

Ten Years to Be an Overnight Success:

Investing in the Future Takes Time

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Friday, May 17, 2024



Khosla Ventures

OpenAI
Commonwealth Fusion
Impossible Foods (burgers)
DoorDash
Square
Instacart
Stripe
Rocket Lab
Hermeus

Ultima Genomics
Guardant Health
Color Genomics
Curai
Atomwise
Cellino
Loyal (dog longevity)
Inflammatix
AliveCor
Synchron
BioAge
Vivodyne
Hello Heart

Sword Health
Q Bio
Flow Neuroscience
Faeth
Siphox
Vicarious Surgical
Mirvie
Karius
Headspace
Everyone Medicines (N of 1)
Limbic AI
eGenesis
Kernel

470 active companies, and over 115 of them in biotech/healthcare

“The best way to predict the future is to create it.”

- Abraham Lincoln

The future is not knowable, but it is inventable.

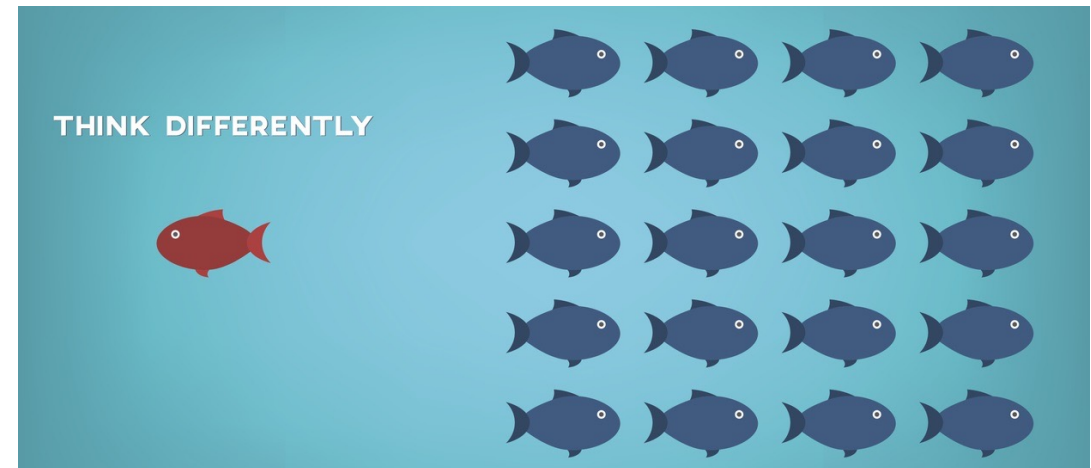
“Reasonable people adapt themselves to the world, the unreasonable [person] adapts the world to them.”

- George Bernard Shaw

Skeptics never did the impossible.

There are always pessimists for every solution.

Most “experts” are experts in the past.



“Nothing in the world is worth having or worth doing unless it means effort, pain, difficulty... I have never in my life envied a human being who led an easy life. I have envied a great many people who led difficult lives and led them well.”

-Theodore Roosevelt

Everything worth doing is hard work, although not everything which is hard work is worth doing.

“All overnight success takes about 10 years.”

-Jeff Bezos

Let's make this concrete

If we had unlimited organs for transplantation, we could solve a lot of problems

Over 100,000 people on transplant wait lists

Every 9 minutes another name added

Most people who might benefit from a solid organ transplant never even get listed

Kidneys, hearts, lungs, livers – all necessary for life, all transplantable

Issue is supply and immune tolerance

Disproportionately distributed in vulnerable populations

Admixed people have a particularly hard time finding good matches

In the limit of 100% matching genetics

Richard Herrick was the first successful recipient of a kidney transplant from his identical twin brother, Ronald Herrick in 1954.

The more genetically similar the surface markers, the better success of transplant.



The Yucatan mini pig – what a cutie!



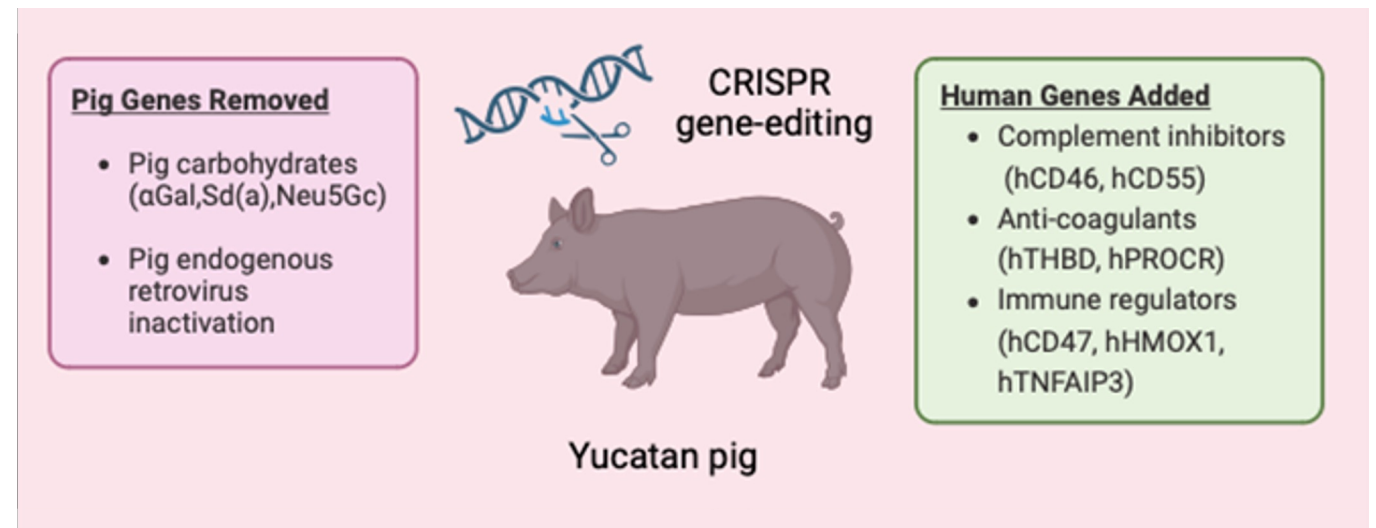
Use CRISPR to edit a pig to be a better an organ donor?

