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

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114, 10, 08

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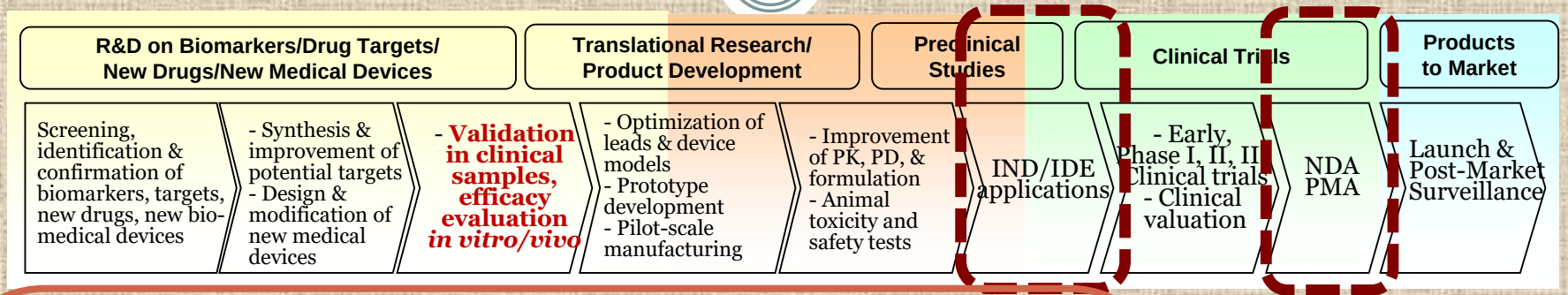
Milestone of New Drug Development

Scope of Today's Presentation



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)

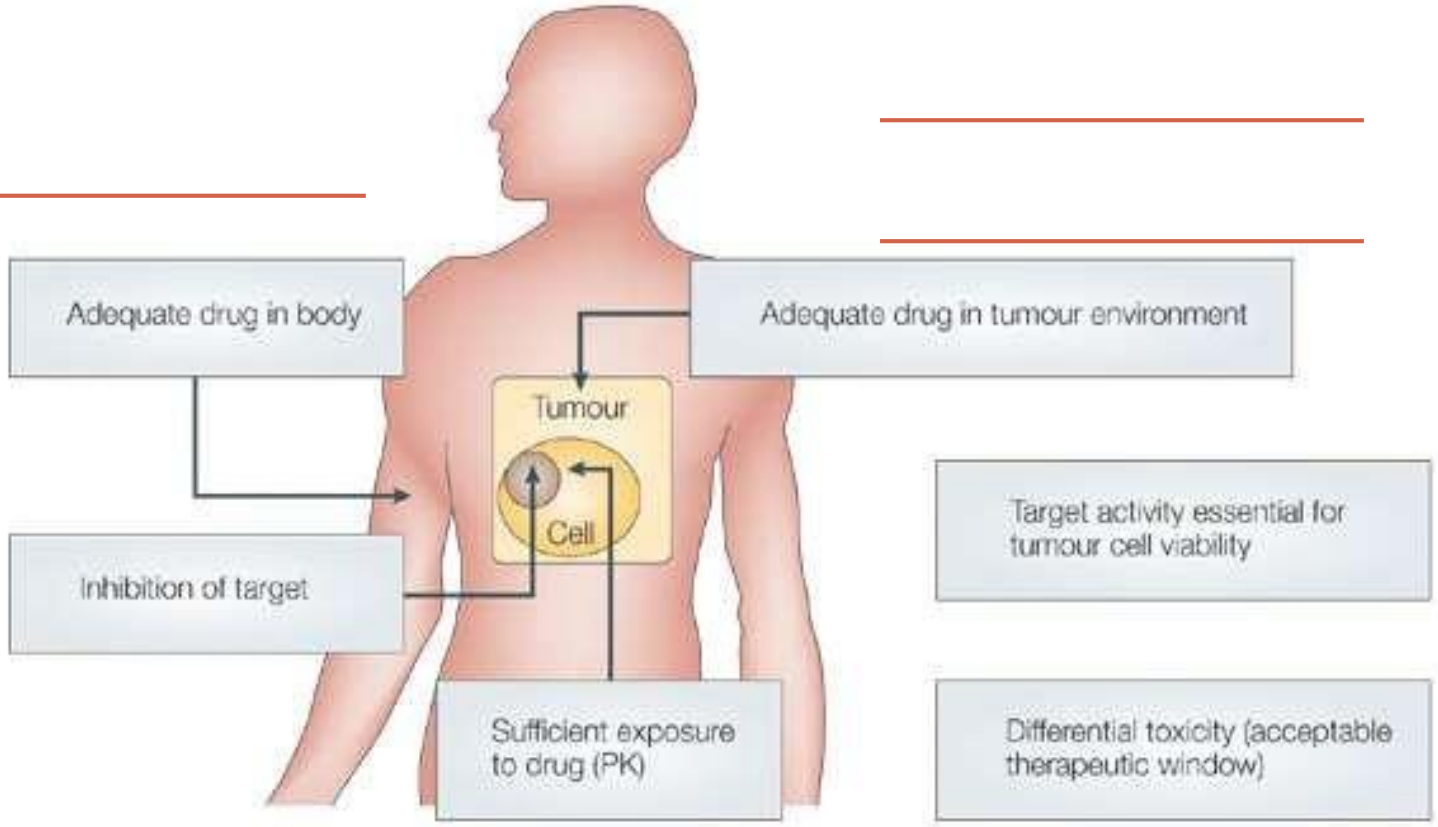
Phase I（安全性）
- 20～80名健康志願者
- 健康人藥物動力學ADME
- 人體耐受劑量研究
- 決定安全性及劑量範圍

