Beyond 3D-Models – Building Confidence in Microphysiological Models

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Drug Development Costs Vs. Approval

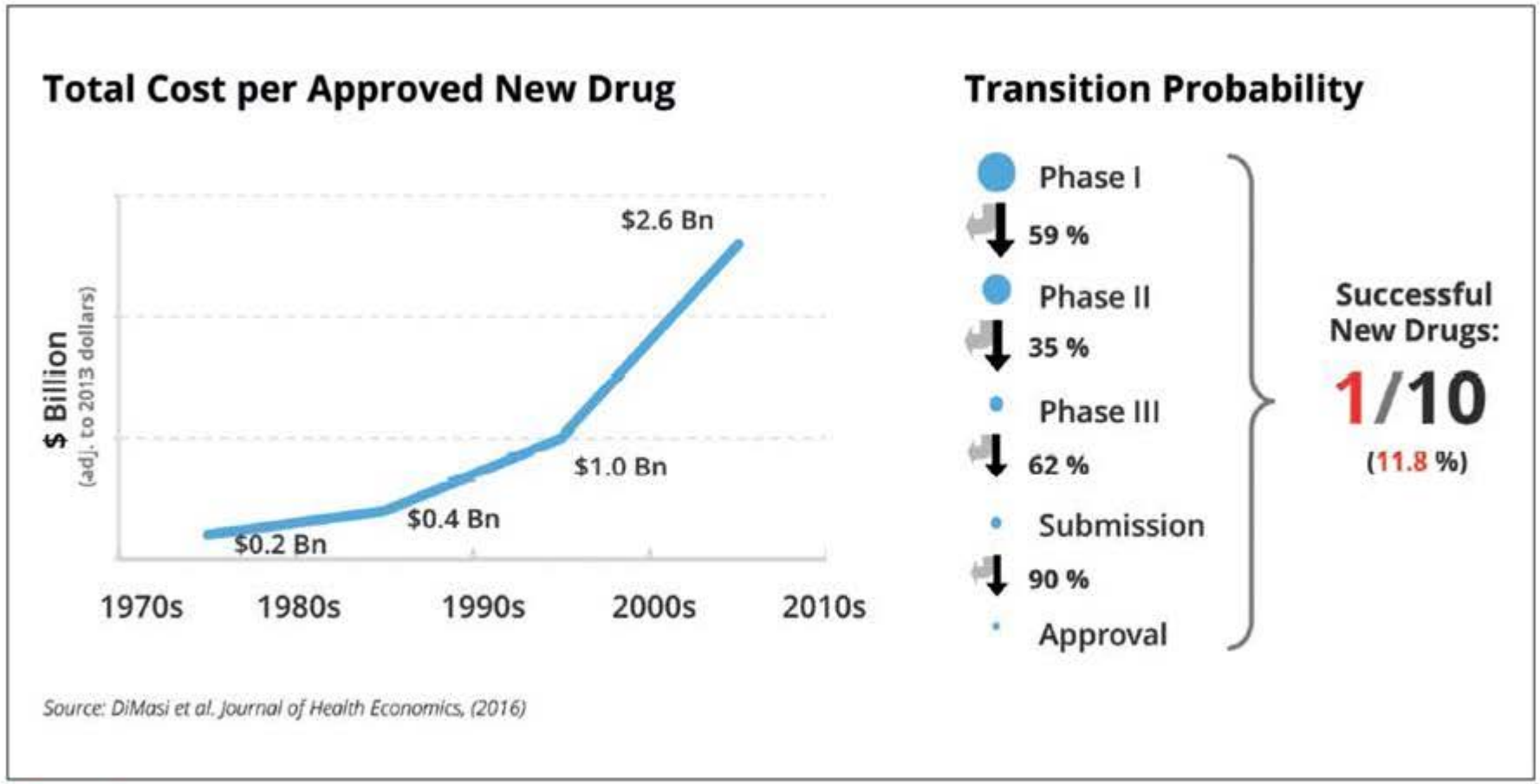

Figure 1 Costs of drug development have risen while overall probability of regulatory approval has reduced[1]. *Image taken from DiMasi JA et al. J Health Econ. 2016;47:20-33*

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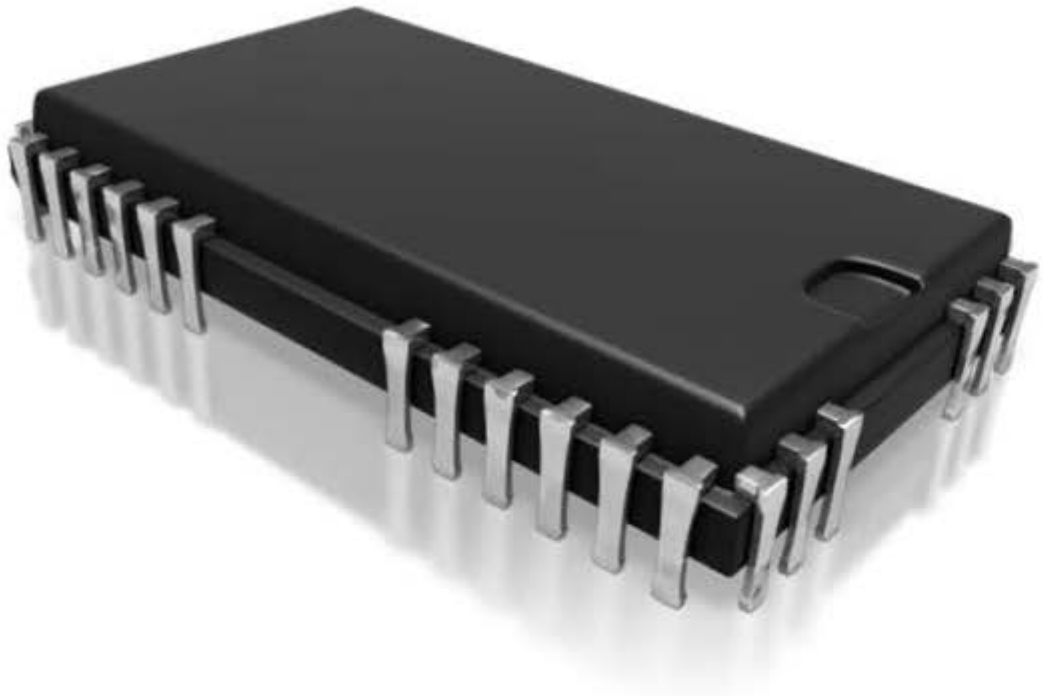

