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Emulate Inc.
www.emulatebio.com

Introduction

Emulate is in the market to commercialize organs-on-a-chip[1] (OOC) or organ chips with the hopes to replace traditional in-vitro (2D cell culture) and in-vivo (animal) models as a human emulation platform that will mimic true human physiology, so that responses to medicines, chemicals and diseases can be accurately predicted. Currently Emulate offers the Human Emulation System™ which consists of 1) instrumentation system (which is the support system for the 6 chips) 2) the actual (disposable) chips which are to be lined with human cells 3) the pods which holds 1 chip and 4) the supporting software & apps.

Emulate originally started off as a project within Harvard University's The Wyss Institute for Biologically Inspired Engineering developing (then) as Biomimetic Microsystems. In the words of several employees Emulate sees "themselves as the bridge between the data from all nomics and health outcomes" advancing better in-silico models, as opposed to just a supplier of technologies. Furthermore it is one of Emulate's vision is to become the standard of precision "personalized" medicine.

Funding

Emulate raised a total of USD $95M, with its most recent funding Series C of $36M[2] announced June 18, 2018 with Founders Fund (Aaron VanDevender as the partner) as the lead at $164M pre and $200M post [3]. Additional investors include Hansjoerg Wyss (who initially funded the Wyss Institute for Biologically Inspired Engineering) and OS Fund.

Emulate also received USD $4M[4] of grant funding from the National Center For Advancing Translational Sciences (NCATS) on June 20, 2017 to study the effects of space travel on human brain cells and again on December 18, 2018[5] to study cellular interactions and better understand the impact of bacterial challenges on gastrointestinal (GI) homeostasis from space.

Competition

Organs-on-chip is relatively new concept that is currently targeting substance testing (drug, chemical and nanoparticle safety) and disease modeling. The hope of OOC is that they can mimic the passage of drugs, chemicals and other particles through the human body better and longer than individual cell types in static culture and with more relevance and accuracy than animal models.

There are several direct, potential and indirect competitors which are:

- Direct Organs-on-Chip (US): Nortis, Hesperos, AxoSim, 4D BioSciences, Organome

[1] The Wyss Institute refers to organs-on-a-chip (OOC) but it can also be organ-on-a-chip and organ-chips
[2] https://www.crunchbase.com/funding_round/emulate-series-c--e3fd5bc8#section-investors
[3] Pitchbook (retrieved Aug 2018)
[4] https://3uyywi3w8psfe6fxn1g4tdb1-wpengine.netdna-ssl.com/wp-content/uploads/2017/06/Emulate_PR_ISS-NCATS_062017.pdf
[5] https://emulatebio.com/press/emulate-intestine-chip-human-gi-infections-international-space-station

- Direct Organs-on-Chip (Worldwide): Mimetas, insphero, Ascendance Biotechnology, TissUse, TaraBiosystems, Cherry Biotech, CN Bio Innovations
- Indirect Lab-on-Chip (LOC) and other: StemoniX, Diagnostics for All,
- Indirect Instrumentation (startups): Thrive Biosciences, Athelas, 10x Genomics
- Diagnostic & Instrumentation: Thermo Fisher Scientific, Merck KGaA (EMD Millipore), Agilent Technologies, Bruker Corporation, Danaher, Illumina, Qiagen, Shimadzu Corporation
- Contract Research Organizations (CRO): LabCorp (Convance), IQVIA (Quintiles IMS Holdings, Inc.), Charles River Laboratories, Pharmaceutical Product Development (PPD), PRA Health Sciences, PRAXEL, Envigo, Syneos Health (INC Research & inVentiv Health), Medpace, Chiltern, PSI
- Small CRO: Taconic Biosciences, The Jackson Laboratory, Harlan Sprague Dawley

Key Risks

Users

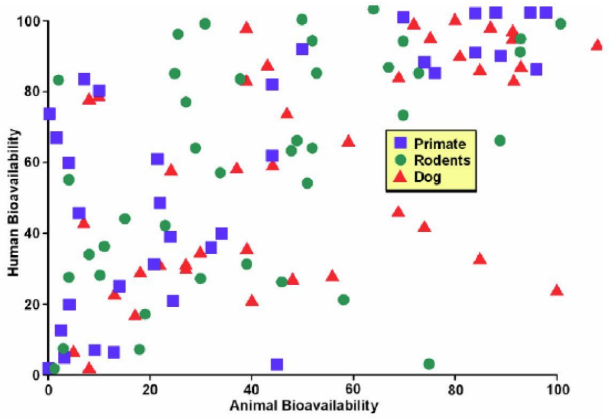
Pharma/Biotech
Current users (specifically pharma and biotech) are using OOC as a "better" predictive models to test drug safety and see it as a possible alternative to animal models. This is because pharma companies are moving away from strictly small molecule to large molecule developments. However there are still challenges with OOC from fabrication of organ-on-a-chip is still a challenging task due to its complexity to the need for very expensive instrumentation systems.

In the words of Emulate's business development team, the biggest challenge for Emulate is that OOC is a disruptive tech and they are still getting researchers (from academic to pharma or any industry) to change their "old ways" (animal models) to use OOC instead.

Alternatives (What exists today)

Pharma/Biotech
The two alternatives today used to optimize a drug (target compound) during the drug discovery process are 1) animal models (usually mice/rats, dogs and non-human primates) which are systemic but not human and 2) human 2D/3D cell cultures which are human but not systemic. These are common and frequently used at the pre-clinical stage for PK/PD[6] modeling and toxicology studies.

[6] PK/PD modeling (pharmacokinetic/pharmacodynamic modeling) is a technique that combines the two classical pharmacologic disciplines of PK and PD. It integrates a PK and PD model component into one set of mathematical expressions that allows the description of the time course of effect intensity in response to administration of a drug dose.



The bioavailability chart shows that the animal model[7] very seldom predicts human pathophysiology and the reactions of sad drugs leading them to being an inaccurate model to test drug efficacy and toxicity.

Current 2D/3D cell models used to predict in vivo drug responses for many targets and pathways and are still very useful in drug discovery, however, it is evident that these 2D cultures suffer disadvantages associated with the loss of tissue-specific architecture, mechanical and biochemical cues, and cell-to cell and cell-to-matrix interactions.

Technique	Advantages	Disadvantages
Spheroids[a]	Easy-to-use protocol Scalable to different plate formats Compliant with high-throughput screening (HTS)/high-content screening (HCS) Co-culture ability High reproducibility	Simplified architecture
Organoids	Patient specific In vivo–like complexity In vivo–like architecture	Can be variable Less amenable to HTS/HCS Hard to reach in vivo maturity Complication in assay Lack vasculature May lack key cell types
Scaffolds/hydrogels	Applicable to microplates Amenable to HTS/HCS High reproducibility Co-culture ability	Simplified architecture Can be variable across lots
Organs-on-chips	In vivo–like architecture In vivo–like microenvironment, chemical, physical gradients	Lack vasculature Difficult to be adapted to HTS
3D bioprinting	Custom-made architecture Chemical, physical gradients High-throughput production Co-culture ability	Lack vasculature Challenges with cells/materials Difficult to be adapted to HTS Issues with tissue maturation

[a]Discussion is limited to low-adhesion plates.

The advantages and disadvantages of different 3D cell culture techniques[8] including OOC.

Current State of OOC

Organs-on-a-chip (OOC) offer the potential for actual human cell mechanisms for disease modeling beyond current technologies. However, the technology itself is still in its infancy and will enable more sophisticated systems that mimic organs, tissues, or whole organisms. Because OOC are still a very young technology, and because no one is yet sure how well they correspond to existing cell and animal models — much less to human biology. For OOC to become an established platform for testing new drugs, both Emulate and its customers will need huge

[7] https://peh-med.biomedcentral.com/articles/10.1186/1747-5341-4-2
[8] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5448717/pdf/10.1177_1087057117696795.pdf

datasets on their performance, which will be much easier to create if their use cuts across institutions.

Contents

Summary

The founding team of Emulate are the pioneers of organs-on-chip (OOC) technology at the Wyss Institute. Emulate develops a wide range of organ-chips and disease models through collaborations with industry partners and internal R&D programs. Emulate is also working with clinical partners to produce OOC personalized with an individual patient's stem cells, for applications in precision medicine and personalized health.

Business

1. Emulate is currently "selling" the Human Emulation System which consists of:
    - Instrumentation: 2 components
        - 1) the life support system for OOC (Zoe)
        - 2) the gas mixer (Orb)
        - This system costs between USD $70-100K
    - S1-Chips (Organs-on-a-chip)
        - The chips are manufactured by a 3rd party Fab (unknown)
        - The cost for each chip are $200-350
    - Pods that house the S1-Chips
    - Software & App (most likely analytics, etc.)

