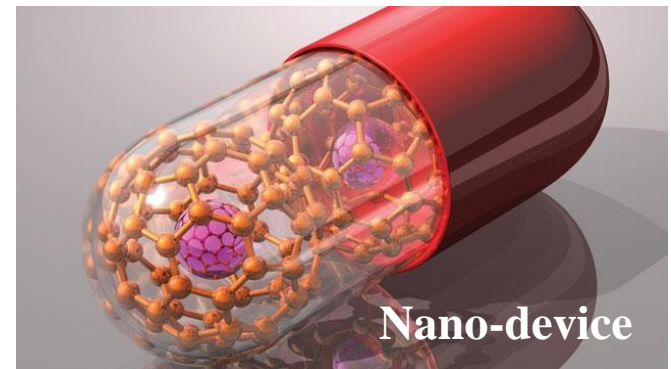
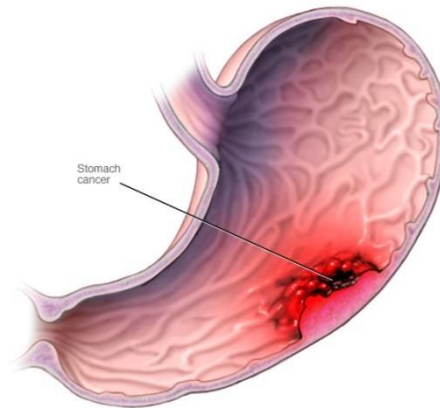


# Nano-medicines for preventing or treating gastric cancer

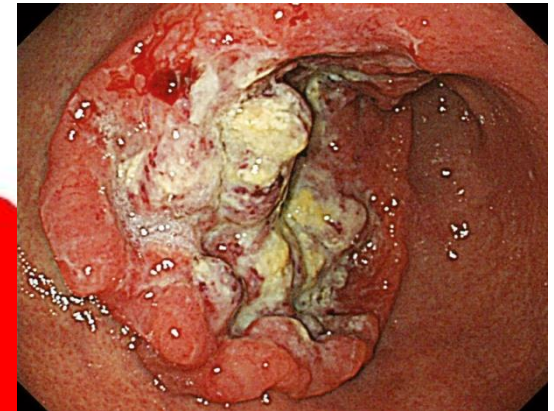
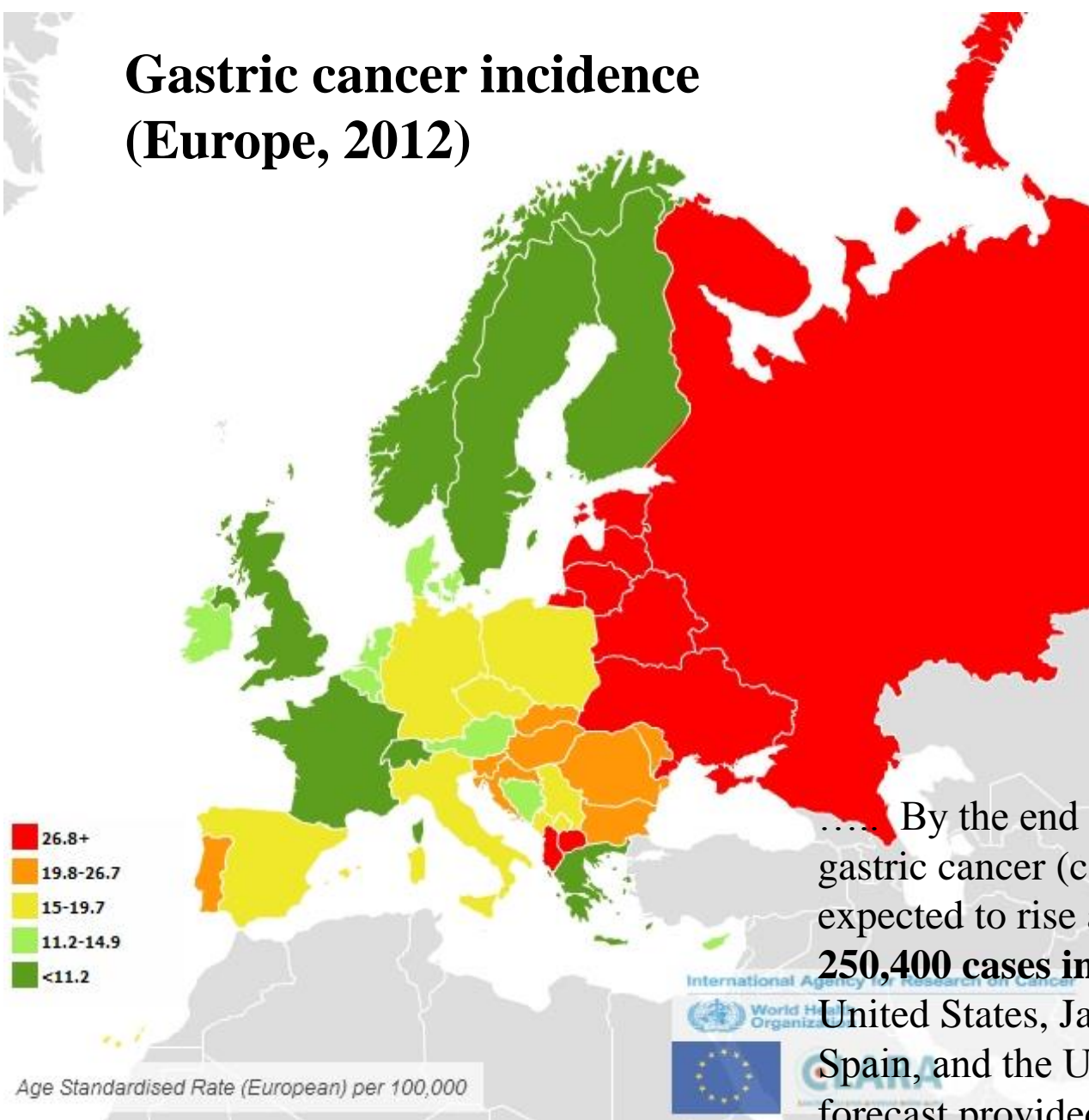
**Ki Baik Hahm, MD, PhD, AGAF**  
CHA University, seongnam, Korea  
*hahmkb@cha.ac.kr*

# Nano-medicines for Gastric cancer

1. Early diagnosis; Raman-Confocal laser endoscopy
2. SERS-Raman for molecular imaging
3. Innovative nano-materials
  - Nano particulated ABC blockers, PPI/P-CAB
  - Nano encapsulated  $\omega$ -3 PUFAs
  - Nano-peptides blocking *H. pylori* virulence, smad7
  - Molecular imaging and therapy (theranostics), chloroquine



# Gastric cancer incidence (Europe, 2012)



Advanced antral gastric cancer

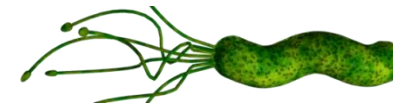
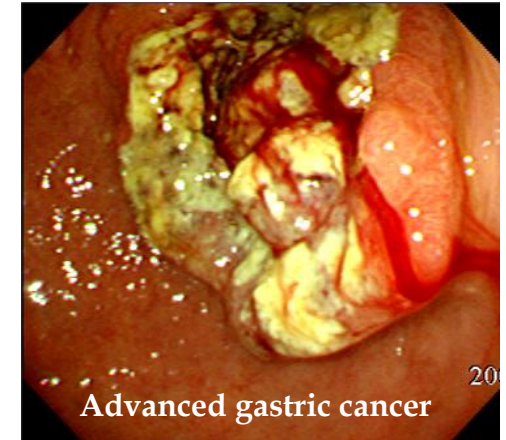
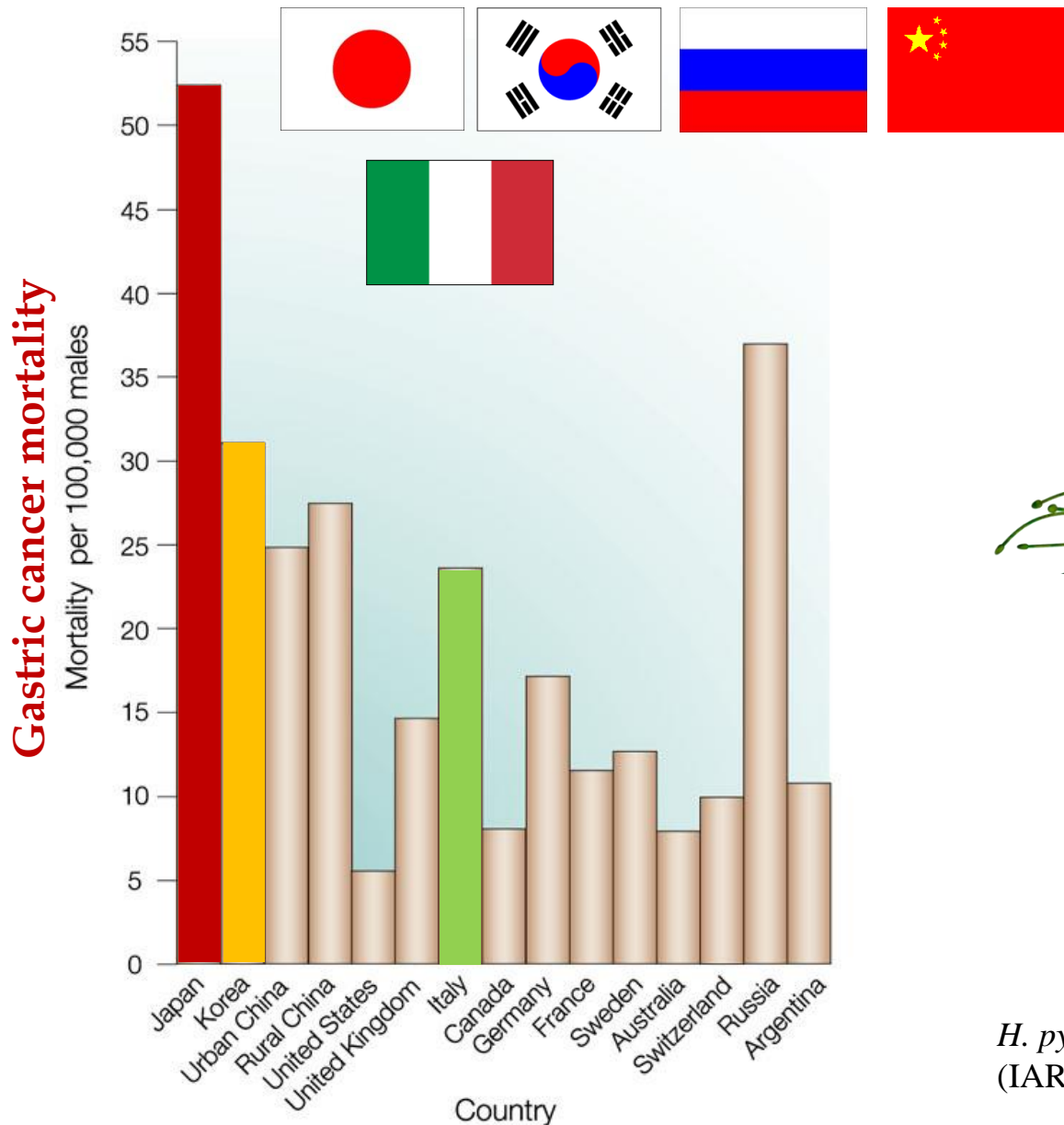
..... By the end of 2020, the incidence of gastric cancer (cancer of the stomach) is expected to rise about 13 percent — **reaching 250,400 cases in seven countries** — the United States, Japan, France, Germany, Italy, Spain, and the United Kingdom. That's the forecast provided by Datamonitor, a business information and analysis company.....

