The first blow is half the battle

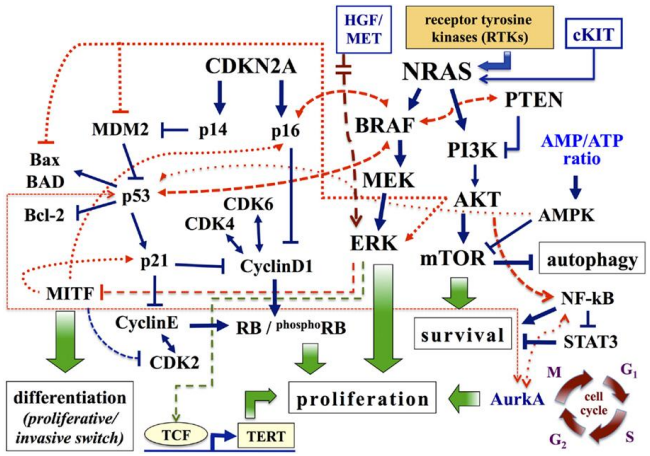
September 2022

CHDR
Centre for Human Drug Research

Landscape (1)

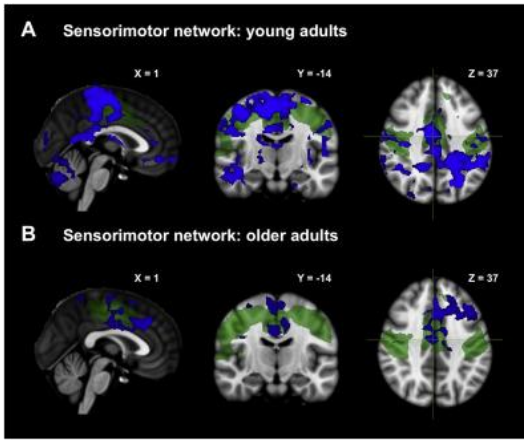
- Developments in systems biology / pharmacology
  - → Better understanding diseases / conditions
  - → Numerous numbers potential targets

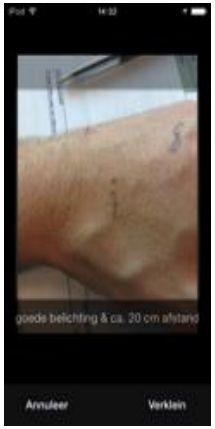
- Molecular biology & high throughput methodologies & -omics
  - → Plethora of modulators (‘drugs’)
  - → Multiple choices for treatment(-strategies)



Landscape (2)

- Technological revolution
  - → Read-outs: including RWD (remote effect monitoring)
  - → Data-analysis
  - → AI / VR Predictive biomarkers for (intended) effects of new treatments are crucially important → likely to be complex

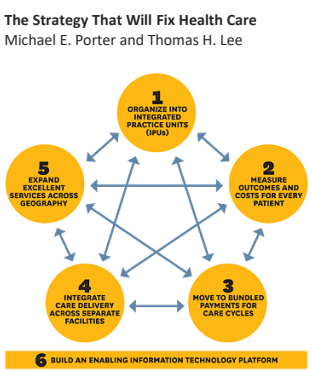




Landscape (3)

- Societal questions / themes
  - Accessibility
  - Increasing pressure cost reduction

- Answers
  - Value-based care
  - Patient-centered care
  - Academia should become more important
  - Return on investment is crucial



Different definitions of value and incentives for value creation

$$\text{Value} = \frac{\text{health outcomes that matter to patients}}{\text{costs of delivering these outcomes}}$$

- Shareholders
- Patients
- Researchers
- Early-stage drug development
  - Value new treatment is only potential
  - Conflicting interests (stakeholders *vs.* shareholders)
  - Are efficiency & rapid (informed) decision by the common answer?
  - Can we achieve that?

Paradigms – drug development

- Classical - Phase I-IV → artificial
  - Phase I-II
    - Safety → cannot be estimated (population size)
    - Tolerability → relative value
      - » most withdrawals perfect tolerability
      - » Acceptance poor outcome (infusion reaction at 1st administration biologics
    - Kinetics: limited value and can be tweaked
  - Phase III
    - 'Hard clinical endpoints' rare, multi-dimensional, time, compared to what (placebo/active)

- Alternative
  - Early and late-stage development → relevant proxy end points and RWD

- Early phase
  - Scientific question based with proper risk/benefit
  - Connect *vs.* collect (integration)

- Is it allowed and possible?

