Humankind 2.0: The Technologies of the Future
6. Biotech

Piero Scaruffi, 2017

See http://www.scaruffi.com/singular/human20.html
for the full text of this discussion

A brief History of Biotech

1953: Discovery of the structure of the DNA

James Watson and Francis Crick Rosalind Franklin

A brief History of Biotech

1969: Jon Beckwith isolates a gene

1973: Stanley Cohen and Herbert Boyer create the first recombinant DNA organism

1974: Waclaw Szybalski coins the term "synthetic biology”

1974 Rudolf Jaenisch and Beatrice Mintz inject viral DNA into the DNA of early mouse embryos and produced the first transgenic mammals

1975: Paul Berg organizes the Asilomar conference on recombinant DNA

Asilomar, 1975

A brief History of Biotech

1976: Genentech is founded

1977: Fred Sanger invents a method for rapid DNA sequencing and publishes the first full DNA genome of a living being

Janet Rossant creates a chimera combining two mice species

1980: Genentech's IPO, first biotech IPO

A brief History of Biotech

1982: The first biotech drug, Humulin, is approved for sale (Eli Lilly + Genentech)

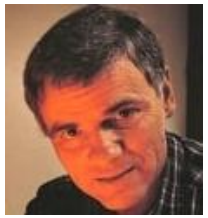
1983: Kary Mullis invents the polymerase chain reaction (PCR) for copying genes

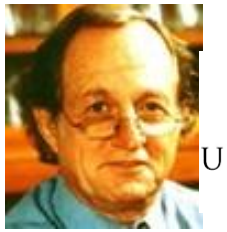
1986: Leroy Hood invents a way to automate gene sequencing

1986: Mario Capecchi performs gene editing on a mouse

1990: William French Anderson's gene therapy

1990: First baby born via PGD (Alan Handyside's lab)





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NATIONAL INSTITUTES OF HEALTH

UNIVERSITY OF LONDON

A brief History of Biotech

1989: AquAdvantage salmon by Memorial University in Newfoundland in Canada (approved for consumption in Canada in 2016)

1994: FlavrSavr Tomato

A brief History of Biotech

1994: Maria Jasin's homing endonucleases for genome editing

1996: Srinivasan Chandrasegaran's ZFN method for genome editing

1996: Ian Wilmut clones the first mammal, the sheep Dolly

1997: Dennis Lo detects fetal DNA in the mother's blood

2000: George Davey Smith introduces Mendelian randomization

Memorial Sloan Kettering Cancer Center

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

THE UNIVERSITY OF EDINBURGH

University of BRISTOL

A brief History of Biotech

1999 fluorescent fish GloFish by National University of Singapore

2000 Nexia Biotechnologies creates goats “augmented” with spider genes so that they produce milk equivalent to spider silk

A brief History of Biotech

2001: Dana Carroll's ZFN-based genome editing in cells

2002: Eckard Wimmer creates the first synthetic virus

2003: Dario Campana's method to make CAR-T cells

2003: The Human Genome Project is completed

A brief History of Biotech

2004: The first international conference on Synthetic Biology is held at the MIT

2005: Jay Keasling (UC Berkeley) artificially produces artemisinin acid

2005: Drew Endy's "Foundations for Engineering Biology"

syntheticbiology.org/Synthetic_Biology_1.0.html

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Synthetic Biology 1.0

The First International Meeting on Synthetic Biology

June 10-12, 2004
at the
Massachusetts Institute of Technology
Cambridge, MA

nature

Nature **438**, 449-453 (24 November 2005)

Foundations for engineering biology

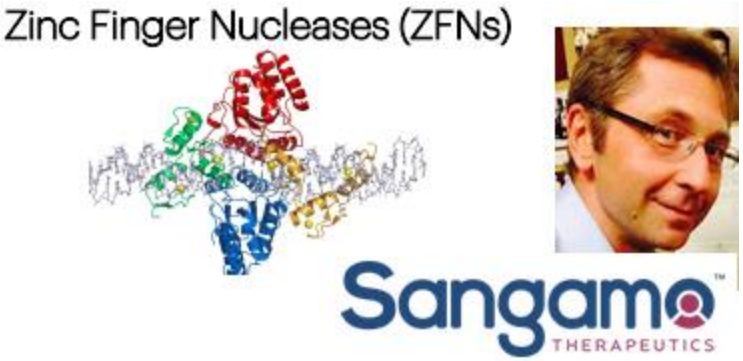
Drew Endy

A brief History of Biotech

2005: Fyodor Urnov uses ZFN to edit human DNA

2007: Personal genomics (Knome, 23andMe)

2007: Shinya Yamanaka converts adult human cells into pluripotent stem cells.



A brief History of Biotech

2008: The TALEN technique for genome editing (Dan Voytas, Feng Zhang)

2009: Jean Bennett's gene therapy restores vision in Corey Haas

2010: Craig Venter and Hamilton Smith (Maryland) reprogram a bacterium's DNA

2010: Cheap printers for living beings (OpenPCR, Cambrian Genomics)

2010: Carl June's CAR-T therapy

2011: The Voytas/Bogdanove TALEN kit




The Children's Hospital of Philadelphia®


A brief History of Biotech

2012: Markus Covert (Stanford) simulates an entire living organism in software

2012: Jennifer Doudna, Emmanuelle Charpentier and Feng Zhang develop the CRISPR-cas9 technique for genome editing

2013: Shoukhrat Mitalipov creates human embryonic stem cells from cloned embryos

2014: Weizhi Ji edits the germ-line of monkeys

2014: the first gene-therapy treatment approved in the West, Glybera by UniQure

uniQure
The leader in gene therapy

A brief History of Biotech

2014: Jef Boeke synthesizes a chromosome (in yeast)

2014: Floyd Romesberg expands life's genetic alphabet with two new bases

2015: Cellectis cures leukaemia in Layla Richards using TALENS editing

2015: Katsuhiko Hayashi's in vitro gametogenesis

2015: First Summit on Human Gene Editing

JOHNS HOPKINS UNIVERSITY

SCRIPPS

cellectis

九州大学
KYUSHU UNIVERSITY

First Summit on Human Gene Editing, 2015

A brief History of Biotech

2014 Valentino Gantz and Ethan Bier experiment gene drive on fruit flies

2015 Recombinetics uses TALEN to create two calves whose offspring should never have horns again

2015 Andrea Crisanti experiments gene drive on mosquitoes

A brief History of Biotech

2017: First gene therapy for cancer treatment approved in the USA

2017: Michele DeLuca combines stem-cell techniques with gene therapy to create artificial skin to cure a skin disease

UNIMORE

A brief History of Biotech

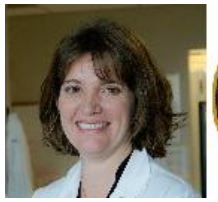
2017: Shoukhrat Mitalipov repairs a genetic mutation in human embryos that causes a heart disease

2018: Jiankui He uses CRISPR to modify human embryos and give birth to the first gene-edited babies

2018 Kimberly Cooper engineers the first gene drive in a mammal (in mice)

2019: Andrew Anzalone's & David Liu's prime editing

2019: CRISPR Therapeutics' gene-editing cure for sickle-cell disease CTX001



UNIVERSITY OF CALIFORNIA · SAN DIEGO

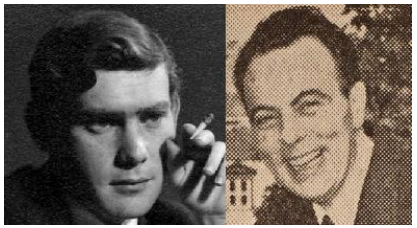
BROAD INSTITUTE

CRISPR THERAPEUTICS

A brief History of Biotech

mRNA medicine

1961: Sydney Brenner, Francois Jacob and Matthew Meselson determine the function of messenger RNA



AN UNSTABLE INTERMEDIATE CARRYING INFORMATION FROM GENES TO RIBOSOMES FOR PROTEIN SYNTHESIS

By DR. S. BRENNER

Medical Research Council Unit for Molecular Biology, Cavendish Laboratory, University of Cambridge

DR. F. JACOB

Institut Pasteur, Paris

AND

DR. M. MESELSON

Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California

A brief History of Biotech

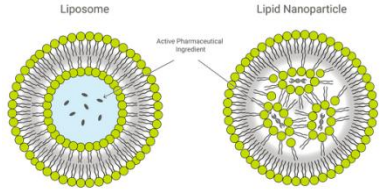
mRNA medicine

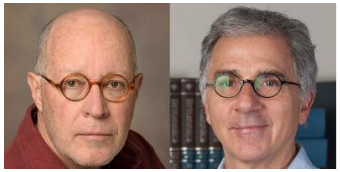
1965: Alec Bangham discovers liposomes

1984: Paul Krieg and Doug Melton synthesize mRNA in a lab

1987: Robert Malone discovers a method to deliver mRNA to human cells so that they begin producing proteins

1990: Katalin Kariko proposes using mRNA as an alternative to DNA-based gene therapy





A brief History of Biotech

mRNA medicine

1992: Gustav Jirikowski's first mRNA-based gene therapy on rats

1995: Robert Conry designs the first mRNA vaccine

1997: Eli Gilboa founds Merix Bioscience, the first mRNA therapeutics company

2005: Katalin Kariko' and Drew Weissman publish their research on how to make mRNA vaccines

Immunity, Vol. 23, 165–175, August, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.immuni.2005.06.008

Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA

Katalin Karikó,[1,*] Michael Buckstein,[2] Houping Ni,[2] and Drew Weissman[2]
[1]Department of Neurosurgery
[2]Department of Medicine
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania 19104

thetic antiviral compound R-848 (Jurk et al., 2(a natural ligand has not been identified.

It has been known for decades that select and RNA molecules have the unique property vate the immune system. It was discovered cently that secretion of interferon in response is mediated by unmethylated CpG motifs acti

A brief History of Biotech

mRNA medicine

2008: Ugur Sahin and Ozlem Tureci found BioNTech

2010: Derrick Rossi (Harvard) discovers a method to make mRNA-based gene therapy and founds Moderna

mRNA-based therapeutics — developing a new class of drugs

Ugur Sahin[1,2], Katalin Karikó[2,3] and Özlem Türeci[1]

Highly efficient reprogramming to pluripotency and directed differentiation of human cells using synthetic modified mRNA

Luigi Warren[1,12], Philip D. Manos[2,3,12], Tim Ahfeldt[4,11], Yuin-Han Loh[2,5], Hu Li[8], Frank Lau[4,6], Wataru Ebina[1], Pankaj Mandal[1], Zachary D. Smith[7], Alexander Meissner[7], George Q. Daley[2,3,5,9], Andrew S. Brack[10], James J. Collins[8], Chad Cowan[4,6], Thorsten M. Schlaeger[2,3], and **Derrick J. Rossi[1]**

[1]Immune Disease Institute, Program in Cellular and Molecular Medicine, Children's Hospital Boston, Harvard Stem Cell Institute, and the Department of Pathology, Harvard Medical School, Boston, MA 02115, USA

A brief History of Biotech

mRNA medicine

2012: Andrew Geall's non-viral technique for making mRNA-based drugs

2017: BioNtech's mRNA cancer vaccine

2020: Moderna's and BioNtech's covid19 vaccines based on mRNA

Nonviral delivery of self-amplifying RNA vaccines

Andrew J. Geall[a,1], Ayush Verma[a], Gillis R. Otten[a], Christine A. Shaw[a], Armin Hekele[a], Kaustuv Banerjee[a], Yen Cu[a], Clayton W. Beard[a], Luis A. Brito[a], Thomas Krucker[b], Derek T. O'Hagan[a], Manmohan Singh[a], Peter W. Mason[a], Nicholas M. Valiante[a], Philip R. Dormitzer[a], Susan W. Barnett[a], Rino Rappuoli[a], Jeffrey B. Ulmer[a], and Christian W. Mandl[a]

[a]Novartis Vaccines and Diagnostics, Cambridge, MA 02139; and [b]Novartis Institutes for BioMedical Research, Cambridge MA 02139

A brief History of Biotech

Trivia… Mutagenesis

1926: Hermann Muller demonstrates that exposure to x-rays caused genetic mutations in the genome of fruit flies

1920s: Lewis Stadler studies corn mutations caused by X-rays and ultraviolet rays

Radiation can speed up evolution

1949 "atomic garden" at Brookhaven National Laboratories in Rhode Island: vegetables exposed to radioactive isotopes like cobalt-60 and caesium-137

1950s: Vogue of "atomic" plants and seeds

Atomic gardens created 2,700 new varieties of plants, including most sweetcorn varieties

A brief History of Biotech

Trivia… Mutagenesis

Most of today's mint oil comes from a disease-resistance peppermint plant developed in 1971 at the Brookhaven National Laboratory

Radiation breeding is responsible for many of the gorgeous orchid, tulip and rose varieties

1958: Edward Knipling's "sterile insect" technique (sterilizing pupae with radiations)

A brief History of Biotech

Cloning

Dolly the Sheep, the first cloned mammal (July 1996 in Britain),

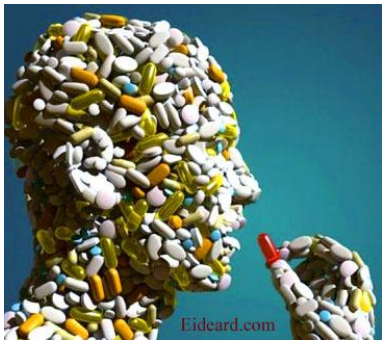
cloning of cattle in Wisconsin (just a few months later in 1997),

cloning cats (the Carbon Copy cat of 2001 in Texas)

cloning of horses (“Prometea” in 2003 in Italy)

cloning of dogs (“Snuppy” in 2005 in South Korea)

Big Pharma



- Big Pharma's revenues: $1.2 trillion (2016)

Big Pharma

- Europe: Novartis and Roche in Switzerland, GlaxoSmithKline and AstraZeneca in Britain, Bayer in Germany
- East Coast: Pfizer and Bristol-Myers Squibb in New York, and Merck, Johnson & Johnson, Wyeth, Sanofi and Organon in New Jersey, ThermoFisher in Boston
- Exceptions:Abbott (Chicago), Lilly (Indiana)
- California: none

1	Johnson & Johnson	9	Bayer
2	Novartis	10	Gilead Sciences
3	Roche	11	Teva
4	Pfizer	12	Amgen
5	Sanofi	13	AbbVie
6	Merck	14	Eli Lilly
7	GlaxoSmithKline	15	Bristol-Myers Squibb
8	AstraZeneca		

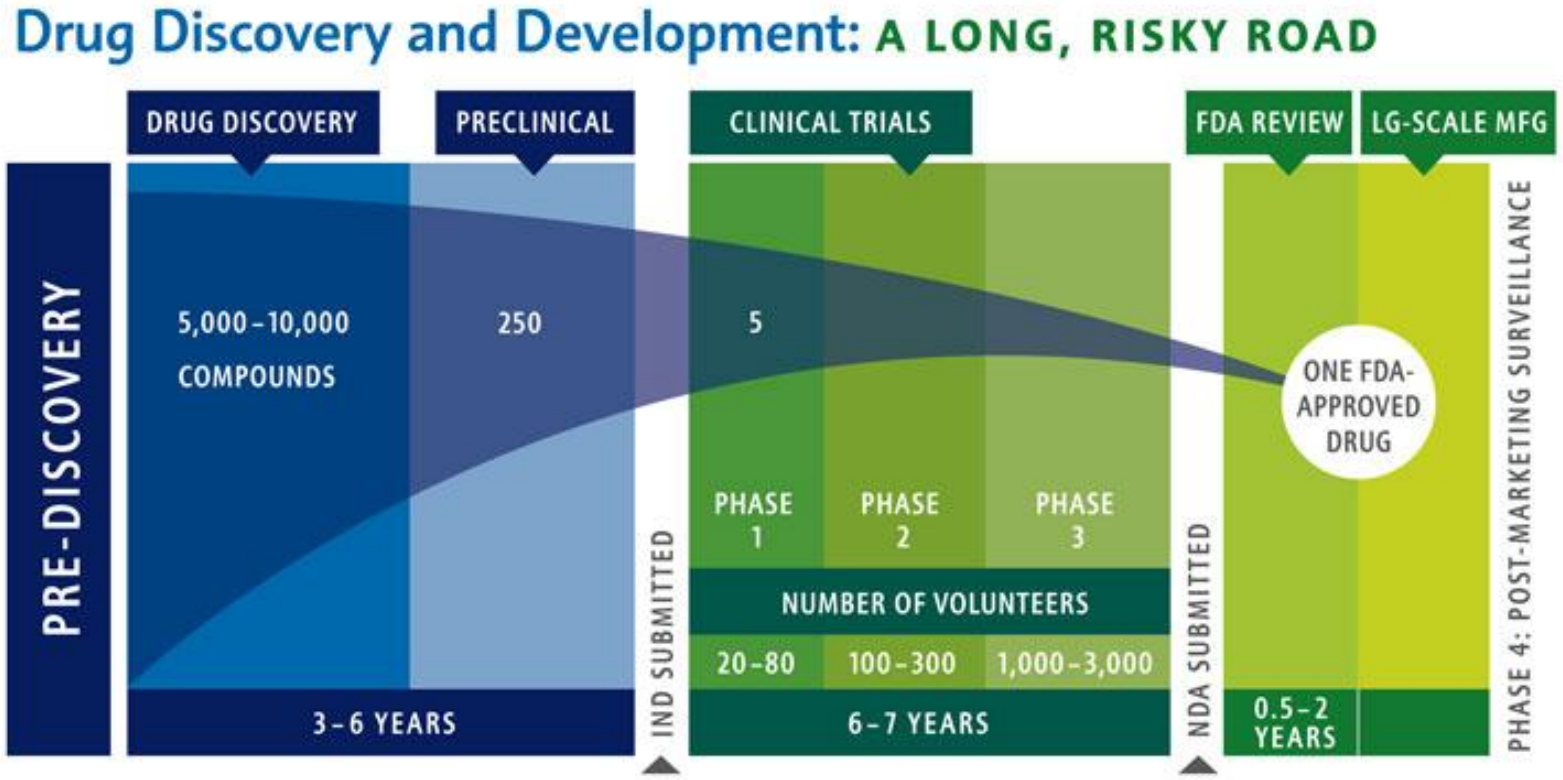
2015

Pharma vs Software

- A biotech startup needs much closer ties to the scientific community than software
- Biotech startups are typically founded by older people than software startups
- A biotech venture is a complex project that requires skills in chemistry, biology, engineering, marketing, and even skills in dealing with the government agency that approves drugs (the FDA) and with the big pharmaceutical companies (that have the power to sell a new drug worldwide).

Pharma vs Software

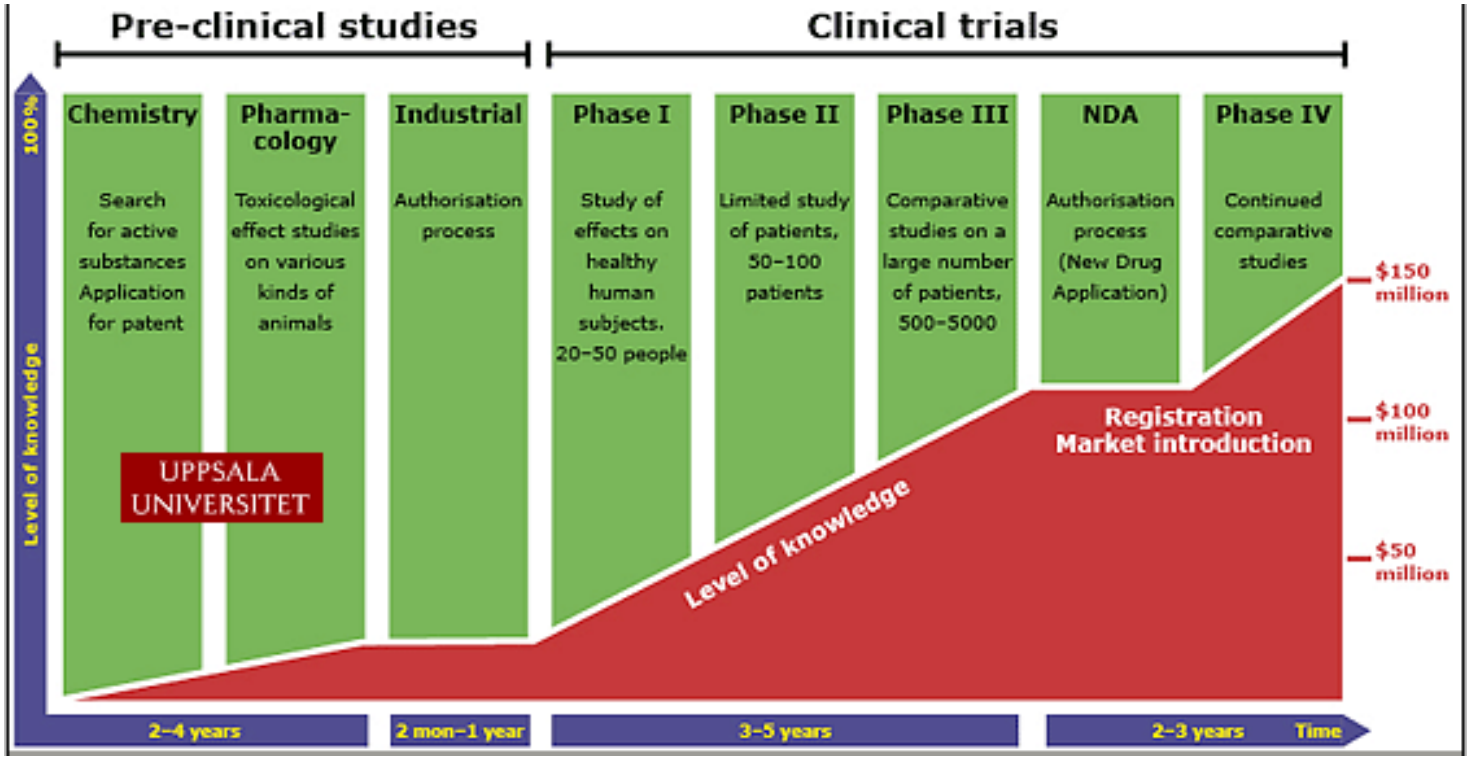
- The cost to develop a new drug is colossal compared with software.



Source: Pharmaceutical Research and Manufacturers of America

Pharma vs Software

- Just the clinical study can easily cost $10 million.
- Time to market: 5 to 10 years.

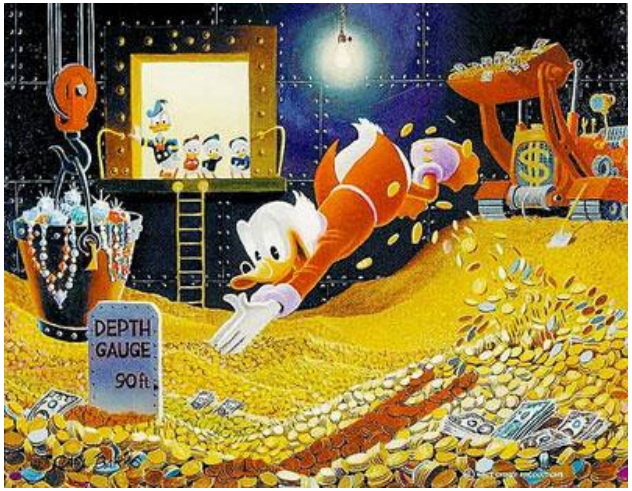


Pharma vs Software

- There are strict rules and regulations to obey that don't exist in software.
- Marketing a new drug is tougher than marketing a software application: drugs don't go viral the way a software app goes.
- Thousands of new software apps and gadgets are launched every year, but instead very few new drugs are approved every year by the FDA, usually less than 50.

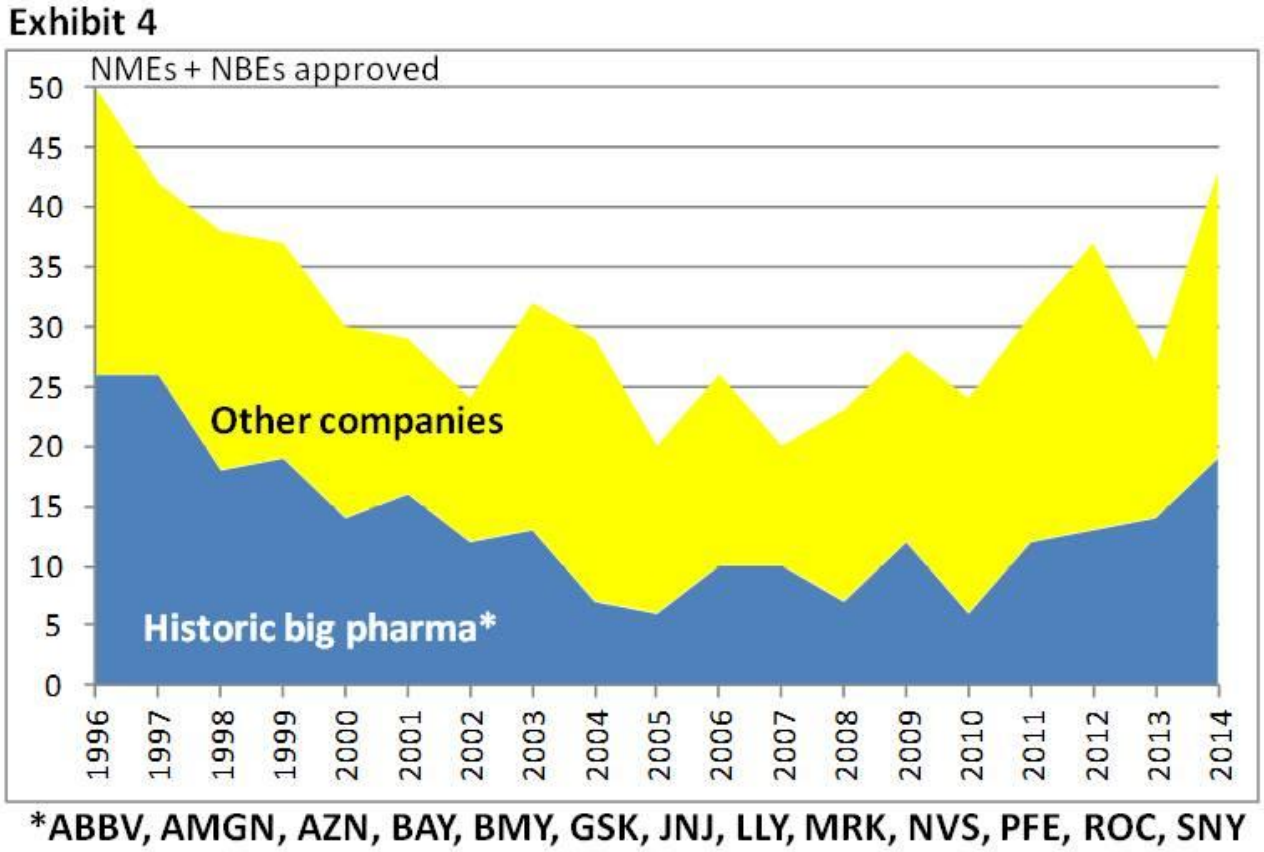
Pharma vs Software

- The risk for the biotech industry is much higher than the risk for the computer industry.
- But the payback can be astronomical…



FDA Approvals

- 1996: all-time record of approved drugs in the USA



FDA Approvals

- 2014
  - FDA approves 44 new drugs, an 18-year high
  - Biologicals: 16 (35%)
- 2015
  - FDA approves 51 new drugs, a 66-year high
  - Biologicals: 20 (39%)
- 2016
  - FDA approves only 22 (lowest number since 2010)
- 2017
  - FDA approves 46

FDA Approvals

- Ten-year trends:
  - Top three: J&J, GSK and Novartis (47 drugs)
  - "Big pharma" has averaged 42% of annual approvals

Company	Last 10 years 2006-2015	Last 5 years 2011-2015
Johnson & Johnson	17	9
GlaxoSmithKline	15	9
Novartis	15	9
Pfizer	11	7
Merck&Co	10	6
Roche	10	8
Bristol-Myers Squibb	9	6
Amgen	7	4
AstraZeneca	7	7
Boehringer-Ingelheim	7	6
Sanofi	7	5
Gilead	6	5
Takeda	6	5

FDA Approvals

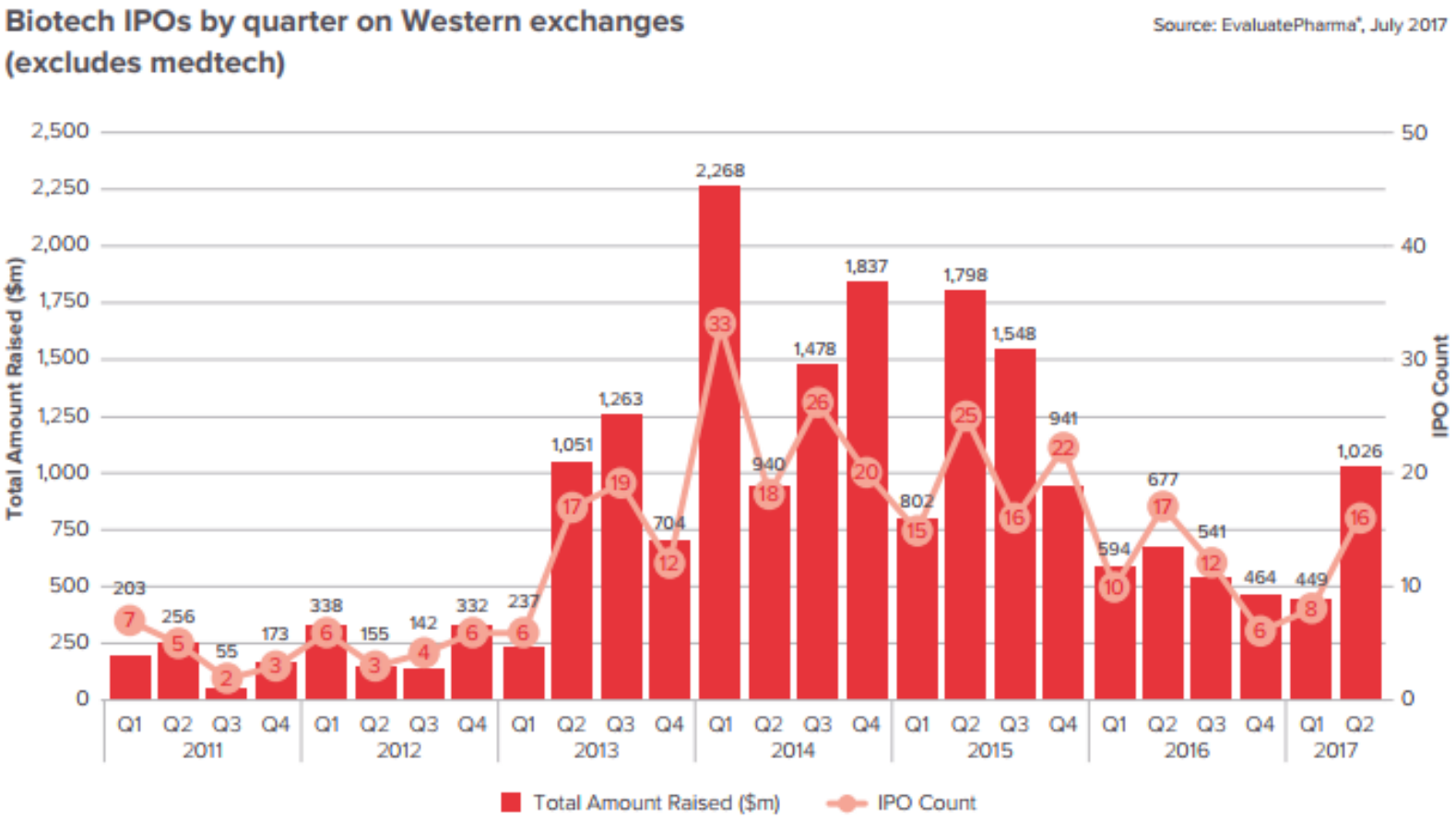
- Three-year trend:
  - Infectious diseases
  - Cancer
  - Rare diseases
  - Hematology
- Future trends (just guessing):

World Health Organization

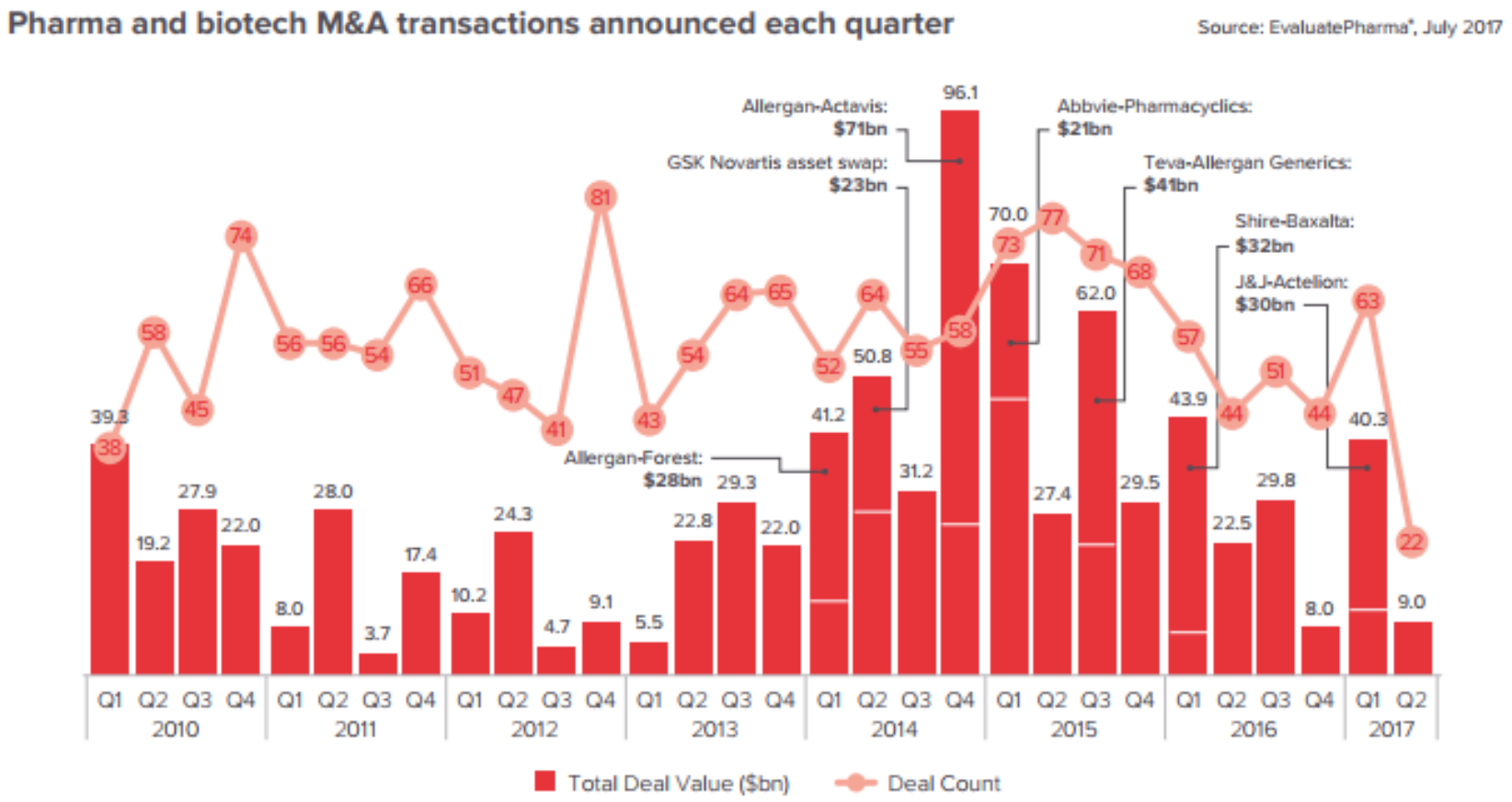
6 APRIL, 2016 | GENEVA - The number of people living with diabetes has almost quadrupled since 1980 to 422 million adults

In 2012, an estimated 1.5 million deaths were directly caused by diabetes

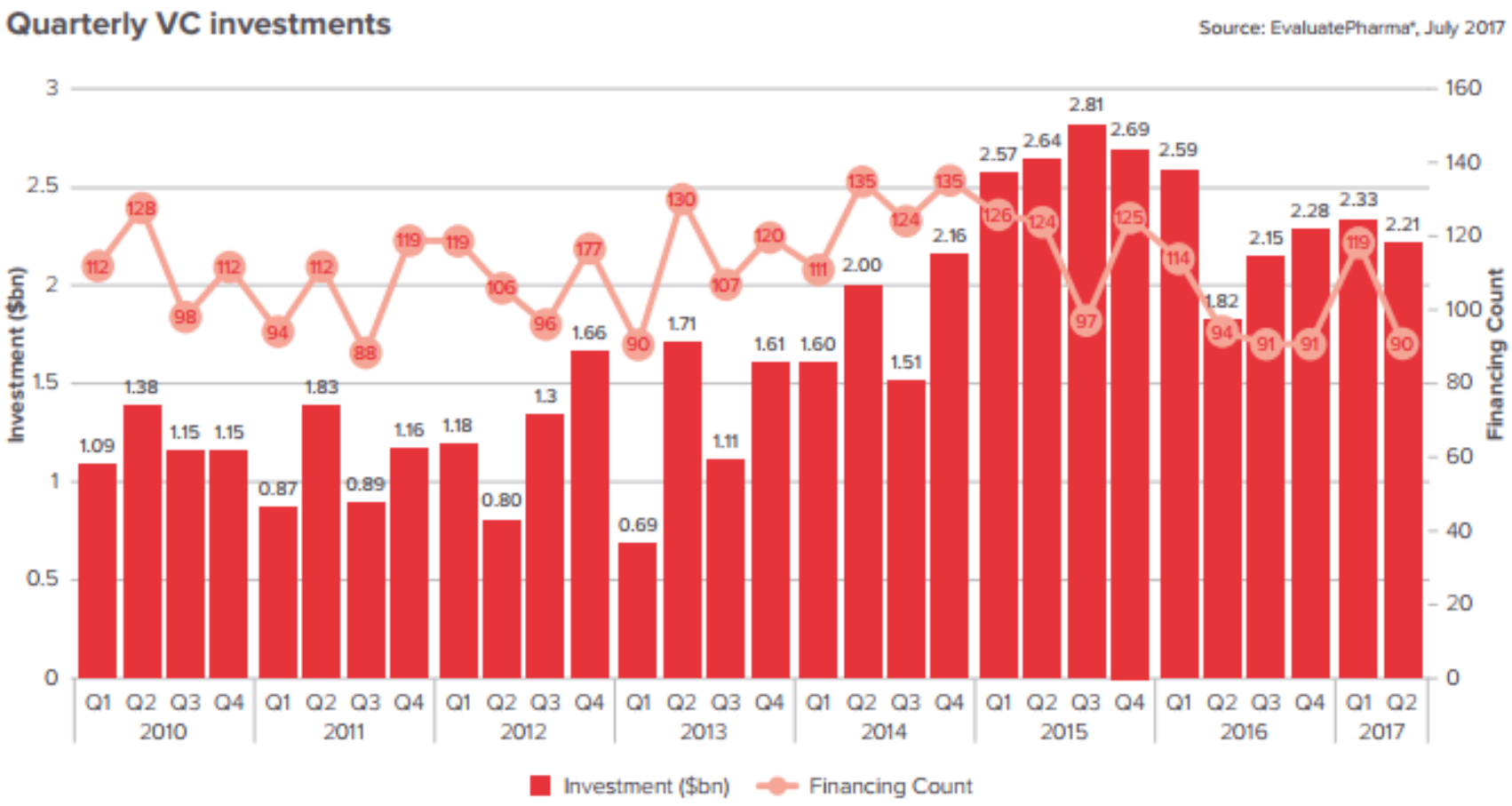
Biotech IPOs



Biotech Acquisitions



Biotech VC Investment



Biotech Case Studies

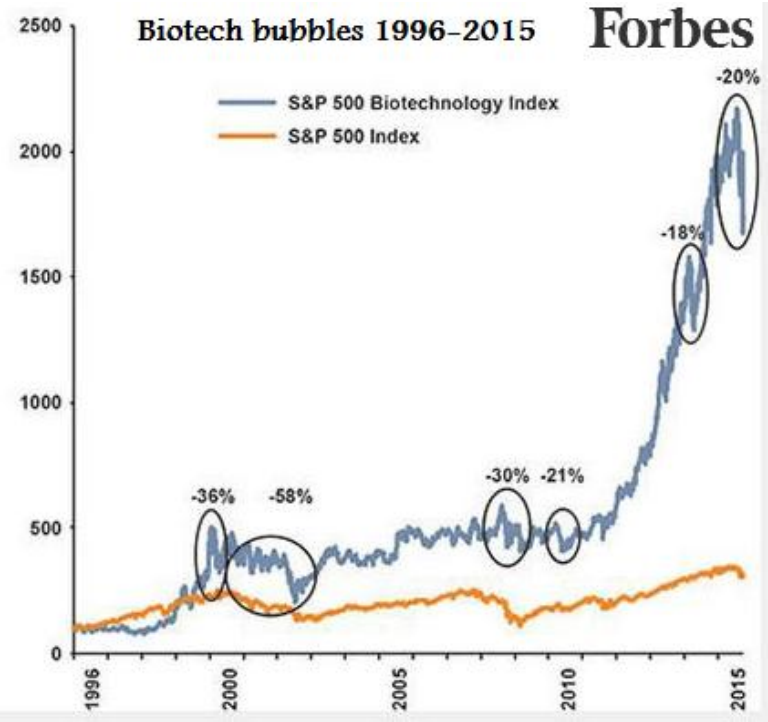
- Genentech (Bay Area, 1976)
  - 1980: Genentech's IPO, first biotech IPO
  - 1982: The first biotech drug, Humulin, is approved for sale
  - 1985: growth hormone Protropin
  - 1990: Roche deal, UCSF lawsuit, Hepatitis B vaccine
  - 1992 revenues: $544 million
- Amgen (Los Angeles, 1980)
  - 1989: Epogen to treat anemia
  - 1991: Neupogen to treat neutropenia
  - 1992: revenues pass $1 billion

Biotech Case Studies

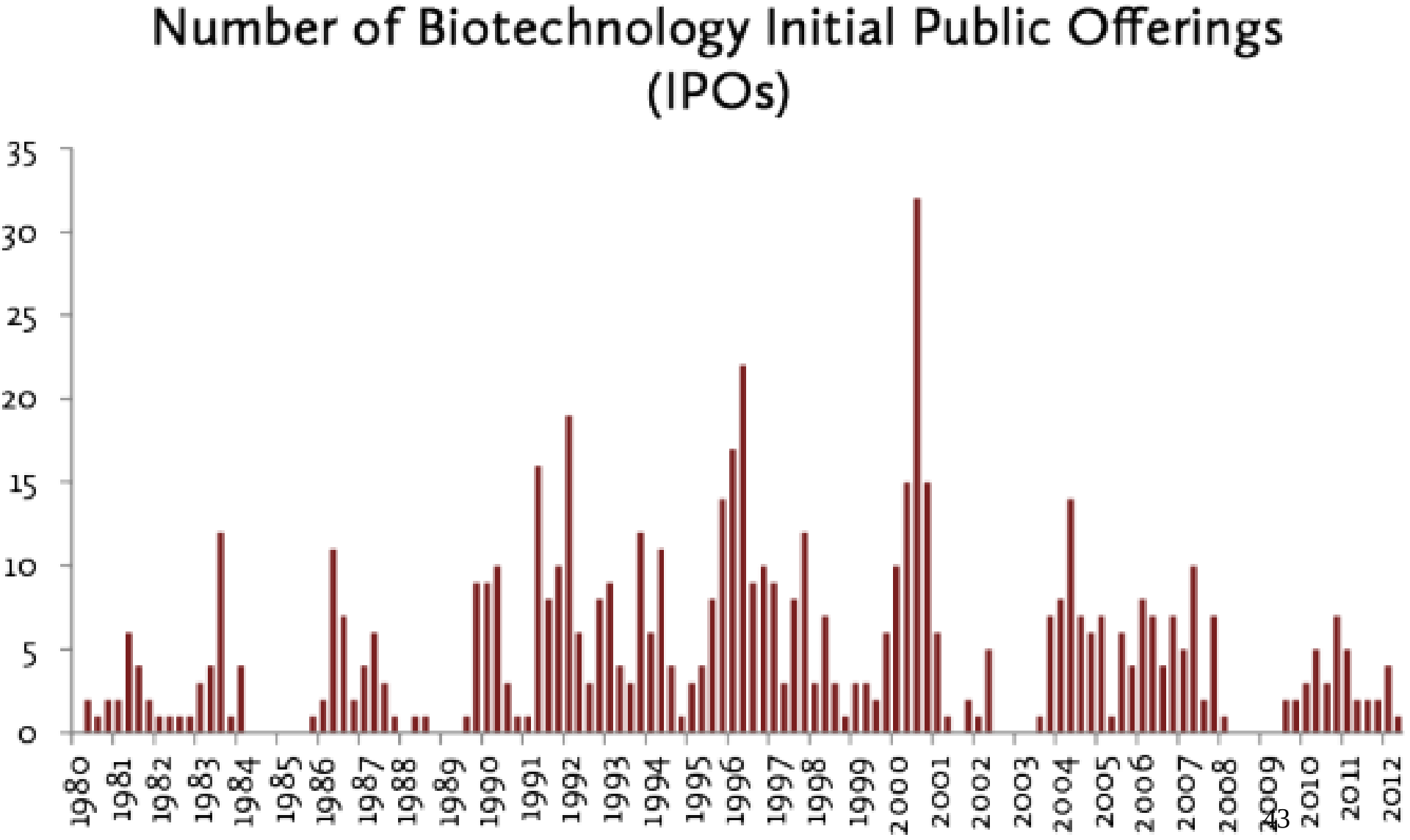
- Gilead (Bay Area, 1987)
  - 1999: anti-flu Tamiflu
  - 2001: anti-AIDS Viread
  - 2013: anti-hepatitis C Sovaldi
  - 2015: largest biotech company, worth $150 billion
  - Fast FDA approval
  - Focus on fighting viruses (harder than fighting bacteria) to treat chronic and global diseases (AIDS, hepatitis C and the influenza).
- All of them founded by venture capitalists
- Time to market from incorporation to first major drug sales is 8-12 years

