NTP
National Toxicology Program

US Strategic Roadmap Goal: Encourage the Use and Adoption of New Methods and Approaches by Federal Agencies and Regulated Industry

Microphysiological Systems as an Exemplar

B. R. Berridge, DVM, PhD, DACVP
Associate Director, NTP

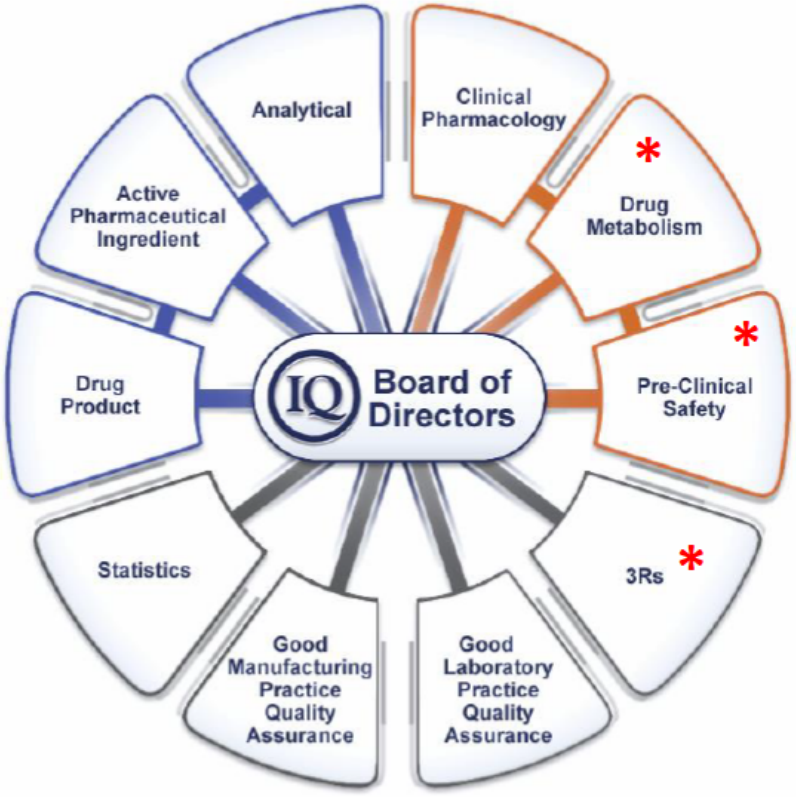
Outline

- End-user perspective for engagement of a novel technology
- Bridge between pharma and NTP contexts
- A guide to building confidence
- Distinguishing ‘validation’ from ‘qualification’
- I’m going to complicate things
  - toxicology contexts
  - organ systems
  - differentiating validation, qualification and confidence

Engaging a novel technology

Linking platform developers to platform users

IQ Consortium- LGs and WGs



Microphysiological Systems WG

Multi-disciplinary team of pharmaceutical scientists representing expertise and interests in drug metabolism and distribution, safety, and the 3Rs of judicious animal use for research

- **Inaugurated late 2014**
- **NCATS request**
- **24 members**
- **16 pharma organizations**

Pharma Challenge

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

Over half of terminations are for things we test preclinically.

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.

Environmental Challenge

National Toxicology Program

Headquartered at the
National Institute of Environmental
Health Sciences NIH-HHS

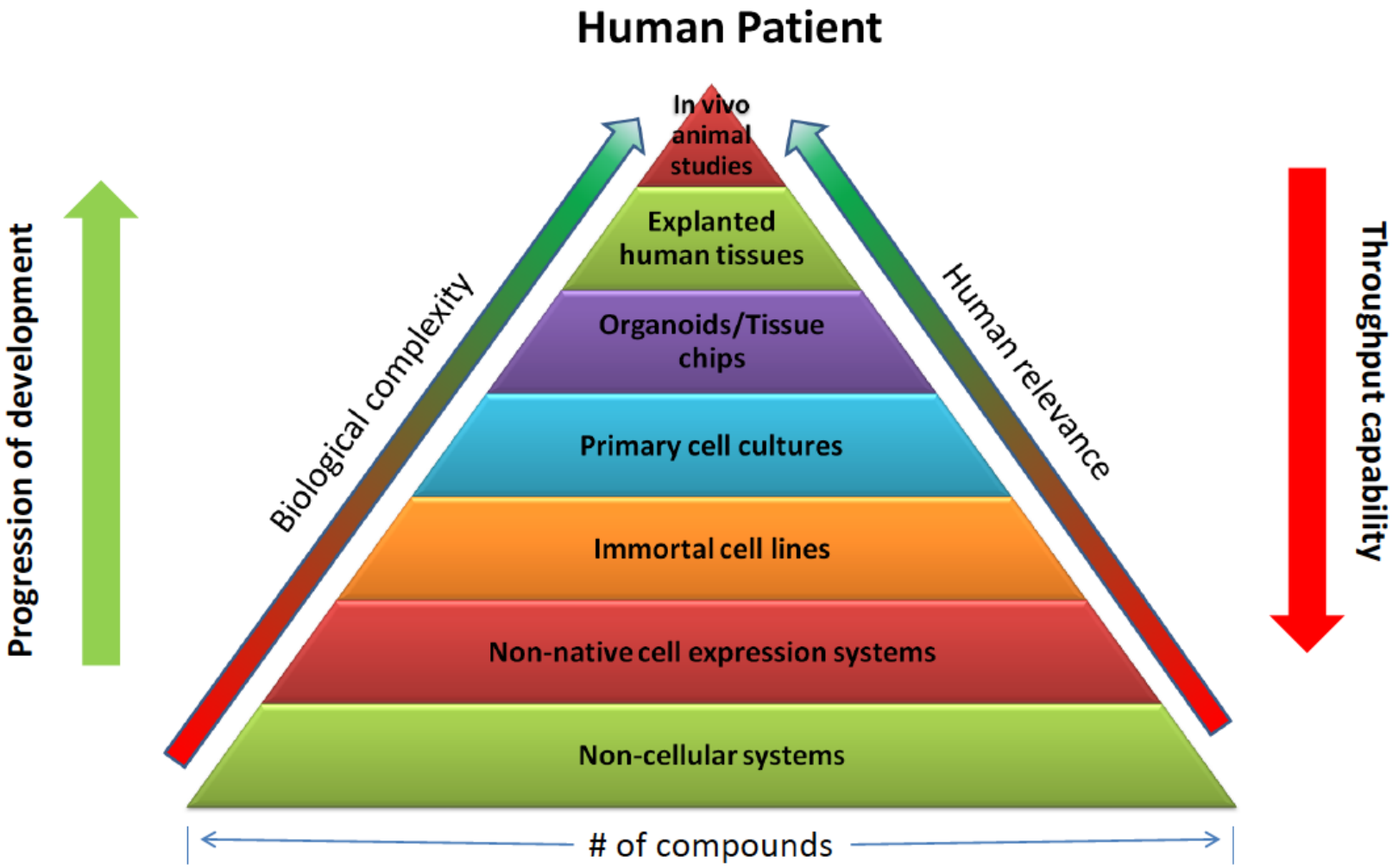
Tox21: Chemical testing in the 21st century