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

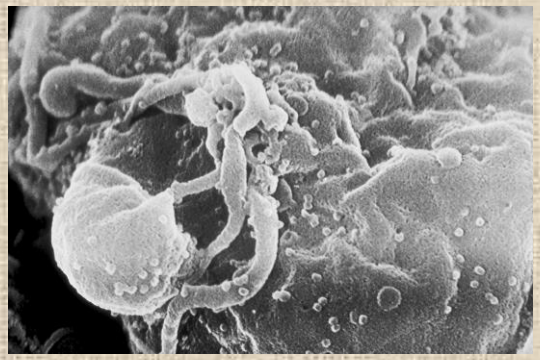


大於

PART I

From Drug Discovery to IND: Preclinical Development and Regulatory Requirement

新藥開發：從解決 _____ (_____) 開始



Need
需求

Benefit
臨床利益

_____

Solution
解決

Differentiation
差異化創新

New Drug Modalities

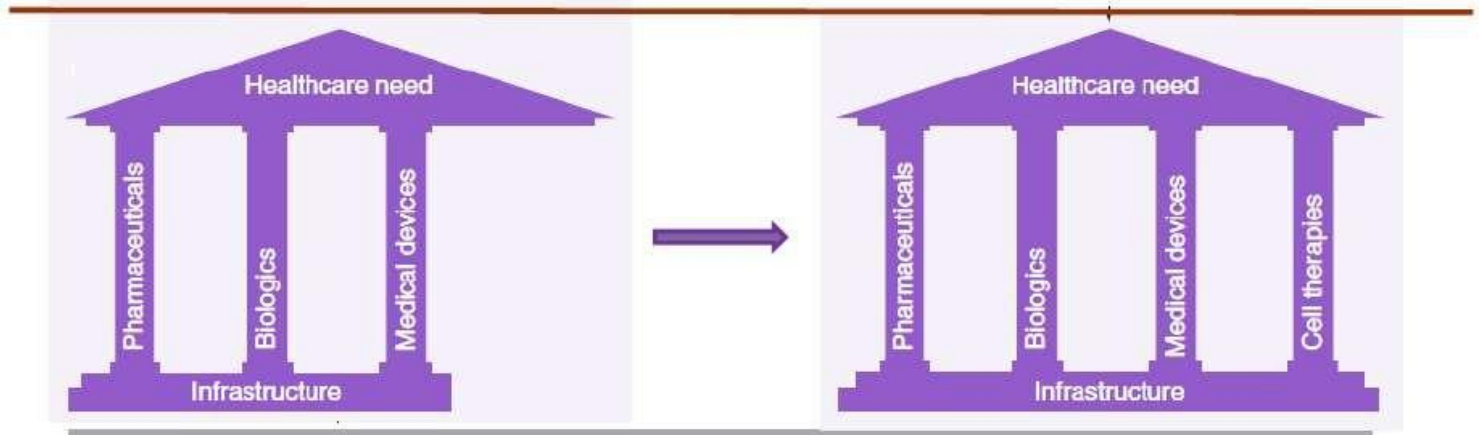


Table 1. Therapeutics and core competencies for the industries that make up the four pillars of healthcare.

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

An Ideal Druggable Target

- Target is disease-modifying and/or has a _____ in the pathophysiology of a disease.
- Target has a favorable '_____' enabling high throughput screening
- Target expression is _____ distributed throughout the body
- It has a _____ situation (no competitors on target, freedom to operate)
- A target/disease-specific _____ exists to monitor therapeutic efficacy.

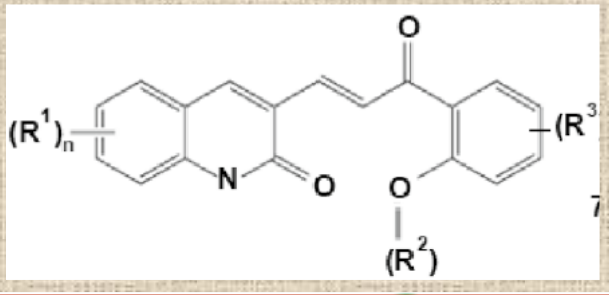
Drug	Covered target classes	Mode of action
Small molecular compound (SM	Enzymes	Inhibitors, activators[a]
	Receptors	Agonists, antagonists, modulators, allosteric activators, sensitizers
	Transcription factors	Inhibitors, activators
	Ion channels	Inhibitors, openers
	Transport proteins	Inhibitors
	Protein–protein 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

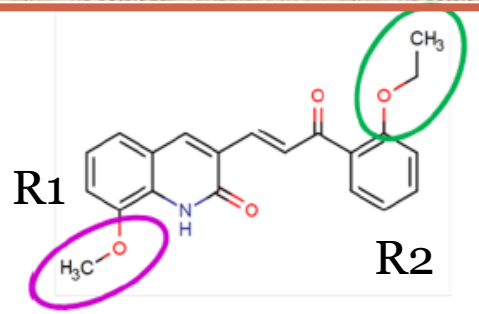
Hit to Lead Optimization: _____ Study

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

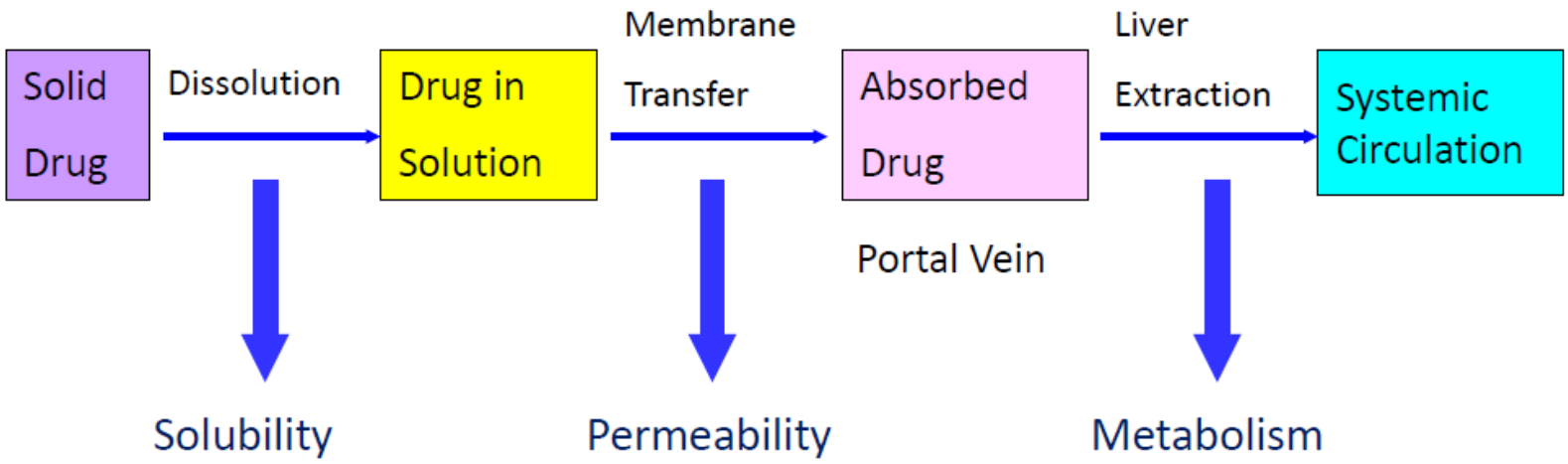
CTR-32
ethoxy group is more cytotoxic than methoxy group. However, it reduces metabolic stability and may target other proteins

