

EXPLORATION OF PHY906, A TCM FORMULA AS ADJUVANT FOR CANCER CHEMOTHERAPY

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Cancer & Viral Chemotherapy

- **Scope of Activity**
 - A. Molecular and Biochemical Pharmacology of Anticancer and Antiviral Compounds**
 - B. Drug Discovery**
 - C. Clinic Protocol Design**
- **Drug Entity of Current Interest**
 - A. Nucleoside Analogs**
 - B. Natural Products**
 - C. Chinese Medicine**

Cancer Associated Viruses

The Current Interests of Our Laboratory

Virus	Infectious Diseases	Cancers Associated
Hepatitis B Virus	<ul style="list-style-type: none">•Chronic infection•Cirrhosis of the liver	Hepatocellular carcinoma
Hepatitis C Virus	<ul style="list-style-type: none">•Chronic infection•Cirrhosis of the liver	Hepatocellular carcinoma
Human Immuno Deficiency Virus	AIDS	Cancer associated with Immuno Deficiency state of patients

Chemicals Discovered in this Laboratory (In Collaboration with Others) Under Different Stages of Clinical Development

Chemical(s)	Indication	Clinical Stage
DHPG (Gancyclovir)*	CMV	Approved
3TC (Lamivudine)*	HBV	Approved
L-FTC (Emtricitabine)	HBV	Approved
L-FMAU (Clevudine)	HBV	Approved (Korea) Phase III (World Wide)
L-OddC (Troxacitabine)	Solid Tumor	Phase I/II
L-Fd4C (Elvucitabine)	HIV HBV	Phase II Phase I/II
D-IPdR (Ropidoxuridine)	Radiosensitizer For solid tumor	Phase I/II Orphan Drug Status
D-4'Ed4T	HIV	Phase Ib/IIa
PHY-906	Cancer	Phase II

*** Do Not Hold Patent**

Strategies for Development of Drugs for Cancer Treatment

1. More selective anti-cancer drugs with less toxicities
2. Decrease the toxicity of current cancer treatment modalities without compromising their anti-cancer activity

“Reductive” single chemical approach could make incremental improvement in most cases

“Holistic” polychemical approach should be entertained

SOME UNIQUE FEATURES OF TCM

- Chinese Medicine has multiple medical claims for the treatment of complicated diseases or multiple symptoms as well as disease prevention and improving quality of life.
- Chinese herbal medicine has many chemicals which could target on multiple sites or act on a single site additively or synergistically through direct or indirect interaction.
- Chinese Medicine takes a holistic approach and is an early form of “system biology” based “integrated medicine”.
- Chinese Medicine is prescribed on an individual basis to optimize its usage. It is “individualized medicine”.

“Chinese medicine could meet some of the current unmet medical needs. It has its own concept and could serve as the basis for developing future medicine”

Toxicity of Anticancer Modalities

- Hematological side-effects
- Nonhematological side-effects
Vomiting, nausea, diarrhea, etc.

PHY 906

Traditional use (since 300 A.D.)

—Diarrhea, vomiting, nausea, intestinal cramping, fever

•Composition

—Spray dried aqueous extract of four botanicals

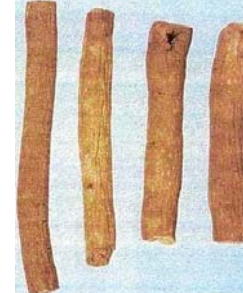
Scutellaria baicalensis Georgi.
Plant and roots



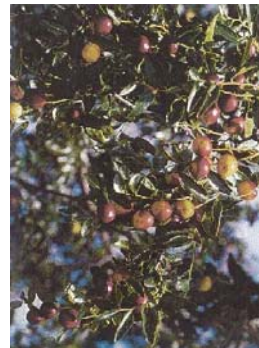
Glycyrrhiza uralensis Fisch
Plant and roots



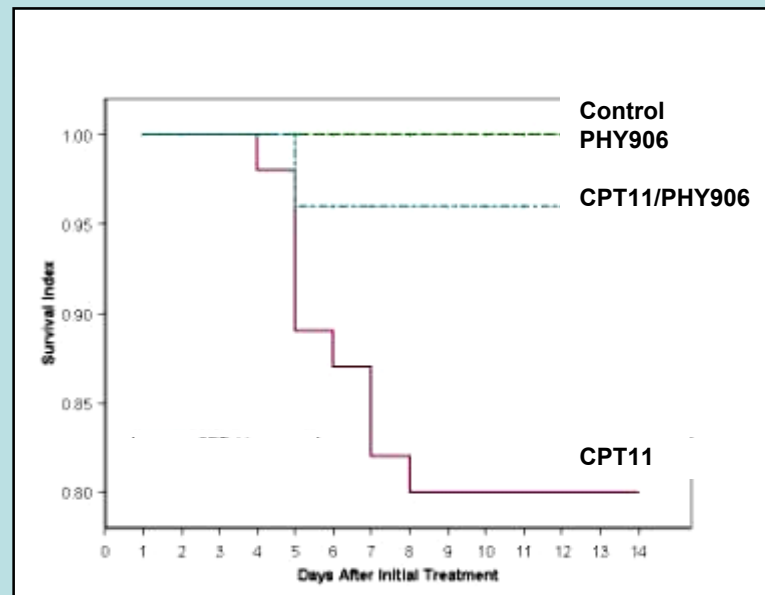
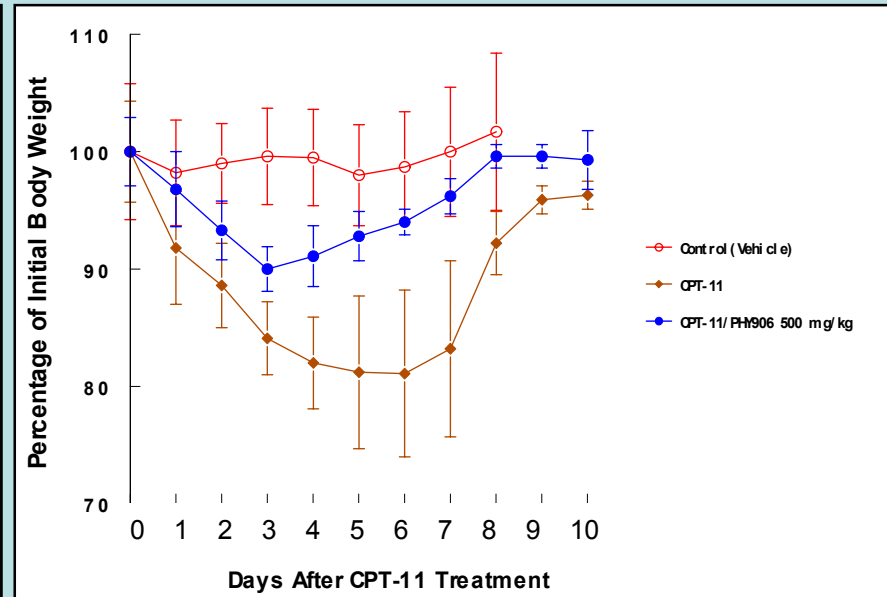
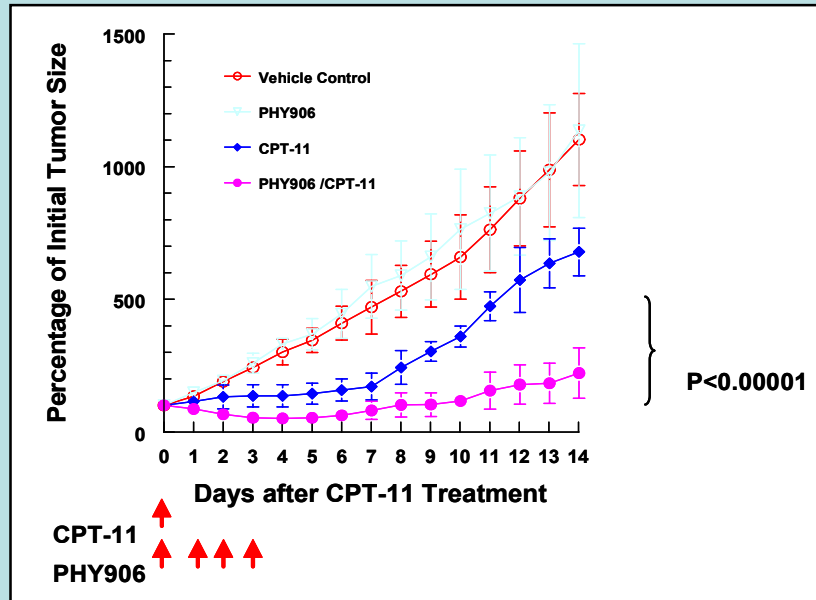
Paeonia lactiflora Pall.
Plant and roots



Ziziphus jujuba Mill.
Plant and fruits



PHY906 enhances the antitumor activity but decreases global toxicity of Irinotecan in colon38 xenograft bearing mice



Effects of Removing one or three Herbs from the PHY906 Formulation on the Potentiation of the Antitumor Activity, the Reduction of induced Body Weight Loss, and the Prevention of Death Caused by CPT-11.

Herbs in Formulation				Potentiation of Antitumor Effect	Reduction of Body Weight Loss	Prevention of Death
S	P	G	Z			
+	+	+	+	+++	+++	+++
-	+	+	+	--	--	+
+	-	+	+	+	+++	+++
+	+	-	+	++	--	++
+	+	+	-	+++	--	+
+	-	-	-	++	+	+
-	+	-	-	+	--	n/a
-	-	+	-	--	--	n/a
-	-	-	+	--	--	n/a

(+++) $P \leq 0.01$ very significant effect; (++) $P \leq 0.05$ significant effect; (+) $P \geq 0.05$ possible effect; (-) no effect.

Basic Regulatory Requirements for Modern Drugs

1. Consistency of preparation
2. Evidence based clinical efficacy
3. Safety
4. Certain Knowledge of its action
 - Sites of action(s)
 - Active ingredient(s)
 - Interactions with other drugs

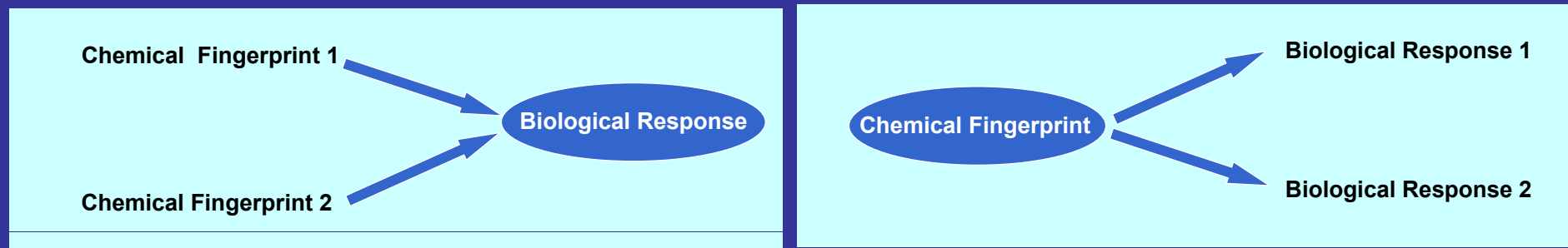
Quality Control for Complex Mixtures

- Regulatory and Scientific Challenge
 - What do you measure?
 - How do you measure it?
 - How do you compare it?

A NOVEL APPROACH IS REQUIRED!!