Seed investment 2015

Over 69 specific edits

Sterile pig cloning farm

Years of primate testing



March 16, 2024

Richard Slayman first person to
successfully receive a
xenotransplanted kidney



Infectious disease is still a problem

Over a thousand people with cancer die of infection every day

Respiratory infections are still one of the top five causes of death in the elderly

10,000,000+ people in the US are immunocompromised

More transplant patients means more immunocompromised

The diagnostics uncertainty is very high – bacteria, virus, fungus, parasite?



Founded 2016

Sepsis kills 700 people a day, but is 80% preventable if identified early

The physiological changes (e.g. blood pressure drop) are lagging indicators, then it's too late

By profiling the gene expression in white blood cells, can identify problems before arise; it's the top of the signaling cascade

Built a box for a rapid POC answer



The image shows a black and white Myma device by Inflammatrix. The device has a screen displaying 'TriVerity' and 'Myma' with instructions: 'Insert cartridge' and 'Insert the cartridge into the device with the tip of the sample tube facing up'. A green arrow points from the device to a cartridge. The cartridge is white with a red sample tube and a green arrow pointing down. The background is a blurred image of a person in a lab coat.

TriVerityTM Acute Infection & Sepsis Test

Testing designed to fit how emergency medicine physicians evaluate hard to diagnose patients

FDA **BREAKTHROUGH** **DEVICE DESIGNATION**
NOVEMBER 2023

Our products are in development, are not for sale, and do not have marketing approval or clearance from regulatory authorities in any jurisdiction.



Founded 2014

Viruses, bacteria, fungi, parasites – they all shed short DNA/RNA pieces into the blood stream

Even when you can't isolate a culturable organism – you can find traces of its existence in short oligonucleotide fragments

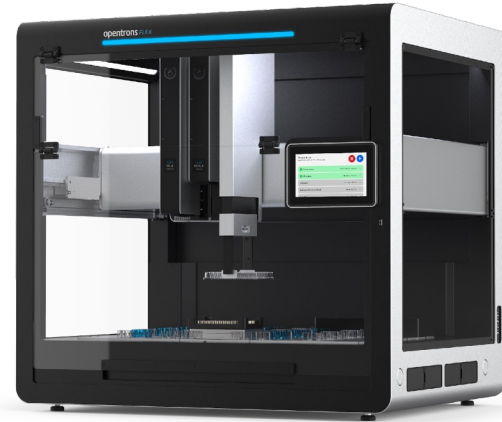
Can identify over 1,300 different infections in 1 tiny blood sample!

Sequencing & lab costs?

OpenTrons – founded 2013

Ultima Genomics – founded 2016

Volta Labs – founded 2018



Automation to drive sequencing (and other assays) toward zero marginal cost
Knowing about where the technology is going leads to next thing and so on...

Larry said COGS (Cost of Goods Sold)!

