

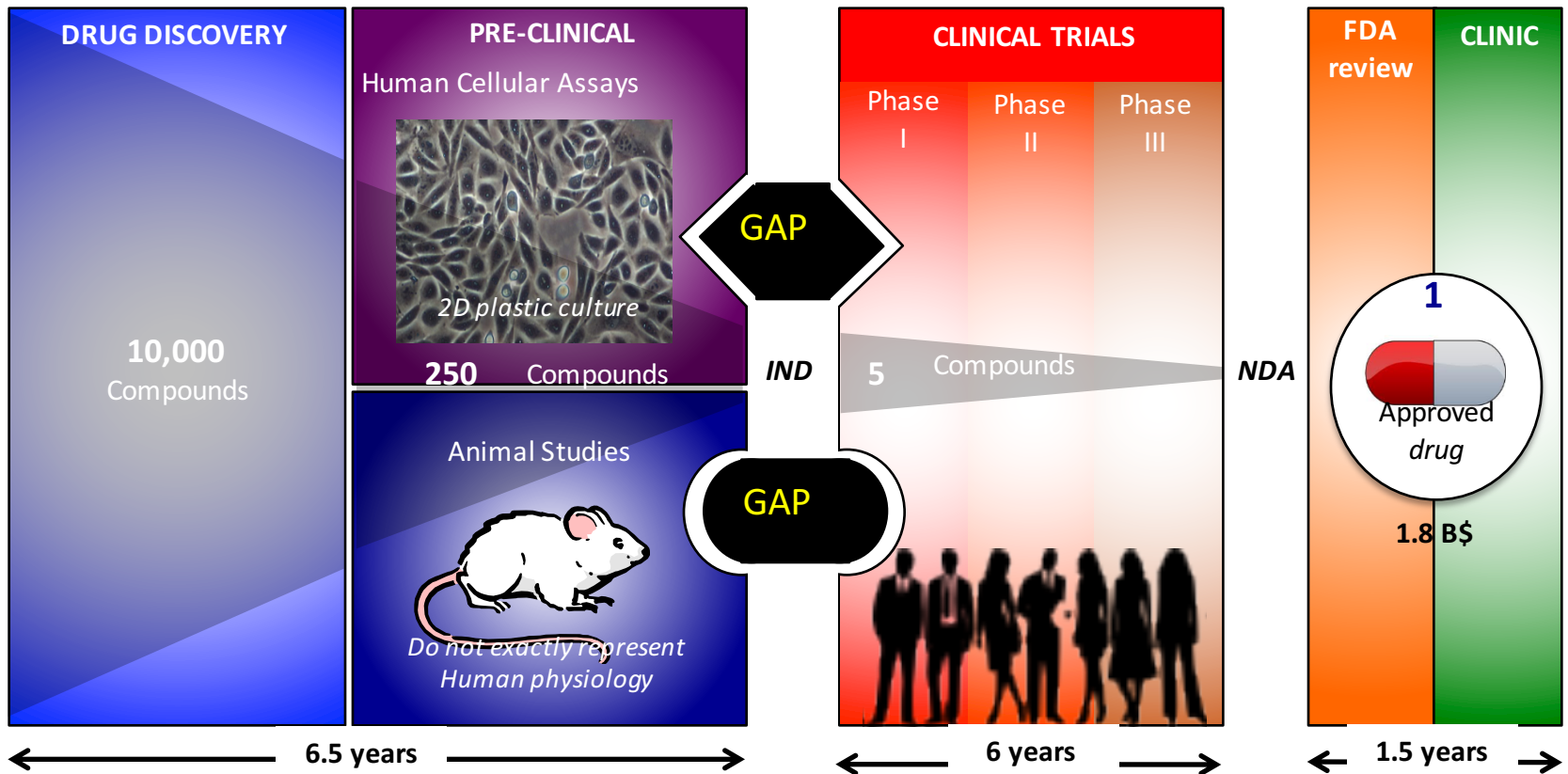


Some challenges in the development of new toxicity assays using *in vitro* methods

J Malcolm Wilkinson , CEO , Kirkstall Ltd.