Tox21 aims to:

- Develop new testing methods that use human cells, called *in vitro* approaches
- Expand the number of chemicals that are tested
- Reduce the time, effort, and costs associated with testing
- Minimize the number of laboratory animals used

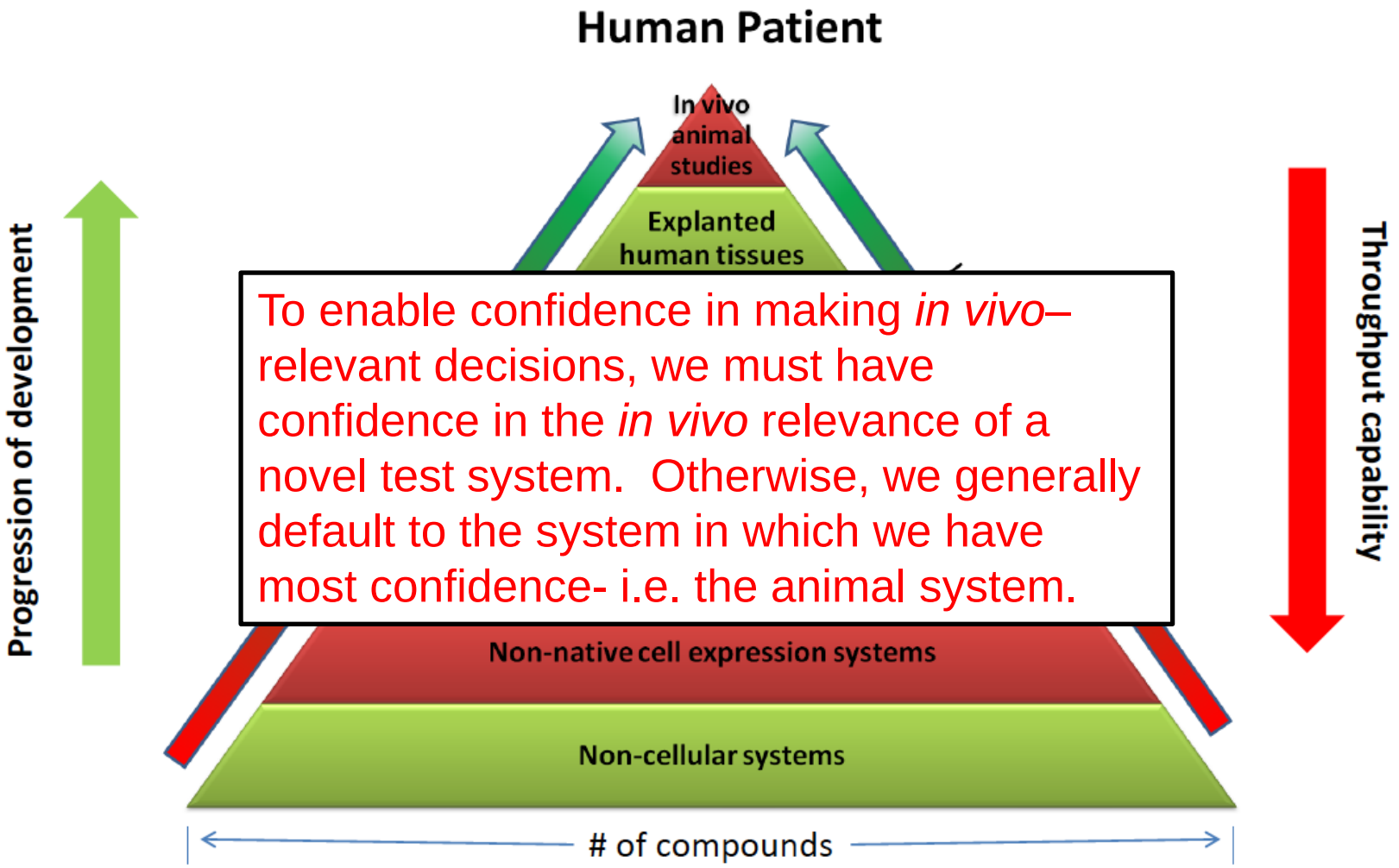
Pharma uses secondary pharmacology screening in a lower throughput context.

Translational Challenge



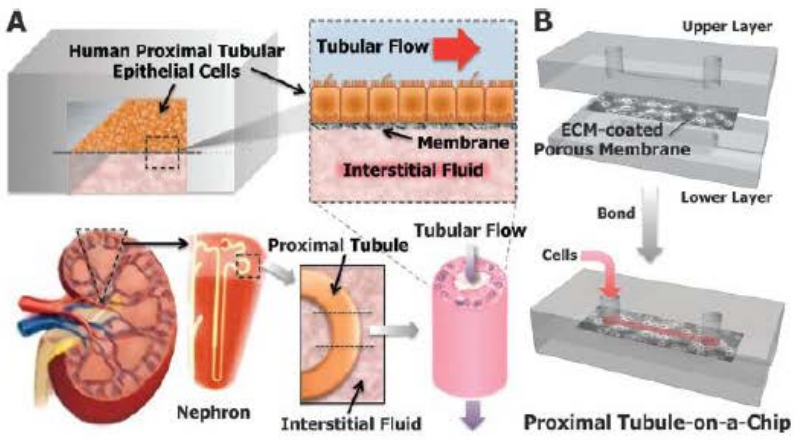
Current approaches trade human in vivo relevance for throughput and analytical clarity.

Translational Challenge

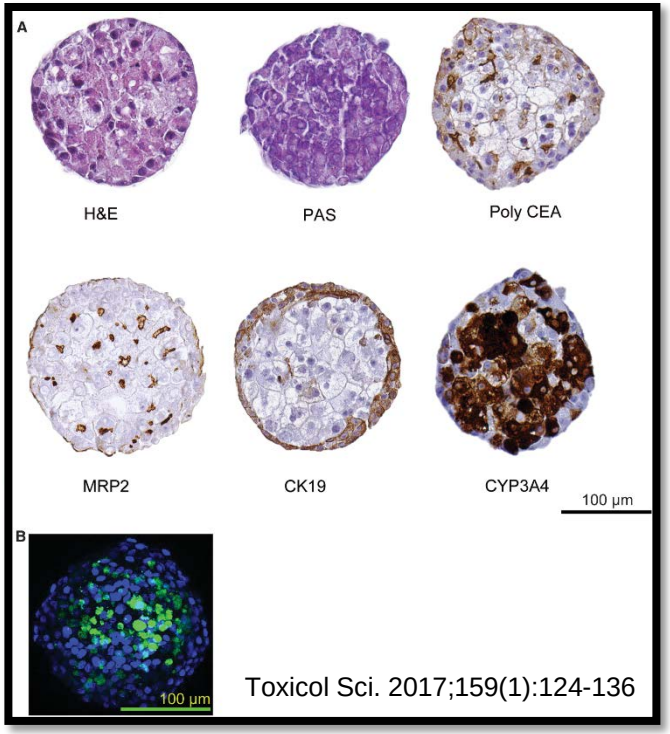


Current approaches trade human in vivo relevance for throughput and analytical clarity.

