AstraZeneca
IMED Biotech Unit

Placing microphysiological systems in the pharmaceutical R&D strategy

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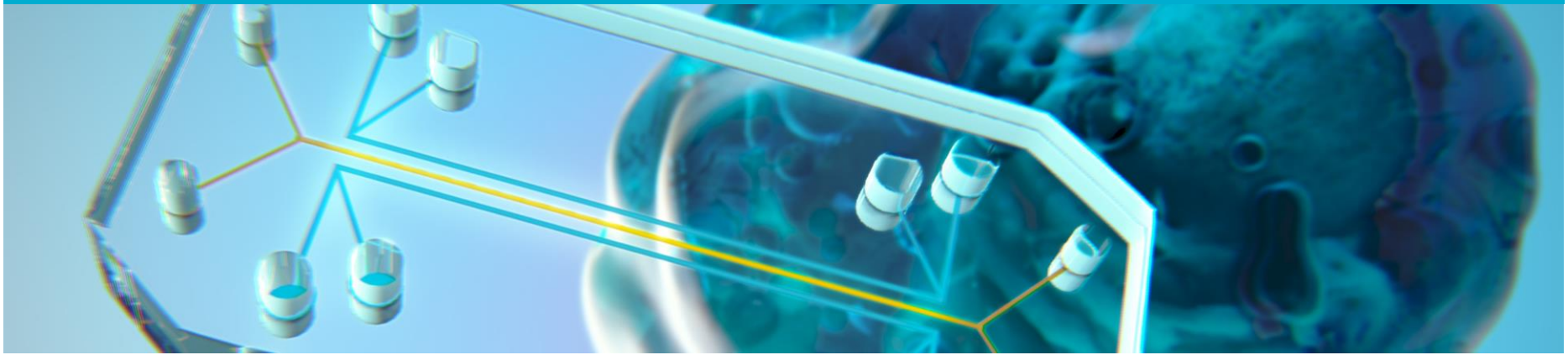
EMA workshop: challenges and opportunities for use of micro-physiological systems, London 5 October 2017



Outline of today’s presentation

- Background
- Introducing the AZ framework for MPS application
- Bringing the framework to life through case examples
- Closing remarks

Background

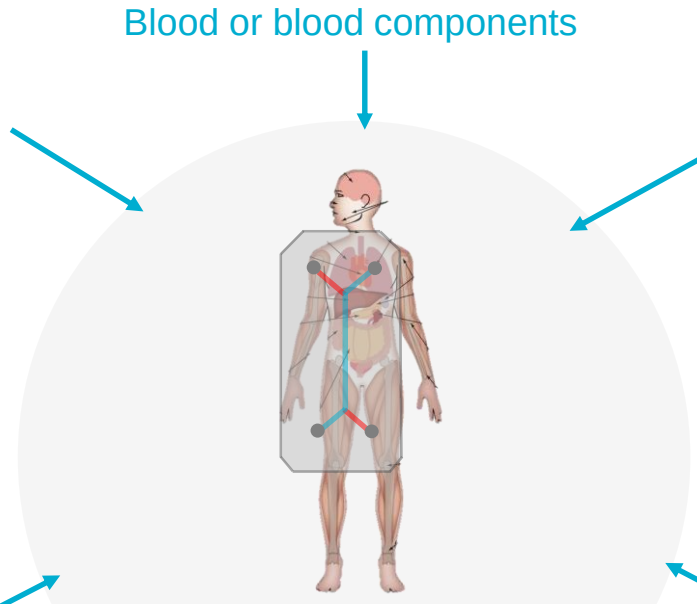
The need for improved mechanistic and predictive modelling: a well described pharmaceutical challenge

The average drug takes 12 to 15 years to develop

It costs $2.6 billion to develop (DiMasi et al., 2016)

Safety and efficacy lead to failure (Cook et al., 2014)

Microphysiological systems enable us to precisely tune cellular biology to produce an accurate model



Successful adoption and application is intimately linked to the correct context of use

- Several potential scenarios for value proposition within drug discovery and development pipeline

- Each scenario has:
  - a different set of technical standards or requirements
  - a standard against which success will be measured
  - a threshold of confidence that would need to be achieved