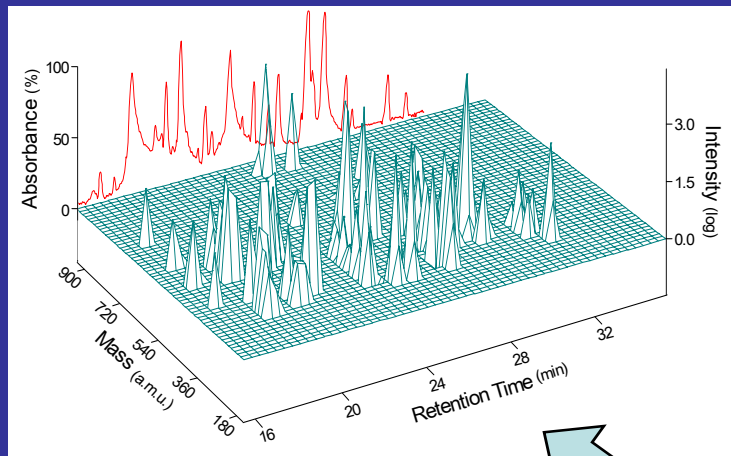
- What can be done now
 - Multiple parameters
 - Inclusive

Comprehensive Quality Control Measures

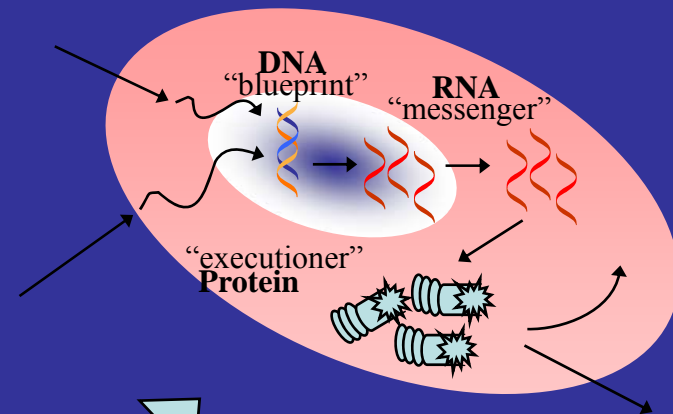


PhytomicsQC™

Chemical fingerprint



BioResponse fingerprint



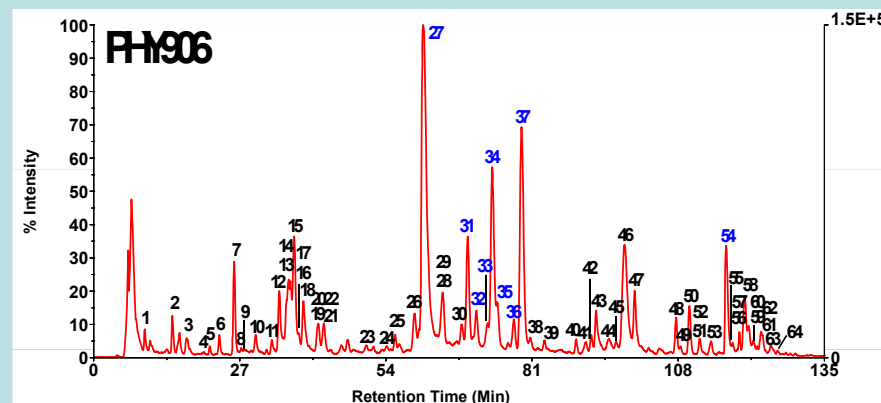
Mr. Mouse / Pharmacology

Provided by PhytoCeutica Inc.
(A Yale University Sponsored Company)

PHY906 can be made consistently based on PhytomicsQC™ analyzed by Phytosimilarity Index (PSI)

Chemical Fingerprint Comparison

	PHY906-6	PHY906-7	PHY906-8	PHY906-F
BATCH 6	1	0.99	0.991	0.729
BATCH 7		1	0.986	0.726
BATCH 8			1	0.722
BATCH F				1



64 compounds were identified from PHY906

Genomic BioResponse Fingerprint Comparison PSI Calculations (based on 20 genes)

	Batch 6	Batch 7	Batch 8	Batch 9	Batch F
BATCH 6	1.00	0.99	0.99	0.92	0.32
BATCH 7		1.00	0.99	0.93	0.36
BATCH 8			1.00	0.95	0.42
BATCH 9				1.00	0.45
BATCH F					1.00

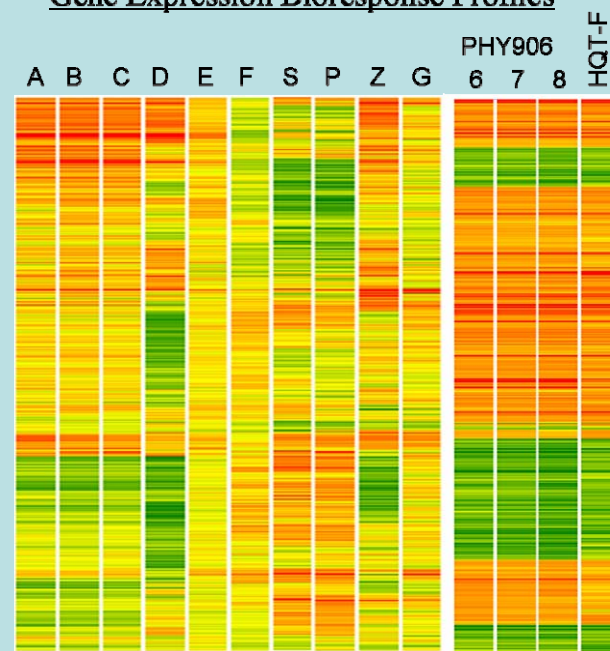
Batch 6, 7, 8 : clinical batches (GMP)

Batch 9: non-clinical batch (manufactured under GMP protocol)

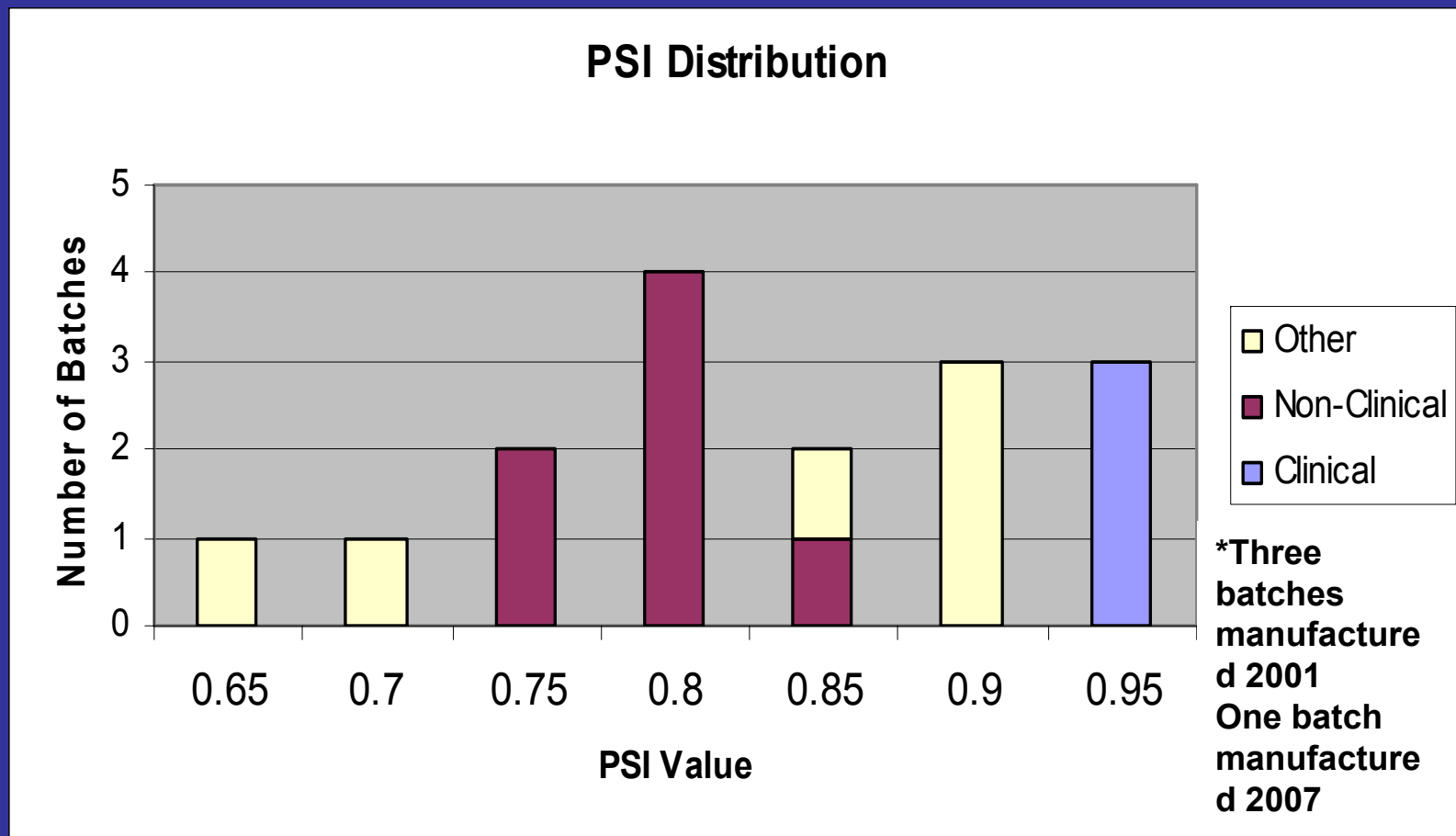
Batch F: non-clinical batch (non-GMP protocol)

Provided by PhytoCeutica Inc. (A Yale University Sponsored Company)

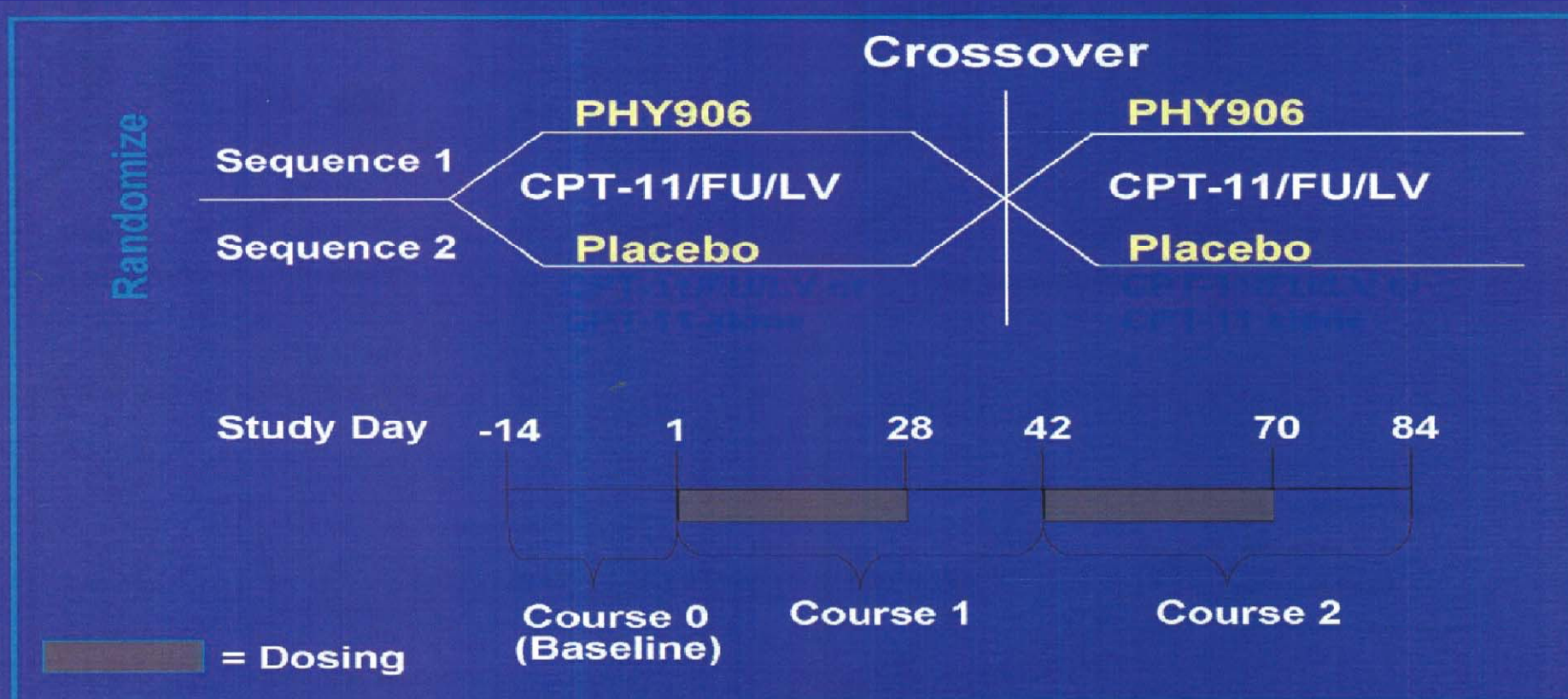
Gene Expression Bioresponse Profiles



PSI Values of Chemical Fingerprint Analysis of 15 Different Batches



A Phase I/IIA Double-Blind, Randomized Study of PHY906 as a Modulator of Irinotecan-Based IFL Chemotherapy in Patients with Advanced Colorectal Cancer



