How the US can best support the careers of promising young biomedical scientists

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Over the past several years, we and others in the biomedical research community have become increasingly concerned about changes in the demographics of our enterprise (*1-4*). We are also convinced that a hypercompetitive atmosphere is having malignant effects on many aspects of our scientific culture, including the choice of research topics (*5*).

These concerns have distressing effects on young investigators: many fewer younger scientists are being supported as independent investigators by U.S. National Institutes of Health (NIH) grants, and newly launched investigators are strongly discouraged from tackling novel scientific problems (*5-7*). These two aspects of academic life in our fields can discourage talented students from aspiring to careers in biomedical research, despite the extraordinary opportunities offered by new technologies and recent discoveries. We view this situation as an existential threat to our profession. There is therefore an urgent need to confront the underlying problems with funding programs that will increase the number of independent scientists at early stages of their careers, accompanied by mechanisms that will encourage new investigators to propose imaginative projects -- even when they seem difficult or uncertain.

In this Policy Forum we propose three steps that could be taken by US funding agencies, especially the NIH (which supports the largest numbers of biomedical scientists), to support young investigators in more constructive and effective ways. We are encouraged to do so by recently released, favorable evaluations of grant programs at both the NIH and the European Research Council (ERC) that emphasize support for young investigators who aspire to tackle new and adventurous goals. We contend that a substantial expansion of such programs, along with changes in other existing grant mechanisms, could do a great deal to reverse two of the most disturbing trends in the conduct of biomedical research.

The nature of the dilemma

Before describing proposed solutions, it is important to summarize the evidence for the two perceived problems: deleterious demographic shifts and discouragement from tackling difficult problems.

The type of NIH grant most often awarded to independent investigators is the R01 award, and tracking their numbers (while including a few similar grants) is

used to monitor the general support of the biomedical sciences in the U.S. By that measure, major changes have occurred in the demographics of the funded investigators in the U.S., with a very striking shift of awards from younger to older scientists (Figure 1A). The factors responsible include the aging of the population (affected in part by the "baby-boomer" generation), the elimination of a mandatory U.S. retirement age, the lengthening of graduate and post-doctoral training, and the often multi-year delay between assuming a faculty position and successfully competing for an NIH grant (*8*).

A cardinal feature of the shift is the dramatic reduction in NIH-funded investigators under the age of 37. That trend is apparent from the data shown in Figure 1B. Despite a large increase in the NIH budget since the early 1980s, there has been more than a five-fold decrease in the number of investigators aged 36 or less who hold R01-type grants: from over 2500 grant-holders to under 500. Expressed in terms of NIH dollars, the proportion of all NIH grant funding awarded to scientists under the age of 36 has dropped from 5.6 percent in 1980 to 1.3 percent in 2012 (*1*). By these measures, the U.S. scientific community is doing a poor job of renewing itself, an inherently unhealthy situation.

The claim that young investigators are reluctant to address the most challenging problems in biomedicine rests on less quantitative observations. But the next generation of scientists—today's graduate students, postdoctoral fellows, and assistant professors—widely report that the peer-review process for grant applications is perceived to be unduly conservative, discouraging them from proposing to conduct highly original work. In conversations with trainees and young faculty, we have repeatedly heard that emerging scientists feel compelled to remain well within the bounds of the research that they and their mentors are already pursuing, because obtaining a research grant requires strong preliminary data and a high probability of success. In addition, many scientists, both junior and senior, operate with the conviction that essential components of the grant-making system, including peer reviewers and agency administrators, currently undervalue research projects that seek to decipher the fundamental principles of living systems -- in favor of projects with shorter-term objectives that address human diseases (so-called "translational biomedical research"). Yet the history of science has repeatedly shown that insightful studies of basic biological mechanisms in easily manipulated model organisms—such as bacteria, yeast, worms, and flies—provide critical, revolutionary insights into life processes. Over the longer term, these discoveries contribute in critical, very profound ways to human health (*9*).

How the NIH and the ERC are addressing the situation

Some ideas on how best to fund young scientists have come out of Europe. In 2007, the European Research Council (ERC) launched its Starting Grants (StG) program, aimed at young scientists who have received their Ph.D. within the

prior 2 to 7 years. At the same time, the ERC initiated a parallel program of "Advanced" grants, open to applicants at any career stage, which likewise emphasize novel interdisciplinary research. Since then, the ERC has added a third category, the Consolidator award, designed to support investigators who have previously received a single grant, such as a StG award, and are 7 to 12 years post-Ph.D. Importantly, the competitions for the three grant categories—Starting, Consolidator, and Advanced—are conducted separately, and the awards are supported from three independent budgets (*2*).