Market

1. Organs-on-a-chip are relatively new and emerging tech but the potential for them are:
    a. Further understand human organs in an isolated setting
    b. Rapid testing of drugs
    c. Precision medicine (personalized meds)

Users and/or Partners (selected)

1. Johnson & Johnson Innovation Center (Janssen Pharmaceutical Company)
2. AstraZeneca (IMED) Biotech Unit
3. Roche (various R&D programs)
4. Merck (lung and GI programs)
5. Pfizer (liver vascular & GI)
6. Takeda (GI drug discovery programs)
7. Cedar-Sinai Regenerative Medicine Institute
8. FDA through CRADA (Cooperative Research and Development Agreement)
9. The Michael J. Fox Foundation

Financials

1. Recently raised USD $35M series C, led by Founders Fund and previously raised $60M.
2. Emulate's estimated revenue is $2M based on a small number of chips and instrumentation devices sold to biotech/pharma and research institutions.

Competition

1. Big players: Thermo Fisher Scientific, Agilent Technologies, Bruker Corporation, Bio-Rad Laboratories, Inc.
2. Small players: Nortis Bio, Hesperos, TissUse, CN Bio Innovations

Team (co-founders and management)

1. James Coon (Co-founder and CEO)
2. Geraldine Hamilton (Chief Scientific Officer & President)
3. Daniel Levner (CTO)

Competitive Analysis

Emulate's immediate competitors in the OOC market are: Mimetas, Nortis Bio, TissUse, Hesperos, AxoSim Technologies, CN Bio Innovations. The top 4 competitors in the space are Emulate, Nortis, Mimetas and TissUse which all have partnerships with AstraZeneca.

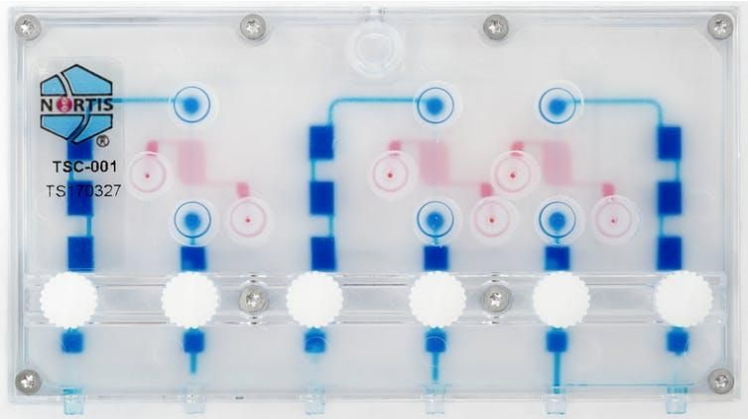
Currently Emulate immediate competitors (in the OOC space) are Nortis Bio and Mimetas and TissUse. It is possible that a large cap company such as Thermo Fisher Scientific which manufactures and sells diagnostic, instrumentation, cell culture and reagents may eventually get into the OOC space.

Nortis Bio

Founded by former University of Washington faculty Dr. Alan Nelson, Nortis was spun-out of the university in 2012, much like Emulate. Nortis has raised $2.5M to date including a $688K[9] NIH Phase II SBIR. Nortis has developed the ParVivo Perfusion System for generating small segments of human tissues and organs in microfluidic chips for the in vitro study of human health and disease. Nortis' vision is to facilitate groundbreaking scientific discoveries and accelerate their impact on improving human health, safety, and quality of life.

Product

The Nortis ParVivo Perfusion System each house just 1 chip and up to six supporting media reservoirs. Three-shelved docking stations that reside in a standard tissue culture incubator enable up to 36 independent experiments to be run at a time. Perfusion through both the tissue lumen and surrounding extralumenal space allow physico-chemical gradients to be created and perfusion fluids and cells to be collected for downstream analysis. Each docking station shelf or an individual perfusion platform can easily be removed using the sealed quick connect fittings allowing easy transport between the cell culture incubator, biosafety cabinets, and microscope stage.

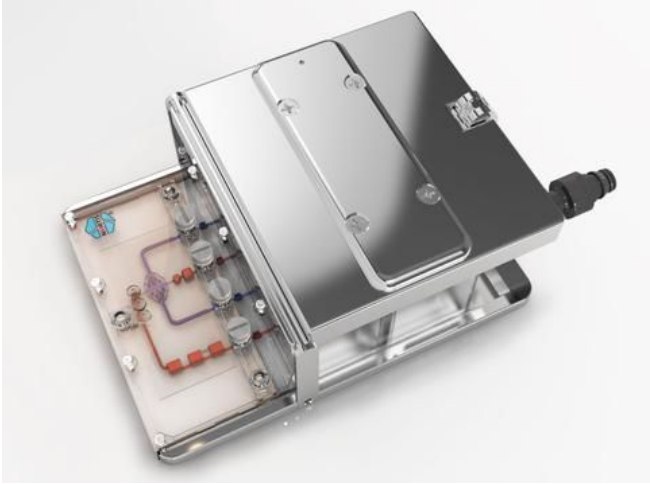


Source: Nortis

The chip[10] are made of PDMS (polydimethylsiloxane), a silicon based organic polymer and encased in polycarbonate shells which allows a wide range of tissue microenvironments can be created in the disposable microfluidic chips. Nortis chips also

[9] https://www.prnewswire.com/news-releases/nortis-awarded-688k-nih-phase-ii-sbir-fast-track-grant-to-develop-living-model-of-human-blood-brain-barrier-300506430.html
[10] https://www.nortisbio.com/#applications

uses a unique tube through biological matrix architecture that allows cells to assemble and migrate in all three dimensions. Where other OOC use a porous PDMS membranes or synthetic scaffolds to create artificially organized structures.



Source: Nortis

The ParVivo perfusion platform that houses 1 organ chip.

Source: Nortis

The ParVivo incubator gas pump (which does the job of somewhat replacing traditional peristaltic pumps) powers the system and provides precise control of flow rates. The pump recirculates incubator air maintaining your specific gas conditions without any additional consumables. This precise flow control enables:

- Creation of vasculature and other tubular tissues

- Delivery of test compounds via the perfusate
- Exposure to shear and flow forces that are present in the body
- Independent perfusion through the vessel and matrix compartments

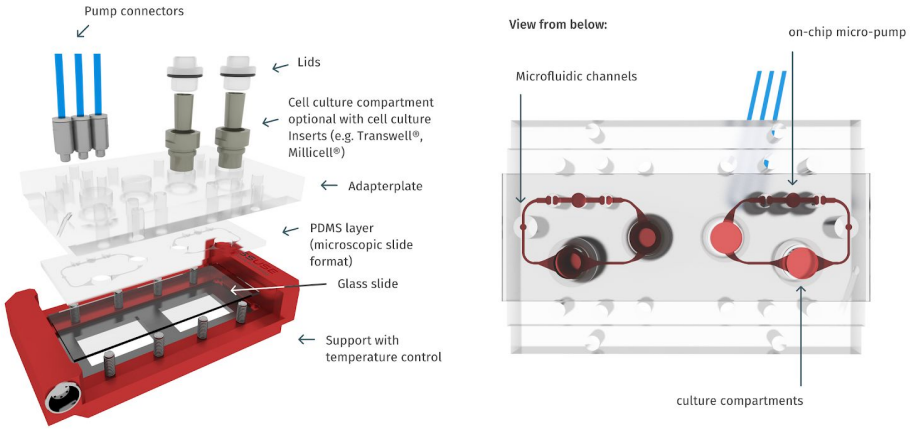
It is important to note that the system is designed to be housed within a standard incubator vs having it's own support system like Emulate.

Currently Nortis has partnerships with Biogen Idec, AstraZeneca, Eli Lilly, EPA, NIH and is considered to be a strong competitor to Emulate.