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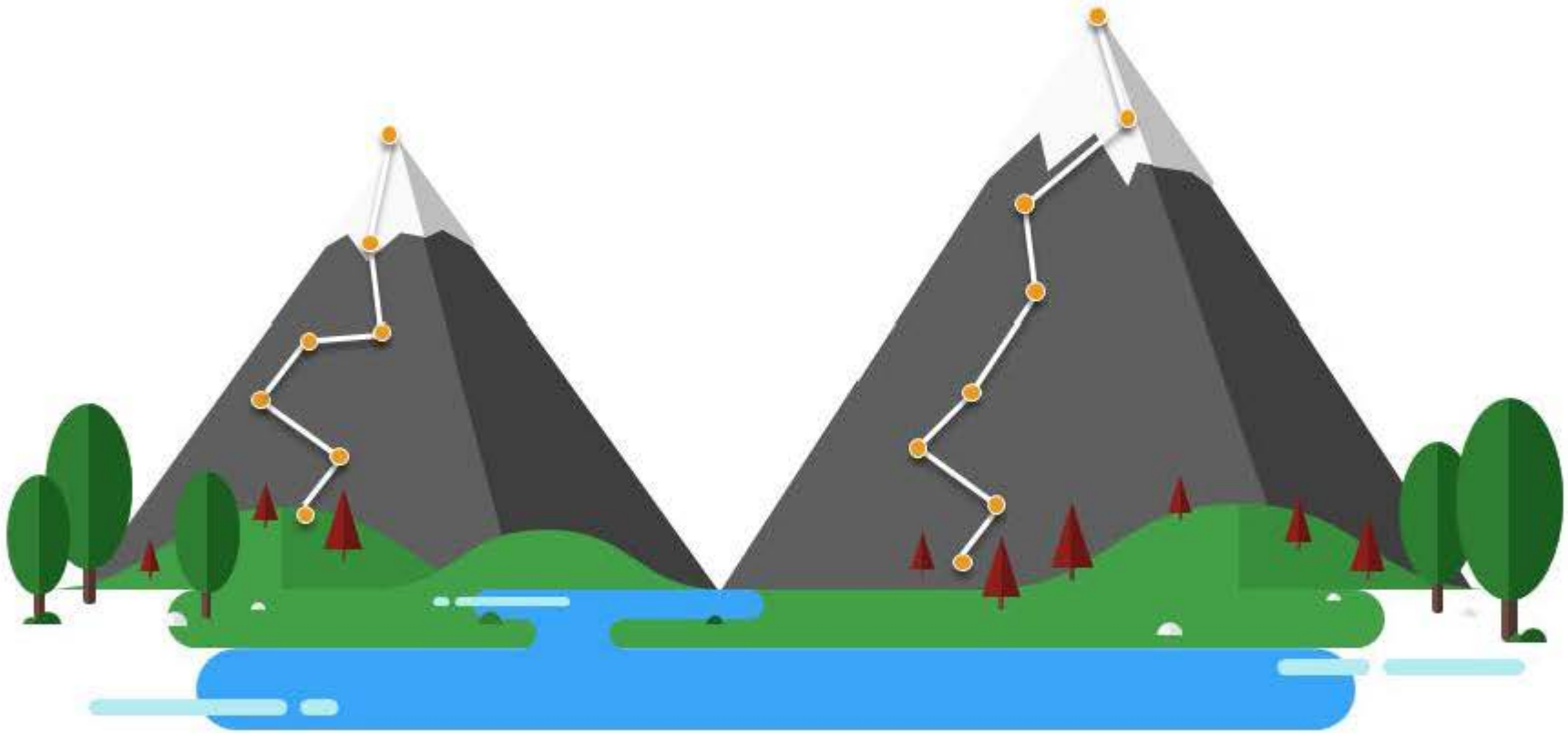

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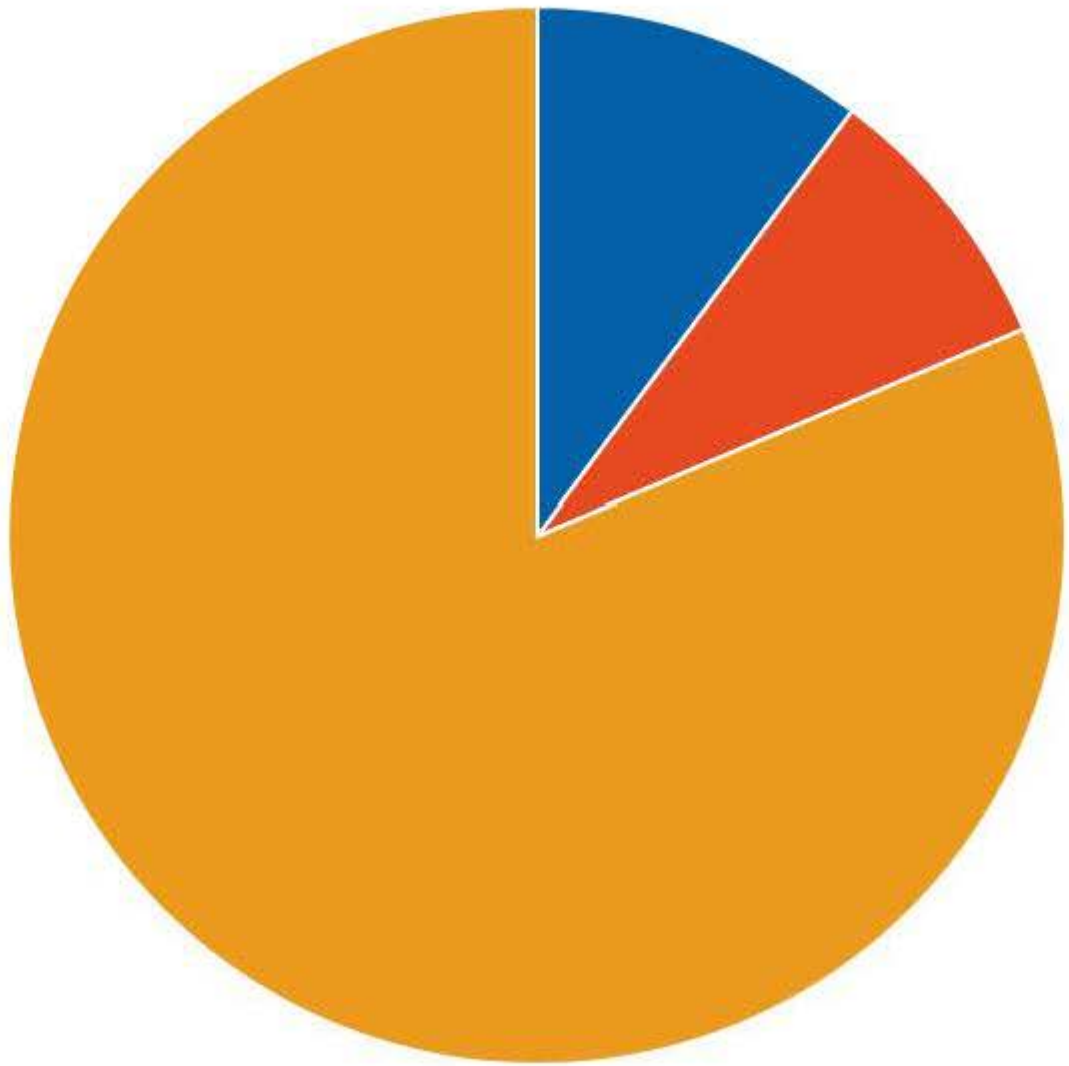