- Uses are not mutually exclusive

Adapted from Ewart et al., 2017 EBM Thematic Issue MPS

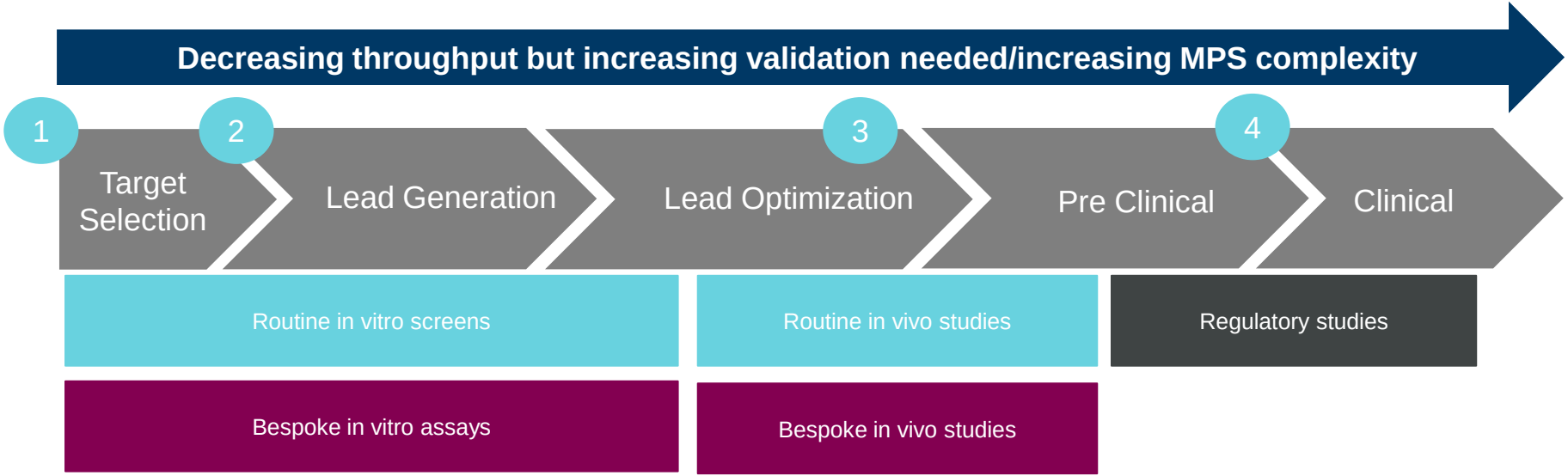
Context of use within the value chain also requires understanding of the problem that needs to be solved

Testing Requirements			
Confirm presence of relevant targets	Baseline effect on physiology	Assess impact on disease phenotype	Identify and assess potential side effects
Thousands of compounds	Tens to hundreds of compounds	Two to three compounds	One to two compounds
High Throughput systems	Medium to high throughput systems	Low throughput systems	Low throughput systems

Adapted from Ewart et al., 2017 EBM Thematic Issue MPS

AZ framework for MPS application

The AstraZeneca framework

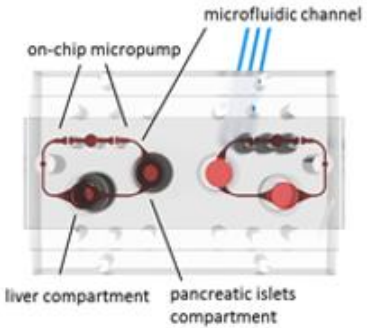


1. Enhance target selection and target biology using disease relevant systems that are agnostic to therapeutic modalities
2. Enhance compound progression with MPS that are “superior” to existing in vitro models
3. Improve in vivo study design and/or reduce the number of in vivo studies
4. Problem solving: Drive understanding of efficacy and/or safety; influence risk assessment and management

