

Consideration: which is the most important in new drug development?

Stability? Mechanism? Safety? Effectiveness? Individualization?

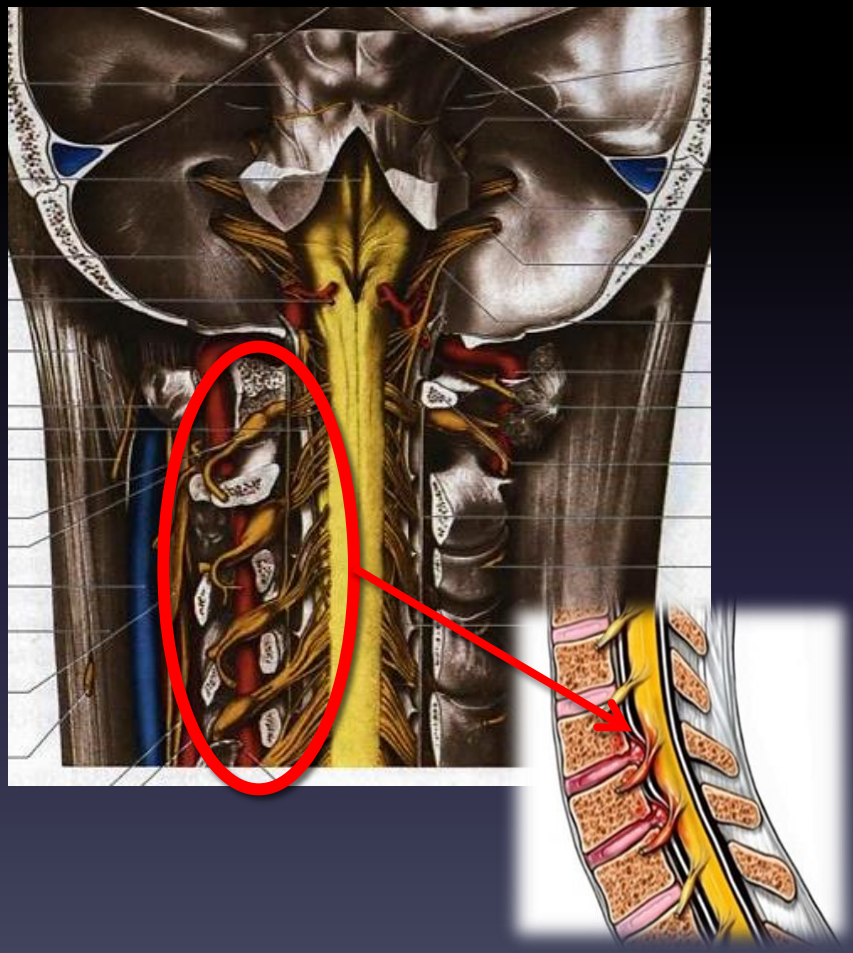
Speaker: Dr. Yue-li Sun
Mentor: Prof. Yong-jun Wang
Shanghai University of TCM
Spine Research Institution

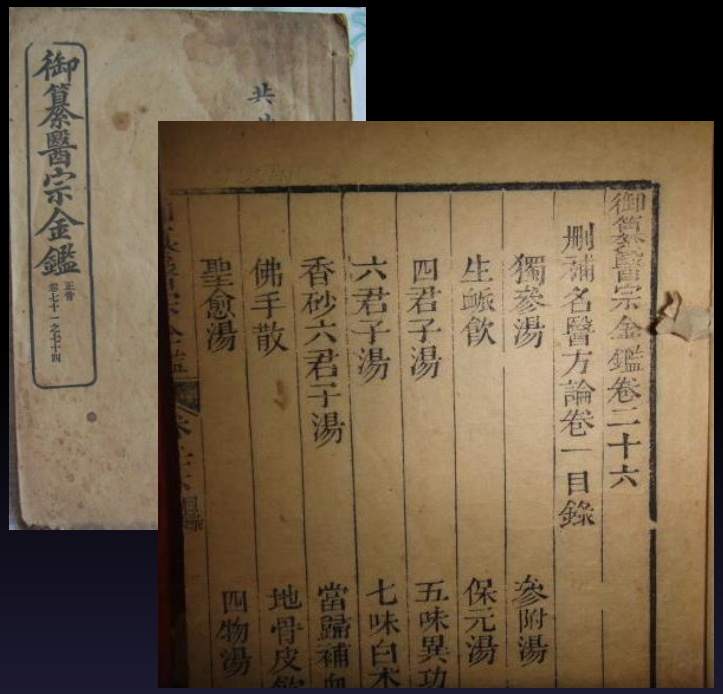
Outline

- Background
  - Neck pain is a common symptom.
  - Many patients use complementary and alternative medicine, including traditional Chinese medicine, to address their symptoms.
- Current studies on the new herb medicine, 'Qishe Pill'
  - To establish the preparation processes of a TCM theory-based Formula
  - To investigate the potential mechanism in *vivo* and in *vitro*
  - To assess the safety and effectiveness in Phase II, III, IV clinical trials
- Challenges and ideas
  - Individualized medicine is a trend.
  - TCM theory-based constitutional types may work.

Cervical radiculopathy

- **A significant public health problem worldwide**
  - **Bad posture , everyday wear and tear, overuse or injury**
- **Related symptoms**
  - Neck pain
  - Neck and arm discomfort.
  - **Pain radiates to the upper or lower arm**
  - **Sensory distribution of the nerve root**





Stage I
Formula Design

- To design the formula as TCM principal
  - To tonify ***Qi*** (vitality)
  - To activate ***Blood*** (circulation)
- To establish the preparation processes
- To provide some pre-trial parameters