Biotech Bubbles

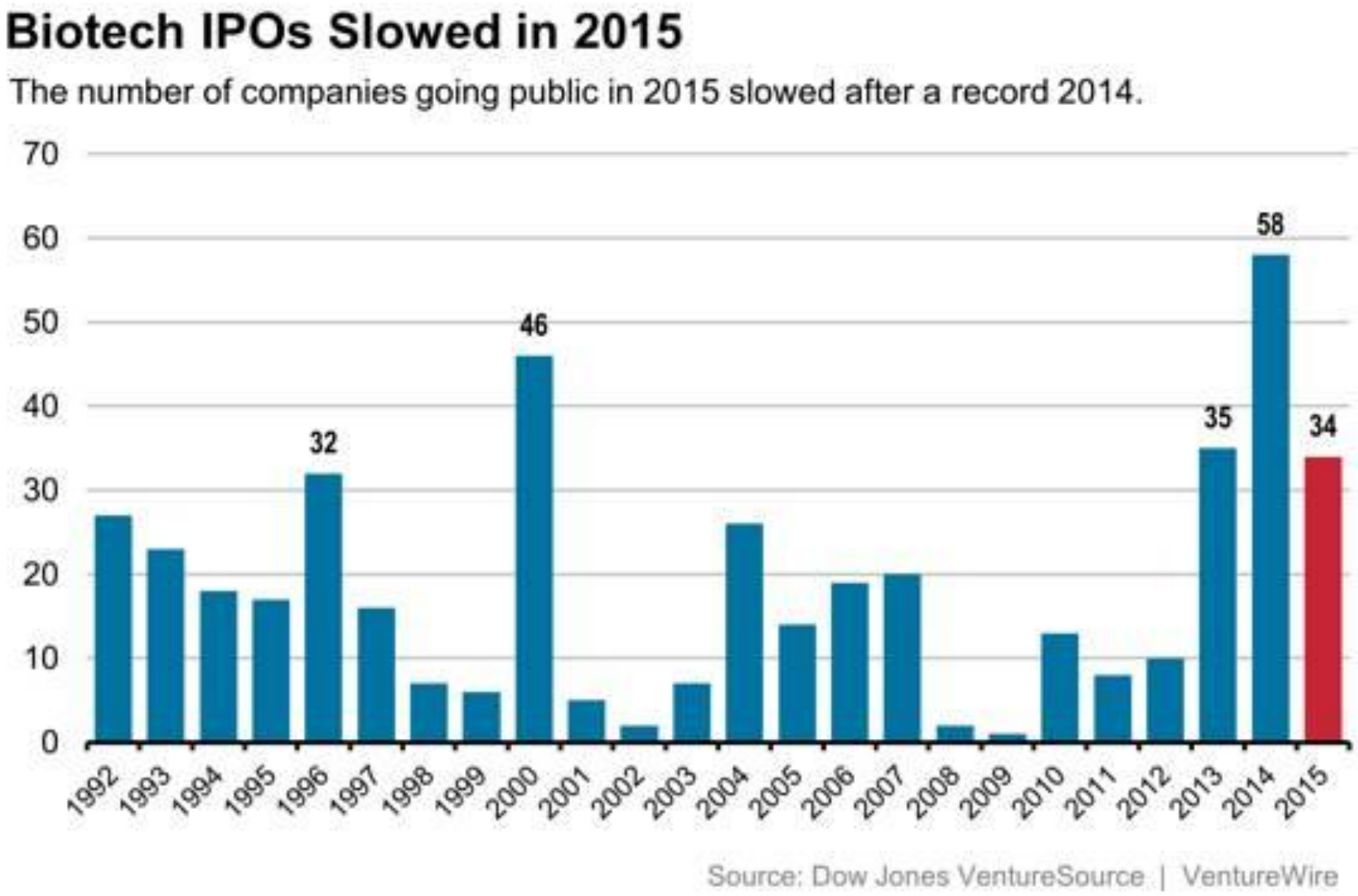
- The S&P 500 biotechnology index skyrocketed more than 400% between July 2010 and July 2015
- Q2 2015: $1.5 billion of venture capital into early-stage companies ($1B in the Bay Area alone)
- Second-longest bull market in biotech since 1992



Biotech Bubbles



Biotech Bubbles



Biotech Bubbles

- The great biotech scandals of 2015/16

The New York Times

Drug C.E.O. Martin Shkreli Arrested on Fraud Charges

By JULIE CRESWELL, STEPHANIE CLIFFORD and ANDREW POLLACK DEC. 17, 2015

MIT Technology Review

Biomedicine

Theranos Promised a Revolution, but Delivered Dangerous Errors

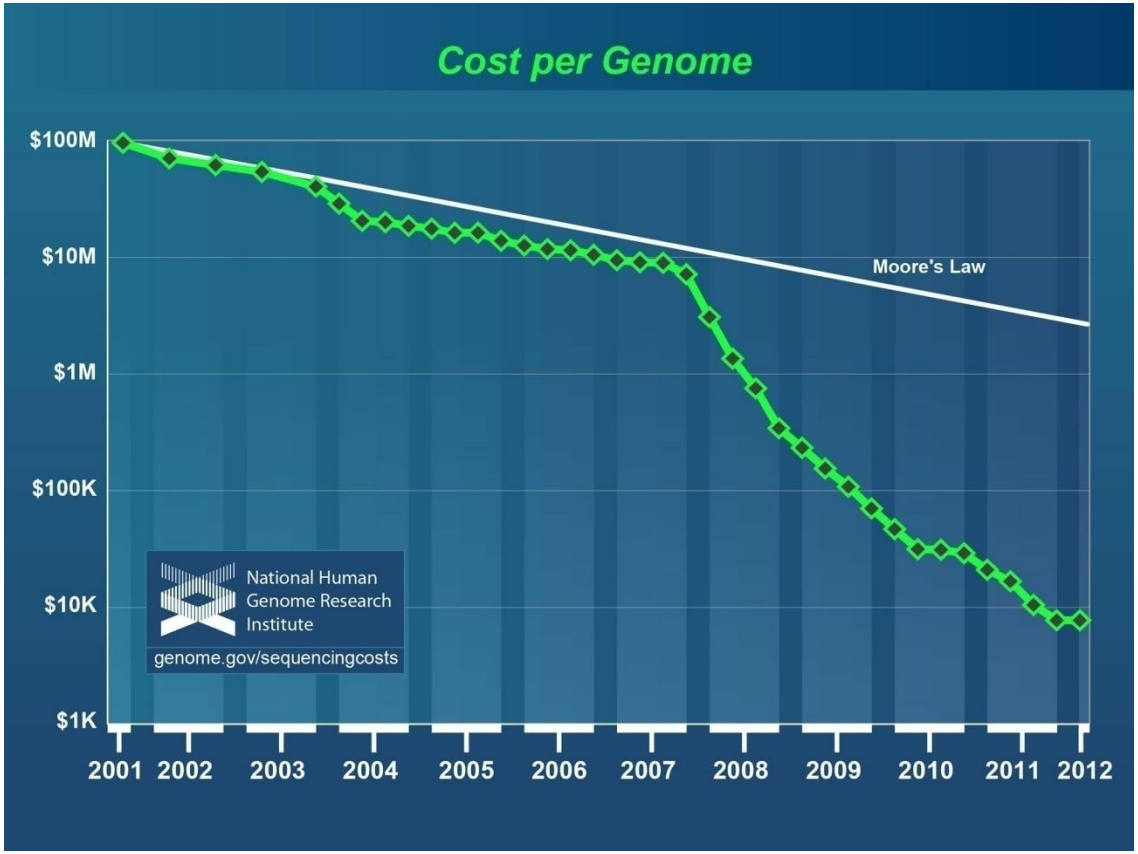
Forbes / Investing

SEP 9, 2015 @ 10:00 AM 201,827 VIEWS

The 30-Year-Old CEO Conjuring Drug Companies From Thin Air

Exponential Progress

- Moore's law vs Cost per genome
  - It took $3 billion and 13 years, from 1990 to 2003, to sequence the first human genome
  - It will soon cost $200, a drop of 99.9% since 2003



Biotech in the Bay Area

- The Bay Area has more biotech startups than the rest of the USA combined
- South San Francisco (birthplace of Genentech)
- Emeryville (near UC Berkeley)
- Mission Bay in San Francisco (UCSF medical campus)
- Silicon Valley

Biotech in the Bay Area

- Incubators
  - QB3 (California Institute for Quantitative Biosciences, 2000)
  - Berkeley Biolabs (2014)
  - Ireland's IndieBio (2014)
  - Johnson & Johnson's Jlab
  - Bayer's CoLaborator
  - Malaysia's BiotechCorp
  - …

Berkeley BioLabs

INDIE BIO

Personal Genomics

- Sequencing the entire human genome
  - Human Genome Project (2003): $3.7 billion
  - Knome (2007): $350,000
  - Veritas Genetics (2015): $1,000

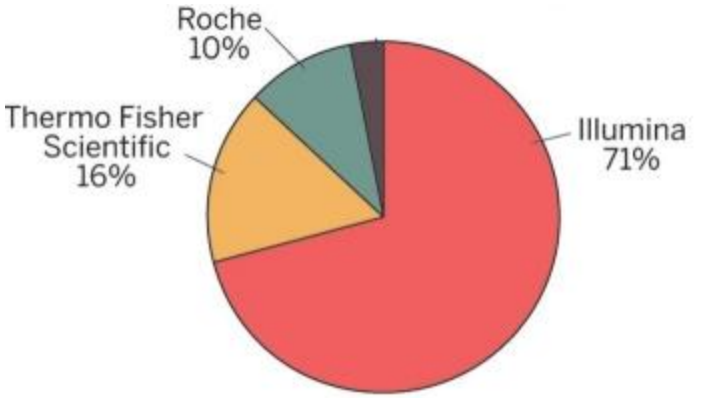
HGP's multinational team

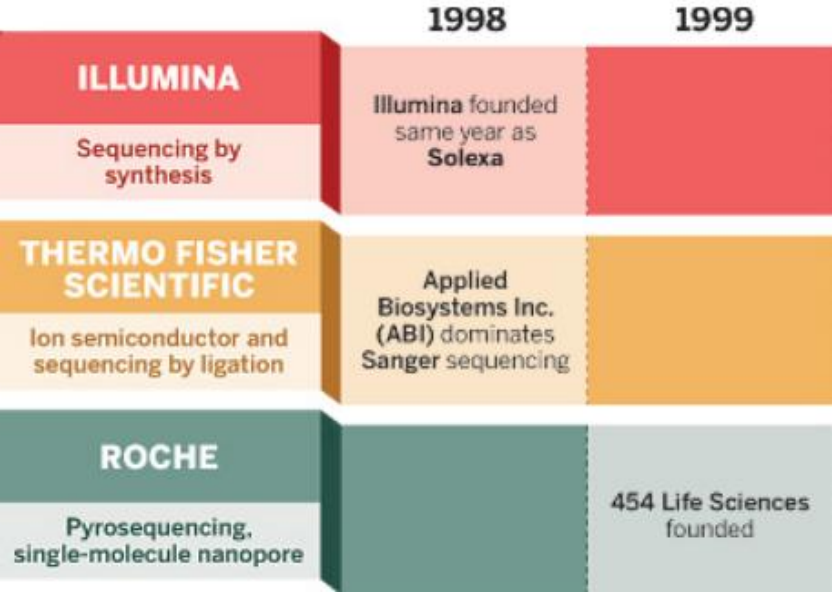
Personal Genomics

- Genome testing
  - 23andme (2006): $200 genome test (millionth customer in 2015)
  - Generations Network's AncestryDNA
  - National Geographic's Genographic Project
  - Family Tree DNA
- But no (actionable) health-related analyses

Personal Genomics

- Gene-sequencing machines
  - Illumina: $1,000 genome test (2015: 70% of the market for genome-sequencing, $1.6 billion revenues)
  - Applied Biosystems (Thermo Fisher Scientific)
  - 454 Corporation (Roche)





2014. Illumina's HiSeq X Ten sequencing costs less than $1,000

Personal Genomics

- Actionable genome testing
  - PierianDx/ Knome (St Louis, 2011): machines for medical labs to provide comprehensive, actionable reports
  - Sure Genomics (Las Vegas, 2014): Sequencing at home for $2,500
  - Veritas Genetics (Maryland, 2014): Sequencing + Interpretation for $1,000

Personal Genomics

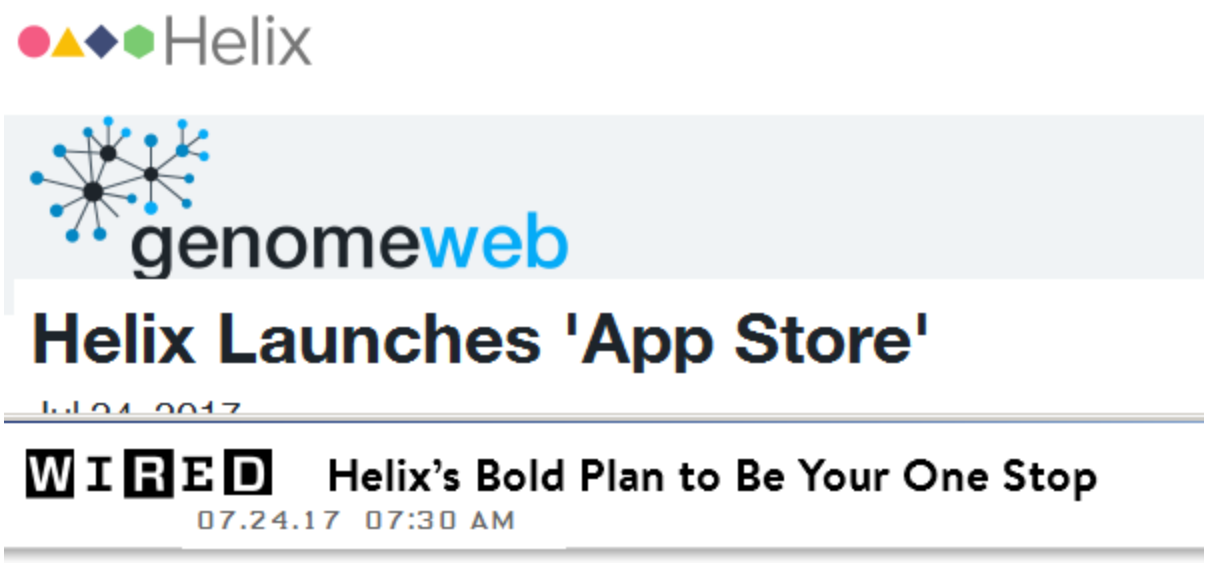
- Actionable genome testing
  - Veritas' MyGenome screens for 1,200 conditions and 100 inherited conditions
  - Inova's MediMap analyzes 31 genes that influence response to 145 prescription medications
  - Inova + Veritas Genetics (2017): MyMap for diet and lifestyle guidance

Personal Genomics

- Portable genome testing
  - Oxford Nanopore's Minion (2015)

Personal Genomics

- Platforms for genomic applications
  - Helix (Illumina spinoff, 2015): an “app store” for personal genomics



Longevity

1993: Cynthia Kenyon (UCSF): disabling Daf-2 gene

1999: Leonard Guarente (MIT) identifies the longevity gene in yeast, sir2

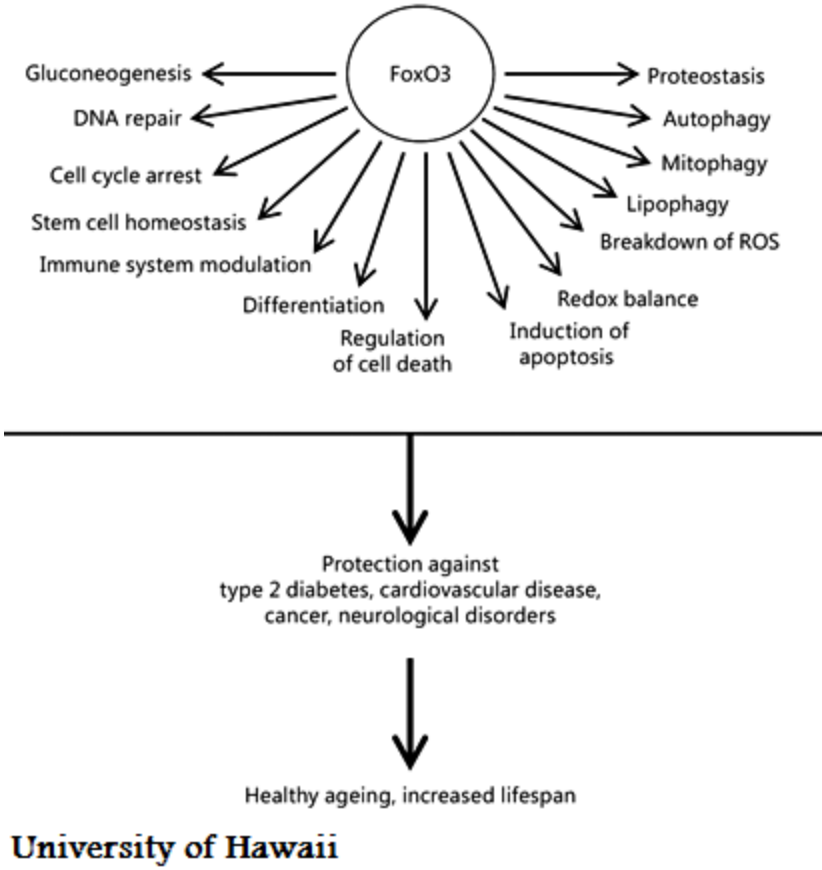
2010: Rochelle Buffenstein (Univ of Texas): NRF2 protects the body against aging

2012: the hydra is “immortal” due to the FoxO gene (Kiel Univ)

2016: Manfred Kayser (Erasmus Medical Centre): MC1R is responsible for looking older

Longevity

- 2008: The FoxO3 gene is very active in centenarians (Univ of Hawaii)
- 2012: the hydra is “immortal” due to the FoxO gene (Kiel Univ)



Longevity

- 1993: Cynthia Kenyon (UCSF): disabling Daf-2 gene can double the life of a worm; sugar shortens it (i.e. aging is not inevitable)
- 1996: Jim Woodget & Vuk Stambolic: Lithium inhibits GSK3
- 1999: Leonard Guarente (MIT) identifies the longevity gene in yeast, sir2
- 2003: Suppressing TOR prolongs the life of worms (Fritz Muller)

Cynthia Kenyon Finds That Mutations In Daf-2 And Daf-16 Genes Cause C. Elegans Worms To Live Over Twice As Long September 15, 1993

PUBLIC RELEASE: 3-NOV-2009

A 'spoonful of sugar' makes the worms' life span go down

UCSF

Jim Woodgett

Vuk Stambolic

MIT

UNI FR

UNIVERSITÉ DE FRIBOURG
UNIVERSITÄT FREIBURG

Longevity

- 2005: Zelton Dave Sharp (Univ of Texas): rapamycin (that targets TOR) prolongs the life of mice
- 2007: David Sinclair (MIT): sir2 and TOR target the same longevity pathway

UT HEALTH SCIENCE CENTER SAN ANTONIO

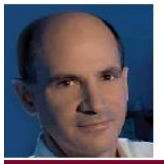
Longevity

- 2005: Tom Rando (Stanford): young blood can rejuvinate old cells
- 2010: Rochelle Buffenstein (Univ of Texas): NRF2 protects the body against aging

THOMAS RANDO LABORATORY
AT STANFORD UNIVERSITY

Young Blood Revives Aging Muscles, Stanford Researchers Find

February 16, 2005 /



Tom Rando

STANFORD SCHOOL OF MEDICINE

UT HEALTH SCIENCE CENTER SAN ANTONIO

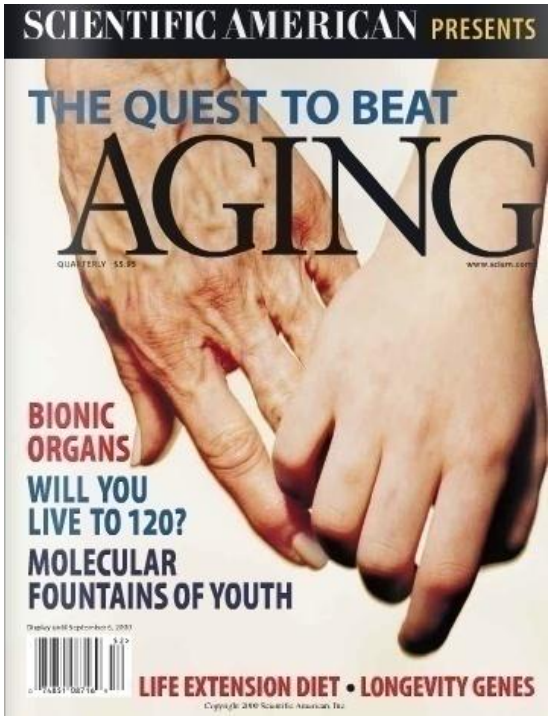
Nrf2, Guardian of Healthspan and Gatekeeper of Species Longevity

Longevity

- 2007: Aubrey de Grey's book "Ending Aging"
- 2010: Special report in Scientific American

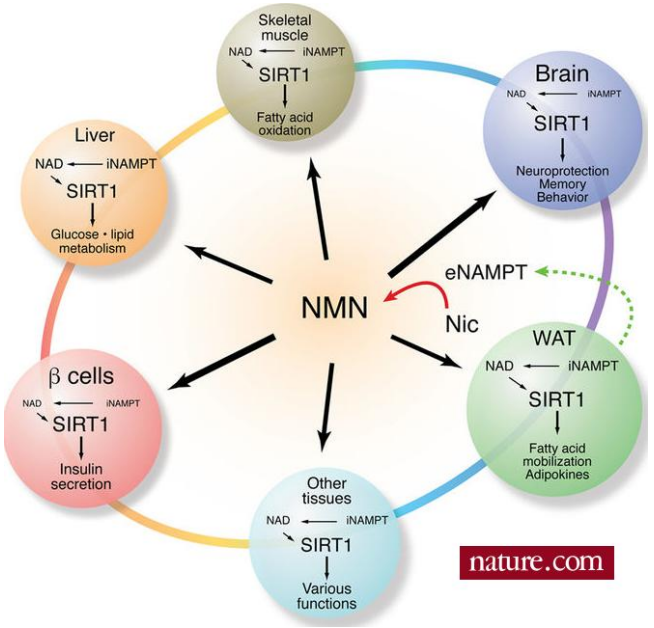
sens research foundation

reimagine aging



Longevity

- 2000: Shinichiro Imai discovers that the action of sirtuins depends on NAD
- NAD enhances the work of mitochondria in the cell
- We produce less NAD as we age
- Boosting NAD via NR or NMN (these boosters activate all seven sirtuins)
- 2013: David Sinclair shows that NMN reverses muscle aging in mice
- 2016: first human clinical study for NMN (Japan)



Longevity

- 2011: Jean-Marc Lemaitre (France) reprogram cells of centenarians
- 2011: Jan Van Deursen (Mayo Clinic) removes senescent cells from mice and founds Unity Biotechnology
- 2013: Google's Calico ("longevity lab")

Longevity

- 2013: Craig Venter's Human Longevity Inc
- 2014: Tony Wyss-Coray & Saul Villeda: young blood reverses aging
- 2014: Leonard Guarente’s Elysium
- 2016: Jesse Karmazin’s Ambrosia (Monterey): transfusions of younger blood

Longevity

- 2016: Juan-Carlos Izpisua-Belmonte (Salk Institute) reprograms cells in mice to express the four “Yamanaka factors”

Longevity

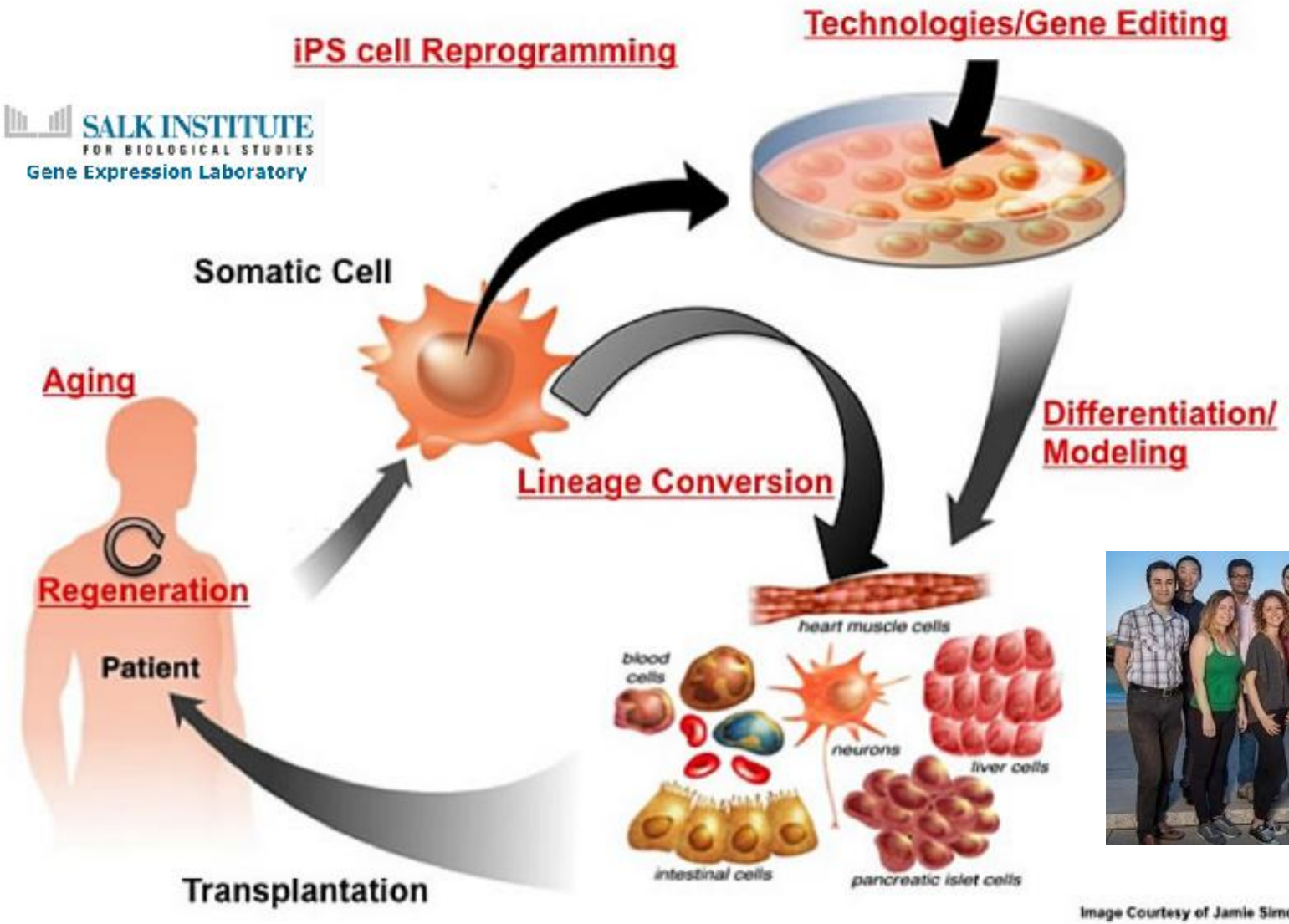
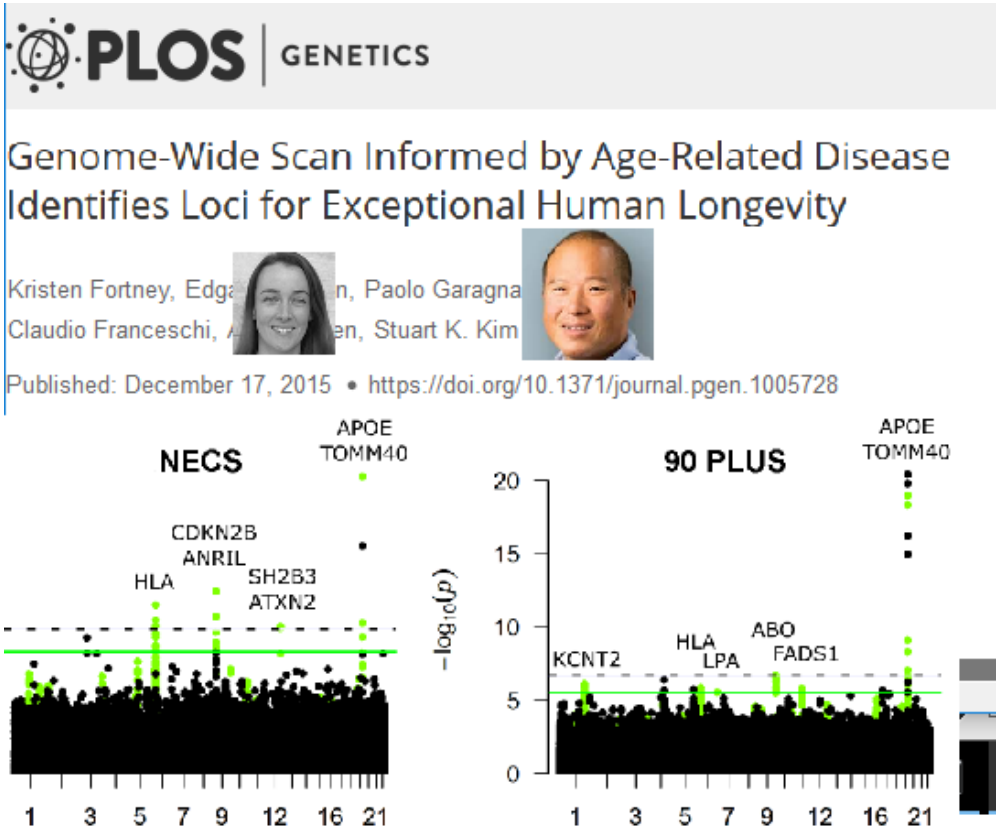


Image Courtesy of Jamie Simon

Longevity

- Stuart Kim (2015): four genes of centenarians



Jeanne Calment[1]	122 years, 164 days
Sarah Knauss[2]	119 years, 97 days
Lucy Hannah[3]	117 years, 248 days
Marie-Louise Meilleur[4]	117 years, 230 days
Violet Brown[5]	117 years, 189 days
Emma Morano[5][6]	117 years, 137 days
Nabi Tajima[5]	117 years, 119 days
Misao Okawa[5]	117 years, 27 days
María Capovilla[7]	116 years, 347 days
Susannah Mushatt Jones[5]	116 years, 311 days

Which genes do they have in common?

Longevity

- Rejuvenate Bio (Boston, 2016, George Church) rejuvenatse dogs using gene therapy
- resTORbio (Boston, 2017): Novartis testing everolimus in hundreds of elderly patients in Australia and New Zealand (everolimus is related to rapamycin)

MIT Technology Review

REJUVENATE BIO

A stealthy Harvard startup wants to reverse aging in dogs, and humans could be next

MIT Technology Review March 28, 2017

Is This the Anti-Aging Pill We've All Been Waiting For?

resTORbio

NOVARTIS

Longevity

- T.A. Sciences (New York, 2002): telomeres
- Humacyte (North Carolina, 2004): regenerative medicine
- Unity Biotechnology (Brisbane, 2011, Ned David)
- Oxstem (Britain, 2013): regenerative medicine
- Life Biosciences (Boston, 2017, David Sinclair)

Longevity

- Regenerative medicine
  - Celularity (Robert Hariri - New Jersey, 2016)
  - BlueRock Therapeutics (2016)
  - Prellis Biologics (Melanie Matheu - San Francisco, 2016)
  - Samumed (Dannis Carson & Osman Kibar - San Diego, 2008)

Longevity

- Samumed

The San Diego Union-Tribune

Samumed raises $438 million for regenerative therapies

August 2018

BUSINESS INSIDER Oct. 24, 2018,

Samumed, a $12 billion startup

Longevity

- Eliminating senescent cells
  - Unity Biotechnology
  - 2018: Paul Robbins & Laura Nidernhofer (Univ of Minnesota)

Longevity

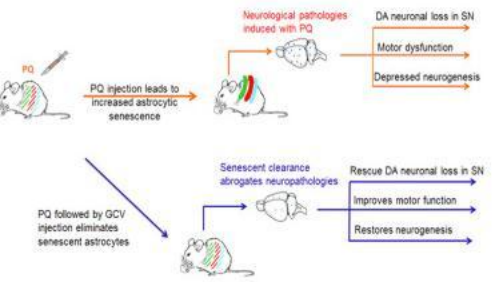
- Eliminating senescent cells
  - 2018: Judith Campisi (Buck Inst)
  - 2018: Darren Baker (Mayo Clinic)

ARTICLE | VOLUME 22, ISSUE 4, P930-940, JANUARY 23, 2018

CellPress

Cellular Senescence Is Induced by the Environmental Neurotoxin Paraquat and Contributes to Neuropathology Linked to Parkinson's Disease

Shankar J. Chinta [5] • Georgia Woods [5] • Marco Demaria [6] • ... David T. Madden • Judith Campisi • Julie K. Andersen [7]



Buck

Campisi

nature
International journal of science
19 September 2018
Nature **562**, 578–582 (2018)

Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline

Tyler J. Bussian, Asef Aziz, Charlton F. Meyer, Barbara L. Swenson, Jan M. van Deursen & Darren J. Baker

MAYO CLINIC

Longevity

- Funds
  - Jim Mellon's and Gregory Bailey's Juvenescence fund
  - James Payer's Apollo Ventures
  - Laura Deming's Longevity Fund
  - Sergey Young's Longevity Vision Fund

JUVENESCENCE

APOLLO VENTURES

Longevity

LONGEVITY VISION FUND

ENDPOINTS NEWS

Peter Diamandis' right hand man Sergey Young wants to reverse aging via his $100M Longevity Vision Fund

February 4, 2019

Longevity

- Funds
  - Coalition for Radical Life Extension
  - Age Reversal Network

Longevity

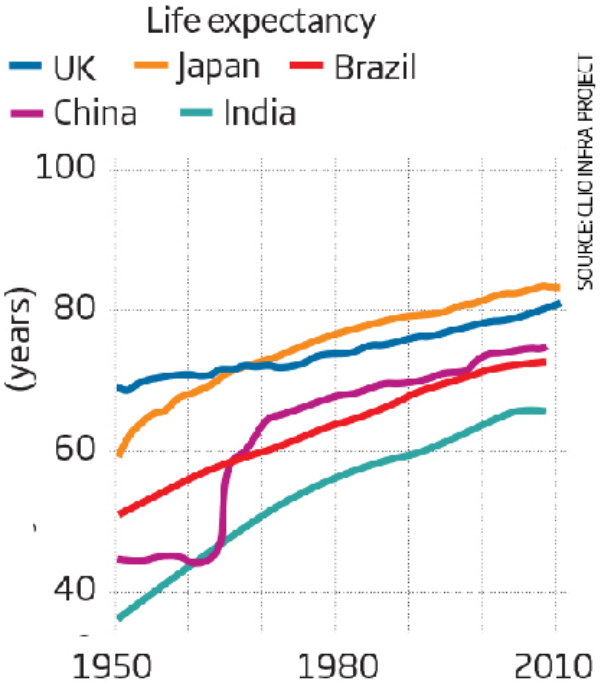
- Today:
  - Anti-aging treatment offered by 100s of clinics...
  - ... but these are all unregulated therapies

Longevity

- 2018:
  - $438 million funding for Samumed (the biggest investment by Finian Tan since Baidu)
  - $712 million IPO for Unity Biotechnology - first clinical trials of "senolytics"
- 2019:
  - $210 million funding for Celularity

Longevity

Record of longevity: Jeanne Calment died at the age of 122 in 1997



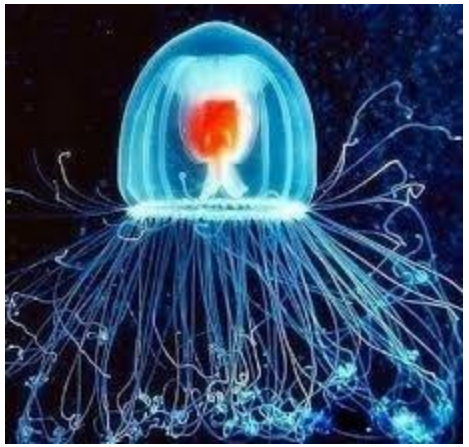
Longevity

- 2016: Linda Partridge (UCL): lithium prolongs the life of fruit flies (inhibits GSK3 and fosters NRF2)
- 2016: Manfred Kayser (Erasmus Medical Centre): MC1R is responsible for looking older

Gene linked to youthful looks has been discovered, scientists claim

Longevity

- The only animal that can reverse its life cycle and rejuvinate: the turritopsis (NOT immortal)
- *"The mystery of life is not concealed in the higher animals. It is concealed in the root. And at the root of the Tree of Life is the jellyfish."* (Shin Kubota, Seto Marine Biological Laboratory, Kyoto, Japan)



Longevitv

Lifespan predictors (DNA-based):

- Yan Zhang's "mortality risk score" (2017)
- Jim Wilson's mortality score
- Steve Horvath's DNAm GrimAge

dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

Published online 2018 Mar 6.

Methylomic survival predictors, frailty, and mortality

Yan Zhang,[1,2] Kai-Uwe Saum,[1] Ben Schöttker,[1,3] Bernd Holleczek,[4] and Hermann Brenner[1,2,5]

Author information ▸ Article notes ▸ Copyright and License information Disclaimer

[1]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg D-69120, Germany

THE UNIVERSITY of EDINBURGH

Jim Wilson

RESEARCH COMMUNICATION Jan 15, 2019

Genomics of 1 million parent lifespans implicates novel pathways and common diseases and distinguishes survival chances

DNA methylation GrimAge strongly predicts lifespan and healthspan

Ake T. Lu[1], Austin Quach[1], James G. Wilson[2], Alex P. Reiner[3], Abraham Aviv[4], Kenneth Raj[5], Lifang Hou[6], Andrea A. Baccarelli[7], Yun Li[8], James D. Stewart[9], Eric A. Whitsel[9, 10], Themistocles L. Assimes[11, 12], Luigi Ferrucci[13], Steve Horvath[1, 14]

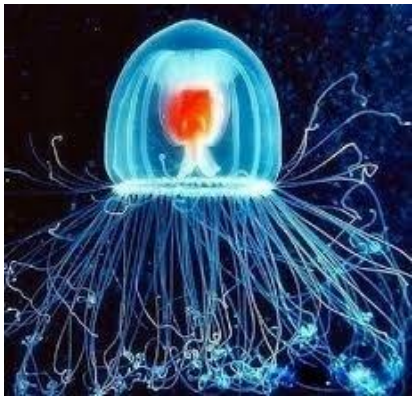
[1] Department of Human Genetics, David Geffen School of Medicine, University of California Los Angeles

Longevity


THE
NEW YORKER
A REPORTER AT LARGE APRIL 3, 2017 ISSUE
SILICON VALLEY'S QUEST TO LIVE FOREVER
Can billions of dollars' worth of high-tech research succeed in making death optional?

The Science of Longevity

Rapid progress in A.I. + rapid progress in Biotech = A whole new discipline and industry, the discipline of Longevity



Why is hydra immortal?
Why the turritopsis can reverse its life cycle and rejuvinate?
Why did Jeanne Calment live to 122

Genomic Databases

- Another attack on privacy
  - Genomic companies collect the genomes of all their customers
  - Apps of the future: who has the "best“ genes for X (eg for longevity)?
  - Gold rush for "rare genes”
  - But we need your genome to make genomics useful (correlation between genes and health)

Genomic Databases

- Rare genes
  - Rare genetic mutations can help improve your genome

The Quest for Rare Genes

Amgen
The biotech in 2012 got genetic data on 160,000 Icelanders via its **$415 million** buyout of DeCode Genetics

Calico
The Google-backed company, searching for longevity genes, has partnered with Ancestry.com, which has collected millions of public family trees and more than **1 million genetic samples**

Regeneron
Working with Geisinger Health System to sequence genes of **100,000 volunteers**

23andMe
The genetic-testing pioneer has genotyped 1 million customers; it has deals with more than **10 drugmakers**, including Pfizer and Genentech

Genomic Databases

- Crowdsourcing + Biotech
  - Personal Genome Project (Harvard Univ, 2005)
  - UK Biobank (2006)
  - 1000Genomes Project (Broad Inst, 2008)
  - 100,000 Genomes Project (Genomics England, 2012)

Personal Genome Project
at Harvard University

George Church

biobank uk

1000 Genomes
A Deep Catalog of Human Genetic Variation

Genomics england
The 100,000 Genomes Project

Genomic Databases

- Crowdsourcing + Biotech
  - Baseline (Google, 2014)
  - DNA.land (Columbia Univ, 2015)

verily Google

THE WALL STREET JOURNAL

Google's New Moonshot Project: the Human Body

Genomic Databases

- P2P+ Crowdsourcing + Biotech
  - The "Internet of DNA" or "Internet of Living Beings"
  - Global Alliance for Genomics and Health (UC Santa Cruz + Broad Inst, 2013): a peer-to-peer network of scientists and volunteers

MIT Technology Review

Internet of DNA

A global network of millions of genomes could be medicine's next great advance.

Global Alliance for Genomics & Health

David Haussler / David Altshuler

Genomic Databases

- And finally Big Pharma
  - 2016: AstraZeneca's project to sequence 2 million genomes (with Human Longevity, Britain's Wellcome Trust Sanger Institute, and Finland's Institute for Molecular Medicine)


nature

22 April 2016

AstraZeneca launches project to sequence 2 million genomes

Drug company aims to pool genomic and medical data in hunt for rare genetic sequences associated with disease.

