Preclinical Drug Development PoC

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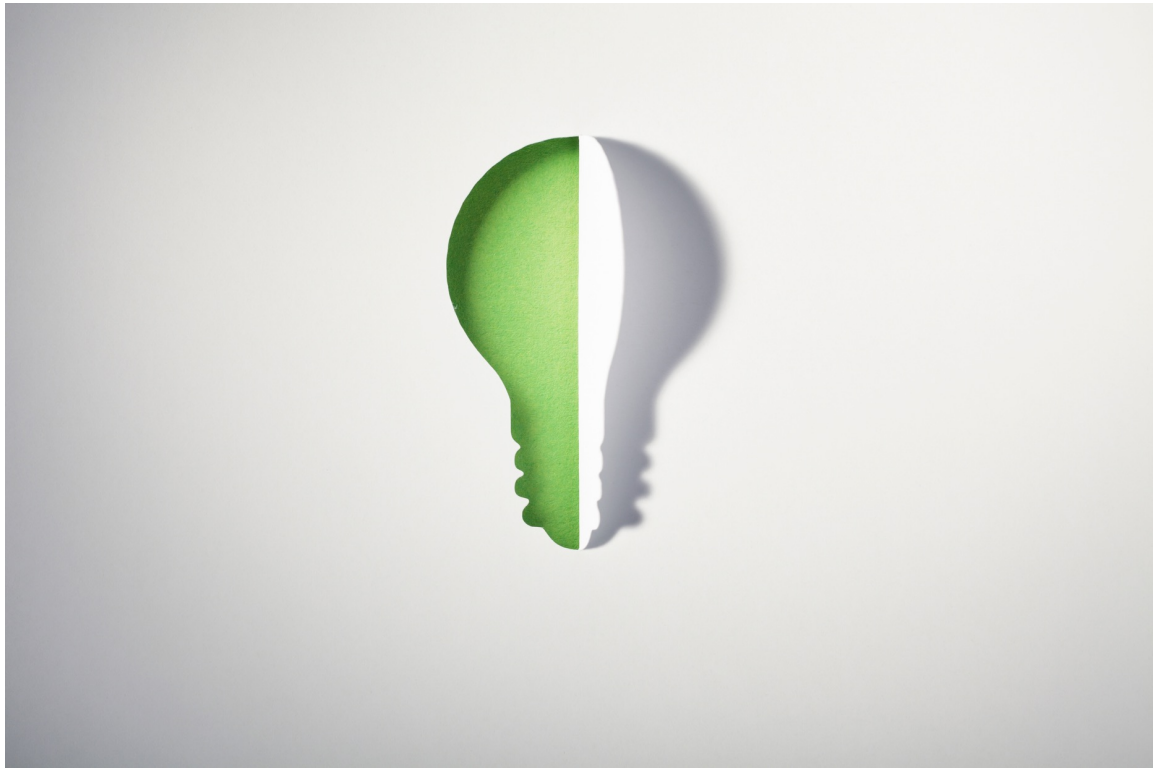
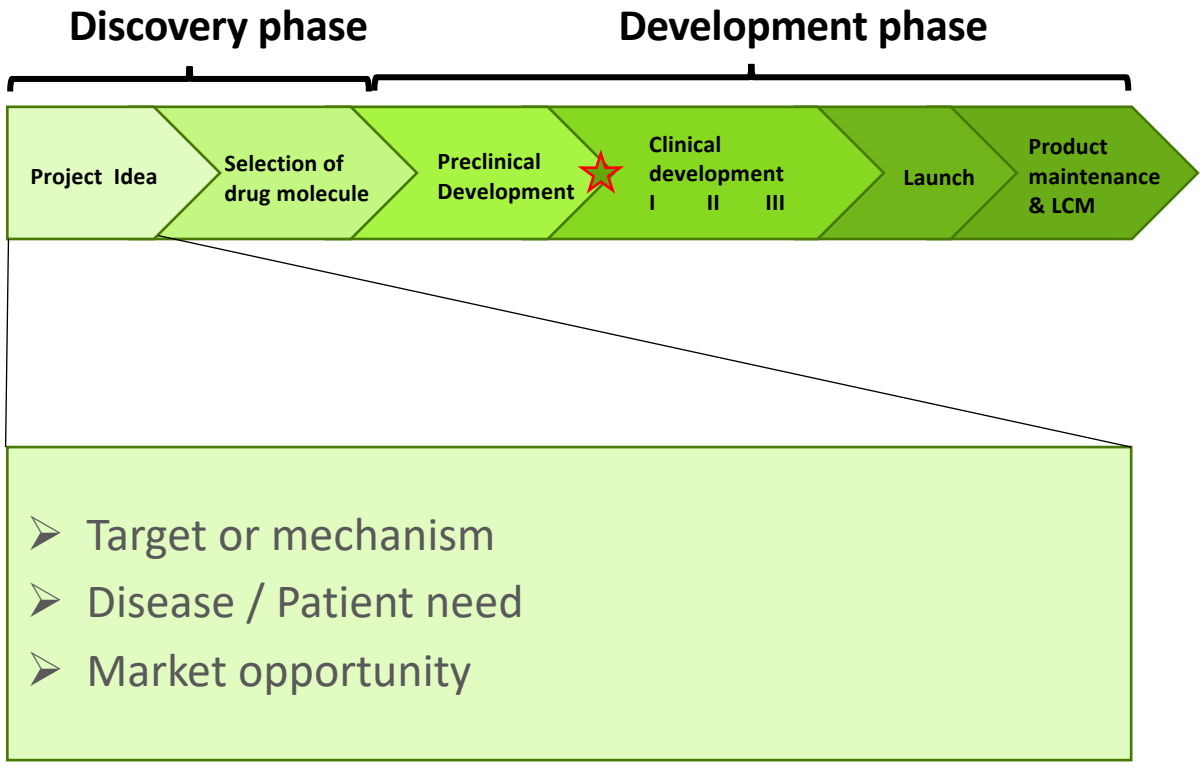
It all starts with a great idea!



