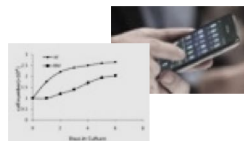**THRIVE** BIOSCIENCE

Analytics. Automation. Better Biology.

CellAssist™
Cell Culture Assistant

Alpaca™
Cell Culture System

Better Data.
Better Biology.™

Thomas Farb-Horch
Takashi Kiyoizumi, M.D., Ph.D.

Big Data Analytics Tokyo
October 24, 2018
Confidential

Thomas Farb-Horch   Thrive Bioscience, Inc.   11 Audubon Road   Wakefield, MA 01880   USA
tom@thrivebio.com   mobile: +1 978-201-9081

Thrive Speakers

CEO & Co-Founder-- Thomas Forest Farb-Horch

- Founder/Board Member of over 10 companies, including:
  - AI: HNC Software (neural networks/acquired by Fair Isaac & Oracle)
  - Devices: Saf-T-Med (safety syringes/acquired by BD)
  - Diagnostics: Exact Sciences (NASD: EXAS) (colon cancer screening)
- General Partner of Shanghai-based venture capital fund
- VP of Strategic Planning & CFO of Cytyc (acquired by Hologic)

EVP of International -- Taka Kiyoizumi, M.D., Ph.D., MBA

- M.D. & Ph.D. (Keio School of Medicine); MBA (MIT)
- Entrepreneur and executive specializing in life sciences
- CEO & Founder of MediciNova (NASDAQ: MNOV)
- CEO of Tanabe Research Laboratories, USA, US affiliate of Mitsubishi Tanabe Pharma

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2019 +
Thrive Instruments

Company Mission: **Provide instruments & software tools for consistently growing healthy cells with accompanying data and analytics**

1952 - 2018

Cell culture is at the center of bio-medical research

- 200,000 "dumb" incubators
- 80,000 labs

1952

Cell culture is conducted similarly to 65 years ago --with significant unsolved pain points

Tuskegee Institute -- HeLa cell line factory

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Q: What is cell culture?

A: Artificially re-creating cells' environments to grow cells *in vitro*.

"Non-Smart" Incubators with Doors	No Images or Data Recorded	Manual, Undocumented, External Processes

Limited process controls

Contamination

LACKS DATA & IMAGES

Stressful Environmental Changes

Lacks Documentation

Lack of reproducibility

Subjective decisions

Difficult to scale

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4

Thrive Bioscience -- Key Points

✓ **Significant Unmet Needs -** Thrive has solved many of the difficult problems of imaging and analyzing unstained, live cells

✓ **Family of Products at Varying Price Points --**
  o Family of instruments using common modules
  o Currently in beta test of first product (CellAssist)
  o Revenues of $100+ million projected in 2023 with significant recurring revenues

✓ **Significant Patent Portfolio** -- 42 applications of which 7 have issued

✓ **Extensive Collaborations** -- The Broad Institute of MIT & Harvard and Harvard Stem Cell Institute

✓ **Financing** -- Raised $18.2 million to-date

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Q: Why Need Thrive? A: There Are Major Problems in Research!

Drug Development Has High Costs & High Failure Rates
(Only 2% - 5% of programs lead to an approval)
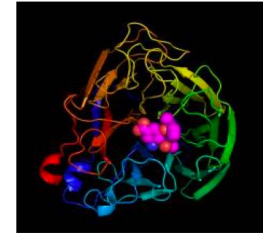
Pre-clinical Research is Not Reproducible

- *Pre-clinical research is the basis of clinical research (testing in humans)*
- *Studies from Amgen, Bayer, NIH and others -- 51% to 89% of pre-clinical research not reproducible!)*

Cell Culture is Not Reproducible
(About half of causes of irreproducibility in pre-clinical research relate to cell culture, directly and indirectly)

Majority of Pre-Clinical Research is Not Reproducible
The Reproducibility Crisis is Becoming Increasingly Recognized

***NATURE* | NEWS FEATURE | 26 May 2016**

"1,500 scientists lift the lid on reproducibility -- Survey sheds light on the 'crisis' rocking research"

**"More than 70% of the [surveyed] researchers have tried and failed to reproduce another scientist's experiments…"**

When asked if there is a Reproducibility Crisis, 52% said:
"Yes, a significant crisis"

AND YET --

Differing results have NOT been resolved in 2/3rds of the cases

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Majority of Pre-Clinical Research is Not Reproducible
Reproducibly is a Necessity in Science
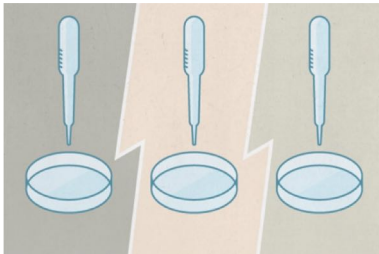
"The reproducibility of published experiments is the foundation of science.