Phase I PHY906 Trial: Grade 3/4 Toxicity

Non-Hematologic Toxicities	CPT-11/FU/LV PHY906	CPT-11/FU/LV Placebo
Diarrhea	0%	31%
Vomiting	0%	15%
Nausea	7%	13%
Fatigue	0%	30%

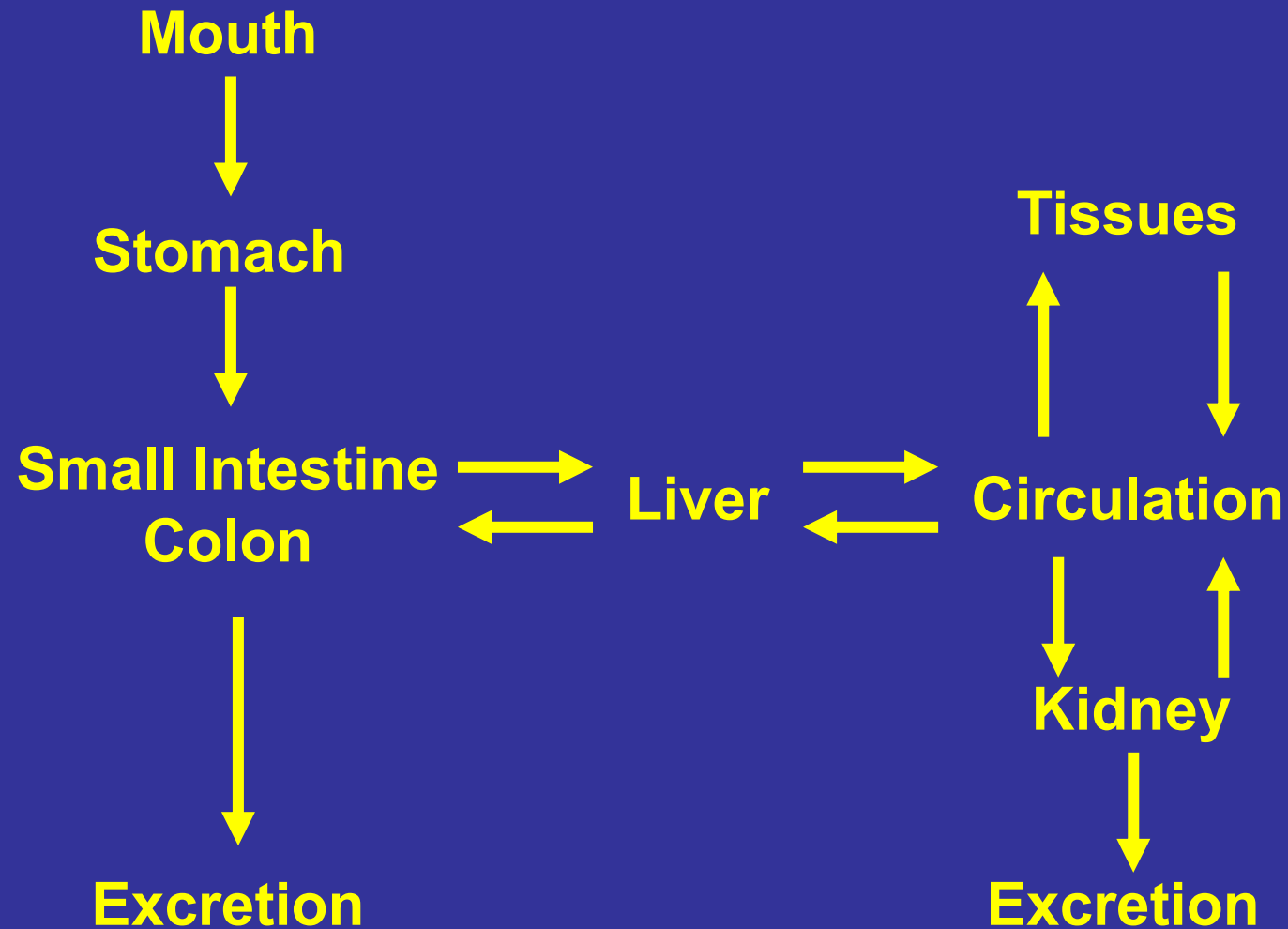
Phase I/II Study of PHY906 + Irinotecan in mCRC

**mCRC
previously treated
by chemotherapy
(2nd-line setting)**

Irinotecan + PHY906

**PIs: Wasif Saif, M.D.
Edward Chu, M.D.**

Passage of Drug Post Oral administration



Different tissues could expose to different chemicals by giving PHY906 orally

Compound	Herb	PHY906 extract	YCC treatment PHY906	mice plasma	patient plasma
Baicalein	S	+	++	-	-
Baicalin	S	+	-	+	+
Baicalin isomer	S	-	-	+	+
Wogonin	S	+	++	-	+
Wogonoside	S	+	-	+	+
Wogonoside isomer	S	-	-	+	+
Wogonin-gluA-gluA	S	-	-	+	+
Paeoniflorin	P	+	+	+	-
Glycyrrhizic acid	G	+	+	+	+
Licorice saponin E2	G	+	+	-	-
Liquiritigenin-gluA	G	-	-	+	+

Principles of Combined Usage of Herbs in TCM Formula

- **Imperial Herb** (君)
The chief herb (main ingredient) of a formula; toxic and nontoxic
- **Ministerial Herb** (臣)
Ancillary to the imperial herb, augments and promotes the action of the main ingredient
- **Assistant Herb** (佐)
Reduces side effects of the chief herb
- **Servant Herb** (使)
Harmonizes or coordinates the actions of the other herbs

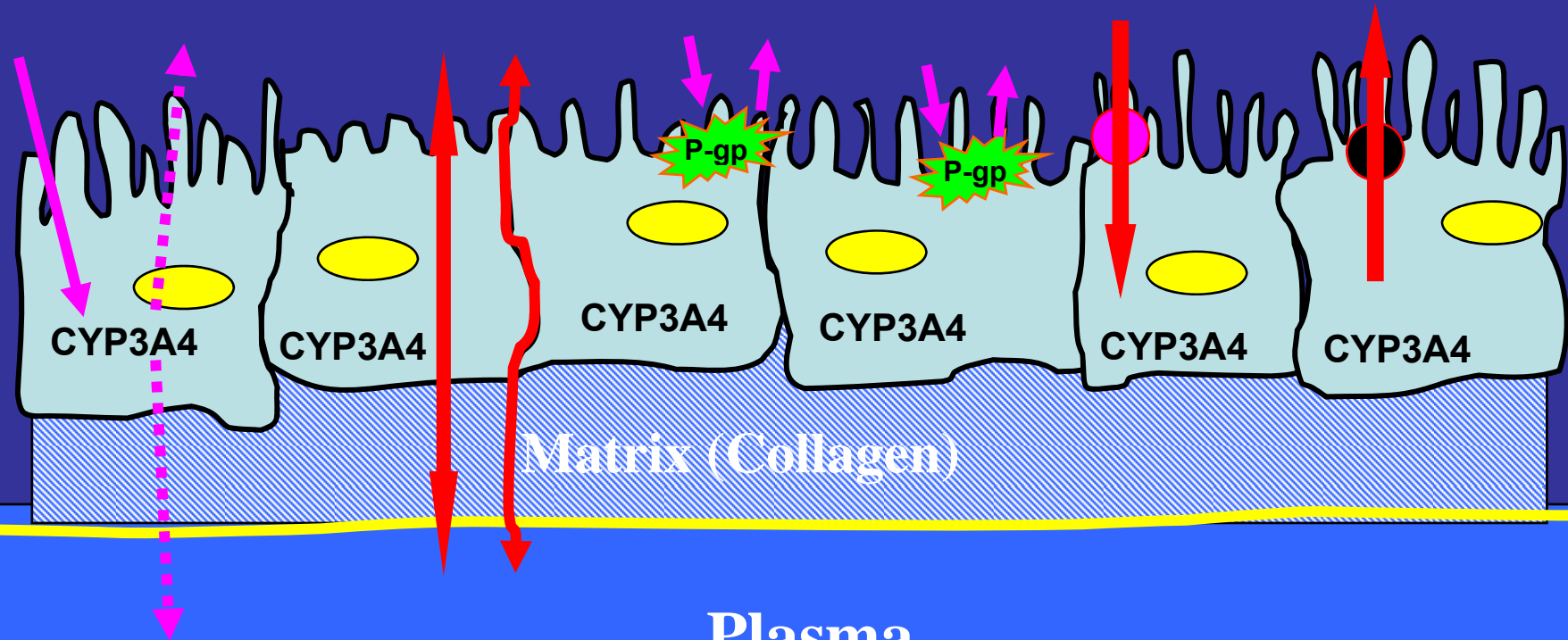
Caco-2 Model for Intestinal Permeability

Apical

Intestine Lumen

Passive Diffusion

Active Transport



Basolateral

Mechanisms of Herb Interaction of PHY906 for Absorption of Phytochemicals into Blood Stream

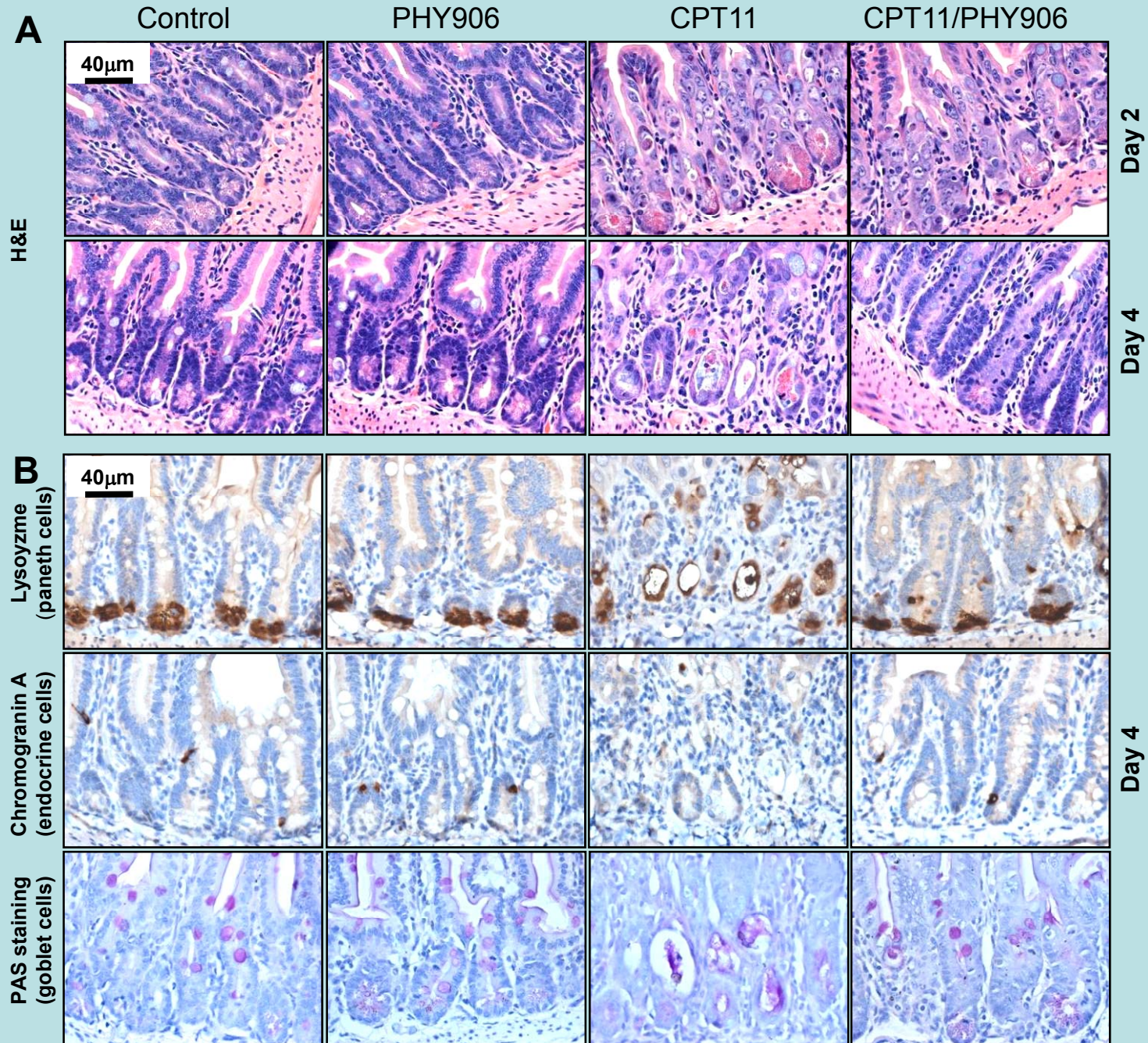
Inhibition of multiple drug resistant protein by Baicalein of Phy906, leading to the increase of oral uptake of certain chemicals.

