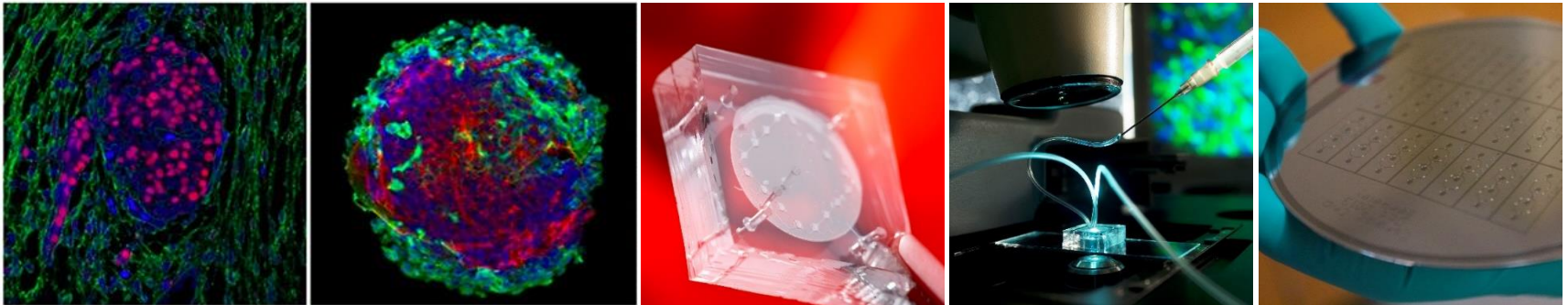


Microphysiological systems as next-generation in vitro models

Jun.-Prof. Dr. Peter Loskill,

Department für Frauengesundheit, Forschungsinstitut für Frauengesundheit am
Universitätsklinikum Tübingen

Fraunhofer Institut für Grenzflächen und Bioverfahrenstechnik IGB
Stuttgart, Germany





TagesAnzeiger

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Medizin & Psychologie Natur Technik Geschichte Weiterbildung Bildstreifen

Miniature devices that mimic human organs could help to replace

BIOTECHNOLOGY

'Organs-on-chip' go mainstream

Drug companies put in vitro systems

Wie Mini-Organ Tierversuche vermindern sollen

Forscher tüfteln an sogenannten Organen auf Chips: Mini-Labore aus Kunststoff, die den menschlichen Körper simulieren. Davon erhofft man sich einiges.

Martina Huber
und Sandra
Niemann

05.12.2016

Facebook
(113)

Twitter (5)

Jede Minute atmen wir 10- bis 15-mal ein und aus, im Verlauf eines Tages ziehen wir 10'000 bis 15'000 Liter Luft durch die Luftröhre und in die immer feiner verzweigten Bronchien hinab bis in die Lungenbläschen, wo der lebensnotwendige Gasaustausch stattfindet: Sauerstoff wird durch die Wände der Lungenbläschen ins Blut aufgenommen, CO₂ in die Atemluft abgegeben.

Infografik: Von der Lunge zum «atmenden» Chip 1

Artikel zum Thema

Der Unmut über Tierversuche wächst



Eine neue Umfrage zeigt, dass in der Bevölkerung Tierversuche immer weniger Rückhalt haben. Bei Versuchen für Alltagsprodukte wie zum Beispiel Spülmittel sei der Gesetzgeber zu lausch. Mehr...
07.11.2013

Über 600'000 Tierversuche in einem Jahr

Die strengereren Auflagen zeigen Wirkung: Die Zahl der Tierversuche hat letztes Jahr in der Schweiz um 8,4 Prozent abgenommen. Es sind jedoch immer noch Hunderttausende. Mehr...
03.07.2013

Die Redaktion auf Twitter

Stets informiert und aktuell. Folgen Sie uns auf dem Kurznachrichtendienst.

@tagesanzeiger



Cyberorganen: een medische revolutie in wording

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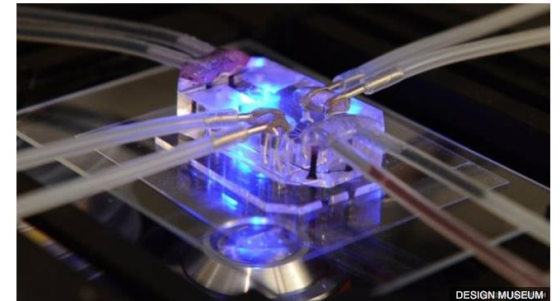
Health

'Organs-on-chips' wins design award

By James Gallagher
Health editor, BBC News website

23 June 2015 | Health

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Silicon chips that mimic the function of living human organs have won the Design of the Year award from the Design Museum in London.

SPIEGEL ONLINE DER SPIEGEL SPIEGEL TV



Anmelden

WISSENSCHAFT

Schlagzeilen

Wetter

DAX 12.257,20

TV-Programm

Abo

Nachrichten > Wissenschaft > Medizin > Medizin > Mini-Chips: Computer-Organ für Medikamententests

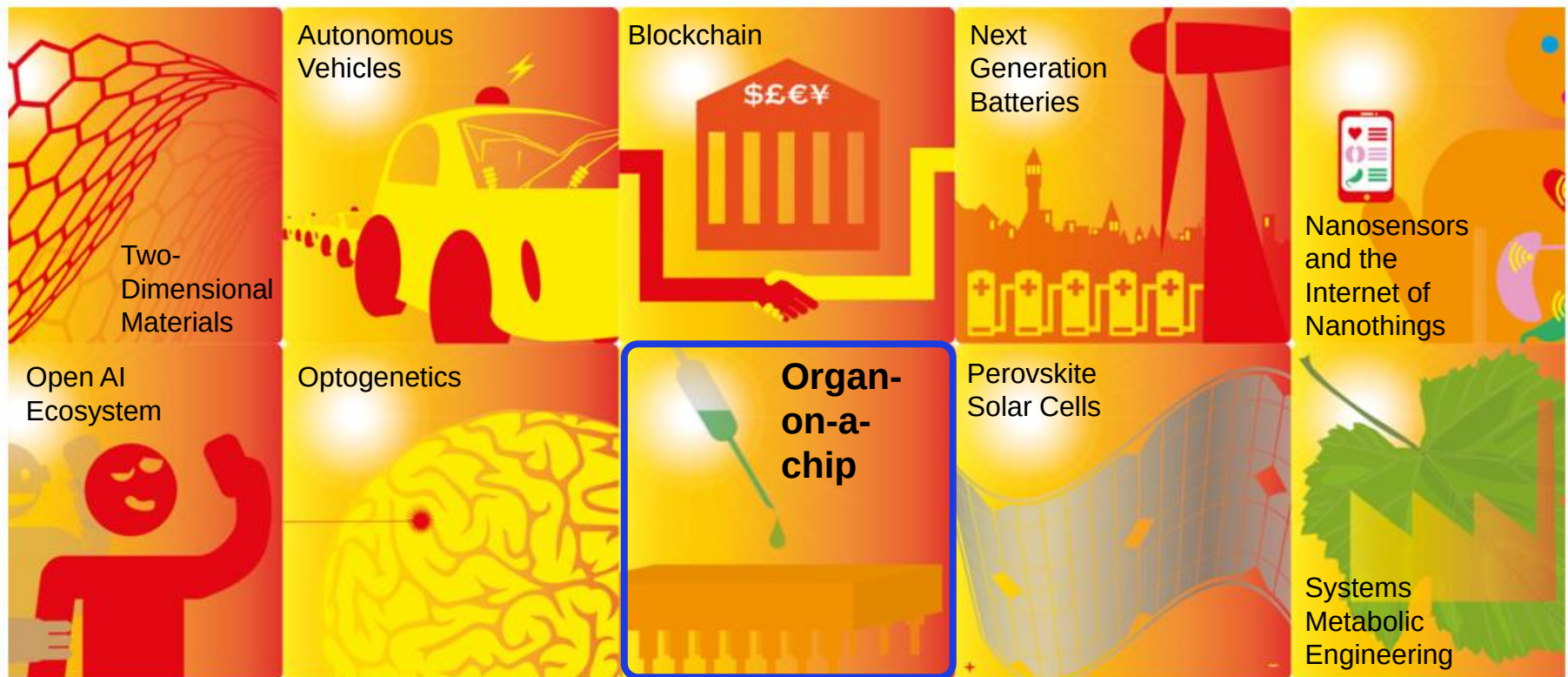
Medikamententests

Forscher basteln am menschlichen Computer-Dummy

Hirn, Leber, Niere: Wissenschaftler bauen menschliche Organe als Computerchips nach. Die Miniaturen sollen Tierversuche bei Medikamententests überflüssig machen - und dabei helfen, Depression, Alzheimer oder Parkinson zu besiegen.

Von Sascha Karberg

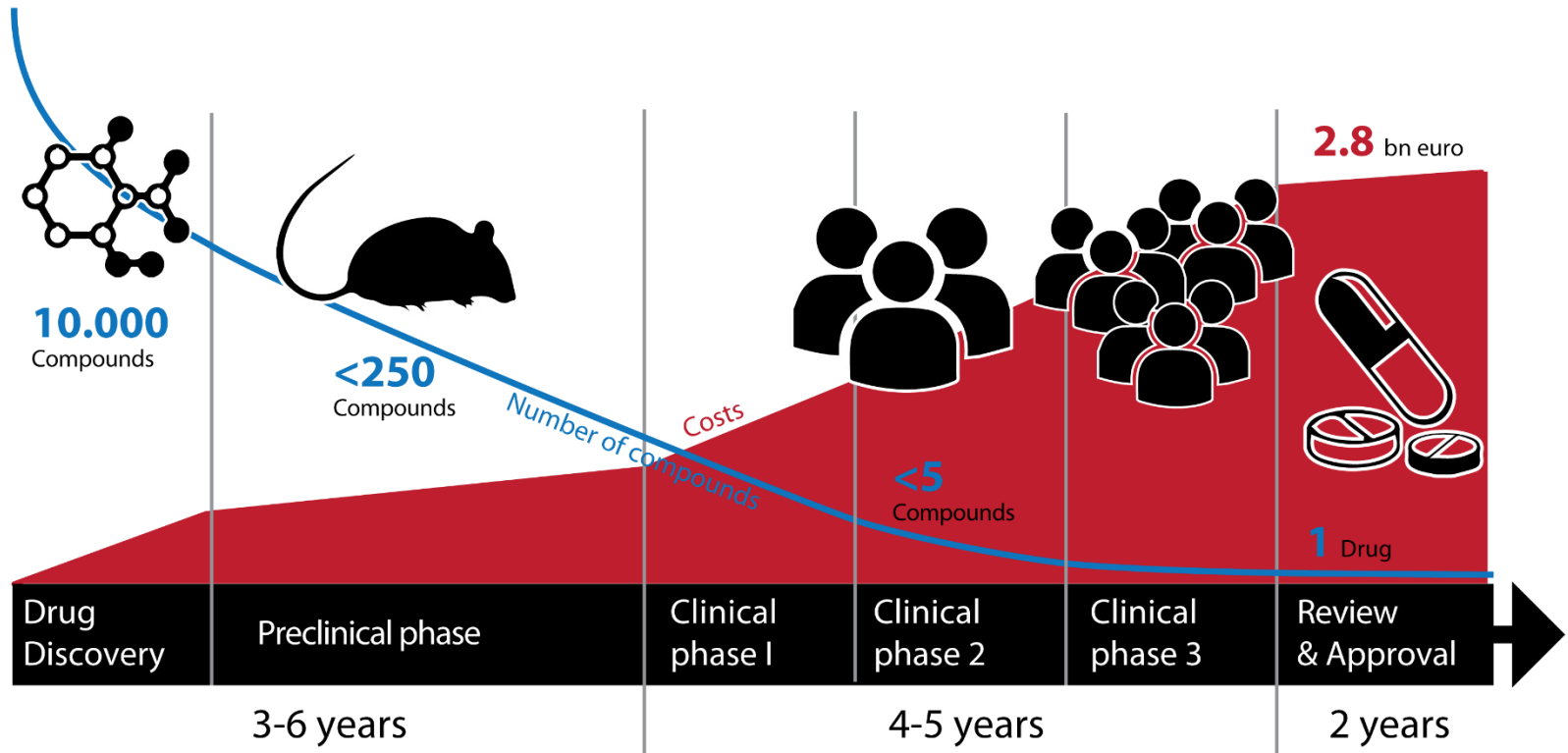
These are the top 10 emerging technologies of 2016



Aims for today

1. Get an introduction into the general concept of the pharmaceutical drug development process
2. Learn about preclinical model systems
3. Understand the underlying concepts of microphysiological systems
4. Get an overview over existing Organ-on-a-chip approaches

Drug development pipeline



A. Mosig, J. Nawroth, P. Loskill DZKF (2017)

- Extremely long process: approx. 10 - 12 years
- Extremely inefficient: 10 000 compounds → 1 drug
- Extremely expensive: >1 bil. €

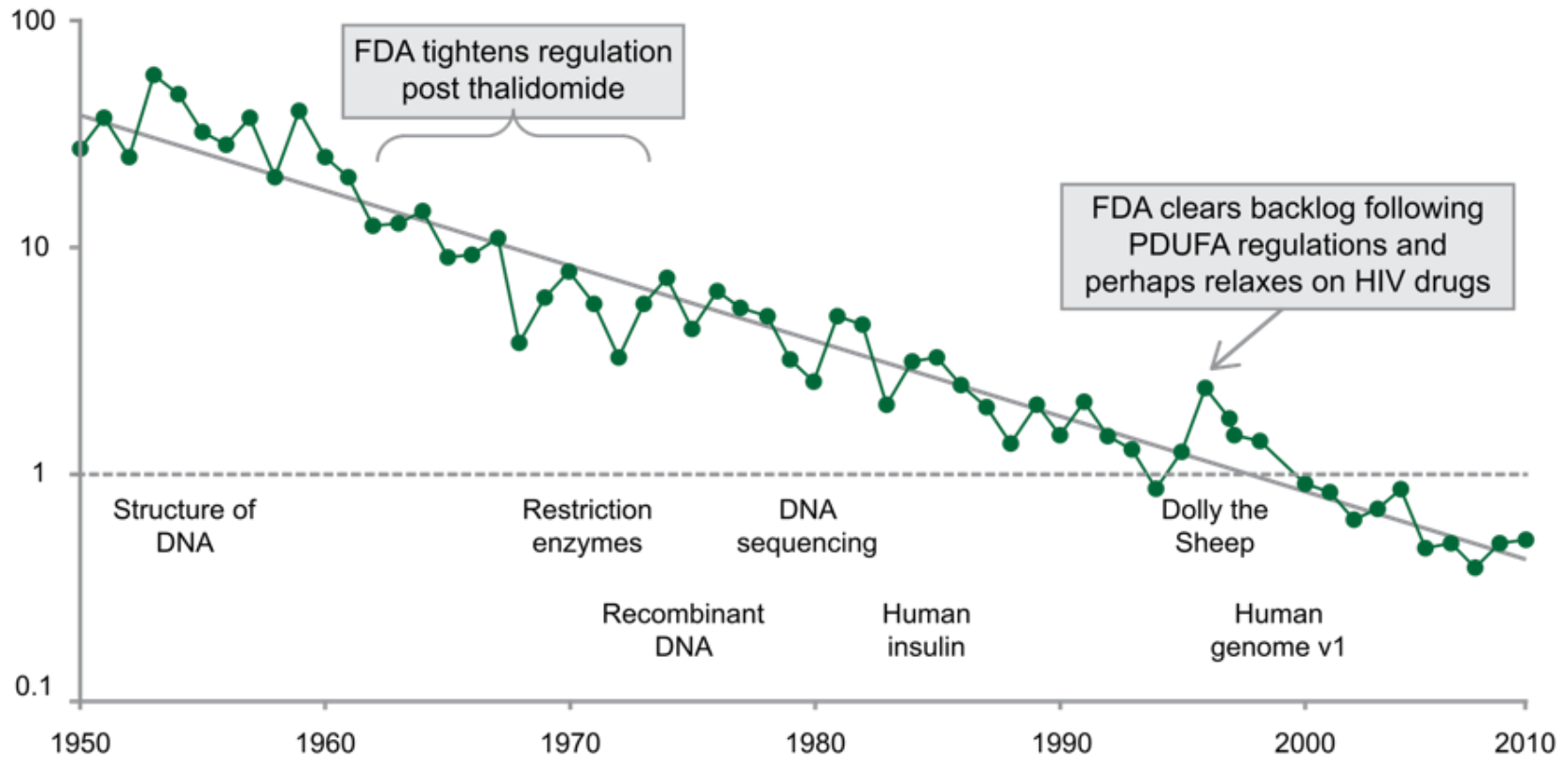
Drug development

Company	Number of new drugs	10 year R&D expenses (bil. \$)	R&D costs per drug (bil. \$)
Abbott	1	13,183	13,183
Sanofi	6	60,760	10,128
AstraZeneca	4	38,245	9,561
Hoffmann-La Roche	8	70,928	8,866
Pfizer	10	77,786	7,779
Wyeth	3	22,702	7,567
Eil Lily	4	26,710	6,678
Bayer	5	33,118	6,624
Schering-Plough	3	18,845	6,282
Novartis	10	60,727	6,073

