

中研院「臨床試驗」系列教育訓練課程

新藥臨床試驗之臨床前試驗設計與要求

Preclinical Study Design and Requirement for Supporting Clinical Trial
of New Pharmaceutical Development

1

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115, 10, 22

葉嘉新簡介

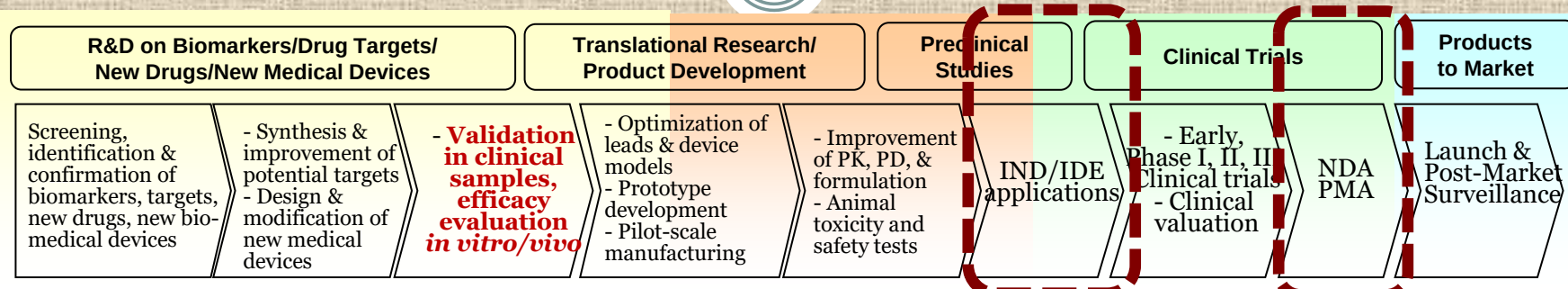
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- **現職**——財團法人醫藥品查驗中心藥劑科技組 組長
- **主要學歷**
 - 北醫藥學系學士
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- **主要經歷**
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 - 台灣生技整合育成中心新藥組總監
 - 行政院科技顧問組生技小組研究員
 - 財團法人醫藥品查驗中心審查員/小組長/組長
 - 台科大、清大、輔大兼任助理教授
- **專門職業**——藥師

Milestone of New Drug Development

Scope of Today's Presentation

3



Hit to lead study

Screening assay
In vitro PD (μM)
In vitro PK

Lead optimization

In vitro PD (sub μM)
In vivo efficacy
In vivo PK
Preliminary tox
Pre-formulation
Scale-up feasibility

IND-enabling study

CMC
GMP production
Primary efficacy
GLP Safety pharm
GLP Tox + TK
PK profile
FIH protocol
IND package (IB + CRF)

Phase I (安全性)

- 20~80名健康志願者
- 健康人藥物動力學ADME
- 人體耐受劑量研究
- 決定安全性及劑量範圍

Phase II (有效性)

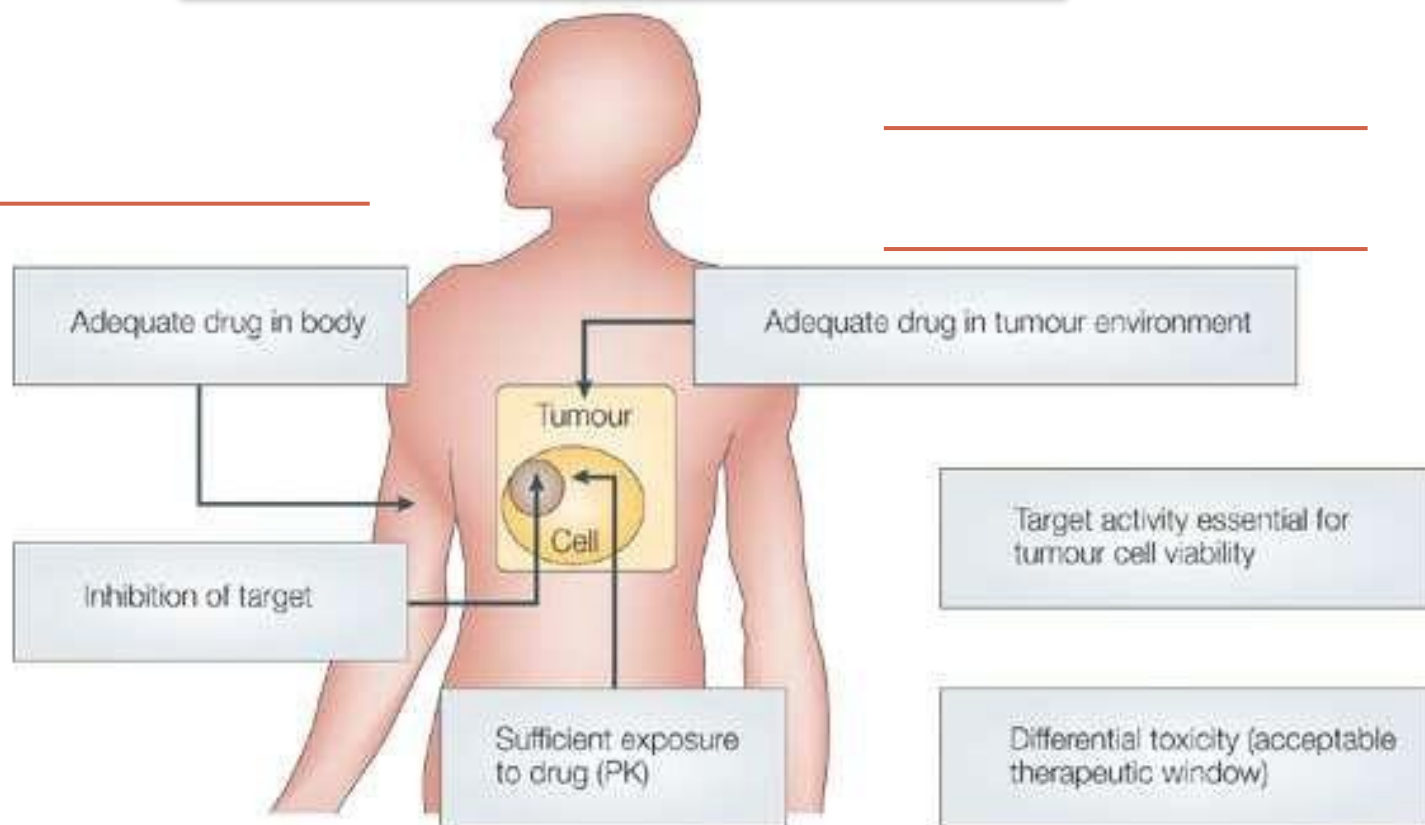
- 100~300名志願病患
- 藥品療效
- 病患藥物動力學ADME
- 決定治療劑量及治療範圍

Phase III (確認使用療效及不良反應)