No reproducibility -- no science."

-- Moshe Pritsker, Ph.D., CEO, Journal of Visualized Experiments

Inability to reproduce results slows down progress on cures and puts patients at risk:

- Undermines our cumulative knowledge / future research is based on past research

- 125,000+ patients in clinical trials based on non-reproducible research from 2000 to 2017 in U.S.

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Cell Culture is Not Reproducible
Current Cell Culture Leads to Inconsistent Results

- **Biology Lacks Data** -- *When an experiment does not work we currently often do not know why*

- **Lack of Control of Process Controls**
  - *Genomic drift from cell stress -- the cells that survive differ from starting cells*

  - *Mislabeling & contamination -- 14% to 36% of cell lines!*

  - *Cells vary across / within labs and over time*

Inconsistent Results

- **Cells are increasingly distant from the "disease model" -- patients!**

Better Data. Better Biology.™

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Cell Biology Databases are Inadequate:

- **Lack of an instrument for rapid imaging and capturing processes and protocols** -- *Thrive is providing the next generation microscope*

- **Biology requires significant amount of contextual data, which is difficult to capture** -- *Thrive captures contextual data from multiple streams (video, sensors, microscopy, 3D microscopy)*

Company Mission:

Provide instruments & software tools for consistently growing healthy cells with accompanying data & analytics.

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Thrive's Cell Culture Systems -- CellAssist & Alpaca

> *Thrive's systems use common image processing, analytics, optics & sensors*

CellAssist Cell Culture Assistant:

- *Bench-top solution ~~improves~~ existing, manual cell culture*

- *Reduces errors from human judgment with image processing & analytics*

Alpaca Cell Culture System:

- *Stand-alone solution ~~replaces~~ & automates cell culture*

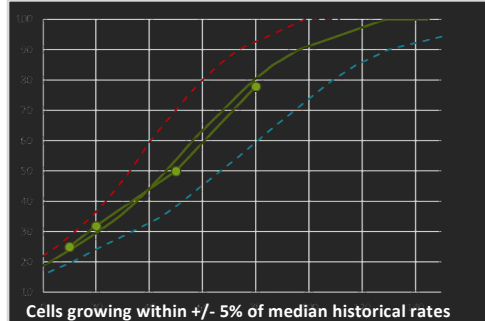- *Reduces errors from human judgment __and__ implementation with robotics*

Good Science Needs Good Cells.™

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The CellAssist Solution: "Cell Metrics in a Box"

- Acquires data & images
- Reports & guidance for cell culture
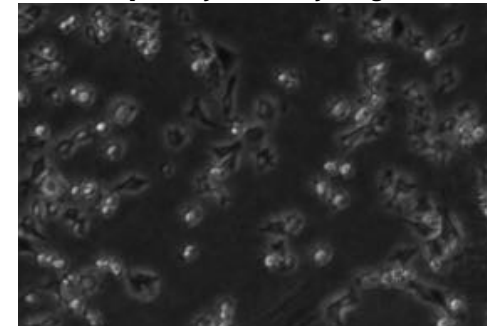- Analytics to improve research
- Documentation of processes

Accurate Cell Counting Across Plates & Time:

Cells growing within +/- 5% of median historical rates

Confluence Analytics Across Plates & Time:

