Drug Discovery and Development: Toxicological Challenges and Opportunities

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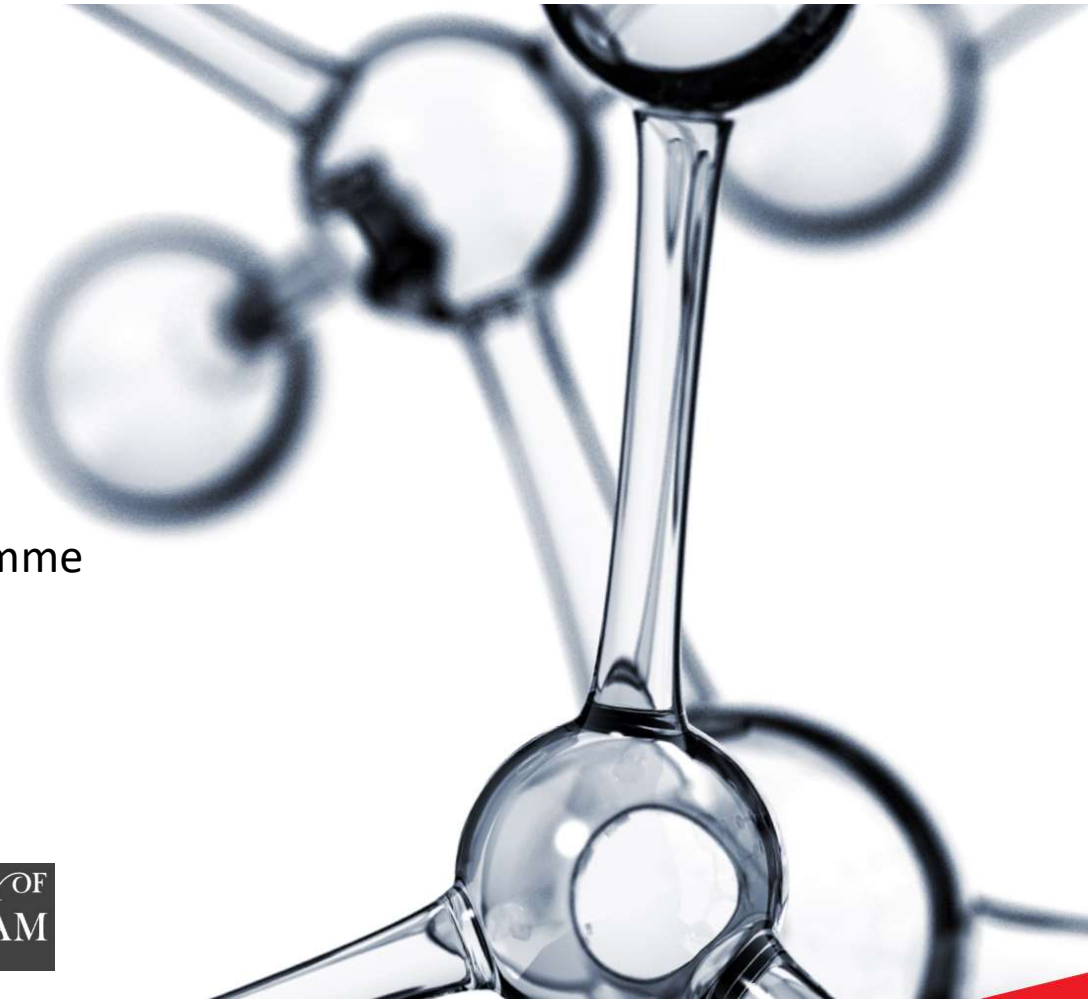
Drug discovery and development: challenges and opportunities

- Outline of drug discovery and development
- Challenges
  - Attrition
  - Concordance
  - 3Rs
- Opportunities
  - Derisking target and chemistry
  - Bespoke design of the nonclinical programme
  - 3Rs
  - Role of new technologies
- Future Perspectives