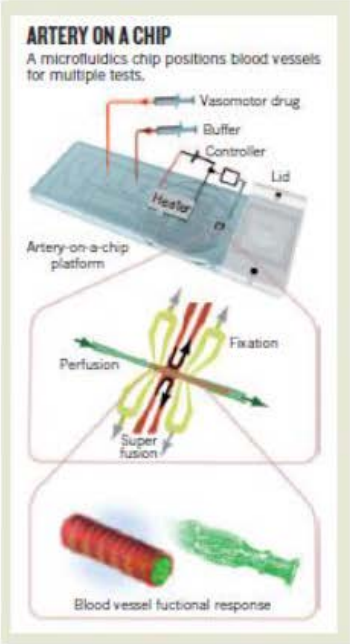
Opportunity- Microphysiological Systems



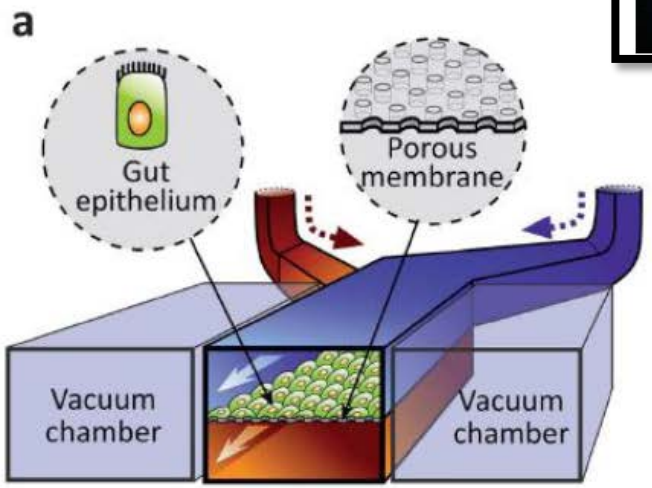
Integr. Biol., 2013, **5**, 1119–1129



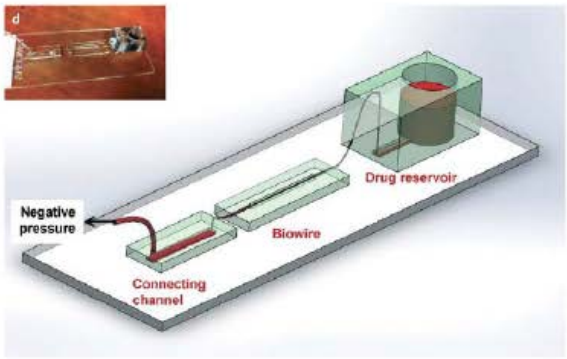
Toxicol Sci. 2017;159(1):124-136



NATURE | VOL 471 | 31 MARCH 2011



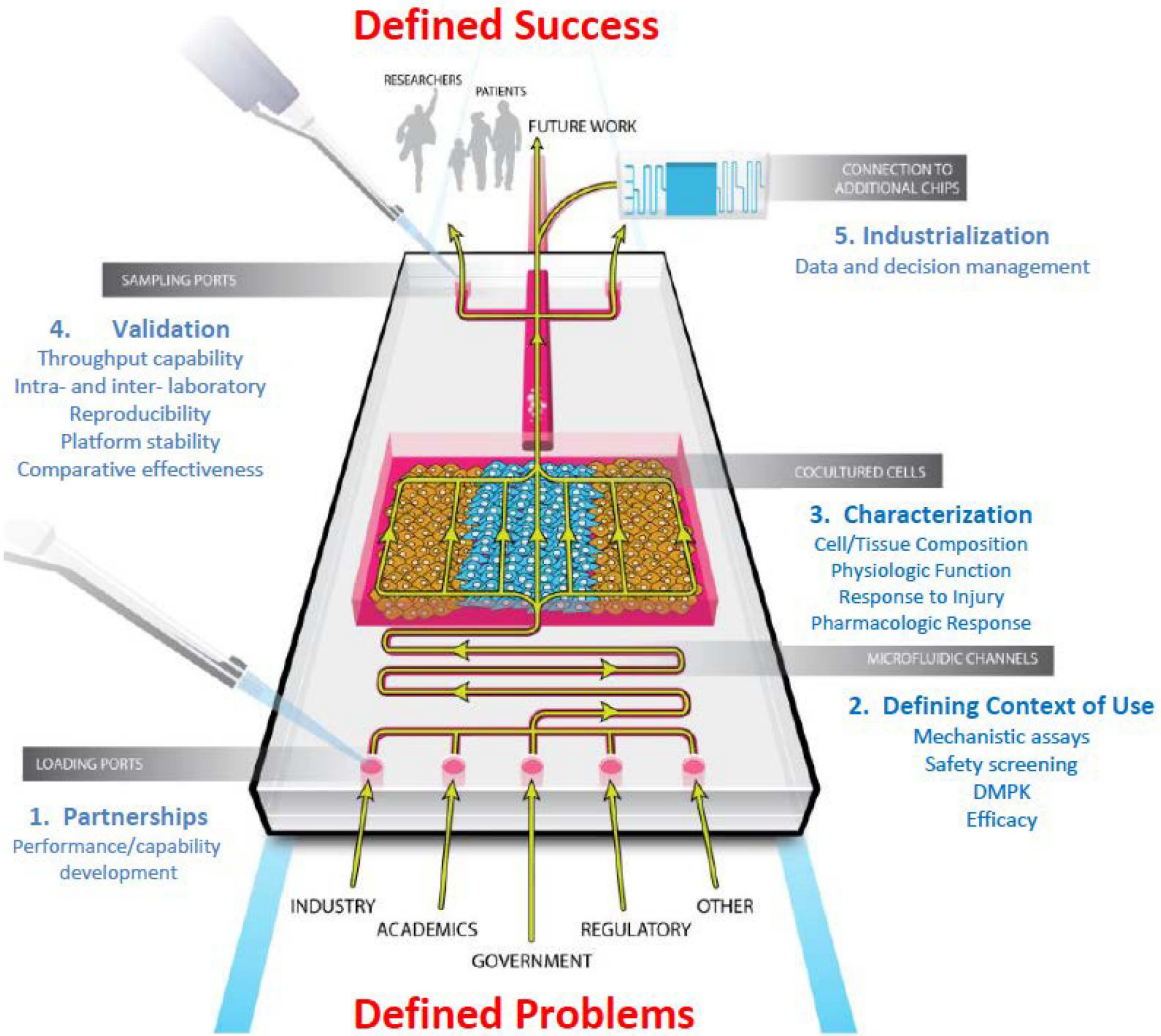
Lab Chip 2012



Lab Chip, 2014, **14**, 869–882

Navigating tissue chips from development to dissemination: A pharmaceutical industry perspective

Lorna Ewart[1], Kristin Fabre[2], Ananthsrinivas Chakilam[3], Yvonne Dragan[4], David B Duignan[5], Jeetu Eswaraka[6], Jinping Gan[7], Peggy Guzzie-Peck[8], Monicah Otieno[8], Claire G Jeong[9], Douglas A Keller[10], Sonia M de Morais[11], Jonathan A Phillips[12], William Proctor[13], Radhakrishna Sura[11], Terry Van Vleet[11], David Watson[14], Yvonne Will[15], Danilo Tagle[16] and Brian Berridge[9]



Experimental Biology and Medicine 2017; 242: 1579–1585.