SAR: Structure Activity Relationship

Scientific Reports | (2021) 11:21576

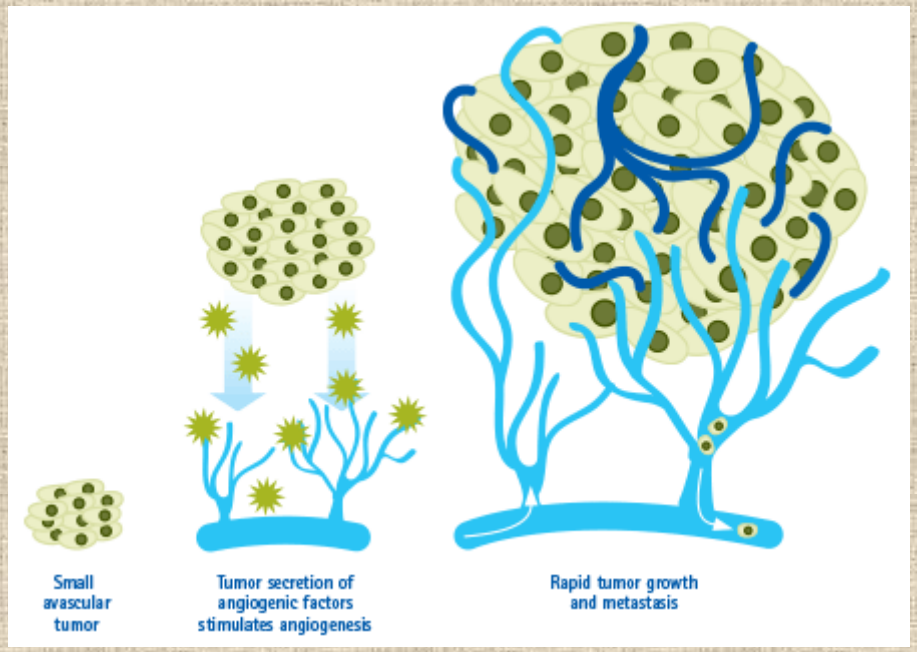
In Vitro PK

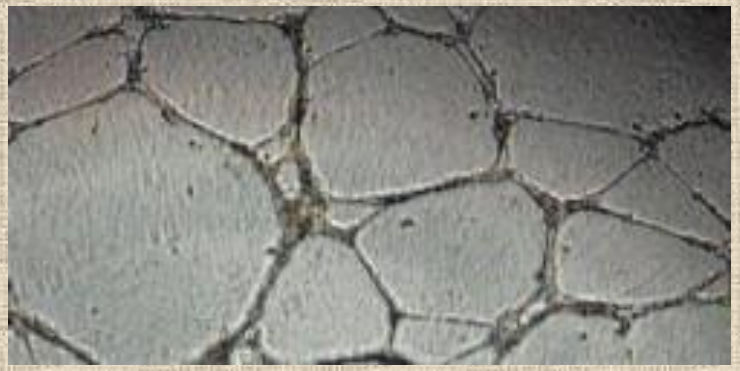
Solubility, Permeability, Chemical and Metabolic Stability Affects Oral Bioavailability



In Vitro PD (Functional Assay)

- 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

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

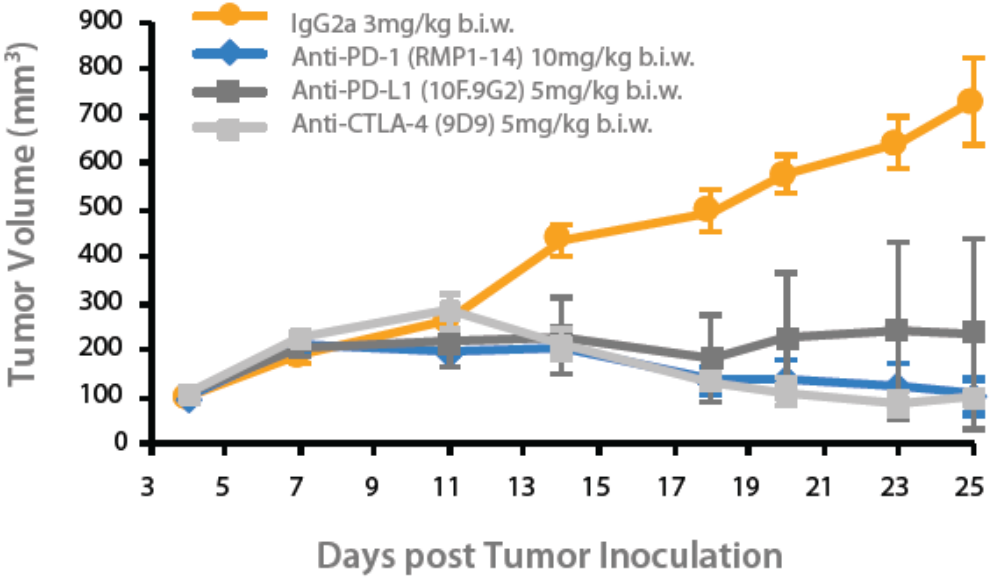
Advanced orthotopic, bioluminescent, and metastic modeling

