Enabling Next Generation Pharmaceutical Safety Assessment: An Evolution

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Opinions expressed are those of the author rather than the employer

Key components

- Motive
- Opportunity
- Strategy
- Partnership

Motive

There are good reasons for us to be interested in novel ways of working!

2015 profile
BIOPHARMACEUTICAL RESEARCH INDUSTRY

KEYFACTS 2015

RESEARCH AND DEVELOPMENT (R&D)[1]

Average time to develop a drug = more than 10 years
Percentage of drugs entering clinical trials resulting in an approved medicine = less than 12%

DEVELOPMENT COSTS

Average cost to develop a drug (including the cost of failures):[2]

- 2000s–early 2010s = $2.6 billion
- 1990s–early 2000s = $1.0 billion*
- 1980s = $413 million
- 1970s = $179 million

R&D SPENDING

Year	PhRMA members[3]
2014	$51.2 billion (est.)
2013	$51.6 billion
2012	$49.6 billion
2011	$48.6 billion
2010	$50.7 billion
2009	$46.4 billion
2008	$47.4 billion
2007	$47.9 billion
2006	$43.0 billion
2005	$39.9 billion
2000	$26.0 billion
1990	$8.4 billion
1980	$2.0 billion

SALES

Generic share of prescriptions filled:[4]

2000 = 49%

2013 = 88%

PhRMA
RESEARCH • PROGRESS • HOPE

An analysis of the attrition of drug candidates from four major pharmaceutical companies

Michael J. Waring[1], John Arrowsmith[2], Andrew R. Leach[3], Paul D. Leeson[3,4], Sam Mandrell[2], Robert M. Owen[5], Garry Pairaudeau[1], William D. Pennie[6,7], Stephen D. Pickett[3], Jibo Wang[8], Owen Wallace[8,9] and Alex Weir[2]

Nat Rev Drug Disc 14: 475, 2015

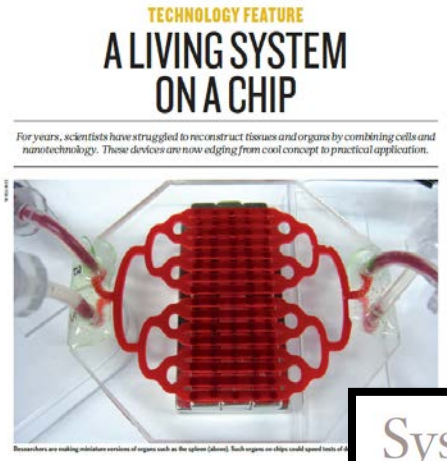
Motive

Table 1 | **Populations of the primary cause of failure categories for terminated compounds***

Termination reason	Overall	Period		Phase		
		2000–2005	2006–2010	Candidate nomination	Phase I	Phase II
Clinical safety	68 (11%)	48 (13%)	20 (8%)	5 (1%)	40 (25%)	22 (25%)
Commercial	40 (7%)	23 (6%)	17 (7%)	26 (7%)	10 (6%)	4 (4%)
Efficacy	55 (9%)	45 (11%)	10 (4%)	10 (3%)	14 (9%)	31 (35%)
Formulation	9 (1%)	4 (1%)	5 (2%)	8 (2%)	1 (0.6%)	0
Non-clinical toxicology	240 (40%)	144 (40%)	96 (40%)	211 (59%)	21 (13%)	7 (8%)
Patent issue	1 (0.2%)	0	1 (0.4%)	1 (0.3%)	0	0
Pharmacokinetics or bioavailability	29 (5%)	19 (5%)	10 (4%)	3 (0.8%)	25 (16%)	1 (1%)
Rationalization of company portfolio	124 (21%)	46 (13%)	78 (32%)	75 (21%)	29 (18%)	19 (21%)
Regulatory	2 (0.3%)	2 (0.6%)	0	1 (0.3%)	1 (0.6%)	0
Scientific	33 (5%)	28 (8%)	5 (2%)	13 (4%)	15 (10%)	5 (6%)
Technical	3 (1%)	3 (1%)	0	2 (0.6%)	1 (0.6%)	0
Other	1 (0.2%)	0	1 (0.4%)	1 (0.3%)	0	0
Total	605	362	243	356	157	89

*Table entries for each column indicate the total number and the percentage in parentheses.

