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REPLACING ANIMAL MODELS WITH COMPLEX 3D TISSUES

October 2019

Animal Testing – The Problem

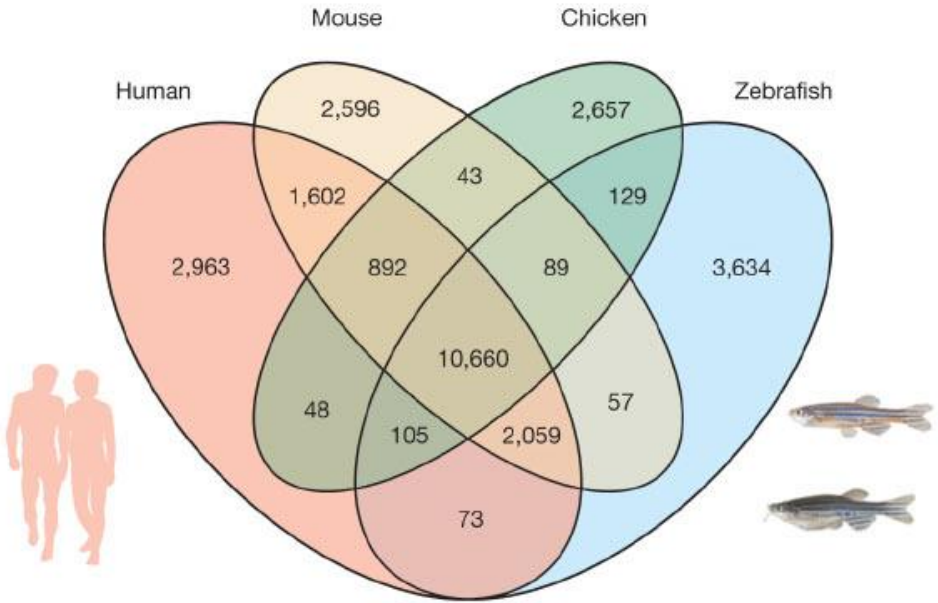
- Animals fail to show true human disease
- Especially true for NASH (fatty liver disease)
- #1 problem cited by researchers in NASH – drugs that work in animals fail in humans
- 100% clinical failure rate in NASH to date

- "We test them [drugs] on animals, and it's not reliable... Ultimately, the ability to develop and test medicines will be you on a chip" – Francis Collins, NIH Director, at TEDMED, discussing the challenges with animal models and the new developments in 3D tissue models

NASH – non-alcoholic steatohepatitis

Animal models are outdated technology

Genetic overlap across species
(number of genes)



Species	% of human overlap
chicken	64%
zebrafish	70%
mouse	83%

Human–mouse overlap is not much more than zebrafish

The gaps with preclinical species result in **drug clinical failures**

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Moving Past the Animal Testing Paradigm

- 3D Bioprinted tissues - ***fully human*** system
- These models show better biology than animals
- Strategy – apply these models in disease areas where clinical failure rate is high
- Viscient blazing a trail in use of these models
- Will transform drug discovery – reduce clinical failures and thus cost of drugs
- $1B+ per approved drug is actually $150M for each drug burdened by an 88% average clincal failure rate
- Reduction of clinical failure rate to 70% would reduce average cost per approved drug to $500M

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- We are experts in using advanced 3D tissues in drug discovery
- Our aim is to produce novel targets and drugs, taking them to clinical proof of concept (POC)
- We are user of bioprinting, not a provider
- We solve biology problems to get to new drugs

- First project NASH (fatty liver disease) due to strong unmet need
- Then expand into new disease areas beyond liver

- Goals for next 12 months:
  - chemistry to generate lead drug molecule with strong data set
  - be on path to IND (Investigational New Drug filing to start Phase 1 clinical)
  - expand process to additional tissues and disease areas

Accomplishments to date

- *In vitro-in vivo* correlation (IVIVC) established for 3D NASH fibrosis model (First in class)
  - Pathologist-confirmed clinically relevant fibrosis patterns
  - Multiple pathology marker assays established
- Map of novel targets provided by single cell gene expression analysis
  - Solved complex experimental and bioinformatics challenges needed to leverage single cell in this context – world class platform
  - Patent applications prepared for filing on selected targets in disease progression
- A second 3D NASH model provides higher throughput screening
  - We have target ID, screening, and validation capability using multicellular 3d tissues that are less complex than bioprints
- Lead target has multiple levels of genetic validation
  - GWAS, single cell gene expression in disease vs. normal, plus additional validation
- We have blazed the trail for new global paradigm of discovery
  - Can repeat same techniques in additional tissues / therapeutic areas