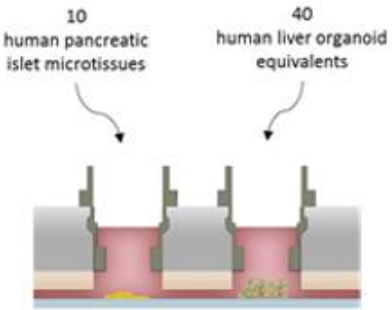
Case examples

Towards disease modelling: enhancing biological understanding

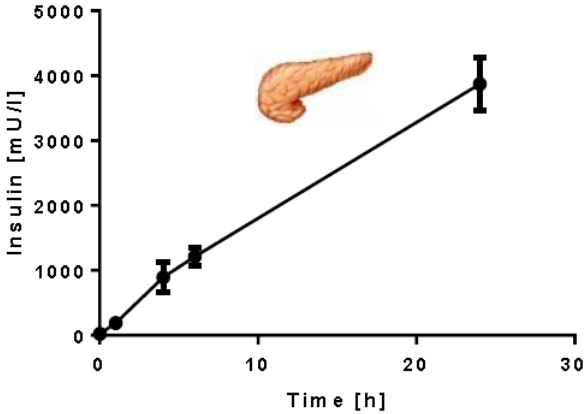
Experimental set up

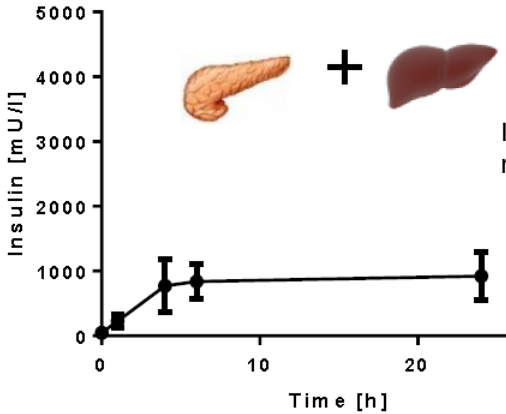


Physiological scaling



Islets only: insulin rises unchecked



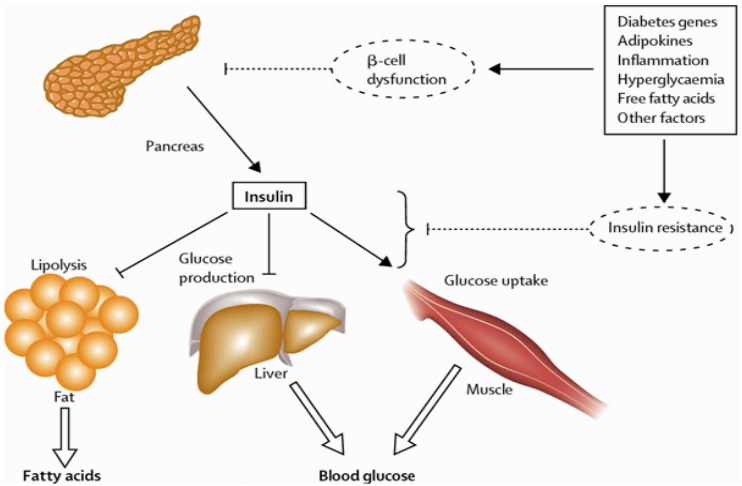


Islets plus liver: insulin levels rise but plateau maintained

Bauer et al., In press Nature Scientific Reports

TISSUSE Emulating Human Biology

Introducing insulin resistance to the liver to explore the impact on beta cell proliferation



Key organ systems in metabolic disease

- Insulin resistance and pancreatic beta cell dysfunction are key interrelated pathogenic factors in the pathogenesis of metabolic diseases such as diabetes
- Pancreas and liver are affected by insulin resistance
- AZ are building an insulin-resistant liver model in three ways: (1) elevated media glucose concentration, (2) pharmacological inhibition of the insulin receptor, (3) creation of hepatocyte cell lines without the insulin receptor using CRISPR
- Can MPS help identify factors that impact beta cell function and/or proliferation?

“Superiority” to existing in vitro models: Case example hematotoxicity assessment

HSC proliferation/CFU

- ✓ High throughput
- ✓ Human cells
- ✓ Small compound amounts (mg) required
- ✗ In vivo BM PK difficult to recapitulate
- ✗ Not amenable to dose scheduling
- ✗ Limited data output for Modelling & Simulation etc.

In vivo

- ✓ In vivo Bone Marrow PK
- ✓ Dose scheduling to mimic clinic
- ✓ Monitor cell recovery
- ✗ Need to translate to human
- ✗ Use of large number of animals
- ✗ Large compound amounts (g) required

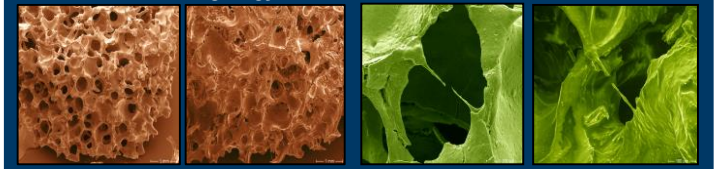
MPS in vitro

- ✓ Human cells with potential to include patient cells
- ✓ Long term cell culture enables investigation of haematopoiesis
- ✓ Recapitulate in vivo environment
- ✓ Kinetic data - potential for enhanced opportunities for systems pharmacology and Modelling and Simulation

