癌症疫苗新藥開發之法規科學考量

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113, 11, 17

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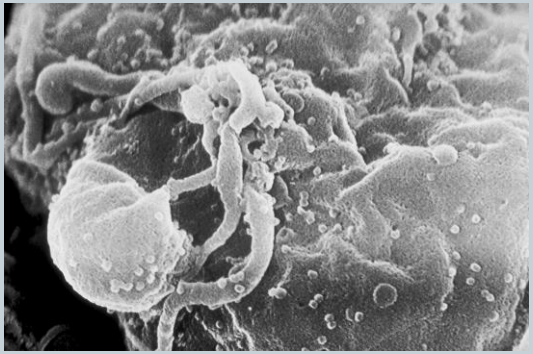
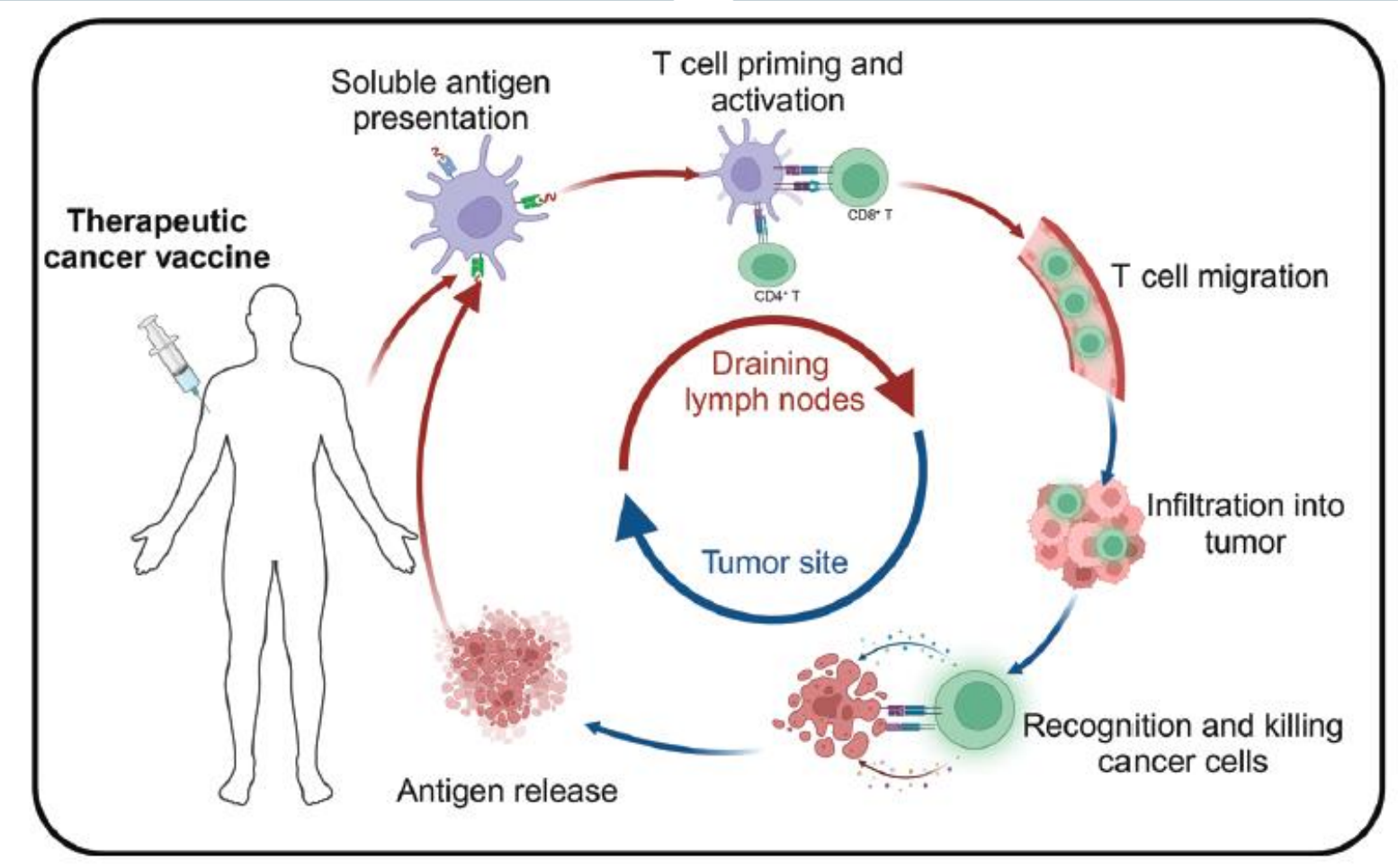
- 專門職業—藥師
- 專長—新藥開發、法規科學、生物科技與法律

