US CHINESE ANTI-CANCER ASSOCIATION
美中抗癌协会

Chinese Society of Clinical Oncology
Beijing Xisike Clinical Oncology Research Foundation

Early Stage Clinical Development

ANTENGENE CORPORATION

Treating Patients Without Borders

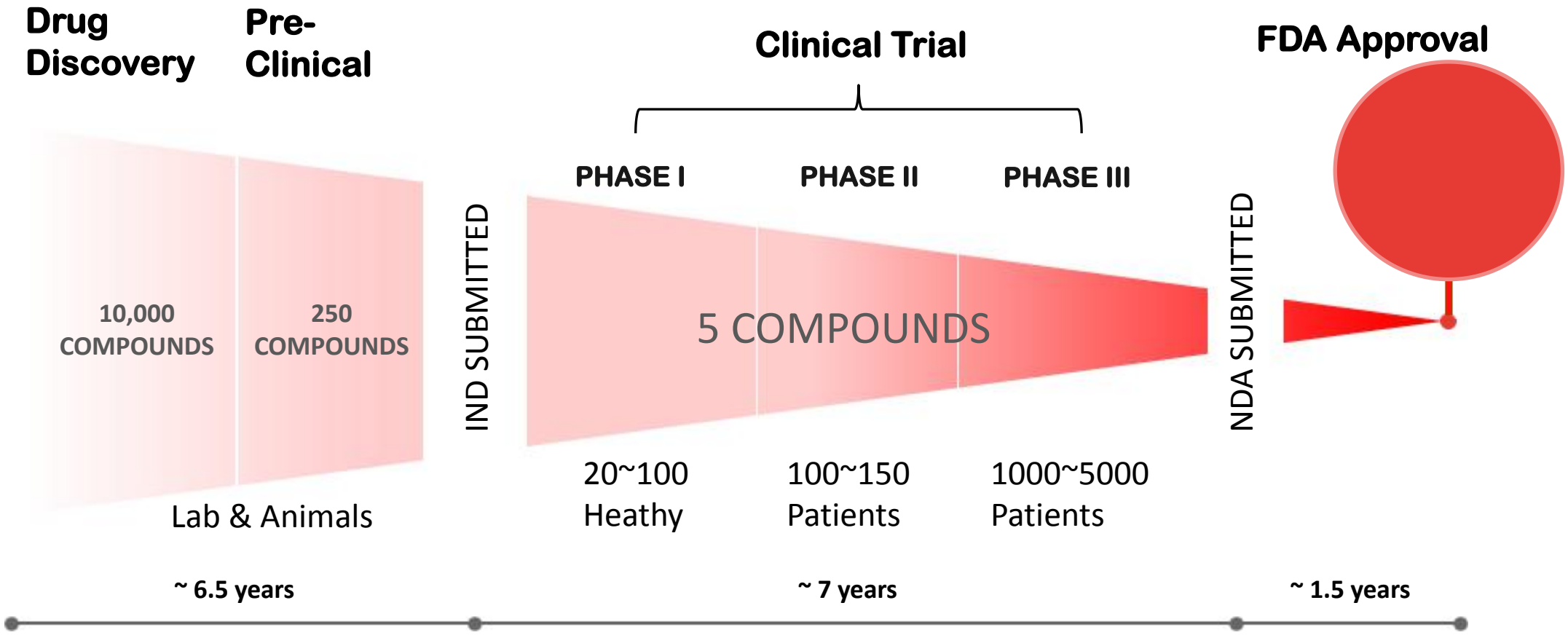
Jay Mei, M.D., Ph.D.