3D Tissues Allow for Better Biology

- **Minimizes plastic interaction**
- **More relevant cell-cell interaction**
- **Four or more cell types**

- **Cells in full contact with plastic**
- **One or two cell types**

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Vicient's custom 3D model from NASH donors

(primary cells from NASH donor tissue)

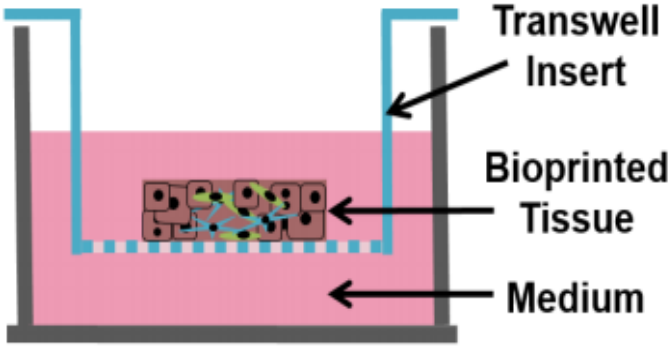
Hepatocytes

Stellate Cells

Kupffer Cells

Endothelial Cells

By careful selection of cells, handling during processing, conditions during culture, the disease is reproduced "in a dish"



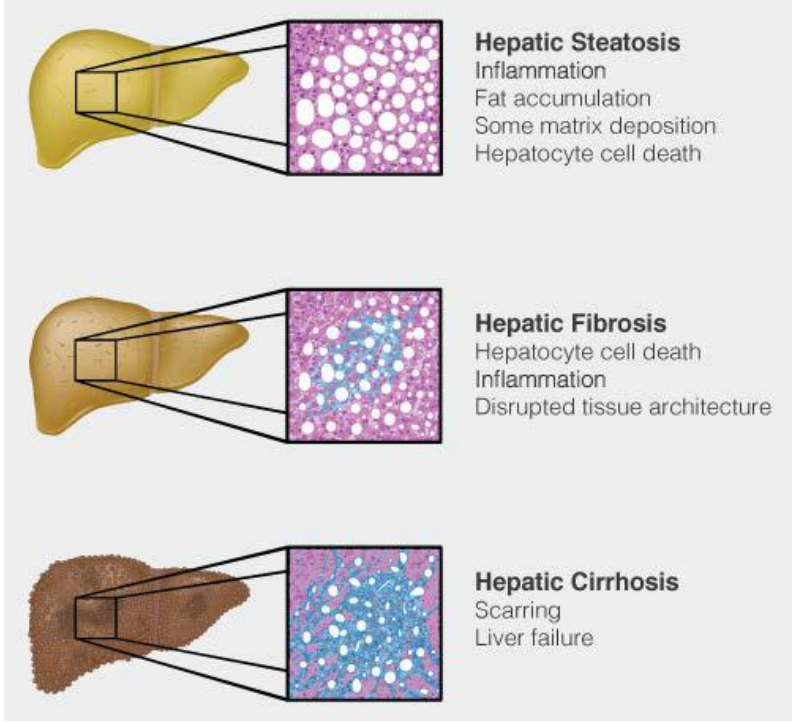
Organovo, AASLD 2017

NASH Disease Pathology Makes 3D Tissue an Optimal Model

1. Liver hepatocytes accumulate fat droplets
2. Surrounding cells detect the change and deposit collagen
3. Collagen builds to a runaway level, known as cirrhosis

No fibrosis can be seen in 2D culture. Viscient model shows collagen "chicken wire" surrounding cells, just as in patients. Model read by Pathologist at major clinical center to confirm patterns match native NASH.