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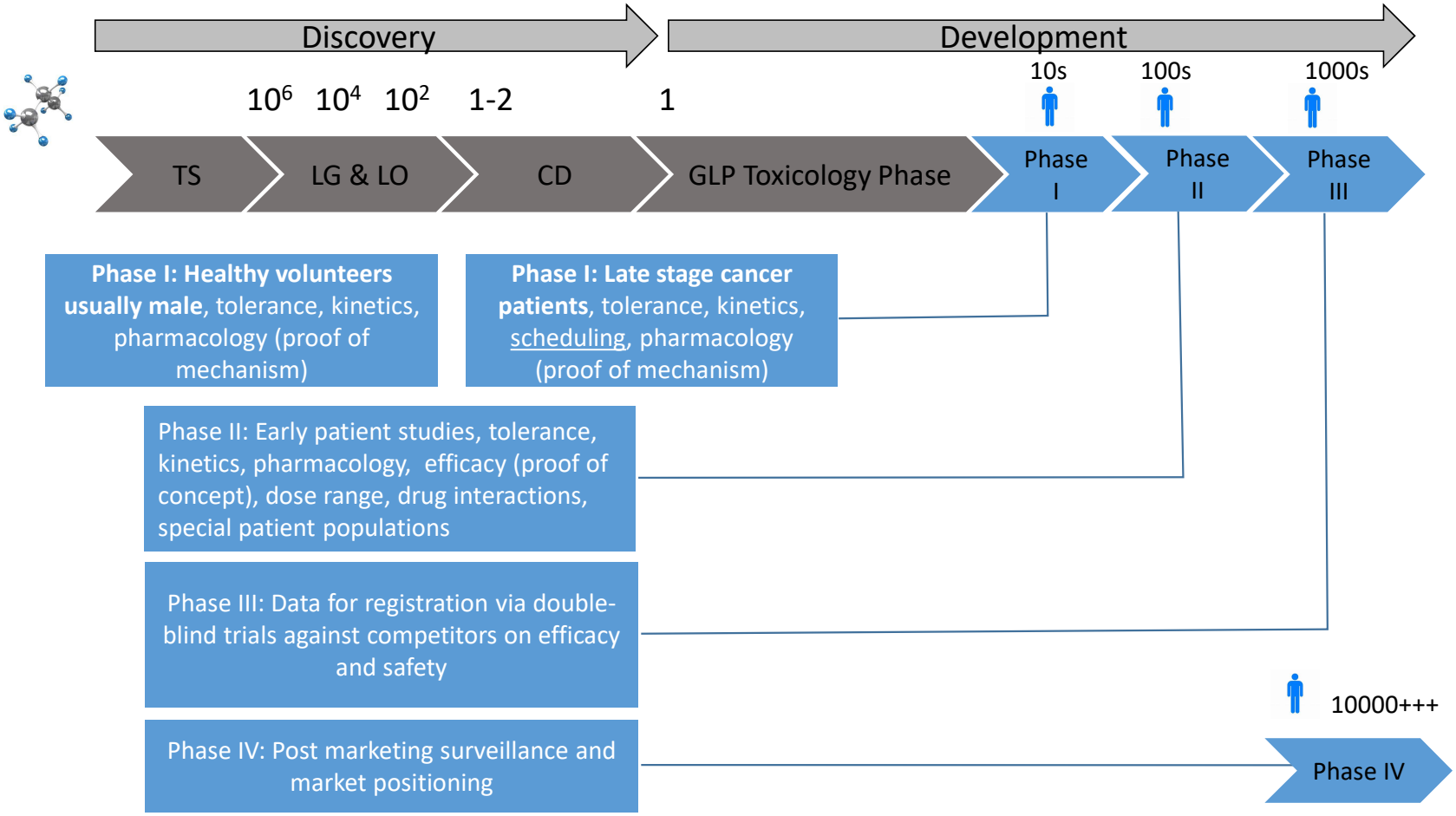