Checkpoint inhibitor benchmarking

Combination therapy strategies

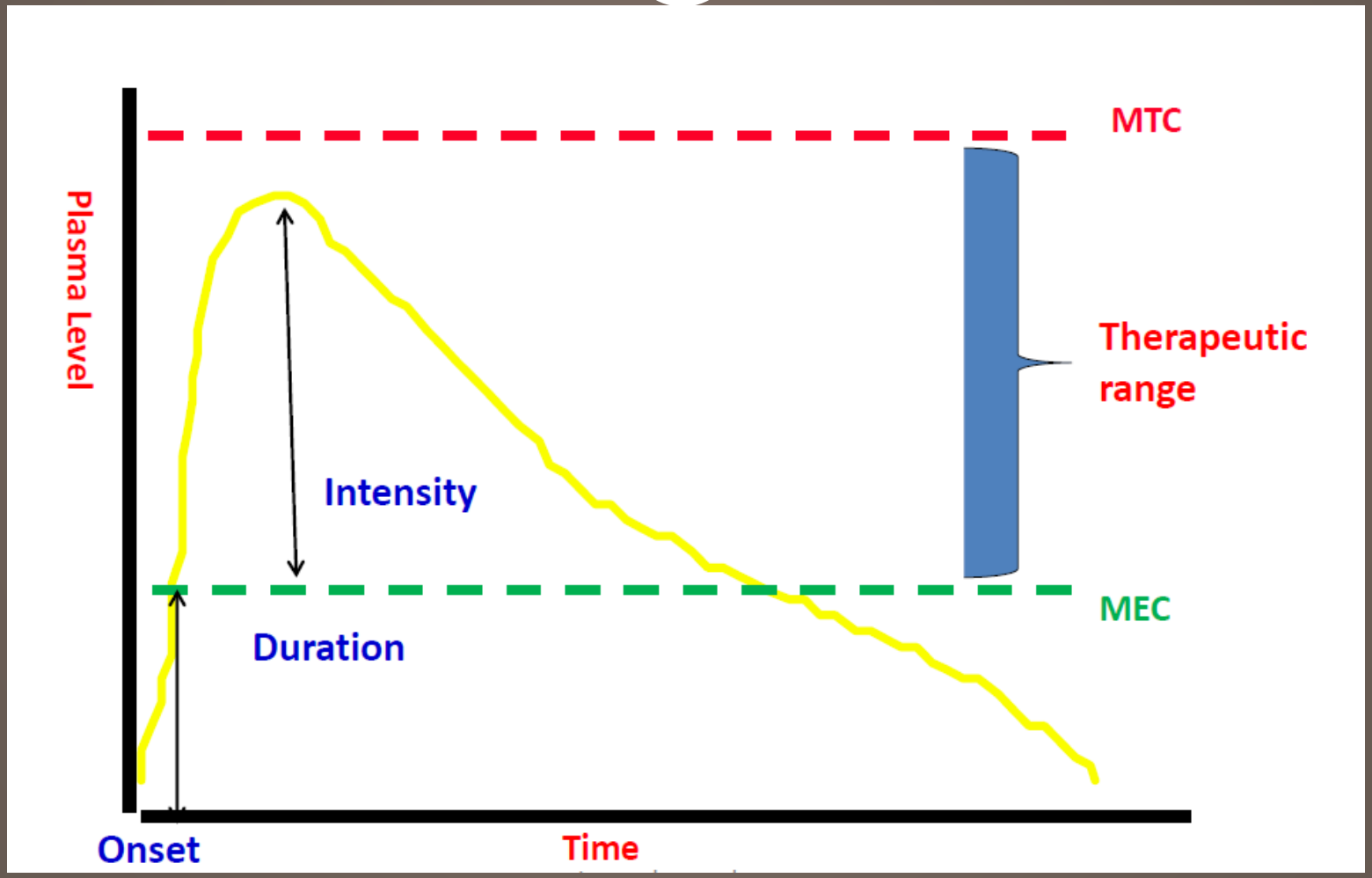
Immune cell profiling

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


MTC
Plasma Level
Therapeutic range
Intensity
MEC
Duration
Onset
Time

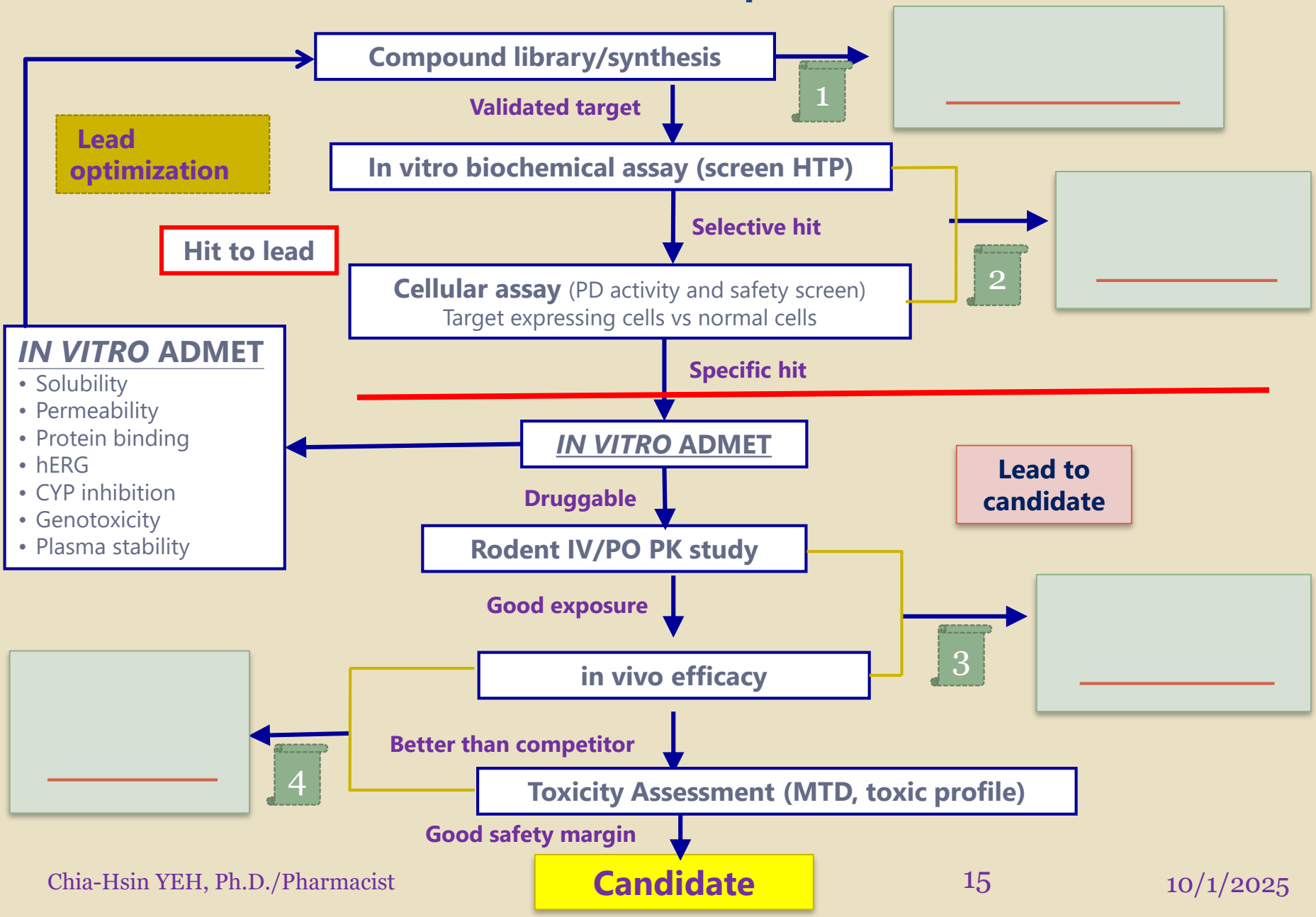
Early Stage Safety Study

eurofins | Pharma Discovery Services

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_A)	•	
DOPAMINE	D_1		
	D_{2S}	•	
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	$5\text{-}HT_{1A}$	•	
	$5\text{-}HT_{1B}$		
	$5\text{-}HT_{2A}$	•	
	$5\text{-}HT_{2B}$	•	
VASOPRESSIN	V_{1a}	•	
TRANSPORTERS			
DOPAMINE	Dopamine Ttransporter		
NOREPINEPHRINE	Norepinephrine Transporter		
SEROTONIN	5-HT transporter		
ION CHANNELS			
GABA CHANNEL	BZD (central)	•	
GLUTAMATE CHANNEL	NMDA		
