“The Life Sciences, Biosecurity, and Dual Use Research”

Project on Dual Use Research in Life Sciences

- Increased concern about bioterrorism and biowarfare amongst policy makers following 9/11 and anthrax letter attacks
- Discussions about the potential for misuse of biological research and how to prevent it
- Interactive discussion amongst practising scientists and decision makers about the possible malign misuse of the life sciences

In many respects, the events of September 11, 2001 and the anthrax attacks in the US that followed afterwards provide the immediate backdrop for this seminar. As I'm sure most of you are aware, since then there has been a significant increase in attention to threats posed by biological weapons. What some of you may not be aware of is that there has also been heightened attention since regarding the possible security implications of life science research. Questions are being asked internationally whether the research, techniques and knowledge in generated in places like universities might not only *prevent* the spread of disease but might inadvertently *facilitate* it. In this sense, research has a 'dual use' potential. And if that is the case, then what should be done in response?

I want to do two things in the seminar today. The first is to inform you about current 'biosecurity' and 'dual use' debates. The second, and much more important, is to generate discussion about these issues. I hope you will respond a lively way based on your individual experiences. With that, let us more to the first slide and case.

For further information:

American Association for the Advancement of Science *Resource: Science and National Security in the Post-9/11* Environment http://www.aaas.org/spp/post911/

Shea, D. 2003. *Balancing Scientific Publication and National Security* Concerns 10 January Washington, D.C.: Congressional Research Service. http://www.fas.org/irp/crs/RL31695.pdf

Wellcome Trust. 2003. *Wellcome Trust Position Statement on Bioterrorism and Biomedical Research.* http://www.wellcome.ac.uk/doc_WTD002767.html

The Life Sciences Today

"The rapid spread of scientific knowledge and applications owes much to a research culture in which knowledge and biological materials are shared among scientists and people move freely between universities, government agencies, and private industry. Large numbers of foreign graduate students and postdoctoral associates have been an essential ingredient of the success of the biological research enterprise. The scientific workforce is increasingly international…"

Notes: So the great success of the modern life sciences in providing for human welfare is based on a system in which people and ideas move with considerable freedom. To close down that freedom of movement would not be sensible unless there are overwhelmingly powerful reasons to do so. That then is the context in which the committee set its discussion of the dual use dilemma.

Biosafety and Biosecurity

"'Laboratory biosafety' is the term used to describe the containment principles, technologies and practices that are implemented to prevent unintentional exposure to pathogens and toxins, or their accidental release.

'Laboratory biosecurity' refers to institutional and personal security measures designed to prevent the loss, theft, misuse, diversion or intentional release of pathogens and toxins."

The Dual Use Dilemma

"The regulation of dual use biotechnology research is a highly contentious technical, political, and societal issue. In the language of arms control and disarmament, dual use refers to technologies intended for civilian application that can also be used for military purposes…"

– "…The key issue is whether the risks associated with misuse can be reduced while still enabling critical research to go forward."

Notes: Given their view of the need for openness in the scientific enterprise and their recognition of the possibility of misuse the committee formulated their key concern as "whether the risks associated with misuse can be reduced while still enabling critical research to go forward". This introductory chapter then makes the risks clear in its sections on the history of biological warfare and briefly introduces the Biological and Toxin Weapons Convention before turning its attention to the new threat.

Synthesis of Polio Virus

- "Wimmer and colleagues reported that they had reconstructed poliovirus from chemically synthesized oligonucleotides that were linked together and then transfected into cells. The report attracted considerable attention in the news media and concern in some segments of the public….This…raised public concern about bioterrorism because it suggested that the Wimmer experiment provided a recipe for terrorists to manufacture the virus…"

Notes: Wimmer published his work in 2002 and following the anthrax letters in the US it again attracted considerable attention and concern enough to provoke a resolution in congress.

Ref:

Cello, J., Paul, A. V., and Wimmer, E. (2002) Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template, *Science* **297**(5583), 1016 – 1018. Available from http://www.sciencemag.org/cgi/content/abstract/1072266

Synthesis of Polio Virus

- “Many scientists concluded that the Wimmer experiment was neither a novel discovery nor a potential threat. The general principle that one could make live poliovirus from a DNA template was already known in 1981, when Baltimore and colleagues reported that a DNA copy of the positive strand RNA genome of poliovirus could be taken up into living cells under appropriate conditions and result in the generation of encapsulated, infectious virus…”

Notes: The Fink committee’s report was rather unconvinced about the threat of bioterrorism arising from misuse of this work, particularly as the method used had been laborious and taken a long time. However, for many people not familiar with life scientist’s interest in matching their capabilities in genome sequencing with capabilities in genome synthesis this work came as something of a surprise. More surprises were to quickly follow as the next slide demonstrates.

Virulence in Smallpox

- "*Variola major* virus causes smallpox, which has a 30 - 40% mortality rate,whereas *vaccinia* virus, which is used to vaccinate humans against smallpox, causes no disease in immuno-competent humans. Both viruses have an inhibitor of immune response enzymes - vaccinia virus complement control protein (VCP) and smallpox inhibitor of complement enzymes (SPICE). The authors focused on a comparison of the genes encoding this inhibitor…"

Notes: This third example used in the Fink report deals with a paper by Rosengard and colleagues which deals directly with an aspect of the virulence of smallpox - certainly a very dangerous potential bioweapons agent.