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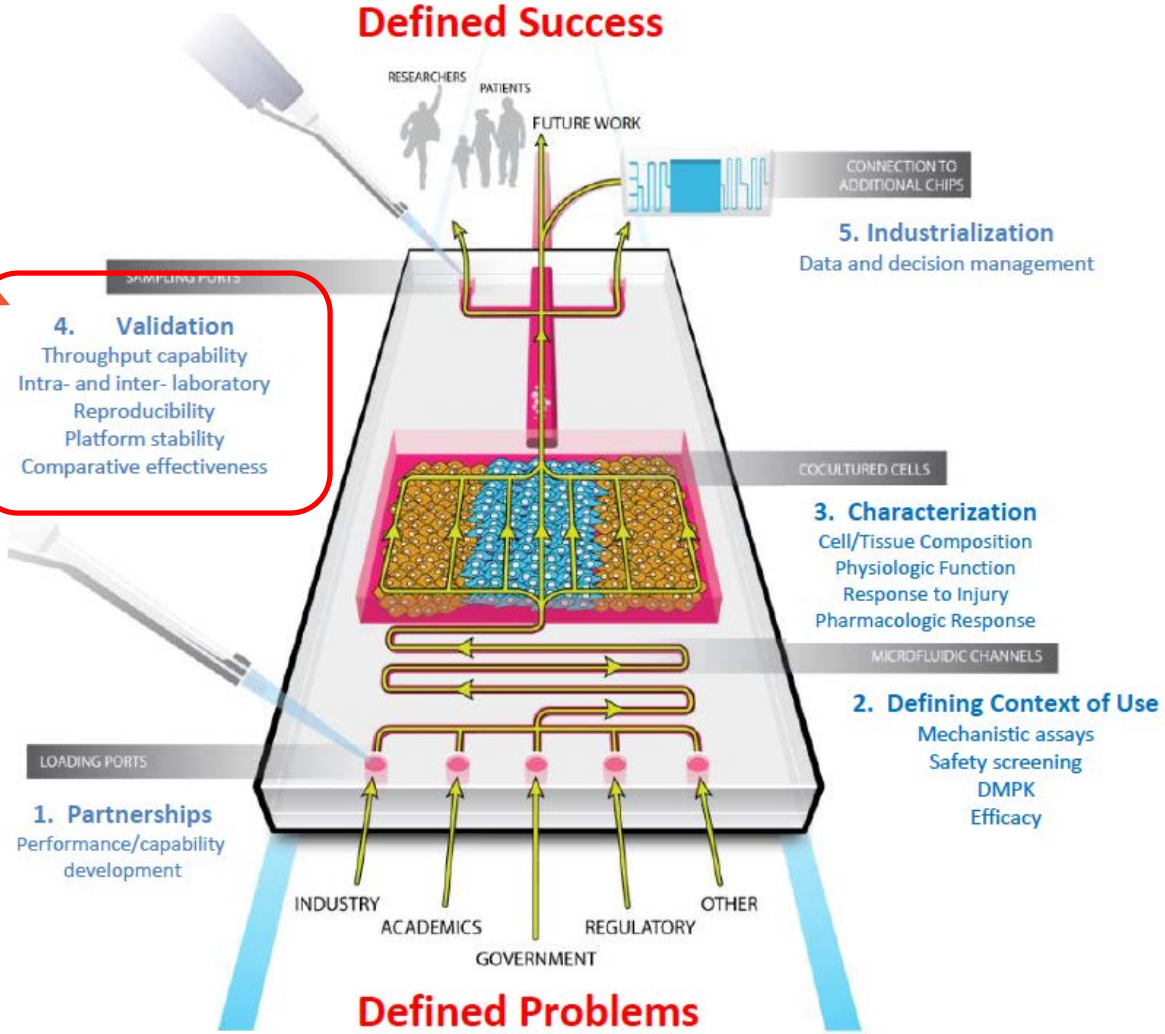
Seen by many as a threshold for success



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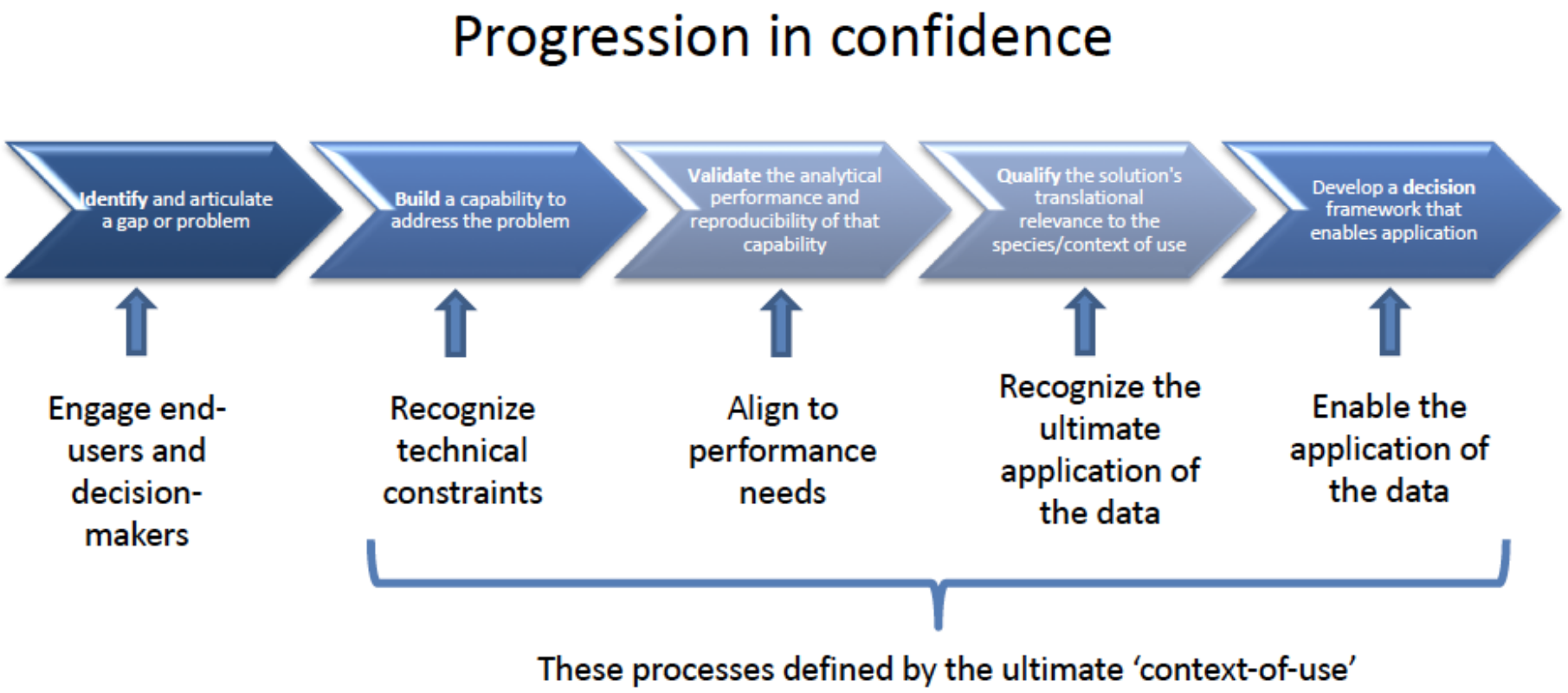
Validation *vs*. Confidence

