Synthetic Biology and Dual-Use Research of Concern

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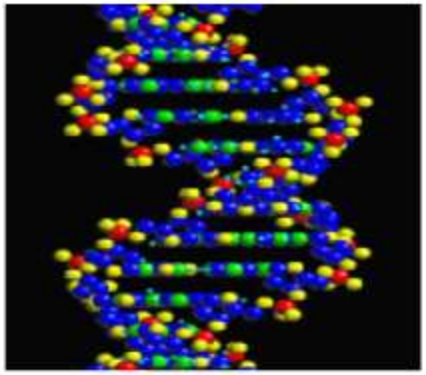
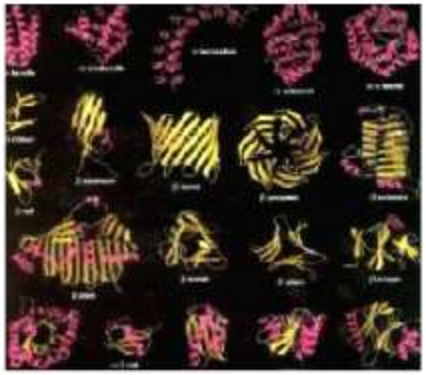
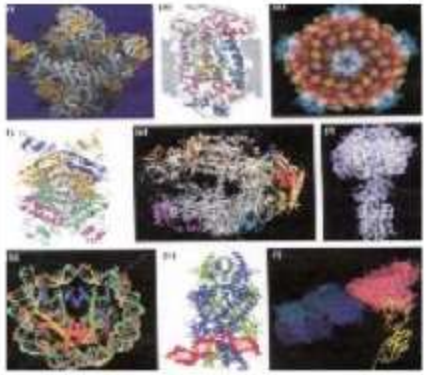
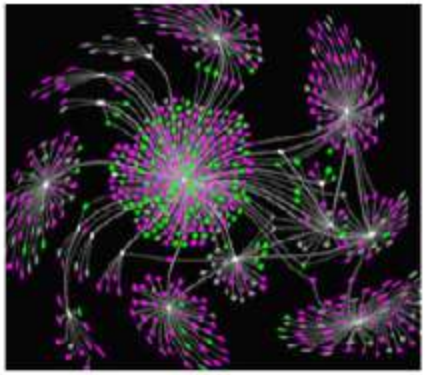
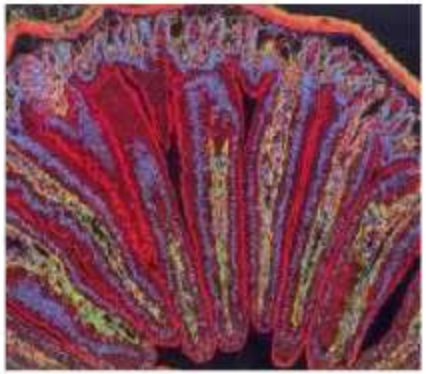
Arizona State University • 25 May 2016

Understanding Biological Organization: The Construction of Increasing Hierarchical Complexity and Mapping the Underlying Instructional Information

common genetic (digital) code in all life forms	tool box of protein motifs for combinatorial assembly (“molecular lego”)	assembly of structurally and functionally diverse proteins	protein interactions and nanoscale intracellular structures
			
			
molecular signaling networks	cells and tissues	organs	organism

Digital Biology (Code) and Synthetic Biology (Construction)

- reprogramming existing biological signaling pathways and networks
- program and assemble new biological functions and organisms based on knowledge of the ‘rule sets’ underlying hierarchical biological systems
- expanding the dimension of explored biospace
  - design, simulation and construction of novel functions/organisms with no known natural evolutionary counter part
  - novel biotic: abiotic combinations
- “directed evolution” and “accelerated evolution”

Synthetic Biology

- emerging technology with myriad applications across diverse industrial sectors

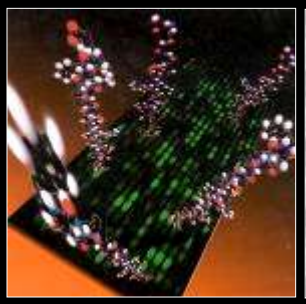
Healthcare

Public Health

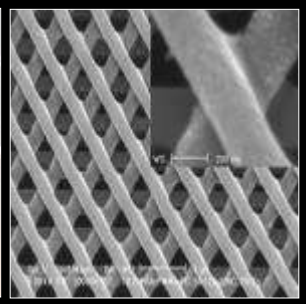
Agriculture

Functional Foods

Novel Materials



Textiles



Bioenergy and Biofuels

Industrial Enzymes

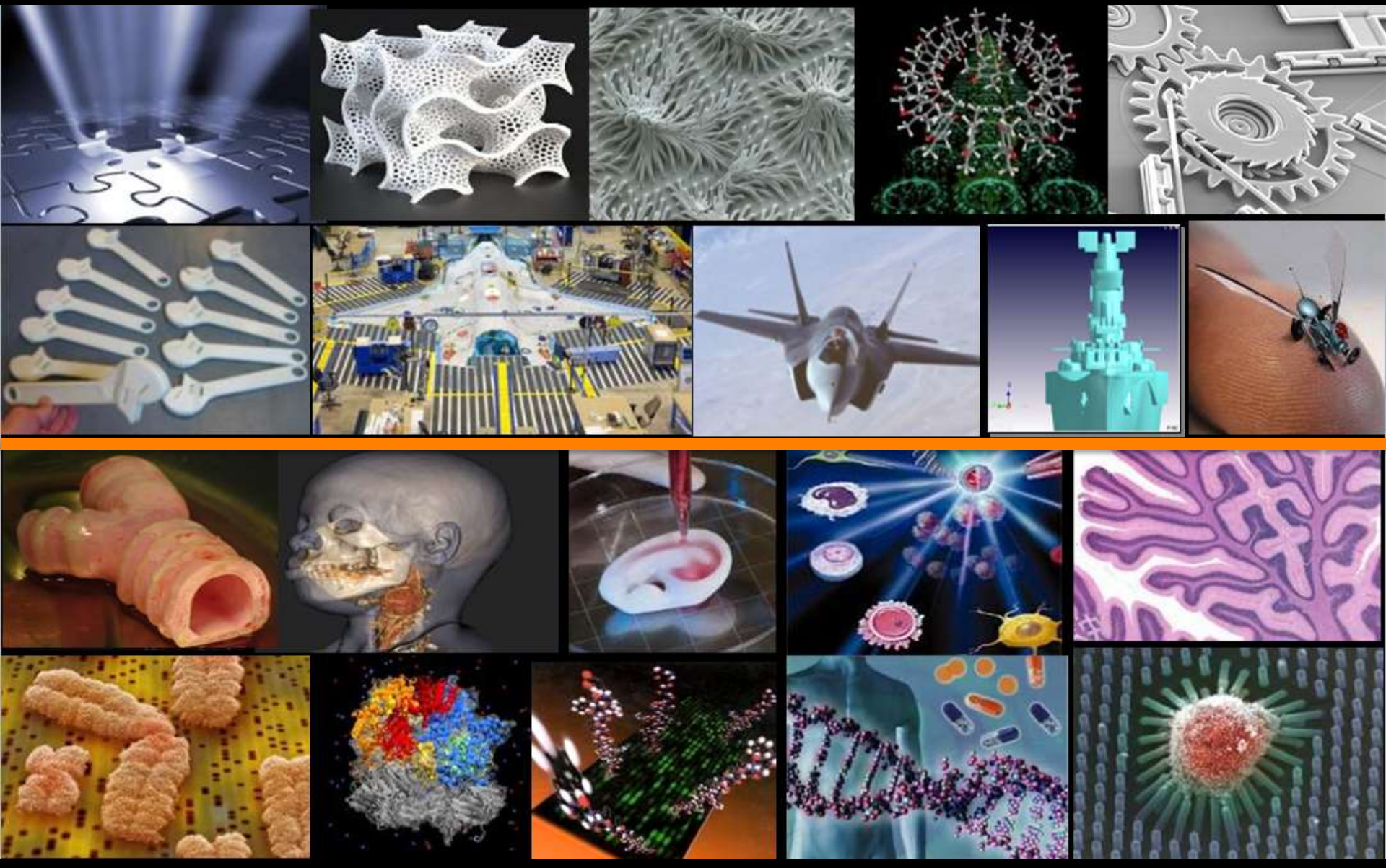
'Green' Mfg

Bio-remediation

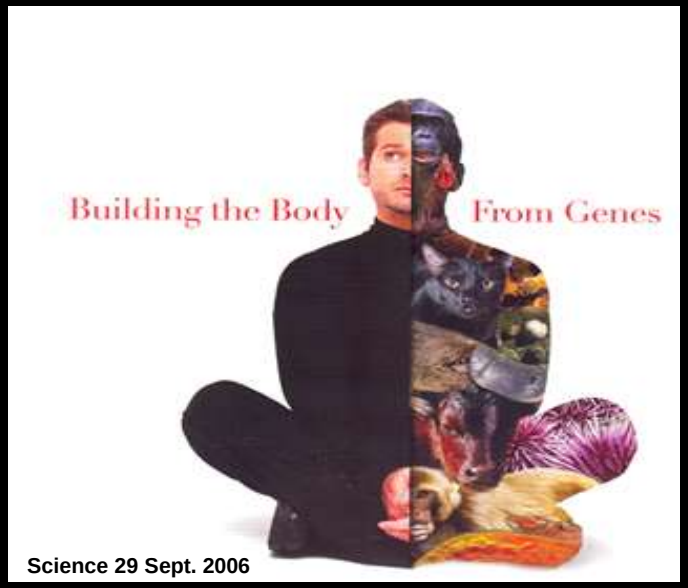
Clean Water

Sensor Networks

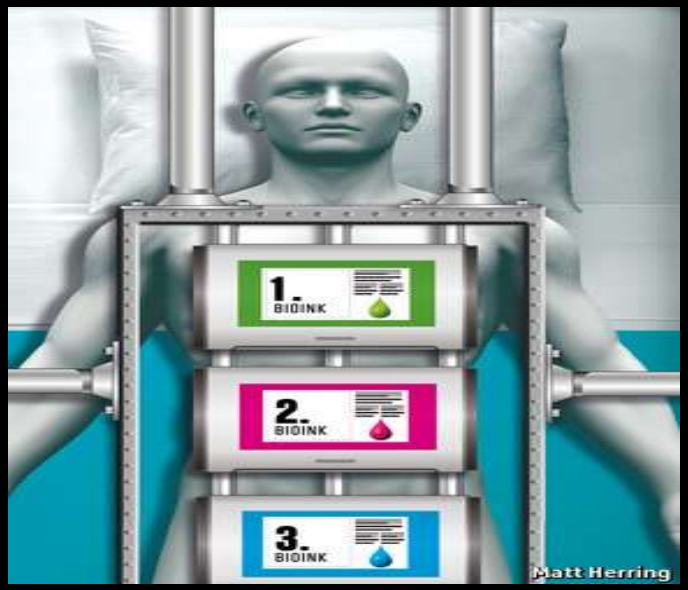
Digital Programming of 3-D Fabrication and Assembly Using Non-Biological and Biological Substrates

