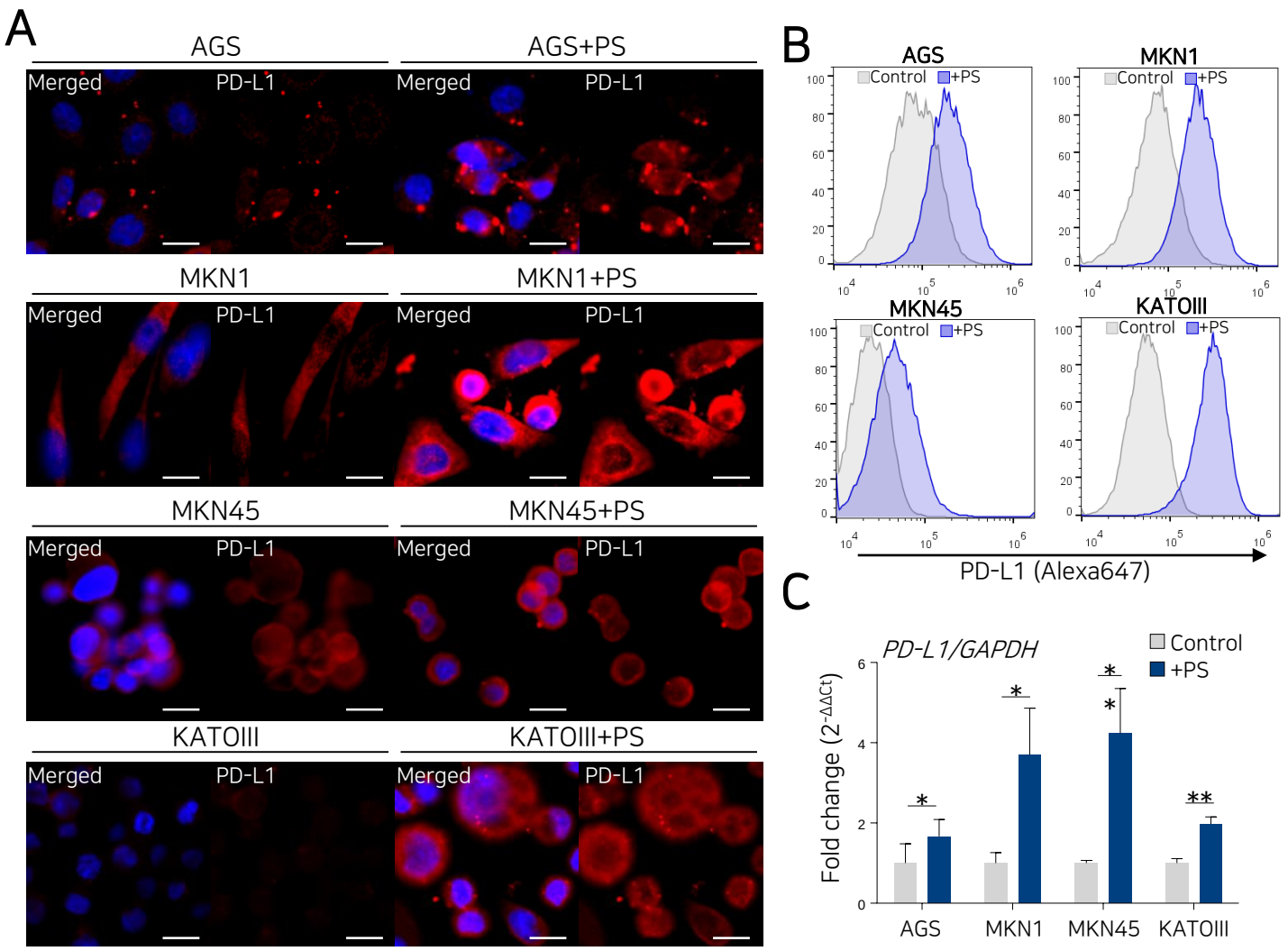
Plastics Promote Drug Resistance (CD44, PD-L1)



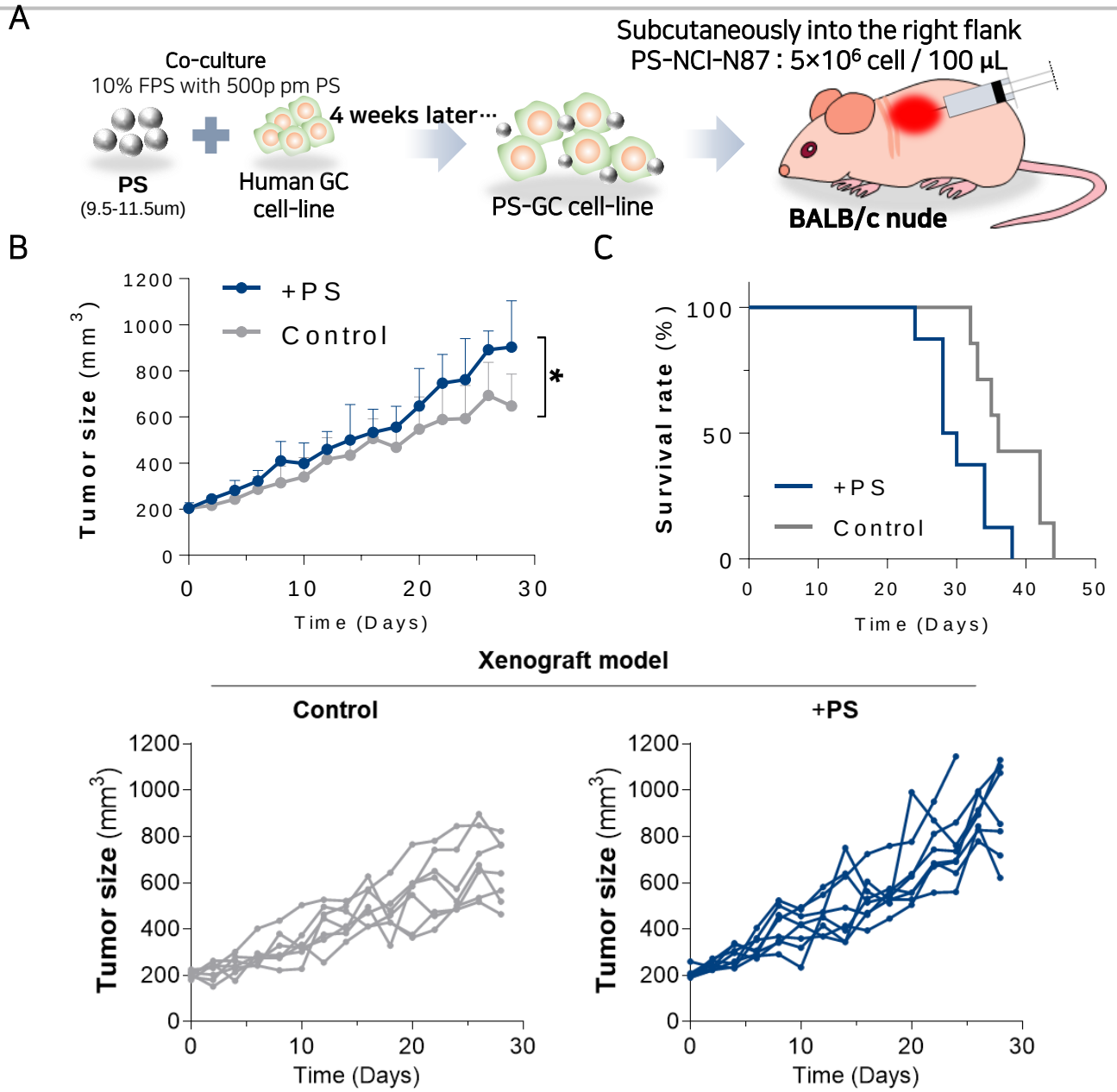
Plastics Promote Drug Resistance (CD44, PD-L1)