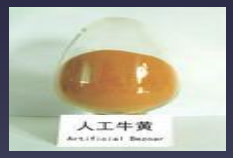




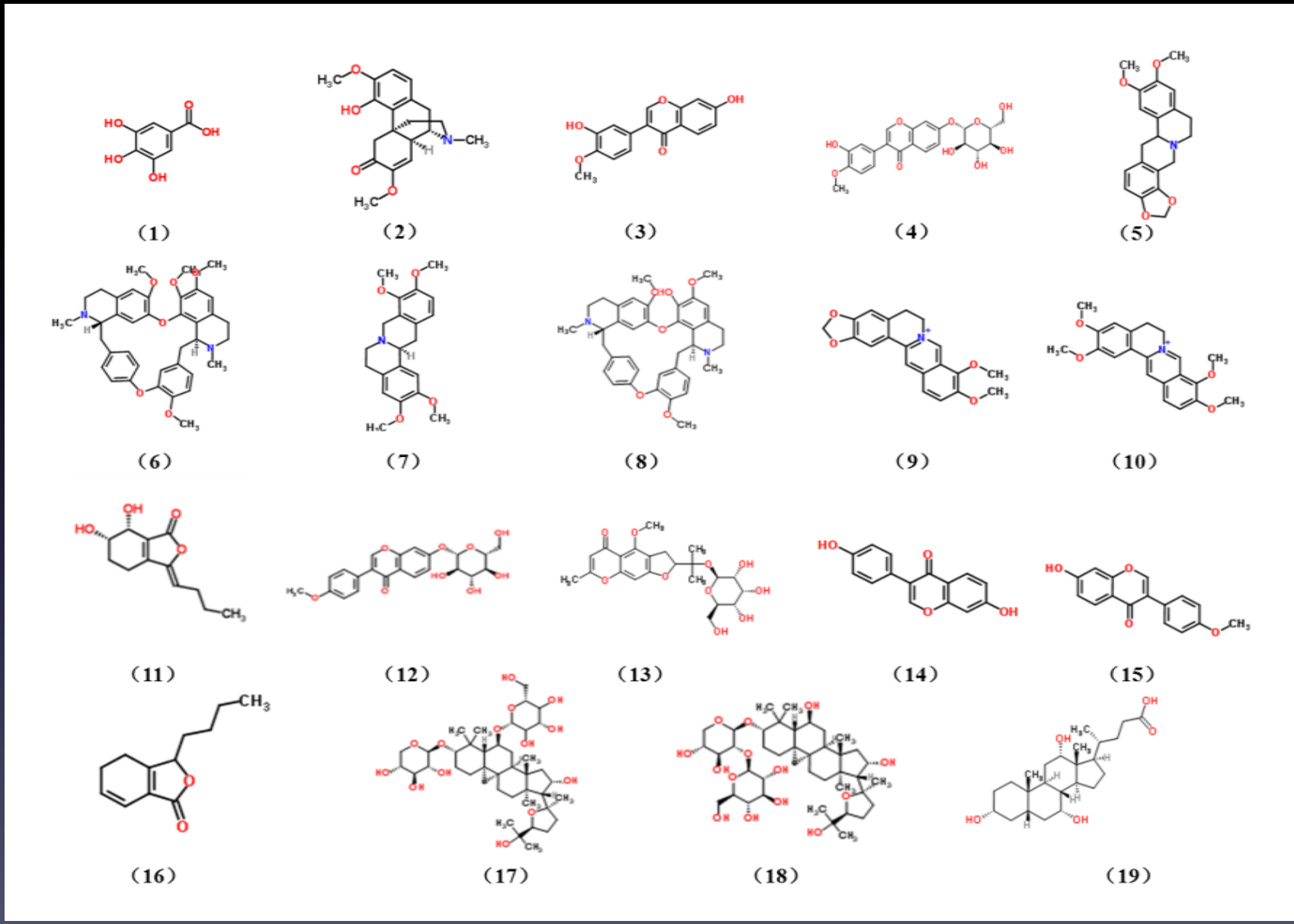


Table 1 Standard formula (Capsule ingredients)*

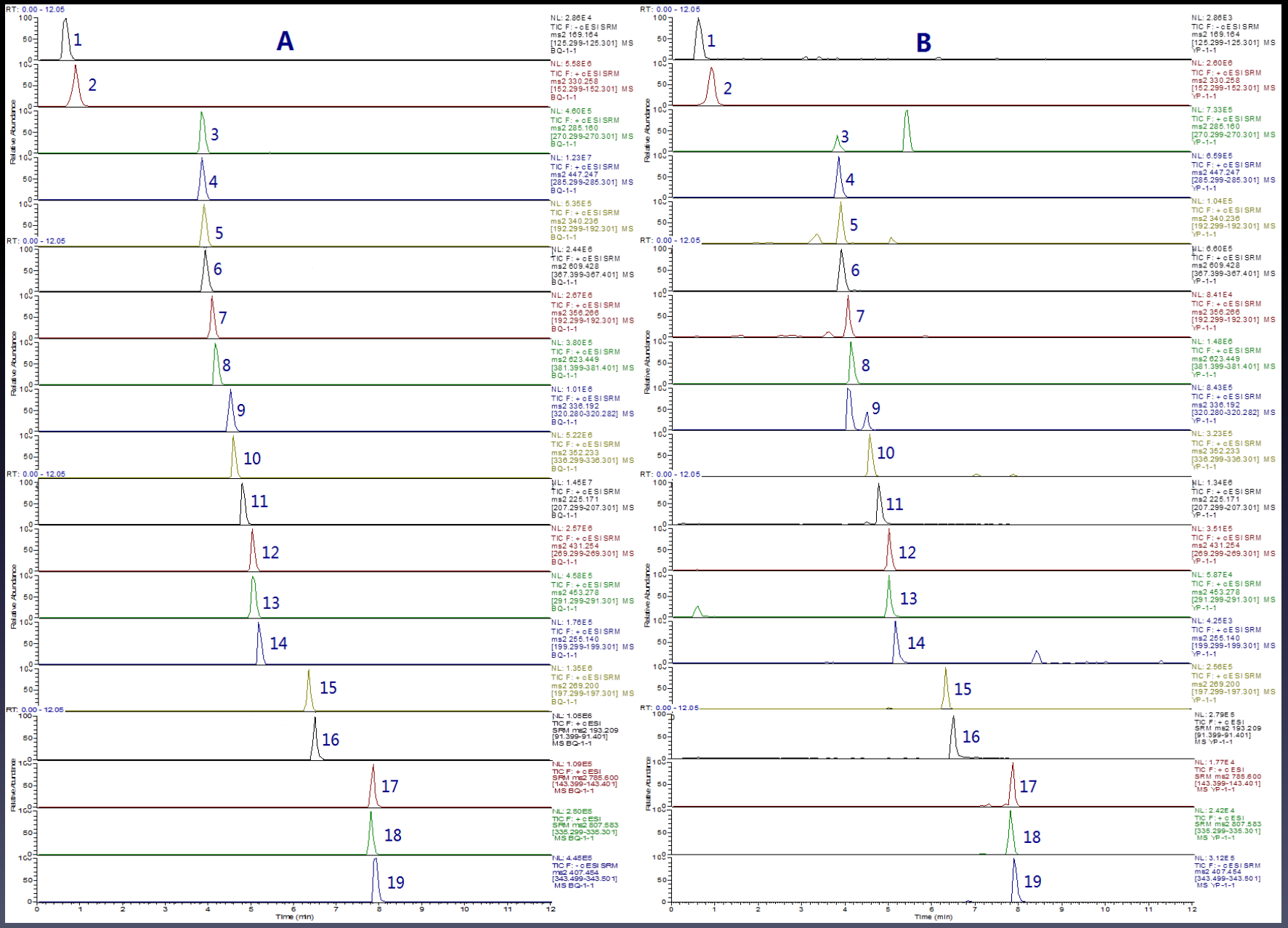
Chinese name	Pharmaceutical name	Powered herb,%
Huang Qi	*Radix Astragali*	28%(13 g)
She Xiang	Muscone	0.06%(0.03 g)
Chuan Xiong	*Szechuan Lovage Rhizome*	26%(12 g)
Fang Ji	*Radix Stephaniae Tetrandrae*	19%(9 g)
Qing Feng Teng	Ovientvine	26%(12 g)
Niu Huang	*Calculus Bovis Artifactus*	0.6%(0.3 g)

*Pharmaceutical Terminology from Hsu [7].

Contents of the 19 active compounds in Qishe Pill



Contents of the 19 active compounds in Qishe Pill

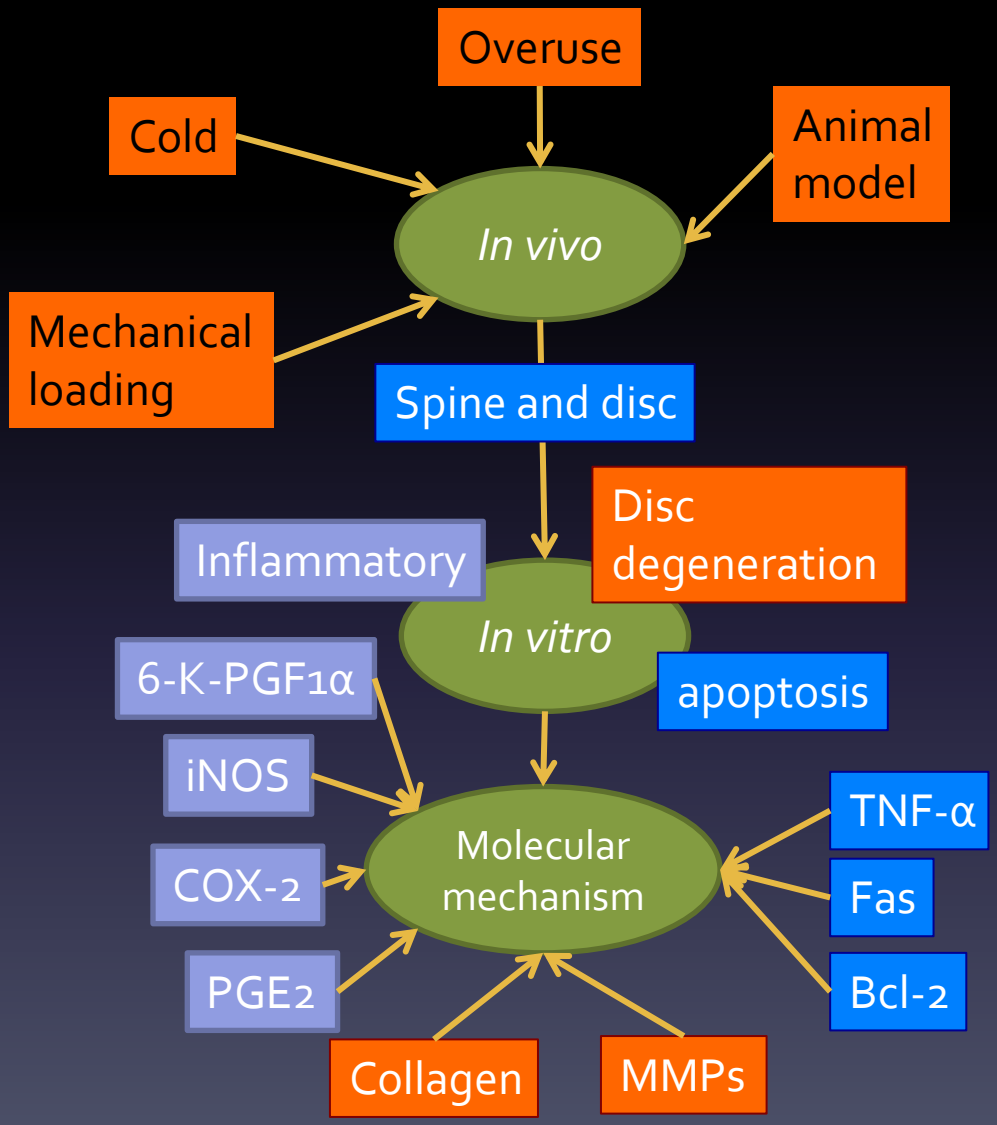


Contents of the 19 active compounds in Qishe Pill

	Content（mg/g）				
	Sample1	Sample2	Sample3	Sample4	Sample5
GA	0.0438	0.0474	0.0432	0.0432	0.0489
SN	6.9353	6.7360	6.3580	5.7984	7.0141
CS	0.9694	0.9320	0.9326	0.8073	1.1504
CSG	0.0466	0.0377	0.0387	0.0318	0.0534
ST	0.0086	0.0108	0.0110	0.0107	0.0118
TR	0.4071	0.6230	0.5329	0.4994	0.5159
TDM	0.0018	0.0024	0.0024	0.0022	0.0026
FCL	20.0805	29.4775	26.7323	24.0118	25.8490
PT	0.0099	0.0116	0.0116	0.0105	0.0125
SI	3.8318	2.1590	2.1099	1.7657	2.6739
GM	0.0483	0.0443	0.0421	0.0373	0.0610
ON	0.0676	0.0628	0.0607	0.0498	0.0861
DZ	0.0037	0.0048	0.0050	0.0038	0.0043
FNT	0.1159	0.1466	0.1441	0.1299	0.1404
AG-IV	0.5317	0.5395	0.5720	0.5922	0.5508
CA	2.9483	2.8714	2.9763	2.7254	3.1097
AG-III	0.0776	0.0992	0.0811	0.0765	0.0829
SA	4.4996	4.1838	3.9999	4.1834	5.4479
BR	0.0018	0.0023	0.0023	0.0019	0.0024

Contents of the 19 active compounds in Qishe Pill Compound

Stage II
Mechanism investigation

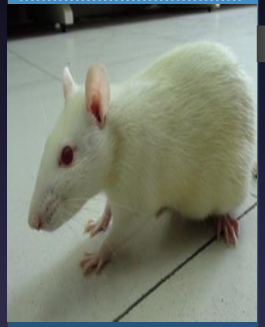


A. To inhibit Inflammatory
B. To decrease apoptosis
C. To prevent angiogenesis and degradation



To establish rat model

01 Normal



02 Nerve root compressed



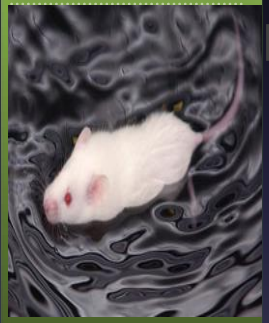
Common Cervical radiculopathy

03 Adrenaline & cortisol



Blood-stasis '*Zheng*'

