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"
1975: Paul Berg organizes the Asilomar conference on recombinant DNA
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)
A brief History of Biotech

1994: FlavrSavr Tomato
1994: Maria Jasins homing endonucleases for genome editing
1996: Srinivasan Chandrasegarans ZFN method for genome editing
1996: Ian Wilmut clones the first mammal, the sheep Dolly
1997: Dennis Lo detects fetal DNA in the mothers blood
2000: George Davey Smith introduces Mendelian randomization
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”
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
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
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
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
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

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

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

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<th>Last 5 years 2011-2015</th>
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FDA Approvals

• Three-year trend:
  – Infectious diseases
  – Cancer
  – Rare diseases
  – Hematology

• Future trends (just guessing):

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

- Three-year trend:
  - Infectious diseases
  - Cancer
  - Rare diseases
  - Hematology

- Future trends (just guessing):
Biotech Acquisitions

Pharma and biotech M&A transactions announced each quarter

Source: EvaluatePharma®, July 2017
Biotech VC Investment

Quarterly VC investments

Source: EvaluatePharma®, July 2017
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

Number of Biotechnology Initial Public Offerings (IPOs)

Biotech Bubbles

Biotech IPOs Slowed in 2015

The number of companies going public in 2015 slowed after a record 2014.

Source: Dow Jones VentureSource | VentureWire
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

Forbes / Investing

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
  - …
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
  - 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)
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
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)
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
Longevity

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

- 2010: Special report in Scientific American
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”)

TIME
can Google Solve death?
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

Somatic Cell

Lineage Conversion

Transplantation

Patient

Aging

Regeneration

iPS cell Reprogramming

Technologies/Gene Editing

Differentiation/Modeling

Image Courtesy of Jamie Simon
Longevity

- Stuart Kim (2015): four genes of centenarians

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)

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

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

Samumed raises $438 million for regenerative therapies

The San Diego Union-Tribune

August 2018

Forbes

Samumed, a $12 billion startup based in California, is on the rise.

October 24, 2018

Business Insider
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)
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

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 rejuvenate: 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)
Longevity

Lifespan predictors (DNA-based):

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

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)
Genomic Databases

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

deCODE’s NextCODE (Iceland, aka Wuxi NextCODE)
PatientsLikeMe’s DigitalMe (Boston, acquired by iCarbonX)
NuMedii’s annotated Stanford database (Silicon Valley)
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
Precision Medicine

- Discovery of gene-disease associations

Accumulation of GWAS findings

>10,000 genome-wide significant associations with common diseases / traits

Discovery of Gene-disease Associations

Visscher et al, 2017
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 consequences of 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
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)
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

- Digitizing 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

Ginkgo Bioworks and Zymergen scale up synthetic biology with robots

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

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

Biotech startup Zymergen nabs $130 million from Softbank
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)
Genome Editing

- ZFN

Source: Dana Carroll
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.

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)
Genome Editing

- TALEN and CRISPR
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
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) invent 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

The Heroes of CRISPR

1993 Discovery of CRISPR
2003 CRISPR is an adaptive immune system
2006 Experimental evidence that CRISPR confers adaptive immunity
2008 Programming CRISPR
2008 CRISPR targets DNA
2010 Cas9 is guided by crRNAs and creates double-stranded breaks
2010 Discovery of tracrRNA
2011 Reconstituting CRISPR in a distant organism
2012 Studying CRISPR in vitro
2012 Genome editing in mammalian cells
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.

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

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

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.

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

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

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.

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**


1UCSF Center for Systems and Synthetic Biology, University of California, San Francisco, San Francisco, CA 94158, USA
2Department of Cellular and Molecular Pharmacology, University of California, San Francisco, San Francisco, CA 94158, USA
3Howard Hughes Medical Institute, University of California, San Francisco, San Francisco, CA 94158, USA
4Department 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 Izpínsúa-Belmonte (Salk Inst, 2015): remove HIV virus from cells
Genome Editing

• Applications of CRISPR
  – Xenotransplantation - Manufacturing transplantable organs (George Church’s eGenesis in 2017)
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
  – Juan Carlos Izsipua-Belmonte
    – 2016: a mouse-rat hybrid
    – 2019: a monkey-human hybrid
Genome Editing

• Applications of CRISPR
  – Changing flower colors (Univ of Tsukuba, Japan)
Genome Editing

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

Rapid improvement of domestication traits in an orphan crop by genome editing

Zachary H. Lemmon, Nathan T. Reem, Justin Dalrymple, Sebastian Soyk, Kerry E. Swartwood, Daniel Rodriguez-Leal, Joyce Van Eck & Zachary B. Lippman

CSH  Zachary Lippman
      Joyce Van Eck
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)

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

- **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)