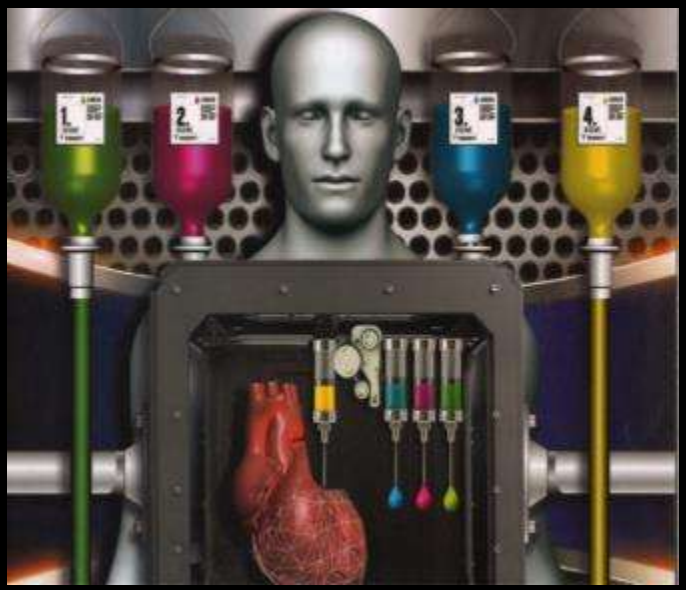


Regenerative Medicine:
Synthetic Biology and Tissue Engineering



Science 29 Sept. 2006






DARPA

Less Inspiring Commercial Applications of Gene Editing Techniques

Chinese Mini-Pigs

Desired Koi Coloration Patterns

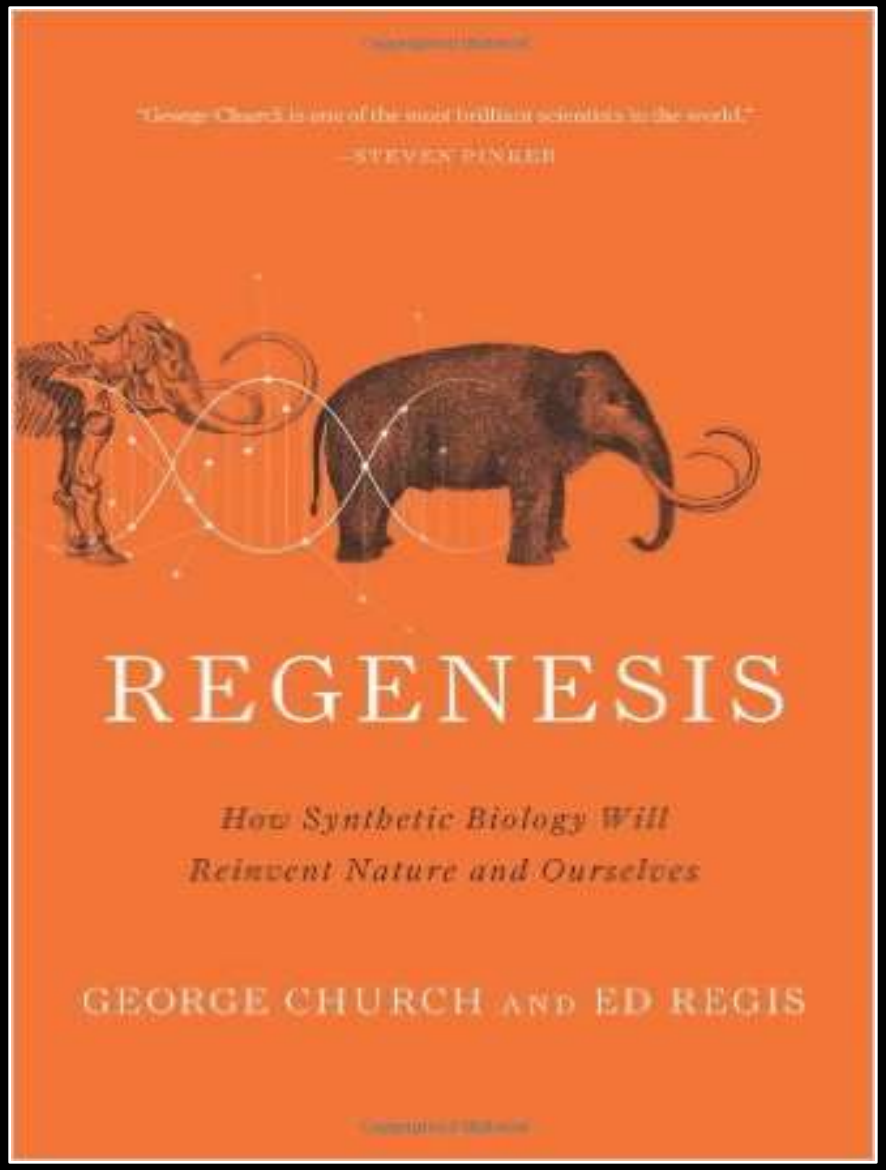
Tech

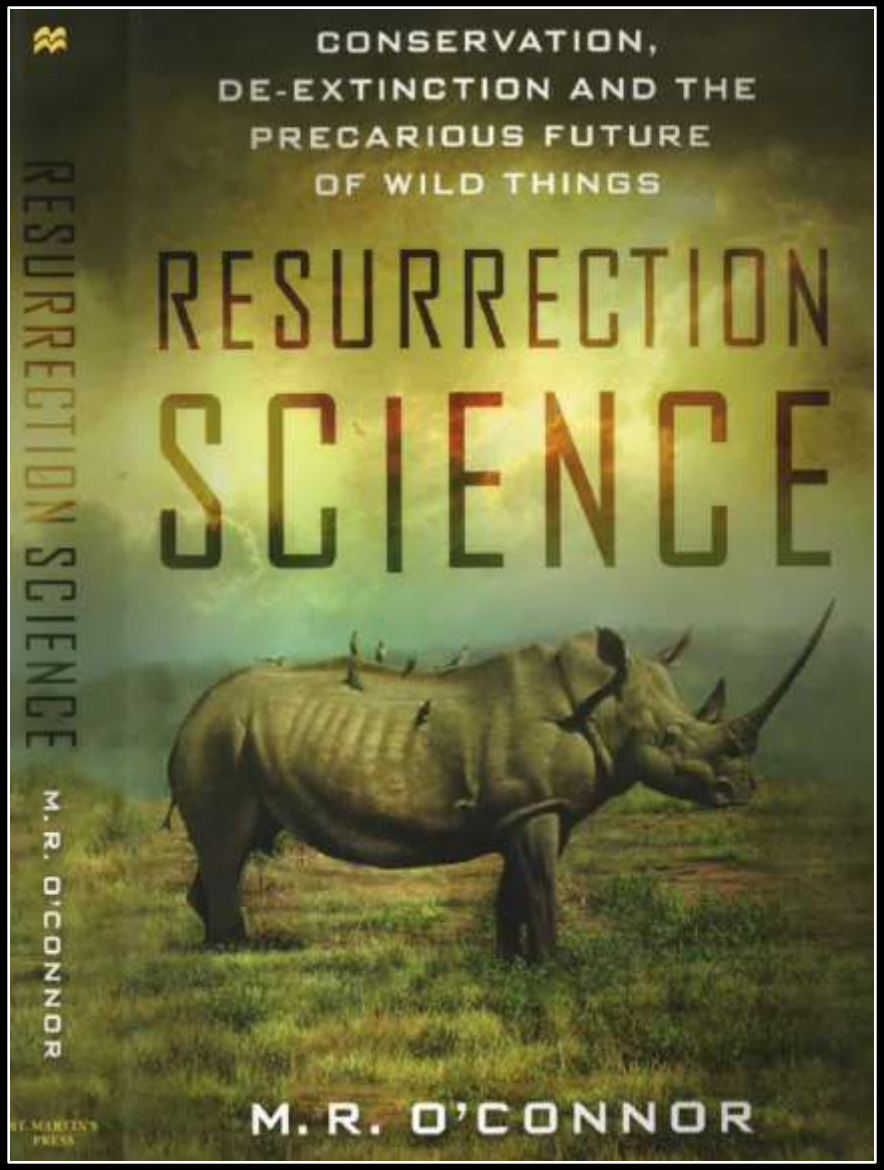
OBJECT OF INTEREST

THE HOTTEST TECH IN SILICON VALLEY MADE THIS MEATBALL

WHAT: A "cultured" meatball from Memphis Meats, a San Francisco startup backed by almost $3 million in venture funding. FRESH MEAT: The company makes its meat in a lab from the cells of cows, chickens, and pigs. One meatball takes three weeks to propagate in a steel tank. "It's not 'lab-grown' meat," says co-founder and CEO Uma Valeti. "It's like a meat brewery." SQUARE MEAL: Cells eat a diet of glucose, vitamins, and minerals to proliferate. "We create the conditions where the cells can grow freely." TASTE TEST: People who tested the cultured meatball couldn't tell that it was grown from cells. "It has an undeniable and intense meat flavor. Our goal was not to be a vegetarian product." CHECK, PLEASE: There's a catch—one pound of ground beef costs Memphis Meats $18,000 to grow. "We're trying to scale it up so that it's cost-effective." HUNGER GAMES: Startups making protein with fewer environmental and health risks are hot: Beyond Meat, which makes protein from plants, counts Bill Gates and two Twitter co-founders as investors; Gates also backed its rival, Impossible Foods. NEXT COURSE: Memphis Meats hopes to sell its product by 2021, Valeti says. "We're still in deep R&D." —*Andrew Zaleski*

Synbio – Fourtune, 05/01/16, 43
http://fortune.com/2016/04/25/memphis-meats-lab-grown-meat/


"George Church is one of the most brilliant scientists in the world."
–STEVEN PINKER
REGENESIS
How Synthetic Biology Will Reinvent Nature and Ourselves
GEORGE CHURCH AND ED REGIS


CONSERVATION, DE-EXTINCTION AND THE PRECARIOUS FUTURE OF WILD THINGS
RESURRECTION SCIENCE
RESURRECTION SCIENCE
M. R. O'CONNOR
M. R. O'CONNOR

Synthetic Biology

- technology acceleration and rapid diffusion
- major strategic national investments in enabling technologies
- rapid growth in corporate investment
- new wave of technologies with national security and military implications
- dramatic expansion in range of dual-use applications compared to historical dimensions of biosciences research
- eugenic implications
  - genome editing
  - synthetic human genomes

Public Fears and Ethical Concerns Regarding Synthetic Biology and Engineered Modification and Design of Living Systems

- ‘unnatural’, ‘Playing God’, hubris
- risk from accident or errors
- malevolent use for military advantage and/or terrorism
- germline modification and eugenics
- social, inequity, discrimination and distributive justice
- undermine the life-machine distinction

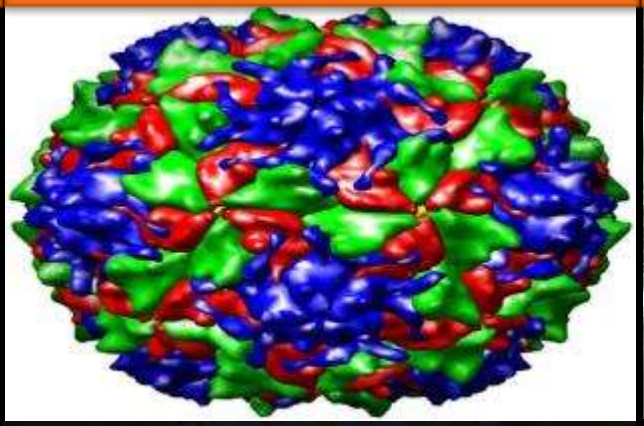
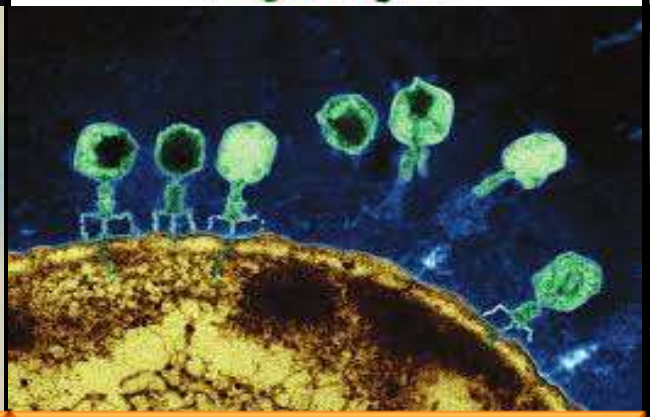
Dual-Use Research

- generation of knowledge that can be used for beneficent or maleficent purposes
- traditional division between civilian applications versus military/terrorism uses
- new genetic technologies expand concept to include myriad civilian applications for modification of diverse species, including humans, and raise profound ethical, legal and social issues

Dual-Use Research of Concern (DURC)

- **dual-use knowledge with the potential to cause profound societal disruptions based on misuse, accident or uncertain risks**

Dual-Use Research of Concern and the Rapid Pace of New Genetic Modification Technologies

Mouse Pox IL-4	Poliovirus Synthesis	Influenza GOF Virulence
		
		
Synthetic Genomes	**CRISPR-CAS Gene Editing**	**Digital Genomes**

DURC With Pathogenic Microorganisms

- increase virulence
- increase agent transmissibility/dissemination/ persistence
- engineer resistance to countermeasures
- evasion of detection/diagnosis systems
- compromise host immunity and increase susceptibility
- alter host range and/or tissue tropism
- reconstitute eradicated or extinct agent
- de novo design of synthetic organisms with these traits

Therapeutic Oncolytic Viruses Designed to Circumvent Immune Detection

- Onco-Vex-GM-CSF (Amgen)
- Reolysin (Oncolytics Biotech)
- JX-594-Jennerex (Biotherapeutics)

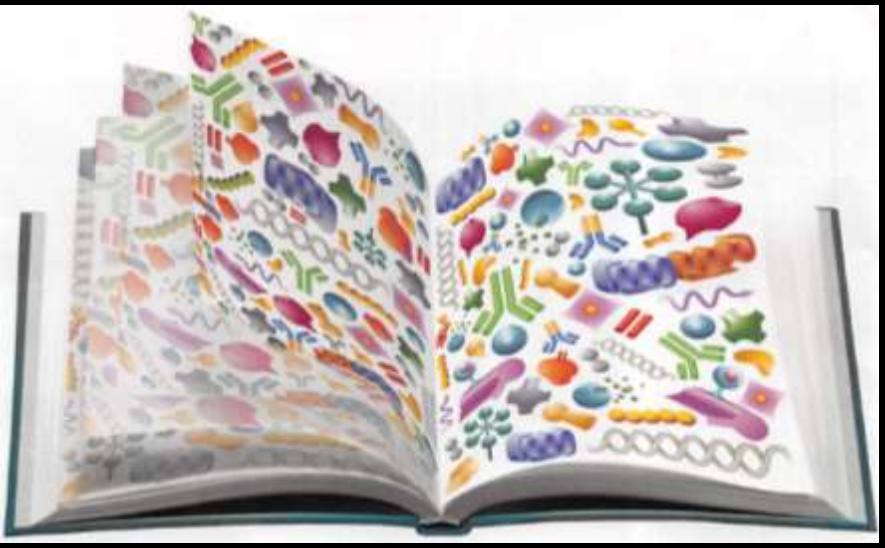
Gain-of-Function (GOF) Research and DURC

- not all GOF research rises to level of dual-use research of concern (DURC)
  - routine use in study of gene function(s) in non-pathogenic context (e.g. cancer research)
- current narrow focus on microorganisms with major public health risks and pandemic potential
- new genetic technologies dramatically expand the potential for DURC
- synthetic organisms
- “beyond bugs”: modification of eukaryotes
- highly targeted “editing” of gene function/regulation in any organism/any biological network