One approach to a Bone Marrow (BM) MPS

3D microenvironment similar to *in vivo*

Scaffold | Human BM | Scaffold | Human BM



Ceramic scaffold mimics human BM structure

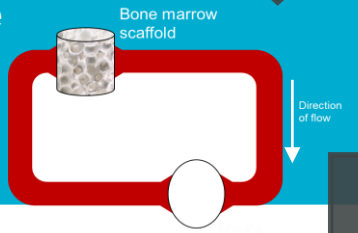
Mesenchymal Stem Cell (MSC) growth similar to *in vivo*

Cytokine-free media for autonomous differentiation

Thrombopoietin (TPO) and Flt3, to encourage autonomous cell differentiation

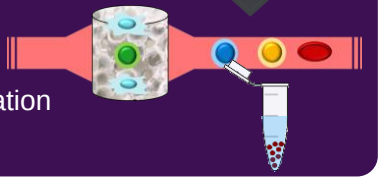
Fluidic system for extended cell culture

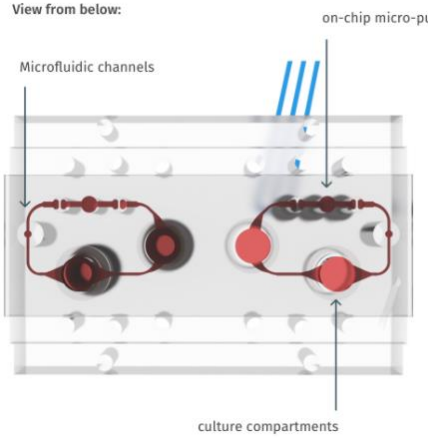
Microenvironment and flow are important for extended viable cell culture



Fluidic system for dynamic cell sampling

Enables monitoring of cell proliferation and differentiation over time





TISSUSE Emulating Human Biology

Model characterisation data and preliminary toxicological data are encouraging

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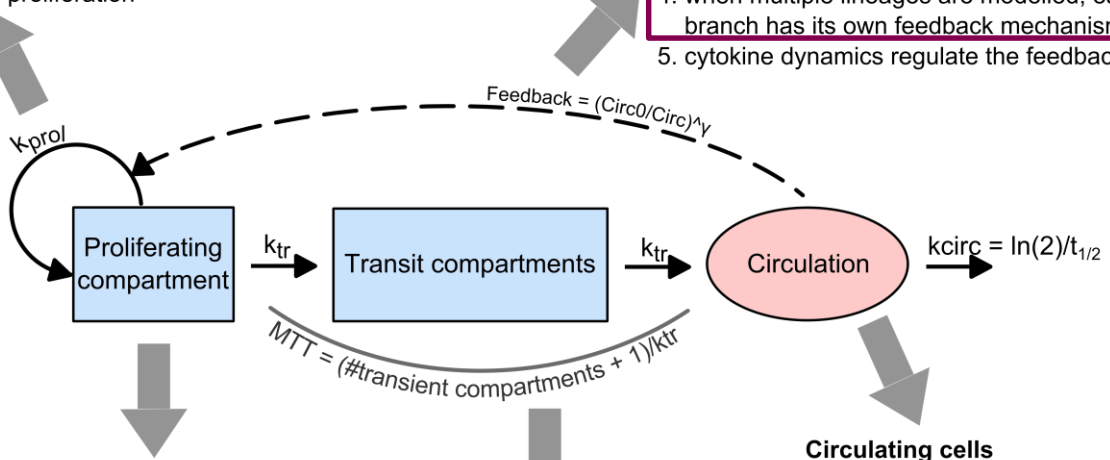
Future: Modelling & Simulation using BM MPS will drive clinical use strategies

Stemness

Proliferation
1. first-order kinetics
2. zero order kinetics
3. cell cycle mechanism
4. fraction of proliferating cells
5. distinction between symmetrical and asymmetrical proliferation

Feedback
1. circulating cells regulate proliferation of mitotic cells (kprol)
2. circulating cells regulate maturation time (MTT)
3. circulating cells regulate probability of symmetric/asymmetric division
4. when multiple lineages are modelled, each branch has its own feedback mechanisms
5. cytokine dynamics regulate the feedback

Neg Feedback



Lineage diff.