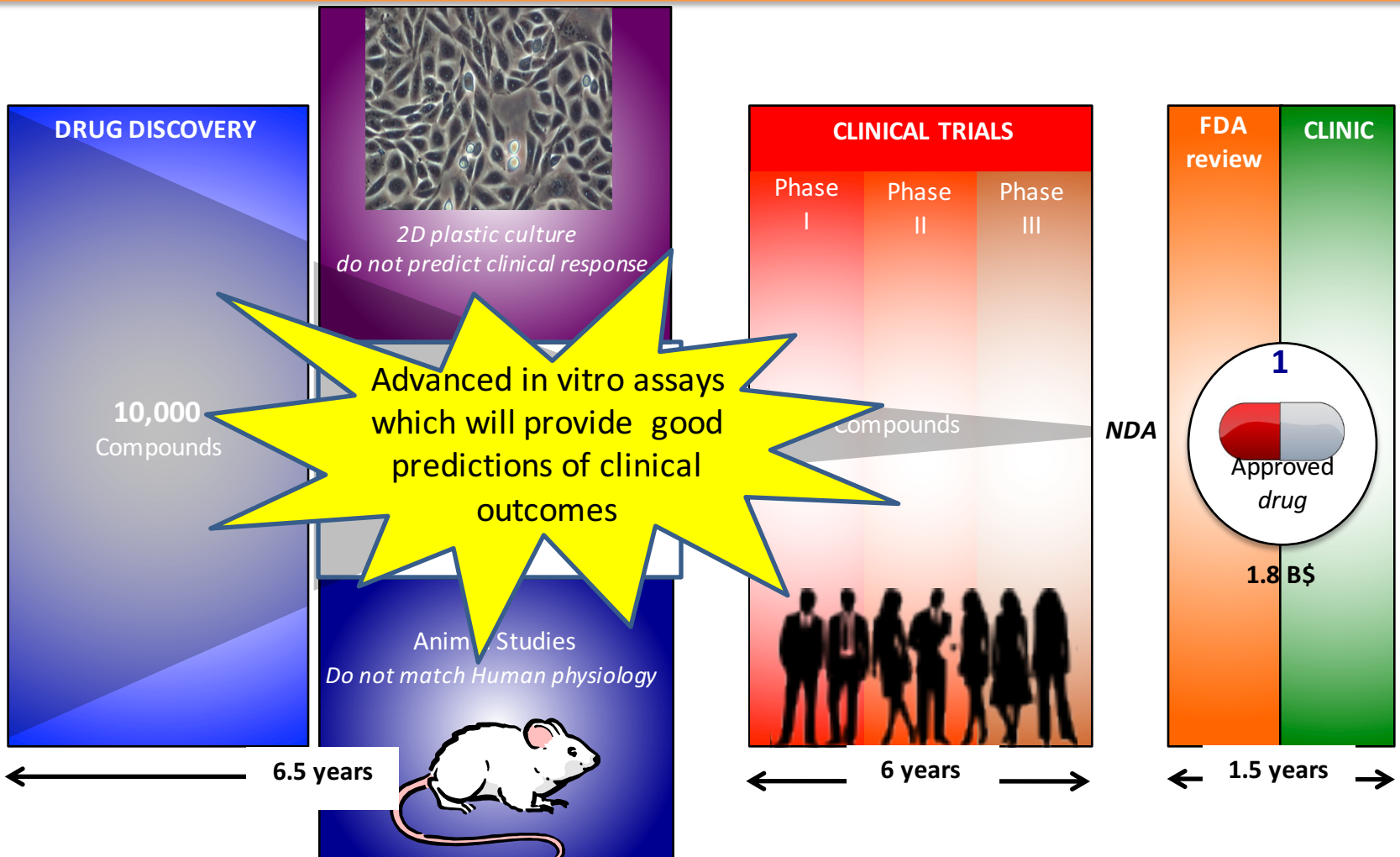
The challenge: long drug development process