新藥開發—
從解決未滿足醫療需求開始：NSDB

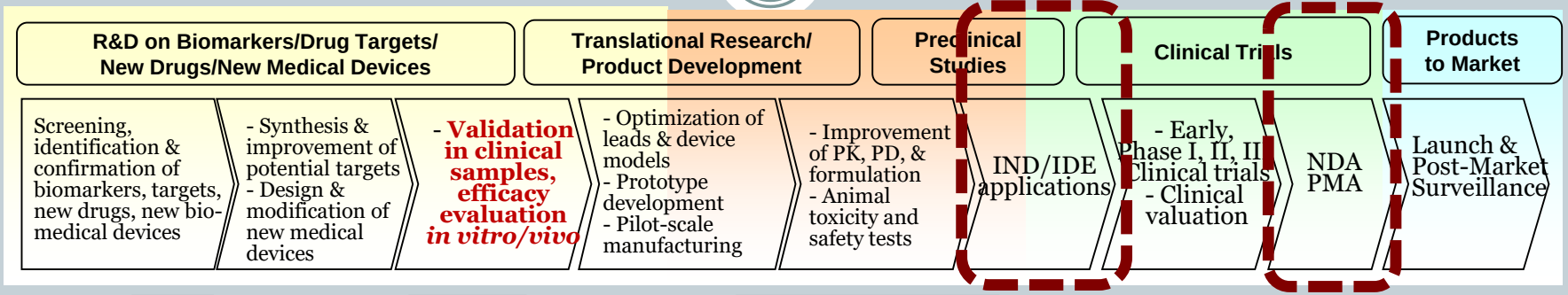


Mechanism of Cancer Vaccine *In Vivo*



Signal Transduction and Targeted Therapy (2023) 8:450

Milestone of New Drug Development



hit → Lead → Candidate

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

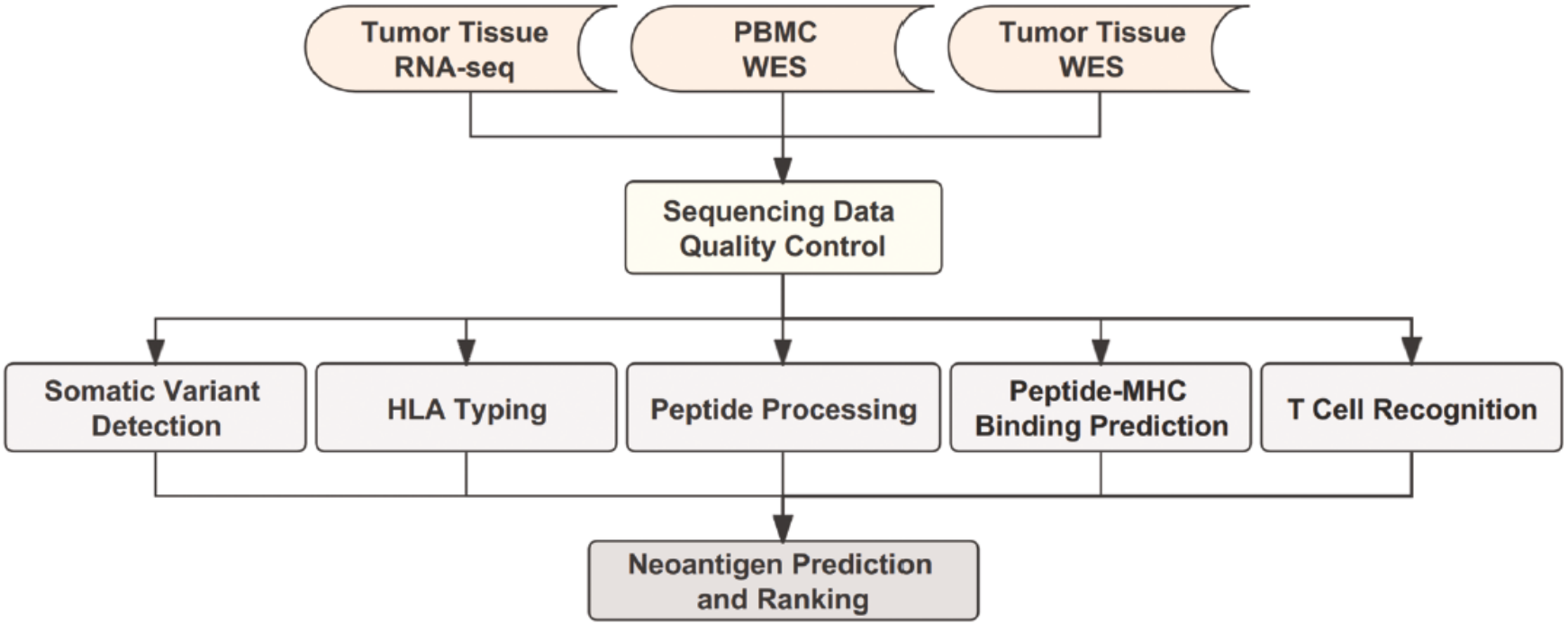
Phase II（有效性）

- 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

