

## “Dual Use” Research: Raising Awareness in the Microbiology Research Community

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Dept of Medicine, Div of Infectious Disease  
UMDNJ-New Jersey Medical School  
Newark, NJ

- Biological weapons (BW) and BW arms control
- What is “dual use research of concern”?
- How can we increase awareness of the issues?

## Sverdlovsk, 1979

- Unusual anthrax epidemic in April/May 1979
- 1986, Meselson in Moscow
  - contaminated animals and meat
  - 96 cases: 79 GI (?) (64 deaths) and 17 cutaneous (0)
- 1990, articles appear in Russian press
- 1992, Yeltsin: “the KGB admitted that our military developments were the cause”

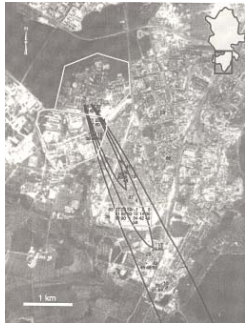


## Sverdlovsk Investigation, 1994

- Geographical distribution of cases
- Interviews
- Medical Records
- Graveyards
- Meteorology



## Sverdlovsk Investigation



Compound 19

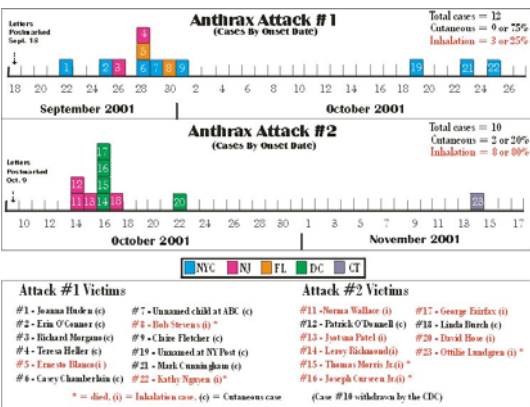
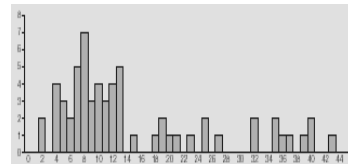


Anthrax killed 18 workers from this ceramics factory, located just downwind of Compound 19



## Sverdlovsk

Accident: April, 1979; 1 gm spores; at least 64 deaths; extensive decontamination



## The letters

- Sept 18, 2001: 5 letters postmarked and mailed to
  - NY: ABC, CBS, NBC, New York Post
  - FL: American Media (Nat'l Enquirer)
  - 16 days later (Oct 3): diagnosis (first case in 25 yrs)
  - Victim died Oct 5
- Oct 9, 2001: two more letters postmarked and mailed
  - Senator Daschle (opened Oct 15; buildings closed)
  - Senator Leahy (found in storage Nov 16)
- Oct 12: NYC anthrax cases confirmed
- Oct 16-17: senate/house buildings closed (reopened 2002)
- Oct 18: NJ mail distribution center closed (reopened 2005)
- Oct 23: cases in Postal Offices confirmed (NJ and D.C.)



## Anthrax attacks

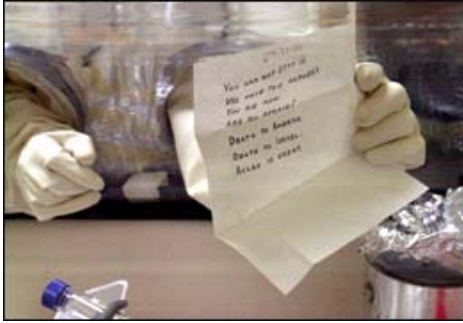
- Last case in U.S. was in 1992
- 2001 - 22 cases: 11 cutaneous, 11 inhalation: 5 deaths
- Letters
- Attribution



09-11-01  
 YOU CAN NOT STOP US.  
 WE HAVE THIS ANTHRAX.  
 YOU DIE NOW.  
 ARE YOU AFRAID?  
 DEATH TO AMERICA.  
 DEATH TO ISRAEL.  
 ALLAH IS GREAT.

