Cell

Healing the NIH-Funded Biomedical Research Enterprise

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Many feel that the R01 grant system supporting biomedical research in the U.S. is broken, discouraging entry of young investigators into the system and inadequately supporting more established investigators. Here, I argue for a "person-not-project"-based scheme that would permit creative, unfettered research by new investigators, better tie ongoing research contributions to continued funding, and help match the number of investigators seeking support with available funds.

Background

An increasing number of commentaries have highlighted the serious problems with the present state of NIH-funded biomedical research in the U.S. (Alberts et al., 2014; Alberts et al., 2015; Casadevall and Fang, 2012; Daniels, 2015; Lorsch, 2015; McKnight, 2015). Several of these papers have emphasized the competition for funding, the associated discouragement of bright individuals from seeking a career in research, the reduction in research progress due to the excessive time spent by investigators preparing grant applications, and the inhibition of creativity resulting from the nature of the grant review process. In many ways, these problems are all linked to the current R01 grant system. What was once a highly effective mechanism for parceling out support to the most deserving scientists has now evolved into what many investigators see as a stultifying, regimented process in which form often counts for more than content and in which any proposal lacking substantial evidence of already having been largely accomplished is unlikely to be supported. It is also a process in which the applicant "dissembles" about the true purpose of the grant, given that most of the proposed aims will necessarily have already been accomplished to satisfy the need for preliminary evidence, and the funding will thus be used for research other than that the grant asks for support to accomplish.

Although these problems affect investigators at all stages of career progression, they are most damaging to those contemplating a future in research or just beginning their independent research careers. In the former case, there is a keen appreciation of the disconnect that exists between how a smart and hard-working student succeeds in moving along the educational pathway versus the likelihood of success as a PI. The ego structure of most scientists is one in which the person believes that a combination of intelligence and effort begets academic success. Accomplishments in high school facilitate entrance into a top college or university, where similar traits allow accomplishments supporting entrance into a top graduate or medical school, and likewise through postdoctoral training, and finally to the offer of a junior faculty position at a top institution. But then the vagaries of the R01 system intrude, disconnecting the two traits that unpinned success to this point from any predictable success going forward (Fang and Casadevall, 2014). The result is that many of the best young "proto-scientists" are opting against pursuing a research career. This was brought home through the anecdotal (but I think cogent) experience of my son who majored in biology and graduated from Stanford in 2009. To his and my surprise, very few of the ~100 students graduating that year with a degree in biology chose to move on directly to Ph.D. programs. Although some entered M.D. or M.D.-Ph.D. programs, many discussions at the departmental graduation ceremony centered on the theme of how much students enjoyed their undergraduate scientific research efforts but wanted or had to plan for careers doing something other than full-time basic science. These choices were largely predicated on the experiences these people had during undergraduate research in top laboratories at Stanford. There they saw the struggles and uncertainty faced by even very successful postdocs and PIs and decided that they did not want to take the career risks the Ph.D./academic research pathway posed.

With respect to those who have made it to a junior faculty research appointment, these individuals must often begin submitting R01 applications within a year or two of starting their labs. This is not only because of the need for additional funding beyond start-up support but also because this is demanded by the employing institution and promotion boards. In the past, when perhaps 10%–15% of one's time was occupied with grant preparation, this was not a problem, and there was merit in the argument that such grant preparation helped focus the thinking of the investigator and resulted in more productive research activity. But now, 50% or more of a faculty member's time can easily be spent in grant preparation. For junior faculty, this drastically hampers their ability to perform experiments themselves, at a time when they are the most accomplished and effective member of their laboratory staff. As a result, far too many young investigators almost immediately retreat to their office, abandoning the bench and relying on students before they have fully established their own research programs or learned how to evaluate data generated by others.

The consequences are clear: much less efficient research and a tendency to be conservative and do experiments that can lead to "preliminary data" required for grant applications, most often next steps from postdoctoral research rather than novel, creative studies, all at a slower pace than should be the case.