Proliferating cells
1. one variable to represent HSCs and MPPs
2. LT-HSCs, ST-HSCs, and MPPs are described by separate variables
3. Bone marrow niche is taken into account

Maturation time
1. transient compartments (ODEs)
2. explicit delay (DDEs)

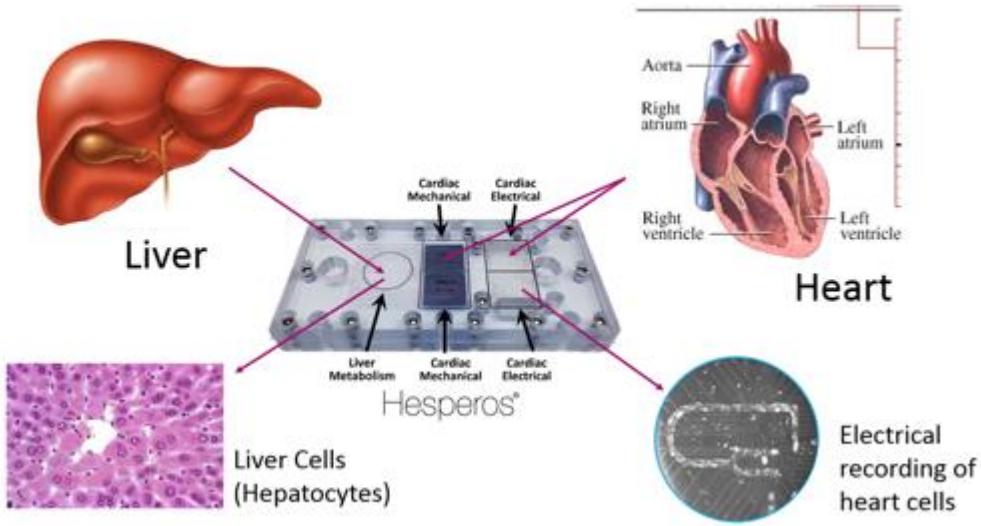
Circulating cells
1. unique pool of circulating cells
2. multi-lineages
3. in case of neutrophils: distinction between circulating cells and marginated pool

Transit time

Improve in vivo study design and/or reduce the number of in vivo studies

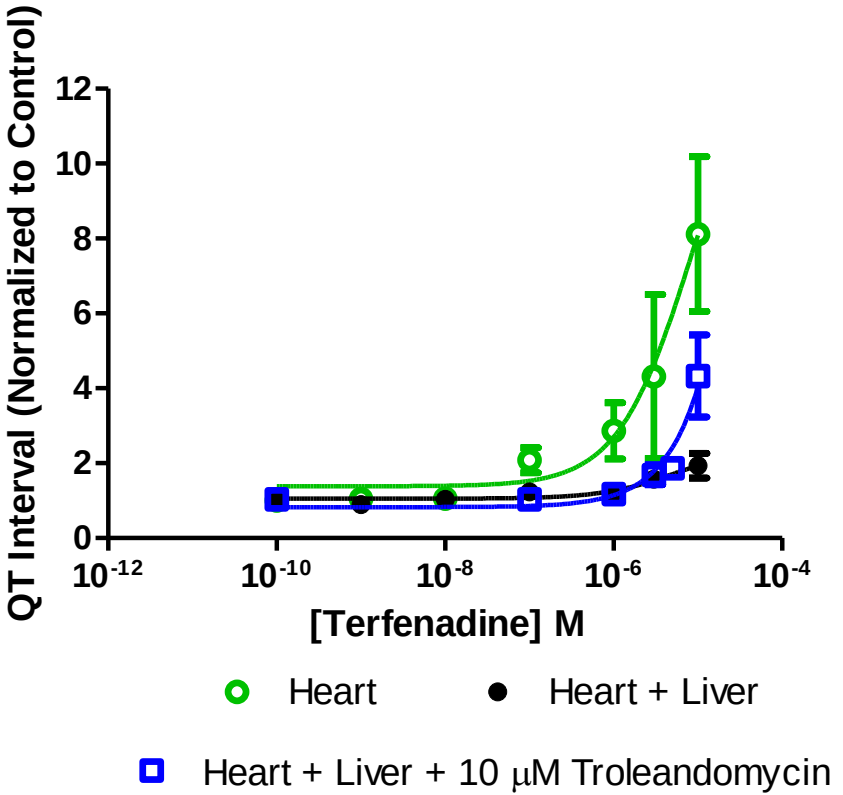
- Despite comprehensive cardiac safety screening, cardiotoxicity sometimes remains undetected until in vivo testing, in part because cardiotoxicity can also be driven by exposures to metabolites instead of the drug itself

