ASU Complex Adaptive Systems Initiative
Arizona State University

PLuS ALLIANCE

Biodefense In The Age of Synthetic Biology and Precision Gene Editing

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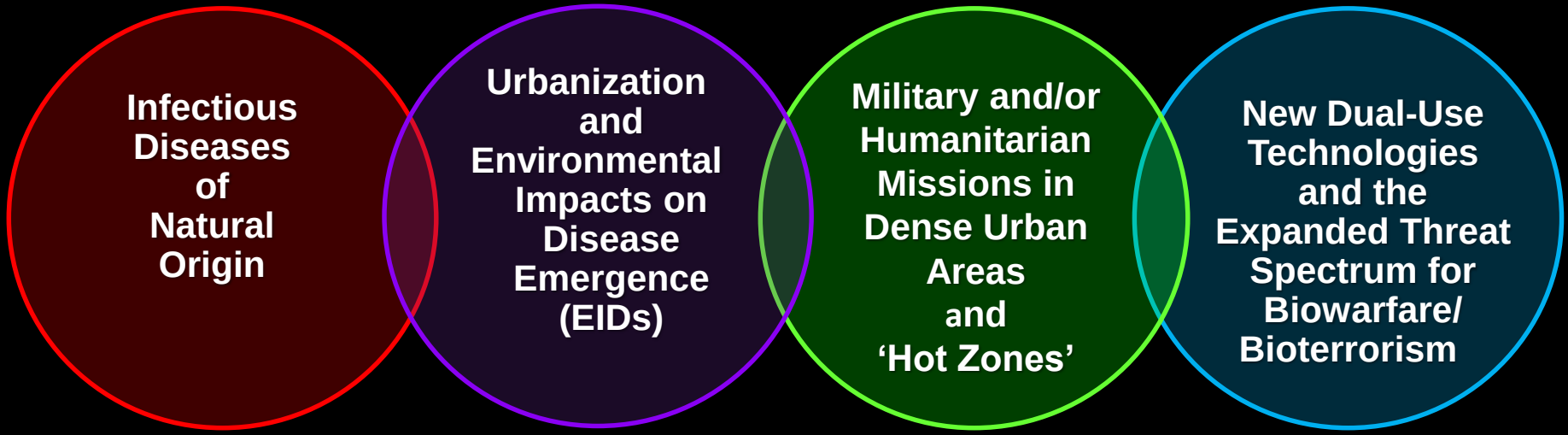
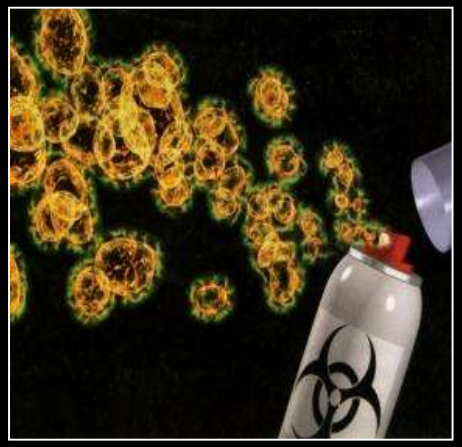
Presentation:
Global Security PLuS and New Approaches to Grey-Zone Threats:
Sydney, 11 September and Canberra 12 September 2018

The Biosecurity Quartet





- shared dimensions in deterrence, prevention, detection, treatment and recovery
- additional requirements in forensics, attribution and retribution for bioattacks

Synthetic Biology 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

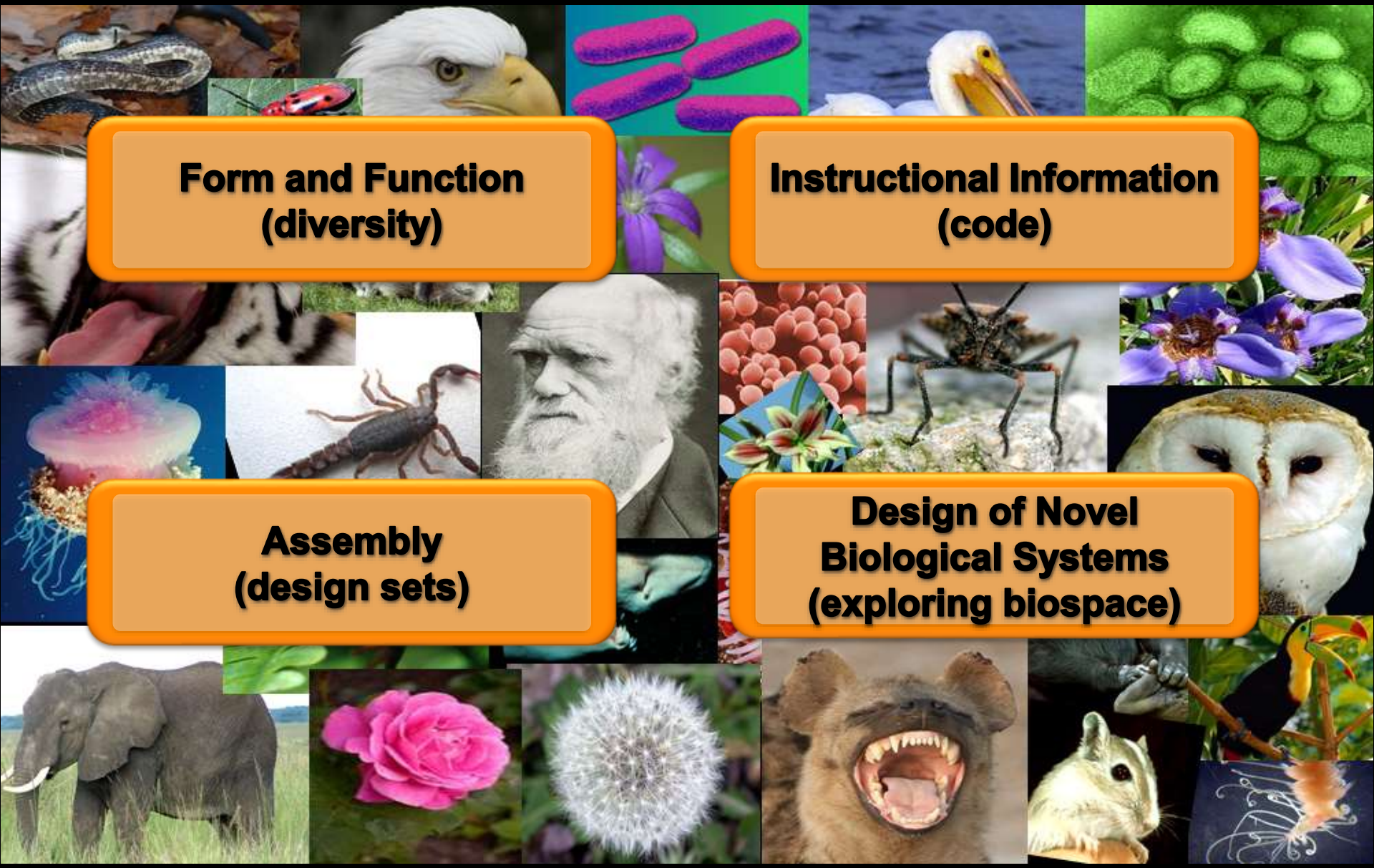
Technology Diffusion, Automation, Simplification and Cost Reduction

New Oversight Mechanisms and International Harmonization

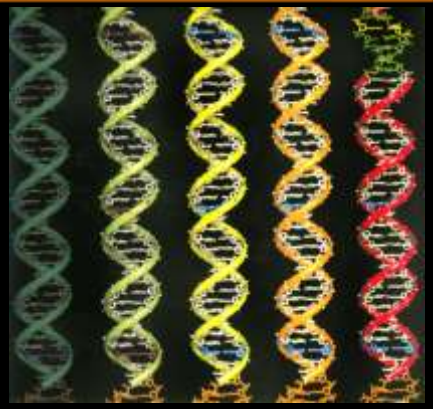
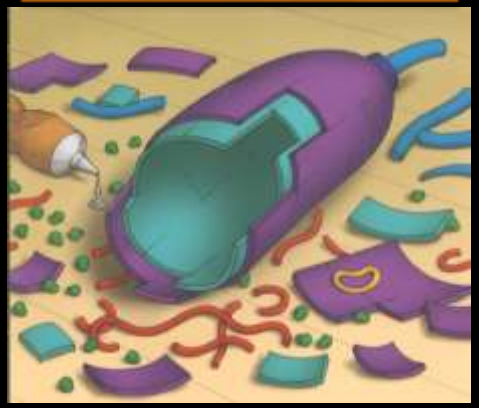
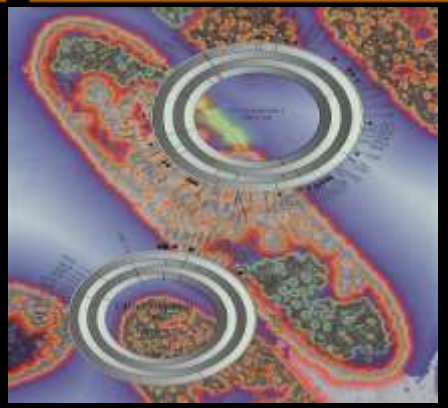
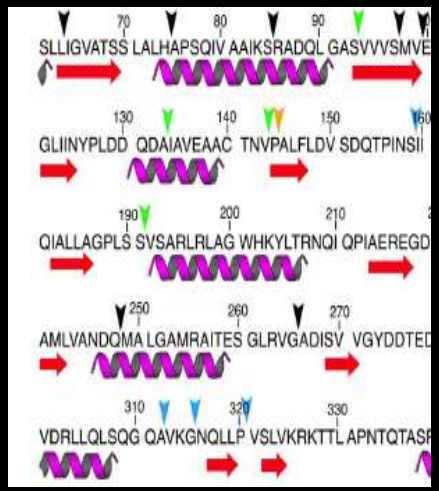
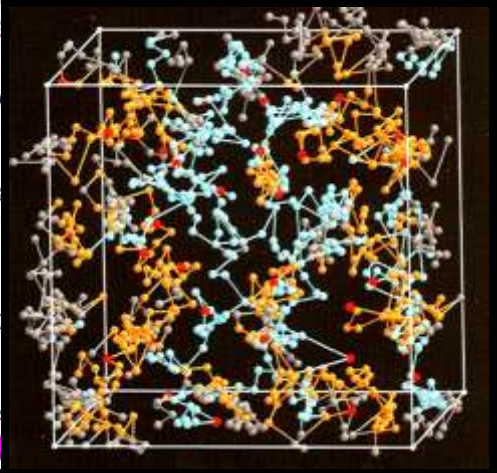
- beneficent and maleficent applications of same knowledge
- potential to cause profound societal disruptions based on misuse, error or accident

Biological Diversity and Variation: "Endless Forms Most Beautiful"

"Endless Forms Most Beautiful"
Systems and Synthetic Biology and Exploring Biospace



Synthetic Biology: Design-Build-Test

Code	Parts	Genome Assembly	Recipient “Chassis”
			
			
Efficient Insertion	**Pathway: Network Optimization**	**Scale Up and Economic Production**	**Oversight: Risk, Regulation and Responsibility**

Digital Biology (Code) and Synthetic Biology (Construction): "It from Bits"

- program and assemble new biological functions and organisms based on knowledge of the instructional 'rules' for synthesis and assembly
- reprogramming existing biological systems
- expanding "biospace"
  - design, simulation and construction of novel functions/organisms with no known natural evolutionary counterpart
  - novel biotic: abiotic combinations
- "directed evolution" and "accelerated evolution"

The Key Technology Platforms for Genome Modification and New Capabilities in Synthetic Biology