Virulence in Smallpox

- "…As live *variola* is not available for study, they used standard techniques to synthesize the SPICE gene. They found that *variola* spice has a greater degree of specificity for human complement and is nearly a hundredfold more active than VCP in inactivating this component of the human immune system (human complement component C3b)…"

Notes: Again the report finds reasons for agreeing that this work should have been carried out, but as we saw in the last lecture they also recommended that an oversight of research projects of this kind was needed. We shall examine oversight systems in more detail in lecture No. 18.

Virulence in Smallpox

Ceppi del virus sono ancora mantenuti presso due laboratori, il *Centers for Disease Control and Prevention* ad Atlanta, USA, e il *Laboratorio di Ricerche Virologiche e Biotecnologiche* di Koltsovo, a Novosibirsk, Russia.
Non si può escludere che ne esistano altre colture nel mondo, in violazione a quanto prescritto.

Il virus doveva essere distrutto nel 1999, ma così non è stato.

Scientist's honor and destroyer's dishonor

(Oct 5, 2008 Yomiuri Newspaper)

Who do you select in the context of "the scientist who damaged the earth most"?

US scientist James Conant (1893 - 1978)

- Took the initiative to produce poison gas in World War I
- Became the president of the Harvard University at his age of forty
- The chairperson of the National Defense Science Committee: Promoted the project of developing atomic bomb

US chemist Thomas Midgley (1889 - 1944)

- Invented leaded gasoline to suppress car knocking
- Succeeded in synthesizing dichlorodifluoromethane: cooling media of refrigerators and air conditioners, abstergent of electronics, gas for sprays

→ Air pollution and the destruction of ozone layer

- Benevolent inventor may become the worst destroyer.
- To what extent should scientists take responsibility to their discovery or invention?

Start point of the problems

Good research projects, Excellent results

But …
we cannot exclude the possibility of hostile misuse

Dual use dilemmas

Why do the life scientists need to know the dual-use issue?

Why do the life scientists need to know the dual-use issue?

1. The development of science and technology, especially in life science such as biotechnology and recombinant DNA technology, is closely related to the development of “new generation” biological weapons.
2. Benevolent and civil research can be used for not only military purposes but also deliberate applications, and it could happen independently of researcher’s opinions.（Dual use dilemma）
3. Now is the age of high-speed internet and anyone can obtain the information of science and technology very easily from websites. Therefore, the scientists need to be responsible for the information that they provide also they have to foster their foresight about dual use research.

This slide clearly show why we research scientists should know the BTWC and the importance of the concept of biosecurity. The concept could perhaps be introduced briefly in advance of the lectures for the BTWC and dual use dilemmas.

Why do the life scientists need to know the dual-use issue?

1. Regarding the publication of research results and new findings, researchers' free and voluntary activity should be maintained. Governments or independent authorities are not the only responsible framework of this issue. Therefore, scientists themselves must tackle on the problems of dual use dilemma.
2. In the Biological and Toxin Weapons Convention, no reliable framework or methods to verify the compliance are established so far. That is the biggest problem in the Convention and simultaneously the life scientist can provide their knowledge to this issue.
3. If the life scientists themselves have an interest in the dual-use issue and participate in related frameworks it will enhance the comprehensive resolution of this issue.

Dual-use concern is not an unrealistic issue but a real problem

- The UK's detailed science and technology review covered 23 separate topics
  （Biological and Toxin Weapons Convention; The Fifth Review Conference of 2001-2002）

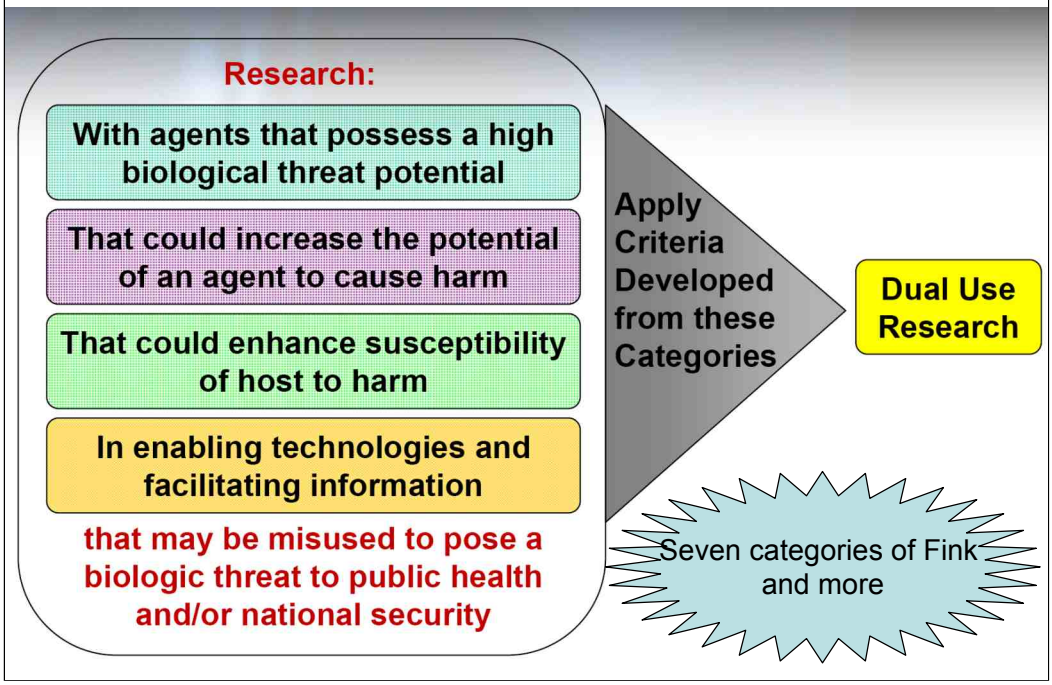
1. Genomics and proteomics
2. Bioinformatics
3. Human Genome Project and human diversity
4. Gene therapy
5. Virulence and pathogenicity
6. Vaccines and novel therapies
7. Recombinant protein expression
8. Toxins and other bioactive molecules
9. Detection and identification technologies
10. Human infectious disease patterns
11. Smallpox destruction
12. Drug resistance
13. Disease in agriculture
14. Pest control in agriculture
15. Global initiatives to tackle disease
16. Molecular biology applications and crops
17. Trends in protein production technologies
18. International co-operation and biosafety: activities under the Biodiversity Convention
19. Means of delivery of agents and toxins
20. Use of pathogens to control weeds and 'criminal' crops
21. Bioremediation: the destruction of material
22. Countering the threat of BW terrorism
23. Impact of the entry into force of the CWC

