Editorial & Letters

EDITORIAL

Making the Case for Federal Support of R&D

President Clinton recognized from the start of his administration that balancing the budget was critical to the future of the nation. At the same time he recognized the need to invest in that future, which included making critical investments in research and development (R&D). The proposed fiscal year (FY) 1999 budget reflects his commitment to R&D, but maintaining that commitment will require support from the scientific community.

As I leave my position as director of the Office of Management and Budget (OMB), I would like to share with you how the scientific community might improve its role in helping to maintain the commitment to R&D by addressing the following questions:

How large a scientific enterprise does the United States need? Last fall hundreds of scientists sent us letters promoting an authorization bill that doubles the research budget but does not address how to fund this doubling. Nor did the bill explain why doubling the budget would produce the correct level of spending. Although not a doubling, the President's FY 1999 budget does provide for aggressive increases for R&D that are fully paid for within very tight funding constraints. Unfortunately, the follow-through by the scientific community has been disappointing. Wish lists do not fund programs—strong justifications, tough choices, good performance, and aggressive follow-through until enactment into law do.

How can we set priorities in the nation's R&D enterprise? If I were to judge from my discussions with university representatives, I would infer that the priority of the research enterprise is to recover indirect costs. I hope that this is not the case, but that the scientific community has something more important to say. We have heard much rhetoric on the importance of setting priorities, and yet we have seen little follow-through. If the scientific community remains silent, priorities will be set without its input, by outside circumstance, by earmarks, and by those outside of the R&D community.

How can we measure the success of our nation's research programs? We appreciate the difficulties of developing performance measures for science, where basic research often results in unpredictable discoveries. Nevertheless, research agencies, as with other federal agencies, must be accountable for how they spend federal dollars. We often hear the success stories that, although necessary, are not sufficient to justify our $70-billion-plus annual investment in R&D. We have to understand not only what new programs and scientific areas are being proposed, but also that they are being conducted in the most effective and efficient ways possible. We must maintain a world-class research enterprise with constrained resources. This can be accomplished through better planning and increased international collaboration in the construction of major scientific facilities and through improved methodologies that lower the cost of research.

How can we strengthen the government-university partnership? I have often heard what the federal government—and the budget—should do to "fix" the problems and stresses at universities, but I have seldom heard what universities and the scientific community are doing to promote and improve our long-standing partnership. For the partnership to continue productively, we must agree on the distinction between support, which connotes entitlement, and assistance, which implies that the federal government is willing to help. We must also emphasize the importance of the peer-review process, or risk simple earmarks that turn science into a high-tech version of pork-barrel politics.

How do we engage the American people in the excitement and wonder of science? The research community first has to clarify its message to the American people. Not every American will become a scientist, and most will not be interested in the arcane details that so excite the scientific community. Yet scientists should make a difference where they can, most importantly by improving the science taught at the K–12 levels. Also, if science is not communicated to policy-makers in a way that they can understand, it will not be supported in the long run.

Although there is general and broad support for investments in R&D, funding is not an entitlement. Annual funding must be justified and earned. The scientific community must learn to be more effective in explaining the scientific enterprise, how priorities are set, and how success is measured. As director of the OMB, I have enjoyed my discussions with the scientific community, and I hope that these discussions will continue with my successor. Together, we can make better decisions about investments in R&D.

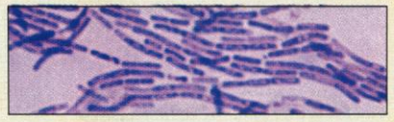
Franklin D. Raines

The author was director of the OMB from September 1996 to May 1998.

LETTERS

Microbes and migrations

Questions about why anthrax infections are lethal and how populations can defend themselves against anthrax attacks are addressed (below, the anthrax bacillus). Novelist Jean Auel reacts to the suggestion that an ancient population migrated from Europe across Asia to the Bering Strait land bridge and on into the Americas. And the histories of black hole theory and of brain area terminology are discussed.



ARTHUR M. SIEGELMAN/VISUALS UNLIMITED

How Anthrax Kills

It was with great interest that I read the report "Proteolytic inactivation of MAP-kinase-kinase by anthrax lethal factor" by Nicholas S. Duesbery *et al.* (1 May, p. 734) and Evelyn Strauss's excellent accompanying Research News article "New clue to how anthrax kills" (1 May, p. 676). I would like to add a couple of thoughts. There is much accumulated evidence that lethal factor (LF) is a central virulence factor in the pathogenicity of *Bacillus anthracis* and is directly responsible for many anthrax disease pathologies (*1*). A previous study provided strong evidence that LF maintains structural elements common to Zn^{2+}-metalloproteases that were required for toxicity (*2*); LF was also shown to hydrolyze the peptide hormones granuliberin R, dynorphin A peptide, neurotensin, kinetensin, and angiotensin-1 (*3*). However, linking these hormones to anthrax biology (beyond acting as test substrates for LF endopeptidase activity in vitro) is problematic. This leads one to ask, "Is inactivation of mitogen-activated protein-kinase-kinases (MAPKKs) by LF any more relevant to anthrax than cleavage of peptide hormones?" Although this remains unaddressed experimentally, a brief comparison of the known activities of LF versus the selective MAPKK inhibitor PD09859 may be useful. Duesbery *et al.* report that LF had a similar activity profile, in a screen of 60 human cancer cell lines, when compared with the chemical PD09859. Both agents are currently believed to inactivate MAPKK and inhibit cellular differentiation. But anthrax lethal toxin also kills

macrophages and is lethal to nearly all species of mammals (*4*–*5*). For example, RAW264.7 cells (and many other macrophage cell types) are rapidly killed in culture by lethal toxin (*4*–*6*). Most mammals are killed in about 24 hours after being given toxin, with the singular example of Fischer 334 rats, which die within 40 minutes (*6*). These are potentially important aspects of LF toxicology. In contrast, PD09859 is not believed to induce such severe acute toxicities either in animals or in cells, including oocytes. In fact, it was recently shown that 50 micromolar PD09859 *protected* RAW264.7 macrophages from nitrogen oxide–induced cell death (*7*). If MAPKK inactivation is responsible for dramatic toxicities, should not other types of selective inhibitors of this enzyme show similar responses?