Genomics Databases

deCODE's NextCODe (Iceland, aka Wuxi NextCODE)

PatientsLikeMe's DigitalMe (Boston, acquired by iCarbonX)

NuMedii's annotated Stanford database (Silicon Valley)

NuMedii

Genomic Databases

2009: Andrey Rzhetsky (University of Chicago)

Comparing two datasets of molecular interactions related to the muscle disease ataxia, the scientists discover genes associated with brain malformations

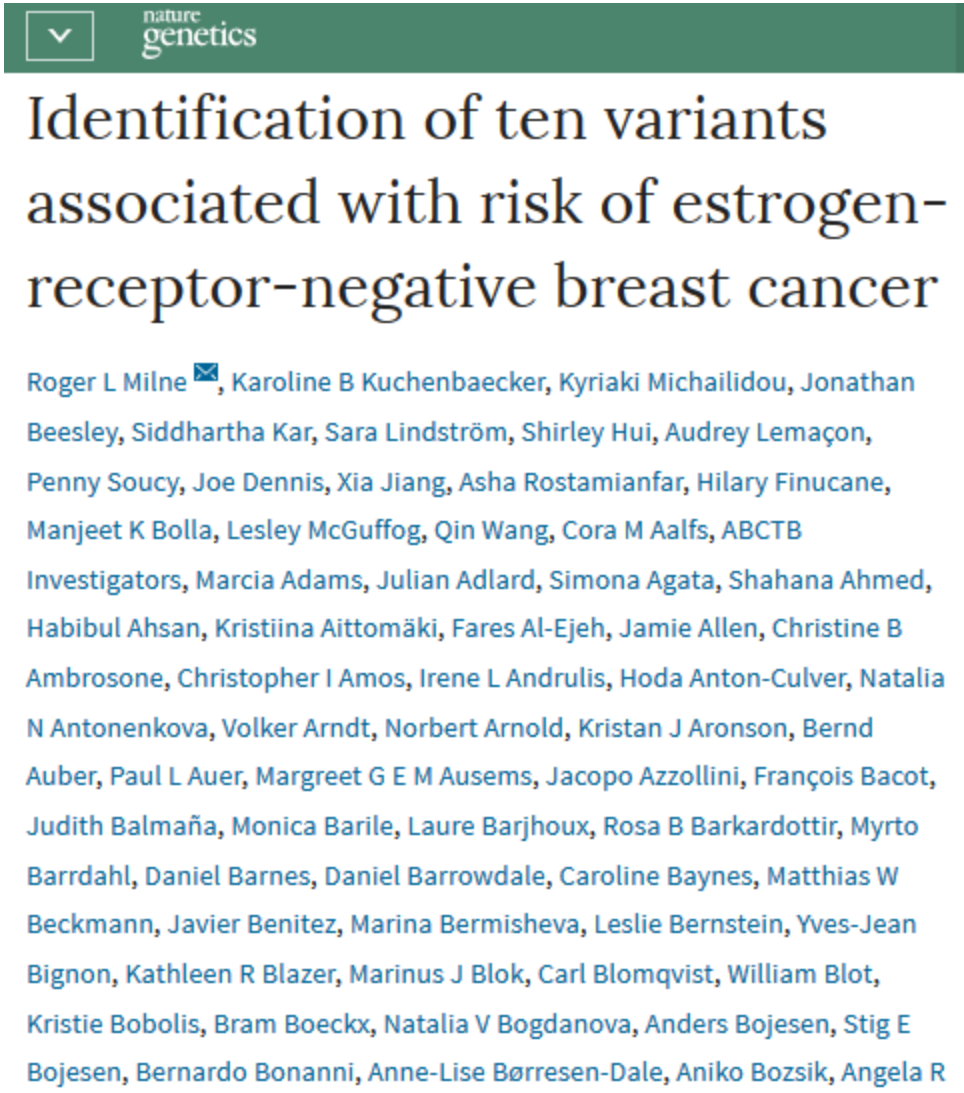
Data from more than 300,000 papers and 8 million abstracts

Genomic Databases

- Steven McCarroll's team at the Broad Institute in Boston publishes the genes involved in schizophrenia (2016)
- Serena Nik-Zainal's team at the Sanger Institute in England publishes the genes involved in breast cancer (2016)

Genomic Databases

- In 2017 the world's largest study on the genetics of breast cancer, done by more than 300 research groups worldwide by analyzing the genomes of over 275,000 women, discovered 72 new gene variants that are likely to cause the disease



Protein Databases

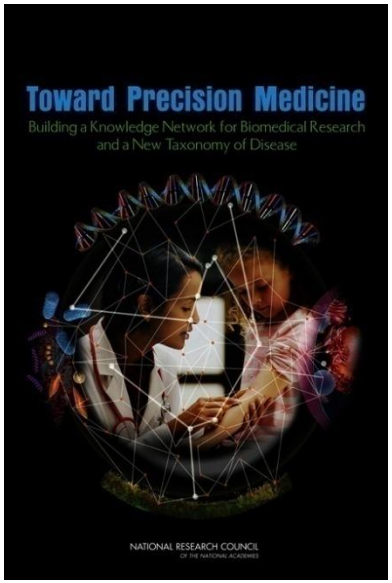
- Protein Data Bank (1971, USA)
- UniProt (2002, EU + USA)
- Kamil Tamiola's Peptone (2016, Holland)
  - Database of structural propensities of proteins for deep learning

Full-body digital simulations

- Insilico Medicine (2014, Baltimore)
- iCarbonX (2015, Shenzhen)
- Virtual Physiological Human Inst (EU)
- Insigneo (Britain)

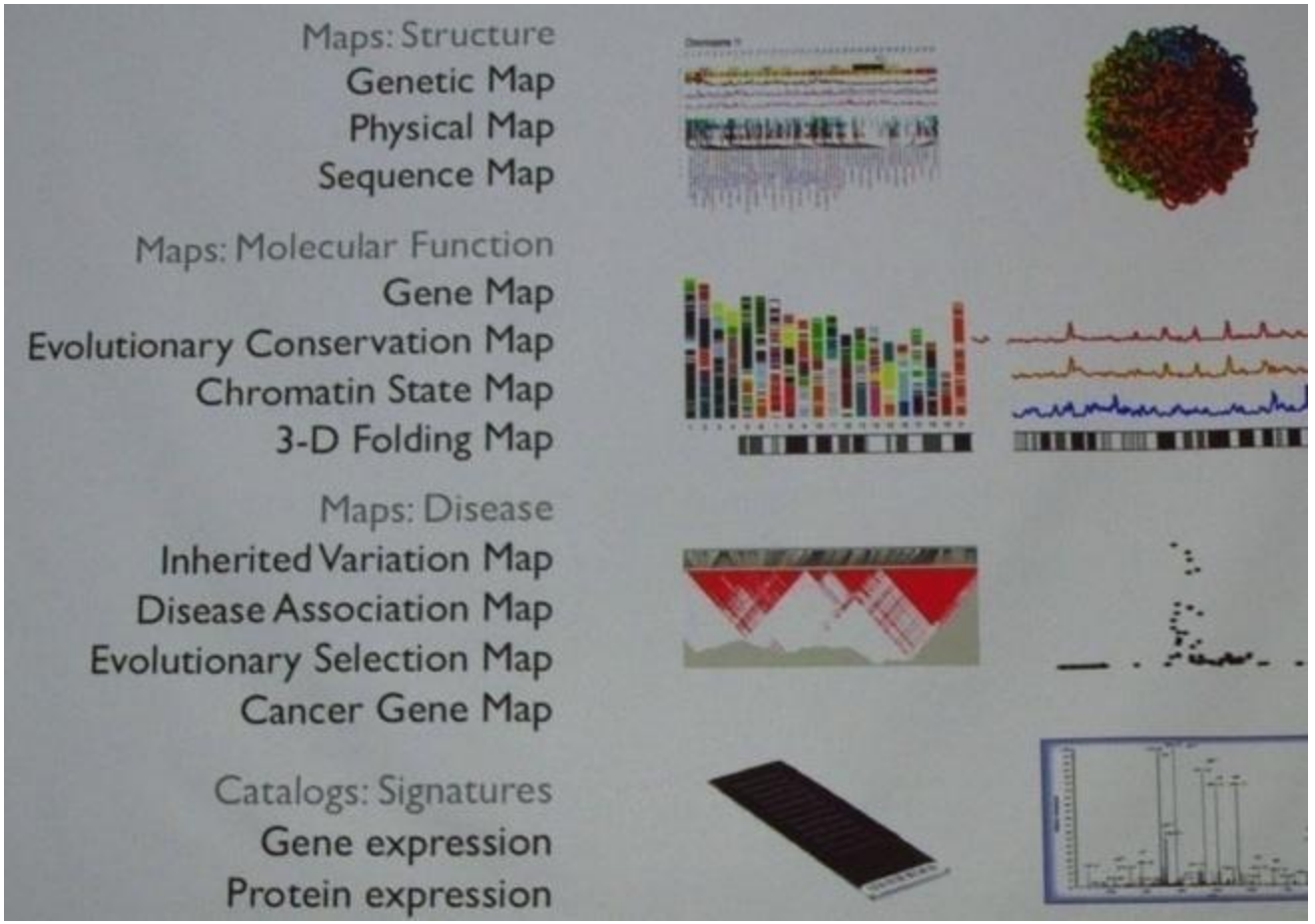
Precision Medicine

- Pharmacogenomics: the right drug for the right patient at the right time and at the right dose
- National Research Council's report "Toward Precision Medicine - Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease" (2011)
- Precision Medicine Initiative (2015)
  - Collect the genomes of one million people



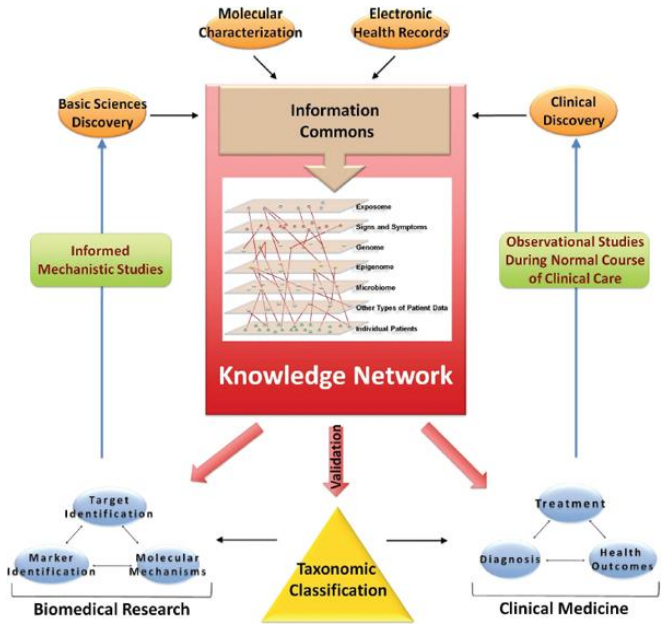
Precision Medicine

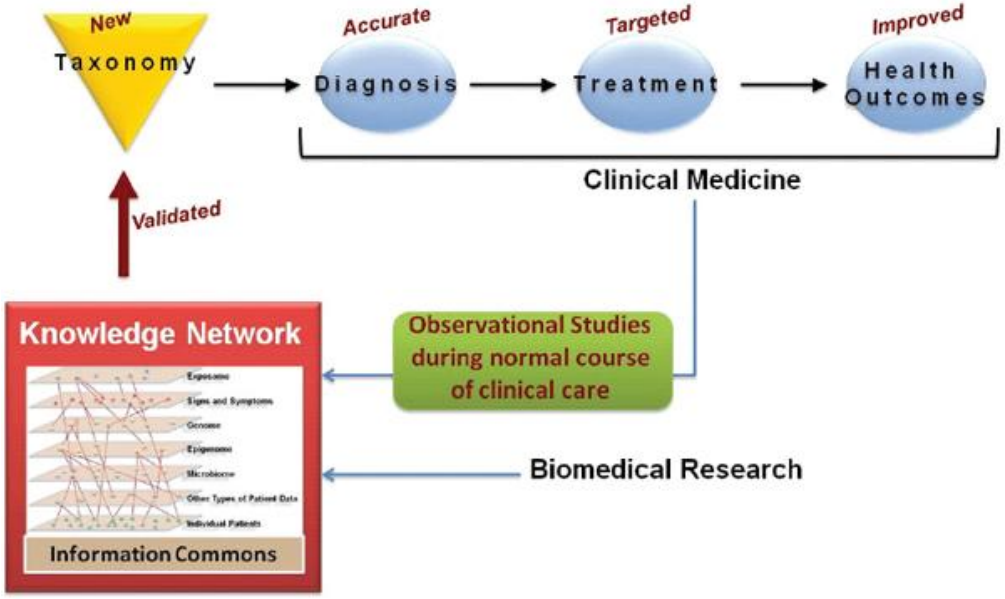
- Big Data drives Biomedicine: maps and catalogs



Precision Medicine

- Big Data drives Precision Medicine
  - Creating an "Information Commons" that will make data on large populations of patients available to all scientists
  - Creating a "Knowledge Network" that will highlight inter-relationships



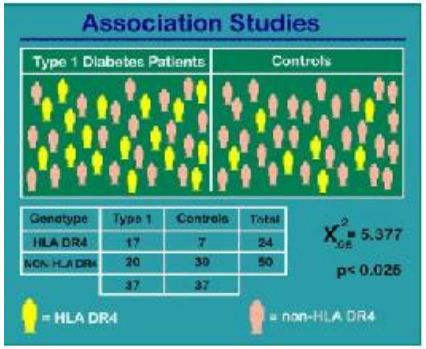


(images taken from "Toward Precision Medicine")

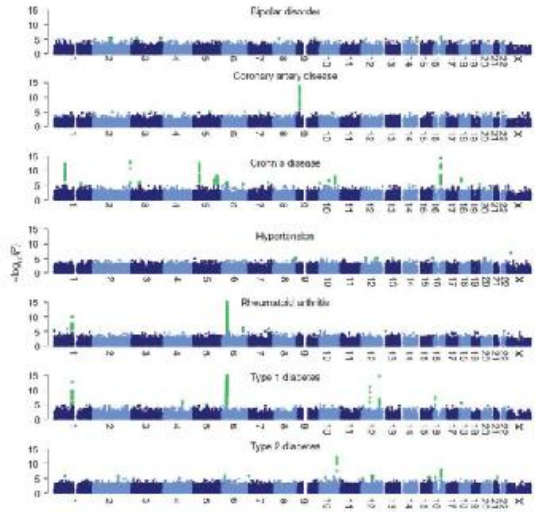
Precision Medicine

- Big Data drives Precision Medicine
- GWAS (Genome-wide Association Study, 2008): relating genetic variants in different individuals to traits

The dawn of genomic big data
Candidate gene studies using GWAS



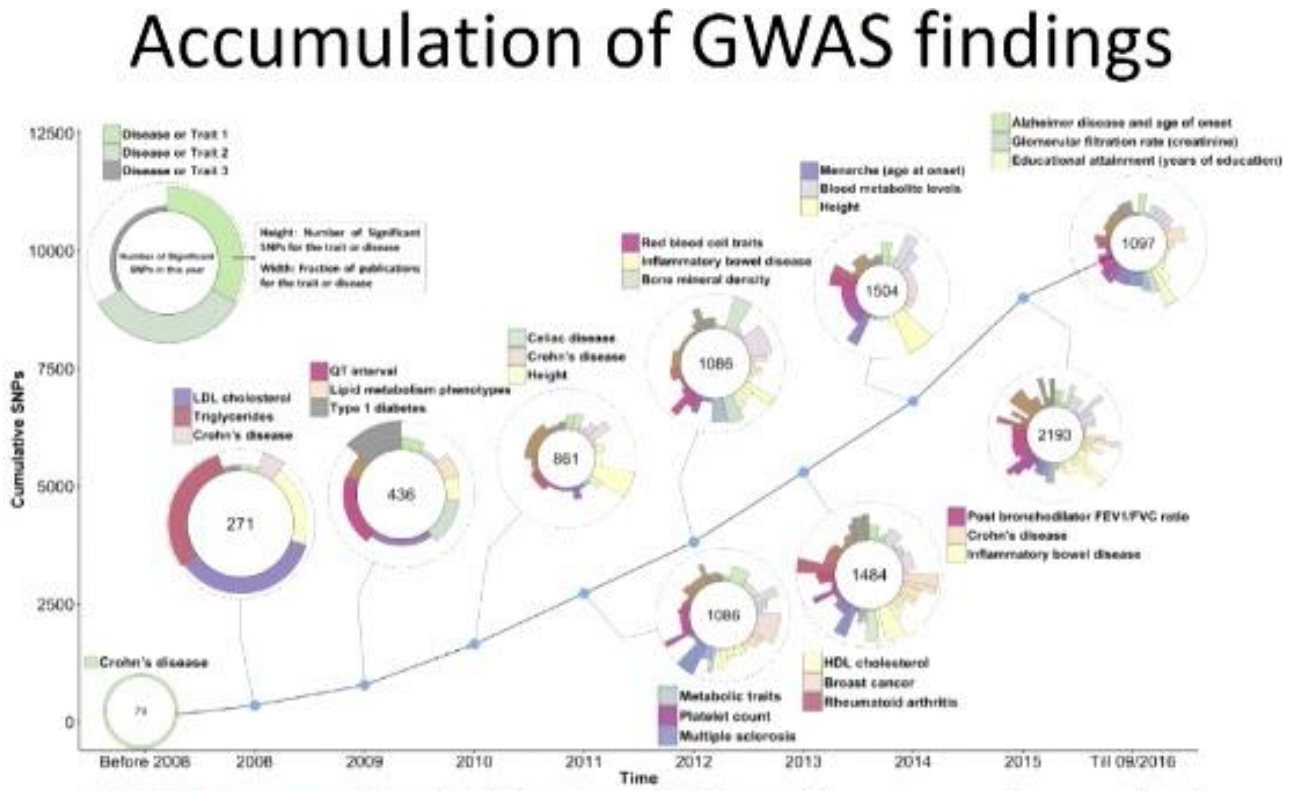
Odds Ratio: 3.6
95% CI = 1.3 to 10.4



The Wellcome Trust Case Control Consortium

Precision Medicine

- Discovery of gene-disease associations



Precision Medicine

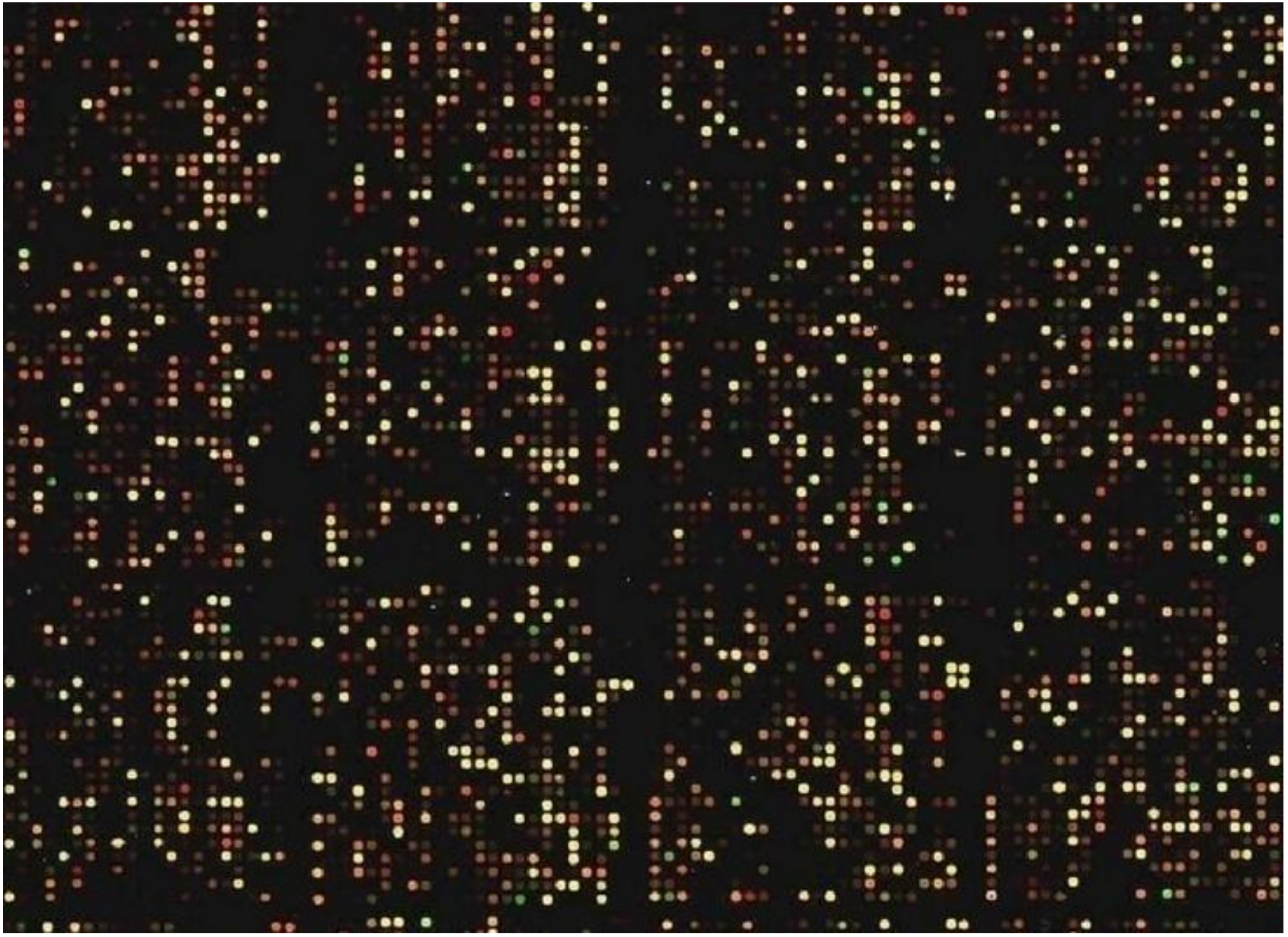
- Future trends

Future Trends

- Large population cohorts with comprehensive assessments of multiple clinical outcomes, intermediate phenotypes, biomarkers, lifestyle and environmental factors (e.g. UK Biobank)
- Large-scale whole-genome sequencing (e.g. UK 100,000K Project), enabling comprehensive assessment of rare variants
- Linking up genetic data with clinical databases and other data domains
- Greater integration of genetic data with functional annotation (e.g. eQTL, Roadmap Epigenome, ENCODE)
- Greater use of functional assays for evaluating the conse genetic mutations

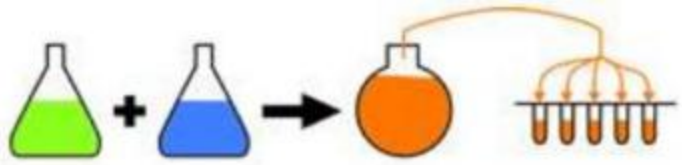
Pak Sham, Univ. of Hong Kong

Bio lab Automation

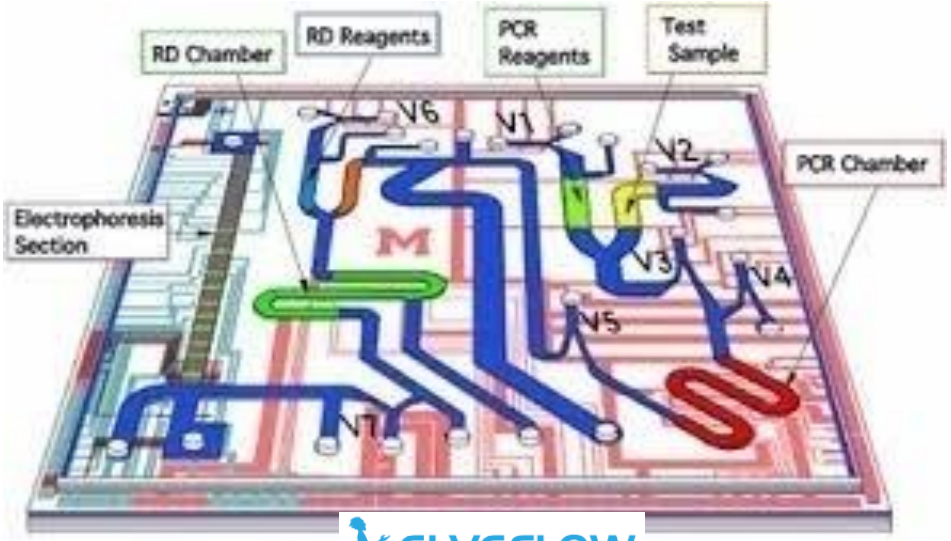


Bio lab Automation

- Many of the procedures involved in drug discovery are routine and repetitive
- Intensive information-processing techniques
- Lab-on-a-chips enable biotech startups to conduct analysis of thousands of DNA and protein samples per day



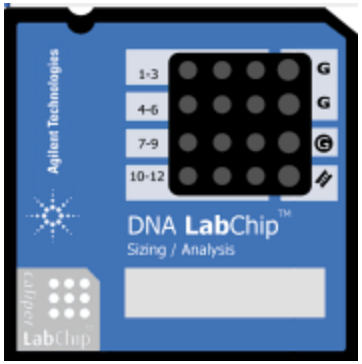
Traditional lab



Bio lab Automation

- 1964: Harvey Nathanson at Westinghouse makes the first MEMS (micro-electro-mechanical system)
- 1979: Stephen Terry at Stanford builds the first “lab-on-a-chip"
- 1983: Richard Feynman’s lecture "Infinitesimal Machinery“
- 1994: Affymetrix introduces the first "DNA chip" (or microarray)
- 1997: DARPA’s Microflumes program to fund research in microfluidics
- Microfluidics: the ability to make millions of microchannels
- 1999: Agilent introduces the first commercial "lab-on-a-chip" product

The first microarray



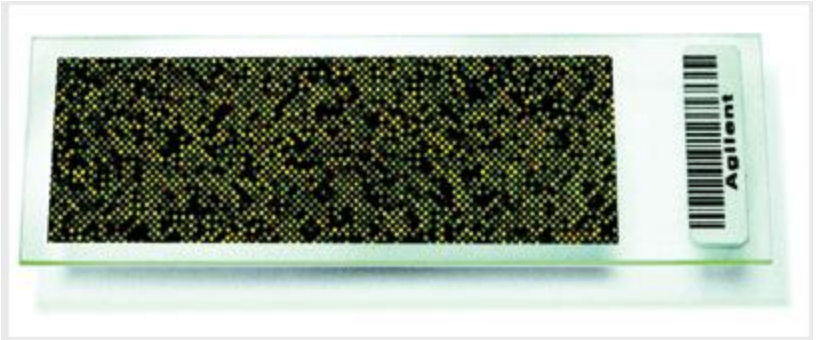
The first lab-on-a-chip

Bio lab Automation

- 2002: Wilhelm Ansorge at EMBL develops the amicroarray with the whole human genome
- 2004: First commercial microarrays of the whole human genome (Affymetrix, Agilent, Applied Biosystems, Illumina, NimbleGen)

affymetrix
Human Genome U133

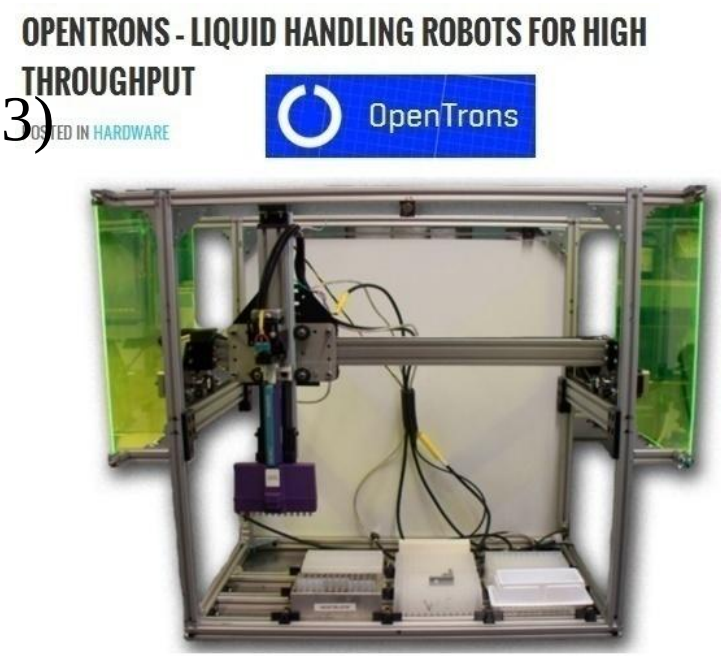
Human Genome Survey Microarray
designed using public and Celera data for all known genes (31,097).



The Agilent Whole Human Genome Microarray represents over 41,000 human genes and transcripts. (Courtesy of Agilent Technology.)

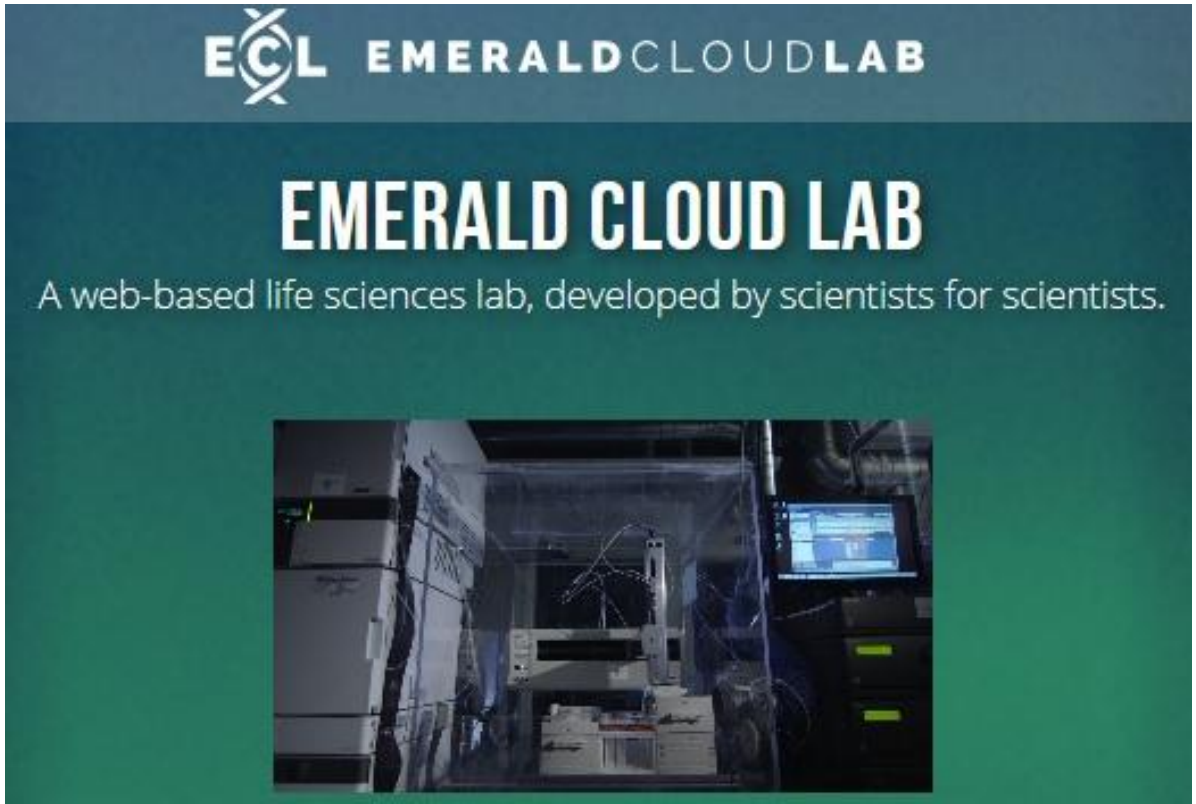
Bio lab Automation

- Cloud-based biotech
  - Transcriptic (Palo Alto, 2012)
  - Emerald (San Francisco, 2010)
- Personal biotech robotics
  - OpenTrons (New York, 2013)



Bio lab Automation

- Emerald Therapeutics (2010, San Francisco): a laboratory on the cloud where robots conduct the experiments. The scientists use a symbolic language to "program" the experiments.



Bio lab Automation

- CAD/AM for biotech
  - Nathan Hillson at JBEI
  - TeselaGen (San Francisco, 2011)

Lab Automation

- Digitazing the laboratory
  - Synthace (2011, Britain): Antha, an operating system and programming language for laboratory scientists, with the aim to digitize the entire process of drug discovery and manufacturing.

Bio lab Automation

- The robotic lab
  - Zymergen (Bay Area, 2013)
  - Ginkgo (Boston, 2008)
  - Twist Bioscience (San Francisco, 2013)

Bio lab Automation

c&en

Volume 94 Issue 45 | pp. 18-22
Issue Date: November 14, 2016

Ginkgo Bioworks and Zymergen scale up synthetic biology with robots

Forbes

SEP 14, 2017 @ 12:02 AM

Bayer And Ginkgo Aim To Make Crops Produce Their Own Nitrogen Fertilizer

TC

Ginkgo Bioworks Takes On Zymergen With $45 Million In Series B Funding

Posted Jul 23, 2015 by Sarah Buhr (@sarahbuhr)

TC

Ginkgo Bioworks grabs $100 million in financing to buy a whole lot of synthetic DNA

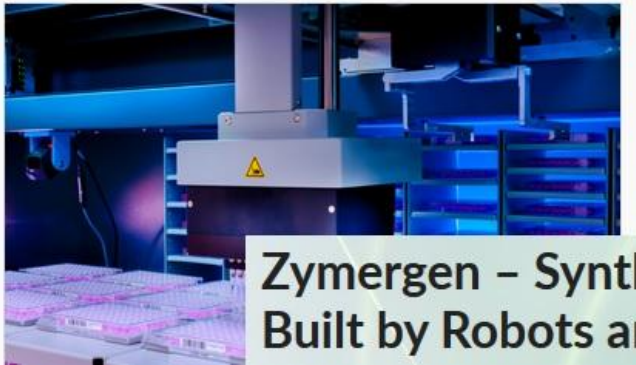
Posted Jun 8, 2016

GINKGO BIOWORKS™
THE ORGANISM COMPANY

TC

With $44 Million In Funding, Biotech Startup Zymergen Is Buying Up Robots To Mass Produce Materials From Microbes

Posted Jun 16, 2015 by Sarah Buhr (@sarahbuhr)



TC

Biotech startup Zymergen nabs $130 million from Softbank

Posted Oct 10, 2016 by Sarah Buhr (@sarahbuhr)

Zymergen – Synthetic Organisms Built by Robots and AI

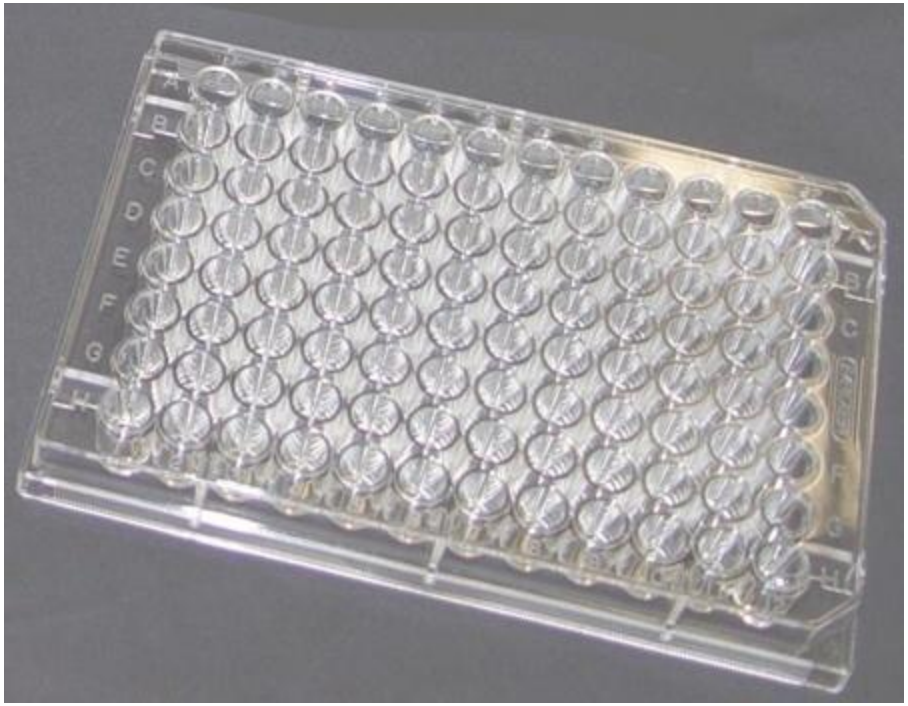
Bio lab Automation

- Twist Bioscience (San Francisco, 2013)
  - Replacing the 96-wells plate with silicon wafers

Emily Leproust of Twist (2016)

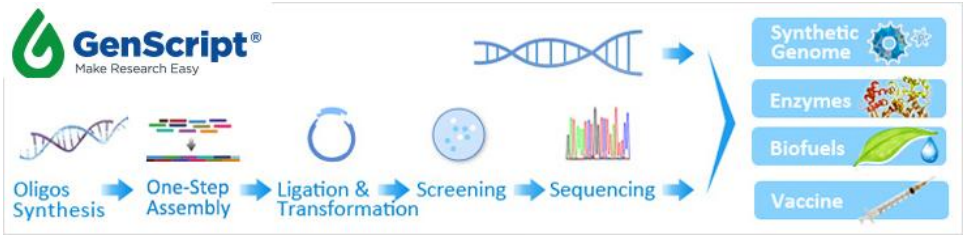
DNA Synthesis

- Manufacturing of synthetic DNA (oligos)
  - The traditional way: the 96-wells plate



DNA Synthesis

- Manufacturing of synthetic DNA (oligos)
  - Gen9 (Boston, 2009)
  - Twist Bioscience (San Francisco, 2013)
  - GenScript (Nanjing)



DNA Synthesis

- Twist Bioscience (San Francisco, 2013)
  - Replacing the 96-wells plate with silicon wafers

Emily Leproust of Twist (2016)

Genome Editing

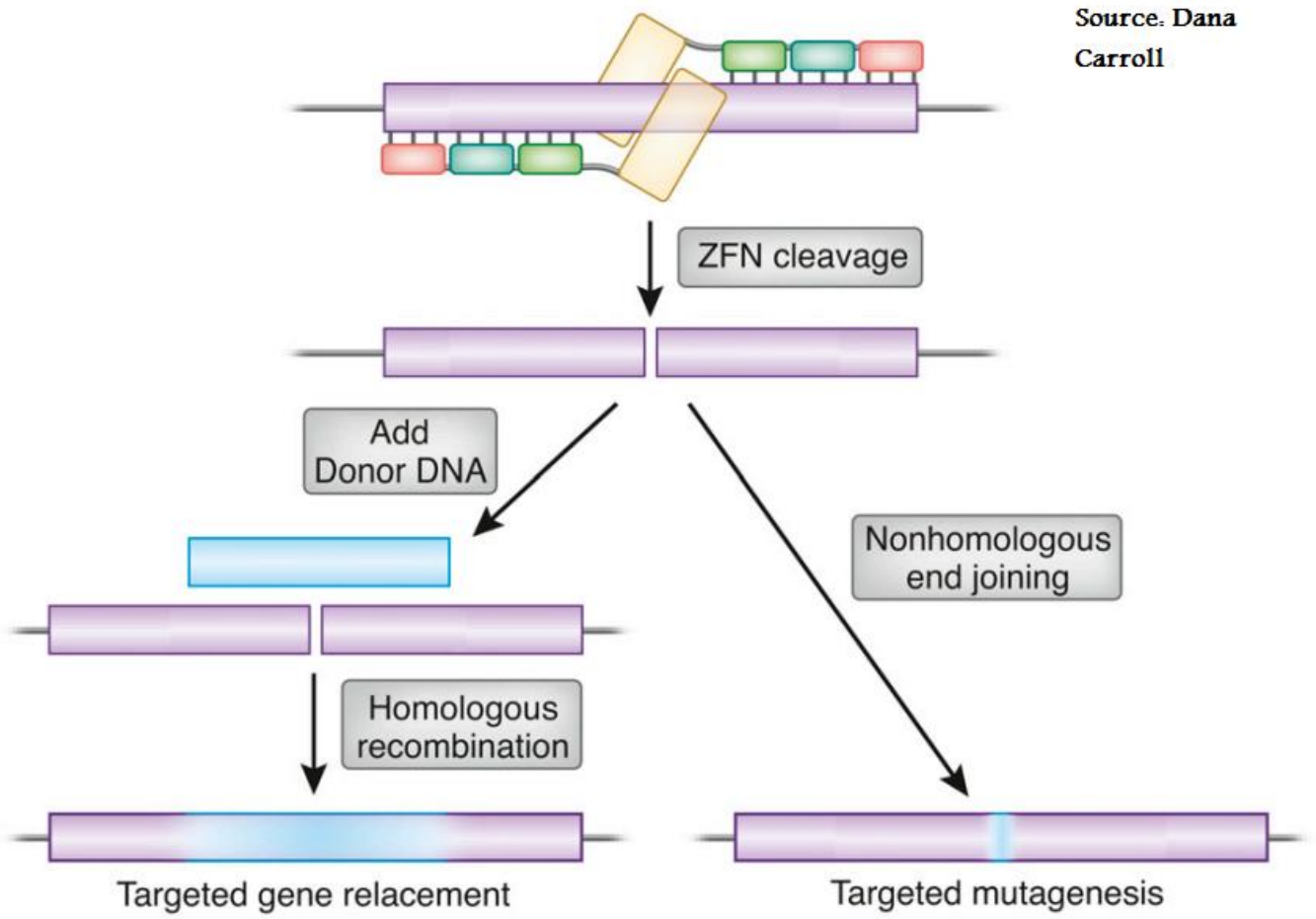
- The missing piece:
  - Lots of progress in reading genetic data (genome sequencing)
  - Lots of progress in writing genetic data (synthesis)
  - But still difficult to edit genetic data
    - The ZFN method, exclusively owned by Sangamo Biosciences

Zinc Finger Nucleases (ZFNs)

Sangamo™ THERAPEUTICS

Genome Editing

- ZFN



Genome Editing

- Why?
- Rare diseases
- Eugenetics

- There are an estimated 6,000~8,000 rare diseases. The rare diseases are estimated to collectively affect more than 200 million people worldwide;
- Three-quarters affect children, over half are life limiting;
- Over 80% of rare diseases are genetic in origin. Most are caused by defects in a single gene;
- Both the central nervous system (CNS), and peripheral organs and tissues are affected in most rare diseases;
- There are treatments for only 6% of rare diseases, of which fewer than 1% are curative;
- It was too expensive, at an average of $1 million per treatment.

Orkin & Reilly. *Science* 2016, 352: 1059-1061.
Melnikova. *Nat Rev Drug Dis.* 2012, 11: 267-268
Boycott & Ardgo. *Nat Rev Drug Dis.* 2018, 17: 151-153.