09-11-01  
 THIS IS NEXT  
 TAKE PENACILIN NOW  
 DEATH TO AMERICA  
 DEATH TO ISRAEL  
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09-11-01  
 THIS IS NEXT  
 TAKE PENACILIN NOW  
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 DEATH TO ISRAEL  
 ALLAH IS GREAT



FBI-Amerithrax site

## Victims of the attacks

- 22 cases: 11 inhalation, 11 cutaneous
- 5 deaths
- 31 “positive” for spores
- estimated 10,000 “at risk” were treated with prophylactics
- 35 postal facilities and mailrooms contaminated



## FBI investigation

- 7 years
- 600,000 person hours
- 17 special agents, 10 US postal inspectors
- 10,000 witness interviews, 80 searches
- 26,000 email reviews
- 4 million MB of computer memory
- 6,000 items of potential evidence
- 5,750 grand jury subpoenas
- 5,730 environmental samples from 60 sites
- More than 1,040 individuals scrutinized, 400 in-depth
- Cooperation of 29 labs (gov’t, academic and commercial)

Monday, October 18, 2010 6:08 AM EDT As of New York 69° 46°

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 Political Insight and Analysis From The Wall Street Journal's Capital Bureau

SEPTEMBER 16, 2010, 1:10 PM ET

**GAO to Take Look at FBI Anthrax Probe**

Article Comments (2)

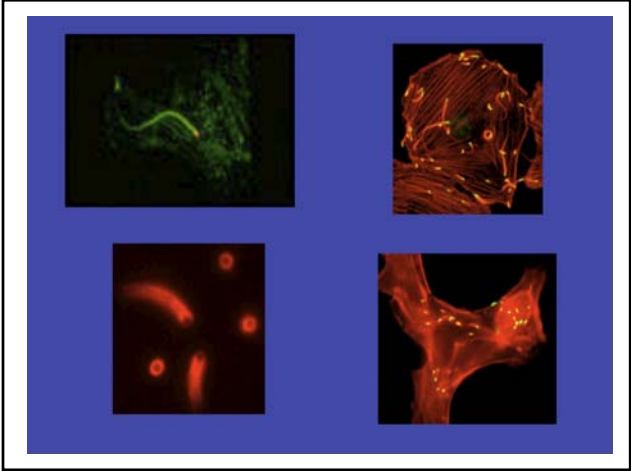

Email Print Permalink Like + More Text

By Evan Perez


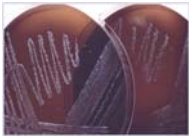
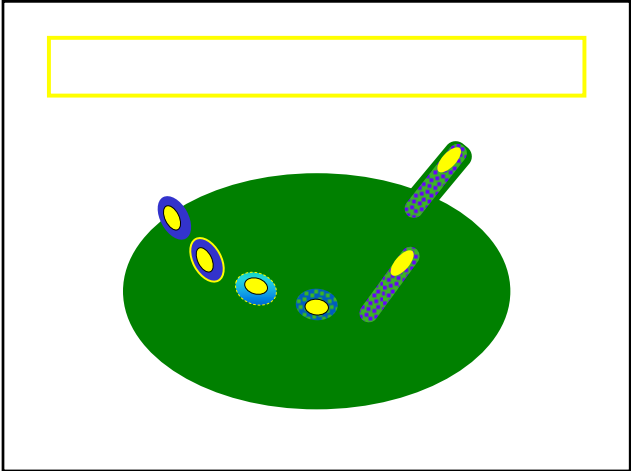
The Federal Bureau of Investigation's eight-year probe of the 2001 anthrax attacks has left many doubters. Now lawmakers are ordering another look at the FBI's investigation.

The Government Accountability Office says it will conduct an examination of some of the science behind the FBI's conclusion that government scientist **Bruce Ivins** was the sole person who carried out the attacks. A separate review of the FBI's work, by the National Academy of Scientists, is expected to be completed this fall.

The GAO examination came at the request of Rep. **Rush Holt** (D., N.J.), an outspoken skeptic of the FBI's work in the case. "The American people need credible answers to many questions raised by the original attacks and the subsequent FBI handling of the case," Holt said in a statement.