- 1,000~3,000名志願病患
- 多中心對照試驗
- 確認適應症，並研究藥物不良反應及交互作用

Regulatory Approval for New Drug Application

5個字詞，12字箴言



大於

Nature Reviews | Drug Discovery

PART I

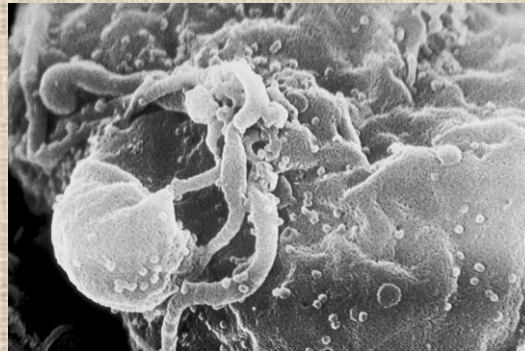
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From **Drug Discovery to IND:** Preclinical Development and Regulatory Requirement

新藥開發：從解決

() 開始

6



Need

需求

Benefit

臨床利益

Solution

解決

Differentiation

差異化創新

New Drug Modalities

7

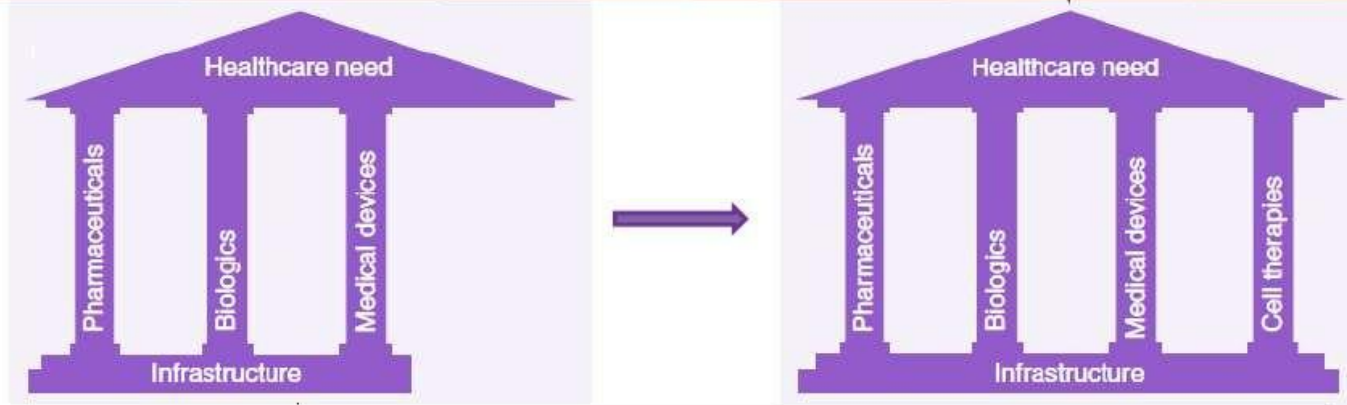


Table 1. Therapeutics and core competencies for the industries that make up the four pillars of healthcare.

Therapeutic product	Core technologies	Industry
Small molecule drug 小分子藥物	Chemistry	Pharmaceutical Industry
Macromolecule drug 蛋白藥物	Genetic engineering Monoclonal antibody	Biotech
Medical device 醫療器材	Physics Engineering	Medical Device Industry
Cell therapy 細胞治療 Gene therapy 核酸藥物	Cells DNA, mRNA, SiRNA	Advanced Therapy Industry

Regen. Med. (2011) 6(3), 265–272

8

- | Drug | Covered target classes | Mode of action |
|-------------------------------|---|---|
| Small molecular compound (SM) | Enzymes | Inhibitors, activators ^a |
| | Receptors | Agonists, antagonists, modulators, allosteric activators, sensitizers |
| | Transcription factors | Inhibitors, activators |
| | Ion channels | Inhibitors, openers |
| | Transport proteins | Inhibitors |
| | Protein–protein interface | Inhibitors of protein–protein interaction ^a |
| | Nucleic acids | Alkylation, complexation, intercalation |
| Biologics (BIOL) | (Extracellular) proteins | Antibodies |
| | Transmembrane receptors, extracellular proteins | Recombinant proteins |
| | Cell surface receptors | Antibody–drug conjugates (ADCs) |
| | Substrates and metabolites | Enzymatic cleavage |
| Nucleic acids | RNA | RNA interference |

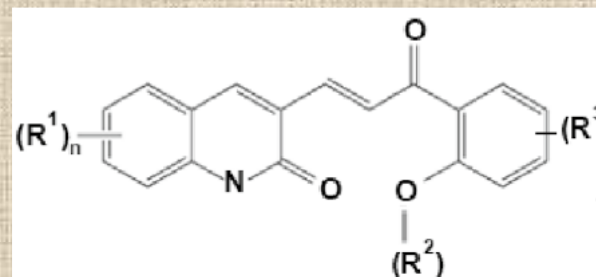
Drug Discovery Today Vol 17S Feb 2012

Hit to Lead Optimization: _____ Study

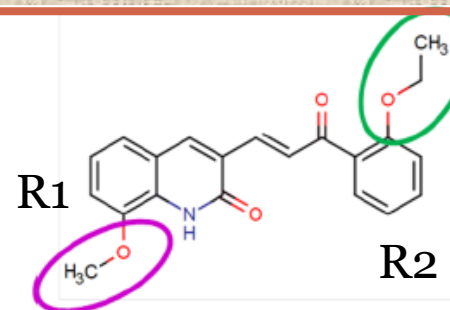
9

Lead optimization of novel quinolone chalcone compounds by SAR study

CTRs	R1	R2	R3
CTR-17	H	methyl	H
CTR-18	6-methyl	methyl	H
CTR-19	7-methoxy	methyl	H
CTR-20	6-methoxy	methyl	H
CTR-21	8-methoxy	methyl	H
CTR-32	H	ethyl	H



	Melanoma cell lines		Breast cancer cell lines	
	MZ-Mel-3	Mel-SOE	MDA-MB435	MDA-MB231
CTR17 (nM)	227 ± 30	786 ± 52	290 ± 66	657 ± 72
CTR18 (nM)	239 ± 13	817 ± 34	307 ± 7	530 ± 119
CTR19 (nM)	6832 ± 957	10,095 ± 64	4723 ± 2761	6506 ± 1388
CTR20 (nM)	98 ± 21	338 ± 78	90 ± 10	216 ± 21
CTR21 (nM)	6 ± 1	27 ± 5	7 ± 2	17 ± 3
CTR32 (nM)	6 ± 2	33 ± 9	13 ± 5	20 ± 2



CTR-21

The move from 6 to 8 carbon makes CTR-21 more cytotoxic and changes the way it binds to tubulin