Lots of new opportunity!

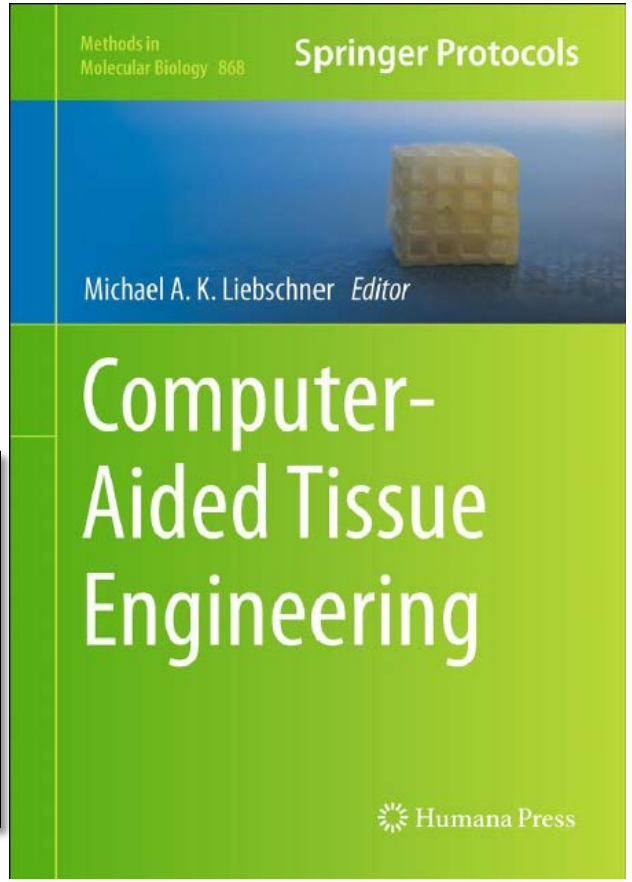

TECHNOLOGY FEATURE

A LIVING SYSTEM ON A CHIP

For years, scientists have struggled to reconstruct tissues and organs by combining cells and nanotechnology. These devices are now edging from cool concept to practical application.

Systems Pharmacology to Predict Drug Toxicity: Integration Across Levels of Biological Organization*

Jane P.F. Bai and Darrell R. Abernethy



ASSOCIATE EDITOR: ERIC L. BARKER

Computational Methods in Drug Discovery

Gregory Sliwoski, Sandeepkumar Kothiwale, Jens Meiler, and Edward W. Lowe, Jr.

Meiler Laboratory, Center for Structure Biology, Vanderbilt University, Nashville, Tennessee

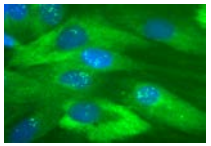
Leveraging the opportunity

- Alignment on the gaps and the opportunities best suited to fill those gaps
- Clearly defined context of use for alternative test systems
- Sense of what it takes to build confidence in a different approach
  - biological relevance, data, experience
- Willingness to accept managed risk
- Freedom to operate
- Collaboration with shared goals