**Listeria monocytogenes**

## Extending the Host Range of *Listeria monocytogenes* by Rational Protein Design

Thomas Wollert,<sup>1</sup> Bastian Pasche,<sup>2</sup> Malke Rochon,<sup>3</sup> Stefanie Deppenmeier,<sup>4</sup> Joop van den Heuvel,<sup>3</sup> Achim D. Gruber,<sup>4</sup> Dirk W. Heinz,<sup>2</sup> Andreas Lengeling,<sup>2,\*</sup> and Wolf-Dieter Schubert<sup>1,\*</sup>

<sup>1</sup>Molecular Host-Pathogen Interactions, Division of Structural Biology

<sup>2</sup>Infection Genetics, Department of Experimental Mouse Genetics

<sup>3</sup>Division of Structural Biology

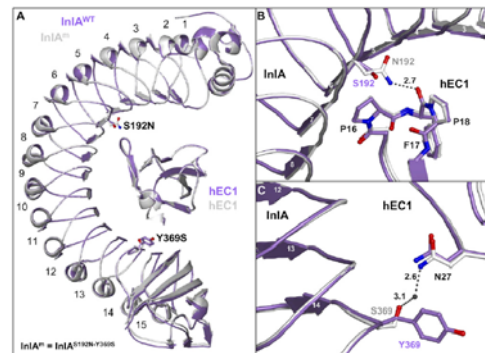
Helmholtz Centre for Infection Research, Inhoffenstr. 7, D-38124 Braunschweig, Germany

<sup>4</sup>Department of Veterinary Pathology, Free University of Berlin, Robert-von-Ostertag-Str. 15, D-14163, Berlin, Germany

\*Correspondence: wolf-dieter.schubert@helmholtz-hzi.de (W.-D.S.), andreas.lengeling@helmholtz-hzi.de (A.L.)

DOI 10.1016/j.cell.2007.03.049

Cell 129, 891–902, June 1, 2007 ©2007 Elsevier Inc. 891



**Figure 1. Re-engineered Variants of Internalin (InIA) in Complex with the N-Terminal Domain of Human E-Cadherin**  
 (A) Superposition of InIA<sup>hEC1</sup> (violet) and InIA<sup>S192N/hEC1</sup> (gray).  
 (B) Critical residues near mutation site S192N<sub>hEC1</sub> are shown as ball and stick. Asn192<sub>hEC1</sub> adds a direct H bond to the carbonyl oxygen of Phe17<sub>hEC1</sub>.  
 (C) The mutation Y369S<sub>hEC1</sub> introduces a water-bridged interaction to Asn27<sub>hEC1</sub>.

### Leading Edge In This Issue

Cell

#### Building a Better Mouse Pathogen



**PAGE 891**  
 Newly emerging infectious diseases are frequently caused by spontaneous mutations in existing pathogens, thereby modifying their host range. Wollert et al. simulated this chance occurrence by manipulating the human pathogen *Listeria monocytogenes* with the goal of extending the host range to mouse. Based on the structure of *Listeria*'s invasion protein InIA in complex with its human receptor E-cadherin, the authors exchanged two amino acids in InIA, which dramatically increased the affinity for both the human and the formerly incompatible murine E-cadherin receptors. Once incorporated into the pathogen's genome, the substitutions enabled *Listeria monocytogenes* to infect the mouse by the oral route, thus creating a versatile animal model of human listeriosis.

washingtonpost.com

## Release of Microbe Study Spurs Bioterror Worries

By Rick Weiss  
 Washington Post Staff Writer  
 Friday, June 1, 2007; A06

Researchers in Germany reported yesterday that they had altered the DNA of a disease-causing bacterium to enable it to infect a species it cannot normally sicken -- a double-edged advance that experts said could deepen scientists' understanding of human diseases but could also speed the development of novel bioterrorism agents.

The change in infectiousness -- the first of its kind ever engineered from scratch -- poses no direct threat to human health, scientists said, because the microbe already causes a human disease: the food-borne illness called listeriosis.