Sample Project - Passage 1 - % Confluence

Time (hrs)	Day 1	Day 2	Day 3	Day 4	Day 5
Control	5%	10%	30%	62%	99%
Drug A	5%	5%	20%	30%	60%
Drug B	4%	5%	8%	12%	18%
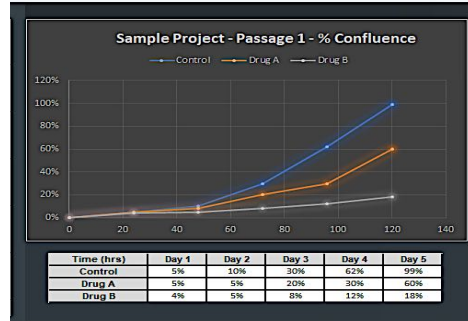
Capture of 1,000's of Images:

CellAssist Features:

- Scans Plates in <1 minute
- Cell Metrics Recording
- AI & Intelligent Image Analysis
- Trend Analysis/Forecasting
- Documentation & Reporting

Data and Images Collected:

- Live/dead cell counts & pH
- Cell morphology features
- Characterization of stem cells
- 4x, 10x, 20x objectives [18]
- 6-well & 96-well plates

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Cell Culture Case Studies

Cell Culture Case Study #1 --
Cells Shaken, Not Stirred?

"A martini. Shaken, not stirred."
– *James Bond, Goldfinger, 1964*

The Sequel:

Q: Do you like your cells shaken or stirred?

"A set of data that was supposed to be completed in a few months took two years to understand and sort out."

from **Sorting Out the FACS: A Devil in the Details** by William C. Hines, Ying Su, et al
Cell Reports, March 13, 2014

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Cell Culture Case Study #1:
Lawrence Berkeley National Laboratory and Dana-Farber Cancer Institute

- "The reproduction of results is the cornerstone of science..."

- "Despite using seemingly identical methods, reagents and specimens, our two laboratories... were unable to replicate each other's... [cell] profiles."

- "The two first coauthors met in Berkeley to work side by side..."

"In the Boston method, tissue was being stirred in a flask...
In the Berkeley method, tissues were digested while rocking...
resulting in a dramatic effect on CD44 antigen presentation."

Cells Expressing CD44 Antigens:

Breast Cancer Cell Lines:
MCF-7
MDA-MB-468
BT549
AU565
MDA-MB-231

Boston:

Berkeley:

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Cell Culture Case Study #2:
How Therapeutics *Really* effect Cells

## Drug Resistance Studies via Cell Counting (Current Practice)

- Drug resistance causes cancer patients to relapse

- Researchers widely study cancer drug resistance using cell culture

- Cancer cell growth is assessed by counting cells over 8 to 15 weeks

  - **Lack of precision**
 - **Time consuming**
  - **Requires training**

Relapse
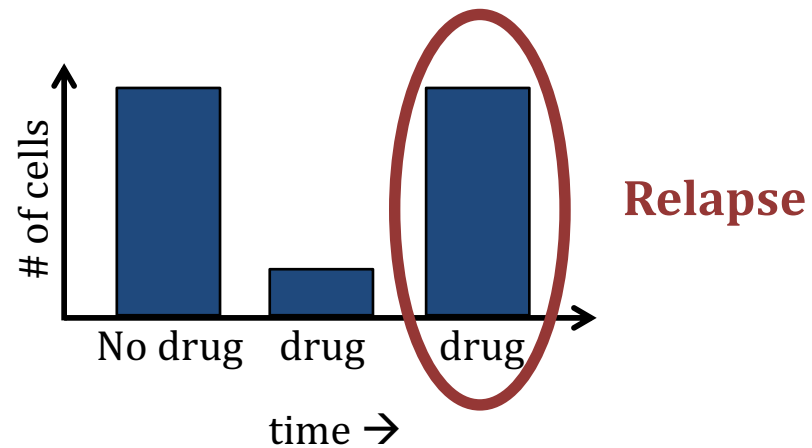
More information is required for meaningful conclusions!