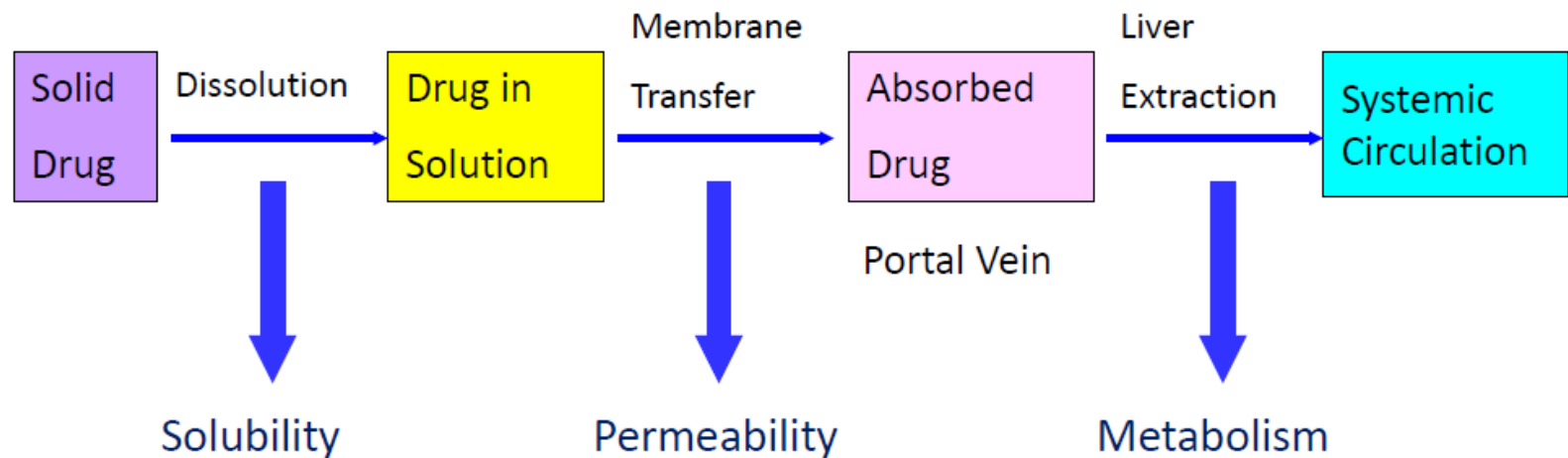
CTR-32 ethoxy group is more cytotoxic than methoxy group. However, it reduces metabolic stability and may target other proteins

SAR: Structure Activity Relationship

In Vitro PK

10

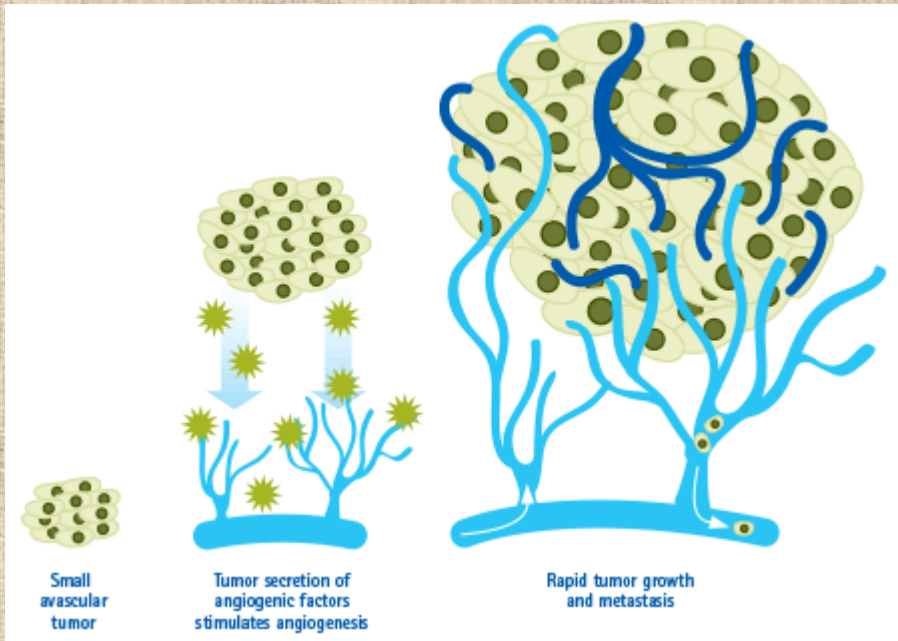
Solubility, Permeability, Chemical and Metabolic Stability Affects Oral Bioavailability



In Vitro PD (Functional Assay)

11

- Screen for anti-angiogenesis drug



HUVEC Cells incubated 6-10 hours at 37°C on ECMatrix™ provided in the *In Vitro* Angiogenesis Assay

In Vivo PD (Efficacy Study)— Syngeneic Models as an Example

12

Historical origins of
in vitro cell line: murine tumor



Implant into original
inbred mouse strain

Syngeneic Models for I/O
Research

Standard subcutaneous models
for I/O agent evaluation

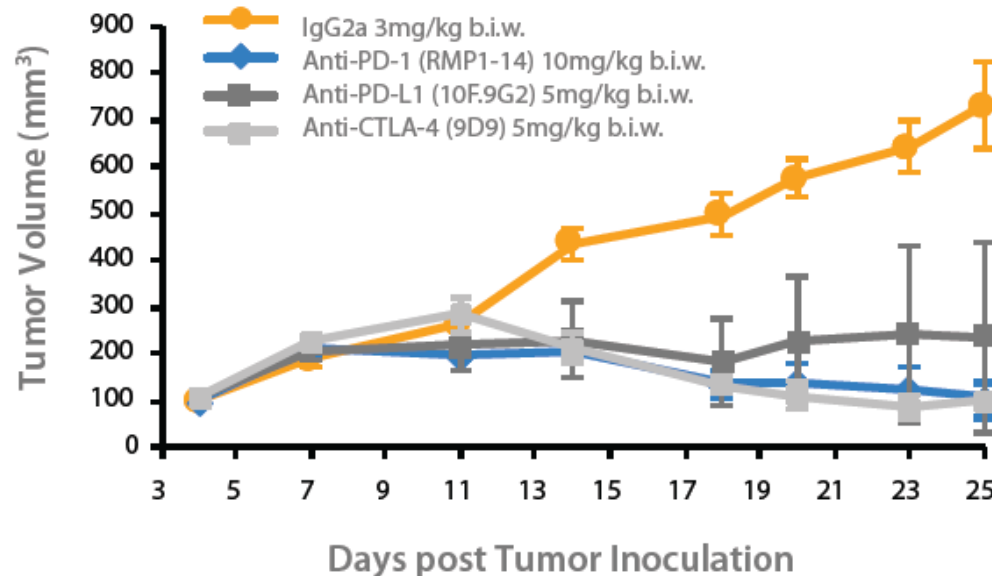
Advanced orthotopic, bioluminescent,
and metastatic modeling