Herper, M., Forbes, 8/11/13

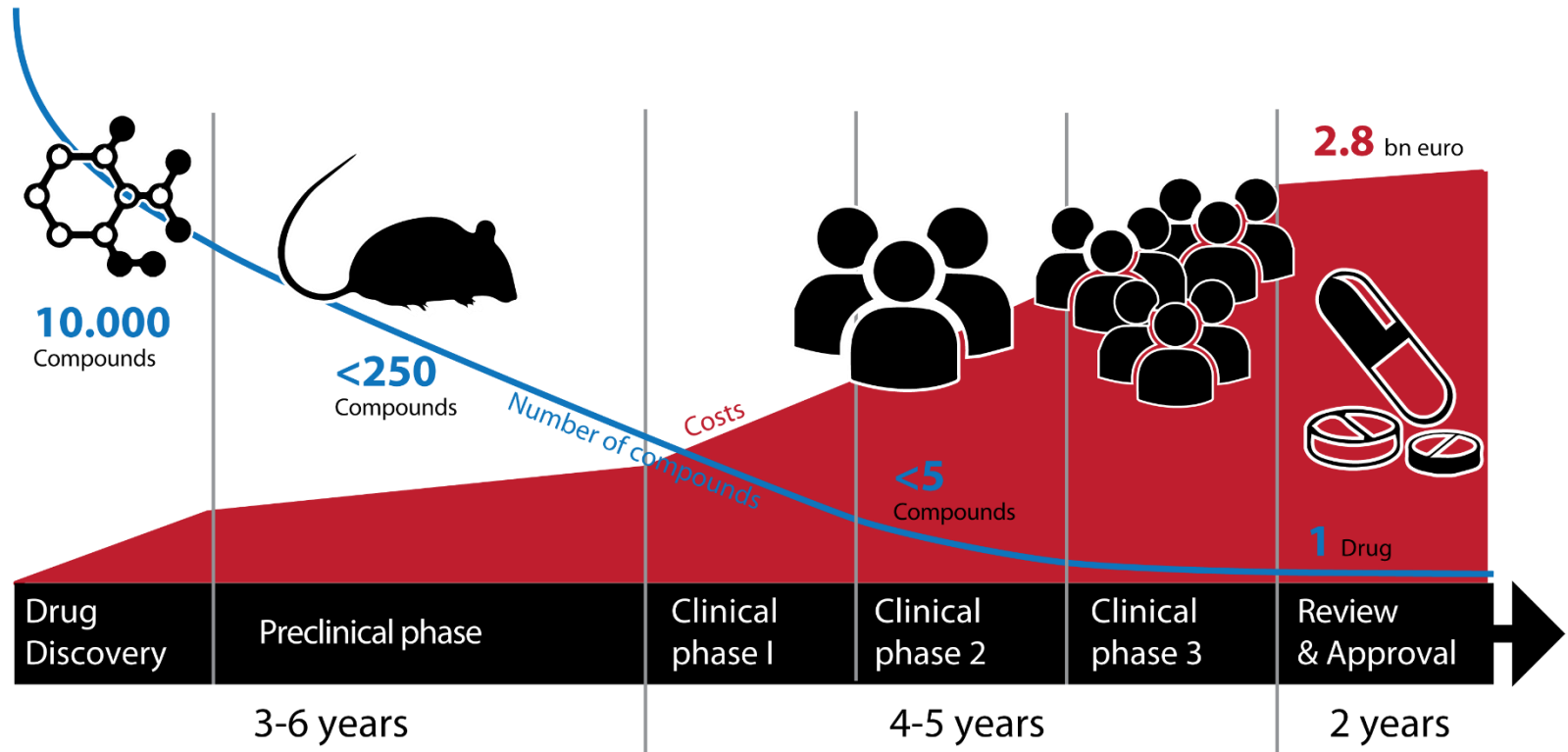
Drug development

Number of new Medical entities (NME) per bil. \$ R&D expenses (corrected for inflation)



■ „EROOM’s law“ – Continuous decline in productivity over the last decades

Transition from preclinical into clinical phases

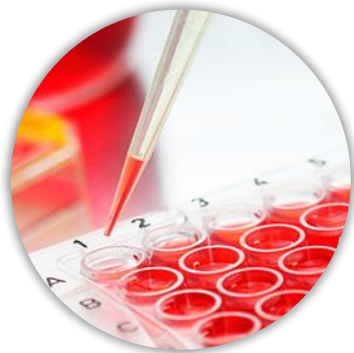


A. Mosig, J. Nawroth, P. Loskill DZKF (2017)

- Extremely important transition, yet inefficient and problematic
- Slight increase in predictability → > 200 Mio \$ cost saving per drug

Preclinical research

*"Education is what survives
when what you have learned
is forgotten" (B.F. Skinner)*



Cell assays



Animal models

➡ What are the advantages and
limitations of those models

Your task:

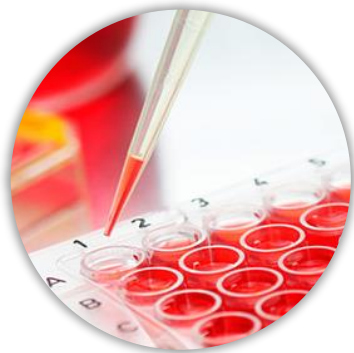
1. Brainstorm for 5 minutes
2. Discuss your ideas with your neighbor(s) for 5 minutes

Preclinical research

"Education is what survives
when what you have learned
is forgotten" (B.F. Skinner)

Cell	Animal
human	similar genome
wrong biomechanical environment	complex tissues + circulation
automation	different sizes
small	multiple species necessary
cheap	diff. behaviour
(no) ethical concerns	behaviour effects
standardization	complicated analysis
non-phys. monoculture	variability
+ environment	
less administrative	
no long-term effects	

Preclinical research



Cell assays

- ✓ Human genetic background
- ✓ Standardized & automated
- ✓ Cost efficient
- ✗ No perfusion
- ✗ No mechanical forces
- ✗ Cell to media ratio too low
- ✗ 2D (mono-)cultures of (cancer) cells on hard plastic

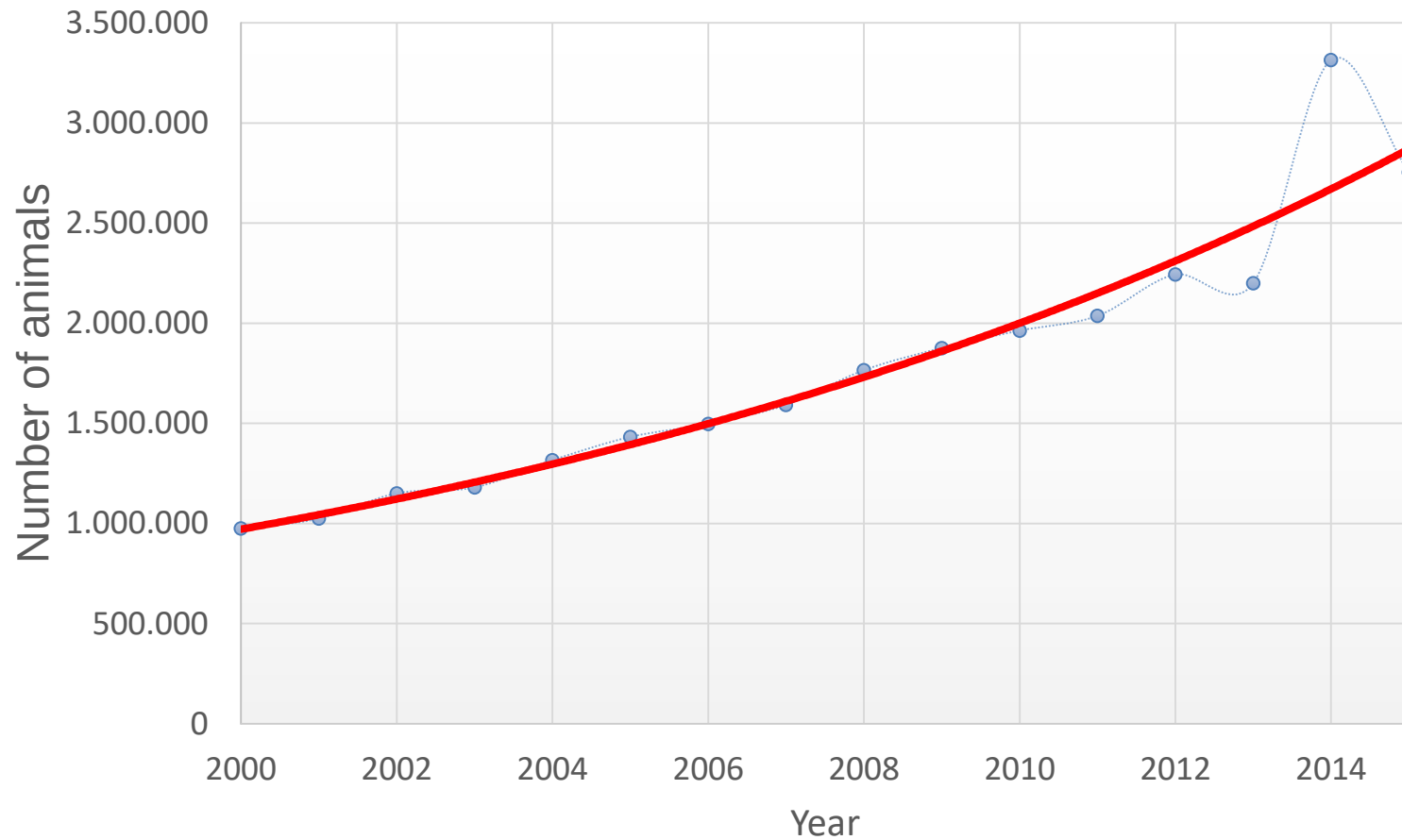


Animal models

- ✓ Complex tissue architecture
- ✓ Circulation
- ✓ Systemic effects
- ✗ Different physiology
- ✗ Different immune system
- ✗ Specific environment & diet
- ✗ Strain-specific results due to (in)breeding

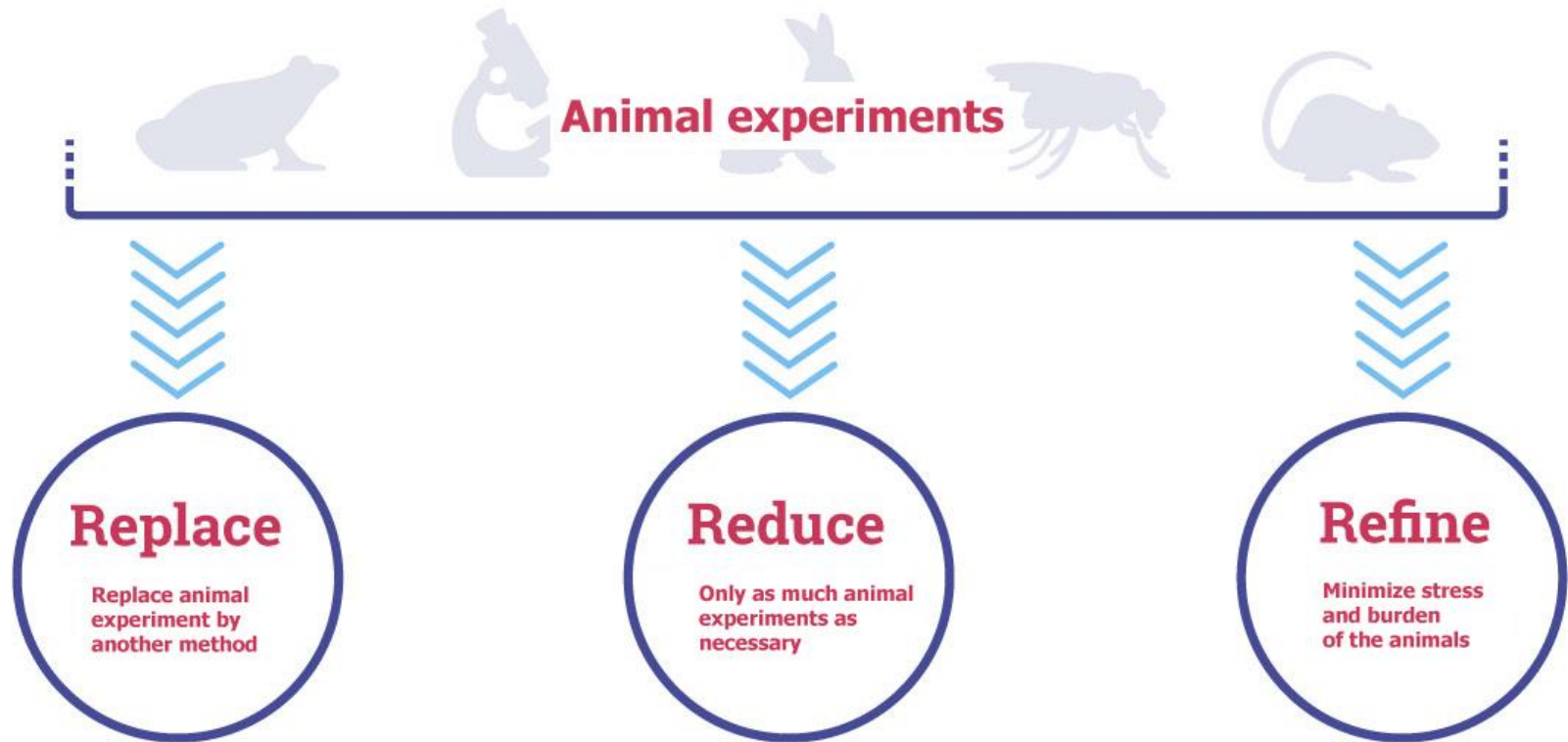
Animal models

Animal experimentation in Germany (Source BMEL)