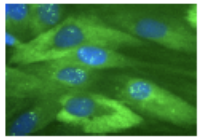


Confidence evolves and is enabled by key elements of the process!

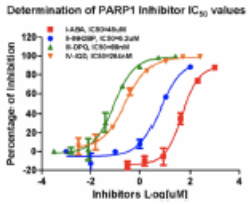
Pharma Context of Use

Capabilities

Bioinformatics

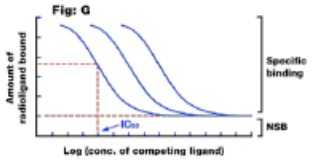


Phenotypic assays

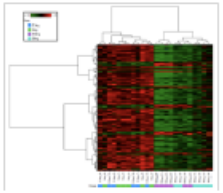


Activity assays

Human tissue

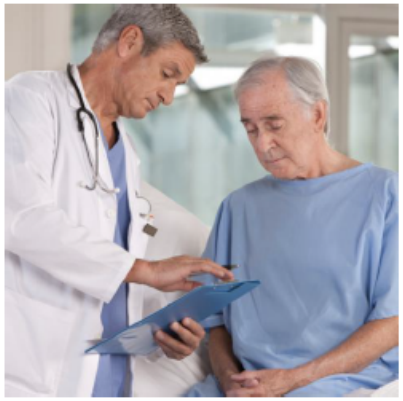


Binding assays



-omics

Animal studies



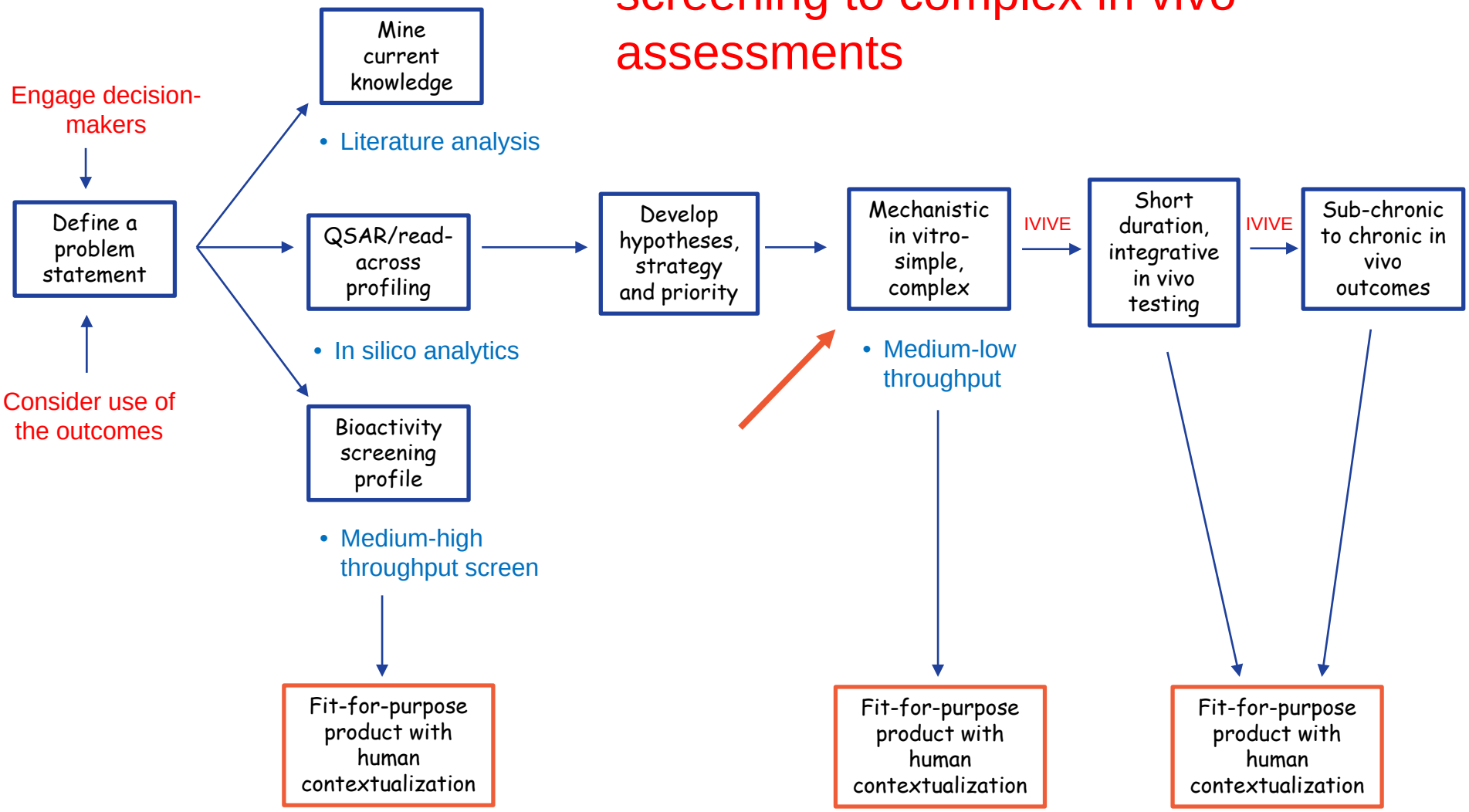
Patient studies

Target ID & validation	Hit/lead discovery	Lead optimisation	Candidate selection	Preclinical safety	Clinical assessment
#compounds	1000's	100's	10's	1-3	

