

# 腸易激綜合征的治疗策略

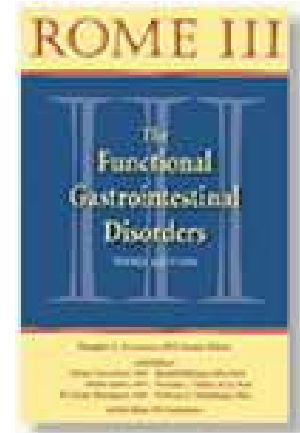
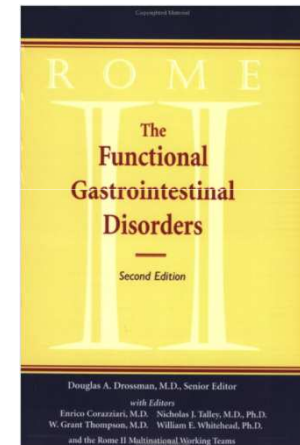


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# 腸易激綜合征 (Irritable bowel syndrome )

- Symptoms of recurrent abdominal pain or discomfort and a marked change in bowel habit for at least six months, with symptoms experienced on at least three days of at least three months. Two or more of the following must apply:
  - Pain is relieved by a bowel movement
  - Onset of pain is related to a change in frequency of stool
  - Onset of pain is related to a change in the appearance of stool

## Manning Criteria



# 病理機制

Visceral Hypersensitivity  
內脏高敏感性

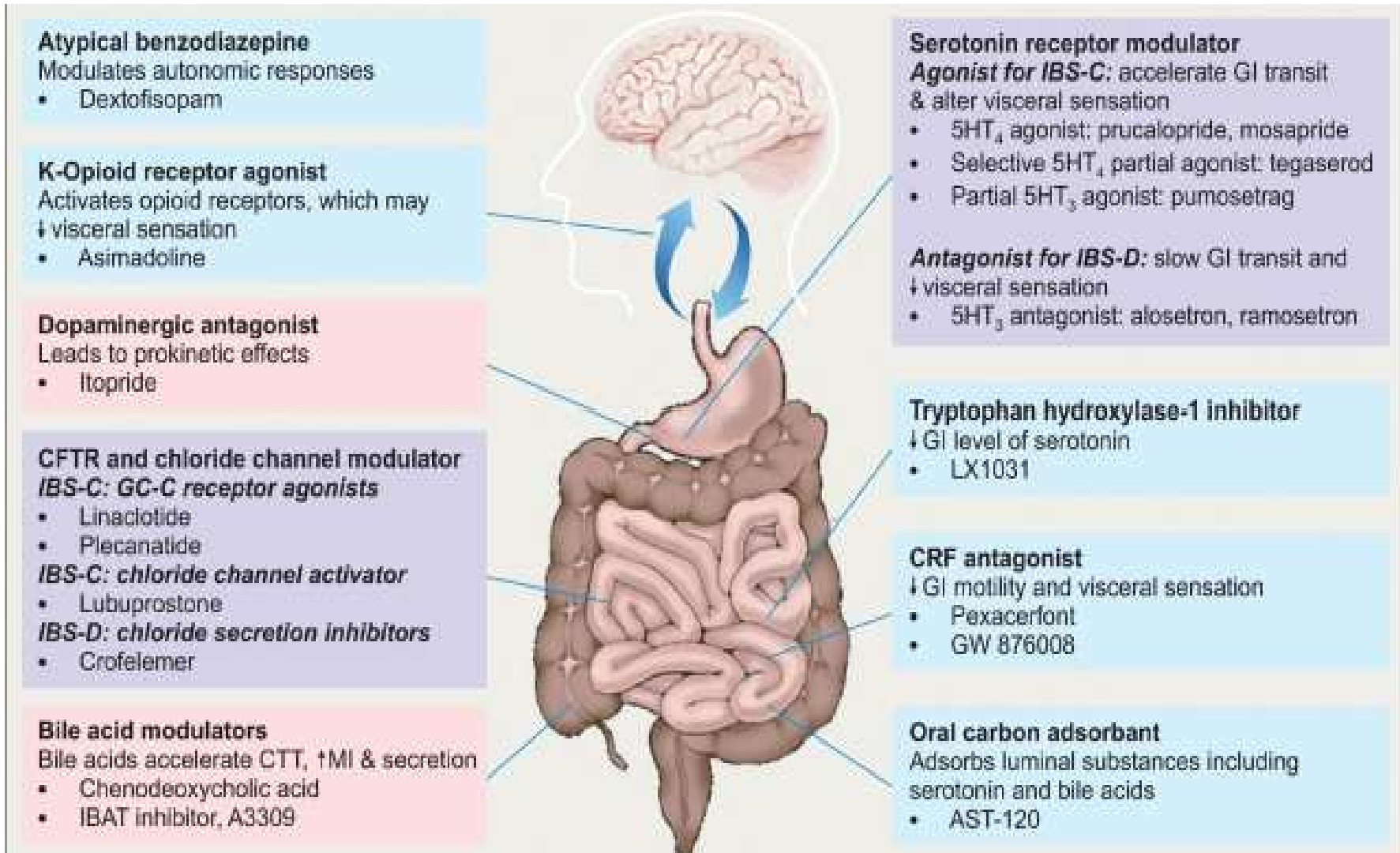
Abnormal Gut Motility and  
Secretory Disorders  
腸道蠕動異常及分泌紊亂

Autonomic Nervous System  
Dysfunction  
植物神經系統功能紊亂

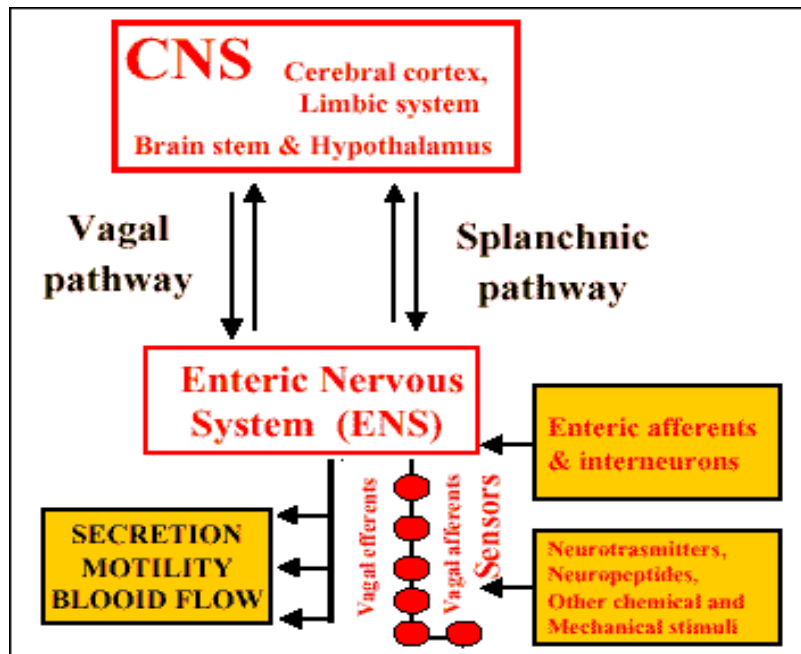
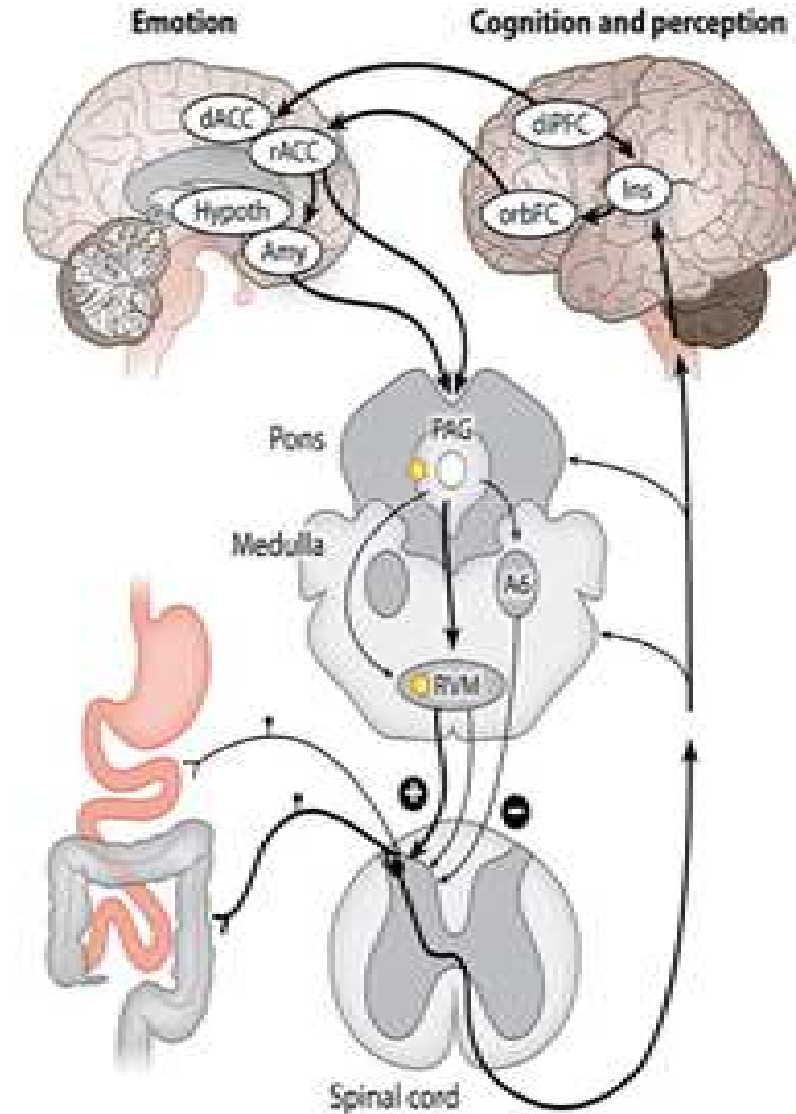
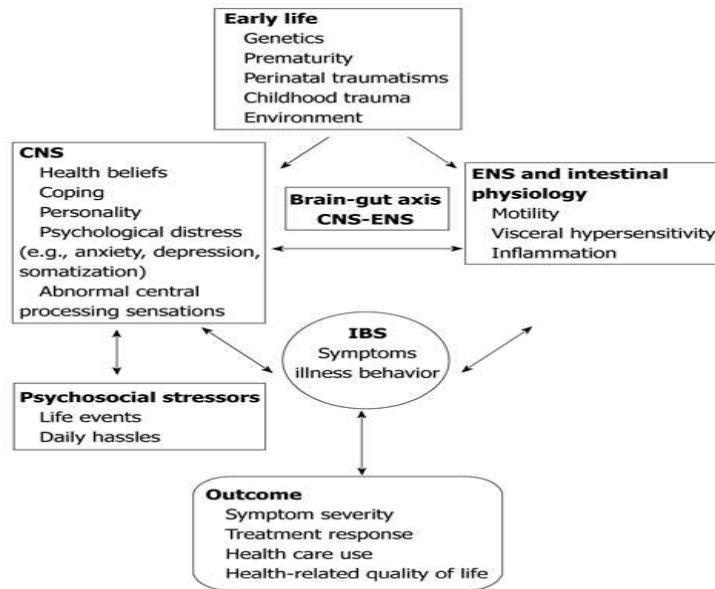
# 腸道菌群與腦腸軸的關係