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AMTRAK


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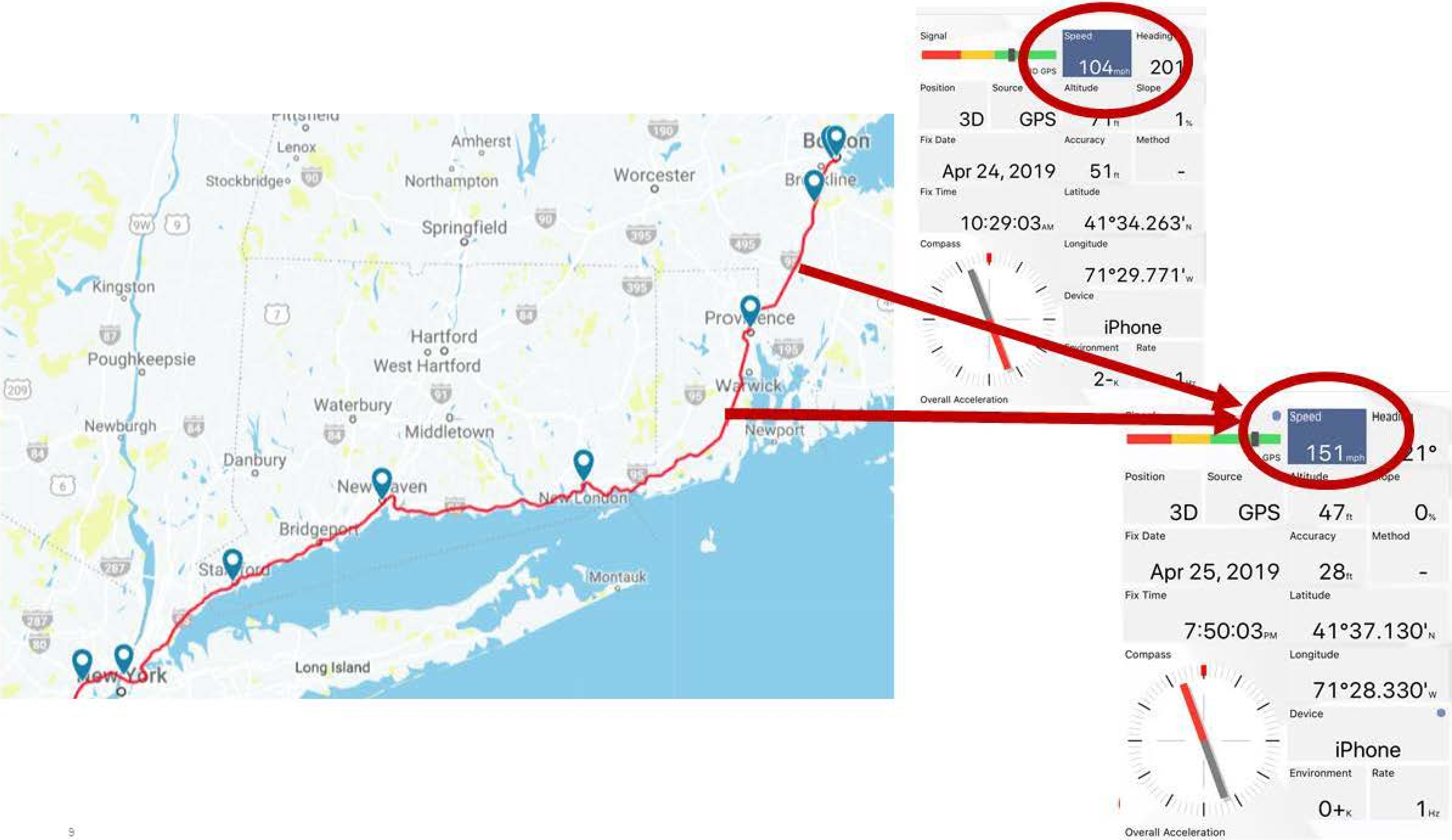
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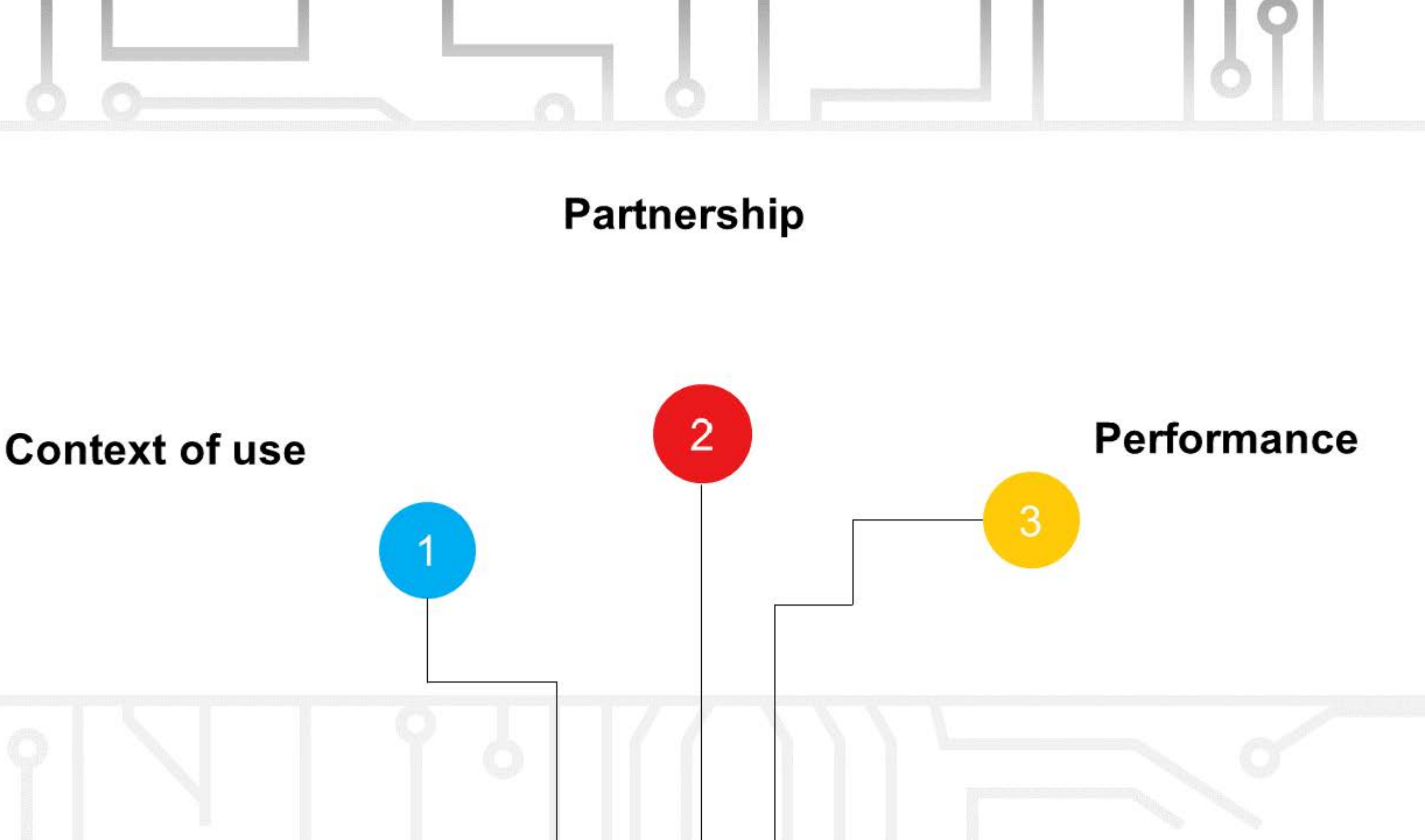
Partnership
Context of use
2
Performance
3
1