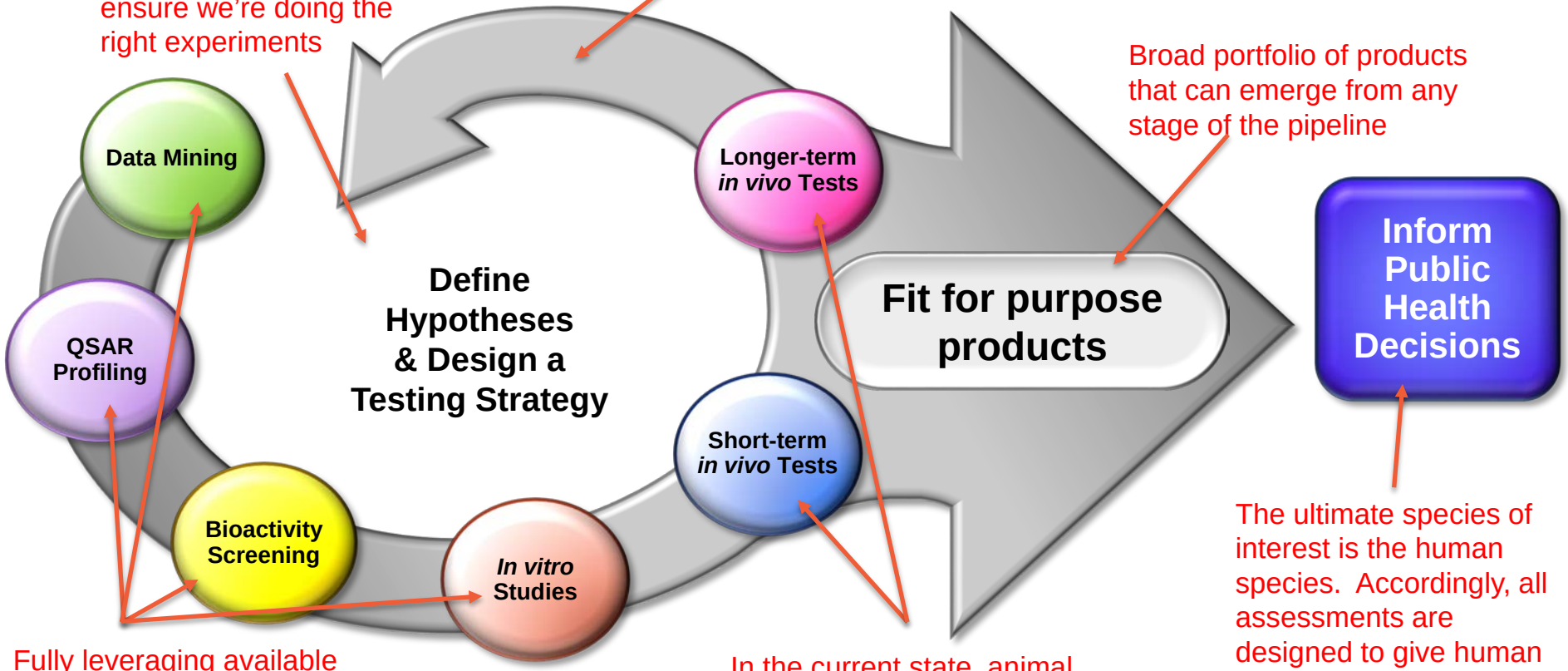
Design compounds by first intent that engage disease-modifying targets at appropriate concentrations without inducing unmanageable liabilities

NTP Context of Use

Building bridges from simple in vitro screening to complex in vivo assessments



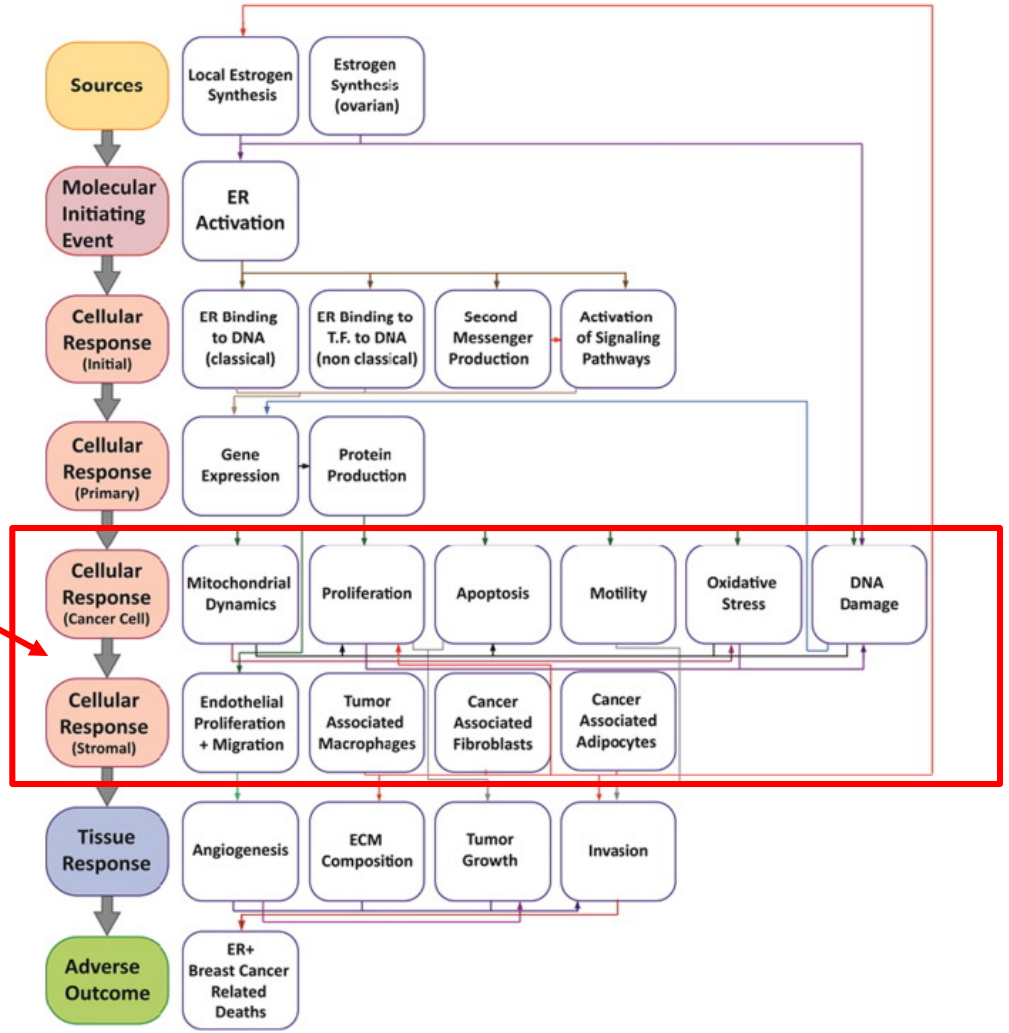
DNTP Translational Toxicology Pipeline Plan