Introduction to Drug Development

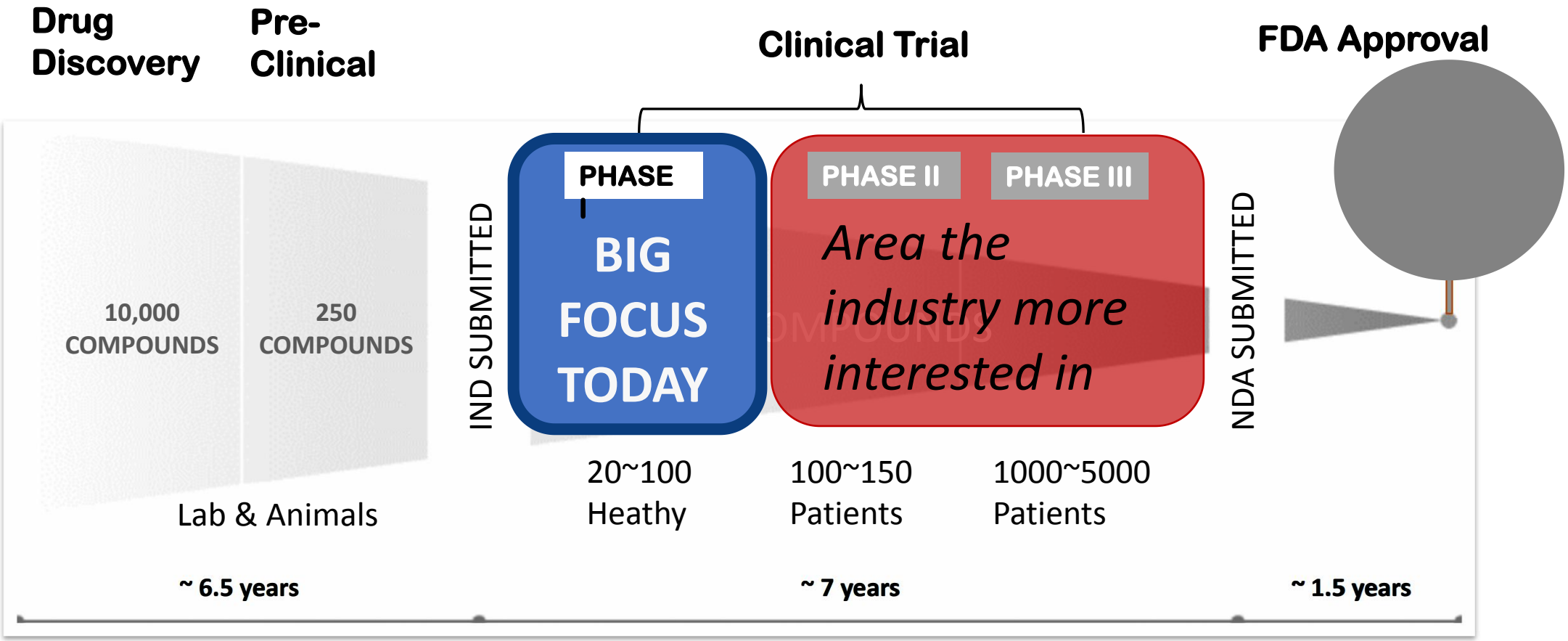
- Today, average R&D cost required to bring a new, FDA-approved medicine to patients is 2.6 billion USD.
- It takes about 7 to 10 years and only 3 out of every 20 approved drugs bring in sufficient revenue to cover their developmental costs, and only 1 out of every 3 approved drugs generates enough money to cover the development costs of previous failures.
- For a drug company to survive, it needs to discover a blockbuster (billion-dollar drug) every few years.

Mullard, Asher. New drugs cost US$2.6 billion to develop[J]. Nature Reviews Drug Discovery, 2014, 13(12):877-877.

Drug Development Process



Drug Development Process



Oncology Clinical Development

	Objectives	Patient Population
Phase I	• Identify maximum tolerated dose • Define key toxicities	• Small (3-6 patients/dose level) • Various tumor types
Phase II	• Evaluate tumor response • Determine whether drug warrants Phase III study characteristics	• Larger than Phase I (10-50 patients/treatment group) • More uniform disease
Phase III	• Compare new treatment with standard • Support marketing approval	• Larger than Phase II (100s patients/treatment group) • Same tumor type • Broader patient pool

Clinical Trial Practice
Issues to be Discussed

What is the design?

Communication with HA

Regulatory Framework

Selection of Clinical Sites for Trials

Extra Support During the Trial

Data Cleaning (Review)

Analysis Results

What is the Design?

What is the Design? (I)

- **Selection of subjects**
  - In most cases, patients with certain type of cancer are conducted.
  - Patients with advanced tumors are often accompanied by extensive distant metastasis, short survival, poor physical condition, and many clinical manifestations of cancer, and often have received various of other toxic methods with side effects before enrolling in the trial. Therefore, strict restrictions of inclusion criteria are needed to reduce the impact of relevant factors. That, in turn, makes it harder to select patients. Thus we must weigh the difficulty of recruiting patients due to excessively strict inclusion criteria.
- **Sample size setting**
  - One possible approach is to expand the number of subjects enrolled in several dose groups where efficacy has been observed.
- **Estimation of the initial dose** (Most important part in Phase I Study)
  - The therapeutic index of most antitumor drugs is very narrow, and the high dose may lead to severe toxicity or even death of patients, thus preventing the development of effective drugs with potential. On the other hand, if the starting dose is too low, the climbing test cycle may be prolonged, which is not conducive to the development process. Moreover, from the perspective of ethics, too many patients should not be exposed to ineffective dose.
  - The results of non-clinical, toxicological and pharmacokinetic studies should be combined, and the previous experience of other drugs with the same structure, target or effect should be taken into account.