Checkpoint inhibitor
benchmarking

Combination therapy
strategies

Immune cell profiling

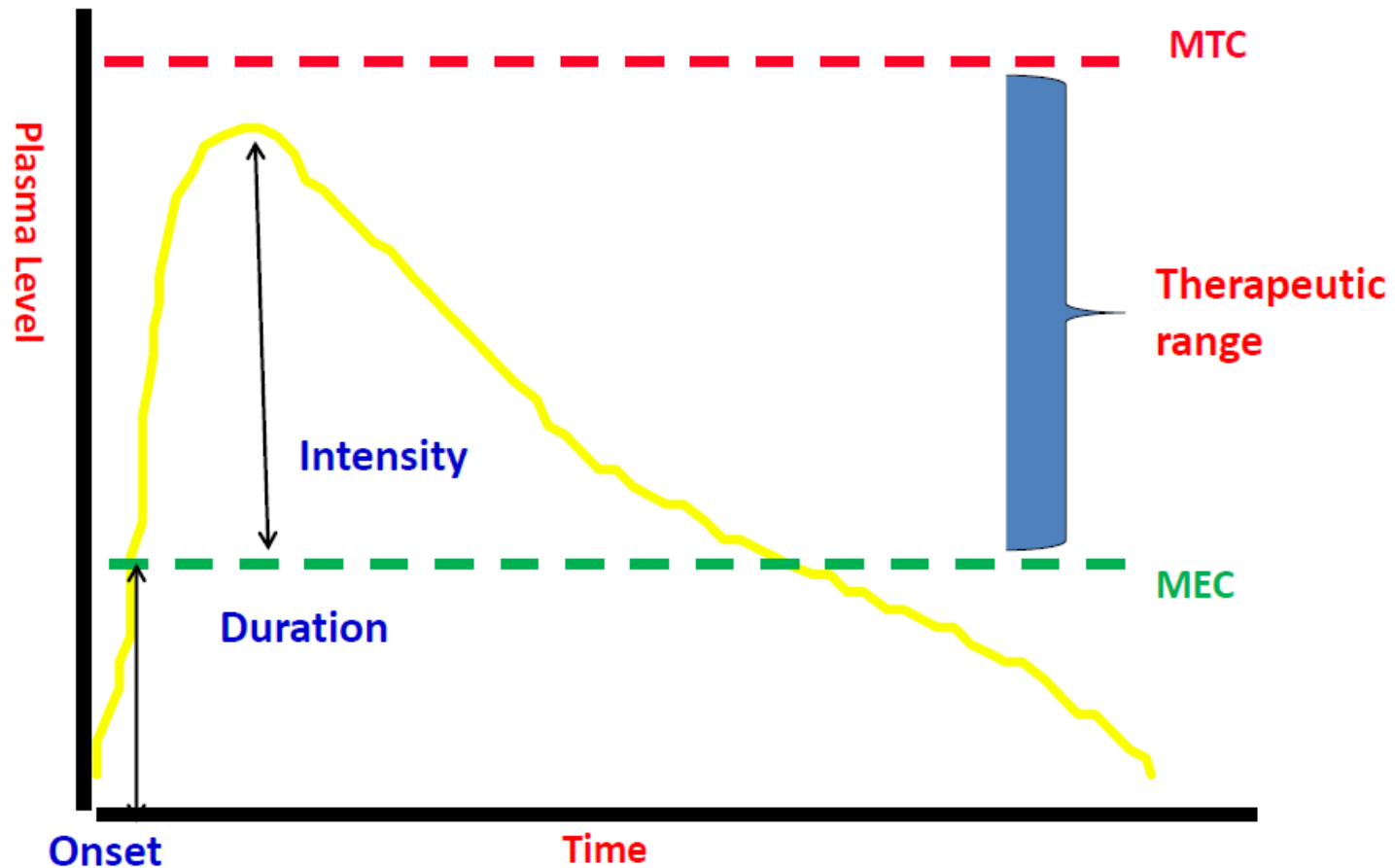
Large scale *in vivo*
screening



Treatment	T/C (%)	TGI (%)	p Value
Anti-PD-1 (RMP1-14)	15	85	<0.001
Anti-PD-L1 (10F.9G2)	32	68	0.042
Anti-CTLA-4 (9D9)	13	87	<0.001