04 Fatigue



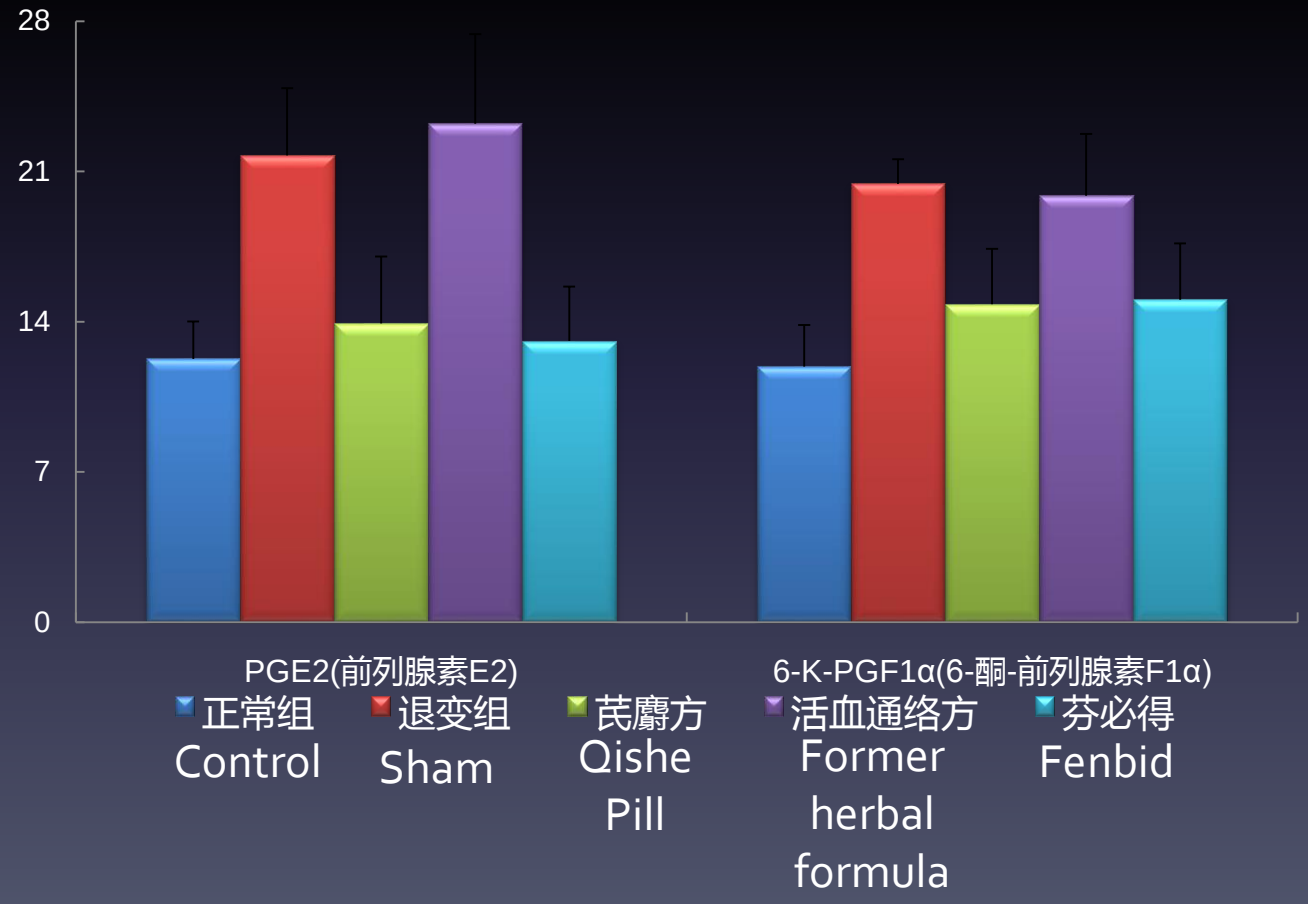
Qi-deficiency '*Zheng*'

05 Disease & '*Zheng*' Model



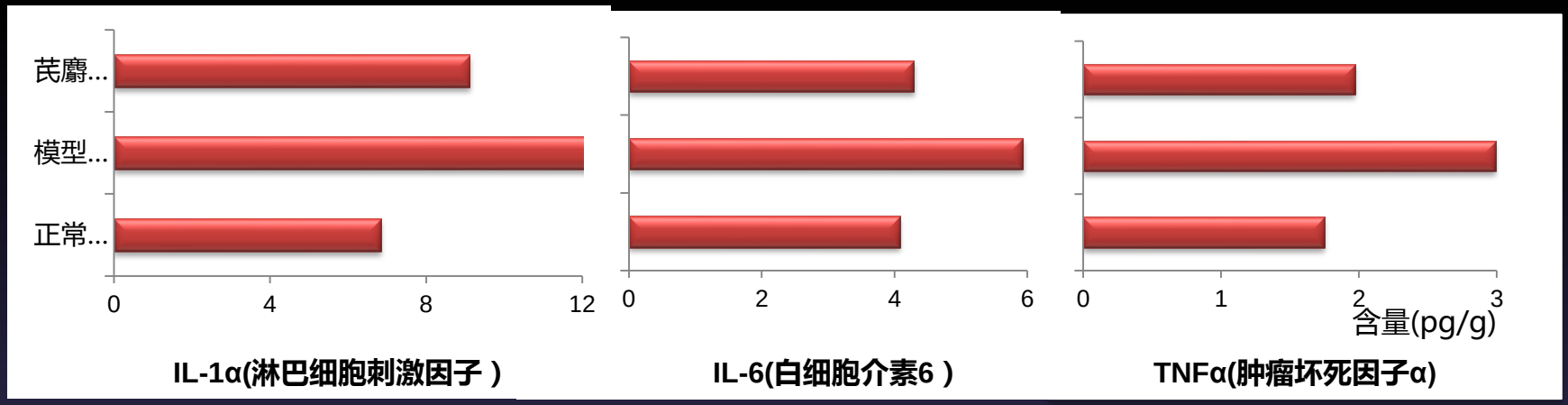
A. To inhibit Inflammatory

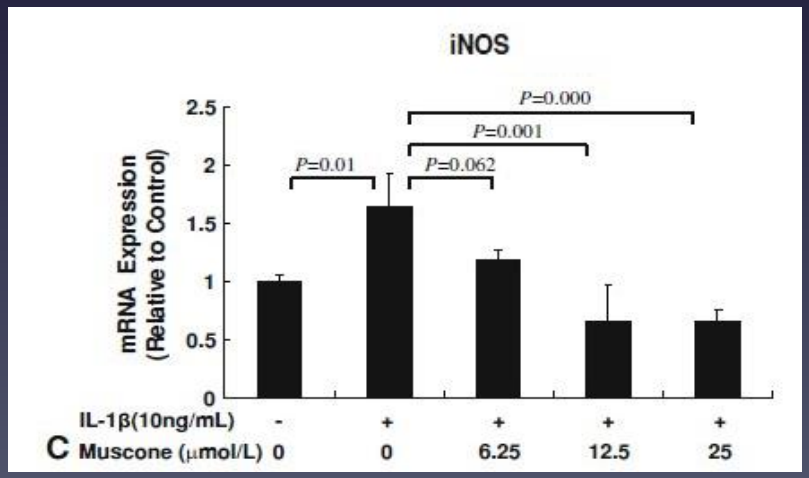
- Decrease the contents of PGE2 and 6-K-PGF1α
- Equal effect with Fenbid
- Prior to other former herbal formula

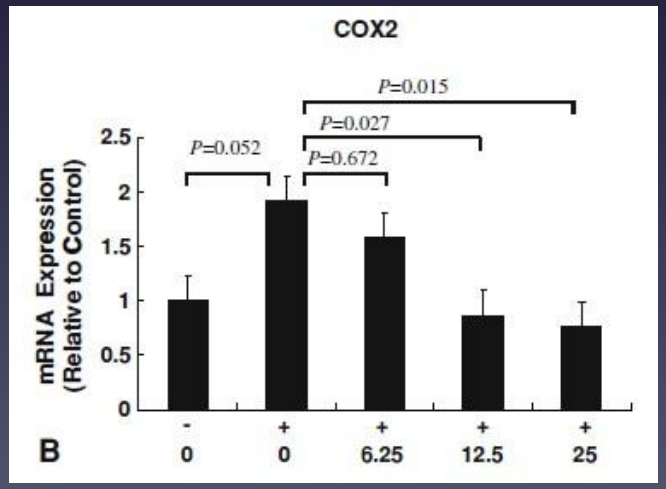


A. To inhibit Inflammatory

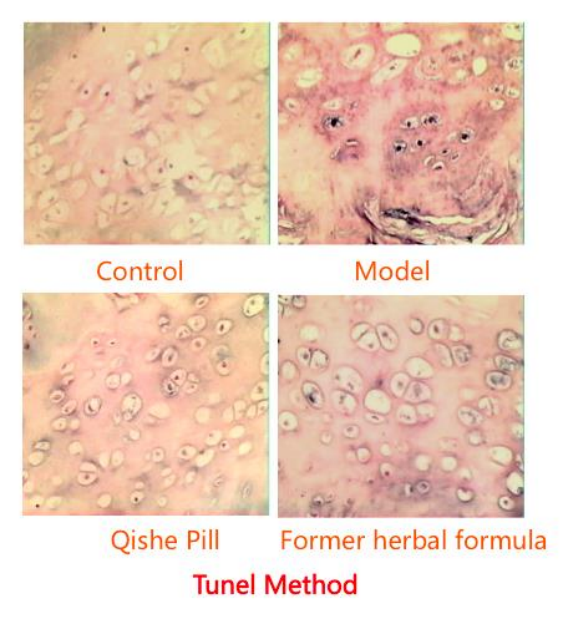
- Decrease the contents of IL-1α 、IL-6、TNFα
- Inhibit mRNA expression of iNOS、COX-2



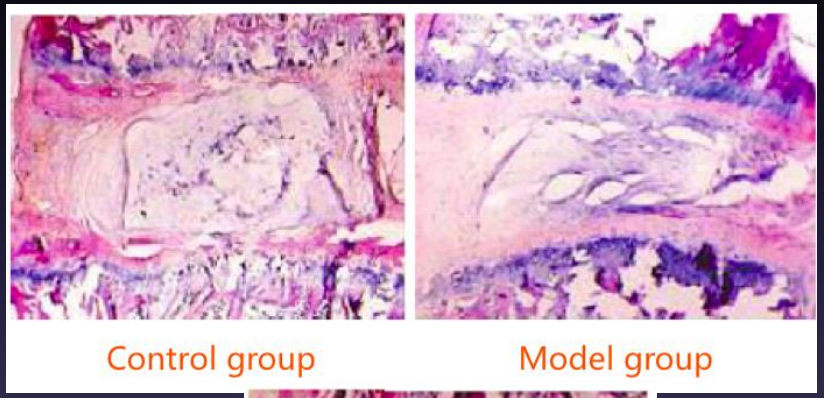




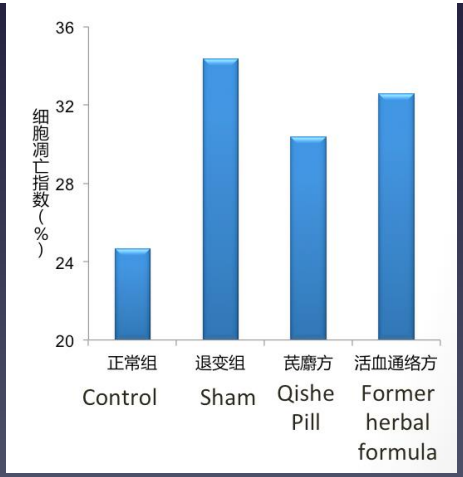
B. To decrease apoptosis



- To decrease apoptosis of nucleus pulposus cell in disc and chondrocytes
- To improve the structure of disc