https://commons.wikimedia.org/wiki/File:NZ_Landscape_from_the_van.jpg

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THE NORTH AMERICAN 3Rs COLLABORATIVE

www.NA3RsC.org

Complex *In Vitro* Models

- Centralized hub for In Vitro Alternatives (IVA)
- IVA Industry Group

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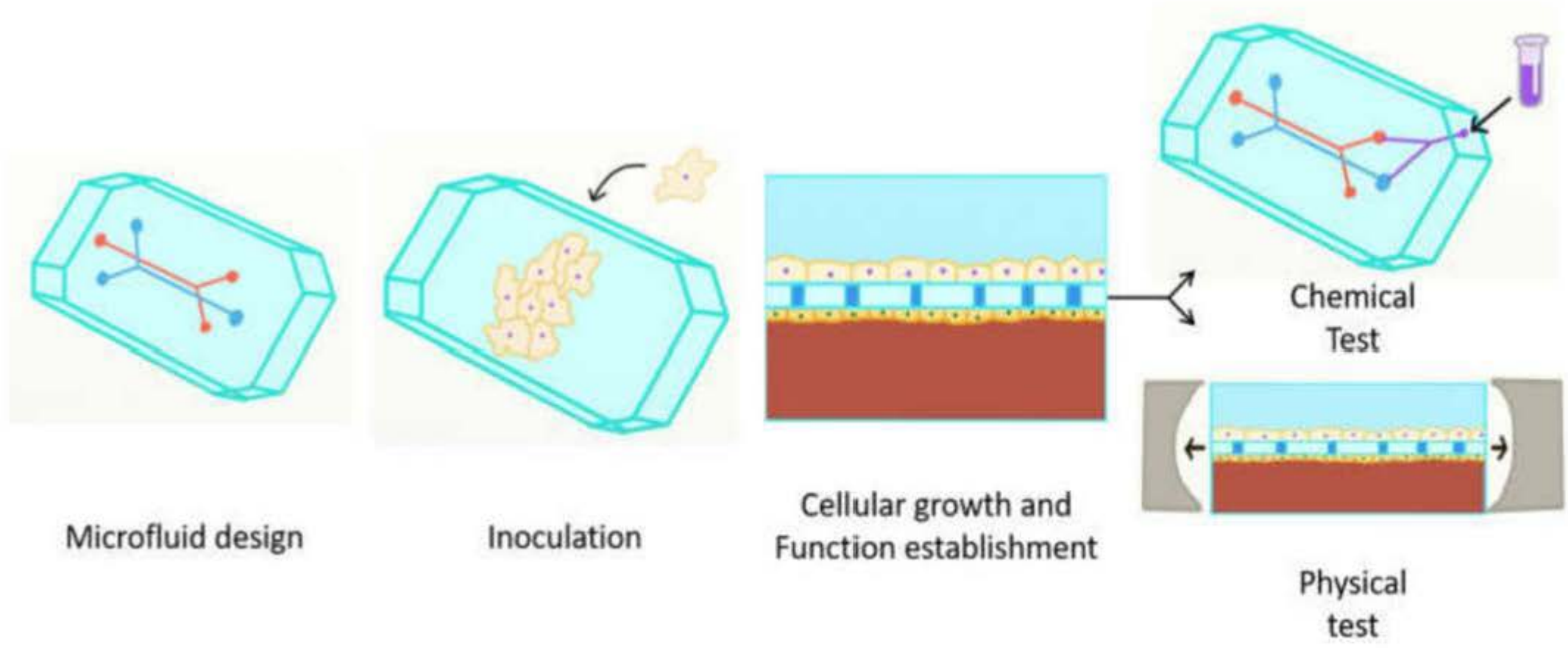

Sosa-Hernandez et al. Micromachines (Basel). 2018 Oct; 9(10): 536. Published online 2018 Oct 22. doi: 10.3390/mi9100536