### *Listeria* receptor modification

- What are some of the implications of this work?
- Should this have been published?
- Should *some* of this information have been published?

# WIRED

## Scientists Build First Man-Made Genome; Synthetic Life Comes Next

By Alexis Madrigal 01.24.08 | 11:00 AM



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Lartigue et al. , pp. 632 – 638

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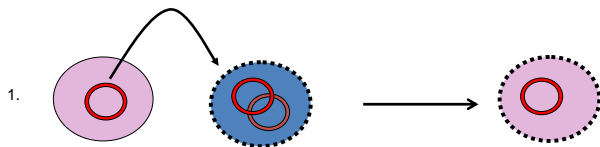
DOI: 10.1126/science.1144622

### RESEARCH ARTICLES

#### Genome Transplantation in Bacteria: Changing One Species to Another

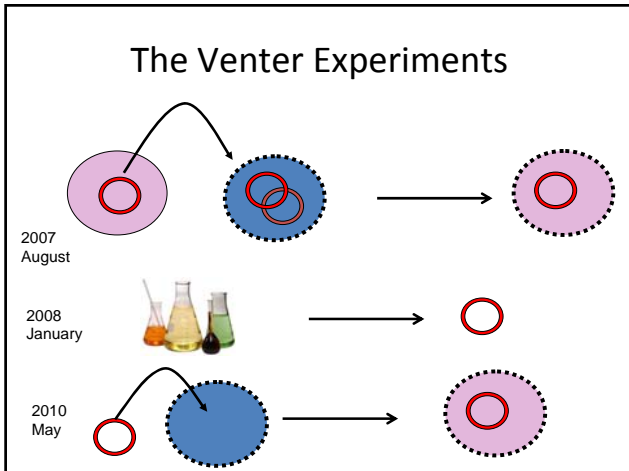
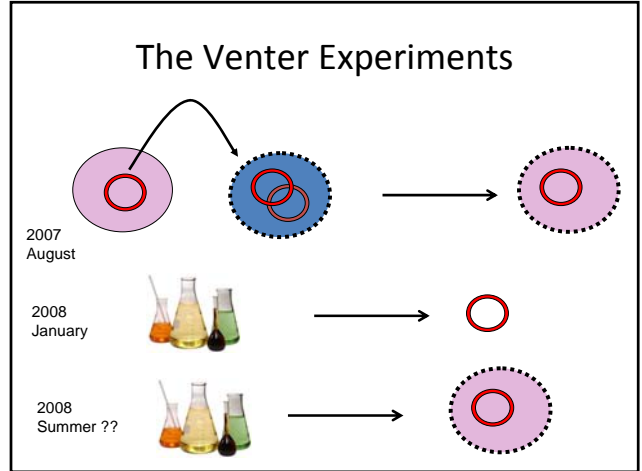
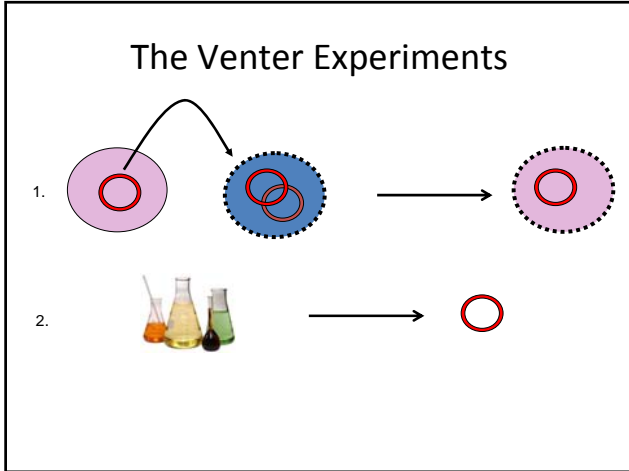
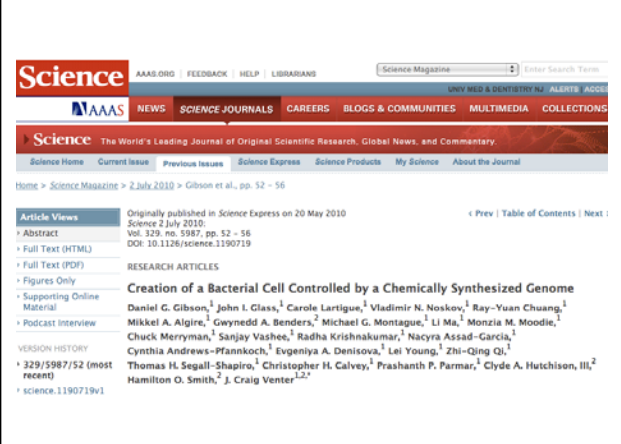
Carole Lartigue, John I. Glass,<sup>\*</sup> Nina Alperovich, Rembert Pieper, Prashanth P. Parmar, Clyde A. Hutchison, III, Hamilton O. Smith, J. Craig Venter

