

**Identify What Technological Advances in the Fields of Science
and Engineering Need to Be Developed (Either New Technology
or Novel Integration of Existing Technologies) to Improve
Rapid Response to New or Emerging Diseases**

WORKING GROUP DESCRIPTION

Background

Only a small fraction of the microbial life on Earth has been actively studied and characterized. Extremophiles have demonstrated the ability of life to exist in environments that appear harsh by existing standards. These adaptations clearly demonstrate the ability of bacteria and viruses to make genomic modifications that result in novel functions. As the rapid movement of people increases around the globe, the probability of becoming infected with or transmitting a previously undiscovered infectious organism is constantly increasing. When one compounds this increased mobility with the naturally changing genomes of existing bacterial and viral pathogens, the result is a precarious balance between pandemic and small isolated outbreaks.

Genetically modified organisms are already in use commercially to enhance milk production as well as to make crops resistant to insects and viruses. Some of these modifications are achieved by selective breeding and others by deliberate genetic modifications. Is it possible to safely create modified organisms that prey on specific target organisms for therapeutic or diagnostic purposes?

The Problem

Using the collective wisdom represented by this team, refine the working group topic into discrete tasks and outline steps required to approach each of the steps.

Initial References

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WORKING GROUP SUMMARY

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Summary

At first glance this working group's charge seemed straightforward: identify some technologies that will help us identify and treat new diseases as they are born or begin harming people. But during our first discussion, it became clear that we had a bigger goal in mind. It seemed to us that in order to address this question, we had to understand—and improve—the entire approach to how we fight emerging disease. Rapid response, our discussions emphasized, involves a broad range of institutions and technologies, from engineering bacteriophages to smart toilets to the marketability of vaccines. And it all seemed so simple—at first.

Our group decided to propose not just technologies but also a framework for a comprehensive response to emerging diseases—whether entirely new or resurfacing. This framework focuses on four sequential stages that compose the strictly technical aspect of rapid response. We sought to improve the effectiveness of the science in each of the four stages such that we could detect new and emerging diseases earlier and respond to them more quickly and effectively. Imagine, for example, that if as soon as the flu of 1918 evolved, scientists identified it immediately in its natural reservoir and stopped it before it harmed a single person. Our group believes this framework can bring us closer to that level of effective rapid response. Here are the four stages of rapid response:

1. Surveillance and monitoring for infectious agents
2. Detection of disease state and identification of causative agent

3. Initial response
4. Later response

Our recommendations to improve each stage:

Surveillance and monitoring: Detecting and identifying potential infectious agents before they spread widely in the human population

The most rapid part of rapid response comes from identifying a problem quickly by using good methods of surveillance. Our group saw two major types of early pathogen detection: biological monitoring and information analysis.

Biological monitoring is a system designed to detect and identify pathogens anywhere in the environment, such as in animal populations, on a public bus, at the scene of a bioterror attack, or in the body of an unknowingly infected person. The group thought that one important way to detect infectious agents this early in the process is through devices that provide constant, widespread environmental monitoring for microbes. These background monitors should focus on some key areas of high risk and high-population density, like hospitals and public transportation. One mechanism to do this would be to install ventilation systems that sample and analyze air as it circulates. In the future these environmental monitors could spread to other locations; surfaces in public buildings, like doorknobs or handrails, could also be surveilled for pathogens. In addition to looking for organisms themselves, environmental monitoring systems can look for early effects of infections in people. For example, during the SARS outbreak, infrared sensors were used to measure the temperature of people's foreheads and faces to see if they had fevers.

A related but somewhat different mechanism to detect the emergence of pathogens is to look more closely at individual people, specifically the systems that most often host small invaders: the respiratory and digestive systems. The group advanced the idea of using "snot chips" and "smart toilets," both of which have the potential to provide a detectable signal in which to look for pathogenic infection. (The use of these types of devices might raise concerns about privacy because they are more traceable than environmental monitors are, but in the surveillance and monitoring stage, we don't need to record people's identities; we're more concerned with detecting the mere emergence of pathogens.)

Another important way to detect emerging pathogens is with indirect monitoring, specifically, watching the purchases of pharmaceuticals as an indicator of infectious outbreaks. In 1993 doctors learned about a *Cryptosporidium* outbreak in Milwaukee only when a perceptive pharmacist noticed a period of particularly strong sales of Imodium (loperamide). We should develop better informatics and meta-analyses to detect outbreaks like these as early as possible. These bioinformatics tools would also help to synthesize and interpret the loads of biological information gleaned from environmental monitoring. This effort should aim to add to, draw on, or connect similar projects that have already been launched, such as NEON, a National Science Foundation-funded network of ecological observatories that could help with environmental monitoring for pathogens (<http://www.neoninc.org/about/> - accessed 2/2/2006); RSVP, an Internet-enabled system that gathers information from thousands of doctors (http://www.ca.sandia.gov/chembio/implementation_proj/rsvp/ - accessed 2/2/2006); and ESSENCE, a Department of Defense-run system to centralize information on infectious outbreaks (<http://www.geis.fhp.osd.mil/GEIS/SurveillanceActivities/ESSENCE/ESSENCE.asp> - accessed 2/2/2006).