Useful in protecting against disease and BW

Many were seen as causes of concern

Some of these developments were seen as useful in protecting against disease and BW, but many were seen as causes of concern.

Emerging concept of dual-use research



Precautionary Principle

The Precautionary Principle (PP) constitutes a principle for decision-making that applies to cases where serious adverse effects can occur with an unknown probability. A fundamental message of the PP is that 'on some occasions, measures against a possible hazard should be taken even if the available evidence does not suffice to treat the existence of that hazard as a scientific fact'.

Notes: As Kuhlau et al note, one frequently quoted formulation of the PP was introduced at the Wingspread Conference in 1998 stating that: 'Where an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically'. Another PP is expressed in the 1992 Rio Declaration: 'Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.'

Ref:

Kuhlau, F., Hoglund, A., Evers, K., and Eriksson, S. (2009) A Precautionary Principle for Dual Use Research in the Life Sciences, *Bioethics*, [Early View] Available from

http://www3.interscience.wiley.com/journal/122499297/abstract

Sign of dual-use problems in life science research

Examples of dual-use research (Papers in a gray zone)

(1) Genetic manipulation of anthrax vaccine

Pomerantsev, A.P., Staritsin, N.A., Mockov Yu, V. and Marinin, L.I. (1997)
Expression of cereolysine AB genes in Bacillus anthracis vaccine strain ensures protection against experimental hemolytic anthrax infection.
Vaccine, **15**, 1846-1850.

→ But … the truth was the addition of toxin genes to the anthrax vaccine

(2) β-endorphin production in *Francisella tularensis*

Borzenkov, V.M., Pomerantsev, A.P. and Ashmarin, I.P. (1993)
[The additive synthesis of a regulatory peptide in vivo: the administration of a vaccinal Francisella tularensis strain that produces beta-endorphin].
Biull Eksp Biol Med, **116**, 151-153.

Combination of biological agent and bioregulator (increase pain sensitivity)

→ The possibility of making a new bioweapon?

Ref:

Pomerantsev, A. P., Staritsin, N. A., Mockov Yu, V. and Marinin, L. I. (1997) Expression of cereolysine AB genes in Bacillus anthracis vaccine strain ensures protection against experimental hemolytic anthrax infection. *Vaccine*, **15**(17/18), 1846-1850. Available from http://www.elsevier.com/wps/find/journaldescription.cws_home/30521/description#description

Borzenkov, V. M., Pomerantsev, A. P. and Ashmarin, I. P. (1993) The additive synthesis of a regulatory peptide in vivo: the administration of a vaccinal Francisella tularensis strain that produces beta-endorphin. *Biull Eksp Biol Med,* **116**(8), 151-153. Available from http://www.labmeeting.com/paper/20603235/borzenkov-1993-the-additive-synthesis-of-a-regulatory-peptide-in-vivo-the-administration-of-a-vaccinal-francisella-tularensis-strain-that-produces-beta-endorphin

Mousepox

"…Probably the most celebrated recent case involving the dissemination of research with the potential for bioterrorist uses was the report of an unexpected effect of the bioengineering of a strain of *ectromelia virus* (mousepox) that was intended to help eradicate mice in Australia…. Some have felt that the publication of this paper provides a blueprint or roadmap for terrorist to engineer a more virulent strain of smallpox that could overwhelm the human immune system in even well-vaccinated individuals…"

Notes: This paper is undoubtedly very well known amongst people concerned with security issues even though it is not very well known amongst practicing life scientists. The original academic paper was published in the Journal of Virology in 2001. It should be carefully studied by students.

Research Update TRENDS in Ecology & Evolution Vol.16 No.8 August 2001

Rodent plagues, immunocontraception and the mousepox virus

Hannu Ylönen

Australian Mousepox Experiment
An Example of Dual-Use Research

- Plagues of hundreds of millions of mice cause millions of dollars of damage in Australia's grain belt.
- To prevent or mitigate such plagues Australian researchers try to induce sterility in mice by altering an infectious virus that affects mice: mousepox.
- They insert egg protein gene into mousepox genome to create antibody response against eggs and thus rejection.
- They also insert the IL-4 gene to enhance the antibody response.

There have been a number of publications in the life sciences which have caused something of a stir because of their dual use potential. Perhaps the paradigmatic case is the Australian IL-4 mousepox experiment. Briefly, scientists at the Australian National University and the Commonwealth Scientific and Industrial Research Institute were trying to find a way of dealing with the plagues of mice which occur in Australia and cause significant agricultural damage. They came up with the idea of using a relatively benign form of mousepox which is usually not lethal to mice, and then to insert the gene for an egg protein from the mouse into this pox virus. The inserted virus then would create an antibody response by the female mice to her own eggs. This worked, but not as well as they hoped, so the researchers decided to add the gene for the cytokine interleukin-4 into the genome of mousepox and in the hopes that this would then elevate the antibody response.