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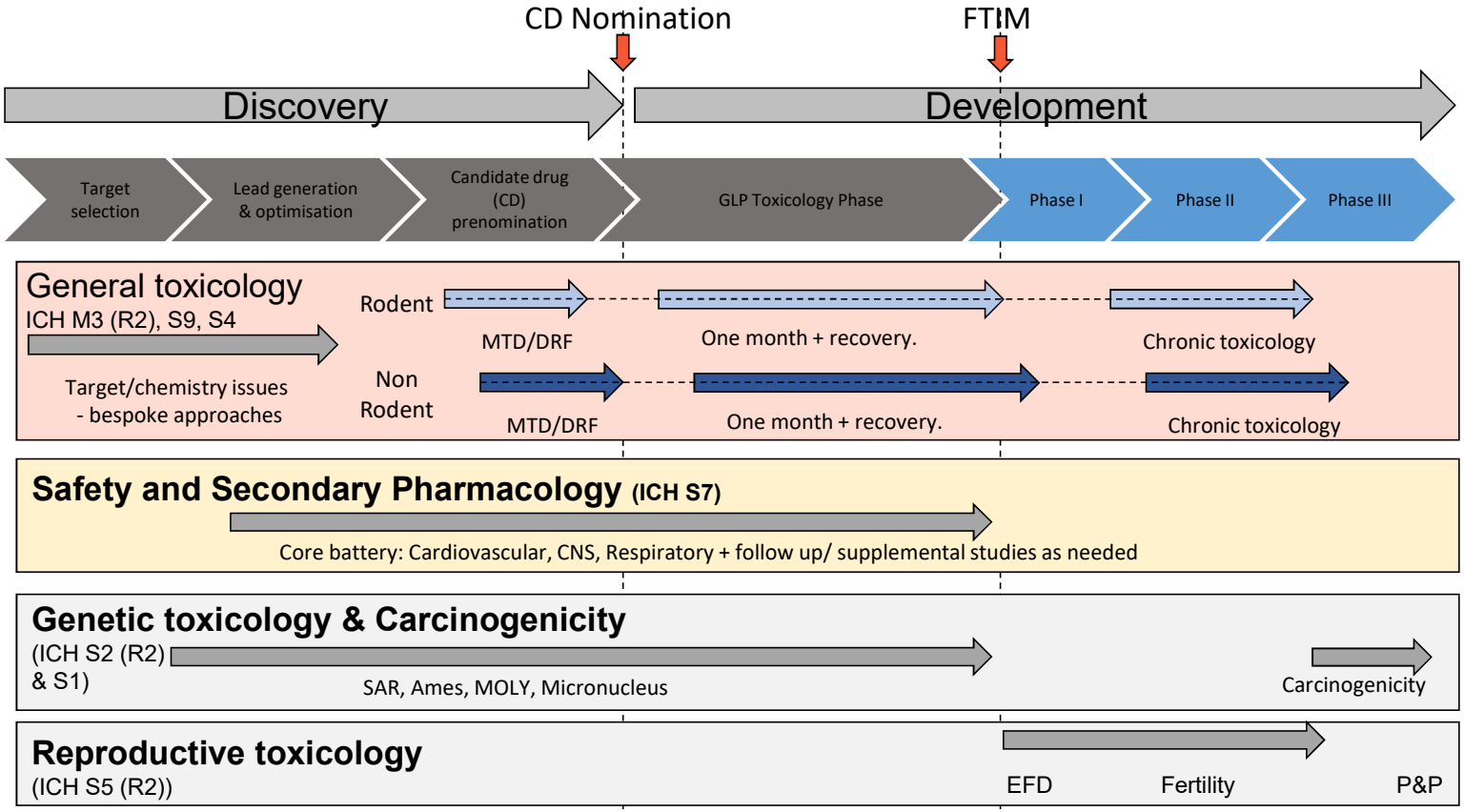
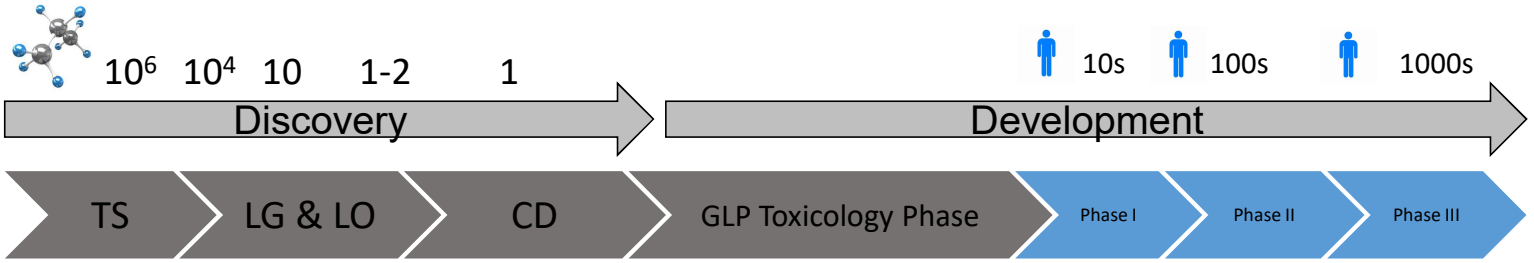
CD: candidate drug; LG: lead generation; LO: lead optimisation; TS: target selection; GLP: good laboratory practice; MOA: mode of action

Navigating the regulatory framework…..