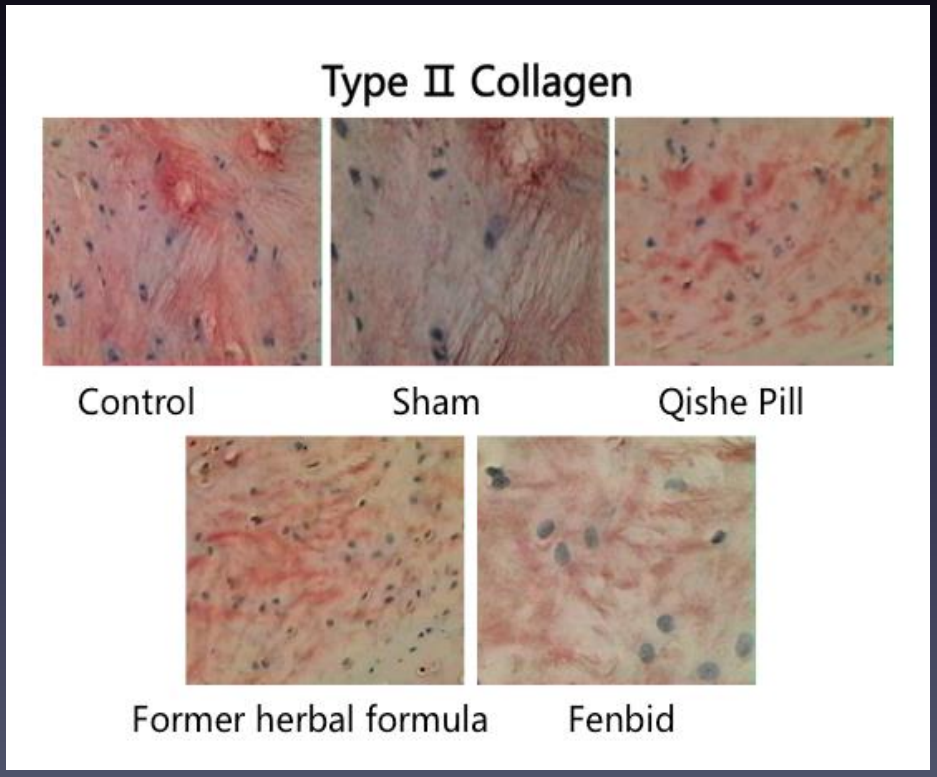


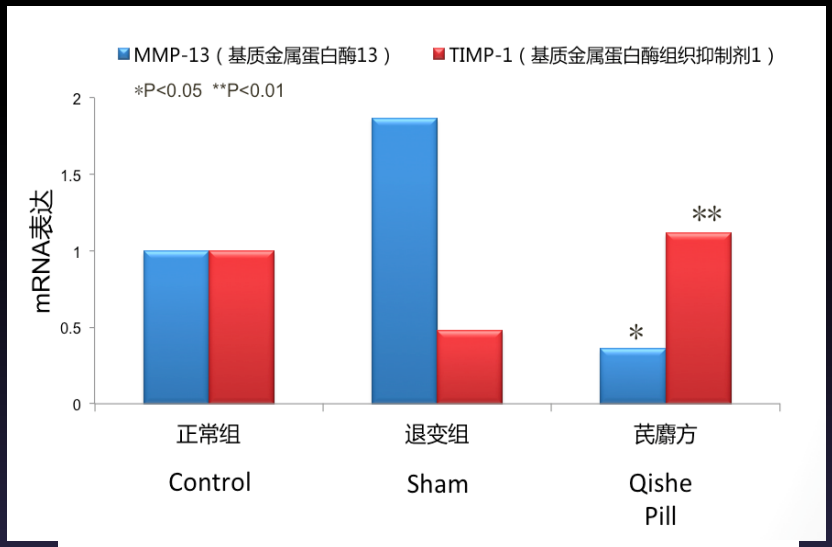


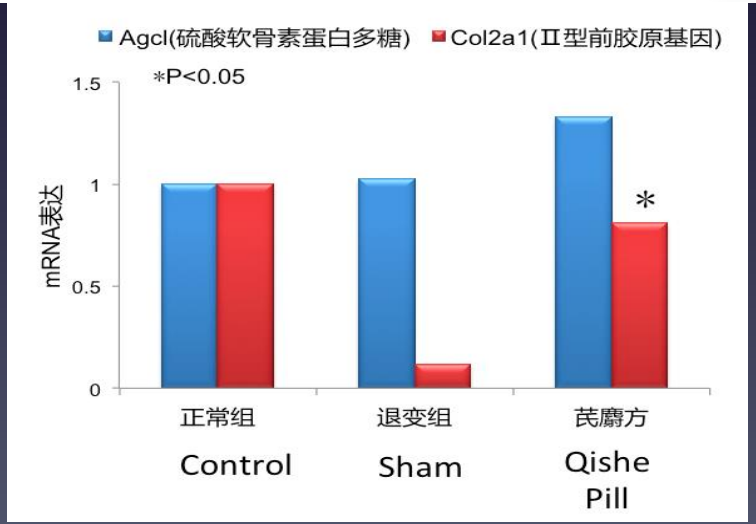


C. To prevent angiogenesis and degradation

- To promote chondrocytes to synthesize extracellular matrix
- To decrease activity of matrix metalloproteinases (MMP)





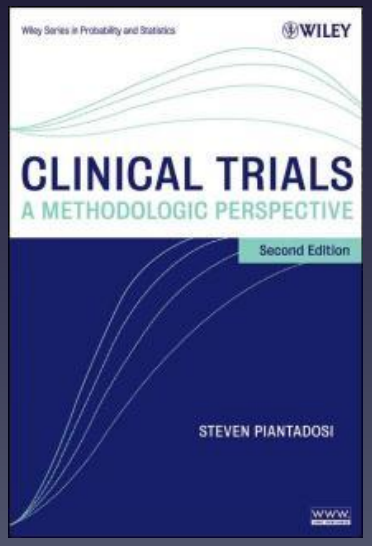




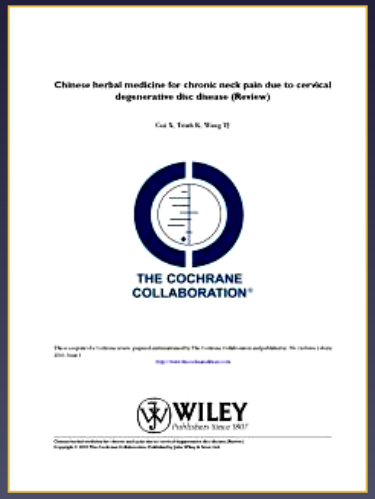
Stage III
Clinical Trials

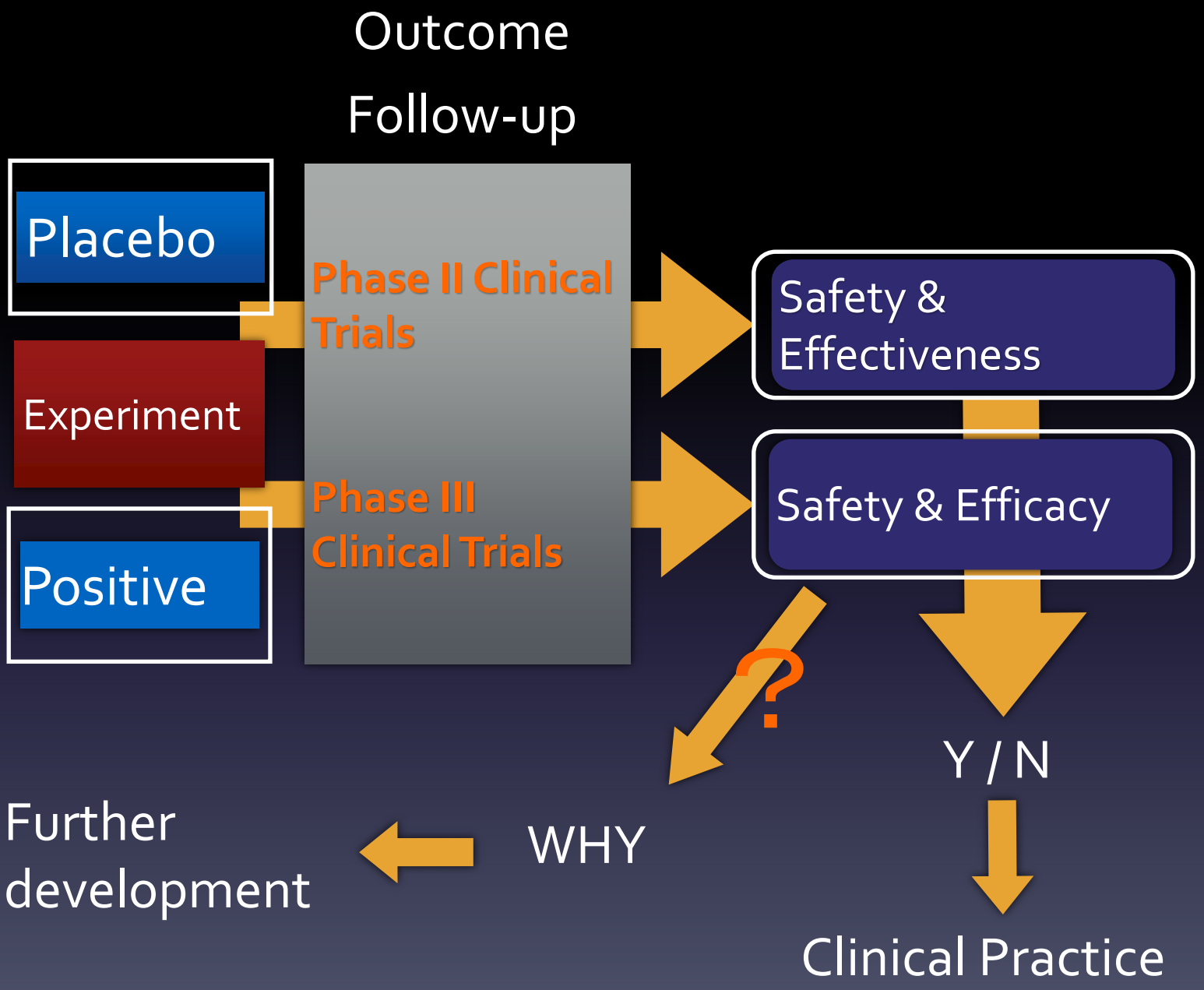
A. **Phase II** —— Safety & effectiveness
B. **Phase III**—— Safety & efficacy
C. **Phase IV**—— Post-marketing surveillance

Challenges and ideas








Outcome
Follow-up
Placebo
Experiment
Positive
Phase II Clinical Trials
Phase III Clinical Trials
Safety & Effectiveness
Safety & Efficacy
?
Y / N
WHY
Further development
Clinical Practice

Challenge 1

How to utilize the information of subjects efficiently ?