Animal models

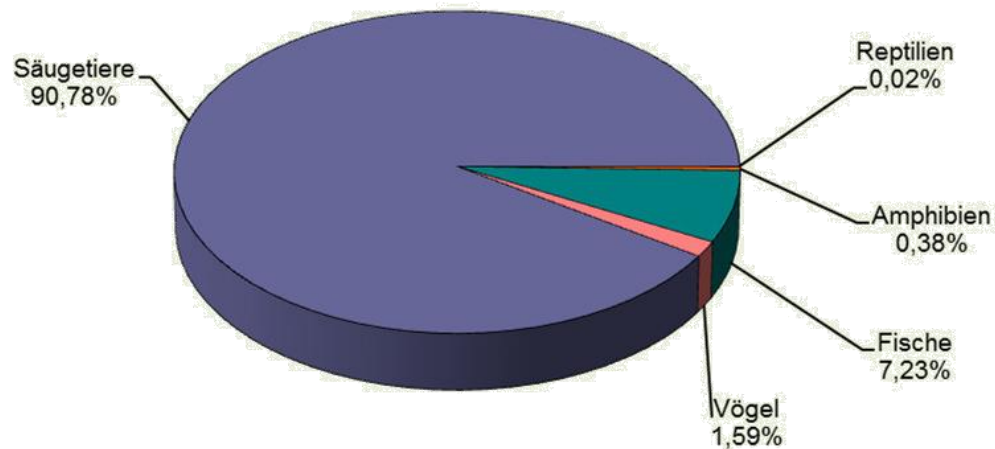
What exactly is the definition of the 3R-Principle



Quelle: Deutsches Zentrum zum Schutz von Versuchstieren (bf3R), 2015

William Russel & Rex Burch (1959) „The Principles of Humane Experimental Technique”

Animal models



Säugetiere	Tierzahlen
Rodents	2.396.475
Rabbits	111.718
Carnivores	6.526
Equines (Horses...)	1.525
Even-toed ungulates	20.643
Primates	3.141
Further mammals	1.590
Total	2.541.618

Source: BMEL 2017

Animal models - Rodent models



Similarities

- 95% of genes are identical to humans
- Similar organ structure

Advantages

- ✓ Fast breeding
- ✓ Small: Advantageous in terms of housing and facility size

Disadvantages

- ✗ Specific environment and diet
- ✗ Different immune system / strategies to fight infections and injuries
- ✗ Different physiology (heart rate 500 – 700 bpm)
- ✗ Strain-specific results due to breeding

Animal models - Rodent models

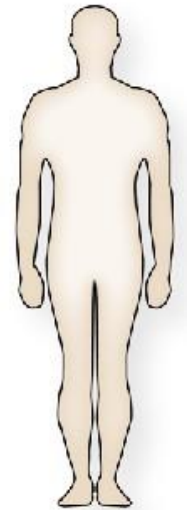
The New York Times

SCIENCE

Mice Fall Short as Test Subjects for Some of Humans' Deadly Ills

By GINA KOLATA FEB. 11, 2013

“But now, researchers report evidence that the mouse model has been totally misleading for at least three major killers—sepsis, burns, and trauma. As a result, **years and billions of dollars have been wasted** following false leads, they say”.

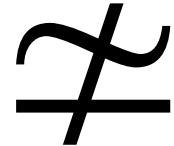


Animal models - Rodent models

PNAS 2013

Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok^{a,1}, H. Shaw Warren^{b,1}, Alex G. Cuenca^{c,1}, Michael N. Mindrinos^a, Henry V. Baker^c, Weihong Xu^a, Daniel R. Richards^d, Grace P. McDonald-Smith^e, Hong Gao^a, Laura Hennessy^f, Celeste C. Finnerty^g, Cecilia M. López^c, Shari Honari^f, Ernest E. Moore^h, Joseph P. Mineiⁱ, Joseph Cuschieri^j, Paul E. Bankey^k, Jeffrey L. Johnson^h, Jason Sperry^l, Avery B. Nathens^m, Timothy R. Billiar^l, Michael A. Westⁿ, Marc G. Jeschke^o, Matthew B. Klein^j, Richard L. Gamelli^p, Nicole S. Gibran^j, Bernard H. Brownstein^q, Carol Miller-Graziano^k, Steve E. Calvano^r, Philip H. Mason^e, J. Perren Cobb^s, Laurence G. Rahme^t, Stephen F. Lowry^{r,2}, Ronald V. Maier^l, Lyle L. Moldawer^c, David N. Herndon^g, Ronald W. Davis^{a,3}, Wenzhong Xiao^{a,t,3}, Ronald G. Tompkins^{t,3}, and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program⁴



PNAS 2014

Genomic responses in mouse models greatly mimic human inflammatory diseases

Keizo Takao^{a,b} and Tsuyoshi Miyakawa^{a,b,c,1}

^aSection of Behavior Patterns, Center for Genetic Analysis of Behavior, National Institute for Physiological Sciences, Okazaki, Aichi 444-8585, Japan; ^bCore Research for Evolutional Science and Technology, Japan Science and Technology Agency, Kawaguchi, Saitama 332-0012, Japan; and ^cDivision of Systems Medical Science, Institute for Comprehensive Medical Science, Fujita Health University, Toyoake, Aichi 470-1192, Japan

Edited by Ruslan Medzhitov, Yale University School of Medicine, New Haven, CT, and approved June 11, 2014 (received for review January 31, 2014)



„It is generally well known and accepted among researchers using animal models that mouse models **mimic only partial aspects of human disorders.**“

Animal models - Rodent models



When Mice Mislead

Couzin-Frankel *Science* (2013)

New stroke therapies:

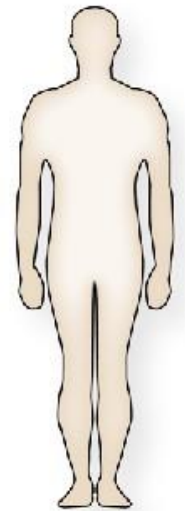
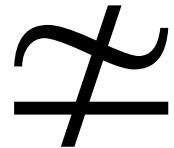
- **603** drugs tested in animals
 - **374** showed positive healing effects
- **97** were tested in humans

➔ **1** worked

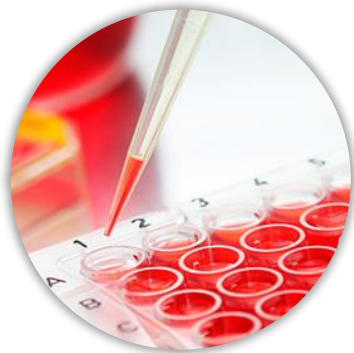
“... wasn’t tested because of animal data at all, but because it had already benefitted patients with heart attacks.”

“The way we do our research with our animals is stone-age.”

—ULRICH DIRNAGL, CHARITÉ UNIVERSITY MEDICINE BERLIN



Preclinical research



Cell assays

- ✓ Human genetic background
- ✓ Standardized & automated
- ✓ Cost efficient
- ✗ No perfusion
- ✗ No mechanical forces
- ✗ Cell to media ratio too low
- ✗ 2D (mono-)cultures of (cancer) cells on hard plastic



Animal models

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Conventional cell culture

Biology on plastic

- Petri dishes, Cell culture flasks, Multiwell plates



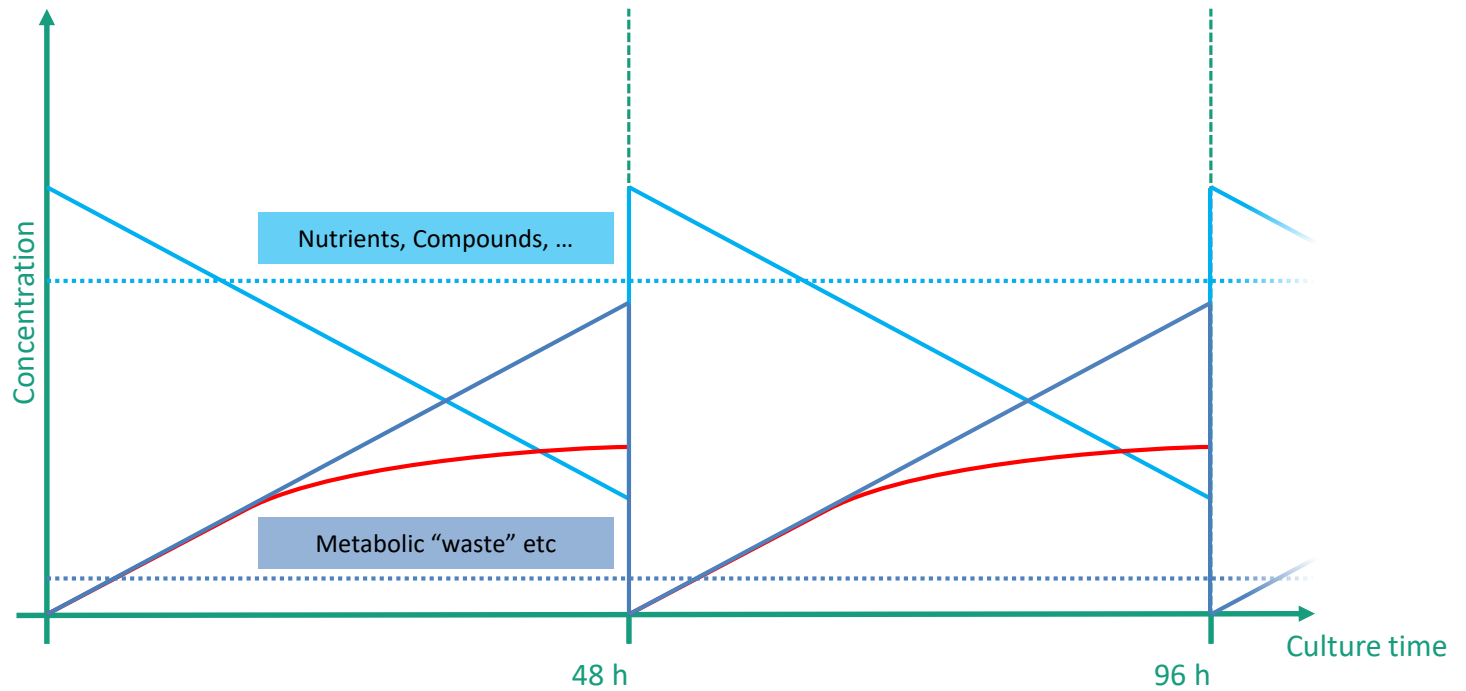
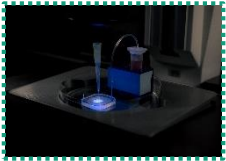
Advantages

- ✓ Standardisable, Automatable, simple handling & logistics, cheap

Disadvantages

- ✗ Monolayers of (cancer)cells on hard plastic
 - ✗ Typically mono cultures
 - ✗ Wrong biomechanical environment
 - ✗ Missing cell-cell / cell-matrix-interactions
- ✗ Lack of perfusion
- ✗ Cell / media ratio magnitudes too low

Conventional cell culture



Conventional cell culture

Biology on plastic

- Petri dishes, Cell culture flasks, Multiwell plates



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- ✗ Lack of perfusion
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“Biologists have constructed an entire, self-consistent biology using monolayer monocultures on plastic.”

—JOHN WIKSWO, VANDERBILT UNIVERSITY, NASHVILLE, USA

Preclinical research



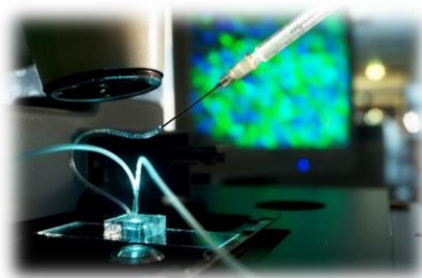
Cell assays

- ✓ Human genetic background
- ✓ Standardized & automated
- ✓ Cost efficient



Animal models

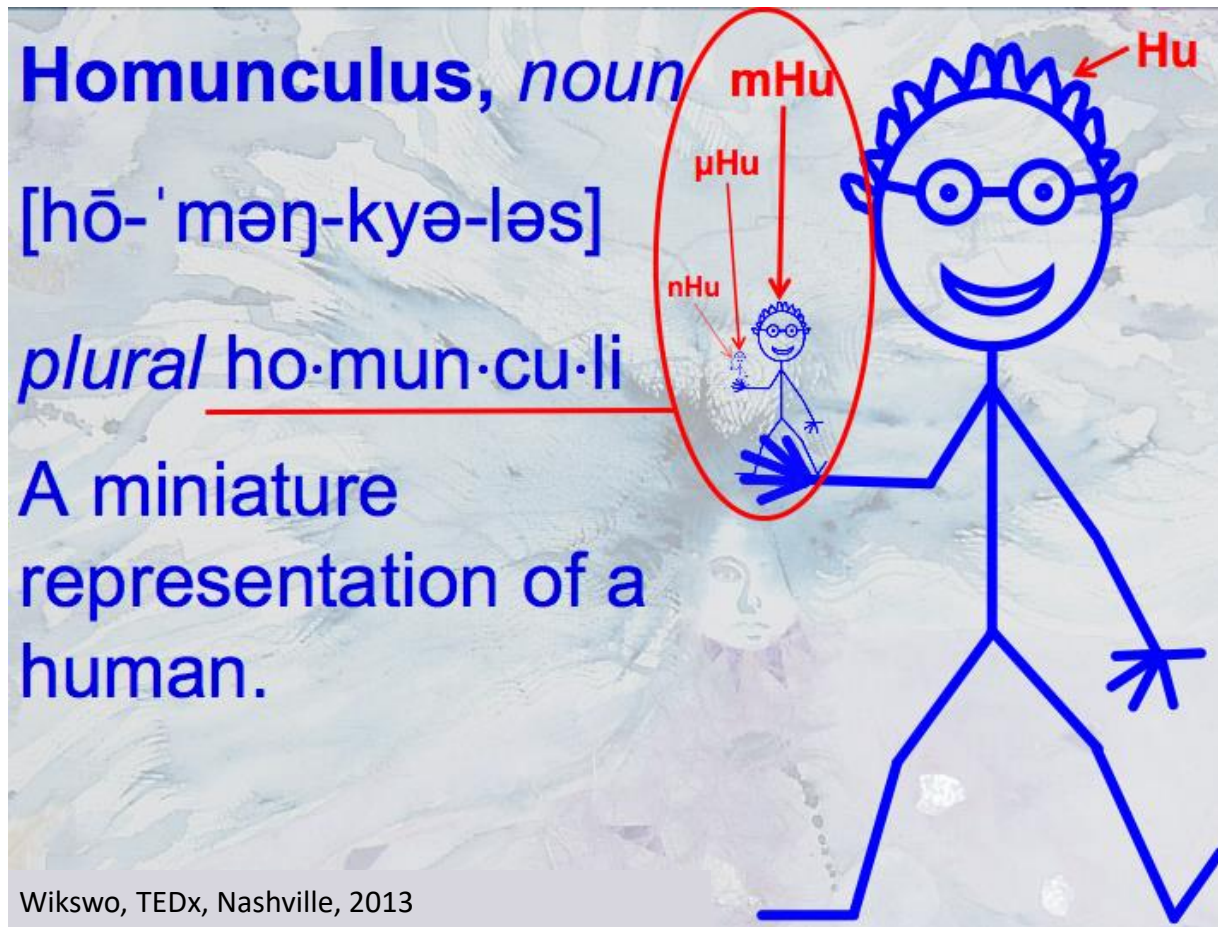
- ✓ Complex tissue architecture
- ✓ Circulation
- ✓ Systemic effects