## The Venter Experiments



- Complete Chemical Synthesis, Assembly, and Cloning of a *Mycoplasma genitalium* Genome.
- Gibson DG, Benders GA, Andrews-Pfannkoch C, Denisova EA, Baden-Tillson H, Zaveri J, Stockwell TB, Brownley A, Thomas DW, Algire MA, Merryman C, Young L, Noskov VN, Glass JI, Venter JC, Hutchison CA 3rd, Smith HO.
- The J. Craig Venter Institute, Rockville, MD 20850, USA.

*Science*, January 24, 2008, published ahead of print

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Home > Science Magazine > 2 July 2010 > Gibson et al., pp. 52 - 56

Originally published in Science Express on 20 May 2010

Science 2 July 2010  
Vol. 328, no. 5987, pp. 52 - 56  
DOI: 10.1126/science.1190719

RESEARCH ARTICLES

**Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome**  
Daniel C. Gibson,<sup>1</sup> John I. Glass,<sup>1</sup> Carole Lartigue,<sup>1</sup> Vladimir N. Noskov,<sup>1</sup> Ray-Yuan Chuang,<sup>1</sup> Mikkel A. Algire,<sup>1</sup> Gwynedd A. Benders,<sup>2</sup> Michael G. Montague,<sup>1</sup> Li Ma,<sup>1</sup> Monzia M. Moodie,<sup>1</sup> Chuck Merryman,<sup>1</sup> Sanjay Vashee,<sup>1</sup> Radha Krishnakumar,<sup>1</sup> Nancy Assad-Garcia,<sup>1</sup> Cynthia Andrews-Pfannkoch,<sup>1</sup> Evgeniya A. Denisova,<sup>1</sup> Lei Young,<sup>1</sup> Zhi-Qing Qi,<sup>1</sup> Thomas H. Segall-Shapiro,<sup>1</sup> Christopher H. Calvey,<sup>1</sup> Prashanth P. Parmar,<sup>1</sup> Clyde A. Hutchison, III,<sup>2</sup> Hamilton O. Smith,<sup>2</sup> J. Craig Venter<sup>1,2,\*</sup>

VERSION HISTORY  
\* 329/5987/52 (most recent)  
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J. Craig Venter  
INSTITUTE

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20-May-2010  
PRESS RELEASE  
FOR IMMEDIATE RELEASE

First Self-Replicating Synthetic Bacterial Cell

First Self-Replicating, Synthetic Bacterial Cell Constructed by J. Craig Venter Institute Researchers

ROCKVILLE, MD and San Diego, CA (May 20, 2010) – Researchers at the J. Craig Venter Institute (JCVI), a not-for-profit genomic research organization, published results today describing the successful construction of the first self-replicating, synthetic bacterial cell. The team synthesized the 1.08 million base pair chromosome of a modified *Mycoplasma mycoides* genome. The synthetic cell is called *Mycoplasma mycoides* JCVI-syn1.0 and is the proof of principle that genomes can be designed in the computer, chemically made in the laboratory and transplanted into a recipient cell to produce a new self-replicating cell controlled only by the synthetic genome.