Time and Attrition

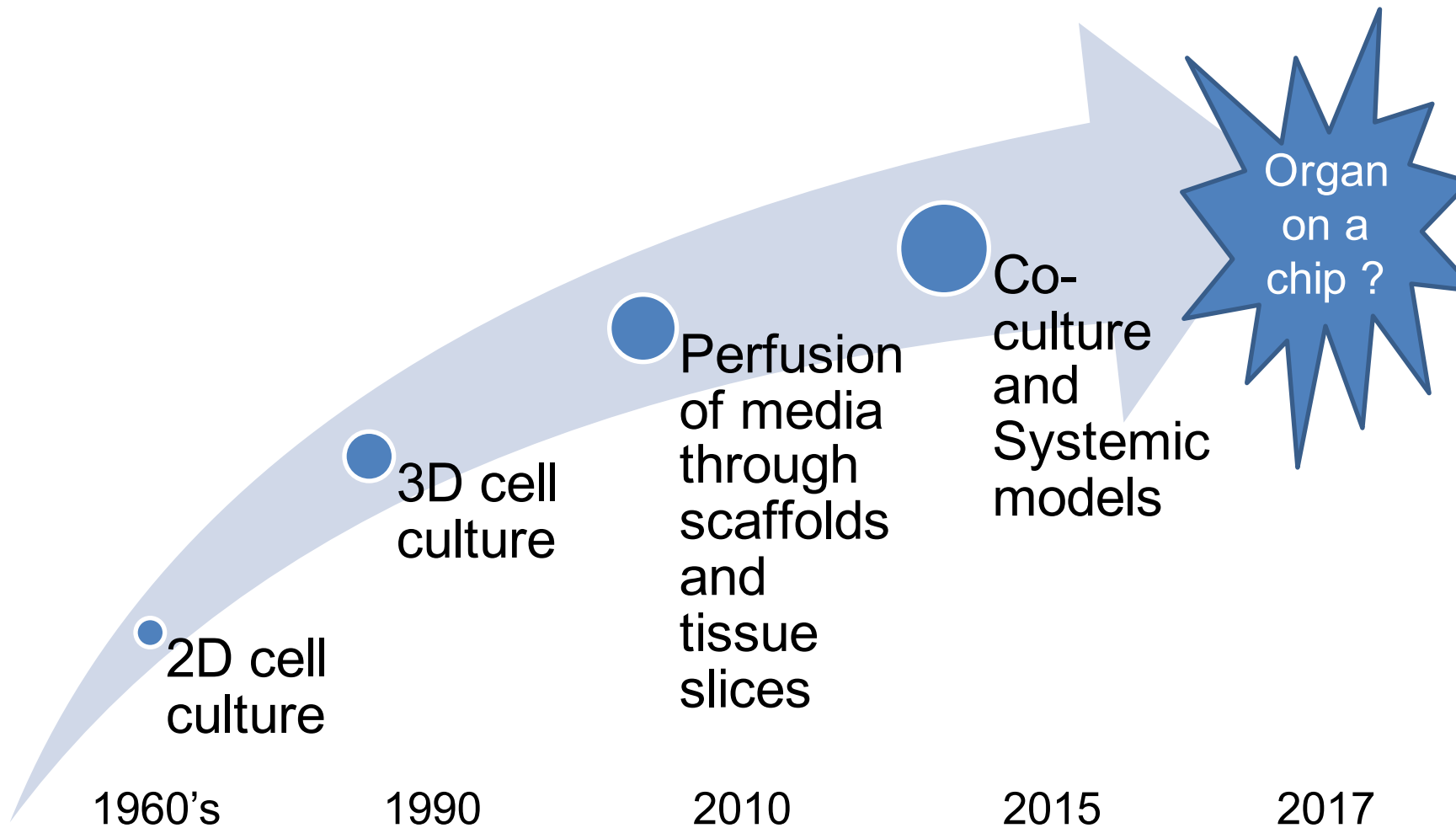
Slide courtesy of Prof Martin Yarmush, Rutgers University & Harvard Medical School

The opportunity for in vitro assays



Time and Attrition

Advances in cell culture



Can we replace animals with advanced *in vitro* cellular assays ?