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Material	Relevant Property	Proposed Application	Reference
Collagen (Chitosan)	Biocompatibility, versatile control of structure and chemistry	Bio-sensing, film assembly	[21,22]
Silkworm (*Bombyx mori*)	Biocompatibility, mechanically robust, flexibility, high mechanical modulus, and toughness	Fabrication of microfluidic channel	[23,24]
Agarose hydrogel	Lox cytotoxicity, biodegradability, mechanical stability at low solid fractions	Cell culture, sensors, and actuators	[25–27]
Teflon	Ease of fabrication with maximum chemical resistance	High precision assay, super clean tools, valves, and pumps fabrication	[28]
Acrylonitrile Butadiene Styrene (ABS)	High resolution, excellent surface finish	Making of the master mold, microfluidics interface (MI), pathogen detection, biological assay	[29–34]
Photocurable resin/polymer	Very high resolution with small features	Biology observation of cell growth	[35,36]
ABS, polycarbonate, polyphenylsulfone, elastomers	Cheap material, ease of support removal	Pathogen detection of bacteria and viruses	[37,38]
Polyamide	Fast build speed, multi-material printing, very durable and high-temperature stable material	Making of the master mold	[39,40]
Hydrogels	Swelling and contraction, act as sensors and actuators	Self-regulating valves, microlens arrays, drug release systems, binding of antigens and proteins and glucose. Flow sensors pH regulators, flooding cooling devices.	[29,41,42]
Polyurethane-methacrylate (PUMA)	Economical to manufacture, biocompatible, nontoxic, strong electroosmotic mobility	High-aspect-ratio microstructures	[43]
Polyethylene glycols (PEGs)	Relatively inexpensive, available in a wide variety of molecular weights, biocompatible, negligible cytotoxicity	Microfluidic valves, Channel cover to improve the microfluidic lifetime	[44,45]
Polyhydroxyalkanoates (PHAs)	Biocompatibility, tunable biodegradability	Microfilm barrier for vapor and oxygen	[46]
Gelatin methacrylate (gel-MA)	Photopolymerizable, porous membrane	Mechanistic vascular and valvular biology cell support matrix	[47,48]
Polylactic acid (PLA) and Polyglycolic acid (PGA)	Tunable biodegradation	Porous scaffold for cell culture with better adhesion	[49]
Poly(polyol sebacate) (PPS)	Biocompatibility, design adaptability, mechanical compliance, low cytotoxicity, degradability	3-D microfluidic system, Microbioreactor	[50]
Poly(ethylene glycol) diacrylate (PEGDA) and gelatin methacryløyl (GelMA)	Biocompatibility, neovascularization potential, multi-material fabrication capability at a high spatial resolution	Tissue engineering, regenerative medicine, and bio-sensing	[51]
Poly(methyl methacrylate)	Favorable mechanical and thermal resistance, chemical compatibility	Genomic analysis	[52]
Styrene Ethylene Butylene Styrene (SEBS)	Biocompatibility, Rheological characteristics	Fabrication of complex and more sophisticated microfluidic networks (μFNs)	[53]
Styrene Ethylene Butylene Styrene (SEBS)	Electrical surface properties, stable and relatively high zeta potential magnitude	Microdevices for Electrokinetic Applications	[54]
Styrene Ethylene Butylene Styrene (SEBS)	Reduced drug absorption, Optical transmittance, Mechanical performance	Cell culture	[55]

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National Center for Advancing Translational Sciences

Tissue Chip Testing Centers

Texas A&M University, College Station

TEX-VAL: Texas A&M Tissue Chip Validation Center

Massachusetts Institute of Technology

"Translational Center of Tissue Chip Technologies" for Quantitative Characterization of Microphysiological

University of Pittsburgh

University of Pittsburgh Microphysiological Systems Testing Database Center

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SCIENTIFIC REPORTS

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Technology Transfer of the Microphysiological Systems: A Case Study of the Human Proximal Tubule Tissue Chip

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Published online: 05 October 2018

Courtney Sakolish[1], Elijah J. Weber[2], Edward J. Kelly[2], Jonathan Himmelfarb[3], Roula Mouneimne[1], Fabian A. Grimm[1], John S. House[4], Terry Wade[5], Arum Han[6,7], Weihsueh A. Chiu[1] & Ivan Rusyn[1]

2D and 3D platforms

University of Pittsburgh Drug Discovery Institute
Microphysiology Systems Database (https://mps.csb.pitt.edu/).

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Internal

External

Duration

- Set up time including cells
- Viability
- Activity / metabolic functionality

System

- Cell composition
- Physiological function
- Capacity
- Maintenance level
- Throughput
- Space requirements
- Equipment requirements
- Microfluidics
- Controls

Abilities

- Sampling
  - -Frequency (some systems do not allow for daily sampling)
  - -Type (liquid, histology)
- Imaging
  - -In situ

Testing Parameters

- Cell sourcing including commercial versus non-commercial
- Media sourcing including commercial versus non-commercial

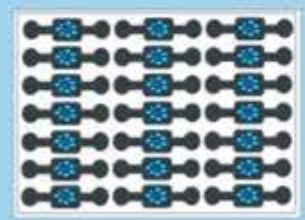
Testing

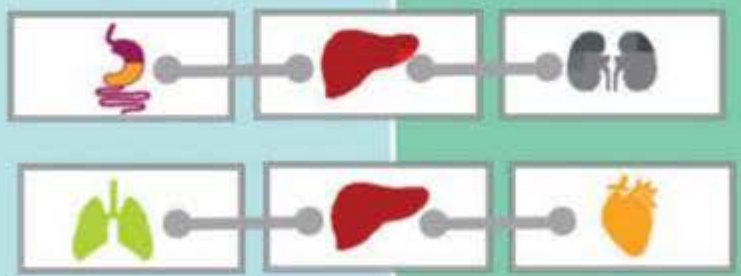
- Protein and gene expression
- Reproducibility level
- Comparisons
  - -2D systems
  - -In vivo models
- Baseline function assays
- Toxicity assays
- In vitro to in vivo extrapolations

Restrictions

- In house only
- Limited cell types

Drug Development	Target ID and Validation	Lead Identification	Lead Optimisation	Preclinical Safety
Testing Requirements	**Hazard Identification**	**Risk Assessment**	**Mechanism of Action**	**Risk Mitigation**
	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
Tissue Chip context of use	Mechanistic understanding or safety profiling	Linked organs e.g. for drug distribution		Boutique individual organs for mechanism or safety





