Empowerment and restraint in scientific communication

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Purpose

- Describe web empowerments
- Describe journal responses to societal concerns
- Discuss recent developments that pose examples of potential constraint on publication.

Technologies of empowerment

- Functional magazines
- RSS feeds
- Social bookmarking
- Blogging
- Semantic web

National Science Advisory Board for Biosecurity

- Overseen by NIH director's office of biotechnology, incorporates ex-officio representatives of all stakeholder departments
- Remit includes: "advising on national policies governing dissemination of research results, including publication"
- Advisory only
- June 2005 meeting established working groups on criteria for dual use results, communication of research results, codes of conduct, international collaboration, synthetic genomics

Public understanding of open science?

- Every scientist finds it difficult or even impossible to imagine non-weaponization papers that should be prohibited.
- To publics and representatives in eg European Parliament and Congress, concerns about genetic and toxic empowerment very strong.
- Synthetic biology community proactive
- NSABB includes people who know that hostile people track the literature
- Bureaucracies commissioned to preserve security don’t always weigh up the benefits of openness
- Bureaucracies highly conservative

Extract, Journal Editors and Authors Group Statement on Scientific Publication and Security

- We recognize that on occasions an editor may conclude that the potential harm of publication outweighs the potential societal benefits. Under such circumstances, the paper should be modified, or not be published. Scientific information is also communicated by other means: seminars, meetings, electronic

(2003)

Nature journal policy

- The editorial staff of Nature journals maintain a network of advisers on biosecurity issues.
- All concerns on that score, including the commissioning of external advice, will be shared within an editorial monitoring group consisting of the Editor-in-Chief of Nature publications, the Executive Editor of the Nature research journals, the Chief Biological Sciences Editor of Nature, and the Chief Editor of the journal concerned.
- Once a decision has been reached, authors will be informed if biosecurity advice has informed that decision.

Journal policy: faq's

- *Why keep security advisors identities and advice confidential?* Usually these are experts assessing paper both technically and for risk, so referee anonymity applies.
- *What happens with paper rejected on security grounds?* Currently, default is that author confidentiality overrides other needs. No alerting or registration system in place. But editors can exercise discretion in alerting appropriate agencies. NSABB needs to take lead on this issue.
- *How international is this agreement? Does it include foreign language journals?* Not very international. No.
- *What questions do you ask risk-reviewers?* We think it inadvisable to be prescriptive as we cannot anticipate non-obvious risks, so we request an open-ended assessment whether publication might be undesirable for security reasons.

So what has happened?

- Nature journals: several papers sent out for dual-use assessment, no decisions affected, but NSABB scrutiny of *Nature* viral genome paper.
- *Science*: no decisions affected, but NSABB scrutiny of viral disease paper
- *ASM*: >500 select-agent ms reviewed by journal editor and chair of publications board, two delayed slightly, none withheld.
- 60% ASM submissions have international or non-US authorships
- *PNAS*: >100 occurrences of Category A agents, no decision not to publish or to delay or modify papers, until Botulinum case.

Emerging ‘line in the sand’

- General consensus: open publication of pathogenic genomes key to public health
- Details of pathogenic mechanisms used by organisms to outwit the immune system are necessary to develop new treatments
- Some experiments with hybrid pathogens against scourges that currently kill many worldwide (like the flu) are worth the risk
- Properly contained experiments in appropriate facilities are crucial
- Public outreach and education crucial to avoid misunderstandings and inappropriate regulation

Biosecurity & openness

- Publication of infectious mechanisms and genomes, as SARS genome demonstrated, can have almost immediate health benefits
- Increase economic health and academic quality
- Openness attracts talent
- Openness encourages international cooperation

Science is international: consensus

- International activities like science need international consensus in what constitutes appropriate action
- Overly tough regulation of publication in one country will be ineffective
- Classifying certain research unilaterally would also create incentives for scientists to move research programs elsewhere

Science is international: trust

- Non-US editors and scientists wary - need to build trust
- Eg Visas - situation affected decisions to enroll in US institutions and business
- Access to government-run information - could PubMed, a critical international information resource run by NLM, excise controversial papers at request of US government?

What is “it”?

R Zilinskas, J Tucker *J Homeland Security* Dec 2002

2002 meeting at Monterey Institute Center for Non-Proliferation Studies considered placing restrictions on research that involves a Select Agent and that aims to achieve one or more of six weaponization-related goals:

1. Enhance pathogen infectivity, pathogenicity, antibiotic resistance, or resistance to host immunological defenses
2. Improve the ability of a microbial pathogen to remain viable and virulent during prolonged storage and/or after release into the environment
3. Facilitate the dissemination of biological agents as a fine-particle aerosol
4. Facilitate the dissemination of a biological agent by contamination of food or water sources
5. Create a novel pathogen or one with characteristics that have been altered to evade current detection methods or host immune defenses
6. Assemble oligonucleotides to synthesize the genome of a pathogenic microorganism.

What are ‘manuscripts of concern’?