Understand the biology you need to represent

ER pathway to breast cancer

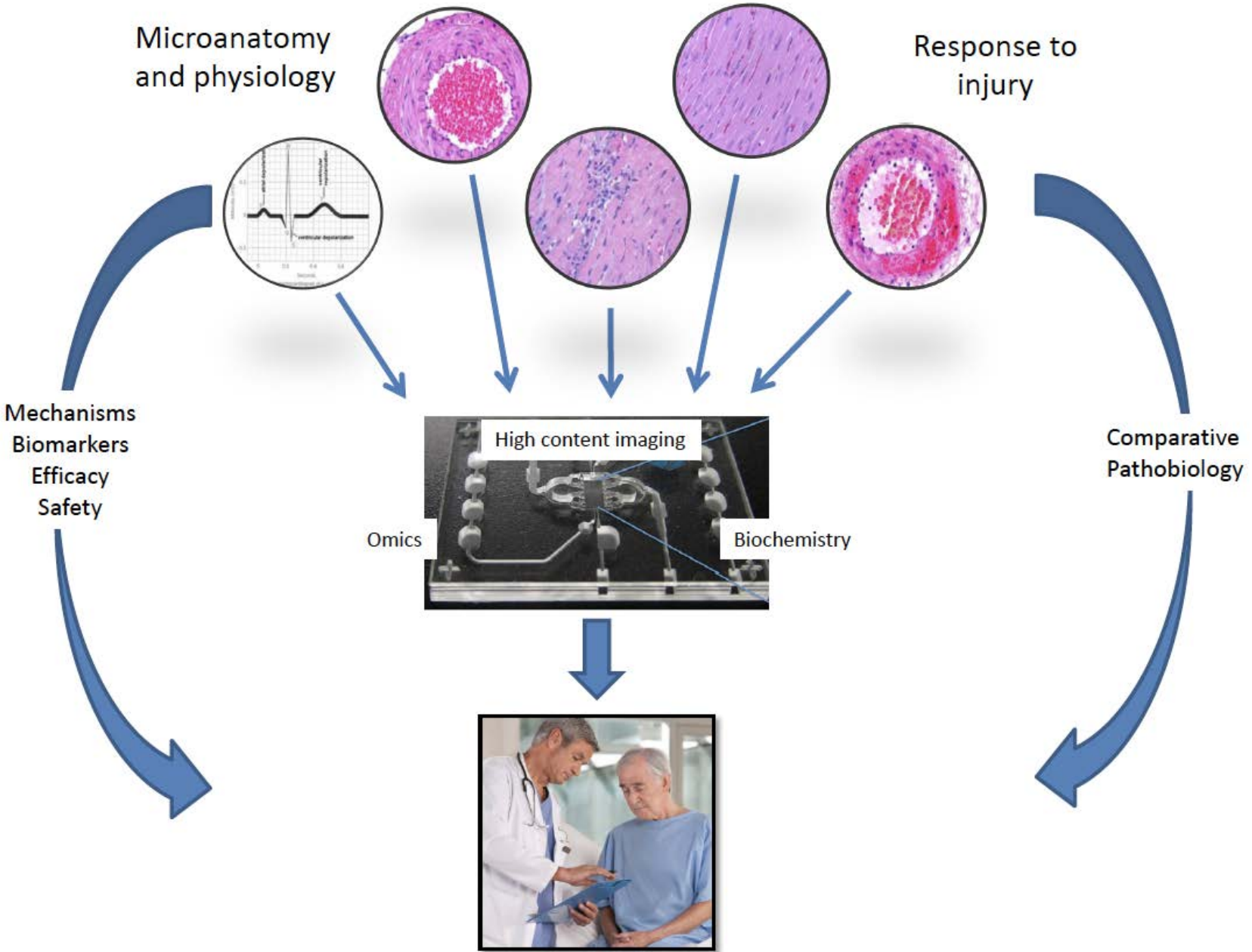
A critical inflection point not generally modeled in simple in vitro systems



From Morgan et al., 2016, Pharmacology & Therapeutics 165: 79-92

Appreciation to Cynthia Rider for introducing me to this.

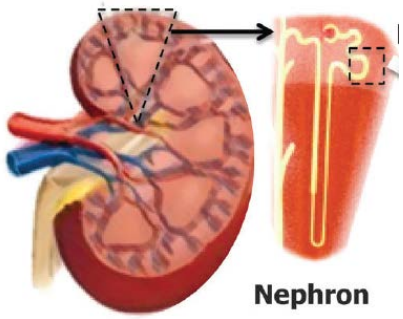
Ensure that biology is translatable

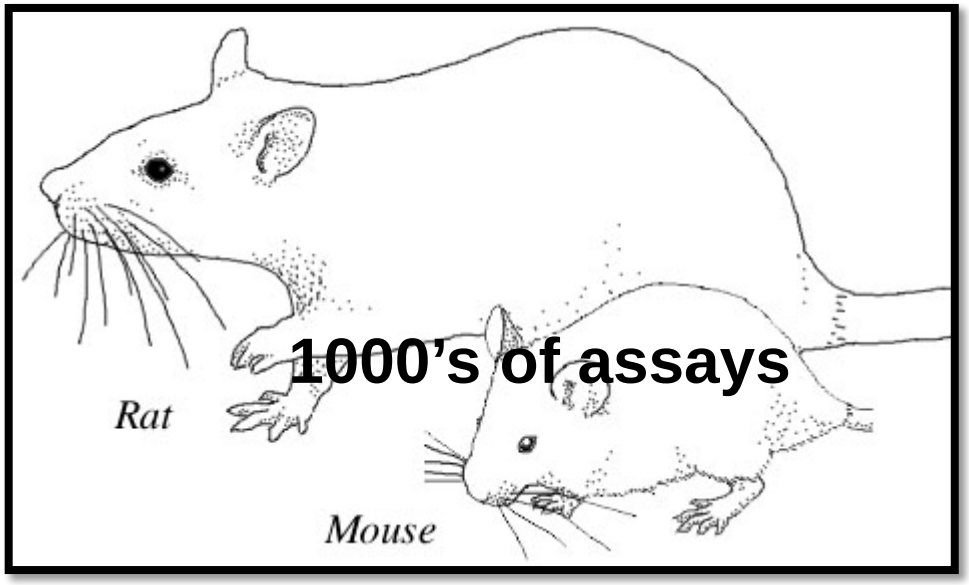


Analytical validation

Consult relevant guidelines or engage your local XVAM!

‘Qualification’ is larger contextualization exercise





cf. Human toxicity
•Tubular toxicity

•cf. Animal assessment
•Tubule cell injury
•Urinary Kim-1, NAG

Qualification of a novel test or modeling system requires-

- an understanding of the how the new system compares to the traditional system
- an understanding of how the pathobiology of interest manifests in the species of interest
- an understanding of how the pathobiology of interest manifests in traditional model species.

Contextualizing the opportunity- What does nephrotoxicity look like in patients?