NASH Progression



NASH – Non-alcoholic steatohepatitis, "fatty liver disease"

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NASH Patient Opportunity

- Historical development is littered with clinical failures
- Failure due to reliance on animal models
- Liver toxins, bile duct ligation used historically in animals versus metabolic imbalance in humans
- Multiple failures in 2019: Gilead Phase 3, Conatus Phase 2b
- Some drugs will likely succeed, but provide benefit to small numbers of patients
- Door open for better drugs that better address disease and demonstrate clinical translation of preclinical promise

Most promising drugs in clinical pipeline will offer minimal benefit and leave significant unmet need:

Intercept

Obeticholic Acid (OCA)
Recent Phase 3 readout
23% of patients benefit vs 12% placebo

Madrigal Pharmaceuticals

THR-β agonist
Phase 2
Biopsy improvement in
~27% patients vs. 6% placebo

NASH Market Opportunity

Non-alcoholic Steatohepatitis

- NASH affects up to 12% of U.S.[1]
- Prevalence doubling every 10 years
- No approved treatment options
- NASH will soon be the leading cause of liver transplants
- NASH drug market future revenue est. $40B/yr [1]

[1]Wall St. Journal, Jan. 2019

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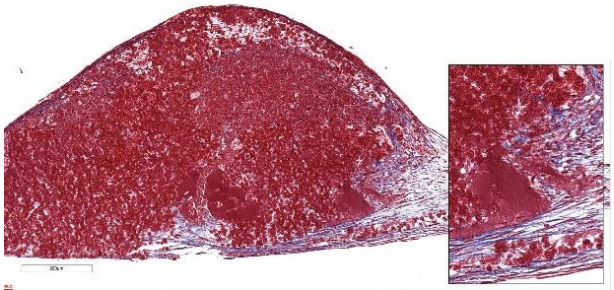
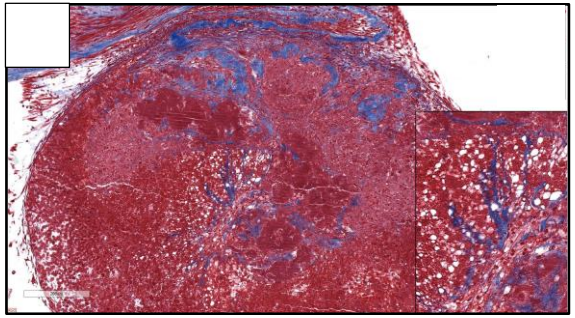
Disease in the dish matches disease in patients

Clear fibrosis (blue) seen in our model matches that seen in patient

Healthy cells, day 14

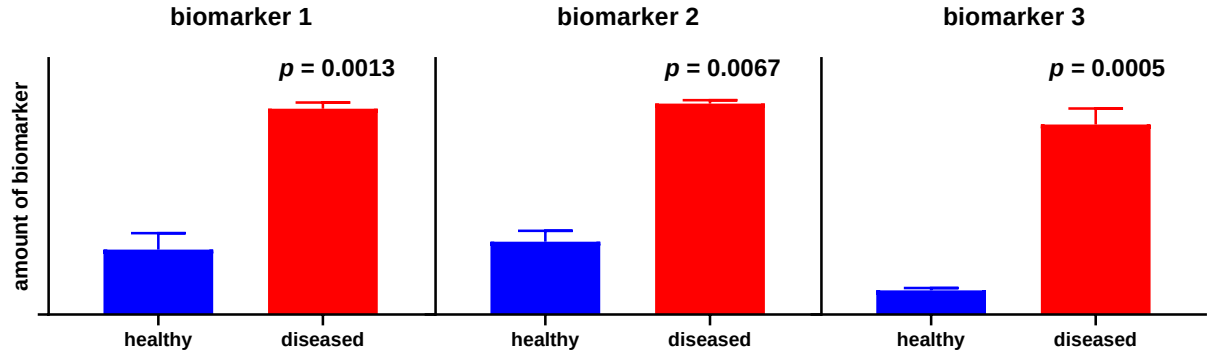


Diseased cells, day 14



All tissues stained with Masson's Trichrome – collagen (fibrosis) shows as blue

Markers of disease seen in patient blood samples are also high in our model



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Traditional Drug Discovery in Animals

TARGET IDENTIFICATION

(find target gene)

Mouse (disease engineered/induced)

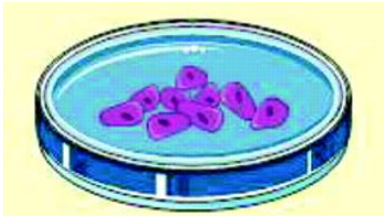
TARGET VALIDATION

(prove gene affects disease)