Inhibition of CYP3A4, a predominant drug metabolic enzyme in the intestine, by chemicals from three of four herbs leading to the increase of oral uptake of certain chemicals.

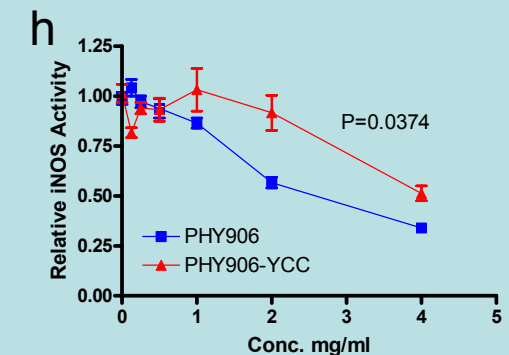
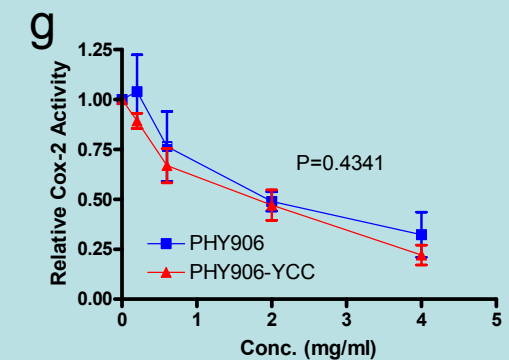
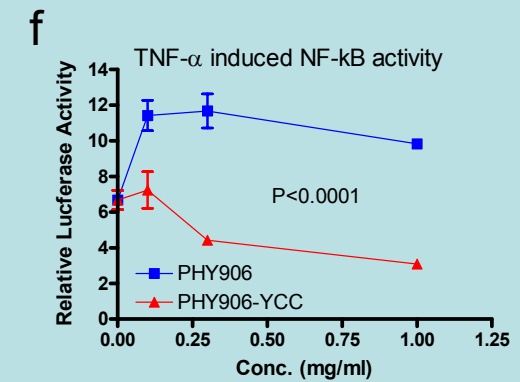
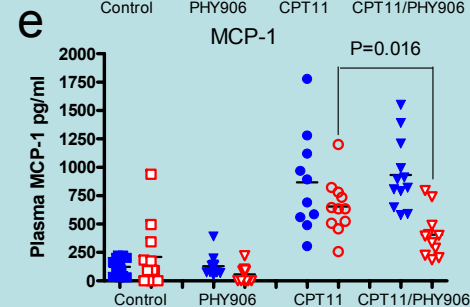
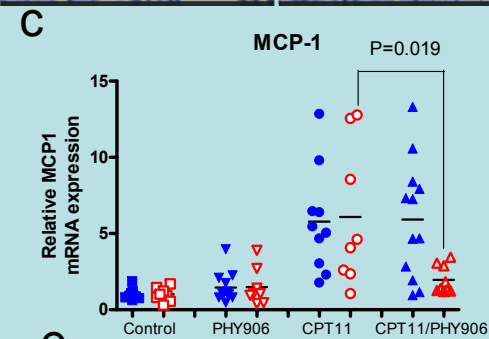
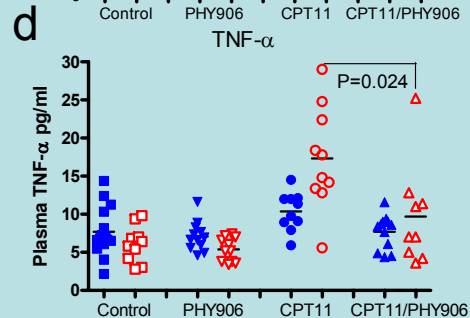
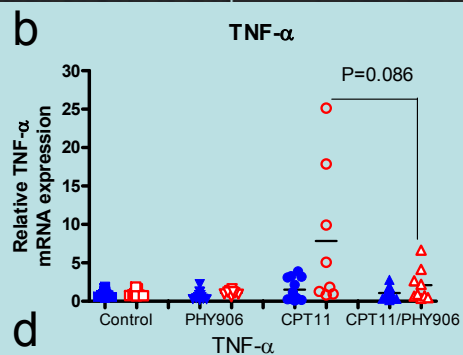
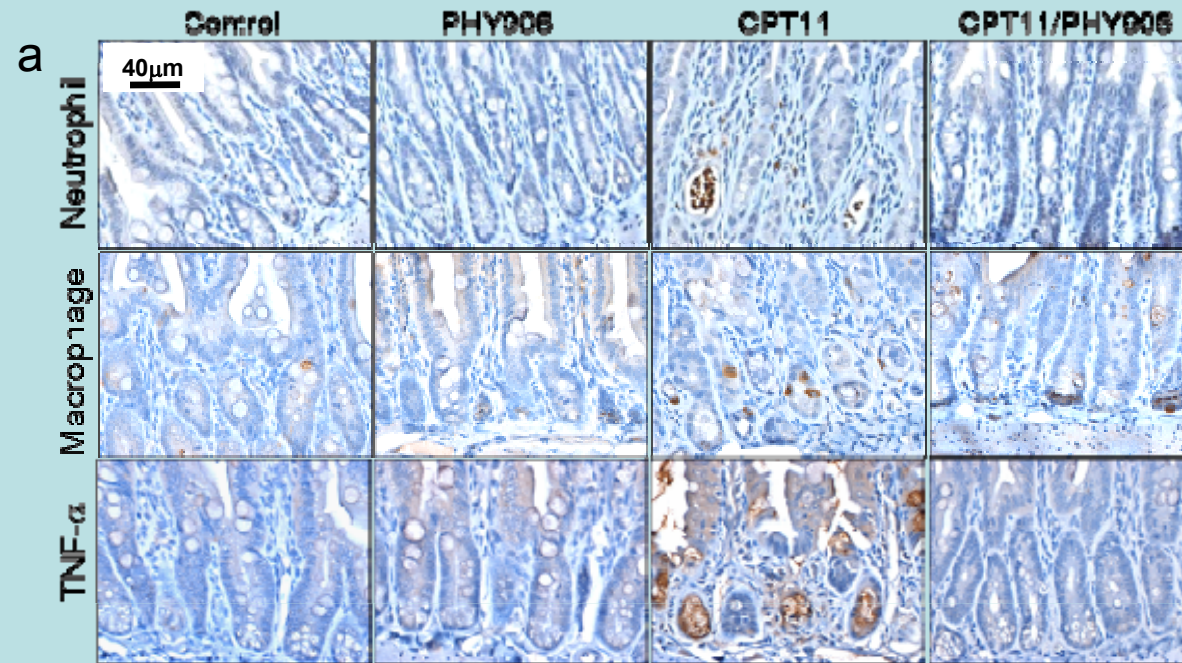
Inhibition of microfloral β -glucuronidase & glucosidase

Stabilization and/or improvement of modification of solubility of certain chemicals.

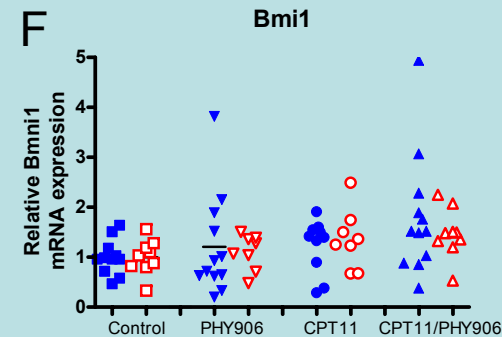
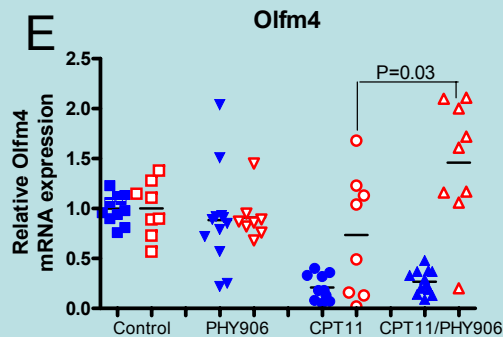
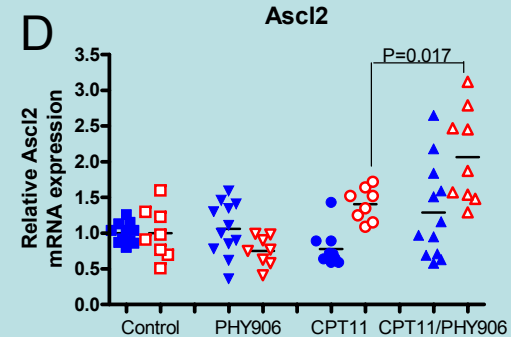
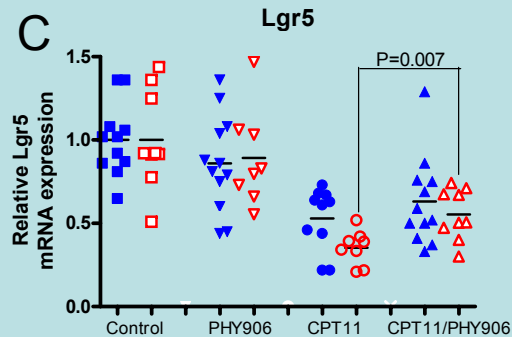
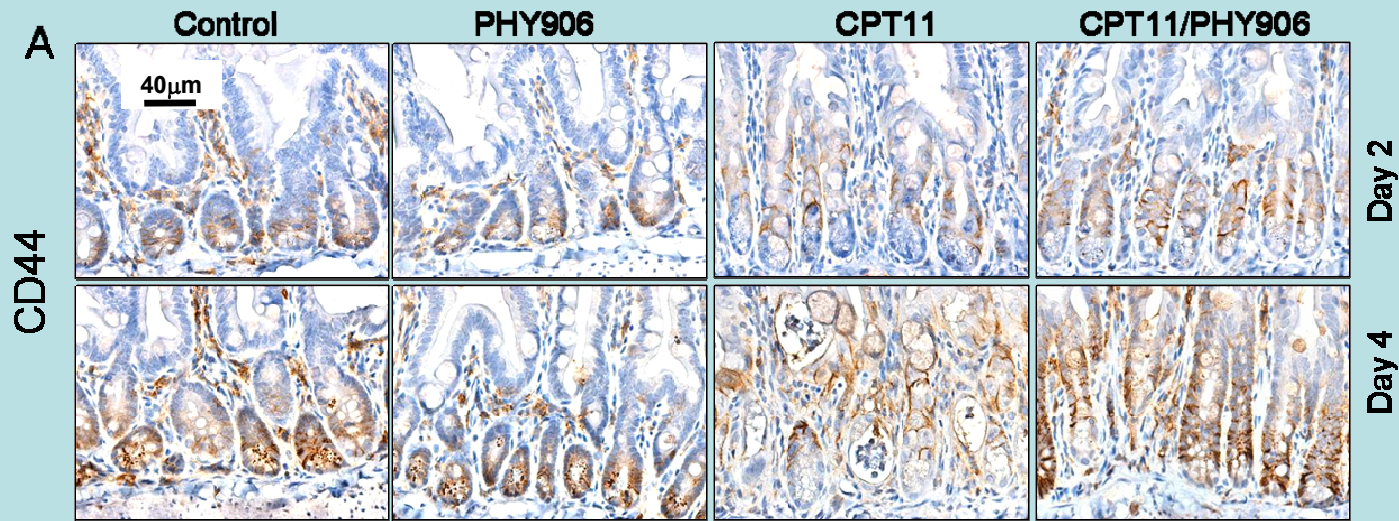
PHY906 promoted the recovery of the intestinal damage caused by CPT-11