Ewart et al. Exp Biol Med (Maywood). 2017 Oct; 242(16): 1579–1585. Published online 2017 Jun 16. doi: 10.1177/1535370217715441

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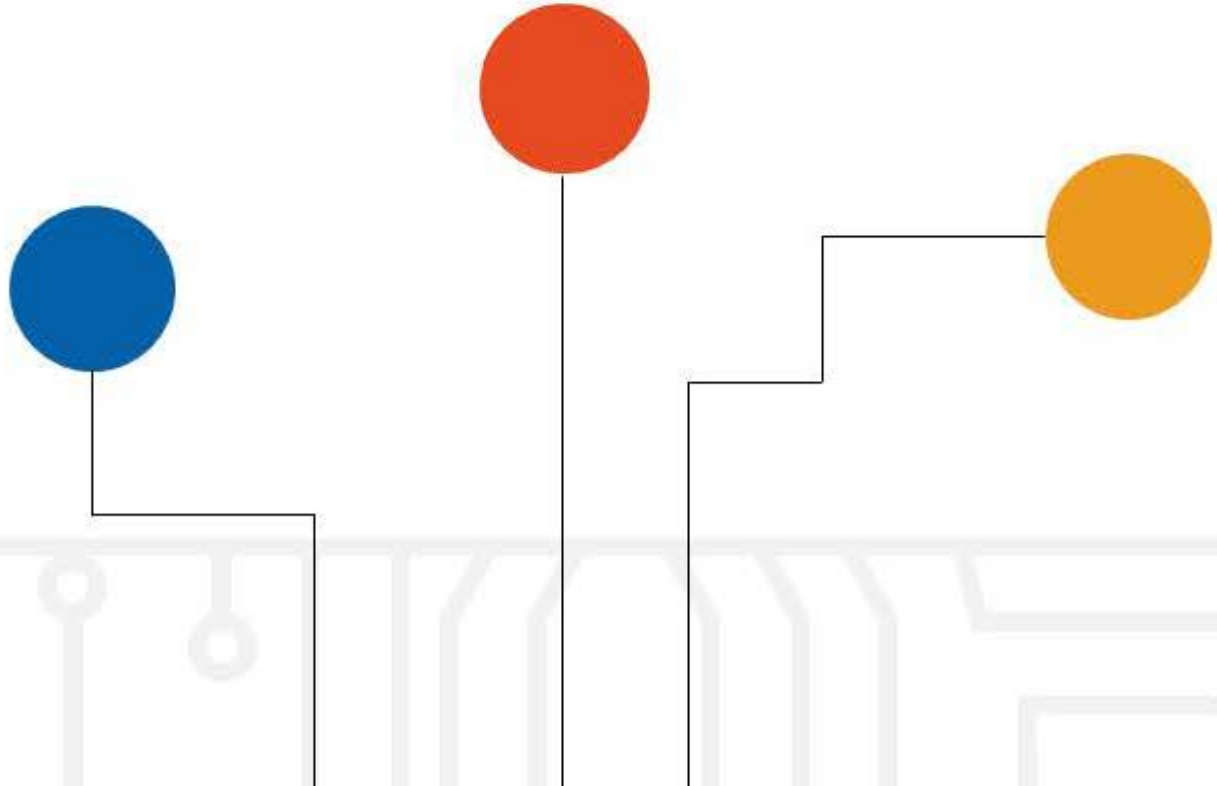
Precision medicine