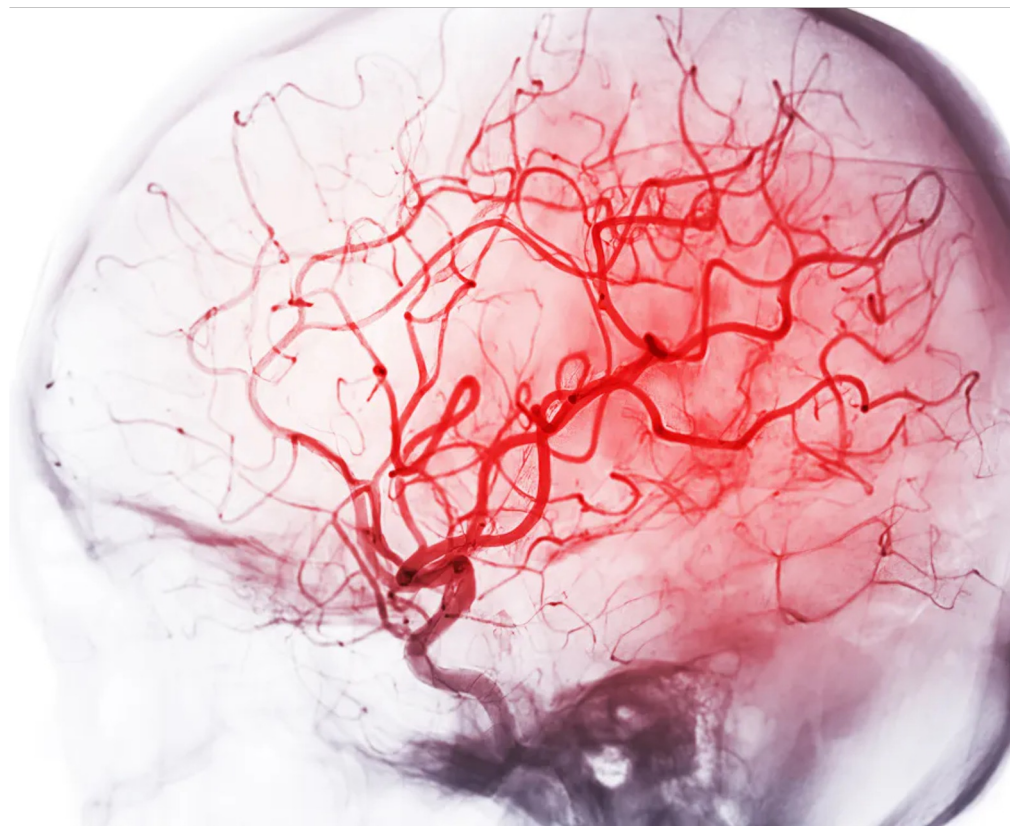
Brain – Consciousness and Personhood

Maybe we can replace hearts, kidneys, livers, lungs, etc. but you can't do a brain transplant, and the brain is what is really important, right?

Can we improve the brain directly?

Brain machine interface – **craniotomy?** **needle arrays?**

The brain has a natural transit system



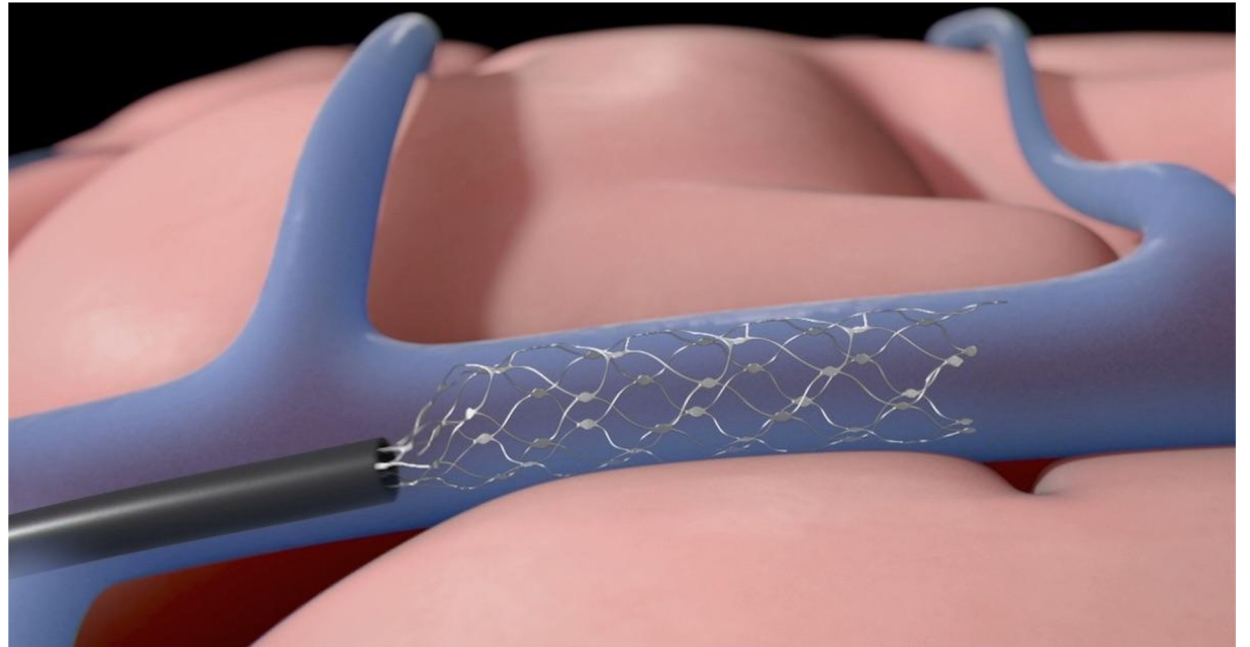
synchron

“Smart” stents

Founded 2012 in Melbourne

We discovered it in early 2021
through an IP search

Invested and helped bring the to NYC



First BCI Tweet – Dec 2021

“Hello World”



BCI is not the endpoint – Brain Therapeutics

Electricity can go both ways

Measure in one area – Stimulate in another

If targeted electricity is the “drug” – information becomes a drug – virtuous cycles of improvement

Epilepsy

Parkinson

Depression

Addiction

Memory Loss – Default mode network activity treat AD?

Metabolism

Et multa cetera...

Also non-implant approaches



Transcutaneous stimulation

Depression and anxiety

Multiple positive clinical trials

Reimbursed in the UK & Switzerland

FDA Breakthrough Designation

Positive pivotal trial in Texas



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'The headset helps my depression so I can be a dad again'

24 March 2024

Share

By **Nikki Fox**, Health Correspondent, BBC East



Nikki Fox/BBC

Ashley Riley says he is calmer and feels "at peace" after using the device for a number of months

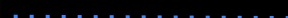
Depression not your problem?

Everybody Sleeps

Over 70M people in the U.S.
struggle with sleep disorders, and
1 in 3 adults are dissatisfied with
their sleep.

*source: NIH 2023

First “closed loop” sleep diagnostic + therapeutic of its kind



Easy to use

User wears Somnee for 15 minutes before bedtime.

Personalized to you

Proprietary EEG+ maps your unique brain signature and patented AI model creates a personalized stimulation session (tES).

Profound results

Somnee delivers results showing more effectiveness than sleeping pills.