In Vivo PK

13



Early Stage Safety Study



Pharma
Discovery Services

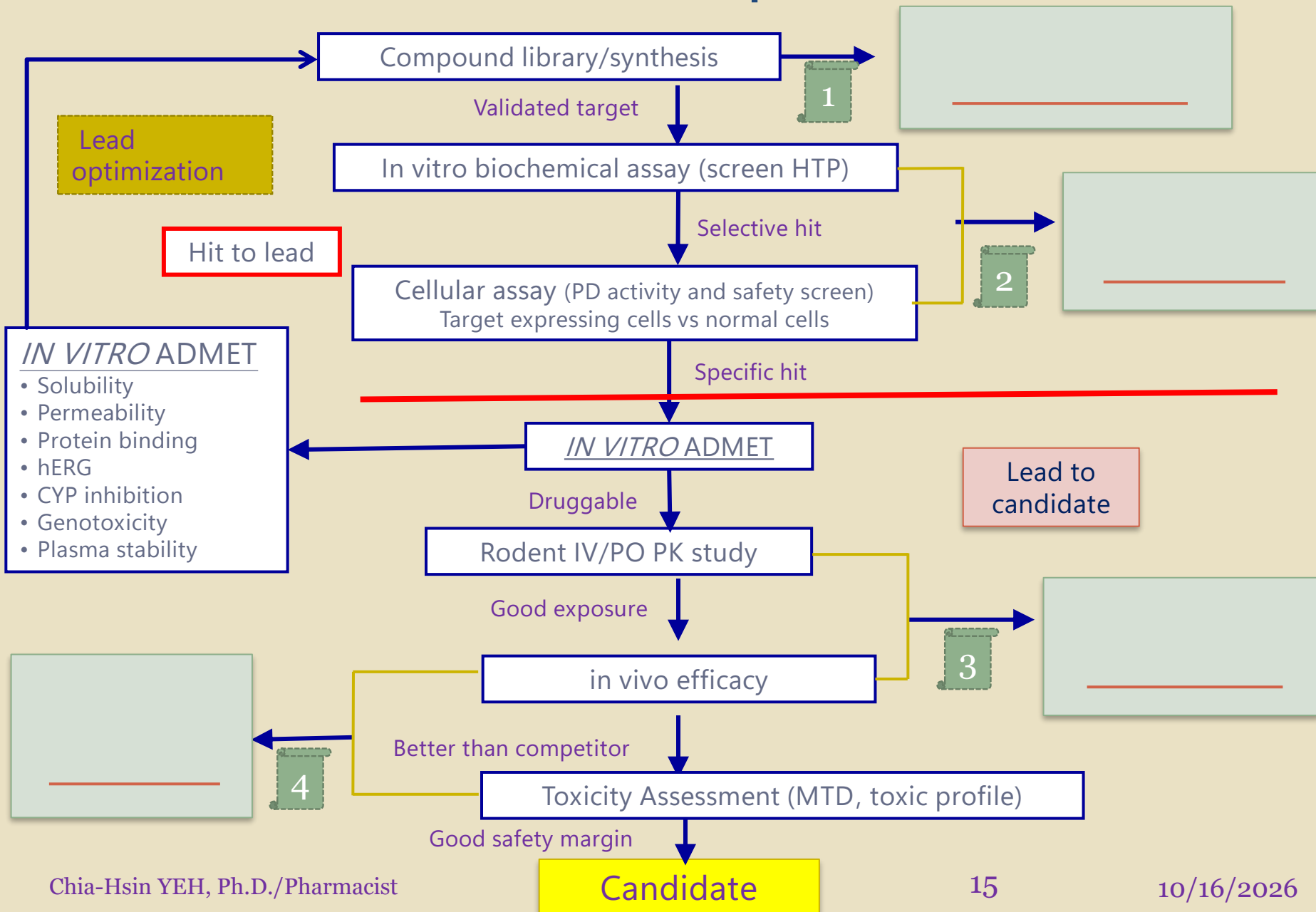
14

SafetyScreen44™ Panel

FAMILY	ASSAY	FORMAT
■ GPCR		
ADENOSINE	A _{2A}	• 📊
ADRENERGIC	alpha _{1A}	📊
	alpha _{2A}	📊
	beta ₁	• 📊
	beta ₂	• 📊
CANNABINOID	CB ₁	• 📊
	CB ₂	• 📊
CHOLECYSTOKININ	CCK ₁ (CCK _B)	• 📊
DOPAMINE	D ₁	📊
	D _{2L}	• 📊
ENDOTHELIN	ET _A	• 📊
HISTAMINE	H ₁	📊
	H ₂	📊
MUSCARINIC	M ₁	📊
	M ₂	📊
	M ₃	📊
OPIOID & OPIOID-LIKE	delta ₂ (DOP)	• 📊
	kappa (KOP)	• 📊
	mu (MOP)	• 📊
SEROTONIN	5-HT _{1A}	• 📊
	5-HT _{2B}	📊
	5-HT _{2A}	• 📊
	5-HT _{2C}	• 📊
VASOPRESSIN	V _{1a}	• 📊
■ TRANSPORTERS		
DOPAMINE	Dopamine Transporter	📊

FAMILY	ASSAY	FORMAT
NOREPINEPHRINE	Norepinephrine Transporter	📊
SEROTONIN	5-HT transporter	📊
■ ION CHANNELS		
GABA CHANNEL	BZD (central)	• 📊
GLUTAMATE CHANNEL	NMDA	📊
NICOTINIC CHANNEL	N neuronal α4β2	• 📊
SEROTONIN CHANNEL	5-HT ₂	📊
Ca ²⁺ CHANNEL	Ca ²⁺ channel (L, dihydropyridine site)	📊
K ⁺ CHANNELS	hERG (membrane preparation)	📊
	K _v channel	📊
Na ⁺ CHANNEL	Na ⁺ channel (site 2)	📊
■ NUCLEAR RECEPTORS		
STERIOD NUCLEAR RECEPTORS	AR	• 📊
	GR	• 📊
■ KINASES		
CTK	Lck kinase	📊
■ OTHER NON-KINASE ENZYMES		
AA METABOLISM	COX ₁	📊
	COX ₂	📊
MONOAMINE & NEUROTRANSMITTER	Acetylcholinesterase MAO-A	📊
PHOSPHODIESTERASES	PDE3A	📊
	PDE4D2	📊

Hit to Candidate Development Flowchart



After Candidate: Pre-clinical Development

16

- Chemistry, Manufacturing and control (_____) – Quality
- Pharmacology and Toxicology (_____) – Animal efficacy and safety
- Pharmacokinetics and Pharmacodynamics (_____) – Dose (concentration)-response relationships, ADME
- Biologics – Quality and preclinical efficacy and safety

CMC Information

17

- Section of IND to describe the composition, manufacturing, and control of the _____ and _____
- Provide _____, _____, _____ and _____ of tested drug
- Allows evaluation of the _____ in the proposed study
 - The identification of a safety concern or insufficient data to make an evaluation of safety is the basis for a clinical hold

Drug Substance

18

- _____ - physical, chemical, or biological characterization (may be brief and limited)
- _____ of its manufacturer
- General method of preparation
- Acceptable _____ and analytical _____ to assure identity, strength, quality and purity
- _____ (COA) for the clinical batch

Drug Product

19

- List of _____ components (active / inactive; appear / not appear in the drug product)(Q1)
- _____ composition (Q2)
- The name and address of _____
- Brief, general description of the method of manufacturing and packaging _____
 - Include sterilization process
 - Flow diagram recommended

Drug Product

20

- Acceptable limits and analytical methods
 - Brief description of acceptable limits and methods
 - Copy of COA of the clinical batch
 - bioactivity and specification should available
- study and test methods
 - Brief report of drug product in proposed container

Placebo and Labeling

21

- ---

 - Brief general description of the composition, manufacture, and control of any placebo to be used
- ---

 - A copy of all labels and labeling to be provided to each investigator
 - Labels must carry “

” statement, e.g.,

Pharmacology

22

Pharmacology = _____ (PD) +
_____ (PK)

- Three categories of pharmacodynamics:
 - _____ **pharmacodynamic**: Studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target
 - _____ **pharmacodynamic**: Studies on the mode of action and/or effects of a substance **NOT** related to its desired therapeutic target
 - _____ **pharmacology**: Studies focused on identifying adverse effects on physiological functions

Pharmacodynamics (PD)