Detection and identification: Isolating and identifying the cause of an infectious human illness

Once an illness has been detected, scientists need to isolate the cause to determine how best to fight it. Our group especially encourages work in a few fields to improve our ability to identify pathogens. Purification, concentration, and array-based analysis of nucleic acids, proteins, and potentially other molecules should be used more broadly to find the signatures of pathogens. Improving culture methods would accelerate the discovery of infectious agents. We should develop better methods for diagnosing disease states and infectious agents by the reactions of parts of the immune system, such as the T-helper cells. We could also assay the major histocompatibility complexes (MHCs) of people's cells—not to learn their MHC genotype but to analyze the mixture of peptides in the complexes and see if particular pathogens are evidenced by distinctive protein signatures.

Initial response: Fast strategies for decreasing the harm done in the first stages of an outbreak

Some of the group's most important work came in the identification of technologies that may provide the scientific basis for improvement of initial responses to emerging diseases—the heart of rapid response. Some of the most promising tools in this stage are bacteriophages, which can be used in a couple of different ways. One recommendation is to keep a permanent and openly accessible library of known bacteriophages. After a new pathogenic bacterium is sequenced and its antigens known, it can be compared against the collection of phages to see which might effectively attack it. As the collection grows, it becomes more likely to include effective counters to new pathogens. Bacteriophages can also be used through phage display to make other antibacterial tools, like antibiotic peptides and antibodies for passive immunotherapy.

Just as a widely accessible library of phages can help respond to new pathogens, a library of rejected drug candidates could do the same. Our group recommends maintaining a catalog of compounds that pass phase 1 of the approval process—they are safe—but they fail in phases 2 or 3 because of a lack of efficacy. But these drugs, ineffective for their original intended goal, may well be invaluable cures against emerging diseases. As new infectious agents are isolated, they could be tested against potential treatments in silico; binding and affinity could suggest efficacy. This approach would demand a substantial organizational change—there is currently no way to administer such a project and reward participating drug makers—but we believe it's possible to develop mechanisms to do so. Both the bacteriophage and recycled-drug libraries would demand new bioinformatics tools to speed the connection of potential cures with new pathogens.

A few more of the group's suggestions for initial responses:

- Use T-helper-cell vaccines to direct the immune system to attack pathogens
- Damp down inflammatory responses to certain infections where the inflammatory response is excessive and harmful
- Locate and contain “superspreaders”

Later response: Follow-on treatments for diseases that have not been contained in the previous step

We hope that the aforementioned strategies will help prevent new diseases from causing widespread illness, but it seems all but inevitable that a pandemic will happen again at some

point. So the group developed some techniques for treating diseases that have already begun to spread.

Again, some of the useful tools to develop for this stage are bacteriophages. If the structure of the pathogen is known but there are no existing phages to attack it, researchers should work to evolve or engineer a new one to do the job. Phages could also be used to alter the composition of the native microflora to compete with or otherwise hinder the reproduction, spread, or virulence of the pathogen.

The group was also hopeful about accelerating vaccine development using the pathogen's sequence, following on from similar work being attempted on HIV. By exposing patients to DNA plasmids that express pathogen proteins and an engineered adenovirus, we hope to be able to provoke an effective immune response. In an urgent or dire situation, the testing of a vaccine might be accelerated so it could be deployed faster than the usual lengthy approval process allows.

Organizational, social, political context

In rapid response to emerging disease, the organizational and political factors are as important as the science; good organization is not enough to make rapid response work, but bad organization is enough to make it not work. Our group focused on technical questions in our discussions, as that was our obvious strength, but we felt we would be remiss not to mention the societal context.

One great concern is the lack of commercial viability of some important parts of rapid response to emerging disease. Vaccines, for example, are seen as unprofitable for drug companies, and are unfortunately ignored. Government and civil society should work together to ensure that such an important health measure is well covered.

Another problem is the increasing secrecy around important reagents and sequences because of intellectual property protections and demands for secrecy from certain governments. Some group members working on vaccines for H5N1 avian flu have run into problems trying to get information on the virus because of restrictions. Intellectual property and other motivations for secrecy must give some ground to safety in the case of potential epidemics or pandemics.

With much of the effort to improve rapid response focusing on accumulating more information more quickly, this search must also be tempered by ethical concerns, especially the privacy demands of laws such as HIPAA (Health Insurance Portability and Accountability Act).

These are the major points raised by the workgroup in our discussions about rapid response to emerging disease. The group feels that each individual step will most likely improve health care by itself. Moreover, this framework can help make sure that our society won't ignore any important links in the chain of rapid response. As one of the group members points out, "Wal-Mart knows that organization is a technology." We hope that it might help scientists and policy makers to guide research and resources in a way that will best protect global health.