Sleep more,
live more.



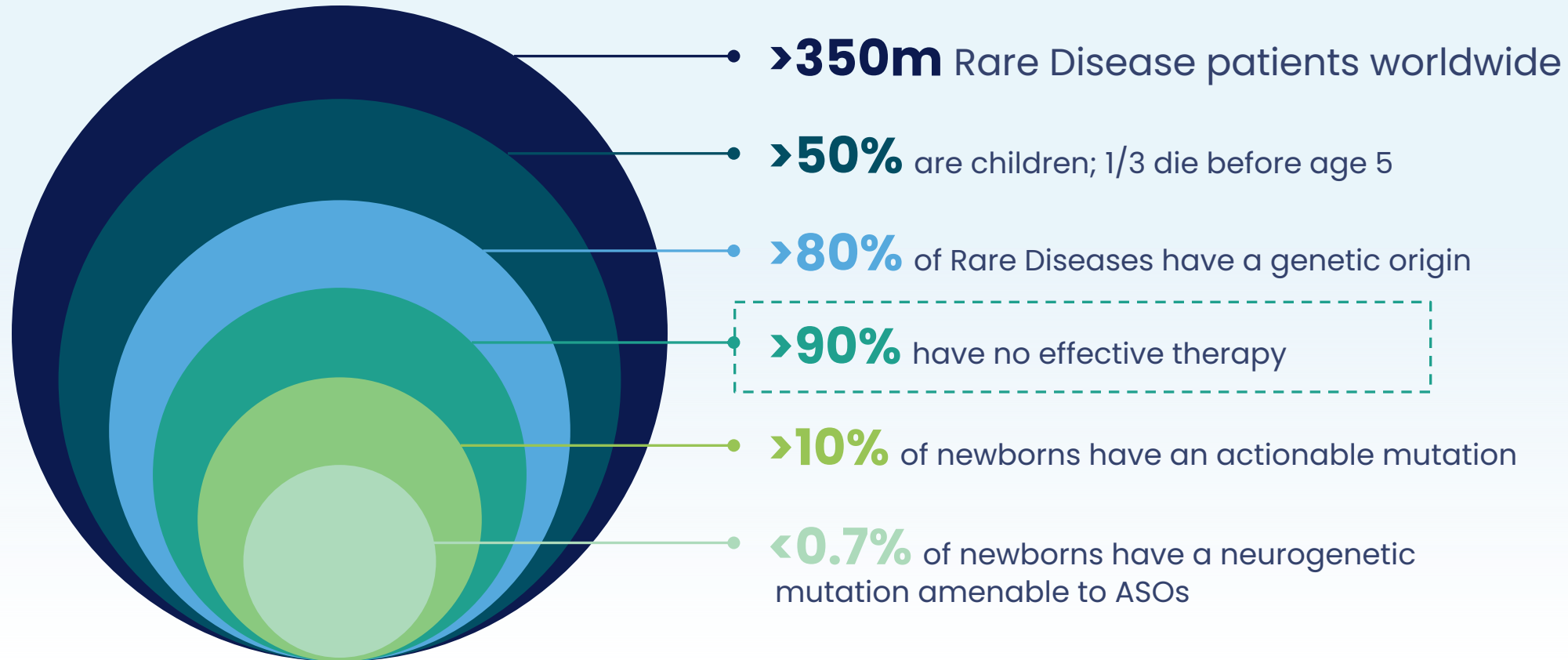
Sleep is important, but...
let's get back to scary diseases

Why don't we still have better drugs for so many serious problems?

“There are a thousand hacking at the branches of evil to one who is striking at the root.”

- Henry David Thoreau

Genetic targets to treat/cure disease



New approaches to genomic medicines

Liberate Bio – Computational discovery of carrier particles, LNPs

Very large edits/inserts – **Stylus Bio**

Ex vivo gene editing – **Kamau**

Bionaut – tiny bots that drive through the body delivering drugs/cells

(think Impossible Voyage)



Also N of 1 - Individualized Medicines Platform

EveryONE Medicines is building a platform for individualized antisense oligonucleotides (ASOs)

- Platform = Systematic, rigorous, cost-efficient development of safe and efficacious medicines
- Platform approval concept endorsed by regulators in Germany and UK
- In discussions with EMA
- Productive discussions on fair reimbursement with HTA bodies and payors

Two Fundamental Problems for Common/Multifactorial

Many of the major areas of unmet need are diseases of aging – aging is a “Principal Component” of much of current human disease. It is hard for researchers to study interventions in human aging, because of the timescales involved and uniquely human features/confounders.

Therapeutics development traditionally requires animal research, and many of the main diseases where we have no good therapies are diseases where we don't have good animal models. If you were a mouse, we'd probably have a cure for whatever ails you.