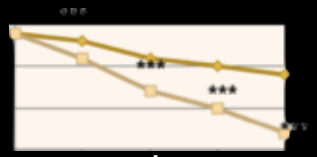
Idea 1



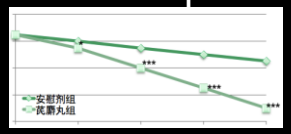
Phase II

Phase III

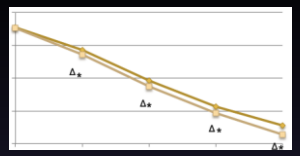
Phase IV



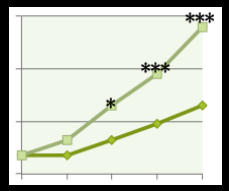
Neck pain



Neck disability



'*Zheng*' assess



ROM of neck

Safety
&
Effficacy



Post-marketing
Surveillance

Subject — Information — Subgroup — Efficacy classification

Challenge 2

How to individualize the treatment from clinical trials

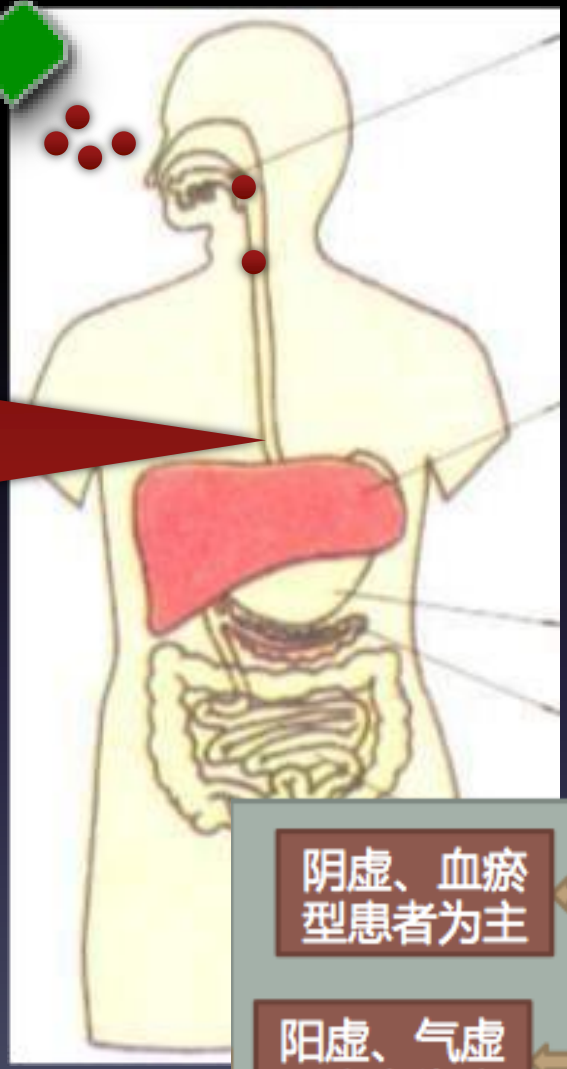
Challenge 2


Aged 18～35岁
BMI 19～24
laboratory indexes
Medical history
Compliance
Drug & alcohol abuse

Idea 2



Subgroup	Characteristic	Self-reported
Blood stasis	Frequent pain	sleeplessness irritability
Qi deficiency	Intolerance of **cold**	**mild diarrhea**
Qi depression	**Depression**	poor appetite
……		



The difference in reaction of medicine shows individual difference in constitutional type

Challenge 3

How to demonstrate the relationship of formula (Monarch, minister, assistant and guide in TCM prescription)

Challenge 3

Evidence？？

扶正祛邪，
一升一降

Monarch
君
黄芪
Radix Astragali

开经络，
透肌骨

佐 Assistant
防己
Radix Stephaniae Tetrandrae
青风藤
Ovientvine

气中之血药



血得气而速生

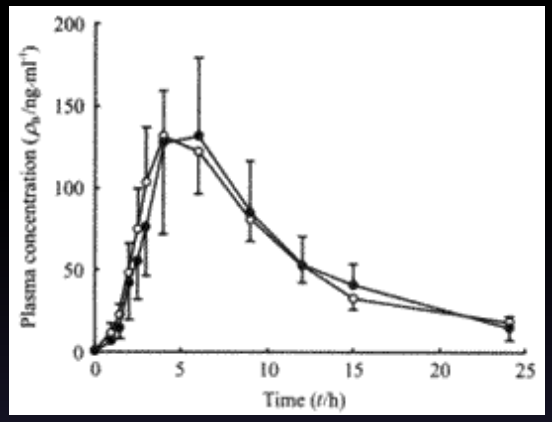
使 Guide
人工牛黄
Calculus Bovis Artifactus
人工麝香
Muscone

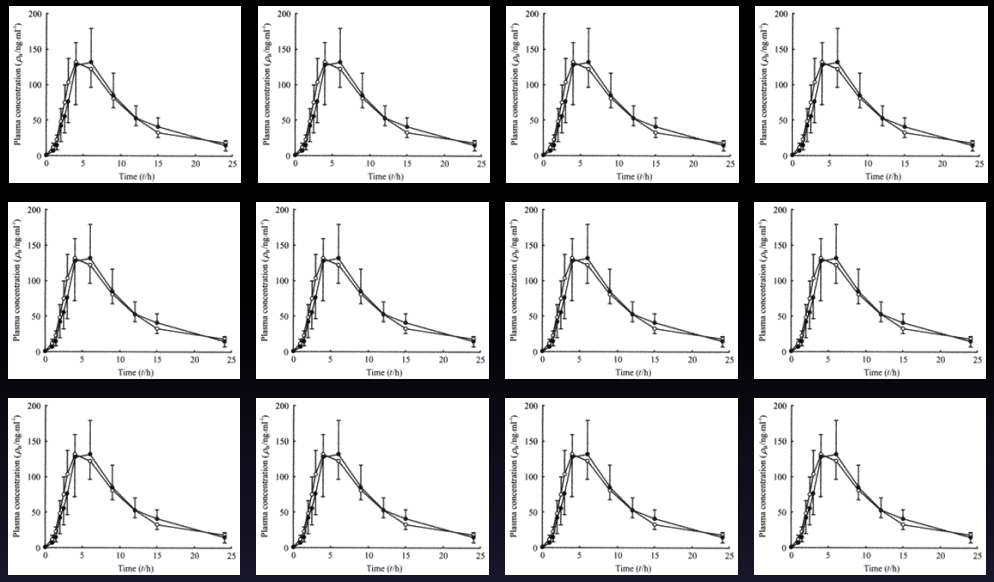
臣 Minister
川芎
Szechuan Lovage Rhizome

藤蔓之属，
皆可通经入络

太阳经的引药
透达头后部

Idea 3





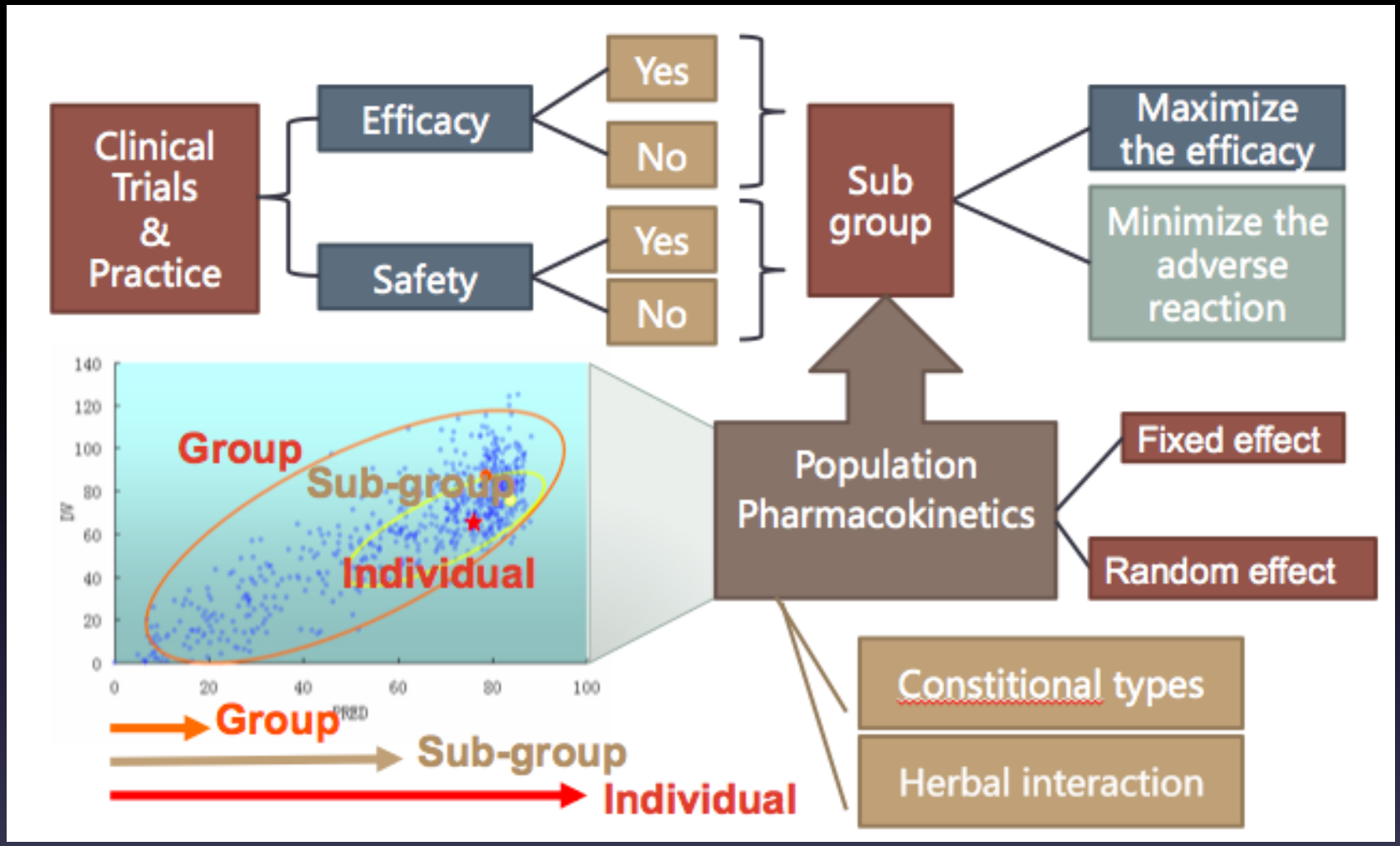
PK of western medicine

Single Ingredient, Multi-dosage

PK of herbal medicine

Multi-ingredient,Multi-dosage

Will clinical pharmacokinetics research data provide some evidence on individual difference or herbal interaction?