Abbs: CD: candidate drug; CNS: Central Nervous System; DRF: dose range finding; EFD: Embryo Fetal Development; FTIM: first time in man; GLP: good laboratory practice; LG/LO: lead generation/lead optimisation; ICH: International Council for Harmonisation; MOLY: Mouse Lymphoma; MTD: maximum tolerated dose; P&P: peri and post natal; SAR: Structure Activity Relationship; TS: target selection

Discovery & Development Toxicology



Project-specific requirements

Identify early safety risks associated with target

Influence chemical design and selection to avoid issues where possible

Regulatory requirement

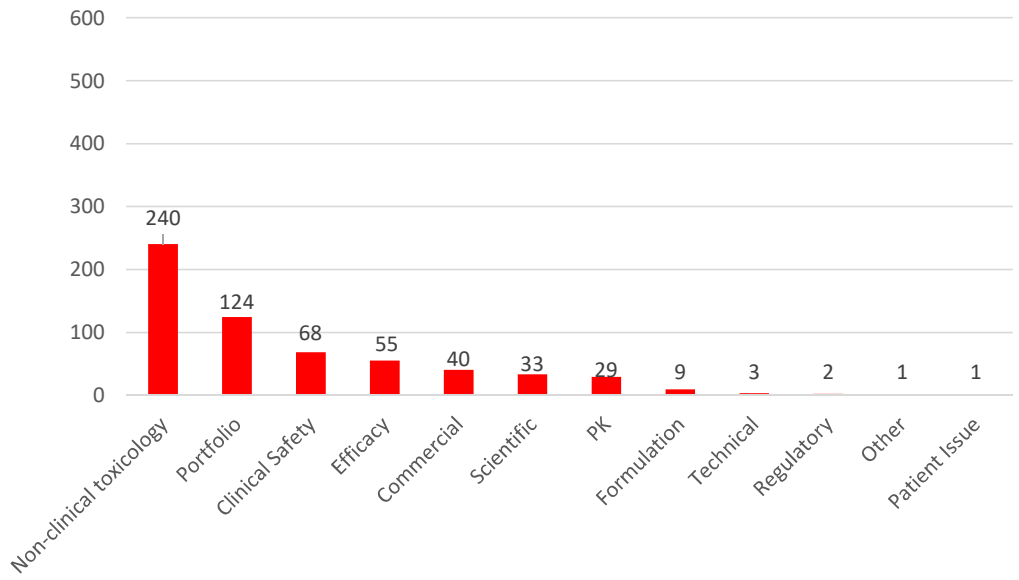
Traditionally the 'home' of pharmaceutical toxicology

Provide safety information on one compound to allow entry into clinical trials and its registration and prescription

Problem solve any findings: MOA and relevance to humans?

CD: candidate drug; LG: lead generation; LO: lead optimisation; TS: target selection; GLP: good laboratory practice; MOA: mode of action

Nonclinical toxicology:
major reason for failure across multiple big pharma



605 projects from AZ, Lilly, GSK and Pfizer

An analysis of the attrition of drug candidates from four major pharmaceutical companies Waring et al., Nature Reviews Drug Discovery, 14, 2015

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Investigating failure

48 AstraZeneca drugs failed during GLP tox alone – reasons?

Roberts *et al* (2014). Reducing attrition in drug development: smart loading preclinical safety assessment. Drug Discov Today. 2014 Mar;19(3):341-347.

Liver Is the Most Frequent Target Organ in Rodent and Non-Rodent FTIM Studies (all projects)

Target Organ	Non-rodent	Rodent
1	Liver	Liver
2	Thymus	Adrenal
3	GI	Spleen Kidneys Bone Marrow
4	Testes	
5	Lymph nodes	

Horner et al (2013) *Regulatory Toxicology and Pharmacology,* 65, 334-343.


Regulatory Toxicology and Pharmacology 65 (2013) 334–343

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Target organ toxicities in studies conducted to support first time in man dosing: An analysis across species and therapy areas