Organ-on-a-Chip Systems

- ✓ Human engineered tissues
- ✓ *In vivo* structure & function
- ✓ Microphysiological environment

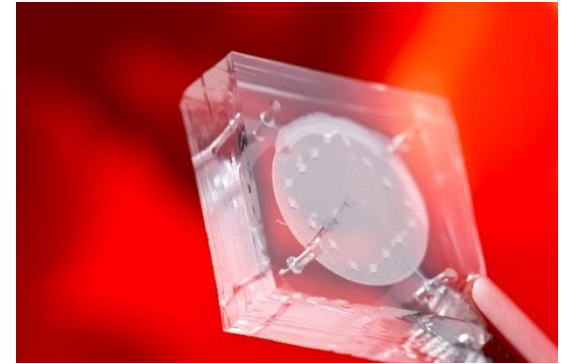
Organ-on-a-Chip



“a fit-for-purpose microfluidic device, containing living engineered organ substructures in a controlled microenvironment, that recapitulates one or more aspects of the organ’s dynamics, functionality and (patho)physiological response in vivo under real-time monitoring”

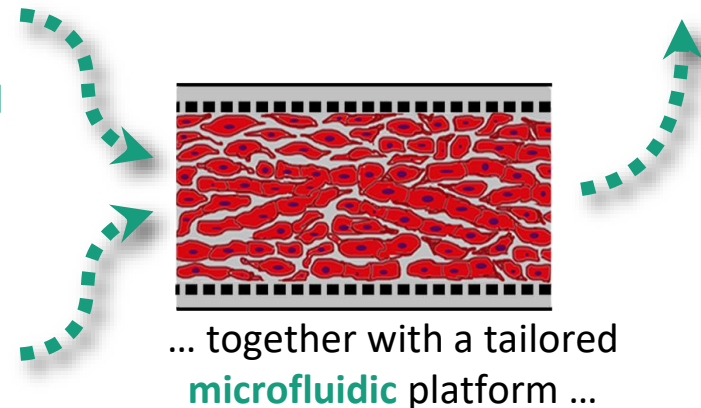
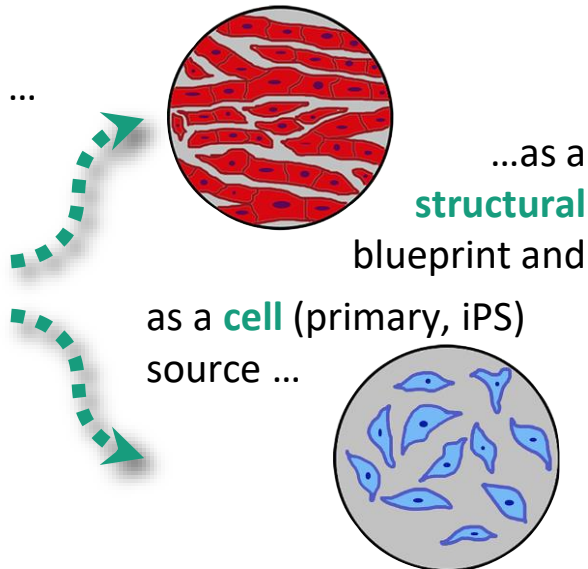
Organ-on-a-Chip

- Human tissue
- In vivo structure & function
- Physiological microenvironment
- Microfluidic perfusion



... yields microphysiological
Organ-on-a-chip systems

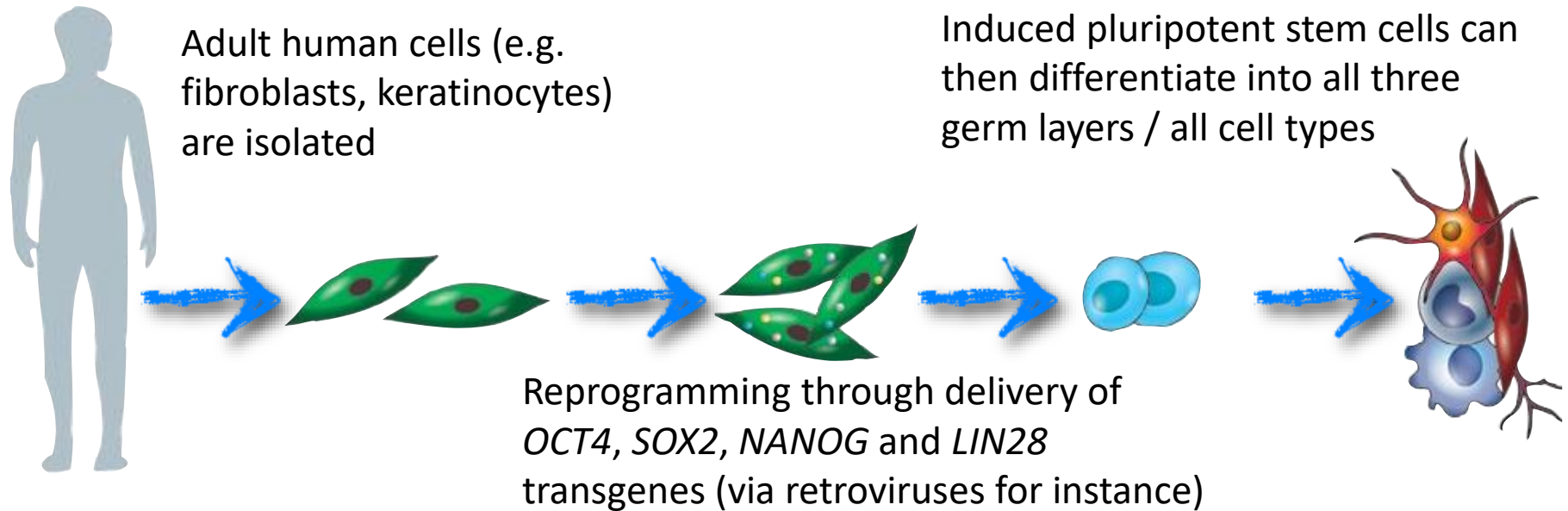
The **human** body ...



A. Mathur, P. Loskill et al., *Stem Cell Res & Ther* (2013)

Induced pluripotent stem cells

- Nobel prize 2012: Shinya Yamanaka, Gladstone Institutes
- Enable patient and disease-specific engineered tissues

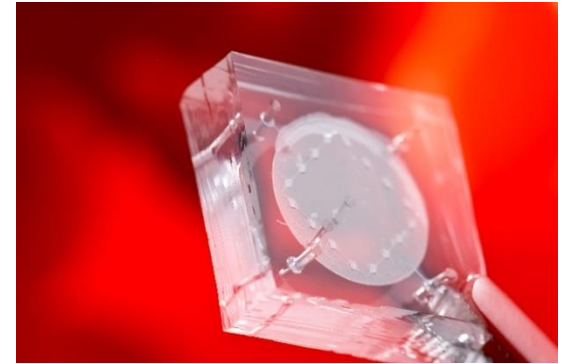


S. Yamanaka, *Cell* 137, 13 (2009)

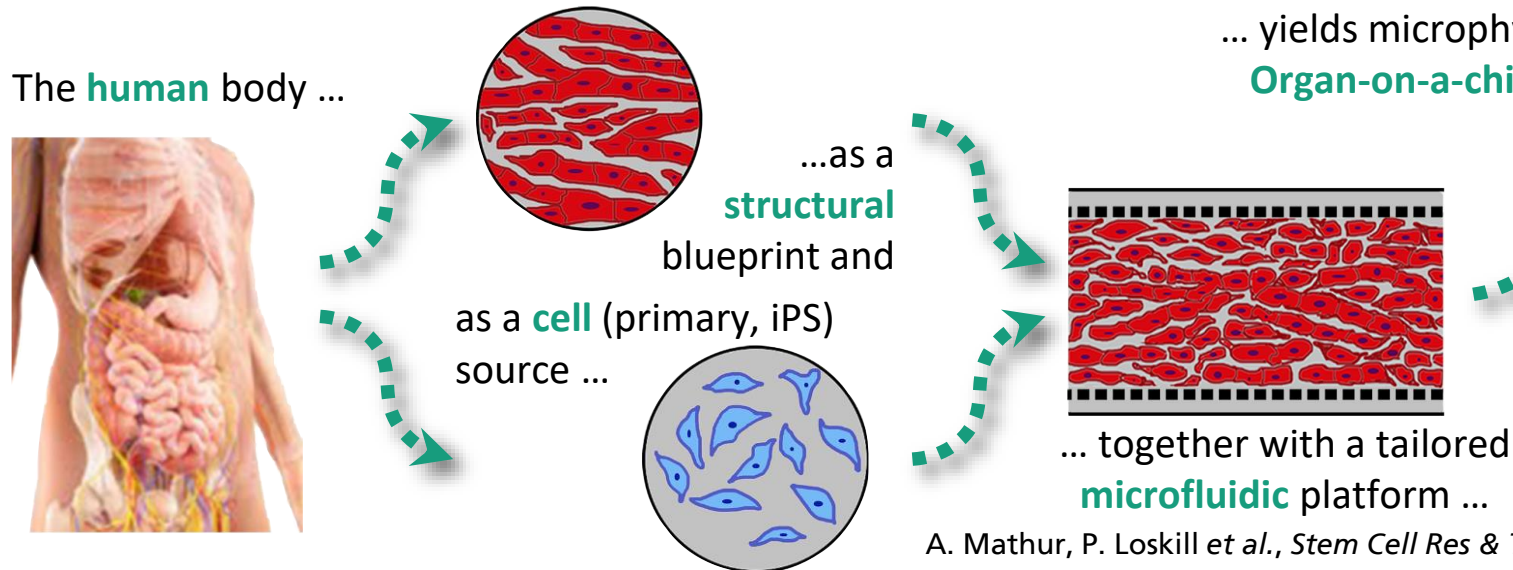
R. Passier et al., *Nature* 453, 322-329 (2008)

Organ-on-a-Chip

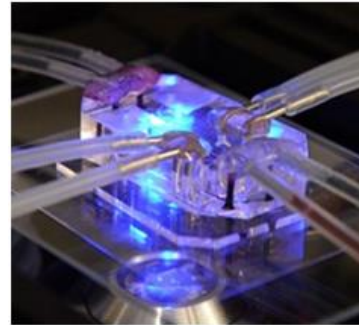
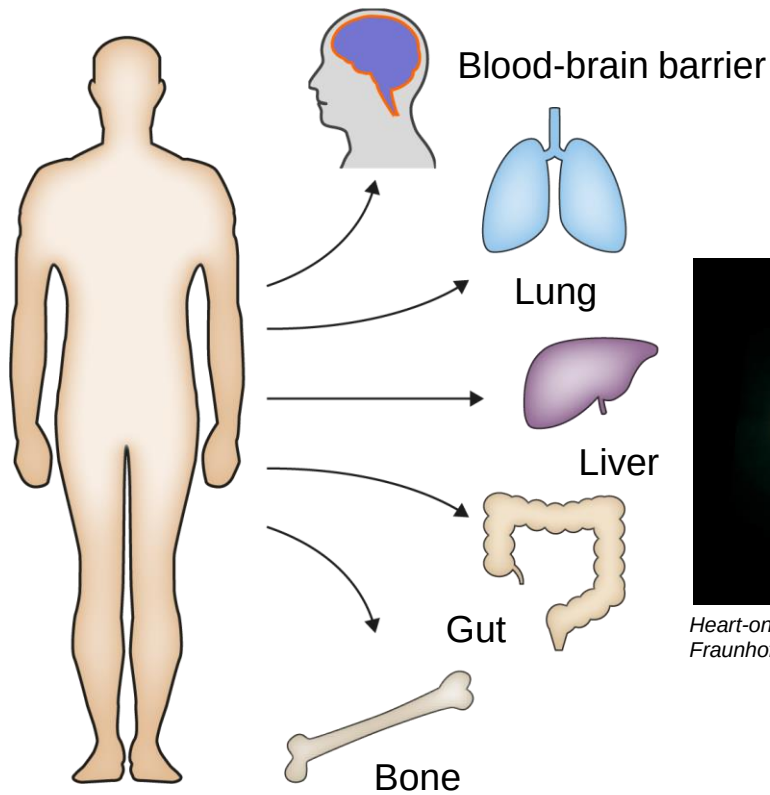
- Human tissue
- In vivo structure & function
- Physiological microenvironment
- Microfluidic perfusion



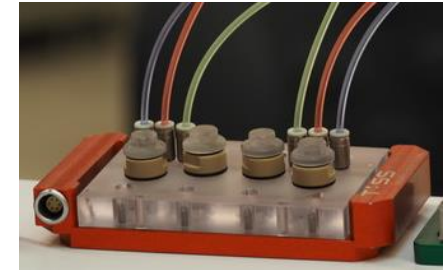
... yields microphysiological
Organ-on-a-chip systems



Organ-on-a-Chip – Diversity in organs, diversity in chips



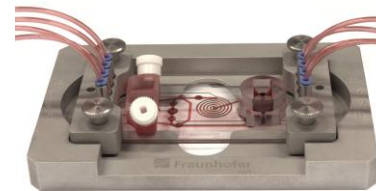
Lung-on-a-chip. Source: Wyss Institute at Harvard University



Multi-organ-chip. Source: TissUse GmbH



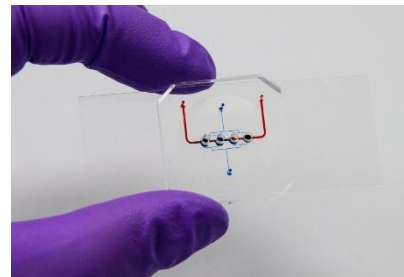
Heart-on-a-chip. Source: Fraunhofer IGB



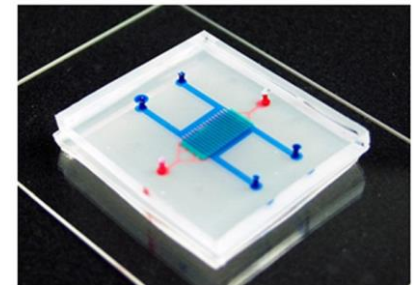
Environment-control-chip. Source: Fraunhofer IWS