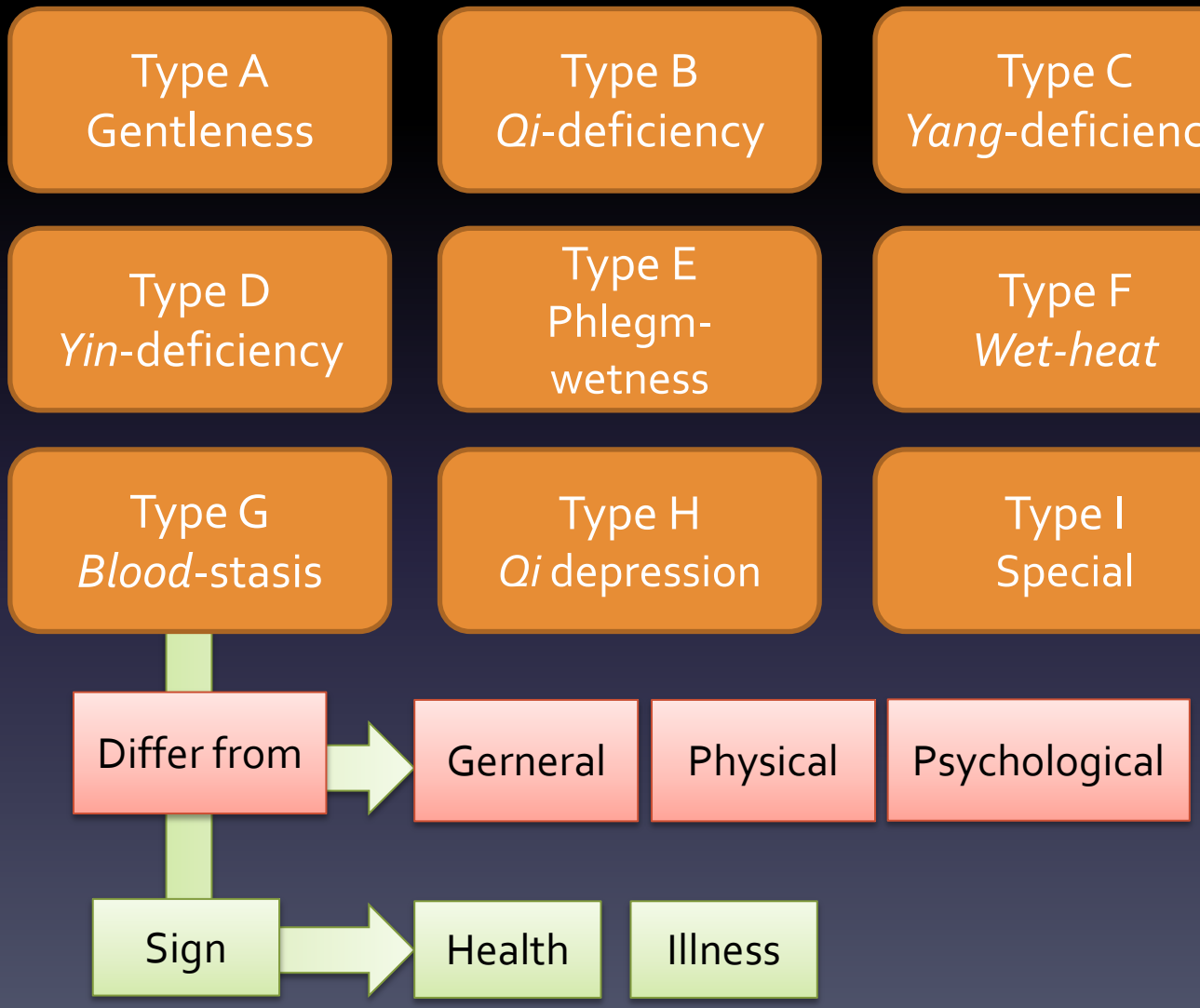
Population Pharmacokinetics (PPK)

A bridge of **formula** and **constitutional type**

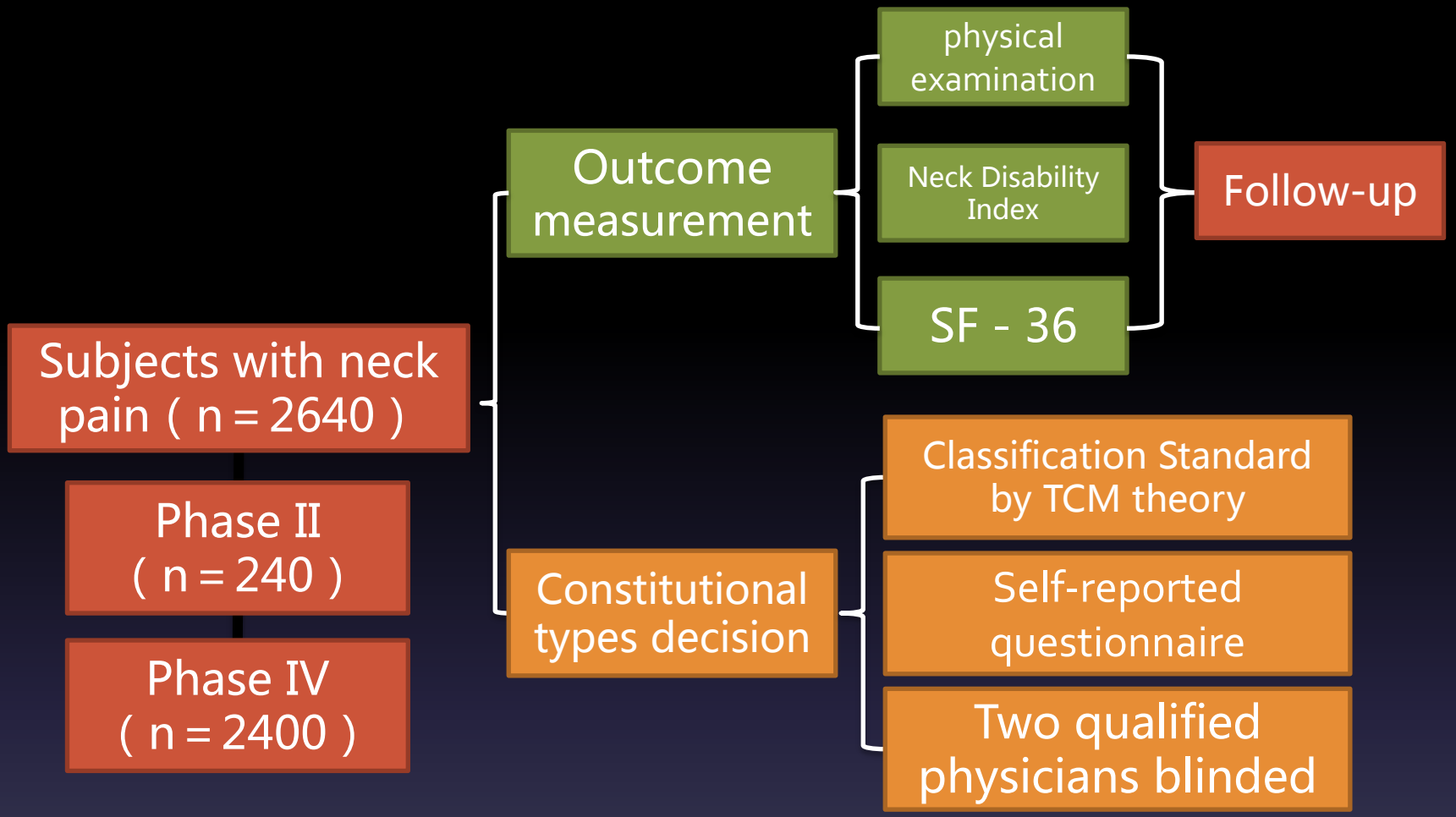
Population

1. How to set ?
2. How to use?

The nine constitutional types



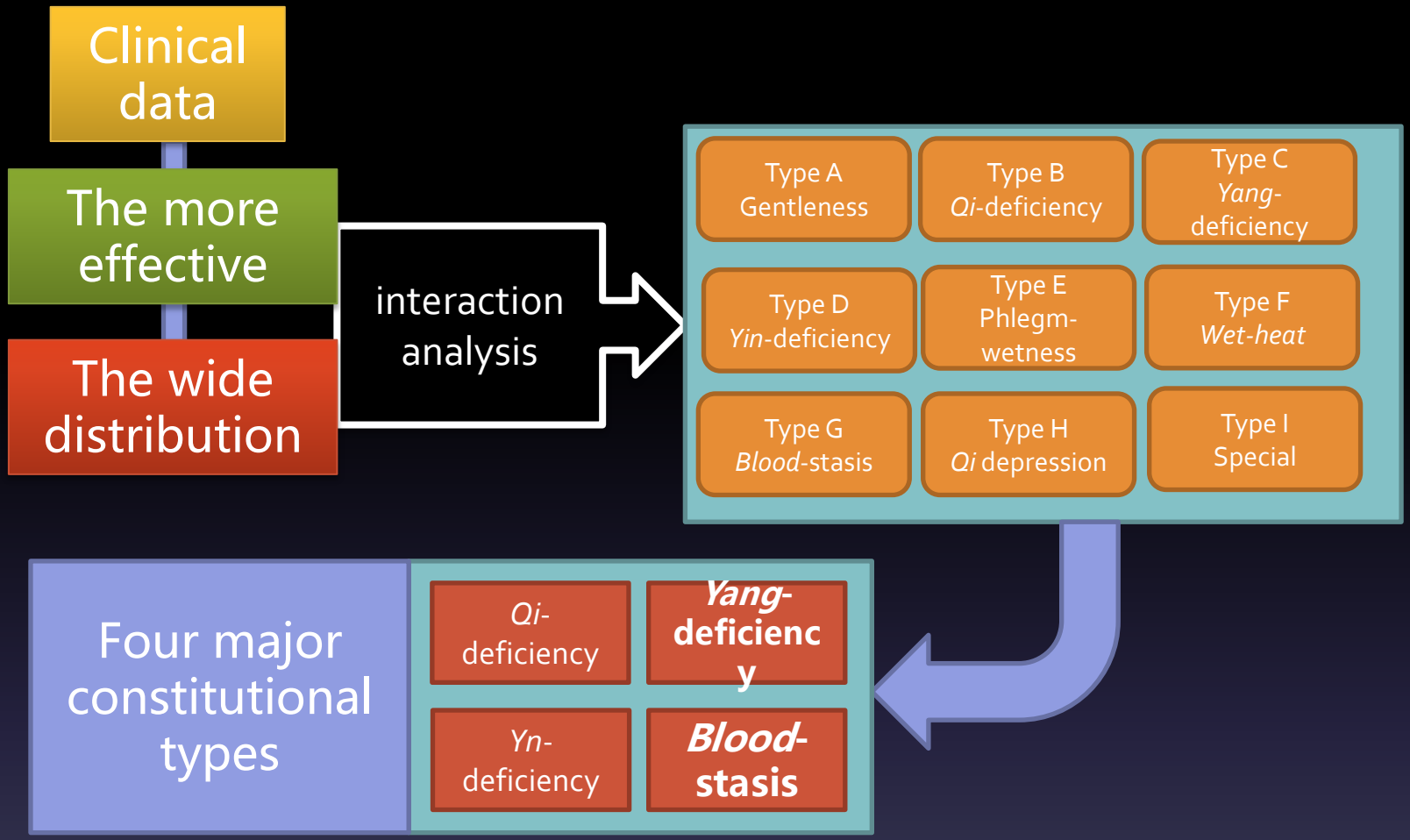
	General characteristics	Physical characteristics	Psychological characteristics	Sign of health	Sign of illness
Gentleness Type A	*Yin-Yang* balanced	Full of vitality and well-proportioned	Mild character	Good cold and hot tolerance, sleep well, good appetite and no fatigue	Less disease
Qi-deficiency* Type B	Insufficiency of primordial *Qi*	Weakened muscle*	No desire to speak	Short of breath, listless and low voice and easy to sweat and fatigue	Palpitations and influenza
Yang-deficiency Type C	More insufficiency of primordial *Qi*	Slightly muscle atrophy	More quiet and introverted	Intolerance of cold, loose stool, clear abundant urine and easy to catch a cold	Diarrhea
Yin-deficiency* Type D	*Yin*-fluid deficiency	Slim body	Quick-tempered	Feverish palms and soles, dry mouth and throat, dry eyes, flushing cheek, and dry skin is usual	Fatigue syndrome, muscle fatigue* and insomnia
Phlegm-wetness Type E	Body fluid stasis and phlegm-wetness aggregation	Obese body with accumulate fat around abdomen	Prudent	Feeling body heaviness, chest distress and excessive phlegm, sticky mouth, and sticky sweating in usual	Stroke and Diabetes
Wet-heat Type F	Internal accumulation of damp-heat	Slim body	Tend to be irritable	likely to suffer from acne, thirsty, bad breath, bitter taste in the mouth in usual	Constipation, scabies and jaundice
Blood-stasis* Type G	Poor blood circulation	All body types	Tend to be annoying and forgetful	Frequent pain* and ecchymosis and g loomy complexion	Chronic pain*
Qi-depression Type H	Depression and stagnation of *Qi*	Slim body	Depressive, sensitive and suspicious	Frequently sigh, distention and pain in chest	hypochondria
Special diathesis Type I	Special diathesis	All body types	All types	Hypersensitiveness	Asthma and urticaria