Many of these problems affecting rising scientists and junior faculty members can be largely rectified by changes in how biomedical science is funded. Rather than supporting the project, it is time for the majority of the R01-equivalent research enterprise to move to the investigator-centric support strategy of the HHMI (HHMI, 2015), NIH intramural program (National Institutes of Health, 2015a), and Wellcome Trust (Wellcome Trust, 2015) (among others), a strategy being considered by some NIH institutes as a replacement to conventional project-oriented grants for at least some established investigators (Kaiser, 2014). I have asked dozens of senior colleagues to answer the following question: "If I gave you $5 million to distribute for research and said you could either have the CV or a grant proposal, but not both, from the applicants, which would you choose to help guide distribution of the funds?" The results are nearly 100% votes for the CV—in contrast to financial investments for which it is said "past performance is no indication of future returns," in science, it is widely accepted that past performance, not a detailed research plan, is the best predictor of future success. So why stay with the fiction that R01 grant proposals are the best method for determining support of the individual scientist, given that, as stated above, these grants now require most of the work to have already been accomplished at least in preliminary form and that true creativity is often cause for lower scores?

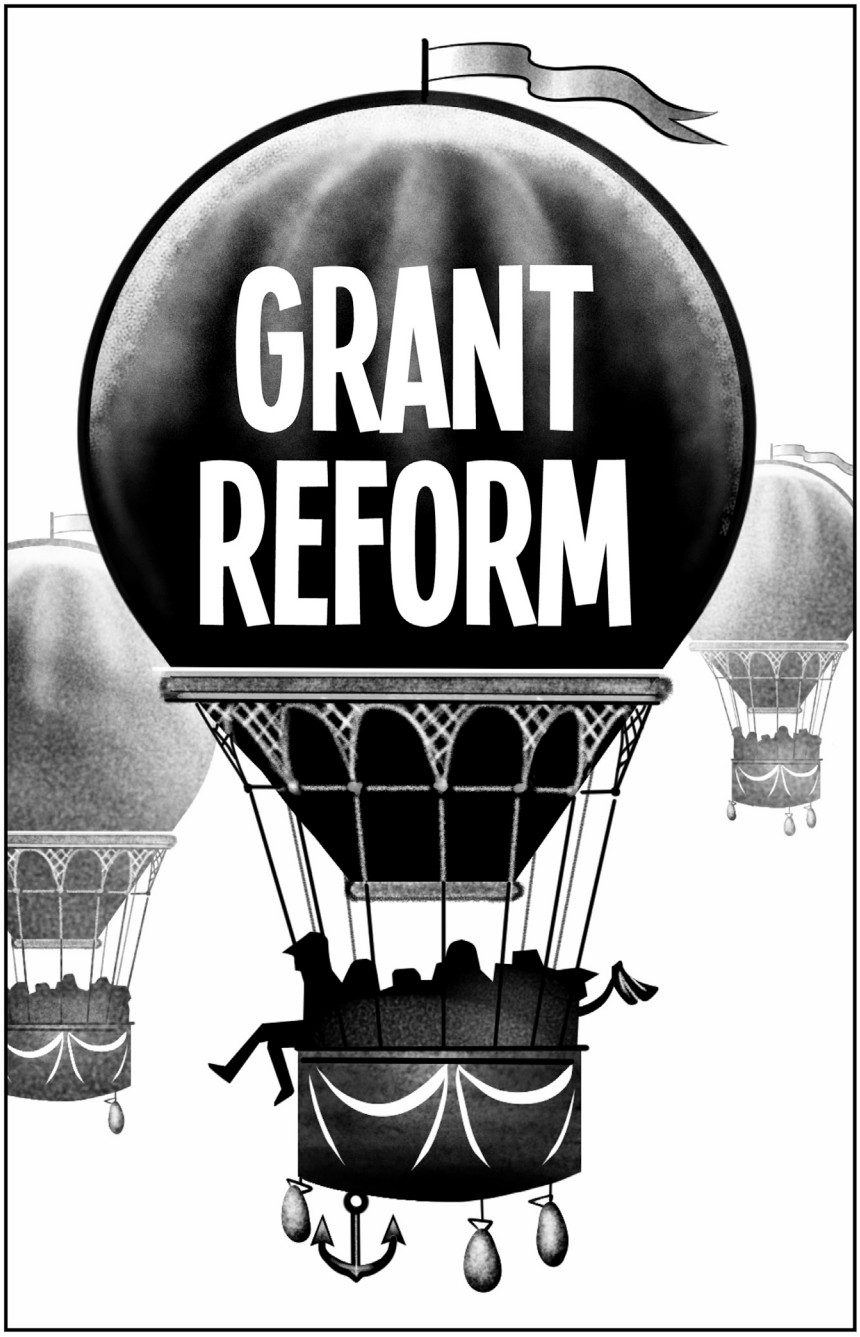
Proposal

To address these problems, including the choice by some of the best and brightest students in the U.S. not to pursue a career in science, I believe the NIH should transition to a system that links getting a first job (faculty appointment) with sufficient funding to support a reasonably sized laboratory (three to five people, including the PI) in terms of staff salaries and supplies, with the institution adding in some support for faculty salary and large equipment. How this linkage between jobs and NIH funding should be accomplished is described in detail below.

Once the new hire is in place, the new faculty member then would have 5–7 years (this could vary among disciplines) to pursue whatever they wish, with no need for conventional project-specific R01 funding. At the end of this time, they would be evaluated for further funding based on what they have accomplished (the review would be ~90% retrospective, 10% on general, not detailed, plans for future work). There would be three main outcomes: (1) failure due to lack of substantial output and contributions to the field, resulting in a cessation of funding, (2) value added to the field that permits continued but not increased funding, and (3) stellar performance (e.g., opening a new area of research), which allows continued funding and a request for expansion. There would be two exceptions to the cutoff of funds for people in the first outcome grouping: (1) cases in which the investigators can show that, within another year, they would likely make a major advance or (2) cases in which investigators tried something extremely original or risky in the earlier years of their appointment; the latter could obtain 1–2 years of bridge funding on a case-by-case basis. In addition, due allowance for family and health-related issues would be made in determining the timing of the initial review point.