NICOTINIC CHANNEL	N neuronal $\alpha4\beta2$	•	
SEROTONIN CHANNEL	$5\text{-}HT_3$		
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			
STEROID 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

- 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

- 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

- _____ - 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

- 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

- 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

- _____
  - 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

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)

The science of what _____ does to _____

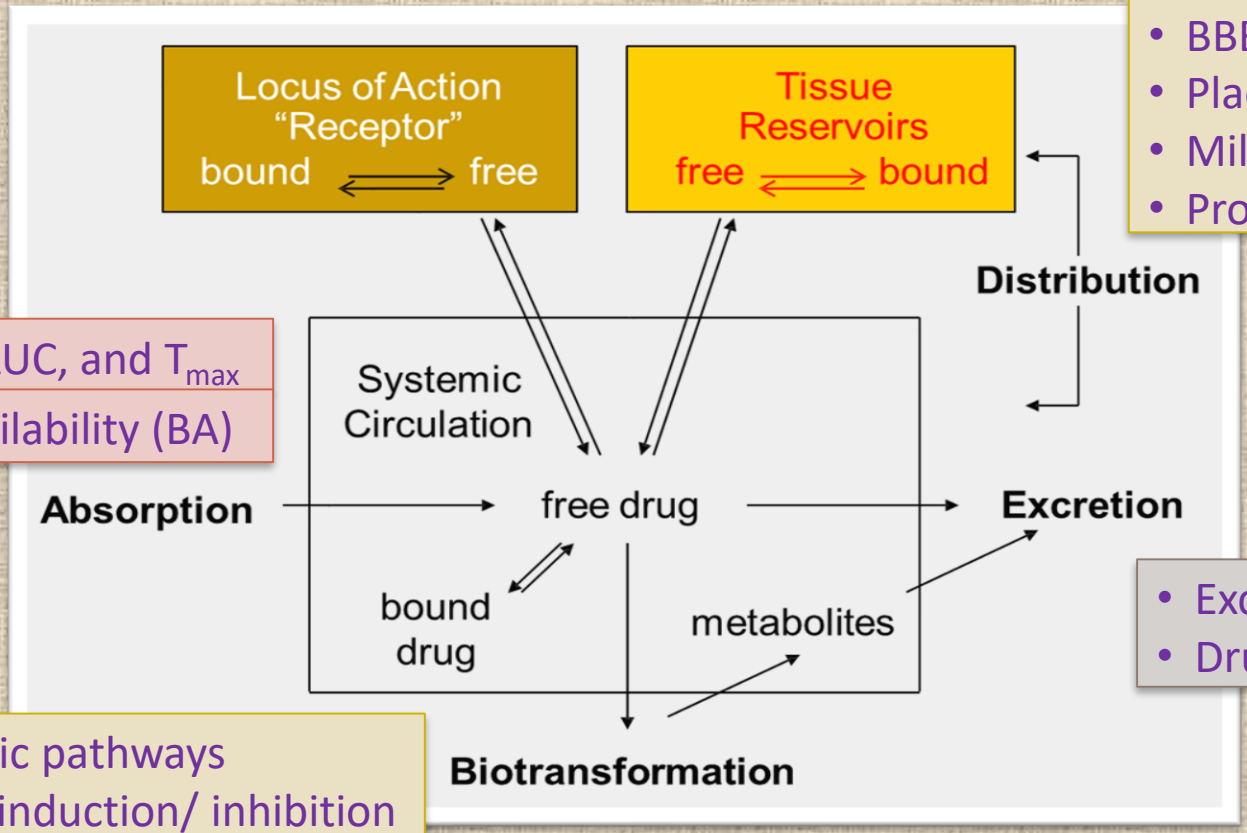
In vitro pharmacological studies

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)