23

The science of what _____ does to

In vitro pharmacological studies

In vivo pharmacological studies

■ For example

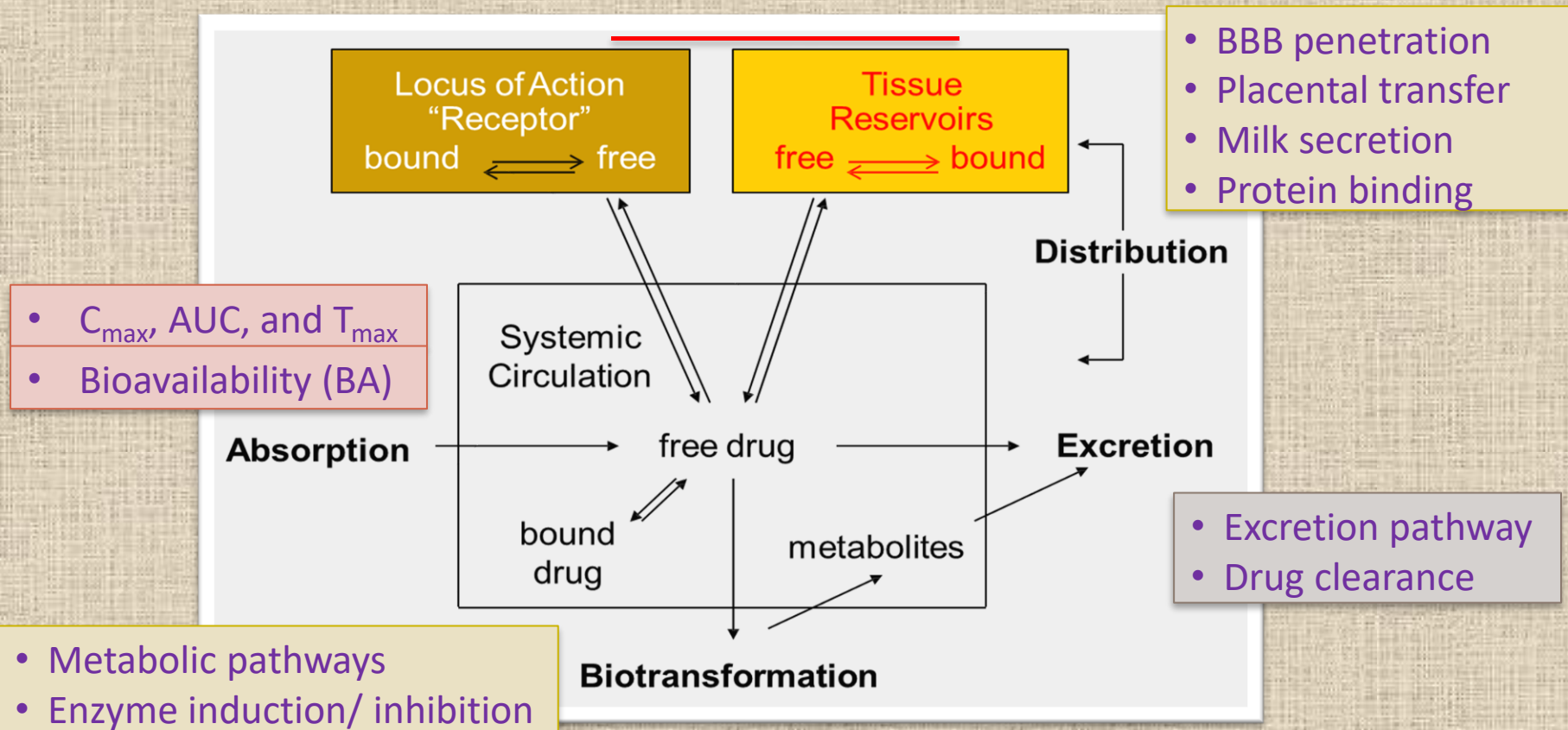
- ❑ Pharmacological/disease model studies
- ❑ Dose-response studies
- ❑ Therapeutic ratio studies
- ❑ Parent vs. active metabolite studies

■ To determine _____ dose in human

Pharmacokinetics (PK)

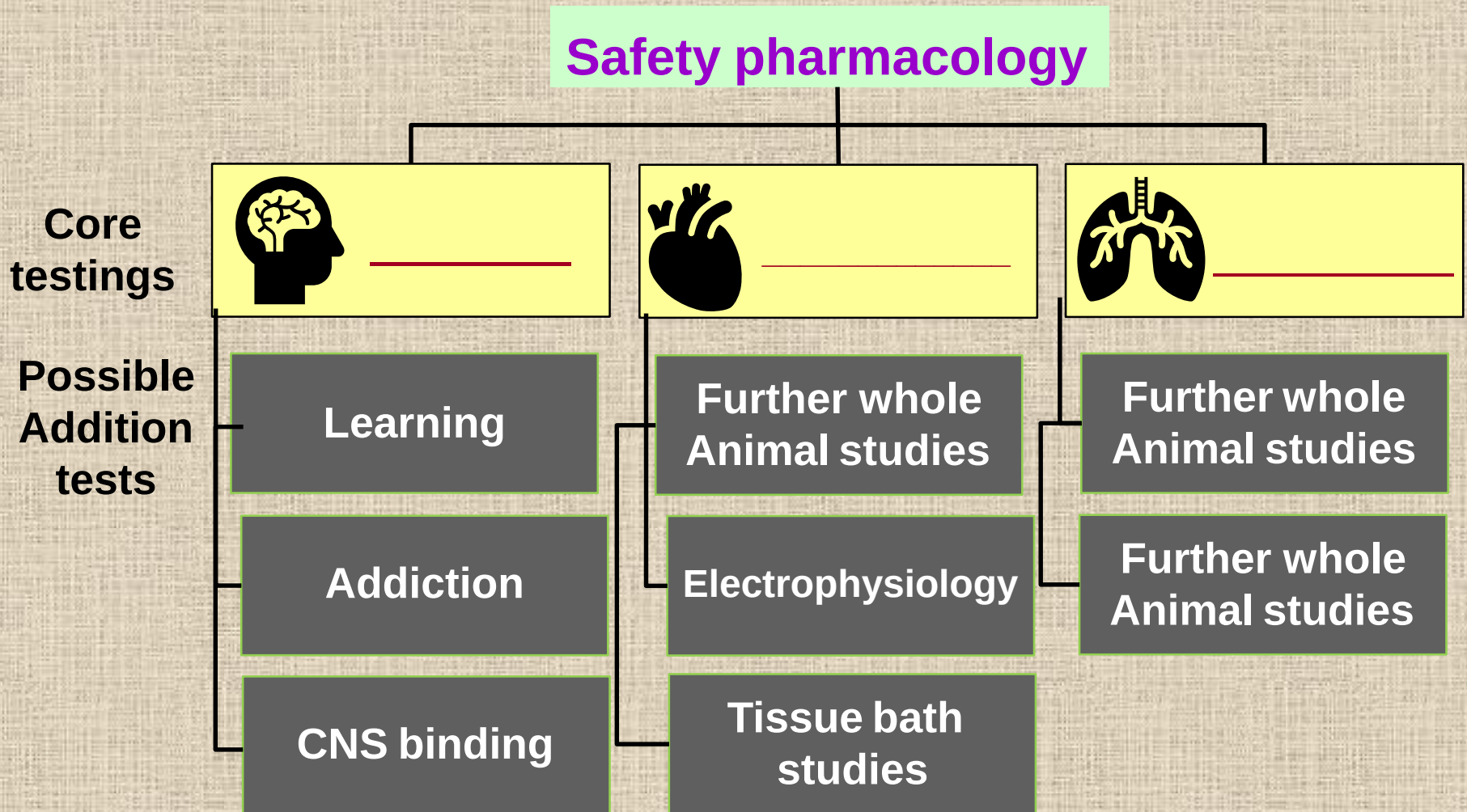
24

The science of what _____ does to



Studies of Safety Pharmacology

25



Animal Toxicology

26

- Recommendation for non-clinical toxicity studies
 - General toxicity studies
 - Reproduction toxicity studies
 - Genotoxicity studies
 - Assessment of carcinogenicity potential
 - Other specialized toxicity studies