Expanding the concept of the Framingham

100 years ago people died of “natural causes”

Study started in 1948 with 5,209 people monitored over time

It was a very low dimensional multi-omics, longitudinal study that gave us the concept that heart attacks were not inevitable, and that **cholesterol** was a risk factor that could be modified

Drug that treats a risk factor - statins – changed the demographics of death

Lovastatin received approval in 1987 – forty years is too long

Alirocumab (PCSK9) approved in 2015 – far, far too long



somalogic

Using computational drug discovery technology applied to advanced proteomics in aging longitudinal study

Clinical stage pharma company

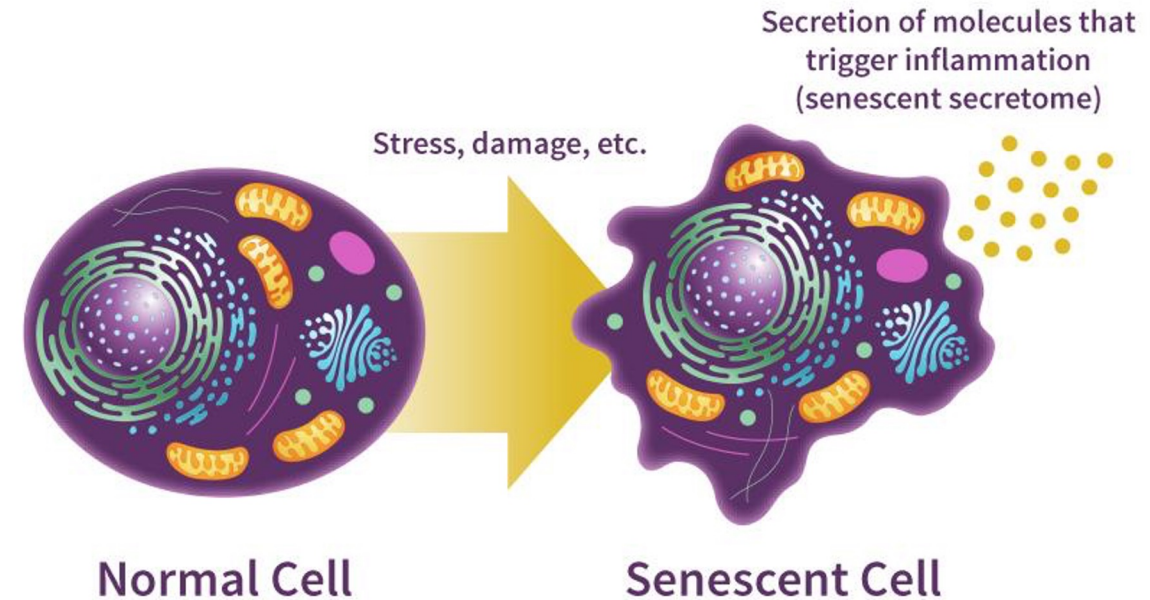
**BioAge Announces Positive Topline Results for BGE-105 in
Phase 1b Clinical Trial Evaluating Muscle Atrophy in Older
Volunteers at Bed Rest**

Senescent cells

Compelling evidence that senescent cells contribute to many of the phenotypes and diseases of aging

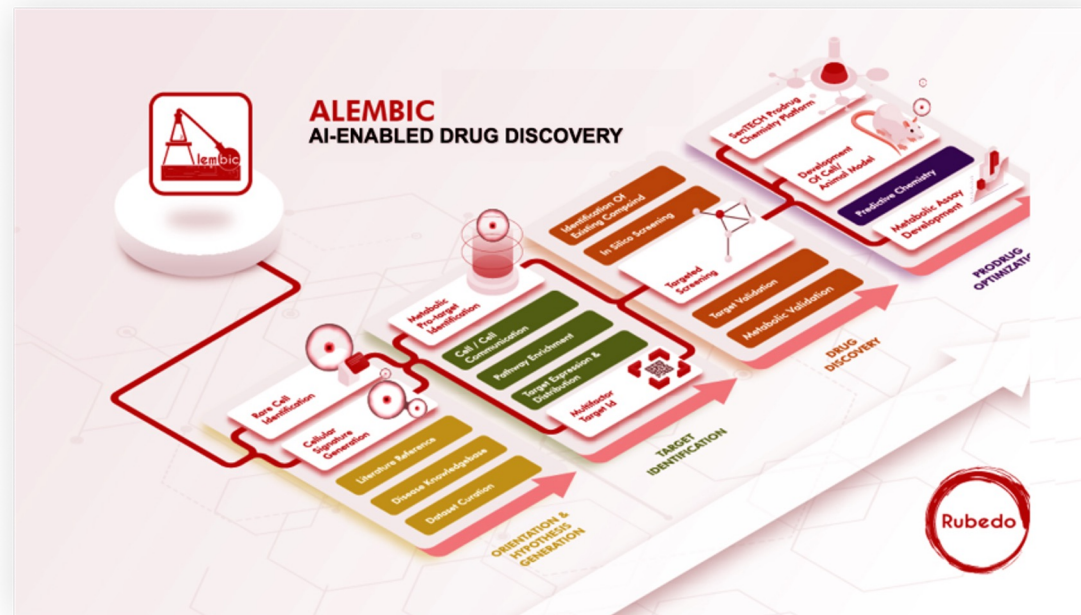
Unity Biotherapeutics raised over 350M in investment to tackle

Rushed to clinic with a not great drug, current \$UBX enterprise value 9.4M



Rubedo – Better Drug Design for Senolytics

Using state of the art computational platform, and clever approaches to chemistry, can try to attack this problem a different way