A typical example of dual-use dilemma in scientific research

infectious immunocontraceptive for wild mice by incorporating a gene encoding an antigen from fertilized mouse eggs into the genome of *ectromelia* virus.

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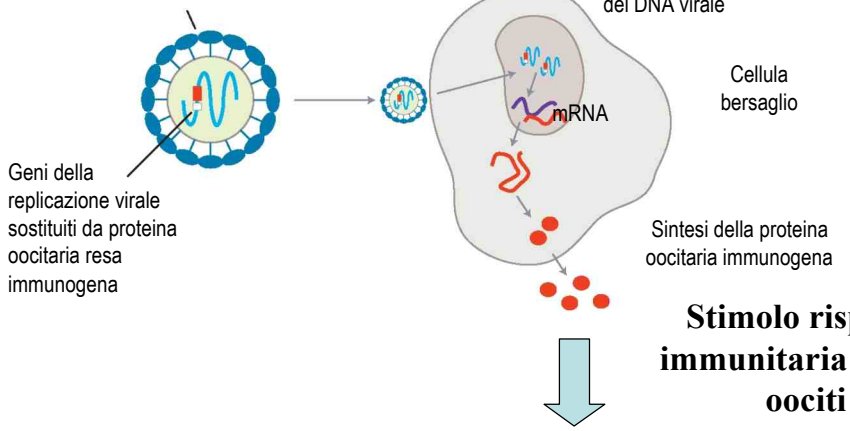
- The vaccine was developed to raise the antibody response to zona pellucida glycoprotein 3, and mousepox virus was used as a simple vehicle to carry it.

PRINCIPLE OF RODENT PLAGUES IMMUNOCONTRACEPTION

Infezione con virus ricombinante



Stimolo risposta immunitaria contro oociti

Diminuzione della fertilità

Come aumentare l'efficienza di sterilizzazione?

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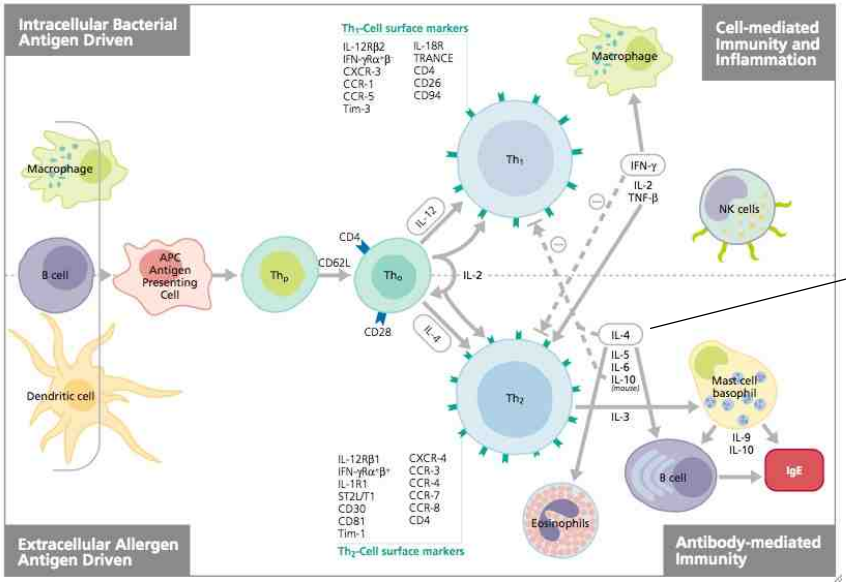
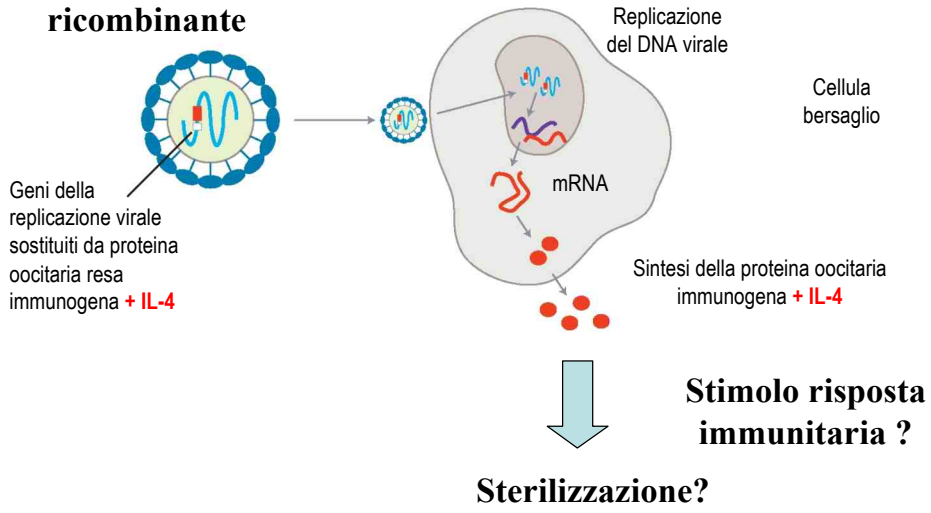
Aumentare la risposta immunitaria



Inserire IL-4 nel genoma del virus ricombinante

RODENT PLAGUES IMMUNOCONTRACEPTION

Infezione con virus ricombinante



Stimolo risposta immunitaria ?

Sterilizzazione?

