Biodefense In The Age of Synthetic Biology and Precision Gene Editing

Dr. George Poste
Chief Scientist, Complex Adaptive Systems Initiative and Regents Professor of Health Innovation
Arizona State University
george.poste@asu.edu
www.casi.asu.edu

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

- Infectious Diseases of Natural Origin
- Urbanization and Environmental Impacts on Disease Emergence (EIDs)
- Military and/or Humanitarian Missions in Dense Urban Areas and ‘Hot Zones’
- New Dual-Use Technologies and the Expanded Threat Spectrum for Biowarfare/Bioterrorism

• 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?

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

Technology Diffusion, Automation, Simplification and Cost Reduction
New Oversight Mechanisms and International Harmonization
Biological Diversity and Variation: “Endless Forms Most Beautiful”
“Endless Forms Most Beautiful”
Systems and Synthetic Biology and Exploring Biospace

- Form and Function (diversity)
- Instructional Information (code)
- Assembly (design sets)
- Design of Novel Biological Systems (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)
- 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

- 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

Microbial CRISPR Defense System Against Viruses

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

Gene/Genome Synthesis
- evonetix
- TWIST BIOSCIENCE

Genome/Protein Engineering
- DMC
- INSCRIPTA

Organism Engineering
- INTREXON
- AMYRIS

Food and Agriculture
- BOOST BIOMES
- WILD EARTH
- PAIRWISE
- INOCUCOR
- Yield10 Bioscience

Tools and Automation
- opentrons
- Bolt Threads

Materials
- SuperMeat
- CustoMem

Biopharma and Health
- AmpliPhi Biosciences Corporation
- OxSyBio

Environment
- HEXAFLY
- Perfect Day

Chemicals
- bioamber
- FRED Sense Technologies

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

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
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
“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
- 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. Noyce¹, Seth Lederman², David H. Evans¹*

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

<table>
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<th>pandemic (avian) influenza</th>
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<td>bush meat food chain</td>
<td>Zika virus</td>
<td>what’s out there?</td>
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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
Purposeful Societal and Economic Disruptions via Design of Ever-Changing Waves of Addictive Illicit Drugs Generated by Synthetic Biology

There are over 40 analogues (variations) of fentanyl. To evade prosecution, chemists alter the fentanyl molecule to create new analogues.
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
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.

By Preetika Rana, Amy Dockser Marcus and Wenxin Fan

Jan. 21, 2018 2:19 p.m. ET
“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

STRATEGIC SECURITY ANALYSIS

Synthetic Biology and ‘Amateur Science’: Dual-use and Challenges of Regulation

by Ioana Puscas
The Governance and Oversight of Synthetic Biology

Growing Gap Between Technological Acceleration and Timely Development of National Policies and International Harmonization
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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.
Export Controls on Technologies for WMD Threats and CBW Weaponization
● 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

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

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

Risk

Beneficent

Maleficent

Assessment

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

Digital Biology

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
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

Synthetic Biology and Digital Biology

Ubiquitous Sensing/Devices

Mega–Data, Advanced Computing and AI

Proliferation of Dual-Use Risks

“Bio-Space”

“Design Space”

“Detection Space”

“Analysis Space”

“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)
The Changing Biosecurity Landscape

- 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

COMPLACENCY!!
"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/