Drug-Induced Nephrotoxicity

CYNTHIA A. NAUGHTON, PharmD, BCPS, *North Dakota State University College of Pharmacy, Nursing, and Allied Sciences, Fargo, North Dakota*

Table 1. Drugs Associated with Nephrotoxicity

Drug class/drug(s)	*Pathophysiologic mechanism of renal injury*
Analgesics	
Acetaminophen, aspirin	Chronic interstitial nephritis
Nonsteroidal anti-inflammatory drugs	Acute interstitial nephritis, altered intraglomerular hemodynamics, chronic interstitial nephritis, glomerulonephritis
Antidepressants/mood stabilizers	
Amitriptyline (Elavil*), doxepin (Zonalon), fluoxetine (Prozac)	Rhabdomyolysis
Lithium	Chronic interstitial nephritis, glomerulonephritis, rhabdomyolysis
Antihistamines	
Diphenhydramine (Benadryl), doxylamine (Unisom)	Rhabdomyolysis
Antimicrobials	
Acyclovir (Zovirax)	Acute interstitial nephritis, crystal nephropathy
Aminoglycosides	Tubular cell toxicity
Amphotericin B (Fungizone*; deoxycholic acid formulation more so than the lipid formulation)	Tubular cell toxicity
Beta lactams (penicillins, cephalosporins)	Acute interstitial nephritis, glomerulonephritis (ampicillin, penicillin)
Foscarnet (Foscavir)	Crystal nephropathy, tubular cell toxicity
Ganciclovir (Cytovene)	Crystal nephropathy
Pentamidine (Pentam)	Tubular cell toxicity
Quinolones	Acute interstitial nephritis, crystal nephropathy (ciprofloxacin [Cipro])
Rifampin (Rifadin)	Acute interstitial nephritis
Sulfonamides	Acute interstitial nephritis, crystal nephropathy
Vancomycin (Vancocin)	Acute interstitial nephritis
Adefovir (Hepsera), cidofovir (Vistide), tenofovir (Viread)	Tubular cell toxicity
Indinavir (Crixivan)	Acute interstitial nephritis, crystal nephropathy
Benzodiazepines	Rhabdomyolysis
Calcineurin inhibitors	
Cyclosporine (Neoral)	Altered intraglomerular hemodynamics, chronic interstitial nephritis, thrombotic microangiopathy
Tacrolimus (Prograf)	Altered intraglomerular hemodynamics
Cardiovascular agents	
Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers	Altered intraglomerular hemodynamics
Clopidogrel (Plavix), ticlopidine (Ticlid)	Thrombotic microangiopathy
Statins	Rhabdomyolysis
Chemotherapeutics	
Carmustine (Gliadel), semustine (investigational)	Chronic interstitial nephritis
Cisplatin (Platinol)	Chronic interstitial nephritis, tubular cell toxicity
Interferon-alfa (Intron A)	Glomerulonephritis
Methotrexate	Crystal nephropathy
Mitomycin-C (Mutamycin)	Thrombotic microangiopathy
Contrast dye	Tubular cell toxicity
Diuretics	
Loops, thiazides	Acute interstitial nephritis
Triamterene (Dyrenium)	Crystal nephropathy
Drugs of abuse	
Cocaine, heroin, ketamine (Ketalar), methadone, methamphetamine	Rhabdomyolysis
Herbals	
Chinese herbals with aristocholic acid	Chronic interstitial nephritis
Proton pump inhibitors	
Lansoprazole (Prevacid), omeprazole (Prilosec), pantoprazole (Protonix)	Acute interstitial nephritis
Others	
Allopurinol (Zyloprim)	Acute interstitial nephritis
Gold therapy	Glomerulonephritis
Haloperidol (Haldol)	Rhabdomyolysis
Pamidronate (Aredia)	Glomerulonephritis
Phenytoin (Dilantin)	Acute interstitial nephritis
Quinine (Qualaquin)	Thrombotic microangiopathy
Ranitidine (Zantac)	Acute interstitial nephritis
Zoledronate (Zometa)	Tubular cell toxicity

(continued)

**—Brand not available in the United States.*

Information from references 10 through 31.

Common Presentations

- Acute interstitial nephritis
- Chronic interstitial nephritis
- Rhabdomyolysis
- Tubular cell toxicity
- Crystal nephropathy
- Altered glomerular hemodynamics
- Glomerulonephritis

But, not in every patient!

Table 2. Patient-Related Risk Factors for Drug-Induced Nephrotoxicity

"Absolute" or "effective" intravascular volume depletion
Age older than 60 years
Diabetes
Exposure to multiple nephrotoxins
Heart failure
Sepsis
Underlying renal insufficiency (glomerular filtration rate < 60 mL per minute per 1.73 m^2)

Information from references 1 through 3, 7, 34, and 35.

Toxicologic Pathology, 40: 14S-86S, 2012

ISSN: 0192-6233 print / 1533-1601 online
DOI: 10.1177/0192623312438736

Proliferative and Nonproliferative Lesions of the Rat and Mouse Urinary System

Kendall S. Frazier[1], John Curtis Seely[2], Gordon C. Hard[3], Graham Betton[4], Roger Burnett[5], Shunji Nakatsuji[6], Akiyoshi Nishikawa[7], Beate Durchfeld-Meyer[8], and Axel Bube[8]

Contextualizing the opportunity- How do we characterize it in animals?

Renal responses to injury

- Degeneration, tubule
- Necrosis, proximal and distal tubules
- Necrosis, papillary
- Infarct, cortex
- Hemorrhage
- Vacuolation, proximal and distal tubules
- Accumulation, glycogen
- Accumulation, hyaline droplets
- Accumulation, pigment
- Cast, hyaline
- Cast, granular
- Crystals, proximal and distal tubules
- Mineralization, tubule
- Mineralization, interstitial
- Hypertrophy, tubule
- Glomerulonephritis
- Glomerulosclerosis
- Infiltrate, inflammatory cell, interstitial
- Edema, interstitial
- Fibrosis, interstitial
- Hyperplasia, tubule
- Hyperplasia, juxtaglomerular
- Adenoma, kidney
- Carcinoma, kidney

Renal biomarkers

- Serum- BUN, Cr
- Urine- Total protein, albumin, sp. gravity, Kim-1, osteopontin, lipocalin-2, NAG

Challenges of Qualification

- Qualifying the *in vivo* relevance of a modeling system (novel or traditional) requires a fundamental understanding of what you're modeling.
- Need to understand how the pathobiology manifests in both the species of interest and the species that has been traditionally used to model that pathobiology.
- Qualifying a novel test system for its *in vivo* relevance to a species of interest is a bit more challenging than validating one but just as important.
- Given the challenges of doing the 'human experiment', *in vivo* experiments in the alternative species may be a component of building confidence in the *in vivo* relevance of a novel system.

Summary

- Engaging end-users and stakeholders of a novel test system or alternative approach is critical to their adoption.
- End-users have a responsibility to guide developers in the construction, validation and qualification of a novel system.
- Building confidence is an evolutionary process with many elements including working the paradigm and seeing the outcomes.
- Acceptance of a novel approach requires a clear line of sight from a problem to a strategy for enabling confidence.

Questions?