This division of career stage into three tiers has a number of advantages. First and most crucially, investigators conducting their first independent projects and those stabilizing their laboratory programs are competing against scientists at the same career stage, not against senior scientists with longer careers and stronger reputations. Second, different criteria for review can be applied to applicants at different career stages. In this way, the StG's encourage applicants to pursue risky and innovative projects when they start their own laboratories, without requiring extensive preliminary data.

The **competition** for these pan-European StG's is held annually, and each of the one to two hundred successful applicants in the life sciences receives substantial funding, €1.5 million over 5 years. A critical feature of the process is the use of 9 review panels, each composed of outstanding senior scientists coming from a broad range of disciplines and many European countries; this serves to minimize narrow specialization and to focus decisions on the broad implications of the proposals (*2*).

The ERC has recently completed an evaluation of the outcomes from the first several classes of investigators who completed the full course of funding from the ERC StGs. The results are very encouraging. Of the 199 individuals evaluated, 43 were judged to have produced a "scientific breakthrough," and 99 were thought to have generated a "major advance" (*10*). The award of an ERC StG is now seen as a stamp of quality for a new investigator and his or her institution, and it is a goal to which most young investigators in Europe aspire.

The NIH leadership has also directed attention to these problems. Over the past few decades, the agency has experimented with several programs designed to fund the next generation of biomedical scientists more effectively and at earlier ages (*2*). Some of these experiments, such as the R29 (FIRST) grant program for new investigators, were discontinued after unfavorable evaluations. Other programs, such as the policy initiated in 2008 to use administrative interventions to raise the success rates of applications from Early Stage Investigators (ESIs; applicants within ten years after receipt of their PhD or completion of clinical training) have made a difference, and they continue. Additional experiments include the Early Independence (DP5) awards and the New Innovator (DP2) grants, popular programs that are very modest in size.

To be eligible for a New Innovator grant, a scientist must be an ESI, as defined above, and cannot have received a major grant previously. Most importantly, the criteria for selection emphasize imaginative and novel scientific goals, without a requirement for preliminary results. These DP2 grants are generous with funds and time, providing $300,000 per year in direct research costs for 5 years. In addition, all of the money is provided at the start of the award period, so that expenditures can be tailored to the needs of each investigator (for example, to purchase major equipment). Although nearly 2200 applications for DP2 awards were received in the initial year (2007), only 30 were awarded. This presumably sent a discouraging signal, since only about 550 applications are now received each year, with 100 finalists selected by a single broad review group. After further evaluation, about 40-60 awards are made (*11*).

The NIH has just completed a careful external evaluation of the first three cohorts of DP2 recipients and deemed the program a success. This grant program is supporting “research that is more innovative, risky, and impactful than research that typically is reviewed and funded using the traditional R01 program." In addition, despite concerns that supporting ESIs to pursue highly original research topics might place their careers in jeopardy, the evaluation found that "the New Innovator Award did not have a significantly more positive or negative impact on the careers of its awardees than did the ESI R01 Award" (*12*).

Encouraged by directives in last year’s 21st-Century Cures Act, and responsive to concerns in the research community, the NIH has announced its intention to enlarge the cohort of young investigators who receive R01-type grants. In a recent opinion piece, the NIH leadership has provided a list of mechanisms by which individual Institutes and Centers might increase the number of awards made to younger investigators and reaffirmed NIH’s commitment to improving prospects for ESI's (*3*). The announcement has also defined a new category of applicants, the Early Established Investigator (EEI) -- a scientist who has received only one R01-type grant and is thus formally analogous to a candidate for the ERC Consolidator Grant. This new NIH policy statement includes a pledge to increase the number of R01-type grants made each year to ESI’s and EEI’s by a few hundred in each category; however, the precise number of additional awards and the definitions of beneficiaries are apparently still under review (13).

Three specific proposals

We are greatly encouraged by the continued engagement of NIH leadership with the plight of young investigators and the commitment to increase the number of awards directed to them. It is in that spirit that we propose that three additional specific steps be taken to enhance the opportunities for early stage investigators.