International Agency for Research on Cancer



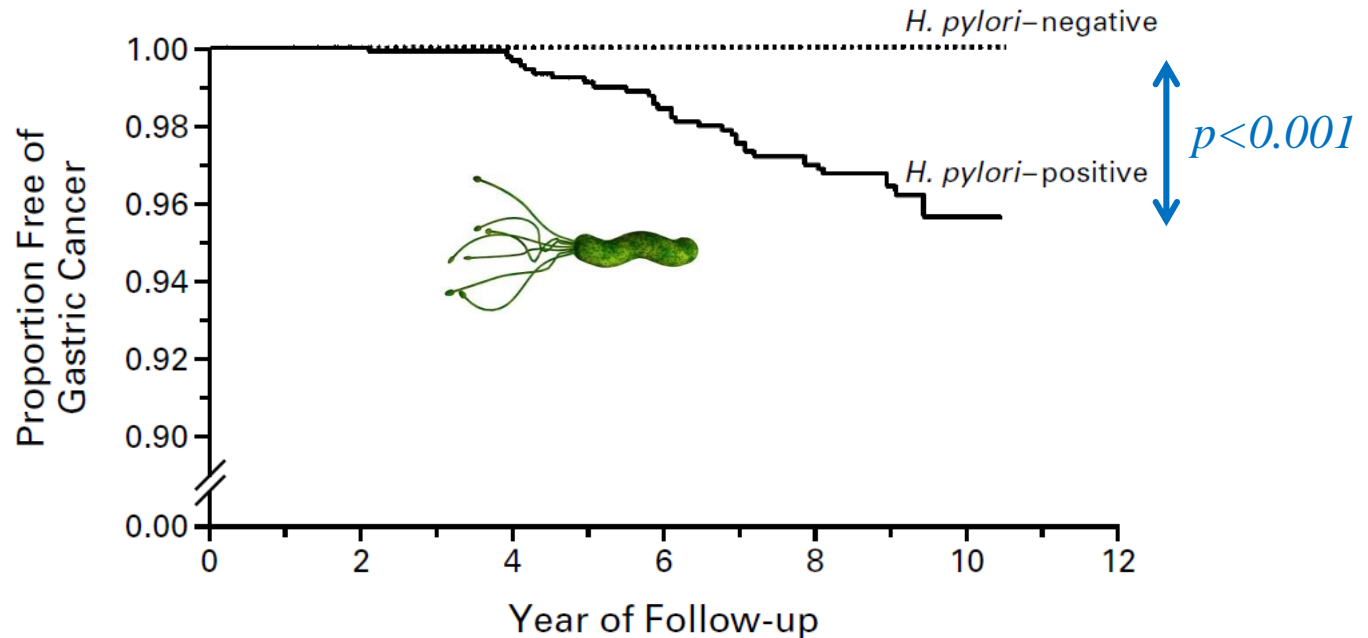
Age Standardised Rate (European) per 100,000

# Gastric cancer mortality (/100,000)



*H. pylori* as class I carcinogen  
(IARC, WHO)

# *H. pylori* infection and the development of gastric cancer



No. AT RISK

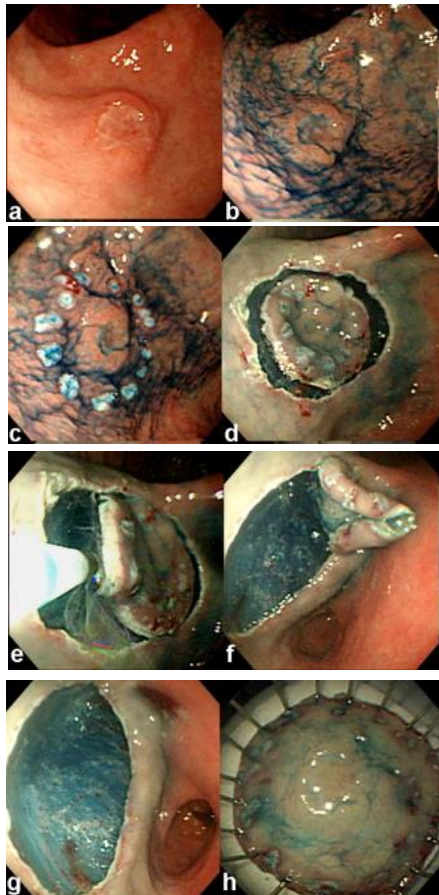
<i>H. pylori</i> -negative	280	272	251	245	213	57
<i>H. pylori</i> -positive	1246	1219	1086	907	782	258

**Figure 1.** Kaplan–Meier Analysis of the Proportion of *H. pylori*-Positive and *H. pylori*-Negative Patients Who Remained Free of Gastric Cancer.

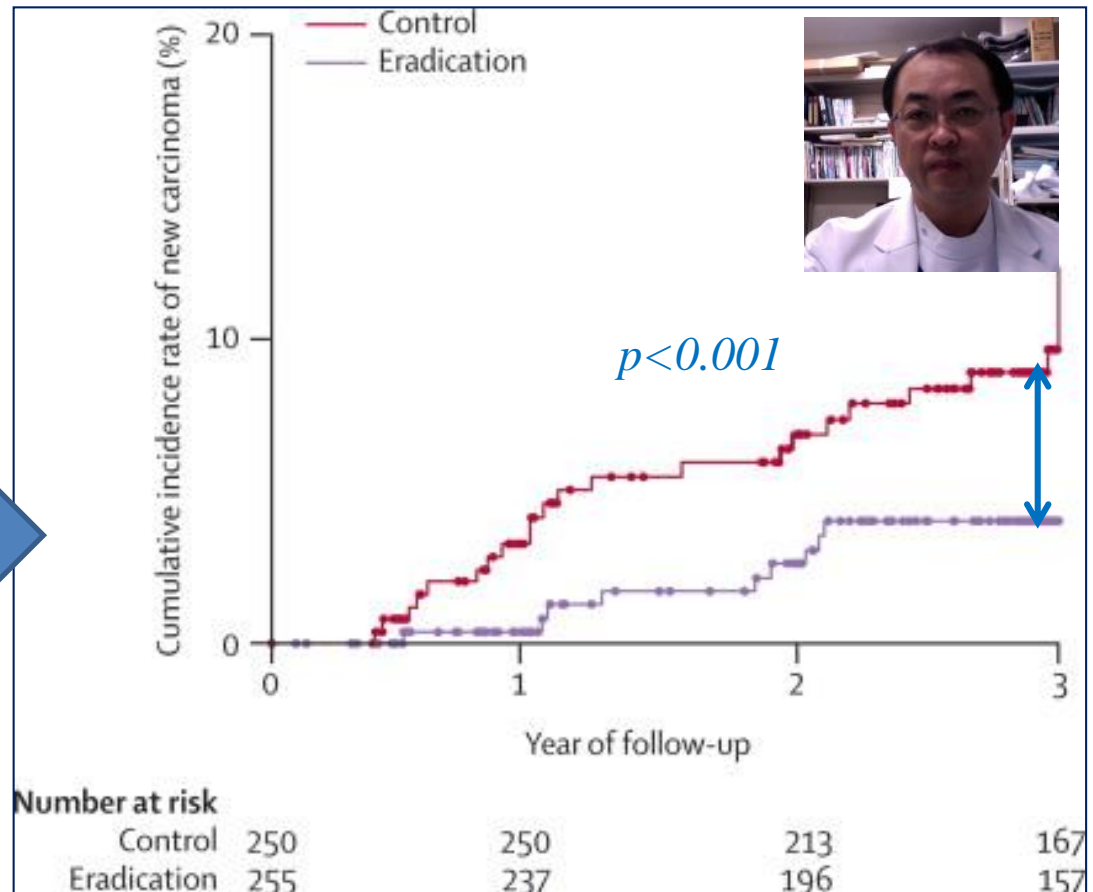
During follow-up, gastric cancer developed in 36 of the 1246 *H. pylori*-infected patients (2.9 percent) but in none of the 280 uninfected patients ( $P < 0.001$ ).