- **read** (sequence)
- **write** (synthesize)
- **edit** (precision changes in known genomes)
- **design** (unique genomes with no natural counterpart)
- **xenobiology** (new genetic codes using non-natural DNA bases)
- **archive** (inventory of global genetic diversity)

Worldwide DNA Sequencing Capacity and Massive Data Flows

- doubling every 6 - 9 months
- 250K human genomes = 35 petabases
- Illumina X-10 sequencing instrument
  - one haploid genome every minute (3 Gbp/min)
  - 18,000 whole human genomes/year
- projected growth of global sequencing information to exabyte/zettabyte scale in a decade

Synthetic Biology:
Myriad Applications in Diverse Industrial Sectors

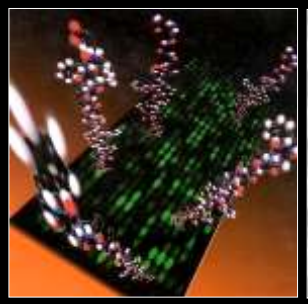
Healthcare

Public Health

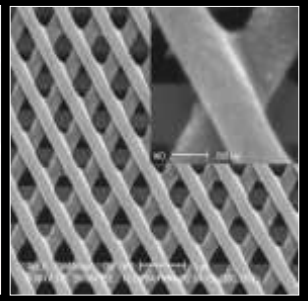
Agriculture

Functional Foods

Novel Materials



Textiles



Bioenergy and Biofuels

Industrial Enzymes

'Green' Mfg

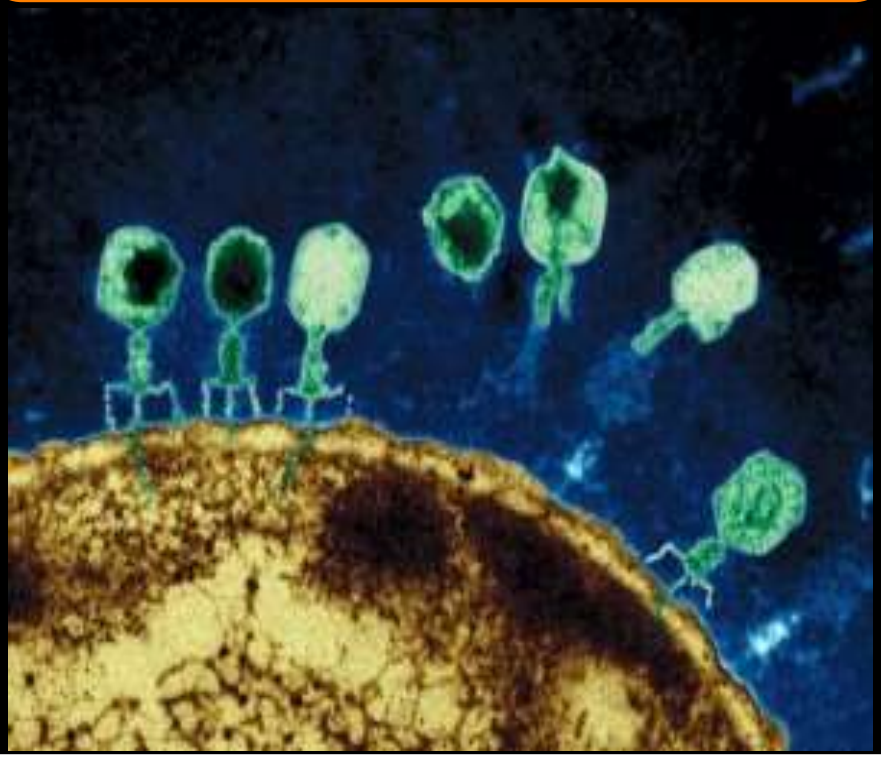
Bio-Remediation

Novel Sensors

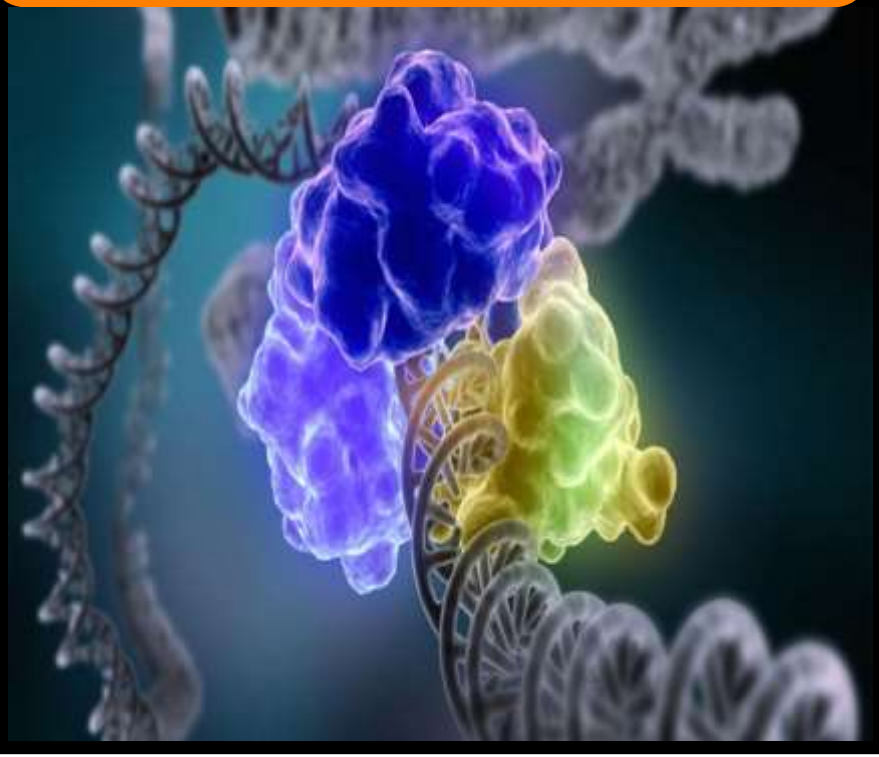
DNA Data Storage

Programmable Nucleases and Genome Editing: The Game Changer in Synthetic Biology

Microbial CRISPR Defense System Against Viruses



CRISPR-Cas Guided Excision and Insertion of New Genes and Substitution of Individual DNA Bases

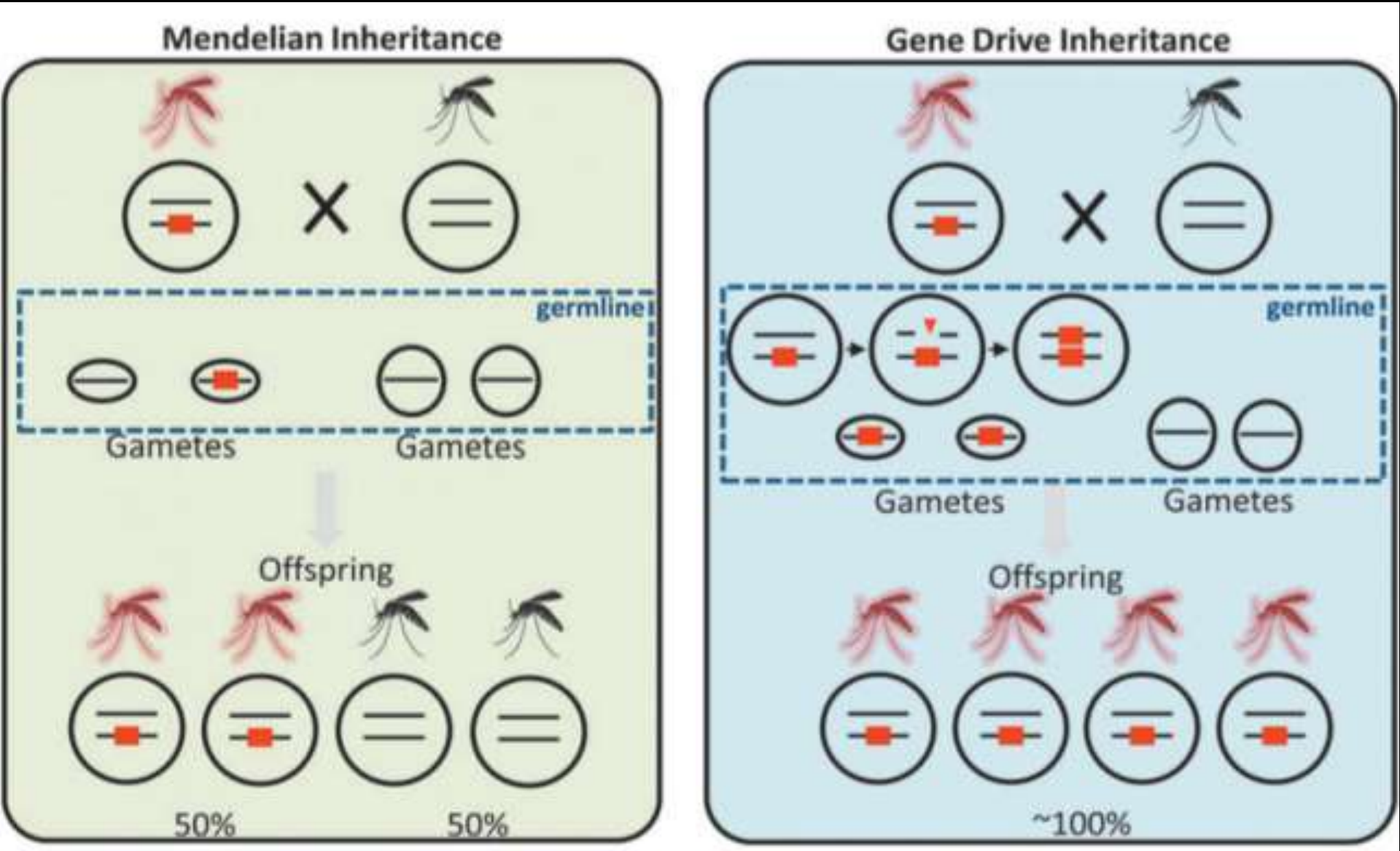


- using an evolutionary mechanism from 3-4 billion years ago for twenty first century genome design
- delete, replace or change genes in any living species, including humans

Gene Editing and Base Editing

- ‘knockout’
  - delete or render non-functional
- ‘silence’
  - switch off expression but DNA code unchanged
- ‘activate’
  - switch on expression of silent genes
- somatic modification (augmentation)
  - changes in non-germ line cells with no inheritance by progeny
- germ line modification (enhancement)
  - changes in gametes (sperm/egg) with inheritance by progeny