Prediction of Neoantigen Candidates

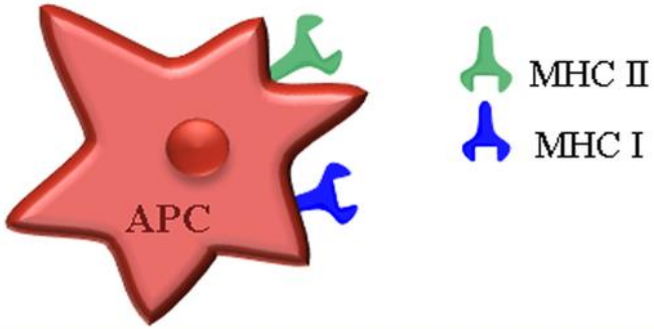


RNA-seq: RNA-sequencing; WES: Whole exome sequencing; PBMC: Peripheral blood mononuclear cell, HLA: Human leukocyte, antigen, MHC: Major histocompatibility complex,

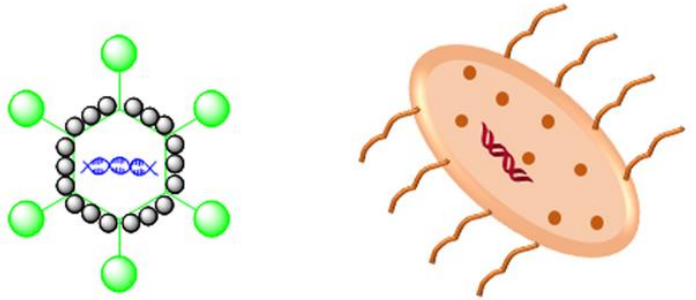
Signal Transduction and Targeted Therapy (2023) 8:450