Genome Editing

- TALEN method (2011) - Dan Voytas (Univ of Minnesota) & Adam Bogdanove (Iowa State Univ)
- CRISPR method (2012) - Jennifer Doudna (UC Berkeley) & Emmanuelle Charpentier (Umeå Univ, Sweden), Feng Zhang (Broad Inst)
- Stanley Qi's dCas9 (2013)



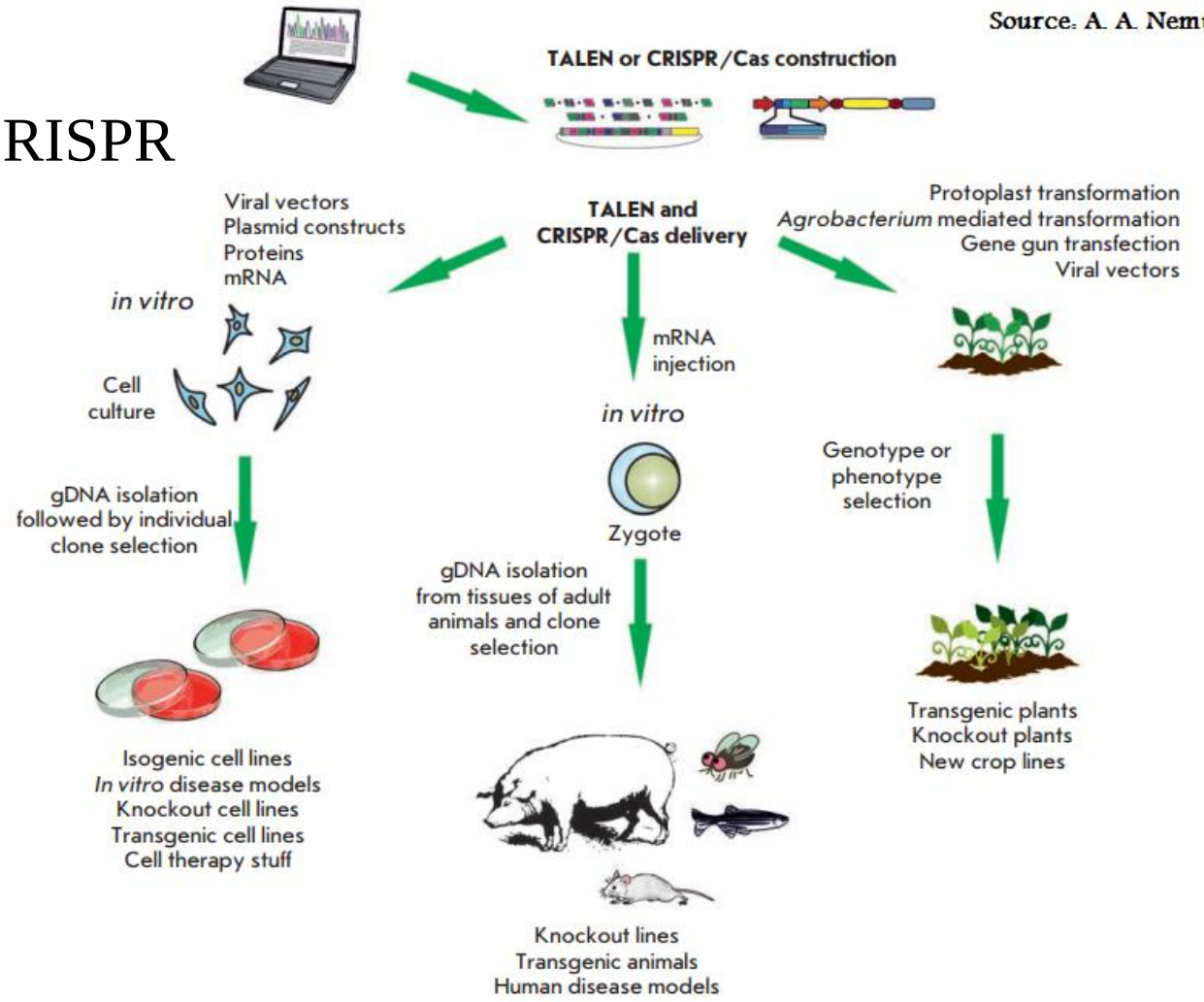



BROAD INSTITUTE

UCSF
University of California
San Francisco

Genome Editing

- TALEN and CRISPR



A general scheme of the strategy for using the TALEN and CRISPR/Cas systems in genomic engineering

Genome Editing

Timeline of CRISPR

1993: Francisco Mojica (Spain) describes CRISPR

2005: Mojica discovers that CRISPR is an adaptive immune system

2005: Alexander Bolotin (France) discovers Cas9

2006: Eugene Koonin (NIH) shows the DNA-repair value of Cas proteins

2007: Philippe Horvath at Danisco (France) prove CRISPR systems are adaptive immune systems

2008: Paper by John van der Oost (Netherlands)

Dec 2008: Luciano Marraffini and Erik Sontheimer (Chicago) show that CRISPR can serve as a general-purpose genome-editing

2010: Paper by Sylvain Moineau (Canada): Cas9 cleaves target DNA

2011: Paper by Virginijus Siksnys (Lithuania)

2012: Jennifer Doudna (UC Berkeley) and Emmanuelle Charpentier (Sweden) describe a CRISPR-Cas9 system to cut DNA in test tube

2012: Feng Zhang and Luciano Marraffini (Broad Inst) invent the first CRISPR system to edit human cells

Apr 2013: Chad Cowan and Kiran Musunuru (Harvard) prove that CRISPR is superior to existing genome-editing tools

Key papers of CRISPR

2008: Marraffini and Sontheimer

2012: Doudna and Charpentier

2013: Feng Zhang

2013: Chad Cowan and Kiran Musunuru

Science. 2008 December 19; 322(5909): 1843–1845. doi:10.1126/science.1165771.

CRISPR Interference Limits Horizontal Gene Transfer in Staphylococci by Targeting DNA

Luciano A. Marraffini and Erik J. Sontheimer*

Science

A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity

Martin Jinek[1,2,*], Krzysztof Chylinski[3,4,*], Ines Fonfara[4], Michael Hauer[2,†], Jennifer Doudna[1,2,5,6,‡], Emmanuelle Charpentier[4,‡]

[1]*Howard Hughes Medical Institute (HHMI), University of California, USA.*

[3]*Max F. Perutz Laboratories (MFPL), University of Vienna USA.*

[4]*The Laboratory for Molecular Infection Medicine Sweden, Umeå Centre for Microbial Research, Department of Molecular Biology, Umeå University, S-90187 Umeå, Sweden.*

Science

Multiplex Genome Engineering Using CRISPR/Cas Systems

BROAD INSTITUTE

Le Cong[1,2,*], F. Ann Ran[1,4,*], David Cox[1,3], Shuailiang Lin[1,5], Robert Barretto[6], Naomi Habib[1], Patrick D. Hsu[1,4], Xuebing Wu[7], Wenyan Jiang[8], Luciano A. Marraffini[8], Feng Zhang[1,†]

[1]*Broad Institute of MIT and Harvard, 7 Cambridge Center, Cambridge, MA 02142, USA, and McGovern Institute for Brain Research, Department of Brain and Cognitive Sciences, Department of Biological Engineering, Massachusetts Institute of Technology (MIT), Cambridge, MA 02139, USA.*

Cell Stem Cell Letter

HARVARD UNIVERSITY

Enhanced Efficiency of Human Pluripotent Stem Cell Genome Editing through Replacing TALENs with CRISPRs

Qiurong Ding,[1] Stephanie N. Regan,[1] Yulei Xia,[1] Leonie A. Oostrom,[1] Chad A. Cowan,[1,2,3] and Kiran Musunuru[1,2,4,*]
[1]Department of Stem Cell and Regenerative Biology, Harvard University, and Harvard Stem Cell Institute, Cambridge, MA 02138, USA
[2]Broad Institute, Cambridge, MA 02142, USA
[3]Center for Regenerative Medicine, Massachusetts General Hospital, Boston, MA 02114, USA
[4]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA 02115, USA
*Correspondence: kiranmusunuru@gmail.com
http://dx.doi.org/10.1016/j.stem.2013.03.006

Diaspora of CRISPR

The first CRISPR startups to go public:

- Charpentier, Novak, Foy, and Cowan: CRISPR Therapeutics
- Zhang, Church, and Doudna: Editas Medicine
- Sontheimer, Marraffini, Rossi, and Barrangou: Intellia Therapeutics

Trivia: Heroes of CRISPR

1993: Francisco Mojica (Spain)

2005: Alexander Bolotin (France)

2006: Eugene Koonin (NIH)

2007: Rodolphe Barrangou and Philippe Horvath (France)

2008: John van der Oost (Netherlands)

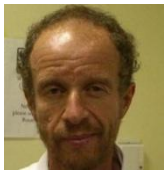
2008: Luciano Marraffini and Erik Sontheimer (Chicago)

2010: Sylvain Moineau (Canada)

2011: Virginijus Siksnys (Lithuania)

2012: Jennifer Doudna (UC Berkeley) and Emmanuelle Charpentier (Sweden)

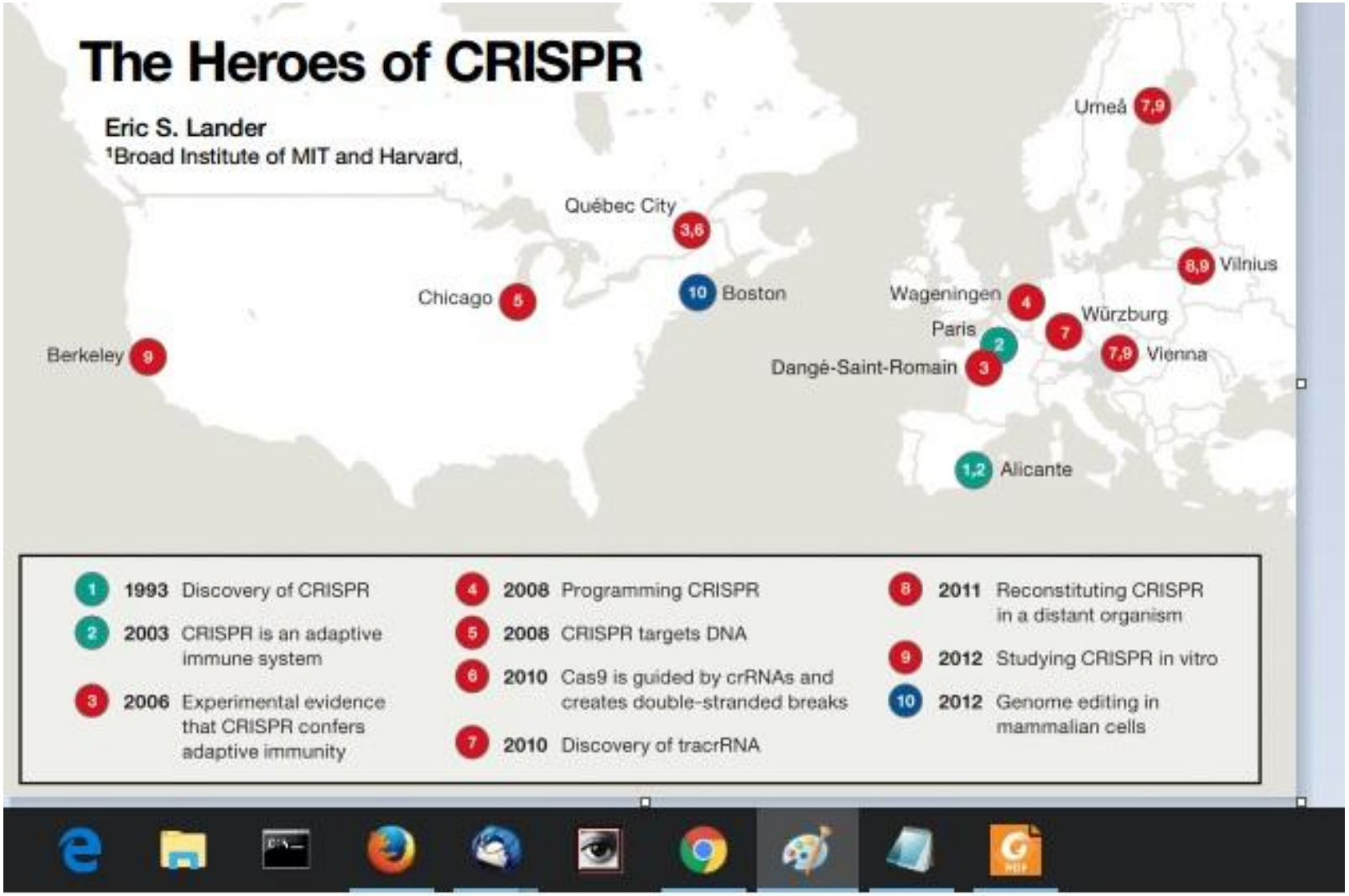
2012: Feng Zhang (Boston) invenst the first CRISPR system to edit human cells



Trivia: Heroes of CRISPR

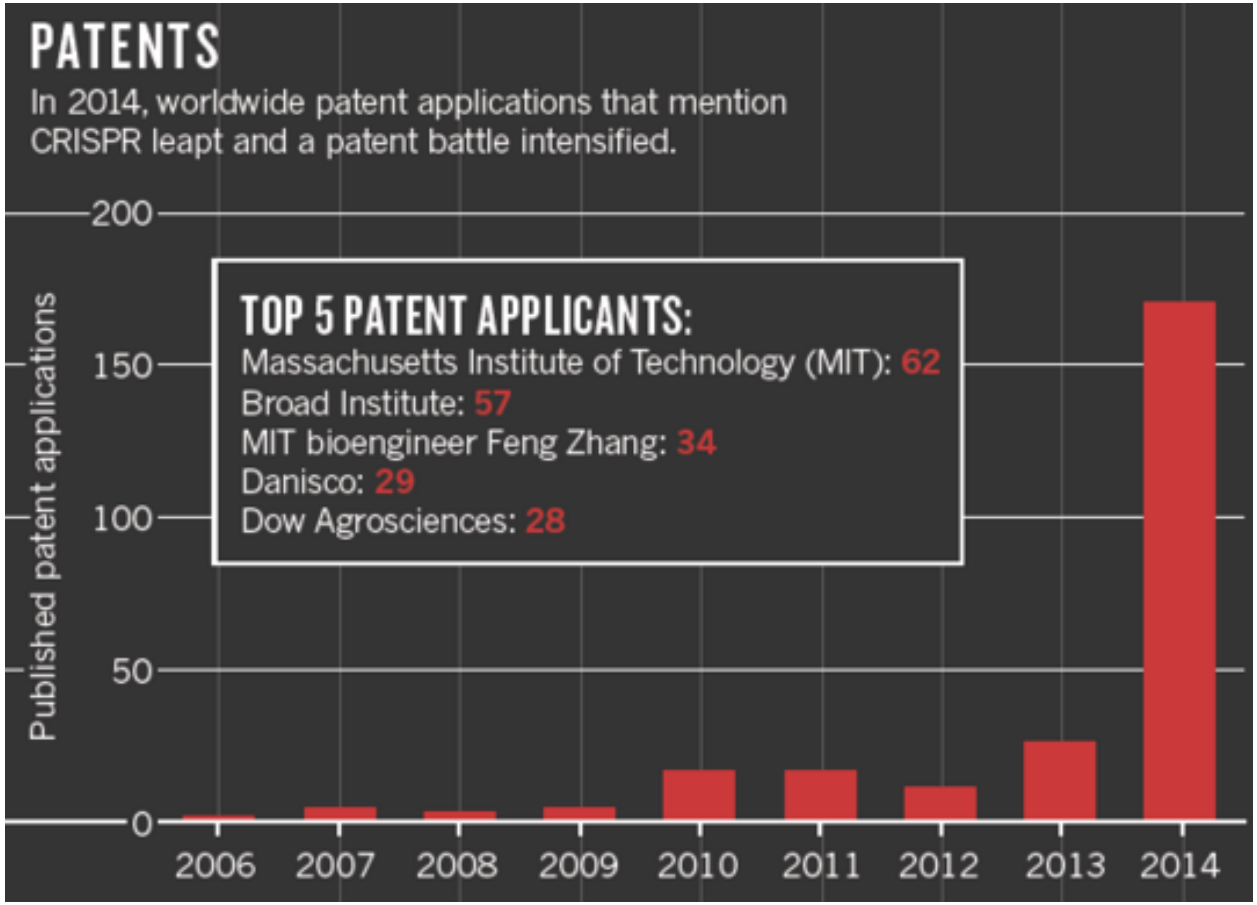
- Mojica, Horvath, Marraffini, Charpentier, Zhang...
- born outside the USA
- didn't work for major universities (Zhang was an independent researcher at MIT, not formally an MIT researcher)
- several of their papers were rejected by journals
- most of them were under 30 years old

Genome Editing



Genome Editing

- The CRISPR rush



Genome Editing

- CRISPR startups
  - Caribou Biosciences (Emeryville, 2011)
  - CRISPR Therapeutics (Switzerland, 2013)
  - Editas Medicine (Boston, 2013)
  - Intellia Therapeutics (Boston, 2014)
  - Color (Burlingame, 2013)
  - Synthego (Redwood City, 2012)

A BRIEF HISTORY OF CRISPR

Key events in the CRISPR story.

December 1987
Researchers find CRISPR sequences in *Escherichia coli*, but do not characterize their function[8].

July 1995
CRISPR sequences are found to be common in other microbes[9].

March 2007
Scientists at food company Danisco determine that the repeats are part of a bacterial defence against viruses[10].

A cluster of biotech companies has sprung up to use CRISPR technology.

October 2011
CARIBOU BIOSCIENCES
Berkeley, California
Focus: Research, industry, therapeutics, agriculture
Raised: $11 MILLION

November 2013
EDITAS MEDICINE
Cambridge, Massachusetts
Focus: Therapeutics
Raised: $43 MILLION

November 2013
CRISPR THERAPEUTICS
Basel, Switzerland
Focus: Therapeutics
Raised: $89 MILLION

November 2014
INTELLIA THERAPEUTICS
Cambridge, MA
Focus: Therapeutics
Raised: $15 MILLION

June 2012
Researchers target CRISPR system to specific DNA sequences, highlighting its potential for genome editing[1].

January 2013
CRISPR is used in mouse and human cells, fuelling rapid uptake of the technique by researchers[11–13].

March 2013
The University of California and others file for a patent on the findings[1].

April 2014
MIT and the Broad Institute are granted a patent on CRISPR gene editing, sparking a fierce patent battle.

March 2015
Report of the first CRISPR gene drive, which can spread an edited gene rapidly through a population[6].

http://www.nature.com

Genome Editing

- Stanley Qi's dCas9 (2013)

Cell. 2013 Feb 28; 152(5): 1173–1183

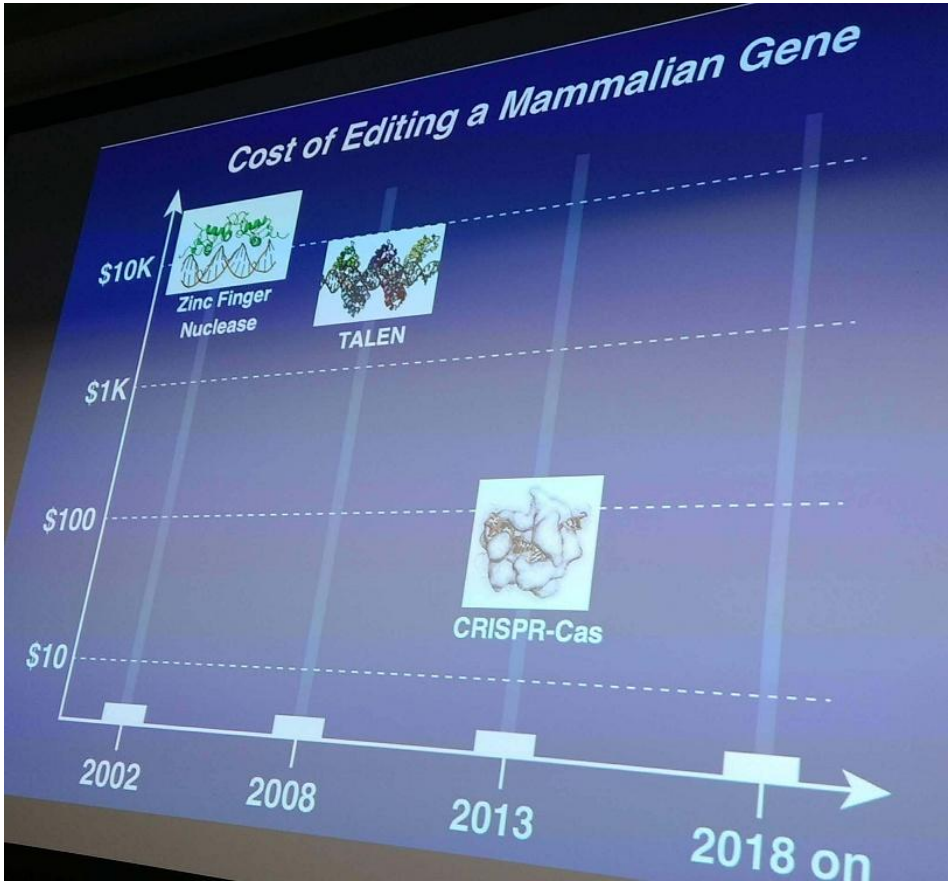
Repurposing CRISPR as an RNA-Guided Platform for Sequence-Specific Control of Gene Expression

Lei S. Qi,[1,2,8,*] Matthew H. Larson,[2,3,8] Luke A. Gilbert,[2,3,8] Jennifer A. Doudna,[4,5,6,8,9] Jonathan S. Weissman,[2,3,8] Adam P. Arkin,[7,8,9] and Wendell A. Lim[1,2,3,8]

[1]UCSF Center for Systems and Synthetic Biology, University of California, San Francisco, San Francisco, CA 94158, USA
[2]Department of Cellular and Molecular Pharmacology, University of California, San Francisco, San Francisco, CA 94158, USA
[3]Howard Hughes Medical Institute, University of California, San Francisco, San Francisco, CA 94158, USA
[4]Department of Molecular and Cellular Biology, University of California, Berkeley, Berkeley, CA 94720, USA

Genome Editing

- Cost of editing a mammalian gene



Source: Stanley Li

Genome Editing

- CRISPR Challenges
  - Standard Cas9 (SpCas9): derived from Streptococcus pyogenes
    - Alternatives: Cas9 orthologs from a different bacterium.
    - Millipore Sigma: FnCas9 (derived from Francisella novicida) and proximal CRISPR targeting (proxy-CRISPR)

Genome Editing

- CRISPR Challenges
  - Software Tools
    - Synthego: ICE (Inference of CRISPR Edits) for analyzing CRISPR experiments

Genome Editing

- CRISPR Challenges
  - RNA Engineering
    - RNA engineering is at a much earlier stage of development compared to DNA engineering
    - Patrick Hsu (Salk Inst): adapting CRISPR to editing RNA
    - DNA targeting is permanent, RNA targeting is potentially reversible

Genome Editing

- CRISPR Challenges
  - Expanding the palette:
    - New nuclease for genome editing: Cpf1 (eg prof Klinestiver)
    - Class 2 CRISPR-Cas systems: Cas9
    - Class 1 CRISPR-Cas systems are more challenging to introduce into eukaryotic cells

Genome Editing

- CRISPR Challenges
  - DETECTR (DNA endonuclease targeted CRISPR trans-reporter) platform (Jennifer Doudna's student Janice Chen) uses CRISPR-Cas12a to analyze cells, blood, saliva, urine, and stool, enabling the detection of genetic mutations, cancer, and antibiotic resistance, and diagnosis of bacterial and viral infections

Genome Editing

- CRISPR Challenges
  - CRISPR-Cas9 = Cas9 nuclease (for creating a DNA double-stranded break) + guide RNA (for targeting the nuclease to a specific region in the genome)
  - Cas9 nuclease: the enzyme that cuts the DNA
  - Selecting the right gRNA sequence is the first challenge facing CRISPR users
  - Fine-tuning gene expression: CRISPRa to activate a gene, CRISPRi to switch off a gene
  - CRISPRi and CRISPRa use deactivated or “dead” Cas9 (dCas9)

Genome Editing

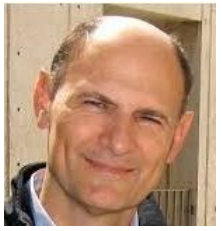
- CRISPR Challenges
  - Cellecta: single-guide RNA libraries for CRISPRi (inhibition) and CRISPRa (activation)
  - Horizon Discovery (formerly Dharmacon): synthetic gRNAs for CRISPRa (gRNAs targeting just one or two genes or whole classes of genes)

Genome Editing

- CRISPR challenges: genetic typos?

Genome Editing

- Applications of TALEN and CRISPR
  - Weizhi Ji at Kunming University in China uses CRISPR to edit the germ-line of monkeys (2014)
  - Chad Cowan and Derrick Rossi (Harvard, 2014): genetic engineering of human cells to make the immune system HIV-resistant
  - Daniel Anderson (MIT, 2014): genetic repair of a mutation that causes a disease
  - JuanCarlos Izpisúa-Belmonte (Salk Inst, 2015): remove HIV virus from cells



Genome Editing

- Applications of CRISPR
  - Xenotransplantation - Manufacturing transplantable organs (George Church's eGenesis in 2017)

egenesis
ENGINEERING LIFE

MIT Technology Review

Scientists have bred gene-edited pigs free of viruses that pose a potential health risk for humans.

by Emily Mullin August 10, 2017

a step toward making pigs suitable organ donors for humans

The Atlantic AUG 10, 2017

Genetically Engineering Pigs to Grow Organs for People

Scientists announce the birth of 37 pigs gene-edited to be better for human transplant.

Genome Editing

- Applications of CRISPR
  - Chimeras
  - Pigs and sheep have organs that are roughly the right size for transplantation into humans
  - Use CRISPR to produce pig embryos and sheep embryos that contain human cells
  - The animal becomes an incubator of transplantable organs
  - JuanCarlos Izpisua-Belmonte
  - 2016: a mouse-rat hybrid
  - 2019: a monkey-human hybrid

SALK INSTITUTE
FOR BIOLOGICAL STUDIES

Juan Carlos Izpisua Belmonte

Aug 05, 2019 Newsweek

A CONTROVERSIAL HUMAN-MONKEY CHIMERA HAS BEEN CREATED IN CHINA, ACCORDING TO A NEW REPORT

Genome Editing

- Applications of CRISPR
  - Changing flower colors (Univ of Tsukuba, Japan)

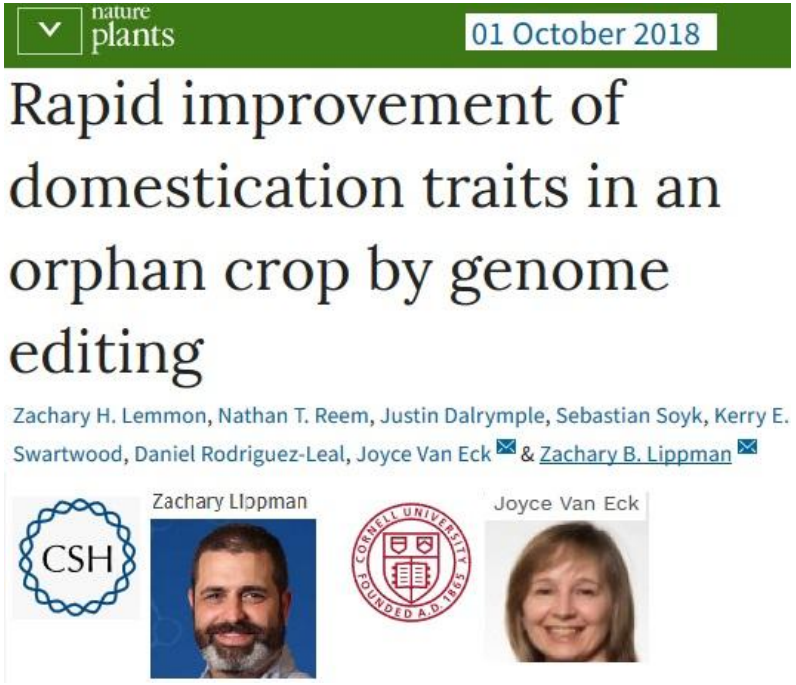
筑波大学
University of Tsukuba

SCIENTIFIC REPORTS 30 August 2017

CRISPR/Cas9-mediated mutagenesis of the *dihydroflavonol-4-reductase-B* (*DFR-B*) locus in the Japanese morning glory *Ipomoea* (*Pharbitis*) *nil*

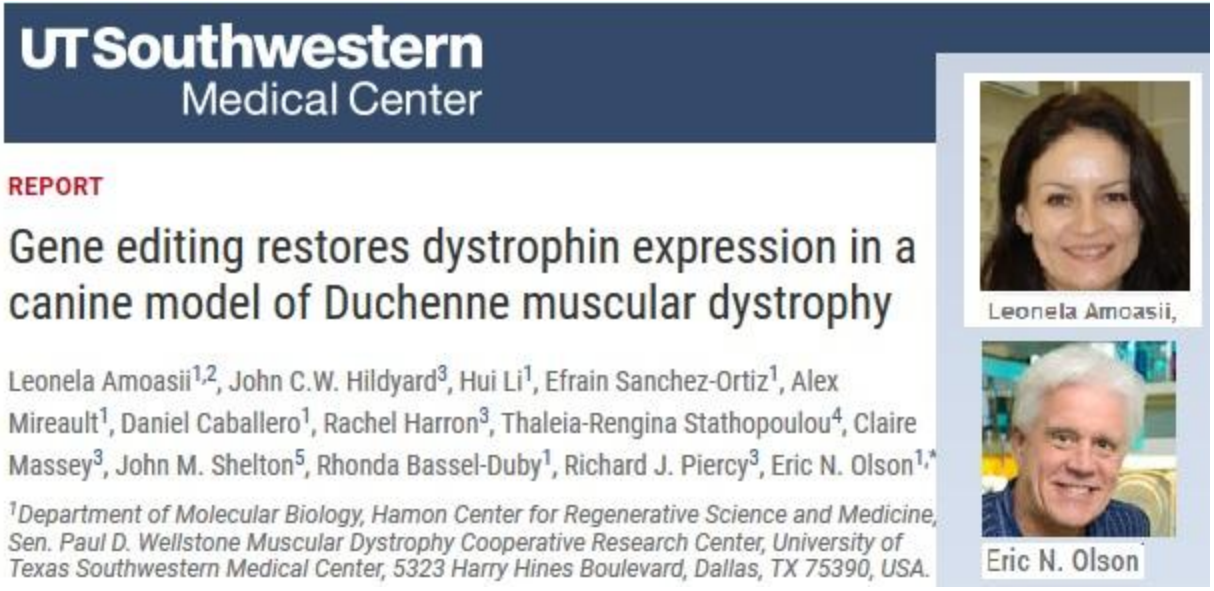
Genome Editing

- Applications of CRISPR
  - Creating new fruit (Joyce Van Eck at Cornell Univ & Zachary Lippman at the Cold Spring Harbor Laboratory)



Genome Editing

- Applications of CRISPR
  - Healing muscular dystrophy (University of Texas Southwestern)



Genome Editing

- Applications of CRISPR
  - Treating sickle cell disease (Emmanuelle Charpentier 's CRISPR Therapeutics & Vertex)

BIOTECH NOVEMBER 19, 2019

First CRISPR treatment for blood diseases shows early benefits in two patients

CRISPR Therapeutics and Vertex Announce Positive Safety and Efficacy Data From First Two Patients Treated With Investigational CRISPR/Cas9 Gene-Editing Therapy CTX001® for Severe Hemoglobinopathies

Genome Editing

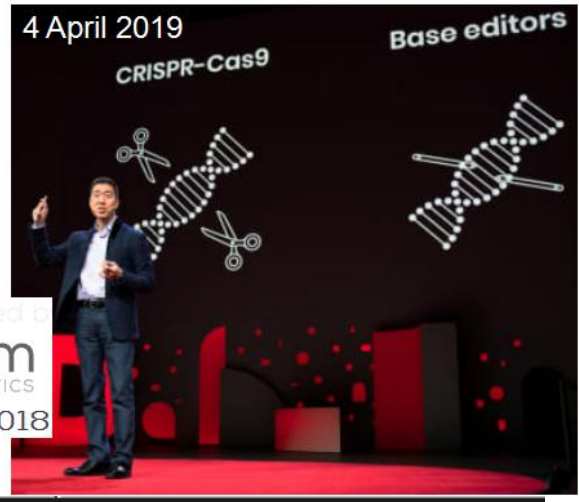
- Applications of CRISPR
  - Cures for blood disorders
  - Cancer therapies (in alternative or in conjunction with CAR-T): CRISPR can also "subtract" not just "add" (CAR-T can only add)

Genome Editing

Base Pairing Rules

Replication	Transcription	Step in Translation	
DNA	DNA	mRNA	tRNA
A	T	A	U
C	G	C	G
G	C	G	C
T	A	U	A

- Beyond CRISPR
  - David Liu (Harvard, 2016): base editing (editing the single letters of DNA)
  - Feng Zhang (MIT, 2017): using CRISPR to edit RNA (which carries DNA's instructions to make proteins)



nature 19 May 2016

Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage

Alexis Komor
David R. Liu

Science 25 Oct 2017

RNA editing with CRISPR-Cas13

David B. T. Cox

Feng Zhang

Broad Institute of MIT

Genome Editing

- Faster better CRISPR
  - Theo Roth (UCSF, 2018)

GEN Genetic Engineering & Biotechnology News

July 12, 2018

Nonviral CRISPR Technology Developed for Faster, Cheaper T-Cell Engineering

Reprogramming human T cell function and specificity with non-viral genome targeting

Theodore L. Roth[1,2,3,4,5], Cristina Puig-Saus[6], Ruby Yu[3,4,5], Eric Shifrut[3,4,5], Julia Carnevale[7], P. Jonathan Li[3,4,5], Joseph Hiatt[1,2,3,4,5], Justin Saco[6], Paige Krystofinski[6], Han Li[8,9], Victoria Tobin[3,4,5], David N. Nguyen[3,4,5], Michael R. Lee[4], Amy L. Putnam[4], Andrea L. Ferris[10], Jeff W. Chen[11], Jean-Nicolas Schickel[11], Laurence Pellerin[12,13], David Carmody[14], Gorka Alkorta-Aranburu[15], Daniela del Gaudio[15], Hiroyuki Matsumoto[16], Montse Morell[16], Ying Mao[16], Min Cho[17], Rolen M. Quadros[18], Channabasavaiah B. Gurumurthy[18], Baz Smith[16], Michael Haugwitz[16], Stephen H. Hughes[10,11], Jonathan S. Weissman[8,9], Kathrin Schumann[3,4,5], Jonathan H. Esensten[19], Andrew P. May[17], Alan Ashworth[7], Gary M. Kupfer[20], Siri Atma W. Greeley[14], Rosa Bacchetta[12,13], Eric Meffre[11], Maria Grazia Roncarolo[12,13], Neil Romberg[21,22], Kevan C. Herold[23], Antoni Ribas[6,24,25,26], Manuel D. Leonetti[8,9,28] & Alexander Marson[3,4,5,7,17,27]*

UCSF

Genome Editing

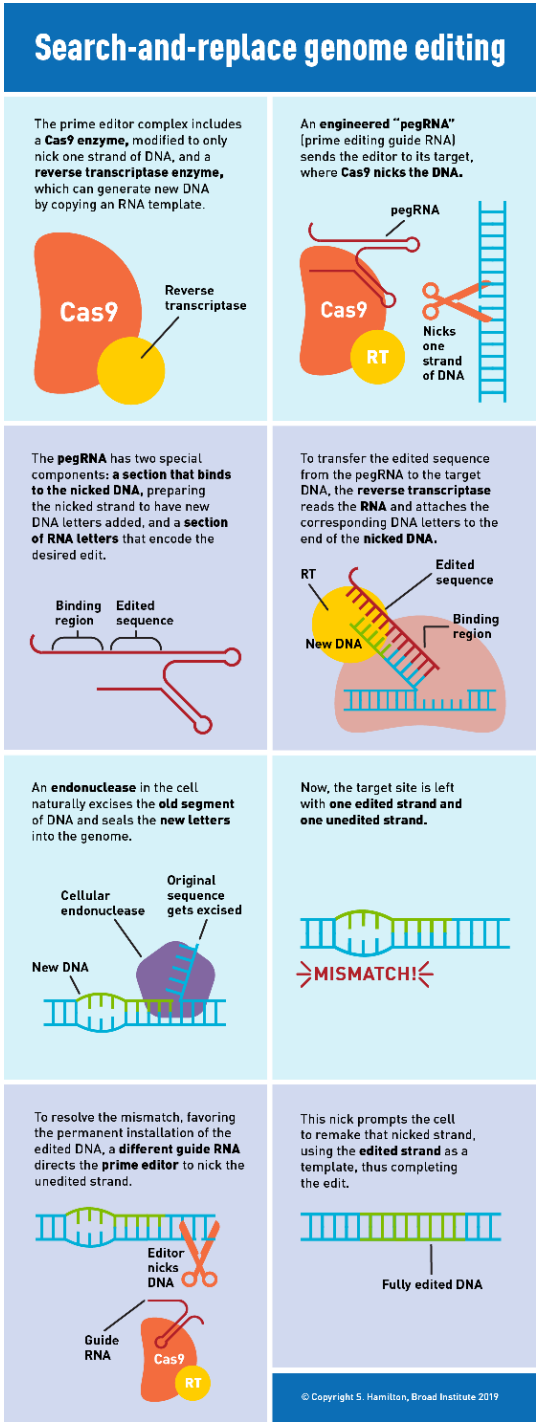
- Prime Editing
  - David Liu & Andrew Anzalone (Broad Inst, 2019)

nature
International journal of science
21 OCTOBER 2019

Search-and-replace genome editing without double-strand breaks or donor DNA

Andrew V. Anzalone, Peyton B. Randolph, Jessie R. Davis, Alexander A. Sousa, Luke W. Koblan, Jonathan M. Levy, Peter J. Chen, Christopher Wilson, Gregory A. Newby, Aditya Raguram & David R. Liu ✉

BROAD INSTITUTE




SECOND INTERNATIONAL SUMMIT ON
HUMAN GENOME EDITING
November 27-29, 2018
The University of Hong Kong
THE ACADEMY OF SCIENCES OF HONG KONG
THE ROYAL SOCIETY
U.S. NATIONAL ACADEMY OF SCIENCES
U.S. NATIONAL ACADEMY OF MEDICINE
SECOND INTERNATIONAL SUMMIT ON
HUMAN GENOME EDITING
27-29 November 2018

Food 2.0

MarketWatch

Opinion: Why 'Food 2.0' is tech's next big start-up craze

By Paul B. Farrell

Published: Oct 6, 2014 3:25 a.m. ET

MIT Technology Review

The Next Startup Craze: Food 2.0

by Ted Greenwald May 7, 2014

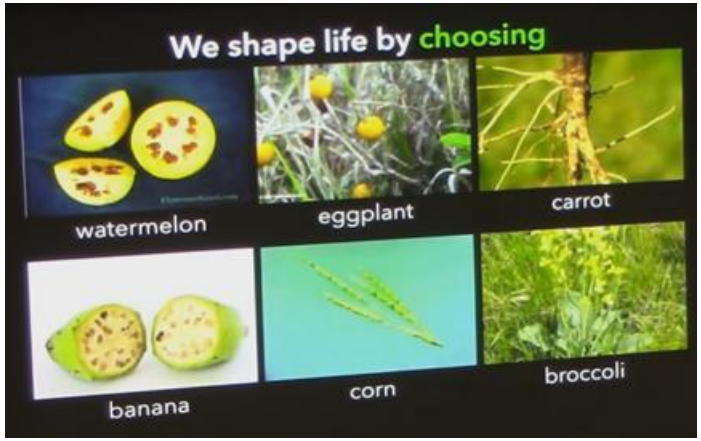
Silicon Valley investors and startups are trying to improve our food.

FOOD 2.0

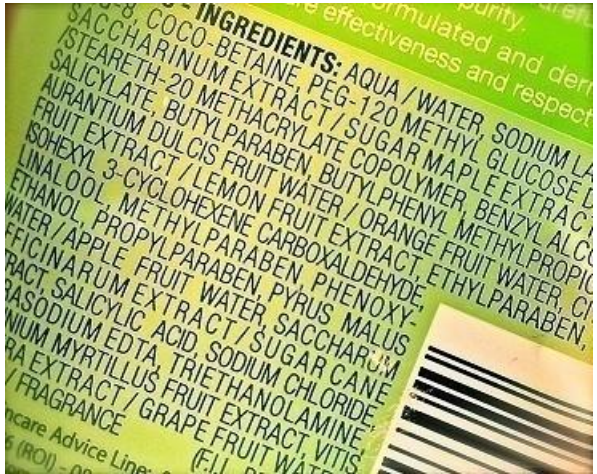
June 7 - 9, 2016 | Los Angeles, CA

Food 2.0

- In defense of GMOs:
  - Farmers have been "genetically engineering" plants and animals for centuries
  - Almost all the fruit that we eat today is genetically engineered
  - And what we eat and drink is hardly “natural”



original plants



Food 2.0

- In defense of GMOs:
  - Dogs are genetically engineered
  - Main difference between selective breeding and laboratory: the speed at which it happens
  - The plant created inside the laboratory is actually more "scientific" than the plant created by the farmer

Food 2.0

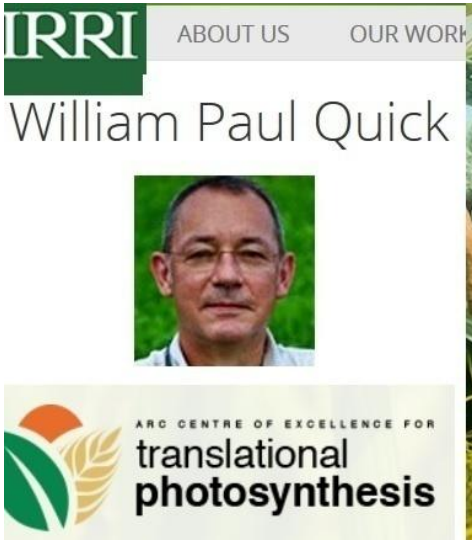
- In defense of GMOs:
  - No transgenic crop has been found dangerous for humans.
  - TALEN and CRISPR techniques can modify a plant without the addition of foreign genes
  - Caixia Gao (China, 2014): genetic engineering of wheat, tomatoes, soybeans, rice, potatoes…

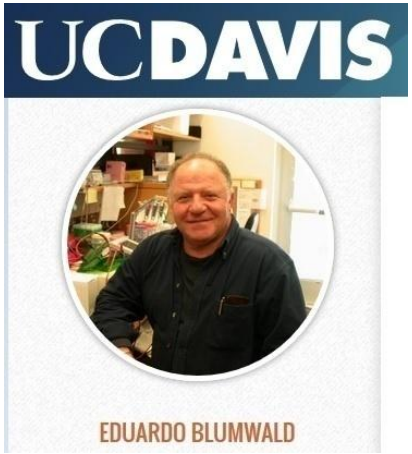
Food 2.0

- Why we need GMOs:
  - To adapt our crops and fruit to the rapid fluctuations of climate
  - Extreme weather will become a common occurrence
  - We cannot afford to wait 10-20 years to improve our plants
  - David Lobell (Stanford) & Wolfram Schlenker (Columbia): *"Climate Trends and Global Crop Production Since 1980"* (2011)

Food 2.0

- Why we need GMOs:
  - Rice feeds 40% of the world's population
  - Paul Quick (Univ of Sheffield) at the International Rice Research Institute (IRRI)
  - C4 Rice Project (2009), funded by the Bill & Melinda Gates Foundation
  - Eduardo Blumwald (UC Davis)

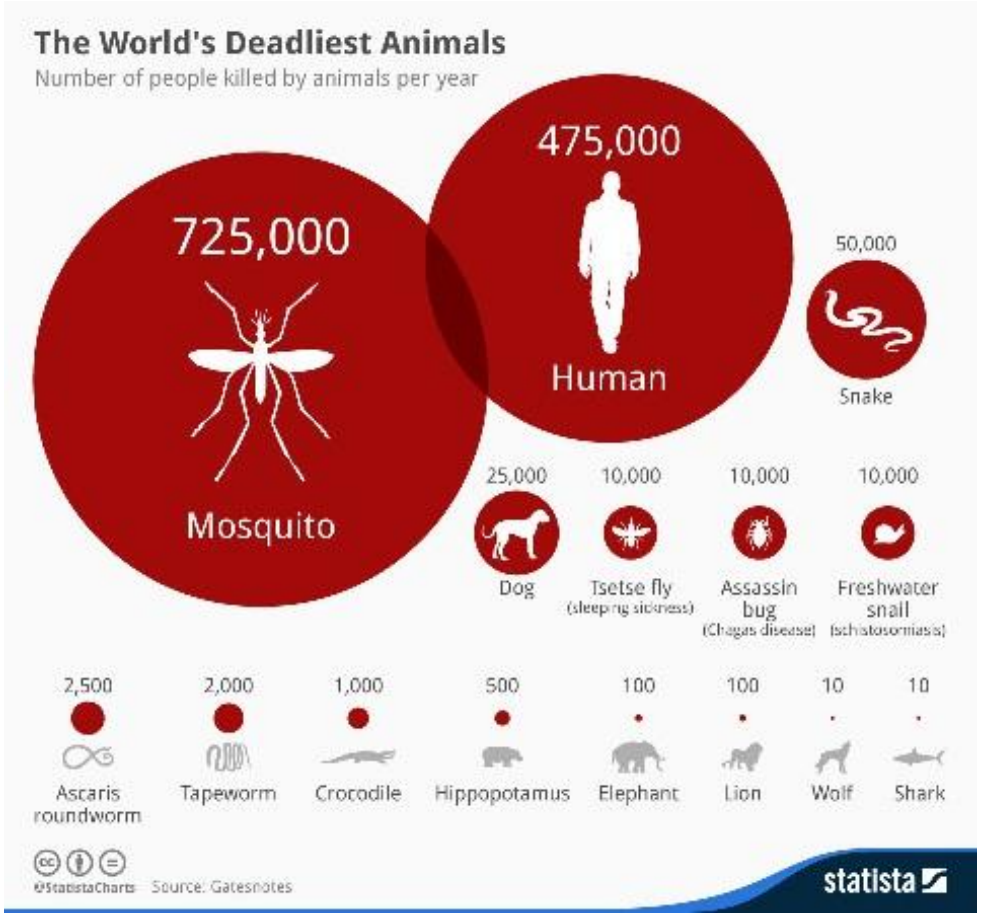


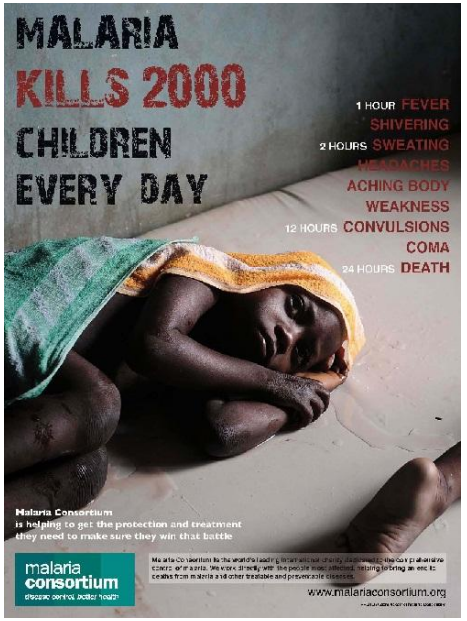


Gene Drive

- CRISPR enables “gene drive” (rapid spread of a genetic change within a population)
  - Ethan Bier and Valentino Gantz (UC San Diego, 2015): gene drive in fruit flies
  - Anthony James (UC Irvine, 2015): gene drive of a malaria-blocking mosquito