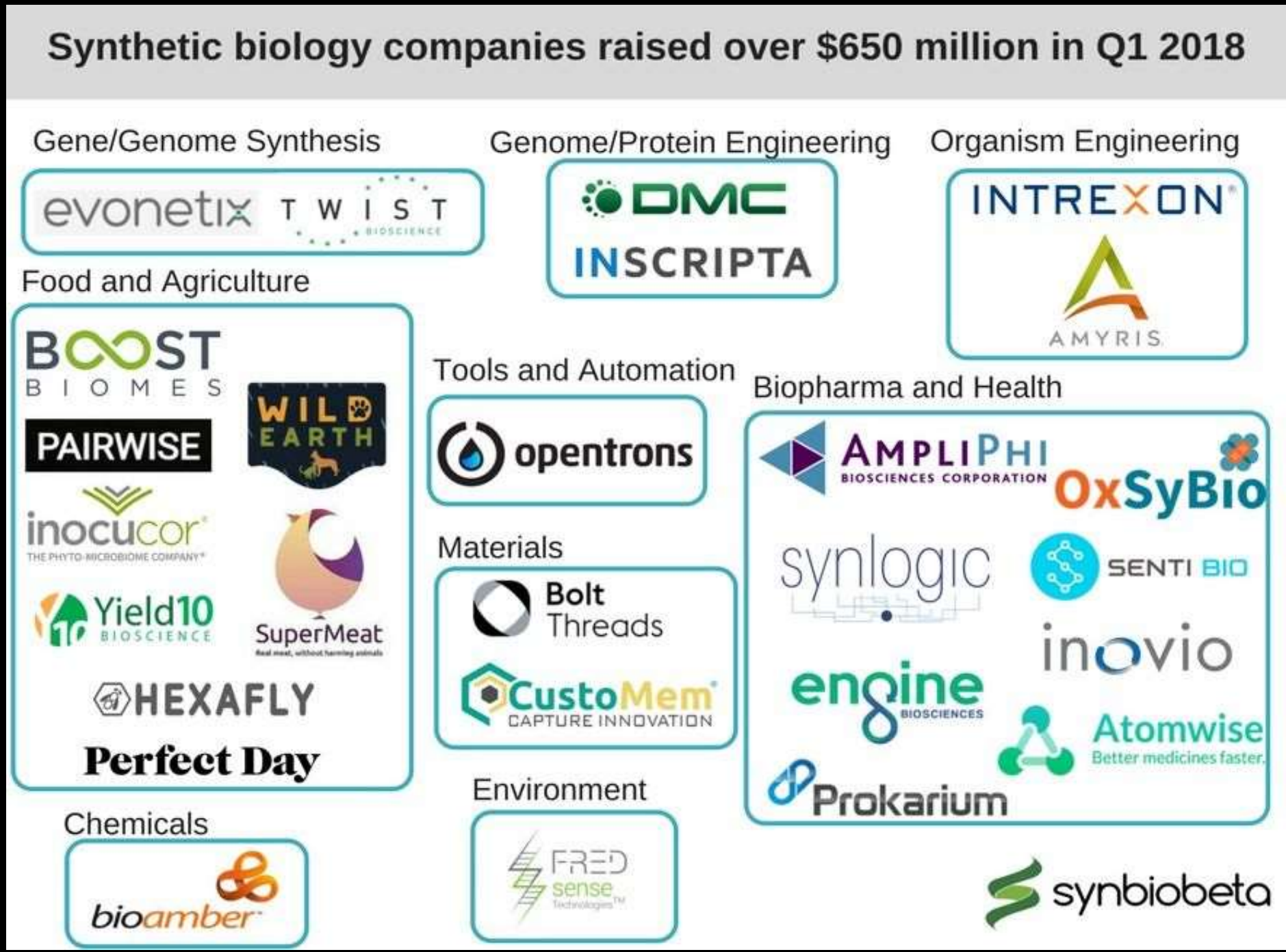
Nuclease-Based Gene Drives: Genetic Modification of a Species to Eliminate Itself



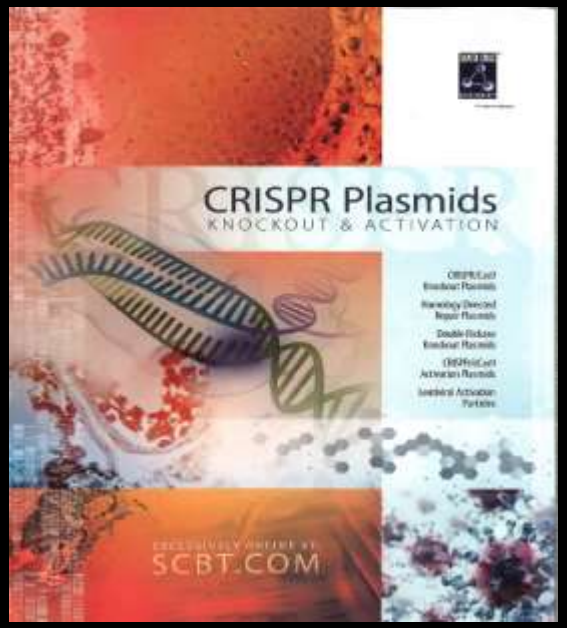
DOI: 10.1089/crispr.2018.29001.tno

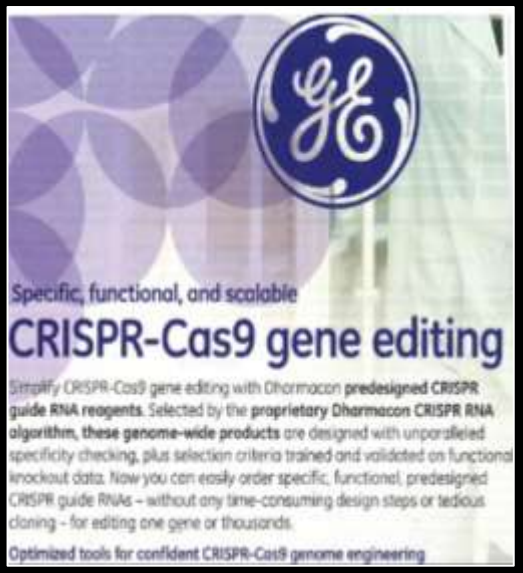
Explosion of the Gene Editing and Gene Therapy Ecosystem

Synthetic biology companies raised over $650 million in Q1 2018



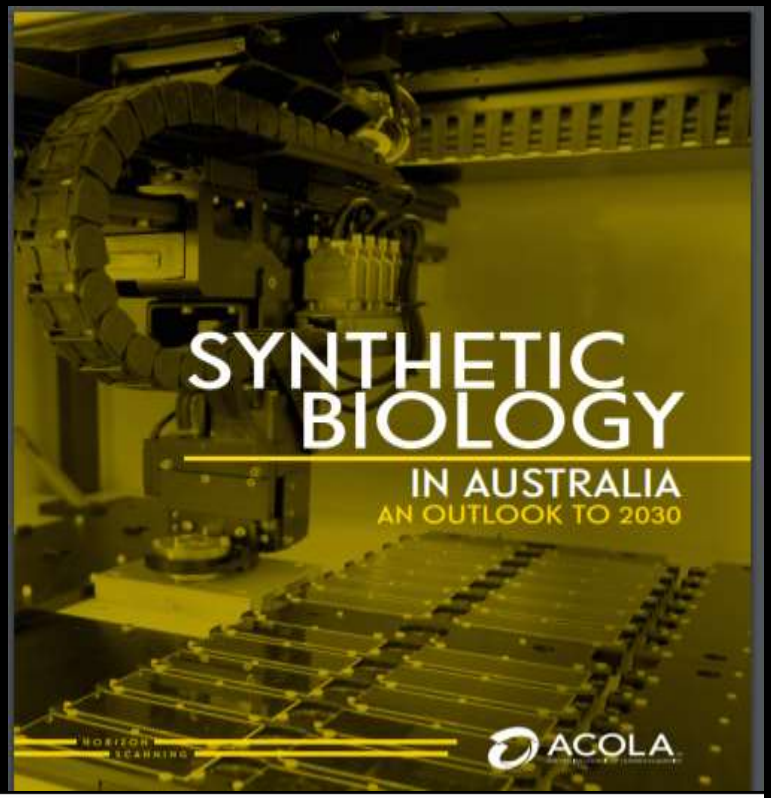
Rapid Growth of a New Industry Supply Chain for CRISPR-Cas Gene Editing Services





SBA

SYNTHETIC BIOLOGY AUSTRALASIA

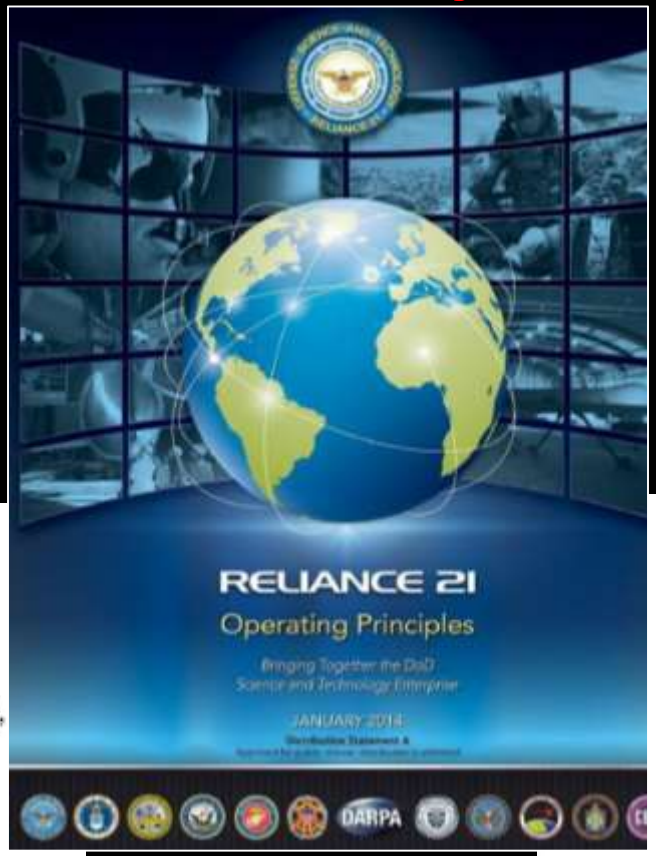


CSIRO

SynBio FSP

Our Synthetic Biology Future Science Platform is positioning Australia to play a role in one of the fastest growing areas of modern science so that we can understand global developments and, where appropriate, contribute to advances in areas including manufacturing, industrial biotechnology, environmental remediation, biosecurity, agriculture and healthcare research.

Synthetic Biology and US Military Science and Technology



DARPA

www.darpa.mil

- Biowarfare defense – advanced diagnostics, decontamination, medical therapies
- Tactical Biomedical Technologies – mobile trauma stabilization, novel therapeutics, generation and storage of blood products
- Restorative Biomedical Technologies – restore complex tissues after traumatic injury, neural-controlled prostheses
- Bio-inspired Platforms and Systems – mimic locomotion and chemical/visual/aural sensing
- Microphysiological Systems – organs-on-chip to mimic human physiological systems
- In Vivo Nanoplatforms for diagnostics and therapeutics
- Living Foundries – create engineering framework for synthetic biology

www.dtra.mil

- Reduce, eliminate, counter, mitigate weapons of mass destruction
  - WMD sensing and recognition
  - Threat containment, filtering, shielding
  - Decontamination
  - Forensics
  - Neutralization of CBRNE materials



Synthetic Biology: applications in Defence



[dstl]