Challenge is removing the senescent cells, without harming the healthy cells

Smart Senolytics

10 years to success – but dogs only get 10

Dogs share much of human exposures and environment

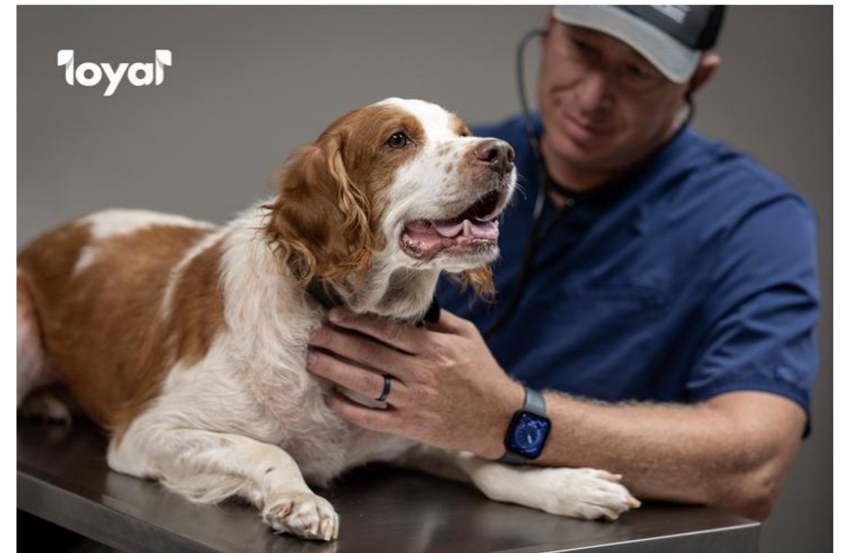
– even when we don't want to share our food

By studying interventions that extend dog life, we can see results on feasible timelines

Families get to spend more time with their pets

2022 – Very contrarian investment

2024 – Mentioned at the Emmy awards



Not just in old age, but also *in utero*

The best way to get QALY boost (quality adjusted life years) is to go early

1,000,000 babies a year die of prematurity

10% of births have some complications

Cell free RNA as a liquid “biopsy”

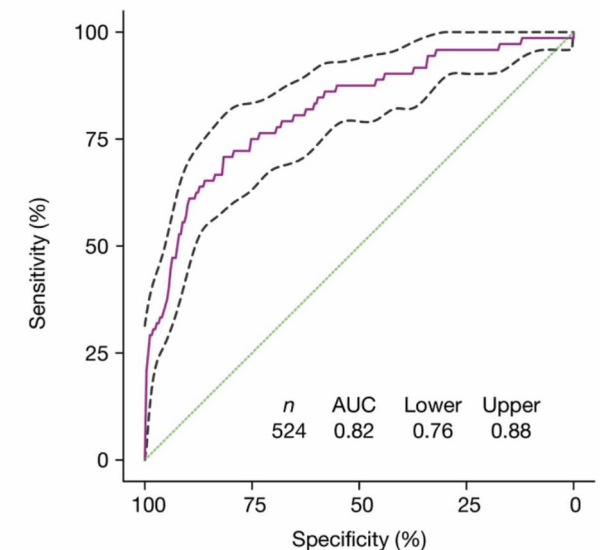
mirvie

Article

RNA profiles reveal signatures of future health and disease in pregnancy

<https://doi.org/10.1038/s41586-021-04249-w>
Received: 9 April 2021
Accepted: 16 November 2021
Published online: 5 January 2022
Open access

Morten Rasmussen^{1,2}, Mitsu Reddy¹, Rory Nolan¹, Joan Camunas-Soler¹, Arkady Khodursky¹, Nikolai M. Scheller², David E. Cantonwine³, Line Engelbrechtsen⁴, Jia Dai Mi⁵, Arup Dutta⁶, Tiffany Brundage⁶, Farooq Siddiqui⁶, Mainou Thao⁶, Elaine P. S. Gee⁶, Johnny Lu⁶, Courtney Baruch-Gravett⁷, Mark K. Santillan⁷, Saisat Deb^{8,9}, Shaaili M. Arne⁸, Said M. Ali⁸, Melanie Adkins¹⁰, Mark A. DePristo¹⁰, Manfred Lee¹⁰, Eugeni Namsaraev¹⁰, Dorte Jensen Gybel-Brask^{11,12}, Lillian Skibsted¹³, James A. Litch¹, Donna A. Santillan¹, Sunil Sazawal¹⁴, Rachel M. Tribe¹, James M. Roberts¹⁵, Maneesh Jain¹, Estrid Hegdall¹⁶, Claudia Holzman¹⁷, Stephen R. Quake^{18,19}, Michal A. Elovitz^{18,19} & Thomas F. McElrath^{18,19}



...and *ex utero*



Ability to bring premature eutherian mammals to full term with no signs of any deficits at all



What about the mice?



If you are opposed to animal testing on ethical grounds, you're not alone:

FDA – you don't need animal testing if you can find alternative

EMA – you have to avoid using animal testing if possible

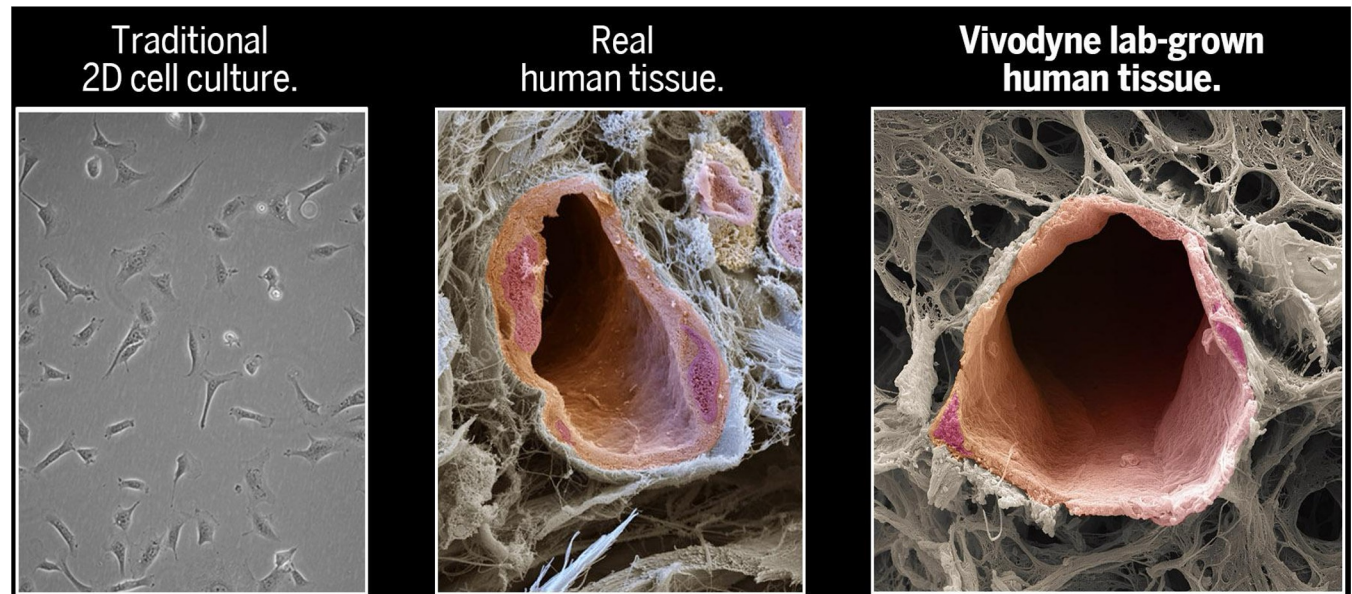
Human testing would be ideal – we are selfishly most interested in human diseases, and new generations of biologics and genomic medicines are very human specific in their targets



Modeling human tissues on highly multiplexed, automated platform

Using AI and automated imaging to collect the results and build predictive models

Can models dozens of different tissues in highly multiplexed replicates



AI in healthcare

For years, many things didn't quite work well enough to be useful in healthcare

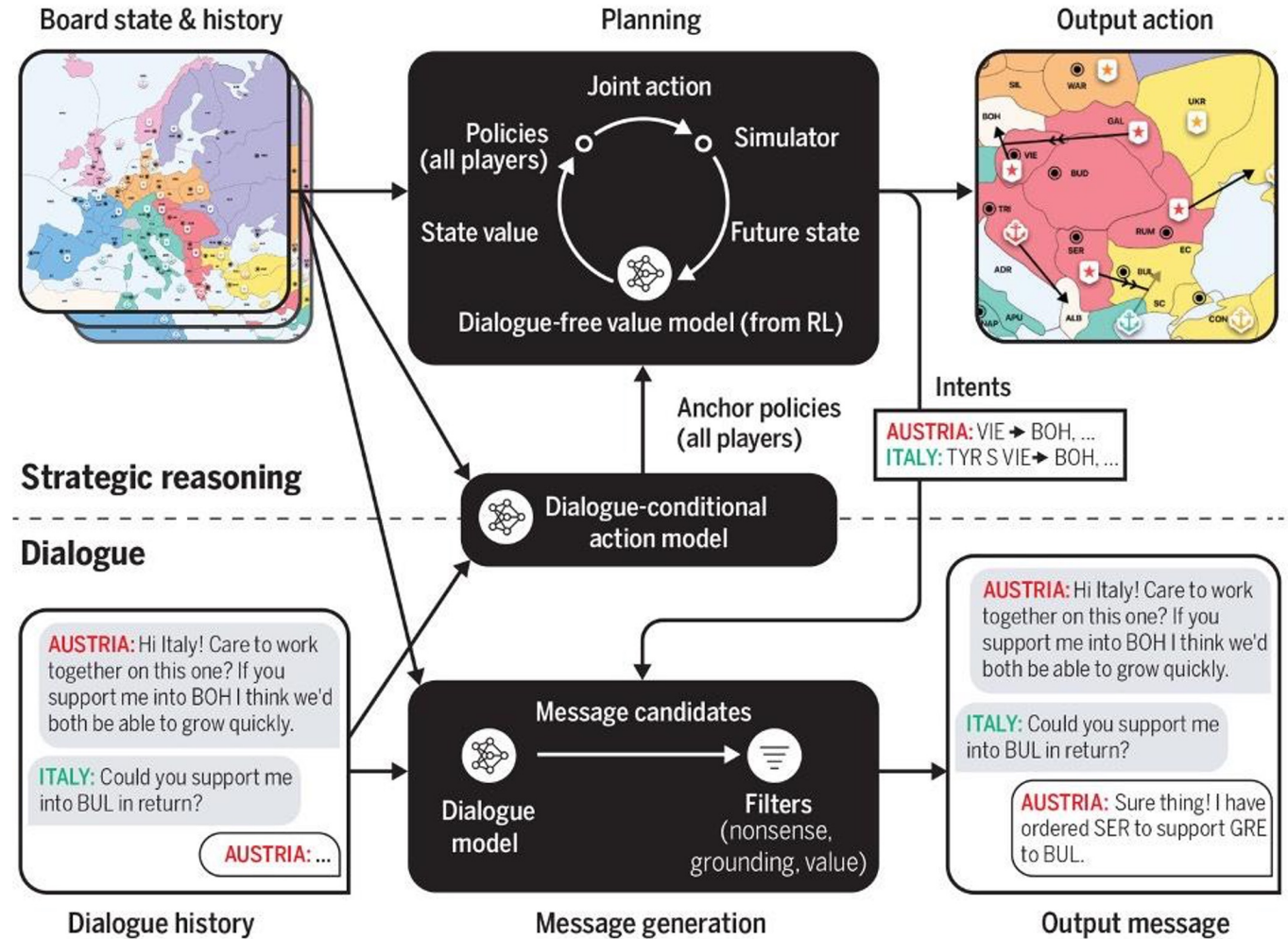
A LOT of things just work now

However, they also work for everyone

Commoditization of many things including language



A lot of healthcare is like Diplomacy



The biggest problem in global health...