To utilize information

Outcome including

Disease & *Zheng*

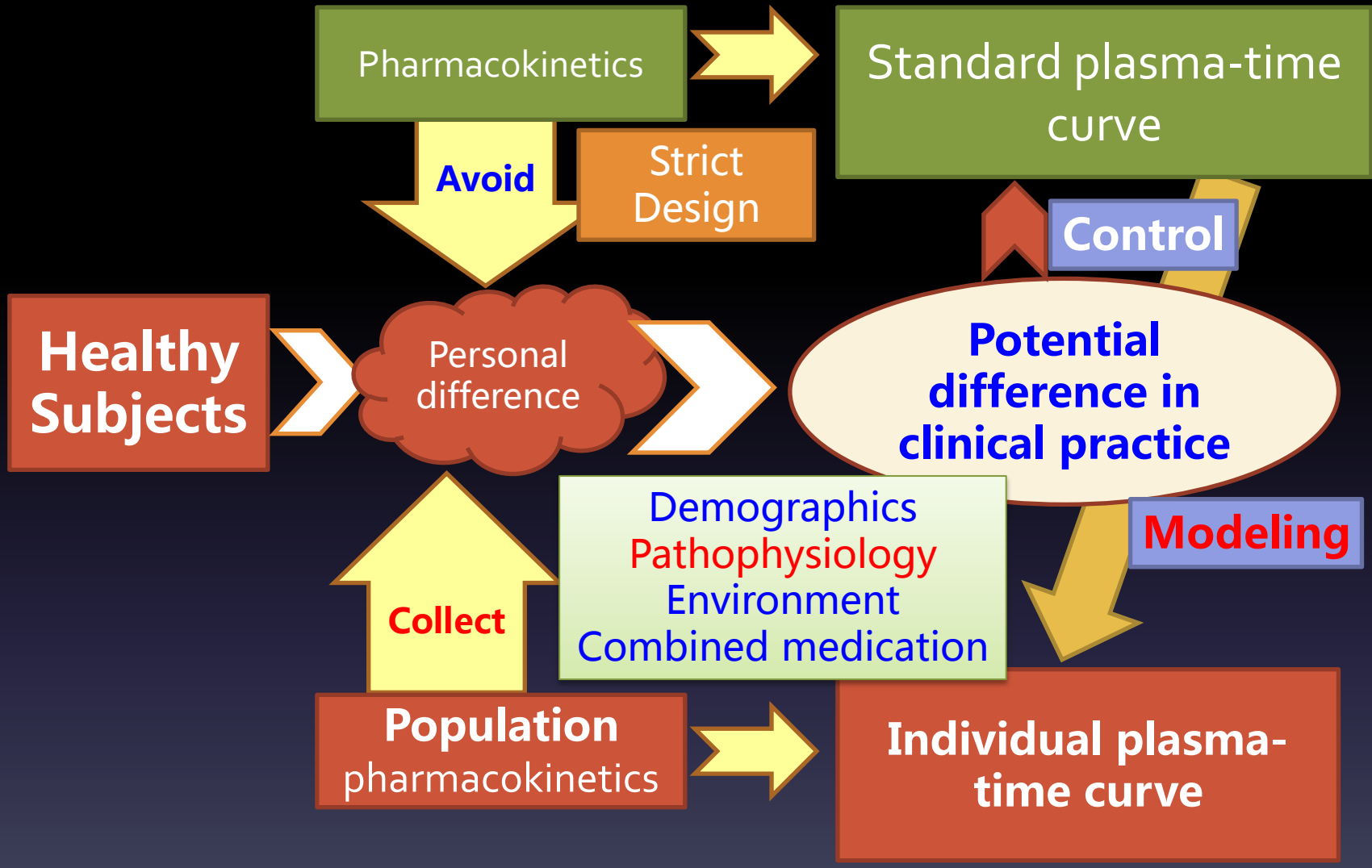


To target population

The wider distribution &
The more effective

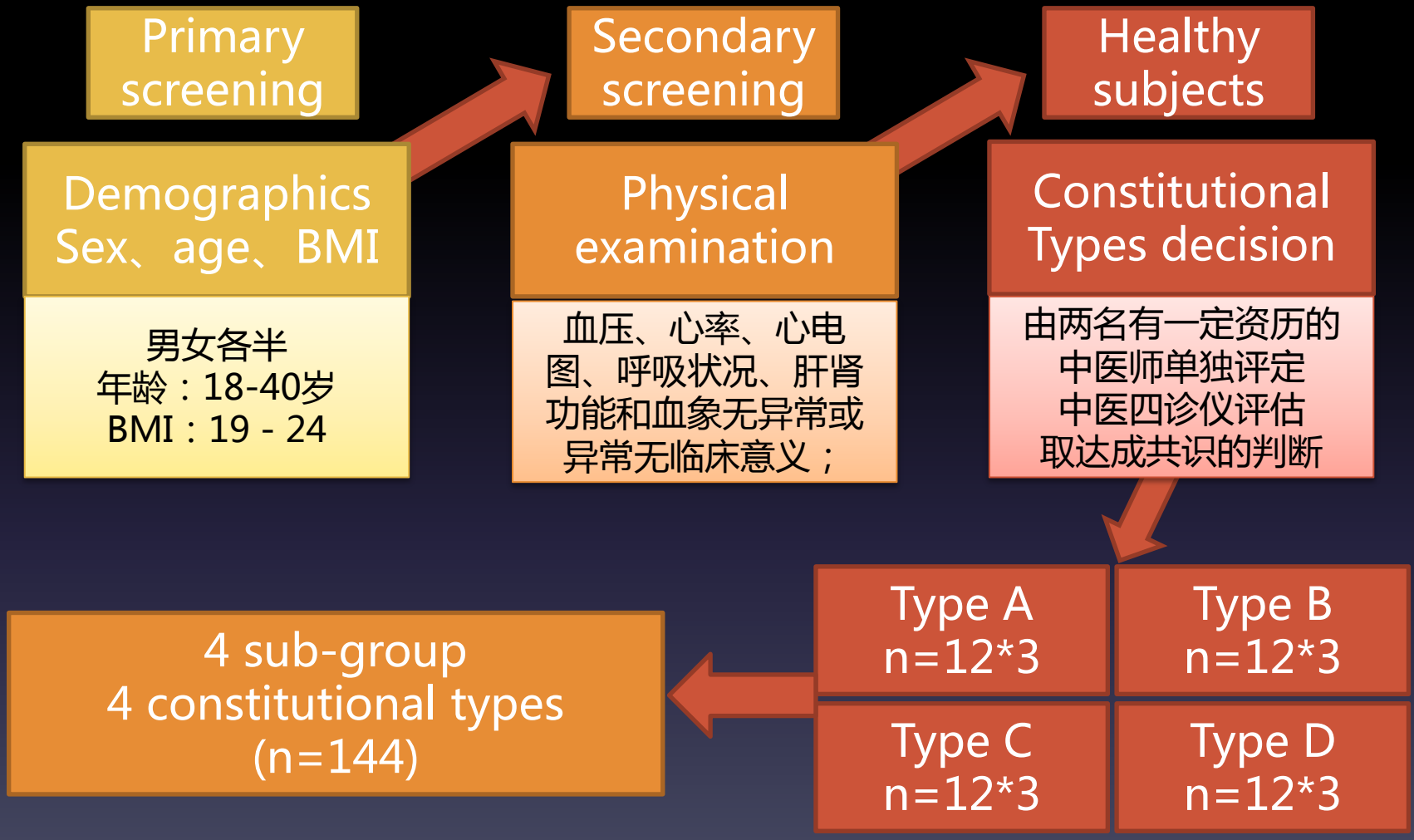
Pharmacokinetics

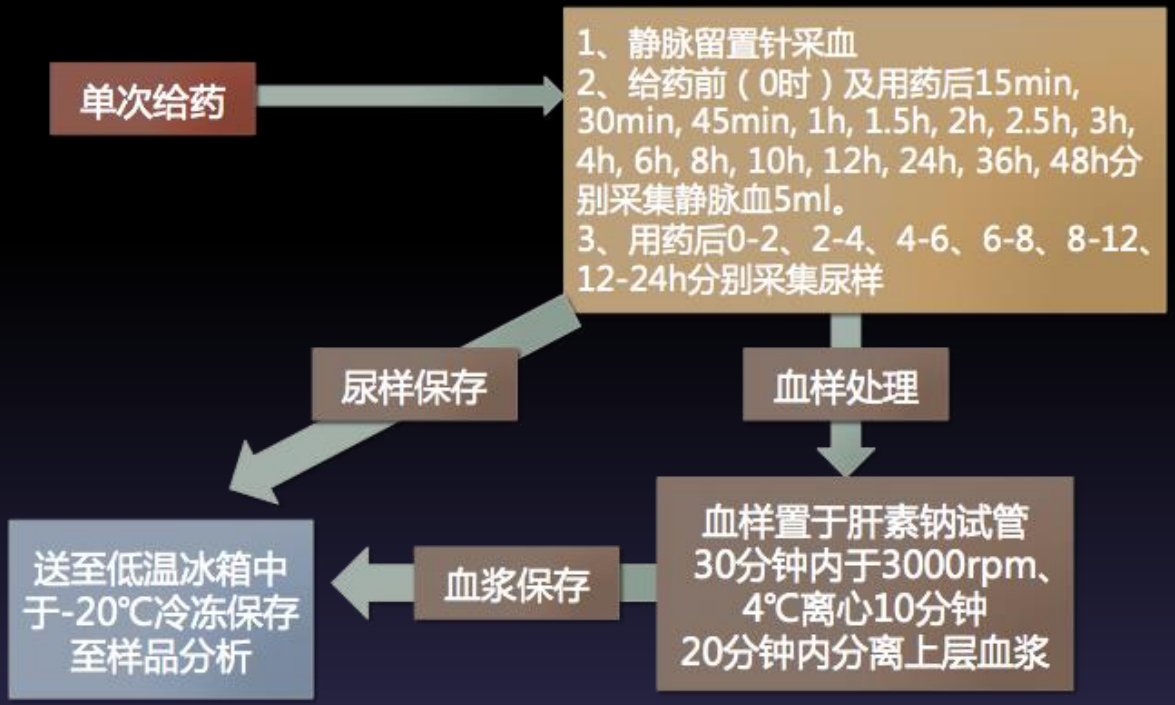
1. Population PK vs classical PK ?
2. Clinical PK of herbal medicine ?