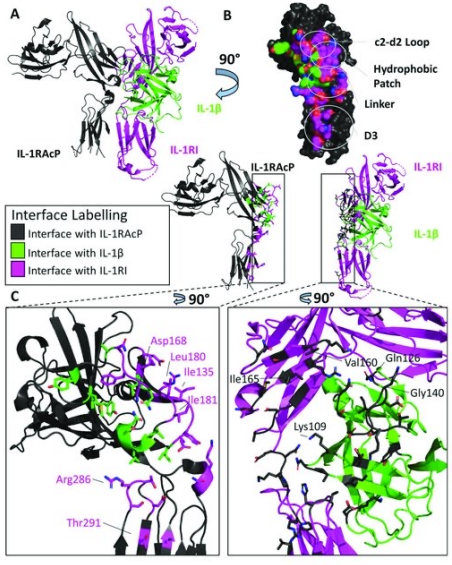
Project idea



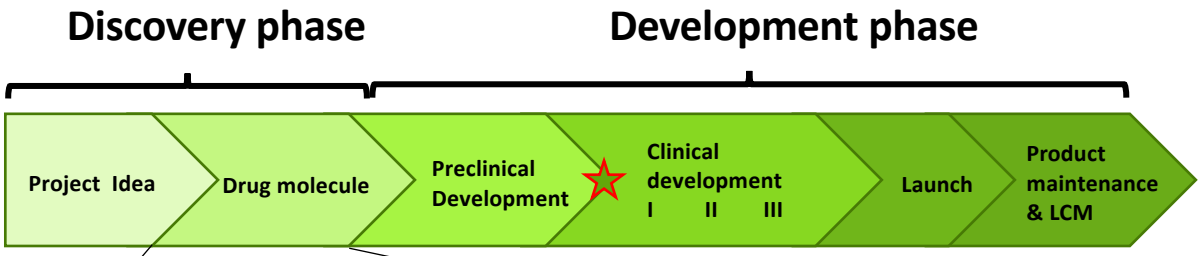
Project idea

"Mechanism or pathway that when modulated generates a positive effect to a medical problem"

- Target molecule
  - Activate or inhibit?
- Disease / Patient need
  - What should the effect of the drug be?
- Market opportunity
  - Is there a market for this product?
- Formulate a draft Target Product Profile, TPP



Drug molecule



- Pharmacological approach:
  - Small molecule
  - Biological
- Route of administration
  - Per oral
  - Intravenous
  - Inhalation

Small molecule or Biological Drug?

Small Molecules

- Chemically synthesized
- Low molecular weight < 1kDa
- May be metabolized to toxic intermediates
- Mostly non-immunogenic
- Can interact with multiple cells or organs
- Often acceptable activity across species