# *H. pylori* eradication to prevent metachronous gastric cancer

Endoscopic submucosal dissection  
(ESD)  
for early gastric cancer



Recurrence  
(MGC)

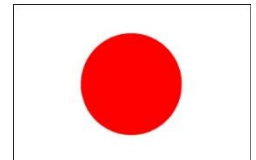


# Approved triple therapy for *H. pylori*-associated gastritis in Japan, Feb 21, 2013

## *Helicobacter pylori* Gastritis Approved as Additional Indication in Japan for *H. pylori* Eradication by Triple Therapy with Proton Pump Inhibitor

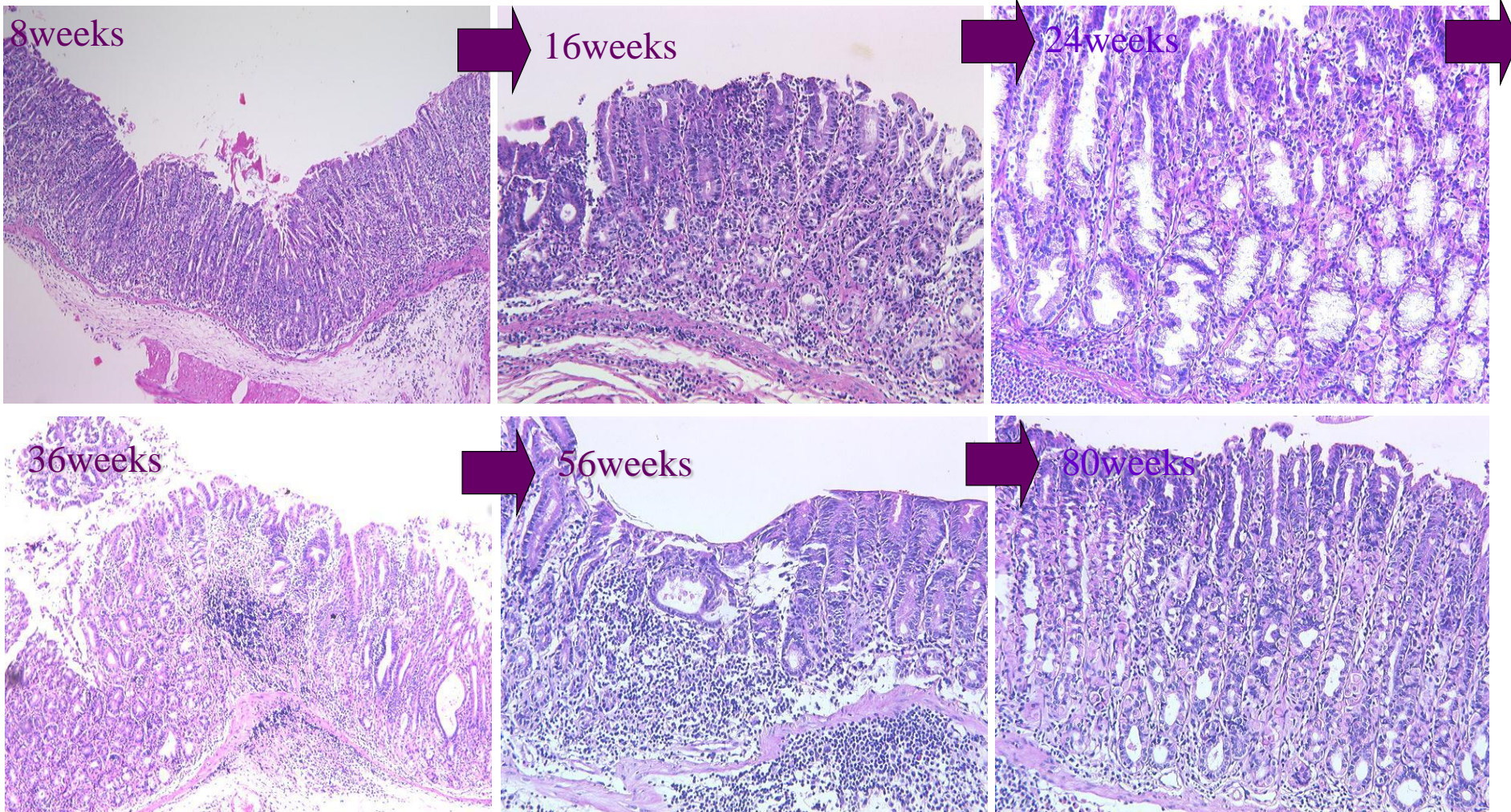
Osaka and Tokyo, Japan, February 21, 2013 --- Takeda Pharmaceutical Company Limited, AstraZeneca K.K., Mitsubishi Tanabe Pharma Corporation, and Eisai Co., Ltd. jointly announced today that ***H. pylori* gastritis has been approved by Japan's Ministry of Health, Labour and Welfare as an additional indication for *H. pylori* eradication by triple therapy with proton pump inhibitors.** This therapy consists of a proton pump inhibitor, amoxicillin, and either clarithromycin or metronidazole.

## New approval of Japanese health insurance for *H. pylori* eradication



# 1. Eradication does not warrant cancer prevention because,

## *H. pylori* infection as promoter for gastric cancer



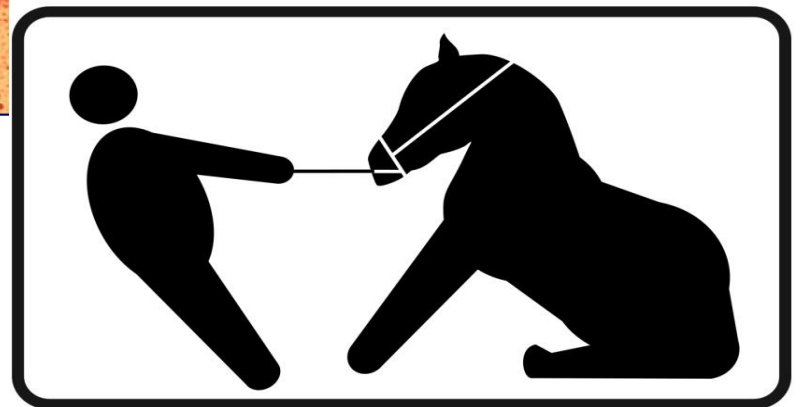


## 2. Eradication does not warrant cancer prevention because,

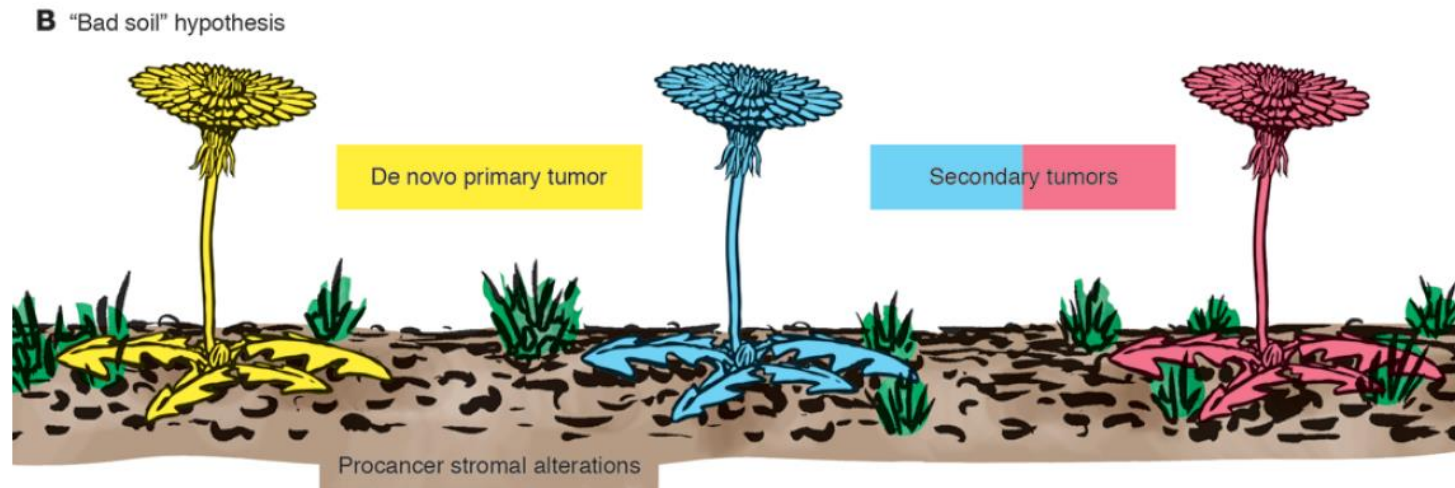
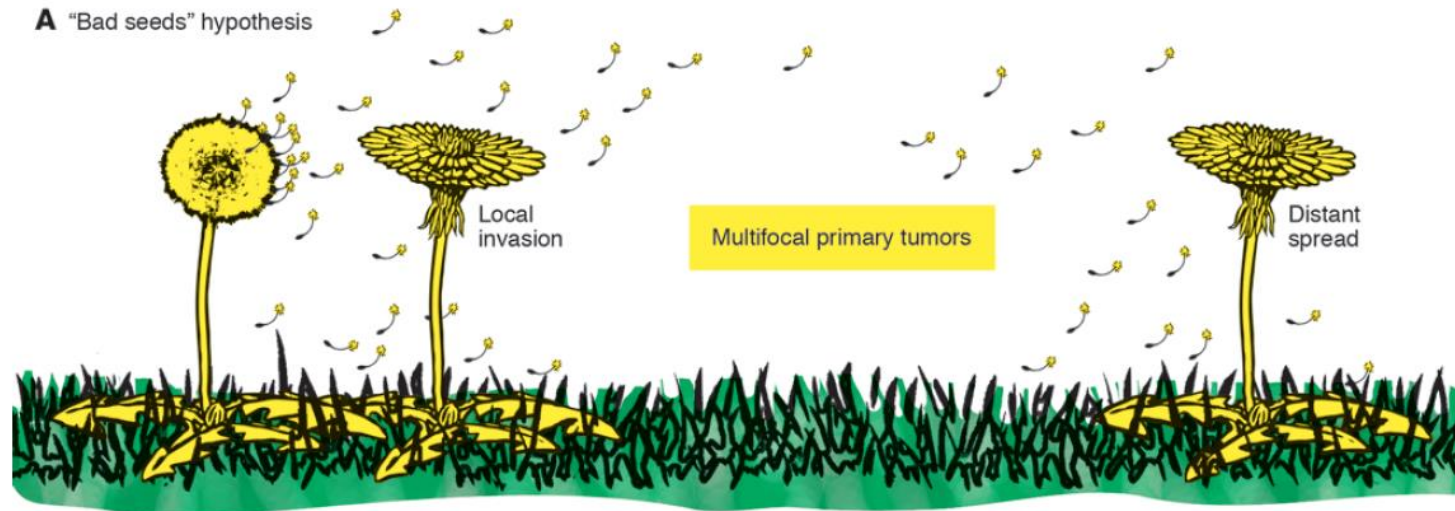
**Simple eradication of bug is not sufficient  
for the prevention of gastric cancer**



**Bacterial Resistance**



### 3. Eradication does not warrant cancer prevention because,



*H. pylori* infection → inflammation → epigenetic changes → **field cancerization**

Dig Dis 2014;32:290-294  
(DOI:10.1159/000357861)

## The Korean Perspective of *Helicobacter pylori* Infection: Lessons from the Japanese Government's Policy to Prevent Gastric Cancer

Park J.-M. · Hahm K.B.