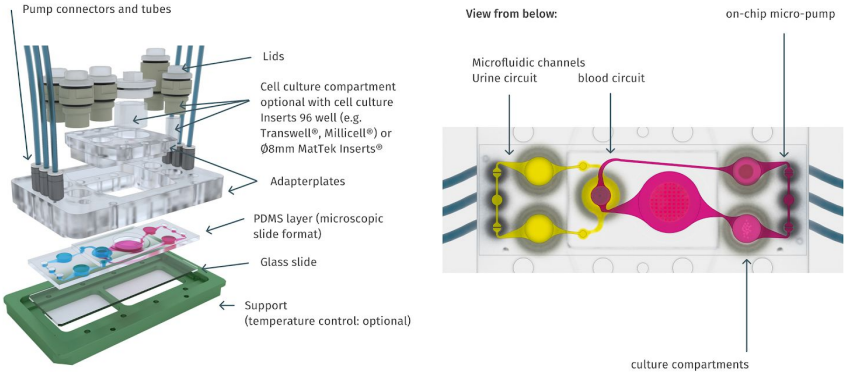
TissUse

Founded in Germany as a spinoff of an organs-on-a-chip research program at the Technical University of Berlin's Institute of Biotechnology. Unlike Emulate and some of the other OOC competitors that are using only single organ chips, TissUse is producing chips that allow two or four organs on each chip. According to Reyk Horland (VP of business development) the reason: "we focus on how to combine different organ models so they are able to interact with each other in a systematic manner."[11]

[11] https://www.cnbc.com/2017/08/14/fda-tests-groundbreaking-human-organs-on-a-chip.html



2-Organ-Chip (2-OC)[12]



4-Organ-Chip (4-OC)[13]

TissUse currently has a partnership with AstraZeneca[14] to look at the unmet need for a physiologically relevant human ex-vivo type 2 diabetes model, resulting in a human microfluidic two-organ-chip model to study pancreatic islet–liver cross-talk based on insulin and glucose regulation for up to 15 days in culture. This work is continuing to further develop the technology into a comprehensive type 2 diabetes-on-a-chip model.

TissUse Smart Hair Transplants (SHT)[15]

TissUse also uses technology for regenerative therapy, and is focusing a use case within the hair transplant technology, where the hair transplant market is expected to be USD +$24.8B[16] by 2024. Currently the sector is dominated by FUE (follicular unit extraction) where hair follicles are extracted from a donor area and replanting them and another method known FUT (follicular unit transplantation) aka strip procedure which involves cutting a strip from the back of the head and extracting. The SHT instead isolates cells from existing follicles (which requires about 30 or so punch biopsies), and “multiply” them externally to produce upwards of 10,000+ neopapilla, which have the potential to form new follicles.

[12] https://www.tissuse.com/en/products/2-organ-chip
[13] https://www.tissuse.com/en/products/4-organ-chip
[14] https://www.epmmagazine.com/technology/astrazeneca-and-tissuse-collaboration-progresses-with-creati
[15] https://www.hairlosstalk.com/news/new-research/tissuse-smart-hair-transplants
[16] https://globenewswire.com/news-release/2018/08/14/1551331/0/en/Hair-Transplant-Market-worth-over-24-8-billion-by-2024-Global-Market-Insights-Inc.html

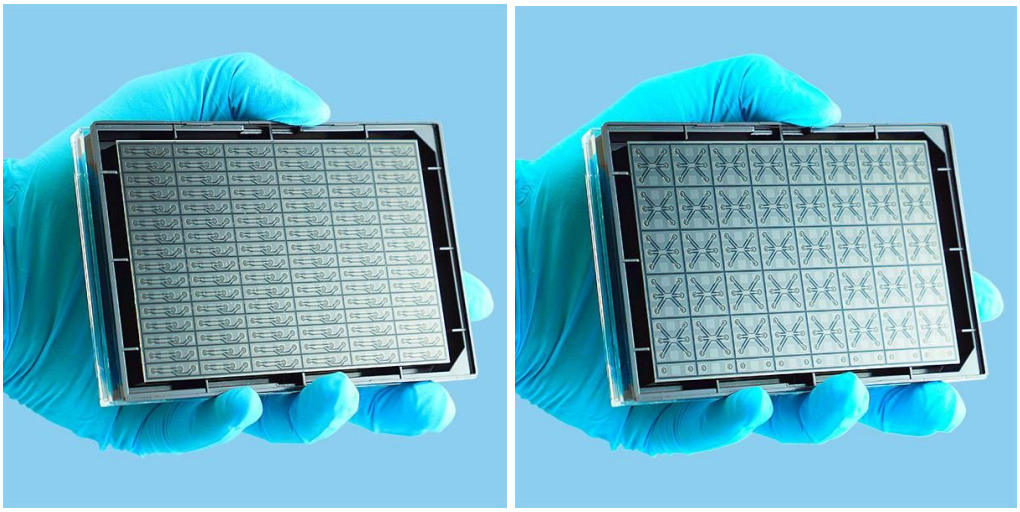
Mimetas

Founded by Paul Vulto and Jos Joore (during a dinner conversation), based in Leiden (NL) Mimetas also maintains a small office in the US Rockville (MD). Mimetas is microfluidic tissue culture technology based on its proprietary OrganoPlate platform that supports 3-dimensional tissue culture under continuous perfusion, via a membrane-free co-culture in a standard 384-well plate format.

The company also received USD $1.6M of grant funding from NC3Rs, GlaxoSmithKline and BASF as a part of the Neuratect CRACK IT Challenge on December 22, 2015. European Regional Development Fund, Sanofi and Abbvie also participated in the round. The company will use the funding to develop, analyze and validate high-throughput neurotoxicity models using its OrganoPlate technology with CDI's iPS neurons.

Products

Mimetas takes a different approach to OOC from Emulate and it's other competitors that all use some sort of microfluidic system to mimic the blood flow of an organ along with various instrumentation systems. Mimetas OrganoPlate platform that supports 3-dimensional tissue culture under continuous perfusion, with membrane-free co-culture in a standard 384-well plate format. This renders the technology suitable for low- to high-throughput screening applications.



Source: Mimetas

The OrganoPlate® 2-lane and 3-lane costs USD $400 per chip.

Source: Mimetas

The Perfusion Rocker Mini costs USD $1,500

Much like some of the OOC companies, Mimetas develops a range of tissue and disease models, including kidney toxicity and disease models, iPSC-derived neuronal brain tissue models and liver models.

Market, Industry & Trends

Emulate focuses on the life sciences sector[17] in biotech, pharma, clinical laboratory services and (possibly) the diagnostics markets. Their system currently targets the drug discovery market by providing a “better” safety testing and in the near future real-time disease modeling capabilities.

Biotech and Pharma

The global pharma market is expected to reach USD $1.12T[18] by 2022 with a CAGR of 6.3% with PhRMA (Pharmaceutical Research and Manufacturers of America) estimating US companies alone investing +$75B[19] annually just in R&D.

The global biotech market is expected to reach USD $727.1B by 2025 with a CAGR of 7.4%

- The global drug discovery technology market is estimated to reach +$85.8B[20] by 2022 with a CAGR of 9.4% from 2017-2022.

The primary use within both biotech and pharma industry for OOC is within drug discovery programs which are long, expensive and have a high number of failure where they involve:

1. finding candidate molecules with a therapeutic effect on the disease state
2. confirming effectiveness through preclinical/clinical trials before being approved

[17] https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-ls-outlook-2018.pdf
[18] http://pharmaceuticalcommerce.com/business-and-finance/global-pharma-market-will-reach-1-12-trillion-2022
[19] http://phrma.org/industryprofile
[20] https://globenewswire.com/news-release/2018/02/13/1340167/0/en/Drug-Discovery-Technology-Market-to-Reach-85-8B-in-2022.html

The entire process can take up to 15 years (where 1 & 2 described can take up to 6 years) and roughly costs USD +$2.7B[21] per drug.

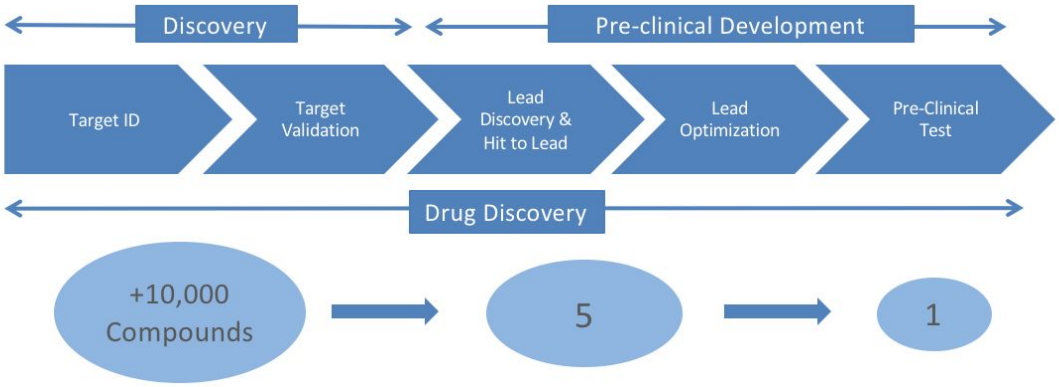
Further refinement of Emulate's instrumentation system will possibly allows Emulate to compete in the clinical laboratory services market[22] worth $146.41B by 2022 and $327B[23] by 2025, $113.44B in 2017 with a CAGR of 5.2%.