PHY906 could decrease CPT11 induced inflammation by inhibiting NF- κ B, iNOS, COX2

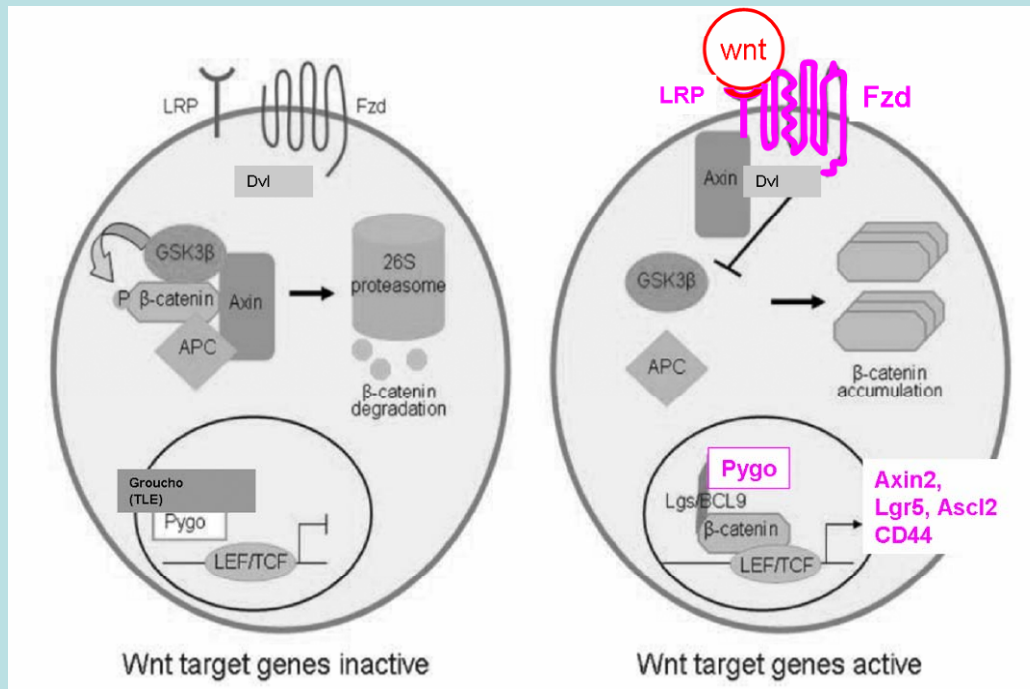
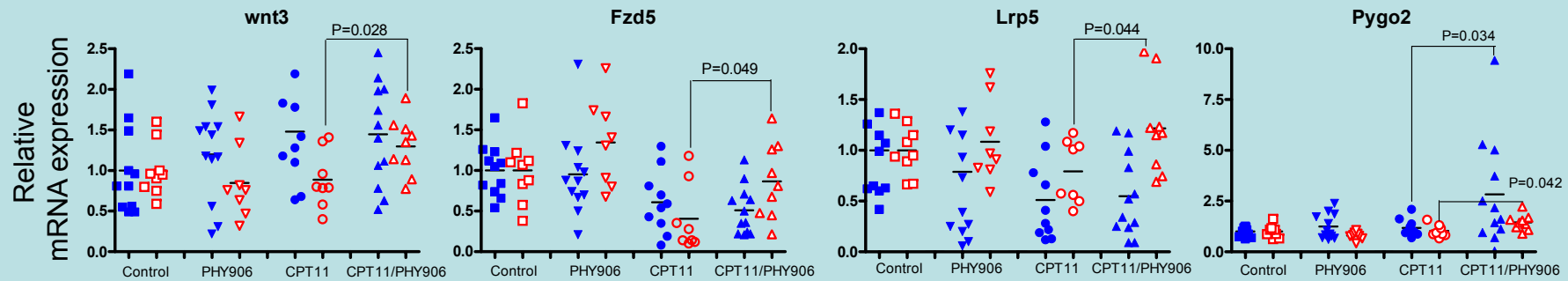


PHY906 Had Positive Impact On The Expressions Of The Intestinal Progenitor Cell/Stem Cell Markers After CPT11 Treatment.

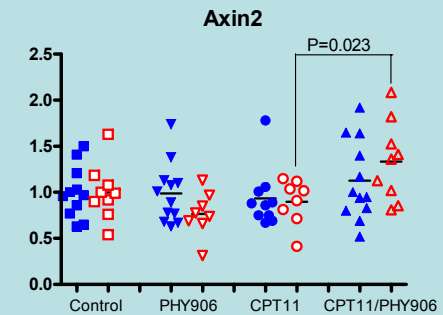


Blue Symbol = Day2
Red Symbol = Day4

PHY906 Increased Expression Of Wnt Signaling Components After CPT11 Treatment



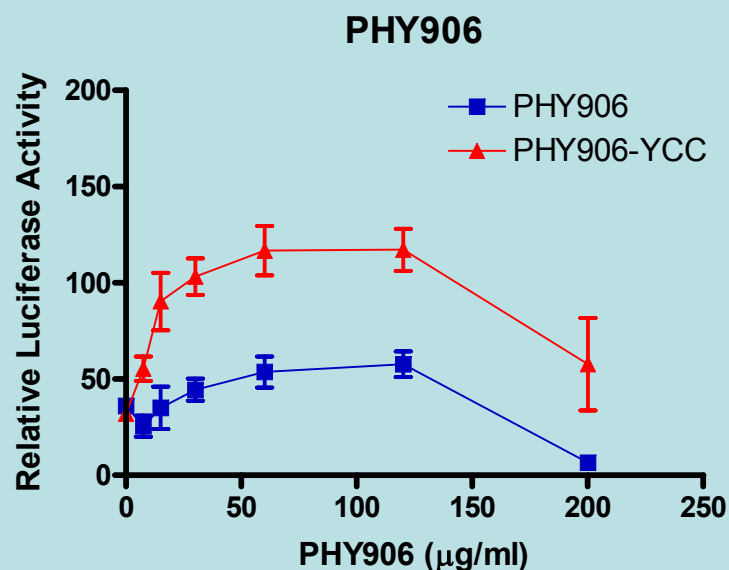
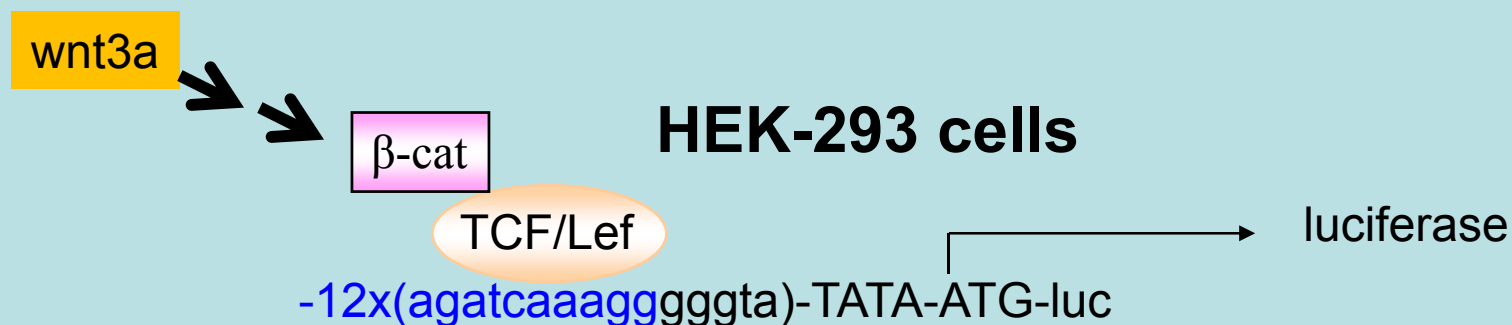
Modify from Jessen S, Gu B, Dai X. Bioessays. 2008 May;30(5):448-56



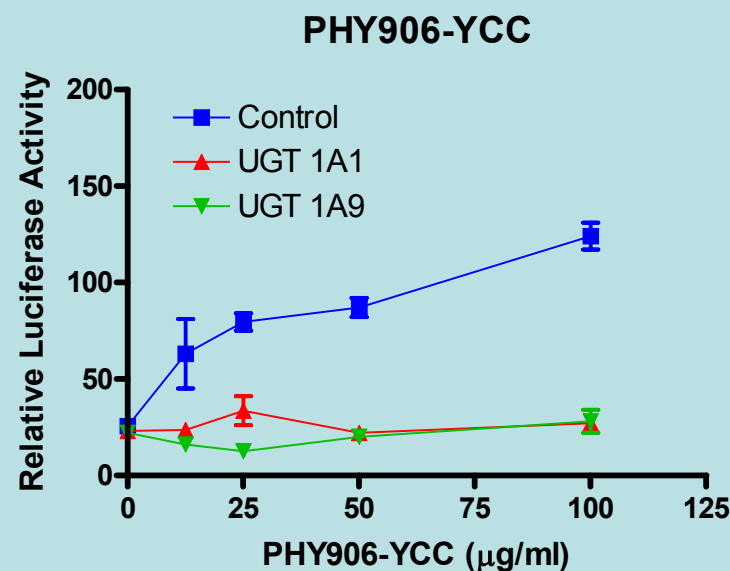
Blue Symbol = Day2
Red Symbol = Day4

PHY906 had no impact on, β -catenin, Dvl, Gsk3b, Apc, Tcf4, Tle, Bcl9, Brg1, Cby1, cdc73

β -glucuronidase Treated PHY906 Could Potentiate Wnt3a Activity In Wnt/B-catenin Signaling In HEK-293 Cells.