Gene Drive


The World's Deadliest Animals
Number of people killed by animals per year
725,000
Mosquito
475,000
Human
50,000
Snake
25,000
Dog
10,000
Tsetse fly
(sleeping sickness)
10,000
Assassin bug
(Chagas disease)
10,000
Freshwater snail
(schistosomiasis)
2,500
Ascaris roundworm
2,000
Tapeworm
1,000
Crocodile
500
Hippopotamus
100
Elephant
100
Lion
10
Wolf
10
Shark
@StatistaCharts Source: Gatesnotes
statista


MALARIA
KILLS 2000
CHILDREN
EVERY DAY
1 HOUR FEVER
SHIVERING
2 HOURS SWEATING
HEADACHES
ACHING BODY
WEAKNESS
12 HOURS CONVULSIONS
COMA
24 HOURS DEATH
Malaria Consortium
is helping to get the protection and treatment
they need to make sure they win that battle
malaria consortium
www.malariaconsortium.org


2014
AFP
Malaria

Gene Drive

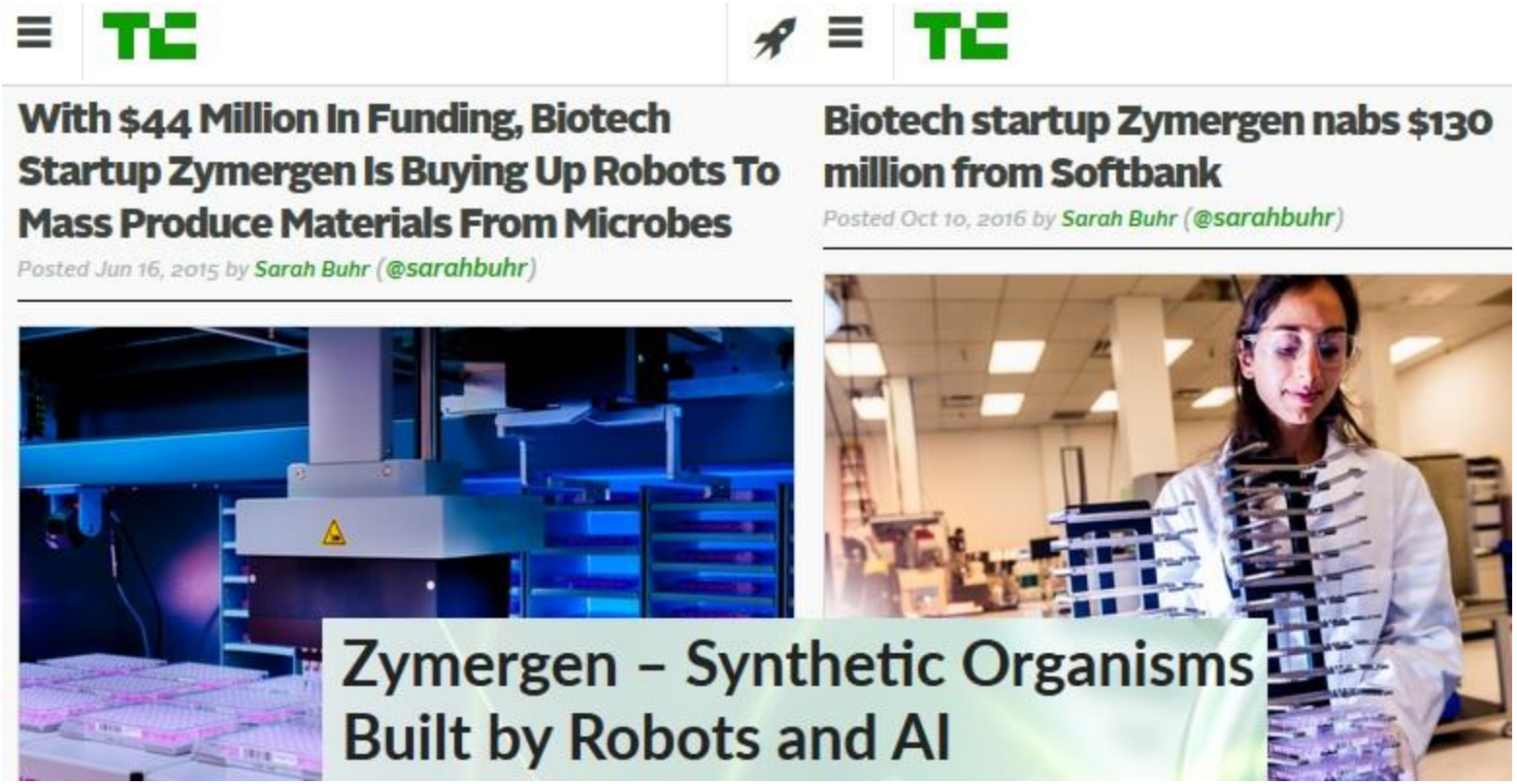
- Andrea Crisanti (UC Irvine, 2018): gene drive of a malaria-blocking mosquito

Biotech & Materials Science

- New materials:
  - Ginkgo Bioworks (Boston, 2008): a foundry to make living organisms on demand (food, cosmetics, etc)
  - Zymergen (Emeryville, 2013): create microbes that can create new materials
  - Modern Meadow (New York, 2011): "print" meat and leather

Biotech & Materials Science

- New materials:
  - Zymergen

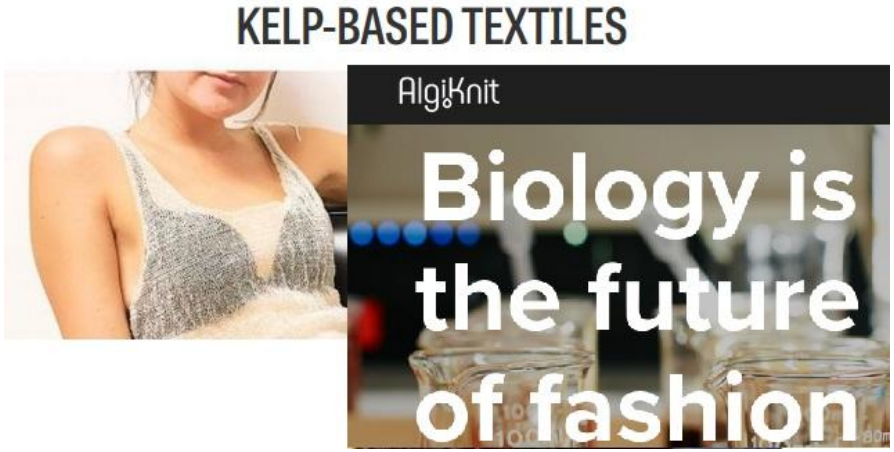


Biotech & Material

- Sustainable Fashion
  - Bacteria-produced dyes
    - Natsai Chieza, designer-in-residence at Ginkgo Bioworks
  - Synthetic leather
    - Modern

Biotech & Materials Science

- Sustainable Fashion
  - Kelp-based textiles
    - AgilKnit
  - Synthetic spider silk
    - Bolt Threads



Designer Babies

- 1978: First baby born via IVF (in vitro fertilization)
- 1990: First baby born via PGD (Alan Handyside's lab)
- Two ways to create human stem cells
  - Shinya Yamanaka (2007)
  - Shoukhrat Mitalipov (2013)
- Basically, it's a way to turn back the biological clock: the DNA of the cell is reprogrammed to the embryonic state

Designer Babies

Rabinowitz-Shendure PGD (2015)

Published online 2015 Apr 8.
doi: 10.1186/s13073-015-0160-4

Whole genome prediction for preimplantation genetic diagnosis

Akash Kumar,[#] Allison Ryan,[#] Jacob O Kitzman, Nina Wemmer, Matthew W Snyder, Styrmir Sigurjonsson, Choli Lee, Milena Banjevic, Paul W Zarutskie, Alexandra P Lewis, Jay Shendure,[✉] and Matthew Rabinowitz[✉]

Designer Babies

Katsuhiko Hayashi & Mitinori Saitou

2012: fertile egg cells from both mouse embryonic stem cells and induced pluripotent stem cells

2015: IVG on mice (“easy PGD”), eggs and sperm created from skin cells

2018: human oogonia

九州大学
KYUSHU UNIVERSITY

Science

REPORT

Science 20 Sep 2018

Generation of human oogonia from induced pluripotent stem cells in vitro

Chika Yamashiro[1,2], Kotaro Sasaki[1,2], Yukihiro Yabuta[1,2], Yoji Kojima[1,2,3,4], Tomonori Nakamura[1,2], Ikuhiro Okamoto[1,2], Shihori Yokobayashi[1,2,4], Yusuke Murase[1,2], Yukiko Ishikura[1,2], Kenjiro Shirane[5,6], Hiroyuki Sasaki[5,6], Takuya Yamamoto[3,4,7], Mitinori Saitou[1,2,3,4,*]

iCeMS KYOTO UNIVERSITY WPI Research Center
Institute for Integrated Cell-Material Sciences
Kyoto University
Institute for Advanced Study

Designer Babies

- Glenn Cohen's article "Disruptive Reproductive Technologies" (2017)

Science Translational Medicine

Disruptive reproductive technologies

. Glenn Cohen[1,*], George Q. Daley[2,3] and Eli Y. Adashi[4]

First baby born after full genetic screening of embryos

8 July 2013

Designer Babies

The Atlantic

May 3, 2017

Would You Edit Your Babies' Genes to Keep Them Healthy?

Designer Babies

2017: Shoukhrat Mitalipov repairs a genetic mutation in human embryos

Correction of a pathogenic gene mutation in human embryos

nature
International journal of science

Hong Ma[1]*, Nuria Marti-Gutierrez[1]*, Sang-Wook Park[2]*, Jun Wu[3]*, Yeonmi Lee[1], Keiichiro Suzuki[3], Amy Koski[1], Dongmei Ji[1], Tomonari Hayama[1], Riffat Ahmed[1], Hayley Darby[1], Crystal Van Dyken[1], Ying Li[1], Eunju Kang[1], A.-Reum Park[2], Daesik Kim[4], Sang-Tae Kim[2], Jianhui Gong[5,6,7,8], Ying Gu[5,6,7], Xun Xu[5,6,7], David Battaglia[1,9], Sacha A. Krieg[9], David M. Lee[9], Diana H. Wu[9], Don P. Wolf[1], Stephen B. Heitner[10], Juan Carlos Izpisua Belmonte[3]§, Paula Amato[1,9]§, Jin-Soo Kim[2,4]§, Sanjiv Kaul[10]§ & Shoukhrat Mitalipov[1,10]§

02 August 2017

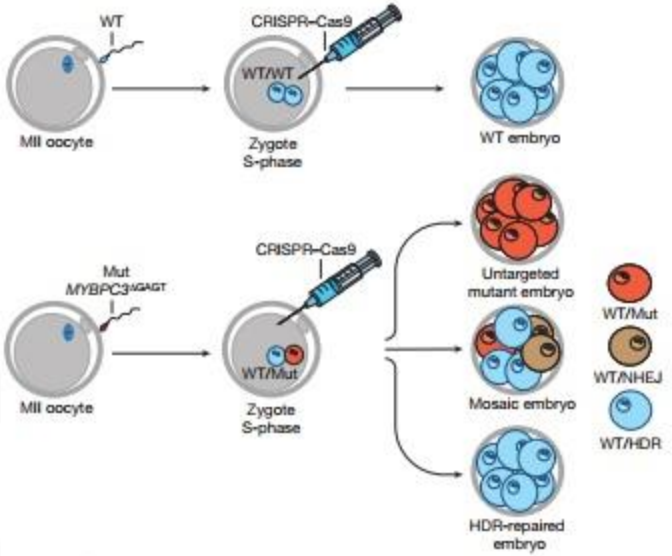


Figure 1 | Gene correction in S-phase-injected human embryos.

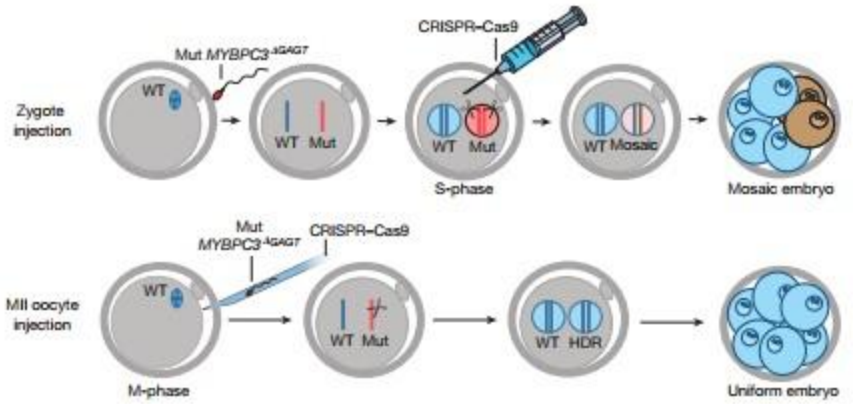
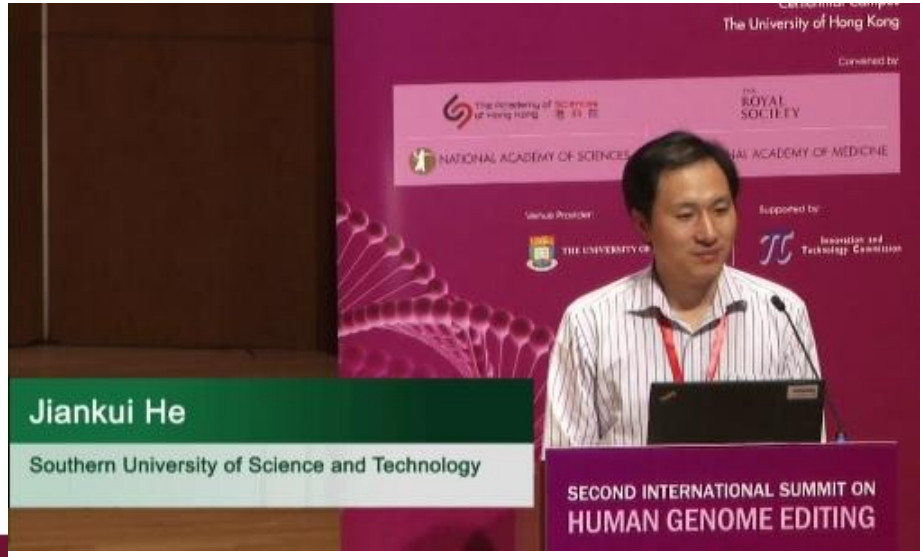
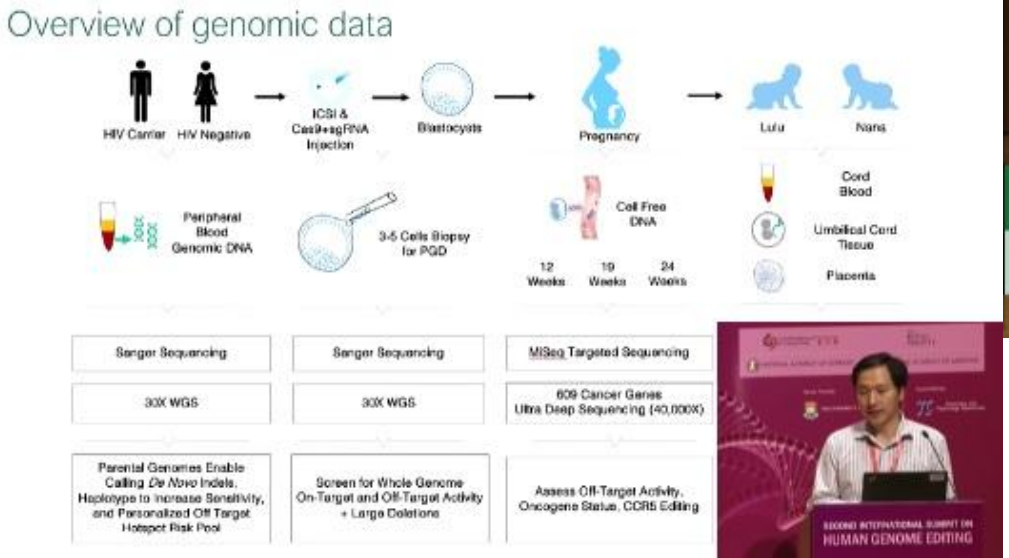


Figure 3 | Gene correction in M-phase-injected human embryos.

Designer Babies

Nov 2018: Jiankui He (Shenzhen) uses CRISPR to modify human embryos (removing the gene CCR5) before they are transferred into a woman's uterus, and claims the first gene-edited babies (immune to HIV)





Designer Babies

Trivia: deleting CCR5 makes mice smarter!

(Alcino Silva, UC Los Angeles)

Deletion of CCR5 gene helps the brain of mice recover

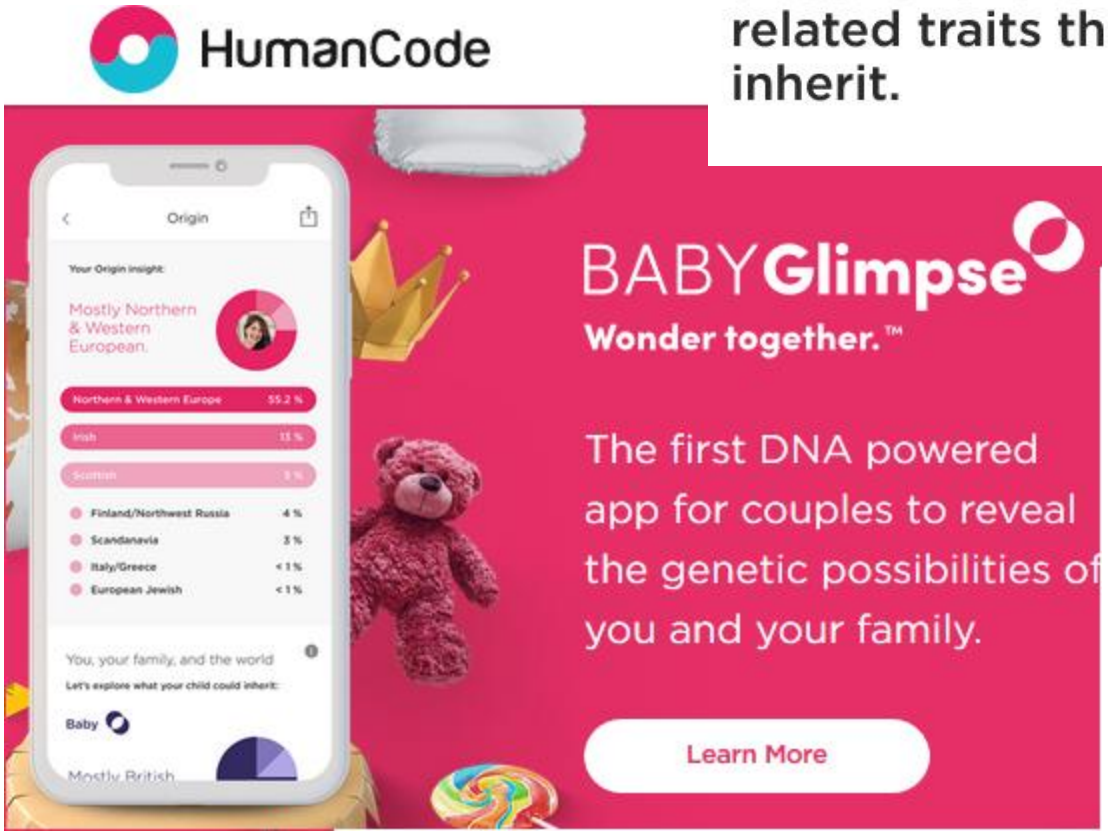
> Will these twins turn out to be "smarter" than the average, and, if so, to see what the public reaction will be: will there be a rush to edit the CCR5 gene from fetuses?

Eugenetics 2.0

- HumanCode

BABYGlimpse is the first DNA-powered app for couples to discover and explore the genetic-related traits their children may inherit.

POWERED BY Helix



Eugenetics 2.0

- Stephen Hsu

Physicist Stephen Hsu developed a genetic "predictor" that uses machine learning to estimate height, to within three centimeters, from a person's DNA.

MICHIGAN STATE UNIVERSITY

genomic prediction

gSEQ
Genomic
Sequence Quantification

EPgT
Expanded
Pre-Implantation Genomic
Testing

Accurate Genomic Prediction Of Human Height

Louis Lello, Steven G. Avery, Laurent Tellier, Ana Vazquez, Gustavo de los Campos, Stephen D.H. Hsu

(Submitted on 19 Sep 2017)

Eugenetics 2.0

- Stephen Hsu (2014): Super-intelligent humans

MIT Technology Review by Antonio Regalado November 1, 2017

Eugenics 2.0: We're at the Dawn of Choosing Embryos by Health, Height, and More

NAUTILUS OCTOBER 16, 2014

Super-Intelligent Humans Are Coming

Genetic engineering will one day create the smartest humans who have ever lived.

BY STEPHEN HSU

MICHIGAN STATE UNIVERSITY

Genetic Engineering of Intelligence

- Genetic engineering of mental and cognitive skills?
  - 1999: Joseph Tsien adds NR2B genes to mice to improve their ability in learning and memory (the “the smart mouse Doogie”)

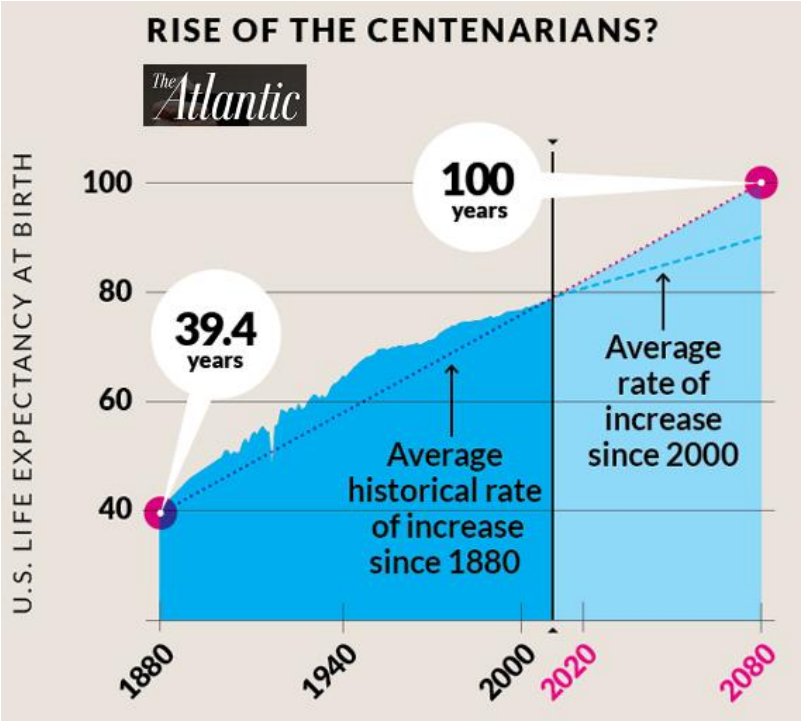
Princeton University

Replacing Surgery

- Positive viral infection
  - Ben Deverman (Caltech, 2015): PCR + natural selection to deliver genes to the brain

An Aging Humankind

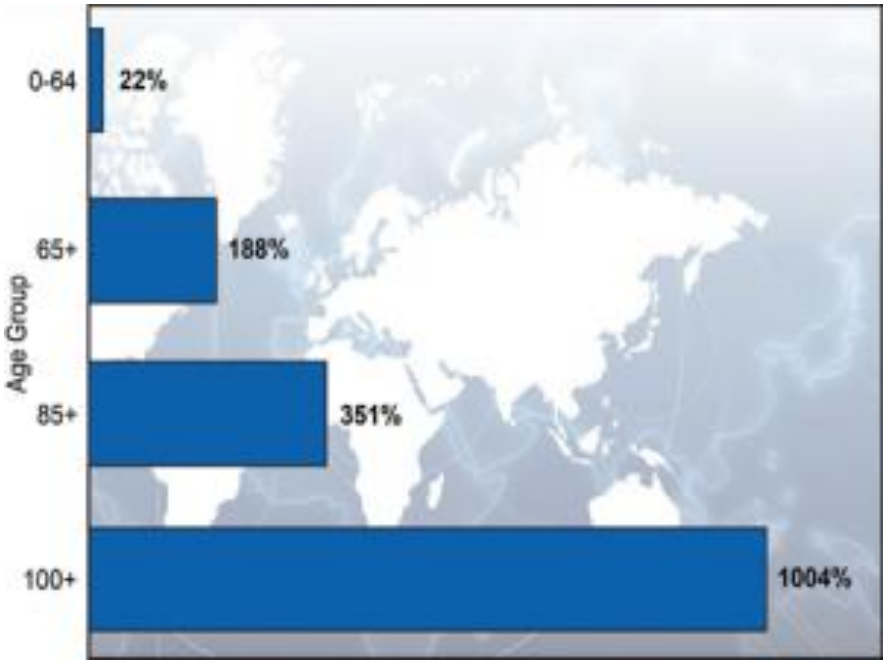
- Life expectancy is increasing: every year by 3 months
- Neurodegenerative diseases increase accordingly
- This means fewer doctors and more diagnostic centers (and their staff)



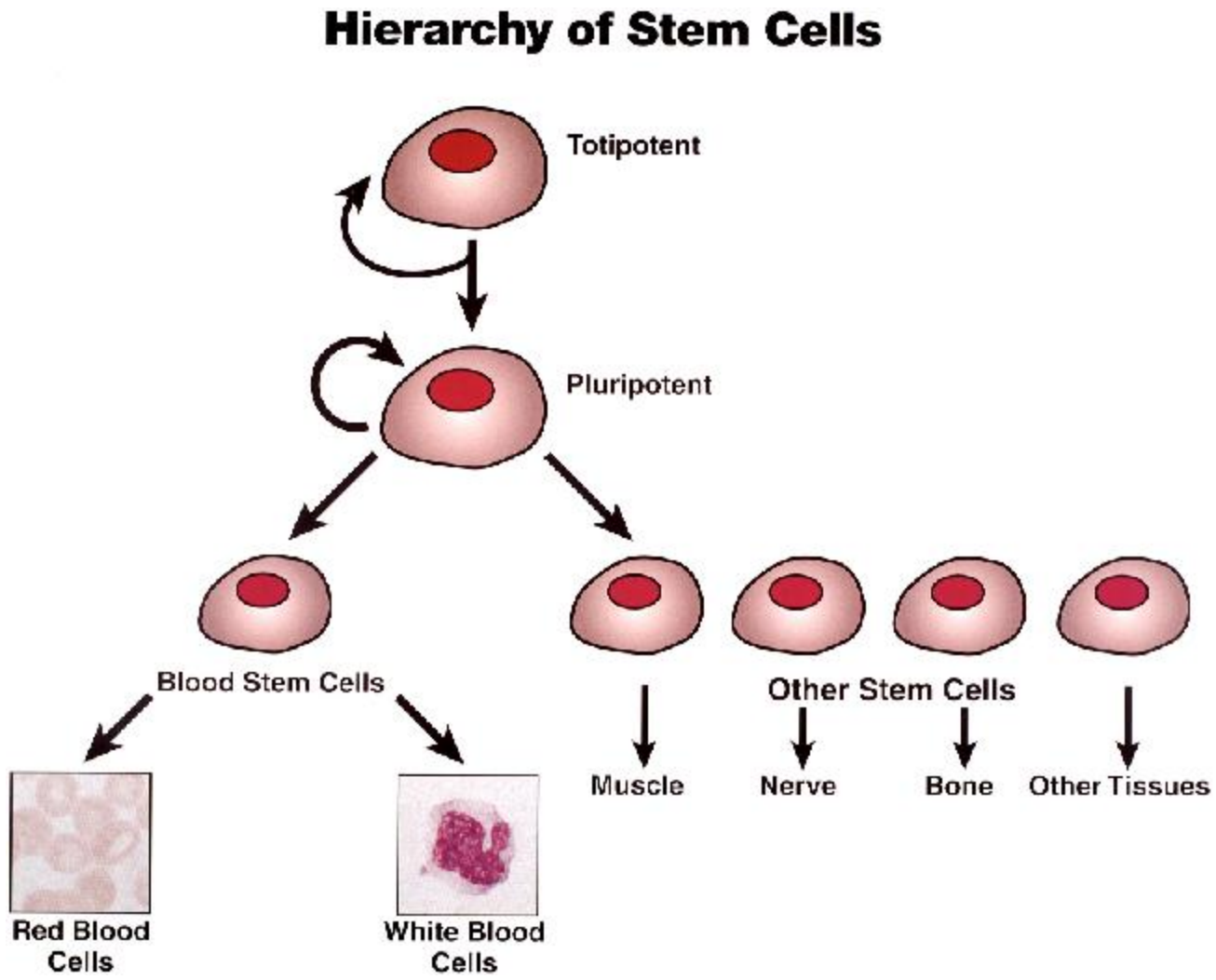
An Aging Humankind

- The most dramatic and rapid gains have occurred in East Asia, where life expectancy at birth increased from less than 45 years in 1950 to more than 74 years today.

% Change in the world's population by age 2010-2050 (UN estimates)

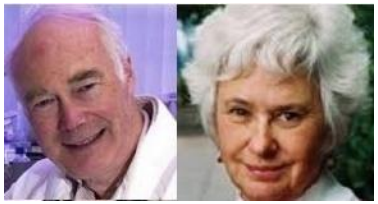


Regenerative Medicine



Regenerative Medicine

- A future of growing replacement tissues and organs for transplantation
- 1981: Martin Evans at Cambridge Univ and Gail Martin at UC San Francisco isolate embryonic stem cells of the mouse
- 1998: James Thomson at the University of Wisconsin isolates human embryonic stem cells
- 2007: Shinya Yamanaka at Kyoto Univ converts adult cells into pluripotent stem cells (iPS cells)
- 2011: Pharmicell gets approval for the first stem-cell drug

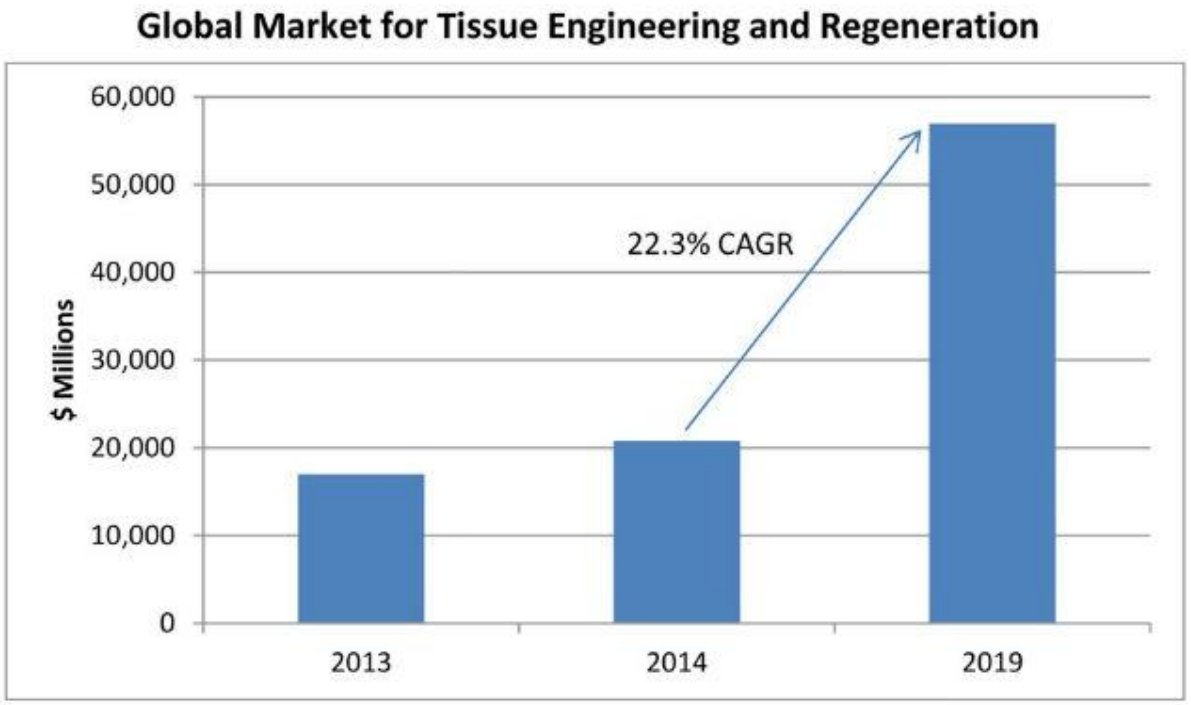


PHARMICELL
ADULT STEM CELL BANK & THERAPY

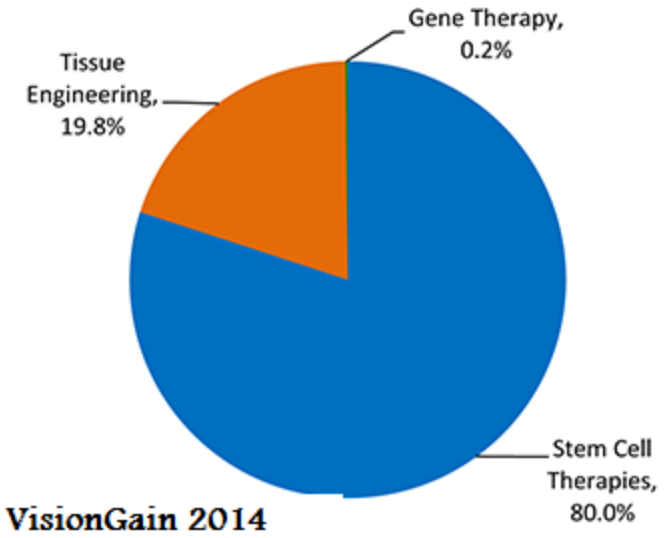
Regenerative Medicine

- Cellectis (France, 1999)
- Mesoblast (Australia, 2004)
- California Institute for Regenerative Medicine (2004)
- Capricor Therapeutics (Los Angeles, 2005)
- Pharmicell (Germany, 2006)
- AlloCure (Boston, 2008)
- Harvard Apparatus Regenerative Technology (Boston, 2012)

Regenerative Medicine



Source: BCC Research (HLC101B), August 2014



Regenerative Medicine

- Madeline Lancaster: using pluripotent human cells to grow three-dimensional tissues (“cerebral organoids”) to model how the human brain develops.

Regenerative Medicine

- Gene therapy for blindness:
  - 2015: Spark Therapeutics' gene-therapy for blindness (spinoff of the Children's Hospital of Philadelphia)

Spark THERAPEUTICS

Children's Hospital of Philadelphia

Regenerative Medicine

- Gene therapy for anti-aging:
  - 2016: Elizabeth Parrish performs gene therapy on herself and improves her "telomere score“
  - 2017: first man to have genes edited directly inside his body

FIRST GENE THERAPY SUCCESSFUL AGAINST HUMAN AGING

American woman gets biologically younger after gene therapies

The First Man to Have His Genes Edited Inside His Body

The Atlantic NOVEMBER 15, 2017

Sangamo Announces Treatment of First Patient in Landmark Phase 1/2 Clinical Trial Evaluating In Vivo Genome Editing for MPS II

Sangamo THERAPEUTICS

Regenerative Medicine

- Gene therapy for general-purpose immunity?
  - 2016: Dusan Bogunovic shows that people without gene ISG15 (about 1 in 10 million people) have a stronger immune system that can fight almost all known viruses.

Regenerative Medicine

- Gene therapy + stem-cell research:
  - Ying Liu (Univ of Texas)
  - Guangbin Xia (Univ of Florida)
  - Joshua Hare (Univ of Miami)
  - Malin Parmar (Lund Univ, Sweden)




Regenerative Medicine

- Gene therapy + stem-cell research:
  - 2017: Michele DeLuca combines stem-cell techniques with gene therapy to create artificial skin to cure a skin disease

Regenerative Medicine

- Khademhosseini Lab (UCLA)

Immune Therapy

- To improve the immune system
- T cells: immune cells that identify other cells infected by a virus or cancer
- 1983: Discovery of how T cells work
- 1994: Tasuku Honjo identifies the gene PD-1 as an inhibitor
- 1996: James Allison identifies CTLA-4 as an inhibitor
- First success story: Ipilimumab for the treatment of skin cancer (2011) by James Allison (UC Berkeley)
- Cellectis (France, 1999)

京都大学
KYOTO UNIVERSITY

Berkeley
UNIVERSITY OF CALIFORNIA

cellectis

Immune Therapy

- Ono's and Bristol-Myers Squibb's Opdivo (2015)

Immunotherapy

- Wendell Lim at UCSF
- AbVitro (Juno Therapeutics)
- Steven Rosenberg at NCI
- Verily (Google's biotech unit)
- KitePharma
- Sean Parker's charity institute (2016)

Woman cancer-free after targeted immune treatment

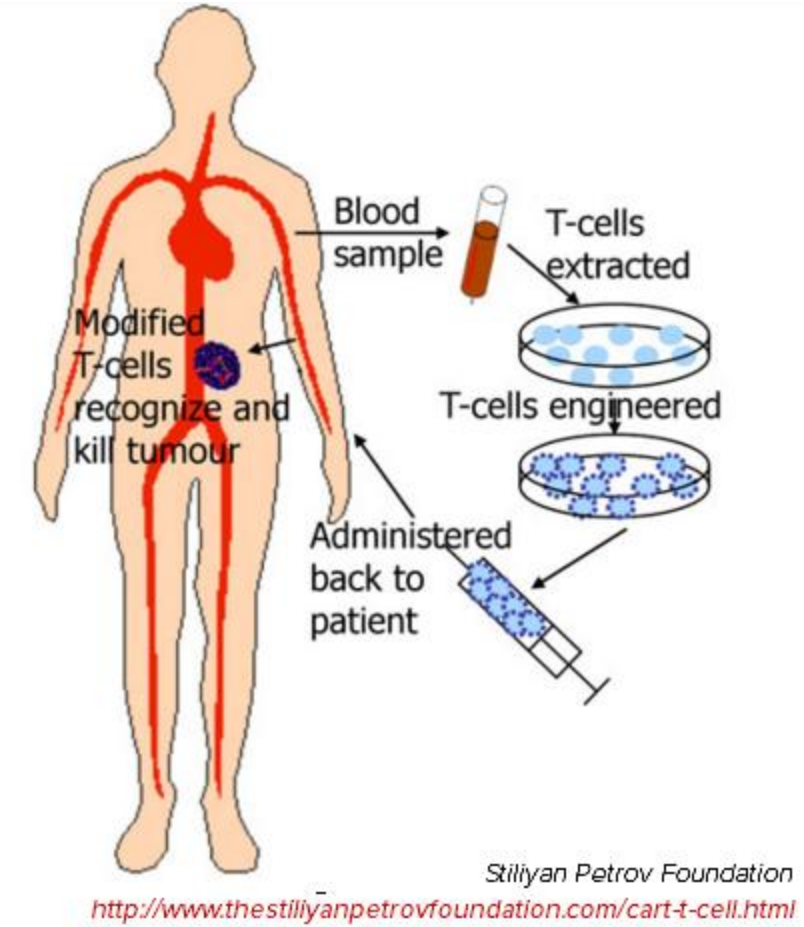
Dec. 8, 2016 Science

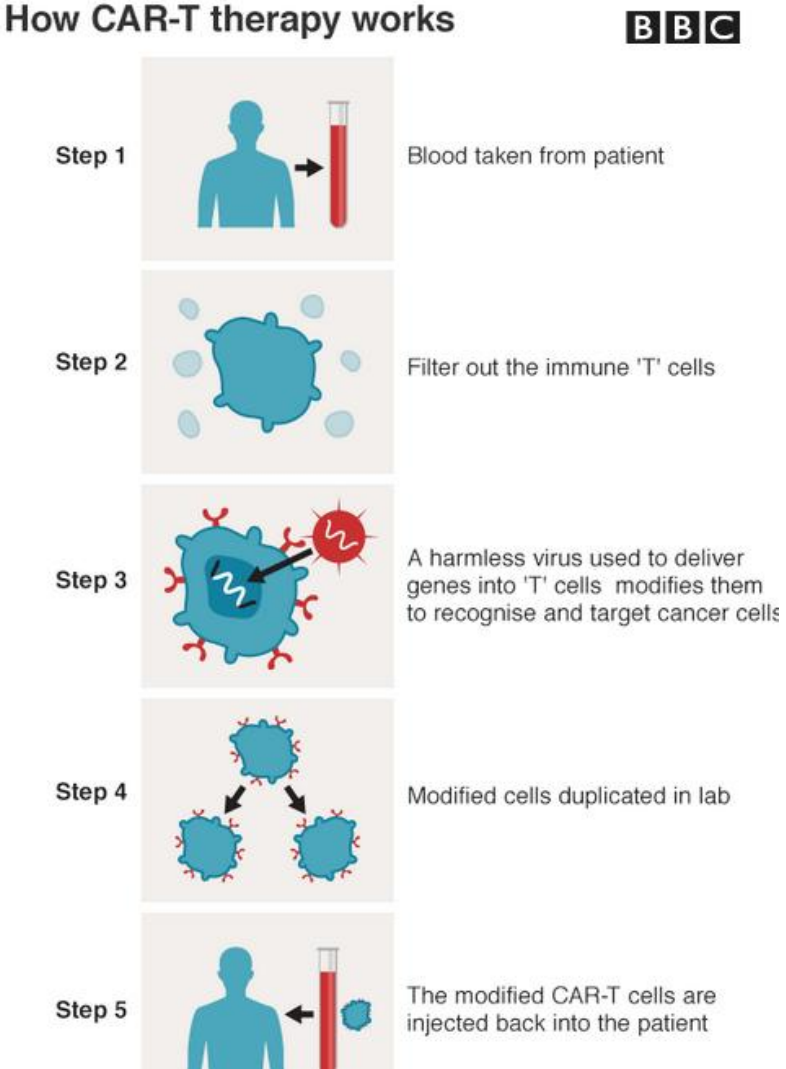
As reported today in *The New England Journal of Medicine*, the 50-year-old engineer and mother of five is the **first to benefit from such a therapy**

The woman was treated in a clinical trial at the National Cancer Institute in Bethesda, Maryland, by a team led by Steven Rosenberg

CAR-T

- Genetically engineered T-cells to fight cancer





CAR-T

- 1991: Brian Seed (Harvard): first generation of CAR-T cells (for HIV)
- 2010: Carl June (Univ of Pennsylvania): CAR-T-cells for cancer
- 2017: first T-cell therapy approved by FDA (Carl June's CTL019, marketed as Kymriah by Novartis)

Perelman School of Medicine
University of Pennsylvania

NOVARTIS AUG 30, 2017

Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah(TM) (CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice

Penn

Carl June

CAR-T

- CAR-T in 2017: Kite (acquired by Gilead), Juno, Bluebird, Celectis, Wendell Lim's Cell Design Labs (acquired by Gilead)
- Three gene therapies approved in the USA: Kymriah by Novartis, Kite Pharma's Yescarta and Spark Therapeutics' Luxturna

Spark THERAPEUTICS

GILEAD

STAT

Gilead agrees to buy Kite Pharma, leaping into CAR-T cancer therapy

AUGUST 28, 2017

MIT Technology Review

December 7, 2017

Genetic Programmers Are the Next Startup Millionaires

celldesignlabs

CAR-T

- Allogene
- Tmunity (Carl June)

Allogene THERAPEUTICS

ENDPOINTS NEWS

Friday, November 9, 2018

Allied with Penn, Tmunity's cell therapy pioneers bag $100M mega-round to back a breakthrough quest on CAR-T, CRISPR