Requirements list:

- Systemic models – eventually the whole organism
 - Long term and repeat dose exposure
 - Cultures that maintain homeostasis (before insult)
 - Good disease models (the use of transgenic mice is growing rapidly but no amount of genetic manipulation will make them human)
 - Lots of scientific evidence on the efficacy of the new tests to reassure the regulators
-and complementary *in silico* methods can support *in vitro*

Contrasting perspectives on new technology



- ACADEMIA
- Driven by curiosity
- Time and PhD skills to fix problems
- If it works once publish quickly!



- INDUSTRY
- Need to be efficient
- Technicians to run standard assays
- Needs to work every day



- REGULATORS
- Risk averse
- Need gold standards for validation
- Needs to work the same in every lab



- PUBLIC
- Need safer medicines
- Need cost effective therapies

Roadmap to new method for toxicity testing

- General platform development and testing
- Focused R&D (for example cardiotoxicity)
- Selecting individual assay/ battery of tests
- Develop robust protocol
- Validate with CRO
- Regulatory approval

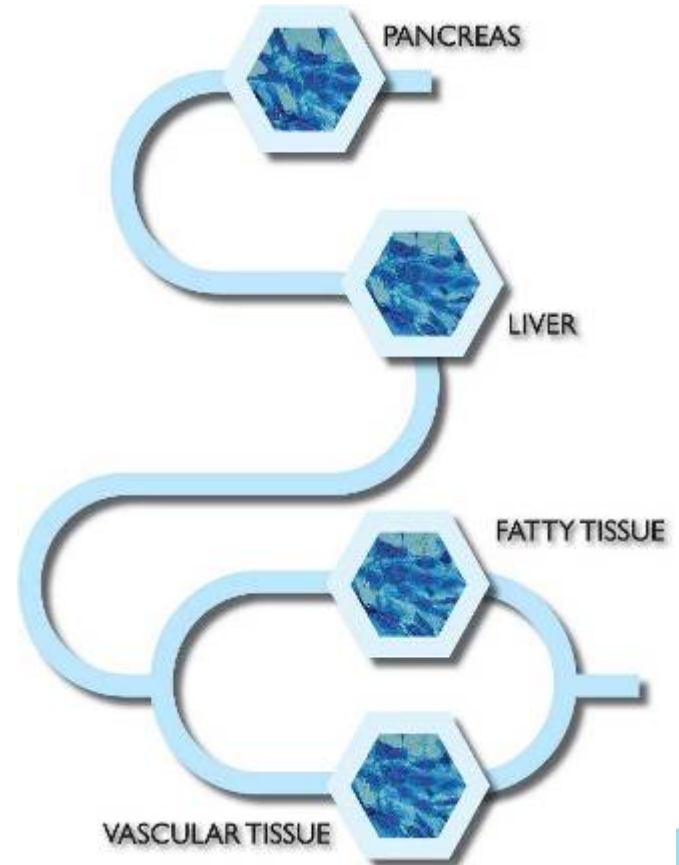
General Platform

Connected chambers

Systemic models

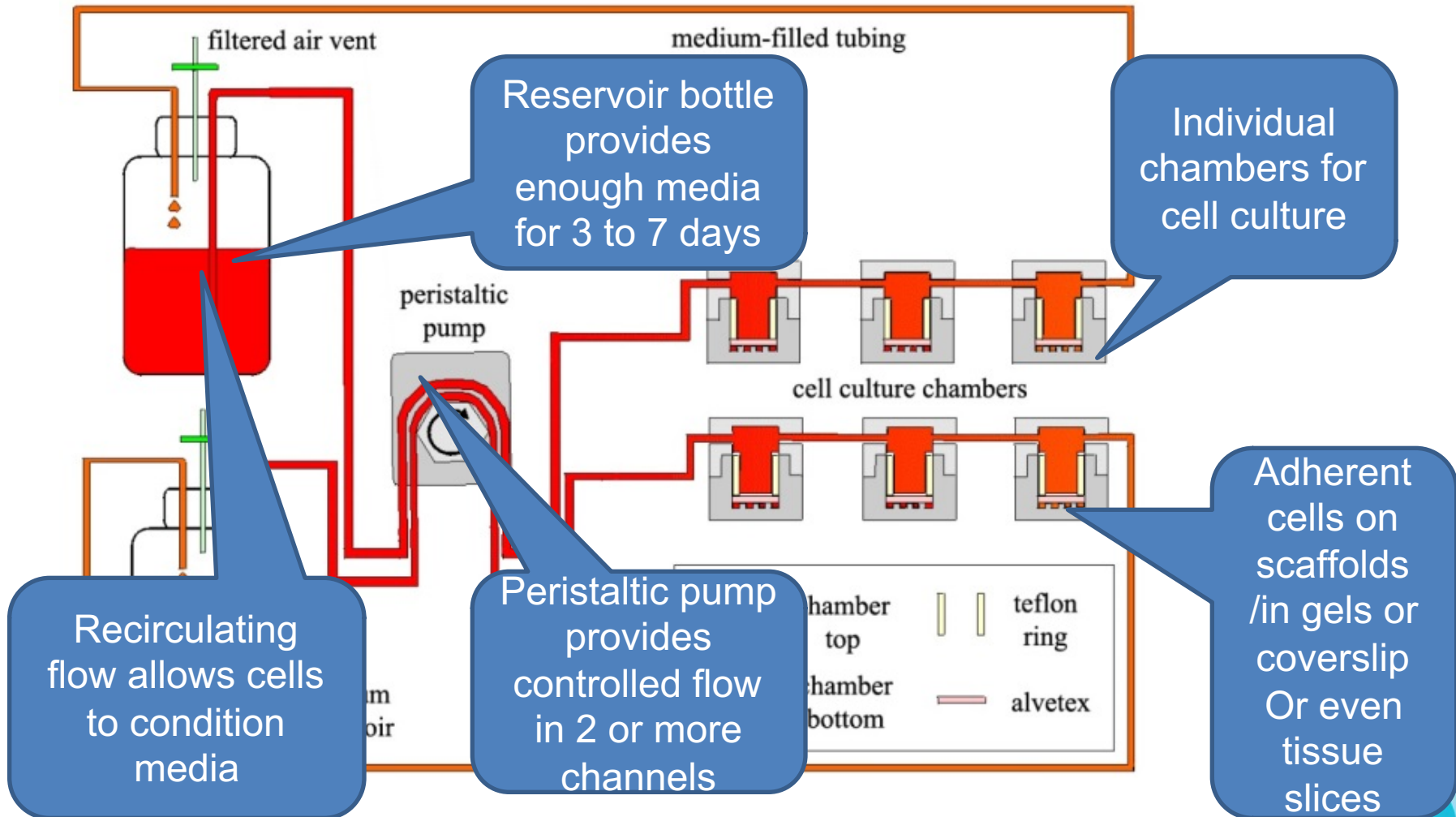


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Lego kit for cell biologists!