- Hypothesis: a heart “chip” connected to a metabolically competent liver “chip” can distinguish parent and metabolite mediated cardiotoxicity in vitro



MPS detects Terfenadine mediated cardiotoxicity

- The anti-histamine terfenadine is cardiotoxic but is metabolized to fexofenadine which is not cardiotoxic
- In the heart “chip” cardiotoxicity is detected (EC_{50} 1.3 µM) but when connected to a metabolically competent liver “chip” the response is right shifted (EC_{50} >10 µM)
- In the presence of a CYP inhibitor at a concentration that reduces metabolism by 50% the response is left shifted (EC_{50} 5.4 µM)

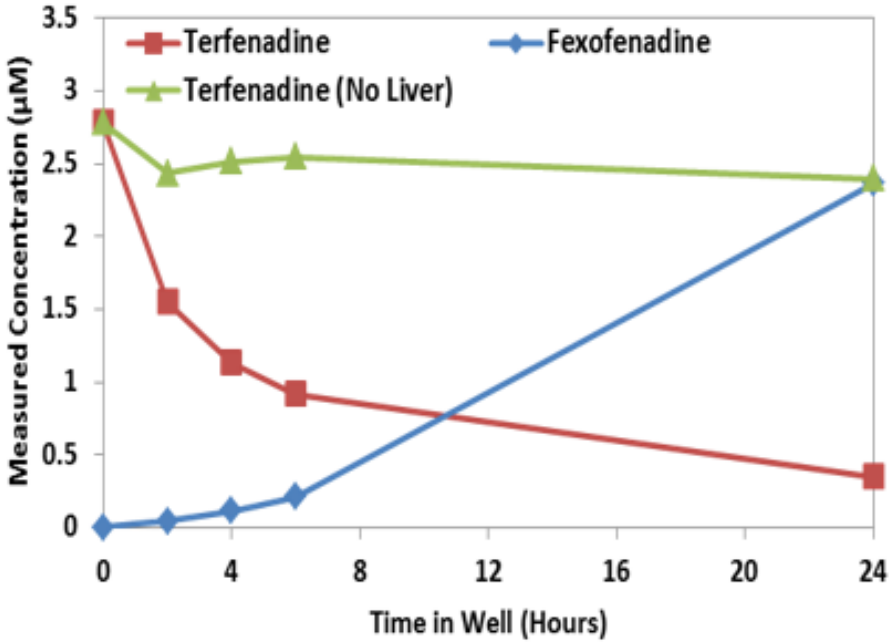


Hesperos®

McAleer et al., Manuscript in preparation

MPS detects Terfenadine mediated cardiotoxicity

- Real time bioanalysis from heart-liver chips supports the pharmacology with a reduction in the terfenadine concentration over time and a subsequent increase in fexofenadine concentration
- Terfenadine concentration is constant in heart only chips



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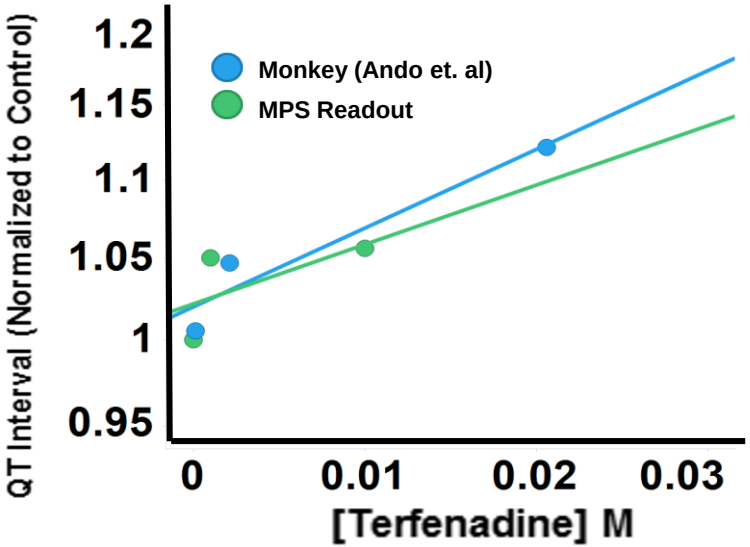
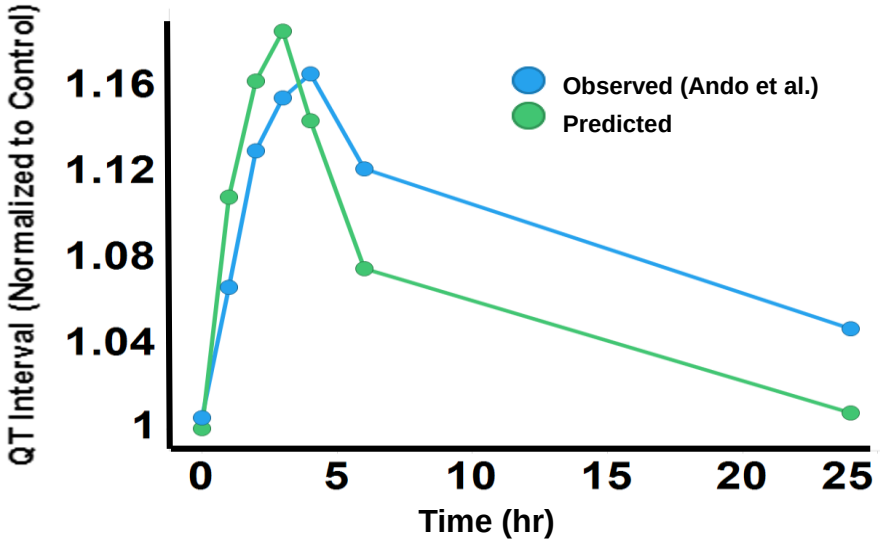
Application of modelling and simulation to MPS data predicts literature in vivo data