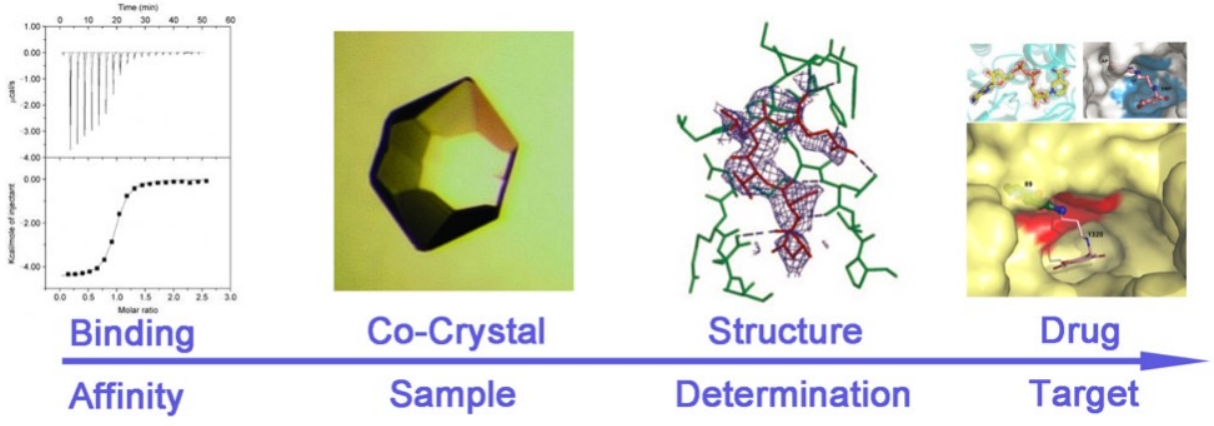
Biologics

- Derived from living cells
- High molecular weight ≥5kDa
- Degraded into non-toxic biological buildingblocks
- May initiate immune response; recognized as foreign
- Able to achieve very high specificity and selectivity
- Often species selective – no activity in distant species

How to find the right hits/leads

Small Molecules

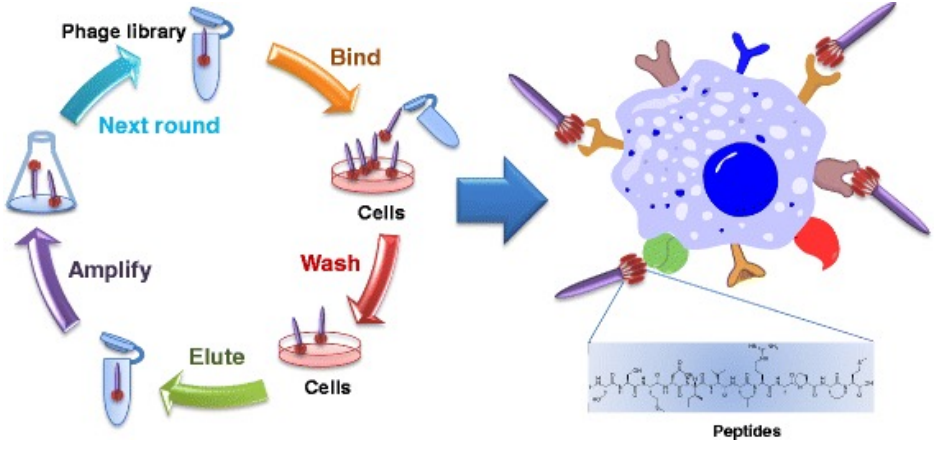
- Structure based design
- Fragment based screening
- HTS
- Published Leads