Problem

The primary and immediate use case for Emulate and OOC is to provide "better" predictive tools for drug discovery and development process because:

- An estimated +92%[24] of all drugs found safe and therapeutically effective from animal tests, fail during human clinical trials due to their toxicity and/or inefficacy.[25]
- More than half of the drugs that are approved by the FDA must later be withdrawn or relabeled due to severe, unexpected side effects that animal testing did not predict.[26]
- Adverse drug reactions (ADR) are the 4th[27] leading cause of death in the US, killing +100K patients annually and costing USD +$4B in direct hospital costs.
- In 2009 more than +2MM[28] Americans received emergency hospital treatment in 2009 for an adverse reaction to a prescribed medication.
- "Currently, 9/10[29] [30]experimental drugs fail in clinical studies because we cannot accurately predict how they will behave in people based on laboratory and animal studies."

Drug Discovery/Development



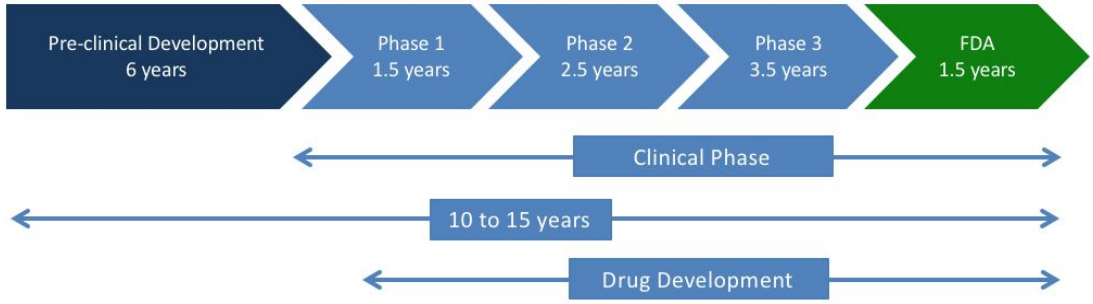
The drug discovery phase (which the pre-clinical phase typically takes +6 years) currently relies on costly and time-consuming animal models for PK studies, efficacy and toxicology studies because existing cell culture models fail to recapitulate complex, organ level disease processes in

[21] https://www.forbes.com/sites/matthewherper/2017/10/16/the-cost-of-developing-drugs-is-insane-a-paper-that-argued-otherwise-was-insanely-bad
[22] http://www.bio-itworld.com/Press-Release/Clinical-Laboratory-Services-Market-Expected-To-Grow-At-a-CAGR-Of-6-0--From-2014-To-2020--Grand-View-Research,-Inc-
[23] https://www.grandviewresearch.com/press-release/global-clinical-laboratory-services-market
[24] https://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.html
[25] http://www.who.int/intellectualproperty/documents/en/FDAproposals.pdf
[26] http://archive.gao.gov/d24t8/141456.pdf
[27] https://www.ncbi.nlm.nih.gov/pubmed/22253191
[28] https://www.samhsa.gov/data/sites/default/files/report_1965/ShortReport-1965.html
[29] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2642860
[30] http://www.understandinganimalresearch.org.uk/news/communications-media/nine-out-of-ten-statistics-are-taken-out-of-context

humans. It's no secret that animal models are regarded as outdated tools with limited predictability, yet they are still used.

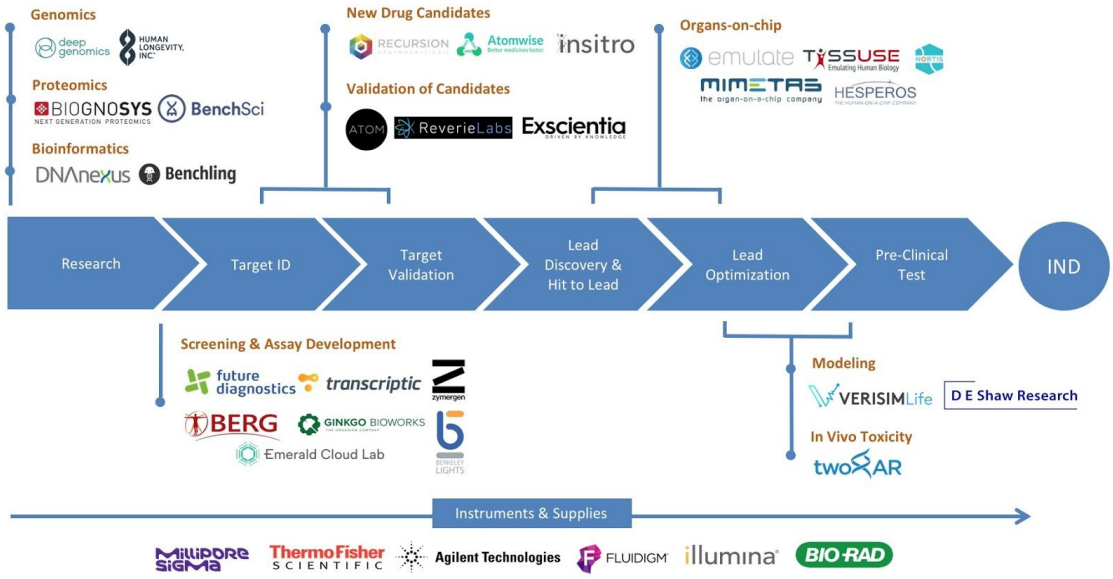
Drug Development	Target ID and Validation	Lead Identification	Lead Optimisation	Preclinical Safety
Testing Requirements	Confirm presence of relevant targets	Baseline effect on physiology	Assess impact on disease phenotype	Identify and assess potential side effects
	Thousands of compounds	Tens to hundreds of compounds	Two to three compounds	One to two compounds
	High Throughput systems	Medium to high throughput systems	Low throughput systems	Low throughput systems

When you look at the value chain, it requires an understanding of the problem that needs to be solved by deploying OOC and using them at certain points of the drug discovery phase the whole entire process can be shortened.



The drug development phase (which takes about 10-15 years) after pre-clinical development.

There are several noteworthy examples of startups tackling drug discovery at the different stages, most of which are using AI and/or ML, however the application for OOC immediately lays within the stages lead discovery/hit to lead and lead optimization.



A general overview of startups and companies involved in the drug discovery sector.

A paper entitled “The ascendance of microphysiological systems to solve the drug testing dilemma”[31] looks at the topic from an industry perspective and importantly highlights the role that regulatory bodies play as any shift to a new technology will require full acceptance by a number of national and international bodies. The review also particularly discusses how a microfluidic platforms address the ADME (absorption, distribution, metabolism and excretion) criteria that are core to the pharmacology community.

Product

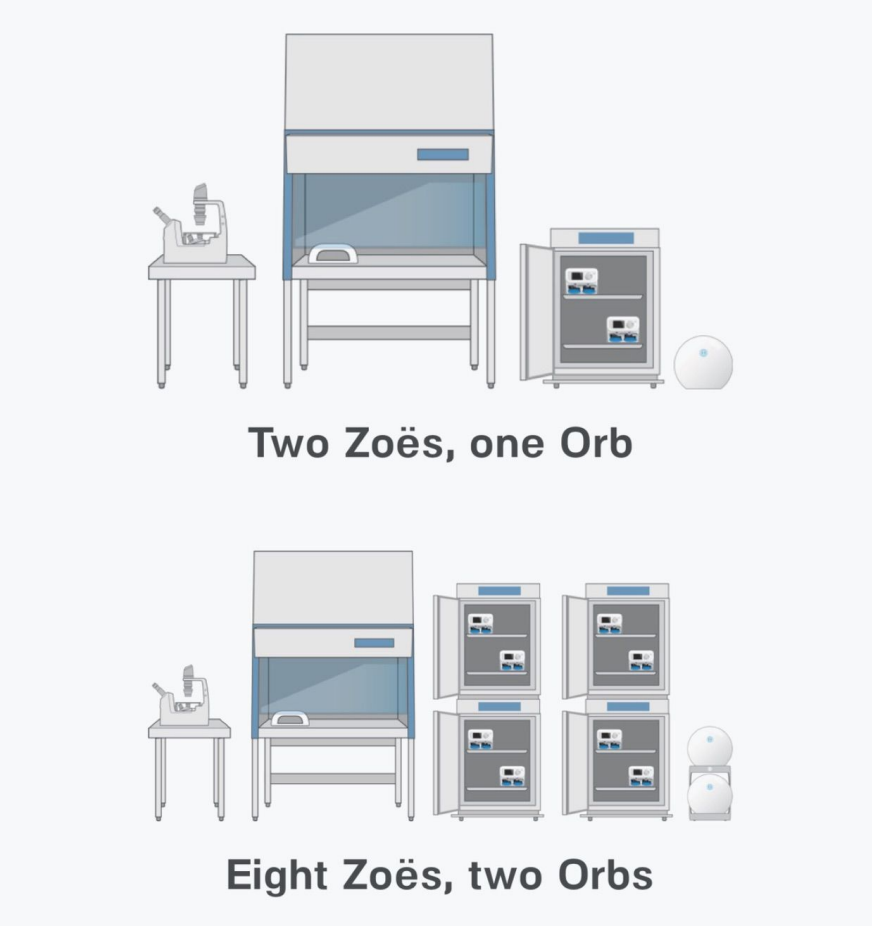
Emulate currently manufactures (through a third party manufacturer) and directly sells the Human Emulation System™ which consists an instrumentation system, the disposable organ chips and it’s software platform. Emulate currently claims which prides itself for being modular/scalable, automated with the ability for reproducible data that is more precise than animal.