The WATERMARKS

2008

- CRAIGVENTER coded as:  
TTAACTAGCTAATGCTCGCAATTGGAGTAGACAGACACAGCACTTAAGTACGCTAA
- VENTERINSTITUTE coded as:  
TTAACTAGCTAAGTAGAAAACCCGAACTAATTACGATTACCGTACTGACTTAAGTACGCTAA
- HAMSMITH coded as:  
TTAACTAGCTAAGTACGCTGATGATTACCCACTTAAGTACGCTAA
- CINDIANDCLYDE coded as:  
TTAACTAGCTAATGCATAAACGACATCCCTAATGACTGCTTTATCATGAATTAAGTACGCTAAGGCTC  
GATGTTTGATGTTATGAGCAGCAACGATGTTACGCGAGGGGAGTCCCTTAACAAAGTTAAAC
- CLASSANDCLYDE coded as:  
TTAACTAGCTAAGTCTAGCTAGTACGGCGAATGACTCCCTATACGATGAG TTAAGTACGCTAA

2010

- "TO LIVE, TO ERR, TO FALL, TO TRIUMPH, TO RECREATE LIFE OUT OF LIFE." – from James Joyce's *A Portrait of the Artist as a Young Man*.
- "SEE THINGS NOT AS THEY ARE, BUT AS THEY MIGHT BE." – a quote from the book, *American Prometheus* which discusses J. Robert Oppenheimer and the first atomic bomb.
- "WHAT I CANNOT BUILD, I CANNOT UNDERSTAND." – attributed to Richard Feynman (physicist, philosopher, badass) as the last words on his blackboard at the time of his death as described in *The Universe in a Nutshell* by Stephen Hawking (physicist, philosopher, badass).

Newsweek's Education Site Photos: Homecoming Newsletter Questions About WikiLeaks Dump SUBSCRIBE @mrbc.com

the G series

Let There Be Life

Five possible implications of Craig Venter's creation of synthetic organisms.

And Craig Venter said, "Let the lab bring forth swarms of living creatures, and let *Mycoplasma mycoides* multiply in the petri dish," and he saw that it was good ...

It's easy to get carried away in the wake of Thursday's announcement that Craig Venter & Co. have created what is in some sense the world's first synthetic organism. Venter's lab typed out the million letters of DNA that comprise the *M. mycoides* genome, had them translated into 1,000-letter chemical chunks, glued the chunks together using yeast and *E. coli*, and transplanted the result into the empty shell of a related bacterium (*M. capricolum*). Voilà: a cell "whose genetic heritage

by Mary Carmichael  
May 21, 2010

Science

crvg venter • genetics • genetic code

Trending on Newsweek

Can We Blame Extreme Weather on Climate Change?

Why Masturbation Helps Procreation

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Venter Takes Genetic Engineering to 'Extreme New Level'

Healthy People Thursday, May 20, 2010

Contact:  
Scott Baumgartner, office 202-222-0751, sbaumgartner@foe.org  
Eric Hoffman, office 202-222-0747, mobile 443-465-2219, ehoffman@foe.org

Venter Takes Genetic Engineering to 'Extreme New Level'  
First organism with entirely synthetic DNA jeopardizes ecosystems and human health

Washington, DC -- Today, the J. Craig Venter Institute announced the creation of the first living organism with an entirely synthetic genome.

Friends of the Earth's genetic technology policy campaigner, Eric Hoffman, responded:  
"Craig Venter's lab has taken genetic engineering to an extreme new level. These new synthetic chromosomes mimic billions of years of evolution.  
"We must ensure that strong regulations are in place to protect the environment and human health from this potentially dangerous new technology. We are far from actually understanding how genes affect the development of life, but it could be difficult to prevent Venter's synthetic biology experiments from eventually entering the natural ecosystem and acting as invasive species, changing out natural living things.  
"The Environmental Protection Agency and the Food and Drug Administration must receive this announcement as a warning bell, signifying that the time has come for our government to fully regulate all synthetic biology experiments and products. It is imperative that in the pursuit of scientific experimentation, we do not sacrifice human health, the environment, and natural ecosystems. Mr. Venter should stop all further research and

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### Synthetic biology: proposed resolutions

1. Insist That All Commercial Gene Synthesis Houses Adopt Current Best Practice Screening Procedures.
2. Create and Endorse New Watch-Lists To Improve Industry Screening Programs.
3. Create a Confidential Hotline For Biosafety and Biosecurity Issues.
4. Affirm Members' Ethical Obligation to Investigate and Report Dangerous Behavior.
5. Create a Community-Wide Clearinghouse for Identifying and Tracking Potential Biosafety/Biosecurity Issues.
6. Endorse Biosecurity/Biosafety R&D Priorities.