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Cell Culture Case Study #2:
How Therapeutics *Really* Effect Cells
Drug Resistance via CellAssist

1. Gather all data from images
   - **Quick**
   - **Precise**
   - **No training**

Relapse
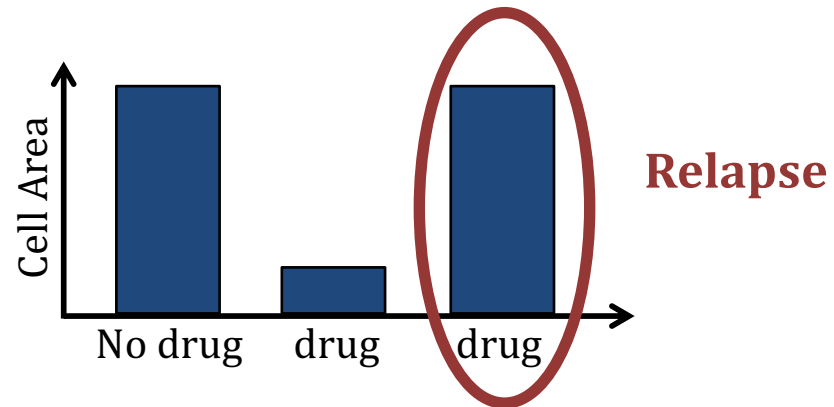
2. Cell Assist provides additional measurements
   - **More information**
   - **No training**
   - **Using AI tools -- can see effect in two weeks that is predictive of what happens in 15 weeks!**
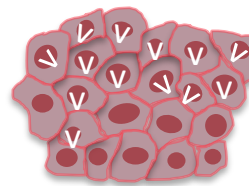
No drug   drug

Resistant cells are different!

CellAssist provides more and better data and earlier results from the same experiment!

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Cell Culture Case Study #3:
The Importance of Confluence & Passaging Cells

- **Confluence** is the percentage of the surface of a culture dish that is covered by cells.

- **Confluence is used to judge when to passage (re-seed or split) cell culture plates**

  - Passaging is the transference of cells from to fresh growth medium

  - When to passage is one of the most important decisions in cell culture

 - Major determinant if the cell line will live and be healthy
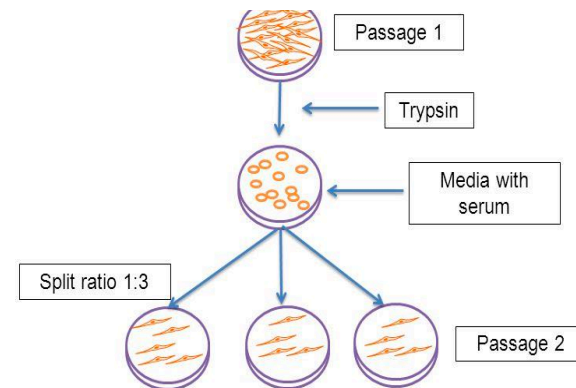
- **Confluence can also be used for determining cell health and and as a measure of consistency and quality**

- **Human estimates are very unreliable.**

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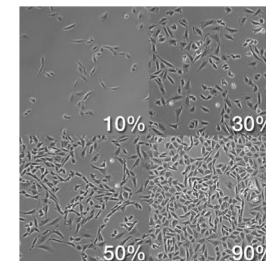
Cell Culture Case Study #3:
## Human Estimates of Confluence Fall Short on Accuracy

Human estimates show a wide spread of values, often materially different from automated calculation:
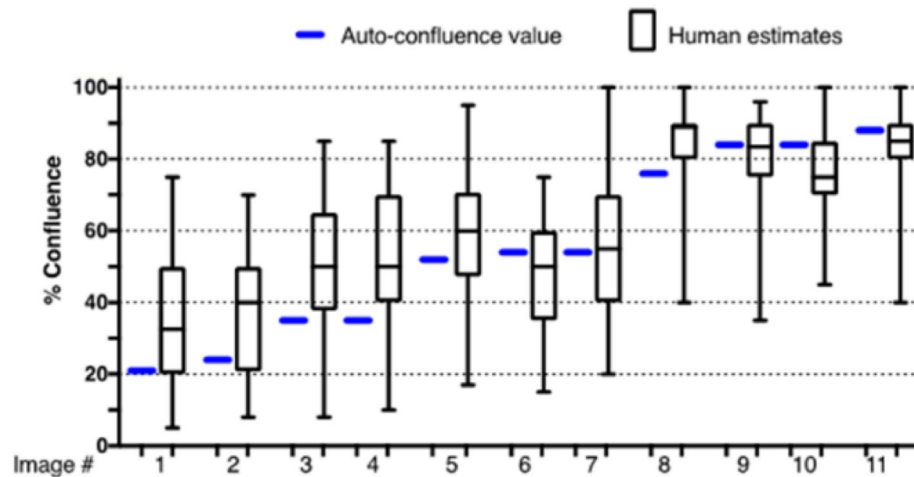

- *Thrive generated data from 2017 ISSCR 2017 conference attendees (N=76 participants) on their confluence estimates for*
- *8 unique images of which 3 duplicated but rotated 180 degrees.*

Cell Culture Case Study #3:
Thrive's Confluence Advanced Data Reporting

- CellAssist records confluence data & tracks according to cell line.