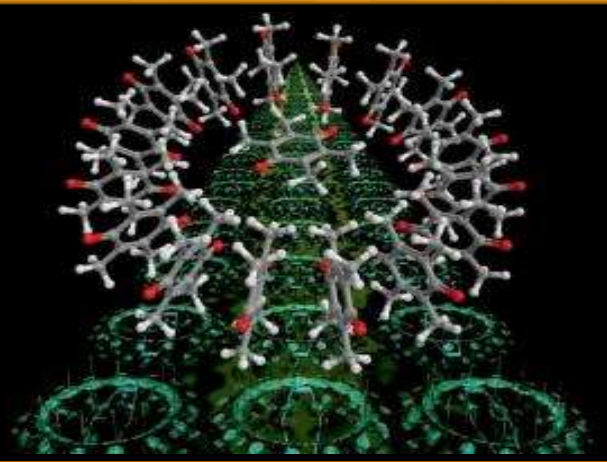
01 October 2014

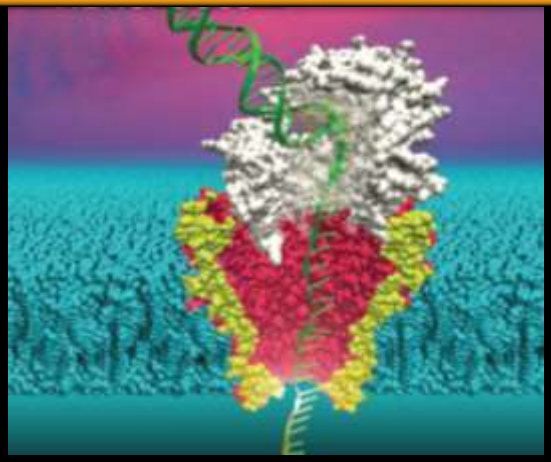
OFFICIAL

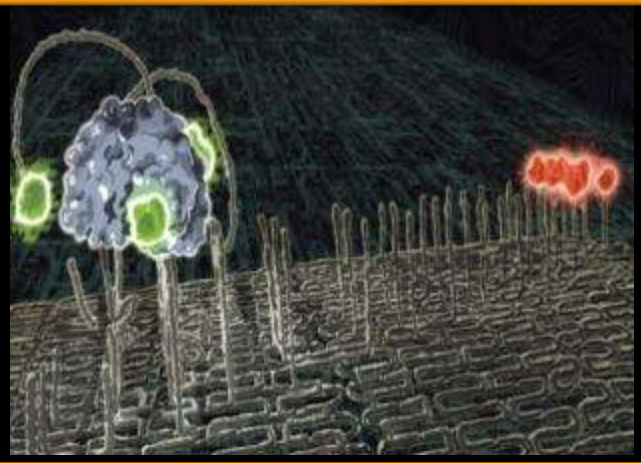
Ministry of Defence

Ångstrom Level Design: Directed Molecular Assembly of Novel Materials and Sensor Displays

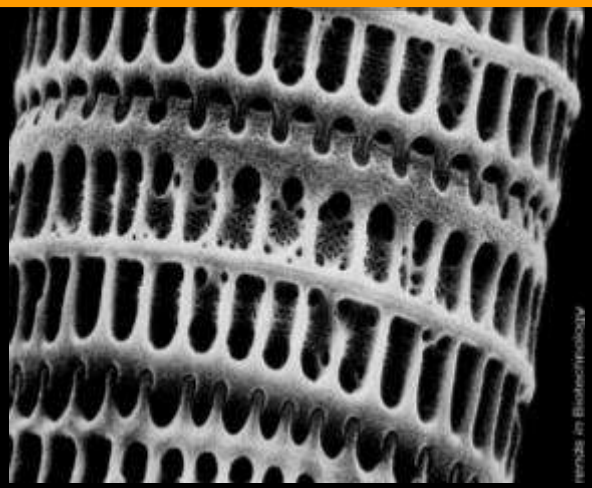
Sensors and Molecular Machines

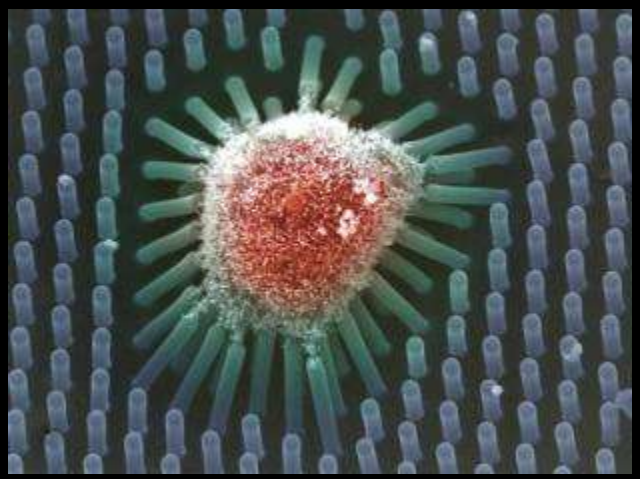




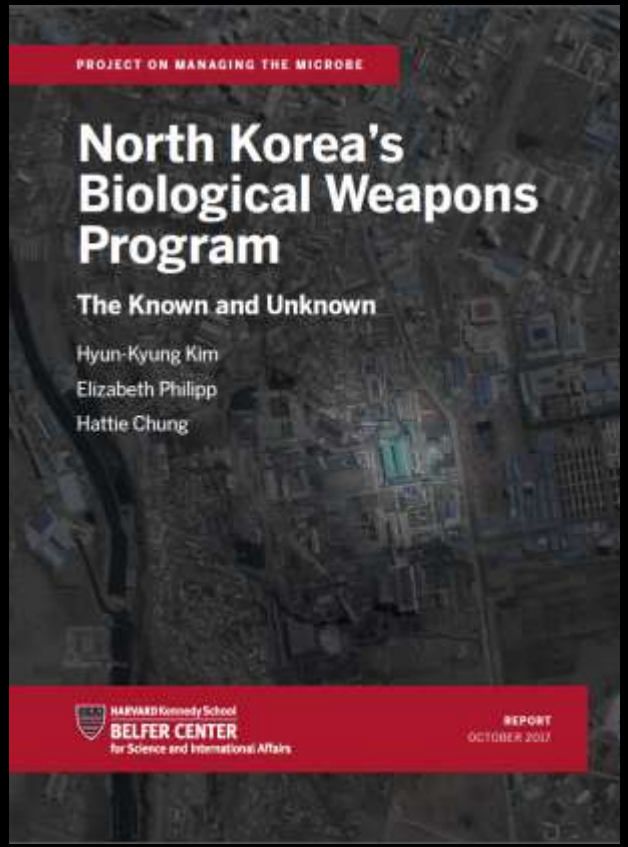


Biomimetic Design: Organic-Inorganic Hybrids

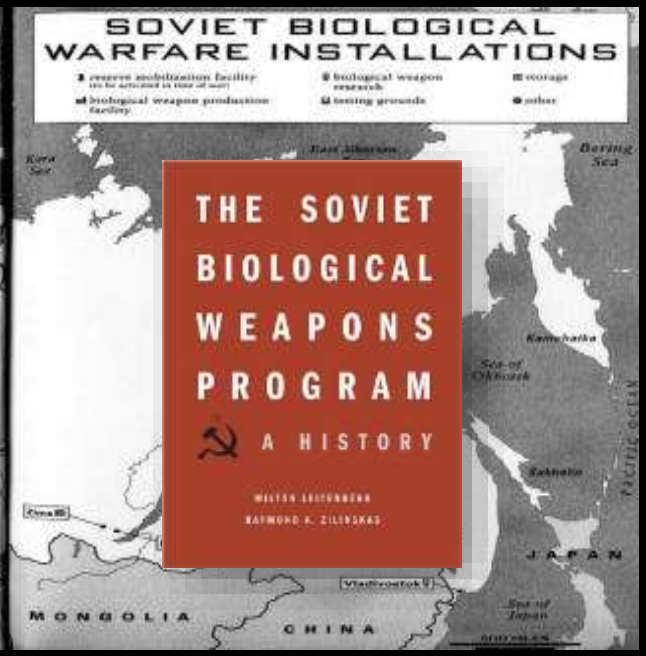


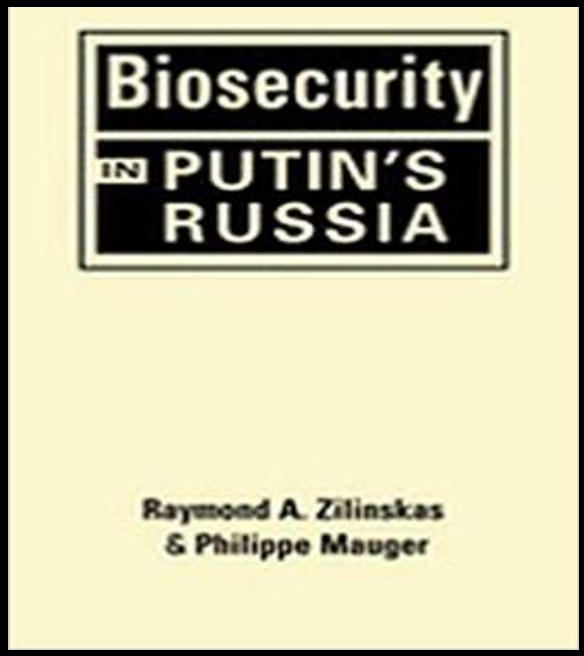


The Appeal of CBW for Asymmetric Warfare and Terrorism



FSU and Russian CBW Programs





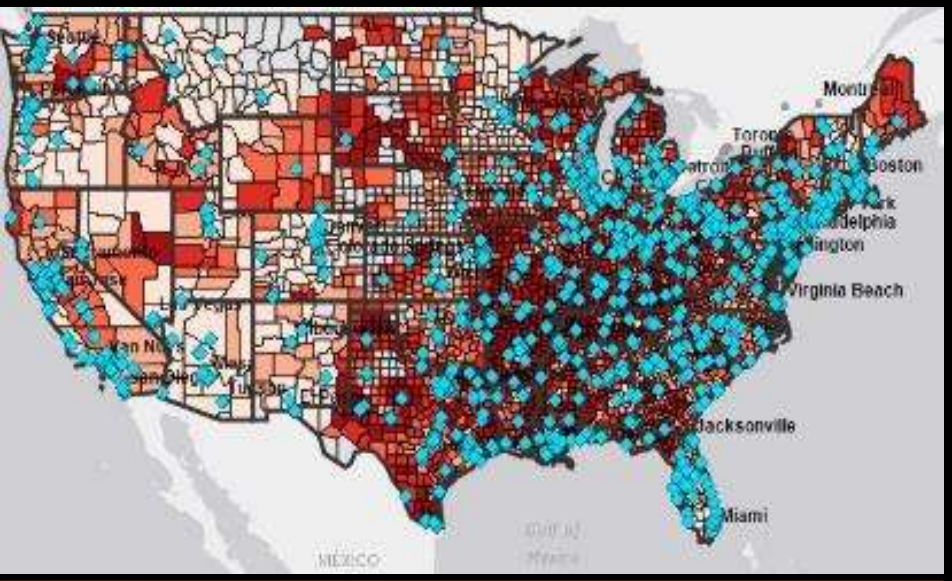
"Armies of the future will need weapons based on new physical principles, including genetic and psychophysical science."

President Vladimir Putin
essay, Rossiyskaya Gazeta, 2012

- major R&D investments and sophisticated expertise in biotechnology and artificial intelligence
- purposeful creation of large diaspora for training in US/EU universities
- relentless industrial espionage and cyber- exfiltration efforts
- mapping the genetic diversity of human populations