[http://syntheticbiology.org/SB2.0/Biosecurity\\_resolutions.html](http://syntheticbiology.org/SB2.0/Biosecurity_resolutions.html)

### Five dangerous experiments

- **Legionella (?) expressing myelin (Soviet)**
  - Fatal autoimmune disease in guinea pigs
- **More virulent strain of *B. anthracis* (Soviet)(US?)**
  - *B. cereus* gene for lipase expressed in *B. anthracis*
- **Defeating mousepox vaccination (Australian)**
  - Ectromelia virus expressing IL-4
- **Synthesis of polio virus de novo (US)**
- **Reconstruction of 1918 flu virus**

### Mousepox: What Should have been Done?

- The potential for increased lethality of mousepox was unforeseen...

#### To popularly publish or not to publish?

"Disaster in the Making: An engineered mouse virus leaves us one step away from the ultimate bioweapon"



Dando/Rappert

#### To publish or not to publish?

"Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox"



### Publishing decisions at ASM

- ASM introduced formal processes for dual use review for its journals
- Manuscripts dealing primarily but not exclusively, with Select Agents
- In 2002: 313 select agents manuscripts received special screening (total of 13,929 submitted)
- Only TWO were sent to ASM publications Board for further review
- In 2003 (Jan-July): 262 select agent manuscripts (of 8557)
- None was referred to the publications board for further review.

ROYAL SOCIETY 2005)



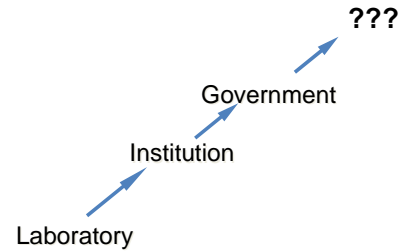
### ASM Code of Ethics- Guiding Principles

(6) ASM members are obligated to discourage any use of microbiology contrary to the welfare of humankind, including the use of microbes as biological weapons.

Bioterrorism violates the fundamental principles upon which the Society was founded and is abhorrent to the ASM and its members.

ASM members will call to the attention of the public or the appropriate authorities misuses of microbiology or of information derived from microbiology.

### Code of Conduct for Biological Sciences? (Hippocratic Oath)



“Dual use research of concern”:  
where are we now?

### The dual use “dilemma”

- Dual use relates to the threat of misapplication, not the the research itself.
- Many types of research of research can be considered dual use.
- Just because a project or approach has dual use potential does not mean it should not be carried out.
- Instead, this designation should be used to flag the work for caution in how it is carried out and how the results are disseminated.

“The number of recorded incidents of civil experiments or publications of true dual-use concern is vanishingly small.

What is truly of concern is the trajectory of the life sciences as a whole, and how the converging technologies that result from complex social innovative processes are to be protected from malign misuse.”

Malcolm Dando, Bulletin  
of the Atomic Scientists, 2011

### Intercalation of “dual use” issues into academic scientific education

- NIH ethics requirement (Responsible Conduct of Research)
- Specific time allotted to discussion during courses - certificates
- Institutional Biosafety Committees
- Laboratory training
- Faculty training

### Final questions:

What types of biological research should be classified and who should decide?

How do you strike a balance between security and scientific progress in the biological sciences?

Should there be limits on publication of genome sequences of pathogens or methods that could be used to make them?

Should scientists withhold information in publications that would enable their misuse? Should scientists be responsible for controlling information flow? What about journals or the government?

NIH case study, 2009