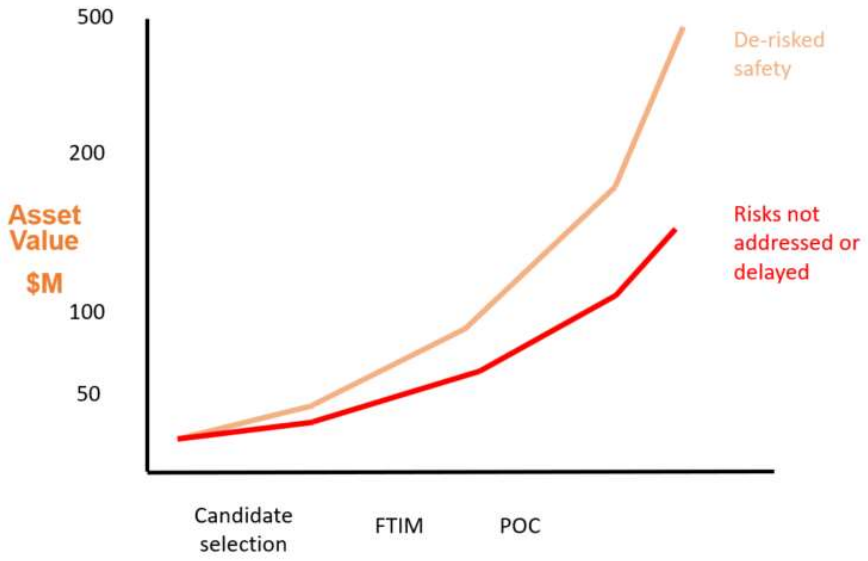
Steve Horner, David Ryan, Sally Robinson, Richard Callander, Katie Stamp, Ruth A. Roberts *

Global Safety Assessment, AstraZeneca, Alderley Park, Macclesfield, UK

This toxicology profile informs:
Starting dose/escalation
Patient exclusion
Monitoring

For those that progress, carrying safety risks into the clinic may……..

- Lower start dose
- Slow recruitment, ↑ exclusions and drop-out rates
- Extend program time, ↑ patient monitoring requirements (and cost)
- May limit exposure below efficacious range
- Regulatory delays and adverse labelling
- Decrease partner/Investigator interest
- Reduce competitiveness and asset value ……



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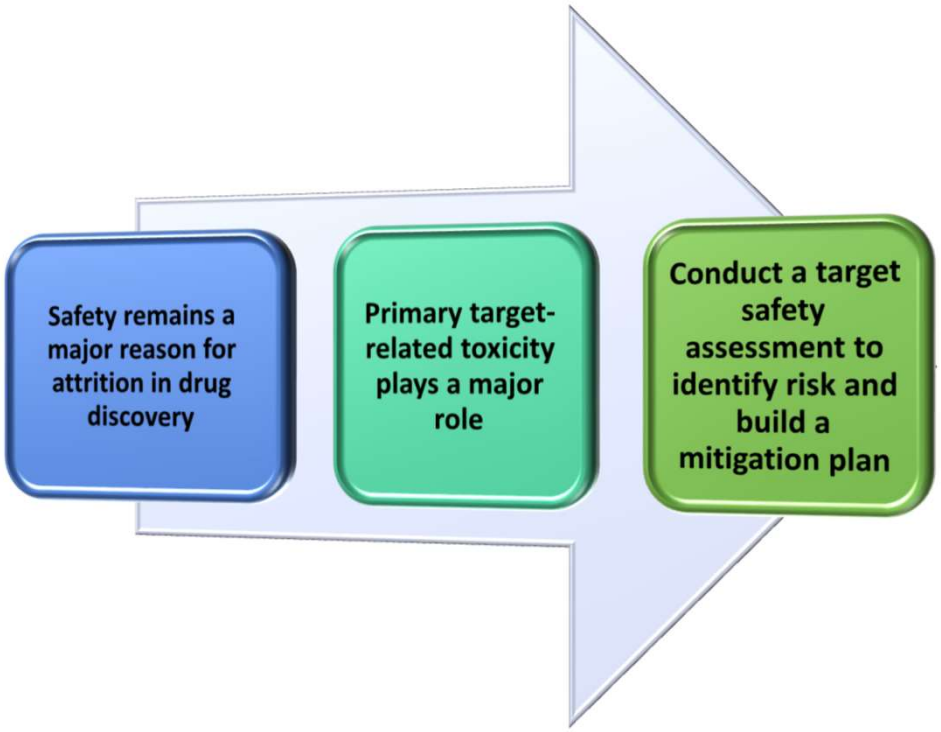
De-risking toxicology:

- **T**arget
  - Target safety assessment to define and mitigate risks
- **C**hemistry
  - Avoiding cardiovascular liabilities such as hERG
  - Early assessment of genetic toxicology
  - PK/PD profile
- **P**atient
  - Appropriate non-clinical safety package tailored to the needs of each project
  - Right patient population



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Target Safety Assessment

	Typical content	
1	**Executive summary**	☑
2	**Background** (aim, nomenclature, homology, distribution and expression, summary of target biology, human mutation phenotype, transgenic mouse phenotype)	☑
3	**Potential safety risks** (including nervous, respiratory, cardiovascular, reproductive, liver, immune and gastrointestinal systems + other relevant for the target)	☑
4	**Competitor compounds***	☑
5	**Suggested risk assessment plan** (in silico, in vitro, in vivo and biomarker including staging)	☑
6	**Powerpoint presentation**	☑
7	**References**	☑

Screening of early chemistry: where should we focus?