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

*Nature*, 19 May 2016

RNA editing with CRISPR-Cas13


Alexis Komor  
David R. Liu

David B. T. Cox  
Feng Zhang

Broad Institute of MIT
Genome Editing

• Faster better CRISPR
  – Theo Roth (UCSF, 2018)
Genome Editing

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

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

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
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”
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
- 25,000 Dog
- 10,000 Tsetse fly (sleeping sickness)
- 10,000 Assassin bug (Chagas disease)
- 10,000 Freshwater snail (schistosomiasis)
- 50,000 Snake
- 2,500 Ascari roundworm
- 2,000 Tapeworm
- 1,000 Crocodile
- 500 Hippopotamus
- 100 Elephant
- 100 Lion
- 10 Wolf
- 10 Shark

Source: GatesNotes

Malaria

Malaria KILLS 2000 CHILDREN EVERY DAY
- 1 HOUR FEVER
- 2HOURS SHIVERING
- 3HOURS SWEATING
- 4HOURS ACHEING BODY
- 5HOURS WEAKNESS
- 6HOURS COMA
- 7HOURS DEATH

Malaria consortium

2014

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 & Materials

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

Introducing Zoa™ Biofabricated Leather.
Biotech & Materials Science

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

Kelp-Based Textiles

Biology is the future of fashion

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)

Whole genome prediction for preimplantation genetic diagnosis

Published online 2015 Apr 8.

Reproductive testing

Natera® is driven by a passion for elevating the science of reproductive testing. We offer highly accurate solutions for noninvasive prenatal testing (NIPT), genetic-carrier screening, preimplantation genetic testing (PGD/PGS), and miscarriage testing.
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
Designer Babies

- Glenn Cohen’s article “Disruptive Reproductive Technologies” (2017)

*Science Translational Medicine*

Disruptive reproductive technologies

First baby born after full genetic screening of embryos

8 July 2013
Designer Babies

Glenn Cohen's Atlantic article

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

Hong Ma1, Nuria Marti-Gutierrez1, Sang-Wook Park2, Jun Wu3, Yeonmi Lee1, Keiichiro Suzuki3, Amy Koski1, Dongmei Ji1, Tomonari Hayama1, Rifat Ahmed1, Hayley Darby1, Crystal Van Dyken1, Ying Li1, Eunju Kang4, A.-Reum Park2, Daesik Kim4, Sang-Tae Kim2, Jianhui Gong5,6,7,8, Ying Gu5,6,7, Xun Xu5,6,7, David Battaglia9,9, Sacha A. Krieg9, David M. Lee9, Diana H. Wu9, Don P. Wolf1, Stephen B. Heitner10, Juan Carlos Izpisua Belmonte8, Paula Amato1,9, Jin-Soo Kim5,6,8, Sanjiv Kaul10, Shoukhrat Mitalipov10

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?

Cell
February 21, 2019

CCR5 Is a Therapeutic Target for Recovery after Stroke and Traumatic Brain Injury

Brain Research Institute | UCLA

Alcino J. Silva
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.
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

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
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”)
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

Hierarchy of Stem Cells

Totipotent

Pluripotent

Blood Stem Cells

Other Stem Cells

Muscle

Nerve

Bone

Other Tissues

Red Blood Cells

White Blood Cells
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
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

Global Market for Tissue Engineering and Regeneration

Source: BCC Research (HLC101B), August 2014

VisionGain 2014

Gene Therapy, 0.2%
Stem Cell Therapies, 80.0%
Tissue Engineering, 19.8%
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)
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

The First Man to Have His Genes Edited Inside His Body

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

American woman gets biologically younger after gene therapies
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

Regeneration of the entire human epidermis using transgenic stem cells

Graziella Pellegrini

Michele De Luca

Tobias Hirsch, Tobias Rothoeft, Norbert Teig, Johann W. Bauer, Graziella Pellegrini, Laura De Rosa, Davide Scaglione, Julia Reichelt, Alfred Klausegger, Daniela Kneisz, Oriana Romano, Alessia Secone Seconetti, Roberta Contin, Elena Enzo, Irena Jurman, Sonia Carulli, Frank Jacobsen, Thomas Luecke, Marcus Lehnhardt, Meike Fischer, Maximilian Kueckelhaus, Daniela Quaglino, Michele Morgante, Silvio Bicciato, Sergio Bondanza & Michele De Luca

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)
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

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

How CAR-T therapy works

1. Blood taken from patient
2. Filter out the immune 'T' cells
3. A harmless virus used to deliver genes into 'T' cells, modifies them to recognise and target cancer cells
4. Modified cells duplicated in lab
5. The modified CAR-T cells are injected back into the patient

Stiliyan Petrov Foundation
http://www.thestiliyanpetrovfoundation.com/cart-t-cell.html
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)

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
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
CAR-T

- Allogene
- Tmunity (Carl June)

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

Perelman School of Medicine
University of Pennsylvania

Carl June
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

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

Michael D. Crowther¹, Garry Dolton¹,³, Mateusz Legut³, Marine E. Caillaud¹, Angharad Lloyd¹, Meriem Attafi¹, Sarah A. E. Galloway¹, Cristina Rius¹, Colin P. Farrell², Barbara Szomolay¹,³, Ann Ager¹,³, Alan L. Parker⁴, Anna Fuller¹, Marco Donia⁵, James McCluskey⁶, Jamie Rossjohn⁷,³,⁷,⁸, Inge Marie Svane⁵, John D. Phillips² and Andrew K. Sewell¹,³*
Programmable Bacteria