The science of what _____ does to _____



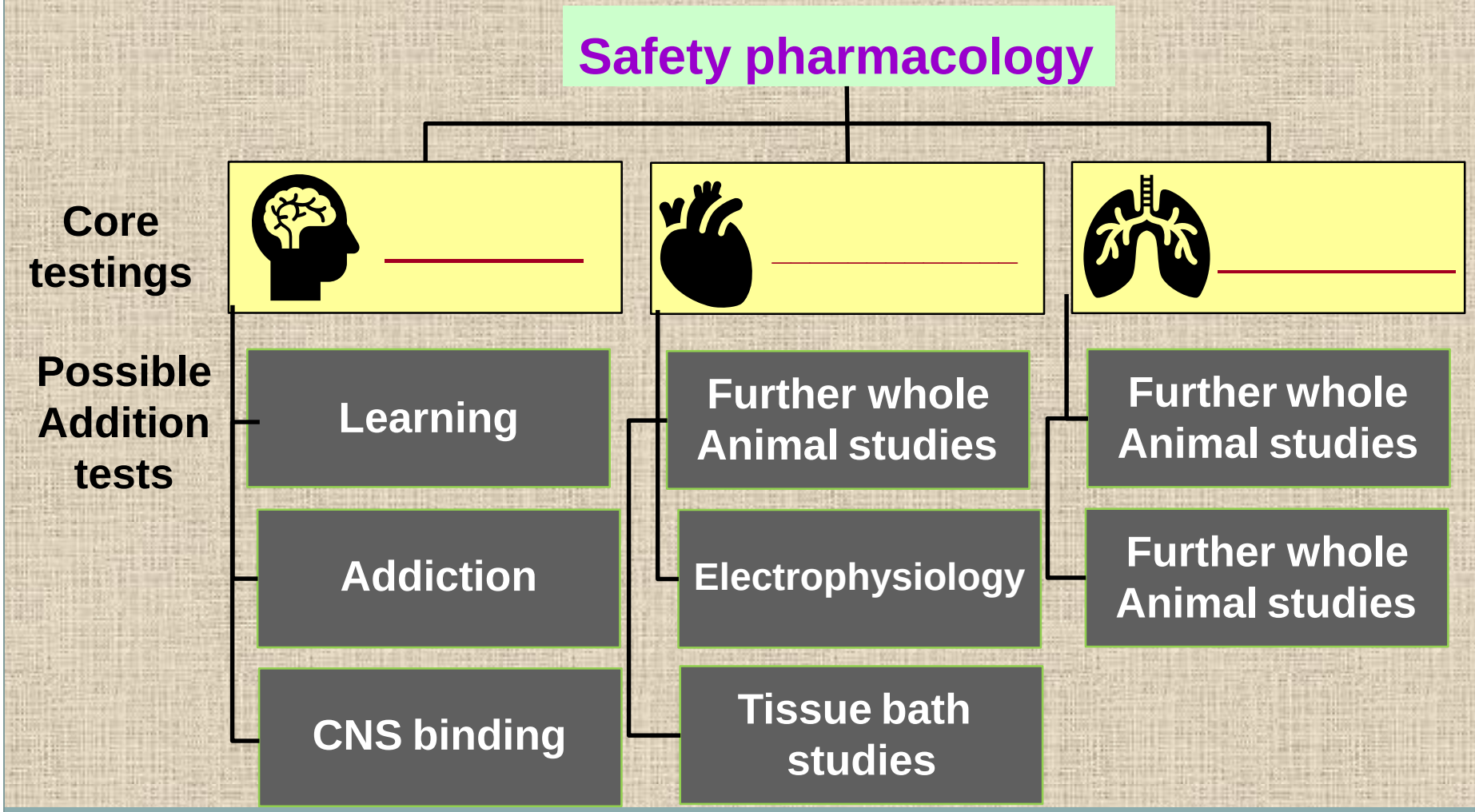
- BBB penetration
- Placental transfer
- Milk secretion
- Protein binding

- C_{max}, AUC, and T_{max}
- Bioavailability (BA)