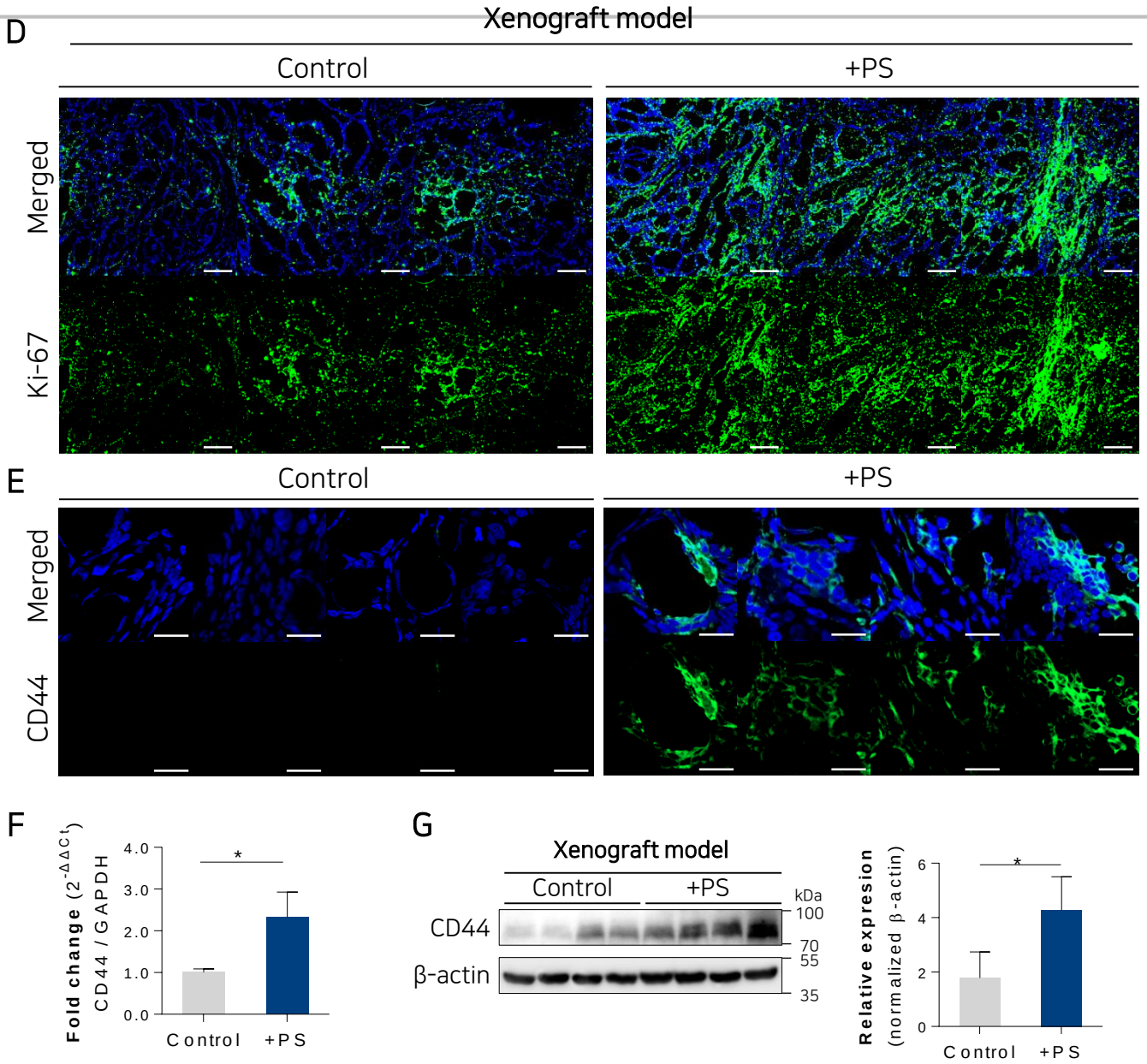
Plastics Promote Drug Resistance (CD44, PD-L1)