Enabling Technologies in Synthetic Biology

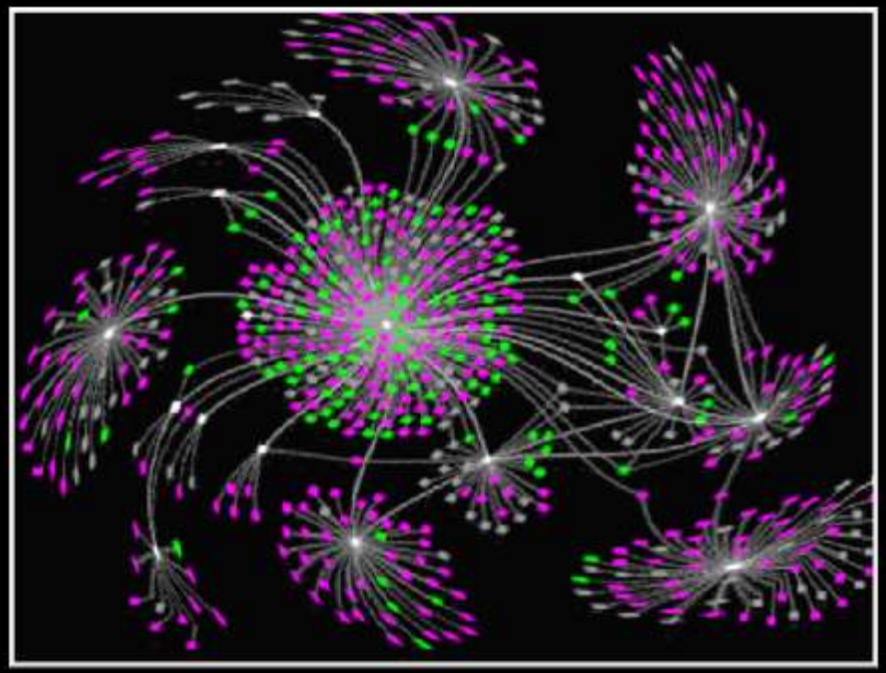
- genome sequencing (reading), synthesis (writing) and targeted modification (editing)
- assembly, delivery and integration of novel genes (targeting)
- designed regulation and control of complex genetic networks (‘system states’)

Enabling Technologies in Synthetic Biology



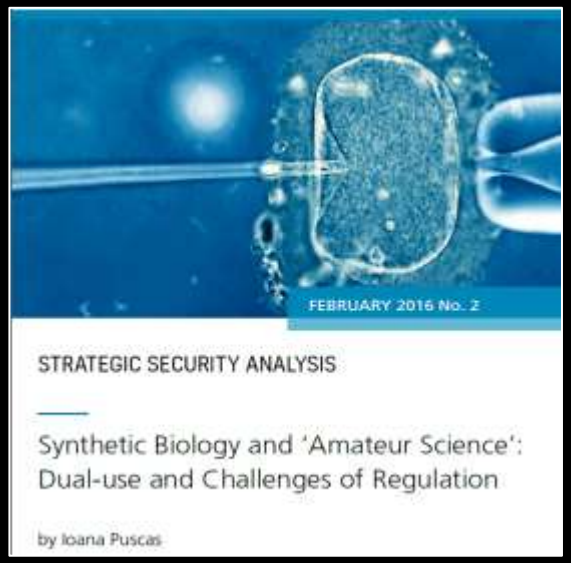
- accelerated directed evolution of molecular components/pathways with novel properties
  - large scale biomanufacturing
  - integration into living systems
- incorporation of non-natural molecular classes (xenobiology)
  - expand genetic code/functional diversity of biological signaling pathways
  - xeno-nucleotides and nucleic acids (XNA)
  - non-canonical amino acids

Enabling Technologies in Synthetic Biology



- comprehensive computational maps/simulation of biological signaling pathways and control systems
  - enhance accuracy of biological network engineering/redesign for increased predictability
- digital biology

DIY Bio



- individuals not necessarily associated with scientific academic or industrial enterprises
- “biohacking”/“garage biology”
- “de-skilling”/“democratization” of biological research
- decreasing costs and automation
- more developed community in USA than elsewhere
- EU GMO regulations apply to GM activities irrespective of physical location or practitioner
- codes of conduct/on line training courses

Synthetic Biology, Genome Editing and National Security: The Ultimate Dual-Use Technology for Modification of Biological Systems?

Statement for the Record

Worldwide Threat Assessment
of the
US Intelligence Community

Senate Select Committee on Intelligence

James R. Clapper

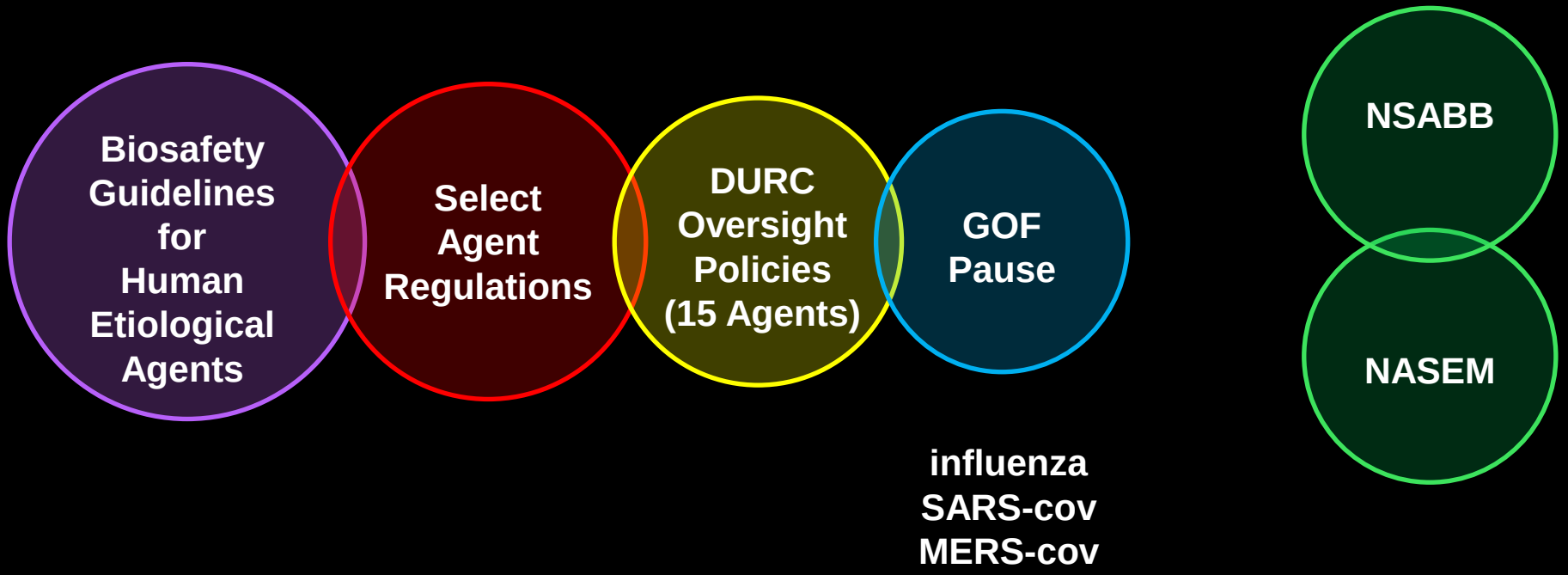
Director of National Intelligence

February 9, 2016

Technology Diffusion, Automation, Simplification and Cost Reduction

New Oversight Mechanisms and International Harmonization

US Government Policy Frameworks for Managing Risk Associated With Life Sciences Research



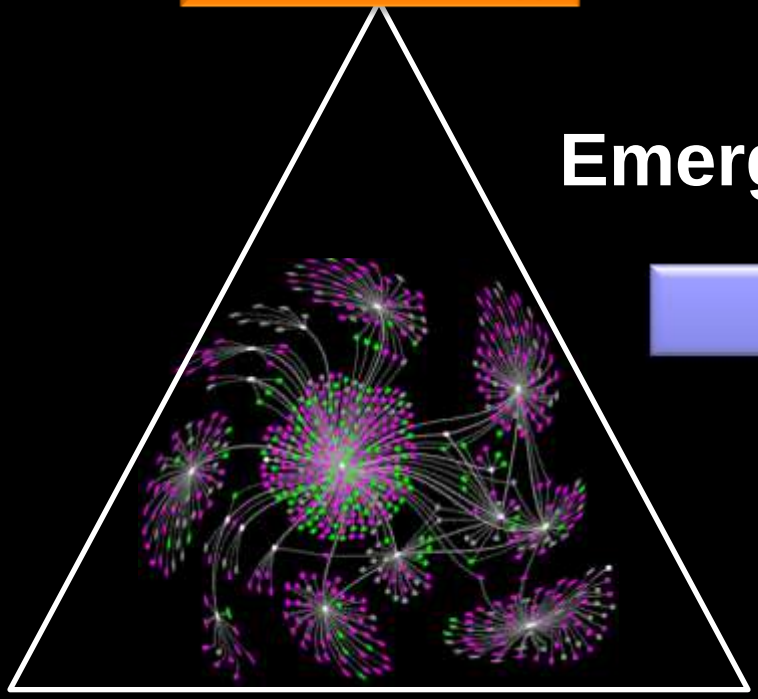
US Policy Landscape for Bioweapons and Bioterrorism

- Biological and Toxin Weapons Convention
- Biological Weapons Anti-Terrorism Act (Public Law 101-298, 1990)
- Antiterrorism and Effective Death Penalty Act (Public Laws 104-132, 1996)
- USA Patriot Act (Public Law 107-56, 2001)
- Public Health and Bioterrorism Preparedness and Response Act (Public Law 107-188, 2002)
- federal and institutional policies for oversight of dual-use research of concern (White House, 2012, 2015)

Thinking “Beyond Bugs”

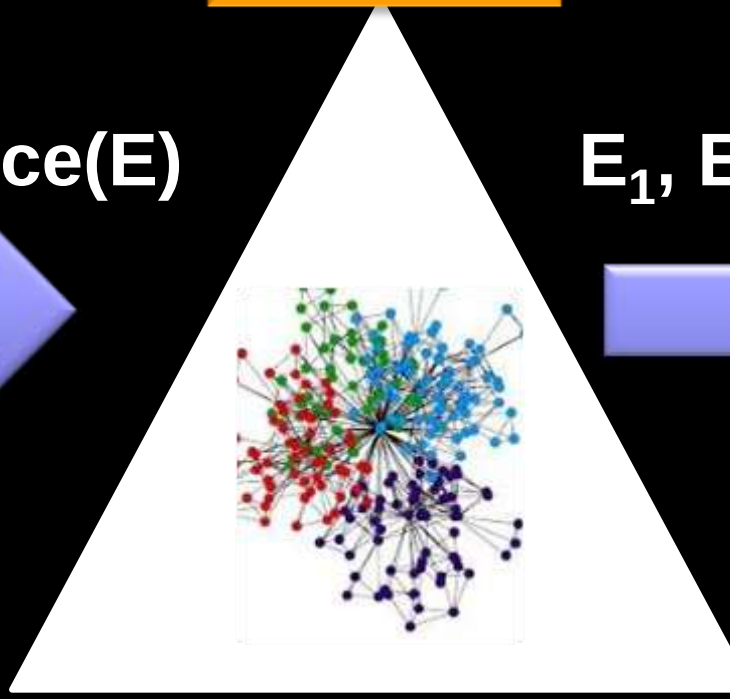
Understanding the Topology of Information Flow and Architecture of Control Networks in Complex Biological Systems

network topology



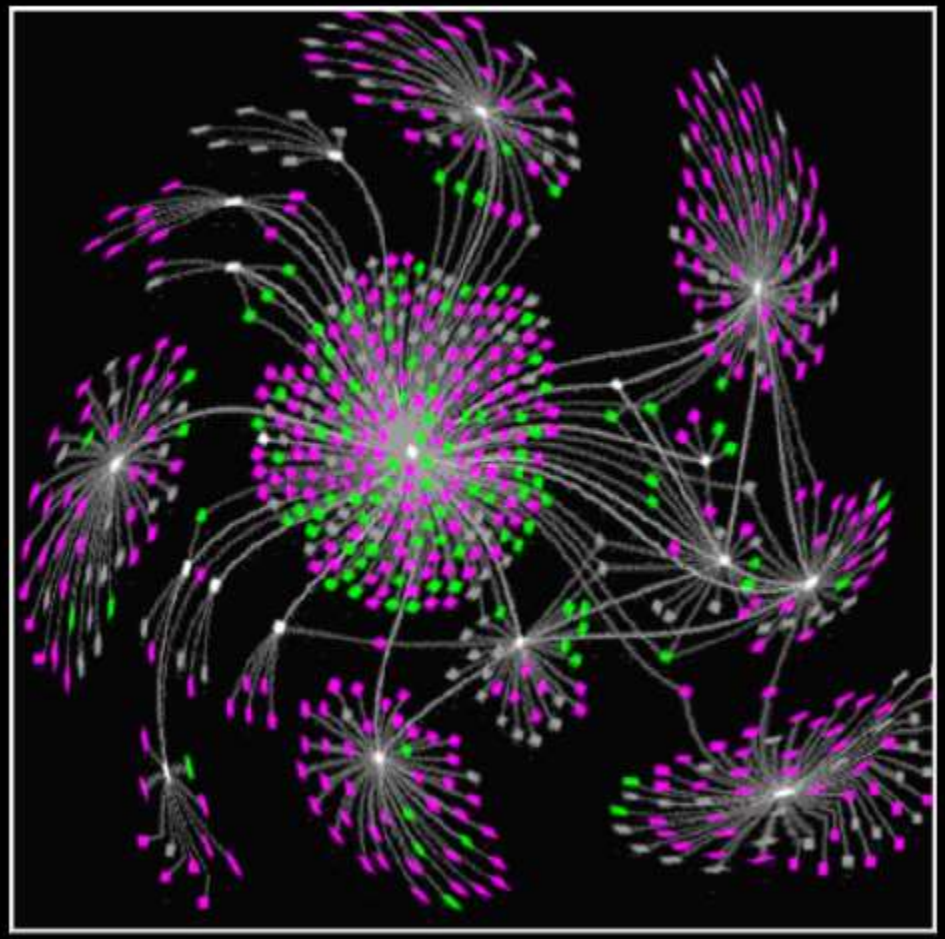
Emergence(E)