Liver-on-a-chip. Source: Jena University Hospital

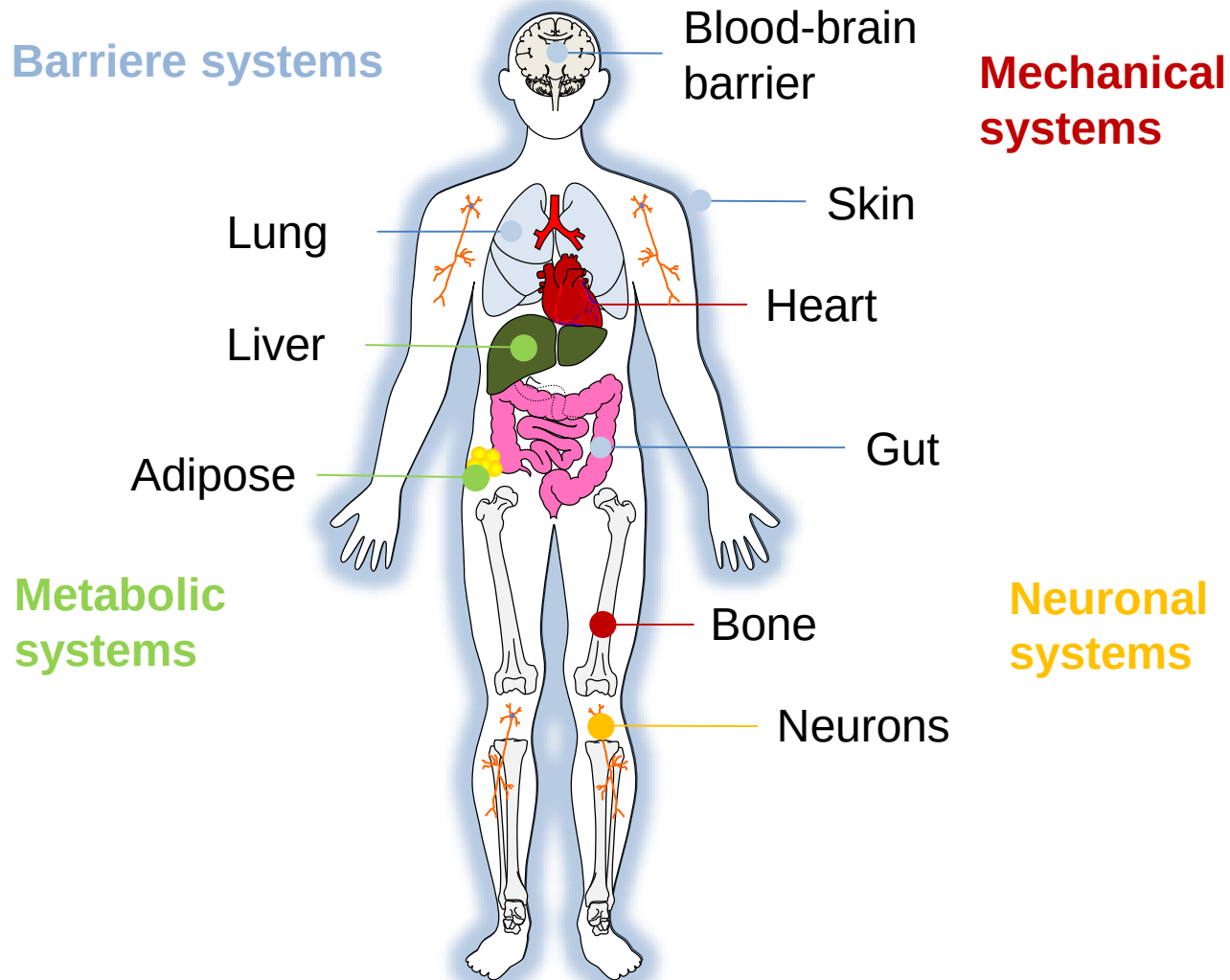


Retina-on-a-chip. Source: Uni Tübingen

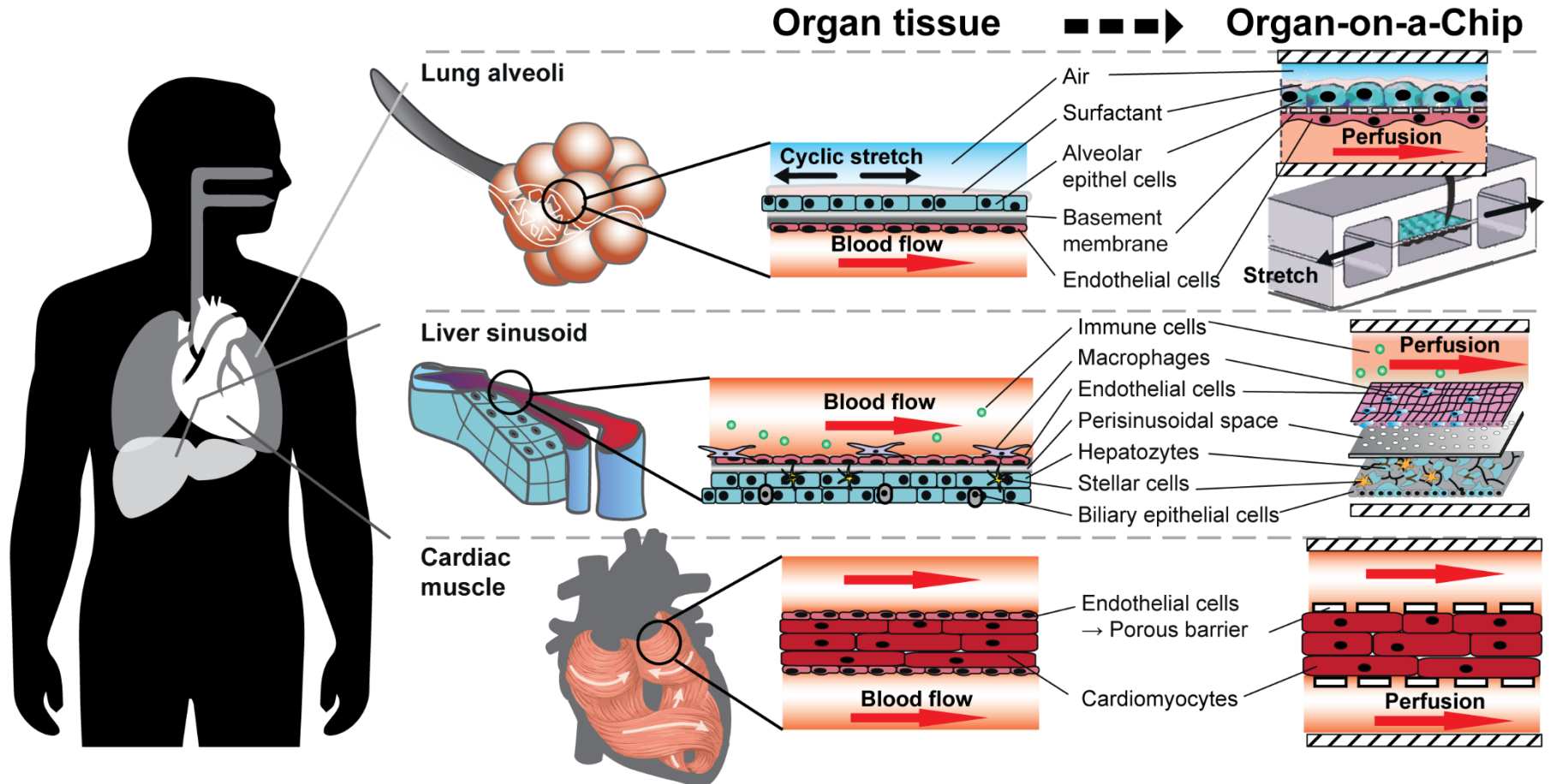


Blood-brain barrier chip. Source: Vanderbilt University

Organ-on-a-Chip – Emulating organotypic functions



Organ-on-a-Chip – Emulating organotypic functions

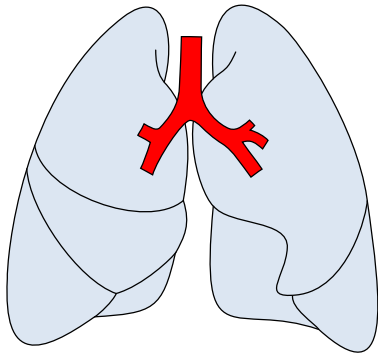


A. Mosig, J. Nawroth, P. Loskill, *Deutsche Zeitschrift für klinische Forschung* (2017)

Lung-on-a-Chip

Major characteristics of lung tissue

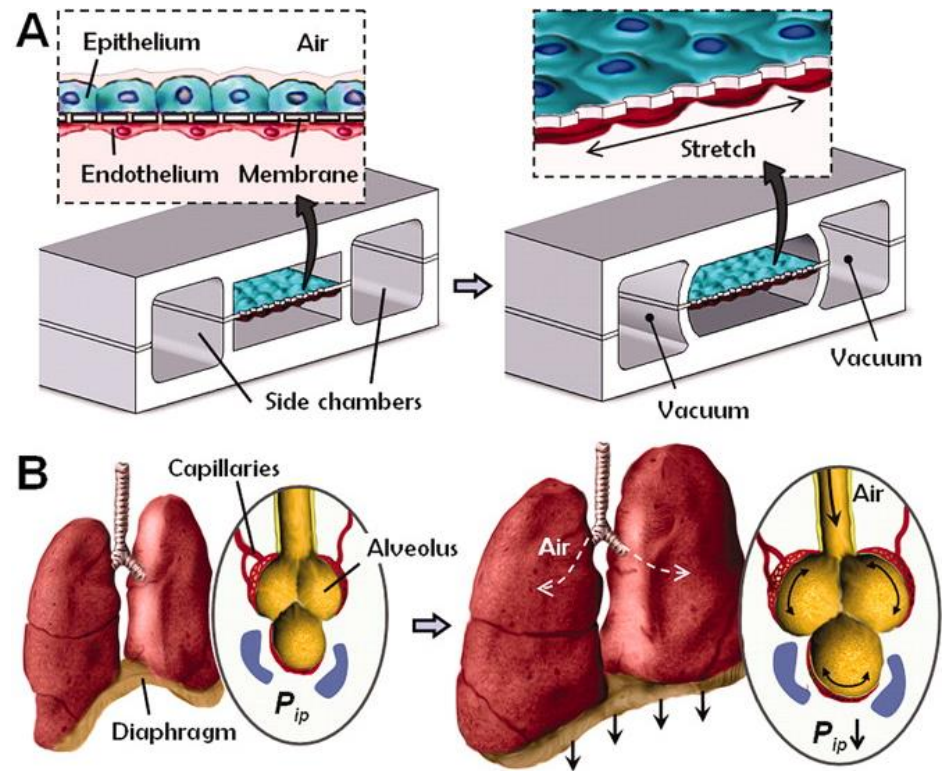
- Breathing motion: Mechanical stimulation
- Air-Blood interface
- Immune competence



Reconstituting Organ-Level Lung Functions on a Chip

Dongeun Huh,^{1,2} Benjamin D. Matthews,^{2,3} Akiko Mammoto,² Martín Montoya-Zavala,^{1,2}
Hong Yuan Hsin,² Donald E. Ingber^{1,2,4*}

Science (2010)



Lung-on-a-Chip

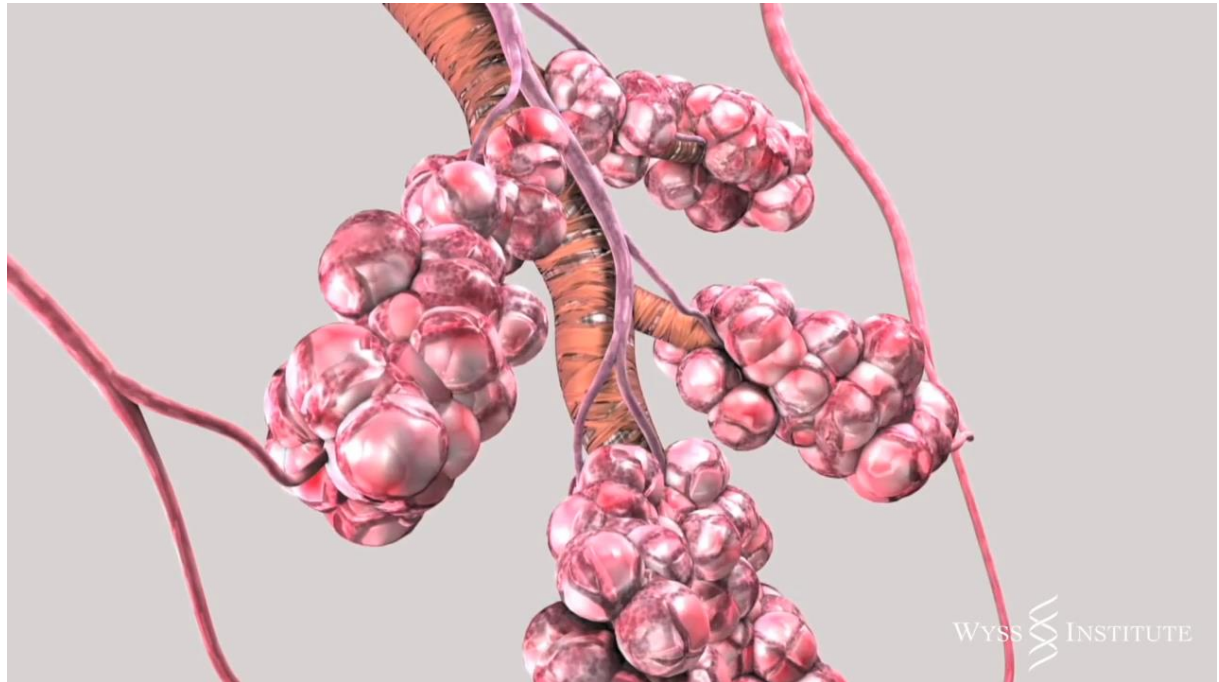
Ingber Lab, Wyss Institute at
Harvard, USA

- Flexible membranes with epithelial cells on one and endothelial cells on the other side

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Science (2010)