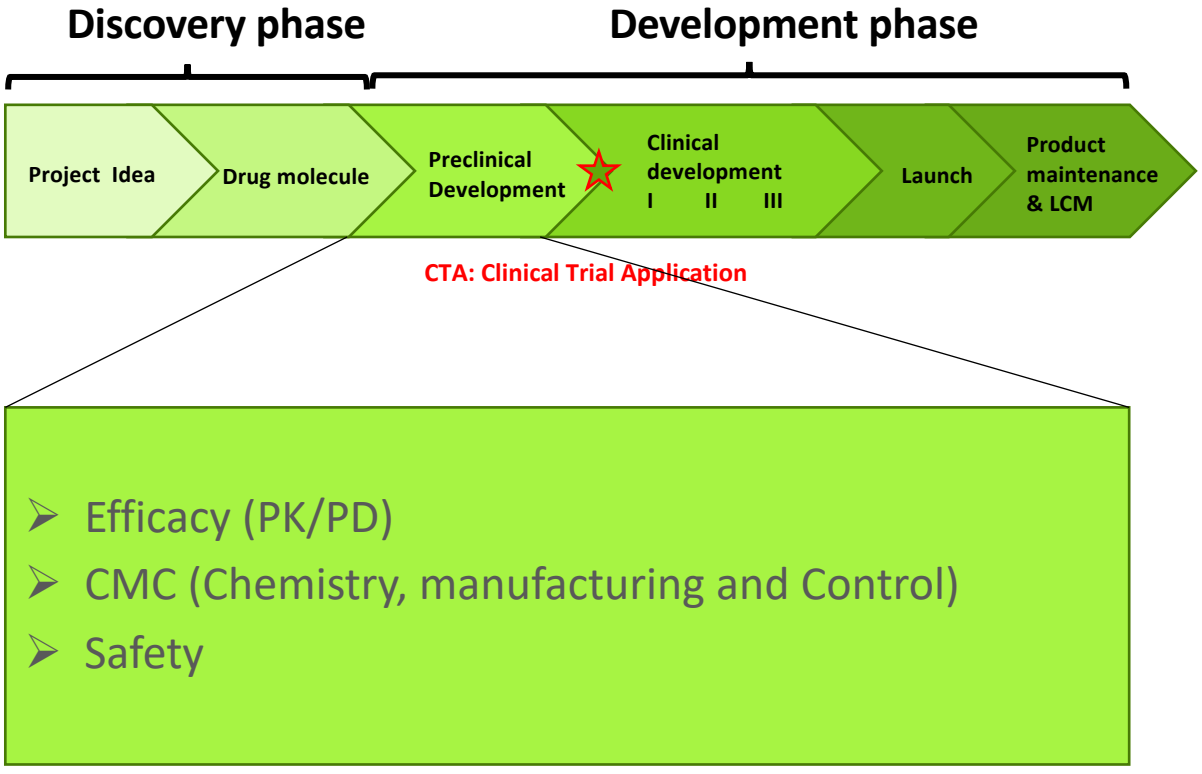
How to find the right hits/leads

Biologics

- Immunizations
- Antibody library selection
- Peptide/Scaffold library selection
- Natural molecules/mimetics



Preclinical Development



Preclinical Development - How to turn leads into drugs

Efficacy

- Optimize potency and efficacy
- Elucidate Mode-of-Action for the drug
- Establish maximal and minimal effect levels in relevant *in vitro* and *in vivo* models
- Characterize the pharmacokinetic profile
- Ensure that you have the right amount of drug at the right place and right time
- Demonstrate Proof-of-Concept (PoC)

CMC

- Appropriate formulation for selected route of administration
- Purity and stability of API
- Manufacturing process

Safety

- *In vitro* tolerability/toxicity and selectivity
- *In vivo* toxicity and safety pharmacology
  - MTD – maximum tolerated dose
  - DRF – dose range finding
  - Pivotal GLP Safety

Pharmacology

"Overall aim is to predict and deliver a safe and effective dose "

Efficacy:

- Enough of the drug should reach the target (Target Engagement)
- Strong enough to translate into a clinically meaningful effect
- Effective dose in animal should have good safety margin

Preclinical *in vitro* models in drug development

Chain of evidence

- Relevant cells
- Human primary cells
- Disease tissues
- Correlation *in vitro/ in vivo*
- Correlation between species

Analytical needs

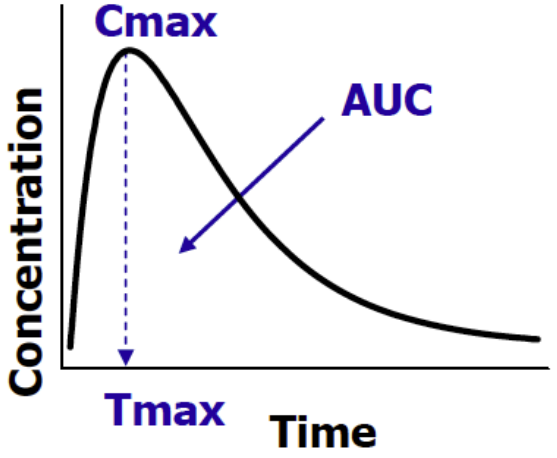
- Sensitivity
- Reproducibility
- Throughput
- Quantitative

Keeping in mind

Pharmacokinetics (PK) – What the body does to the drug

- Several processes determine the PK
  - Absorption, Distribution, Metabolism, and Excretion

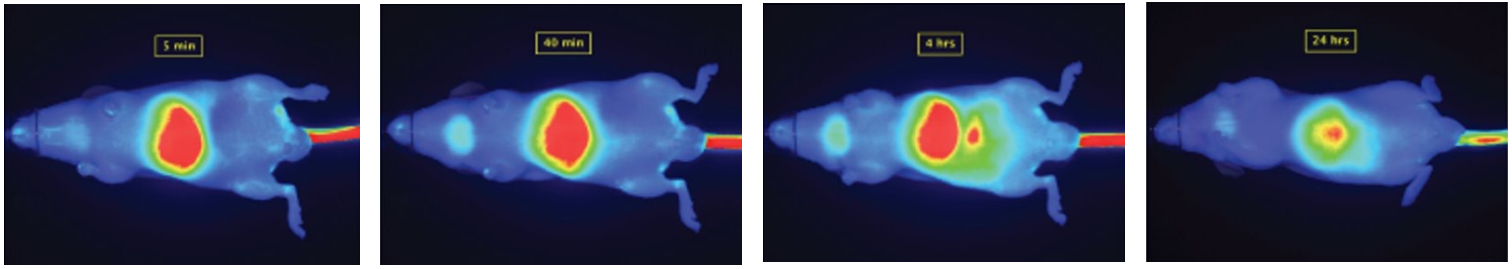
- May differ between
  - Species
  - Strains/Individuals
  - Gender