We have traditionally thrown human labor/training at the problem

No way to create an equitable system

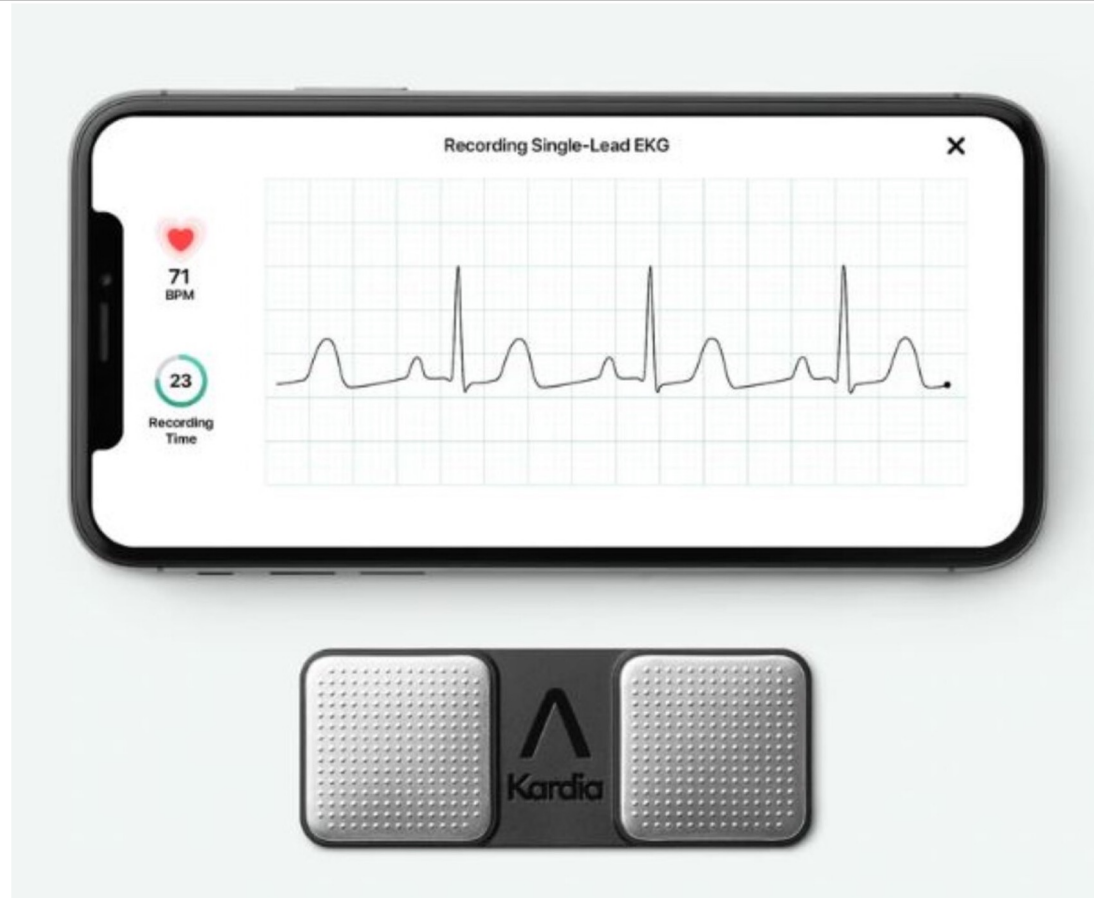
We need to leverage economies of scale via technologies

Also: Human biases are very hard to fix; AI biases are scary, but once identified are fixed with a software update

The difference a few years makes: Scaling with technology vs scaling with labor



AliveCor Named No.1 Artificial Intelligence Company in *Fast Company's* 2018 Most Innovative Companies Ranking



Advice to entrepreneurs

Institutions are made of individuals

The goals of individuals are not always the goals of their organization

If you want to predict behavior – put someone in a situation where they can work toward their short-term personal gain

Example: Trying to sell an AI automation tool to the person whose job will be replaced or even just their prestige/power in an organization will diminish

The goal is to generate value not raise money

A company which raises a lot of money and has a high valuation

- Makes it much harder to increase in value

- Much harder for stock options to be worth anything

Just because a company has raised a lot of money doesn't mean it is any good: e.g. FTX

There is a lot of daily grind growing value

Pitching to an investor – grow value over time

“Give me \$100,000,000, and step back for 10 years, and I will sequence a bunch of people and make a bunch of new drugs and make a bunch of money - that’s a billion dollar idea!”

Investors need to make returns

Many investment professionals need to get promoted or raise new funds within 2-3 years

Need to have a plan to show some incremental value creation – even if it takes 10 years to really be successful

Hopefully you saw something new

It does take a lot of hard work and a lot of time to improve the world, so the sooner you get started, the better for all of us...

... happy building!