The neural, immunological, endocrine and metabolic pathways by which the microbiota influences the brain, and the proposed brain-to-microbiota component of this axis. Putative mechanisms by which bacteria access the brain and influence behaviour include bacterial products that gain access to the brain via the bloodstream and the area postrema, via cytokine release from mucosal immune cells, via the release of gut hormones such as 5-hydroxytryptamine (5-HT) from enteroendocrine cells, or via afferent neural pathways, including the vagus nerve. Stress and emotions can influence the microbial composition of the gut through the release of stress hormones or sympathetic neurotransmitters that influence gut physiology and alter the habitat of the microbiota. Alternatively, host stress hormones such as noradrenaline might influence bacterial gene expression or signaling between bacteria, and this might change the microbial composition and activity of the microbiota.

# 以腸道為主要靶點的藥物治療



# 腸易激 + 腦易激 (Irritable bowel + irritable brain?)

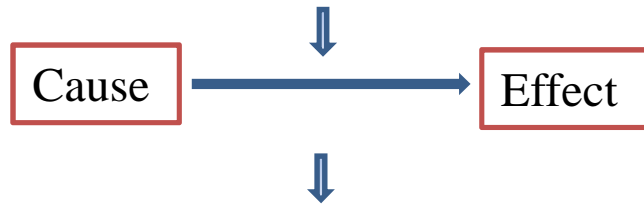


# 針對IBS的藥物治療及其效果

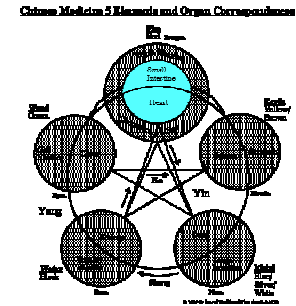
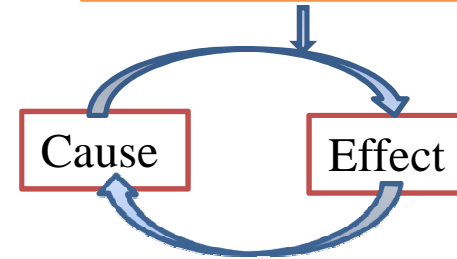
We found reasonable evidence to support the use of smooth-muscle relaxants for abdominal pain. In contrast, the benefits of bulking agents remain unproved despite a large number of trials. Loperamide seems to be effective for diarrhea. The potential efficacy of psychotropic agents should be confirmed in well-done, adequately powered trials. Newer agents, specifically 5-hydroxytryptamine–receptor antagonists, seem promising, but the amount of evidence to allow a definitive statement on their efficacy is insufficient at this time. Finally, the durability of treatment effects over longer intervals requires careful examination.