National Security Implications of Genome Data on Populations

Population Databanks



Individual Profiles

Foreign Access to Data

iCarbonX

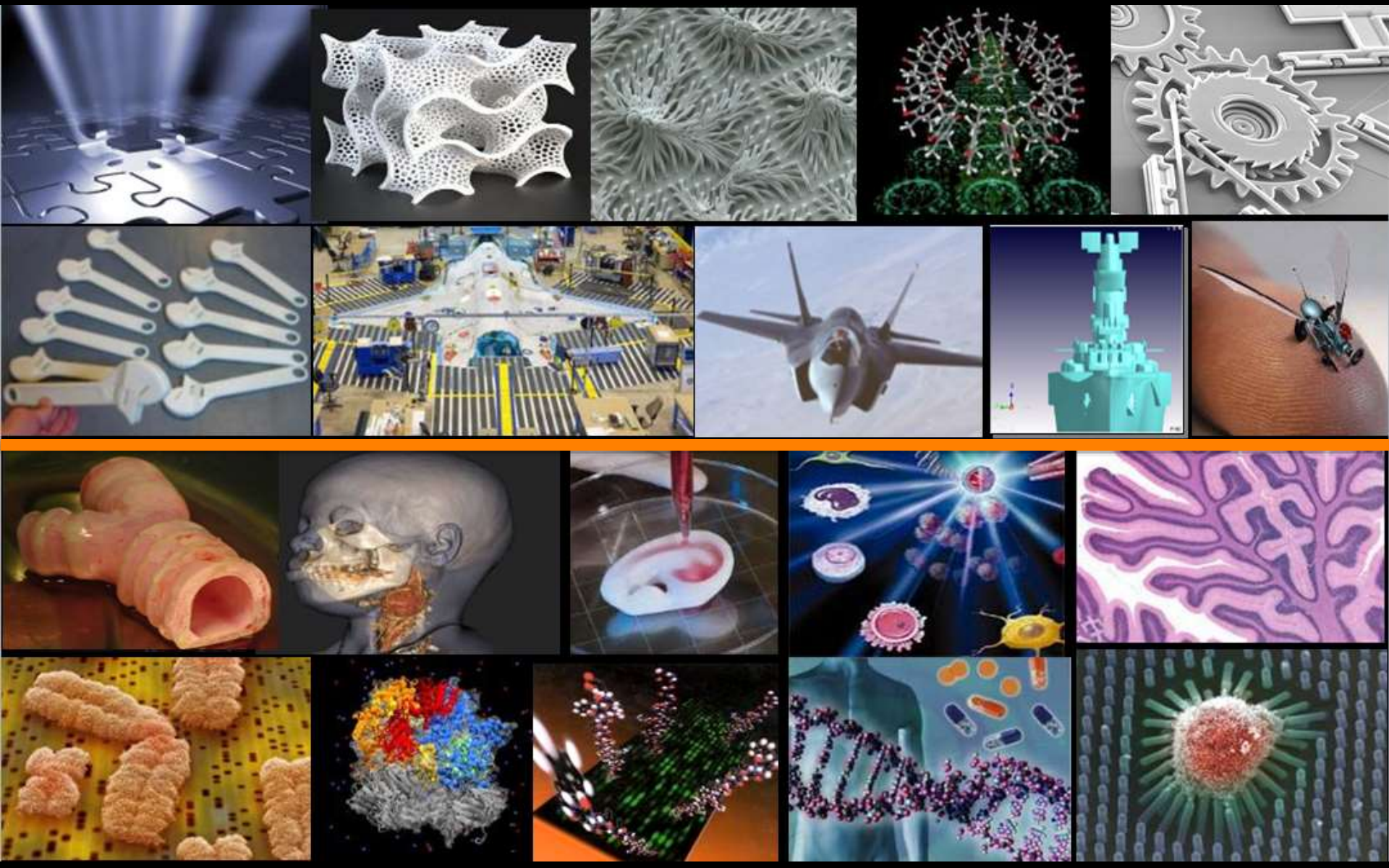
华大基因
BGI

Data Security

Digital Biology

- DNA is a digital code
- biology at internet speed
  - transmission of digital instruction code to any location
  - geographic uncoupling of design (code) from manufacture (synthesis and assembly)

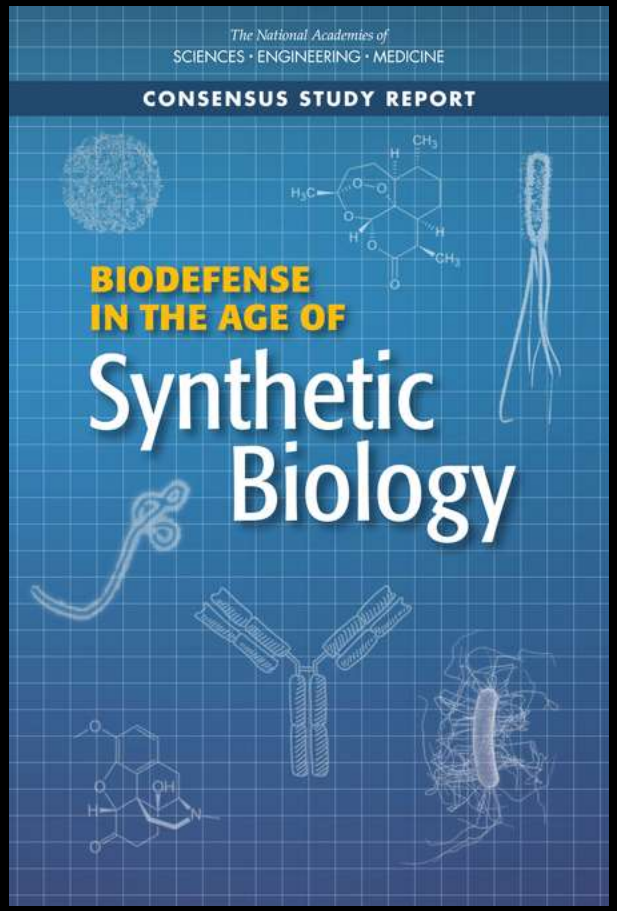
Advanced Manufacturing Digital Programming of New 3-D Fabrication and Assembly Technologies



Biodefense in an Era of Synthetic Biology and Precision Gene Editing

- what are the implications for the future biothreat spectrum?
- what are the timeframes that particular novel threat categories are likely to evolve?
- what new surveillance and counter-measures will be needed?
- how do current international agreements regarding WMD/CBW need to be updated to address the changing threat spectrum?
- gray-zone complexity

A Risk Scale for Synthetic Biology: Dual-Risk Research of Concern (DURC)



high

- alterations of known pathogens
- engineering of pathogenic microbes with entirely novel properties
- modification of microbial metabolic pathways and synthesis of novel materials

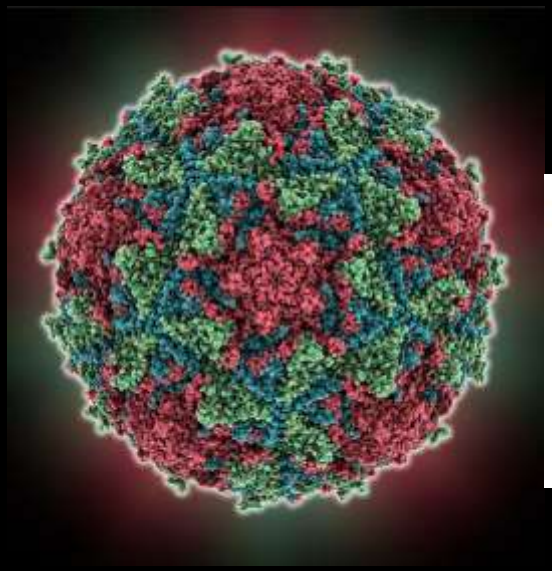
high to medium

- modification of human organ systems
  - microbiome, immune defenses
  - brain

medium to low

- gene drives and ecosystem disruption
- large scale eugenics

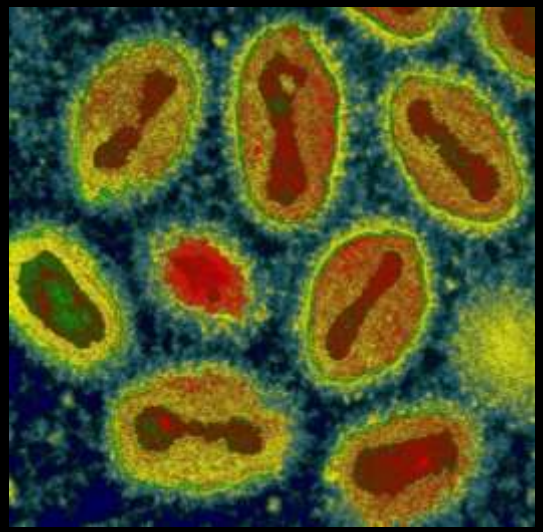
De Novo Synthesis of Pathogens



Science (2002) 297, 1016

Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template

Jeronimo Cello, Aniko V. Paul, Eckard Wimmer*



PLOS ONE https://doi.org/10.1371/journal.pone.0188453
January 19, 2018

Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments

Ryan S. Noyce[1], Seth Lederman[2], David H. Evans[1]*

1 Department of Medical Microbiology & Immunology and Li Ka Shing Institute of Virology, University of Alberta, Edmonton, Alberta, Canada, 2 Tonix Pharmaceuticals, Inc., New York, New York, United States of America

DURC With Pathogenic Microorganisms

known pathogens

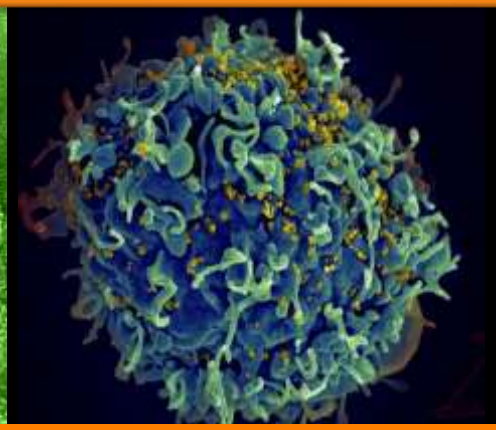
- increase virulence/transmissibility/dissemination/persistence
- evasion of detection/diagnosis
- engineer resistance to countermeasures
- compromise host immunity
- alter host range and/or tissue tropism

novel threats

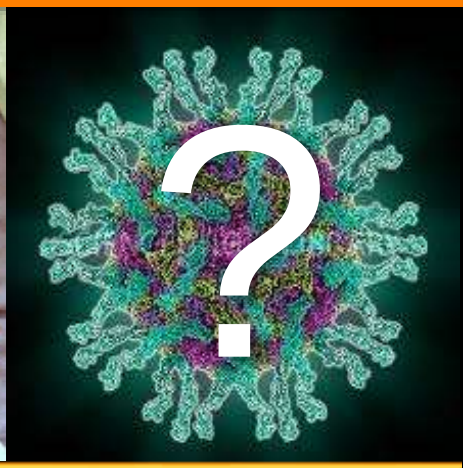
- reconstitute eradicated or extinct microorganisms
- de novo design of synthetic organisms with these virulence traits
- immunologically naive populations

"One Health"
Zoonotic Diseases as Major Human Health Threats:
A Rich Reservoir for Microbial Manipulation

pandemic (avian) influenza	HIV	West Nile virus	MERS- CoV



Ebola virus	bush meat food chain	Zika virus	what's out there?