- This enables the cell culturist to compare how their cells grow compared to past observations and identify anomalous growth.
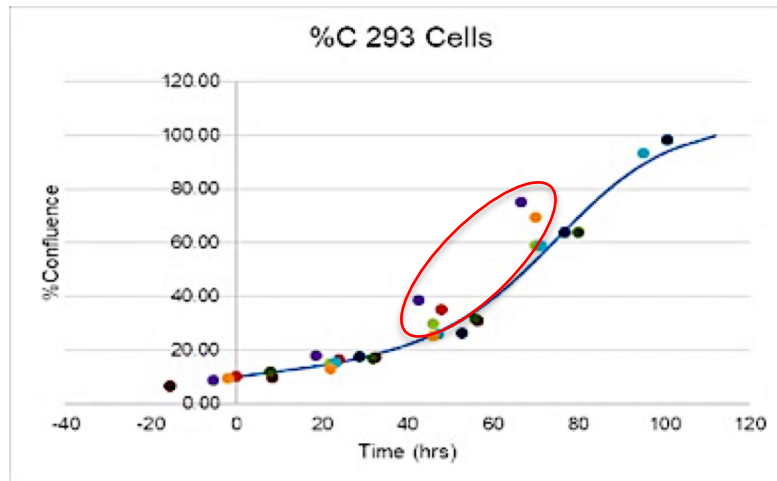
(statistical anomaly highlighted)

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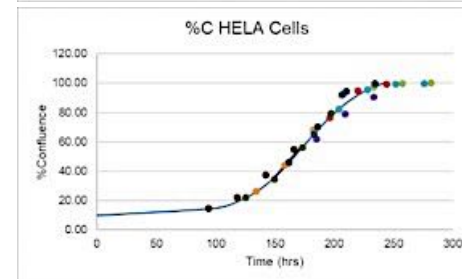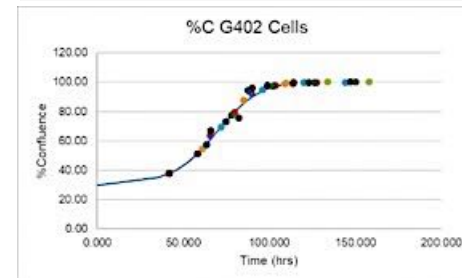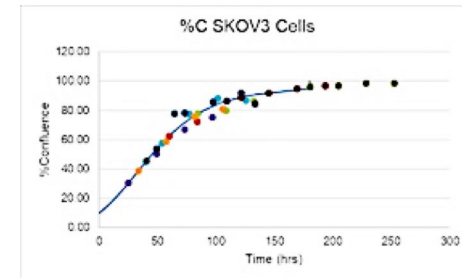
Cell Culture Case Study #4:

CellAssist -- Solving Problems in Directed Differentiation

Humans using phase-contrast microscopy cannot easily distinguish the quality of iPSC's by their appearance and resolve undesirable vs desirable differentiation.

End-point validations are costly and limited in providing into measuring the quality of the iPSC's, plus, they kill the cells.

Process & cell status information is lost due to a combination of the lack of vendor solutions, cost (time and equipment), and complexity (image processing).

Quality is determined later in the process than is ideal, even though there is value to researchers and to patients in determining the outcome at the earliest point in time, rather than reactively.

Simply growing iPSCs over and over does not inform us sufficiently on leading indicators of downstream quality.

> **CellAssist Addresses the Problems:**
> The CellAssist, combines routine full-well 4X imaging for growth and spread measurements with 10X sampled imaging for morphological characterization to provide interpretable image data.