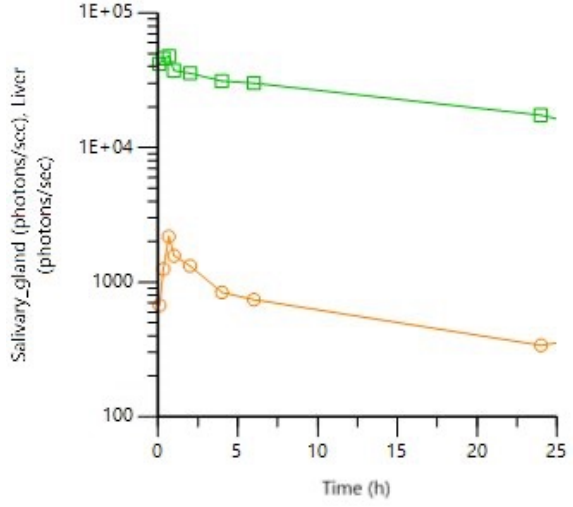


- Exposure parameters (Cmax and AUC) are important in preclinical safety studies and thus for what exposure / dosing that can be used later in clinical development

PK imaging using Pearl Trilogy

In vivo biodistribution and tissue localization of intravenously administered Cy7.5 labelled peptide Z





Non-compartmental analysis (NCA) indicate terminal half-life liver= 15 h

Pharmacodynamics (PD) -
What the drug does to the body

The study of:

- biochemical and physiological effects of drug on the body
- mechanism of action (MoA)
- the relationship between drug concentration and effect (PK/PD)

Pharmacological studies

PK/PD Model

- Demonstrating dose-response relationship (PK/PD)

Proof of Mechanism (PoM) = PD model

- Showing drug exposure at the target site of action
- Showing that the drug interacts with the intended target – Target Engagement
- Showing that the drug effects cell biology in the desired manner and direction

Proof of Concept (PoC) = Disease relevant model

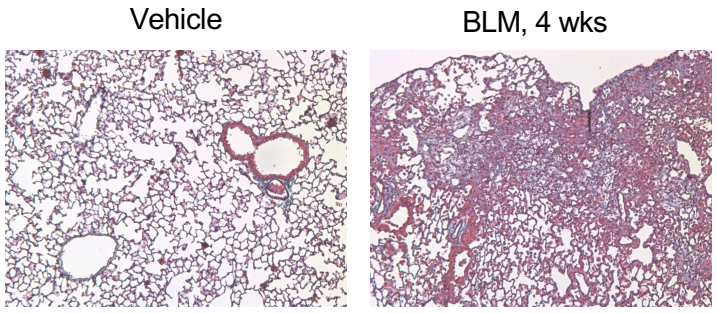
- Showing statistically significant evidence of preclinical efficacy (endpoints of the condition)

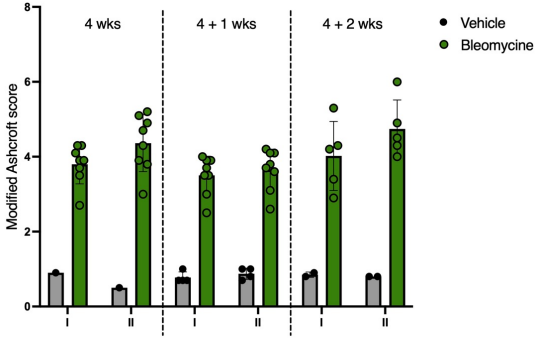
Animal disease-relevant model

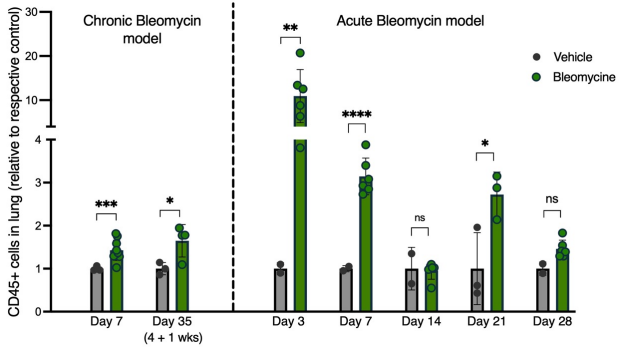
- Similar endpoints & biomarkers should if possible exist for preclinical and clinical studies