(i). *Greatly expand the use of the DP2 mechanism*. The New Innovator award has now been used for a decade and evaluated favorably. We believe it deserves expanded use as part of a multi-faceted plan to improve the prospects for talented young biomedical scientists. We propose that the NIH move in a step-wise manner towards a goal of providing approximately half of the total NIH resources for ESIs through DP2 grants. In 2016, the NIH funded 908 of the 3937 applications from ESI's for R01-type grants (*14*); if that number rises to about 1100 ESI grants annually under new NIH policies, we propose that 550 eventually be awarded in the New Innovator category. This number of New Innovator-type awards would greatly increase the probability that ESIs will be funded to explore novel approaches to important biological problems. As a result, all new independent investigators -- as well as the younger graduate students and postdocs still preparing for their careers -- would be liberated from the widely perceived tyranny of conventional thinking.

These changes could also affect the age at which investigators receive their first R01-type grant. The ability of the DP2 program to launch careers at relatively early ages is evident from the age distribution of the DP2 awardees over the past decade (Figure 2). As shown, these awards have generated a small cohort of researchers who began their independent careers at a median age of 36 years. (Notably, the age distribution for DP2 recipients is similar to that observed for recipients of the ERC's StGs in the life sciences, for which the median age has been 35 years; Figure 2). Thus, greatly expanding the number of DP2 grants to approximately 550 awards per year (2750 total, since each is for 5 years) would both stimulate novelty and help to counteract the loss of PIs under 37 years old who are funded with R01-type grants (see Figure 1B). The average age of first-time grant recipients could be further reduced by gradual changes in the eligibility criteria for a DP2 award from the current ten years or less post-Ph.D. to 7 years (as discussed again below).

One can question whether a major expansion of the DP2 program would be able to reduce the average age at which new investigators in the US are funded, given the large backlog of post-doctoral fellows who have been in a "holding pattern", competing for the limited number of independent positions in US research institutions. In the current conservative funding environment, why would a university hire a scientist proposing to undertake a novel research program after only a few years of post-doctoral training, when the institution could hire someone with several more years of training, many more publications, and a plan to continue an already productive research program? We propose that, by providing sufficient amounts of funding to new faculty without a pre-existing publication record on a proposed research topic, the NIH would free university search committees to think more imaginatively about the type of science (and scientists) that they want for their institutions.

To encourage this type of hiring, we recommend that the NIH adopt two current practices of the ERC. The first is to allow a postdoctoral fellow to apply for a DP2 Award provided that he or she has secured a position that is conditional on the award decision. This is the case for the ERC StGs, where, in addition, a successful applicant retains the option of shifting institutions after the grant has been awarded. The second is to restrict DP2 grants, over time, to applicants who are between 2 to *7* years post PhD or clinical training, instead of the current 10-year limit. Reducing the number of years of eligibility for ESI status would encourage two healthy trends: less time in post-doctoral training and earlier research independence.

(ii). *Increase the funding of young investigators through Requests for Applications (RFAs)*. It is often underappreciated that NIH Institutes and Centers issue substantial numbers of R01-type grants to applicants responding to RFAs, not just to applicants for the traditional investigator-initiated awards. Ideally, RFAs can be used to attract more investigators into fields of research that warrant greater attention because the public health needs are great or because new findings or technologies offer unexpected opportunities for progress. Yet it is generally perceived that RFA's are designed for more senior scientists who are already working in relevant areas of research. (In 2016, the total number of new NIH R01s was 4,541; of these, 333 (7.3%) were awarded via an RFA.)

We propose that the NIH mandate that a substantial percentage of grants (perhaps a quarter) be awarded to ESI's as part of both Institute-sponsored RFAs and NIH-wide initiatives, such as the Cancer Moonshot and the BRAIN Initiative, and that the ESI competition be conducted using the selection criteria already used for DP2 awards. Reserving funds in each case for a separately reviewed, DP2-type competition among ESI's would then advance the goal of the program in two ways: by attracting new scientists into the targeted field and by encouraging novel approaches to an important problem.

(iii). *Experiment with separate competitions for ESI's when awarding traditional investigator-initiated R01 grants*. For several years, the NIH has encouraged its Institutes to favor ESI applicants when selecting recipients of new grants. This has produced higher success rates for ESIs at some Institutes, but it has not achieved a substantial change in the demographics shown in Figure 1.