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Cell Culture Case Study #4:
Directed Differentiation on CellAssist:
Thrive's Time Series Analysis of Differentiation

Tracking cells in a fixed location over time – including over multiple media changes – allows identification of differentiating cells

Day 1   Day 3   Day 5

Day 9   Day 8   Day 6

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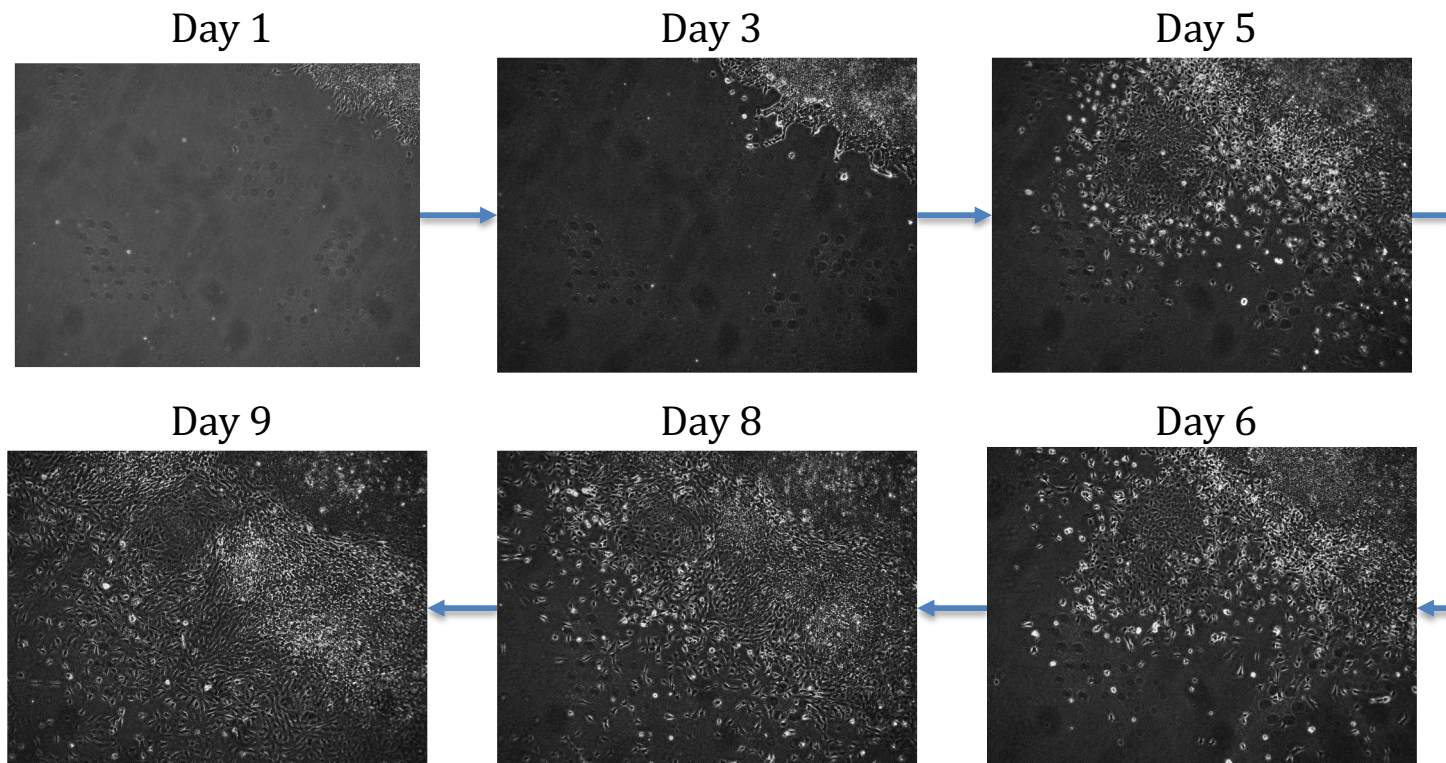
Cell Culture -- An Important, Ignored Problem

Example Statements from 1,000 Labs Market Research Conducted by Thrive

" **We have a complete lack of tools to help us in this increasingly important task of cell culture.** "

-- University Principal Investigator

" **Cell culture may be the only remaining island of outdated manual processes surrounded by an ocean of automation.** "

-- Research Institute Lab Director

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Thrive Bioscience, Inc.   11 Audubon Road   Wakefield, MA 01880   USA

tom@thrivebio.com   mobile: +1 978-201-9081