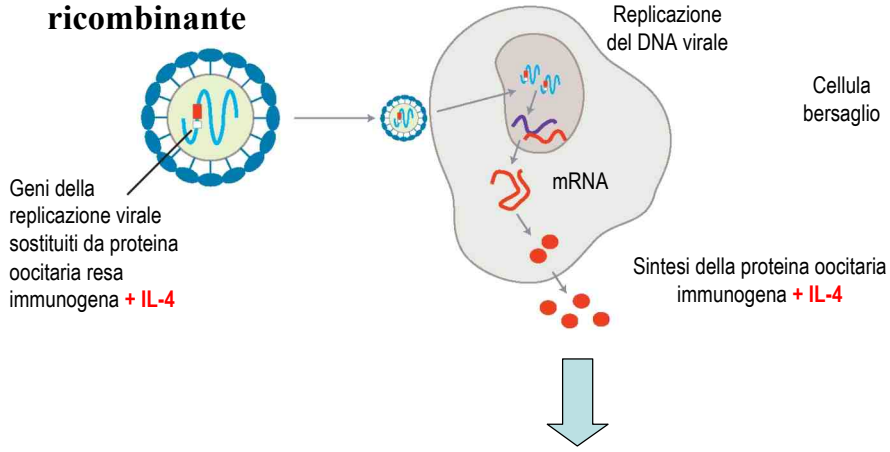
Mousepox

- “Since the expression of this egg antigen of the virus did not result in infertility, the authors attempted to increase the virulence of *ectromelia* with the hope that this would increase the immune response…”

Notes: The civil objective of the work was clear. In order to deal with rodent plagues a naturally infective pox virus was modified so that it produced an egg protein. This it was hoped would generate a sufficient immune response to lead to the rejection of the eggs by mice and thus prevent the build up of the plague of mice (which if you have seen film of such a plague is quite startling).

RODENT PLAGUES IMMUNOCONTRACEPTION AND THE MOUSEPOX VIRUS

Infezione con virus ricombinante

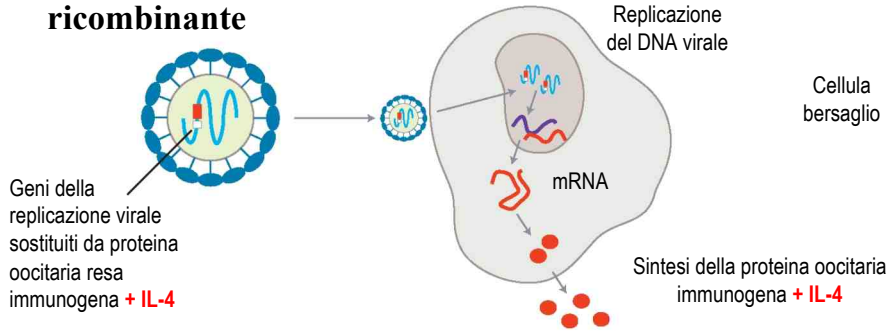


Morte dei topi

Genetically manipulated new virus showed unexpectedly strong virulence to kill the mice

RODENT PLAGUES IMMUNOCONTRACEPTION AND THE MOUSEPOX VIRUS

Infezione con virus ricombinante



Morte dei topi ma sensibilità di ceppi altrimenti resistenti all'infezione!

Mousepox

- "…They then demonstrated that this engineered mousepox virus was much more virulent than the parent virus and killed 60% of infected mice, even if the mice were from a genetically resistant strain. Even more unexpected was their observation that mice that had been vaccinated and were completely resistant to the parent virus…were now killed by the IL-4 gene-expressing virus."

Notes: What the scientists did not expect was that the doubly modified mousepox virus now killed mice which has been vaccinated against the original virus. Moreover they had used quite simple techniques that were described in the methods section of the paper. The Fink Committee's report then goes on to discuss the pros and cons of publication in the academic literature (though it should be noted that prior to publication in the Journal of Virology there was an major article and editorial about the work in the popular science New Scientist which made the potential connection to a modified smallpox very clear).

Come aumentare l'efficienza di sterilizzazione?

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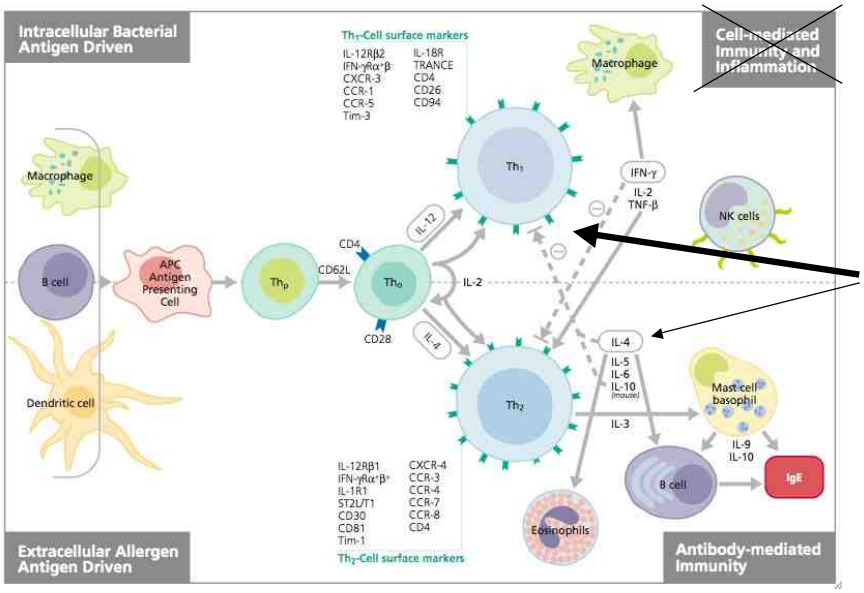
Aumentare la risposta immunitaria