# 思維模式與藥物

Linear thinking model



Circle thinking model



**One Drug  
for One Target  
for One Disease**

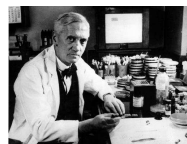


**One formula  
for multi-Targets  
for One Syndrome**

**Clear cause, with single  
target/pathway**

**New drug development**

**Bacteria-induced disease  
Peptic Ulcer**



**Chinese medicine system**

**3000+ years**

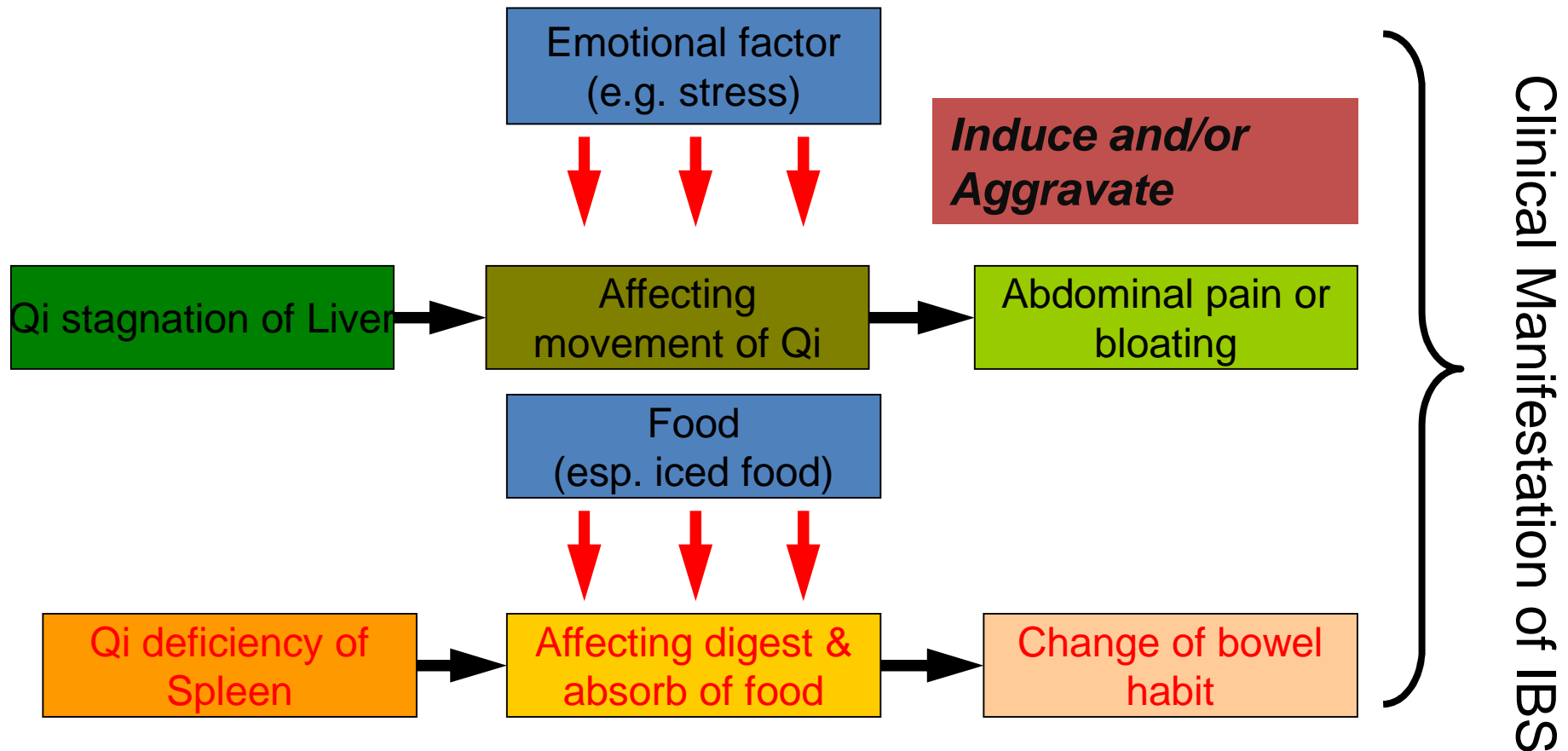
**100,000+ formulas**

**Syndrome-based approach**

**Personalized therapy**



# 系統思維下的中醫藥對**IBS**病機及治療的認識

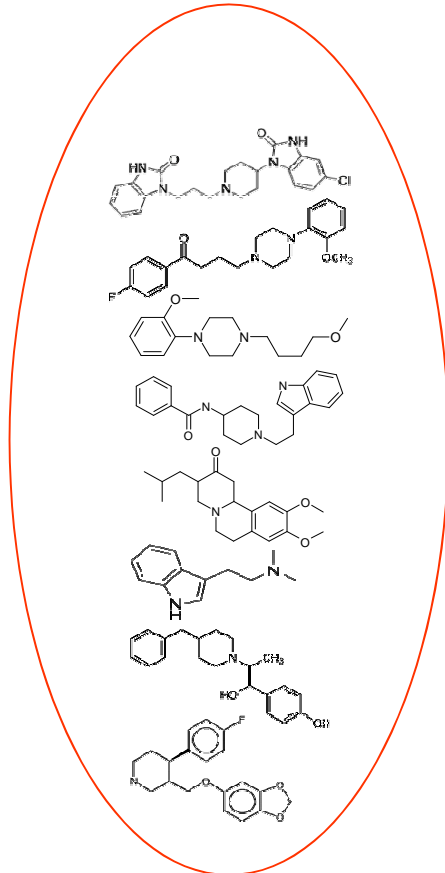


**Very importantly: Stagnation of Liver and Deficiency of Spleen are the key mechanism of IBS, not just for the abdominal pain, diarrhea or constipation, and also the major reason for IBS recurrence.**

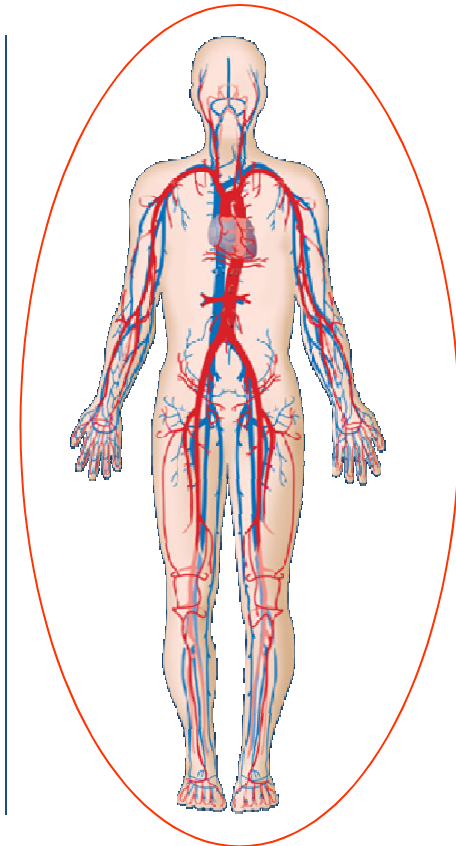
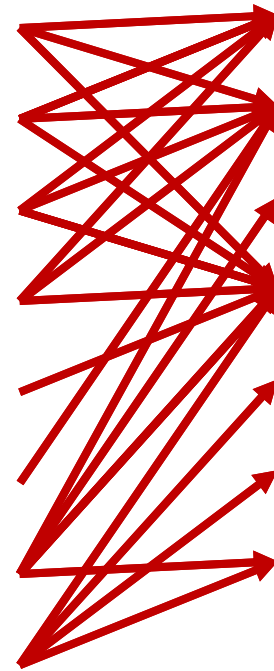
# 中藥的特征-是多系統、多靶點、多途徑！



**Chinese herbal formula**

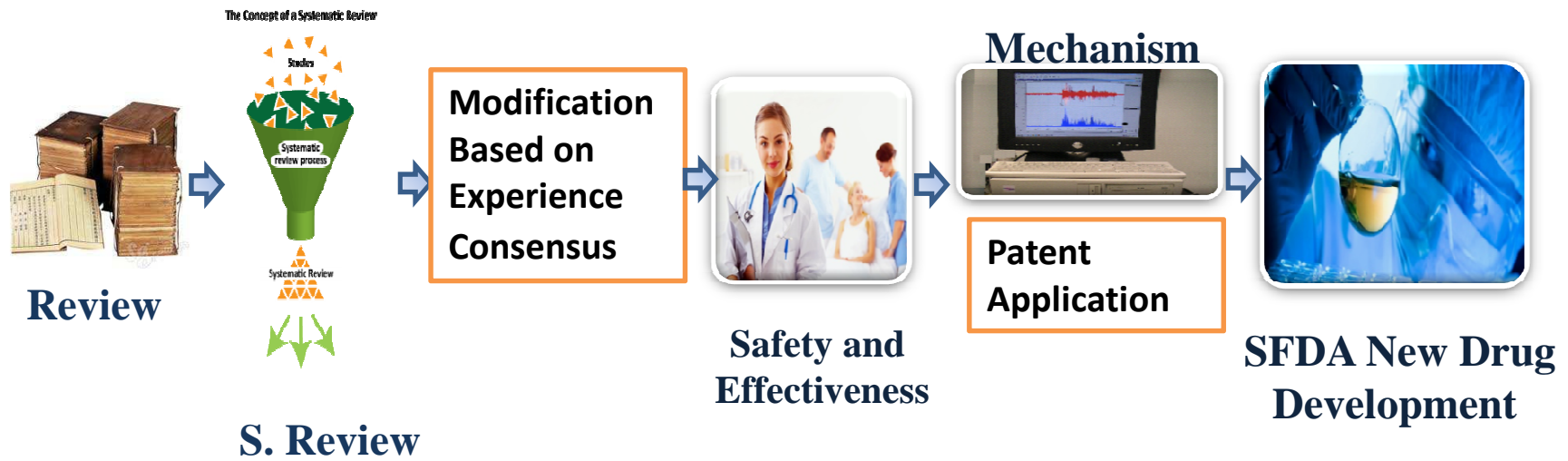


**Multi-components**



**Multi-targets**

# JCM16-02



# 系統評估 Systematic review

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1. 200+ classic formulas
2. Key—Important formula for painful diarrhea (IFPD)
3. Systematic review about IFPD effect for IBS patients-  
(Publication in J Altern and Complement)

## ○ Important Formula for Painful Diarrhea (痛瀉要方)

- Rhizoma Atractylodis Macrocephalae (Bai zhu/白朮)
- Radix Paeoniae Lactiflorae (Bai shao/白芍)
- Pericarpium Citri Reticulatae (Chen pi/陈皮)
- Radix Saposhnikoviae (Fang feng/防风)

Conclusion: There is evidence to indicate the potential usefulness of IFPD-A for IBS patients. The results were limited by the poor quality and heterogeneity of these studies. Further studies with carefully designed, randomized double-blinded placebo-controlled trials will be needed to confirm the effectiveness of IFPD or IFPD-A for IBS.

# 臨床經驗與專家共識

## Clinical experience + Consensus among experts

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### 1. Why delete?