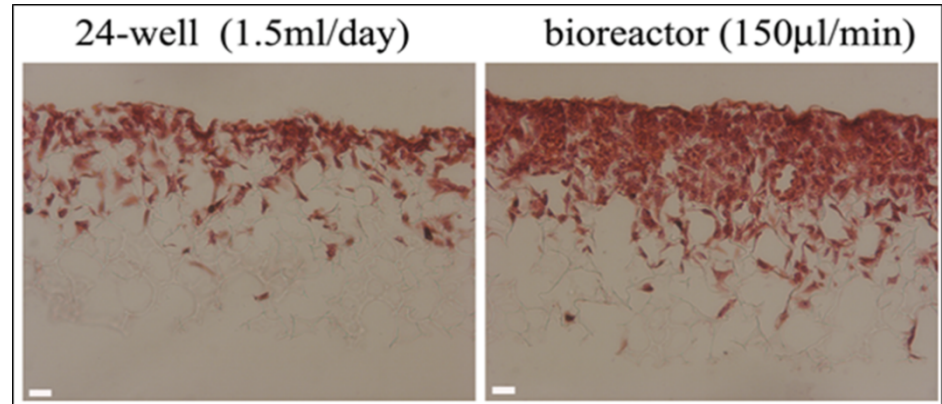
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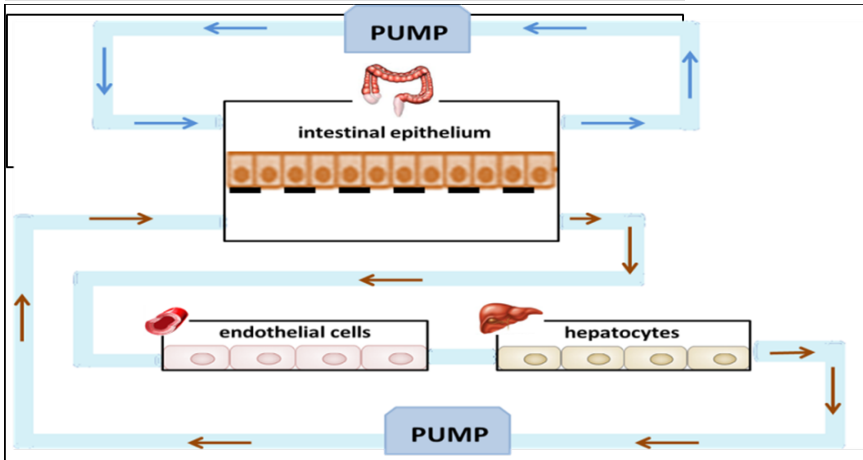
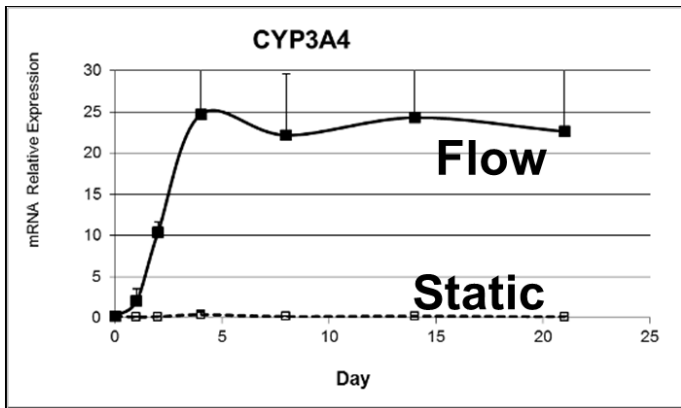
Quasi Vivo® - saving lives through better science