WYSS INSTITUTE

Lung-on-a-Chip

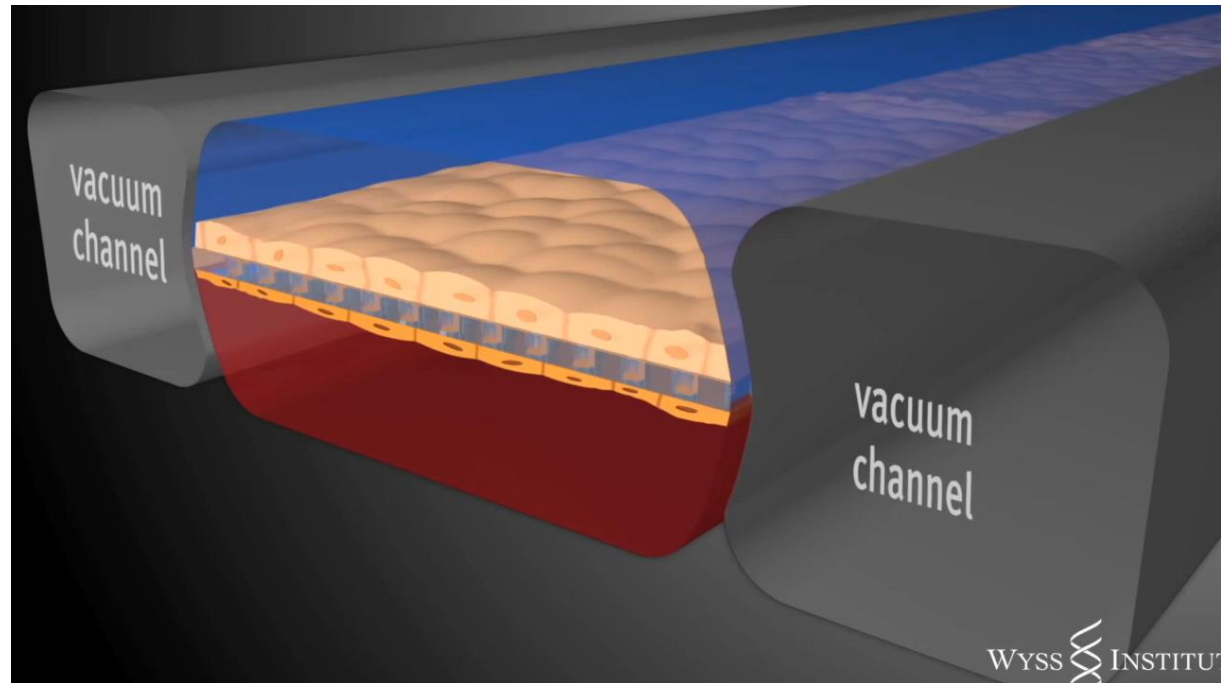
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- Recapitulation of breathing motion

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Science (2010)



Lung-on-a-Chip

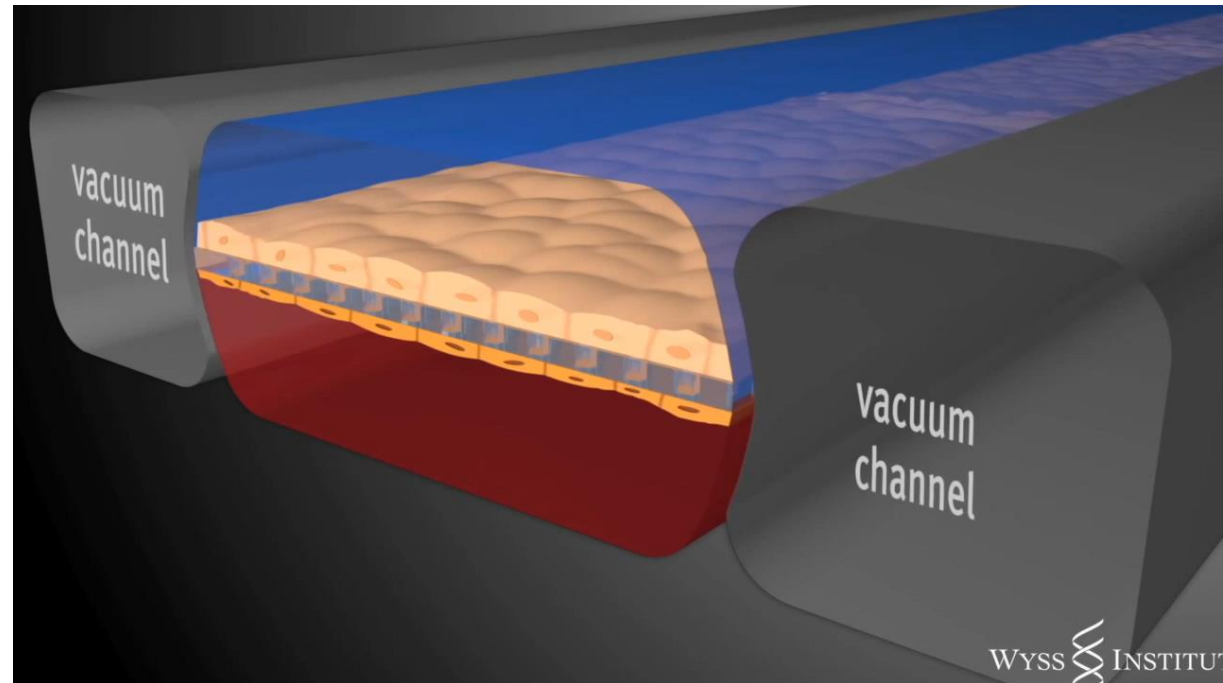
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Reconstituting Organ-Level Lung Functions on a Chip

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Science (2010)



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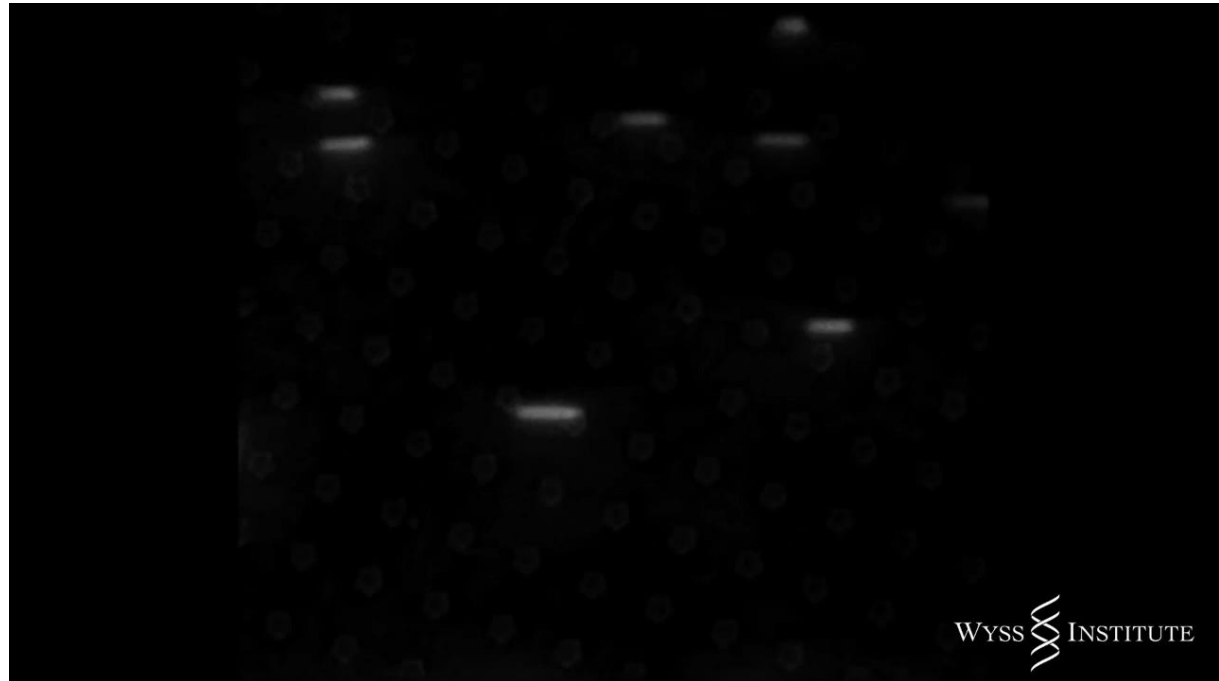
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Science (2010)



Lung-on-a-Chip

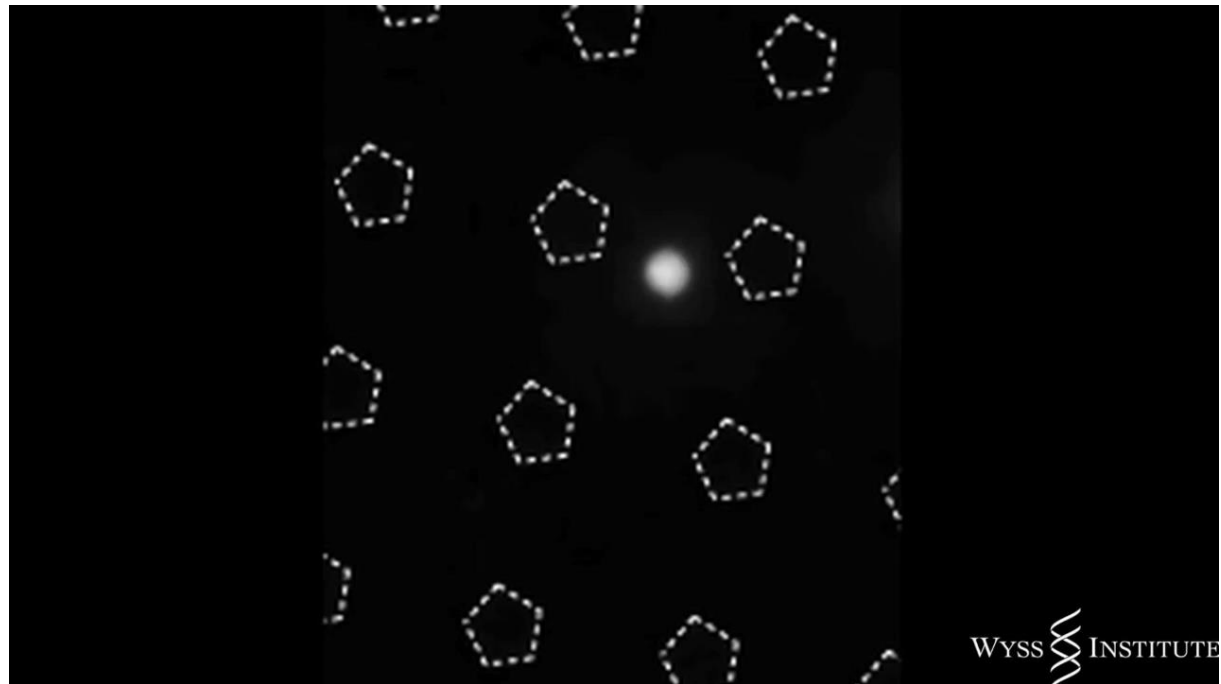
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Reconstituting Organ-Level Lung Functions on a Chip

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Hong Yuan Hsin,² Donald E. Ingber^{1,2,4*}

Science (2010)



WYSS  INSTITUTE

Lung-on-a-Chip

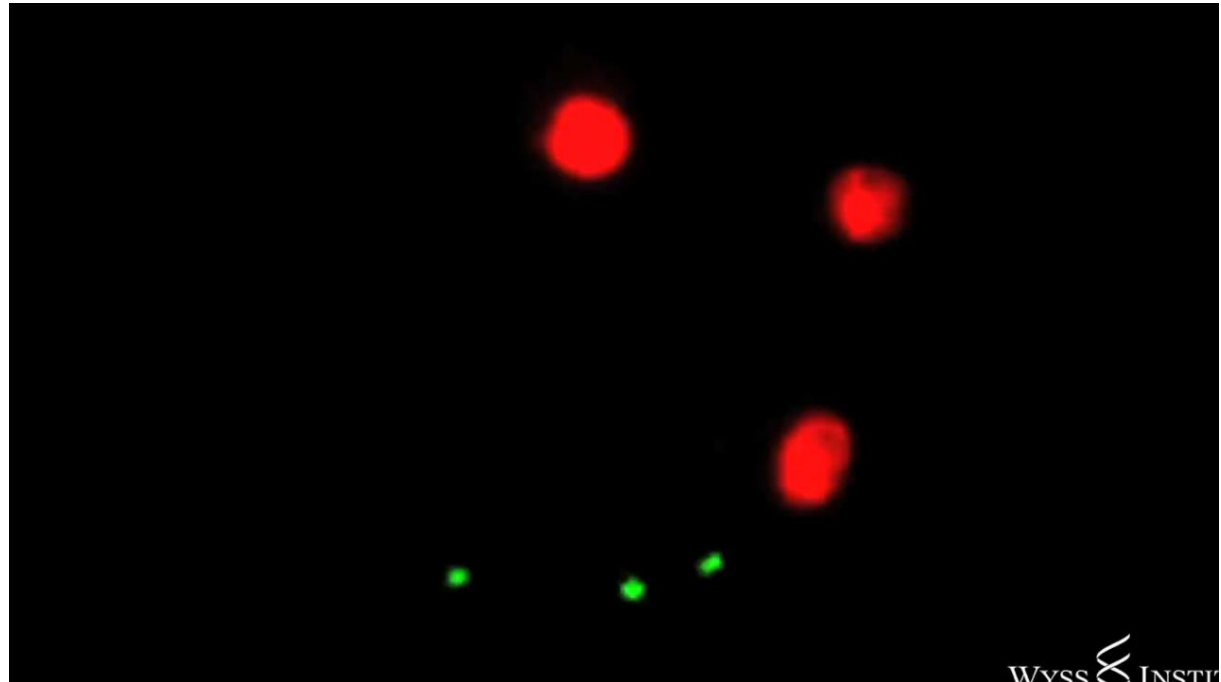
Ingber Lab, Wyss Institute at
Harvard, USA

- Flexible membranes with epithelial cells on one and endothelial cells on the other side
- Recapitulation of breathing motion
- Recapitulation of an immune response

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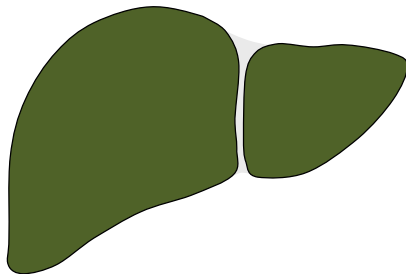
Science (2010)



Liver-on-a-Chip

Major characteristics of hepatic (liver) tissue

- Multilayer structure
- Integration of non-parenchymal cell types
- Long-term maintenance of metabolic and clearance capacity



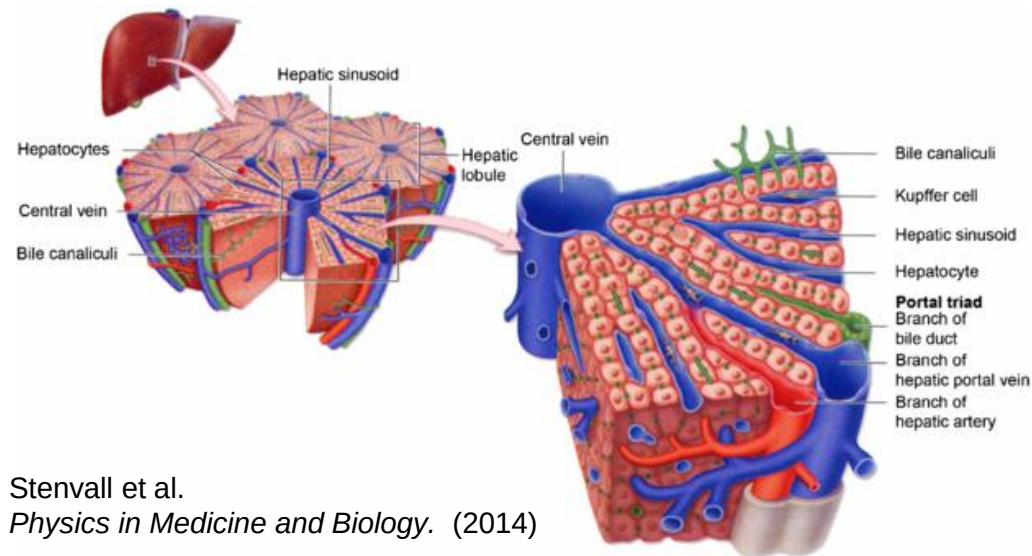
Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