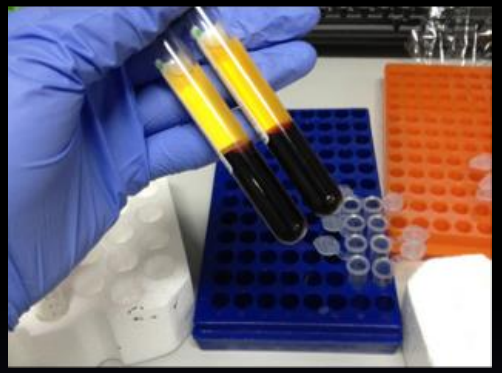


Face it or Avoid it ?

PPK VS PK


Primary screening
Secondary screening
Healthy subjects
Demographics
Sex、age、BMI
Physical examination
Constitutional Types decision
男女各半
年龄：18-40岁
BMI：19 - 24
血压、心率、心电图、呼吸状况、肝肾功能和血象无异常或异常无临床意义；
由两名有一定资历的中医师单独评定
中医四诊仪评估
取达成共识的判断
Type A
n=12*3
Type B
n=12*3
Type C
n=12*3
Type D
n=12*3
4 sub-group
4 constitutional types
(n=144)









- 16 time windows for blood collection (5ml) in 3 days
  - 2304 samples for PK anlysis of each ingredient
- 6 time windows for urine collection in 3 days

Ingredient

黄芪甲苷、5-o-甲基维斯阿木醇苷、毛蕊异黄酮、
毛蕊异黄酮葡萄糖苷、芒柄花素 、芒柄花素苷、黄芪皂苷Ⅲ、黄芪皂苷Ⅰ、洋川芎内酯A 、洋川芎内酯I 、粉防己碱、防己诺林碱、木兰花碱 、盐酸巴马汀、四氢巴马汀、盐酸小檗碱 、四氢表小檗碱 、青藤碱、蛇床籽素 、大豆素、异补骨脂素 ……

PK parament

C_{max} T_{max}

$AUC_{0\text{-}t}$ $AUC_{(i,\ i+1)}=(ti+1-ti)(Ci+Ci+1)/2$

$t_{1/2}$

$t_{1/2}=In(2)/\ k_e$

$AUC_{0\text{-}}$

$AUC_{0\text{-}\infty}=AUC_{0\text{-}t}+\ C_t/k_e$

SNP on pharmaco-metabonomics

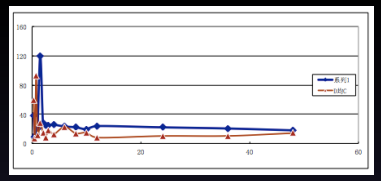
CYP1A1、CYP1A2、CYP2D6、CYP2C9、CYP2C19、CYP2E1、CYP3A4和CYP3A5

Constitutional type and vital sign

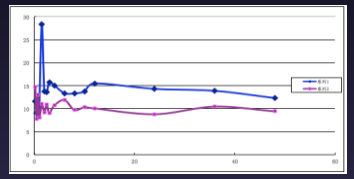
试验前后生命体征监测
一般体格检查，血尿常规，血生化及心电图检查。
试验前后体质分型判定

芪麝丸临床药代动力学前期预试验结果

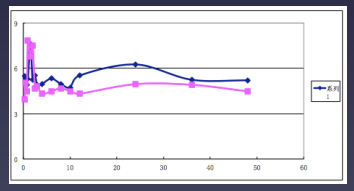
Stephaniae Tetrandrae



粉防己碱

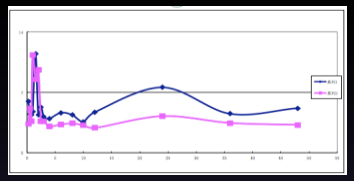


防己诺林碱

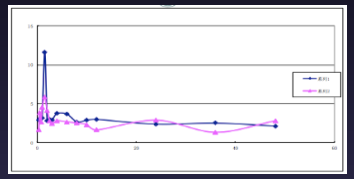


5-O-甲基维斯阿米醇苷

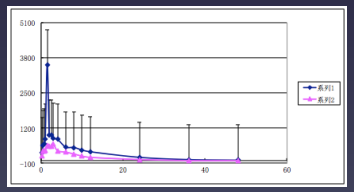
Ovientvine



芒柄花苷

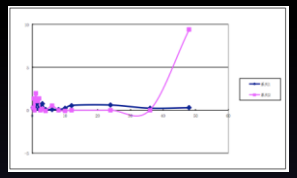


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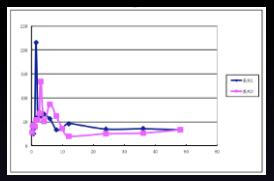


青藤碱

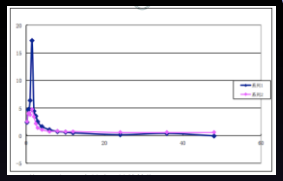
Ovientvine & Stephaniae Tetrandrae



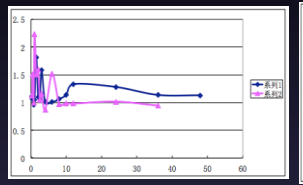
盐酸巴马汀



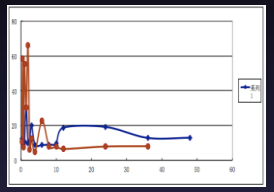
木兰花碱



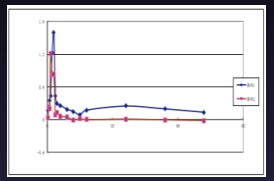
四氢小檗碱



盐酸药根碱

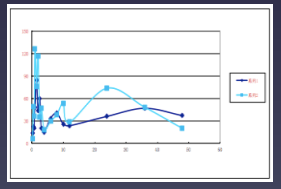


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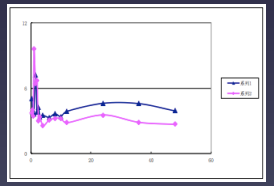


四氢巴马汀

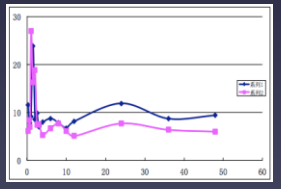
Radix Astragali



黄芪甲苷

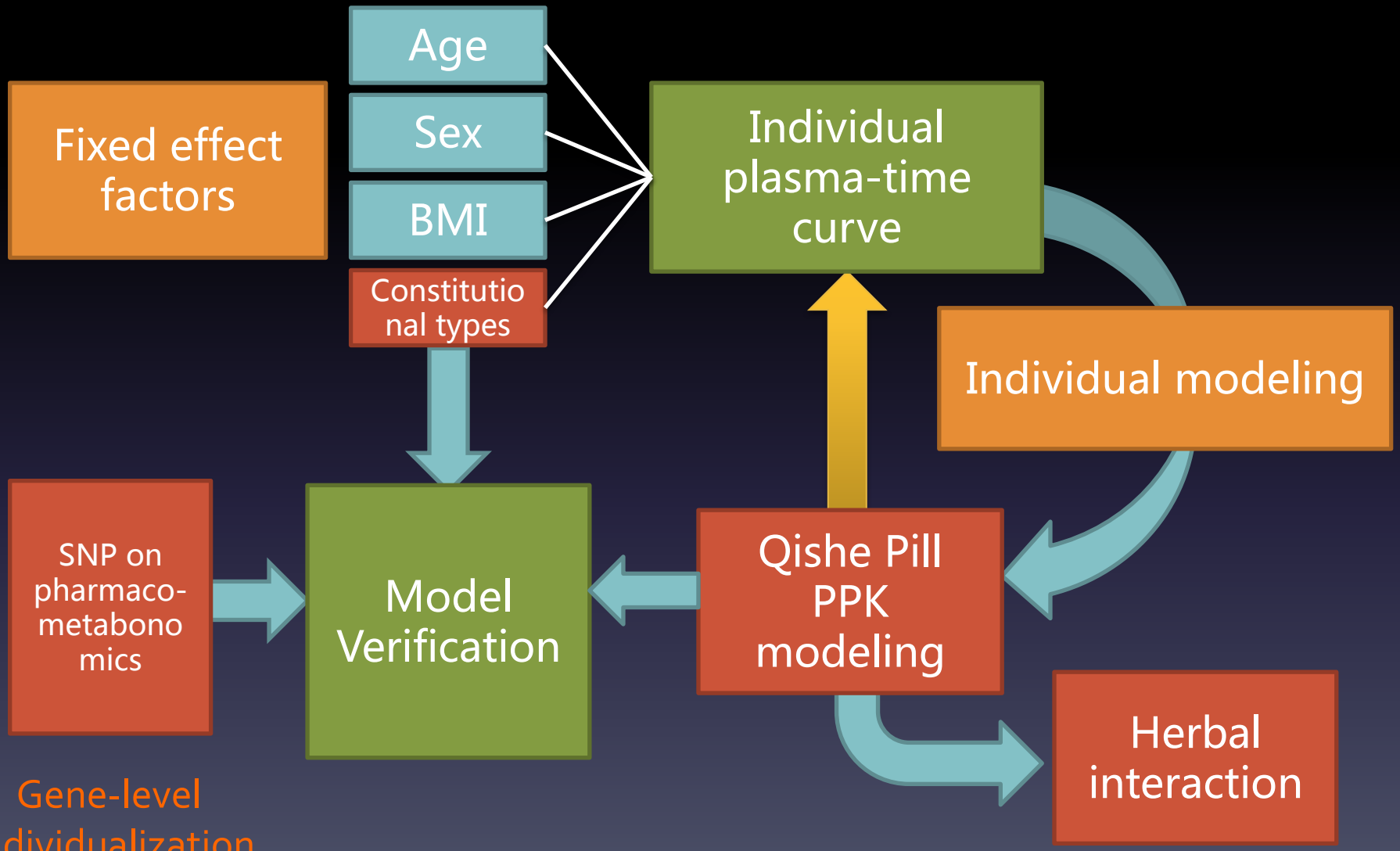


毛蕊异黄酮



毛蕊异黄酮葡萄糖苷

Qishe Pill PPK modeling



上海中医药大学附属龙华医院
Longhua Hospital, Shanghai University of TCM

- Founded in 1960, one of earliest National TCM Clinical Research Bases
- National demonstration hospital of TCM
- National model establishment, Regarded as spiritual civilization unit in Shanghai for 12 years
- National TCM Clinical Research Base (2008)
- Ranked 1st in the national re-evaluation of A hospital of TCM
- Ranked 2st in the national hospital competitiveness of TCM(2014)





Thank you for your attention!