To reach a greater representation of young investigators among grant recipients, we suggest that NIH experiment with the kind of strategy adopted by the ERC, in which ESI's compete separately for pre-designated numbers of R01 awards, rather than against the entire pool of applicants.

We recognize, as does the NIH leadership (*3*), that the earmarking of funds to

support more young investigators will come at a cost to older scientists, as analyzed in detail by others (*4*). Nevertheless, it is important to make this shift in support, which we consider to be essential for the future vitality of biomedical research. These changes would have the support of Congress, which has been concerned about the status of young investigators. They will also be easier to make if the Congressional appropriations for NIH continue to grow, as signalled in this year's House and Senate appropriation bills (*15*).

Summary

An ideal funding program for young biomedical scientists would enable the country to sustain a vibrant academic research enterprise. Such a program should award enough independent grants to young investigators to inspire the most talented students to aim for scientific careers, and it should encourage them to solve important biological problems. Reaching these goals requires two things: (i) re-engineering the grant-making process at the NIH to guarantee that there are substantial cohorts of funded investigators in early phases of their independent careers and (ii) reducing the current pressures on new investigators to continue research programs similar to those of their mentors, by emphasizing originality when making funding decisions. To these ends, we propose a large expansion of the NIH New Innovator (DP2) Program and the awarding of more R01-type grants to ESI's through both RFAs and traditional investigator-initiated mechanisms. If properly implemented, our proposals will substantially increase the number of scientists who receive independent research support while still in their 30's, while enhancing the originality of their research.

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Figure Legends

Figure 1. The increasing age of principal investigators funded by the US National Institutes of Health. (A) The age distribution of NIH R01-type funded PIs in 1980 and 2016. (B) The percent of NIH PIs with R01-type funding plotted against year, selecting out older and younger age brackets. R01-type grants are defined as R01, R23, R29 and R37 awards. Data were synthesized from files posted for NIH’s New and Early Stage Investigators at https://grants.nih.gov/policy/new_investigators/index.htm.

Figure 2. The age distribution of recipients of ERC Starting Grants in Life Sciences compared with the age distribution of recipients of the NIH New Innovator (DP2) awards. NIH data were obtained by a FOIA request. ERC data were provided courtesy of Jose Labastida, head of the ERC Scientific Department. Values for DP2 PIs 30 and younger and 44 and older were not provided by the NIH due to privacy concerns.

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Figure 1

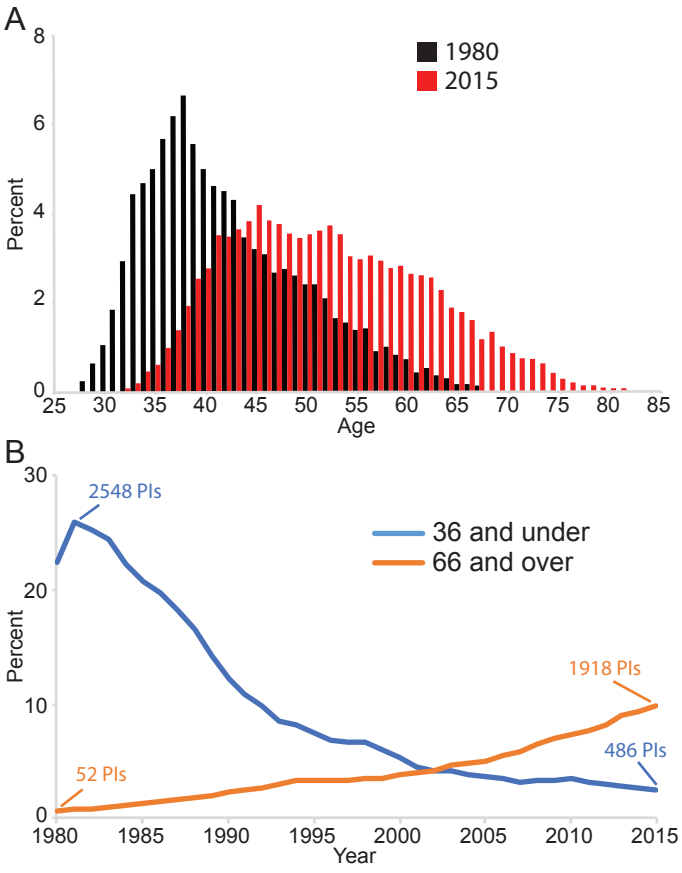

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Figure 2