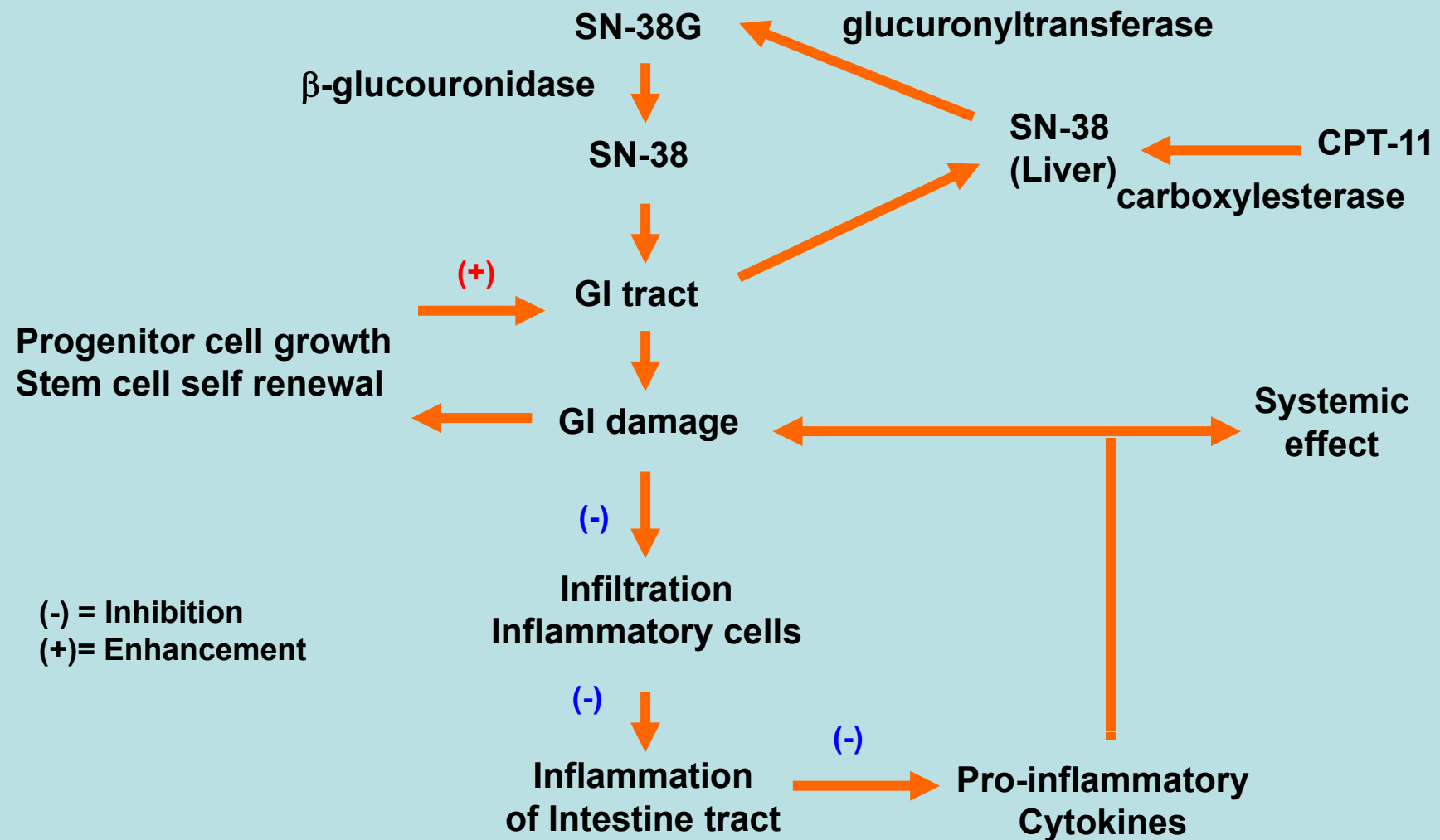


YCC
(HCl treatment and β -glucuronidase treatment)

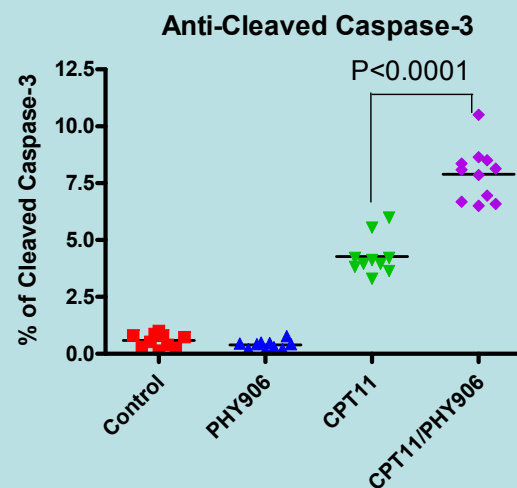
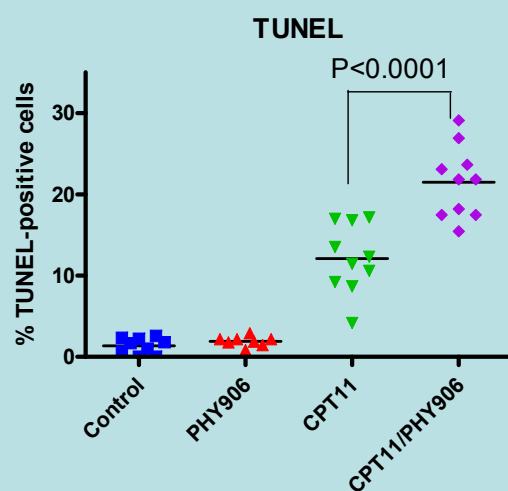
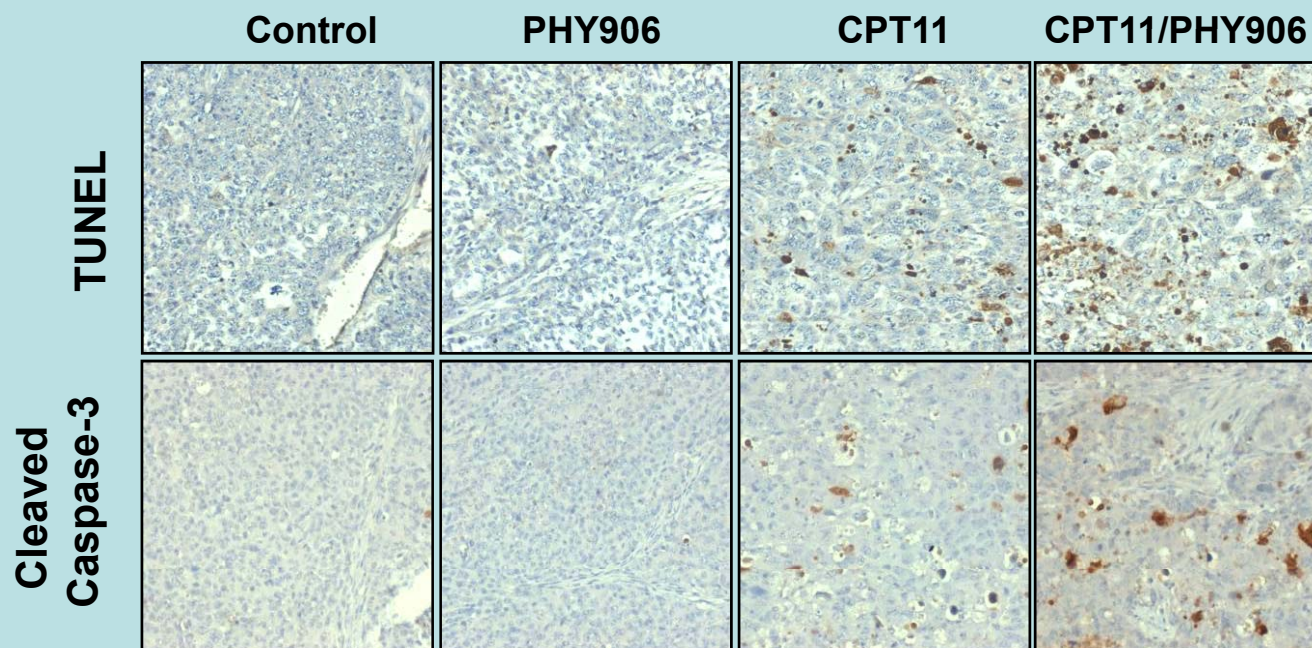


UGT
(UDP-glucuronosyltransferases)