Zoe & Orb

According to Emulate their “easy-to-use automated instrumentation system (Zoë-CM1™ culture module) and it’s external gas mixer (Orb-HM1™ hub module) maintains the organ chips and enables the end-user to conduct experiments, while Emulate’s software suite facilitates experimental design and execution, analysis of data, modeling of outcomes, data storage, and mining”. Despite released images and some data of the system, not much is actually known about the actual instrumentation system and it is hypothesized that the system can actually be much smaller through advancements in microfluidics.

Emulate’s instrumentation system currently has 2 separate trays (underneath) that each holds 6 organ chips. The instrumentation system is put inside an incubator (with an external gas mixer) and currently 4 fits in one Thermo Fisher CO2 incubator.

[31] https://www.future-science.com/doi/10.4155/fsoa-2017-0002

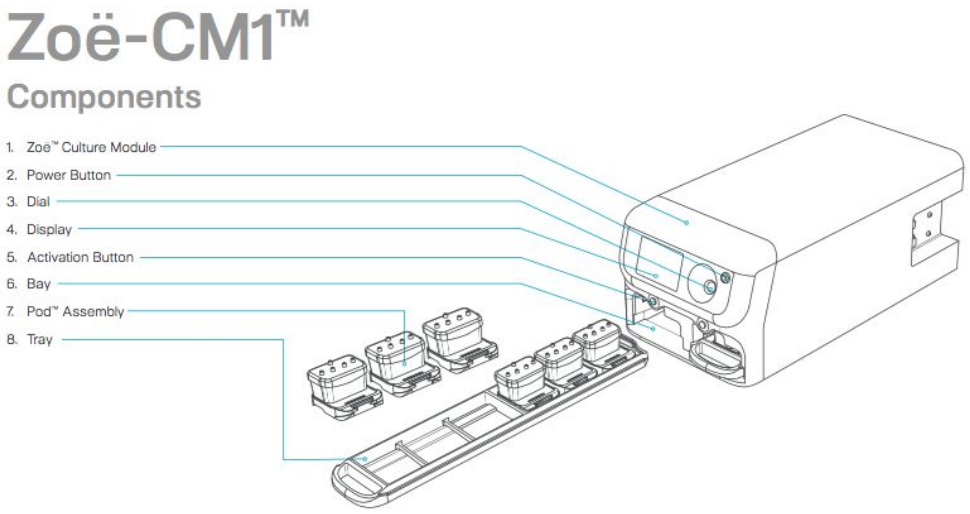


The Diagram shows the various configuration in a lab either 2 Zoes + 1 Orb or 8 Zoes (with 2 incubators) + 2 Orbs. (Source: Emulate)

What is known is that there is an instrumentation system roughly the size of a large desktop printer (roughly 1-2 ft x 3-4 ft x 8-10 inches or so) that sits inside an incubator and an “orb” that provides gas mixture. Before Jan 2019, the whole system (instrument + orb) costs roughly $70K-90K (with a life cycle of roughly 3 years) to the pharma and research institutions. The instrumentation system provides pressure for flow and vacuum for the stretching along with the software to control the system.

As of Aug 2018, Emulate is in the process of scoping version 2.0 of Zoe and is expected to release a beta version sometime between Q4 2019 - Q2 2020. Based interviews with [redacted] it is estimated that they are most likely looking to have a product vision of something “that is more smaller, stand alone and integrating with existing instrument.”

An image of the instrumentation system (Zoe) and an external CO2 (Orb) incubator with the 2 trays holding the OOC. (Source: Emulate)



Zoe diagram[32] (Source: Emulate)

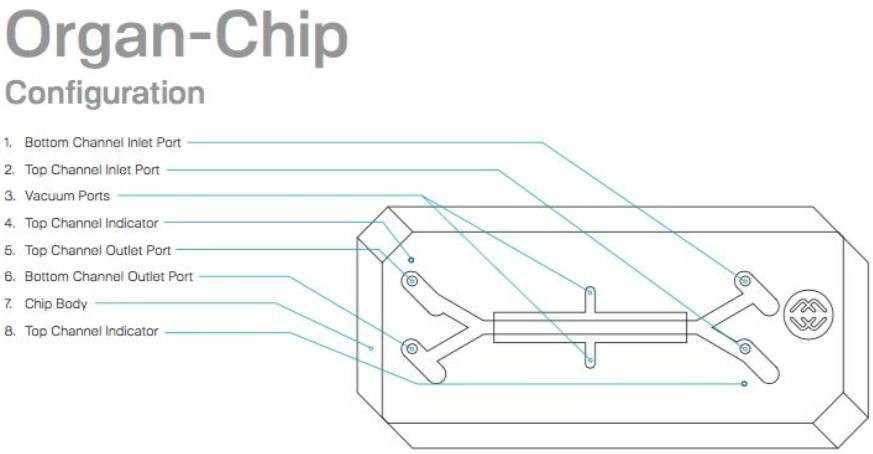
[32] https://emulatebio.zendesk.com/hc/en-us/articles/360010125293-Zo%C3%AB-Introduction

Based on past systems, the first generation Zoe is a significantly smaller verses the instrumentation system from when Emulate was still part of Wyss Institute and was funded through the $37M grant from DARPA[33]. (Source: Wyss Institute)

Chip-S1

The Emulate OOC chips (Chip-S1) are not integrated organs-on-a-chip, but a microfluidic chip that is made of silicon and involves 3 key elements:

1. a microfluidic chip that is polymer based,
2. live microtissues that are cultured onto the chip,
3. components for stimulus loading to mature the microtissues.



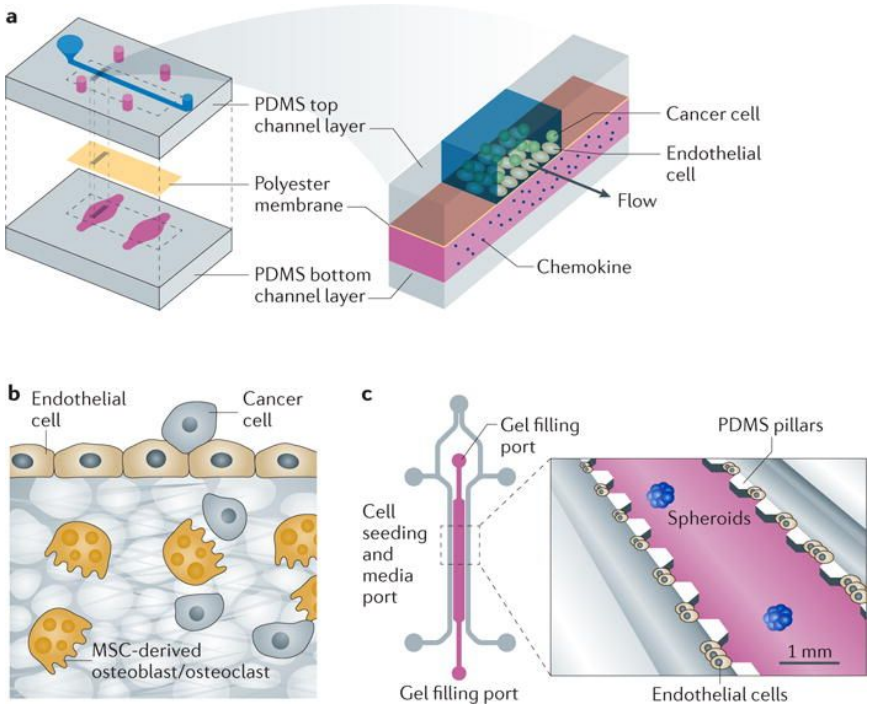
The actual chips sold are all clear and do not have the red blue dies (Source: Emulate)

Use Case of S1

The S1 has the ability to recapitulate the structural and functional complexity of various human organs such as the liver, heart, lung, intestine, kidney, brain and bone. An example of the S1 is the lung-on-a-chip. This example features a mechanically active alveolar–capillary barrier in the

[33] https://wyss.harvard.edu/wyss-institute-to-receive-up-to-37-million-from-darpa-to-integrate-multiple-organ-on-chip-systems-to-mimic-the-whole-human-body

human lung with the ability to mimic physiological breathing motions. An example with this type of chip is used to study pathogenic bacteria's interaction to the lung to modeling lung diseases[34] [35].