What is the Design?(II)

- **Dose escalation method**
  - Design based on rules or algorithms and model-based design
  - At present, the clinical research on anti-tumor drugs generally adopts the "improved" Fibonacci method according to the trial requirements, but there may be a situation in which it is difficult to determine the relationship between the definition of adverse events and the study drug due to many non-drug-related problems. In the test, it is necessary to combine the various aspects of information to judge whether it is worth climbing or climbing.
  - However, even if the active target of the drug is saturated or the effect is observed when there is no significant toxicity, it is still recommended to study a higher dose, mainly based on the desire to obtain the best effect at the maximum tolerated dose.

What is the Design?(III)

- **Dosing intervals**
  - Tumor drugs are time- and concentration-dependent, and their efficacy and toxicity are closely related to the dosing regimen. Because, in addition to each dose, we have to consider whether the new drug is administered multiple times or a single dose? How often do subjects taken the medicine? At what frequency of administration, can the patient tolerate the toxicity of the drug while at the same time achieving tumor suppression? E.g. Some targeted drugs are usually considered to take a solution that continuously inhibits the concentration of the target.
  - In addition, the convenience of clinical administration should also be considered.
  - The pre-clinical exploration of new drug regimens is relatively general, and it is often not possible to find the optimal dosing regimen in Phase I clinical trials, while it is necessary to continue into Phase II studies.

What is the Design?(IV)

- MRCT can be considered to accelerate the completion of clinical trials, however, it may undermine researchers' understanding of the toxicity of new drugs. Therefore, it is essential to share and report on the latest research progress on a regular and timely basis.
- Once the clinical trial dose of phase II has been obtained in the phase I study, the specific subject can be enrolled according to the mechanism of drug action to investigate the initial efficacy at the dose level of the phase II clinical trial, meanwhile, the target subjects who are most effective for the study drug can be identified and confirmed.

- Important to receive KOLs' feedback on the feasibility of your study and overall design

Communication with HA

Pre-IND Meetings

Meetings with regulatory boards provide guidance to sponsors who seek to comply with regulatory requirements and ease the drug approval process

- confirm the requirements of the development process
- focus on specific scientific or regulatory issues

- clinical trial design, pharmacology studies, toxicology studies, acceptability of novel formulations, dosing limitations, data requirements for an IND application, and regulatory requirements for demonstrating safety and efficacy

Other Formal Meeting During Drug Development

Building a strong relationship with HA is essential for success in drug development

Divided in phases:
- End-of-phase 1 meetings
- End-of-Phase 2 meetings
- Pre-NDA meetings / Pre-BLA meetings

Divided in functions:
- Multidisciplinary Meeting
- CMC-Specific Meeting

(CMC-Specific meetings separately or as a supplement to multidisciplinary meetings)

- Proper utilization of meetings with HA during drug development may reduce the R&D time to market and ensure that the proposed studies are designed to provide useful information

Regulatory Framework

Regulatory Framework

- Understand the regulatory environment of today (global and local) and in the future if you are planning to make a claim
  - OS is still gold standard in Oncology for FDA
- Follow religiously regulations
  - If deviations have occurred, document them and how you will address/correct them
- Keep your IRB/Ethical committee in the loop
  - Report deviations to study conduct
  - File amendments
  - Report SAEs and INs
- Have a clear understanding of your roles and responsibilities as a sponsor according to GCP
  - Make your staff fully aware of their and your responsibilities
- Use or create a local SOP for common activities related to clinical trials:
  - Local master file, SAE reporting and archiving, drug supply, etc.