Different Types/Platforms of Cancer Vaccines

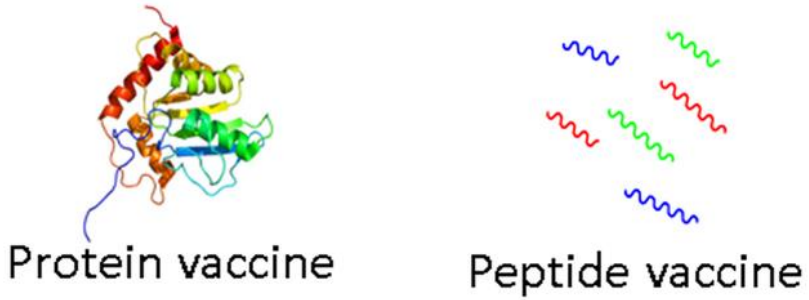
Cell-based vaccines



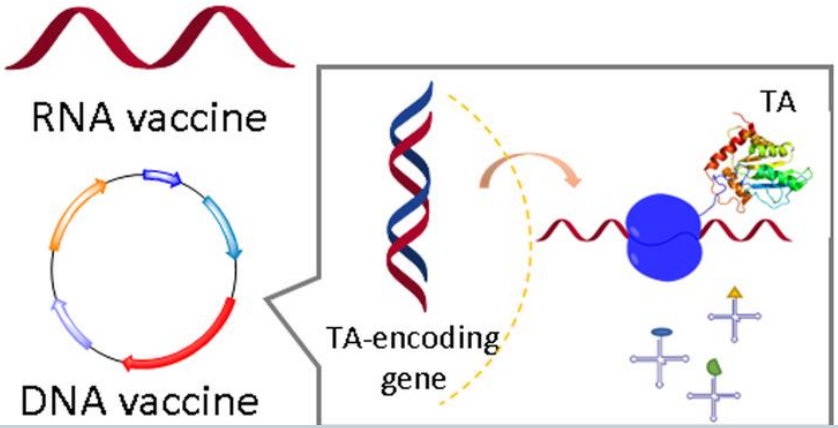
Viral/bacterial-based vaccines



Protein/peptide-based vaccines

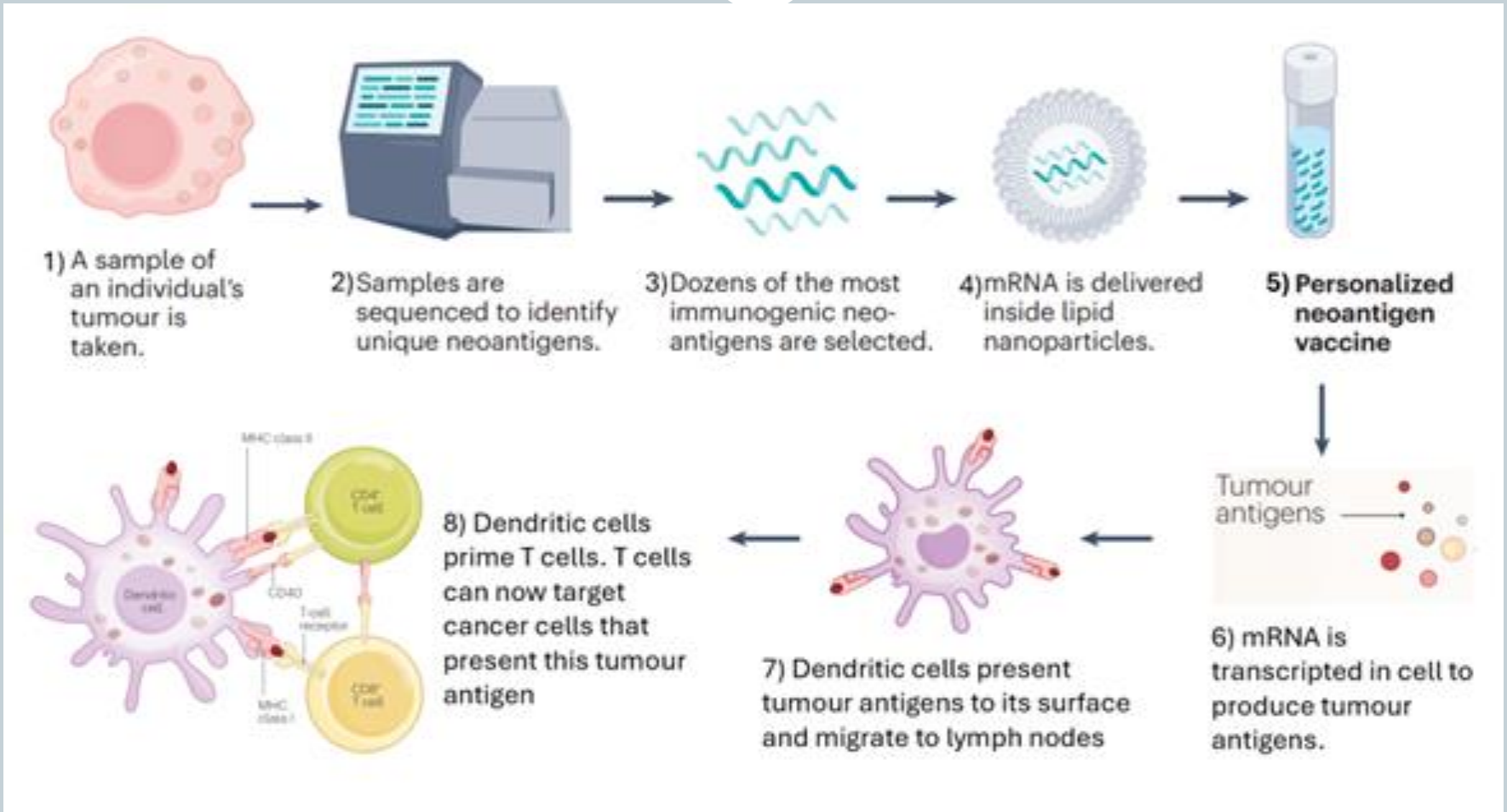


Gene-based vaccines



J Exp Clin Cancer Res 38, 146 (2019)