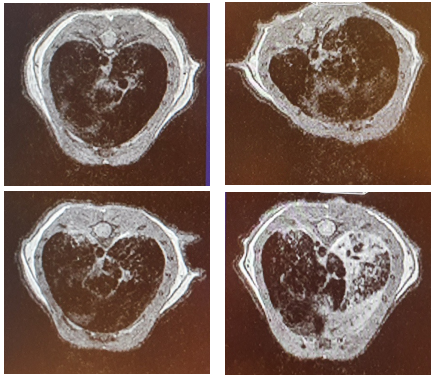
Animal model of lung fibrosis

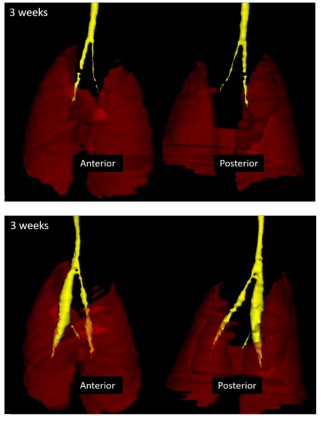
- Chronic exposure to Bleomycin 35 (iU/g) i.p. twice a week for 4 weeks











Distribution

The physical and chemical properties of the drug determines the distributes from the blood stream into different compartments of the body

If the drug;

Binds to plasma proteins

- difficult to leave the blood

Low lipid solubility

- difficult to enter into cells

Substrate for drug transporters

- influx or efflux

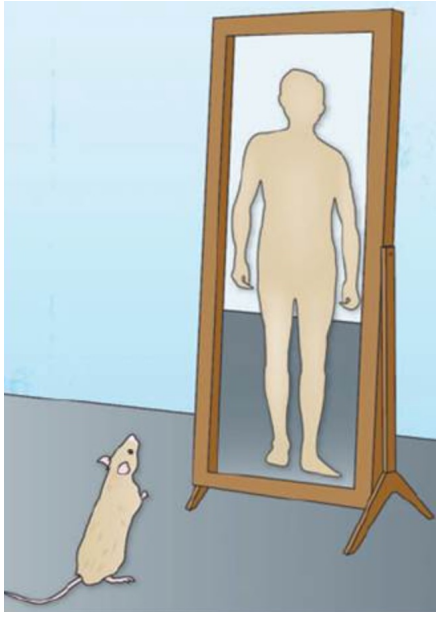
High specific binding

- accumulates in organ/tissue

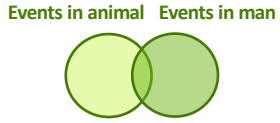
High lipid solubility

- accumulate in fat

Preclinical *in vivo* models in drug development



Animal model is not a disease, but the closest thing you will get to disease before a human trial.



Poor model

Good model

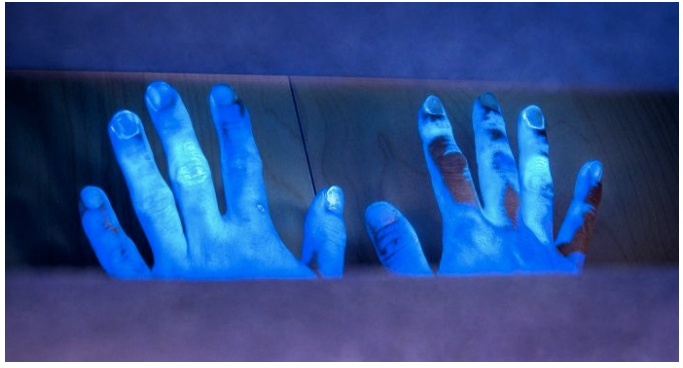
- Animals are used to predict efficacy, PK, safety and toxicity
- Naïve animals – 'mechanistic' PD models ➔ Drug action at binding site and the physiological/chemical/ behavioral effect produced by this action.
- Disease models – 'disease signature' ➔ translational aspect is crucial