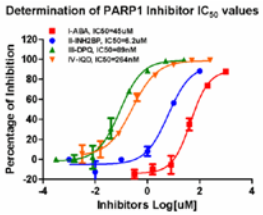
Strategic Context of Use

Capabilities

Bioinformatics

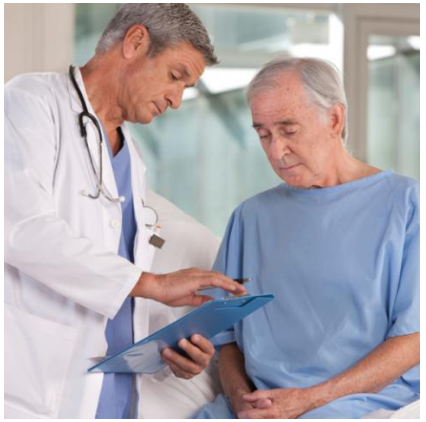


Phenotypic assays

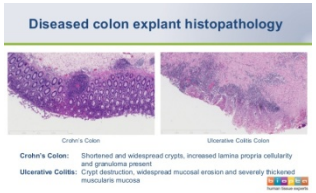


Activity assays

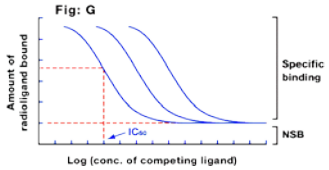
Animal studies



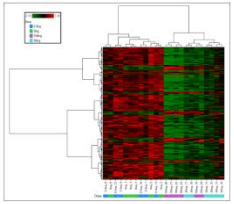
Patient studies



Human tissue



Binding assays



-omics

Target ID & validation → Hit/lead discovery → Lead optimisation → Candidate selection → Preclinical safety → Clinical assessment

#compounds	1000's	100's	10's	1-3

Freedom to operate ← | → Regulated expectations

Liability characterization at molecular design- opportunity for non-animal platforms

Challenges of applying a novel modeling strategy early in discovery

- Sufficient biological complexity with adequate throughput
- Accounting for the biology not in the platform (novel platforms, though less reductionist, will be reductionist)
- Defining what you're measuring against
- Accounting for dose/exposure extrapolation
- Interpreting more mechanistic endpoints
- Considering rapid changes in scope of drug modalities (small molecules, Ab therapies, oligonucleotides, cell/gene therapy)
- Designing a different intellectual framework
- Impacts on cost and time
- Building a reason to believe!

We know where to start

- IQ Dru Safe Attrition of Pharmaceuticals during Preclinical Development
  - 282 compounds
  - 16 pharma contributors
  - contemporary data

- Primary target organs
  - CV, liver, kidney, GI, CNS, testes
  - ~70% of preclinical safety attrition
  - We don’t have to replicate the 15K data points in a 28d rat study

Design-Test-Implement- IQ/NCATS/FDA partnership as a model

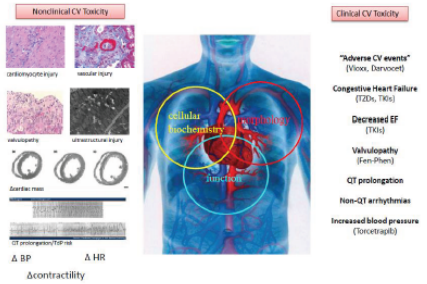
IQ Microphysiological Systems Working Group
Organotypic Standards- Cardiovascular

Berridge, B. R., IQ MPS Working Group, HESI Cardiac Safety Technical Committee

Introduction

- The cardiovascular system is dynamic and integrated with significant adaptive function, intra-system interdependencies and non-CV influences
- It is an important source of drug safety liabilities for which the in vivo mammalian system has been important for identifying and characterizing
- The myocardium, heart valves, and intra- and extra-cardiac arteries are primary targets of both structural and functional toxicity
- Contemporary assessments of CV safety include assessment of cardiac rhythm and contractility, systemic blood pressure, heart mass and morphology of the heart and blood vessels
- An appropriately robust, human-relevant MPS system could provide near term opportunities for early screening as well as a means to differentiate species-specific effects
- MPS systems are likely to be more mechanistically informative

What does cardiovascular toxicity look like?



Important physiological features of the CV system

- Integrated system with significant interdependence, reserve capacity and dynamic function
- Significant biological integration at the system (heart and blood vessels), tissue (cardiomyocytes and capillaries) and cellular (cardiomyocyte ion channels) levels
- High energy requirements- substrates = fatty acids > glucose, oxygen, high number of mitochondria
- Relative lack of regenerative capacity in the myocardium
- Functional changes manifest in changes in fluid dynamics. Changes in fluid dynamics can induce structural changes.
- Cardiomyocytes express drug transporters and they can be mediators of toxicity but they're not very well characterized.