CHA Cancer Prevention Research Center, Seoul, and CHA University Bundang Medical Center, Seongnam, South Korea

[Abstract](#)[Purchase](#)[FullText](#)[PDF](#)[Login / Register](#)

### Abstract

The guideline of the Korean College of Helicobacter and Upper Gastrointestinal Research group for *Helicobacter pylori* infection was first produced in 1998, when definite indication for *H. pylori* eradication is early gastric cancer in addition to the previous indications of peptic ulcer (PUD) including scar lesion and marginal zone B cell lymphoma (MALT type). Though treatment is recommended for the relatives of a patient with gastric cancer, unexplained iron deficiency anemia, and chronic idiopathic thrombocytopenic purpura, a consensus treatment guideline is the treatment of PUD,

## 3 major reasons against drastic eradication executed in Japan





## Korean strategy

**Early detection (malignant potential) and early sweeping**

Earlier detection, Raman Spectroscopy/ SERS base

Earlier sweeping; Nano-molecules

*siTRP (short-term intervention To Revert Premalignant lesion)*

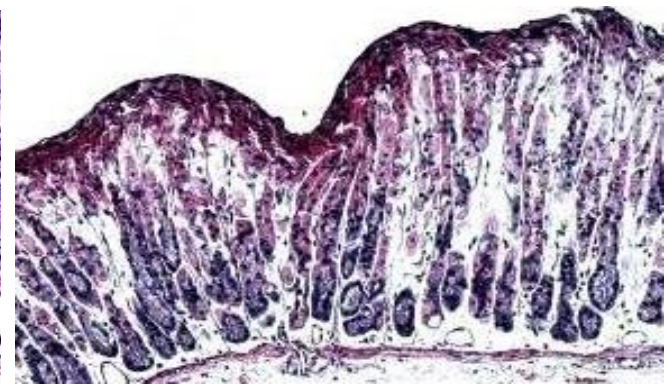
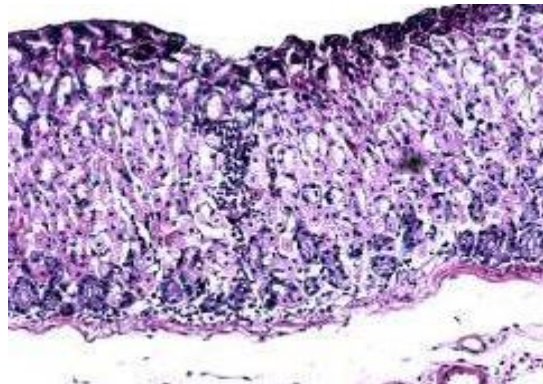
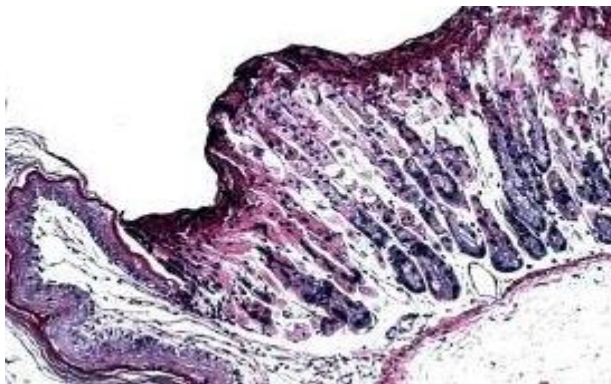
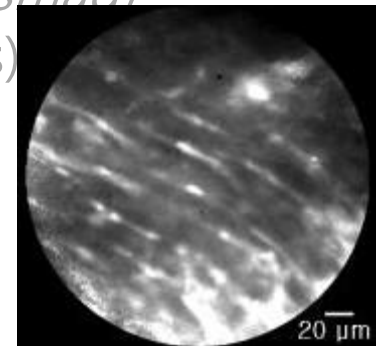
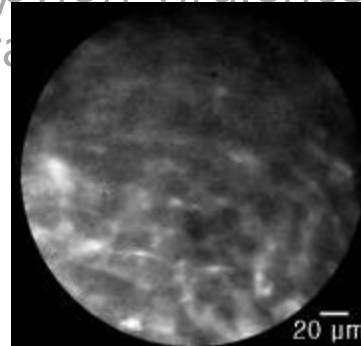
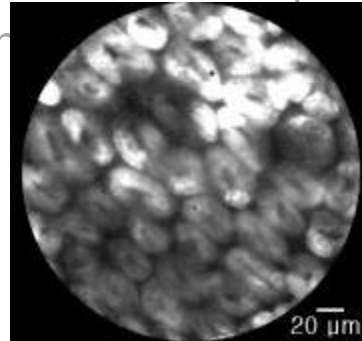
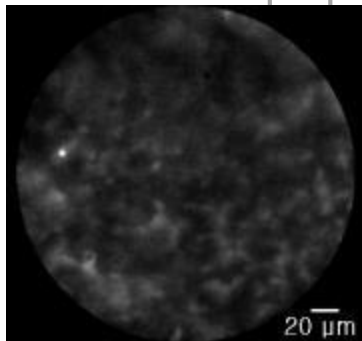
# Nano-medicines for Gastric cancer

1. Early diagnosis; Raman-Confocal laser mini-probe endoscopy
2. SERS-Raman for molecular imaging
3. Innovative nano-materials