Of more immediate concern are the quotes in Strauss's article by Vande Woude concerning a potential role of new LF protease inhibitors in combating anthrax as a weapon. Inhibitors of LF action could very well be effective medicines. But, at numerous levels, there are reasons why LF protease inhibitors may not be the panacea projected in the particular instance of bioterrorism. Only a few examples need to be offered.

1) Other *B. anthracis* virulence factors in addition to LF may influence overall pathogenicity during inhalation anthrax infections. The current U.S. anthrax vaccine (now given to military personnel) raises strong humoral immunity specifically to lethal toxin antigens and protects against natural anthrax exposure, but its efficacy in inhalation (biowarfare) anthrax is questionable.

2) The early symptoms of inhalation anthrax are nondescript ("flu-like"), and the time to death may be as short as 24 hours after exposure. Exposed victims may not even seek medical attention until *after* lethal toxin has been expressed and irrevocable damage has been done to the body.

3) "Altered" *B. anthracis* strains could be created by adding foreign genes from other toxic organisms or for multiple-antibiotic resistance (or protease-inhibitor-resistance), characteristics that might change the molecular nature of the disease.

4) Stockpiling enough of *any* drug (including protease inhibitors, penicillin, and tetracycline) and delivering and treating potentially thousands of exposed people within the available window of time is a task well beyond our current infrastructures. This important logistical issue is superbly described in Richard Preston's article "The Bioweaponeers" (*8*) and has recently been made a national priority by President Clinton.

The devious efforts of despots and terrorists add tremendously to today's challenges of infectious diseases. To combat the problem of microbes adapted to be weapons raises problems that require vigilance and the dedicated, long-term, and coordinated efforts of many, not just researchers.

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Response: Hanna discusses our recent report in the context of his own work demonstrating the central role of macrophages in anthrax infection in mice (*1*). Among other points, he questions whether the finding that LF cleaves MAPKK is any more relevant to anthrax pathogenesis than his own previous demonstration (*2*) that LF slowly cleaves several small peptide hormones. In our report, we did not say that the cleavage of MAPKK fully explains anthrax pathogenesis, but only that one important protein substrate had been found that is cleaved in the cytosol of cells exposed to the toxin. It would be surprising if the rapid cleavage of MAPKK leading to the loss of mitogen-activated protein kinase (MAPK) activity did not contribute to pathogenic effects in some cells and tissues of some animal species. In fact, our own continuing studies on cells transformed by activation of the MAPK pathway reveal dramatic effects of LF on the transformed phenotype. We agree that there may be other relevant substrates waiting to be identified, particularly in mouse macrophages, which, like the Fischer 344 rat, are rapidly killed. Our report acknowledged the possible existence of additional substrates, and the accompanying News article accurately reported that we "aren't certain that LF owes its toxicity to its ability to cleave MAPKK."

Hanna states, "Both agents [anthrax LF and PD09859] are currently believed to inactivate MAPKK and inhibit cellular differentiation," which may lead the reader to believe that they are truly similar. In fact, these two agents differ dramatically in activity against MAPKK, acting by very different mechanisms and targeting substrates differently. For example, PD09859 only slows oo-

cyte maturation (3), while LF prevents it. Moreover, LF irreversibly inactivates both MAPKK 1 and 2, while PD09859 preferentially prevents phosphorylation and activation of MAPKK 1 (4, 5), an inhibition that can be easily overcome by upstream agonists (5) and is reversible (4). Thus, we expect that LF should be more toxic than PD09859 and that it is unlikely that PD09859 can prevent MAPKK activation to the same extent as LF. Further, the reference to PD09859 preventing nitric-oxide induced apoptosis (6) appears to be an unrelated argument, because LF induces total and rapid macrophage lysis and is not known to be apoptotic, while nitric oxide-mediated cell death is much slower and less efficient, and is apoptotic.

Hanna's comments regarding the medical and logistical difficulties of dealing with terrorist or military use of anthrax are topical and deserve the attention of policy-makers. These issues were not the subject of our research report, and we do not claim expertise in these areas. However, we believe that we were justified, during discussions with the correspondent preparing the accompanying News article, in speculating that an inhibitor of LF might limit the pathogenesis associated with anthrax infection, in the same way that protease inhibitors are effective in treating AIDS, a process that our colleagues at Frederick helped initiate.

Like Hanna, we anticipate that defense against use of anthrax as a weapon will require a combination of measures, including vaccines and antibiotics. We hope that our findings will facilitate development of inhibitors of LF protease activity, and that such drugs may constitute one additional medical intervention to limit the effects of anthrax infection.

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Early Americans

I read with great interest Virginia Morell's Research News article "Genes may link ancient Eurasians, Native Americans" (24 Apr., p. 520). The general theory that has been proposed to account for a genetic marker that appears in people from Europe and Asia Minor, and Native Americans, but not in Asians, does not seem logical to me. I have to question the concept of a small group of people remaining cohesive without detrimental inbreeding, and without leaving any trace, while traveling all the way across the European and Asian continents, and then across the Bering Strait land bridge. And what could possibly have motivated them to continue such a trek over the generations it would have taken to travel that far?

Some years ago a theory was proposed that at least some of the original settlers in