Harnessing new science is vital for biodefense and global health

With the impending Congressional approval of Project Bioshield (S. 15 and H.R. 2122), the United States will be taking new steps to prepare itself against the prospect of bioterrorism. The bills provide incentives to the private, for-profit sector to develop diagnostics, vaccines, and drugs against biological threats. In addition, through a program launched in fiscal year 2003, the National Institutes of Health is providing major funding for research aimed at uncovering the knowledge required for the development of protective agents.

How can we mobilize the best science to protect the nation and the world from future possible biological disasters? We are convinced that, without a special effort, many critical resources are likely to be left untapped in this important mission. These resources include the community of academic scientists who do not ordinarily study pathogens but who have highly relevant expertise that can supplement the research programs of the virologists and microbiologists who focus on microbial threats.

This view caused the two of us to encourage the test project from the National Academies, “Discovery of antivirals against smallpox,” whose results appear in this issue of PNAS (1). We chose smallpox as the focus for the effort because the variola virus that causes this disease ranks at the very top of the Centers for Disease Control and Prevention’s list of high-threat (Class A) agents, due to its high human lethality (up to 40%) and ease of transmission. There is, therefore, a demand for new countermeasures to the virus, including antiviral drugs that could rapidly stop smallpox if an outbreak occurred—while also being valuable for decreasing the risks associated with vaccine complications.

To explore smallpox antivirals, a 2-day workshop was modeled after an earlier National Academies project proposing new research directions for understanding the devastating mental disease schizophrenia (2). During the first half-day, a handful of experts on poxviruses and on antiviral drugs presented brief talks and answered questions to educate the remaining 25 or so specialists representing other areas of research, including cellular, structural, computational, and biochemical biology. The total group was limited to approximately 30 to give everyone a chance to engage actively in the dialogue. Subsequent brainstorming led to the formation of breakout groups that explored specific topics in depth before reporting back to the entire group for further discussion.

The specialists (and the two of us) who previously knew very little about either variola or other poxviruses found the 2 days both intellectually invigorating and highly productive. Twelve of those who had been invited to attend the workshop were selected to form a National Academies committee tasked with writing a report and developing recommendations. This committee was chaired by Stephen Harrison, a distinguished leader in the analysis of viral and protein structure. With one important exception (Bernard Moss), the report was produced by a group of scientists who were not poxvirus experts. In their briefings on variola and other poxviruses during the workshop, the virologists revealed a set of scientific puzzles that seem ripe for new discovery. These include the mysterious development of membrane “crescents” during the early assembly of poxvirus particles, possibly derived from the membranes of the endoplasmic reticulum or the Golgi; the little understood mechanisms of viral DNA replication and transcription in the host cell interphase cytoplasm, a site for these activities that is unique to poxviruses among animal DNA viruses; and the puzzle of how the virus exploits the cytoskeleton: microtubules for directed movements within its host cell and actin bundles to push it outward toward a new cell. Overall, it was clear to every one that the intricate, highly specialized process of variola replication provides a wealth of scientific opportunities for the development of new drugs that should be able to stop viral infection without damaging normal human tissues.

We believe that infectious disease research is too critical to our future not to involve leading investigators from fields in addition to virology and microbiology. Interdisciplinary workshops based on the model of the smallpox antiviral meeting are promising avenues for exploring and catalyzing interest in the biology of many microbial threats. Even with a primary focus on agents of bioterrorism, it is almost certain that progress made on this set of pathogens will have a spillover effect on important diseases that spread naturally, including HIV, influenza, the severe acute respiratory syndrome (SARS) coronavirus, monkeypox, West Nile Virus, and avian flu.

In summary, it is in all of our interests to stimulate new contributions in this important area of national priority from outstanding researchers who have highly specialized knowledge and expertise. A broad range of scientists can play a role in meeting the challenges described here. But the very best scientists whom we need to involve will be already busily occupied in their own areas of research, so that carefully tailored events such as the workshop described will be important for extending their ambitions to new fields. By creating opportunities for constructive collaborations among scientists who normally do not know of each others’ work, we can promote more powerful and innovative strategies to solve critical problems in infectious disease, thereby improving health and enhancing human security.

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