- Nano particulated ABC blockers, PPI/P-CAB

- Nano-*Helicobacter pylori*-infected stomach

- Nano-peptides blocking *H. pylori* virulence, *smad7*



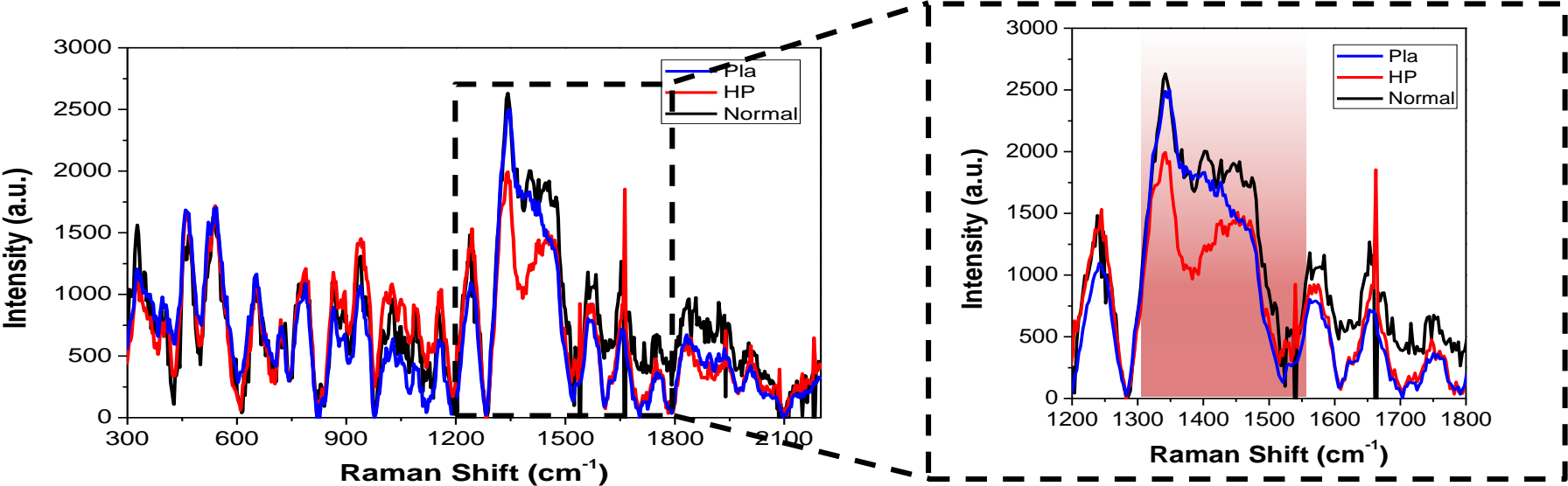
# Nano-medicines for Gastric cancer

## Portable Raman System

Laser-line : 785 nm

Sample power : 60 mW

Acquisition time : 30 sec



Normal

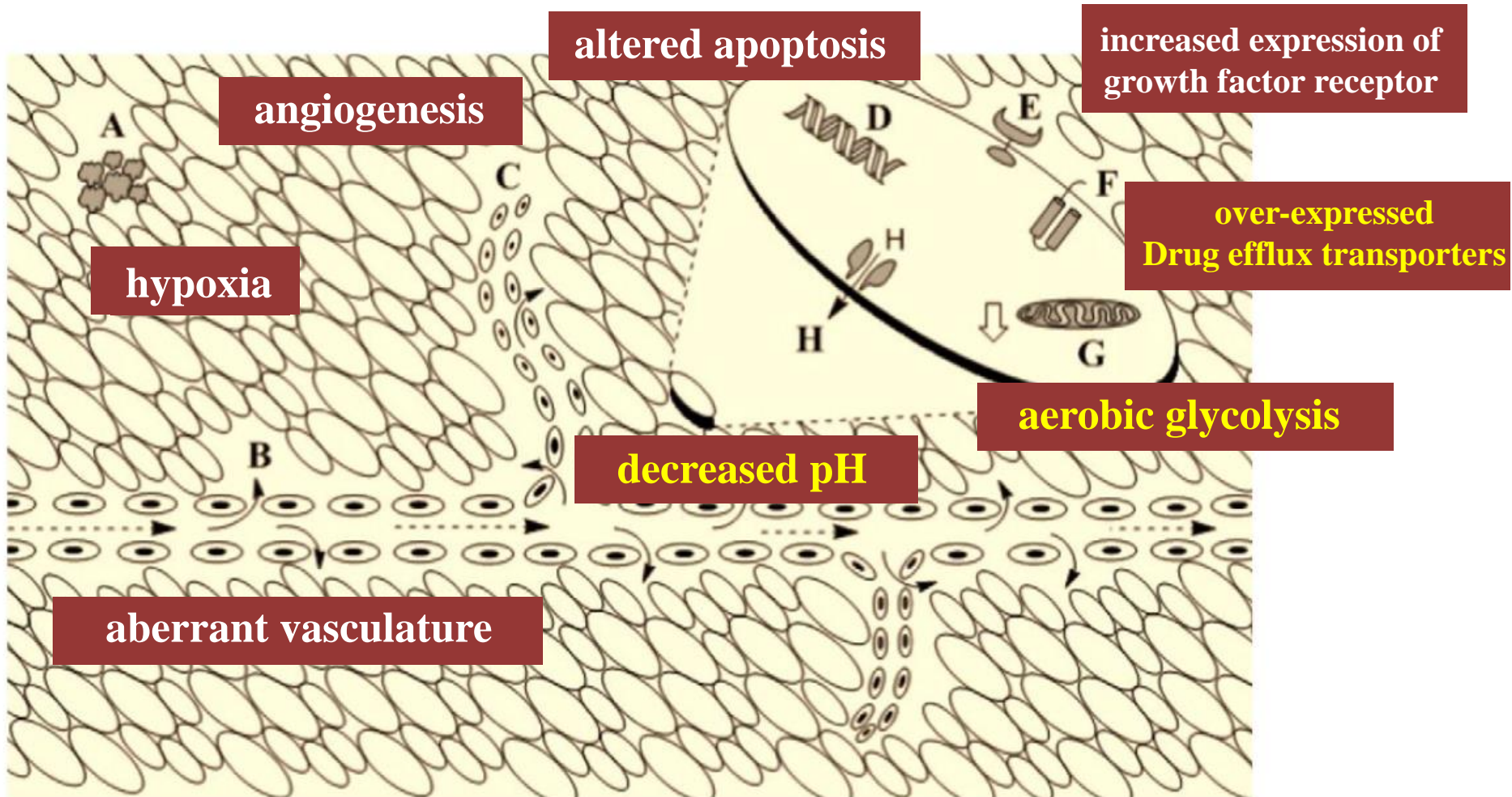


H. pylori-chronic atrophic gastritis



H. pylori-chronic atrophic gastritis treated with stem cells

# Tumor Microenvironment



# Warburg effect

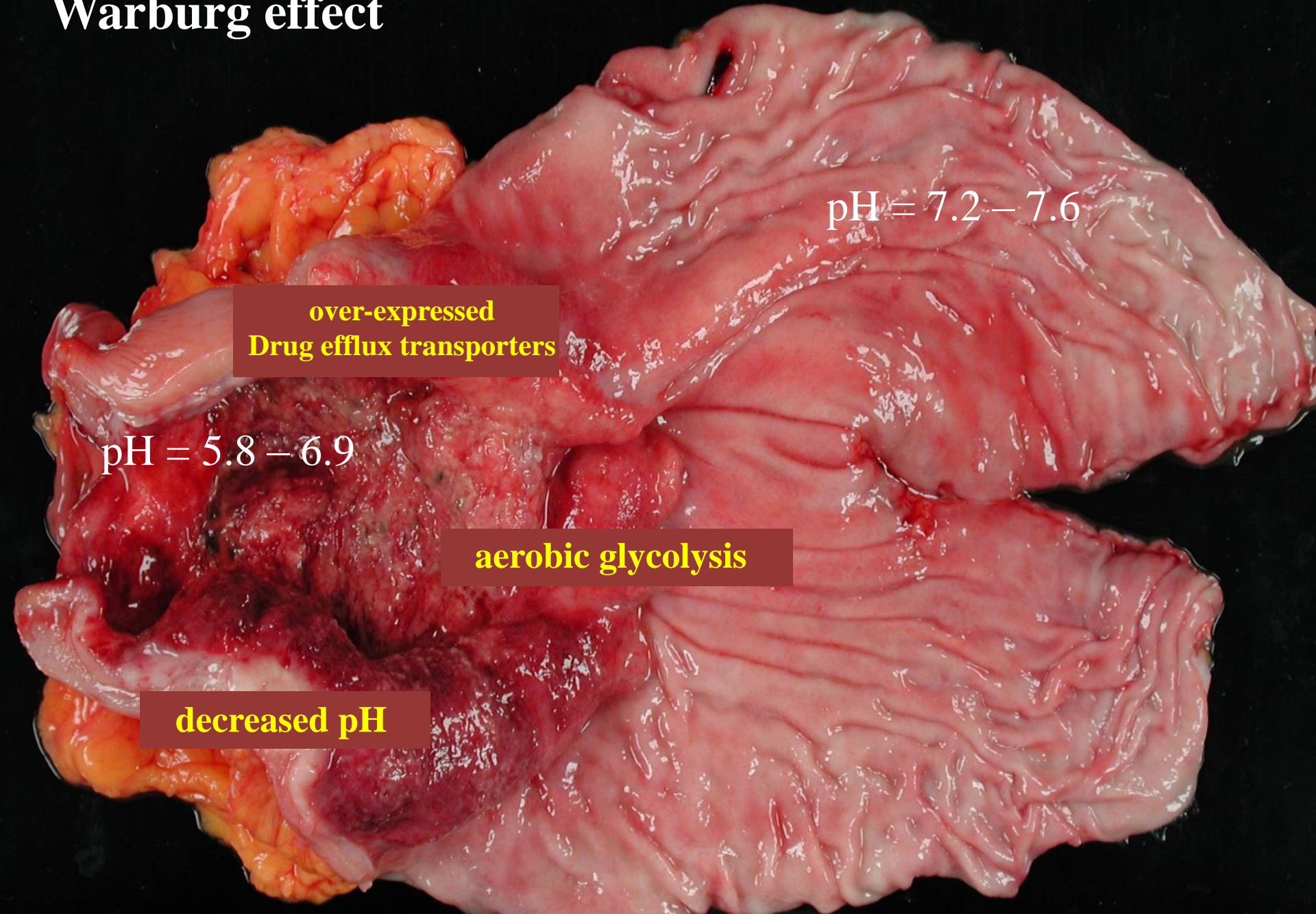
pH = 7.2 – 7.6

**over-expressed  
Drug efflux transporters**

pH = 5.8 – 6.9

**aerobic glycolysis**

**decreased pH**





# Warburg effect

## Proton Pump Inhibitor beyond the acid inhibition

anti-inflammation, apoptosis, differentiation, defense enhancement

Vol. 10, 8687–8696, December 15, 2004

Clinical Cancer Research 8687

### Selective Induction of Apoptosis with Proton Pump Inhibitor in Gastric Cancer Cells

Marie Yeo,<sup>1</sup> Dong-Kyu Kim,<sup>1</sup> Young-Bae Kim,<sup>1</sup>  
Tae Young Oh,<sup>1</sup> Jong-Eun Lee,<sup>1</sup> Sung Won Cho,<sup>1</sup>  
Hugh Chul Kim,<sup>2</sup> and Ki-Baik Hahm<sup>1</sup>

<sup>1</sup>Genomic Research Center for Gastroenterology and <sup>2</sup>Department of  
Hematology-Oncology, Ajou University School of Medicine, Suwon,  
Korea

#### INTRODUCTION

The H<sup>+</sup>/K<sup>+</sup>-ATPase of gastric parietal cell exchanges luminal K<sup>+</sup> for cytoplasmic H<sup>+</sup> and is the enzyme primarily responsible for gastric acidification (1–3). The enzyme consists of two subunits, a 114 kDa  $\alpha$ -subunit and a 35 kDa  $\beta$ -subunit. The  $\alpha$ -subunit containing ATP and cation binding sites carries out the catalytic and transporting function of the proton pump.

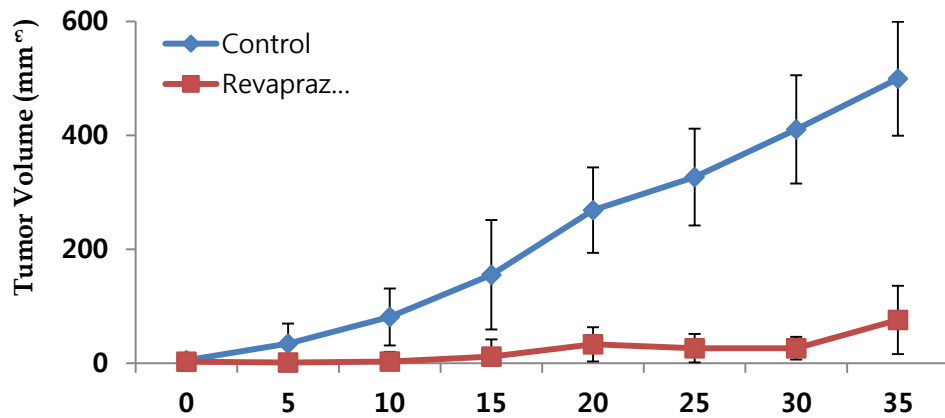
# Warburg effect

## Chemoquiescence through ablating CSCs with acid blockers

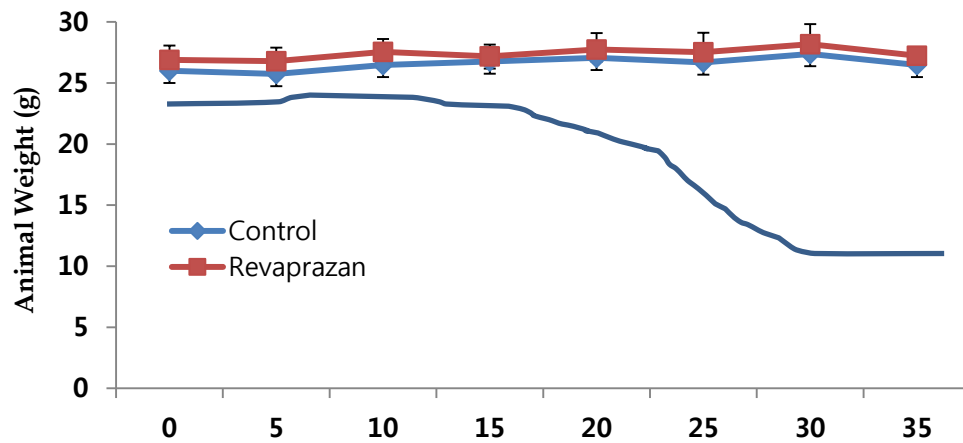
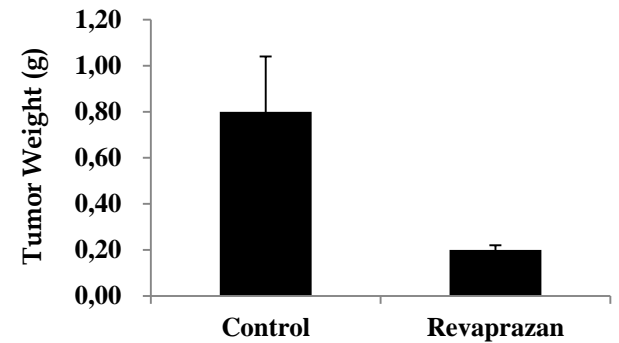
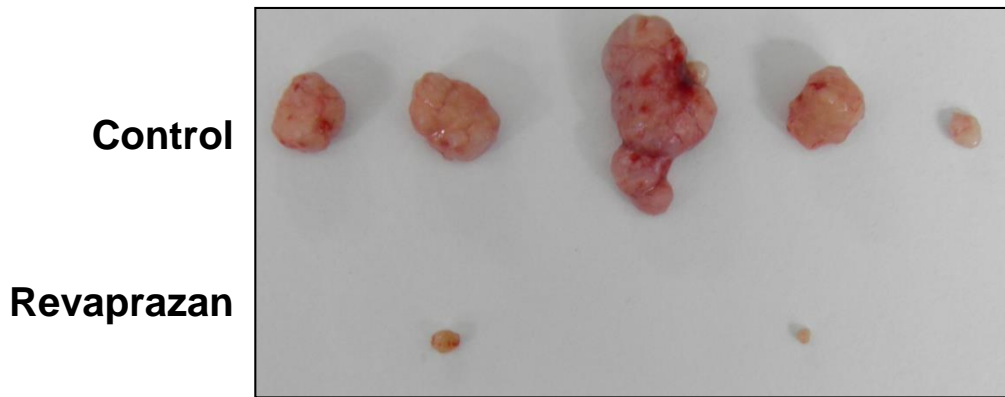