Resolve disease by gene edit or tool compound

COMPOUND SCREENING

(find chemistry hits to affect gene/pathway)



2D cells in dish 1536 tests/plate

LEAD SELECTION

(create drug based on hits, show efficacy in animal)

Reduction in disease by lead compound

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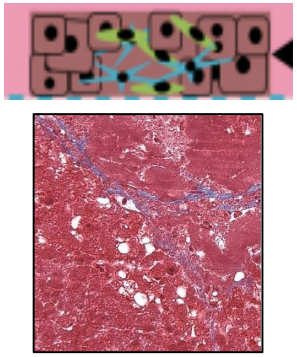
Viscient performs the same steps, replacing the animal with a bioprinted model

TARGET IDENTIFICATION

(find target gene)

Bioprinted tissue (disease direct from patient cells)



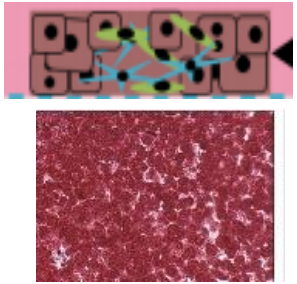
Diseased (fibrosis in blue)

Comparison to normal using single cell gene expression etc.

TARGET VALIDATION

(prove gene affects disease)

Disease reduction



CRISPR/ Other gene edits or tool compounds

COMPOUND SCREENING

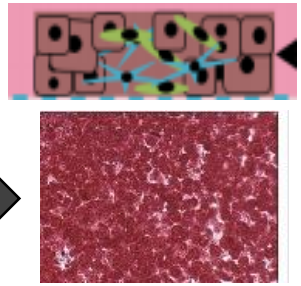
(find chemistry hits to affect gene/pathway)

Proprietary higher throughput model

Better biology than 2D cells 384 tests/plate

LEAD SELECTION

(create drug based on hits, show efficacy in the tissue)



Disease reduction

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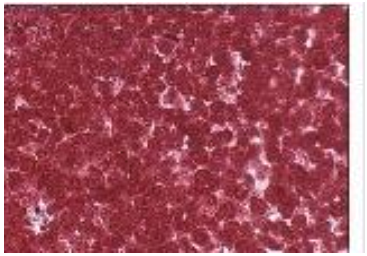
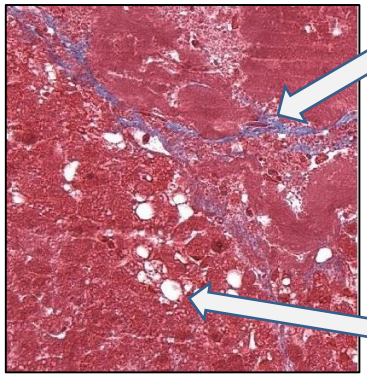
Viscient's lead program leveraged key input from multiple 3D models



Bioprinted control tissue



Viscient disease model

Measure which genes differ from control to diseased

Test which genes on list affect disease

Select best gene to target with a drug

"Target ID"

Build screening methods to test drug compounds

Screening to pick best drug hits and chemistry

"Select lead"

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Lead program target validation

- We will have multiple levels of validation for our lead program target
- Genomic association – known upregulation in disease
- Single cell gene expression in 3D models
  - Upregulated in disease cell model versus healthy
  - Additional levels of validation
- Pharma collaboration possible within 6-12 months on:
  - Lead program
  - Our novel targets that we are not pursuing
  - Drug discovery platform in NASH

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Team

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Keith Murphy, Co-Founder and CEO

- Founder, former CEO and Chairman Emeritus, Organovo (3D bioprinting)
  - Launched 2007, public 2012, high return to early investors
  - Signed collaborations with Pfizer, Merck, more
  - Launched commercial products, >150% revenue growth/year
- Ten years at Amgen, Global Ops. Leader, Prolia/Xgeva, (>$4B/yr sales)
- MIT; UCLA Anderson
- Board Member, Adgero Biopharmaceuticals
- Board of Directors, California Life Sciences Association