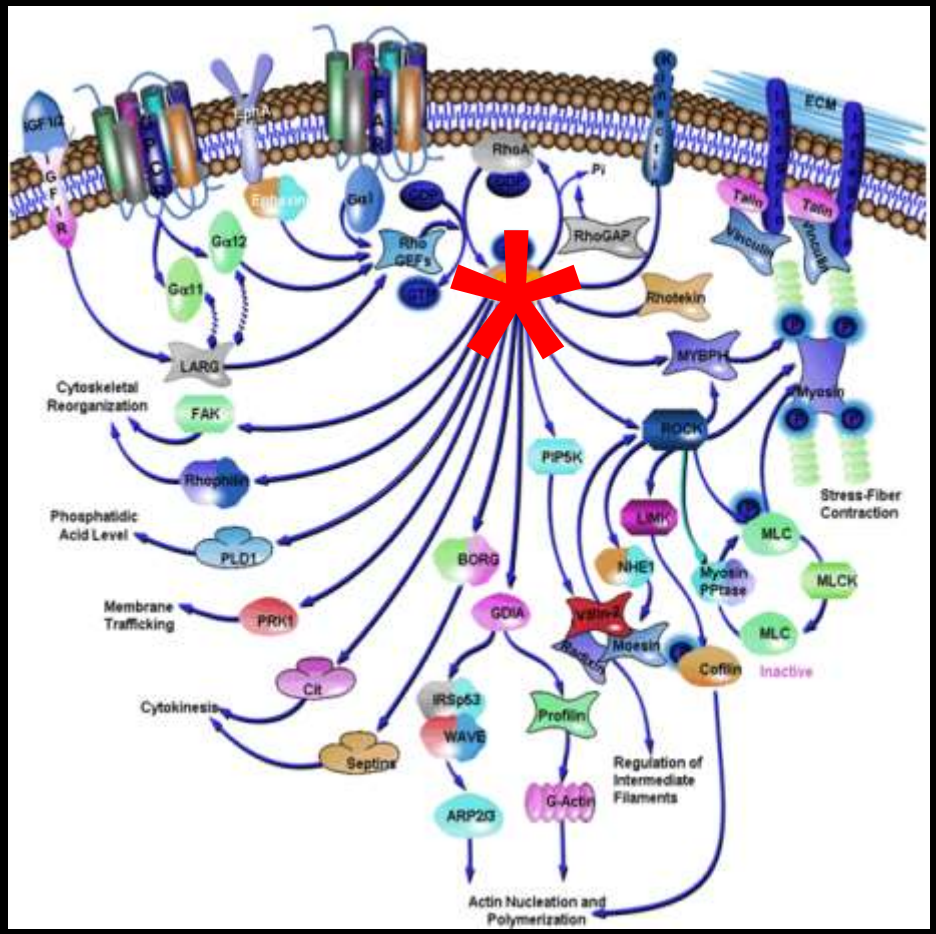
state shifts

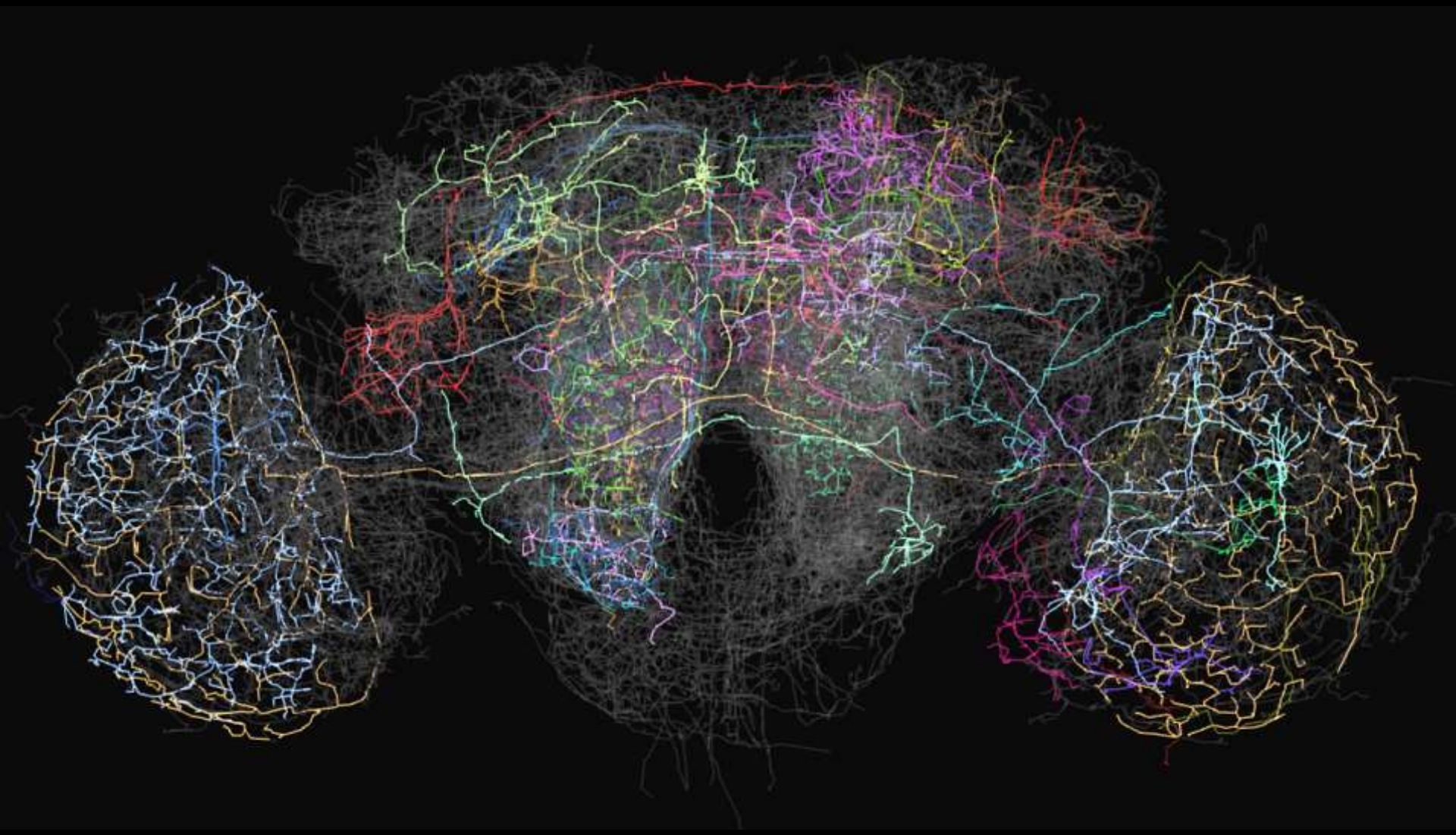


$E_1, E_2 \ldots E_n$

- Black Swans
- dislocations
- tipping points
- irreversible cascades
- phase shifts
- perturbations
- inflection points
- unintended consequences
- critical thresholds
- bifurcations
- trigger points



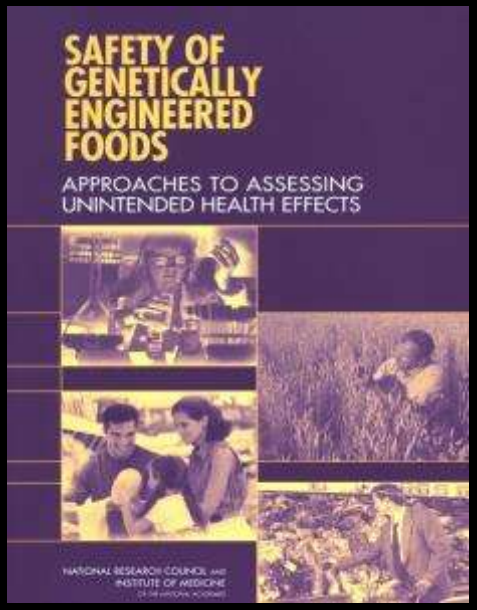

ECM
RhoA
Pi
RhoGAP
Talin
Vinculin
Gα12
Gα11
Rho GEFs
Rhotekin
LARG
MYBPH
Myosin
Cytoskeletal Reorganization
FAK
ROCK
PIP5K
Rhophilin
Stress-Fiber Contraction
Phosphatidic Acid Level
PLD1
LIMK
MLC
BORG
NHE1
Myosin PPtase
MLCK
Membrane Trafficking
PRK1
GDIA
Ezrin-4
Moesin
Cofilin
Inactive
Cit
Cytokinesis
IRSp53
WAVE
Profilin
Septins
Regulation of Intermediate Filaments
G-Actin
ARP2/3
Actin Nucleation and Polymerization

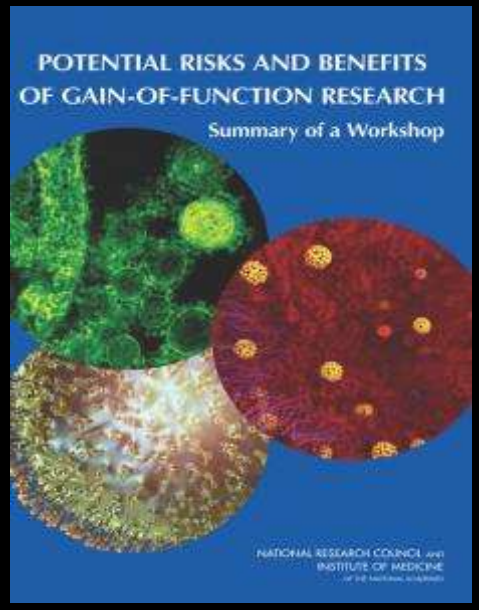


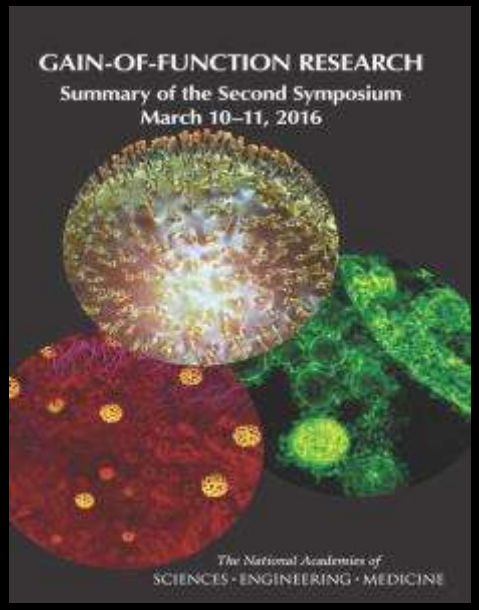
The Complexity of Dual-Use Issues

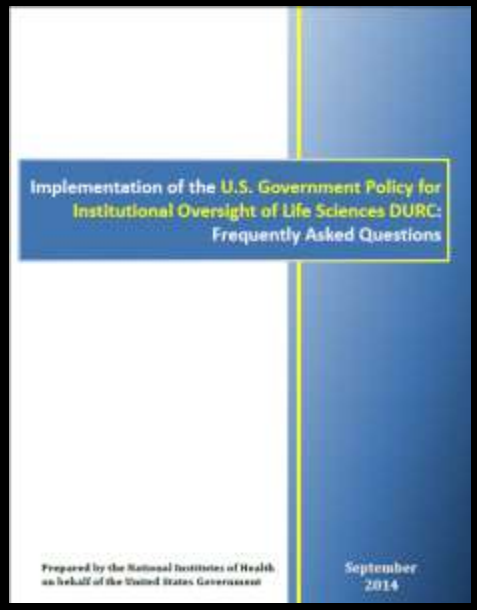
- multifactorial, non-linear events and rude surprises
- deliberate misuse versus error/accident
- intent and risk spectrum
- capacity, cost and probability of successful translation
- ease of detection/mitigation/attribution
- oversight, regulation, compliance
- international harmonization

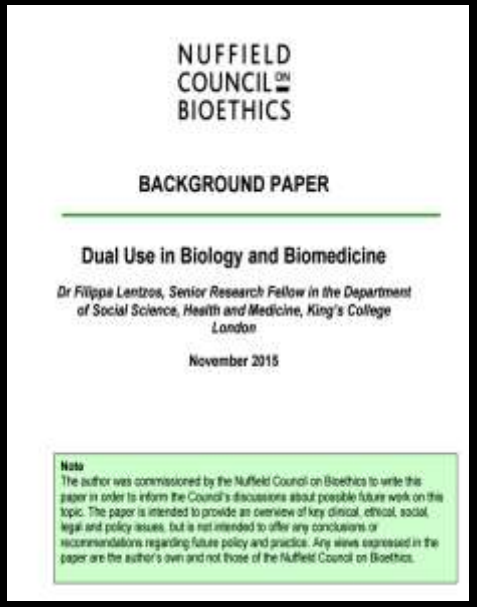
Risk, Regulation and Responsibility

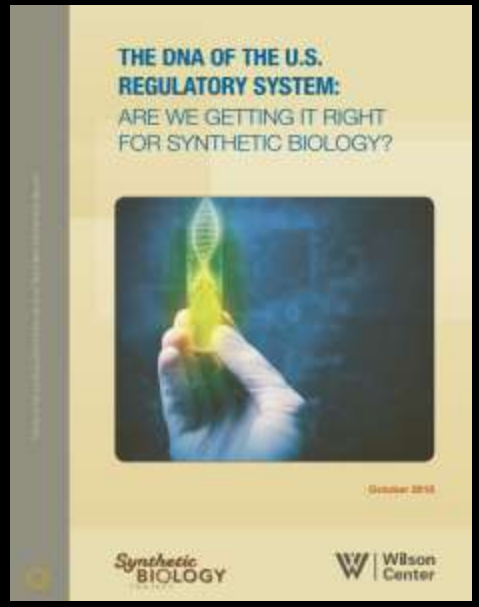

SAFETY OF GENETICALLY ENGINEERED FOODS
APPROACHES TO ASSESSING UNINTENDED HEALTH EFFECTS
NATIONAL RESEARCH COUNCIL AND INSTITUTE OF MEDICINE