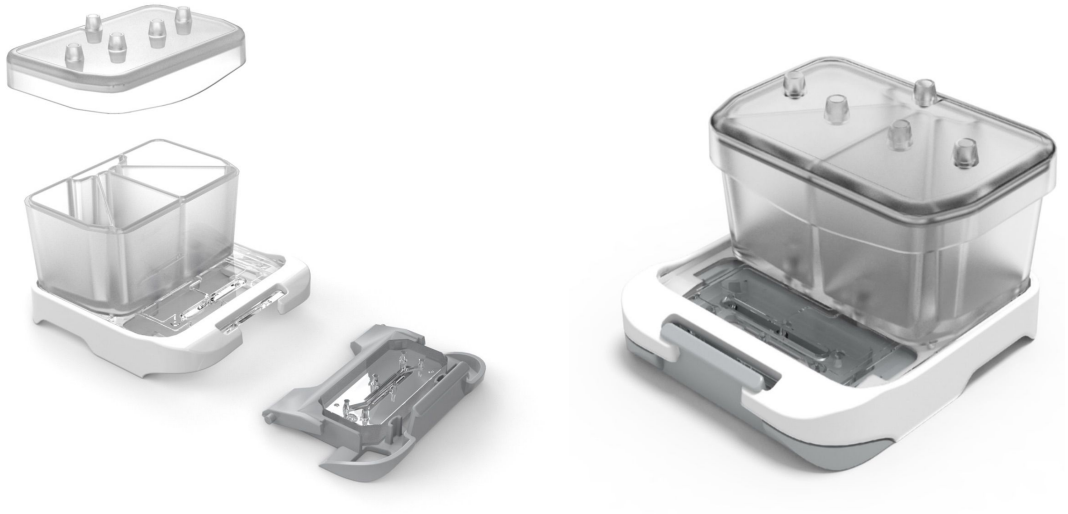


This diagram shows how a lung-chip is was used to reveal breathing's critical role in lung cancer development[36].

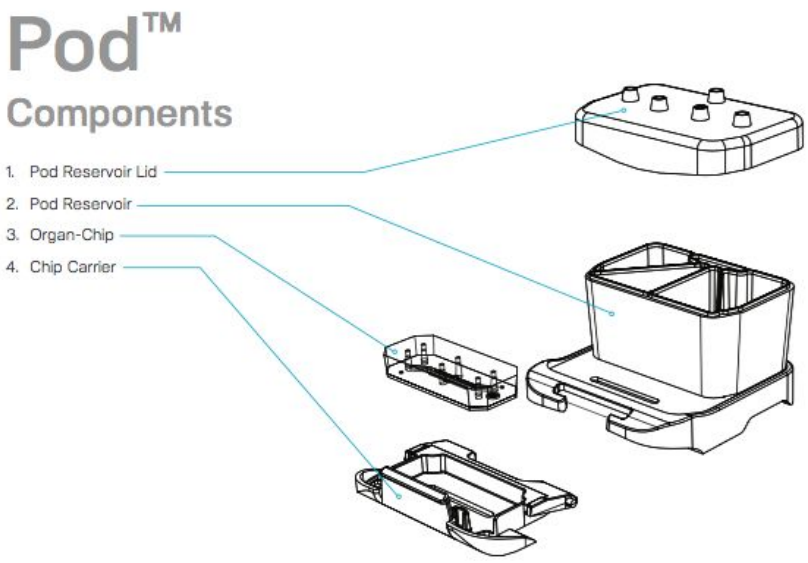
Pod-1

Emulate's chips has an additional outer component known as Pod-1, that consists of 2 reservoir used to supply fresh media to the cells and 2 reservoirs to collect bypass liquids for analysis. The top of the unit features ports where the pump from the instrumentation system connects to. 1 Zoe can contain

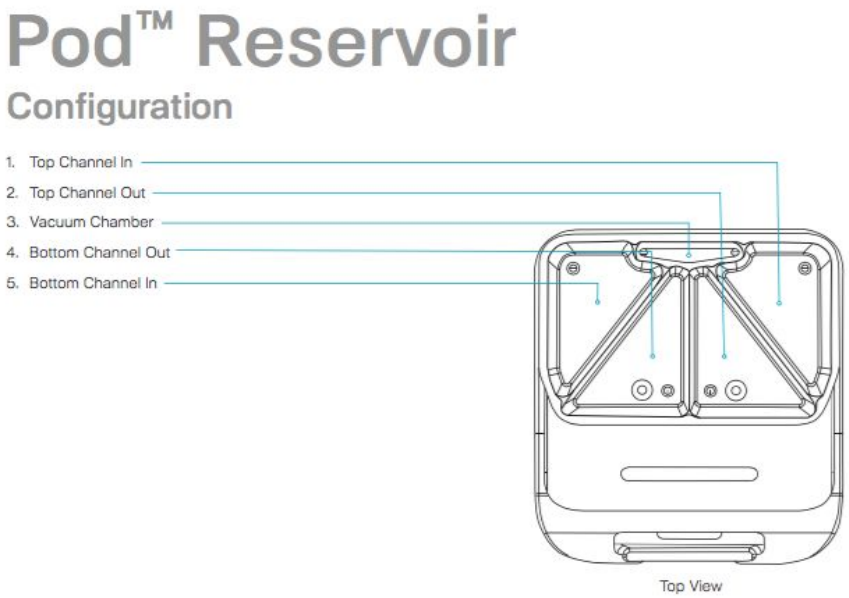
[34] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4826389
[35] https://vector.childrenshospital.org/2017/10/lung-cancer-organ-chips
[36] https://vector.childrenshospital.org/2017/10/lung-cancer-organ-chips



Source: Emulate



Source: Emulate



Source: Emulate

According to internal sources at Emulate, it is estimated that 1 chip and containment has a unit cost of at least $500 to pharma/biotech companies and can go as high as $750. (Source: Emulate) with each unit costing around $100 to manufacture.

Through the Emulate Shop (their ecommerce store), Emulate offers the Basic-Kit for USD $8,000 [37] which includes 3 chips with 3 pods, reagents and training for first time users. This kit seems to be something for on-off purchase or academic researchers (Source: Emulate)

Source: Emulate

[37] https://shop.emulatebio.com/basic-kit

Business Model

Emulate currently (before Jan 2019) solely sold to pharma/biotech companies and academic institutions directly (to use and test) and through announced partnerships (to be used in official drug discovery programs).

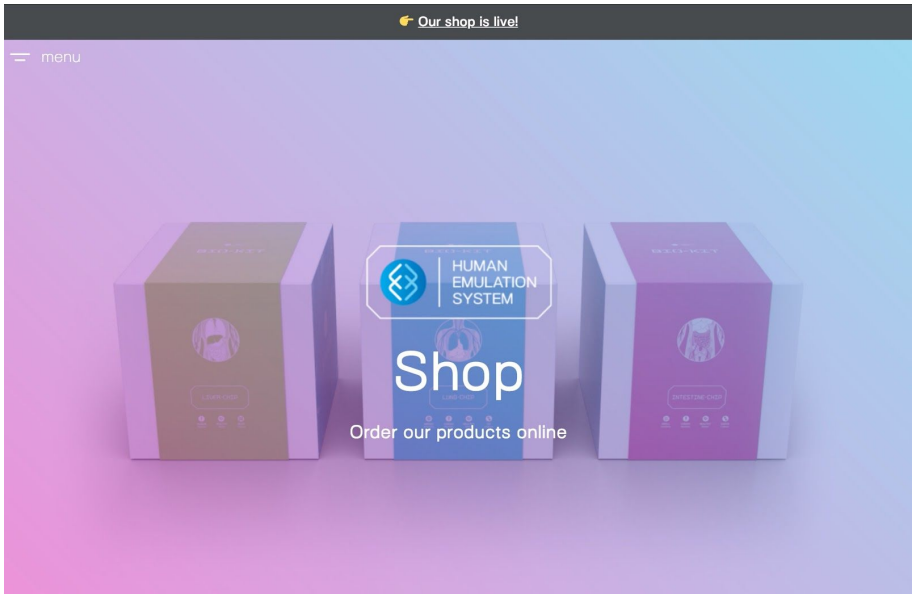
It is estimated that Emulate sells roughly 100-500 chips (+ the outer “pod” component) per month at a price point of $500 (low) and $1000 (high)