Jeffrey N. Miner, Co-Founder and Chief Scientific Officer

- Exec. Director, Biology, Ardea Biosciences / AstraZeneca (AZ)
  - Developed Zurampic for gout, led to AZ buying Ardea for $1.25B
- Head of molecular and cellular biology, Ligand Pharmaceuticals.
- Developed Oncology program & sold to Bayer, Co-developed Promacta/Revolade follow-on with GSK
- Top team members from Ardea followed Jeff to Viscient
- Ph.D., Oregon State University; Post-doc, UCSF

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Viscient Biosciences- Torrey Pines Site

- Access to a vibrant biotech community
- UCSD, Salk and other major research institutes in walking distance
- Newly renovated office and lab
- General Atomics incubator with full service infrastructure

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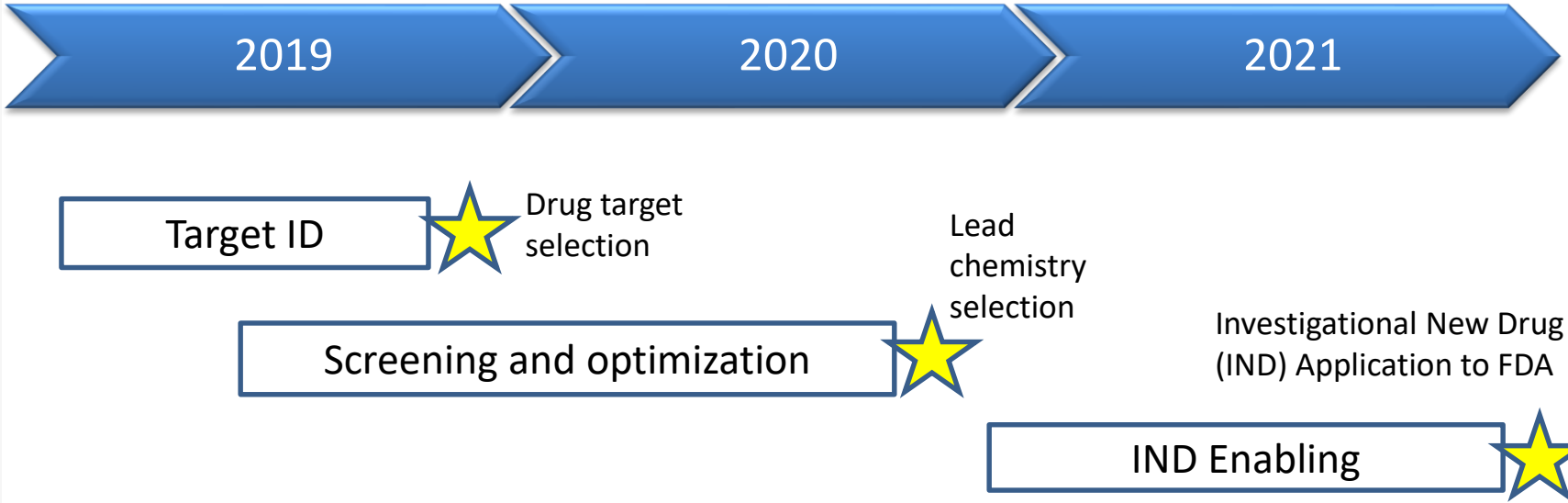
Timeline to clinical trials



Next steps:

-Optimize drug chemistry
-Test drug safety
-Determine dosage form
-Understand drug mechanism of action
-Develop clinical and regulatory plan
-Drive to clinical proof of concept (show drug works in humans)

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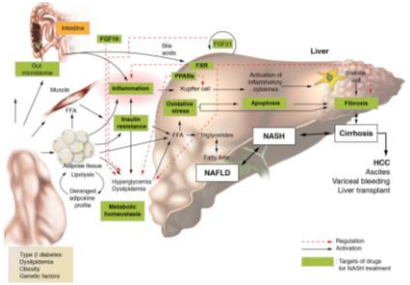
Exit Strategy



- Pharma R&D spending is down
- Pharmas now largely purchase innovation
- >50% of pharma pipeline is bought or in-licensed from outside, mostly small biotech
- Recent NASH deals done by Boehringer Ingelheim, Genentech, Gilead. Active NASH interest from Merck, Allergan, Takeda, others
- Typical deal >$1B total deal value, Viscient can be at the stage to allow that in 3 years

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Thank You!

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