**CSCs are responsible for**

- Cancer recurrence
- Cancer metastasis
- Chemoresistance
- Radioresistance



**Revaprazan**  
(Potassium Competitive Acid Blocker)  
Nanoparticulated P-CAB



Cancer cachexia

ORIGINAL ARTICLE

## Mongersen, an Oral SMAD7 Antisense Oligonucleotide, and Crohn's Disease

Giovanni Monteleone, M.D., Ph.D., Markus F. Neurath, M.D., Ph.D., Sandro Ardizzone, M.D., Antonio Di Sabatino, M.D., Massimo C. Fantini, M.D., Ph.D., Fabiana Castiglione, M.D., Maria L. Scribano, M.D., Alessandro Armuzzi, M.D., Ph.D., Flavio Caprioli, M.D., Ph.D., Giacomo C. Sturniolo, M.D., Francesca Rogai, M.D., Ph.D., Maurizio Vecchi, M.D., Raja Atreya, M.D., Ph.D., Fabrizio Bossa, M.D., Sara Onali, M.D., Ph.D., Maria Fichera, M.D., Gino R. Corazza, M.D., Livia Biancone, M.D., Ph.D., Vincenzo Savarino, M.D., Roberta Pica, M.D., Ambrogio Orlando, M.D., and Francesco Pallone, M.D.

### ABSTRACT

#### BACKGROUND

Crohn's disease–related inflammation is characterized by reduced activity of the immunosuppressive cytokine transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1) due to high levels of SMAD7, an inhibitor of TGF- $\beta$ 1 signaling. Preclinical studies and a phase 1 study have shown that an oral SMAD7 antisense oligonucleotide, mongersen, targets ileal and colonic SMAD7.

#### METHODS

In a double-blind, placebo-controlled, phase 2 trial, we evaluated the efficacy of

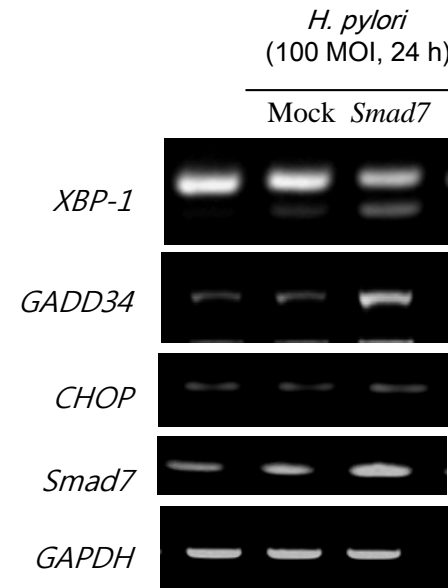
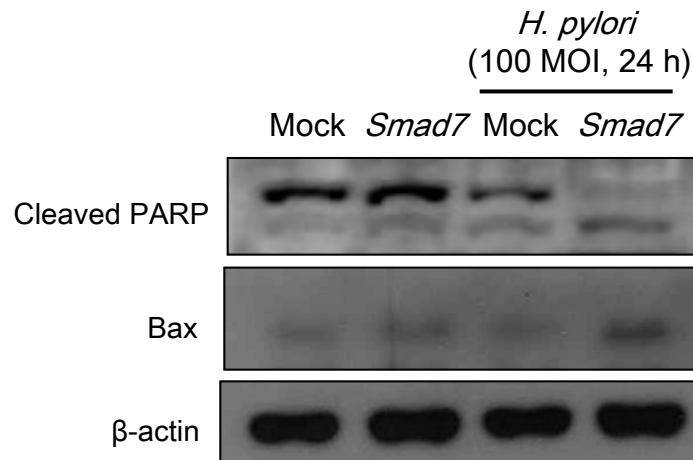
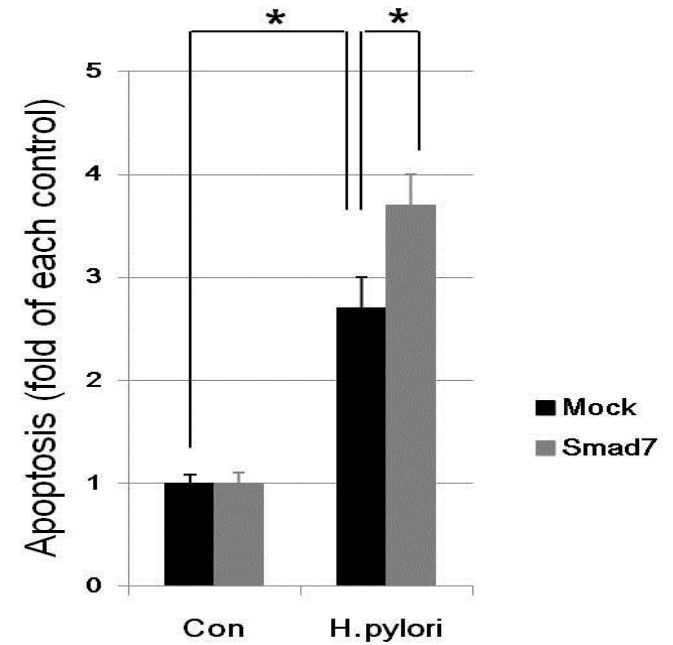
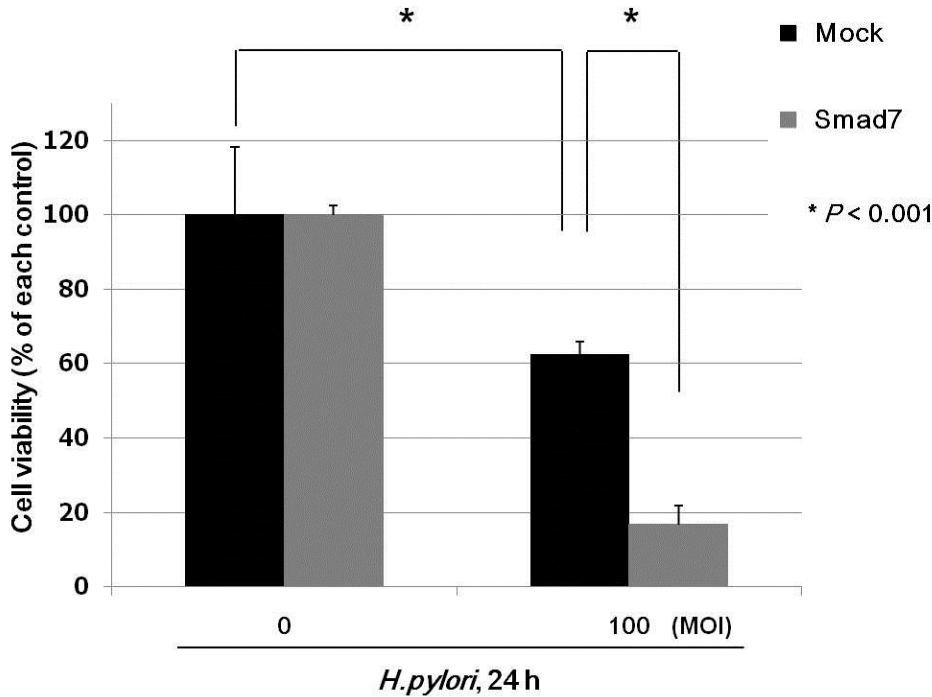
The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Monteleone at the Department of Systems Medicine, Università Tor Vergata, Via Montpellier, 1–00133, Rome, Italy, or at gi.monteleone@med.uniroma2.it.

N Engl J Med 2015;372:1104–13.