**Pericarpium Citri Reticulatae (Chen pi/陈皮) and  
Radix Saposhnikoviae (Fang feng/防风)**

### 2. Why add?

**Cortex Magnoliae Officinalis(Hou Po/厚樸)**

**Semen coicis Lachryma-jobi (yiyiren /薏苡仁)**

**Polygonaceae (Huo Tan Mu/火炭母)**

**Fructus Terminaliae Chebulae(he zi/訶子)**

**Rhizoma Corydalis Yanhusuo(Yan Hu Suo/延胡索)**

## 未定方 Pre-JCM 1602

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Go through the case study in clinic

Rhizoma Atractylodis Macrocephalae (Bai zhu/白朮)

Radix Paeoniae Lactiflorae (Bai shao/白芍)

Cortex Magnoliae Officinalis (Hou Po/厚樸)

Semen coicis Lachryma-jobi (yiyiren /薏苡仁)

Polygonaceae (Huo Tan Mu/火炭母)

Fructus Terminaliae.Chebulae(he zi/訶子)

Rhizoma Corydalis Yanhusuo(Yan Hu Suo/延胡索)

# 預試 **Preclinical study about JCM 1602 effect**

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- 1. Analgesic effect in mice model**
- 2. Anti-diarrhea effect in Castor oil-induced diarrhea and magnesium sulphate-induced diarrhea in Mice model**

## 定方 Finalization of JCM 1602 with fixed dosage

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Rhizoma Atractylodis Macrocephalae (Bai zhu/白朮)

Radix Paeoniae Lactiflorae (Bai shao/白芍)

Cortex Magnoliae Officinalis (Hou Po/厚樸)

Semen coicis Lachryma-jobi (yiyiren /薏苡仁)

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Fructus Terminaliae Chebulae (he zi/訶子)

Rhizoma Corydalis Yanhusuo (Yan Hu Suo/延胡索)

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# 基金與隊伍

## **Funding source and Team**

- **ITC of HKSAR**
- **Team**

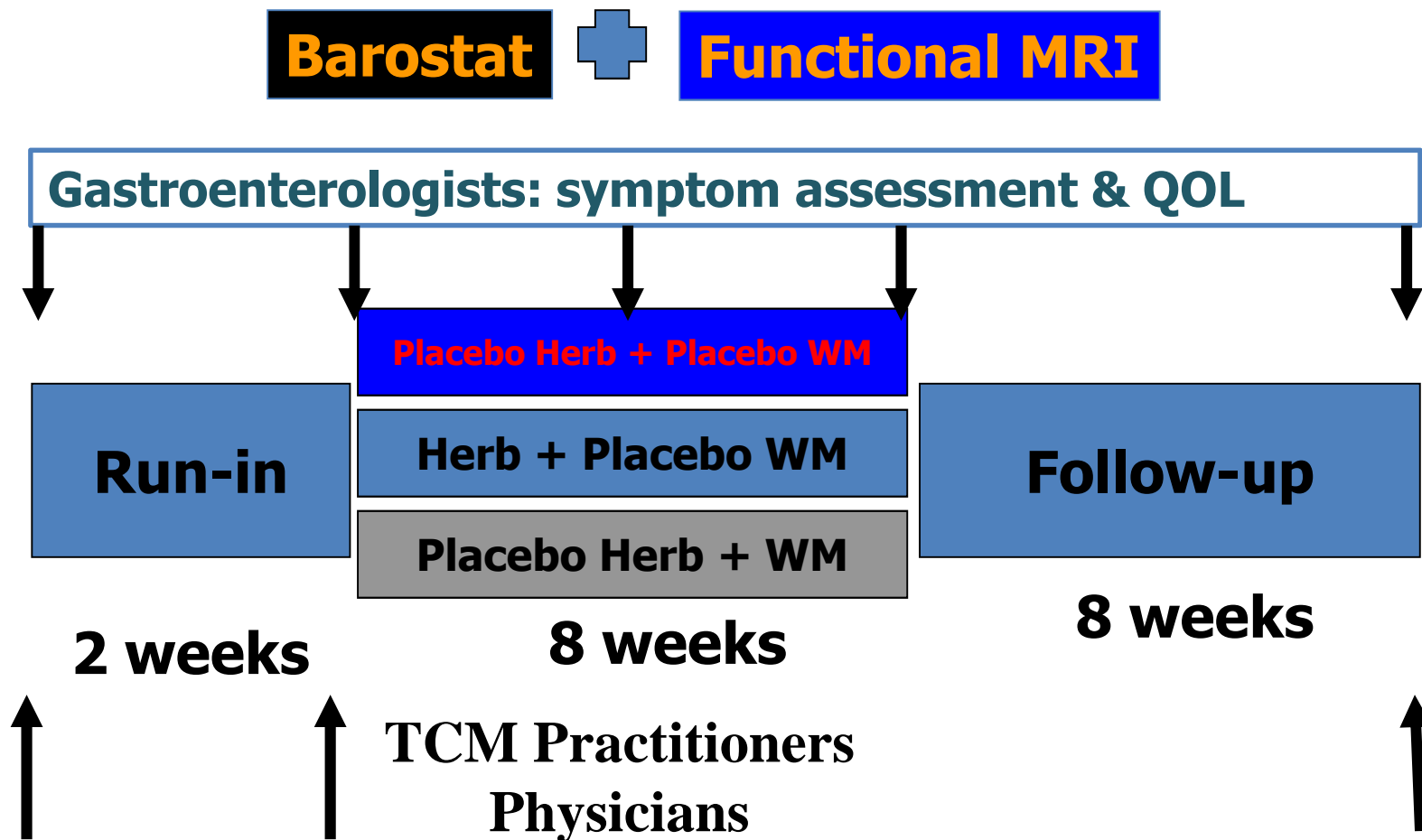
**Faculty of Medicine/ CUHK**

**School of Chinese medicine/HKBU**

# 臨床試驗 Clinical Trial Design

Following Rome II criteria

Randomized double blinded placebo controlled study



# 實驗結果 Trial Results

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- 8 weeks TCM > placebo > holopon
- 16 weeks TCM > placebo > holopon
- 系統思維方式與線性思維方式！

# Patent

ZL2006-1-0146331.1

Rhizoma Atractylodis Macrocephalae (Bai zhu/白朮)

Radix Paeoniae Lactiflorae (Bai shao/白芍)

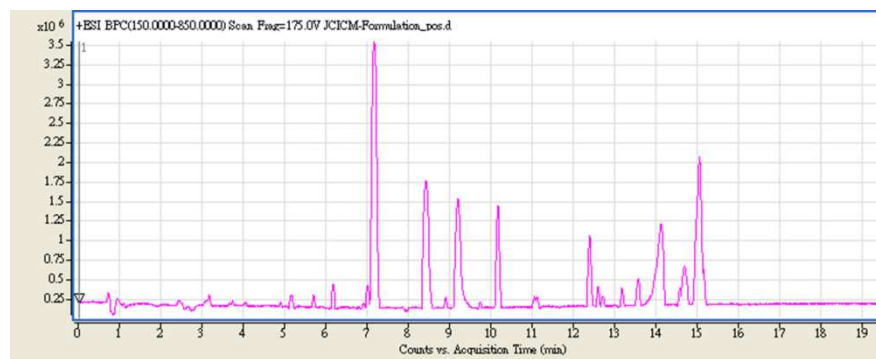
Cortex Magnoliae Officinalis (Hou Po/厚樸)

Semen coicis Lachryma-jobi (yiyiren /薏苡仁)

Polygonaceae (Huo Tan Mu/火炭母)

Fructus Terminaliae.Chebulae(he zi/訶子)

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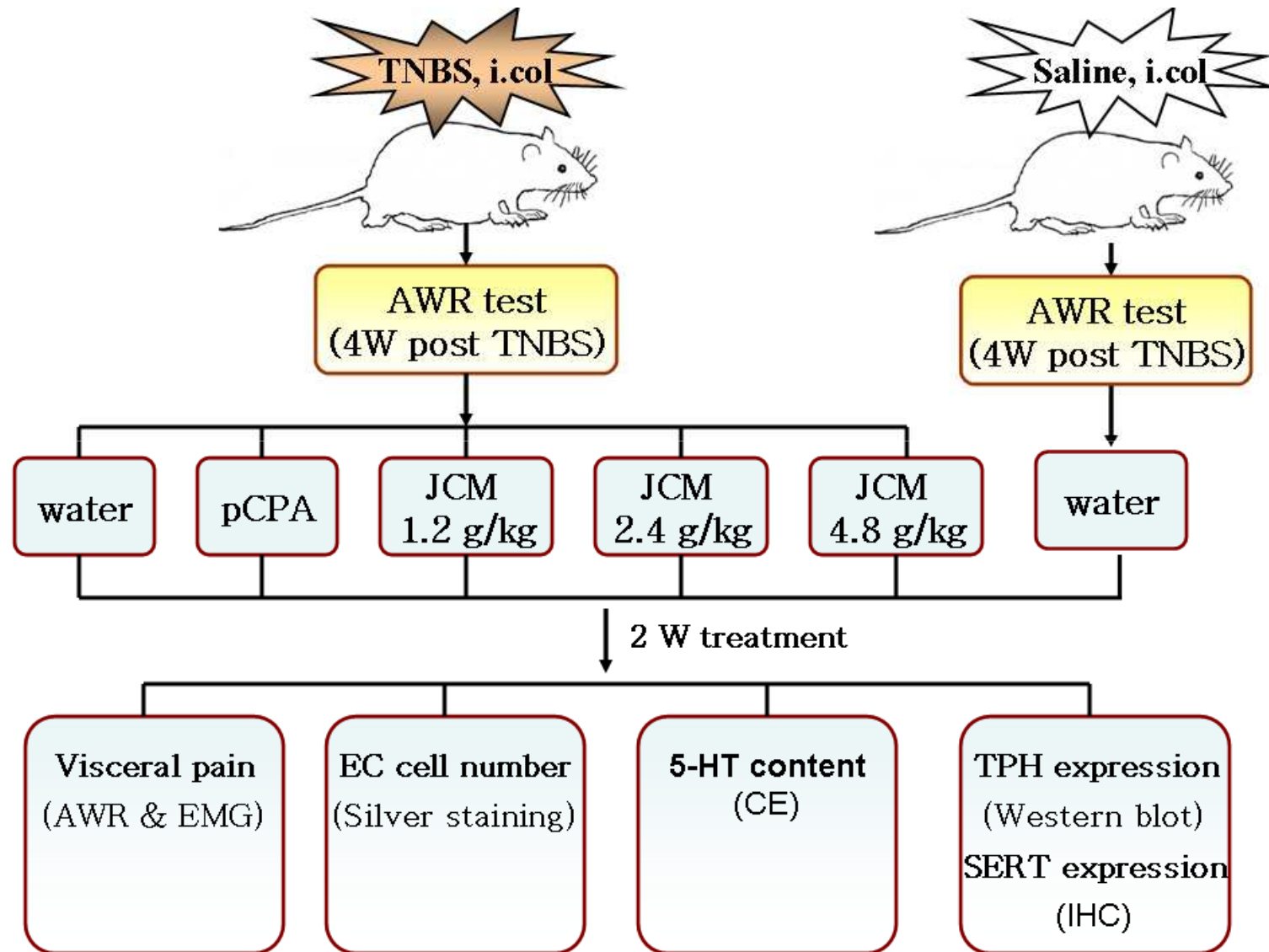