A microfluidically perfused three dimensional human liver model

Knut Rennert ^{a,1}, Sandra Steinborn ^{a,1}, Marko Gröger ^{a,i}, Birgit Ungerböck ^b, Anne-Marie Jank ^c, Josef Ehgartner ^d, Sandor Nietzsche ^e, Julia Dinger ^f, Michael Kiehntopf ^g, Harald Funke ^c, Frank T. Peters ^f, Amelie Lupp ^h, Claudia Gärtner ^b, Torsten Mayr ^d, Michael Bauer ^{i,j}, Otmar Huber ^{a,j}, Alexander S. Mosig ^{a,j,*}

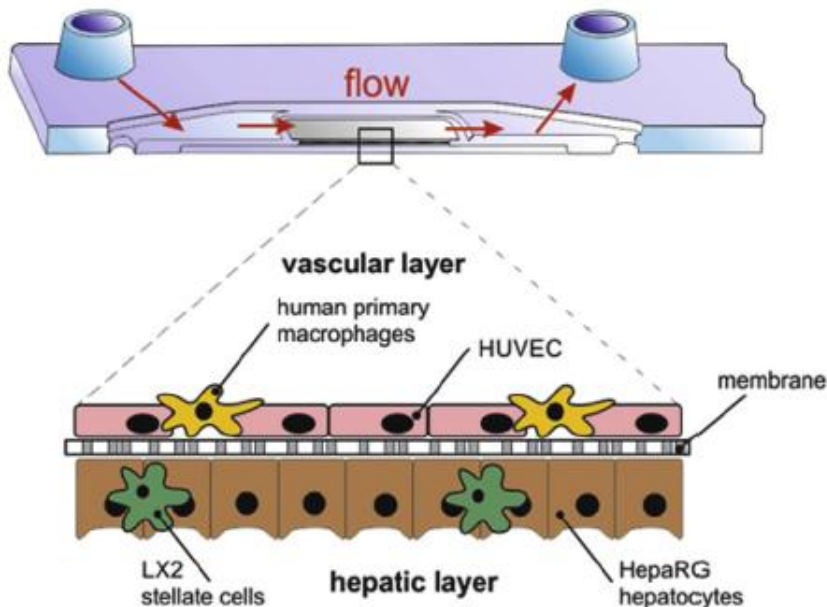


Stenvall et al.
Physics in Medicine and Biology. (2014)

Liver-on-a-Chip

Mosig Lab, Universität Jena

- Two channel platform with endothelial side (upper) and hepatic side (lower)



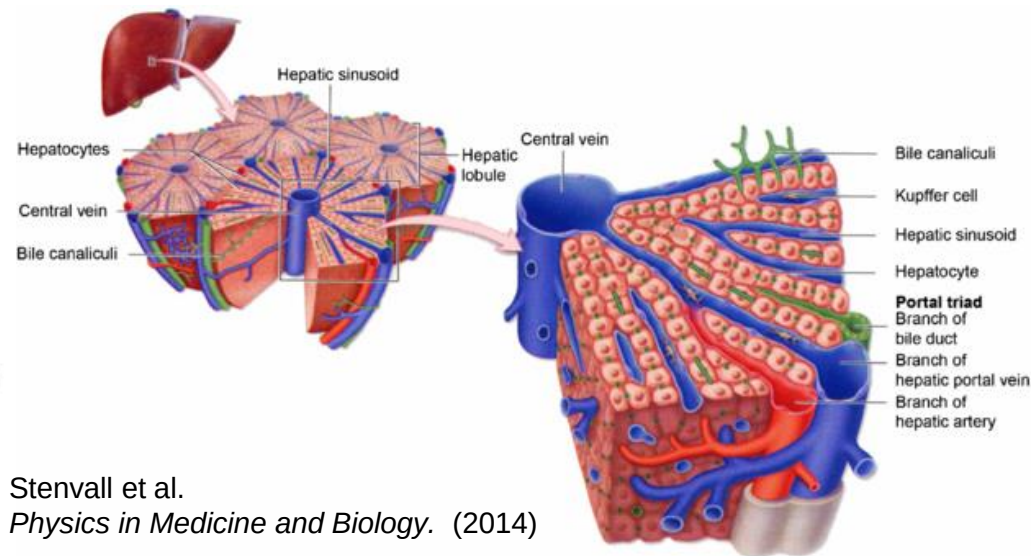
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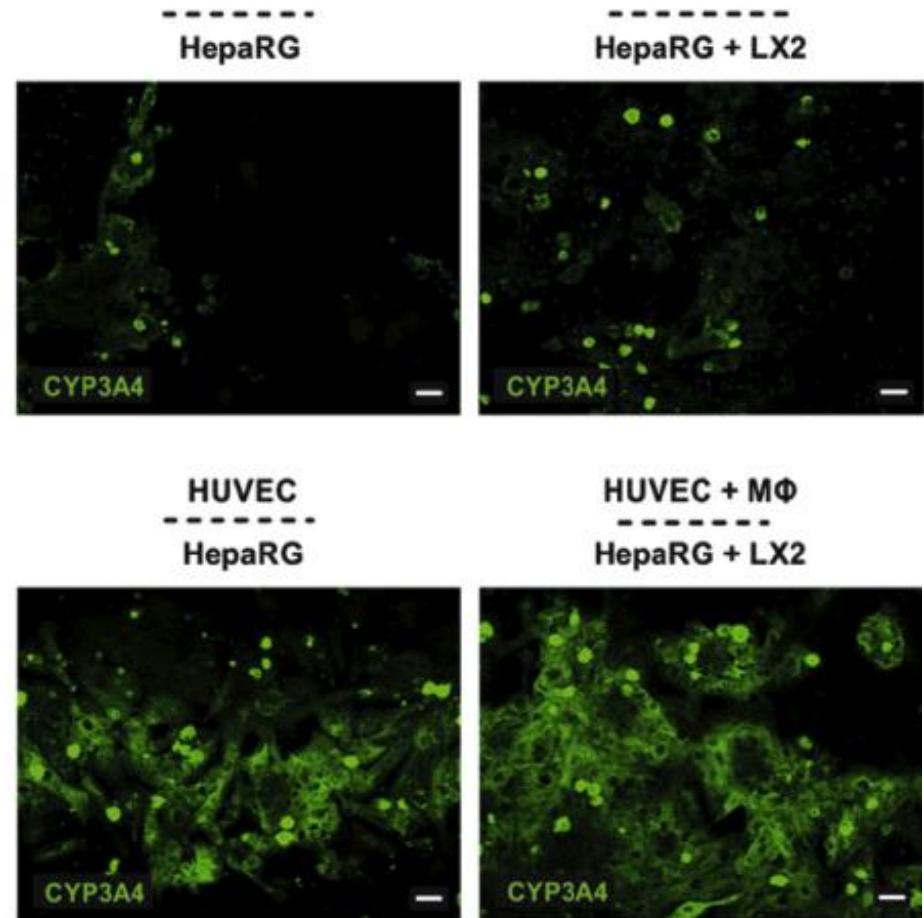
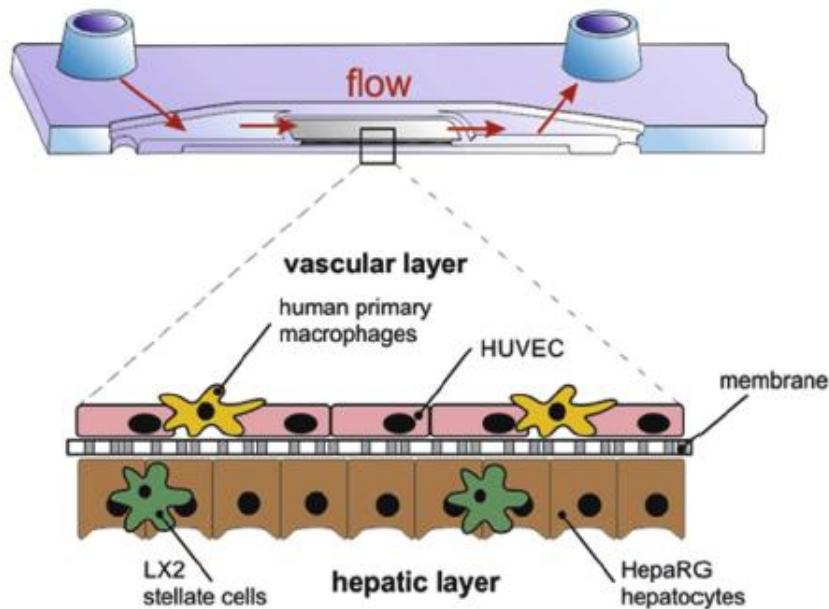


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Liver-on-a-Chip

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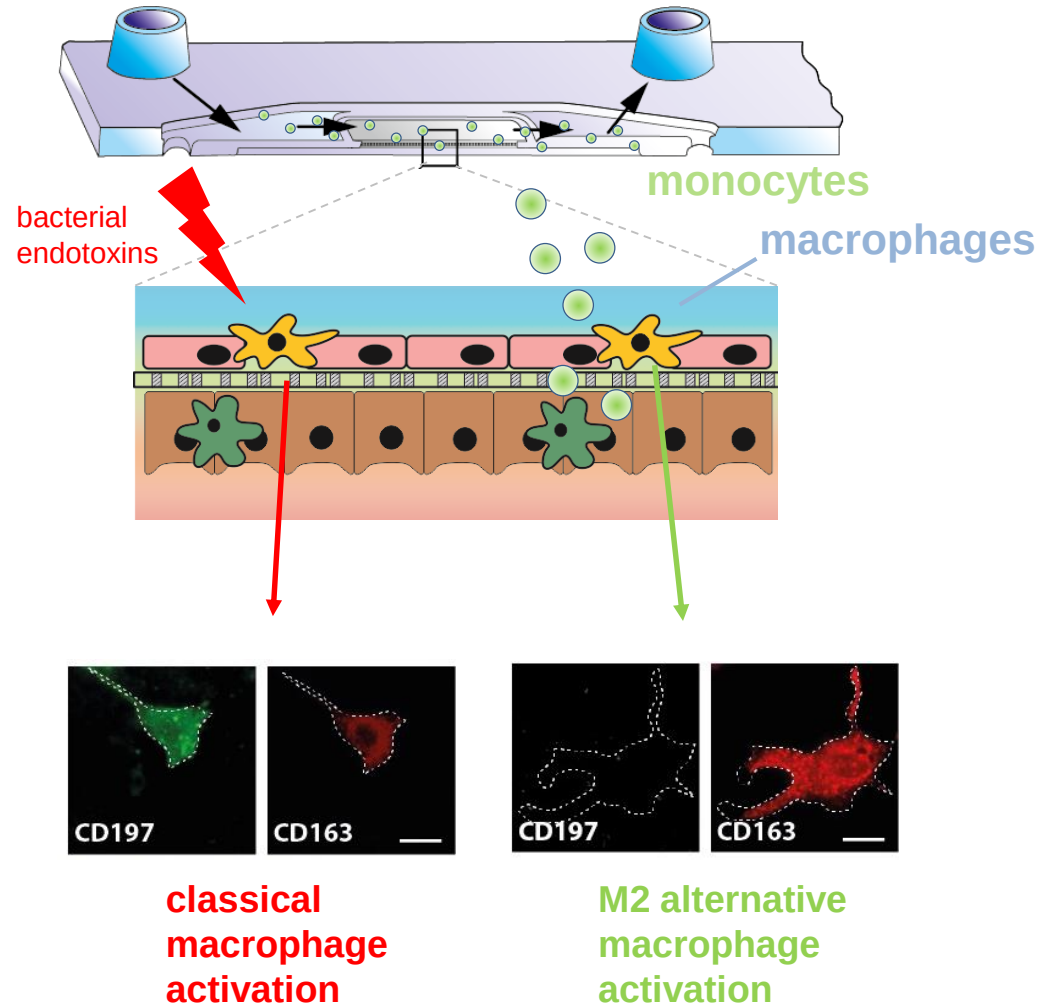


Rennert et al. *Biomaterials* (2015)

Liver-on-a-Chip

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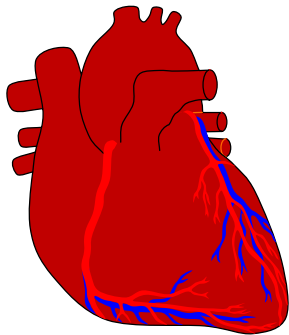
- Two channel platform with endothelial side (upper) and hepatic side (lower)
- Immune response
 - Inflammation
 - lose of central metabolic functions
 - sustained inflammation
 - cellular dysfunction / cell death
 - Regeneration
 - Reconstitution of organotypic functionality
 - immune tolerance
 - prevention of cell death



Heart-on-a-Chip

Major characteristics of cardiac (heart) tissue

- 3D fiber structure
- Spontaneous contraction
- coordinated stimulus transmission

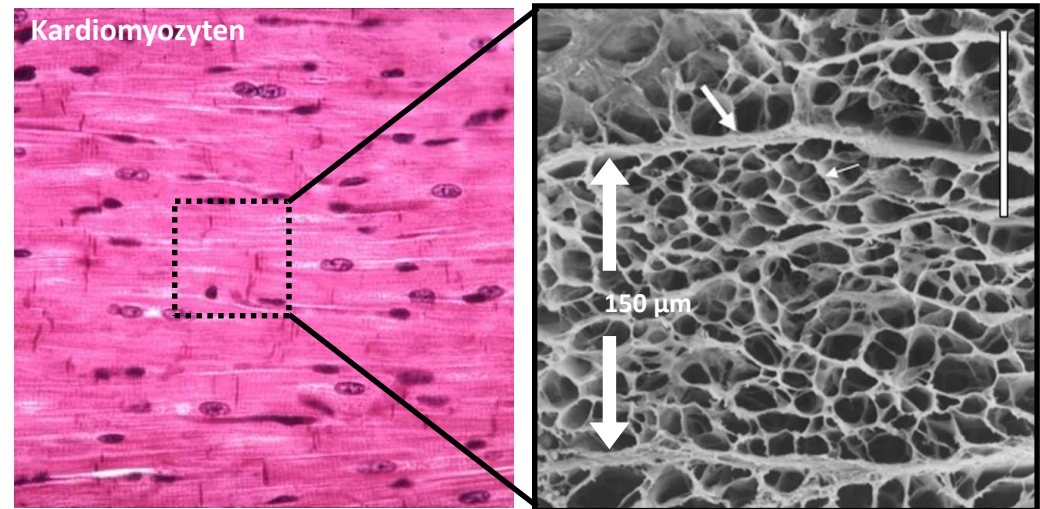


Human iPSC-based Cardiac Microphysiological System For Drug Screening Applications

Anurag Mathur^{1,2}, Peter Loskill^{1,2}, Kaifeng Shao¹, Nathaniel Huebsch^{4,5}, SoonGweon Hong¹, Sivan G. Marcus¹, Natalie Marks¹, Mohammad Mandegar^{4,5}, Bruce R. Conklin^{4,5}, Luke P. Lee^{1,3} & Kevin E. Healy^{1,2}

A. Mathur, P. Loskill, et al. *Sci. Rep.* (2015)

Kanzaki et al., *Circulation* (2010)