- Genetic toxicology
- A simple cytotoxicity assay
- Secondary Pharmacology (CEREP panel, Bowes *et al*. 2013)
- CV risk: designing out unwanted ion channel activity
  - hERG
  - CiPA
- For cause: de-risking predicted issues (failed projects, the target, the chemistry, competitor projects….)

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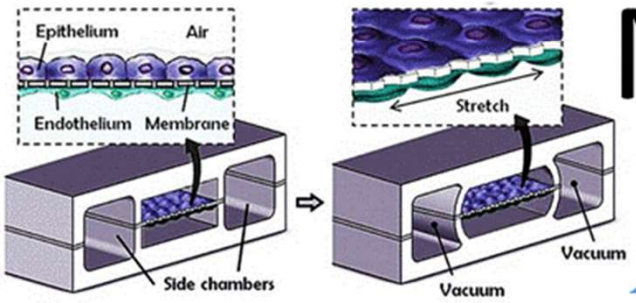
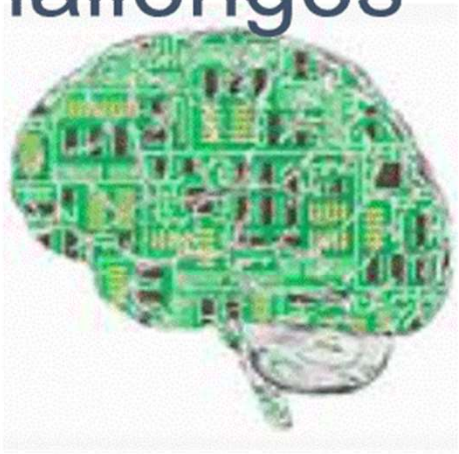
Connect new technologies to challenges



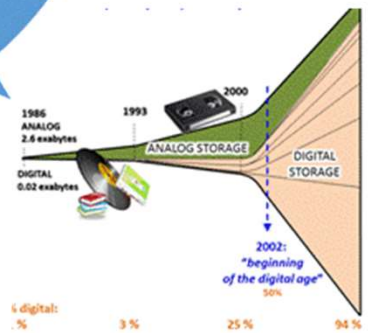
MPS

AI



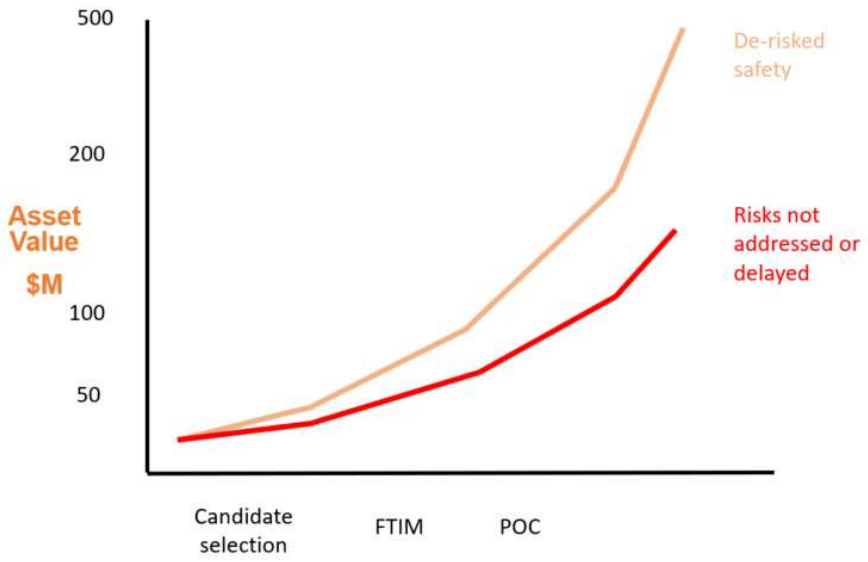
Animal testing
Attrition
Translation

Big data



Collaboration between all disciplines across all sectors:

- **Facilitates data-driven assessment of risk-benefit in the context of each project**
- **Facilitates cost effective design and derisking of projects early while we still have choices**
- **Manages risks that cannot be avoided**
- **Delivers a cost and time-effective programme of nonclinical safety**



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