Problems from the viewpoints of dual-use

1. The purpose of this study was to improve antibody production by IL-4 gene insertion into ectromelia virus, but the recombinant virus suppressed cellular immunity very strongly. (Unexpected products for researchers)
2. The researchers show the possibility of making a new pathogenic virus by manipulating the gene that directly involves in immune response. (The possibility of making new pathogenic viruses using similar concept)
3. The recombinant virus exerted strong immunosuppressive effect to the host that already has acquired immunity to the same virus strain. (Warning to the vaccine programme)
4. Novel vaccine research regarding cancers and other diseases may produce unexpected products such as killer viruses. (Similar research may produce harmful viruses?)
5. Research reports published in medical journals and anyone can read them. (Easy provision of information)
6. Simple gene manipulation may lead to the production of novel viruses. (No need of high technology and specialized knowledge)

Communication Questions

- The researchers produced a recombinant virus with greatly increased lethality.
- The virus with IL-4 killed mice genetically resistant to mousepox and those immunized against it.
- Concerns arise because of the potential for increased lethality of other pox viruses, including smallpox.

Do you agree with the decision to publish?

If so, why? If not, why not?

What follows on from your views?

It certainly elevated the response. What it did in fact was to close down the cell mediated arm of the immune system. They ended up with a recombinant virus which killed mice genetically resistant to mousepox and even those immunized against it. It didn't take very long for the researchers to ask 'Hang on a minute, what if somebody was to do this with smallpox?'. Potentially at least, you might then have a form of smallpox that could overcome existing vaccinations. The first question then is do you think the Australians should have gone ahead and published these results in a standard scientific article in the *Journal of Virology*? If so, why? If not, why not? Would there be any additional follow on implications that would follow from what you said?

For further information:

Jackson, R. Ramsay, A., Christensen, C., Beaton, S. Hall, D., & Ramshaw, I. 2001. 'Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox' *Journal of Virology* 75(3): 1205-1210.
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pubmed&pubmedid=11152493

ABSTRACT

Genetic resistance to clinical mousepox (ectromelia virus) varies among inbred laboratory mice and is characterized by an effective natural killer (NK) response and the early onset of a strong CD8+ cytotoxic T-lymphocyte (CTL) response in resistant mice. We have investigated the influence of virus-expressed mouse interleukin-4 (IL-4) on the cell-mediated response during infection. It was observed that expression of IL-4 by a thymidine kinase-positive ectromelia virus suppressed cytolytic responses of NK and CTL and the expression of gamma interferon by the latter. Genetically resistant mice infected with the IL-4-expressing virus developed symptoms of acute mousepox accompanied by high mortality, similar to the disease seen when genetically sensitive mice are infected with the virulent Moscow strain. Strikingly, infection of recently immunized genetically resistant mice with the virus expressing IL-4 also resulted in significant mortality due to fulminant mousepox. These data therefore suggest that virus-encoded IL-4 not only suppresses primary antiviral cell-mediated immune responses but also can inhibit the expression of immune memory responses.

Kind of Communication

- Published in *Journal of Virology* Feb. 2001.

target => to the scientific community

- Editorial and article in the *New Scientist* 13 January 2001

target => larger Public

JOURNAL OF VIROLOGY, Feb. 2001, p. 1205–1210 Vol. 75, No. 3
0022-538X/01/$04.00+0 DOI: 10.1128/JVI.75.3.1205–1210.2001

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

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ABSTRACT

Genetic resistance to clinical mousepox (ectromelia virus) varies among inbred laboratory mice and is characterized by an effective natural killer (NK) response and the early onset of a strong CD8+ cytotoxic T-lymphocyte (CTL) response in resistant mice. We have investigated the influence of virus-expressed mouse interleukin-4 (IL-4) on the cell-mediated response during infection. It was observed that expression of IL-4 by a thymidine kinase-positive ectromelia virus suppressed cytolytic responses of NK and CTL and the expression of gamma interferon by the latter. Genetically resistant mice infected with the IL-4-expressing virus developed symptoms of acute mousepox accompanied by high mortality, similar to the disease seen when genetically sensitive mice are infected with the virulent Moscow strain. Strikingly, infection of recently immunized genetically resistant mice with the virus expressing IL-4 also resulted in significant mortality due to fulminant mousepox. These data therefore suggest that virus-encoded IL-4 not only suppresses primary antiviral cell-mediated immune responses but also can inhibit the expression of immune memory responses.

Another Kind of Communication

- January 2001Australian researchers worked with a popular magazine to publish a preview of their paper.
- *New Scientist* published an article with the following title:

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

Rationale: "We wanted to warn the general population that this potentially dangerous technology is available…We wanted to make it clear to the scientific community that they should be careful, that it is not too difficult to create severe organisms." -- R. Jackson

How do you view the decision to popularly publish (why, what follows on from this, etc.)?

Let's just slightly later the line of reasoning. The Australian researchers did not just communicate their results through a standard article in the *Journal of Virology,* rather they did so through the *New Scientist* as well. The month before article appeared in the *Journal of Virology*, *New Scientist* carried an editorial and an article about the experiment. That first article was entitled 'Disaster in the Making – an engineered a mouse virus leaves us one step away from the ultimate bioweapon'. It noted that a forthcoming issue of the *Journal of Virology* would be carrying the scientific article. The logic the Australian researchers used to justify the *New Scientist* coverage was that 'We wanted to warn the general population that this potentially dangerous technology is available…We wanted to make it clear to the scientific community that they should be careful, that it is not too difficult to create severe organisms.'