Increasing complexity

Biomarkers a tool in Translational Medicine

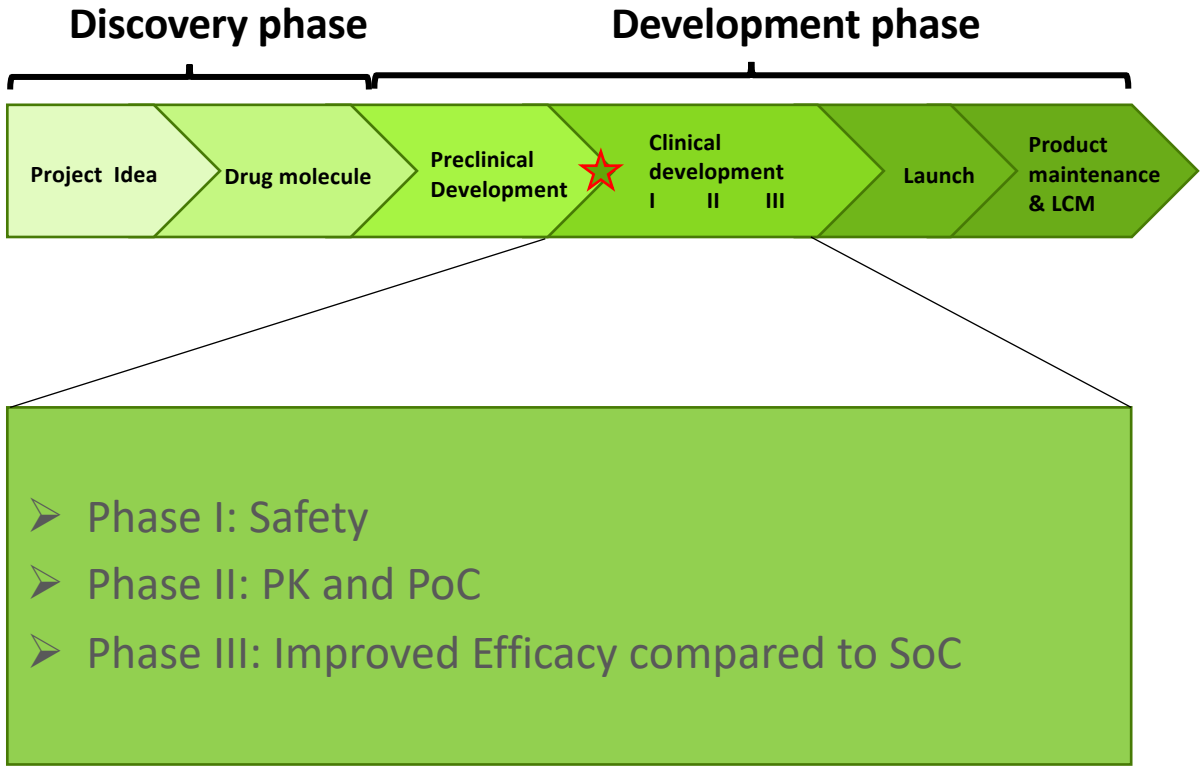
A characteristic that is measured and evaluated as an indicator of:

- normal biological processes
- pathogenic processes
- pharmacological responses to a therapeutic invention



Detection of Bacteria after handwash.
“Biomarker” in everyday health care.

Clinical Development



Phase I

- Is the drug Safe?
- What doses are safe?
- Identify most common side-effects
- Mostly conducted in healthy subjects

➢ If possible also include assessment of efficacy.

➢ Use of biomarkers will be important for both Safety and Efficacy

➢ Around 70% of drugs pass to next phase

Phase II

- Is the drug effective? (Proof-of-principle/Proof-of-Concept)
- Continued focus on safety and tolerability
- What is the best dose?

➢ Conducted in patients

➢ Larger cohorts

➢ Deliver conditions for Phase III pivotal studies

➢ Around 1/3 of drugs moves forward to phase III

Phase III

- Is the drug good enough to get registered on the market?
- Comparative studies with current Standard of Care
- Is the drug effective? (Proof-of-principle/Proof-of-Concept)
- Placebo controls

- Conducted in patients. Preferably “natural cohorts”
- Large cohorts with mixed background
- Basis for claims and registration
- Around 1/3 of drugs starting a Phase III proceed to registration

Non-clinical data for a clinical trial application –
CTD Module 4

Pharmacology

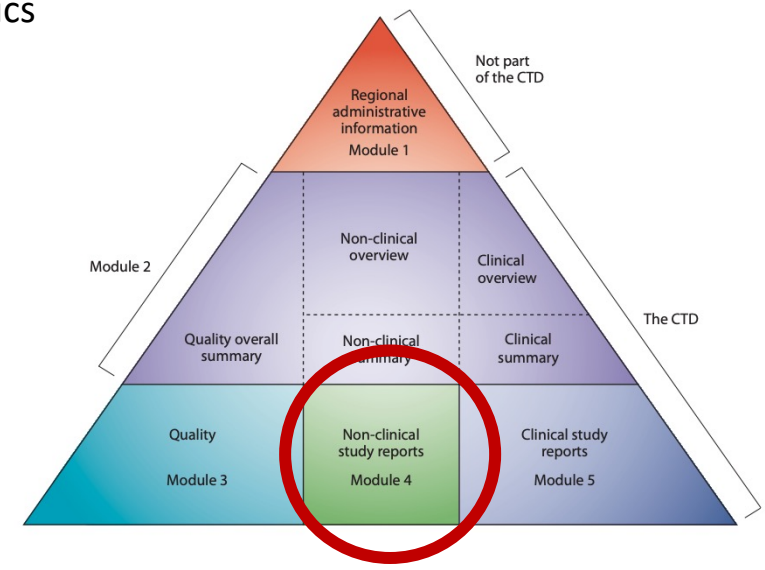
- Primary pharmacodynamics
  - In vitro & in vitro potency
- Secondary pharmacodynamics
- Safety pharmacology

