The best-kept secrets to winning grants

With competition for research funding approaching an all-time high, experts reveal their top tips and tricks.

BY KENDALL POWELL

An aesthesiologist and clinical researcher Peter Nagele started his first independent position in good shape. It was 2007 and he had already earned two early career grants for his laboratory at Washington University in St Louis, Missouri. But when he applied for his first major research grants from the US National Institutes of Health (NIH) he got two crushing rejections.

Nagele had made some rookie mistakes: one proposal, for a 10,000-patient clinical trial, was too large in scope to be eligible, and the other was not a priority research area for the agency. "Those projects never saw the light of day," he says, "and rightfully so."

By his third attempt he had learnt some invaluable tips and tricks. He got feedback from colleagues on his draft proposal, he talked to a grants programme officer at the NIH to work out the best strategy, and he added experienced co-investigators to his proposal.

In 2015, his homework paid off. His application for a smaller clinical trial to look at the use of beta-blockers to prevent post-surgery heart problems was funded for roughly US$500,000 a year. The difference between between failure and success, in his

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opinion, was "significance of the research and feasibility." He demonstrated to reviewers that he and his collaborators would be able to do the work on time and on budget.

Competition for funding is ruthless, and the stakes are particularly high at the NIH — the largest single source of funding for biomedical research in the world. The agency's research-project grants — R01s and other, similar grants — are the main mechanism for funding investigator-initiated biomedical research in the United States, supporting about 27,500 investigators at any given time. The 5-year average success rate is 18% of the applicant pool — a historic low that shows little sign of moving, given the relatively flat NIH budget since 2008 and uncertainty about its prospects. As a result, grant reviewers resort to finding any flaw they can to weed out applications.

"Damned if you do, damned if you don't sometimes seems like a theme at NIH."

That creates a daunting challenge — particularly for young investigators, who don't yet know the ropes. "The system has many biases in it — unintended, by and large. But certainly the more experience someone has, the more these biases work in their favour," says Jon Lorsch, director of the National Institute of General Medical Sciences (NIGMS) in Bethesda, Maryland, which awards more than 11% of the research grants funded by the NIH.

Experienced researchers and grant managers know that scientists can increase their chances of success, for example, by taking full advantage of the programmes designed to help new investigators, teaming up with senior colleagues when appropriate, choosing the right budget and funding mechanisms, and talking early and often with NIH staff who are there to advise. *Nature* spoke with experts in 'grantsmanship' and delved into the data to find out what works — and what common advice is best ignored. Much of the guidance translates to grant applications elsewhere in the world, particularly for the young scientists that many funders are looking to court and nurture.

Early-career investigators are unknown quantities to a grant-review panel, says Lorsch. "But they are no less important" to the system.

EMBRACE YOUR INEXPERIENCE

Since 2008 the NIH has tried to reverse the tilt in the playing field that gives established investigators a funding advantage. One strategy has been to prioritize 'new investigators', those who have never had NIH funding for an independent project. New investigators who obtained their final research degree or completed their medical residency within the past ten years are considered early-stage investigators (ESIs). When applications come in, they are split into groups; those from new investigators are compared against one another, but not against those from more-established researchers. This allows scientists to compete against applicants who have similar experience and resources.

Applications from new investigators and ESIs must win funding for new applications at roughly the same rate as do those from established investigators. And half of the successful proposals from new investigators must be from ESIs. Age is no barrier: in 2016, about 300 investigators won their first R01 awards aged 50 or older.

The data show that these rules even out the success rates across age groups. But they have done less to spread out total funding dollars (see 'The NIH's long tail'). Just 10% of NIH-funded investigators receive more than 40% of NIH funding. So, the NIH also conducts 'special council reviews' of any proposal from investigators who already hold $1 million or more in funding. This month, it announced a points system, called the Grant Support Index, to limit the amount of funding and the number of large grants that any one scientist can hold. The proposed index assigns a value to each type of grant and limits researchers to 21 points — the equivalent of three R01 grants at a time.

It's important that researchers with new-investigator or ESI status use it to their advantage, says John D. Robertson, owner of the Grant Writers' Seminars and Workshops, a company based in Buellton, California, that helps researchers with their grant applications. Young investigators should also enquire about extending their ESI status if their research has been interrupted for reasons such as parental leave, medical leave, extended medical training beyond residency, active military duty or even natural disasters.

But applications from such researchers must still demonstrate competence and independence in ways that might not be required of more established researchers, who are well known among reviewers. ESIs must provide enough detail in their proposals to show that they can carry out the planned research.

