Dual-use results and scientific journals

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Purpose

- Briefly to review history of journal policy and experience
- Provide an overview of key issues as I see them.

Journal Editors and Authors Group, January 2003

- **Ronald Atlas, President ASM, Editor CRC Critical Reviews in Microbiology**
- **Philip Campbell, Editor, Nature**
- **Nick Cozzarelli, Editor, PNAS**
- **Greg Curfman, New England Journal of Medicine**
- **Lynn Enquist, Editor, Journal of Virology**
- **Gerry Fink, MIT**
- **Annette Flanagin, Managing Senior Editor JAMA, President, Council of Science Editors**
- **Jacqueline Fletcher, President, American Phytopathological Society**
- **Beth George, DOE**
- **Gordon Hammes, Editor, Biochemistry**
- **David Heyman – CSIS**
- **Thomas Inglesby, Editor, Biosecurity and Bioterrorism**
- **Samuel Kaplan, Chair, ASM Publications Board**
- **Donald Kennedy, Editor Science**
- **Judith Krug, American Library Association**
- **Rachel Levinson, OSTP**
- **Emilie Marcus, Editor, Neuron (Cell Press)**
- **Henry Metzger, NIAMS, NIH**
- **Stephen S. Morse, Columbia University**
- **Alison O'Brien, Editor, Infection and Immunity**
- **Andrew Onderdonk, Editor, Journal of Clinical Microbiology**
- **George Poste, Health Technology Networks**
- **Beatrice Renault, Editor, Nature Medicine**
- **Robert Rich, Editor, Journal of Immunology**
- **Ariella Rosengard, University of Pennsylvania**
- **Steven Salzburg, TIGR**
- **Thomas Shenk, ASM President-Elect, Past Editor, Journal of Virology**
- **Mary Scanlan, American Chemical Society**
- **Herbert Tabor, Editor, Journal Biological Chemistry**
- **Eckard Wimmer, SUNY Stony Brook**
- **Keith Yamamoto, Editor, Molecular Biology of the Cell**

Meeting also included…

- OSTP, Department of Homeland Security, FBI, CIA…
- These ‘representatives’ were concerned that the scientific community should put its own house in order. They were not at that time advocating greater restrictions.
- Potential action by Congress loomed large.

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 Under such circumstances, the paper should be modified, or not be published.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

Editorial controversy

Objections to editorial censorship:

- Stanley Falkow in *Science*: need definition
- Public Library of Science: anti censorship

Objections to openness:

- Richard Meyer, Center for Disease Control – restrict key details
- George Poste: “collision course”

Follow-up by *Nature*

- Established informal group of advisers with defence connections, including scientists at national labs in the US and at Porton Down in the UK. Informal discussions held.
- Established internal framework for consultation.
- Published policy.

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.
- *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.
- *Science*: no decisions affected (to be checked).
- *ASM*: >500 select-agent ms reviewed by journal editor and chair of publications board, 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.

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
- Acoustic disruption – bone pain, airway modulation, ultrasonic skin heating.
- “Sophisticated, but not beyond the bounds of state actors”

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

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.

Virulent flu in mice from 1918 strain proteins

(Kobasa et al, *Nature*, Oct 2004)

- H5N1 rampant in SE Asia, able to infect humans, not so far reassorted in humans by simultaneous avian and human infection, pandemic predicted.
- Single anti-flu drug on market. Need new antivirals to attack virus from various angles to avoid escape, and immunomodulators to enhance antiviral host defence mechanism.
- Reverse genetics technique to clone cDNA to generate infectious virus previously published.
- **Pinpointed gene responsible for high pathogenicity out of those previously identified in PNAS.**
- Inconclusive as it's mouse model.
- **Underlying mechanism – neutrophil influx and associated inflammatory foci in lungs – novel and important for drug design even if we don't know how particular haemagglutinin modulates effect.**

Virulent flu in mice from 1918 strain proteins

(Kobasa et al, *Nature*, Oct 2004)

- Post-publication concern in media about safety, but was level 4 and enhanced level 3 labs.
- Concern as to why do the work. See previous justification, but maybe journals and/or authors need to provide more explicit justification.
- Concern over lack of transparency and democratic accountability of journal's dual-use risk assessment. (Paper was seen by experts within the US risk assessment system.)

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

(Lawrence Wein & Yifan Liu, PNAS in press)

- 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, refs approved
- HHS contacted NAS following reporter contact
- NAS delayed briefly, discussed with government representatives, likely now going ahead

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 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

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.

Protein-mediated error correction for *de novo* DNA synthesis

Carr et al (MIT), Nucleic Acids Research 32 e162 (2004)

- The availability of inexpensive, on demand synthetic DNA has enabled numerous powerful applications in biotechnology, in turn driving considerable present interest in the *de novo* synthesis of increasingly longer DNA constructs. The synthesis of DNA from oligonucleotides into products even as large as small viral genomes has been accomplished.
- Despite such achievements, the costs and time required to generate such long constructs has, to date, precluded gene-length (and longer) DNA synthesis from being an everyday research tool in the same manner as PCR and DNA sequencing. A critical barrier to low-cost, high-throughput *de novo* DNA synthesis is the frequency at which errors pervade the final product.
- Here, we employ a DNA mismatch-binding protein, MutS (from *Thermus aquaticus*) to remove failure products from synthetic genes. This method reduced errors by >15-fold relative to conventional gene synthesis techniques, yielding DNA with one error per 10 000 base pairs. **The approach is general, scalable and can be iterated multiple times for greater fidelity.**
- **Reductions in both costs and time required are demonstrated for the synthesis of a 2.5 kb gene.**

Synthetic biology visions

Extract, Oliver Morton, *Wired* January 2005

- The goal, as Endy puts it, is nothing less than to "reimplement life in a manner of our choosing."
- And what might the practitioners of this emerging science do with such godlike capability? Within a decade, some hope to create bacteria able to mass-produce drugs that currently have to be painstakingly harvested from rare plants. Others talk about making viruses encased in protein sheaths that can be used to produce fabric with molecular circuitry woven into its warp and weft.
- In the more distant future, synthetic biologists envision building more complex organisms, like supercoral that sucks carbon out of the biosphere and puts it into building materials, or an acorn programmed to grow into an oak tree - complete with a nifty tree house.
- And there's the opportunity to add new chromosomes to the human genome, ushering in a panoply of human augmentations and enhancements.

Synthetic biology

- Engineering as well as science
- Precision design, not “DNA bashing”
- Focus on artificial production of cell components (genes, networks)
- Methods literature
- 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.

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

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.
- 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.
- 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. [Monterey workshop August 2002]

Possible restrictions processes

E Harris, J Sensenbrenner, *CBW Conventions Bull*. March 2005

- 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

Peer review exercise at U. Maryland

Elisa Harris, talk, 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?

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

Key truisms

- Journal editors must show responsibility
- Scientists must show responsibility
- Science's integrity needs to be preserved:
- "*The traditions and structure of research in the U.S. today depends on replication and refutation, which means that sufficient data and methods to allow that must be published in peer-reviewed journals. Such publication also mitigates fraudulent results, sloppy science, and political biases guiding important policy decisions. Recent, well-publicized incidents of scientific misconduct underscore the merits of this system.*" MRC Greenwood, Chancellor, UC Santa Cruz