## Mechanism study design

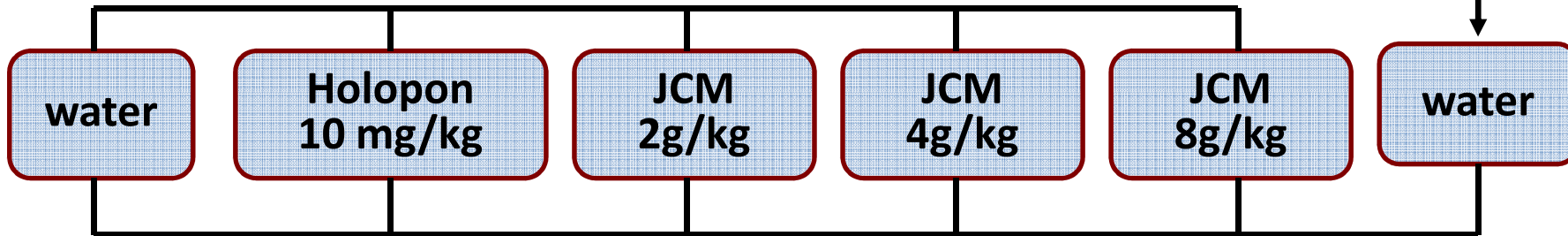
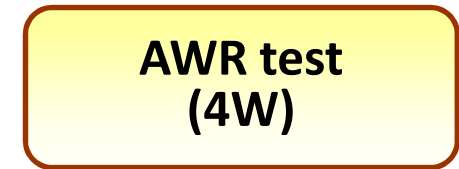
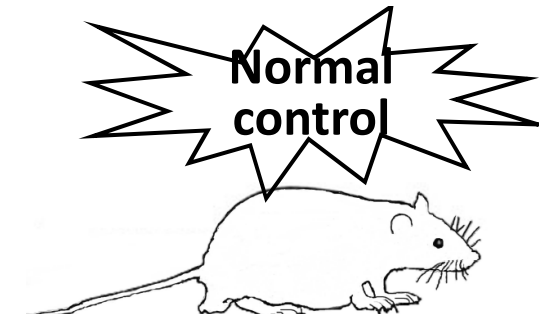
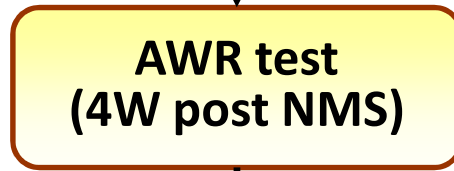
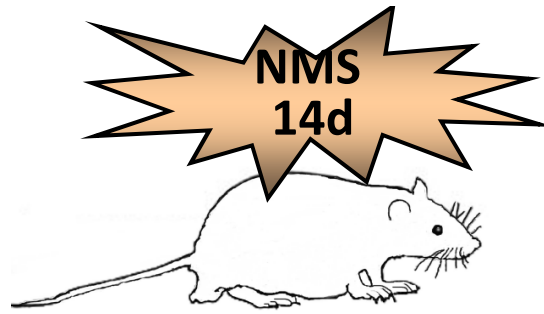
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- **Post-infection IBS model**
- **Early life stress IBS model**