ADD SOMEONE SENIOR — MAYBE

Scott Fears, a psychiatrist and geneticist at the VA West Los Angeles Medical Center in California, has struggled to earn his own R01 for work studying the developing brains of vervet monkeys (*Chlorocebus pygerythrus*). But in another line of research, he earned a smaller, two-year grant known as an R03 after including a more-established collaborator to make it a multi-investigator grant. The reviewers, Fears says, indicated that his collaborator's experience was a factor in their scoring. "Adding her has gotten me nothing but positive comments," he says.

Many young investigators wonder if teaming up with a better-known researcher in their field would boost their chances, too. Anecdotally, the approach seems to help some researchers, but experts warn that the strategy can backfire.

There are two ways to include other investigators in an application. One is to add a co-investigator who brings specific expertise or equipment to a project. The other, for projects that are multidisciplinary in nature, is for two or more scientists to apply for a multi-investigator grant; in this case, each researcher is responsible for different components of the project.

At the NIH, multi-investigator applications come with some caveats: ESIs who team up with non-ESIs will negate their early-career advantage for that application. And under the current vision for the Grant Support Index, a share in a multi-investigator grant scores nearly as highly (6 points) as a single-investigator R01 (7 points). Robertson advises adding a senior person as co-investigator instead, which does not jeopardize the ESI status and, at least for now, doesn't add points to the co-investigator's Grant Support Index.

Nagele tried this in his third attempt at an R01, and

included two co-investigators who had the experience and expertise to get his project done. It worked, he says. But this strategy could have drawbacks, too. The partnership must make sense from a scientific perspective, otherwise reviewers could see it as an attempt to ride the coat-tails of a bigger name. And if the co-investigator is a past supervisor, reviewers might criticize the applicant as not being sufficiently independent — a consideration that could also affect tenure decisions even if the application is successful.

"It's only an advantage if the person is really a co-investigator, doing the work as a collaborator," Robertson says.

ASK FOR MORE MONEY

Another decision young investigators face in their first R01 application is whether to go with a research budget that fits the modular-budget mechanism — that is, one for budgets of less than $250,000 a year. Applications for more than that must include a detailed accounting of how the money will be spent on personnel, equipment, travel and research. Many young investigators report that senior departmental colleagues advise them not to ask for more than $250,000 in their first applications — the rationale being that the NIH won't want to hand big sums to an inexperienced scientist.

"This is a consistent refrain," says Casey Greene, a computational biologist at the University of Pennsylvania School of Medicine in Philadelphia. "As I scientist, I did not view the evidence as compelling."

Taking a modular budget, especially in light of the yearly budget-slimming cuts that the NIH applies to all awards, might hurt a young lab's research. And the data suggest that it won't improve the chances of winning a grant. Of the 22,765 R01s that were being funded in 2016, 55% had budgets of less than $250,000 and 45% had budgets of between $250,000 and $5 million. About 56% of new awardees aged 45 or under held 'non-modular' budgets, of more than $250,000. And nearly half of those investigators were classified as new investigators (see 'The 'mod' squad').

When the NIGMS analysed the new grants it had awarded in the past five years, it found that although only 14% of ESIs apply for non-modular budgets, their success rate, of 25%, was better than that for established investigators. It was even slightly better than for their ESI peers who applied for the lower, modular budgets. Experts advise researchers to apply only for as much money as they genuinely need.

Even so, perceived inexperience with large budgets can be a hindrance in the review room. Fears confronted the budget issue with his monkey experiments, which are notoriously expensive. Reviewers' feedback told him that they thought his study was statistically underpowered, but they were unwilling to give him the bigger budget that he would need to increase the sample size. "Damned if you do, damned if you don't sometimes seems like a theme at NIH," he says.

DON'T BANK ON THE R21

Wendy Walwyn, an addiction researcher at the University of California, Los Angeles, thought she had stumbled on exactly the kind of translational research that the NIH was interested in when she found a connection between dietary omega-3 fatty acids and reduced anxiety during opioid withdrawal. It suggested that a simple change in diet might help drug addicts to quit.

She called various programme officers at the National Institute on Drug Abuse to ask which study section, or reviewer panel, was most appropriate. "They all said the same thing: you shouldn't combine preclinical research and clinical work in the same application," she recalls.

They suggested that, instead, she split the proposal into two applications for a two-year grant mechanism designed to fund exploratory studies: the R21. "I had already tried that. Twice," says Walwyn. It wasn't a successful strategy.

The R21 is often a go-to grant for young investigators starting up labs. Many look at it as a way to gather preliminary data to support an R01 application, or as 'bridge' funding to tide them over once they've exhausted their start-up funds, until they get an R01.