POTENTIAL RISKS AND BENEFITS OF GAIN-OF-FUNCTION RESEARCH
Summary of a Workshop
NATIONAL RESEARCH COUNCIL AND INSTITUTE OF MEDICINE

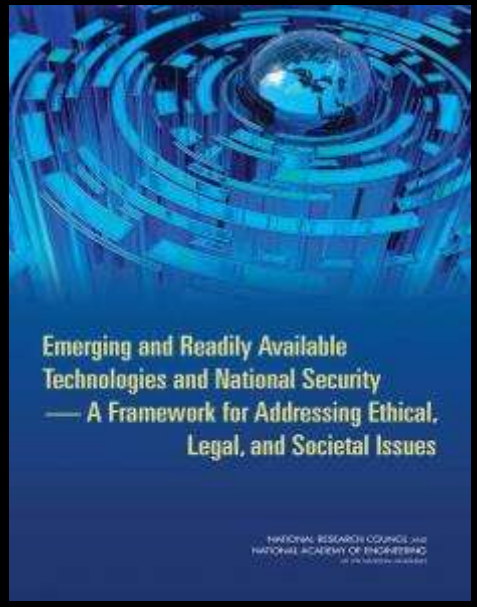

GAIN-OF-FUNCTION RESEARCH
Summary of the Second Symposium
March 10–11, 2016
The National Academies of
SCIENCES · ENGINEERING · MEDICINE


Implementation of the U.S. Government Policy for Institutional Oversight of Life Sciences DURC: Frequently Asked Questions
Prepared by the National Institutes of Health on behalf of the United States Government
September 2014


NUFFIELD COUNCIL ON BIOETHICS
BACKGROUND PAPER
Dual Use in Biology and Biomedicine
Dr Filippa Lentzos, Senior Research Fellow in the Department of Social Science, Health and Medicine, King's College London
November 2015
Note
The author was commissioned by the Nuffield Council on Bioethics to write this paper in order to inform the Council's discussions about possible future work on this topic. The paper is intended to provide an overview of key clinical, ethical, social, legal and policy issues, but is not intended to offer any conclusions or recommendations regarding future policy and practice. Any views expressed in the paper are the author's own and not those of the Nuffield Council on Bioethics.


THE DNA OF THE U.S. REGULATORY SYSTEM:
ARE WE GETTING IT RIGHT FOR SYNTHETIC BIOLOGY?
Synthetic BIOLOGY
Wilson Center


Scientific Committee on Health and Environmental Risks
SCHER
Scientific Committee on Emerging and Newly Identified Health Risks
SCENIHR
Scientific Committee on Consumer Safety
SCCS
Opinion on
Synthetic Biology II
Risk assessment methodologies and safety aspects
Scientific Committees
The Scientific Committees adopted this Opinion:


Emerging and Readily Available Technologies and National Security
— A Framework for Addressing Ethical, Legal, and Societal Issues
NATIONAL RESEARCH COUNCIL AND NATIONAL ACADEMY OF ENGINEERING

Coordinated Framework for Regulation of Biotechnology

Food and Drug Administration Modernization Act

Federal Food, Drug and Cosmetic Act

Federal Insecticide, Fungicide and Rodenticide Act

Toxic Substances Control Act

Plant Protection Act

National Environment Policy Act

Food Safety Modernization Act

Export Control Act

The Complexity of Risk-Benefit Assessment for DURC

- multi-disciplinary, multi-dimensional
- evaluation in context of entire life cycle (from research to tangible utility/threat)
- diverse stakeholders
  - scientific, clinical, public health and military/security communities
  - social, behavioral and decision science
  - public and private sectors
  - general public
- oversight mechanisms
  - law, guidelines, best practices, codes-of-conduct
  - compliance, enforcement and penalties
  - moratoria and/or prohibition

Risk, Restraint and Responsibility: Purported Claims By The Academic Research Community

- intrinsic value of “knowledge”
- scientists are not responsible for harmful uses of their research (the gunmaker’s defense)
- individual scientists cannot affect the overall trajectory of a research field
- publication as deterrent to misuse
- publication as critical vehicle to inform countermeasure development

Regulatory Oversight of Synthetic Biology Products

- current biosafety/containment requirements
- current environmental release requirements
- modified organisms as biosensors
  - containment, release and classification as devices?
- modified endosymbiont organisms as probiotic/dysbiosis therapeutics
  - drug approval requirements?
- next-generation genetic and synthetic biology technologies?
  - gene drives, gene editing
  - synthetic organisms

Evaluation of DURC

- from focus on method/process of production to risk assessment of end product, its properties and societal impact

Genetically-Designed Safeguard to Limit Survival of Modified and/or Fully Synthetic Organisms: 'Kill' and 'Suicide' Switches

- auxotrophic dependency
  - survival requires chemical(s) not available in natural environments
- induced lethality
  - two gene system in which activation of 'toxic' second gene silences the first gene and kills the organism
- toxin-antitoxin pairs
  - plasmid-borne toxic peptide neutralized by genome-encoded antitoxin
  - when both expressed the cell survives but plasmid transfer to another cell without anti-toxin results in toxin-mediated death of receiver cell

International Gene Synthesis Consortium

- screening and reporting orders for potentially dangerous sequences
  - focus on select agents
- likely increasing irrelevance as a biosafety/surveillance tool
  - low cost of synthesis machines
  - digital genome computer codes bypass screening and surveillance tools
  - new gene editing tools makes any gene a target

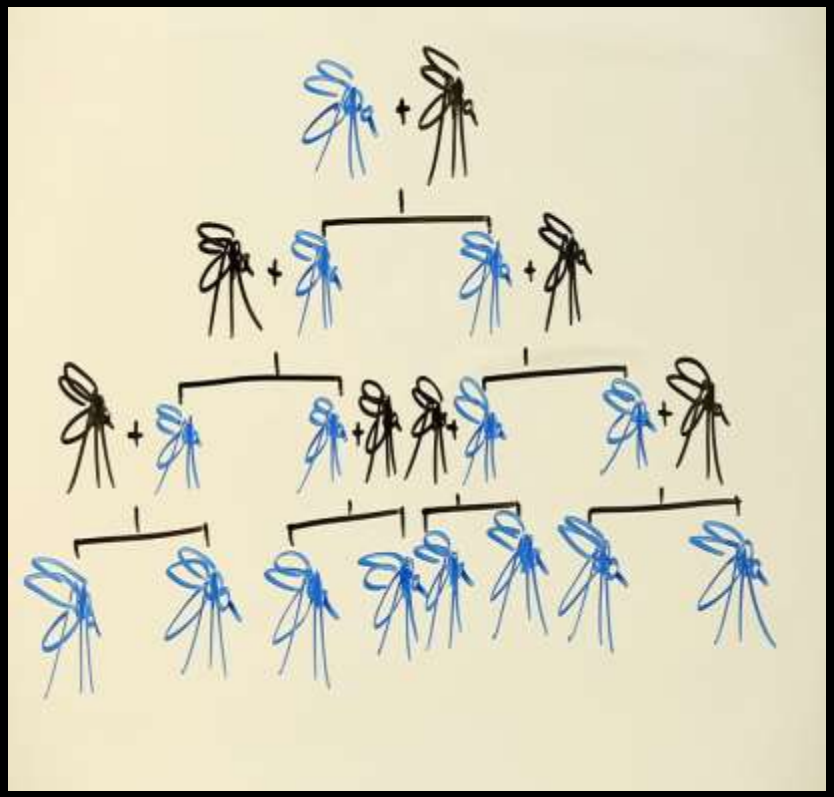
Game Changers

Gene Drives

Precision Gene Editing

Digital Genomes

Gene Drives
Rapid Penetrance of New Traits



CRISPR-Cas and Precision Genome Editing

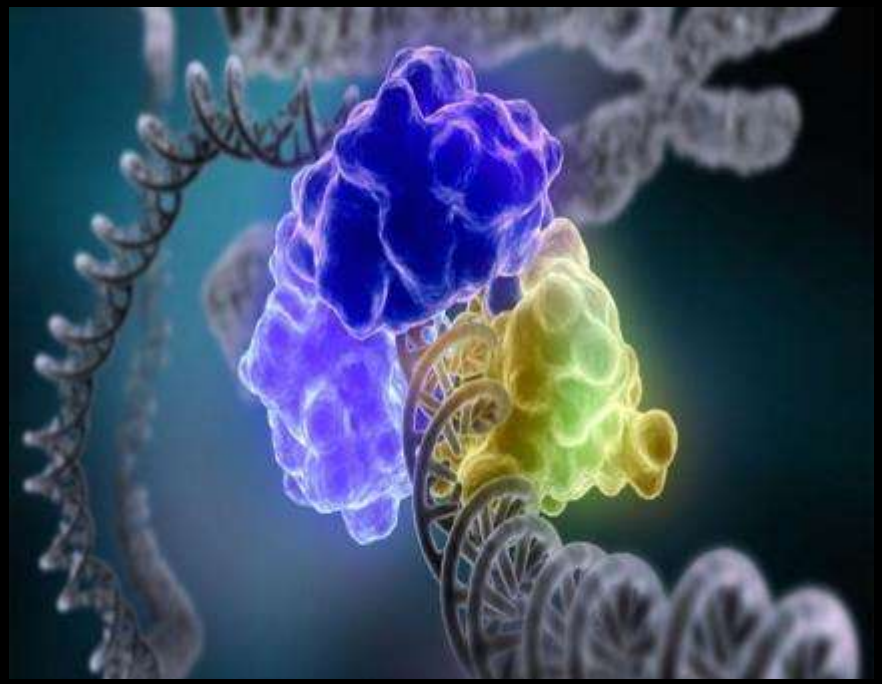
Using An Evolutionary Mechanism from 3-4 Billion Years Ago for 21st Century Genome Design