Orphan diseases

Nanomedicine



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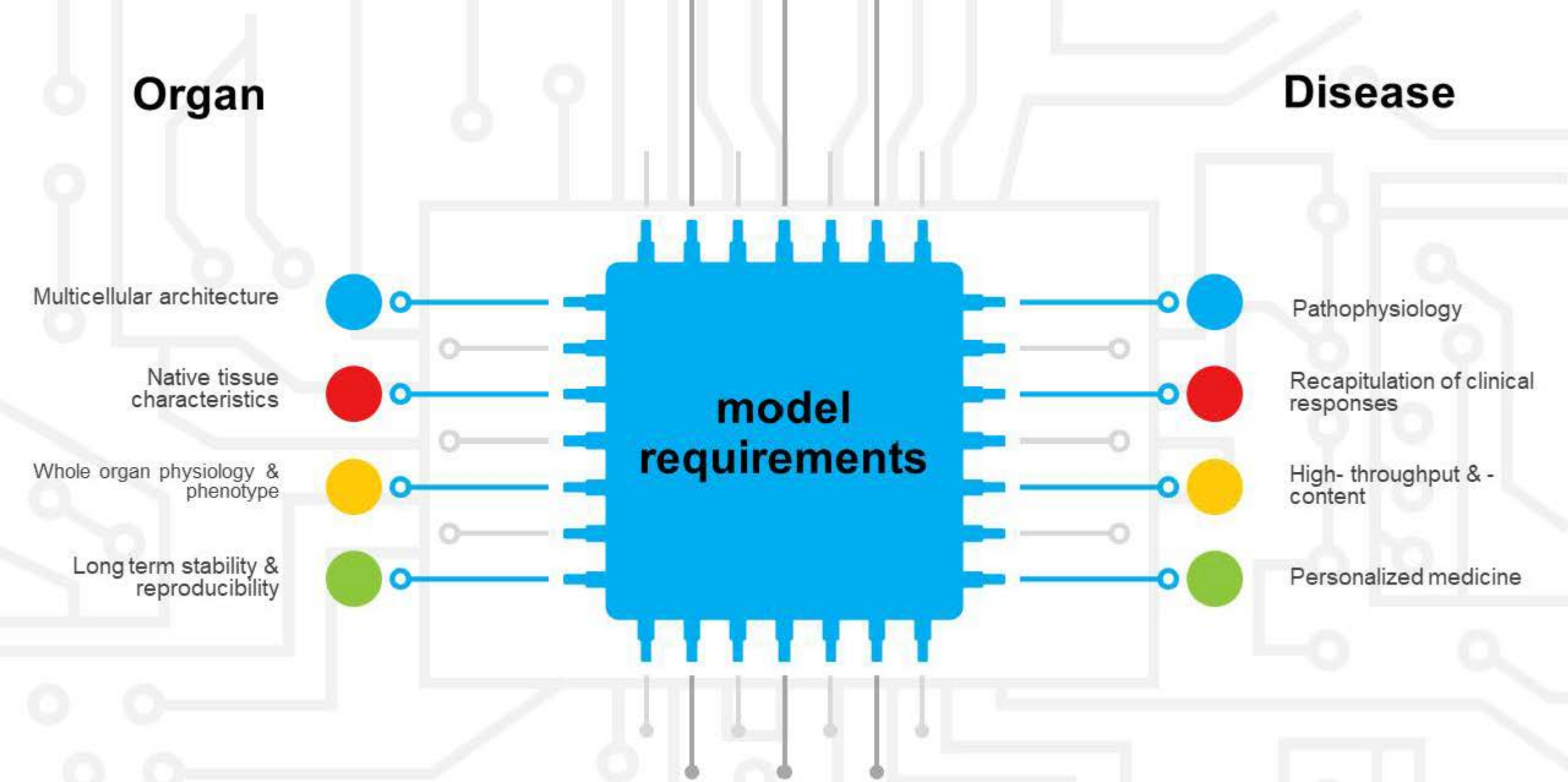
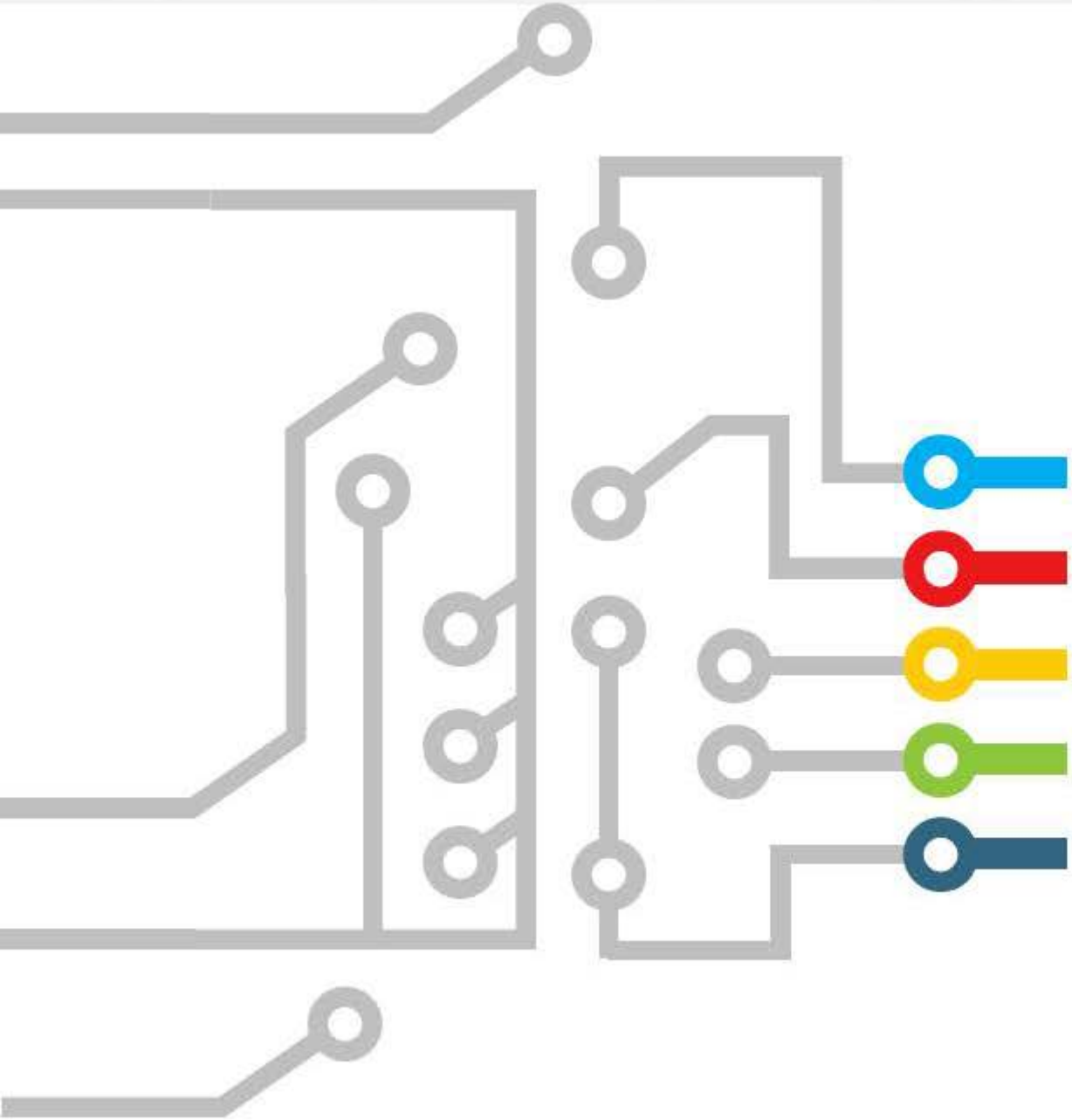


Adopted from Rothbauer M et al. Curr Opin Biotechnol. 2019 Feb;55:81-86. doi: 10.1016/j.copbio.2018.08.009. Epub 2018 Sep 4



