We Have Met the Enemy, and He Is Us: Redesigning The American Biomedical Research Enterprise

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The Problem

Biomedical research in the USA in is a crisis. Established scientists with decades of accumulated knowledge and wisdom are permanently losing their research programs or positions due to their inability to obtain research grants. After graduating from college, junior scientists are spending ten to fifteen years in "training" at wages and circumstances that repel many of the most talented and ambitious individuals. The trainees that manage to obtain coveted tenure track positions (perhaps 10% of PhD recipients) face severe pressure in obtaining their initial grants (rewarded at the astonishing average age of 43), and particularly their first renewals, forcing them to abandon promising research careers (with an uncertain future at nearly 50 years old). Those who manage to survive the funding crunch perpetually face the imminent threat of defunding, and spend a significant, and ever-increasing portion of their time writing grant proposals to maintain their labs.

These problems are obvious to every working scientist who relies on the NIH extramural grant system to support their research, but who is to blame? Is it the executive and legislative branches of the US governments, who simply don't provide enough money to support the research establishment? Not in my opinion. The fundamental problem is that with every increase in the NIH budget, the US biomedical establishment expands well beyond what the increase can support. This bubble-based cycle exerts an enormous toll in both human misery and inefficient use of human resources.

This pattern, which has persisted for at least 20 years, principally results from the unregulated expansion of US biomedical research, where every dean is a potential entrepreneur angling to increase the size and prestige of their institution. Merging of the biomedical training and labor pools (*i.e.*, nearly all of the work is done by graduate students and post-docs) compounds the problem. Expanding universities recruit far more graduate students and post-docs than the number of new faculty positions created, *decreasing* the fraction of trainees who attain assistant professorships, and prolonging the time until independence, as competition for the limited number of tenure track positions increase and *c.v.s* of applicants lengthen.

Uncertainty in successfully funding research grants leads investigators to maintain a super-optimal number of grants to buffer against dipping below the optimal funding level: *i.e.* the amount necessary to maintain a lab of sufficient size and expertise to progress on a research topic. Such overfunding of the most successful labs (defined in terms of funding, not necessarily science) fuels a negative feedback loop of decreasing grant success and increasing pressure to obtain them.

Here's the big picture of the current situation. We biomedical scientists have created a system in which highly intelligent, extremely hard-working individuals who spend years in training at low wages must struggle to maintain a career that serves the public good. Bluntly put, this is crazy. Why should talented and ambitious youngsters sign up for such misery? Is there any doubt why so many wind up on Wall Street? We scientists can do better than this for ourselves and for the future of science, which is inextricably linked with the economic, health, and social well being of our society and nation.

A Possible Solution

Ending the boom-bust cycle of NIH funding requires rationally planning the number of NIH supported investigators and trainees. But, how to create such order from the chaotic system in place? I suggest extending the model of the NIH intramural funding system to the entire NIH funding system.

US government of funding of biomedical research is so pervasive through direct and indirect mechanisms, that with exceptions (*e.g*. HHMI investigators, public employees of state universities), NIH funded investigators are already essentially *de facto* employees of the US government. The idea is for the government to employ grantees *in situ* (like HHMI investigators), where they would maintain their positions in their institutions and their participation in teaching and other institutional obligations.

Rather than submitting grant proposal to fund their research, investigators would be allocated funds based on quadrennial reviews of their productivity and general direction of their research. This would have enormous benefits. It would end the fiction that important discoveries can be accurately predicted in advance by grant proposals. It would end the corrupting prevarication that the "proposed" research hasn't already been started (if not finished), and the common practice of using grants to fund more promising ideas not included in the proposal (which is increasingly running afoul of auditors, clueless of how science actually advances). It would save enormous amounts of time in writing and reviewing grants. It would prevent grant reviewers from filching ideas from proposals. It would free the imagination of investigators, who would be able to pursue their *best* ideas, and not their most *fundable* ideas.

But here's the deal. No more super-sized labs, unless mandated by special circumstances. Again the model is the intramural program, with an average group size of approximately 8 investigators (one PI, one technician, one PhD level staff scientist, 5 post-doctoral fellows/students). Although it is common knowledge that large labs are typically inefficient, their PIs typically have mastered the art of funding. Trimming such labs would free resources to support more independent investigators. It would also greatly encourage collaboration between groups with different expertise, increasing collegiality and scientific excitement in institutions. Efficiency should increase too, since expertise will be shared between groups and not have to be created by each group.

The productivity of the proposed "extra-intramural" system is a critical issue. Given the advantages of a direct funding mechanism described above, true productivity, as measured

in important discoveries should increase. A key to maintaining productivity will be the effectiveness of the review process. The NIH intramural system provides an example of fair yet rigorous peer review process that occurs on a quadrennial basis. Non-productive laboratories are typically closed after two consecutive substandard reviews (*i.e.* over an 8-year period), and the resources re-assigned to a newly recruited, typically tenure track, investigator.

Such junior investigators are hired by the standard process employed by universities: a nation wide search is conducted to identify the best candidates who are selected by a committee composed of senior scientists in the field of interest, with the ultimate hiring decision made by the department chair (whose leadership is also subject to quadrennial review). The potential of junior scientists is judged after a 5 to 6 year period principally by the quality of their publications, with advice sought from 8 to 10 world experts in their field. Candidates must have demonstrated that their productivity is largely due to their efforts, and is not based on collaboration. The offer of "tenure", *i.e.* becoming a full government employee, is made only on the advice of two Promotion and Tenure committees: one at the Institute level, the other at the NIH level. Further promotions through the academic ranks (with commensurate salary increases) are made via the Institute committee, but with oversight from the institute and NIH intramural directors.

The greatly relaxed competition for funding will have huge payoffs in the psychological state of individual scientists and the entire scientific enterprise. Today's intense pressure brings out the worst in human nature, eroding the integrity of the research culture: fudging and outright fraud is increased in such circumstances, particularly in grant proposals, where data are preliminary and not subject to the crucible of reproducibility by other labs. The cycle of pain that accompanies repeated grant rejections contributes to a poisonously critical atmosphere that saps creativity and kills the spirit and joy of science. It extends to reviewing manuscripts where it is particularly devastating for young scientists, whose efforts are typically subject to the brutal criticism of reviewers (us!) demanding more and more data, in what typically leads only to incremental findings that do little to modify or improve the major findings of a study.

Don't get me wrong. Constructive criticism and vigorous competition are essential to the scientific process. The truth can only be approached by constantly proposing, testing, and remolding hypotheses. Human nature is such that this process is greatly accelerated by competition between investigators with common interests. The competition must be collegial, however, and based on respect, not fear.

Obviously, it is not possible to immediately remedy the present state of affairs. We can, however, begin to offer top level investigators as well as tenure track investigators the opportunity to become extra-intramural investigators as a carefully monitored pilot program to compare the productivity and happiness of investigators in the new vs. traditional grant system. If warranted, over a 20-year period, we can gradually move to the new system.

We American scientists got ourselves into this mess, and it is our responsibility to find a solution. We must bequeath to future generations a sustainable system of biomedical research that rewards productivity, rigor, creativity, and honesty. One of the great national traits we Americans seem to have misplaced in recent years in our indomitable can-do attitude. We need to attack our problems with an open mind and an eye to the future. Science is an essential element of modern society, and our principal mission as scientists is to ensure that the torch of the scientific method is passed from generation to generation.

We can and must do better.

The author is supported by the Division of Intramural Research, NIAID. The views in this essay are strictly the personal opinions of the author, and do not reflect the official policies or opinions of NIAID