So what I want to ask you then is not was it a good idea to publish in the scientific press, but should they have gone ahead and 'popularly published' their results?

For further information:

New Scientist 13 January 2001

http://www.newscientist.com/contents/issue/2273.html

Mousepox

- “Some have felt that the publication of this paper provides a blueprint or roadmap for terrorists to engineer a more virulent strain of smallpox that could overwhelm the human immune system in even well-vaccinated individuals…. It has been suggested that either the paper should not have been published, or at the very least the ‘materials and methods’ section…should have been altered or omitted entirely from the published article…”

Notes: The authors consulted about whether the paper should be submitted for publication and the editors of the journal also sought guidance. Eventually, however, the paper was published exactly as submitted.

Mousepox

- Reasons for publication?
  - "…First, knowledge of these experiments allows the scientific community to explore how to overcome such engineered viruses…"
  - "…Second, it suggests that we should be prepared to treat infections caused by such an engineered virus with antibodies that inactivate the relevant cytokine, with gamma interferon that would counter the effect of IL-4, or with both…"

Notes: Notwithstanding the fact that even vaccinated mice were killed by the doubly modified mousepox the report gives reasons to support the publication as shown in the quotations given in this slide. Of course, given the prominence of this experiment there is a large literature on the topic that students could easily explore on the internet. An example of earlier work of relevance is given in the first link below to another paper in the Journal of Virology in 1998. Later work can be followed in the link to the 2008 paper in Antiviral Research provided in the second link below.

Ref:

Parker, S., Touchette, E., Oberle, C., Almond, M., Robertson, A., Trost, L. C., Lampert, B., Painter, G.., and Buller, R. M.(2008) Efficacy of Therapeutic Intervention with an Oral Ether-lipid Analogue of Cidofovir (CMX001) in a Lethal Mousepox Model. *Antiviral Research* **77**(1):39-49. Available from

http://www.ncbi.nlm.nih.gov/pubmed/17904231

Another Model for Communication

- Suggestion that British researchers had previously obtained similar results to the Australian mousepox research.
- The researchers were said to have informed Health and Safety Executive, but deliberately avoided discussing or alluding to bioweapons implications in their publication.
- A literature search revealed a **1998** *Journal of Virology* article that might be research in question:
  - IL-4 insertion in modified vaccinia virus (VRBm)
  - "A mortality of 100% was observed for mice immunized with VRBmIL-4 [modified vaccinia with IL-4 gene]… This contrasted with that for mice immunized with rVV expressing low levels of IL-4…which showed no ill effects…"

What are the merits of this "softly-softly" approach?

OK, up to this stage I have asked questions about whether something should be published or not. Now I want to ask a more nuanced question about how one should publish. There has been a suggestion that similar results to what the Australians found had been achieved elsewhere but communicated in a much different manner. This story involves researchers in the UK who were working with IL-4 in the late 1990s. The idea is that the scientists unexpectedly came across similar results about the lethality of IL-4 in a pox virus, but choose to take a very low key approach to communicating their results. So rather than warning the general population through an article in *New Scientist* or raising flags within scientific communities through their specialized publications, what these researchers did was to inform the Health and Safety Executive of their 'dual use' concerns. The UK Health and Safety Executive is in charge of ensuring laboratory biosafety. Then they continued on with the civilian animal research they were interested in.

This is a story that is told in UK policy circles without any identification of who was involved, so it is not possible to know what research is being referred to in this story. Looking back with a sense of hindsight, though, it is possible to identify research that could fit this description. For instance, a 1998 article in the *Journal of Virology* dealt with the effects of cytokine genes on the immune system. If you read the article closely, you can see the researchers made some interesting findings regarding the effects of IL-4 on vaccinia virus. Specifically, these researchers were able to achieve a 100% mortality rate for immunized with a form of vaccinia expressing high levels of IL-4 which contrasted with that of a form of vaccinia expressing low levels of IL-4 which showed no ill effects.

Funding

Ideas of restricting research and publications are generally treated as matters of concern by practicing life scientists. However, the funding of various lines of research has also provoked discussions of interest in relation to dual use research.

Development of Biosafety Oversight

- In 1970's life scientists began to manipulate genomes.
- Many countries have instituted review procedures to ensure biosafety of such experiments.
- In US, Asilomar Conference in 1975 led to NIH funded research subject to rDNA review procedures.

James Watson and
Sydney Brenner at Asilomar

Before getting into dual use specific issues, let me make some initial remarks about oversight in general. Oversight is not a new issue to life science research, indeed concerns about the need for such measures have been around for some time. This slide notes some examples related to the safety of experiments.

The Fink Report

BIOTECHNOLOGY RESEARCH IN AN AGE OF TERRORISM (2004)

The great achievements of molecular biology and genetics over the past 50 years have produced advances in agriculture and industrial processes and have revolutionized the practice of medicine. The very technologies that fueled these benefits to society, however, pose a potential risk as well—the possibility that these technologies could be used to create the next generation of biological weapons. Biotechnology represents a "dual use" dilemma in which the same technologies that can be used to better society can also be misused for bioterrorism with devastating results.

National Academy of Sciences • National Academy of Engineering • Institute of Medicine • National Research Council

US National Academies Fink Report *"Biotechnology Research in an Age of Terrorism"*

- Expand **existing** local and national *biosafety* review **funded** rDNA research to include *biosecurity.*
- Apply new procedures to 'experiments of concern' in **US** e.g.:
  - Making vaccines ineffective
  - Altering host range or enhancing virulence of pathogens
  - Conferring resistance to useful antibiotics or antivirals
- Establish National Science Advisory Board for Biosecurity to:

  review, survey and educate bioscientists including to 'develop guidelines for the oversight of dual-use research, including guidelines for the risk/benefit analysis...'