Rules - regulatory guidance

TABLE 1.—AN APPROACH TO CLASSIFYING CLINICAL STUDIES ACCORDING TO OBJECTIVE

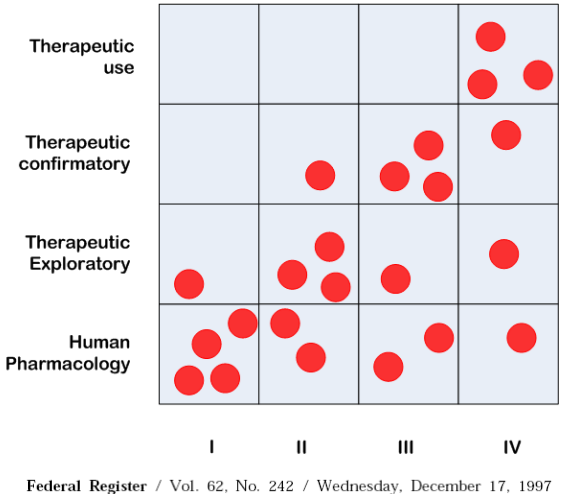
Type of Study	Objective of Study	Study Examples
Human Pharmacology	• Assess tolerance • Define/describe PK[1] and PD[2] • Explore drug metabolism and drug interactions • Estimate activity	• Dose-tolerance studies • Single and multiple dose PK and/or PD studies • Drug interaction studies
Therapeutic Exploratory	• Explore use for the targeted indication • Estimate dosage for subsequent studies • Provide basis for confirmatory study design, endpoints, methodologies	• Earliest trials of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures • Dose-response exploration studies
Therapeutic Confirmatory	• Demonstrate/confirm efficacy • Establish safety profile • Provide an adequate basis for assessing the benefit/risk relationship to support licensing • Establish dose-response relationship	• Adequate, and well controlled studies to establish efficacy • Randomized parallel dose-response studies • Clinical safety studies • Studies of mortality/morbidity outcomes • Large simple trials • Comparative studies
Therapeutic Use	• Refine understanding of benefit/risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendation	• Comparative effectiveness studies • Studies of mortality/morbidity outcomes • Studies of additional endpoints • Large simple trials • Pharmacoeconomic studies

[1] Pharmacokinetics
[2] Pharmacodynamics

NOTE FOR GUIDANCE ON GENERAL CONSIDERATIONS FOR CLINICAL TRIALS
(CPMP/ICH/291/95)
Federal Register / Vol. 62, No. 242 / Wednesday, December 17, 1997

No phases but science-driven objectives

Regulatory guidance



Federal Register / Vol. 62, No. 242 / Wednesday, December 17, 1997

- Objectives of early human studies
  - Human pharmacology studies
  - Estimation of initial safety and tolerability
  - Pharmacokinetics
  - Early measurement of drug activity (PD)
  - Integration (PK/PD, drug-disease, variability)

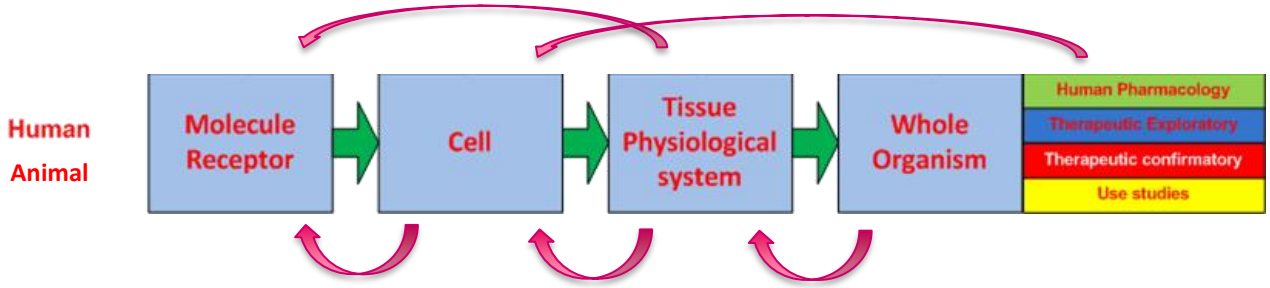
→ There is no regulatory reason for safety and tolerability as primary objectives for human pharmacology studies