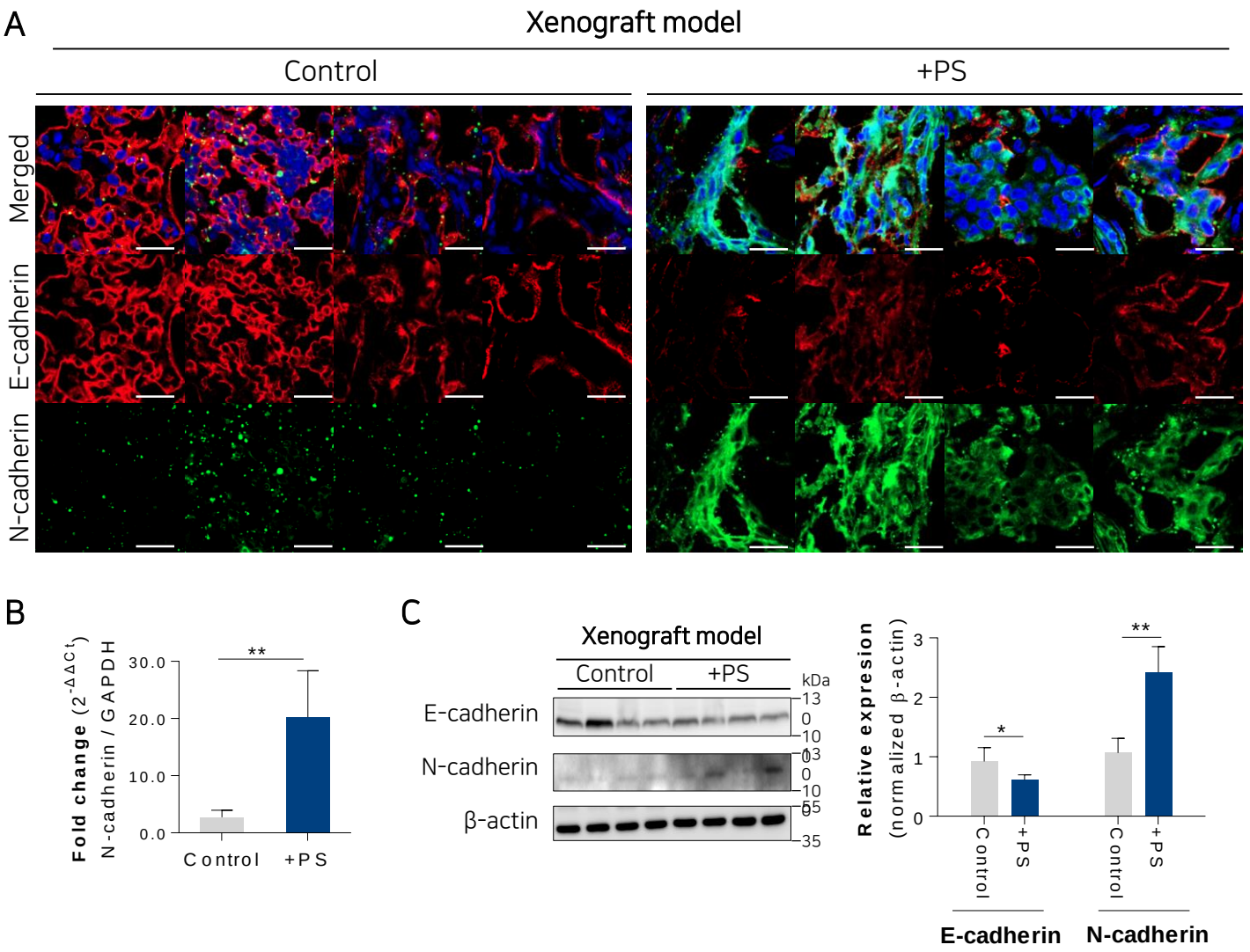
Survival Rate Reduction in Xenograft Model



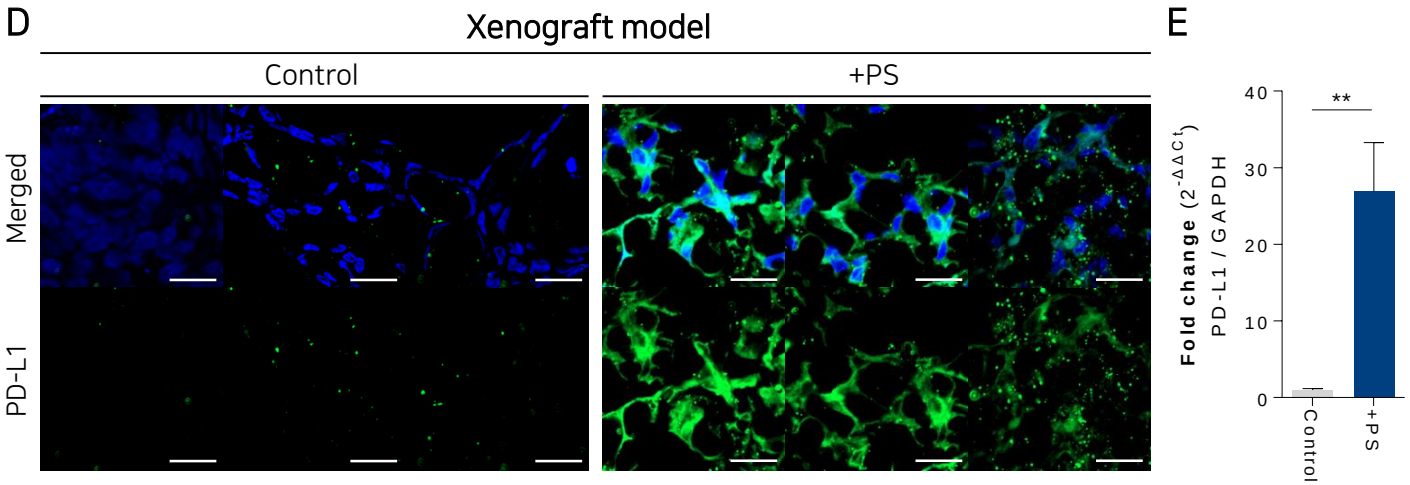
Ex vivo (Higher CD44)



