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Sustainability in Biomedical Research

We hear a lot about sustainability these days–sustainability of health and environment, of economic prosperity, of conservation of nature, and so on (3). Great! But what about sustainability in an area that makes so much other sustainability possible? Scientific research . . . and more specifically for our purposes, biomedical research.

This editorial continues a theme that I introduced on two previous occasions (1, 2): the funding and management of scientific research. I can only comment on how these matters pertain to my home country, but I suspect that they strike a chord with investigators elsewhere.

Why Worry About Sustainability?

This section is going to be a bit depressing. In the USA, youngsters destined for careers as independent or "principal" investigators (PIs) invest 4 years in high school, another 4 in college, and then 5 or more to earn a Ph.D. And then the promising young scientist–now in his/her late 20s–begins one or more stints as a postdoctoral fellow. In today's climate, successful applicants may not finally win a position as an assistant professor until his/her late thirties. The newly minted young faculty member, transiently euphoric, now sets up a new laboratory, hires and trains new personnel, and gathers preliminary data to bolster that first grant application. The average age for the first major independent NIH research grant (the R01) is about 42. (This figure includes physicians who have a more protracted training period than the straight Ph.D.).

The cost (paid by the student or subsidized by taxpayers or others) to reach this stage of one's career is staggering. Imagine $40,000 for a high-school education, perhaps $160,000 for a college, and then perhaps $150,000 in graduate stipends, plus $50,000 in tuition and $50,000 in laboratory costs . . . just to reach the Ph.D. For, say, 6 years of postdoctoral fellowship, we may invest an additional $300,000 in salary and fringe benefits plus another $60,000 in laboratory expenses. A typical start-up package at a medical school basic-science department–including equipment, salary, and additional personnel–usually exceeds $1.0 million. Throw in some renovations and other less transparent expenses, and by the time the PI receives that first grant–and some never do–society has invested $2,000,000 . . . not to mention someone's entire adult life.

In the competition for grants, the NIH generally gives a bonus to the new investigator. Thus the hard-working assistant professor has a reasonable chance of obtaining initial funding. Five years later, as the grant expires, the no-longer-so-young faculty member has assembled a team of trained laboratory members who have established a rhythm and a measure of efficiency. By this point, society has invested another $1.25 million in grant support, not to mention the portion of salary and fringe benefits not covered by the grant . . . and the cumulative tab stands now at about $3.5 million, just as the PI faces the stiffest test of his/her career when attempting to obtain the second 5 years of grant support. With NIH paylines (the percentile you must achieve to receive a grant) in the range of the 10th to the 15th percentile, some will succeed in renewing the grant immediately, some after only two or more attempts, and some will be unable to renew the grant despite several attempts. For those in the last category, a once-promising career is in shambles, with the erstwhile PI in his/her late 40s.

What about the PIs in the second category, the ones who are able to obtain that first renewal, but only after two or more attempts? During the lean times between grants, the novice PI, with a tight budget, may experience the pain of releasing laboratory personnel or of not being able to replace personnel who plan to leave. Once funding is finally reestablished, the PI must now rebuild the group, having lost some or even most of the "corporate memory" that he/she worked so hard to assemble during the first 5-year funding period. Efficiency is initially suboptimal, putting the PI at a selective disadvantage 5 years down the road, when the now-mature PI is in his/her early 50s. At this point, the aggregate career investment is now on the order of $5 million. The grant renewal, as 5 years earlier, could be successful on the first attempt (optimal), after two or more attempts (major laboratory inefficiency), or never (total PI-career meltdown).

All the while, undergraduates, graduate students, and postdocs are observing just how frustrating the above business plan can be, even for a talented PI. These younger potential PIs may choose a different career path. This is especially an issue for women thinking of becoming mothers . . . can we as a society afford to discard all this talent?

Is this any way to run a business?

Why Do We Have This Problem?

The fundamental problem is an unfavorable balance between the *numerator* (the number of dollars that the NIH invests in investigator-initiated or R research grants) and the *denominator* (the number of PIs or applications that they submit). The *quotient* determines how much money is available to support the average PI, and thus the payline.

Over the years, the quotient certainly has changed–generally for the worse. When I was a graduate student in the mid-1970s in the Department of Physiology and Biophysics at Washington University, the PIs took their grant applications seriously. However, I never had the sense that PIs were overly concerned about their prospects for success, and it seemed to me that virtually every PI had an R01. I was not privy to the business model for that highly successful 1970s Department, but the place was humming with about 1 grant per PI. I understand that the School paid more than 50% of the PI's salary, far more than a typical private school does today (e.g., my university targets 30% School/70% grants). The result was stability, which was probably one reason why that department had quite a few M.D. researchers.