- October 2003 US National Academy of Sciences committee chaired by Gerald Fink
- Identified some categories of experiments should be cause for concern:
  - Render vaccines ineffective
  - Confer resistance to useful antibiotics or antivirals
  - Enhance virulence of microorganisms
  - Increase transmissibility of pathogens
  - Alter host range of a pathogen
  - Render a pathogen harder to detect
  - ‘Weaponize’ biological agents or toxins

Other bio-weaponry to come?

George Poste, NAS meeting 2003 (not formally published):

- Microbiology just a part of the landscape
- Deliberate engineering of immune escape, stealth viral vectors
- Overproduction of host inflammatory mediators to produce toxic shock
- Knocking out genes that regulate key cell processes such as cell proliferation.
- Small molecules that disrupt molecular circuits, eg networks in immune response, blood clotting system, higher brain function
- “Sophisticated, but not beyond the bounds of state actors”

More ‘dual-use’ publications

After the Jan 2003 meeting dual-use publication continues

- May 2003 *Nature* - anthrax genome
- May 2003 *Science* - SARS sequence
- Mar 2004 *Science* - crystal structure of 1918 pandemic influenza hemagglutinin
- Aug 2004 *Nature* - anthrax toxin-receptor structure
- Oct 2004 *Nature* - construction of virulent flu in mice with 1918 HA
- Dec 2004 *Nature* – gene synthesis
- June 2005 *PNAS* – botulinum toxin and milk supply

Benefits of anthrax genome

"If the *Bacillus anthracis* genome had not been released, we would not have been able to develop the high resolution system that is currently so important [to the investigation of last year's anthrax attacks]." (Paul Keim, quoted in New Scientist 2002)

Note: available on internet, independent of journal.

Accurate multiplex gene synthesis from programmable DNA microchips.

Tian et al,Nature 432 1050-4 2004

- Testing the many hypotheses from genomics and systems biology experiments demands accurate and cost-effective gene and genome synthesis.
- Here we describe a microchip-based technology for multiplex gene synthesis. Pools of thousands of 'construction' oligonucleotides and tagged complementary 'selection' oligonucleotides are synthesized on photo-programmable microfluidic chips, released, amplified and selected by hybridization to reduce synthesis errors ninefold. A one-step polymerase assembly multiplexing reaction assembles these into multiple genes.
- **This technology enabled us to synthesize all 21 genes that encode the proteins of the Escherichia coli 30S ribosomal subunit, and to optimize their translation efficiency in vitro through alteration of codon bias.**
- This is a significant step towards the synthesis of ribosomes in vitro and should have utility for synthetic biology in general.

Synthetic biology

Report of 'New & emerging science and technology' group FP6

- Applying engineering to biology
- Device fabrication and characterization

  -inputs (cell surface proteins), regulators (inverters, logic gates, transcription...), outputs (pathways)
- System design (gene networks, non-natural genomes, in-cell synthesis of materials, drugs)
- Enabling infrastructure (sequencing, gene circuit simulation, ...)

Synthetic biology- benefits

Report of 'New & emerging science and technology' group FP6

- Biomedicine: eg complex molecular devices for tissue repair
- In-vivo synthesis of small-molecule drugs: eg artemesinin from bacteria
- Expanding chemistry of life: eg nucleic acid drugs for RNAi therapies with altered backbone structures for easier membrane transport
- Sustainable chemistry industry: in-vivo synthesis
- Environment and energy: solar energy plus waste converted to biofuel
- Smart materials and biomaterials: eg proteins with artificially evolved recognition properties as glue

Synthetic biology - risks

Report of 'New & emerging science and technology' group FP6

- Dangerous organisms for health and environment, deliberate or by chance
- Personalized bioweapons

Synthetic biology

Methods literature, widely available

- Cost reductions: technology widely available within two years of publications
- Registration of equipment?
- Need for engagement with stakeholders.
- Asilomar-type moratorium impractical.

Synthetic biology ethos

- Engineering => potentially binding professional codes and standards, emerging from a biology community unused to them
- Community small enough to establish a new national or even international society
- Institutions may develop compliance frameworks (compare with stem cells research)
- Information, not materials, is key transferable.

Codes compliance frameworks

- Well established in universities for safety and research involving animals and humans, less well established for other codes of practice.
- Well established in journals for materials sharing, data deposition and research on humans, less systematic for ethical boundaries and reporting cases of misconduct externally.
- No inter-journal framework for biosecurity concerns, or national or international framework that incorporates journals.

Peer review exercise at U. Maryland

Elisa Harris, talk, BWC Geneva June 2005

- Day-long exercise, 5 scientists proposing biodefense studies
- 20 peer reviewers assessed proposals
- Consensus on validity of process and criteria
- Emergent criteria: Public health advanced? In response to validated threat? Biosafety risk minimized? No alternative way of achieving results? Current biodefense necessity? Genuine new knowledge?