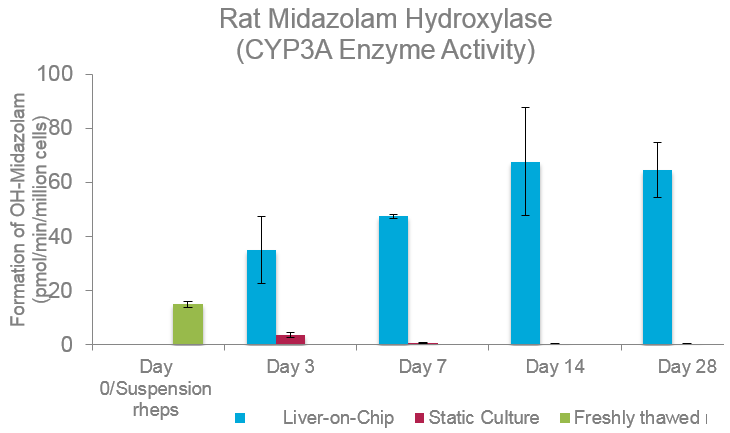


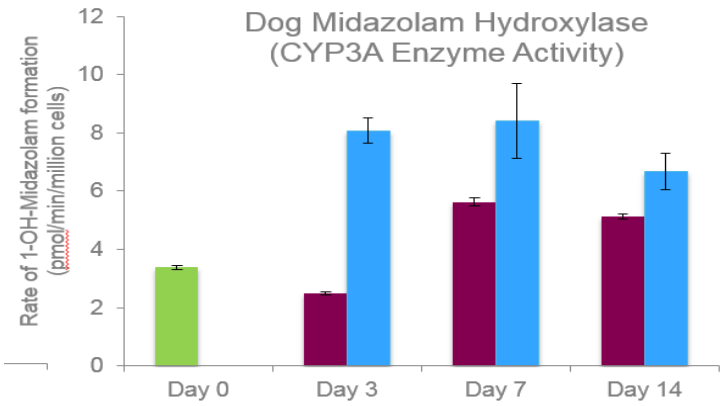


McAleer et al., Manuscript in preparation

Application in risk assessment within preclinical safety

- Prior to first time in human administration, new chemical entities are tested in 2 preclinical species
- Translating the relevance of a signal to human is critical to risk assessment
- Development of species “chips” will enhance our confidence in the risk assessment
- AZ in partnership with Emulate have developed rat and dog liver chips





Jang et al., Manuscript in preparation

Application in risk assessment within preclinical safety

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Jang et al., Manuscript in preparation