In 1981, when I applied for my first R01, the payline at my NIH institute was around the 35th percentile. At this level, solid investigators felt confident that–if they worked hard and continued to push the field forward–they would continue to be funded on the first or, at the worst, second try. There was competition, but it was a healthy competition that drove you to do your best.

In 1989, the year I became chair of physiology at Yale, NIH paylines suddenly fell from the upper 20s in my institute to–I distinctly remember–the 19th percentile. As a result, several elite colleagues lost their R01 support. This was the beginning of tough times at the NIH and angst among faculty nationwide. Since then, paylines transiently have sunk below the 10th percentile in some institutes. During the days of the doubling of the NIH budget (1998–2003), paylines temporarily often exceeded the 20th percentile, but now we are generally back down to the range of the 10th to 15th percentiles.

Thus, the general trend has been for the quotient to shrink . . . too many PIs (predators) chasing too few dollars (prey). When Congress and the NIH direct more dollars to R grants (prey), as happened during the NIH doubling, the quotient rises and things temporarily look rosy . . . that is, until deans hire more predators, uh, faculty. Then the quotient falls, efficiency falls, and the *PI misery index* (PIMI) rises.

Where Would We Like to Be?

I should first state what we scientists should *not* want: scientific socialism. Society does not owe us a living! What society wants is good health, and they hire us to do research that will lead to discoveries that will improve their health.

What we scientists should, I think, want is a model of *sustainable* scientific research, one that operates at the highest possible level and thereby optimizes human health. We want the best and the brightest to choose careers in scientific research (represented by Ph.D. programs and postdoctoral fellowships), and then we want to choose the best among them to become the next generation of PIs. PIs should work hard to keep their edge, but the competition should be healthy (as opposed to destructive or brutal) so that PIs have a reasonable expectation of continued, long-term success. Failure or even intermittent success drives candidate PIs away from research careers, reduces the efficiency of those who remain, and can degrade an otherwise collegial atmosphere and thereby further reduce efficiency. I propose that "we" work toward an NIH payline at about the 30th percentile. This value would represent a level of competition that would ensure that all work perceived as "outstanding" be funded, and will also make room for proposals not judged–at the time–to be outstanding (perhaps because they were judged too risky or perhaps because nobody knew what was behind the next door) but which nevertheless sometimes lead to major breakthroughs. Sounds idyllic. Sounds like the 1970s.

How Could We Get There?

Obviously, we need to increase the quotient, the prey-to-predator ratio. This will lead to an increase in efficiency and a decrease in PIMI, eventually producing more, better science, and thus better health.

The prey. One approach is to increase the numerator, the NIH budget, the prey. This strategy is attractive to the research community, and it is also necessary. Nevertheless, if this is the only action, we will fail . . . repeating the experience of the last NIH doubling as the predators expand to match the prey. Moreover, the NIH budget cannot continue to rise indefinitely.

Before we leave the subject of prey, I would like to make a proposal for *sustainability in NIH funding*. Scientific research is too important to depend on the whims–and the backroom deals aimed at satisfying powerful constituencies–of Presidents and Congresses. Rather, we ought to have an NIH trust fund–sustainable prey–created by levying an across-the-board tax (e.g., 1%) on all health and dental expenditures. The USA recently adopted a more selective but steeper tax as part of health-care reform, triggering some whining. However, a tax directed at improving health would be better received. Moreover, it would relieve the general budget of the NIH's expenditure of over $30 billion. Finally, there is precedent for such trust funds, an example being the one supported by gasoline taxes and used to pay for highways and transportation projects.

The predators. The other approach is to decrease the denominator, the predators. I think that this option has been anathema among deans and faculty, who are strong proponents of a free market–at least as applied to expanding the biomedical research enterprise. However, the free market that we are in right now is not as free as it seems (after all, the government controls the prey), and it is ultimately counterproductive for science. What can we do?

One option that I have heard discussed is to limit the number of NIH grants that one PI could hold. However, because the average number of R01 grants per PI is only in the range of 1.2–1.3, imposing this rule would have only a modest effect on paylines. Moreover, it would penalize those perceived as the most productive among us and put them at a selective disadvantage to those supported by the other agencies (e.g., HHMI) or in other countries.

Another option–limiting the number of dollars per grant–has already been partially accomplished by inaction: failing to adjust the size of modular NIH grants for inflation. I believe that this action is unwise and will eventually stifle research.

I would also argue that neither of the previous two options really reduces the number of predators, only the size of their quantum bite. I would like to see fewer, better-fed, more ferocious predators . . . .