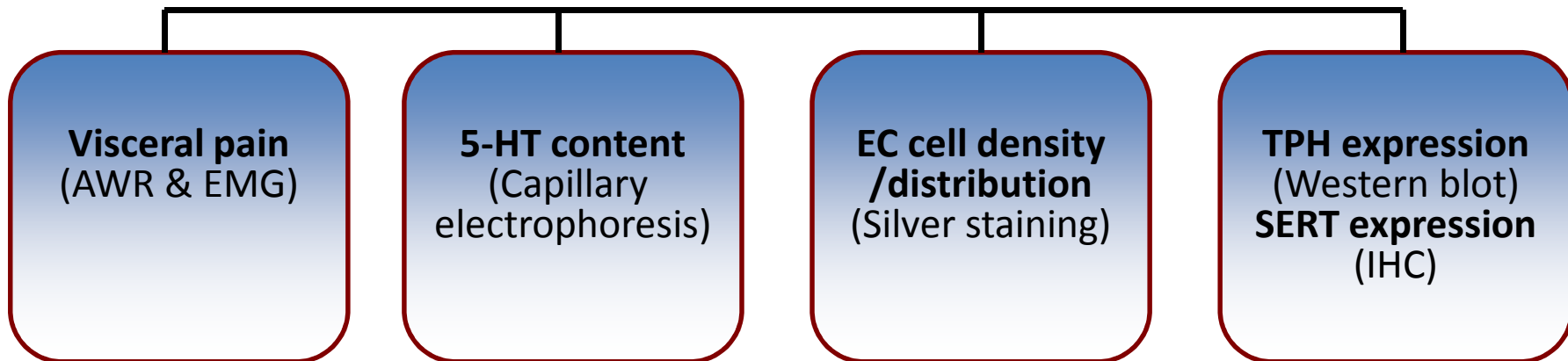
# Study design: JCM1602 for PI-IBS rats



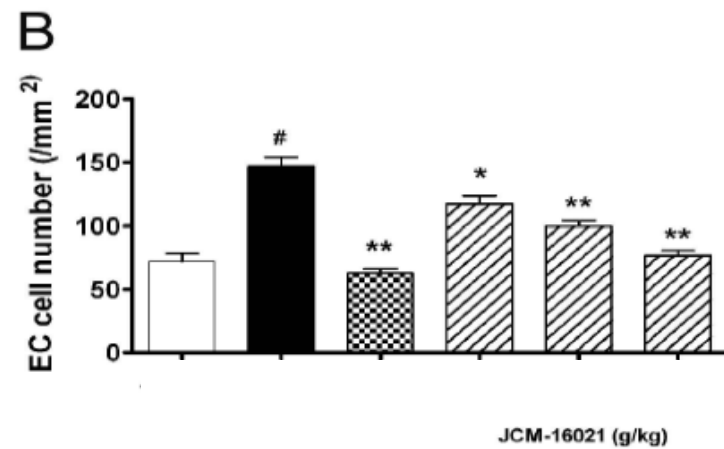
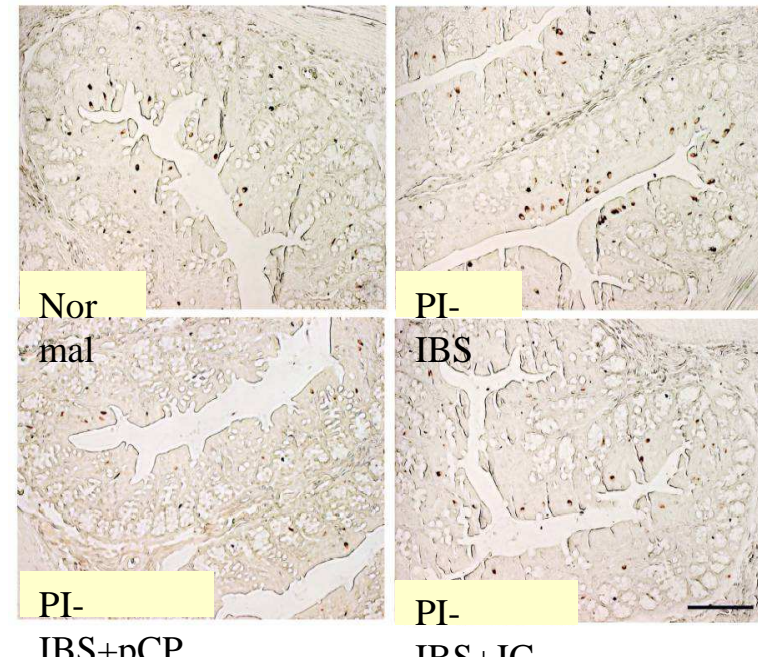
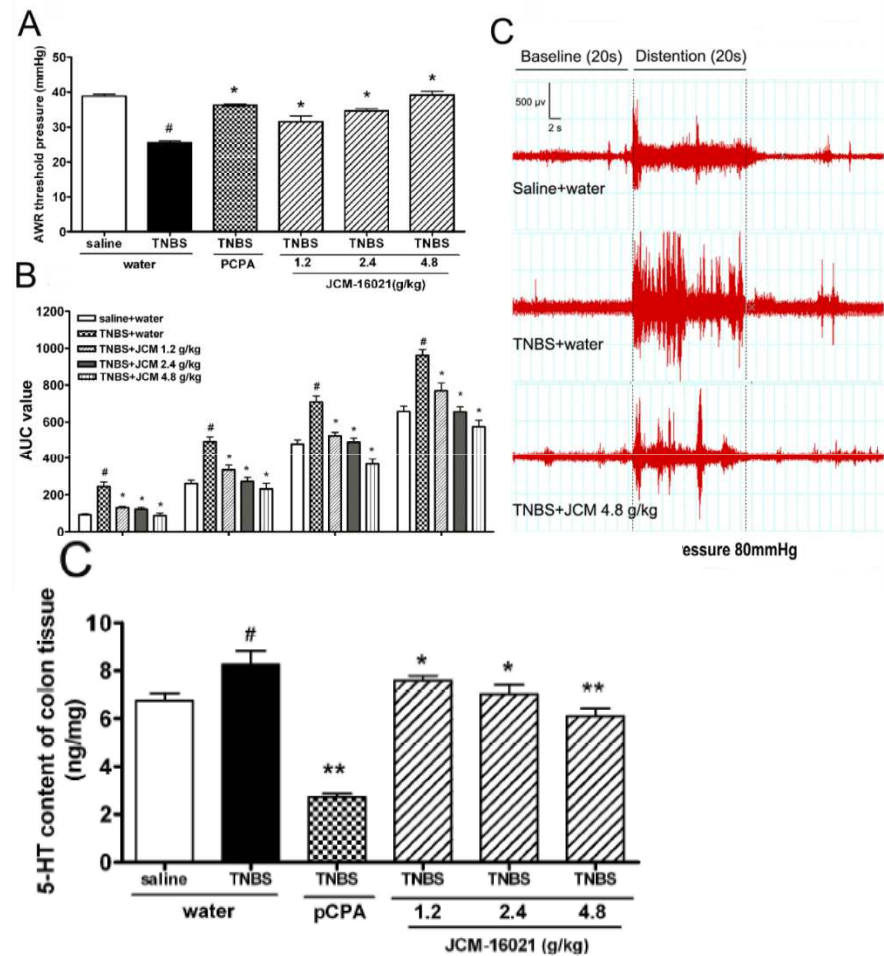
**Study design:  
JCM1602 for  
NMS rats**



2 W treatment



# Effect of JCM-16021 on visceral hypersensitivity in PI-IBS rats

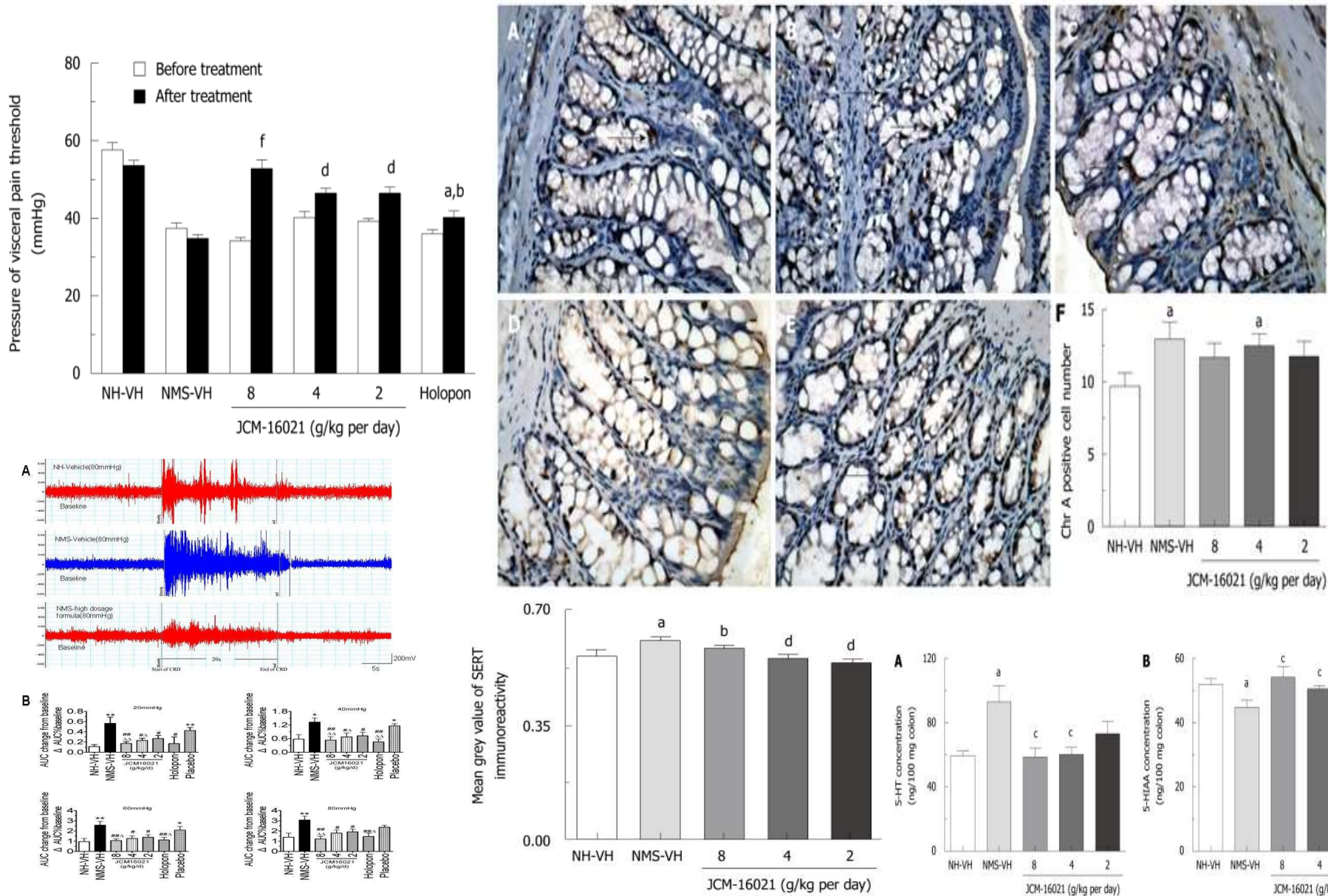


(#  $p < 0.05$  vs. normal rats, \*  $p < 0.05$ , vs. PI-IBS rats)