New platform has clear benefits

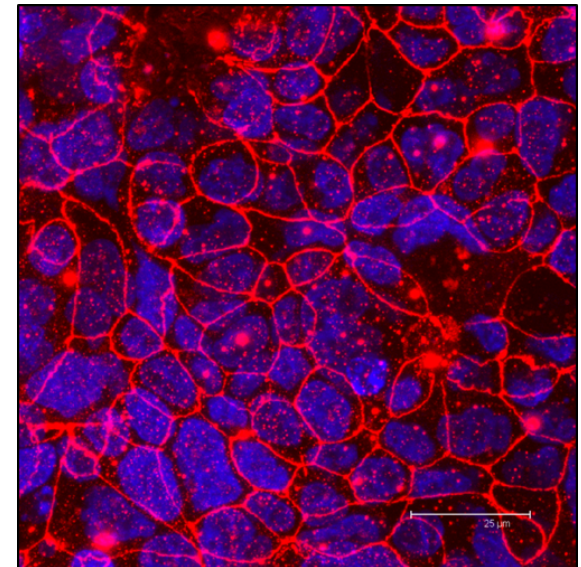
Improved cell viability



Improved metabolic function




Co-culture and barriers




Improved barrier function

Route map

- 
- R&D Feasibility Study
 - Cumulative spend :£250,000

- 
- Industrialisation of Assay
 - Cumulative spend: £1,500,000

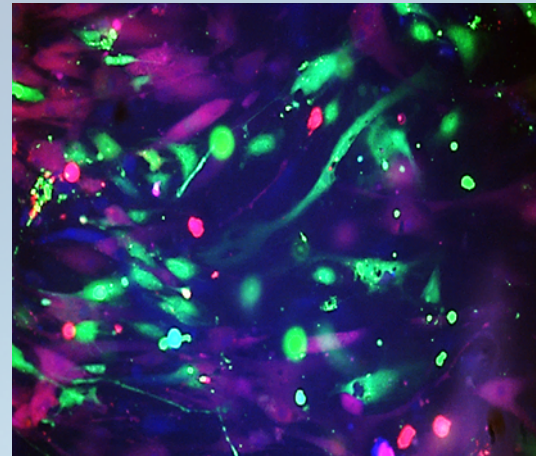
- 
- Validation & Regulatory and Market Acceptance
 - Cumulative spend: £5,500,000

R&D Feasibility Study (example)

- **CVTOX- Innovate UK project number 131728**

This project is investigating the creation of a co-culture representing cardiac tissue: human cardiomyocytes (HCMs), smooth muscle cells (HSMCs) and endothelial cells (HECs).

Goal is long term stable culture for repeat dose testing of drug and chemical safety



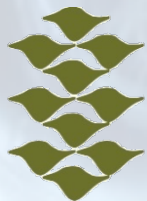
7 day co-culture of HCM's (blue) HEC's (green) and SMC's (red) marked using fluorescent stains

'Development of an in-vitro tri-culture of primary human cardiac microvascular toxicological model'

A collaborative project funded by UK Government



Manchester
Metropolitan
University



CICY



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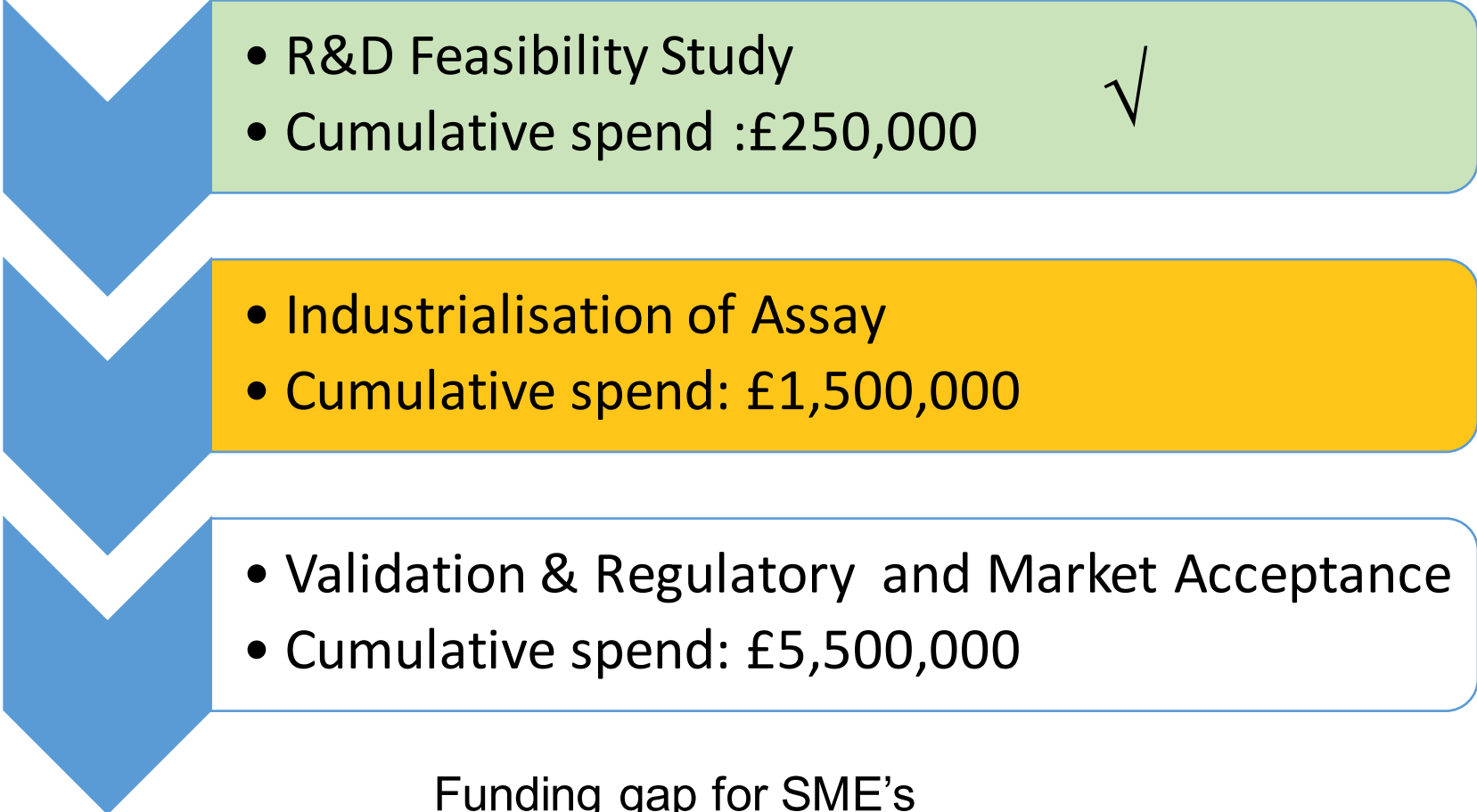
ELISHA