This plan for new faculty would be connected to a rolling change in the present R01 grant mechanism among more senior investigators by switching to retrospective review in 5–7 year cycles as the major grants of an individual come due. If possible, it would be best to roll all R01 grant award into one or two new awards (if the breadth of research requires support from more than a single NIH institute) at a particular point for each investigator, rather than to have different reviews for different grants and topics at varying times.

Several issues arise in terms of the starting junior faculty proposal, first among them being the source of the funding. I believe that the best mechanism is to provide the appointing institution with block grants that can only be used for such new faculty support. This



is because the institutions make the appointments, and a national parsing of support would be hard to coordinate with such hiring decisions in advance. This is clearly a point of contention, with many of those I spoke to about this issue being opposed to institutional award and favoring instead a national NIH-operated competition on an individual basis. I find the latter hard to imagine as workable—there are at least 200 open junior biomedical faculty positions every year spread across institutions and departments, with >200–300 applicants for each opening. Even accounting for a 5× overlap in applicants for similar positions, this would lead to >4,000 applications to evaluate per year and brings us to the problem of study sections and their make-up. Further, it would be difficult to align award with open faculty positions on a field or department basis. Other limitations to a scheme of individual funding would be institutional hiring based on a candidate having money and not necessarily based on merit or potential (the judgment of NIH study sections is very likely not to match that of faculty at the hiring institutions). More discussion is certainly welcome, and an even better scheme might emerge from further consideration of this point.

Which institutions would get funding in the proposed scheme and how would the scale of the institutional awards be determined? One logical possibility is that, at the beginning of the launch of this new plan, all institutions presently with K22, K99, R21, R01, etc. awards for their junior faculty would receive grants whose scale is based on historical data reflecting the institution's receipt of such awards over the past 10 years, factoring in the increased costs associated with full funding of a 3–5 person laboratory for 5–7 years. In this way, one does not need new dollars to get the program started and there will be natural "population control" in that institutions will be constrained in the number of new appointments they can make. By making renewal of the institutional block award contingent on the funding rate of that institution's appointees upon their initial retrospective review in the "new R01 regime" I outline above, the institutions would be forced to provide a high level of support and mentoring to the junior faculty to help ensure their success.