Change, Delete or Replace Genes in Any Living Species, Including Humans

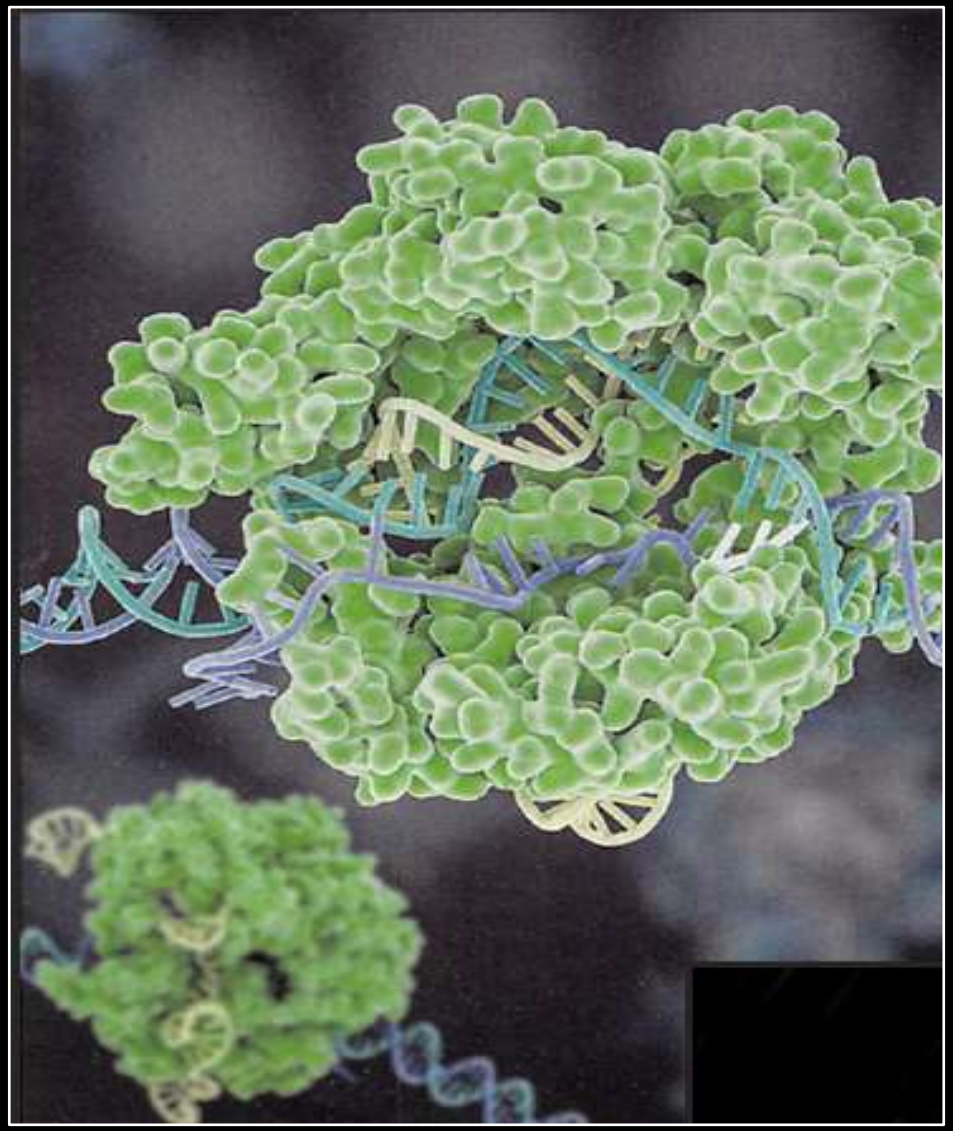
Genome Editing

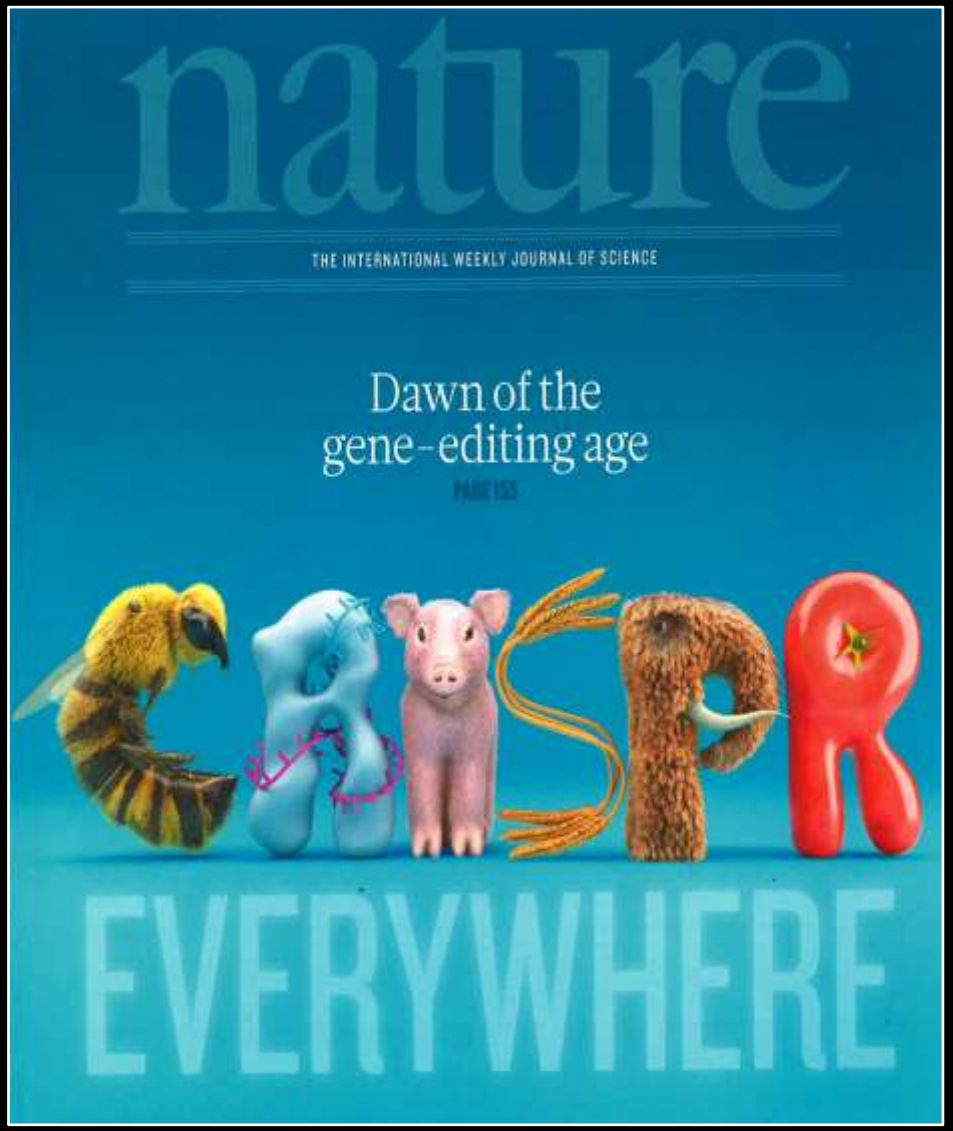
Microbial CRISPR Defense System Against Viruses

CRISPR-Cas Guided Excision and Insertion of New Genes

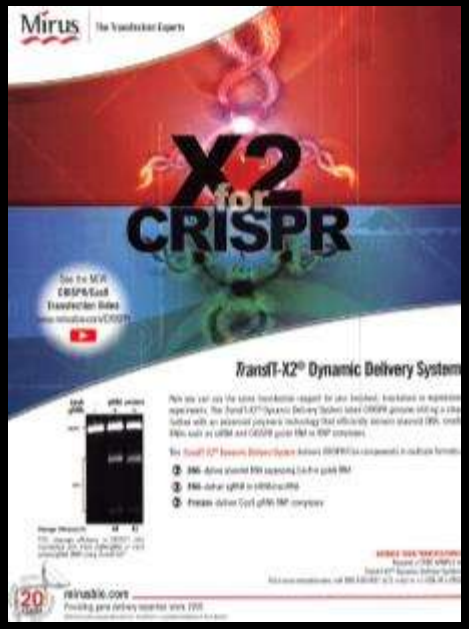


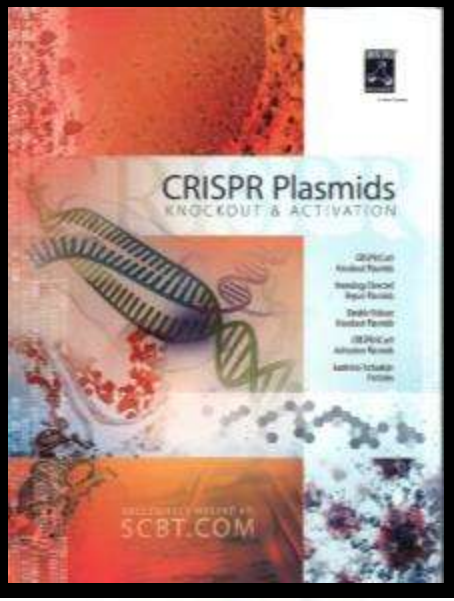
CRISPR-cas9 and Precision Gene Editing

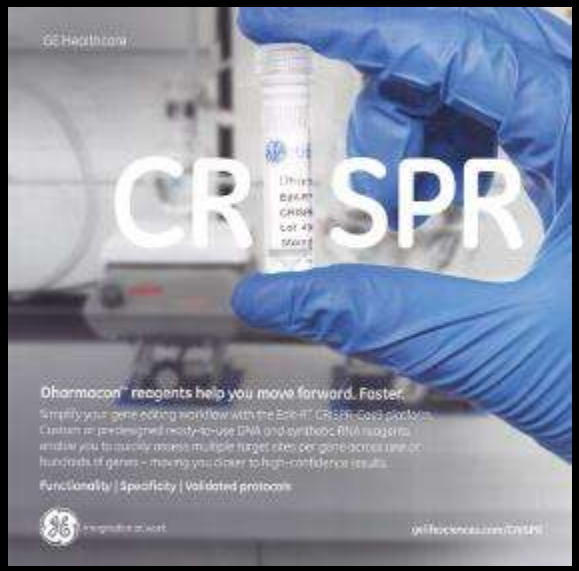




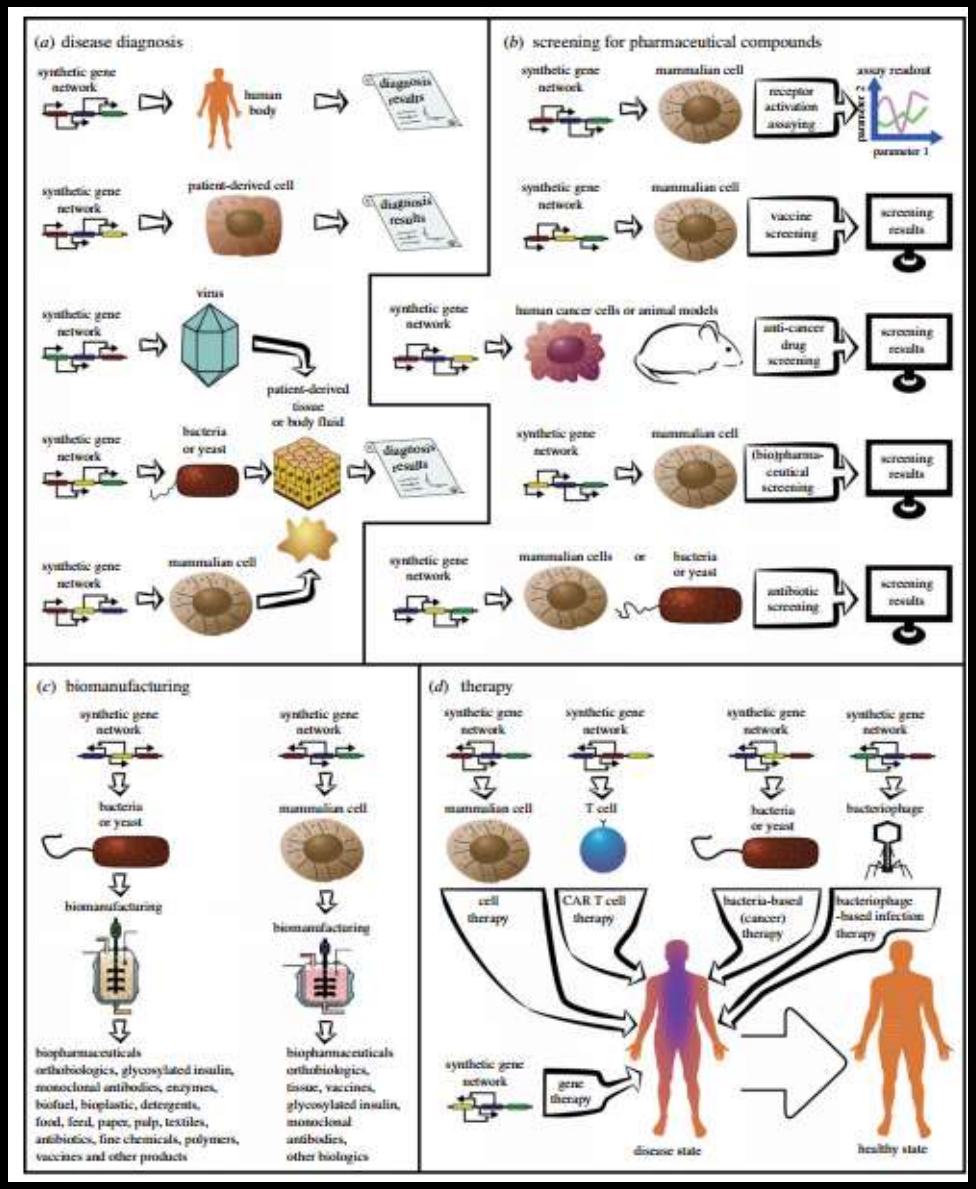
The Rapid Growth of a New Industry Supply Chain for CRISPR-Cas Gene Editing Services







Applications of Synthetic Biology in Healthcare: Z Kis et al. (2015) J. Roy. Soc. Interface 12, 201410000

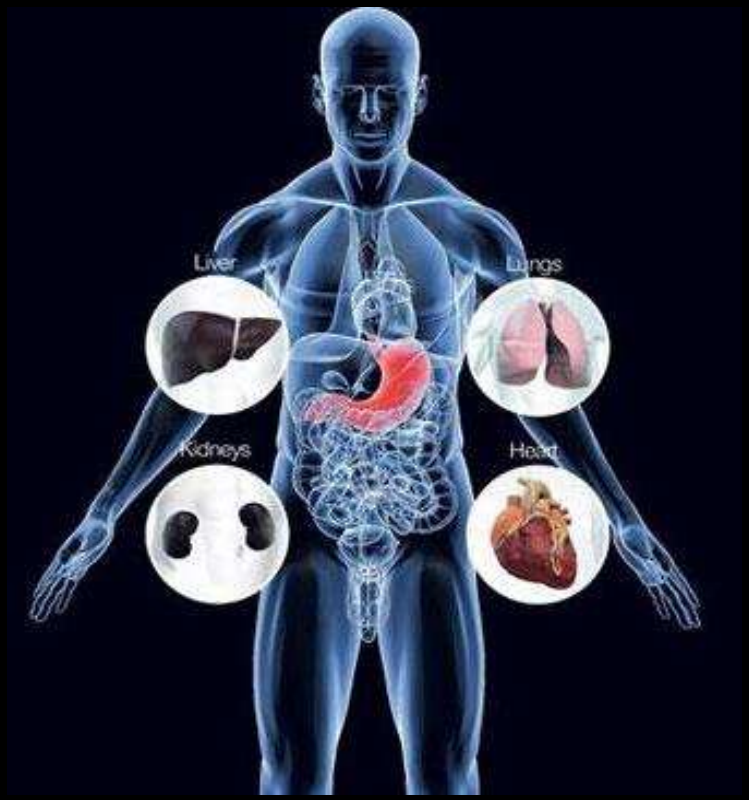


CRISPR-Cas Precision Gene Editing and Engineered Resistance to Viral Diseases

susceptible to
African swine fever (ASV)

transfer ASV resistance
genes to domestic pigs

CRISPR-Cas and Gene Editing to Design Pig Organs for Xenogeneic Transplantation to Humans



122K Americans on Waiting List for Organ Transplants

Elimination of Pig Genes That Trigger Transplant Rejection

CRISPR-Induced Mutation in MECP-Z Gene in Macaques and Induction of Rett Syndrome/Autism Spectrum Disorder Models

Z.Liu et al. (2016) 530, 98

Regulatory Review of Genome Editing

- dramatic expansion of potential applications
  - microorganisms, plants, animals
  - human therapeutics
- advocacy that GMO-type oversight based on transgenic technology should not apply
  - use of naturally occurring gene modification and repair systems
  - homologous (precision) spatial localization of gene modification(s)

Gene Editing of Humans

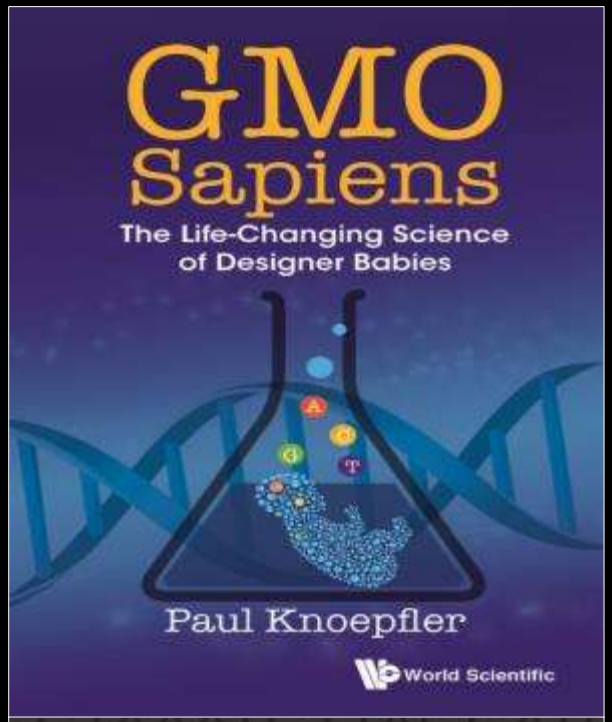
Somatic Cell Modification and Augmentation (non-heritable)