Effect of PHY906 on CPT-11 GI Injury

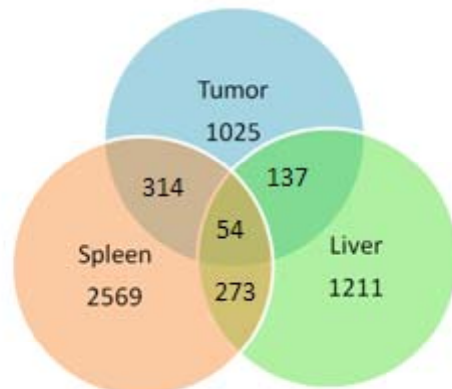


Impact of PHY906 and/or CPT-11 treatment on apoptosis of Colon38 tumor

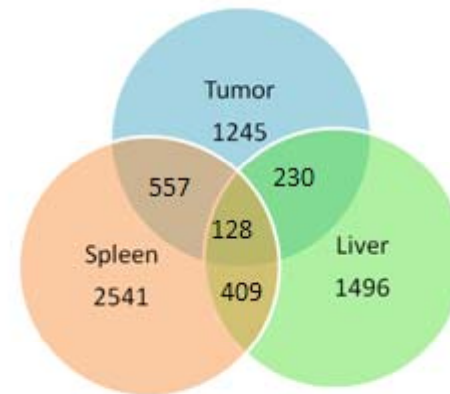


IMPACTS OF PHY906, IRINOTECAN AND THEIR COMBINATION ON GENE EXPRESSION ARE DIFFERENT IN DIFFERENT TISSUES

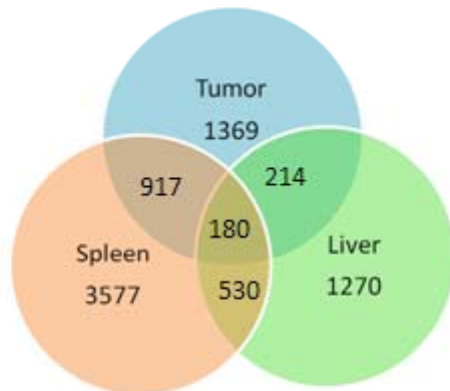
PHY-906 vs. PBS $p < 0.05$



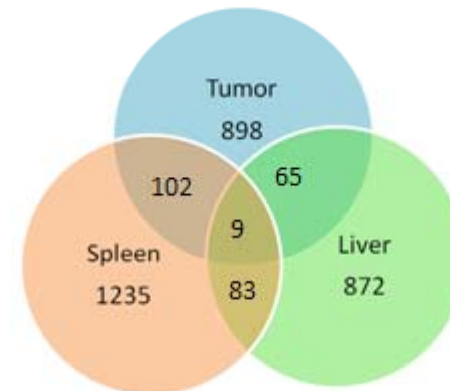
CPT vs. PBS $p < 0.05$



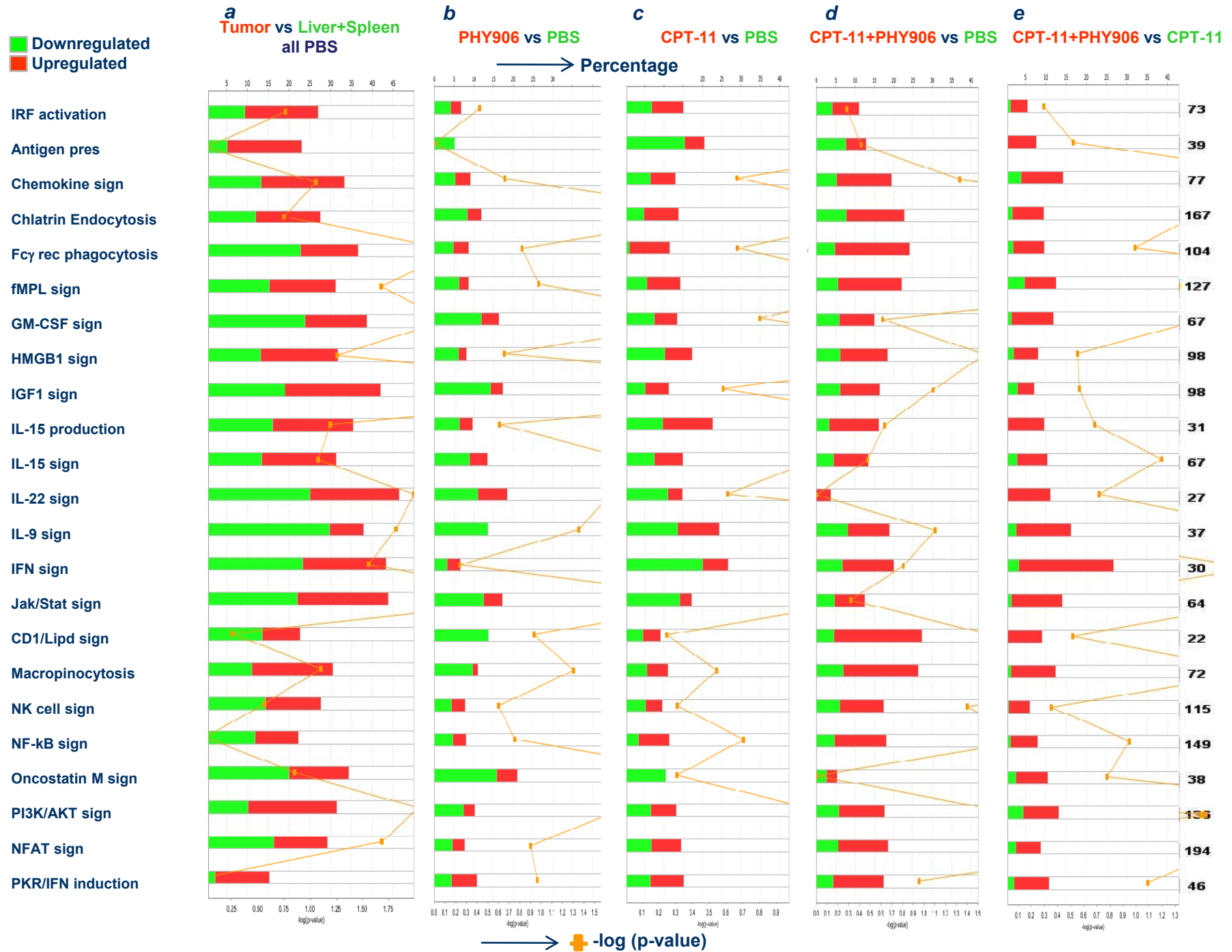
CPT+PHY906 vs. PBS $p < 0.05$

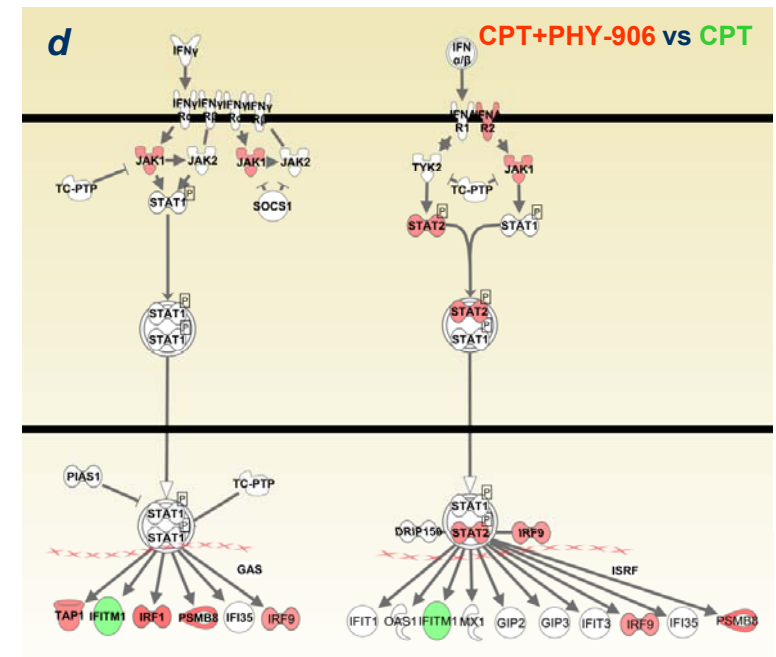
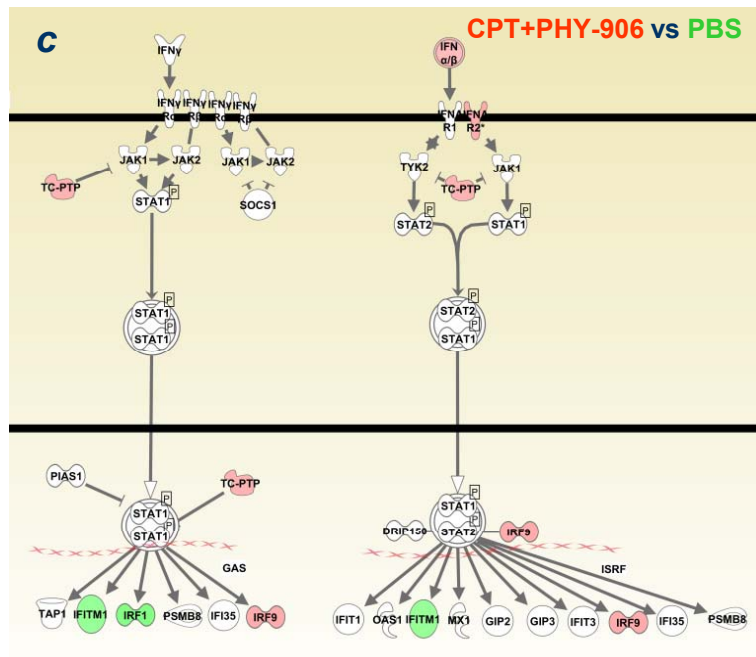
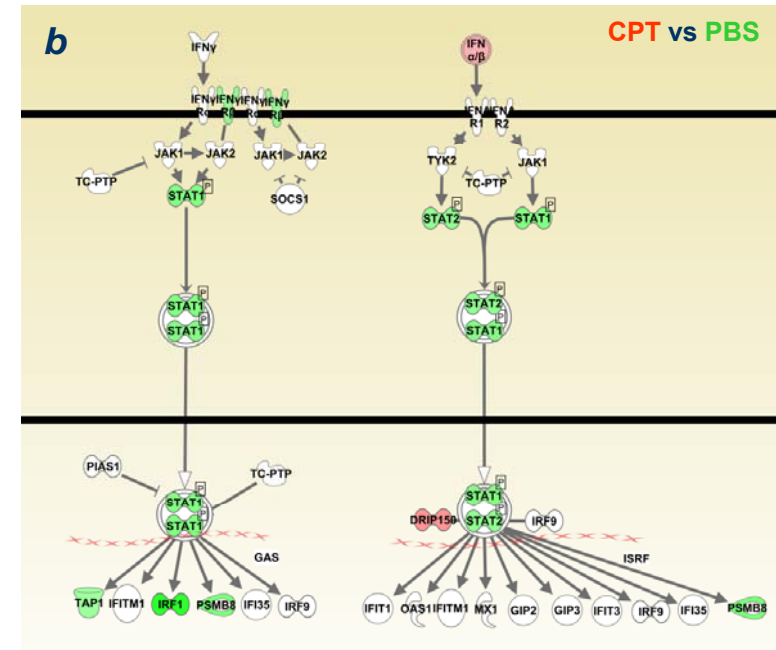
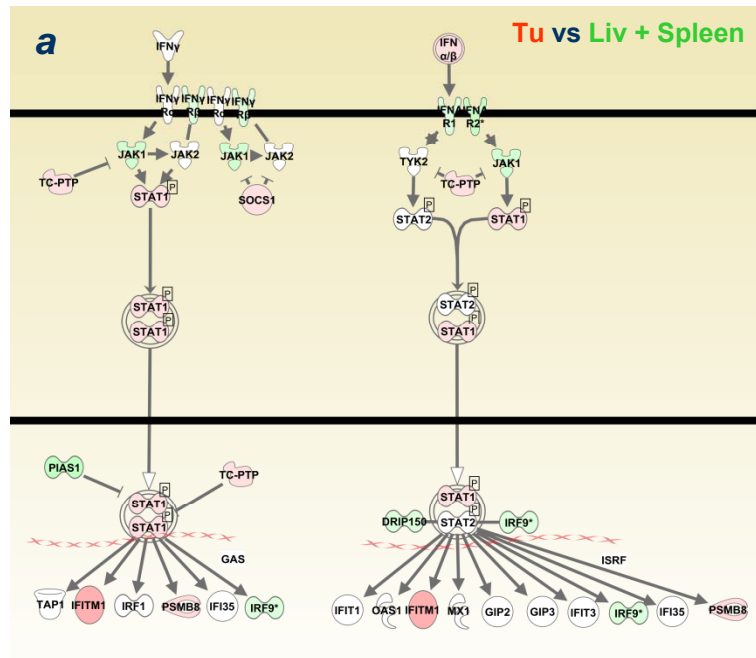


CPT+PHY906 vs. CPT $p < 0.05$

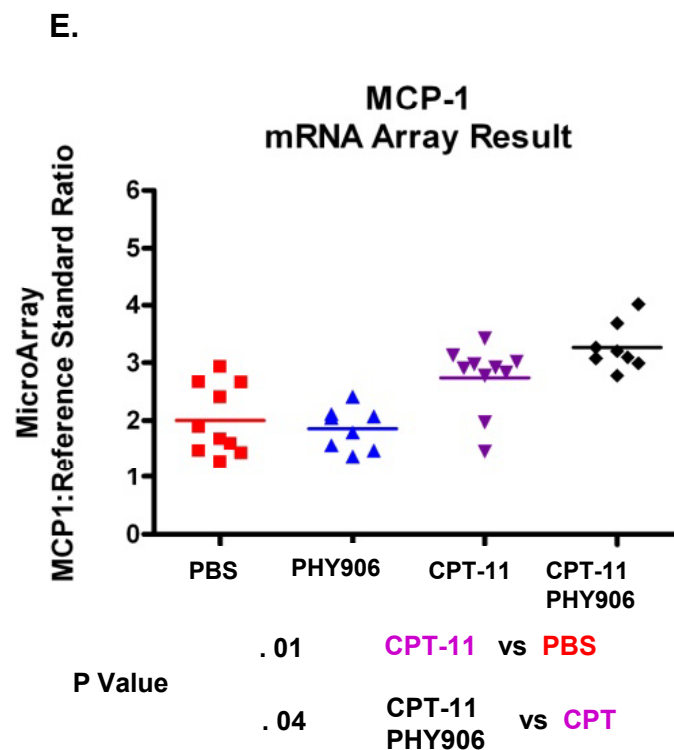
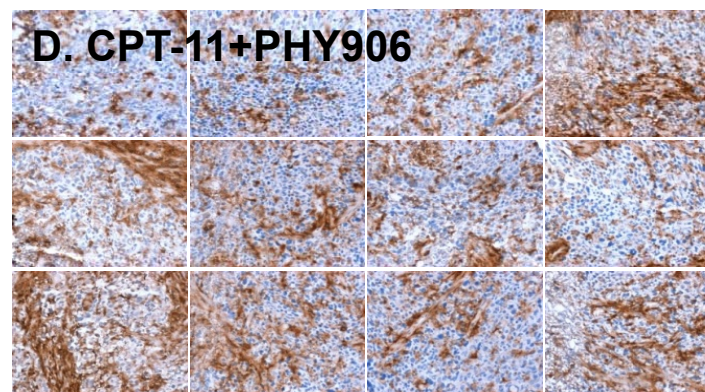
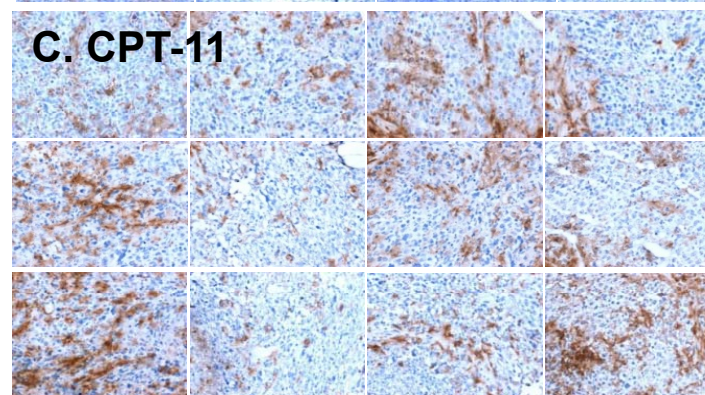
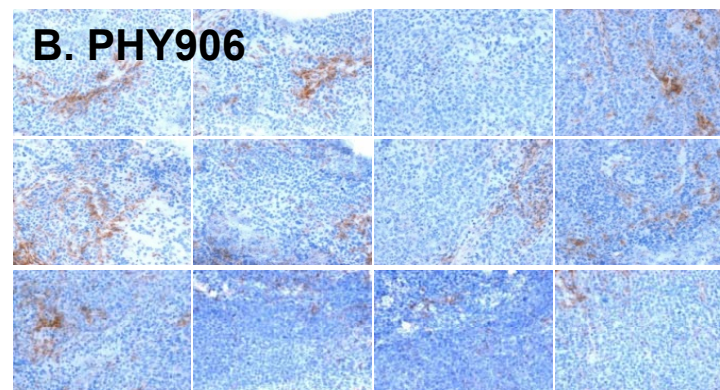
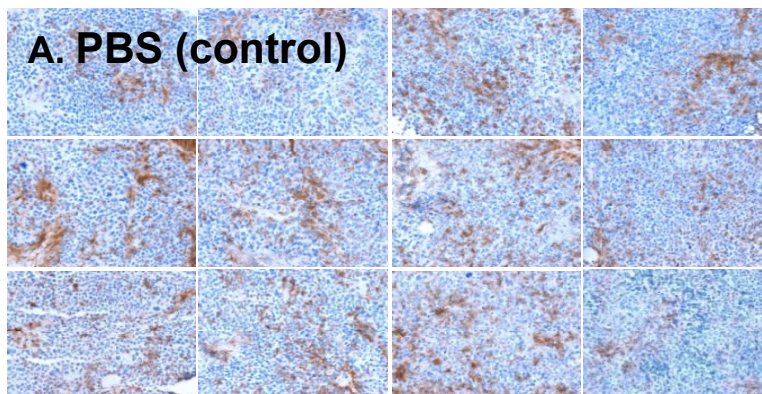


■ Downregulated
■ Upregulated





Impact of CPT-11 and /or PHY906 Treatments on Macrophage Infiltration in Tumor Tissue



Mechanisms of PHY906 in Enhancing CPT-11 Antitumor Actions

- Increasing Apoptosis
- Increase Macrophage Infiltration
- Change of Chronic State of Inflammation in Tumor Microenvironment to Acute State.
- Etc.