Carl June

Perelman School of Medicine University of Pennsylvania

TMUNITY

CAR-T

- Wendell Lim & Carl June: Roadmap for the development of next-generation therapeutic cells (2017)

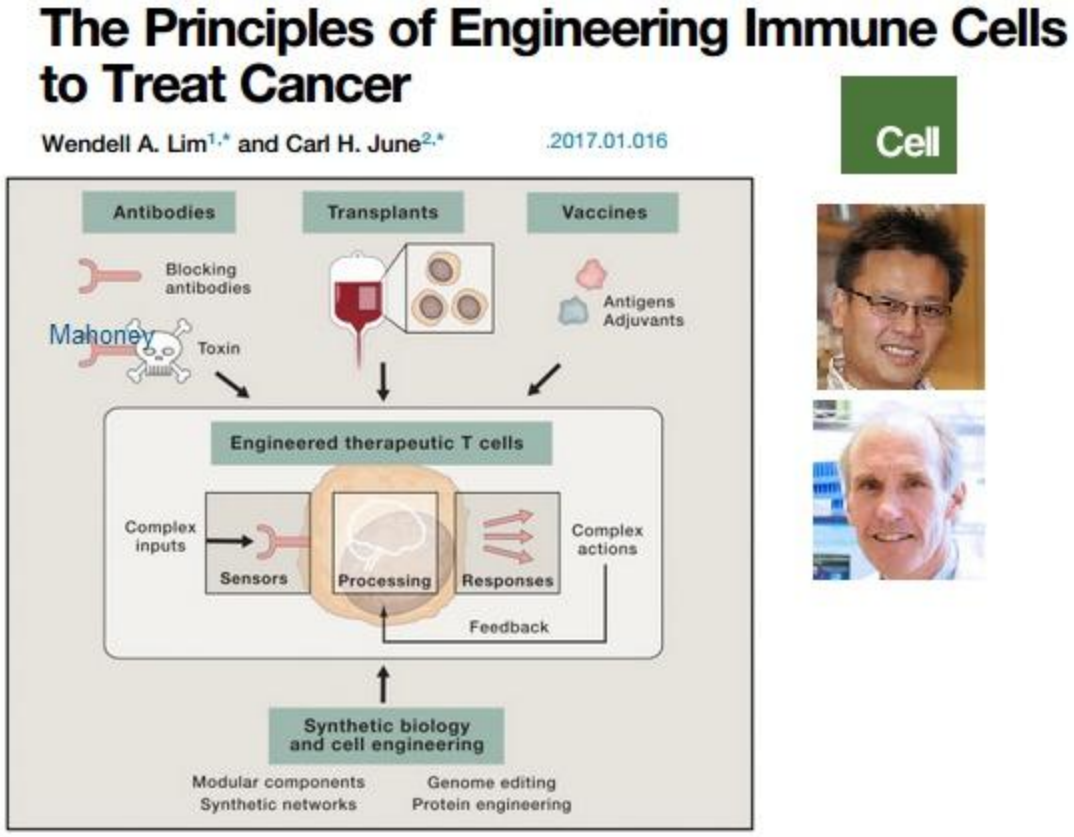


Figure 1

Engineered Therapeutic T Cells Provide a Transformative New Platform for Interfacing with Complex Diseases such as Cancer

CAR-T

- Andrew Sewell discovers universal T-cells (2020)

Discovery of new T-cell raises prospect of ‘universal’ cancer therapy

20 January 2020

CARDIFF UNIVERSITY

nature immunology

VOL 21 | FEBRUARY 2020 | 178–185

Genome-wide CRISPR–Cas9 screening reveals ubiquitous T cell cancer targeting via the monomorphic MHC class I-related protein MR1

Michael D. Crowther[1,9], Garry Dolton[1,9], Mateusz Legut[1], Marine E. Caillaud[1], Angharad Lloyd[1], Meriem Attaf[1], Sarah A. E. Galloway[1], Cristina Rius[1], Colin P. Farrell[2], Barbara Szomolay[1,3], Ann Ager[1,3], Alan L. Parker[4], Anna Fuller[1], Marco Donia[5], James McCluskey[6], Jamie Rossjohn[1,3,7,8], Inge Marie Svane[5], John D. Phillips[2] and Andrew K. Sewell[1,3*]

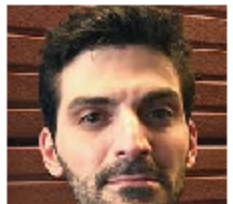
Programmable Bacteria

- Nicholas Arpaia & Tal Danino (2019, Columbia Univ): Genetically modified microbes release “nanobodies” that help the immune system attack cancer in mice

Nature Medicine **25**, 1057–1063 03 July 2019

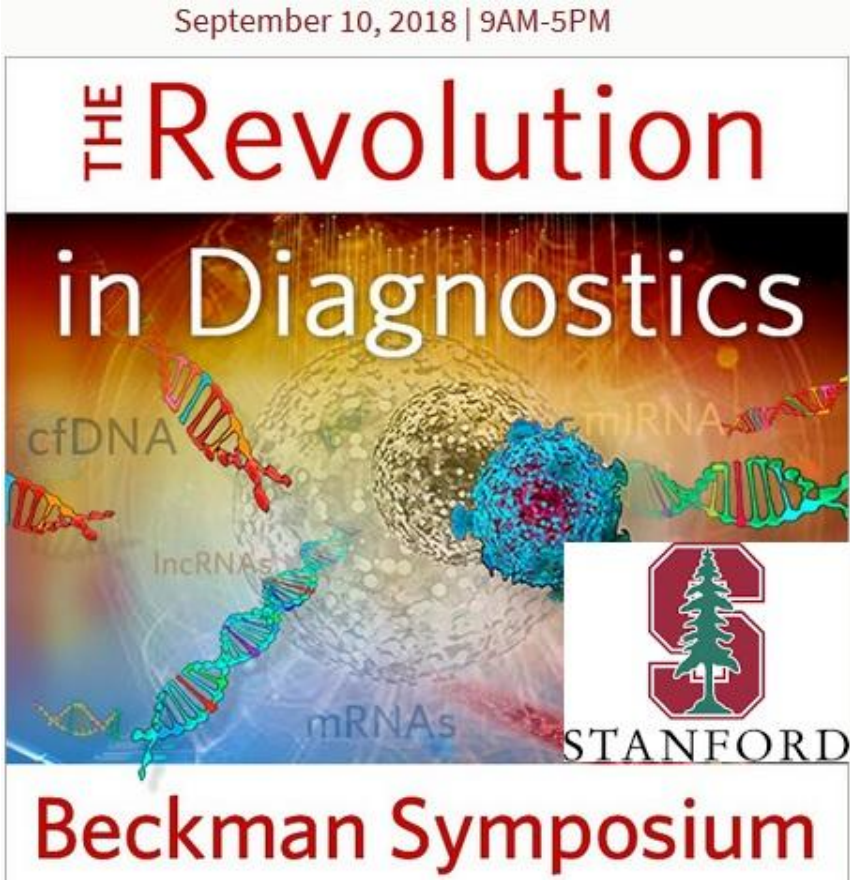
Programmable bacteria induce durable tumor regression and systemic antitumor immunity

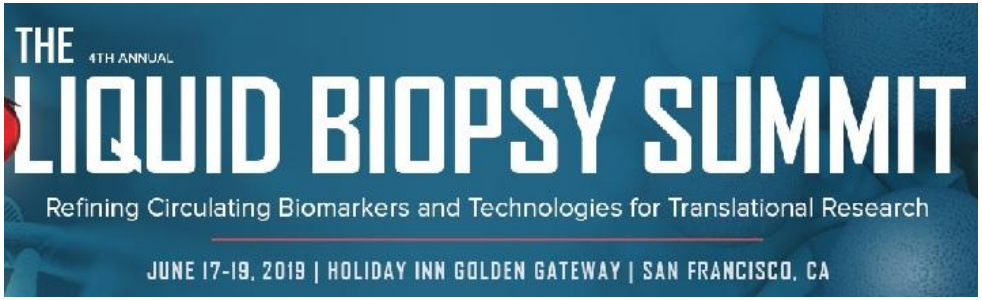
Sreyan Chowdhury, Samuel Castro, Courtney Coker, Taylor E. Hinchliffe, Nicholas Arpaia ✉ & Tal Danino ✉



Liquid Biopsy

- Cancers shed DNA into blood





Liquid Biopsy

- Cancers shed DNA into blood
- Pioneered by Bert Vogelstein in 1989
- BioFluidica (North Carolina, founded in 2007 by Steven Soper of University of North Carolina)


Vogelstein

Mon, 01/11/2016

ECN

'Liquid Biopsy' Blood Test Replaces Painful Bone Marrow Biopsy for Leukemia

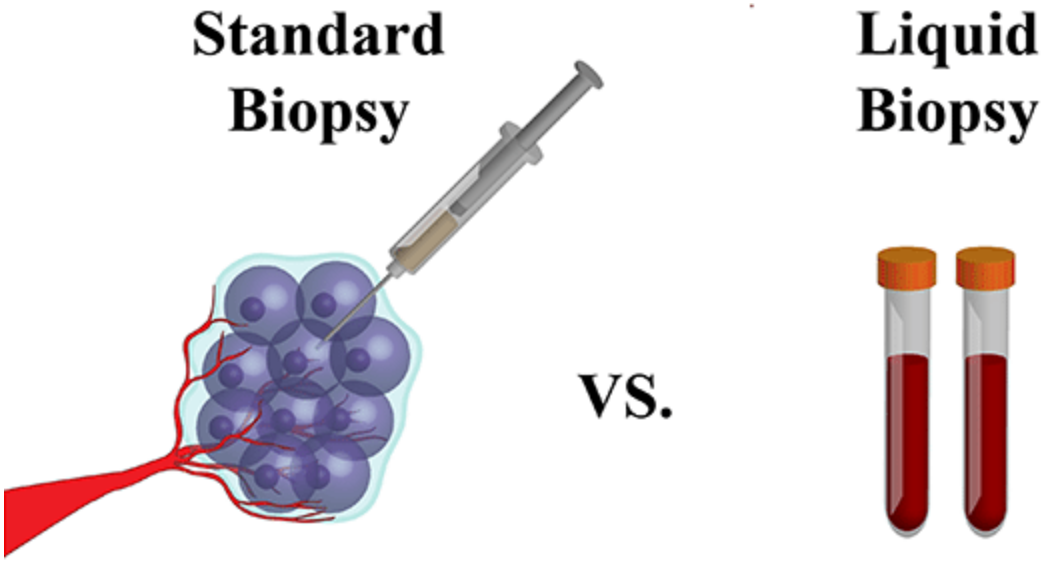

Steven Soper

BioFluidica

UNC SCHOOL OF MEDICINE

Liquid Biopsy

- Guardant Health (Redwood City, 2013)
- Grail (Menlo Park, 2016)
- Apostle (Sunnyvale, 2017)



Revolution in Diagnostics

- Liquid biopsy startups (2018):
  - Grail - Funding: $1,000 m
  - Guardant Health - Funding: $550 m
  - Human Longevity - Funding: $300 m
  - T2 Biosystems - Funding: $185 m
  - Epic Sciences - Funding: $100 m
  - Genalyte - Funding: $92 m
  - RainDance Technologies
  - Qiagen
  - Trovagene
  - Biocept
  - Genomic Health

Grail's ex-CEO and ex-Googler Jeff Huber: *Grail's aim is to create "a test*

Liquid Biopsy

- Liquid biopsy for brain tumors: Florent Mouliere (Cambridge Univ, 2018)
- Bert Vogelstein (Johns Hopkins, 2018)

EMBO Molecular Medicine 06.11.2018

Detection of cell-free DNA fragmentation and copy number alterations in cerebrospinal fluid from glioma patients

Florent Mouliere, Richard Mair, Dineika Chandrananda, Francesco Marass, Christopher G Smith, Jing Su, James Morris, Colin Watts, Kevin M Brindle, Nitzan Rosenfeld

Florent Mouliere (f.mouliere@vumc.nl)*,[1,2,3,[Link]], Richard Mair[1,2,4,[Link]], Dineika Chandrananda[1,2], Francesco Marass[1,2,5,6], Christopher G Smith[1,2], Jing Su[1,2], James Morris[1,2], Colin Watts[7], Kevin M Brindle (kmb1001@cam.ac.uk)*,[1,2,8,†] and Nitzan Rosenfeld (nitzan.rosenfeld@cruk.cam.ac.uk)*,[1,2,†]

[1]Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge, UK

UNIVERSITY OF CAMBRIDGE

Science

REPORT *Science* 23 Feb 2018: Vol. 359, Issue 6378, pp. 926-930

Detection and localization of surgically resectable cancers with a multi-analyte blood test

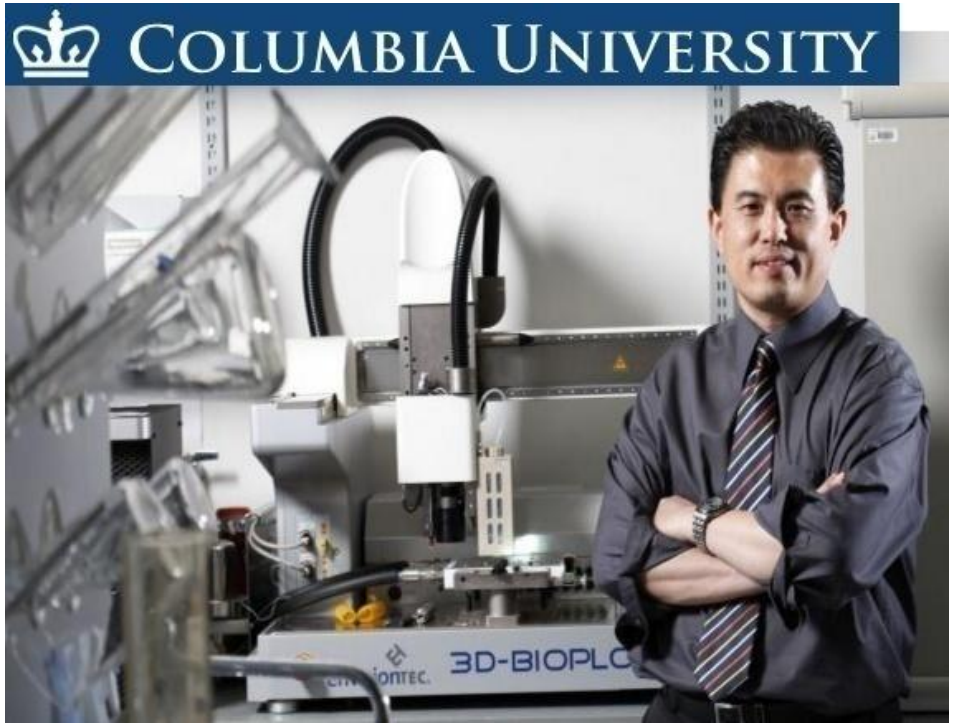
Joshua D. Cohen[1,2,3,4,5], Lu Li[6], Yuxuan Wang[1,2,3,4], Christopher Thoburn[3], Bahman Afsari[7], Ludmila Danilova[7], Christopher Douville[1,2,3,4], Ammar A. Javed[8], Fay Wong[1,3,4], Austin Mattox[1,2,3,4], Ralph H. Hruban[3,4,9], Christopher L. Wolfgang[8], Michael G. Goggins[3,4,9,10,11], Marco Dal Molin[4], Tian-Li Wang[3,9], Richard Roden[3,9], Alison P. Klein[3,4,12], Janine Ptak[1,2,3,4], Lisa Dobbyn[1,3,4], Joy Schaefer[1,3,4], Natalie Silliman[1,2,3,4], Maria Popoli[1,3,4], Joshua T. Vogelstein[13], James D. Browne[14], Robert E. Schoen[15,16], Randall E. Brand[15], Jeanne Tie[17,18,19,20], Peter Gibbs[17,18,19,20], Hui-Li Wong[17], Aaron S. Mansfield[21], Jin Jen[22], Samir M. Hanash[23], Massimo Falconi[24], Peter J. Allen[25], Shibin Zhou[1,3,4], Chetan Bettegowda[1,3,4], Luis A. Diaz Jr.[1,3,4,*], Cristian Tomasetti[3,6,7,†], Kenneth W. Kinzler[1,3,4,†], Bert Vogelstein[1,2,3,4,†], Anne Marie Lennon[3,4,8,10,11,†], Nickolas Papadopoulos[1,3,4,†]

JOHNS HOPKINS UNIVERSITY

Vogelstein

3D Bioprinting

- Wake Forest University (North Carolina): printing skin cells on burn wounds (2016)
- Jeremy Mao at Columbia University: printing cartilage



3D Bioprinting

- Organovo (San Diego): first commercial bioprinting
- Cyfuse (Japan)
- Regenovo (Hangzhou, China)
- Prellis Biologics (Melanie Matheu - San Francisco, 2016): laser-based printing of human tissue with capillaries (demonstrated in 2018)

organovo

CYFUSE

Regenovo
杭州捷诺飞生物科技有限公司

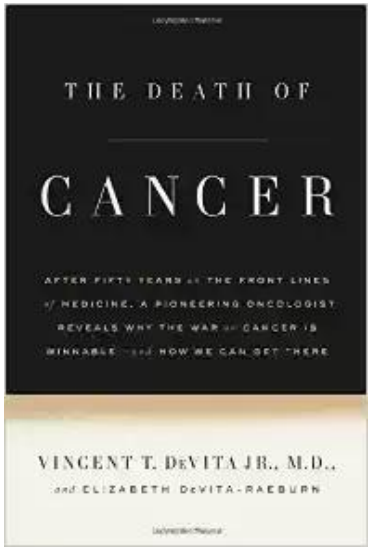
PRELLIS BIOLOGICS
building life with light

June 20, 2018

Prellis Biologics Achieves Unprecedented Speed and Resolution in 3D Printing of Human Tissue With Capillaries

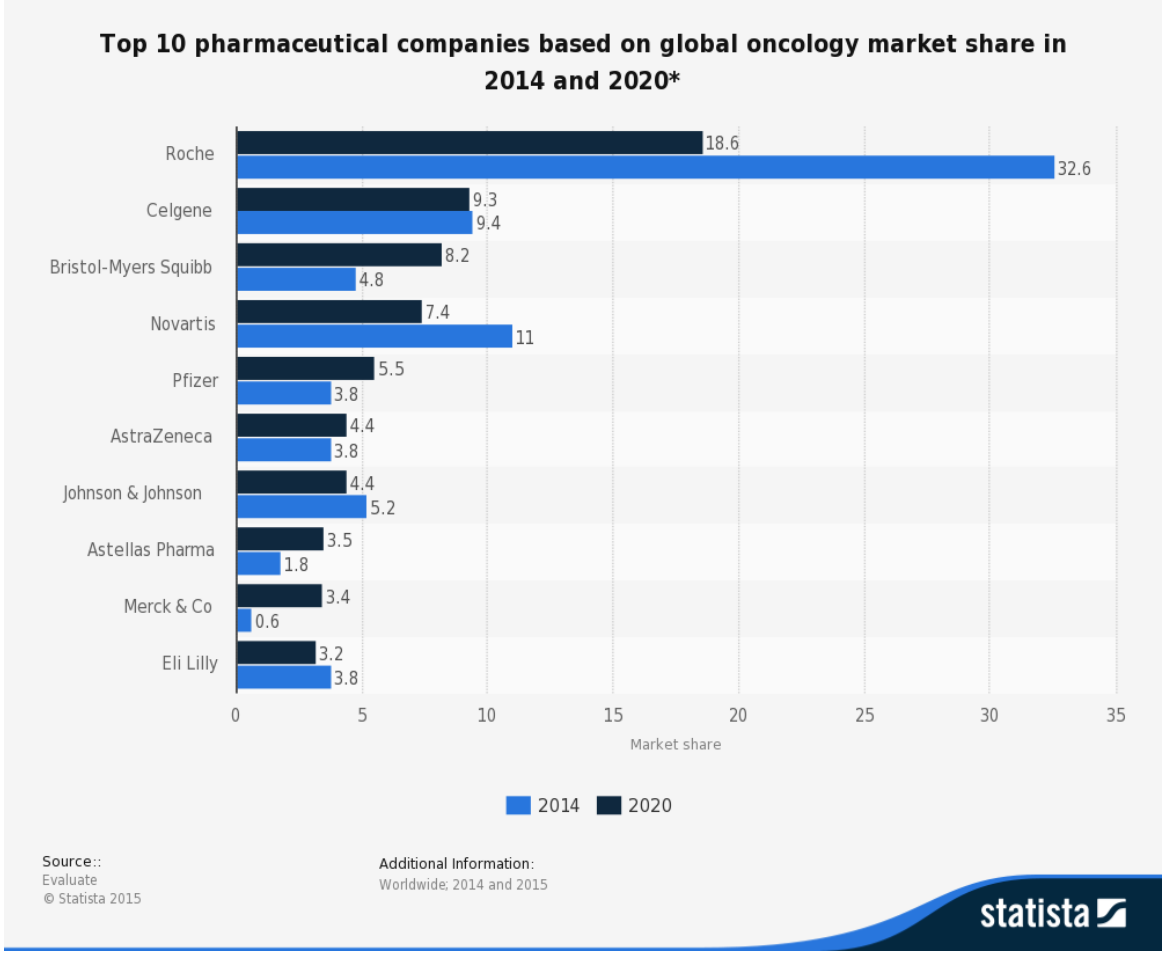
Government, Big Pharma, or… the crowd?

- 1971: USA declares "war on cancer“ and sets up National Cancer Institute
- Promise: the cure for cancer in 5 years
- 1976: No cure for cancer
- 1984: NCI promises a 50% reduction of cancer-related deaths by 2000
- 2000: only 17% reduction
- 2003: National Cancer Institute promises to cure cancer by 2015
- 2015: 1.5 new million cases of cancer and 590,000 people die of cancer in the USA

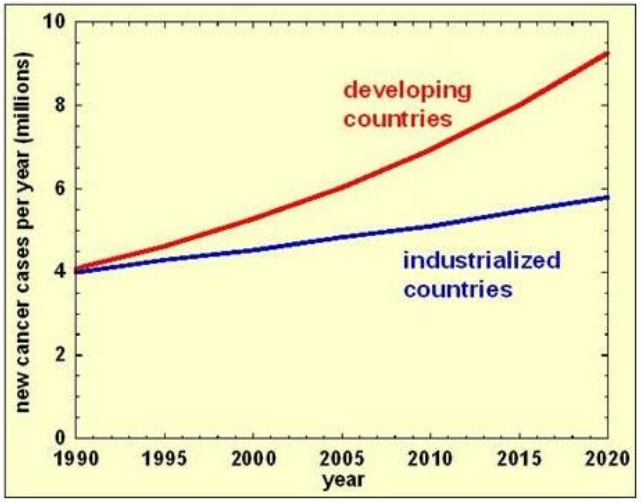


Government, Big Pharma, or… the crowd?

- Big Pharma's revenues from oncology



Number of New Cancer Cases



Government, Big Pharma, or… the crowd?

- Volunteers who pool together their computers or smartphones to allow scientists to carry out independent research on cancer
- UC Berkeley Rosetta@home
- World Community Grid (run by IBM)
- Australia's DreamLab app

Government, Big Pharma, or… the crowd?

- “Big Data" projects that collect billions of data about cancer patients
- CancerLinQ (American Society of Clinical Oncology, 2013)
- Genomics Evidence Neoplasia Information Exchange or GENIE, (American Association for Cancer Research, 2015)

ASCO®
American Society of Clinical Oncology

AACR
American Association for Cancer Research

Biohacking

www.nytimes.com/2015/04/24/health/chinese-scientists-edit-gene

Steve Fuller, author of

HEALTH | Chinese Scientists Edit Genes of Human Embryos, Raising Concerns

HEALTH

Chinese Scientists Edit Genes of Human Embryos, Raising Concerns

By GINA KOLATA APRIL 23, 2015

230 COMMENT

THE NEW YORKER

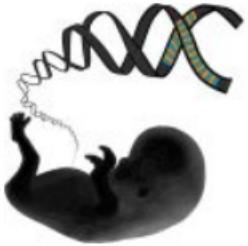
ANNALS OF SCIENCE | NOVEMBER 16, 2015 ISSUE

THE GENE HACKERS

A powerful new technology enables us to manipulate our DNA more easily than ever before.

BY MICHAEL SPECTER

FROM THREE-PERSON IVF TO GENOME EDITING



THE SCIENCE AND ETHICS OF ENGINEERING THE EMBRYO

Progress Educational Trust conference, London, 9 December 2015

Book HERE

Biohacking

- A community of worldwide hobbyists
- Public-domain databases of genetic parts
- “Open source” biotech
- Global grassroots synthetic-biology revolution

Biohacking

- BioBricks (Tom Knight, MIT, 2003)
- Registry of Standard Biological Parts (Drew Endy, MIT, 2003)
- iGEM Jamboree (Drew Endy, MIT, 2004)
- AddGene (MIT, 2004)

SBC@MIT
Synthetic Biology Center @ MIT

addgene
The nonprofit plasmid repository

A Better Way to Share Plasmids

We distribute 45,000 plasmids on behalf of 2,000 labs from around the world. Find plasmids for your next experiment.

Biohacking

- DIYbio (Boston, 2008)
- Genspace (New York, 2009)
- BossLab (Boston, 2009)
- Sage Bionetworks (Seattle, 2009)
- BioCurious (Silicon Valley, 2010)

Biohacking

- Meredith Patterson's "Biopunk Manifesto" (UCLA, 2010)
- Rob Carlson's "Biology is technology" (2010)

Biohacking

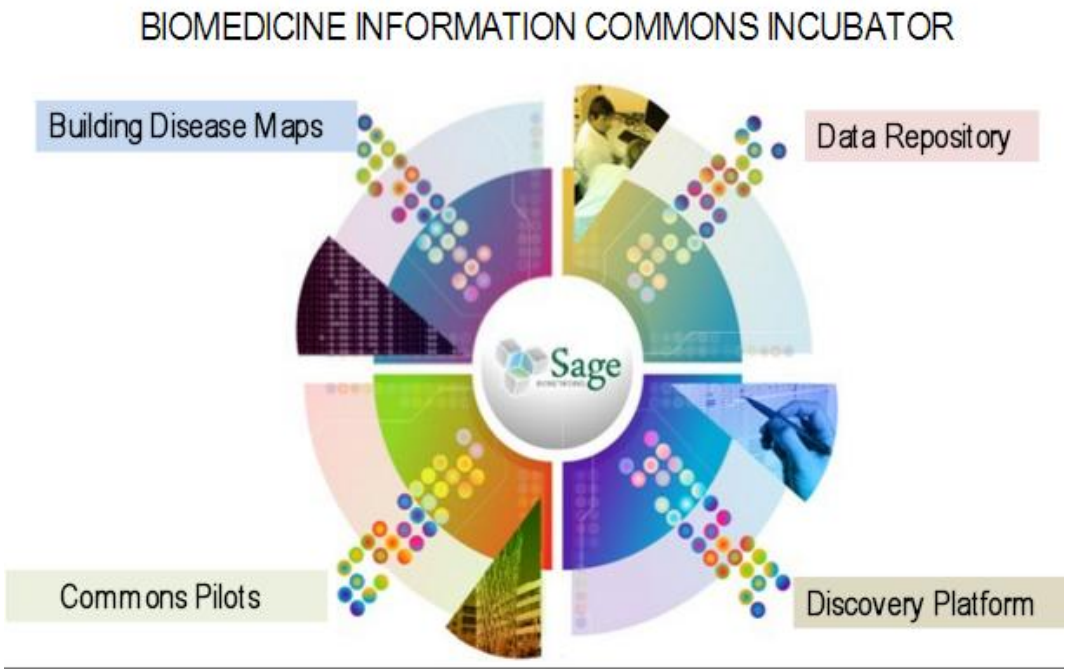
- iGEM = International Genetically Engineered Machine
- Student bioengineers from all over the world create new life forms and race them every year at the iGEM Jamboree in Boston (since 2004)
- 2014: 2,500 competitors from 32 countries
- Repository of 20,000 biological parts (biobricks)
- They create mostly microbes (e.g., organisms detecting and eliminating water pollutants)

Drew Endy (Stanford), iGEM and BioBricks Foundation

Biohacking

- Open networks of scientists and patients are needed to solve complex scientific problems
- Sage Bionetworks (Seattle, 2009): nonprofit organization that promotes open science and patient engagement
- Inspired by GitHub

Stephen Friend



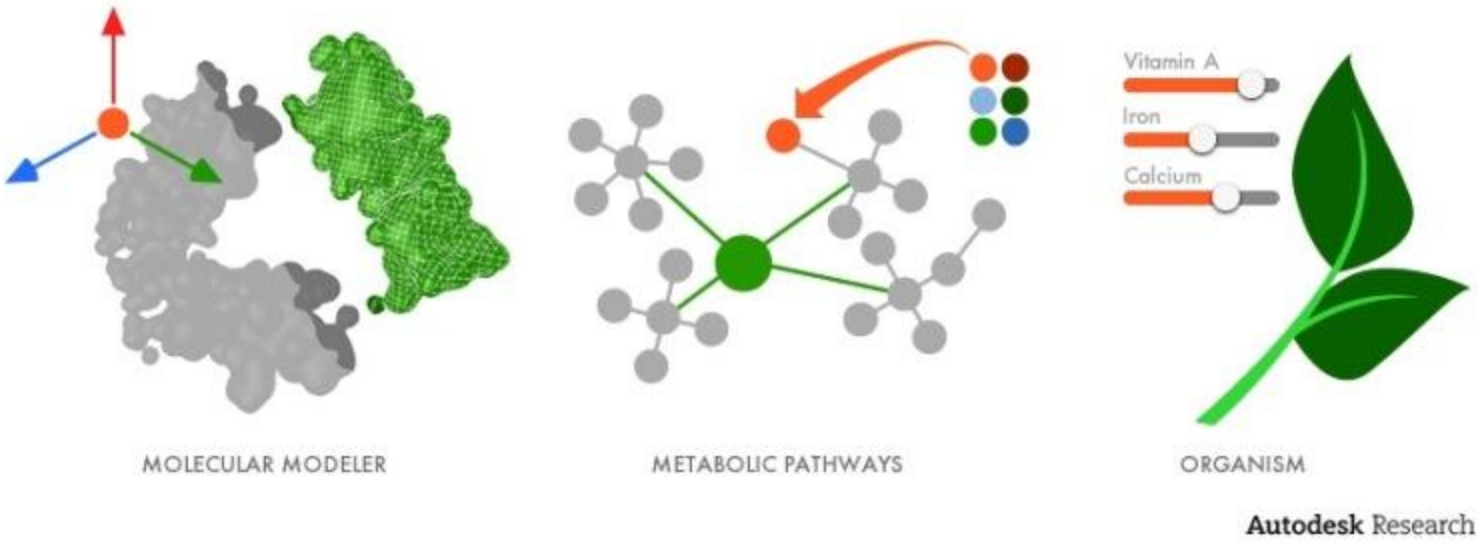
Biohacking

- PCR printers (identify a piece of DNA and make copies of it)
  - OpenPCR (cheap Polymerase Chain Reaction printer)
  - Cambrian Genomics: a laser printer for living beings

DNA LASER PRINTING.™
CAMBRIAN GENOMICS

Biohacking

- Autodesk's Project Cyborg: design tools for biohackers (quote: "Project Cyborg is a cloud-based meta-platform of design tools for programming matter across domains and scales")



Biohacking

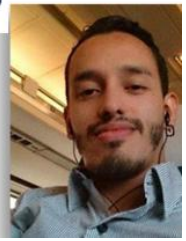
- Biohacking spaces all over the world

DIYBIO BCN
DIY BIO BARCELONA

BIOFOUNDRY
Australia

LA PAILLASSE

SynTechBio
Latin America



London Biohackspace

DIYBioBA - Biohacking Buenos Aires

Fab Lab Lima

Biohacking

- Biohacking spaces all over the world

Biohacking

DIY CRISPR Kits, Learn Modern Science By Doing

San Francisco, United States Technology

Story Updates 9 Comments 5 Backers 256 Gallery 1

If you had access to modern synthetic biology tools. what would you create?

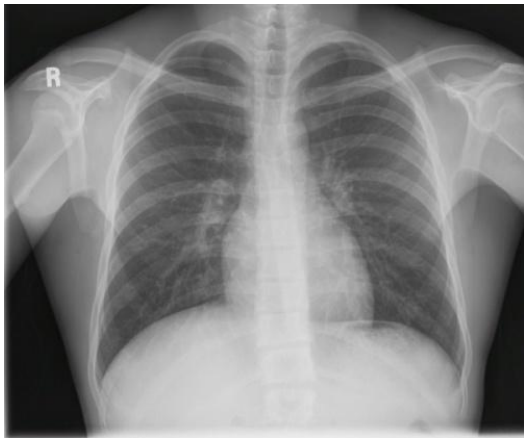
$65,554 USD
total funds raised

DIY Bacterial Gene Engineering CRISPR Kit

Jo

A.I. and Biotech

- Analysis of medical images: X-Rays, MRIs, Computed Tomography (CT), etc
- Philips Health Care: 135 billion medical images, 2 million new images every week
- Helping radiology, cardiology and oncology departments understand images



Philips and Hitachi Data Systems to deliver next-generation data management solution for healthcare organization-wide access to billions of medical images

February 18, 2016

A.I. and Biotech

- Enlitic (San Francisco): deep learning to detect lung cancer in CT images
- Arterys (Stanford StartX): deep learning to detect cardiovascular disorders in MRI scans
- A4L (Toronto): to detect heart diseases

A.I. and Biotech

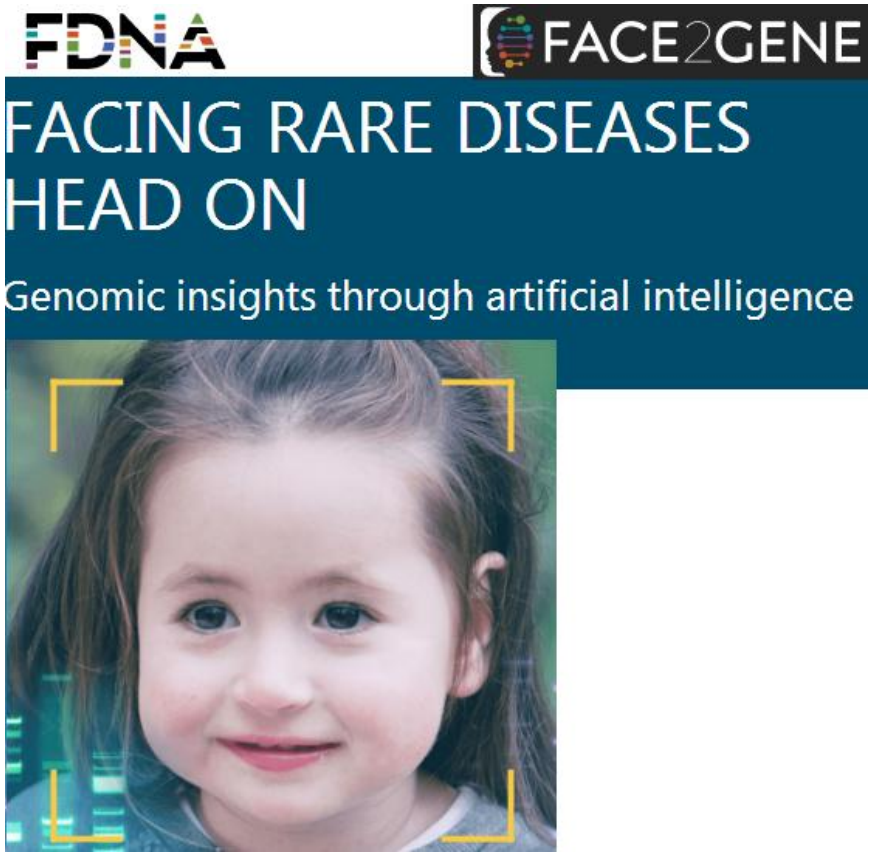
- Zebra Medical Vision (Israel): automated analysis of all medical images.
- Biogen (Boston 1978, thir d largest biotech company in the world): generate automated "risk reports" from the 1.6 billion records of genomic data that it owns.
- IBM: Watson Genomic Analysis

A.I. and Biotech

- The dream
  - to store all medical images in a cloud
  - To have the equivalent of a search engine's "spider robots" crawl this cloud and check each new image for signs of trouble.
  - automatically, all the time
  - New "releases" of the spider robots will automatically re-check all images based on whatever new medical knowledge has become available

A.I. & Biotech

- FDNA
  - Facial analysis (2011, New York)



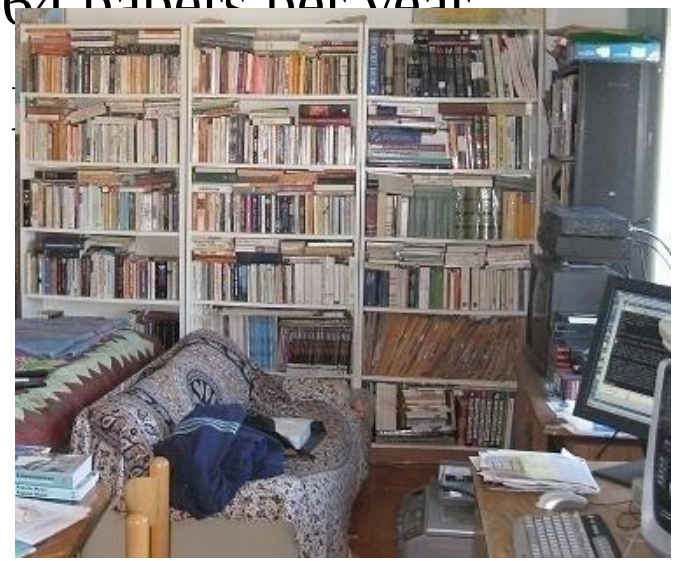
Deep Learning in Bioinformatics

Help!

- 2016: more than 1.2 million papers were published in life science journals alone, on top of the 25 million already in print
- A new article is being published every 30 seconds
- On average a scientist reads about 264 papers per year


The Greatest Web Site of All Time

but Piero Scaruffi has become an Internet destination with his ecle



Piero Scaruffi is one of the victims of information overl

Data Analytics/Diagnostics

Sophia Genetics (Switzerland)

DNAlytics (Belgium)

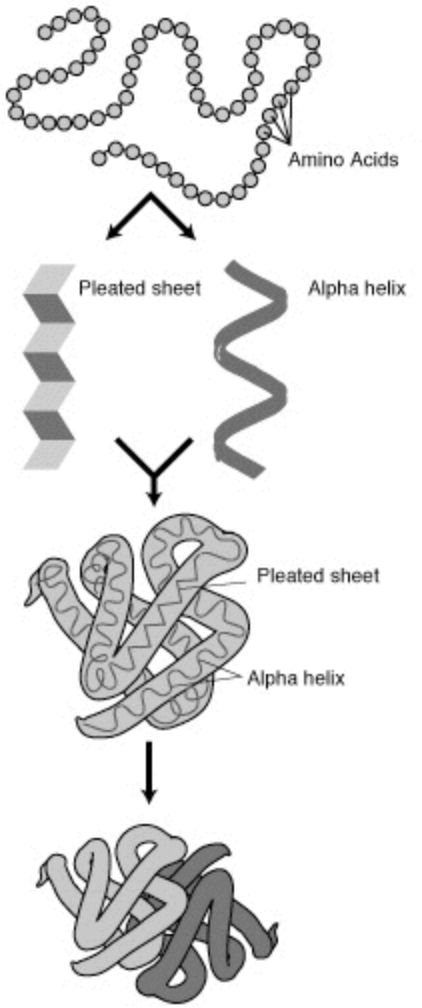
Innoplexus (Germany)

DL in Bioinformatics

- “Omics” research (genomics, transcriptomics, epigenomics, proteomics, metabolomics, etc)
  - Protein structure prediction
    - Primary structure (sequence of amino acids)
    - Secondary structure (Linus Pauling, 1951)
    - Tertiary structure (three-dimensional structure)
  - Gene expression regulation
  - Protein classification

DL in Bioinformatics

- Predicting the structure of proteins
  - Problem: tertiary structure predictions are increasingly demanded due to the rapid discovery of proteins; tertiary structure prediction depends on secondary structure prediction
  - Protein SS prediction has been extensively studiedto predict both 3-state SS and a few to predict 8-state SS



DL in Bioinformatics

- Predicting the structure of proteins
  - Ning Qian & Terrence Sejnowski (1987)
  - David Jones developed the two-stage neural network method PSIPRED (1999)

Journal of Molecular Biology

Volume 202, Issue 4, 20 August 1988, Pages 865-884

Predicting the secondary structure of globular proteins using neural network models

Ning Qian, Terrence J. Sejnowski

Department of Biophysics The Johns Hopkins University Baltimore, MD

Journal of Molecular Biology

Volume 292, Issue 2, 17 September 1999, Pages 195-202

Communication

Protein secondary structure prediction based on position-specific scoring matrices [1]

David T Jones [a] ✉

DL in Bioinformatics

- Predicting the structure of proteins
  - Three-state accuracy of SS prediction :

69.7% by PHD in 1993

76.5% by PSIPRED in 1999

80% by Structural Property prediction with Integrated Neural nEtwork (SPINE) in 2007 - Ofer Dor & Yaoqi Zhou, State University of New York at Buffalo

82% by Structural Property prediction with Integrated DEep neuRal network 2 (SPIDER2) in 2015 - Yaoqi Zhou's team, Griffith University in Australia

84% by Deep Convolution Neural Field network (DeepCNF) in 2015 –Sheng Wang and Jian Peng, University of Chicago

	Q3
Jpred4	0.751
SPINE X	0.769
PSIPRED 3.3	0.780
SCORPION	0.805
SPIDER2	0.798
PORTER 4.0	0.798
DeepCNF	0.821

DL in Bioinformatics

- Predicting the structure of proteins
  - SPIDER2 (2015)

OPEN

Improving prediction of secondary structure, local backbone angles, and solvent accessible surface area of proteins by iterative deep learning

Received: 04 March 2015
Accepted: 19 May 2015
Published: 22 June 2015

Rhys Heffernan[1], Kuldip Paliwal[1], James Lyons[1], Abdollah Dehzangi[1,2], Alok Sharma[2,3], Jihua Wang[4], Abdul Sattar[2,5], Yuedong Yang[6] & Yaoqi Zhou[4,6]

DL in Bioinformatics

- Predicting the structure of proteins
  - Problem: challenging to predict the tertiary structure of proteins that do not have a close homolog with known structure (“ab initio”); accuracy stagnated at 65%
  - Jianlin Cheng (2015, Univ of Missouri): DNSS, a deep learning approach to 3-state SS prediction
  - 1425 proteins from the Protein Data Bank

IEEE/ACM Trans Comput Biol Bioinform. 2015 ; 12(1): 103–112. doi:10.1109/TCBB.2014.2343960.

A Deep Learning Network Approach to *ab initio* Protein Secondary Structure Prediction

Jianlin Cheng
Department of Computer Science, University of Missouri, Columbia, MO 65211.

DL in Bioinformatics

- Predicting the structure of proteins
  - Jian Zhou and Olga Troyanskaya (2014, Princeton Univ): ICML2014 deep learning approach to 8-state SS prediction

---

Deep Supervised and Convolutional Generative Stochastic Network for Protein Secondary Structure Prediction

---

Jian Zhou
Olga G. Troyanskaya
Princeton University Princeton, NJ 08540 USA

DL in Bioinformatics

- Predicting the structure of proteins
  - Sheng Wang and Jian Peng (University of Chicago) in collaboration with Toyota Technological Institute (2015)
  - DeepCNF (Deep Convolutional Neural Fields) for both 3-state and 8-state SS prediction.
  - Datasets: (1) CullPDB53 of 6125 proteins, (2) CB513 of 513 proteins, (3) CASP1054 and (4) CASP1155 datasets containing 123 and 105 domain sequences, respectively, and (5) CAMEO
  - DeepCNF pushed the 8-state accuracy to beyond 70%.