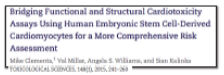
Cardiovascular response to toxic injury, endpoints and test compounds

Cellular components	Structural features	Functional features	Responses/manifestations of injury	Potential endpoints	Test compounds
Cardiomyocytes	Terminally-differentiated with mature phenotype (e.g. contractile apparatus, $Ca2+$ apparatus, physiologic mitochondrial mass; sMHC, transporter and connexin expression),	rhythmic contractility with reserve capacity (paced beating with positive force-frequency, action potential morphology, Starling's forces)	Necrosis/apoptosis	LDH, cTnI/T, TUNEL	LFS, CEM, Doxorubicin, ischemia
			Vacuolation (lipidosis, mito-swelling, ER dilation, lysosomal accum., glycogen accum.	morphology, lipid stain, mito dyes, lysosome label,	etomoxir (lipid), doxorubicin (ER), chloroquine (lysosomes), ischemia (mitochondria), pharmacol (mitochondria, ER)
			Mineralization	$Ca2+$ staining	
			Hypertrophy	Cell size quantitation	testosterone, phenylephrine, clenbuterol
			Organellar (e.g. mitochondrial) dysfunction	Oxidative stress, ATP production, O2 consumption	
			Inotropic dysfunction	contractile force/shortening	pimobendan, amrinone, finaconazole, atenolol, digoxin
			Lusitropic dysfunction	rate of relaxation (?)	milrinone
			Chronotropic dysfunction	beat rate	isoproterenol, lidocaine
			Rhythmic dysfunction	action potential measures	terfenadine, cisapride
Fibrocytes	Vimentin expression, no SMA	Contractile (though generally not rhythmic), collagen production	Activation to myofibroblast, proliferation, increased collagen production	SMA expression, proliferation	TGFb
Valve stromal cells	Mature phenotype expressing SMA, βMHC, cTnI, ECM production; SHT2B expression	ECM production, contractile (though not rhythmic)	Activation to myofibroblast, proliferation, increased ECM production	SMA expression, proliferation	ALK 5 inhibitors, fenfluramine-phentermine
Capillary endothelial cells	Mature phenotype (CD31 expression, vWF, fenestrated intercellular bridging, Weibel-Palade bodies, pinocytotic vesicles)	selective permeability, anti-coagulation	Necrosis/apoptosis	LDH, morphology	LFS, tubulin inhibitors, cyclophosphamide
			Pro-inflammatory activation	PECAM expression	LPS
			Retraction	Loss of intercellular bridging, edema	IL-2?
			Hypertrophy	Cell size quantitation	
			Proliferation	PCNA, BrdU incorporation	
			Pro-thrombotic activation	platelet adhesion, surface markers	LPS
			Altered NO/ET expression	NO, ET	endothelin inhibitors, L-NAME
Smooth muscle cells	Mature phenotype (SMA expression,)	contractile and responsive to NO, ET, adrenergic signals	Necrosis/apoptosis	LDH, TUNEL	
			Lipid accumulation	lipid stain	TZDs
			Lysosomal accum.	Lysosomal marker	
			contraction/relaxation	Functional measure	NO, endothelin, hydralazine, minoxidil, fenoldapam
Arterial endothelial cells	Mature phenotype (CD31 expression, vWF, fenestrated intercellular bridging, Weibel-Palade bodies, pinocytotic vesicles)	NO/ET production, anticoagulant	Necrosis/apoptosis, retraction, pro-thrombotic activation, hypertrophy	See capillary endo cells	

Relating in vitro to in vivo endpoints

In vivo	In vitro	Comments
Heart rate	Beat rate	± autonomic influence
ECG	Field potential, conduction velocity?	Tability to model re-entrant action potentials
QA interval/dP/dT max	Force of contraction, contraction velocity, calcium flux	Direct contractility measures
Blood pressure	NO production, blood vessel diameter	Measure of direct vasoactivity
Cardiomyocyte hypertrophy–heart weight	Cell size, gene expression	Measure of direct anabolism or catabolism
Cardiomyocyte injury–microscopic morphology, cTnI, special staining procedures	Cell size, morphology and viability, gene expression, protein content	Restricted to direct effects but potentially mechanistically insightful
Endothelial injury–microscopic morphology, coagulation factors, inflammation	Gene expression, barrier function	