100 chips/component x $500 = $50,000/mth and $600,000/yr (min)
300 = $1.8M (max)

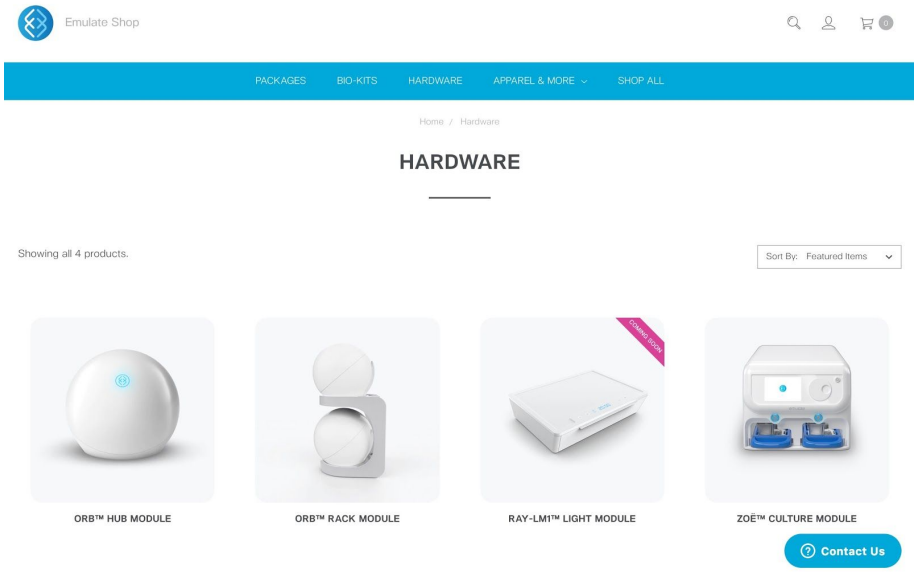
100 chips/component x $1000 = $100,000/mth and $1,200,000/yr (min)
500 = $6M (max)

These numbers would be just in organ-chips and the pods alone.

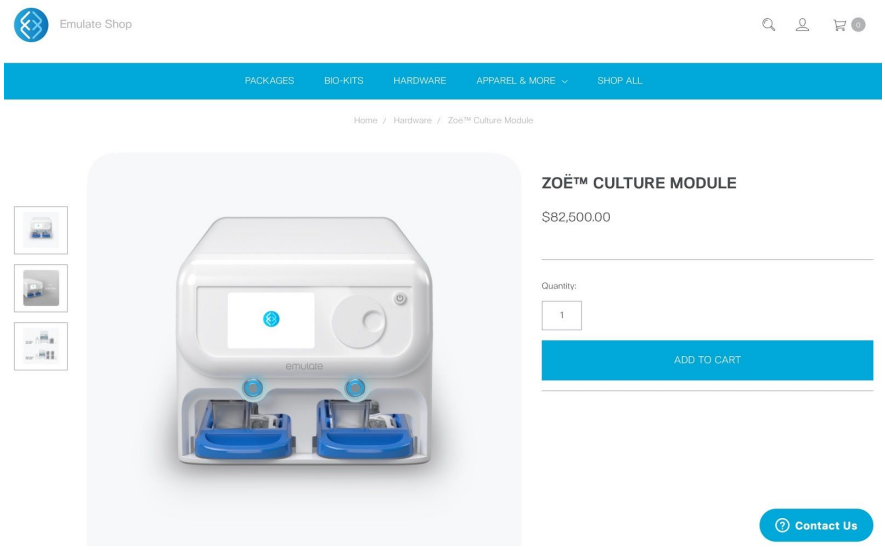
However as of Jan 2019, Emulate has announced details of Zoe, Orb, Pod-1 and Chip S-1 along with having an ecommerce store that allows non partnered companies or individuals purchase the system starting at $82,500 for just the Zoe or a Research Starter Package for $195,000 which includes 2 Zoes, 1 Orb and a 24 organ-chip pack (Basic Kit).



An actual screen cap of the live Homepage for the Emulate Store.



Source: Emulate



Source: Emulate

Users

Current users of the Emulate's Human Emulation Systems are Johnson & Johnson, AstraZeneca, Roche, Merck, Pfizer, Takeda, Cedar-Sinai Regenerative Medicine Institute and The Michael J. Fox Foundation.

According to senior management staff at Emulate, about 12 or so pharma partners currently on board "about 25% are paying customers" (the actual names who which companies were paying were not disclosed).

Johnson & Johnson

Emulate formed a research collaboration with Janssen Biotech, a division of Johnson & Johnson in 2015 (which was their first commercial partner[38]) to deploy Emulate's thrombosis-on-chip and liver-on-chip (which J&J helped validate) to better predict the potential human response of drug candidates and improve the drug development process [39]. During this period the thrombosis-on-chip has demonstrated[40]:

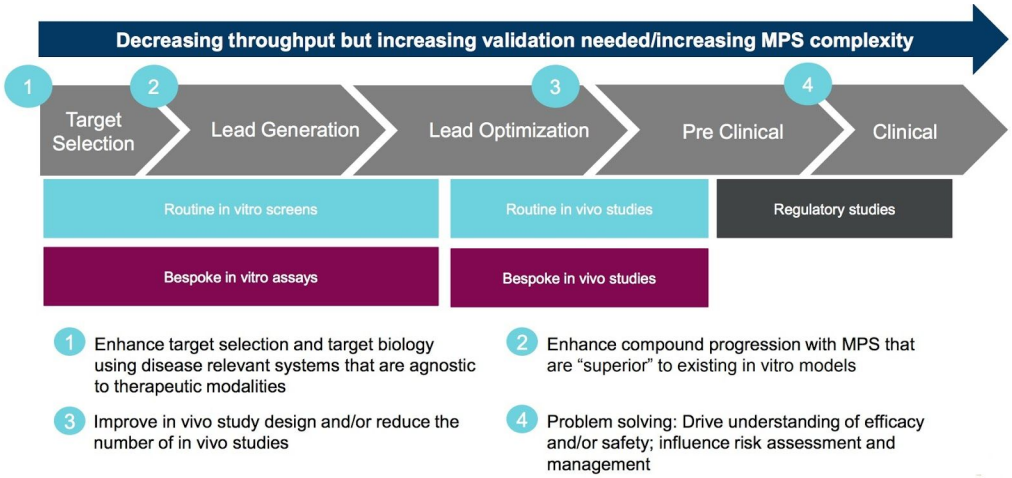
- Creating a microenvironment to emulate the physiological function of endothelium-platelet interactions, flow of blood, and related mechanical forces involved in platelet aggregation and clot formation
- Engineering a microfluidic-based system and integrated analytical methods that embodied an in vitro approach to assess the dynamic functions of platelet interactions with living endothelial cells
- Demonstrating molecular and cellular level resolution to evaluate platelet activation and aggregation and interaction of endothelial dysfunction and blood-derived factors in causing thrombosis or bleeding
- Analyzing platelet-endothelial interactions under pathophysiological conditions relevant for thrombosis research.

According to Geraldine Hamilton (Chief Science Officer): "For the first time, Emulate's Organs-on-chips have demonstrated the ability to recreate the key drivers of thrombosis within a chip in a way that mirrors what happens in the human body. We accomplished this Thrombosis-on-Chip milestone working alongside our colleagues at Janssen and Harvard, and we are proud to advance the frontiers of organs-on-a-chips technology to provide insights into the mechanisms of action of thrombosis."[41]

AstraZeneca

In 2018, Emulate announced its collaboration with AstraZeneca's Innovative Medicines and Early Development (IMED)[42] Biotech Unit within the labs of the IMED Drug Safety organization. So far IMED has invested in $1B in research[43] and $90M in diagnostic partnerships[44] since its inception in 2010.