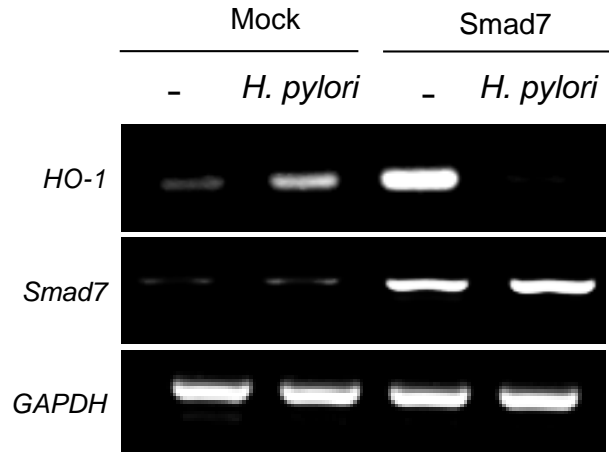
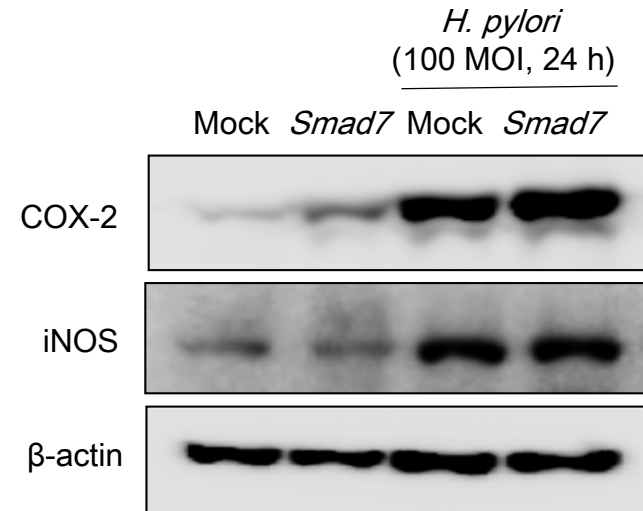
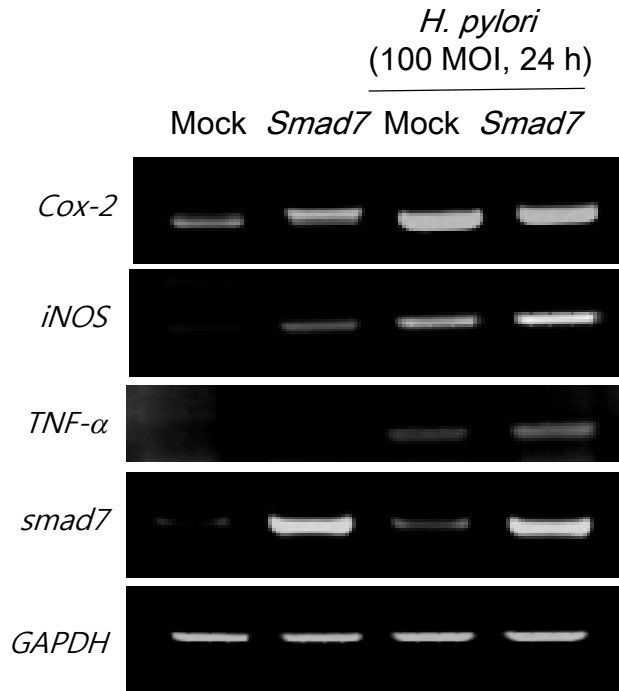
DOI: 10.1056/NEJMoa1407250

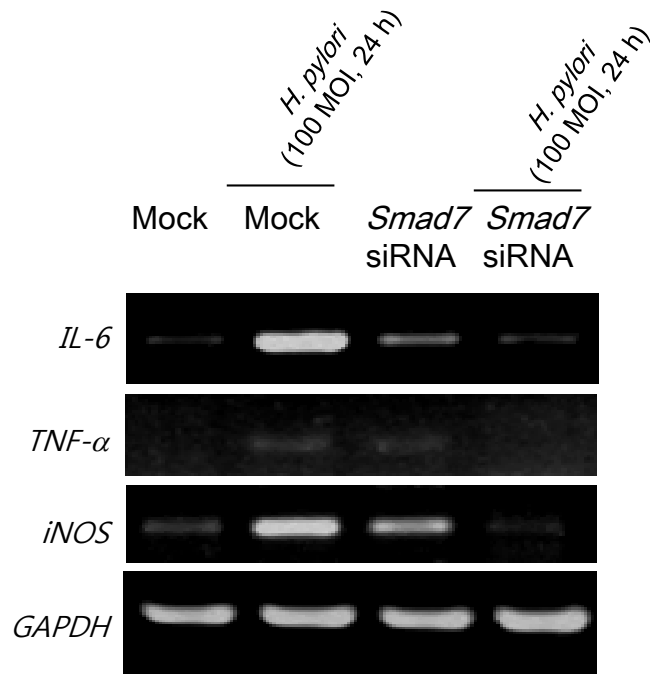
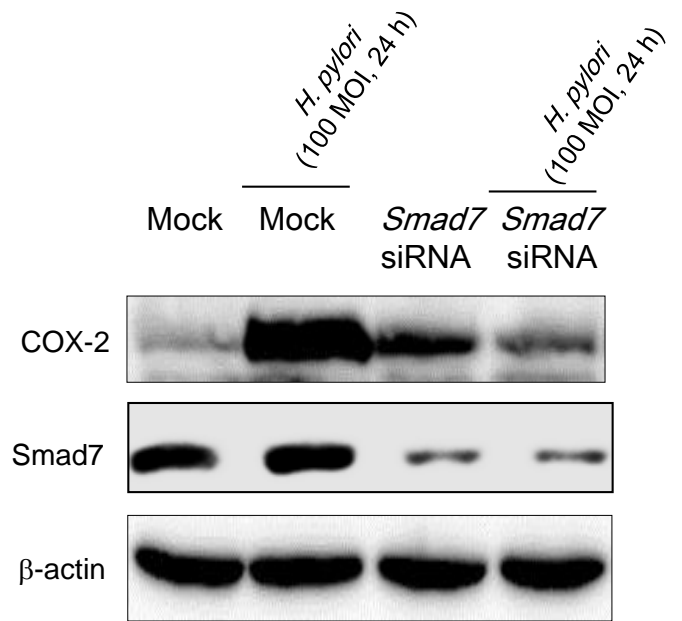
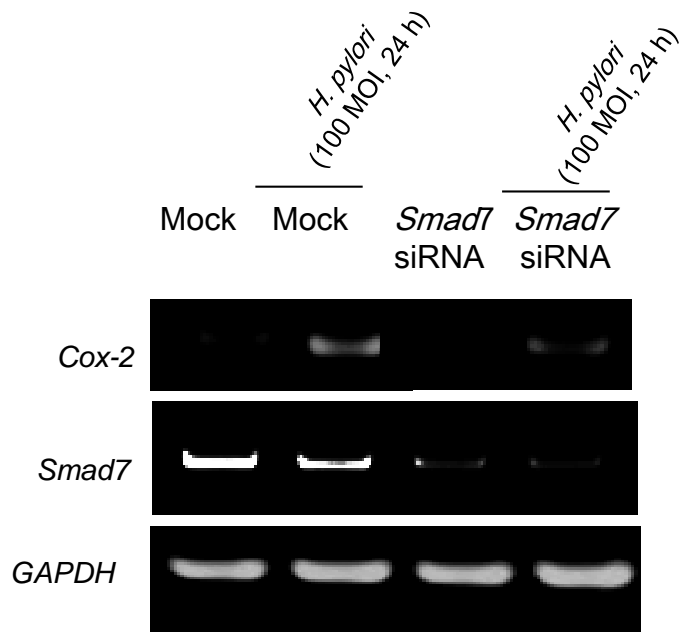
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# increased cytotoxicity relevant to *H. pylori* under smad7 overexpression



# Increased inflammatory mediators relevant to *H. pylori* under smad7 overexpression

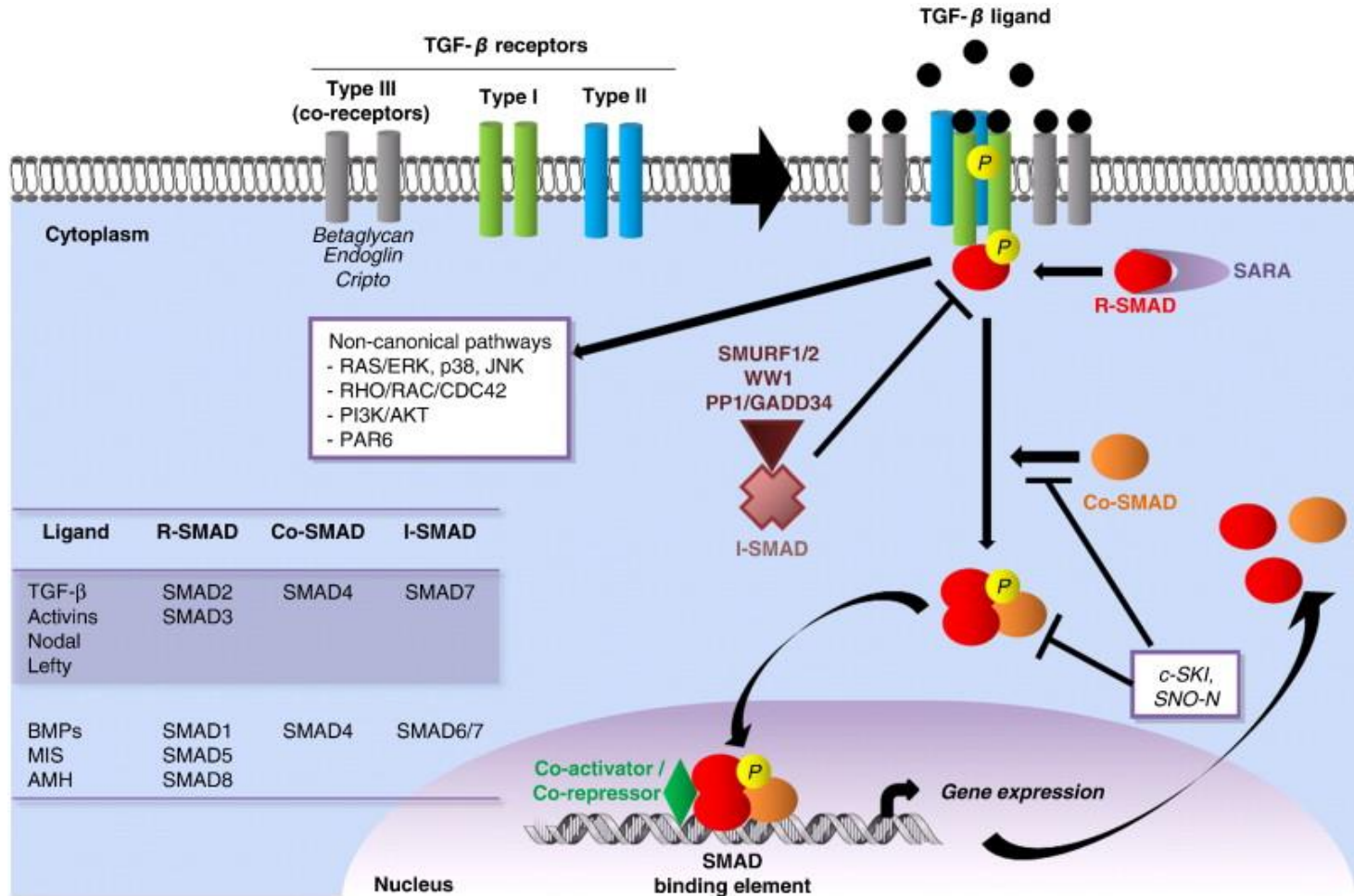




# Nano-medicines for Gastric cancer

Nano-peptides blocking *H. pylori* virulence,

*smad7* anti-sense nanomolecules





# Nano-medicines for Gastric cancer

Nanomedicine to block field cancerization,

**Nano encapsulated  $\omega$ -3 PUFAs**

[www.impactjournals.com/oncotarget/](http://www.impactjournals.com/oncotarget/)