Pharmacokinetics

- Pharmacokinetics
- Biodistribution
- Metabolism
- PK/PD

Toxicology

- Single-dose toxicity
- Repeated-dose toxicity
- Genotoxicity
- Immunotoxicology
- Local tolerance



Potential Novel Translational Biomarker: Comparison[^{18}F]FDG PET-MRI / ^{89}Zr-FAP PET-CT

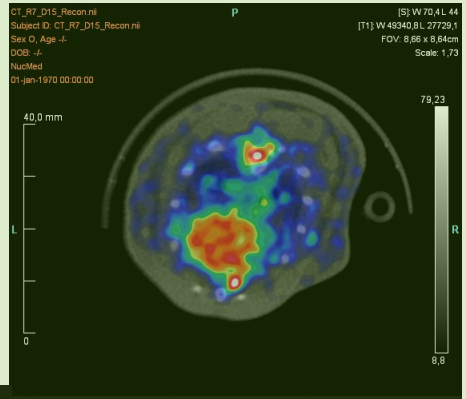
Control group: Animal R7

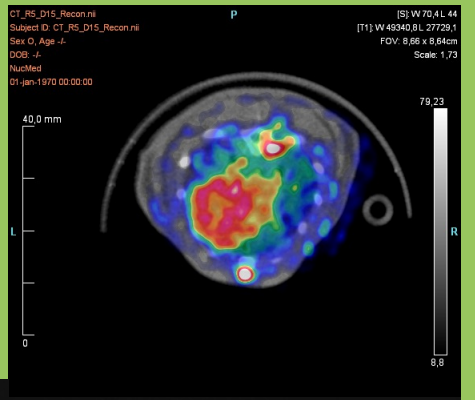
Acute Bleomycin model

Bleo group: Animal R5

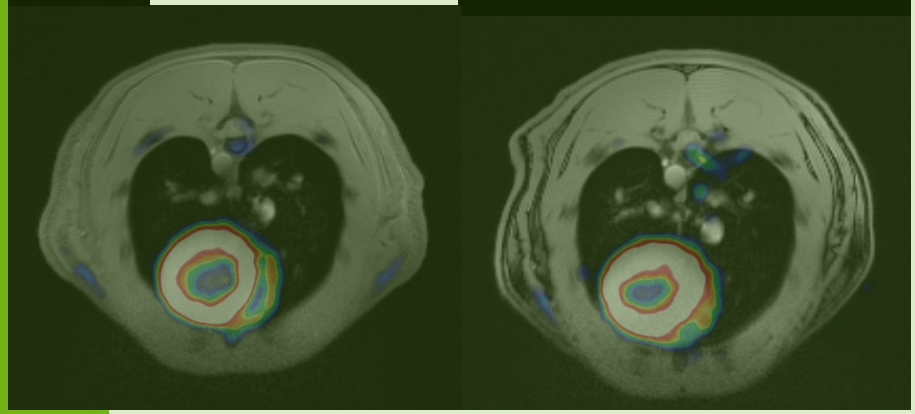
Acute Bleomycin model

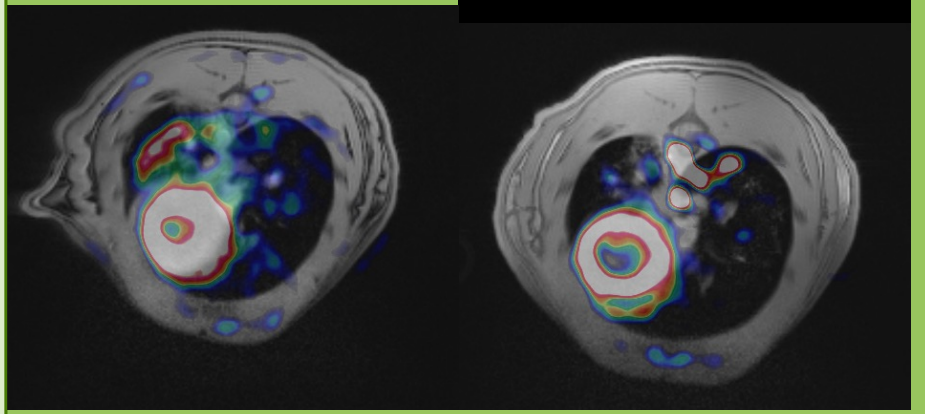
aFAP





FDG





Imaging D7

Imaging D14/15

Imaging D7

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Thank you!