Committee on Dual Use Research of Concern: Options for Limited Communication

Michael Imperiale

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H5N1 influenza: a case study

Experimental adaptation of an influenza H5 HA confers respiratory droplet transmission to a reassortant H5 HA/H1N1 virus in ferrets

Masaki Imai[1], Tokiko Watanabe[1,2], Masato Hatta[1], Subash C. Das[1], Makoto Ozawa[1,3], Kyoko Shinya[4], Gongxun Zhong[1], Anthony Hanson[1], Hiroaki Katsura[5], Shinji Watanabe[1,2], Chengjun Li[1], Eiryo Kawakami[2], Shinya Yamada[5], Maki Kiso[5], Yasuo Suzuki[6], Eileen A. Maher[1], Gabriele Neumann[1] & Yoshihiro Kawaoka[1,2,3,5]

Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets

Sander Herfst,[1] Eefje J. A. Schrauwen,[1] Martin Linster,[1] Salin Chutinimitkul,[1] Emmie de Wit,[1*] Vincent J. Munster,[1*] Erin M. Sorrell,[1] Theo M. Bestebroer,[1] David F. Burke,[2] Derek J. Smith,[1,2,3] Guus F. Rimmelzwaan,[1] Albert D. M. E. Osterhaus,[1] Ron A. M. Fouchier[1]†

H5N1 influenza: a case study

- avian H5N1 has high human mortality rate
  - no human-to-human transmission
  - can it spread?
- debate in virology community
- Fouchier and Kawaoka test experimentally

The NSABB saga

- original recommendation: publish nature of finding, omit specific mutations
- briefing by Francis Collins
  - FOIA
  - cybersecurity
- new recommendation based on binary decision

US government policies

- NSDD-189
  - fundamental research published openly unless classified
  - NIH does not fund classified research
- Sensitive But Unclassified
  - “Controlled Unclassified Information”
- Export controls

Scientific community

- publication is norm
  - allows reproducibility
  - builds foundation
- pressure to publish
- other venues for dissemination
  - conferences

Journals

- detail necessary
  - proper peer review
  - reproducibility
- reviewers nor editors properly trained

Other Considerations

- Internet
  - blogs
  - preprint servers
  - cybersecurity
- International concerns
  - collaboration
  - cultural differences

What information do we want to control?

- pandemic pathogens
- new technologies
- new applications of existing technologies
- other…

Is limited communication feasible?

Box 1 | Properties of the ideal gene therapy vector

Easy production
The vector should be easy to produce at high titre on a commercial scale. This consideration stems from the wide range of cell numbers that must be transduced — from a handful of stem cells capable of reconstituting the entire haematopoietic repertoire to 10^{11} or more cells to infect 5–10% of the liver. For widespread use, the vector should be amenable to commercial production and processing (such as concentration technology for delivery in small volumes), and should have a reasonable shelf-life for transport and distribution.

Sustained production
The vector, once delivered, should be able to express its genetic cargo over a sustained period or expression should be regulable in a precise way. Different disease states have different requirements (for example, regulated expression in diabetes and lifetime expression in haemophilia).

Immunologically inert
The vector components should not elicit an immune response after delivery. A humoral

Box 1 | Properties of the ideal gene therapy vector

dispersed throughout the body (such as in the haematopoietic system), or if the cells are part of a heterogeneous population (such as in the brain). It is also important to avoid certain cells, such as dendritic cells, the 'professional' antigen-presenting cells of the body, because of their role in mediating the immune response. Cell or tissue-targeted vectors present a great challenge, but also offer rich dividends for gene therapy approaches.

Size capacity
The vector should have no size limit to the genetic material it can deliver. The coding sequence of a therapeutic gene can vary from 350 base pairs for insulin, to over 12,000 base pairs for dystrophin. Furthermore, addition of appropriate regulatory sequences may be required for efficient transduction and expression of the foreign genetic material.

Replication, segregation or integration
The vector should allow for site-specific integration of the gene into the chromosome of the target cell, or should reside in the nucleus as an episome that will faithfully divide and segregate on cell division. Site-specific integration is a very desirable attribute because it eliminates the uncertainty of random integration into the host chromosome, and endogenous regulatory regions will control its expression under physiological conditions. The ability of the vector to be maintained as an episome could make the genetic elements independent of local chromatin environments, but faithful replication and segregation is needed if the vector is to be effective in systems such as stem cells.

Infection of dividing and non-dividing cells
As large numbers of cells (such as neurons, hepatocytes and myocytes) are postmitotic, vectors capable of efficiently transducing non-dividing cells are very desirable.

Somia and Verma, *Nature Rev. Genet.* 2000

Properties of the Ideal Limited Communication System

- overall conclusions freely available
- specifics available on ‘need to know’ basis
  - unique experimental details omitted
  - worrisome data omitted
- secure storage
  - release once perceived threat reduced/gone

Questions

- who decides what needs to be controlled?
- who needs to know?
  - who decides?
- who stores the data?
- how are data secured?

Another approach: enhance the status quo

- emphasize responsible science
  - responsibility to public
- more diligence up front
  - identify projects with potential issues
  - proactive communication plan