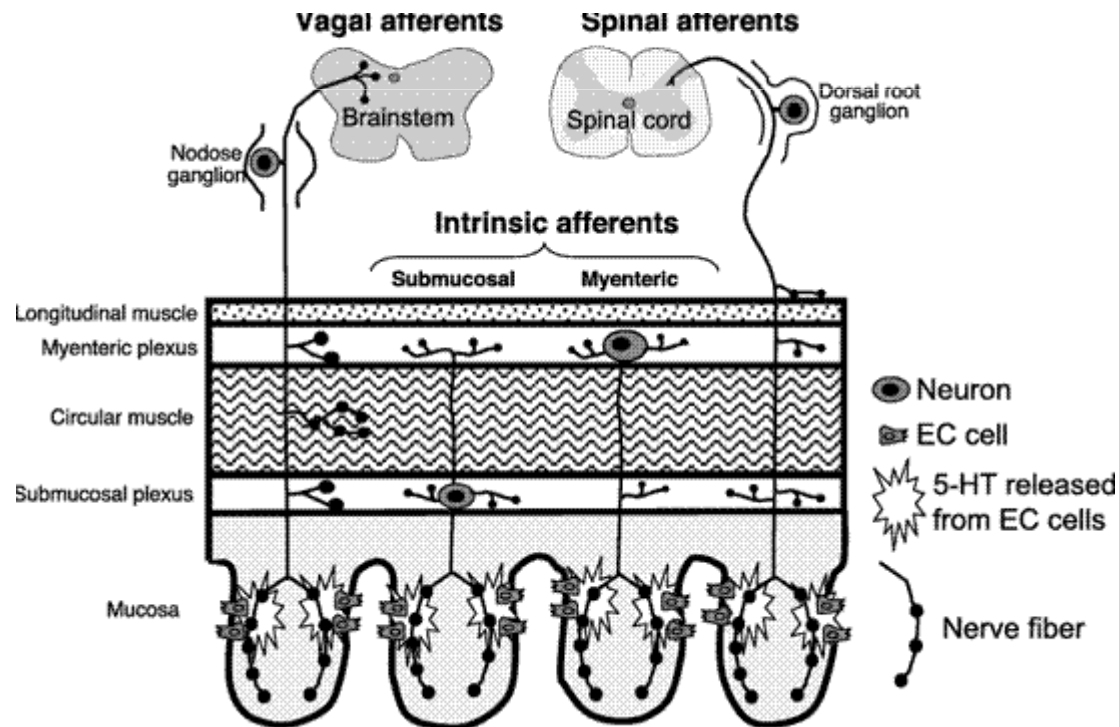
JCM-16021 attenuated visceral hyperalgesia in PI-IBS rats



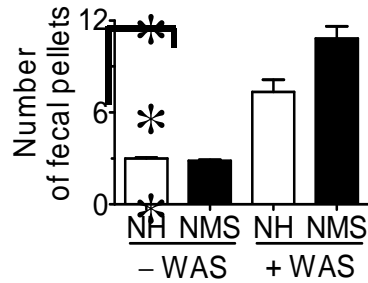
# JCM 16021 and visceral pain in NMS rats



# JCM 16021 for Serotonin pathway

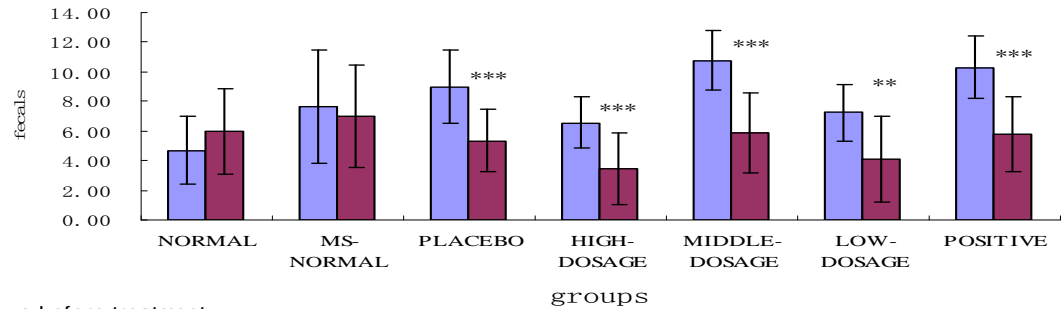


# JCM-16021 對鈣通道的影響



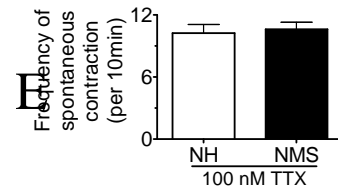
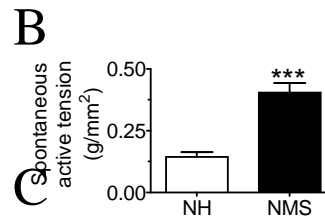
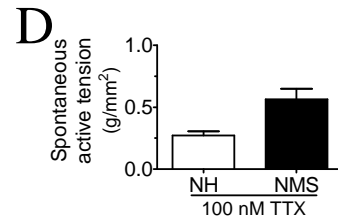
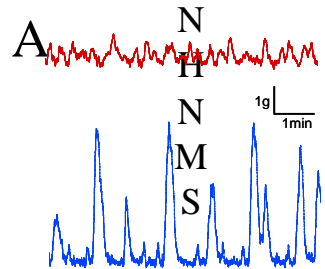
水应激1小时内的粪粒数