And this leads us to the first key question: Just how many PIs does society need? I think that solving this problem begins with determining how many research projects we need and then reducing the number to how many we can actually afford. Dividing that result by 1.25 gives us the number of PIs that can have active projects at any one time. Finally, based on a 30-percentile payline, an actuary should be able to tell us how many PIs we ought to be bringing in (through recruitment) or pushing out (through retirement or re-assignment to non-PI activities) per year to achieve the desired number of PIs in our national pool. The calculated number of recruits should be less than the actual number of new PIs that we are hiring in now, and the number of re-assignments of more senior PIs should be less, being limited to those whose productivity has fallen below some threshold. The re-assignment decision would be made, as it is now, by funding agencies.

This brings us to a second key pair of questions: Who is the gatekeeper that decides who enters the PI pool? And at what career stage is that decision made? I would argue that the career stage should be in the late postdoctoral period, giving the candidates adequate time to show their promise. As to the gatekeeper, I can think of at least four mechanisms.

1) Mentoring. In principle, the mentor of a postdoctoral fellow could advise the mentee as to his/her suitability for a career as a PI. However, this task could be difficult for the mentor (no one likes to deliver bad news) and could be of questionable accuracy (it is difficult to judge someone so close to you). A departmental or university committee could make the decision, but I would worry that politics and expertise could be problematic.

2) Lowering the salary cap. A PI investing 50% effort on a research project can charge 50% of his/her salary and fringe benefits to an NIH grant, up to a maximum that increases annually. The present cap is about $200,000, so that a PI with 50% effort and a $200,000 salary can charge $100,000 of salary (plus the associated fringe benefits) to the grant. If the PI has grants totaling 90% effort (the effective maximum), the university would pay little of the salary, and its only risk would be that the PI loses funding. And even then, the university can eventually release the PI if he/she does not have tenure. One way of lowering the number of predators would be for the NIH to freeze the cap in absolute dollars (i.e., not increasing it for inflation) or even reduce the cap gradually. Thus, universities could not afford so many PIs above a certain salary. However, I fear that universities would skirt this ploy by capping faculty salaries and thereby making the profession less attractive.

3) Lowering the fraction of faculty salary that can be charged to a grant. In this scenario, the NIH could state that, even if a PI devotes 50% of his/her effort to a research project, only a fraction of that (e.g., half) could be charged to the grant. In this example, if the PI had a total of 90% effort on research grants, only 45% of the salary could be charged to those grants, leaving the university to cover the remaining 55%. Here, the university would not be able to afford as many PIs at any rank. However, as a good university citizen, I feel queasy about this approach. In the long run, research at a university is a money-losing proposition. The more you do, the more money you lose, making up the difference from philanthropy, royalties, and other mechanisms. It is not easy to raise money, and the NIH would not have to lower its salary contribution by much to put some universities out of the research business.

4) Requiring universities to cost share at the outset of the PIs career. The NIH could require that the university give the new PI a start-up package that matches some fraction of the PIs first NIH grant. This happens now for new tenure-track, basic-science PIs at major research universities, where a start-up package roughly equals 5 year's support by the first R01 grant. The large university investment obviously limits the number of people that can be recruited. However, universities also have a backdoor hiring mechanism that one might call *speculative hiring*. They encourage a clinical instructor or a non-tenure-track advanced postdoctoral fellow in a basic-science department to apply for an R01, perhaps with the mentor's help. The successful applicant is appointed as an assistant professor, but without the major investment in a start-up package. Thus universities have a vested interest in creating backdoor predators, whose careers sometimes work out just fine. However, backdoor predators are at a selective disadvantage compared to the tenure-track predators (who received large start-up packages). For this reason, my dean has voiced concern over the backdoor approach.

5) Requiring candidate PIs to prove themselves at the national level. In this scenario, one could not apply for an NIH grant unless he/she had previously passed muster in a nationwide competition. I imagine a mechanism akin to the present K awards for senior postdoctoral fellows. However, in my plan, the written grant application would only be the first step in the process. The highest-ranked candidates–perhaps after a few years of support–would then interview with and present a seminar to the review panel, which would choose the ultimate winners. If this process sounds time consuming, you have not recruited faculty lately. If it sounds expensive, think of how much money is wasted in the current system when careers melt down at the PI stage. And if it sounds brutal to triage PI candidates before they even apply for a faculty position, think of how much more brutal it is to shut down a PI's lab when he/she is 50 years old.

We must take bold steps to make scientific research sustainable. I favor the prey option (a jump in NIH spending on R grants plus the creation of an NIH trust fund) together with some combination of *predator options 1* (mentoring), *4* (cost sharing), and *5* (nationwide competition). Now, how do we get the ball rolling? ■

References

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