[38] https://www.xconomy.com/boston/2015/06/18/with-jj-deal-emulate-nabs-first-partner-for-organ-on-chip-tech
[39] http://www.bio-itworld.com/2015/6/18/johnson-johnson-harvard-spinoff-emulate-unveils-new-organs-chips.html
[40] https://wyss.harvard.edu/emulate-announces-strategic-collaboration-with-johnson-johnson-innovation-to-use-organs-on-chips-platform-to-better-predict-human-response-in-drug-development-process
[41] https://www.marketwatch.com/press-release/emulate-announces-strategic-collaboration-with-johnson-johnson-innovation-to-use-organs-on-chips-platform-to-better-predict-human-response-in-drug-development-process-2015-06-18?reflink=MW_news_stmp
[42] https://www.biospace.com/article/emulate-inc-and-astrazeneca-collaborate-on-organs-on-chips-technology
[43] https://www.astrazeneca.com/content/dam/az/Our-Science/IMED-Biotech-Unit/IMED_Brochure_20pp_Version%20v3%2013-7.pdf
[44] https://www.astrazeneca.com/content/dam/az/our-company/our-company-052017/investor-relations/presentations-and-webcast/2014/IMED---Mene-Pangalos.pdf



AstraZeneca's strategy[45] to deploy OOC/MPS across their value chain. (Source AZN)

The initial focus for AstraZeneca will be the liver-chip for safety testing of drug candidates across the AstraZeneca's pipeline with the goal of submitting organ-chip data within the regulatory framework for new drugs. An example of AstraZeneca's efforts with the liver-chips are investigating insulin resistance[46] to the liver to explore the impact on beta cell proliferation.

Upon the success with the lung-chips, AstraZeneca plans to further develop (3) other chips, in which they hope to imitate a lung tumor, lung, and glomerulus in the kidney.

Roche

In 2018 Roche announced a partnership with Emulate across multiple R&D programs in a three-year partnership, with the aim of discovering and developing new classes of therapeutic antibodies and drug combinations. Though not much is known but one goal of the partnership is to use patient-derived cells to make headway on the idea of personalized drug safety, using the chips to test how a patient or patient group might respond to a drug. The research will initially focus on using lung-chip and "brain-chip with the opportunity to expand to use other OOC.

Merck

Merck (known as MSD outside the US) announced a partnership with Emulate in 2015[47] to use organ-chips on Merck's discovery programs to improve models of human inflammatory diseases and better predict the potential human response of therapeutic candidates. The research will focus on using Emulate's small airway lung-chip (specifically asthma and COPD) and intestine-chip to enable predictive modeling of inflammatory processes in the human lung and the gastrointestinal system.

Takeda

Takeda[48] announced its partnership with Emulate in 2018 to specifically use Emulate's "Intestine-Chip" for gastrointestinal disease R&D. According to Geraldine: "the ability to

[45] http://3d-tissuemodels.com/wp-content/uploads/sites/189/2017/09/0900-Kristin-Fabre-ilovepdf-compressed.pdf
[46] http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2017/11/WC500238316.pdf
[47] https://emulatebio.com/press/lung-chip-new-capabilities
[48] https://emulatebio.com/press/advisory-emulate-takeda-partner

accurately model the intestinal epithelium is a key to opening up new insights into the complex pathways of GI diseases and drug mechanisms of action, and we are delighted to apply our Intestine-Chip to support drug innovation with Takeda, a world leader in developing treatments for GI diseases,"

FDA

In 2017, FDA[49] Signed a collaborative agreement with Emulate, Inc. through a Cooperative Research and Development Agreement (CRADA) to advance OOC as a toxicology testing platform that will be used to understand how a product (including foods, dietary supplements and cosmetics) affects human health and safety.

According to Geraldine regarding the FDA, "we are looking forward to combining our expertise with leading researchers at FDA to explore how our Organs-on-Chips technology integrates with existing product testing frameworks – opening the potential for a new paradigm for establishing improved standards, creating more predictive models, and helping to better evaluate safe products for human use."[50]

Issue[51]

Despite the continual advancements of OOC and the rapid commercialization of the technology, the entire systems themselves have their downsides and has several issues. Currently the OOC are still a niche market at ~$7.5M (estimated in 2016) reaching somewhere between $60-$117M by 2022[52].

The first issue starts with the creation of the OOC systems, which are not a simple process. According to Dr. Yu Shrike Zhang (instructor of medicine/associate bioengineer, Harvard Medical School) "Challenges include reproducing the architectural complexity of the human tissues and organs in vitro in a miniaturised fashion, and how to link them in the right format (arrangement) that the interconnected systems also recapitulate the human tissue/organ interactions,"

Another example with OOC points specifically to the membrane itself is often made of some sort of plastic (silicon), it can disrupt cell interactions and skew results. Professor Abhinav Bhushan[53] from Illinois Institute of Technology sought to create a more natural membrane that would encourage the normal growth and development of human cells. In a paper co-authored by Zhang titled *Multisensor-integrated organs-on-chips platform for automated and continual in situ monitoring of organoid behaviors*, the research also pointed out "PDMS at this prototyping stage, which is not optimal for organs-on-chip applications due to their potential adsorption and absorption of hydrophobic small molecules and drugs.[54]"

Along with the challenges of development of OOC, another problem that can also occur with their adoption is validation, which is seen by many as one of the biggest hurdles. Expert Pharmaco-Toxicologist Dr. David Jones (Clinical Trials Unit, MHRA) describes how "Given the

[49] https://emulatebio.com/press/fda-collab-agreement-emulate
[50] https://emulatebio.com/press/fda-collab-agreement-emulate
[51] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5661765/pdf/10.1177_1535370217700523.pdf
[52] https://www.i-micronews.com/images/Flyers/MedTech/YDMT17013_Organs-on-Chips_Market_and_Technology_Report_March_2017_Flyer.pdf
[53] https://www.researchgate.net/publication/319248695_Organs-on-a-Chip_A_Future_of_Rational_Drug-Design
[54] https://www.pnas.org/content/pnas/114/12/E2293.full.pdf

enormous potential these models hold, Regulators like myself believe that it is vital that we work alongside investigators and industry in the development and validation processes because this presents a new challenge to Regulators and Industry alike.[55]" It is hoped that these collaborative efforts will help to ease the widespread adoption of these models. Adding Dr. Jones further mentions "Given the complexities of organ function and regulatory requirements, it is unlikely that organ-on-chip models will replace the current animal based pivotal safety assessment testing paradigm anytime soon. Data from them can, however, inform and add to the information gained from these pivotal safety studies, especially in investigating unexpected effects seen either in animals or in the clinic."

Even though the promise of OOC with its main value efficiently performing assays that is closer to human physiology (as opposed to in vitro and in vivo methods), the technology will need years to validate the technology, though it shows that Emulate is in the best position to be at the forefront of OOC innovation.

Team

Emulate originally started off at The Wyss Institute through DARPA's MPS (Microphysiological Systems) program where a lot of it's early researchers formed Emulate. The key executive management team are as follows:

James Coon (Co-founder and CEO) most recently served as an EIR at the Wyss Institute, with a focus on providing researchers with insights on commercialization and product development, target markets, and fundraising strategies in both Nanotherapeutic and OOC technologies. Coon has served as a co-founder, executive management, and strategic partner for numerous healthcare and biotech startup companies, including roles as President of RxGen, President and CEO of BCS, Inc., President and CEO of HepatoTech, Inc., Executive Vice-President of CellzDirect, and the Senior Director of Business Development for RTI International. He received his undergraduate degree in Biochemistry from the Rochester Institute of Technology, and completed his graduate work in liver cell biology at the University of North Carolina at Chapel Hill School of Medicine.

Geraldine Hamilton (Chief Scientific Officer & President) prior to joining Emulate's founding team, she served as Lead Senior Staff Scientist with the Wyss Institute. At the Wyss Institute, Hamilton lead the OOC program and managed the multidisciplinary team responsible for developing, translating and commercializing the OOC technology. Hamilton's career spans industry, academia and the start-up world. Prior to her tenure at Harvard University, Hamilton spent more than 11 years in the pharmaceutical industry in leadership roles managing drug discovery teams. Her research achievements helped advance the development and application of human relevant in vitro models for drug discovery. Hamilton was a founding scientist and VP of Scientific Operations for CellzDirect and was responsible for the successful translation of CellzDirect's technology from academia to broad use and acceptance across the industry.

[55] https://www.technologynetworks.com/drug-discovery/articles/organs-on-chips-applications-challenges-and-the-future-288031

Daniel Levner (CTO) prior to joining Emulate's founding team, he was a Senior Staff Scientist with the Wyss Institute, where he led the advanced engineering team responsible for developing Emulate's OOC platform. Levner played a key leadership role in managing the multidisciplinary OOC team by formulating innovative approaches for fostering close collaboration and in-depth exchange between biologists and engineers. Levner brings this tight integration of disciplines to Emulate, where it is a defining part of the company's culture. Prior to directing the OOC program, Levner worked with world-renowned Harvard geneticist Dr. George M. Church in programs related to medical diagnostics, DNA/RNA sequencing tools, and multiplexed analysis techniques. As an entrepreneur, Levner co-founded a medical diagnostics startup company, and earlier in his career, an optical telecommunications startup company.