Thinking Beyond Select Agents: The Impact of 'Agent X'(Natural or Nefarious)

atypical disease clusters and novel features

quarantine logistics

incident management

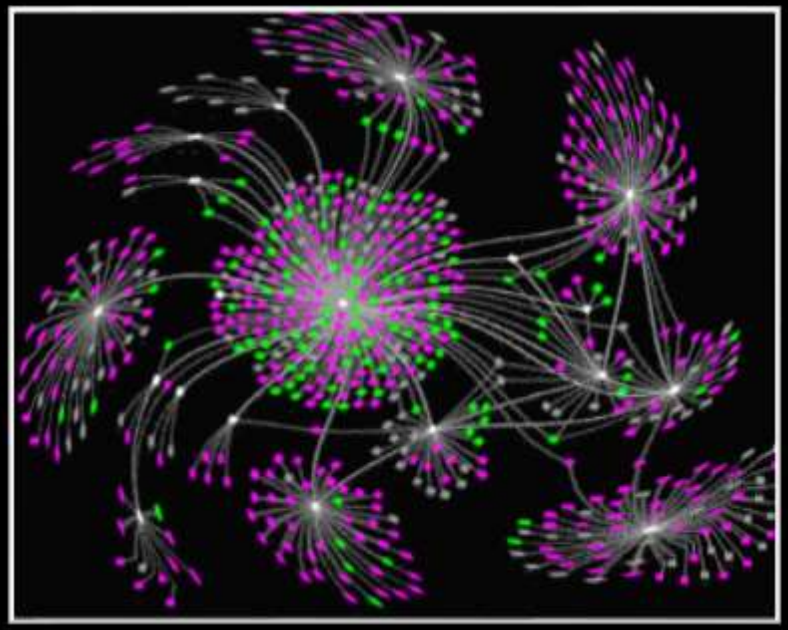
Engineering Microbial Pathogens: Shifting the Disruption Impact from Acute to Chronic

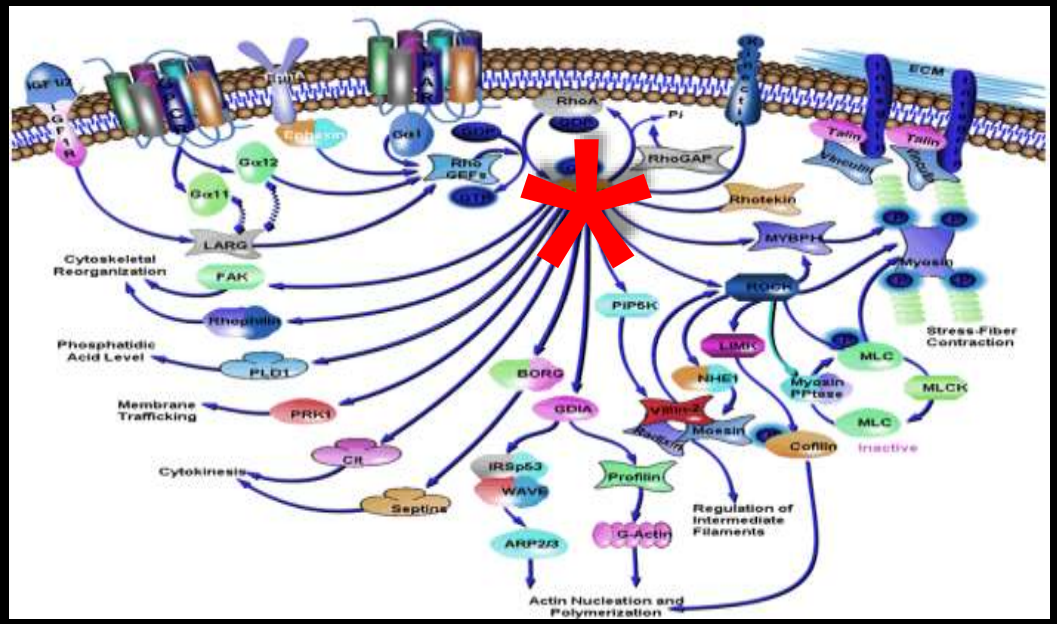
- overwhelm preparedness resources and paralyze healthcare delivery systems
- high chronic morbidity in survivors and resulting clinical burden (human) or economic loss (agriculture and trade)
- racial and ethnic selectivity (human) and genetic bottlenecks (agricultural livestock and crops)
- acute (panic) and enduring long term psychological impact (erosion of trust in government)

Latent Agents: Activation on Demand

- ‘silent’ integration into host genome
  - targeted insertion in specific organs/cell types
- co-infection and co-insertion of activation trigger (gene enhancers)
- activation on demand by exposure to enhancer triggers
  - from targeted effects on individuals/groups to widespread population effects
  - silent insertion into germ line (sperm, eggs) and trans-generational vulnerabilities

Synthetic Biology and DURC: "Thinking Beyond Bugs"

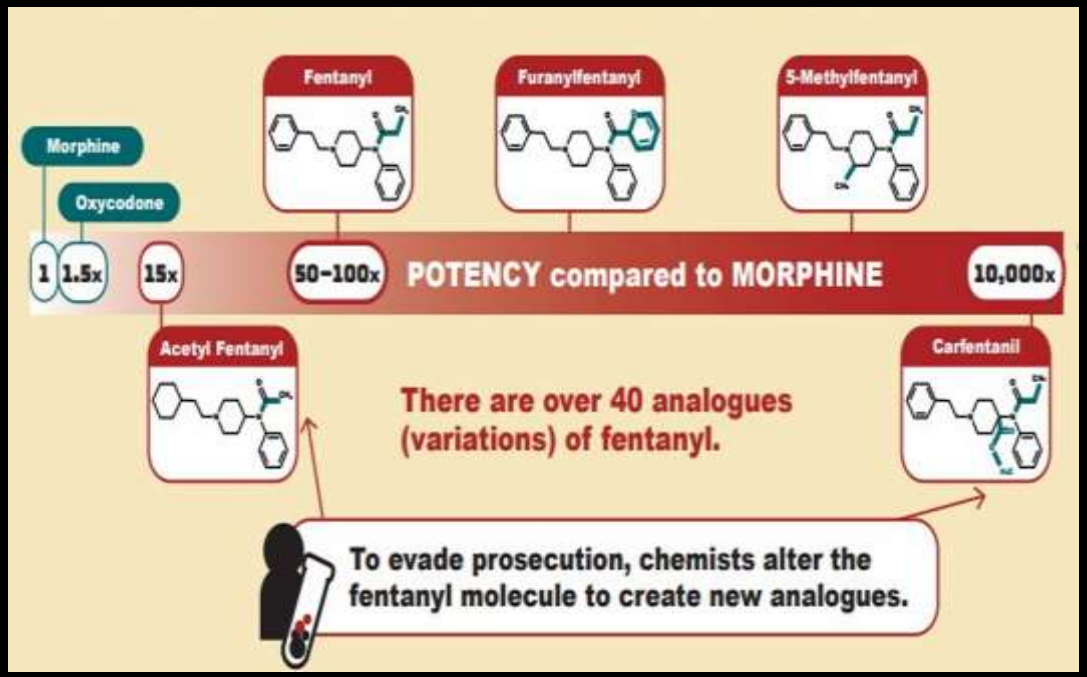




- precision medicine
  - mapping the molecular networks (circuit diagrams) of every cell type in the body and circuit disruptions in disease
- creates roadmap for next-generation chemical warfare agents to target specific molecular circuits

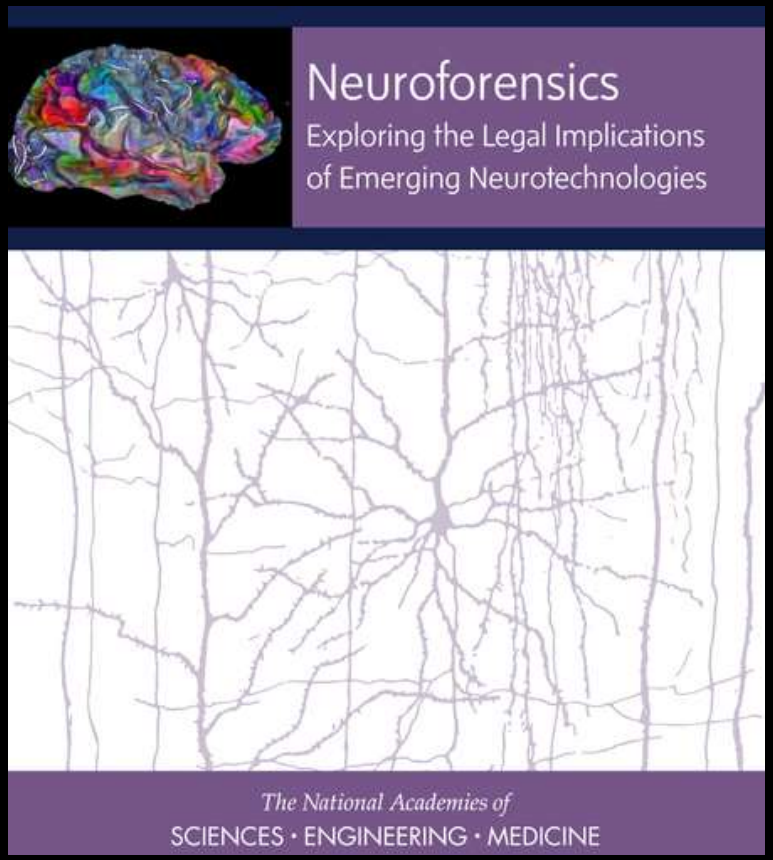

СЕВЕРНЫЙ

Purposeful Societal and Economic Disruptions via Design of Ever-Changing Waves of Addictive Illicit Drugs Generated by Synthetic Biology



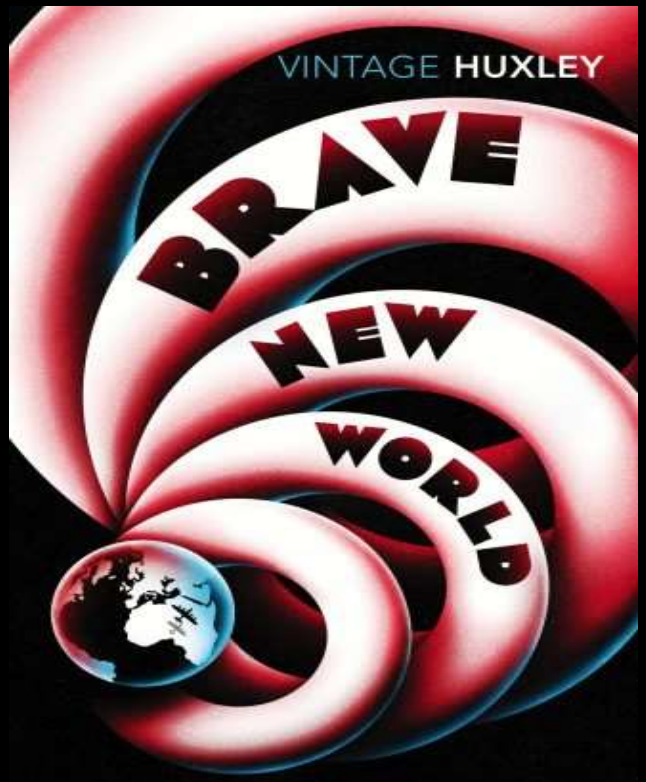
Dual-Use Implications of Advances in Brain Science

Chemical or Electronic Modulation of Specific Neural Circuity: New Warfare Capabilities and Societal Vulnerabilities



- fear, paranoia depression, suicidal ideation
- aggression
- disruption of sleep patterns
- memory modulation
- addiction
- lethargy
- hallucinations

Editing Humanity:
Moral and Legal Constraints or Hubris and Irresistible Inevitability?