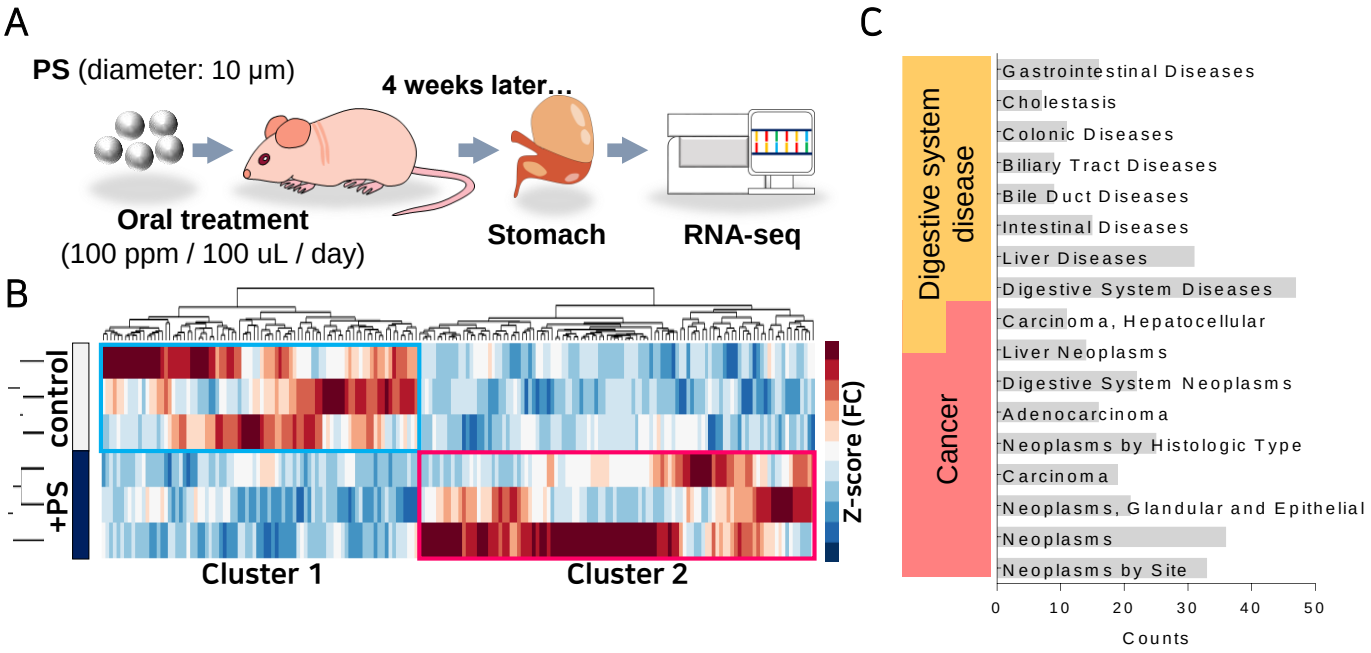
Confirmation of Metastasis Marker in Xenograft Data



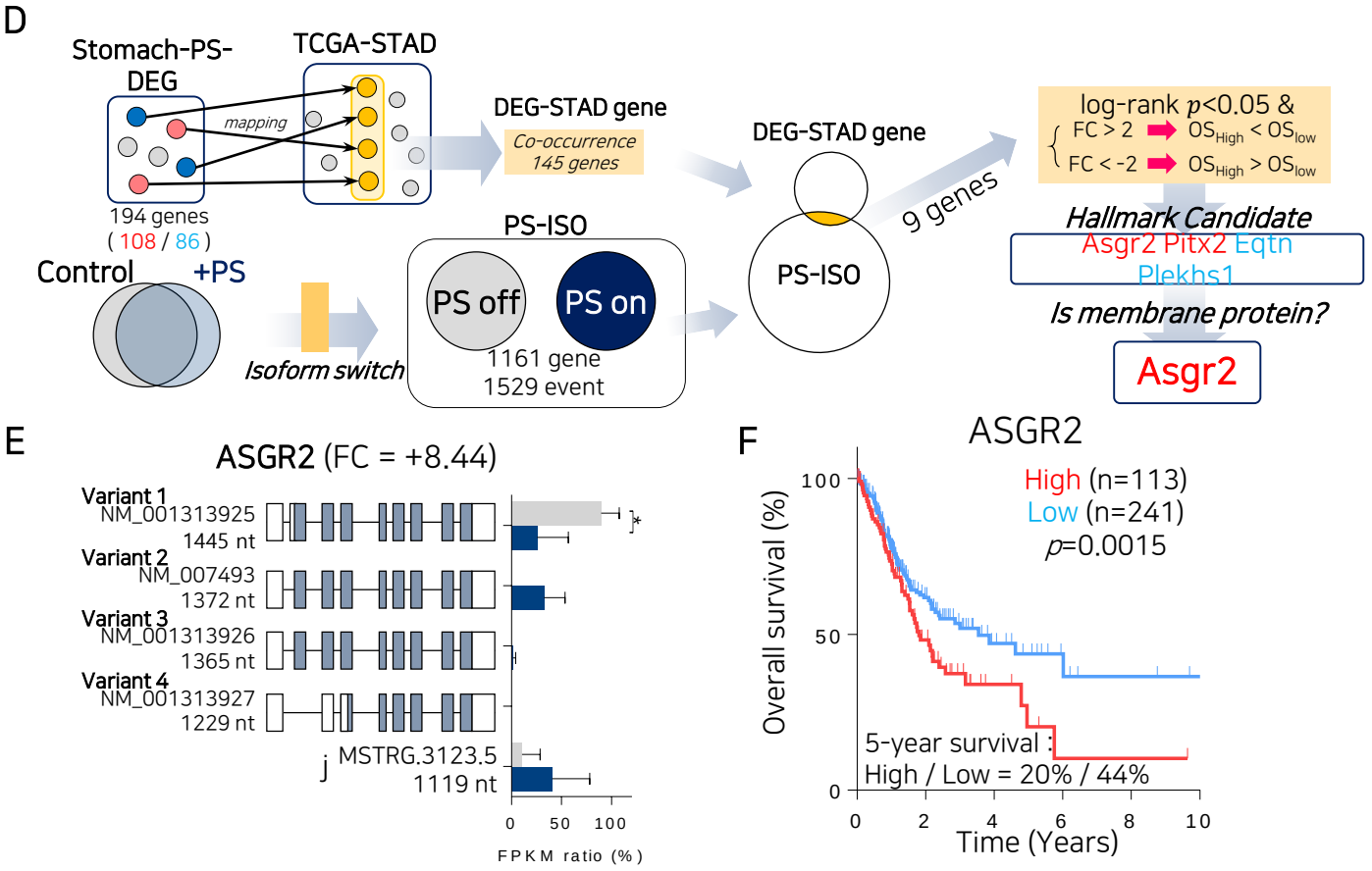
Xenograft Model (ex vivo data)