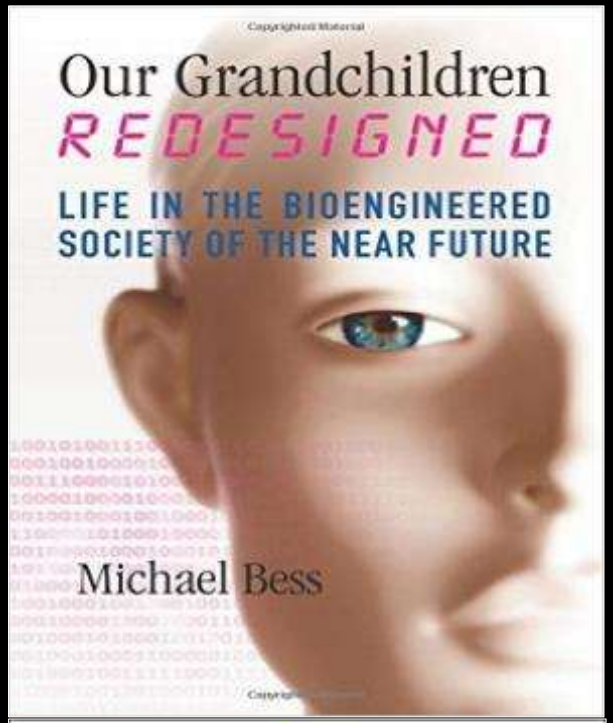
Germ Line Modification Enhancement (heritable)

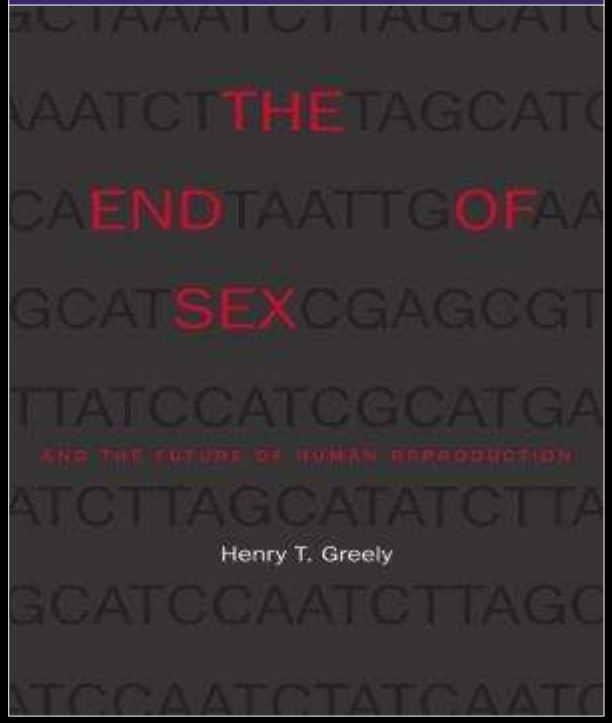
Very Different Ethical, Legal and Social Implications

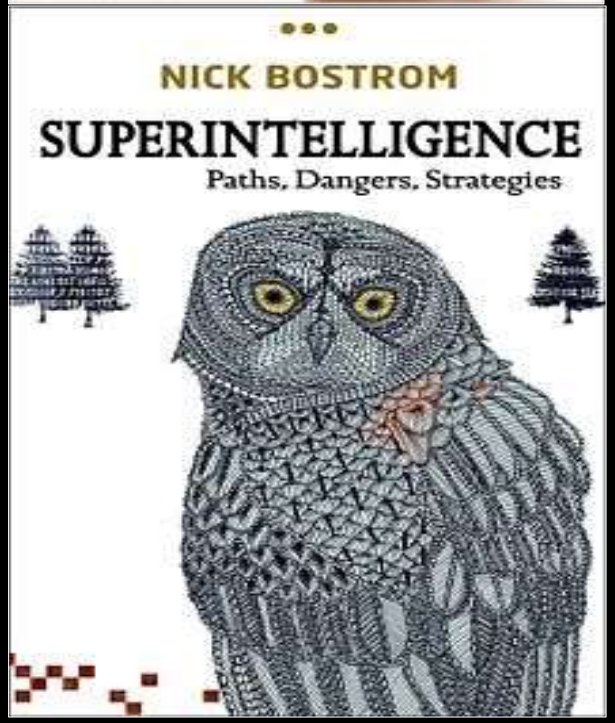
Somatic Cell Gene Editing

- monogenic versus multigenic diseases
- ex vivo modification versus targeted in situ modification
- detection of off-target effects
- confirmation that germ line not modified inadvertently
- epistatic interactions and gene-environment interactions of modified gene(s)
- creation of new risk/susceptibilities
  - T cell CCR5 gene modification confers resistance to HIV but increases susceptibility to W. Nile virus infection


GMO
Sapiens
The Life-Changing Science
of Designer Babies
Paul Knoepfler
World Scientific


Our Grandchildren
REDESIGNED
LIFE IN THE BIOENGINEERED
SOCIETY OF THE NEAR FUTURE
Michael Bess


THE
END
OF
SEX
AND THE FUTURE OF HUMAN REPRODUCTION
Henry T. Greely


NICK BOSTROM
SUPERINTELLIGENCE
Paths, Dangers, Strategies

Editing the Human Germ Line: No Longer An Abstract Question

Research article

CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes

Puping Liang[1], Yanwen Xu[1], Xiya Zhang[1], Chenhui Ding[1], Rui Huang[1], Zhen Zhang[1], Jie Lv[1], Xiaowei Xie[1], Yuxi Chen[1], Yujing Li[1], Ying Sun[1], Yaofu Bai[1], Zhou Songyang[1], Wenbin Ma[1], Canquan Zhou[1] ✉ and Junjiu Huang[1] ✉

(1) Guangdong Province Key Laboratory of Reproductive Medicine, the First Affiliated Hospital, and Key Laboratory of Gene Engineering of the Ministry of Education, School of Life Sciences, Sun Yat-sen University, Guangzhou, 510275, China

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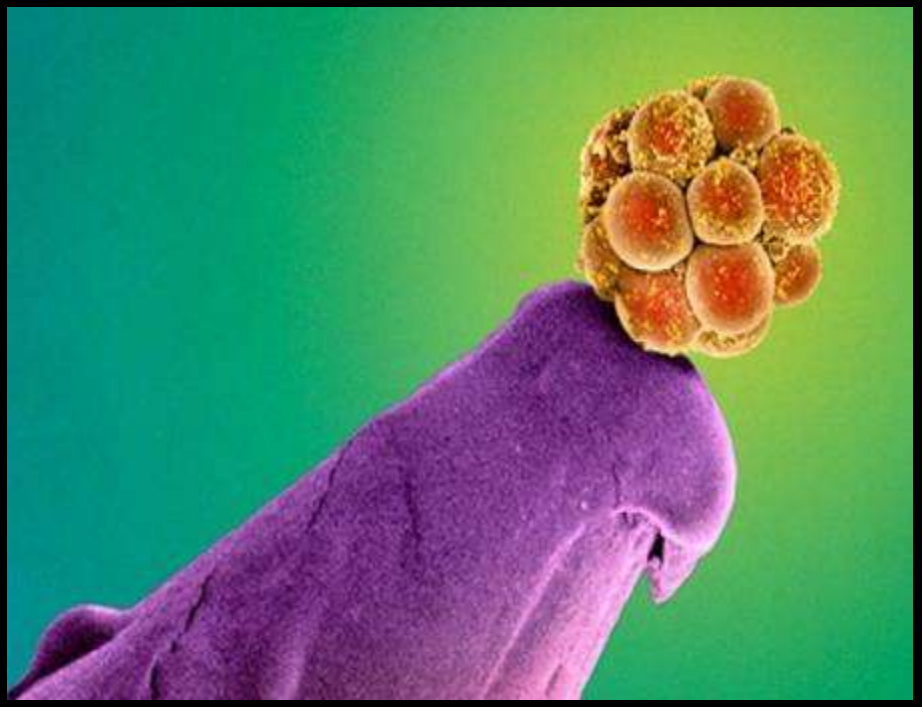


International Summit on Human Gene Editing: Washington, DC 1-3 December 2015

"Today, we sense that we are close to being able to alter human heredity. Now we must face the questions that arise. How, if at all, do we as a society want to use this capability?

Dr. David Baltimore

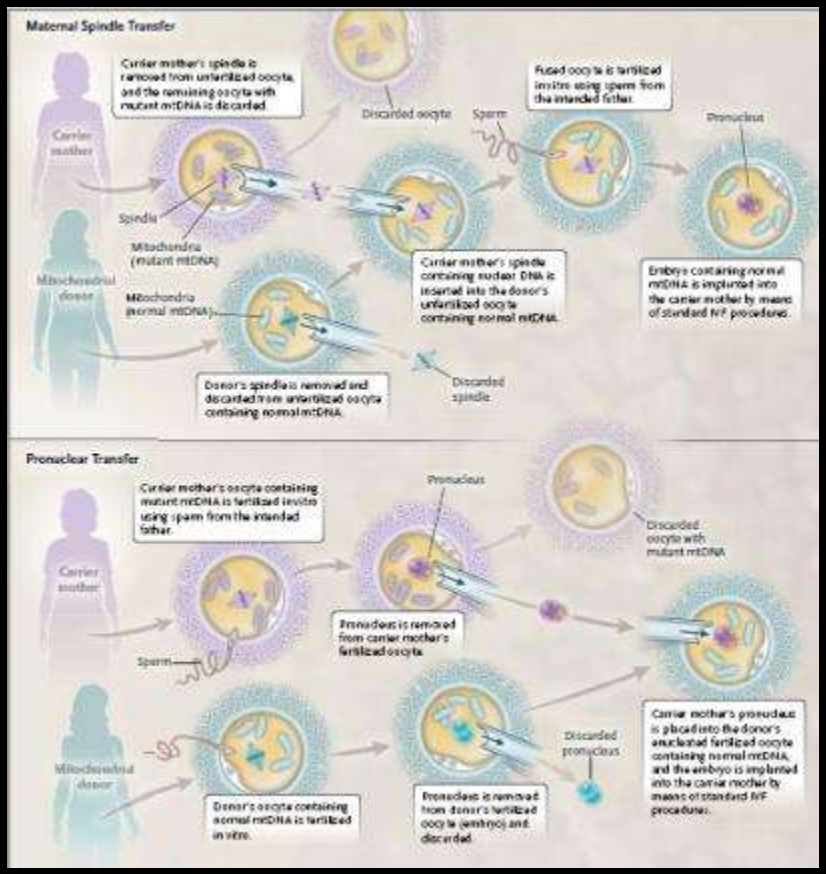
Production of Autologous Germ Cells from Reprogrammed Somatic Cells

- production of oocytes, spermatids and spermatozoa from induced pluripotent stem cells (iPSCs)
- accomplished in mice and production of healthy offspring
- prospect of gene editing of iPSCs and subsequent induced differentiation of primordial germ cells
- critical safety concerns regarding genomic instability of iPSCs

Human Fertilisation & Embryology Authority

THE FRANCIS CRICK INSTITUTE

Mitochondrial Replacement Therapy



From: M.J. Falk et al. (2016) NEJM 374, 1103

Germ Line Gene Editing

- heritable change
- complex ethical, social and legal issues
  - impact on future generations
  - moral status and rights of the unconsented embryo
- varied responses of patient advocacy groups affected by inherited disorders
  - “hell yes, do it” versus “let’s wait to see the technology mature”
- the lurking spectre of eugenics
  - social justice, equity, coercion
  - economic forces
  - who decides?

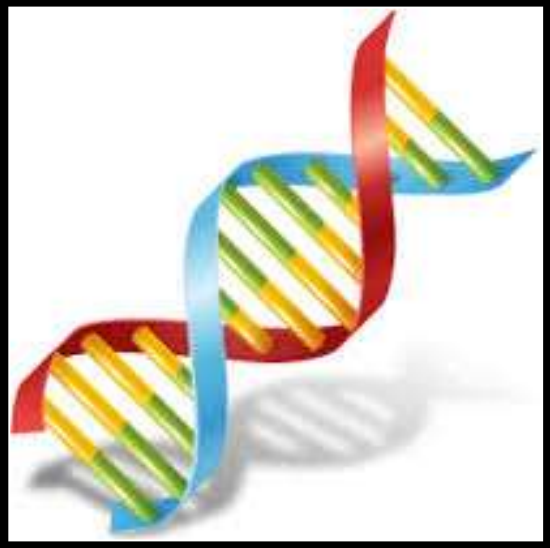
Medical Tourism

Offshore Surrogate Mothers, Stem-Cell Treatments and Organ Transplants

Market Precursors for Next Phase of Customized Gene Edited Human Embryos?

Democracy

(Re)Design



“What rights do we now hold (see) as self-evident?”