Possible restrictions processes

E Harris, J Steinbruner, *CBW Conventions Bull*. March 2005
See also: www.cissm.umd.edu/documents/pathogensmonograph.pdf

- Multi-tier, nationally binding to all, and also internationally by agreement.
- Local (like IRBs), national (like RAC), international (like WHO advisory committee on Variola virus research)
- Proposals peer reviewed for risks vs benefits, including need for dissemination restrictions.
- Dissemination restriction like NAS 2002 study of agricultural bioterrorism or via password-accessible database.
- Security clearance required for national body
- Non-disclosure agreements, with penalties
- **NB These are upstream processes.**

“Sensitive but unclassified information”

Concerns:

- Currently, no definition of what constitutes "sensitive" information, so no standardized criteria for identifying sensitive information warranting removal from public access. Work on such a definition is underway at NSABB.
- Possible removal of methodology sections in scientific papers and self-censorship by scientists threaten the basis of verification and publication that science is based upon.
- The progress of research may be impeded if scientific information is removed from the public domain or if access by scientists is otherwise restricted.
- Removal of "critical infrastructure information" such as locations of hazardous materials, may compromise public safety and health.

Possible restrictions processes

R Zilinskas, J Tucker *J Homeland Security* Dec 2002

- Prime responsibility on funding agency at outset
- At publication stage, submission of paper about "Restricted" research project accompanied by a letter from the funding agency denoting which portions of the paper were sensitive and warranted restrictions on distribution. ***Potentially contravenes definition of science, public paper becomes advertisement.***
- Dissemination of the embargoed material to legitimate scientists (identified through a simple vetting process) would then be controlled by the journal editor, in cooperation with the funding agency. ***Not so simple, takes resources and a database***
- For example, access to sensitive data might be provided through secure, password-controlled websites, with substantial fines and other sanctions (such as denial of access) imposed in cases of unauthorized transfers. ***How to police, who imposes fine and restricted access?***

[Monterey workshop August 2002]

Restrictions problems

- No definition or consensus on what needs to be restricted.
- Needs to be international
- Does not prevent internet distribution or conferences
- Who would be allowed access?
- Who'd pay to maintain the restricted archives?
- Most journals not well resourced for extra compliance
- University opposition: "opens [us] to potentially arbitrary dictates – however well intended" (MIT)
- See also 'Limiting the contribution of the open scientific literature to the biological weapons threat' by RA Zilinskas and JB Tucker, *J Homeland Security*, December 2002

Analyzing a bioterror attack on food supply: Botulinum toxin in milk

(Lawrence Wein & Yifan Liu, PNAS)

- Input: various scenarios of toxin introduction (nothing new or hard to discover for terrorists)
- Output: range of impacts on health and mortality, analysis of responses to protective measure highlighting security needs
- Author checked with HHS, HHS advised against, author denies getting response.
- PNAS followed full procedures, referees approved
- HHS contacted NAS following reporter contact
- NAS delayed briefly, discussed with government representatives, proceeded to publish despite official request not to.
- Subsequent agonizing in government about how it was handled.

PNAS/Botulinum episode: issues

- Responsibilities of researcher and HHS to pursue an initial alert rigorously
- Lack of robust system for such alerts
- Should paper be submitted to high-profile journal, and accepted?
- What is sensitive research, how should government respond, what is appropriate code and system for researchers for communicating dual-use results?
- Lack of guidelines leads to overly precautionary measures by officials at expense of appropriate access to the literature

Science on NSABB and flu

- Extracts from editorial by Don Kennedy, 14 October 2005
- “To begin with, *Science* did the right thing in consulting with the proper authorities, both our own and those at HHS.
- “The 11th-hour intervention from the secretary's office, it has been explained to us, was to give the NSABB a real experience with a "live" issue.
- “There is a real question of authority here. Government officials can advise, and should be listened to thoughtfully. But they can't order the nonpublication of a paper just because they consider the findings "sensitive." No such category short of classification exists, as the Reagan-era Executive Order National Security Decision Directive 189, still in force, makes clear. If a paper should not be published because of biosecurity risks, then it should be classified.
- “Second, the NSABB should regard this first exercise as a helpful one-off and turn to its mandate of developing principles rather than making decisions on individual papers.
- “So would I, given our own convictions, the timing, and what we had learned from our consultations with Gerberding, Fauci, and others, have published the paper even if the NSABB had voted otherwise? Absolutely--unless they had it classified.”

1918 flu papers

- Papers published on genetics (*Nature*) and virulence (*Science*) of flu virus
- NSABB had belated closed discussion of papers the week before publication, to give experience of live issue.
- NSABB considered publication was acceptable but asked for additional wording clarifying strict containment.
- Some news reports suggested NSABB could have prevented publication. Formally and in the circumstances, not true. In principle, could have put pressure on authors to withdraw.
- Don Kennedy editorial explained that all editorial processes had been followed and that NSABB request not to publish would have been resisted. But didn't acknowledge the right of authors to withdraw and too gung-ho: we will take input from anyone and if good reasons are given but authors wish to continue, we will consider and reserve right not to publish.
- Ad hoc arrangement for scrutiny – nascent system. What does this presage for the future? NSABB pre-publication review committee? Not its job.
- Does that make papers vulnerable to institutionalized clashes of precautionary versus open cultures?