Overview of mRNA Cancer Vaccine Therapy



https://www.rcpath.org/resource-report/an-update-on-mrna-cancer-vaccines.html

Pre-Clinical Development

- Chemistry, Manufacturing and Control (CMC) – Drug substance and drug product **quality**
- Pharmacology and Toxicology (Pharm/Tox) – Pre-clinical **efficacy** and non-clinical **safety**
- Pharmacokinetics and Pharmacodynamics (PK/PD) – Dose (concentration)-response relationships, ADME

Regulatory Consideration on Quality

- Provide CMC Information on the identification, quality, purity and strength of study material (including drug substance and drug product)
  - 化學(Chemistry)—了解藥品各物質的物化性質，擬定適當的配方組成、製造與管制策略
  - 製造(Manufacturing)—藥品從起始、原料藥物到成品的製程，須符合GMP的要求，並對關鍵製程進行確效
  - 管制(Control)—對於影響藥品安全性與療效的關鍵屬性訂定規格，以經確效的分析方法做檢驗，確保符合所定之允收標準

Regulatory Consideration on Pre-Clinical Efficacy

- Accepted scientific principles
  - Understanding the therapy's putative mechanism of action
  - Demonstrating the "**Proof of Efficacy**"
- Pharmacology and/or microbiology
  - *In vitro* and *in vivo* disease (**activity**) models
  - Dose-response relationship
  - Biomarker and PK profile
- Provide essential information on
  - Minimal effective human dose (consider the Minimal Anticipated Biological Effect Level' (**MABEL**) approach)
  - Rationale of dosing regimen and duration
- For life-threatening indication
  - Efficacy data is a **safety** concern

Regulatory Consideration on Non-Clinical Safety

Product-based scientific review

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

For cancer vaccine, case by case approach is necessary

Clinical Development

Phase I (安全性)

- 20～80名健康志願者
- 健康人藥物動力學ADME
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Phase II (有效性)

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Early phase clinical trials

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

Phase IV (上市後安全性監測)