Selection Clinical Sites for Trials

Selection of Clinical Sites for Trials (I)

- Credential and qualification of the investigators: ICH-GCP requirement
- Adequate education, training and experience to conduct trials
- Provide curriculum vitae
- IRB/EC
- Be familiar with the use of the investigational drug and IB, and the ability to follow the protocol
- Comply with GCP, and permit monitoring/auditing by the sponsor; inspection by HAs
- Maintain a list of qualified personnel with delegated trial-related duties (study nurses, pharmacists and SC)

Selection of Clinical Sites for Trials (II)

- Criteria based on the trial needs
  - Phase I vs phase II; or III
  - Special monitoring or testing needs
- Experience with a particular tumor type and/or use of a specific regimen
- Number of patients with the relevant target disease seen in clinic
- Prior trial experience
- Able to allocate time for the study
- Competing trial(s) at the site
- Facility and accessibility of the site for patients

Extra Support During The Trial

Extra Support During The Trial

- Monitoring
  - Identify misunderstanding or lack of clarity from the protocol
  - Identify serious issues -e.g. safety early on and react appropriately
  - Evaluate if information is properly collected
  - Good monitoring help to get the database cleaner
  - Identify if site needs help
- Biomarkers collections
  - Collection of tumor blocks and blood sample
  - Are tissue and blood samples allowed to leave the countries? (If not, can local lab facilities be utilized?)
  - Require central collection, identification (patient, timing, type of sample), shipment to a central lab facilities, analyses and reporting results
  - Require a separate consent form
  - Require ongoing analyses if you want to maximize the benefit of it

Data Cleaning (Review)

Data Cleaning Leads to Data Consistency

- Data cleaning starts with the design of the protocol, Case Record Form (CRF) and statistical tables at the same time (along with the tools, organized by priority and guidelines)
  - Establish patient profiles, set of listings and priority for cleaning in regard to the endpoint of your study (survival ⇨listing of date of death).
  - It is never too early to start to look at the data – spot patterns of data error, correct current data.
- Data consistency is a very efficient way to achieve high quality data required for database lock, which increase alignment between data collection and data reporting
- Goal is standardized CRF that allows seamless output of patient profiles, tables, and reports.

When?

- At the design stage
  - Remember all the issues from the last DBL and apply solutions.
  - Investigator meetings are golden opportunities to explain to investigators/study nurses how you want the data to be collected.
- During the Trial
  - Cleaning the trial data on a real time basis offers numerous advantages:
    - Identify monitoring issues
    - Identify design issues
    - Identify safety/efficacy issues
    - Understand why accrual is low
    - Give an unprecedented opportunity to correct them while you still have a chance to do so!
  - Data review should occur at least monthly (more frequent review for early stage)
    - Identification of safety issues, preparation and discussion with investigators for dose escalation

What Needs to be Cleaned?

- The clinical database
  - All data captured on the CRF need to be reviewed/cleaned
  - GCP-based data collection
- Serious adverse events
  - In a different database (Pharmacovigilance)
  - Clinical and PV databases must contain consistent data
  - Often done on the spot, when the SAE happens and not necessarily by the Investigator
  - Diagnoses or syndromes reported may not be reflected in the database ⇨stresses the importance of an appropriate follow-up
  - Not a stricto-senso GCP-based data collection
    - SAE forms are sent on an emergency basis, contain a lot of errors compared to the CRF until the reconciliation occurs
  - Some will be required to be written as narratives in the CSR

Four Major Type of Data Cleaning Tools

- Data Listings
  - Listings display data by type (blood chemistry, AE, response) across the study
  - Regular, standard listings
  - Customized listings (I-review allows you to customize listings)
- Patient profiles
  - Display all data for a given patient
- Statistical tables
  - A dry run of the tables may be useful to identify and correct issues in the databases
  - Should occur early (agreement with statistician and programmers)
- SAE listings including reconciliation listings and SAE narratives

How?

- Patient profiles are useful to make data cleaning effective by patient (make sure the records are consistent)
  - Key review tool for Phase I dose escalation
- Listings have to be used in combination with patient profiles
  - Listings by topic (lab, AE, demography, etc.)
    - Allows for review of data trends and data consistency across the trial
  - Listings customized to check particular points (e.g. proteinuria by 24hr urine collection)
  - SAE listings
  - SAE narratives (but remember that SAE database is not GCP)

Analysis Results

Analyzing Data

- Data is analyzed based upon pre-specified clinical endpoints in protocol, and outlines in statistical analysis plan

- Other clinical endpoints are analyzed and reported in FIR

  - Exploratory statistics (not pre-defined) can be conducted for hypothesis generating and scientific interest. But results not accepted for any claim.

人类和肿瘤的斗争不会停歇，抗肿瘤新药临床研究工作任重而道远。

The struggle between human beings and tumors will not stop. The clinical research of anti-tumor new drugs still has a long way to go.

Thank You