- long standing science fiction scenarios and philosophical, religious, ethical, legal debates on the societal implications
- previous luxury of theoretical debate because the technology was not available

WORLD

China, Unhampered by Rules, Races Ahead in Gene-Editing Trials

U.S. scientists helped devise the Crispr biotechnology tool. First to test it in humans are Chinese doctors

A cancer patient at Hangzhou Cancer Hospital goes through a procedure that includes infusing his own cells after genetic editing using Crispr.
PHOTO: QILAI SHEN FOR THE WALL STREET JOURNAL

By Preetika Rana, Amy Dockser Marcus and Wenxin Fan

Jan. 21, 2018 2:19 p.m. ET

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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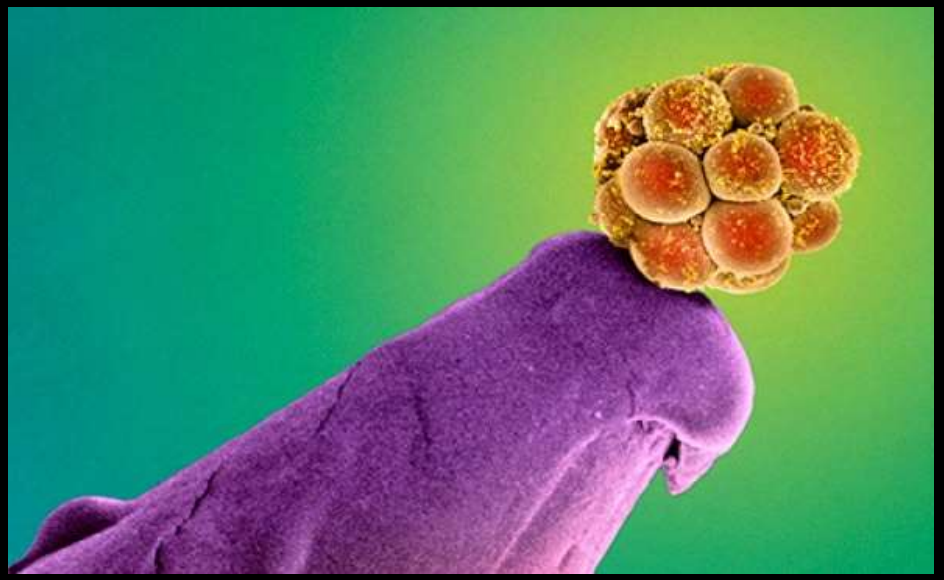
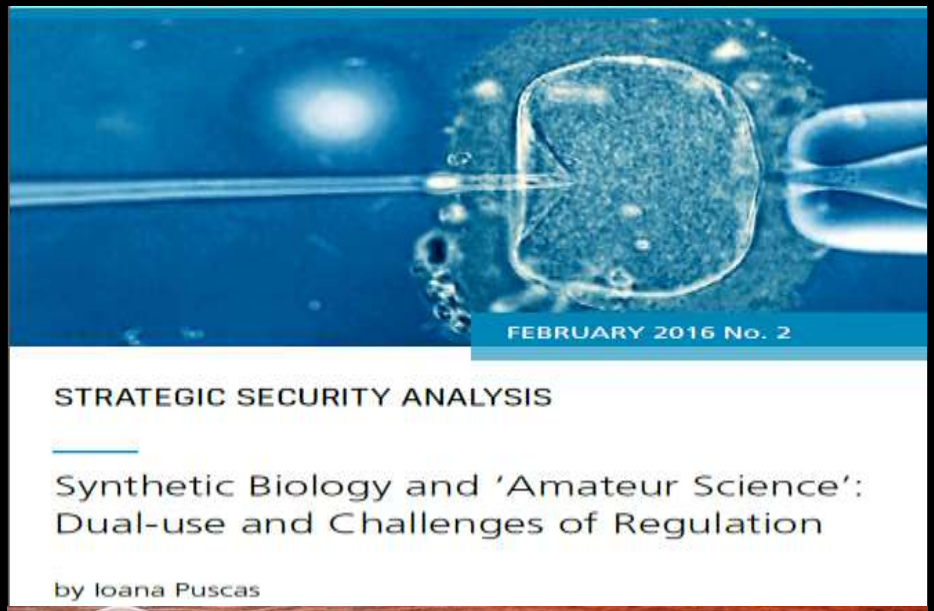


"Today, we sense that we are close to being able to alter human heredity. Now we must face the questions that arise. How, if at all, do we as a society want to use this capability?

Dr. David Baltimore

Biohackers and DIY Bio



The Governance and Oversight of Synthetic Biology

Growing Gap Between Technological Acceleration and Timely Development of National Policies and International Harmonization

Design	Build	Test	Synthetic Biology Technologies and Applications	Factors to Assess Capability for Malicious Use			Factors to Assess Capability for Mitigation			
				Use of Technology	Use as a Weapon	Attributes of Actors	Deterrence and Prevention Capabilities	Capability to Recognize an Attack	Attribution Capabilities	Consequence Management Capabilities
			Automated Biological Design							
			Metabolic Engineering							
			Phenotype Engineering							
			Horizontal Transfer and Transmissibility							
			Xenobiology							
			Human Modulation							
			DNA Construction							
			Editing of Genes or Genomes							
			Library Construction							
			Booting of Engineered Constructs							
			High-Throughput Screening							
			Directed Evolution							

A Proposed Framework for Identifying Potential Biodefense Vulnerabilities Posed by Synthetic Biology: Interim Report (2017) NAP

Current Frameworks for Technology Oversight and Bioincident Preparedness Response are Outdated

- historical focus on “one purpose” industries
- biothreat focus on ‘select agents’
- major gaps in governmental expertise to interpret and regulate accelerating technological change
- inter-agency communication and decision authorities
  - monitoring global supply chains and multiple intermediaries
  - internet crime
  - digital biology and data security
- poor linkage and integration of global public, health frameworks (natural infections) and biodefence efforts (nefarious assaults)

China Has Withheld Samples of a Dangerous Flu Virus

Despite an international agreement, U.S. health authorities still have not received H7N9 avian flu specimens from their Chinese counterparts.

Health workers attending to an H7N9 avian flu patient in Wuhan, China, in 2017.

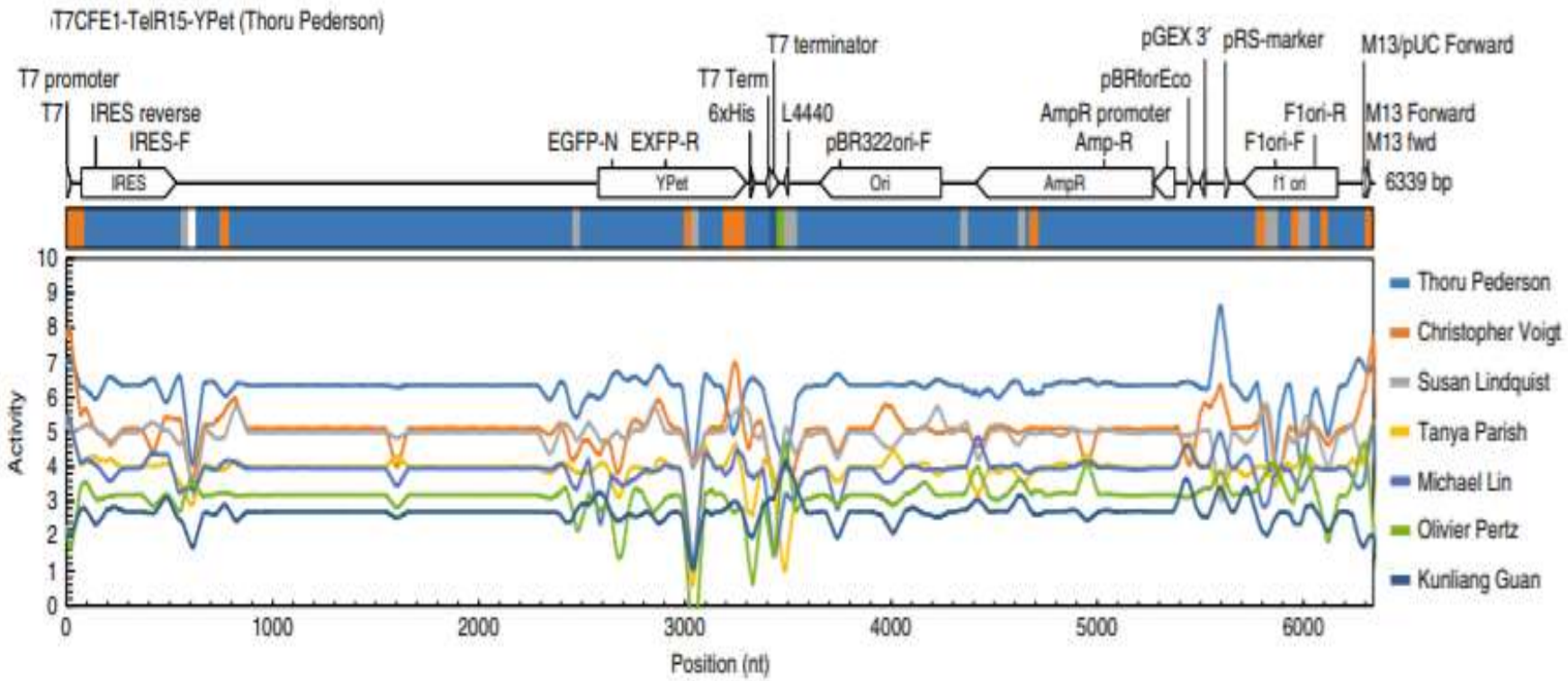
Agence France-Presse — Getty Images

Export Controls on Technologies for WMD Threats and CBW Weaponization

Screening of Gene Sequences of Concern

- screening orders to synthesize 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

Deep Learning Convolutional Neural Networks Profiling of Plasmids and 'Lab-Specific Drift' Patterns

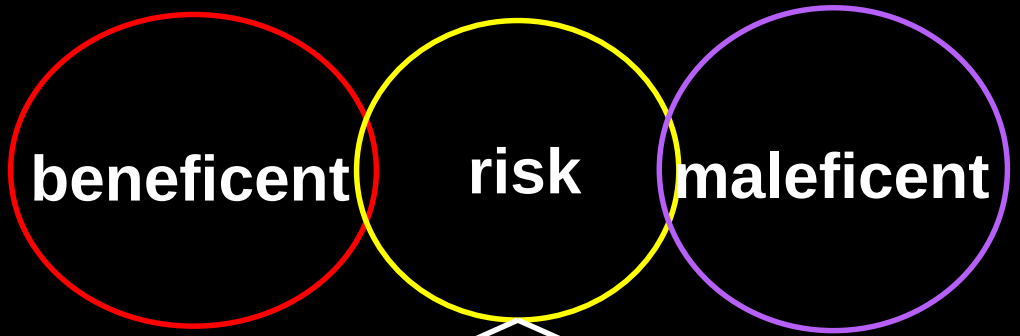


new class of potential signatures to predict lab-of-origin in engineered DNA sequences

From: A. A. K. Nielsen and C. A. Voigt (2018) Nature Comm. s41467-018-05378-z

Automated Remote Monitoring of Bioprocess Equipment to Ensure Integrity of Synthetic Program as Declared

Dual Use Technologies



assessment

- actors
- technical feasibility
- timing
- scale of threat
- threat signatures
- accidents/errors

digital biology

- data protection
- data corruption
- national security
- industrial espionage
- personal privacy

mitigation

- deterrence
- prevention
- detection
- counter-measures
- recovery
- attribution
- retribution

Complex, Multi-dimensional Problems Cannot be Solved by Uni-dimensional Approaches

Reactive, Incident Driven, Episodic Investments

Versus

Proactive Sustained Systems-Based Investment to Develop Resilient Systems and Agile Response Capabilities

Massive Gaps in Preparedness for Large Scale Bioincident(s) (Natural or Nefarious)

Massive Gaps in Bioincident Preparedness

World Health Organization

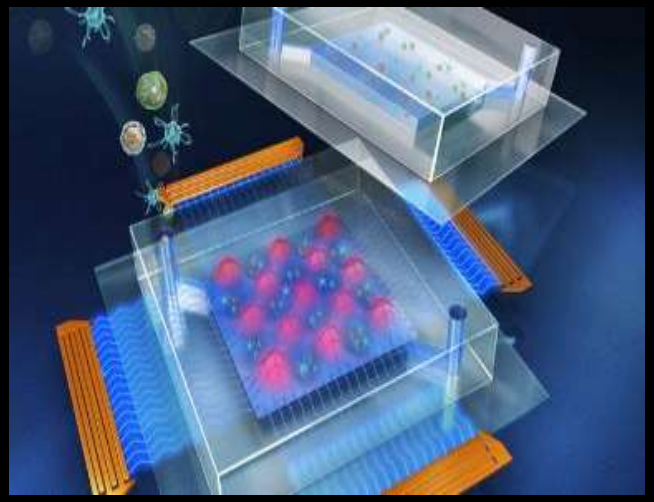
UNSW SYDNEY

Kirby Institute

Faster Diagnosis Saves Lives:
The Primacy of Diagnostics in Biosurveillance and Preparedness Mobilization