RNA seq

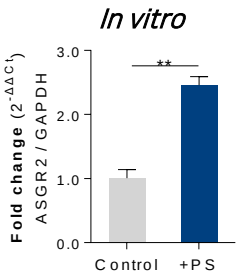

A
PS (diameter: 10 μm)
4 weeks later…
Oral treatment
(100 ppm / 100 uL / day)
Stomach
RNA-seq
B
control
+PS
Z-score (FC)
Cluster 1
Cluster 2
C
Digestive system disease
Cancer
Gastrointestinal Diseases
Cholestasis
Colonic Diseases
Biliary Tract Diseases
Bile Duct Diseases
Intestinal Diseases
Liver Diseases
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 Discovery

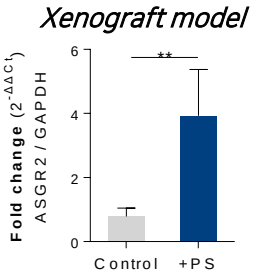


in vitro & ex vivo confirmation (ASGR2)

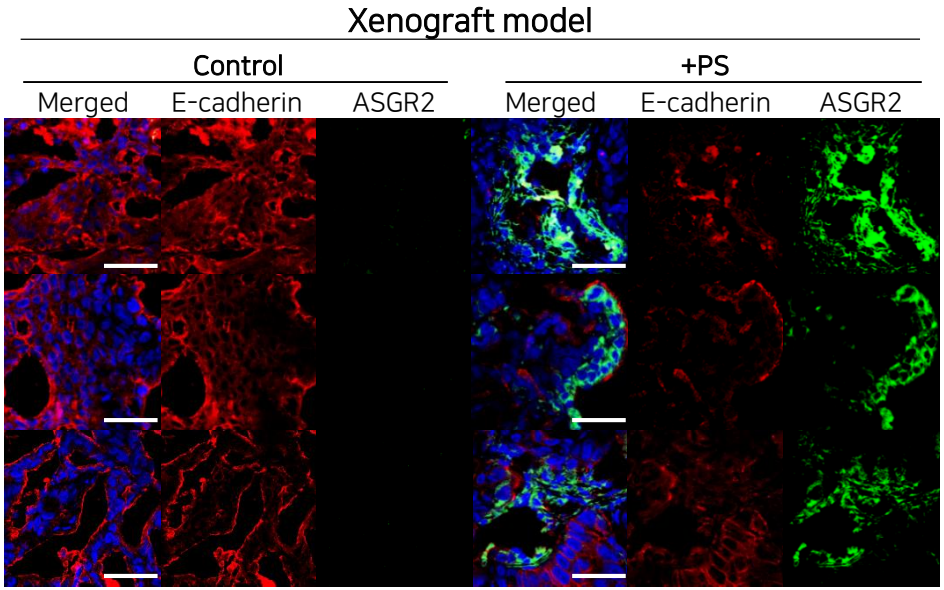
G



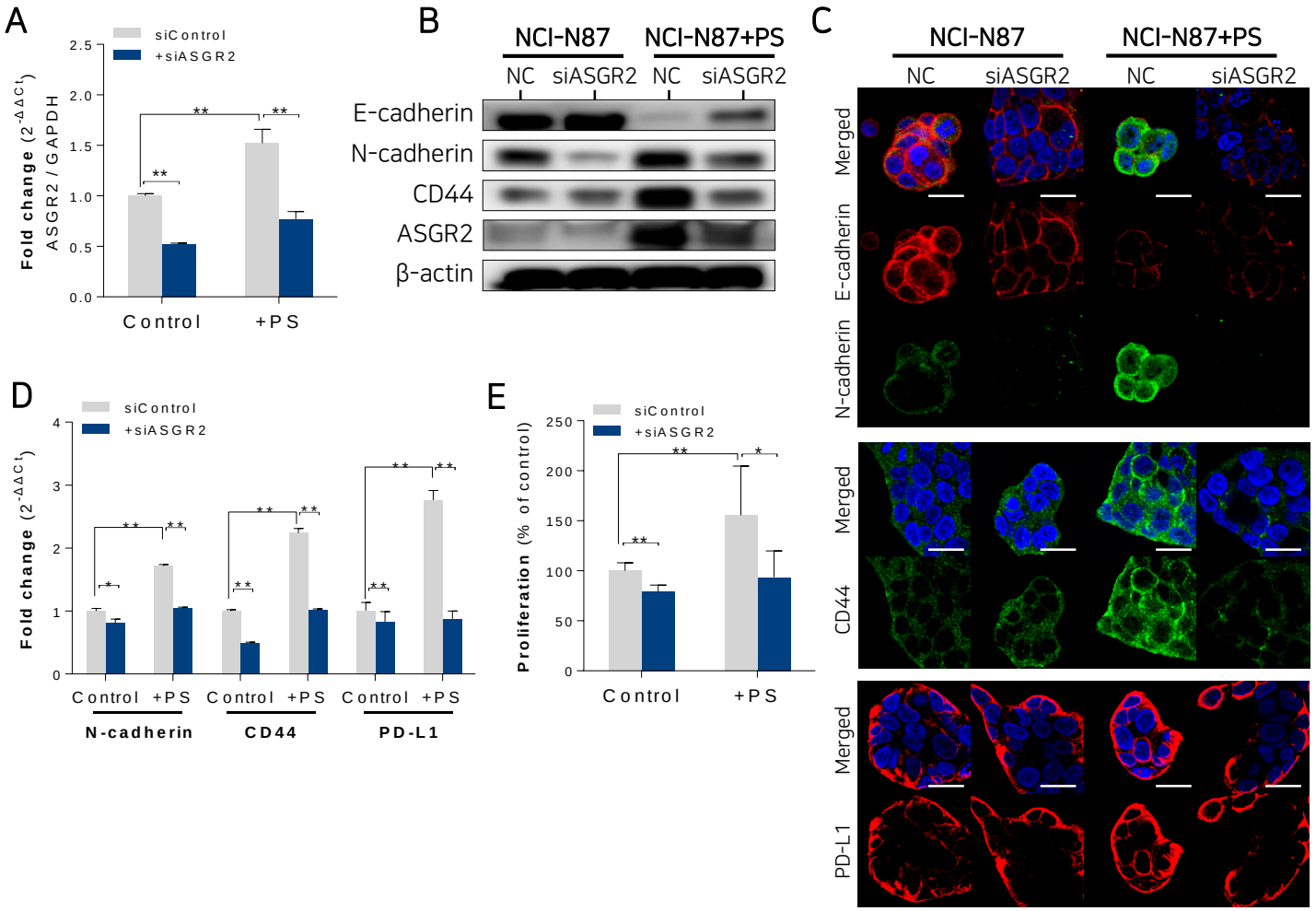
H



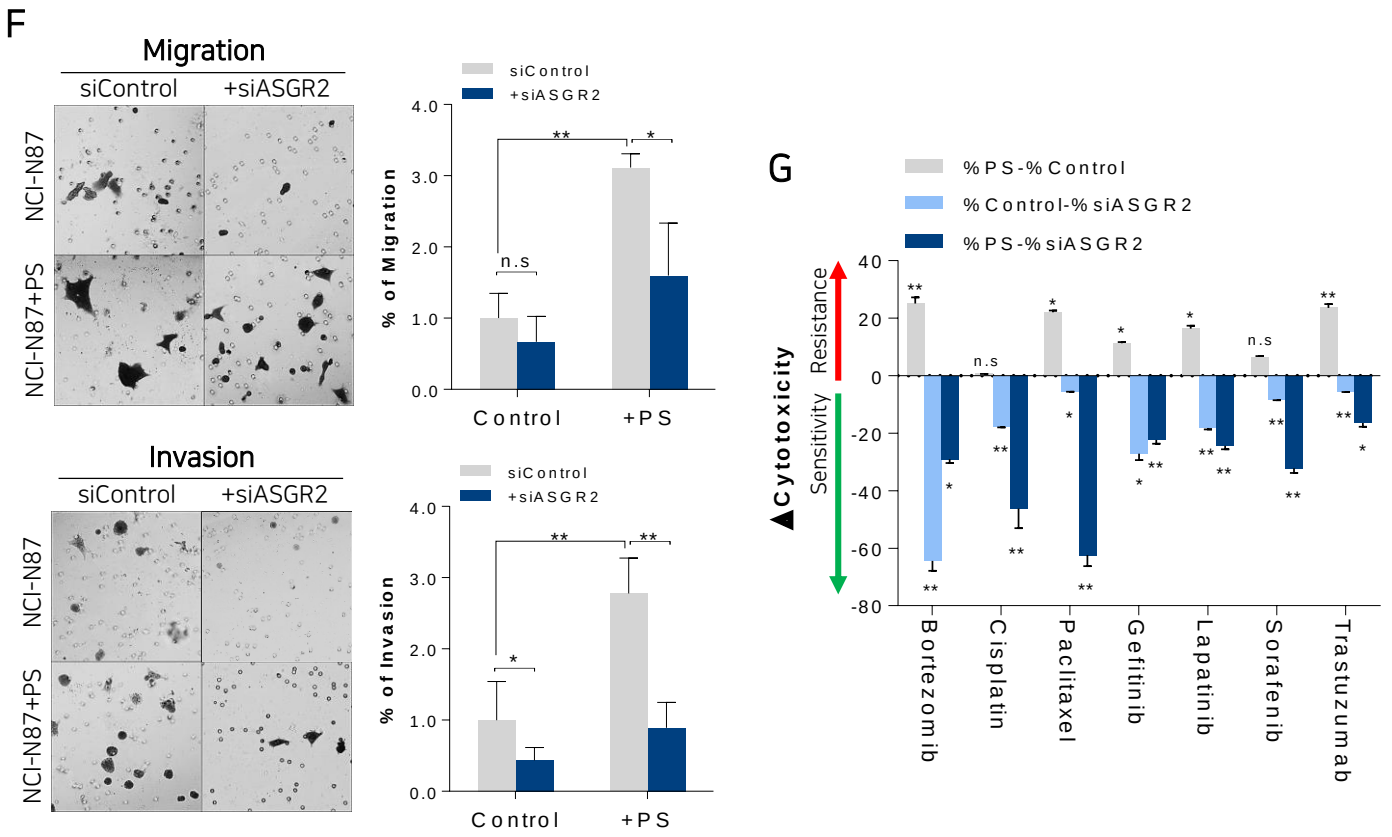
I



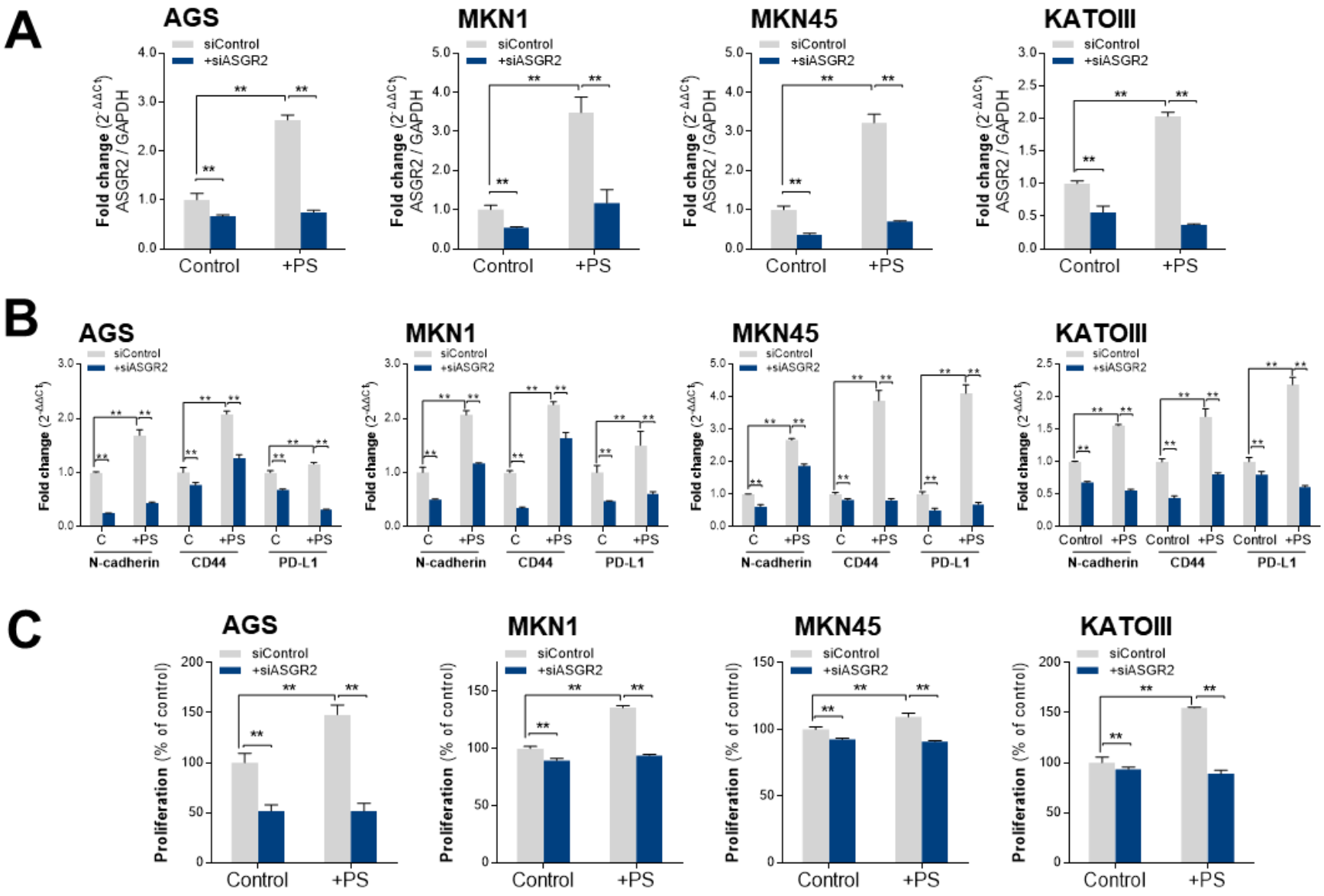
Confirmation of ASGR2