Oncotarget, Advance Publications 2016

## Suppressed *Helicobacter pylori*-associated gastric tumorigenesis in Fat-1 transgenic mice producing endogenous $\omega$ -3 polyunsaturated fatty acids

Young-Min Han<sup>1,\*</sup>, Kyung-Jo Kim<sup>2,\*</sup>, Migyeung Jeong<sup>1</sup>, Jong-Min Park<sup>1</sup>, Eun-Jin Go<sup>1</sup>,  
Jing X Kang<sup>3</sup>, Sung Pyo Hong<sup>4</sup>, Ki Baik Hahm<sup>1,4</sup>

<sup>1</sup>CHA Cancer Prevention Research Center, CHA Cancer Institute, CHA University, Seoul, Korea

<sup>2</sup>Department of Gastroenterology, University of Ulsan, Seoul Asan Medical Center, Seoul, Korea

<sup>3</sup>Laboratory for Lipid Medicine and Technology, Massachusetts General Hospital, Harvard Medical School, Boston, USA

<sup>4</sup>Department of Gastroenterology, CHA Bundang Medical Center, Seongnam, Korea

\*These authors have contributed equally to this work

Correspondence to: Ki Baik Hahm, email: hahmkb@cha.ac.kr

Keywords: Fat-1 transgenic mice, COX-2, 15-PGDH,  $\omega$ -3 PUFAs, anti-proliferation

## ABSTRACT

**Dietary approaches to preventing *Helicobacter pylori* (*H. pylori*)-associated gastric carcinogenesis are widely accepted because surrounding break-up mechanisms are mandatory for cancer prevention, however, eradication alone has been proven to be insufficient. Among these dietary interventions, omega-3-polyunsaturated-fatty**

have been reported, likely based on inconsistent dietary administration. In this study, we developed an *H. pylori* initiated-, high salt diet promoted-gastric tumorigenesis model and conducted a comparison between wild type (WT) and Fat-1 TG mice

# Nano-medicines for NSAID-associated GI damages

Nanomedicine  $\omega$ -3 polyunsaturated fatty acids

Nano encapsulated  $\omega$ -3 PUFAs

[www.nature.com/scientificreports](http://www.nature.com/scientificreports)

## SCIENTIFIC REPORTS

OPEN

### Mitigation of indomethacin-induced gastrointestinal damages in *fat-1* transgenic mice via gate-keeper action of $\omega$ -3-polyunsaturated fatty acids

Received: 17 May 2016

Accepted: 06 September 2016

Published: xx xx xxxx

Young-Min Han<sup>1,\*</sup>, Jong-Min Park<sup>1,\*</sup>, Jing X. Kang<sup>2</sup>, Ji-Young Cha<sup>3</sup>, Ho-Jae Lee<sup>3</sup>, Migeyong Jeong<sup>1</sup>, Eun-Jin Go<sup>1</sup> & Ki Baik Hahm<sup>1,4</sup>

Non-steroidal anti-inflammatory drugs (NSAIDs) damage the gastrointestinal (GI) epithelial cell membranes by inducing several signals through lipid raft organization after membrane incorporation, whereas  $\omega$ -3 polyunsaturated fatty acids (PUFAs) relieve inflammation, reduce oxidative stress, and provide cytoprotection, consequent to lipid raft disorganization. Therefore, we hypothesized that

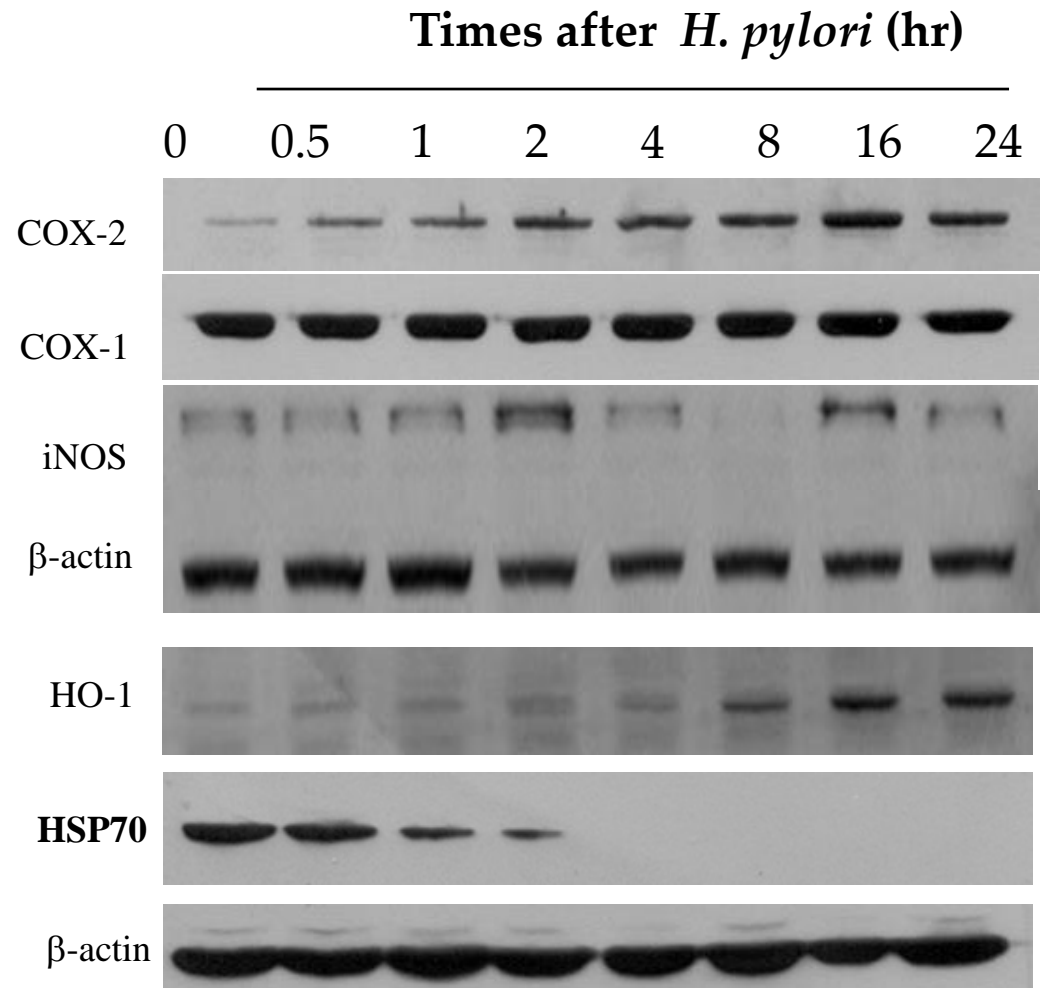
Released today

# Nano-medicines for Gastric cancer

- ✓ Nano-particulated HSP70 inducer;  $\omega$ -3 PUFAs



**Burn bridges, e.g, stress**

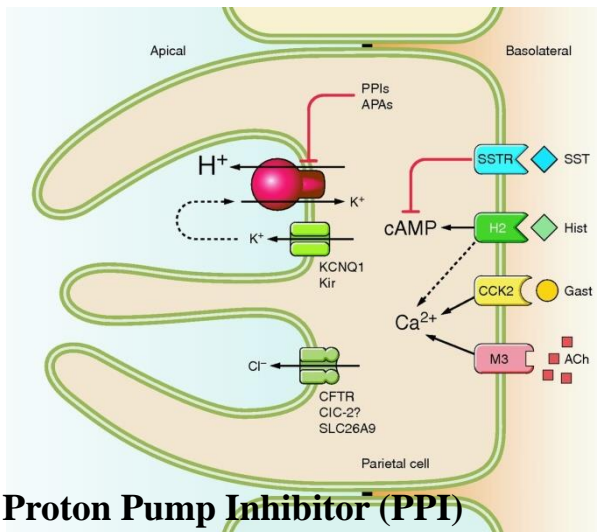


# Nano-medicines for Gastric cancer

1. Early diagnosis; Raman-Confocal laser endoscopy
2. SERS-Raman for molecular imaging

## 3. Innovative nano-drugs for gastric cancer

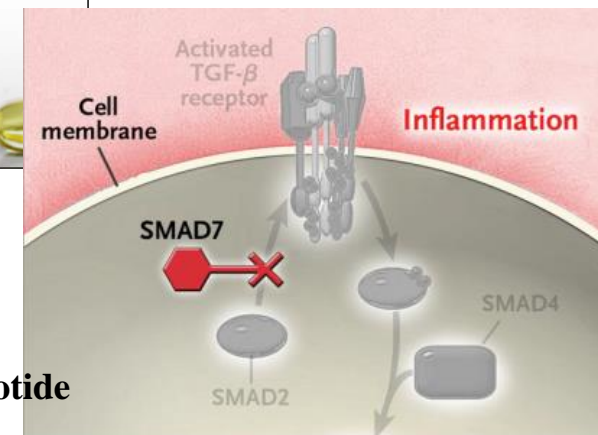
- Nano particulated ABC blockers, PPI/P-CAB, HSP inducer
- Nano blocks field cancerization, Nano encapsulated  $\omega$ -3 PUFAs
- Nano-peptides blocking *H. pylori* virulence, *smad7*
- Molecular imaging and therapy (theranostics)



**Proton Pump Inhibitor (PPI)**  
**Potassium competitive acid blocker (P-CAB)**  
**on nano-based particle**



**Nano-particulated  
n-3 PUFAs**



**Anti-sense oligonucleotide  
*Smad7* (Mongersen)**  
**Other nano-form for stomach**

# CHS (CHA University Health System)

1984-1995



CHA hospital at Gangnam, Seoul, Korea

1995-2000



CHA hospital at Gumi, Gyungsangdo



CHA hospital at Los Angeles, CA, USA

2000-2012

Regenerative Medicine and Stem Cell



CHA Bio Complex at Pangyo



CHAUM at Chungdam, Seoul

Research Oriented Hospital Project (2013~2023)



CHA Medical Center at Bundang, Seongnam

2023~



**CHA University Bundang Medical Center**  
**Government nominated Research Oriented Hospital**

# Nano Roma, September, 20-23 2016 **Innovation** Conference & Exhibition



**World without gastric cancer**

**Thank you for attention**  
**Q&A?**