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

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)
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 that will detect all of the major cancer types*
Liquid Biopsy

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

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

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)
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

### Top 10 pharmaceutical companies based on global oncology market share in 2014 and 2020*

<table>
<thead>
<tr>
<th>Company</th>
<th>2014</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche</td>
<td>18.6</td>
<td>32.6</td>
</tr>
<tr>
<td>Celgene</td>
<td>9.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>8.2</td>
<td></td>
</tr>
<tr>
<td>Novartis</td>
<td>7.4</td>
<td>11</td>
</tr>
<tr>
<td>Pfizer</td>
<td>5.5</td>
<td>3.8</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>4.4</td>
<td>3.8</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>4.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Astellas Pharma</td>
<td>3.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Merck &amp; Co</td>
<td>3.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>3.2</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Source: Evaluate
© Statista 2015

Additional Information: Worldwide 2014 and 2015
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)
Chinese Scientists Edit Genes of Human Embryos, Raising Concerns

By GINA KOLATA  APRIL 23, 2015

FROM THREE-PERSON IVF TO GENOME EDITING
THE SCIENCE AND ETHICS OF ENGINEERING THE EMBRYO

Book HERE

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

BY MICHAEL SPECTER
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)
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
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
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

DIYBioBCN
DIY Bio Barcelona

BIOfoundry
Australia

SynTechBio
Latin America

DIYBioBA - Biohacking Buenos Aires

London Biohackspace

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

$65,554 USD  total funds raised

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

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, third 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

More than 70,000 papers have been published on the tumor suppressor p53.

Piero Scaruffi is one of the victims of information overload.
Data Analytics/Diagnostics

Sophia Genetics (Switzerland)
DNAllytics (Belgium)
Innoplexus (Germany)
DL in Bioinformatics

- “Oomics” 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 studied to 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)
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
DL in Bioinformatics

- Predicting the structure of proteins
  - SPIDER2 (2015)

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

Rhys Heffernan, Kuldip Paliwal, James Lyons, Abdollah Dehzangi, Alok Sharma, Jihua Wang, Abdul Sattar, Yuedong Yan, & Yaocai Zhou
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

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

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
  – 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%.
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

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 \( \sim 1000 \) 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 \( \sim 1.3 \) 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)
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 Li1,2, Wenqiang Shi1, and Wyeth W. Wasserman*1

1Centre 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*

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


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

Jian Zhou<sup>1,2</sup> and Olga G Troyanskaya<sup>1,3,4</sup>

<sup>1</sup>Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, New Jersey, USA
<sup>2</sup>Graduate Program in Quantitative and Computational Biology, Princeton University, Princeton, New Jersey, USA
<sup>3</sup>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. Kelley¹ Department of Stem Cell and Regenerative Biology, Harvard University,
Jasper Snoek²
John L. Rinn¹
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)
DL in Bioinformatics

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

Reproductive testing

Natera is driven by a passion for elevating the science of reproductive testing. We offer highly accurate solutions for noninvasive prenatal testing (NIPT), genetic-carrier screening, preimplantation genetic testing (PGD/PGS), and miscarriage testing.
Designing Babies

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

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

Disruptive reproductive technologies

Super-Intelligent Humans Are Coming

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

Lab Automation + Pattern Recognition + Theory Formation

Data ➔ Correlations ➔ Drug/Therapy
Drug Discovery

And maybe even…
Drug Discovery

- Exscientia (Britain)
- Berg (Boston)
- Numerate (Bay Area)
- BenevolentAI (Britain)
- Atomwise (San Francisco)
- Insilico Medicine (Baltimore)
- Desktop Genetics (Britain)
- 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
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.
Drug Discovery

- Insitro (South San Francisco, 2018)
Drug Discovery

• Desktop Genetics

Desktop Genetics launches a new Gene Editing Platform

DESKGEN™ CRISPR Libraries
AI-designed for more effective and affordable guides, with fewer false negatives.
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”

Our Platform

Our platform offers cloud-scale artificial intelligence support for every design decision at each stage of drug discovery
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 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

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.
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".

First FDA Approval For Clinical Cloud-Based Deep Learning In Healthcare
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)
DNA Computing

- 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 Högborg, Franziska Graf, & William M. Shih
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)
- 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)
DNA Origami

- George Church (Harvard): DNA origami nanobot (2012) with Shawn Douglas and Ido Bachelet

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

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
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
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)
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

- Technologies for people over 80:
  - IoT
  - Sharing Economy
  - VR for virtual tourism
  - Wearables for health monitoring
  - 3D printing
  - Robots for medicine reminders, deliveries and pickups, shopping
  - Social media for socializing
  - Space for supersonic travel
  - Biotech for health
  - Cloud/ Big Data/ AI for analysis of health conditions and prescription of activities, medicines, diets
Longevity Economy

• And what else?
• 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
Bibliography
Contact

• www.scaruffi.com

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