_____ * is required for _____ studies

GLP: Good Laboratory Practice

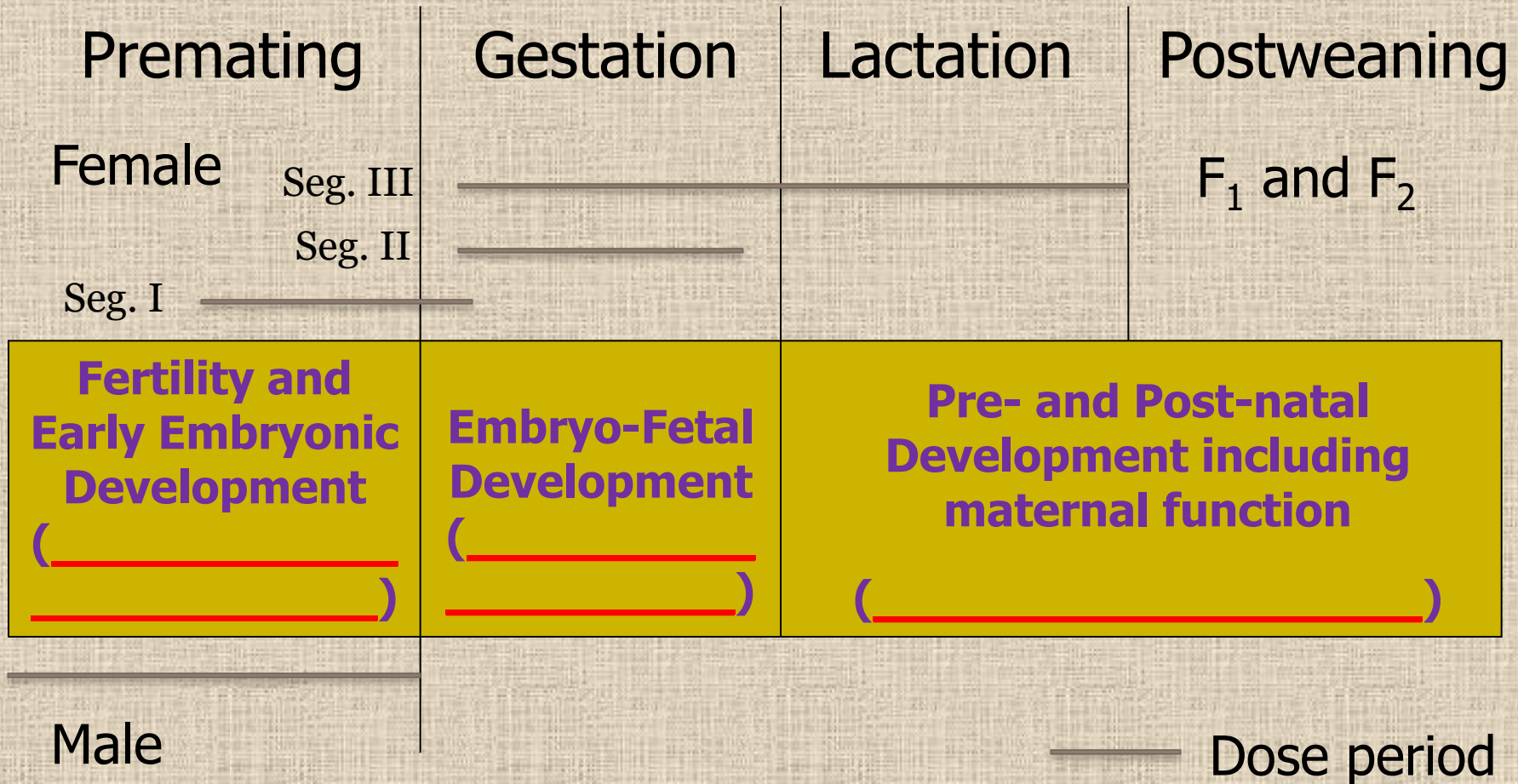
General Toxicity Studies

27

- _____ of toxic effects with respect to target organs, dose dependence, relationship to exposure, and potential reversibility
- Important information for estimation of an initial _____ starting dose for human trials and identification of parameters for clinical monitoring for potential adverse effects

ICH Reproductive Segmental Studies

28



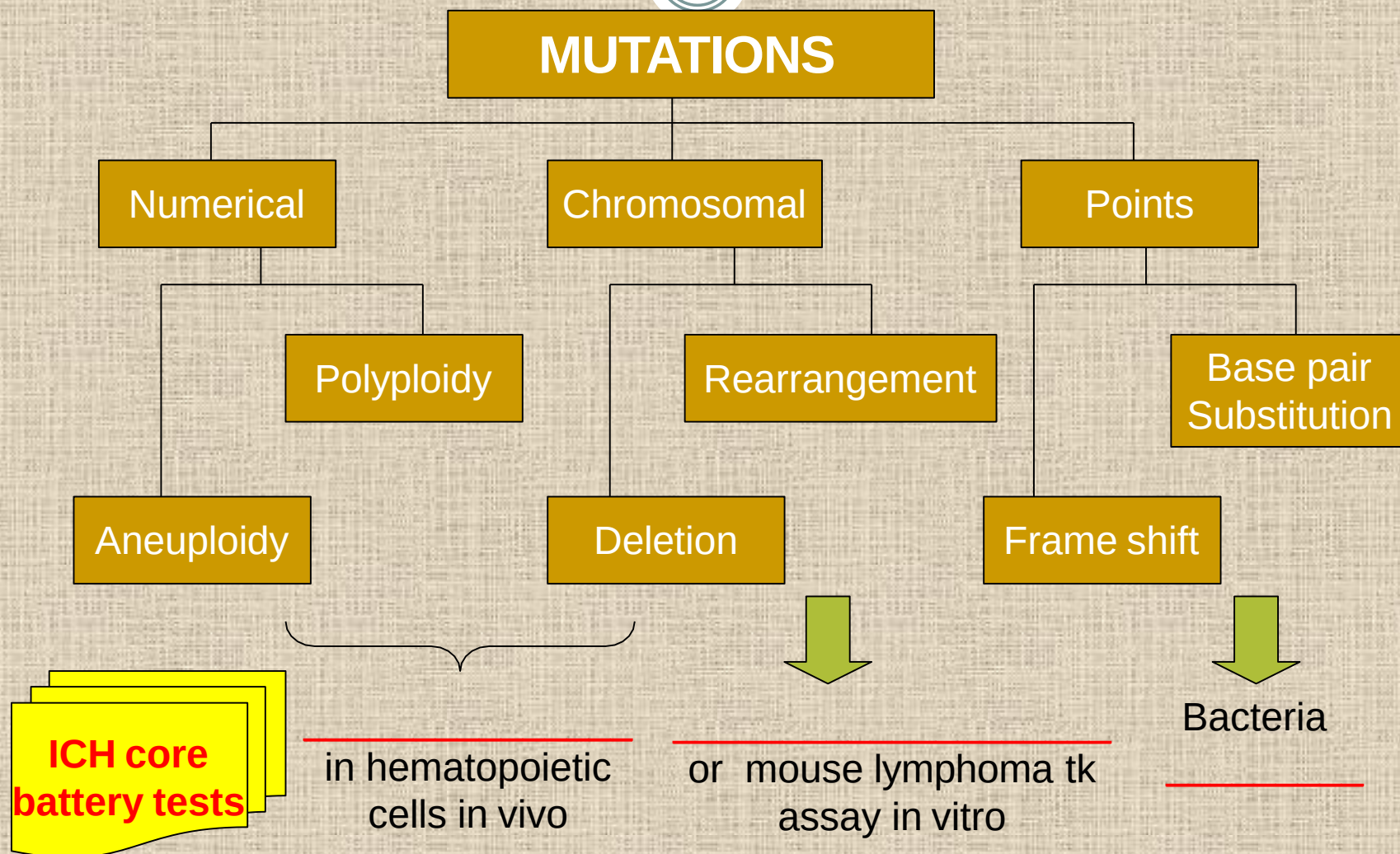
Reproductive toxicity studies

29

- Population to be exposed
 - _____: may be included in Phase I and II, but not III trials without male fertility study
 - _____: may be included in clinical trials without reproduction toxicity studies
 - _____: may be included in carefully monitored studies without reproduction toxicity studies
 - _____: all reproduction toxicity studies should be conducted. The safety data from previous human exposure are generally needed