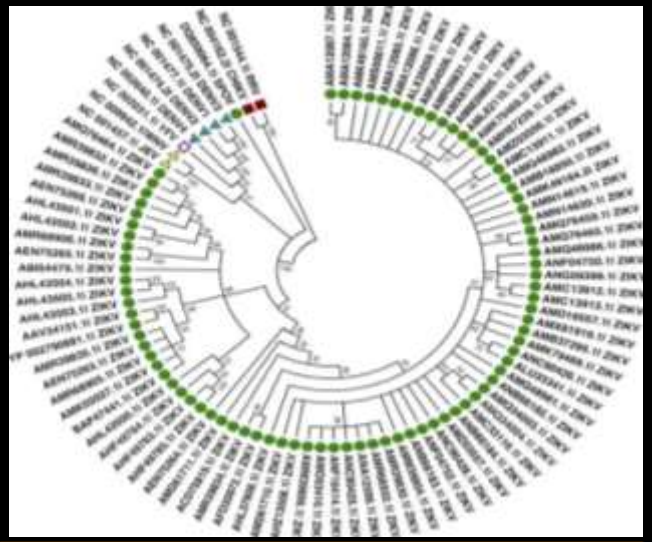
Profile:
signatures of infectious agents

Detect:
rapid automated PON/POC diagnostics



Act:
real-time situation awareness, decisions

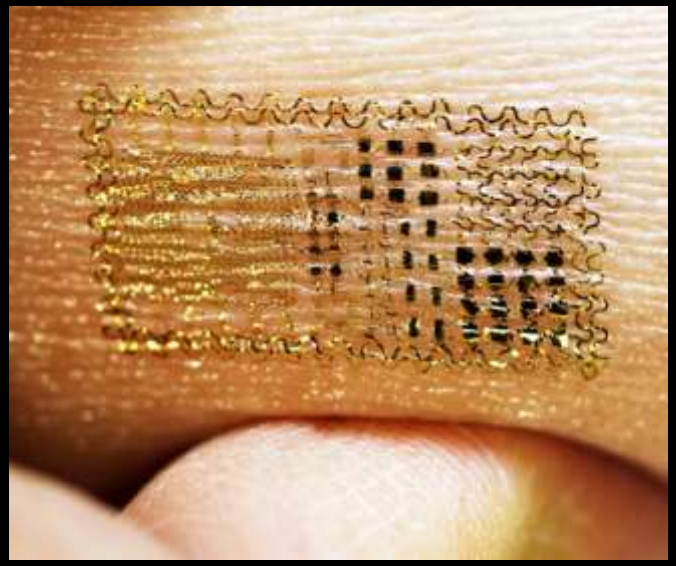
surveillance
sans frontières



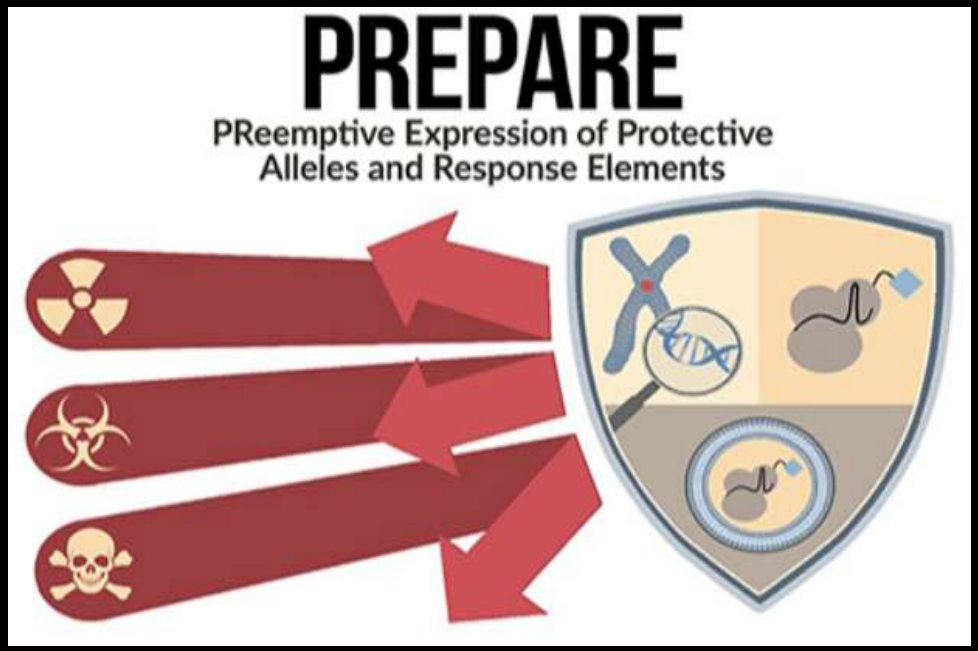
pathogen evolution

dual-use research and
engineered biothreats

Remote Monitoring Technologies: Faster Detection of Emergent Infections



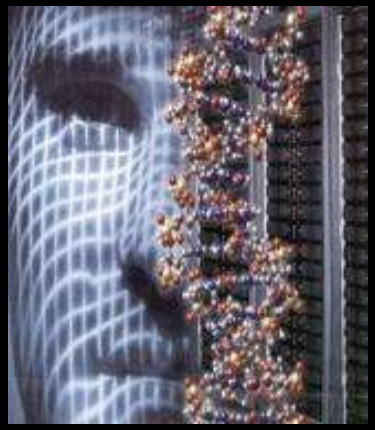
PReemptive Expression of Protective Alleles and Response Elements (PREPARE)



- proposals to reversibly "tune" innate body defenses against biological, chemical and radioactive threats
  - influenza
  - opioid overdose
  - organophosphate poisoning
  - gamma radiation

Technology Acceleration and Convergence: Escalating Complexities in Biosecurity

First Generation Biotechnology



“Bio-Space”

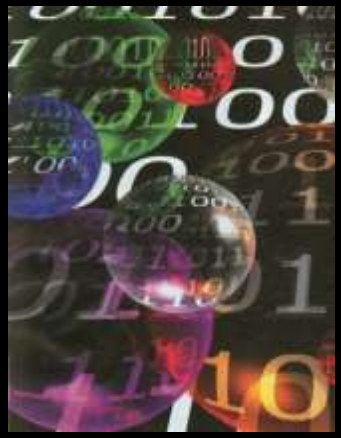
Synthetic Biology and Digital Biology

“Design Space”

Ubiquitous Sensing/ Devices

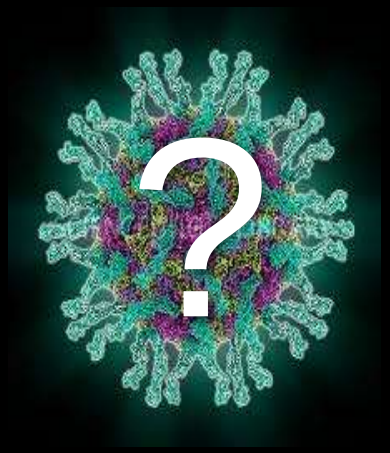
“Detection Space”

Mega–Data, Advanced Computing and AI



“Analysis Space”

Proliferation of Dual-Use Risks



“Preparedness Space”

Technology Acceleration and the Changing Biosecurity Landscape

- convergence (technology)
- context (dual-use and intent)
- capabilities (risk assessment)
- computing (digital biology, threat expansion, data security)
- consequences (preparedness and incident management)
- compliance (oversight, regulations, laws, codes of conduct)
- controls (export, publications)

PROCRASTINATE
NOW
AND
PANIC
LATER

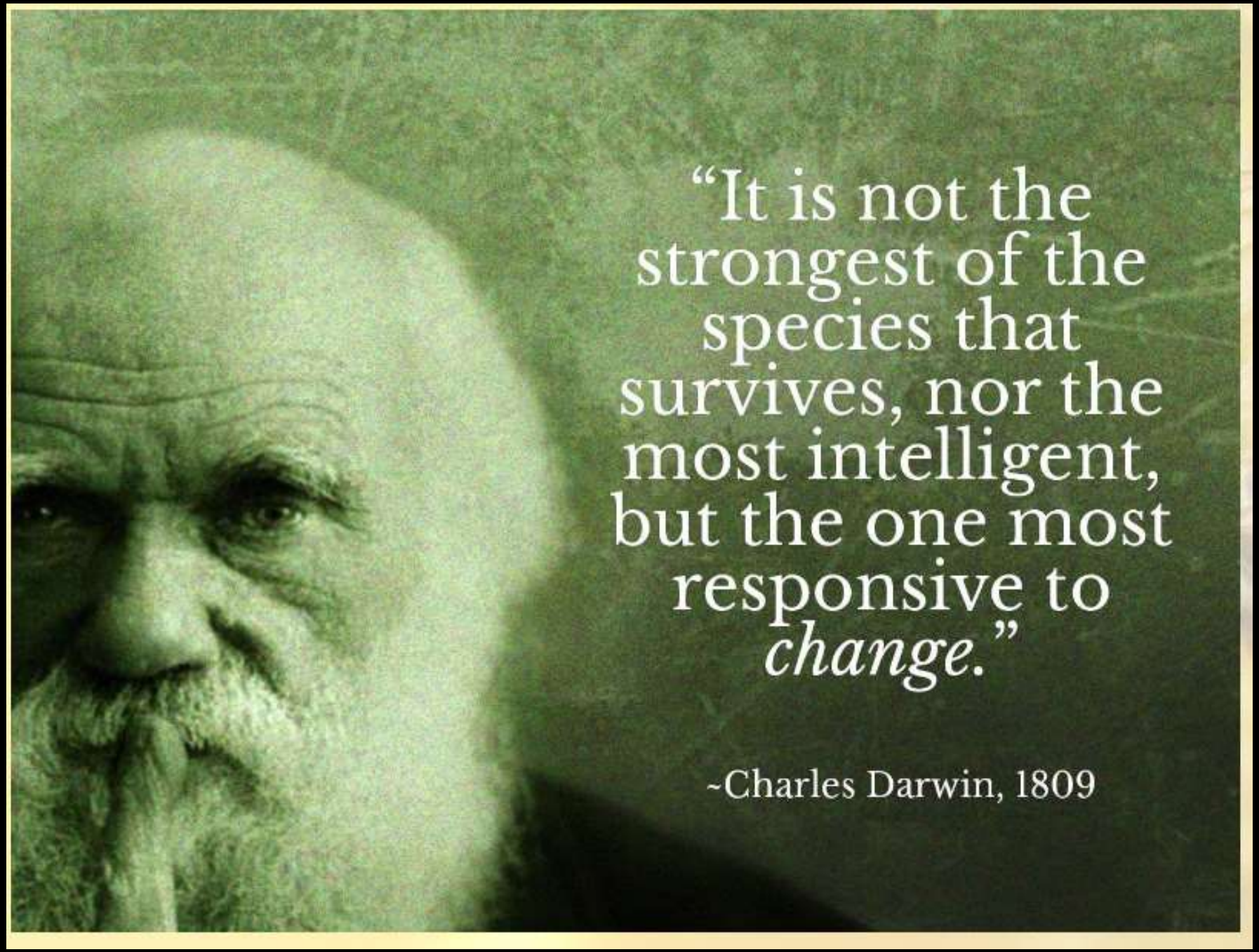
Choices

KEEP
CALM
AND
EDIT ON

The Changing Biosecurity Landscape

COMPLACENCY!!

- need for higher priority of biosecurity in national security strategy and international engagement
- development of more sophisticated threat assessment capabilities
- strengthen surveillance, analysis and deterrence capabilities in national security, IC, law enforcement
- greater investment in robust threat mitigation capabilities
  - obligate private sector engagement
  - logistics and operational integration (and training) for complex bioincident management
- agile oversight mechanisms and international harmonization


"It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to *change*."
~Charles Darwin, 1809

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