Protein Secondary Structure Prediction Using Deep Convolutional Neural Fields

Sheng Wang ✉, Jian Peng, Jianzhu Ma & Jinbo Xu ✉

Scientific Reports **6**,
Article number: 18962 (2016)
doi:10.1038/srep18962

Received: 28 June 2015
Accepted: 26 November 2015

DL in Bioinformatics

- Gene expression regulation
  - Problem: DNA- and RNA-binding proteins play a central role in gene regulation and knowing their sequence is important to explain the regulatory processes and for investigating the genetic causes of diseases
  - Babak Alipanahi (2015, University of Toronto): DeepBind for DNA-protein binding
  - Training: datasets of DNA binding in vivo and in vitro + RNA binding in vitro

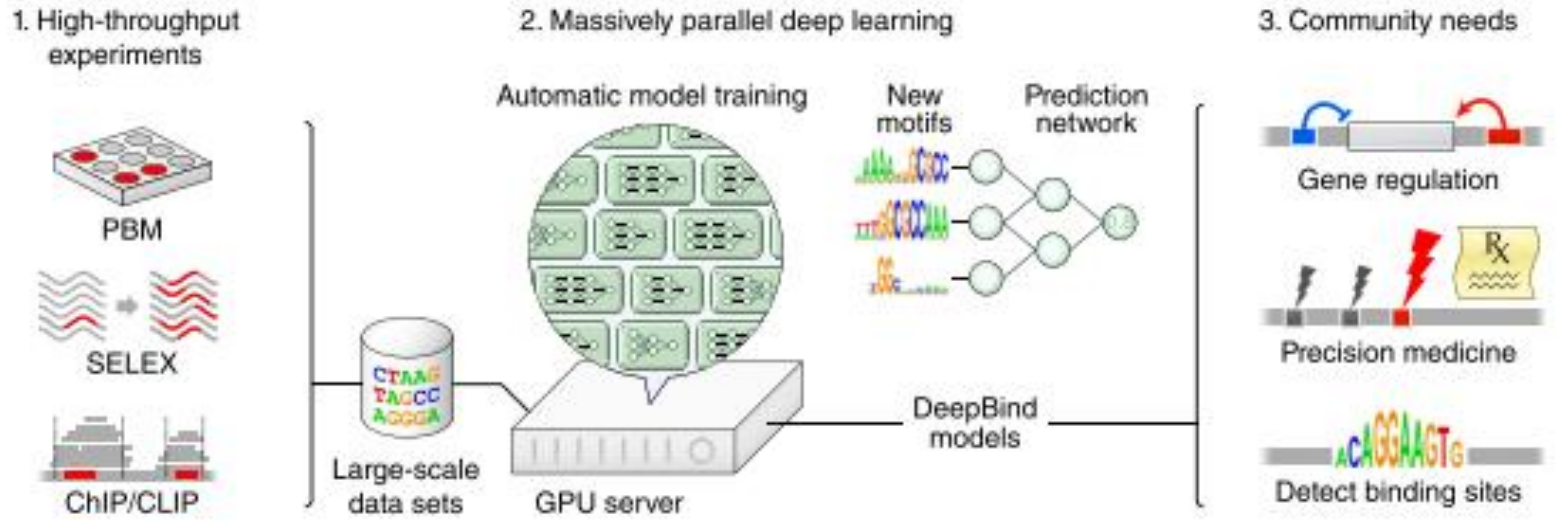
DL in Bioinformatics

- Gene expression regulation
  - Babak Alipanahi : DeepBind

Nature Biotechnology **33**, 831–838 | Received: 28 November 2014

Predicting the sequence specificities of DNA- and RNA-binding proteins by deep learning

Babak Alipanahi, Andrew Delong, Matthew T Weirauch & Brendan J Frey



DL in Bioinformatics

- The authors founded Deep Genomics (2015)…
- … it helps to have good neighbors

DL in Bioinformatics

- Gene expression regulation
  - Problem: NIH's Library of Integrated Network-Based Cellulanatures or LINCS: to save costs, profile the expression of only ~1000 landmark genes from the Connectivity Map (CMap) project and inferring the expression of remaining target genes (whose gene expression is correlated to the landmark genes) via linear regression. This way the LINCS program has generated ~1.3 million gene expression profiles, but LR ignores the nonlinearity within gene expression profiles.

DL in Bioinformatics

- Gene expression regulation
  - Xiaohui Xie (2016, UC Irvine): D-GEX to infer the expression of target genes from the expression of the "landmark" genes
  - Dataset: Gene Expression Omnibus dataset (111,000 expression profiles)

Gene expression February 3, 2016

Gene expression inference with deep learning

Yifei Chen[1,4,†], Yi Li[1,†], Rajiv Narayan[2], Aravind Subramanian[2] and Xiaohui Xie[1,3,*]

[1]Department of Computer Science, University of California, Irvine, CA 92697, USA, [2]Broad Institute of MIT And Harvard, Cambridge, MA 02142, USA, [3]Center for Complex Biological Systems, University of California, Irvine, CA

DL in Bioinformatics

- Gene expression regulation
  - Problem: regulation depends on promoters and enhancers, but detecting the locations of promoters and enhancers (a focus of bioinformatics for twenty years) is not trivial.
  - Wyeth Wasserman (2016, Univ of British Columbia): DECRES for the identification of enhancer and promoter regions in the human genome
  - Datasets: Encyclopedia of DNA Elements (ENCODE) and the Functional Annotation of the Mammalian Genome (FANTOM)

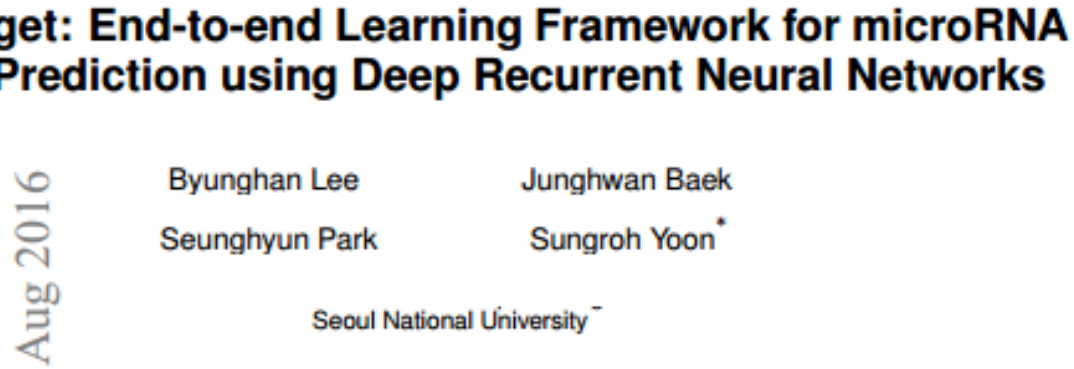
Genome-Wide Prediction of *cis*-Regulatory Regions Using Supervised Deep Learning Methods

Yifeng Li[1,2], Wenqiang Shi[1], and Wyeth W. Wasserman*[1]

[1]Centre for Molecular Medicine and Therapeutics, Child and Family Research Institute, Department of Medical Genetics, University of British Columbia, Vancouver

DL in Bioinformatics

- Gene expression regulation
  - Problem: MicroRNAs (miRNAs) are short sequences of ribonucleic acids that control the expression of target messenger RNAs (mRNAs) by binding them
  - Robust prediction of miRNA-mRNA pairs is important to understand gene regulation
  - Seoul National University (2016): DeepTarget for microRNA-mRNA prediction



deepTarget: End-to-end Learning Framework for microRNA Target Prediction using Deep Recurrent Neural Networks

Aug 2016

Byunghan Lee Junghwan Baek

Seunghyun Park Sungroh Yoon*

Seoul National University

DL in Bioinformatics

- Gene expression regulation
  - Problem: noncoding variants are statistically associated with human disease, but determining their mechanism is not trivial
  - Jian Zhou and Olga Troyanskaya (2015, Princeton Univ): DeepSEA to predict the functional effects of noncoding variants from DNA sequence

Nat Methods. 2015 October ; 12(10): 931–934. doi:10.1038/nmeth.3547.

Predicting effects of noncoding variants with deep learning–based sequence model

Jian Zhou[1,2] and **Olga G Troyanskaya**[1,3,4]

[1]Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, New Jersey, USA

[2]Graduate Program in Quantitative and Computational Biology, Princeton University, Princeton, New Jersey, USA

[3]Department of Computer Science, Princeton University, Princeton, New Jersey, USA

DL in Bioinformatics

- Gene expression regulation
  - David Kelley (2016, Harvard): open-source deep-learning framework Basset to learn functional activities of DNA sequences, annotate every mutation in the genome with its influence, etc
  - Databases from ENCODE Project Consortium and Roadmap Epigenomics Consortium

Basset: Learning the regulatory code of the accessible genome with deep convolutional neural networks.

David R. Kelley[1] Department of Stem Cell and Regenerative Biology, Harvard University,
Jasper Snoek[2]
John L. Rinn[1]

DL in Bioinformatics

- Gene expression regulation
  - Problem: RNA splicing is a critical step in gene expression whose disruption contributes to many diseases, including cancers and neurological disorders; and tens of thousands of genetic variants may alter splicing
  - Hui Xiong, Babak Alipanahi, Leo Lee (2015, Univ of Toronto) predict the splicing activity of individual exons (in particular, the genetic basis of spinal muscular atrophy, hereditary nonpolyposis, colorectal cancer and autism)

Science. 2015 January 9; 347(6218): 1254806. doi:10.1126/science.1254806.

The human splicing code reveals new insights into the genetic determinants of disease

Hui Y. Xiong[1,2,3], Babak Alipanahi[1,2,3], Leo J. Lee[1,2,3], Hannes Bretschneider[1,3,8], Daniele Merico[4,5,6], Ryan K.C. Yuen[4,5,6], Yimin Hua[7], Serge Gueroussov[2,6], Hamed S. Najafabadi[1,2,3], Timothy R. Hughes[2,3,6], Quaid Morris[1,2,3,6], Yoseph Barash[1,2,9], Adrian R. Krainer[7], Nebojsa Jojic[10], Stephen W. Scherer[3,4,5,6], Benjamin J. Blencowe[2,4,6], and Brendan J. Frey[1,2,3,4,6,8,10,@]

[1]Department of Electrical and Computer Engineering, University of Toronto

DL in Bioinformatics

- Gene expression regulation
  - Hui Xiong, Babak Alipanahi, Leo Lee (2015, Univ of Toronto)

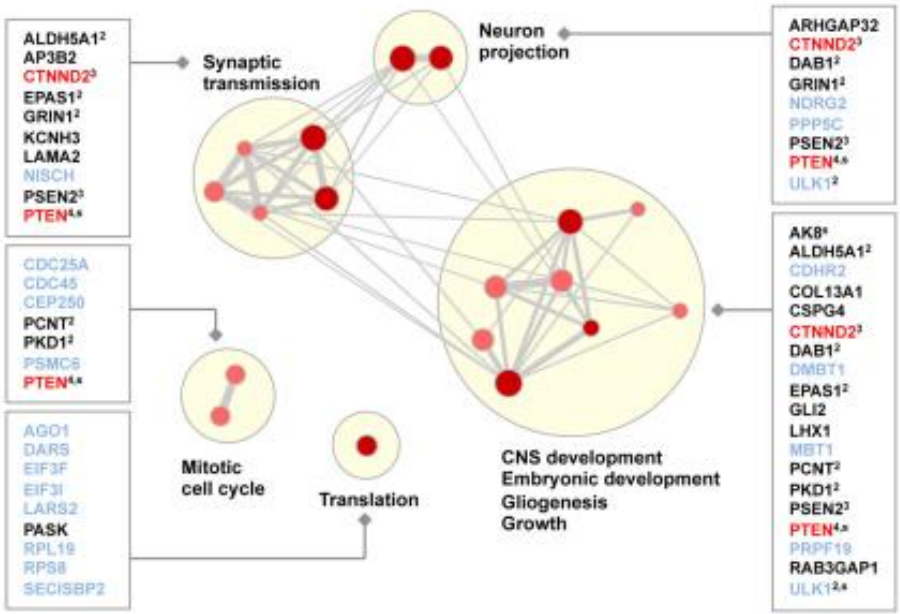


Figure 8. Misregulated genes and functional categories enriched in individuals with autism

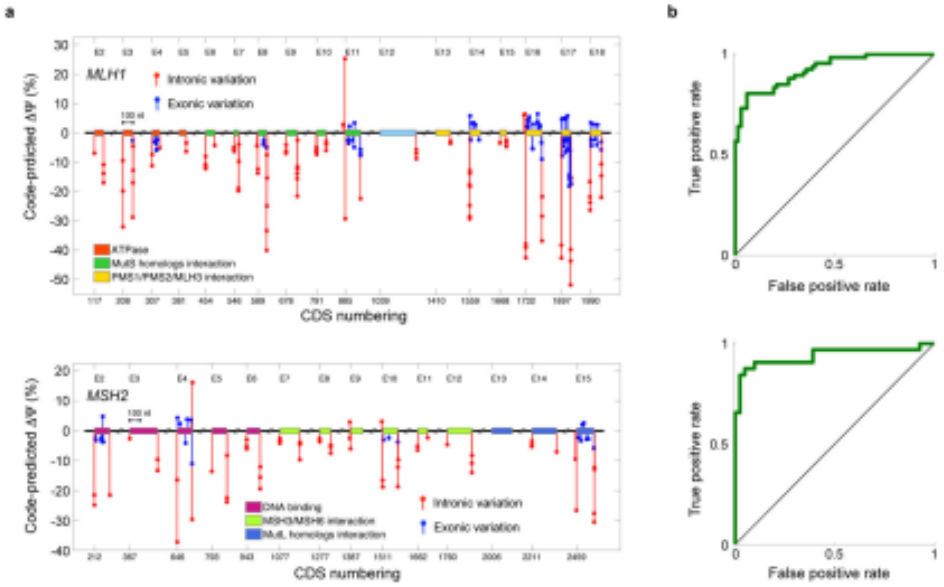
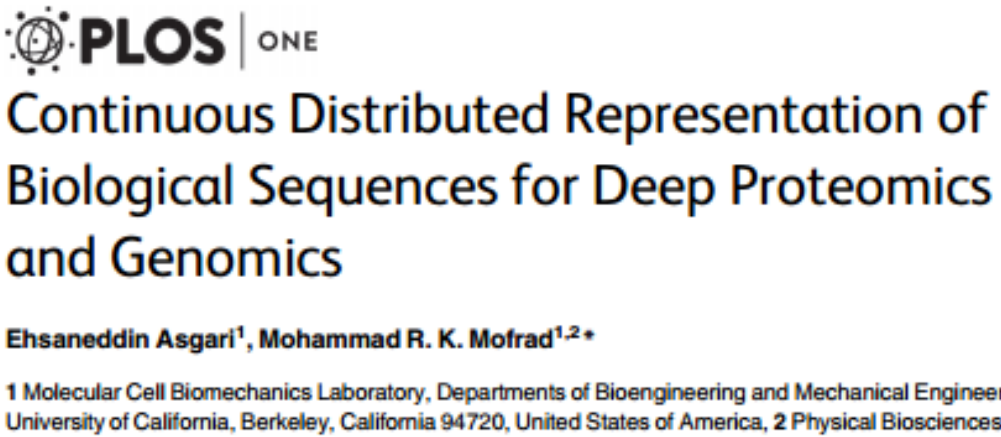


Figure 6. The mutational landscape of nonpolyposis colorectal cancer

DL in Bioinformatics

- Protein classification
  - Problem: a general representation that can be employed in a wide array of bioinformatics research such as family classification, protein visualization, structure prediction, protein-protein interaction prediction, etc
  - Ehsaneddin Asgari and Mohammad Mofrad (2015, UC Berkeley): ProtVec to classify 324,018 protein sequences from Swiss-Prot belonging to 7,027 protein families



DL in Bioinformatics

- Multitask networks for drug discovery
  - Quantitative Structure-Activity/Property Relationship (QSAR/QSPR) studies are important to predict the drug properties called ADME (absorption, distribution, metabolism and excretion).
  - George Dahl (2012, University of Toronto) wins a Merck contest with a multitask deep neural networks for classifying QSAR

Multi-task Neural Networks for QSAR Predictions

George E. Dahl

Department of Computer Science, University of Toronto

DL in Bioinformatics

- Multitask networks for drug discovery
  - Vijay Pandey's group (2015, Stanford) designs a multitask network for drug discovery that even improves as additional tasks and data are added.

Massively Multitask Networks for Drug Discovery

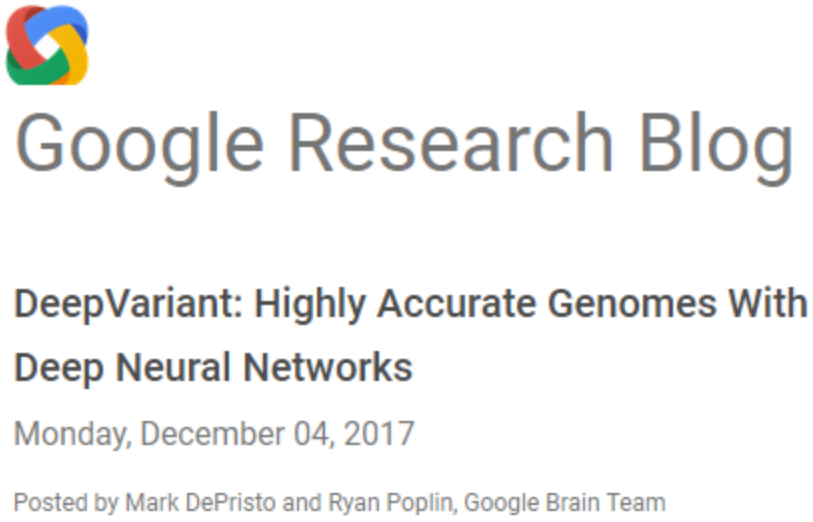
Feb 2015

Bharath Ramsundar[*,†,°]
Steven Kearnes[*,†]
Patrick Riley[°]
Dale Webster[°]
David Konerding[°]
Vijay Pande[†]
([*]Equal contribution, [†]Stanford University, [°]Google Inc.)



DL in Bioinformatics

- Tools to interpret your genome:
- GATK
- VarDict
- FreeBayes
- Google DeepVariant (2017)
- Problem: Processing the high-throughput sequencing output into a single, accurate and complete genome sequence



Designing Babies

1978: First baby born via IVF (in vitro fertilization)

1990: First baby born via PGD (Alan Handyside's lab)

Two ways to create human stem cells

Shinya Yamanaka (2007)

Shoukhrat Mitalipov (2013)

Basically, it's a way to turn back the biological clock: the DNA of the cell is reprogrammed to the embryonic state

Designing Babies

Rabinowitz-S[illegible] PGD (2015)

Published online 2015 Apr 8.
doi: 10.1186/s13073-015-0160-4

Whole genome prediction for preimplantation genetic diagnosis

Akash Kumar,[#] Allison Ryan,[#] Jacob O Kitzman, Nina Wemmer, Matthew W Snyder, Styrmir Sigurjonsson, Choli Lee, Milena Banjevic, Paul W Zarutskie, Alexandra P Lewis, Jay Shendure,[✉] and Matthew Rabinowitz[✉]

Designing Babies

Katsuhiko Hayashi (2015): IVG on mice ("easy PGD"): we can make eggs and sperm from skin cells

九州大学
KYUSHU UNIVERSITY

Designing Babies

HumanCode (2017, Denver):
predict babies' height without AI

Stephen Hsu (2017): predict babies' height with AI

Physicist Stephen Hsu developed a genetic "predictor" that uses machine learning to estimate height, to within three centimeters, from a person's DNA.
MICHIGAN STATE UNIVERSITY

Accurate Genomic Prediction Of Human Height

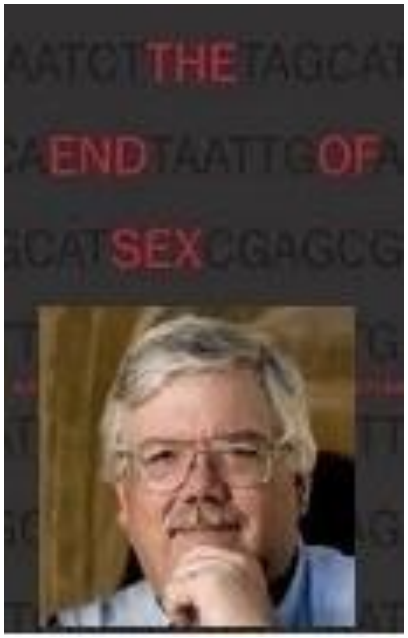
Louis Lello, Steven G. Avery, Laurent Tellier, Ana Vazquez, Gustavo de los Campos, Stephen D.H. Hsu

(Submitted on 19 Sep 2017)

Will A.I. help parents "design" their babies?

MIT Technology Review by Antonio Regalado November 1, 2017

Eugenics 2.0: We're at the Dawn of Choosing Embryos by Health, Height, and More



Hank Greely

Science Translational Medicine

Disruptive reproductive technologies

. Glenn Cohen[1,*], George Q. Daley[2,3] and Eli Y. Adashi[4]

NAUTILUS OCTOBER 16, 2014

Super-Intelligent Humans Are Coming

Genetic engineering will one day create the smartest humans who have ever lived.

BY STEPHEN HSU

MICHIGAN STATE UNIVERSITY

Drug Discovery

According to the Tufts Center for the Study of Drug Development, it takes an average of 12 years and about $2.6 billion to put a new drug on the market.

Drug Discovery

Automating and accelerating the process of drug discovery

Drug Discovery

Rein Vos' *"The Enigma of Drug Discovery"* shows that the process of drug discovery can be modeled, and therefore automated

Can it be accelerated?

Can we design better molecules, enzymes, peptides to cure diseases?

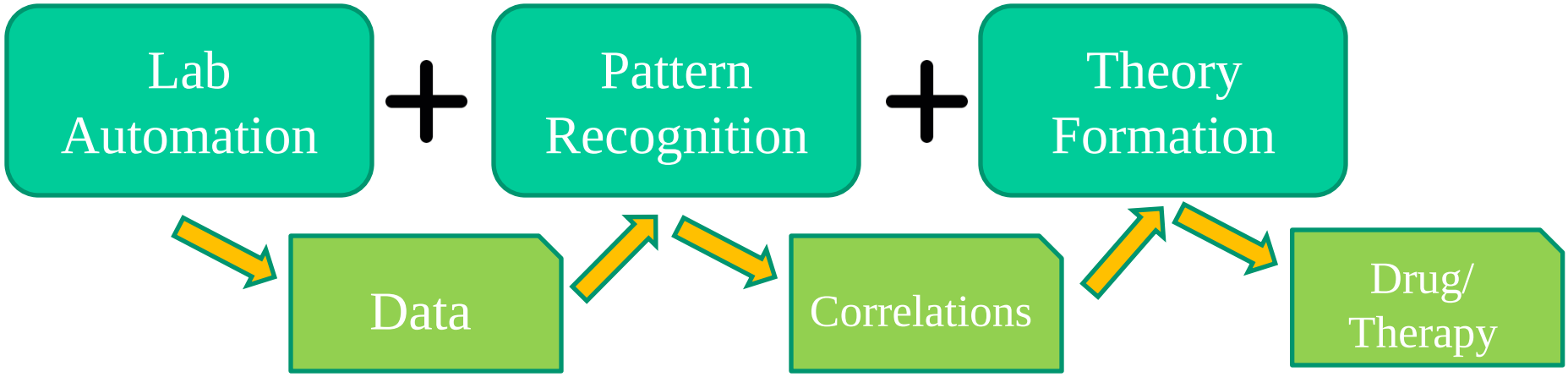
OXFORD GLOBAL

Artificial Intelligence in Drug Development Congress

27-28 September 2017, London, UK

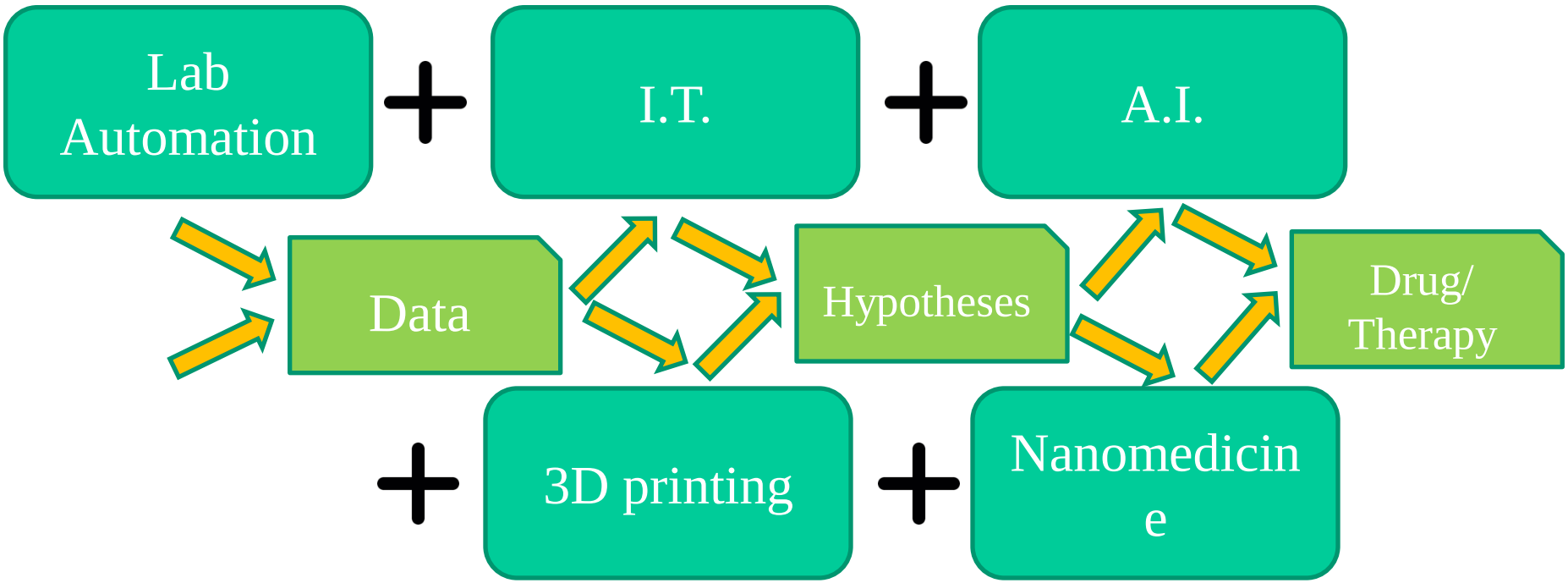
Drug Discovery

Automation and acceleration of drug discovery



Drug Discovery

And maybe even…



Drug Discovery

- Exscientia (Britain)
- Berg (Boston)
- Numerate (Bay Area)
- BenevolentAI (Britain)
- Atomwise (San Francisco)
- Insilico Medicine (Baltimor
- Desktop Genetics (B
- Sophia (Switzerland)
- PathAI (Boston)
- Recursion (Utah)
- Insitro (Bay Area)

Drug Discovery

- Exscientia (2012, Britain): rapid-prototyping platform that automates drug design via an expert system that is equipped with a repertory of best practices acquired from experts of the sector. This system can design millions of novel compounds and calculate for each how effective it is likely to be for a specific project. Then it can select the best ones for experiments.
- Collaborations with GSK, Sanofi and Evotec

Drug Discovery

- Atomwise (2012, San Francisco): neural network AtomNet to combine millions of molecular structures and infer the most likely to target a disease
- Working with IBM Watson
- Projects ranging from multiple sclerosis to ebola
- Collaborations with Merck

Merck is working with Atomwise to explore the frontiers of drug discovery using artificial intelligence and machine learning.

TC

YC Alum Atomwise Raises $6 Million To Further The Advancement Of Artificial Intelligence In Drug Discovery

Posted Jun 3, 2015 by Sarah Buhr (@sarahbuhr)

Drug Discovery

- BenevolentAI (2013, Britain)
  - Analyzing scientific papers
  - Nvidia's DGX-1 supercomputer
  - $800 million deal in 2014 to deliver two Alzheimer drug candidates to bigpharma
  - 2017: 24 drug candidates

Drug Discovery

- Berg (2006, Boston): analyze genomic and clinical data about a disease and then infers the network of protein interactions that cause the disease
- Collaboration with AstraZeneca (2017) to discover new treatments for Parkinson's disease and other neurological disorders.

REUTERS
AUGUST 28, 2017

AstraZeneca

AstraZeneca taps AI for drug discovery in deal with Berg

BERG
BERG
Back to Biology for a Healthier Tomorrow

Drug Discovery

- Insitro (South San Francisco, 2018)

insitro

Daphne Koller

Gilead Sciences, insitro Launch Up-to-$1B+ AI-Based NASH Drug Collaboration

April 16, 2019 0

Stealthy Insitro opens up—starting with Gilead deal worth up to $1.05B

by Amirah Al Idrus | Apr 16, 2019 7:00am

Drug Discovery

- Desktop Genetics

Drug Discovery

- Insilico Medicine (2014, Baltimore)
  - looks at drugs that are already safe to use and see if they can be re-purposed for other uses

Drug Discovery

- TwoXAR (Silicon Valley, 2014): identified a potential drug for liver cancer in just four months by screening 25,000 potential candidates in a joint project with Stanford (the only treatment approved by the FDA took five years to develop).

Drug Discovery

- Numerate (2007, Bay Area) can “virtually assay 25 million compounds from a library of 1 trillion compounds against a handful of accurate activity, selectivity and ADME models at a cost of one-one hundredth of a penny per compound, in about one week”

Drug Discovery

- Recursion (2013, Utah): computer vision to look at cells and analyze more than 1,000 features to determine whether a sick cell is being "cured" by the compounds that it massively produces.
- image-processing software developed by Anne Carpenter at the Broad Institute
- committed to discovering 100 disease treatments by 2025
- 2017: identified 15 potential treatments for rare diseases
- 2016: partnership with Sanofi

Drug Discovery

- BioAge Labs (2015, Berkeley): accelerate a the discovery of drugs for longevity

Drug Discovery

- PathAI (2016, Boston): end-to-end data-driven pathology analysis + clinical decision support tools
- Andrew Beck at Stanford built one of the earliest A.I. systems for cancer pathology
- Working with Philips to diagnose breast cancer

Andrew Beck
Aditya Khosla

PathAI

PHILIPS

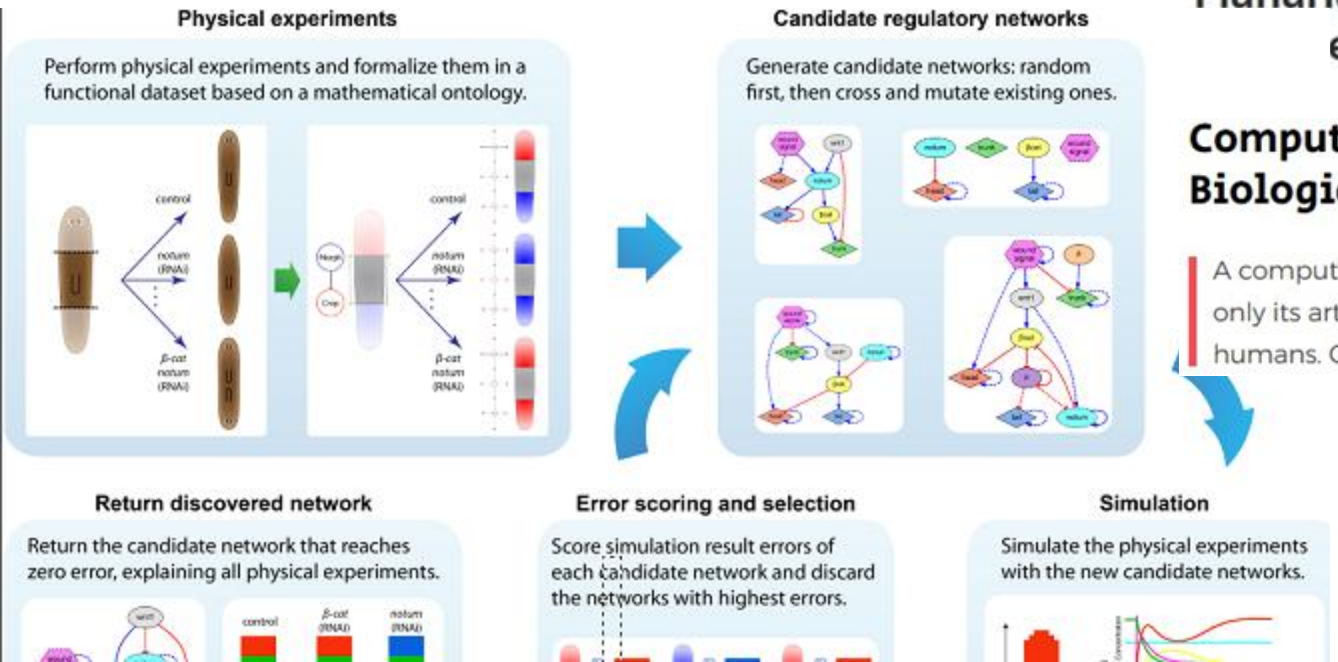
News center

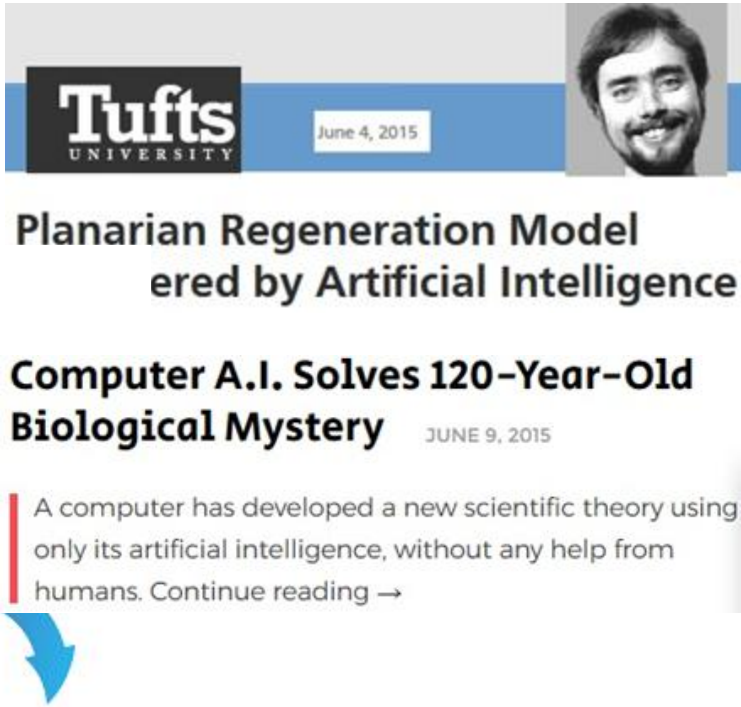
March 29, 2017

Philips and PathAI team up to improve breast cancer diagnosis using artificial intelligence technology in 'big data' pathology research

Drug Discovery

- 2015: Michael Levin's evolutionary algorithm reverse-engineers the regeneration mechanism of planaria (which had eluded human scientists for over 100 years)
- Planaria can regenerate its organs





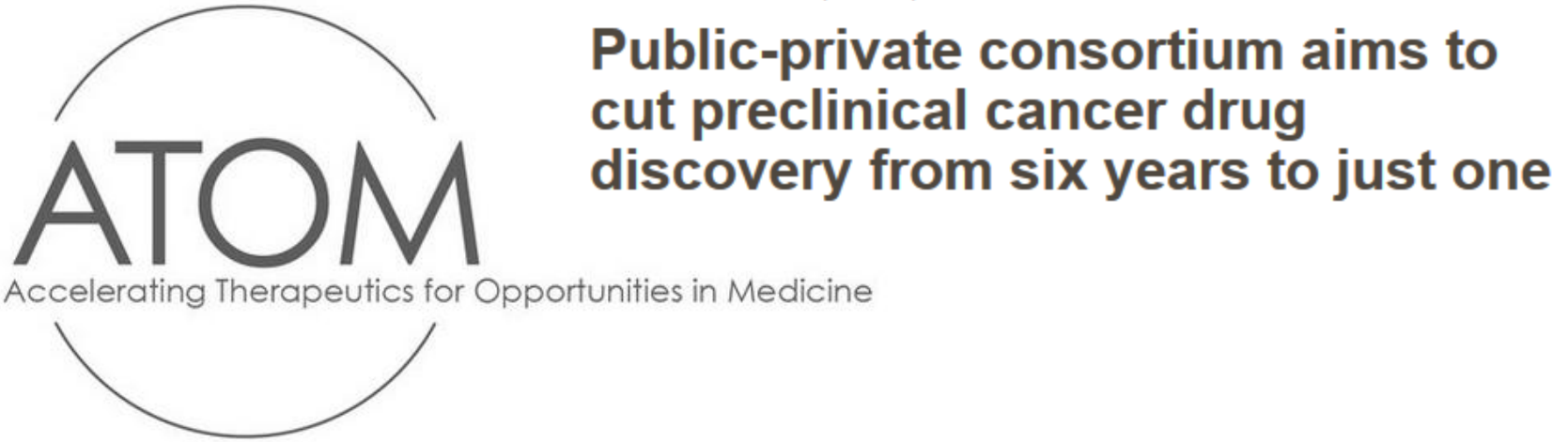
Drug Discovery

- 2016: IBM Watson discovers ALS genes
- It analyzed all published literature related to ALS and ranked genes based on the probability that they would be responsible for the proteins known to be associated with the disease: eight of the top ten genes are indeed associated with the disease, and five of them were previously not suspected.

Barrow Neurological Institute

Drug Discovery

- 2017: GlaxoSmithKline + Lawrence Livermore Lab + National Cancer Inst form ATOM consortium to transform drug discovery from the slow, sequential and failure-prone process that is today into a rapid and accurate process (from target to patient-ready in less than one year).



Drug Discovery

- 2017: First A.I. based system approved by FDA (a medical imaging platform by Arterys to detect heart problems)
- Not quite "biotech", but an important first step towards accepting A.I. as a "cure".

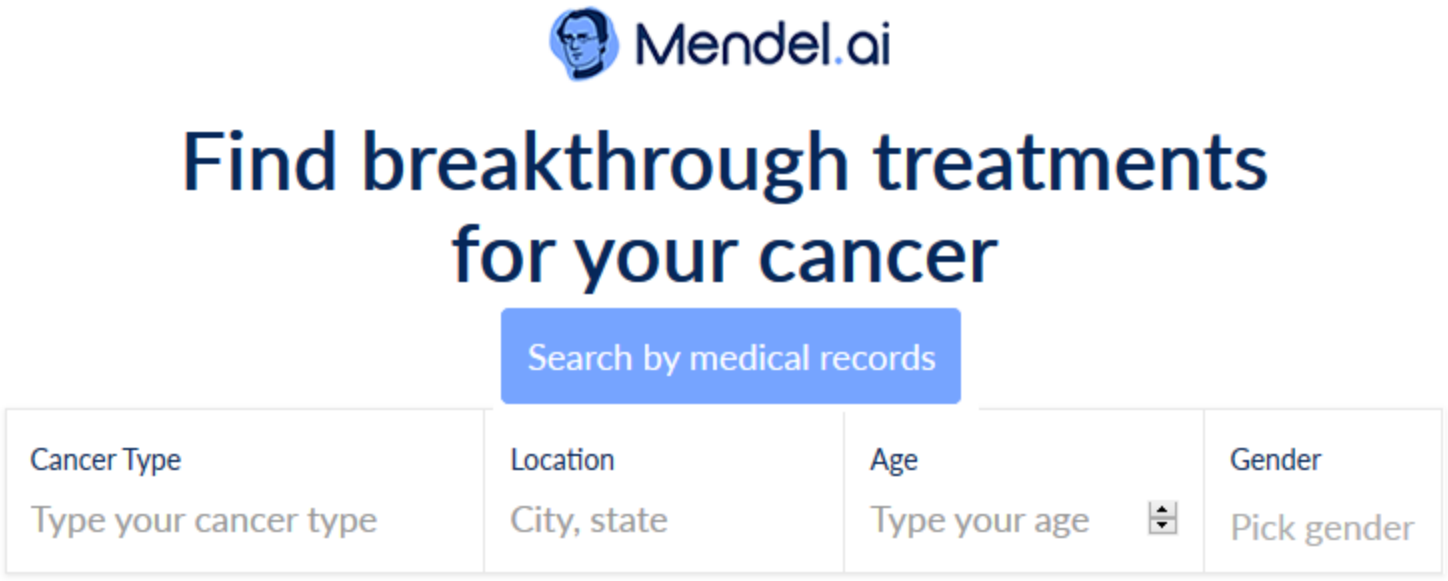
Towards Precision Medicine

A.I. could mark the end of the mass-produced drug

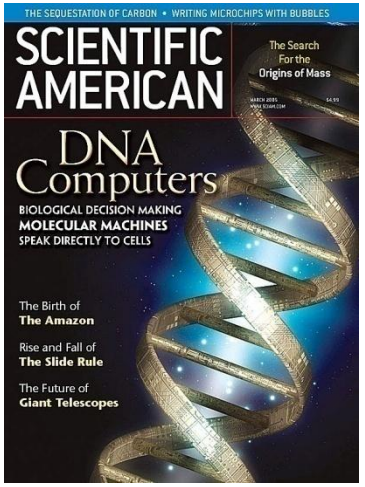
It could discover the specific drug that works best for your specific case

Towards Precision Medicine

- Mendel.ai (2016, San Francisco): provide customize treatments to cancer patients based on the latest published data (NLP tech to analyze medical publications and ANN to compare content with a patient's medical record)



DNA Computing



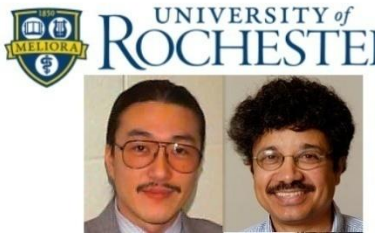
- DNA is a natural substance for computing
- You can encode a string of data in the sequence of nucleotides and use the properties of DNA to do the calculation.
- 1994: Leonard Adleman (Univ of Southern California) creates a DNA computer
- 1995: Richard Lipton (Princeton Univ): computational power of DNA (a DNA computer can break NSA's encryption)

USC University of Southern California

PRINCETON

DNA Computing

- 1999: Mitsunori Ogihara and Animesh Ray (Univ of Rochester): "Simulating Boolean Circuits on a DNA Computer"
- 1999: Ehud Shapiro (Israel): "A Blueprint for a Biomolecular Computer".
- 2002: First practical DNA computer (Akira Suyama)
- 2013: Drew Endy's biocomputer

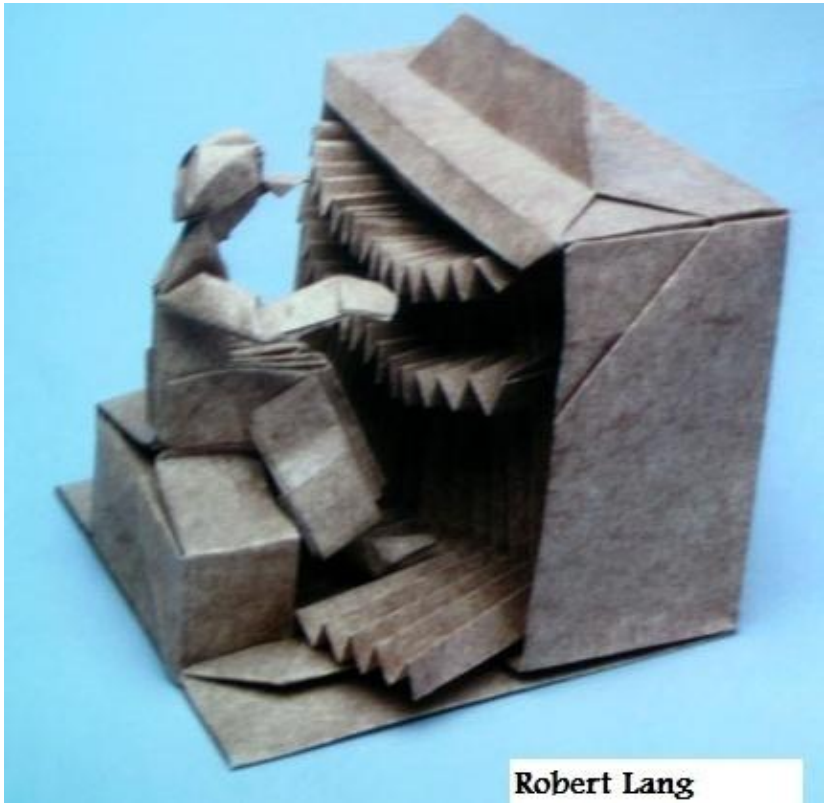


DNA Computing

- Difference with electronic computers
  - Biocomputers are slow but…
  - Biocomputers can interact naturally with living systems
  - Biocomputers can be deployed in places where electronics cannot be deployed
  - Biocomputers can be deployed in the body and act like sentinels

DNA Origami

- Bottom-up nanomanufacturing



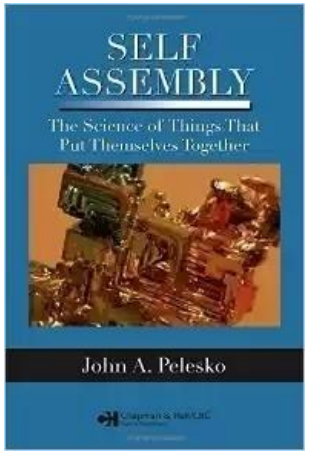
Self-assembly of DNA into nanoscale three-dimensional shapes

Shawn M. Douglas, Hendrik Dietz, Tim Liedl, Björn Högberg, Franziska Graf, & William M. Shih

Nature. 459:414–8. 21 May 2009.