Are biosecurity oversight mechanisms to be welcomed? Why or why not?

In the United States, where perhaps more attention has been given to the issues surrounding the malign use of life science research, the National Academy of Sciences set up a committee to look at what possibly could be done in response. This was headed by Gerald Fink of the Whitehead Institute. After about 18 months of study, they produced a report that has become known as the Fink Report. One of its recommendations was that there should be an expansion of the current NIH recombinant DNA review procedures to include a review of so-called 'experiments of concern'. These experiments would be of concern in the sense that they might come up with findings that could readily and significantly aid malign purposes. Seven categories of research of concern were proposed, of which a few are noted on the slides. The report suggested that the proposals to carry out research in these areas should be submitted to local institutional biosafety for assessment and that there should be a National Science Advisory Board for Biosecurity set up to review any case which could not be handled at a local level. The Bush Administration accepted most of the recommendations of Fink report and established the National Science Advisory Board for Biosecurity to give advice on how such and oversight system should function. By 2006, the Board had had a number of meetings and began to formulate specific recommendations. So the question I would like to ask is: should such an oversight system be welcomed?

For further information:

'Fink Report'- *Biotechnology Research in an Age of Terrorism*

http://www.nap.edu/catalog/10827.html

US National Science Advisory Board for Biosecurity

The Fink Report

- The Committee's 2004 report, *Biotechnology Research in an Age of Terrorism*, is usually referred to as the Fink Report.
- The Fink Report contained seven recommendations to ensure responsible oversight for biotechnology research with potential bioterrorism applications.
- One of these recommendations was to create a National Science Advisory Board for Biodefense within the Department of Health and Human Services to provide advice, guidance, and leadership for a system of review and oversight of experiments of concern.

14. Experiments of concern (Seven categories)

—Fink Report (NAS 2004)—

1. **Would demonstrate how to render a vaccine ineffective**.
   This would apply to both human and animal vaccines.
2. **Would confer resistance to therapeutically useful antibiotics or antiviral agents.**
   This would apply to therapeutic agents that are used to control disease agents in humans, animals, or crops. Introduction of ciprofloxacin resistance in *Bacillus anthracis* would fall in this class.
3. **Would enhance the virulence of a pathogen or render a nonpathogen virulent.**
   This would apply to plant, animal, and human pathogens. Introduction of cereolysin toxin gene into *Bacillus anthracis* would fall into this class.
4. **Would increase transmissibility of a pathogen.**
   This would include enhancing transmission within or between species. Altering vector competence to enhance disease transmission would fall into this class.
5. **Would alter the host range of a pathogen.**
   This would include making nonzoonotics into zoonotic agents. Altering the tropism of viruses would fit into this class.
6. **Would enable the evasion of diagnostic/detection modalities.**
   This could include microencapsulation to avoid antibody based detection and/or the alteration of gene sequences to avoid detection by established molecular methods.
7. **Would enable the weaponization of a biological agent or toxin.**
   This would include environmental stabilization of pathogens.

Important points in the report are …

- Ensure that Research is Not Limited
- Educate the Scientific Community
- Enhance the Review System for Experiments
- Rely on Self-governance for Review of Publications

- Create a National Science Advisory Board for Biodefense

- Improve Communication between Security, Law Enforcement, and Life Science Organizations

- Review Physical Containment and Personnel Issues

- Coordinate International Oversight

AGENCIES

- Exec. Office of the President
- Department of Health and Human Services
- Department of Energy
- Department of Homeland Security
- Department of Veteran's Affairs
- Department of Defense
- Environmental Protection Agency
- United States Department of Agriculture
- Department of Interior
- National Sciences Foundation
- Department of Justice
- Department of State
- Department of Commerce
- National Aeronautics and Space Administration
- Intelligence community

Arms Control

- Geneva Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous, or Other Gases, and of Bacteriological Methods of Warfare
- Biological and Toxin Weapons Convention
- Chemical Weapons Convention
- Convention on the Prohibition of Military or Any Other Hostile Use of Environmental Modification Techniques

Core responsibilities of life scientists regarding dual use research of concern

Individuals involved in any stage of life sciences research have an ethical obligation to avoid or minimize the risks and harm that could result from malevolent use of research outcomes.

Toward that end, scientists should:

•Assess their own research efforts for dual use potential and report as appropriate;
•Seek to stay informed of literature, guidance, and requirements related to dual use research;
•Train others to identify dual use research of concern, manage it appropriately, and communicate it responsibly;
•Serve as role models of responsible behavior, especially when involved in research that meets the criteria for dual use research of concern; and
•Be alert to potential misuse of research.

What Else Might be Done

If Fink recommendations *not welcomed*, what about…

"We're looking for the scientific community to come forward itself because the government will not do this very efficiently and not do it very well at all. We are looking for scientific community to come forward to help establish these kinds of criteria [for the oversight of research], to debate them openly."

-- Penrose Albright (2003)
Office of Homeland Security
White House Office of Science & Technology Policy

OK, given that some of you expressed reservations about the system of community self-governance proposed by the Fink report, I can put up this quote from someone at the US Department of Homeland Security. What Albright said, and it is a sentiment that have been echoed by others in and outside of the US, is that the failure of the scientific community to come up with oversight suggestions will necessitate others stepping in, such as politicians. The implication being: don't complain if this happens. I offer this quote just to see what sort of reactions you might have to it.