- Start doses and escalation steps
  - NOAEL is only one of possibilities among Pharmacological Active Dose (PAD) and Minimum Anticipated Biological Effect Level (MABEL)
- Not dogmatic, but science-oriented
- Particularly useful for new drugs / drug classes

Contains Nonbinding Recommendations

Guidance for Industry[1]
Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

Requirements translational approach - clinical



- Develop methods that can be used in early phase clinical development
  - Pre-study preparations to identify informative biomarkers
- Flexibility - innovative trial designs
  - Adaptive designs / Umbrella protocols
- Multidisciplinary / Integration
  - On-line integration / PK-effects*

- What can we do to get this into practice ?

Approaches / tools for translational approach

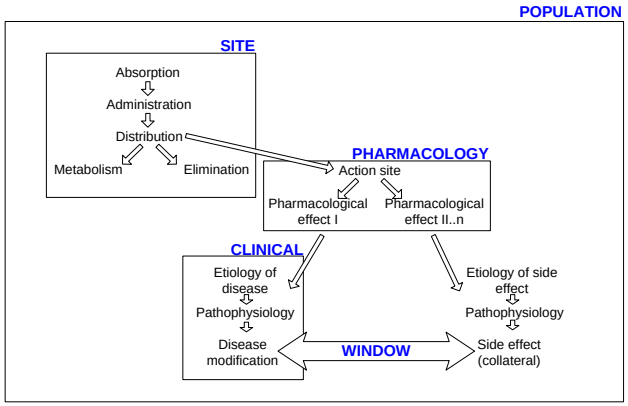
1. Question Based Development (QBD)

2. Structured risk analysis

Establishing risk of human experimentation with drugs: lessons from TGN1412. Kenter and Cohen. Lancet 2006; 368: 1387-91

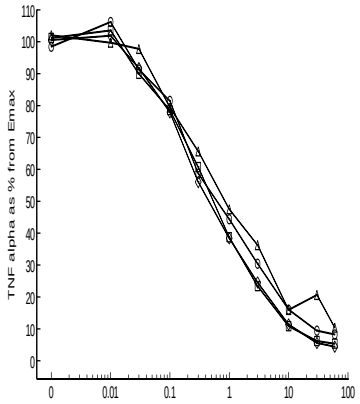
Question Based Development

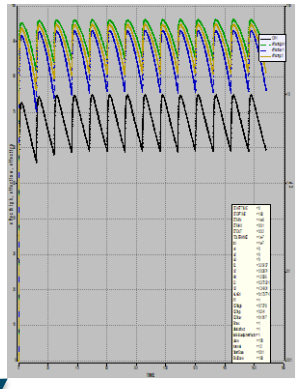
1. Does the biologically active compound get to the **site** of action?
2. Does the compound cause its intended **pharmacological**/functional effect(s)?
3. Does the compound have beneficial effects on the disease or its **clinical** pathophysiology?
4. What is the therapeutic **window**?
5. How do the sources of **variability** in drug response in the target **population** affect the development of the product?

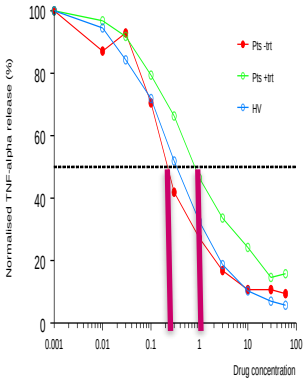


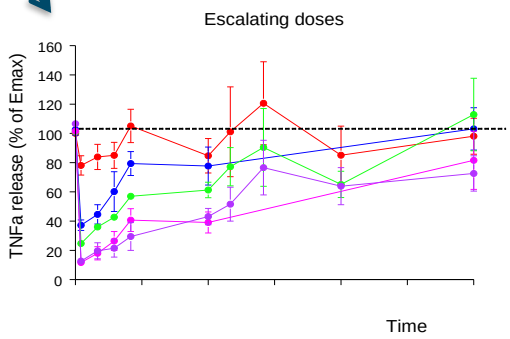
Biomarker-driven drug development

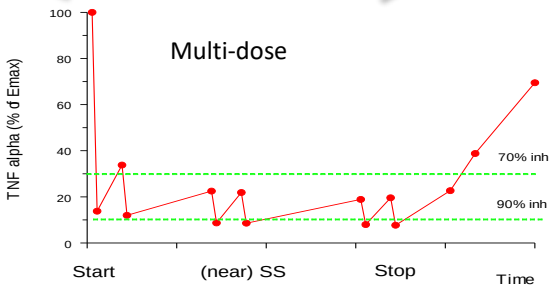
Tissue → **Organism** → **Integration** → **Organism** → **Tissue patients**