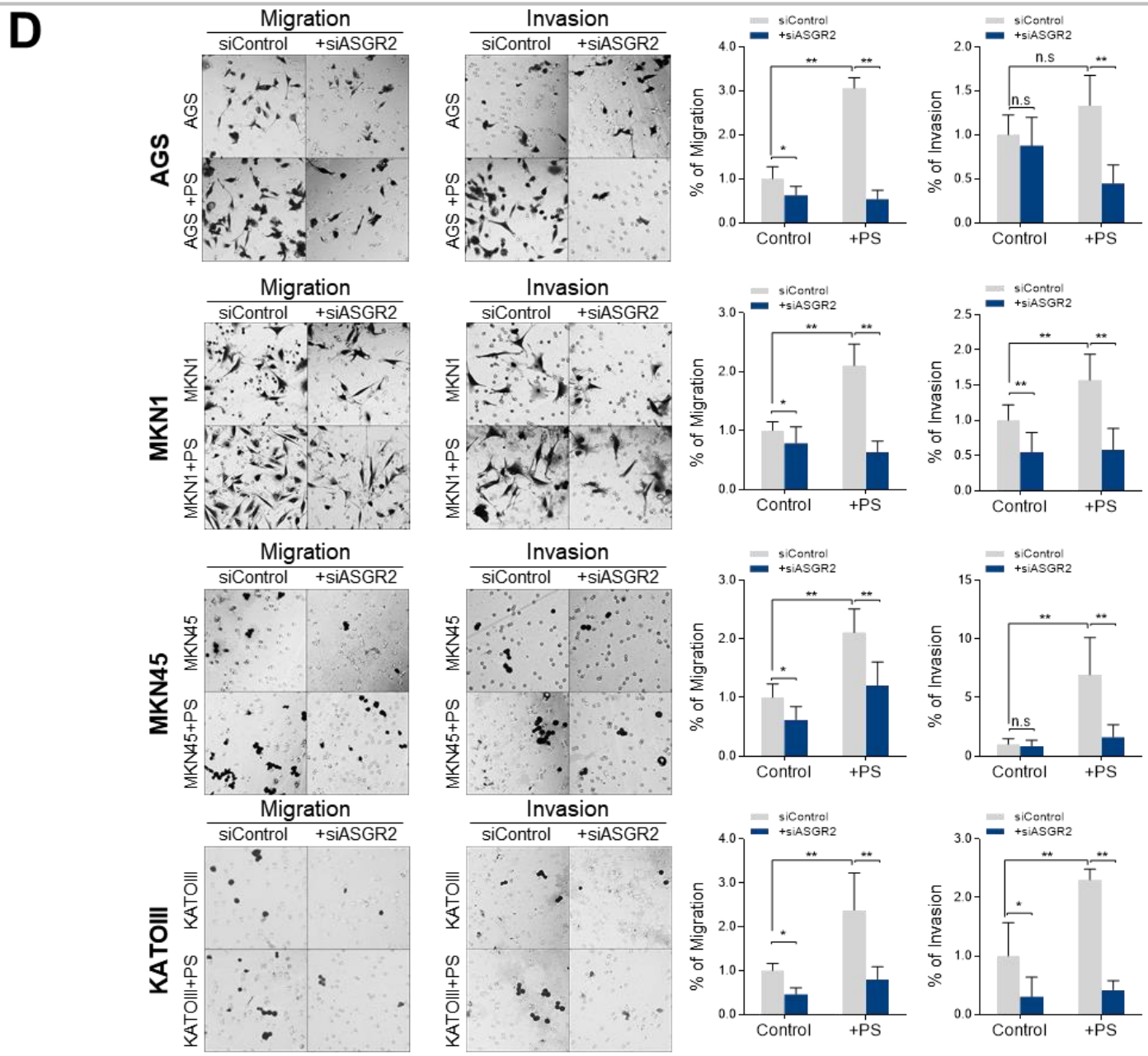
Confirmation of ASGR2

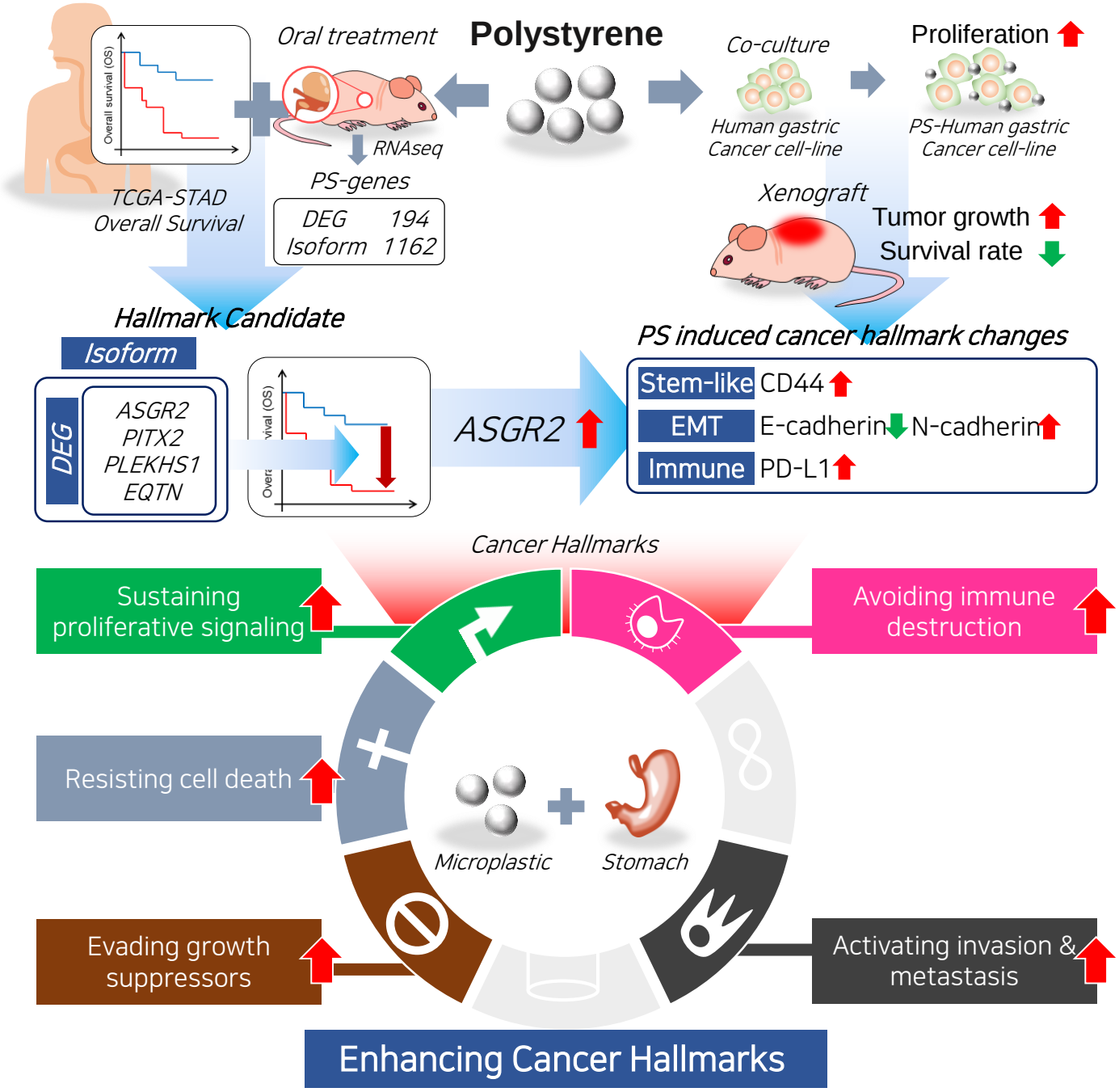


Confirmation of ASGR2



Confirmation of ASGR2




Oral treatment
Polystyrene
Co-culture
Proliferation
Human gastric Cancer cell-line
PS-Human gastric Cancer cell-line
RNAseq
PS-genes
DEG 194
Isoform 1162
TCGA-STAD Overall Survival
Xenograft
Tumor growth
Survival rate
Hallmark Candidate
Isoform
DEG
ASGR2
PITX2
PLEKHS1
EQTN
ASGR2
PS induced cancer hallmark changes
Stem-like CD44
EMT E-cadherin N-cadherin
Immune PD-L1
Cancer Hallmarks
Sustaining proliferative signaling
Avoiding immune destruction
Resisting cell death
Microplastic
Stomach
Evading growth suppressors
Activating invasion & metastasis
Enhancing Cancer Hallmarks