Responses to Additional Caveats Raised by Others

I have discussed this specific plan with various HHMI investigators, tenured and non-tenured faculty at diverse institutions, postdoctoral fellows, and students around the U.S. The responses range from substantial interest to enormous enthusiasm, most at the latter end of the scale. The major questions raised about the plan beyond those dealt with above have been the following:

1. How would the money be apportioned to support the program? I have addressed this in part above, but some have broached the question of whether this would

make the "rich richer" and also pose political problems because of the skewed distribution of grants and faculty in the current research landscape. I think that both points are valid but can be addressed. First, no institution would get less on average than they get now, so the distribution is not "unfair" in that regard. As to disadvantaging an institution that is trying to "up its game," even in the present situation, this usually requires a large upfront internal financial investment from the institution (typically utilizing private or state dollars) to attract faculty that it wouldn't otherwise be able to compete for, so this would remain the same. However, as renewal applications of existing new faculty support block awards come in, one would imagine that some institutions will do more poorly than others. Up-and-coming institutions, if they can show a high rate of success when their internally funded new hires go into the retrospective review program, would be able to outcompete the present block grant holders whose new hire success rate is at the low end of the scale and capture the block funding going forward. So the system can accommodate changes in institutional strength over time.

2. What about the geographic distribution of funding and the concern of Representatives and Senators about institutions in their districts/states? Again, the distribution is not different from what exists now, so it is unclear there would be reason for complaint, but of course, this issue isn't always debated in a completely dispassionate manner. I am not such a purist that I don't see some value in insuring minimal base funding for major (state) institutions even if their historical record wouldn't support making a large block award (though I note that many state universities are strong research centers). This is not just for political reasons. Often such institutions are the only places some students can afford to go to college, and exposing these students to active research would allow capture of some potentially outstanding future scientists who would otherwise lack mentors and the experience of laboratory research to propel them further in this direction.
3. Is the recommendation for termination of funding at the end of any given cycle due to "non-performance" too harsh? Aside from the exceptions listed for new investigators that would result in bridge funding for 1–2 years (imminent major progress or investment in a potentially important but risky project), should the result of a poor review for either the first or any subsequent cycle be a drastic reduction in funding continued for a full cycle rather than cessation of an award, with the hope that such a cut would lead the investigator to focus intently on a limited question and make sufficient progress to pass muster at the next review? I have doubts about this alternative—with 5–7 years of support per round and 1–2 years of bridge funding available, I think it is unlikely that a highly competent investigator will fail to produce enough during 6–9 years of research to warrant a "passing grade" without further extensions, except in extenuating circumstances. Further discussion will be needed to develop a policy dealing with accommodations in grant term related to family and health-related issues. It should also be noted that the current R01 system possesses the same "deficiencies," as R01 renewal is also a binary outcome. Although current investigators with multiple grants can afford to fail to renew some funding sources without shutting down their laboratories, in the plan proposed here, PIs similarly funded to perform a broad range of projects would also be "protected" against complete loss of funding by being able to show progress in subsets of these diverse projects.

A related issue is whether there can and/or should be an opportunity for additional funding during the initial 5–7 year new faculty support period—for example, if an unexpected result looks like it would open a new area and there is a desire to add work in that direction to ongoing efforts. I think in the main that the support I am proposing should be adequate for the PI to take advantage of such observations by terminating less productive activities in the lab and redirecting funds and personnel to this more promising avenue. Of course, some allowances may need to be made at times in deference to graduate student and postdoctoral fellow career issues. There will also be occasions when the nature of the work is such that only additional funding will allow the new opportunity to be properly pursued, so a limited number of awards in support of such novel projects could be part of the plan. I worry that application for such funds would quickly become routine, but perhaps a mechanism to allow such funding on rare occasions could be found that avoids this pitfall. One possibility is to give institutions the ability to hold back a small fraction of their block grant funds and disburse these in response to requests from their own investigators hired through this mechanism. Such a scheme would make the institutions responsible for ensuring that the money was well employed, as the outcome of such supplemental awards would be taken into account during the institution block grant review process that is based on the success of the new career hires.