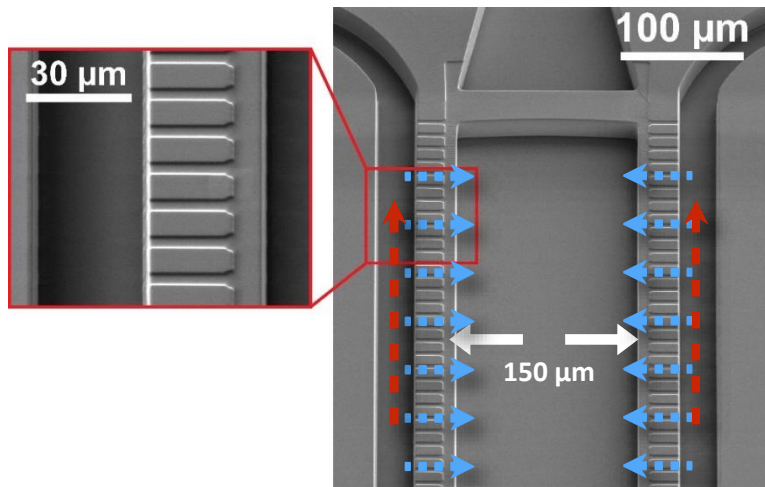


Heart-on-a-Chip

Healy Lab, UC Berkeley, USA

Loskill Lab, Universität Tübingen

- Central tissue chamber and adjacent vasculature-like media channels connected via micropores
- Separation of transport processes (diffusive vs convective)



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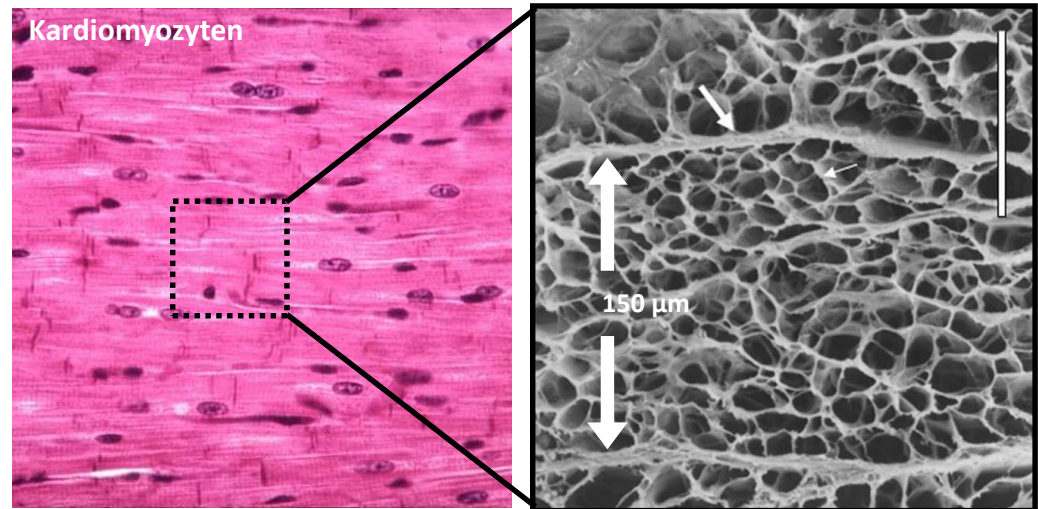


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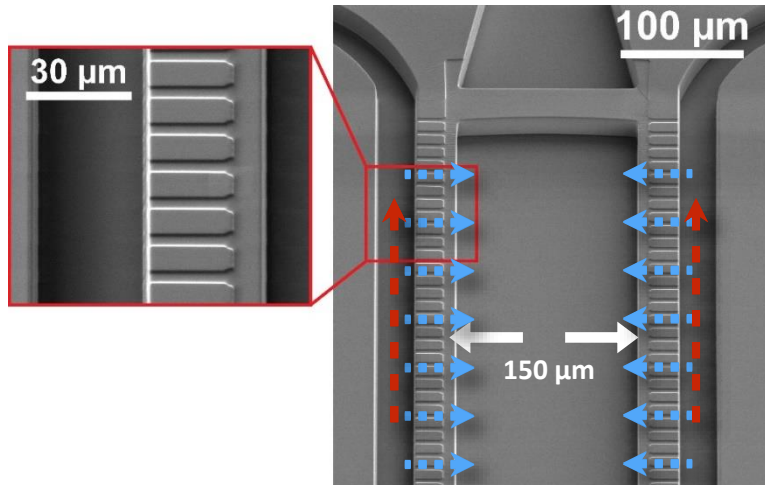


Heart-on-a-Chip

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- Central tissue chamber and adjacent vasculature-like media channels connected via micropores
- Separation of transport processes (diffusive vs convective)
- Aligned human iPSC-Cardiomyocytes



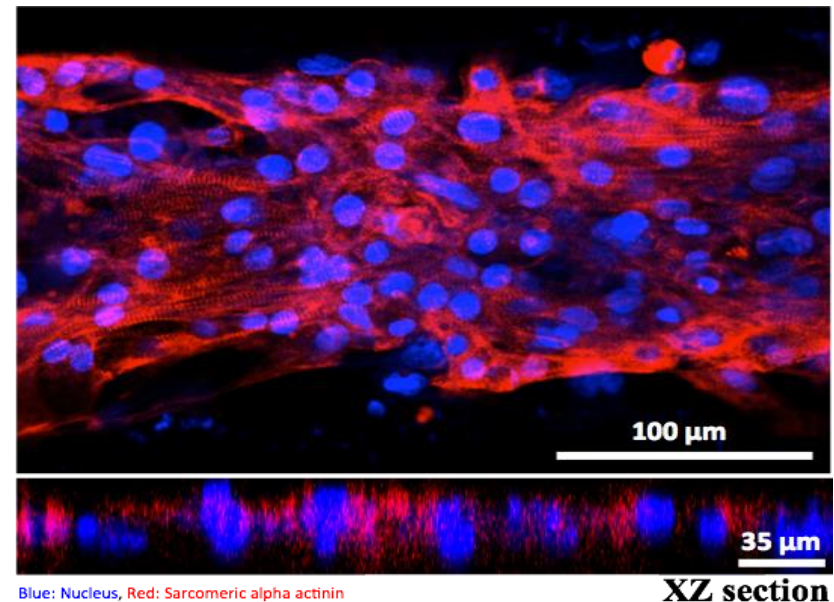
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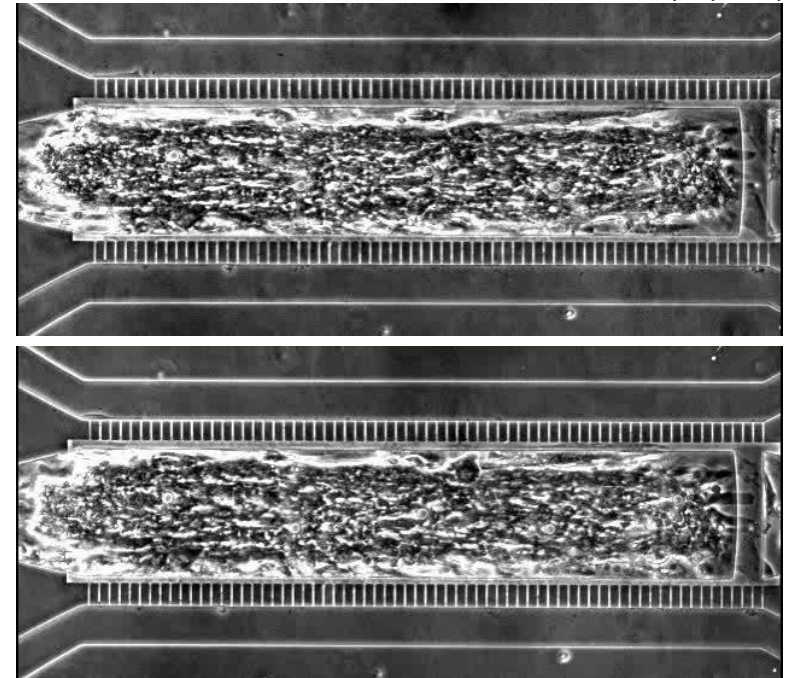
- Central tissue chamber and adjacent vasculature-like media channels connected via micropores
- Separation of transport processes (diffusive vs convective)
- Aligned human iPS-Cardiomyocytes
- Physiological effect of exposure to drug compounds: Increase in contraction force and beating rate



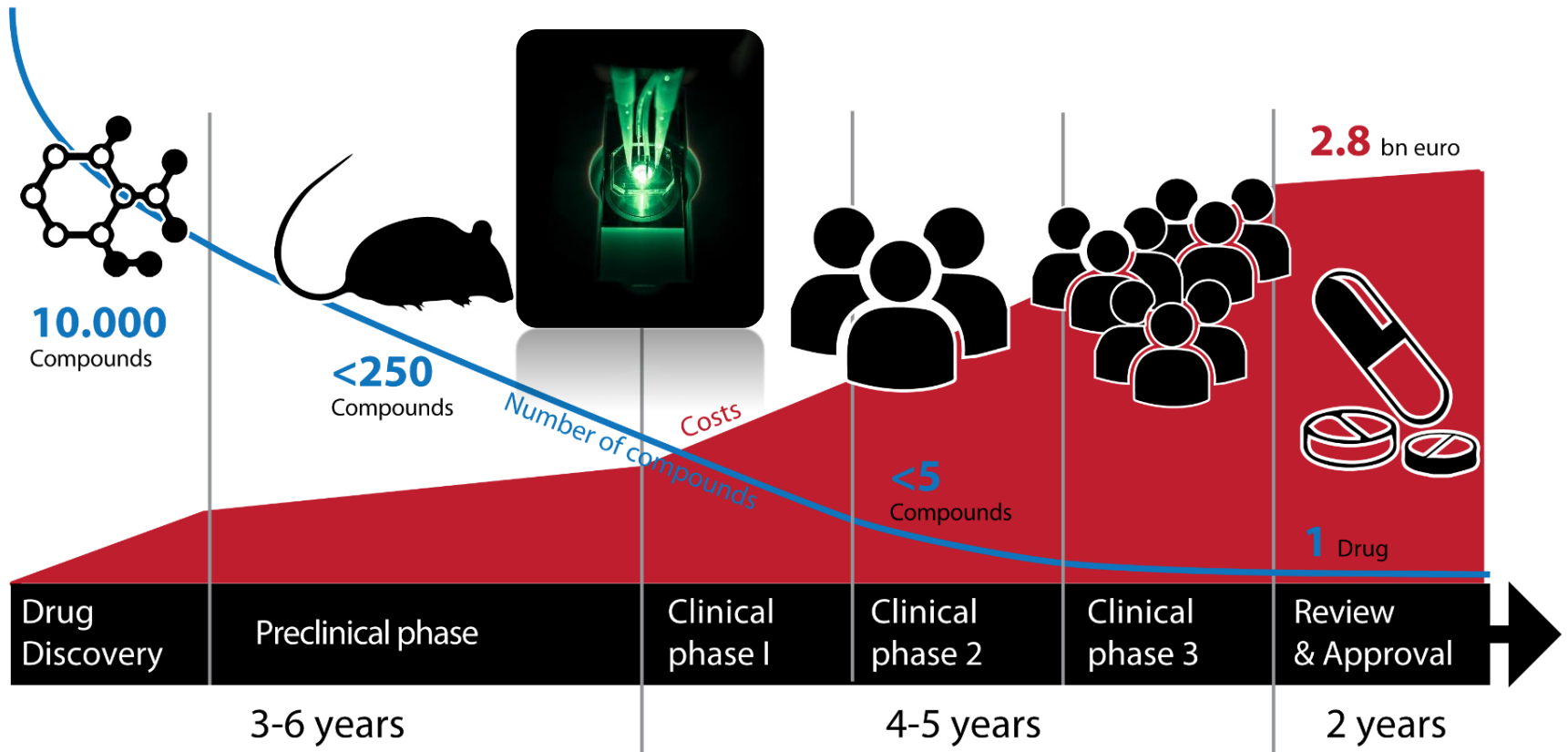
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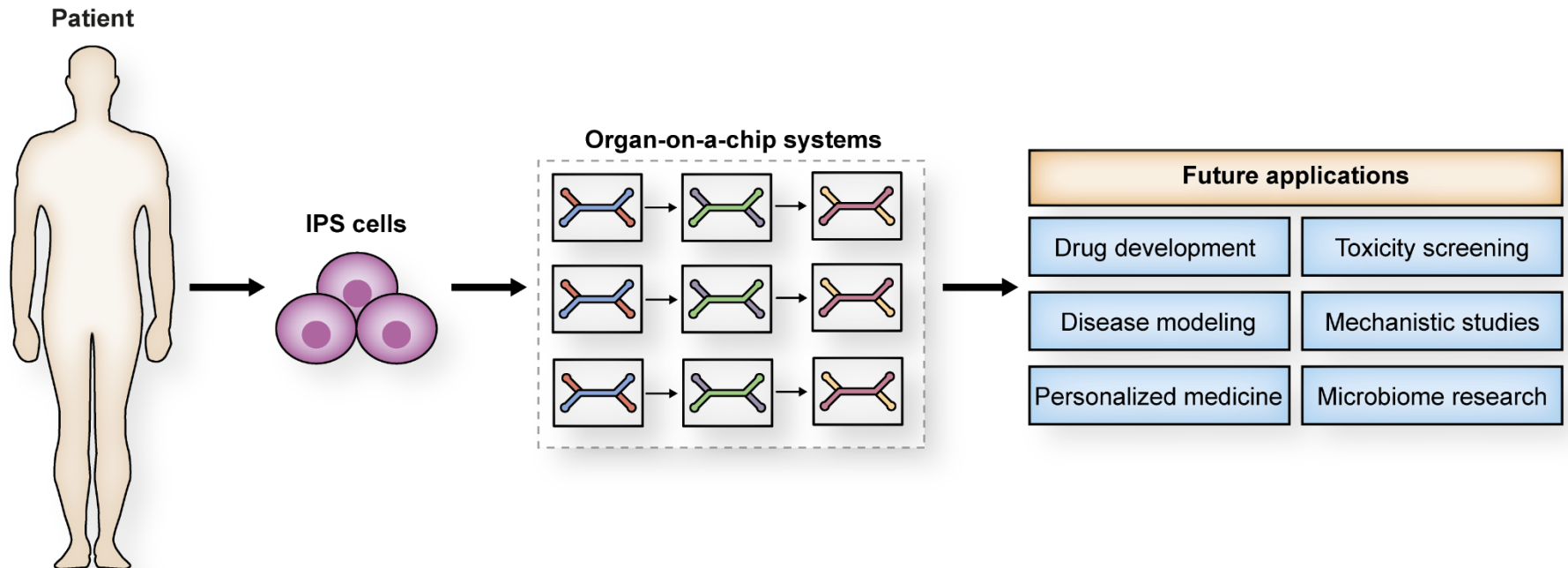


New opportunities provided by Organ-on-a-Chip



- Organ-on-a-Chip as enabling technology for the transition of compounds from the preclinical phase into the clinical phases.
 - Increase in predictivity → Safer, faster and more economical drug development

New opportunities provided by Organ-on-a-Chip



➡ More than just a drug screening tool

Thank you for your attention!

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