emulate

Cytotoxicity confirmed by automated confocal and live cell imaging

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Data redacted

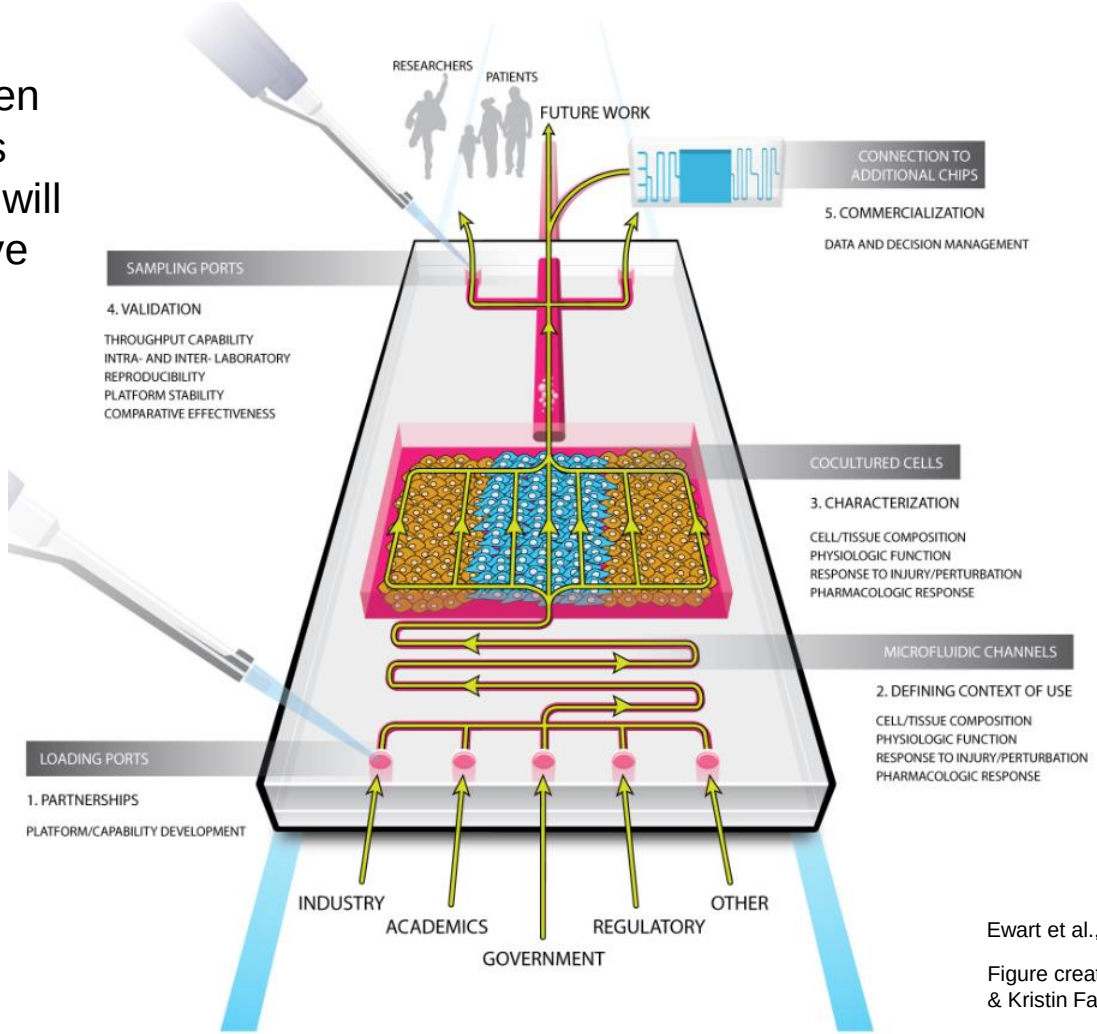
Peel et al., Manuscript in preparation

Jang et al., Manuscript in preparation

emulate

Closing remarks

- Partnership between the chip innovators and the end users will be essential to drive this technology deeper into our strategies



Ewart et al., 2017 EBM Thematic Issue MPS

Figure created by Kyle Brimacombe & Kristin Fabre

Challenges to address for near term application of MPS

- PDMS – oxygen permeable and transparent for imaging but binds lipophilic drugs
- Platform – standardization from one platform to another to enable comparison between systems and the potential to connect chips should this be required (e.g. for “body-on-a-chip approaches)
- Building a discipline – the high content nature of these models needs to be differentiated from standard in vitro plate models; patience and partnership required to enable the technology to blossom
- The vexing drug discovery issues that might be addressed in the near term with MPS need to be clearly articulated by the end user to the developer
- Agreeing on the “truth” - are animal studies really useful comparators for building confidence in in vitro to in vivo extrapolations?

Summary

- Microphysiological systems provide an opportunity to be more mechanistic and predictive in our preclinical modeling at several points across the drug discovery value chain

- Emerging data build confidence that MPS add value in specified situations

- Near term impact won’t come without significant partnership and deliberate intent. It will also require development of complementary technologies.

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