The effect on anti-diarrea of the formula

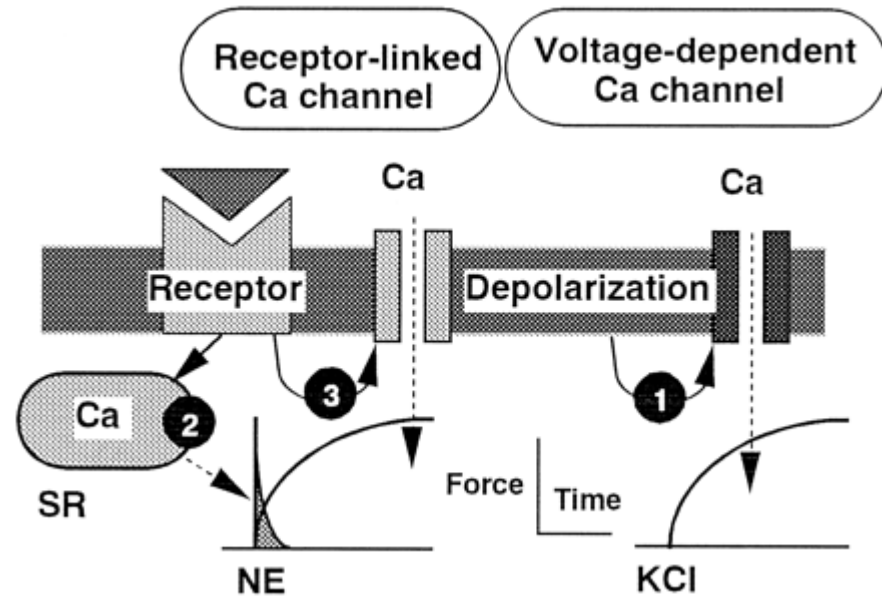


vs. before treatment, \*\* $p < 0.01$ , \*\*\* $p < 0.001$

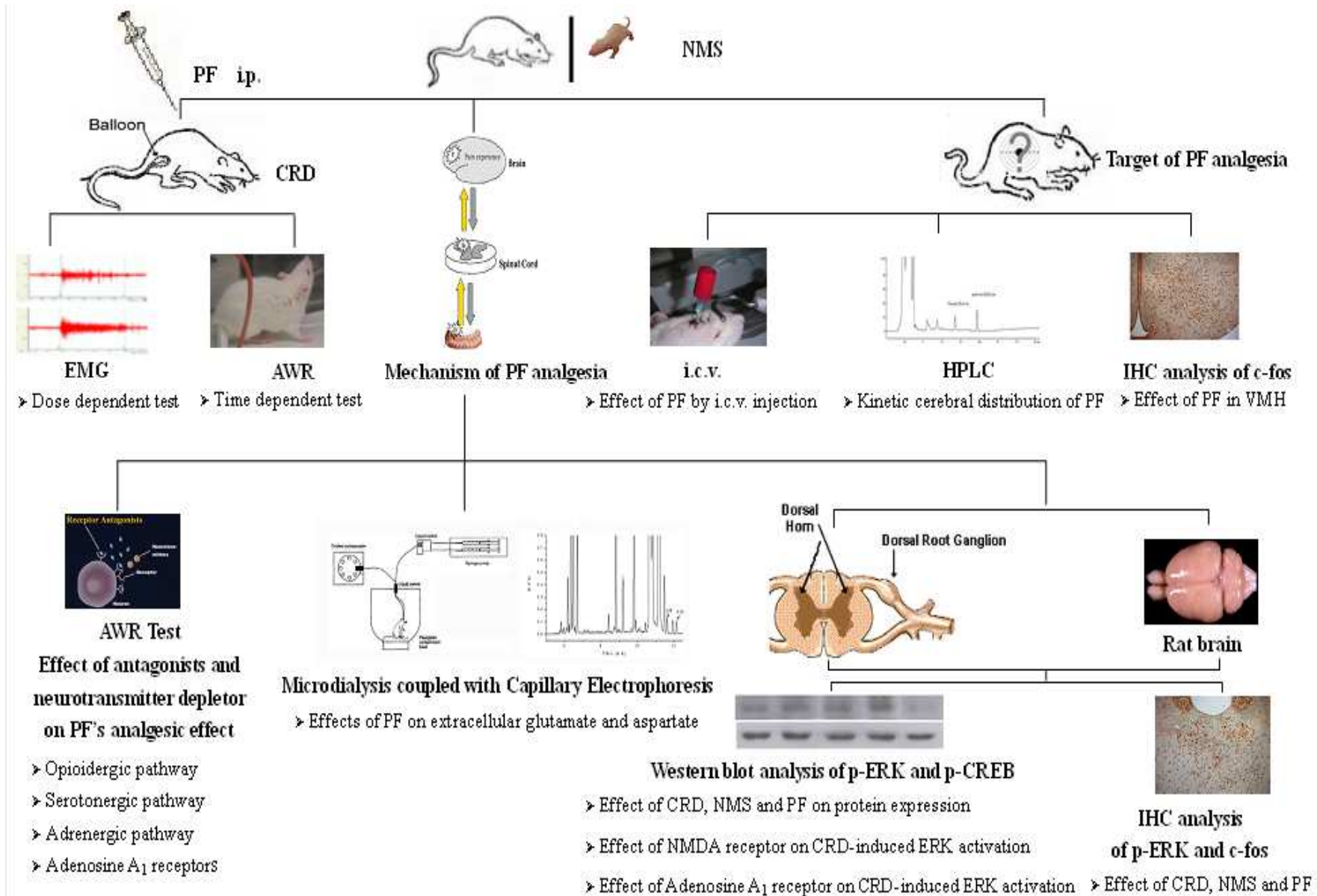
■ BEFORE TREATMENT ■ AFTER TREATMENT



离体肠道运动检测

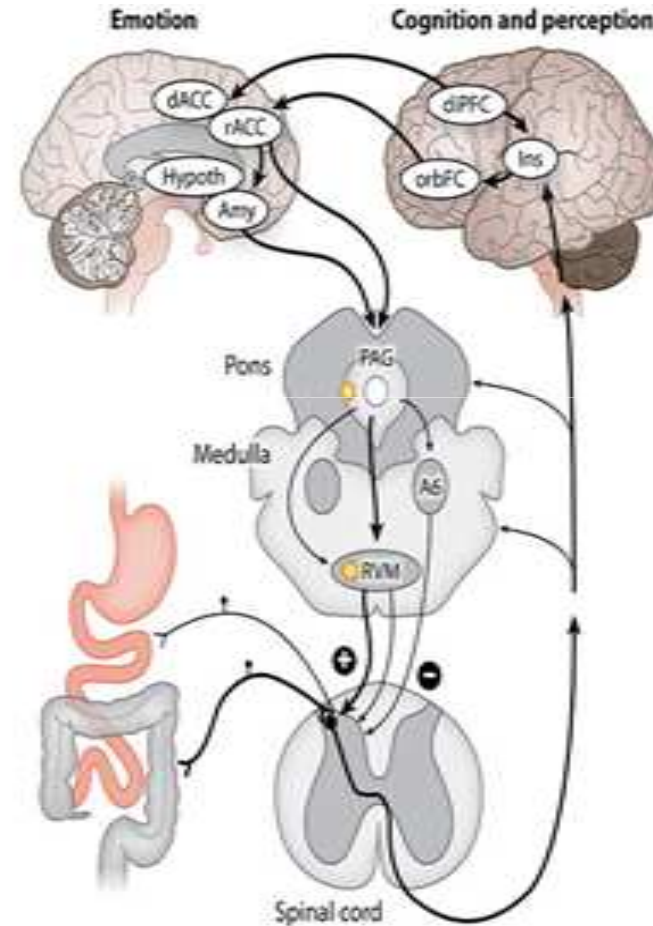


# JCM16021 對 MAPK pathway 的作用



# JCM16021 的作用途徑

- **Serotonin pathway**
- **MAPK pathway**
- **Calcium Pathway**
- **PAR-2 Pathway**
- .....



# IBS治療的變革

- 從臨床症狀層面，不僅要針對腸，還要針對腦；
- 從病理機制層面，不能只針對單一病理靶點，還需綜合考慮針對多系統病理通路

# 从传统多“靶點”出发

1、基於中醫理論指導

2、藥物作用“靶點”是針對不同的症狀特征的證候，所謂的“君臣佐使”，其作用靶點，有可能同一，如四君子湯的補氣(氣虛為君臣佐使的靶點)，有可能不同，如小承氣湯的熱結津傷(熱、結、津傷是靶點)等

3、傳統意義上的靶點，與現代藥理概念上的靶點並不一致，或者起碼在初始概念上並不一起，传统药物配伍并非针对靶点，虽然有可能有吻合

但是這種方藥的設計，特別是在療效驗證基礎上的方藥組合，為多靶點藥物治療的設計提供了可能

從传统多“靶點”出發。。。。

從以辨證論治為指導的“多靶點”方向，尋求藥物療效的最大化—理想復方

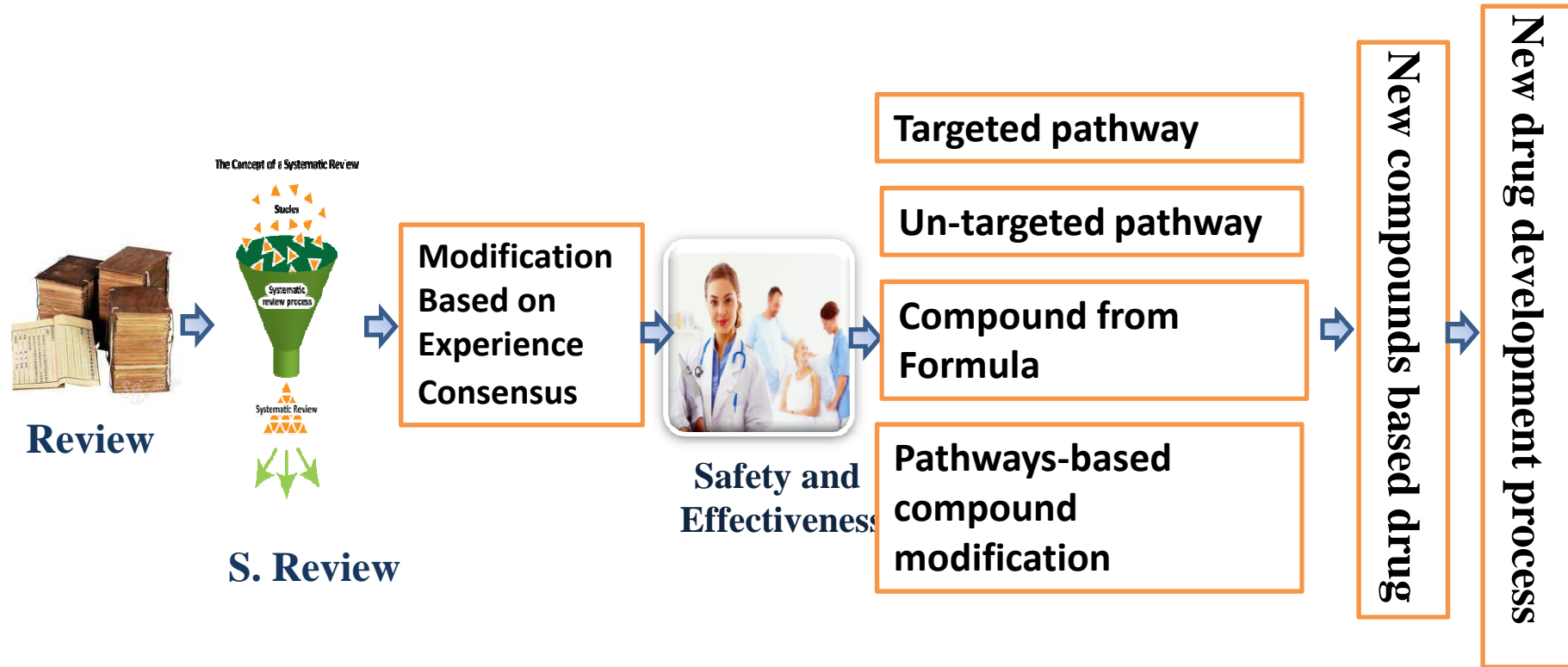
從系統生物學為指導，尋求疾病治療中病理環節的反映通路—治療靶向

從藥物化學為指導的有效組分分析—單體組合

三方面結合，一定能够走出一條新藥研發路徑



# 復方為導向的系統藥物設計



JCM1602的方向: Version 2

# 綜合途徑

- 以證候為基礎的多靶點治療
  - 以病理網絡為基礎的多通路探索
  - 以藥物化學為基礎的成份分析
  - 以線性思維與環性思維的結合
- 
- 不只是治療腦與腸，應針對病理系統
  - 不只是對**IBS**，系統病
  - 。。。

# 致謝

- **CUHK**
- **HKBU**
- **ITC/JCICM**
- **RGC/GRF**