Genotoxicity Testings

30



Carcinogenicity Studies

31

- To identify a tumorigenic potential in animals and to assess the relevant risk in humans
- Experimental approaches
 - A long-term _____ study in rodent, the rat is recommended to be selected
 - _____ *in vivo* tests for carcinogenicity
 - Short or medium-term rodent test systems
 - A life-span carcinogenicity study in a second rodent species

The Need for Carcinogenicity Studies

32

- Duration of _____
 - Expected clinical use in continuous for at least _____ months (FDA: 3 months)
 - Expected to be used _____ in the treatment of chronic or recurrent conditions (e.g., allergic rhinitis, depression, anxiety)
 - Certain delivery systems which may result in _____
- Short term use but _____

Special Toxicity Studies

33

- Local tolerance studies
- Skin sensitization and skin irritation studies
- Eye irritation studies
- Immunotoxicity studies
- Photosafety evaluation
- Assessment of QT prolongation

請依據

相關指引

請參考

相關指引

PART II

34

STUDY DESIGN OF GENERAL TOXICOLOGY REPEATED-DOSE TOXICITY STUDIES

General Consideration

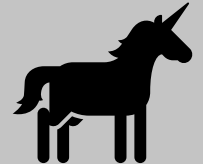
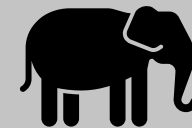
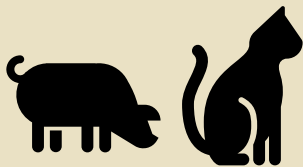
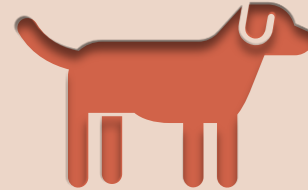
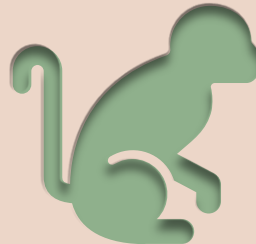
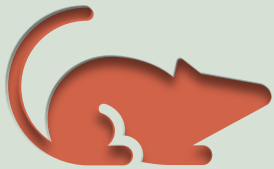
35

- Tested article
- **Species** and numbers of animals
- **Dosage levels**
- **Duration of studies**
- Route of administration
- Parameters measured during studies
- Toxicokinetics

Species of Animal

36

- Two species (_____ & _____) are always required
- What species is adequate?



- Biologics: one _____ species is essential, if justified

Selection of Three Dosage Levels

37

Dosage group	Effect level	Note
	Lethal dose level	
High dose	Adverse effect level	(Maximum toxic dose, MTD)
Middle dose	No observed adverse effect level (<u>NOAEL</u>)	A high non-toxic dose for estimating
Low dose	Pharmacological active dose (PAD) or Proposed human dose	dose

Study Duration to Support Clinical Trial

38

Maximum Duration of Clinical Trial	Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials	
	Rodents	Non-rodents
Up to 2 weeks	2 weeks ^a	2 weeks ^a
Between 2 weeks and 6 months	Same as clinical trial ^b	Same as clinical trial ^b
> 6 months	6 months ^{b, c}	9 months ^{b, c, d}

PART III

39

Non-clinical Assessment on IND

No, There would be Some Imperfections

40

- Too good to be true (less _____ to believe?)
- The wrong dosage (less _____ to detect?)
- The wrong species (less _____ to human?)
- The wrong _____? And others?



Consideration for Data Evaluation

41

- Adequate study design according to the current guideline
- Perform study in compliance with GLP regulation
- Setup safety margins for clinical use
- Characterize drug-related toxicity for risk assessment



Evaluation of Toxicological Safety

42

- The extent of human _____
 - No-Observed Adverse Effect Level (NOAEL)
 - Safety margins
 - Maximum safe starting dose
- The _____ effects on various biological systems
 - Nature of effect, target, magnitude of response per unit dose, etc.
- The basis of _____ similarity to known toxicants
- _____ class

Indication—Cancer

43

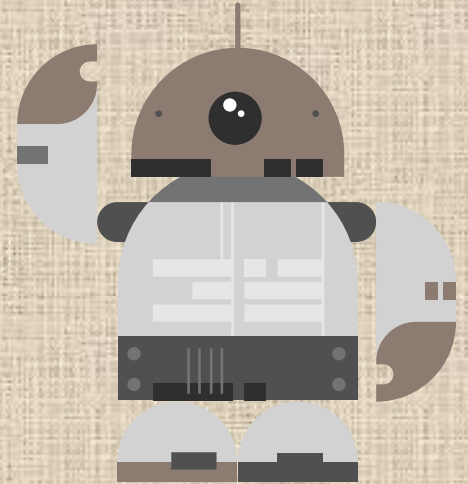
- Without effective therapy, patients will die
- If survival is 0% without new therapy, how much toxicity will be tolerated?
- Almost all cancer drugs have lethal side effects, but if they can cure some patients, these toxicities are acceptable

Therefore, the pharm/tox data is _____ expected to be massive in size or devoid of toxicities

Indication—Sleep Aid

44

- No one dies from insomnia
- Any evidence of toxicity observed in preclinical studies will put the drug' s success at risk



Therefore, the preclinical program will have to be _____, _____, and nearly _____ of significant toxicities

Factors to Consider Before Initiating Clinical Trials

45

- Type of the medicinal _____
- Type and severity of _____
- _____ to be treated
- Type of clinical _____
- _____ and treatment _____

Questions Relating to a Clinical Study Protocol

46

- Is the _____ sufficiently supported?
- Is the proposed dosage _____ supported by animal safety data?
- Is the _____ program appropriate to ensure safety?
- Are the inclusion and exclusion _____ appropriate to ensure safety?

First Time Exposure in Man— Questions Asked

47

- Did the test system exhibit any _____?
- Were the effects _____-related?
- Are the effects toxicologically _____?
- Are the effects _____?
- Are the effects _____ relevant?
- Can the effects be _____ clinically?



Thanks for Your⁴⁸ Attention

It is highly welcome for your kind feedback