- Excretion pathway
- Drug clearance

- Metabolic pathways
- Enzyme induction/ inhibition

Studies of Safety Pharmacology



Animal Toxicology

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

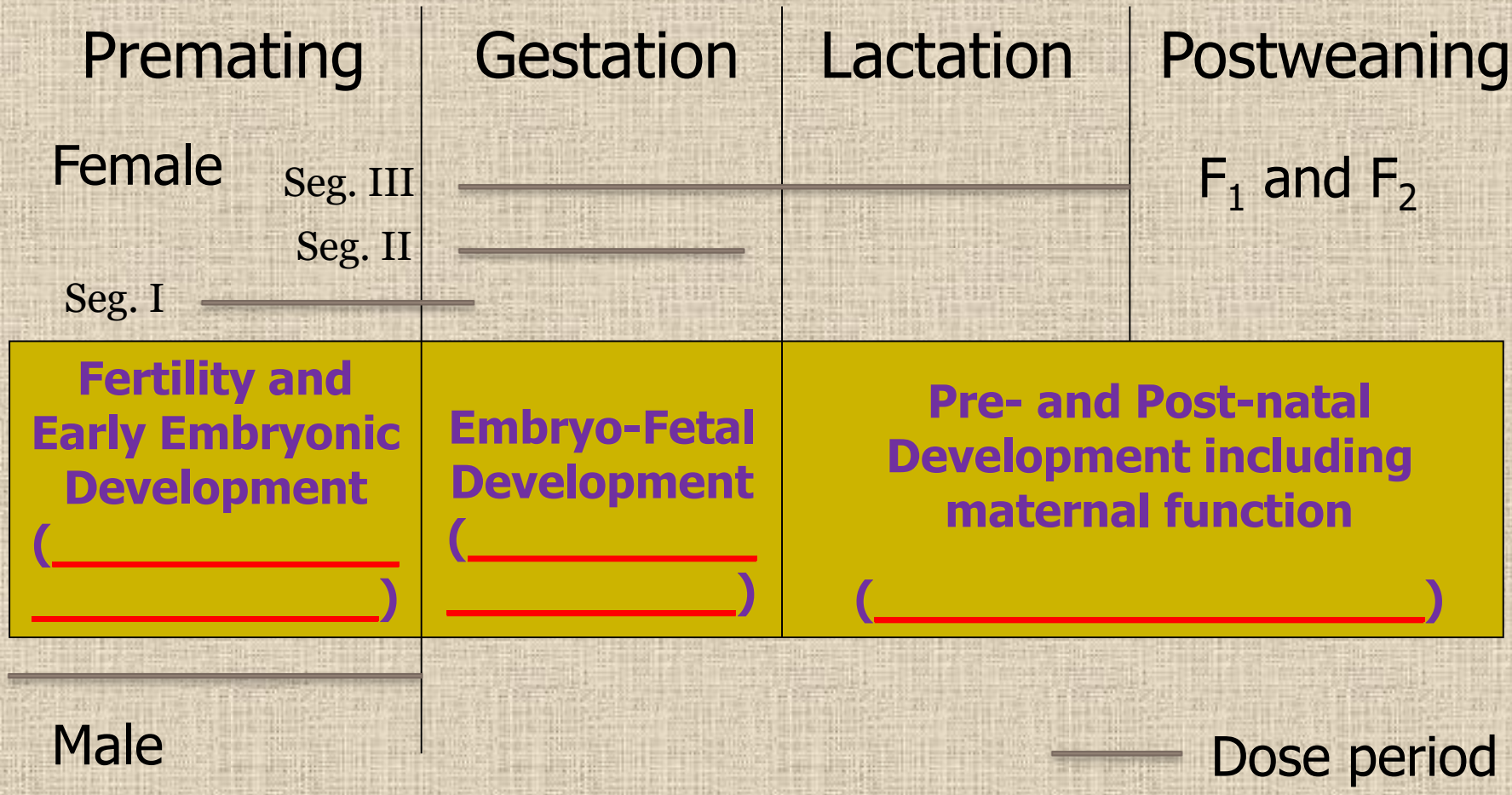
_____* is required for _____ studies

GLP: Good Laboratory Practice

General Toxicity Studies

- _____ 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

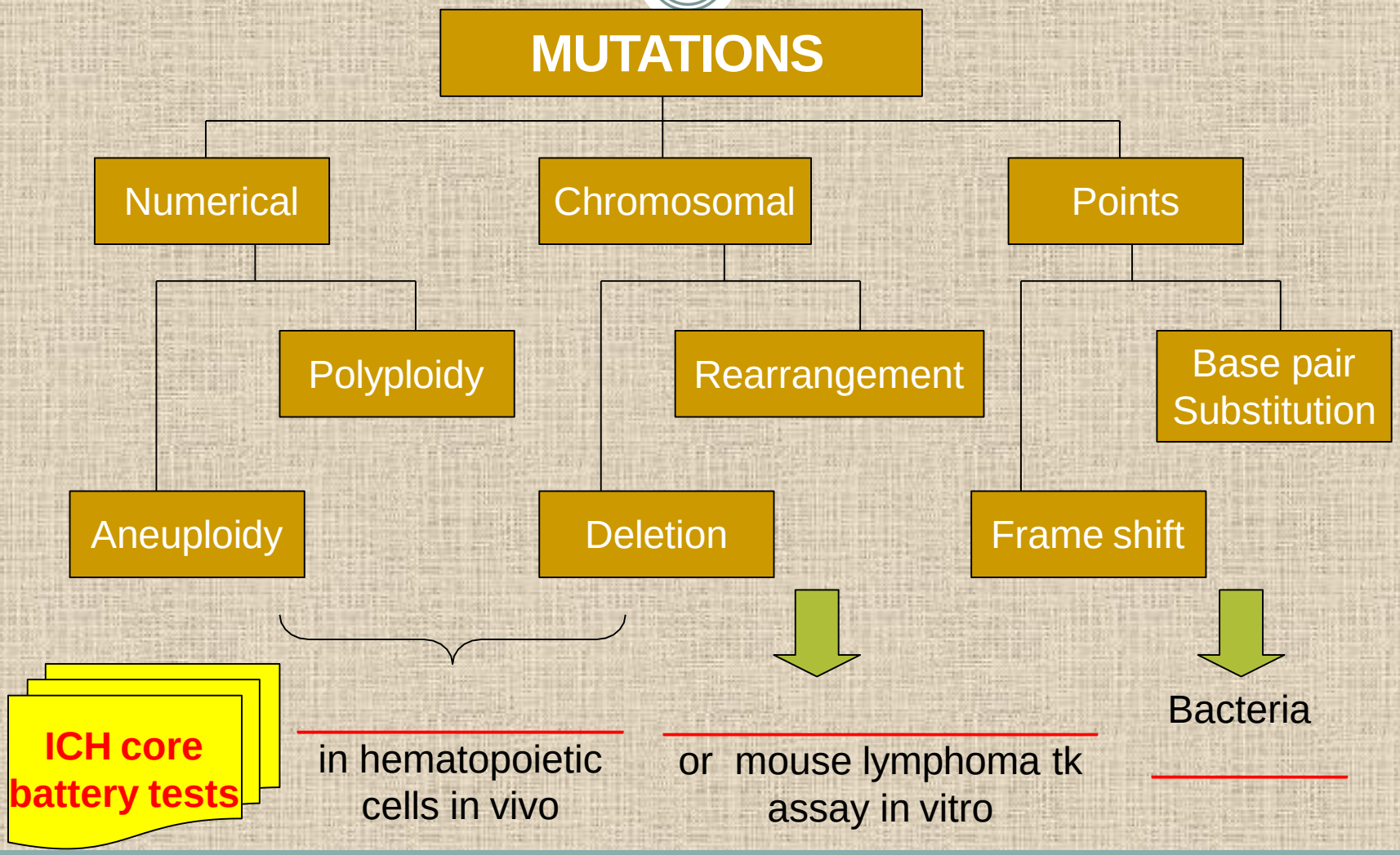
ICH Reproductive Segmental Studies



Reproductive toxicity studies

- 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



Carcinogenicity Studies

- 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

- 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 rhinities, depression, anxiety)
    - Certain delivery systems which may result in _____
- Short term use but _____