Materials

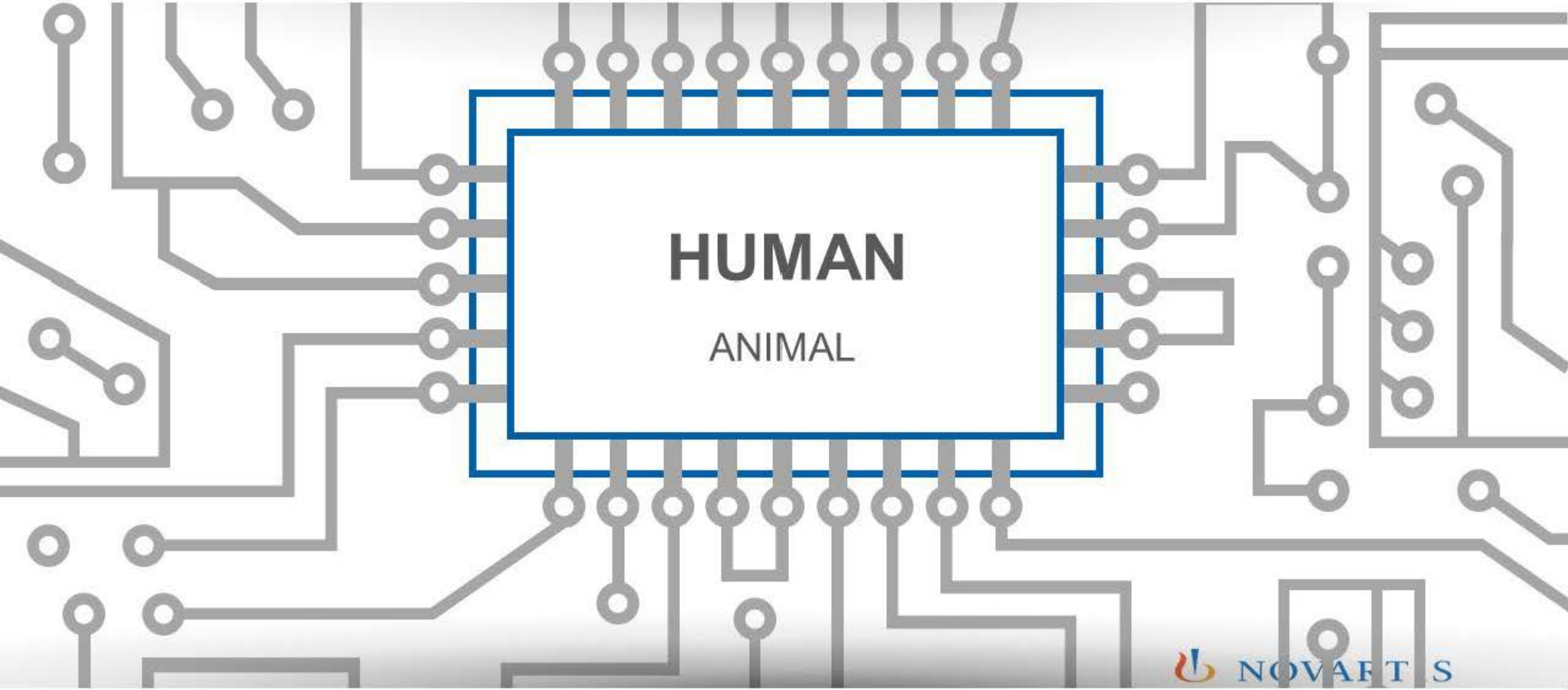
Large-scale manufacturing

Cells and media

Samples for analysis

Readouts

Species?



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COMPLEXITY
PRACTICALITY


IN
CHIPS
SPACE
NCATS
NIBIB
CASIS

Reproducibility

Robustness

Relevance

Reliability

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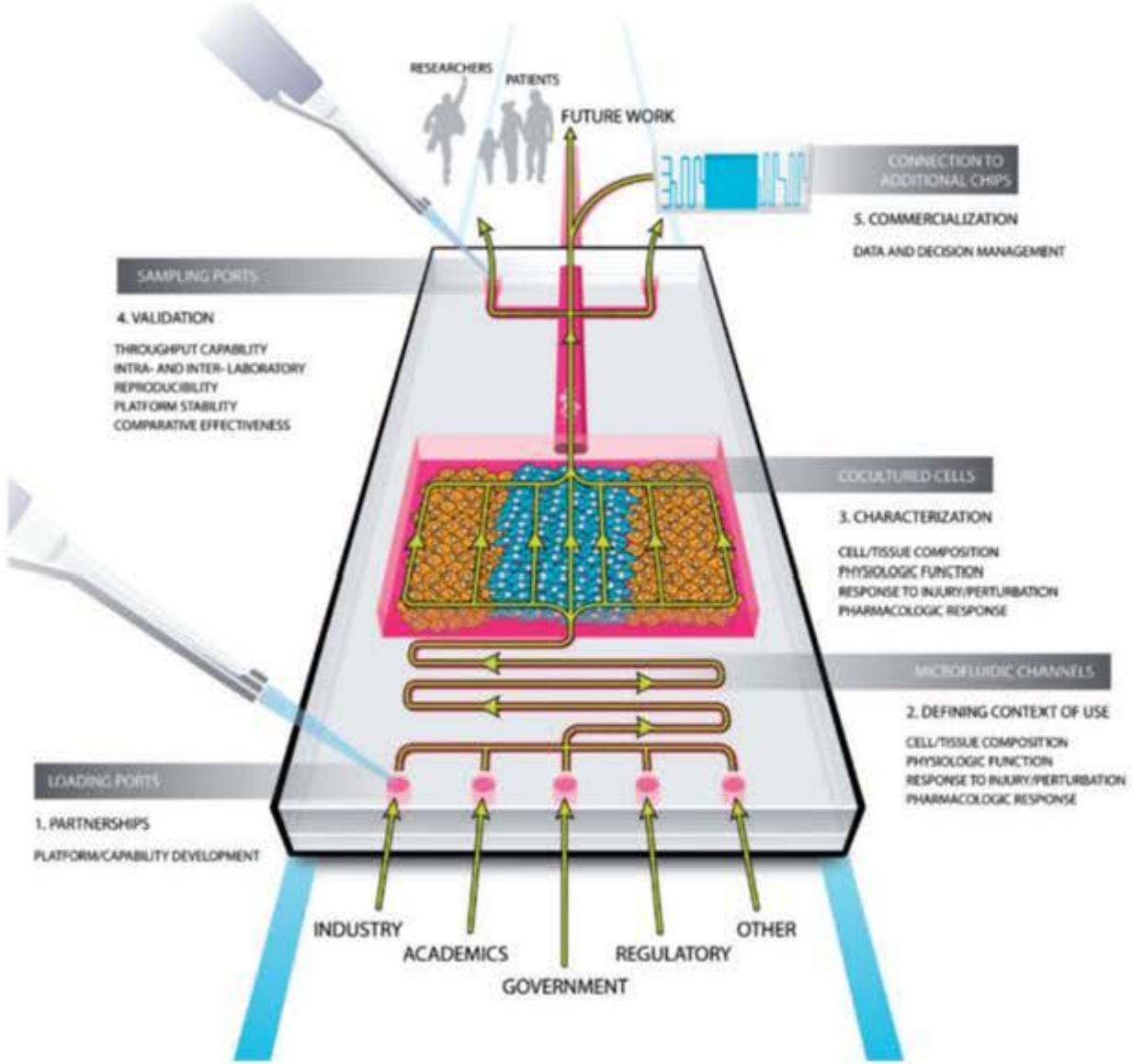

Navigating tissue chips from development to dissemination: A pharmaceutical industry perspective

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