Contextualizing other capabilities


Bridging Functional and Structural Cardiotoxicity Assays Using Human Embryonic Stem Cell-Derived Cardiomyocytes for a More Comprehensive Risk Assessment


Structural and functional screening in human induced-pluripotent stem cell-derived cardiomyocytes accurately identifies cardiotoxicity of multiple drug types

Building Confidence

- Relate the platform to a specific component of the integrated system
- Demonstrate relevant in vivo morphologic and functional attributes
- Test known positive and negative compounds for specific outcomes
  - representing a spectrum of mechanisms
  - at relevant in vivo doses
  - with pre-defined success criteria
- Know how to respond to the data- e.g.
  - stop development
  - needs further characterization
  - mitigates animal data
- Be able to represent appropriate context of use, throughput, value proposition, weaknesses

Contact Information

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Roadmap

Define critical target organs of tox and AOPs

+

Define critical DMPK organs, processes and endpoints

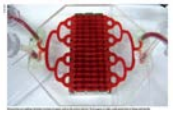
Define biological and analytical standards for these target organs/processes

Evolution of Application

Pre-animal Safety Screens

Seek ready now solutions

Seek ready soon solutions



Comparative application with in vivo safety studies

Co-develop and/or test those solutions

PPP Incubator

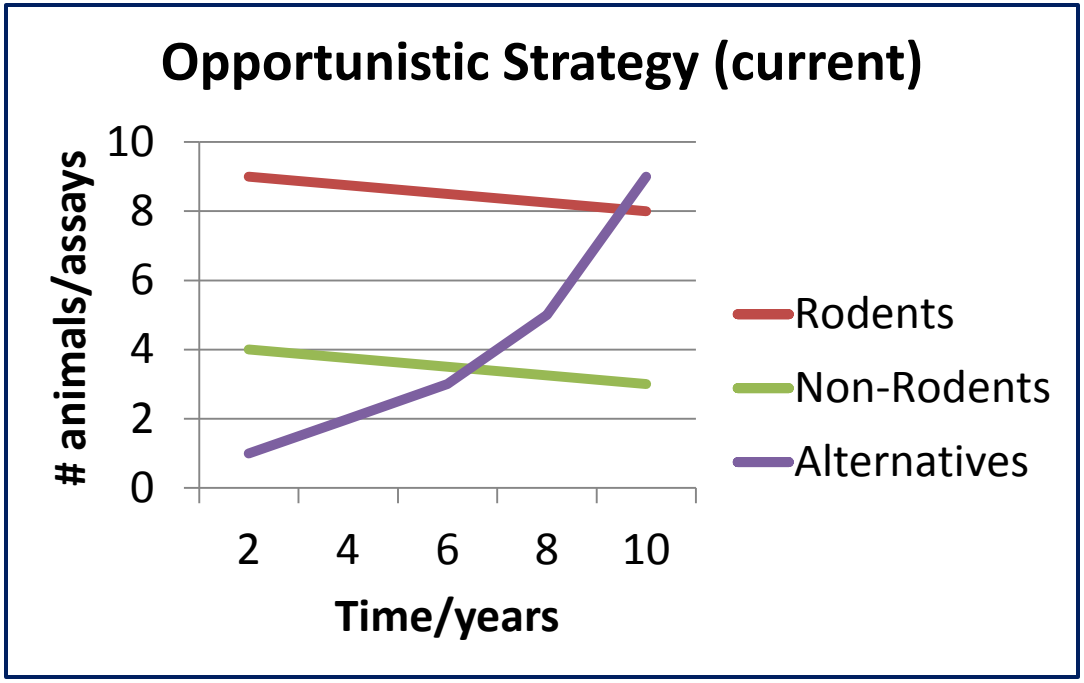
Virtual second safety species

Embed/industrialize

The ultimate value proposition

- Improved predictive validity of early preclinical models = lower attrition
  - DMPK + safety in the first instance
  - Parallel application of the principles of this approach to specific disease areas improves efficacy modeling in the second
- Decreased cycle time by bringing the best lead forward the first time (avoids iterative assessment of multiple leads pre-CS)
- Enables early risk:benefit integration
- Decreases animal use
- Lowers development costs
- Efforts in innovation more efficient and impactful in the near term