Special Toxicity Studies

- 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

STUDY DESIGN OF GENERAL TOXICOLOGY

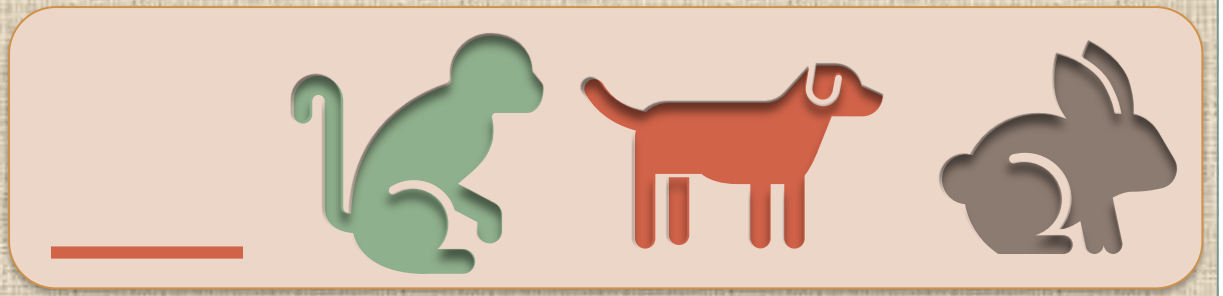
REPEATED-DOSE TOXICITY STUDIES

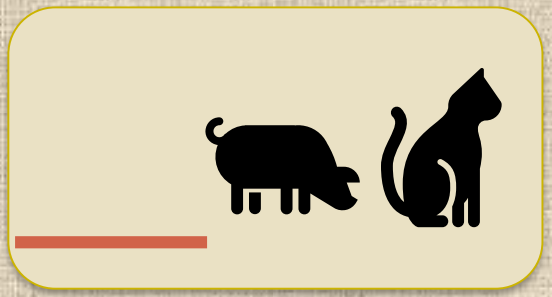
General Consideration

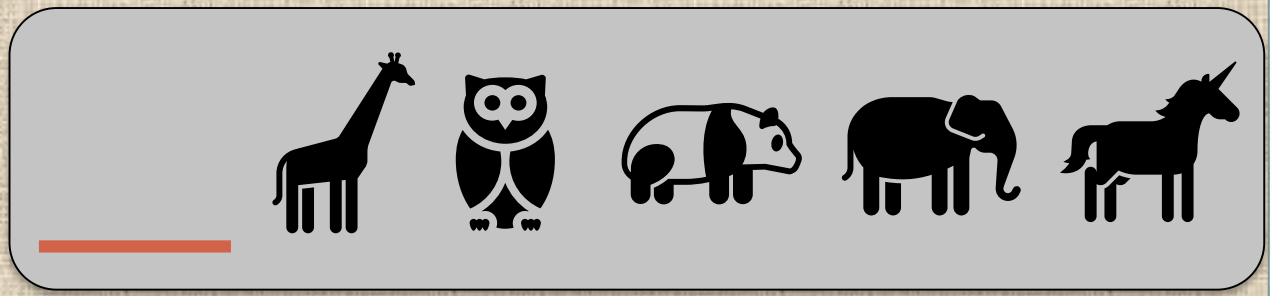
- Tested article
- Species and numbers of animals
- Dosage levels
- Duration of studies
- Route of administration
- Parameters measured during studies
- Toxicokinetics

Species of Animal

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

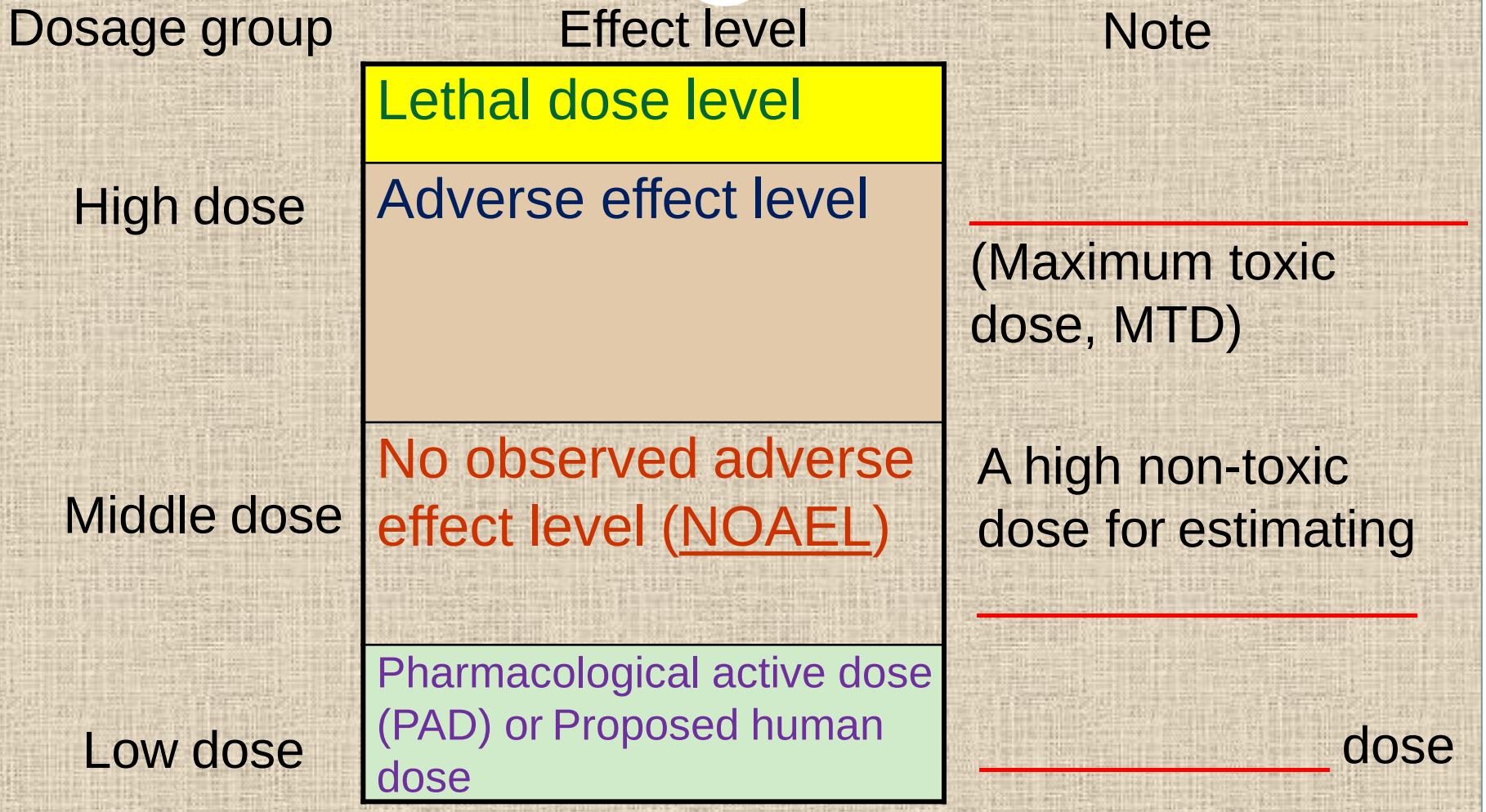






- Biologics: one _____ species is essential, if justified

Selection of Three Dosage Levels



Study Duration to Support Clinical Trial

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

Non-clinical Assessment on IND

No, There would be Some Imperfections

- 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

- 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

- 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

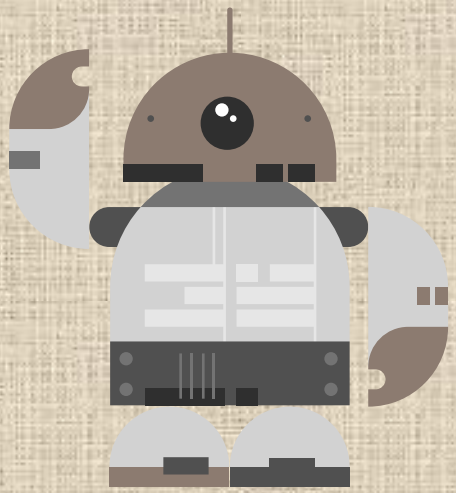
Indication—Cancer

- 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

- 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

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

Questions Relating to a Clinical Study Protocol

- 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

- 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 Your Attention

It is highly welcome for your kind feedback