The Journey to the Anthropocene: The Long History of Technology-Enabled Human Augmentation

- improved health, shelter, labor, education
- improved nutrition, clean water, sanitation, infrastructure
- transportation
- public policies and protection of individual rights
- advances in clinical medicine and therapeutics
- devices, implants, prostheses
- computing, connectivity and communication
- in vitro fertilization
- somatic cell gene therapy

Arguments Against Bioenhancement

- “ ‘Playing God’ or secular version as ‘altering the natural balance of nature”
- subversion of human dignity by commodification of human traits and capabilities
- disruption/destruction of qualities that render us human
- inequitable access, prejudice and fragmentation of the species
- unknown and unintended consequences

Arguments in Favor of Bioenhancement

- limit human suffering
- intrinsic human drive in the Promethean quest for new knowledge, new capabilities and richer experiences
- next phase in the technological trajectory of human control of the natural world (the anthropocene)
- future evolution by Darwinian selection combined with purposeful design of desired new states
- who decides?, what is selected?, who has access?

Secret Meeting Of Scientists To Discuss Creating Synthetic Human Genome Fuels Speculation

May 16, 2016 | by Josh L Davis

Scientists Talk Privately About Creating a Synthetic Human Genome

By ANDREW POLLACK MAY 13, 2016

Sixty trays can contain the entire human genome as 23,040 different fragments of cloned DNA. James King-Holmes/Science Source

Scale Matters!

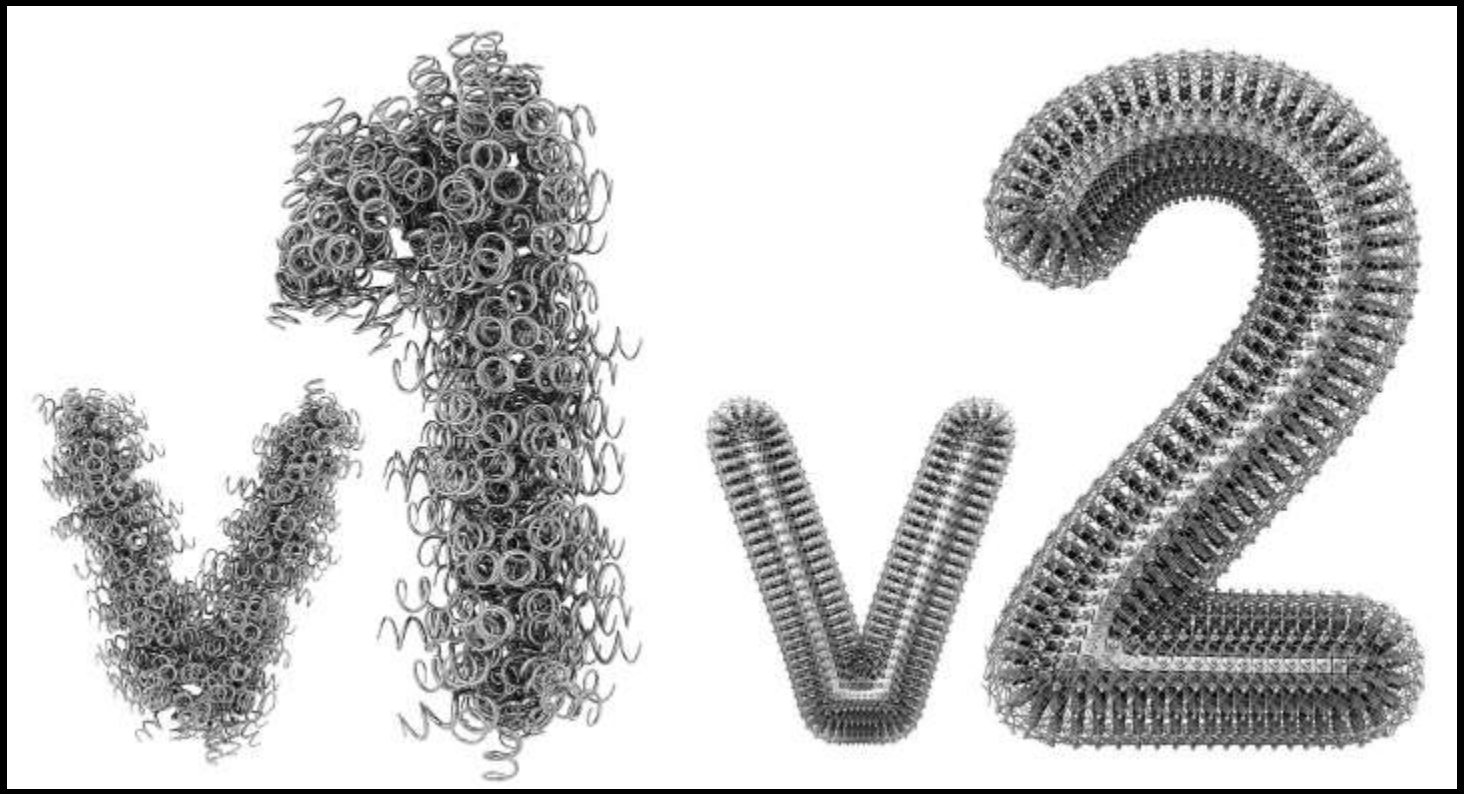
Worldwide DNA Sequencing Capacity

- doubling every 9-12 months
- 35 Petabases/year (2015) ≡ capacity for 250K human genomes
- Illumina X-10 sequencer instrument
  - 18,000 whole human genomes/year
- projected growth from petabyte to exabyte scale in a decade

Digital to Biological Conversion: The Next Phase in Biotechnology and Synthetic Biology

- genome sequences are digital
- transmission of digital code(s) for distributed dissemination and production
- prototype instruments for fully automated integration of complex biological signaling pathways
  - gene sequence → digital code → gene synthesis → mRNA and gene expression → protein product
- geographic uncoupling of knowledge of source code from product manufacturing

Technology Acceleration and Refinement

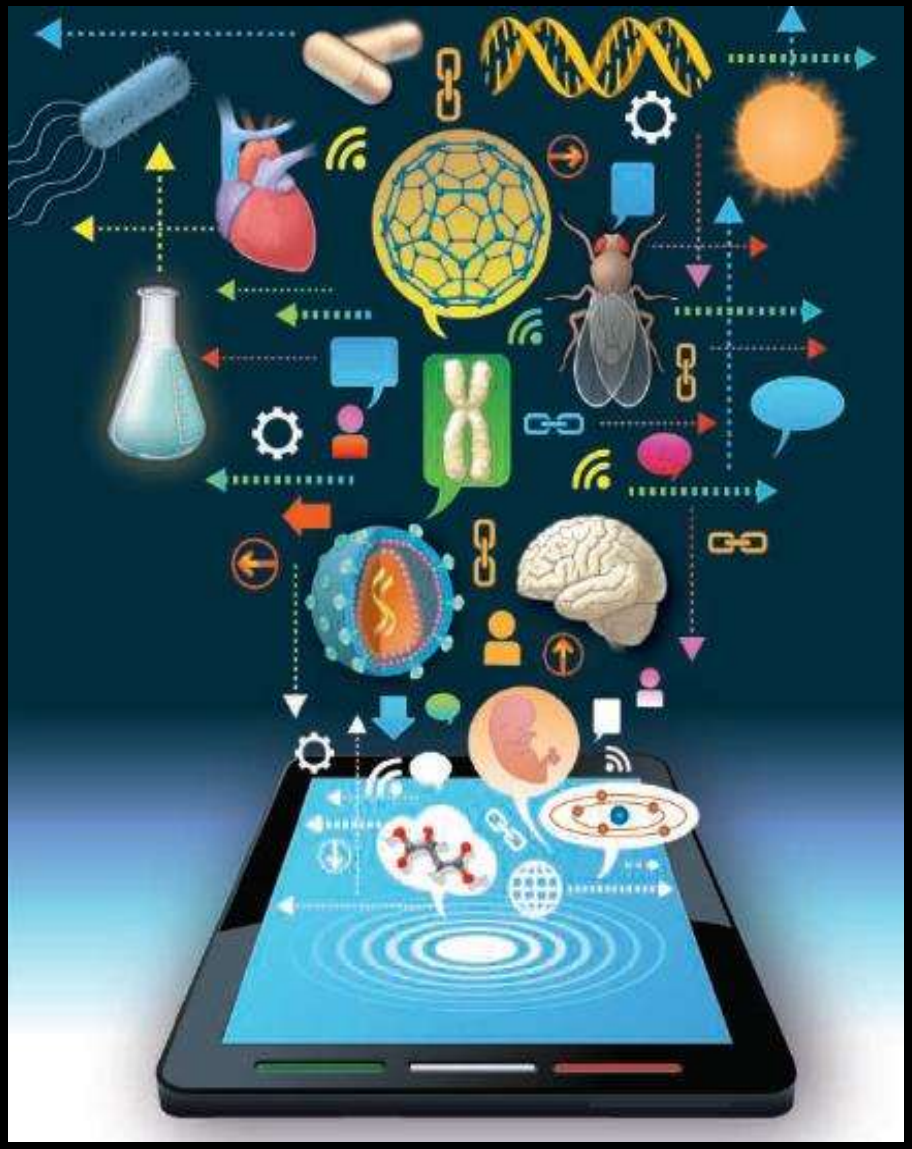


Big Biology and Biomedicine Meets Big Data

The Pending Zettabyte Era
1,000,000,000,000,000,000,000

Integration of Large Scale,
Multi-Disciplinary Datasets

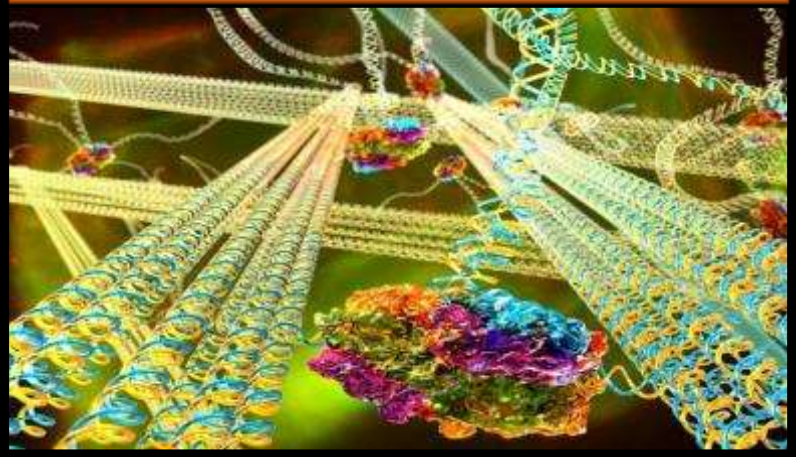
The Pending Era of Cognitive Systems: Overcoming the "Bandwidth" Limits of Human Individuals



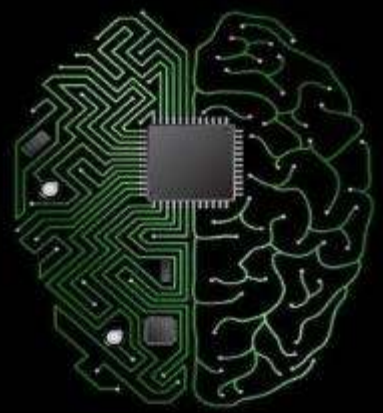
- limits to individual expertise
- limits to our multi-dimensionality
- limits to our sensory systems
- limits to our experiences and perceptions
- limits to our objective decision-making

Technology Convergence and Synthetic Biology: Biology and Medicine Meet Engineering and Computing

Modeling and Simulation of Biological Networks



Automation/Miniaturization and Robotic Production Suites



Exabyte and Zettabyte Computing Scale

Advanced Computing, New Analytical Tools and Machine Intelligence

“Digital Darwinism”

- a pending digital divide
- growing imbalance in sophistication of different end users and their ability to embrace data scale and complexity
- institutions unable to access and analyze large data sets will suffer ‘cognitive starvation’ and relegation to competitive irrelevance

Data Security

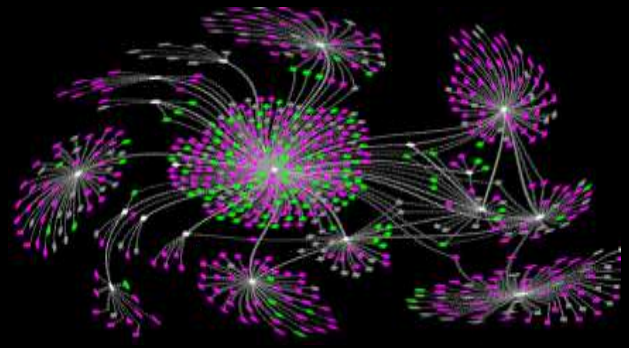
- data theft
- data corruption
- intellectual property
- ownership of personal genetic data
- genomic code as a target

Synthetic Biology, Genome Editing and Engineered Construction of Biological Circuits

digital biology: "it from bits"

engineered virulence

de novo synthesis of organisms



targeted modification of any biological circuit in any organ

mapping neural circuitry brain – machine interfaces

华大基因学院
BGI college
华大基因研究院
BGI research

accelerating technological diffusion

New Genetic Modification Technologies and Regulatory Oversight

- gene editing and gene drives represent an inflection point in genomic modification technologies
- technology is outpacing risk:benefit assessment and oversight mechanisms
- current regulations focus primarily on containment but new technologies are designed primarily for widespread use and dissemination

Synthetic Biology and Dual-Use Research of Concern (DURC)

- new classes of bioweapons and bioterrorism threat
- accident/error in manipulation of pathogens with pandemic potential
- generation of fully synthetic organism and introduction into natural ecosystems
- human germ line modification and eugenics
- engineered life forms and blurring the life-machine distinction
- social and distributive justice
- existential threats: real or imagined.

Synthetic Biology and Dual-Use Research of Concern (DURC): Seeking Balance

- risk:benefit
- safety and security
- hierarchical governance and oversight
  - codes of conduct, guidelines
  - regulation and legislation
  - moratoria and/or prohibition
  - international harmonization
- freedom of scientific enquiry and publication versus prudent constraint

Slides available @ http://casi.asu.edu/