A last point on this topic is what to do with rising stars who wish to expand their laboratories earlier than the usual 5–7 year point of entry into the retrospective review system. I think that there is every reason to allow investigators to try their luck with the review process earlier than the maximally permitted period. It is a risk of course in that those doing the review may not agree that the work is quite so stellar, so I suspect only those with the strongest programs will opt for this possibility. This makes it likely that only a small number of such early renewals with

a request for expansion will come in, and I see no reason to deny such (putatively) successful PIs a chance to build more rapidly.

4. The description of this change in funding is cast above as if NIH is a monolithic organization, but of course, it consists of nearly two-dozen institutes that make grant awards. Substantial thought (and political will) will be necessary to put this plan into operation in the context of the separate budgets for these institutes and their different primary areas of research support. This is not a simple matter to parse, as the most obvious solution requires some adjustment of budgets among institutes (a politically fraught issue), but if the basic tenets of the proposal are accepted as desirable goals, I believe this problem can be resolved.
5. This proposal does not deal explicitly with the difficulties that exist in creating more opportunities for minority and underserved populations to enter and succeed in the biomedical research arena. Augmenting such representation requires changes at all stages of education before the faculty entry point of the funding system described here. However, I do think that this scheme provides those who make it to the first tier in such a career (a junior faculty appointment) a more egalitarian path forward based on documented performance with resources in hand, a process that is typically more objective than project review. This can only have a salutary effect in fostering a more diverse population of investigators. Nonetheless, special attention will need to be paid to ensuring that biases, subconscious or otherwise, do not skew the choices of new faculty or the retrospective renewal process.
6. Mechanisms will be needed to deal with gaps in research careers or entry into the system other than as a starting faculty member. Interruption of a research career for short periods, for health or family reasons, shouldn't exclude an individual from continuing to function as a PI. For those already successfully competing in the proposed system, it should be reasonably straightforward to craft mechanisms for postponing ongoing funding for short periods (a few years at most) and then restarting the flow of dollars when the individual returns to the laboratory. In other cases, individuals might wish to enter a research track later in their career, whether an M.D. moving from clinical work to research or someone who has been in a lab but not functioning as a PI. Two ways to accommodate such transitions could be easily imagined—allowing institutions to use some of their block funds to initiate research careers for these individuals, with the same post hoc review of the success of these choices, or reservation of a modest amount of funding for direct application in the style of the current R01 system. Keeping open the possibility of entry into a research career other than through the first hire funding scheme that is at the core of this proposal would help ensure that the system isn't a "one size fits all" that excludes those who either come late to the "calling" or who may be on the border of award of a funded junior faculty position and need to prove their worth in the research arena to qualify for retrospective review funding going forward.
7. Finally, although this proposal deals primarily with R01 funding, there will also need to be attention paid to other mechanisms used for research support. Large, collaborative efforts are necessary to attack certain problems. However, stronger requirements for data qualification, deposition, and sharing are essential for larger projects supported by such mechanisms as U01 or U19 awards, so that the substantial amount of money spent on such efforts benefits the entire research community and so that the growing cadre of bioinformaticians can re-use the data for potentially novel discoveries at the earliest possible time. I support such large efforts, but not in their current form—my experience is that too often, vast sums are consumed in disproportion to the advances made, and in many (most?) cases, the PIs feel that they should have exclusive ownership of the resources and data for an unreasonably long time. There should be stricter rules controlling when data are made available publicly and greater accountability to insure investment translates into outcome, especially when the activities do not involve creation of new technologies where success cannot be assured, but rather involve application of known methods on a large scale to an important problem (see the new NIH rules on data access for genomic information for efforts to move forward in this direction [National Institutes of Health, 2014]). The issue of credit allocation and career advancement for individuals engaged in large, collaborative projects is also a crucial one but beyond the scope of this piece, though it may be instructive for readers to examine the revisions made in the past few years to the NIH Intramural Research Program tenure policy to specifically recognize the importance of team science in the biomedical research arena (National Institutes of Health, 2015b).