Innovate UK

Technology Strategy Board

Route map

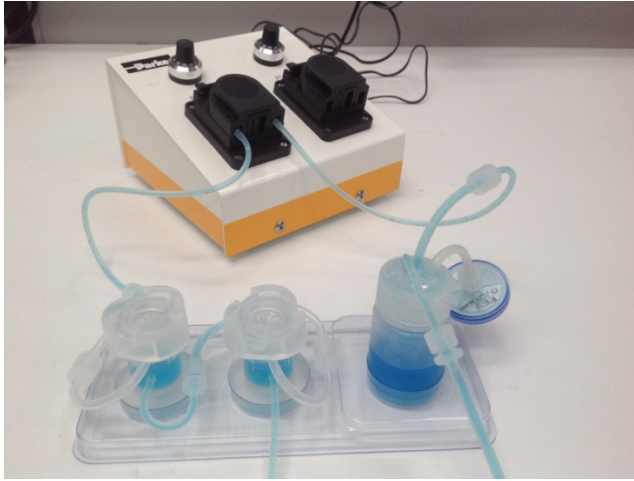
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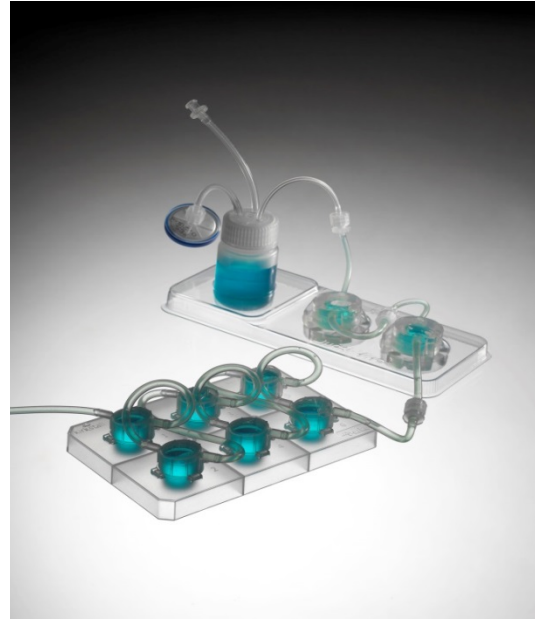
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Funding gap for SME's
Need a Large Enterprise Sponsor

Technology Commercialisation Route



Flexible R&D capability



First stage of standardisation and scale up



Prototype industrial test system



Conclusions / Lessons Learned

- Good science is needed
- A business case has to be made (even for academic grants!)
- Technology translation from academia to industry has to be managed
- Pioneers (risk takers) needed all the way through the process
- Even regulators will need to be innovative (what is the gold standard for validation if you are replacing an animal test)



Thanks for your attention !

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