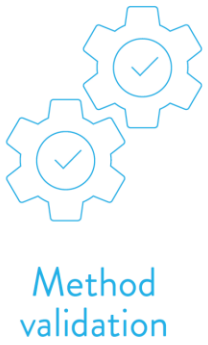








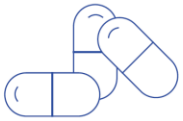
Early-stage development - summary



Method validation

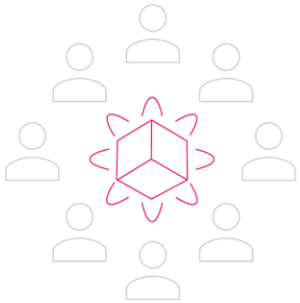
HEALTHY VOLUNTEERS (SAFETY / PKPD)

Single ascending dose



Multiple ascending dose

INTERMEDIATE POPULATIONS



Pharmacological challenges

Behavioural challenges

TARGET POPULATIONS (MONOCENTRE APPROACH)

Surrogate endpoints in patients

Efficacy in patients

POP: Proof-of-Pharmacology

POM: Proof-of-Mechanism

POC: Proof-of-Concept

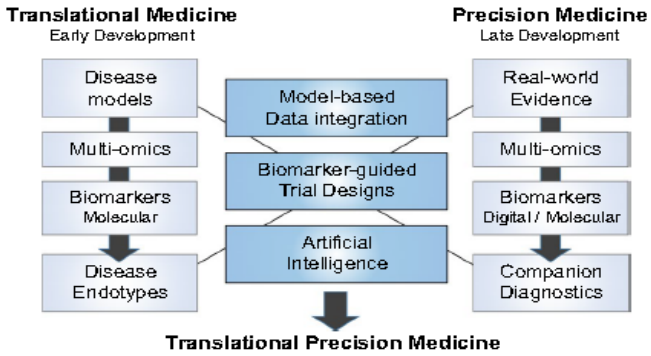
Added value of biomarkers in early-stage drug research

- Only 7.1% of all drug development paths using biomarkers use them in all stages of development (5.7 % in phase I)
- Trials using biomarkers exhibit almost twice the overall probability of success compared to trials without biomarkers (10.3% vs. 5.5%)
  - 1.3x more successful for phase I to II
  - 1.4x more successful for phase II to III
- Imagine what the success rate c/would be for combined early drug development (aka phase I/II)

Wong et al. Estimation of clinical trial success rates and related parameters (MIT-report 2019)

Added value of biomarkers in (early-stage) drug research

- Translation
  - **Forward**: mechanistic insights → early clinical development (bench-to-bedside)
  - **Reverse**: late clinical development insights → drug discovery (bedside-to-bench)
- Data-driven mechanism-indication pairing
- Identify clinically-relevant biomarkers and endotypes
  - omics signatures / models / deep-learning
- Tailored to patient
  - Patient engagement / companion diagnostics / etc.



"In combination, these emerging concepts …. hold promise to make drug discovery and development more efficient and less burdensome to patients….."

Hartl et al. Translational precision medicine: an industry perspective. J Transl Med. 2021

Summary

→ Paradigm shift from classical phase 1 to early human (proof of) pharmacology studies as basis

- Careful integration of preclinical studies
  - Starting dose based upon pharmacology and toxicology
- Integration between preclinic and clinic
  - PK / Effect measures / Combine *in vitro* and *ex vivo* data
- Validated methodology
  - Biomarkers: based on disease char's ↔ drug mechanism
  - Enabled by technological developments including analysis tools
- Efficiency
  - Faster entry in later phases (or 'early kill') / lower chance overdosing
- Further align with regulators for modernized review

The first blow is half the battle

Starting with data dense human pharmacology studies using validated biomarkers early in drug development using a cyclical translational approach and based on integration of data increases the chance of successful drug development

Acknowledgements

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Thank you!

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