- 數萬~數十萬名志願病患
- 臨床用藥觀察
- 追蹤各類型病人使用藥物的不良反應及交互作用

Late phase clinical trials

Regulatory Consideration on Clinical Efficacy/Safety

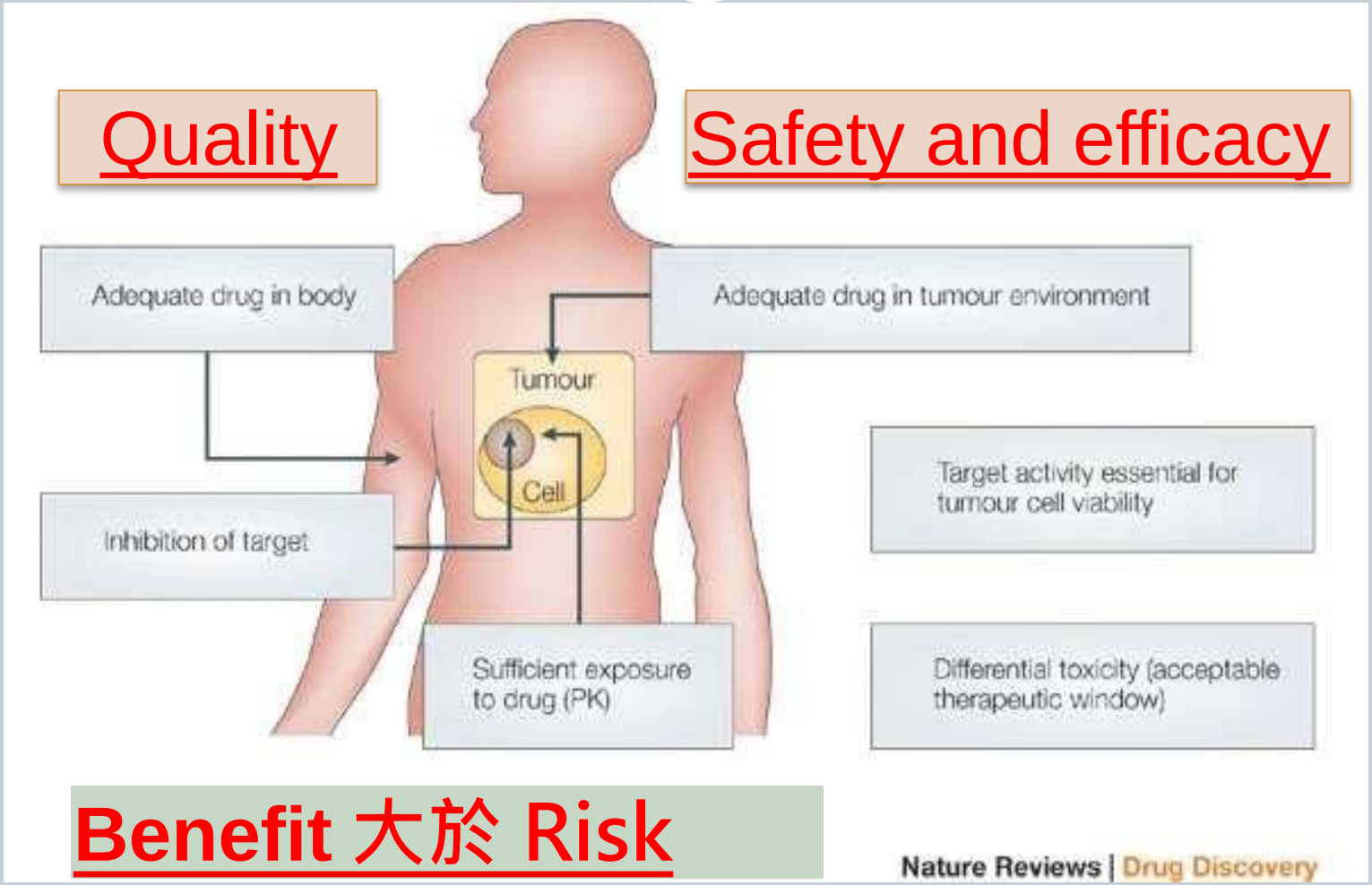
Efficacy

- Monitoring the immune response in early phase clinical trials for proof-of principle: At least two immunological assays, if possible
- Biomarkers as evidence of efficacy, and co-development of cancer vaccines and tests for targeted antigen during development
- Superiority trial design to demonstrate cancer vaccine treatment effect on chosen clinically meaningful endpoints

Safety

- 3 + 3 design may not be the most suitable approach to early phase trials of cancer vaccines
- Induction of autoimmune reactivity (cellular and humoral) and induction of tolerance should be carefully monitored during the progress of the trial and in long-term follow-up

Regulatory Approval of New Drug



Regulatory Guidance for Cancer Vaccine

- ICH guideline topics for quality, safety, efficacy and multidisciplinary: Q5、M3(R2)、S6(R1)、S9、S12…
- EMA: Guideline on the clinical evaluation of anticancer medicinal products, 2023

- WHO: Guidelines for assuring the quality and nonclinical safety evaluation of DNA vaccines, 2007
- USFDA Guidance for industry: Clinical Considerations for Therapeutic Cancer Vaccines, 2011

- USFDA: Cellular & Gene Therapy (CGT) Guidances, 2024
- EMA: Guidelines relevant for advanced therapy medicinal products (ATMP)

Case by Case—Consultation

- To increase predictability of regulatory requirement
  - Meet regulatory requirement
- To identify the gap between sponsor and regulatory agency
  - To balance between reality and regulatory demand
- Do the documentation right starting from development to marketing approval
  - Translation development
  - Clinical trial application
  - New drug application

Early Communication is highly encouraged

Regulatory Strategy for Unmet Medical Need

Guidance for Industry
Expedited Programs for Serious Conditions – Drugs and Biologics

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2014
Procedural

OMB Control No. 0910-0765
Expiration Date: 03/31/2017
See additional PRA statement in section X of this guidance.

Expedited Development Program

Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
February 2019

Regulatory Knowledge Guide for Cell and Gene Therapies and Biological Products.
NIH SEED

Shortened Review; Rolling Submission

Full or Conditional Approval

Serious or life-threatening disease or condition

Regulatory Philosophy

- Science-based regulation
- Product innovation can be facilitated by regulation
- Efficient government and regulatory process make markets-both win
- Benefit-risk balance

Innovative research

- Improve health
- Bio-tech industry

Public health safety

- Biosafety
- Patient safety


Thanks for Your Attention
It is highly welcome for your kind feedback
Chia-Hsin YEH, Ph.D./Pharmacist
11/19/2024