Alternatives Development Strategy Impact



Opportunity-driven

Salient features

- Representative of current 'crowd-sourced' innovation
- Adoption and confidence in alternative platforms will steadily increase with development out-pacing adoption
- Animal use will be impacted as confidence grows

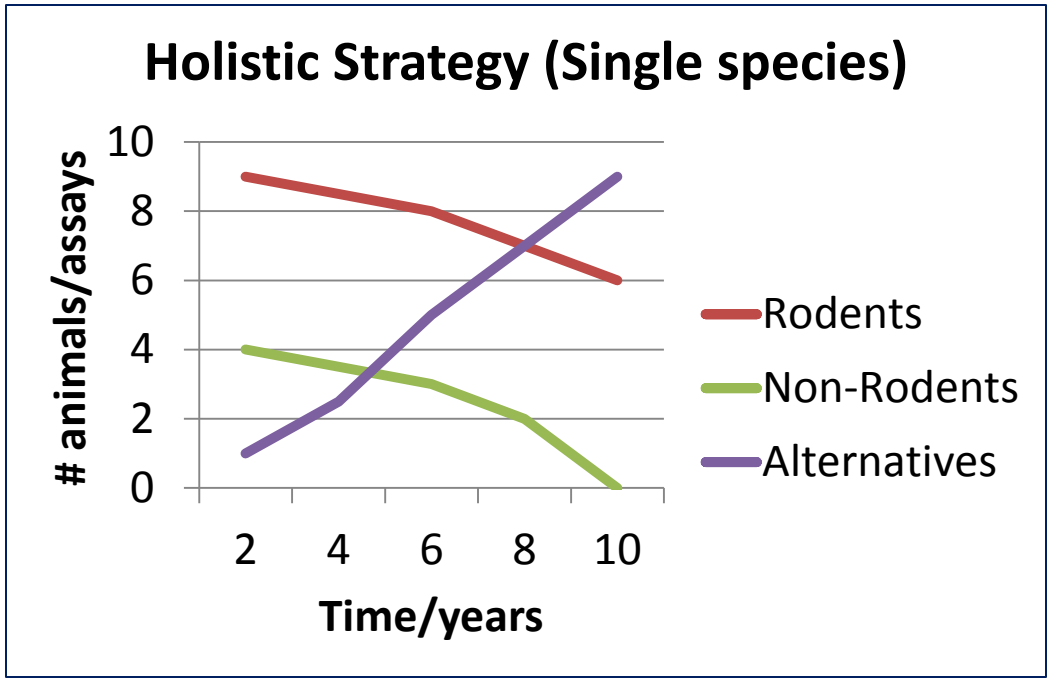
Pros

- Slow gradual change in behaviour
- No change in investment
- Animal use will decline as confidence increases
- Clinical predictivity could increase
- Unrestricted innovation
- Regulatory acceptance not needed

Cons

- Investment not optimally leveraged; lots of wasted resource
- Progress slow
- Improvements in clinical predictivity and decreases in animal use minimal over the short term (5-10 yrs.)
- Additive assessments

Alternatives Development Strategy Impact



Incentive-driven

Salient features

- Defined by a bold aspirational goal- i.e. single species safety package
- Alternatives development defined by the prioritized scope of in vivo assessments
- Rate of animal use impact increases with time

Pros

- Deliberate innovation defined by current standards
- Significant alignment and complementarity of investment
- Signficant decrease in animal studies- particularly for non-rodents
- Clinical predictivity could/should increase

Cons

- Significant global coordination
- Regulatory acceptance required for full impact
- Structured development and qualification process
- Innovation directed