PHY906

MODERN USE (2000 A.D.) : AN ADJUVANT FOR CANCER CHEMOTHERAPY

- Decrease of non-hematological side effects
 - Enhancement of antitumor activity of chemotherapeutic agents
-

Chemotherapeutic Agent

- CPT-11
- Capecitabine (5-FU Prodrug)
- CPT-11/5-FU/LV
- VP-16
- L-OddC
- Gemcitabine
- Oxaliplatin
- Sorafenib
- Taxol
- Sunitinib

Indication

- Colorectal Cancer
- Colorectal and Liver Cancer
- Colorectal Cancer
- Lung Cancer
- Leukemia, Pancreatic Cancer
- Pancreatic Cancer
- Colorectal Cancer
- Renal and Liver Cancer
- Lung, Breast and Ovarian Cancer
- Renal and Liver Cancer

* U.S. Patent 7,025,993 B2 ; IND: 62,627

Comparison of Patient Characteristics, Outcome and Selected Grade 3 or 4 Drug-Related Side Effects Between Sorafenib and PHY906+Capecitabine Studies

Patient Characteristics, outcome and side effects	Sorafenib Phase III	Sorafenib Phase III	PHY906 (600/800 mg) + Capecitabine ⁽¹⁾	PHY906 (600/800 mg) + Capecitabine ⁽²⁾
# of Patients	299	150	27	20
% of Child-Pugh A	95	97	74	100
% of HBV	19	71	37	50
% of HCV	29	11	26	20
Study Sites (%)	EU/US (88/9)	Asia (100)	US (100)	US (100)
Response % (PR/MR/SD)	2.3 /0/ 71	3/ 0 / 54	0/ 14.8/ 51.9	0 / 0 /65
Median TTP (months)	5.5	2.8	3.4	2.8
Median OS (Months)	10.7 ⁽³⁾	6.5 ⁽⁴⁾	9.2	10.9
12 Month Survival Rate (%)	44	28	41	50
Grade 3/ 4 drug-related Toxicities (%)				
Hand-Foot Skin Reaction	8	11	3.7	0
Diarrhea	8	6	0	0
Fatigue	4	3	0	0
hypertension	2	2	0	0
Abdominal pain	2	NA	0	0
Hypophosphatemia	11	NA	0	0
Thrombocytopenia	4	NA	0	0

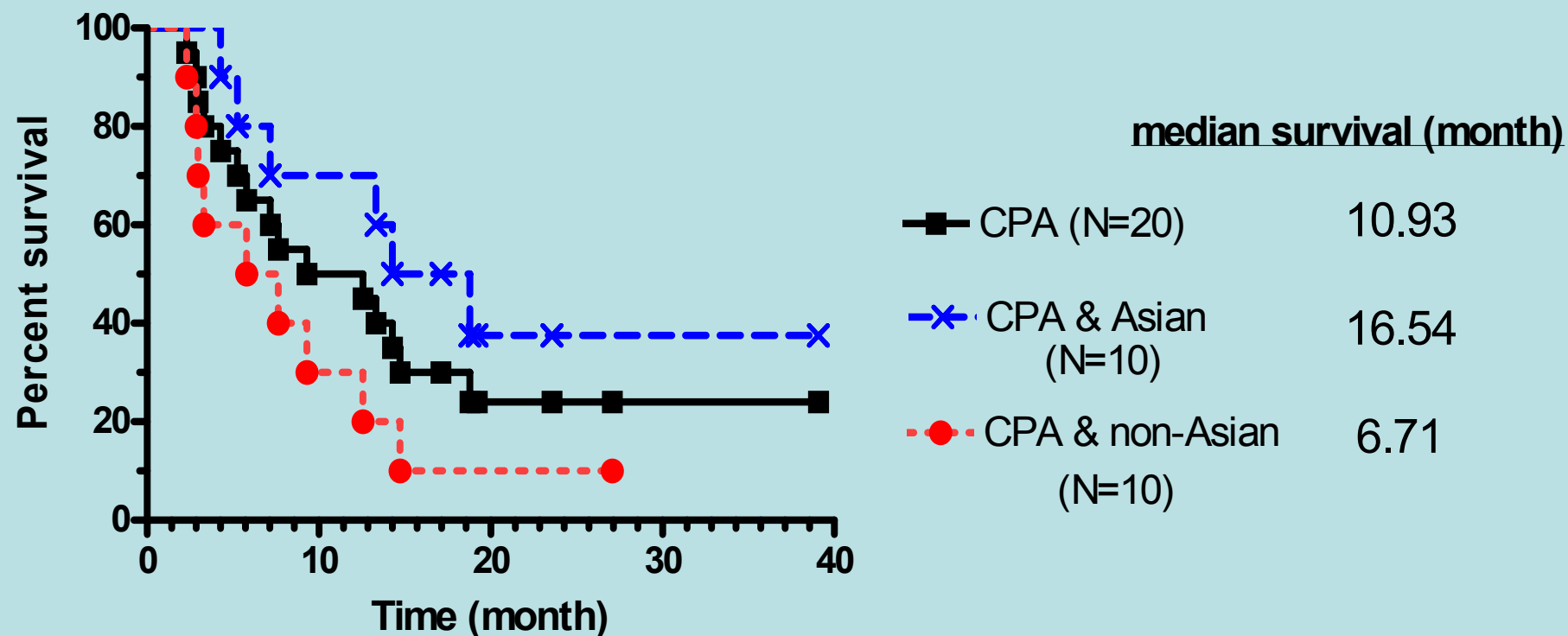
1. Phase II patients treated with either 600 mg or 800 mg of PHY906 together with capecitabine (750 mg/m²)

2. Subset of (1). All the patients in this group were classified as Child-Pugh A.

3. Median OS for the placebo group in the US/EU trial was 7.9 months. *N Engl J Med.* 359:4, 378-390 (2008).

4. Median OS for the placebo group in the Asia trial was 4.2 months. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 4509).

Kaplan-Meier Survival Curve of Asian vs non-Asian Patients with Child-Pugh A Treated with PHY906 (600+800 mg) +Capecitabine(N=20)



Medium OS for placebo group in US/EU was 7.9 months and in Asia it was 4.2 months (historically)

US Sites Only

New Paradigm for Future Medicine

- Multiple targets
- Polychemical medicine instead of one chemical medicine with system biology approach in mind

Two approaches to polychemical medicine

- Conventional “step by step”
- Revisiting history as the basis of reinventing medicine

Basic Study of Herbal Medicine

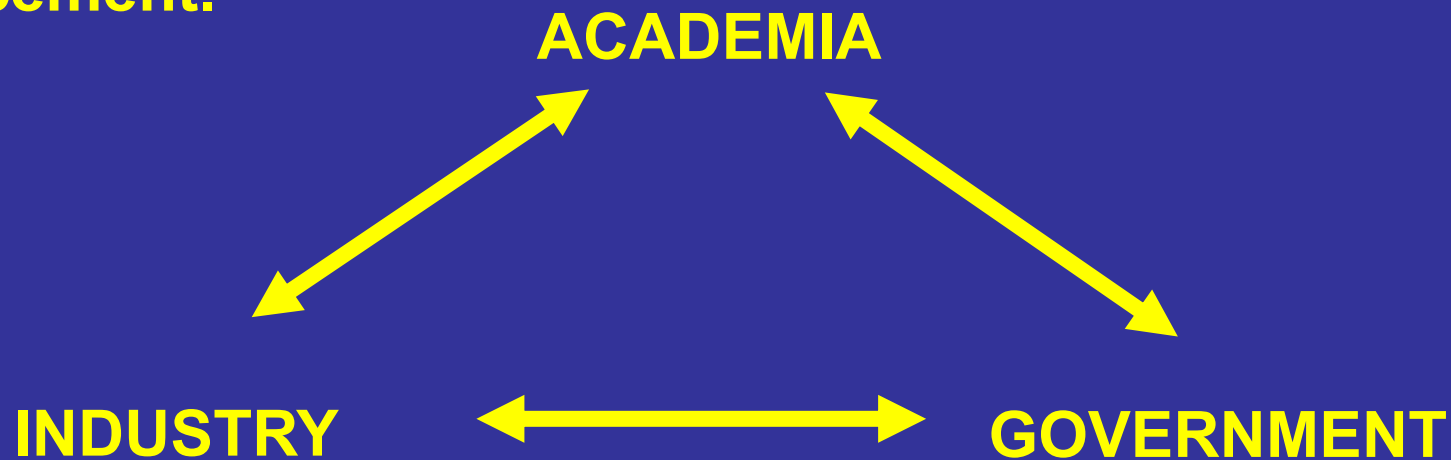
- Rigorous preclinical and clinical studies
- Multiplex analysis
- Systems biology approach
- Information driven
- Data mining

“The Technologies Are Here Today”

The discovery using approaches outlined for herbal medicine could facilitate the single targeted orientation approach in Western Medicine

“Collaboration is Critical”

To globalize Chinese and herbal medicine, close collaboration among academia, industry and government is needed. Given the limitation of resource (human, technology and financial) international collaboration is critical for the advancement.



**-INTRA-REGIONAL COLLABORATION
-INTER-REGIONAL COLLABORATION**

Consortium for Globalization of Chinese Medicine (CGCM)

Global
Non-profit
Non-discriminatory
Non-political

Founded on December 15, 2003

- 126 Institutional Members
- 10 Industrial Affiliate Members

www.tcmedicine.org

Mission

To advance the field of **Chinese Herbal Medicine** to benefit human kind through joint efforts of worldwide academia, industry and regulatory agencies in the spirit of **contributions and sharing**.

Platform Technologies

- Quality Control
 - Informatics
 - Clinical
 - Herbal Resource
 - Molecular Mechanisms & Active Compounds
-
- Intellectual Properties
 - Education
 - Industrial Liaison

The Evolution of Medicine

Traditional Chinese Medicine (TCM)



Modern Chinese Medicine (MCM)
(China, Japan, Korea, etc)



Globalized Chinese Medicine (GCM)



Future New Medicine (NM) ←← **Other Folk Medicine (FM)**
(Tibet, India, Europe, Africa, etc)



Current Mainstream Medicine (CMM)



Western Medicine (WM)

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- Dr. Cheng is a Fellow of the National Foundation for Cancer Research.
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- The input of Professor E. Chu of Yale University is critical for the clinical design of studies of PHY906
- Part of the work is in collaboration with Dr. Marincola (HHH/NCI) and Dr. Zhao (Yale)

Conflict of Interest

- I am the scientific founder of PhytoCeutica, Inc and a share holder.

I am the co-inventor of the use of PHY906 as adjuvant therapy for cancer chemotherapy as well as some of the platform technologies. The patents are owned by Yale University and licensed to PhytoCeutica, Inc. I will receive some royalties from Yale University based on the license agreement.