I believe that, if changes along the lines I propose could be accomplished, the funds already available to the NIH would be put to much better use. The review process would become much less onerous, with salutary effects on the reviewers (and on who is willing to serve in such a position) and perhaps diminished administrative costs and more funds available for science itself. Indeed, review panels could be much more multi-disciplinary than at present because of the retrospective nature of the review that considers mainly published work and is not concerned with the discipline-specific nitty-gritty of how one would conduct a future study. Under such conditions, one does not necessarily need to be an expert in the field to contribute to evaluation of the portfolio of the person

under review—this was the case with the HHMI when I was on the review board, where having a mix of expertise on the panel worked extremely well. This broadening of the review boards would decrease the perceived unevenness in the rigor with which grants that go to different study sections are reviewed, as well as reduce the effects of parochial thinking on the overall award pool and research portfolio.

Many readers might suggest at this point that I have missed a key issue—the number of dollars devoted to biomedical research. Wouldn't many of the problems I seek to rectify by this proposal be obviated if there were simply more money available? Others have already noted that as desirable as an increase in the NIH budget would be, especially a correction of the 25%–30% erosion in constant dollars that has occurred over the past decade, it is extremely unlikely that the problems afflicting the research enterprise can be solved in this manner (Alberts et al., 2014). The reason is simple math—depending on what one considers the likely size of laboratories (reliable data are sparse and estimates range from as few as 3–4 to 10+, as seems to be the case from acknowledgment slides after talks at major meetings of even junior faculty speakers), then with 5 years on average in postdoctoral training, each PI is replicating herself or himself an average of every 6 months to a year. Even if this number is inflated by 2-fold due to second postdoc periods, drop-outs from the system, and non-trainee staff, and assuming that only 25% of fellows become PIs as has been reported (Rockey, 2012), then the effective population doubling rate is every 4–8 years. I doubt any of us think that, however much of the GDP we feel should be devoted to biomedical research, the compound budget increases approaching the 12%–25% per year above inflation needed to sustain such growth are conceivable. The person-centric, block-grant system I propose would impose "natural" population control through limitations in the number of new laboratories formed and their size expansion over time. Together with other changes to the sociology of scientific training and to the structure of laboratory groups—more research associates/staff scientists, fewer trainees as mere hands in the lab—a better balance between potentially sustainable budget growth and expansion of research can be attained, while maintaining the creativity that comes in large part from the influx of new trainees and young investigators. At the same time, this rebalancing of the laboratory staff structure will improve research efficiency. These changes would also likely foster more collaboration, given the constraints of overall group size and the increasing appreciation that multidisciplinary efforts are often needed to make major advances. I am fairly sure we will not see the power law budget increase needed to keep up with the current explosive production of new scientists arising from ongoing practices, but I am perhaps unduly optimistic that, after a correction of the inflationary losses of the past several years, we may be able to attain an "inflation plus" growth rate that would support a robust research enterprise of the type I think we all envision and to which this change in funding strategy could contribute.

A final point of tension is over the fraction of the budget devoted to basic versus translational or clinical research, with a fear among more basic investigators that the balance is shifting too far toward the latter (Wadman, 2012). There is little doubt that successful translational work that improves human health (the end goal of the overall NIH mission) depends on new discoveries made in basic science laboratories, and strangling the latter will only diminish effective clinical advances. But it is also fair for the society that supports research to expect a return on its investment. Beyond the funding scheme changes that constitute the heart of this essay, I end by noting that there are ways to provide stable support to basic investigators while also recruiting their knowledge and talents more directly in support of the rapid movement of discoveries into the translational realm; indeed, some of the mechanisms for doing this can make basic scientists more aware of new areas ripe for study and also generate collaborative enterprises that together make for exciting and rewarding scientific interactions. If we are creative and open in our thinking about re-structuring not only the major support scheme for biomedical research from a project to a person-centric model as I propose, but also in how we organize our research efforts, it is not too difficult to imagine a future in which much of the angst about support and career stability can be turned into a new era of sustainable and rewarding research activities, one that satisfies the "seeker" in each scientist while providing society with the new knowledge and application of this information that it deserves for its support.

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