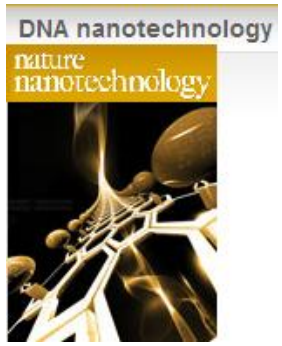
DNA Origami

- Ned Seeman (NYU, 2005): “From genes to machines - DNA nanomechanical devices”
- Paul Rothemund (CalTech, 2006): self-assembly of DNA molecules
- John Pelesko’s “Self Assembly” (2007)



DNA Origami

- Nature Nanotechnology's special section (2009)
- William Shih (Harvard): "Self-assembly of DNA into nanoscale three-dimensional shapes" (2009)
- Tim Liedl (Munich): "Self-assembly of DNA into nanoscale three-dimensional shapes" (2009)
- Shawn Douglas (UCSF): first BioMod (Bio-Molecular Design Competition) at Harvard (2011)
- Hiroshi Sugiyama (Kyoto University): "DNA origami technology for biomaterials applications" (2012)



BIOMOD
WYSS INSTITUTE

DNA Origami

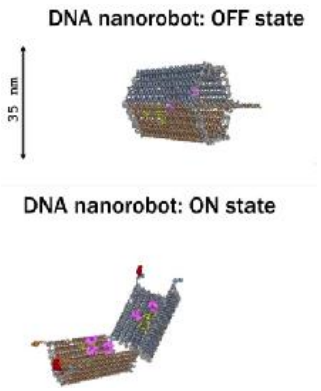
- George Church (Harvard): DNA originami nanobot (2012) with Shawn Douglas and Ido Bachelet
- Daviel Levner (Harvard) & Ido Bachelet (Israel): DNA origami robot in living being (2014)
- Ido Bachelet (Israel): Human trial of DNA origami nanobot & partnership with Pfizer (2015)

December 27, 2014

Ido Bachelet announces 2015 human trial of DNA nanobots to fight cancer and soon to repair spinal cords

May 15, 2015

Pfizer partnering with Ido Bachelet on DNA nanorobots



DNA Origami

- Open-source software
  - CADnano (William Shih, 2009 + Autodesk + Harvard + UCSF…): Rapid prototyping of 3D DNA origami shapes
  - CanDo (MIT, Mark Bathe, 2011): Computer-aided engineering for DNA origami - can convert a 2-D DNA origami blueprint into a complex 3-D shape

cadnano

DANA-FARBER CANCER INSTITUTE

AUTODESK. RESEARCH

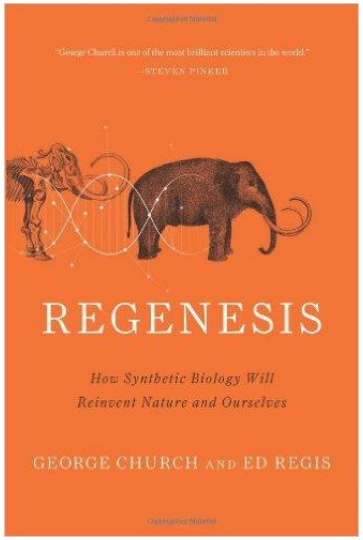
CanDo

MIT

DNA Origami

- Open-source software
  - Hao Yan (Arizona State Univ, 2009): Tiamat, a 3D editing tool for complex DNA structures
  - Cello (MIT, William Voigt, 2016): programming language to design DNA circuits

DNA Origami



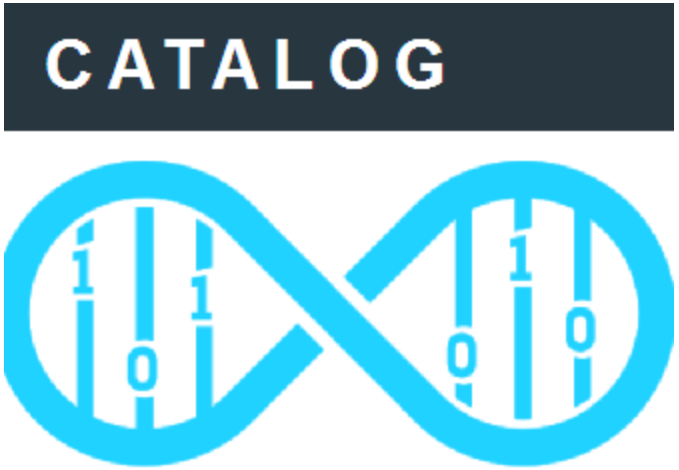
- DNA storage
  - Slow but lasts tens of thousands of years
  - 2012: George Church encodes his latest book into DNA.
  - 2013: Ewan Birney (European Bioinformatics Institute) encodes 739 Kbytes in DNA
  - 2014: Ok Go record an album on DNA
  - 2016: Microsoft & Univ of Washington

DNA Origami

- DNA storage
  - Cost: $12,000 per Mbyte using machines that cost millions of dollars…
  - … vs my 16Gbyte flash drive that cost $20, and it costs zero to rewrite the information on it…
  - … but all texts of human civilization (50 billion Mbytes) can be stored in the palm of your hand.

DNA Origami

- DNA storage
  - Catalog DNA (Boston, 2016)

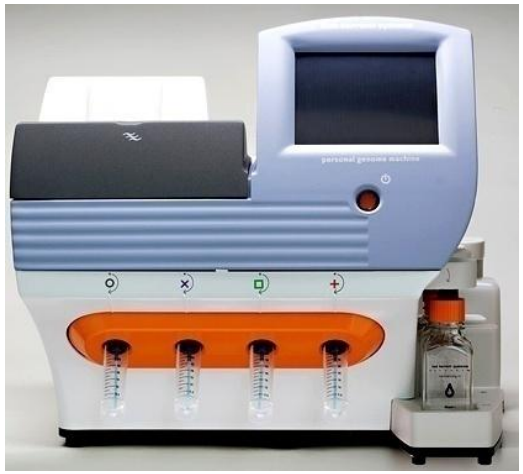


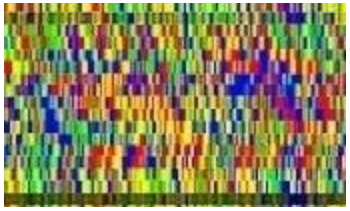
DNA Origami

- The dream
  - DNA origami robots traveling nonstop around your body and communicating with each other
  - Run some A.I. program on them so that they can monitor and interpret what is happening inside your body in real time

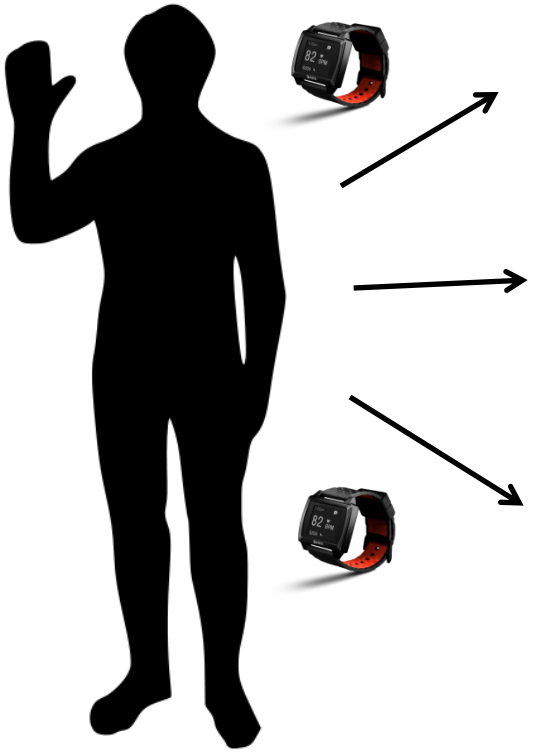
Big Data and Wearables in Biotech

1) DNA Sequencing

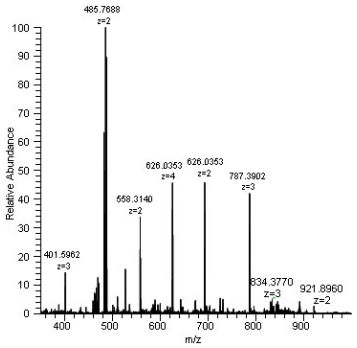




2) Wearables



3) Mass Spectrometry



Predispositions due to mutations

ABCC8: Hyperinsulinemic hypoglycemia

APC: Colon cancer

BRCA1: Breast & ovarian cancer

CHEK2: Breast cancer

HNF1A: MODY mutation

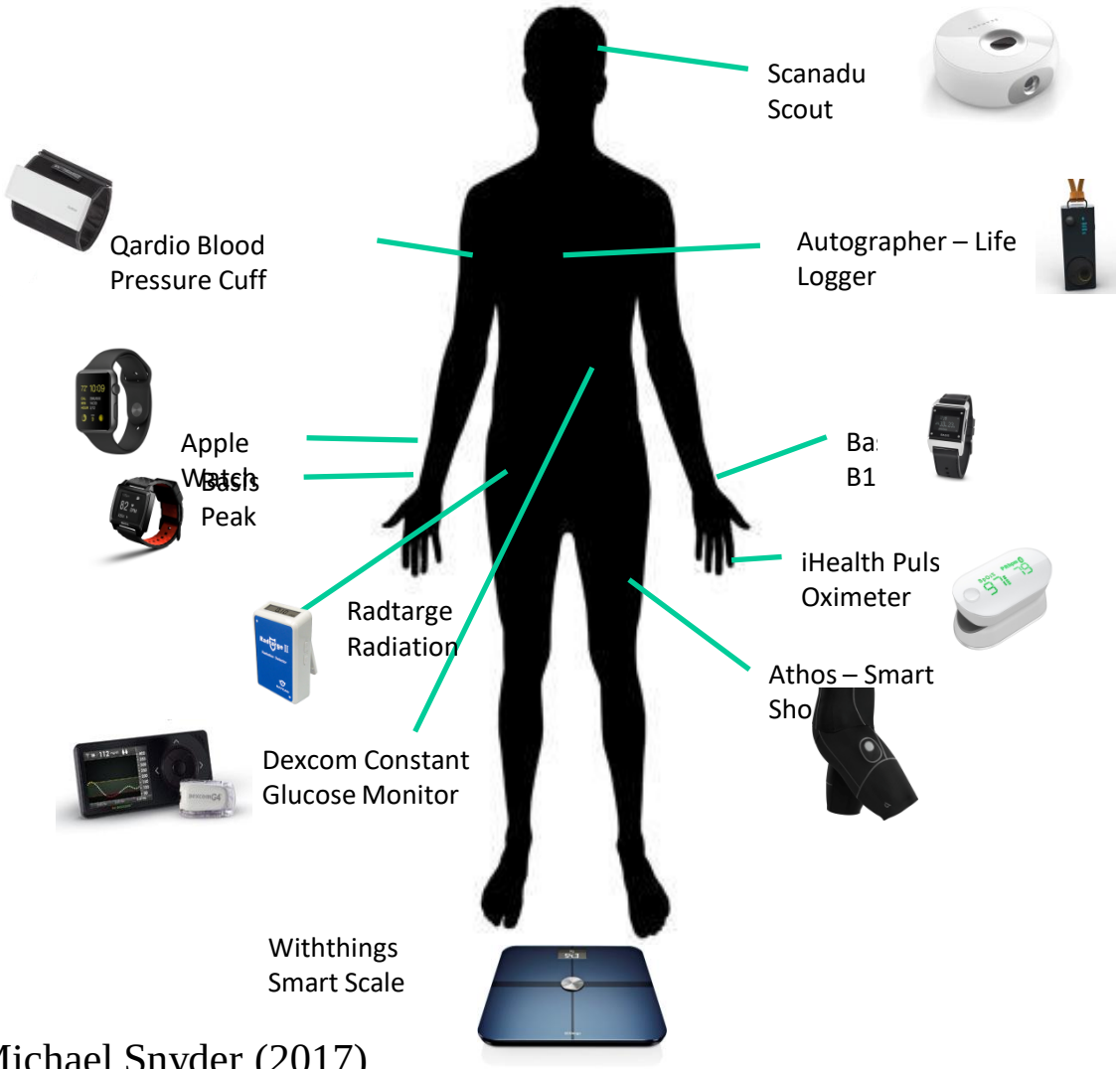
MUTYH: Colon cancer

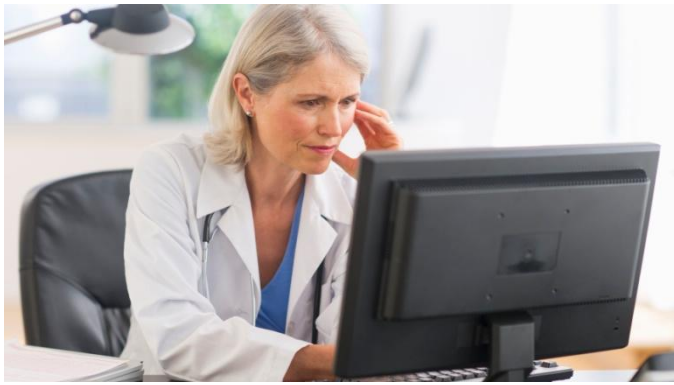
PROC: Affects coagulation

RBM20: Dilated cardiomyopathy

SLC7A9: Cystinuria

Biosensors





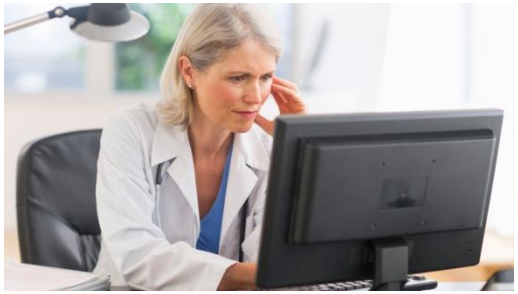
Michael Snyder (2017)

Data-driven Health Control

Genome

Exercise

Molecular Info

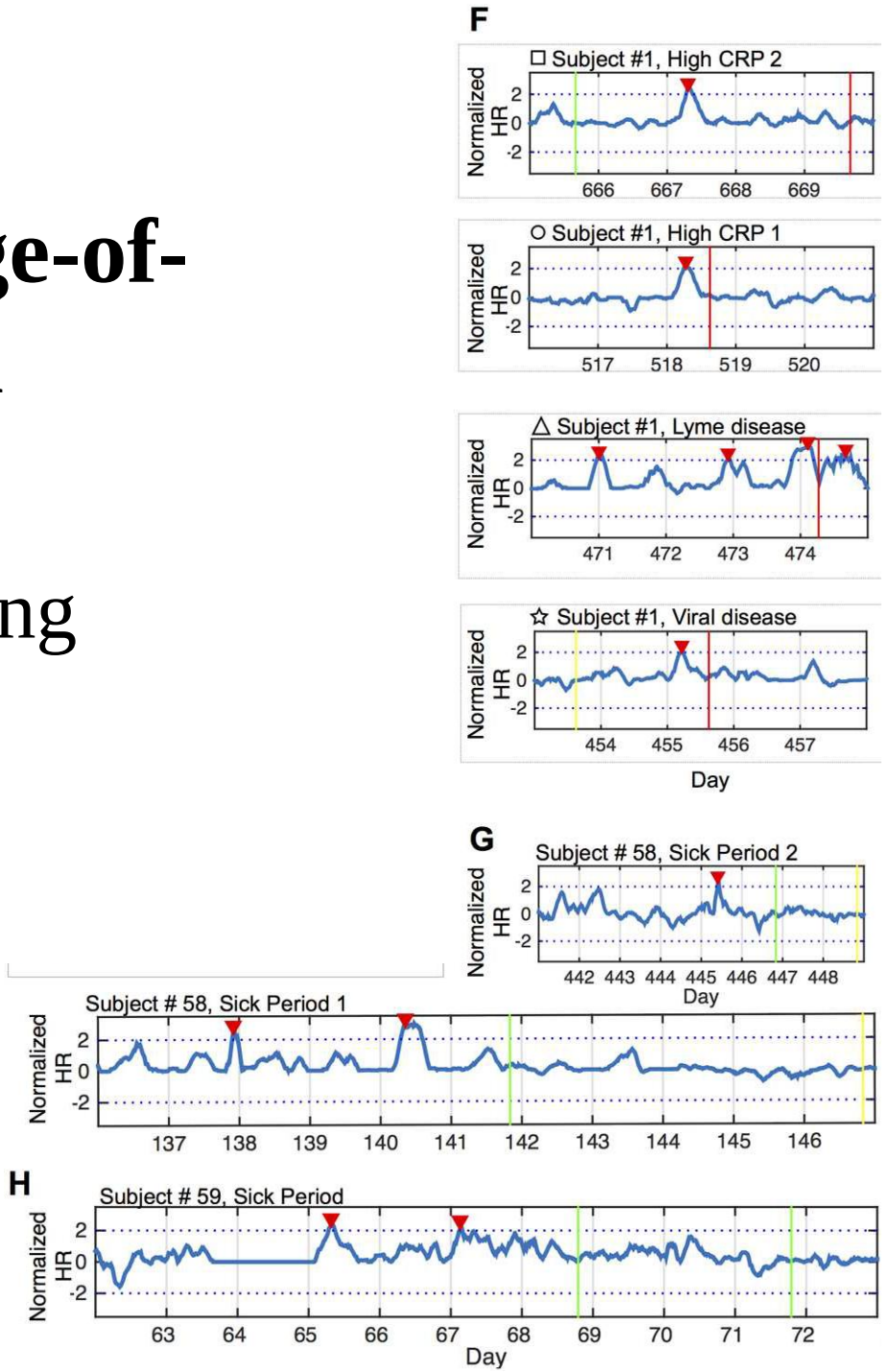


Diet

Michael Snyder (2017)

Example: Change-of-Heart Algorithm

Detecting illness using wearable devices



Li, Dunn et al.
PloS Biol 2017

Expanding the Genetic Alphabet

- 2014: Floyd Romesberg at the Scripps Research Institute in San Diego expands life's genetic alphabet with two new bases in a living bacterium

SCRIPPS

Dangers

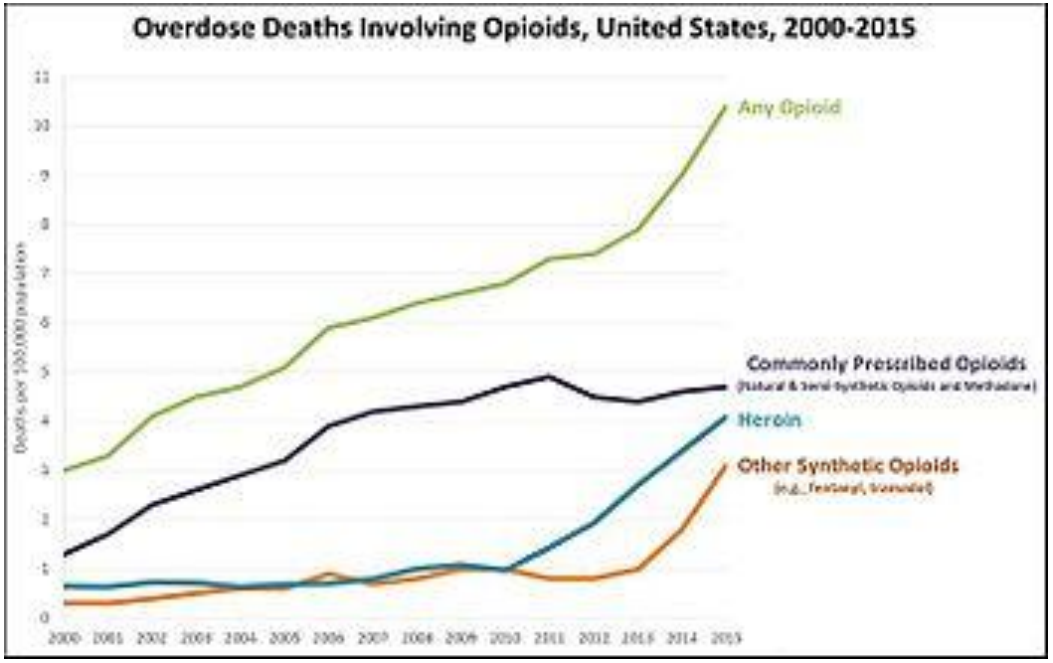
- The "undo" command doesn't exist in biotech. Biohackers may create something that will not be easily "undone".
- Who am i? Is it ok to change one of my genes or reprogram one of my cells? Am I still me? Would you like a brain transplant? Would you like a genome transplant?
- We still know very little about genomics. The human genome contains 25,000 genes, but rice contains 50,000. So a grain of rice is more complex than me?

Dangers

- I am not afraid of Biotech.
- I am afraid of
  - Pesticides
  - Infectious diseases (flue, malaria, ebola, AIDS, sika…)
  - Cancer
- Biotech can eliminate all of these.

Dangers

- Unfortunately we are also afraid of Big Pharma…



Dangers

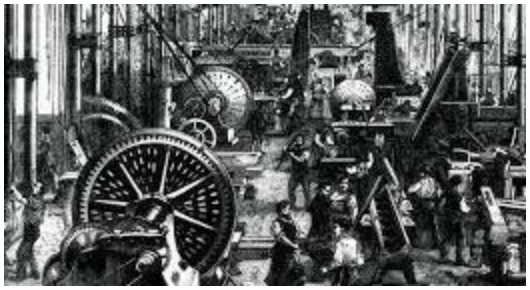
- The pharmaceutical industry is still stuck in the age of batch manufacturing
- All other industries moved on to continuous manufacturing (an integrated flow from raw materials to finished product)
- It can take one month to manufacture a drug that could be made in two days
- 2007: Novartis + MIT: Center for Continuous Manufacturing
- 2012 Continuous: spinoff of MIT + Novartis
- 2013 Glaxo in Singapore
- 2016: MIT prototype (portable drug making)

NOVARTIS

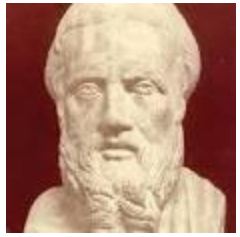
CONTINUS™ pharmaceuticals

Benefits

- We solved the problem of starvation with the agricultural revolution.
- We solved the problem of housing with the industrial revolution.



- There is still one big problem to solve that neither the agricultural nor the industrial revolutions solved: diseases.
- That requires the "biological revolution" that is going on today.
- Centuries from now the historians will write books about the biological revolution of the 21st century.



Longevity Economy

- The best birth control: education and wealth.
- Disruptive demographics: more and more old people, fewer and fewer young people
- By 2020: the population of people over 60 will control 30% of global spending, the equivalent of China's entire GDP ($9 trillion)
- Every business will be disrupted (retirement, real estate, tourism, smart cities, international affairs, ...)
- We don't have rituals, habits, sports, etc for old people.

Longevity Economy

- Longevity Science is multidisciplinary
- A new field that needs new thinking to seize an unprecedented opportunity
- What people want:
  - Longer lives
  - Better lives
- Longevity Technology must start from the day that the baby is born, planning the baby's behavior to maximize the chances of living as long as possible as healthy as possible

Longevity Economy

- Life will extend way beyond 65
- Society needs to keep "old" people active
- Today's children: no return on investment
- Society needs to keep "old" people productive
- Problems:
- 1. Today tech is developed by young people for young people
- 2. Old people neither invent nor adopt new technologies
- Who can develop tech for old people?

Longevity Economy

- Assisted Living Technology of the past
  - Hearing aids
  - Glasses
  - Microwave oven
  - Garage opener

Longevity Economy

- Prevention of Obesity
  - Semaglutide for weight loss
  - Micropeptide boosts physical fitness and prevents obesity
- Mitochondria tuneups
  - Elamipretide helps restore function to flagging mitochondria
- Supercentenarian Sequencing
  - Decoding the genomes of supercentenaria

Longevity Economy

Prevention of Alzheimer's Disease

- Devices stimulate the brain and prevent cognitive decline

mRNA Vaccines for Cancers

- Vaccines that exploit mRNA technology for several cancers

CRISPR-Based Cures

- Gene-editing tool to treat blood disorders, cancer, etc

Longevity Economy

Exercise-simulating Pills

- Drugs that mimic benefits of exercise

Artificial Young Blood

- Treatments that mimic the chemistry of young blood

Customized Microbiomes

- AI-controlled medications and diets to optimize the populations of microbes in our gut

Stopping the Epigenetic Clock

- Drugs that slow or reverse epigenetic clocks

Longevity Economy

Lab-Grown Organs

- Bladders cultivated in labs have already been implanted in humans

Pruning out aging Cells

- Drugs that kill or neutralize “senescent” cells

Anti-Aging Drugs

- Rapamycin stretches the lives of mice by more than a third
- Metformin (used by patients of Type 2 diabetes) may lower mortality for all
- Alpha-ketoglutarate extends life span in mice

Longevity Economy

Nanobots

- Nano-scale robots that travel inside the body and sense conditions and repair problems including cancers and deliver precisely targeted drugs

Cellular Reprogramming

- Gene-editing to rejuvenate organs

A Clinic in our Home

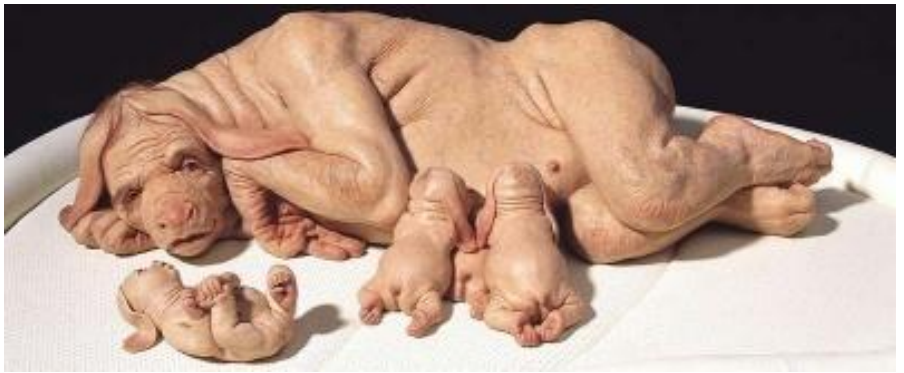
- Wearables, robotics and cloud computing to monitor people’s health without any need for doctor’s visits

Longevity Economy

- Can people over 80 innovate and create their own economy?

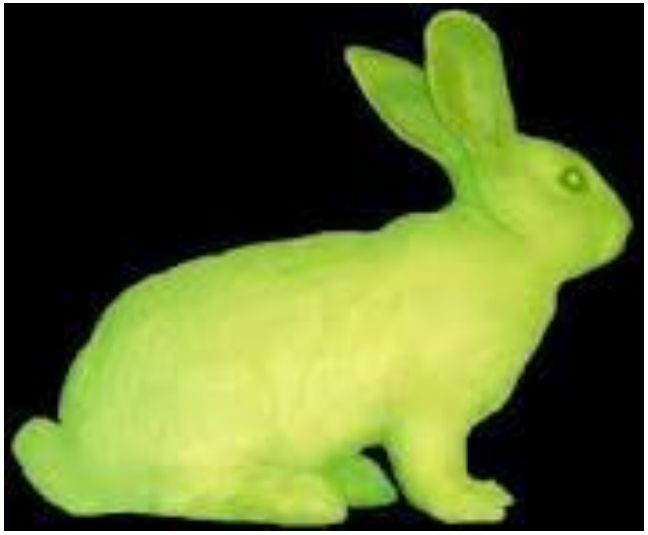
Bioart

- Damien Hirst (1994)
- Patricia Piccinini (2002)



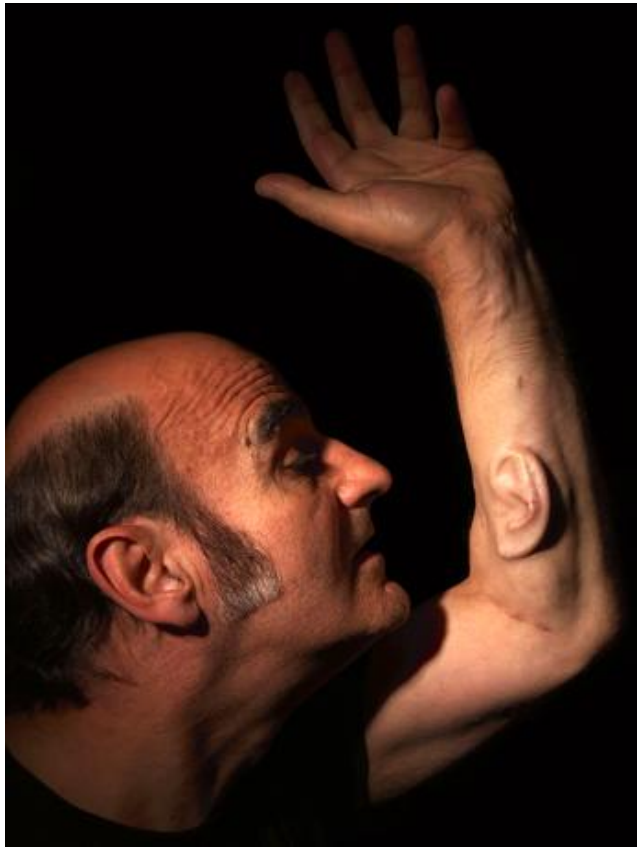
Bioart

- Oran Catts (2004)
- Eduardo Kac (2000)



Bioart

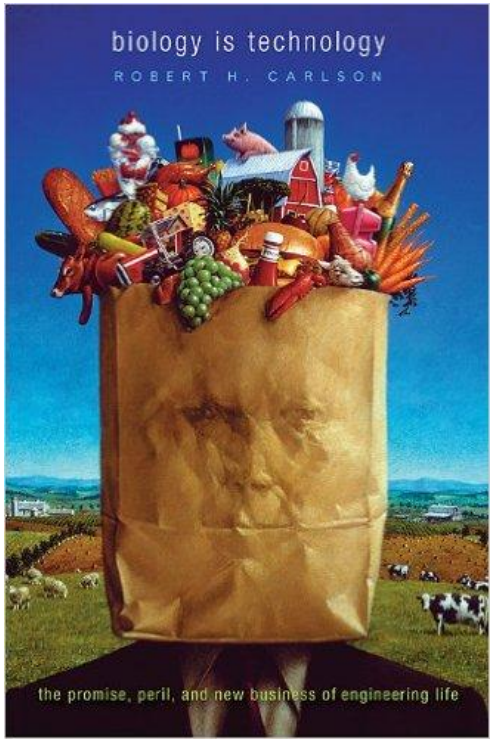
- Stelarc (2007)
- Jae Rhim Lee (2011)
- Philip Ross (2012)

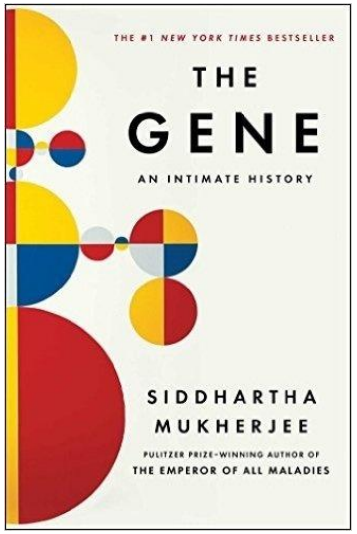


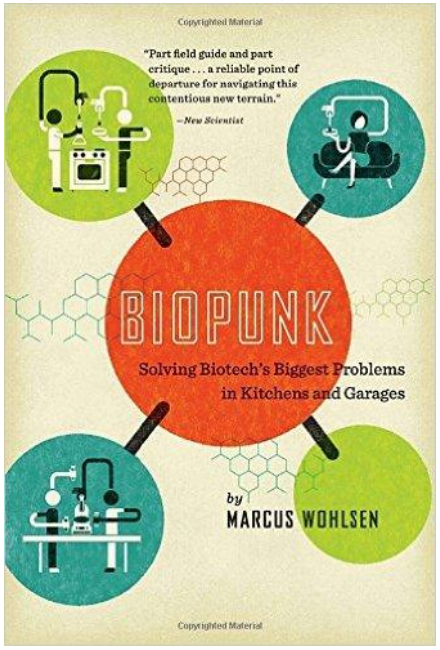
Bioart

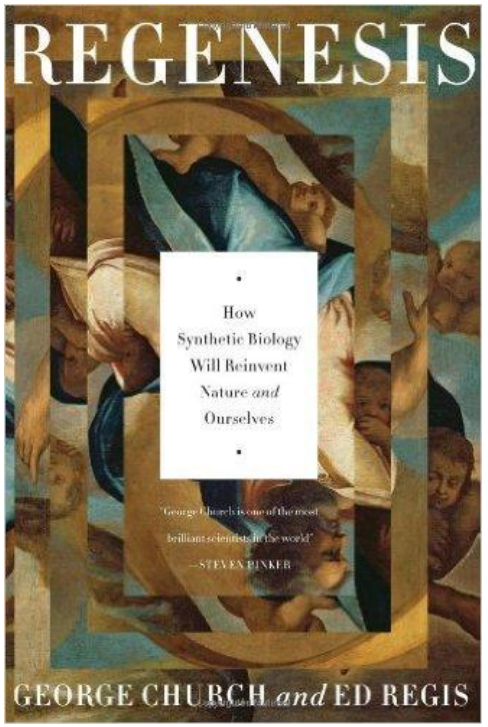
- Joe Davis
  - "Malus ecclesia" (2014)
  - To place the entire Wikipedia into DNA
  - The DNA version of Wikipedia to spread across several trees, a modified Garden Of Eden that literally includes a tree of knowledge
  - Forbidden fruit: US law does not permit the eating of unregulated plants that have been genetically modified

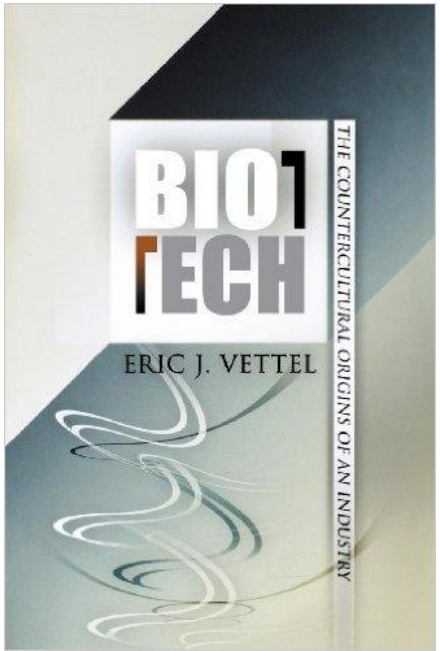
Bibliography

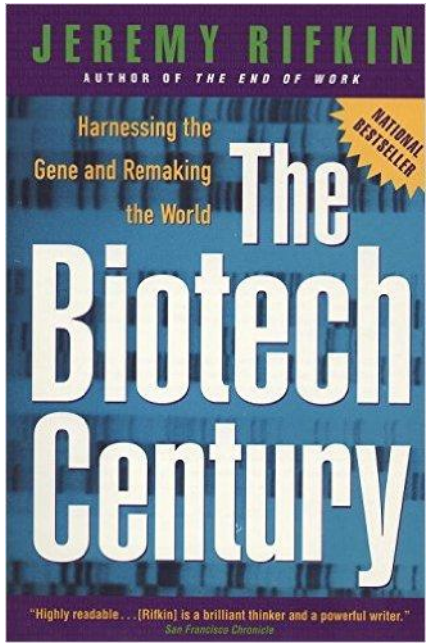


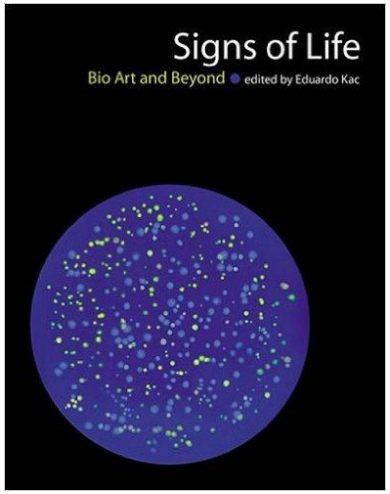


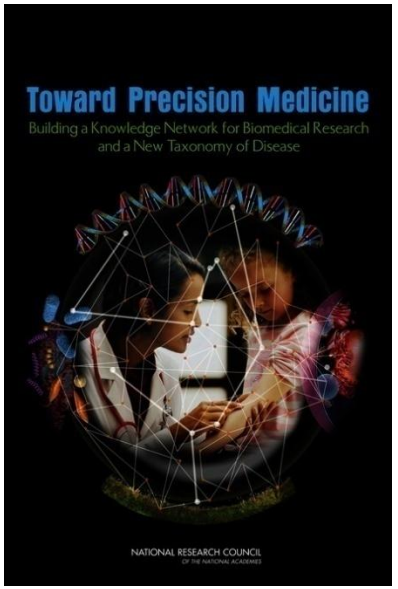












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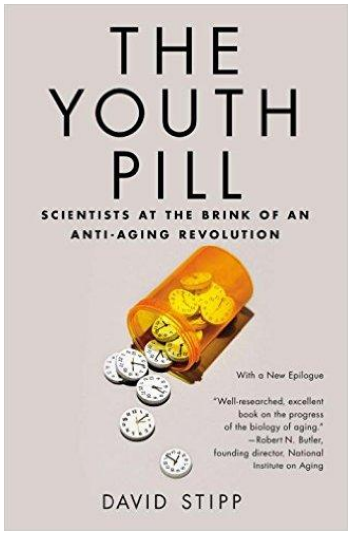
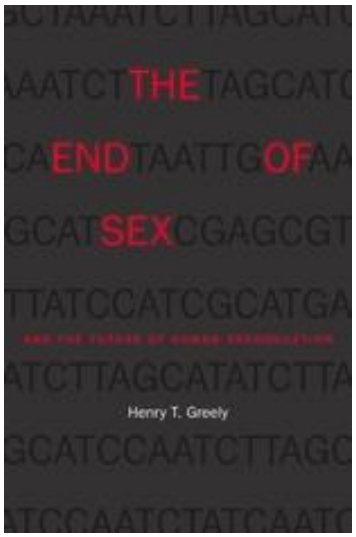
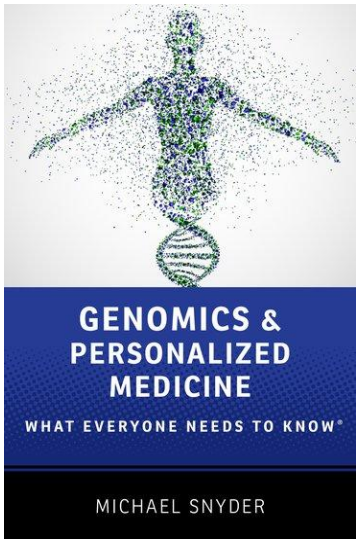
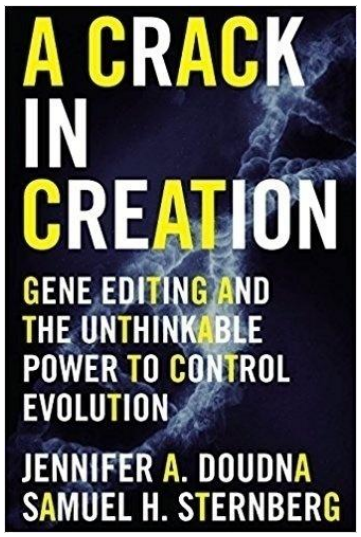
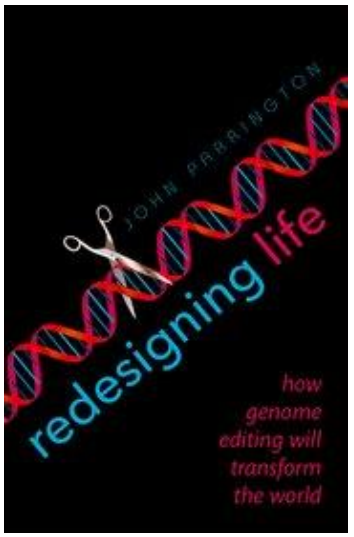
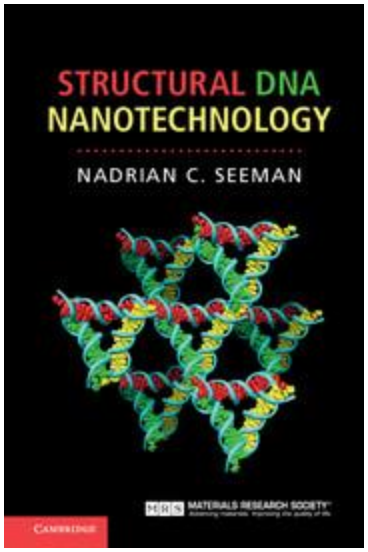


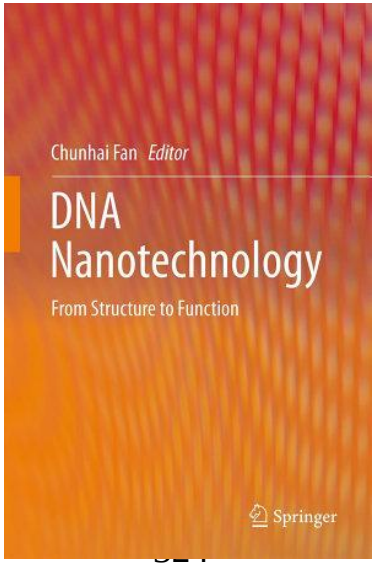






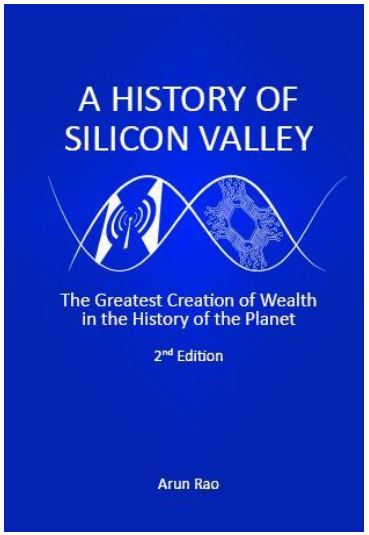


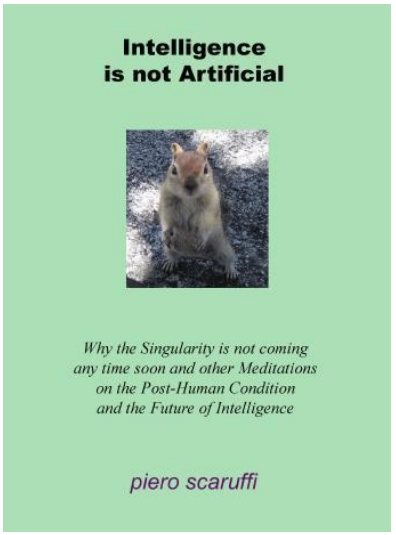


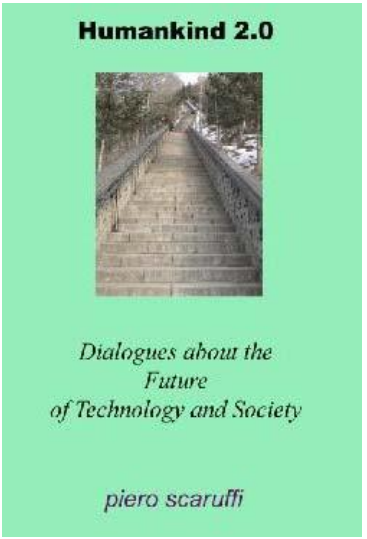


Contact

- www.scaruffi.com







See http://www.scaruffi.com/singular/human20.html for the full text of this discussion