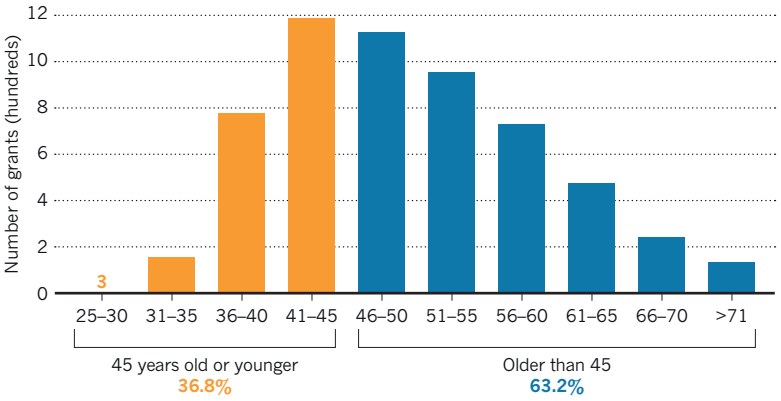
But Walwyn's story of R21 failure and frustration is not uncommon. Many investigators feel that the R21's two-year payout is not worth the time and effort spent writing the application: "I only bother writing R01s — as opposed to R21s — for the amount of science one can do for the amount of headache," says Greene.

Not only that, but fewer R21s are given out each year — just 2,219 in 2016, compared with 6,065 R01s and equivalent grants. And they are harder to get: the overall success rate for R21s in 2016 was 15%, several percentage points lower than for R01s.

Stephen Piccolo, a bioinformatician at Brigham Young University in Provo, Utah, learned this lesson personally. He had been told to stay away from R21s, but he ignored that advice when he saw an announcement requesting applications from people in his field of cancer informatics. His proposal earned a competitive percentile score, but he found out in April that it is unlikely to be funded. He's still optimistic about the R21 mechanism and plans to

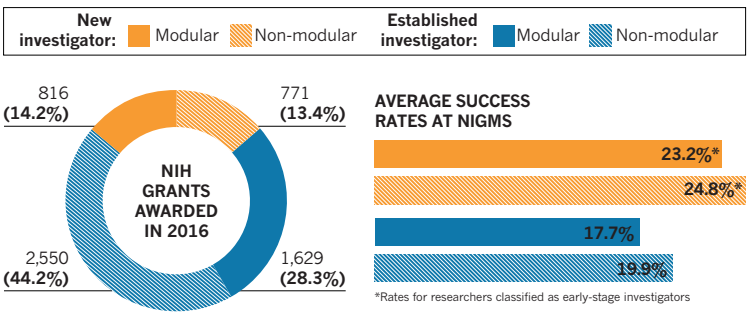
The NIH's long tail

Although investigators aged 41–45 won more R01 and equivalent grants than did any other age group in 2016, the majority of awards go to researchers over the age of 45.



The 'mod' squad

Early-career investigators are often advised to apply for a modular budget (<US$250,000), but many scientists who were awarded their first grant in 2016 sought and won higher amounts (left). An analysis by the National Institute of General Medical Sciences (NIGMS) found that over the past five years, the average success rate for young investigators applying for non-modular budgets was higher than for those seeking modular funding (right).



GRANT GUIDANCE
Quick tips you've never heard

- Watch a video of a mock study-section discussion by the National Institutes of Health Center for Scientific Review (go.nature.com/2qhspcc)
- Do not name potential reviewers in your cover letter. This will immediately disqualify those people as having a potential conflict of interest.
- Do name names when requesting in your cover letter that a direct competitor should not review your grant application.
- Look for 'funding opportunity announcements' or 'requests for applications' that identify institutes' specific research priorities. Often, success rates for these dedicated pools of funding are higher than for general review pools.
- Do not oversell medical significance or pop a disease name into your title, if your research is really fundamental in nature. It could send your application to the wrong institute or study section, significantly lowering your chances. K.P.

submit a revised proposal. But he is also practical about its limitations. "If you feel like your project is the right scope for an R01, then don't go for the shorter grant — keep trying until you get the R01."

TALK TO THE PROGRAMME OFFICERS

Programme officers, also called programme directors, are NIH employees who shepherd grant applications through the system, from submission to award. Their role includes advising investigators by e-mail and on the phone — but not every scientist takes full advantage of this opportunity.

"There's not any question that is off-limits," says Alexandra Ainsztein, a programme director in the division of cell biology and biophysics at the NIGMS. New investigators should ask about the various institute missions and research priorities that can affect the decision to fund, says Stacia Friedman-Hill, a programme director at the National Institute of Mental Health.

These considerations can often mean that proposals with scores outside the fundable range, especially from ESIs, might get a 'reach' and be funded, she says. Programme officers can also advise on each institute's favoured grant mechanisms and probable paylines — the percentile-score cut-offs for funding. The best time to start talking is before a proposal is written. From just a page or outline of specific aims, a programme officer can help to guide researchers to the right study section or a specific funding opportunity, or can suggest adjustments that align with the institute's current research priorities.

They will also point out if experimental approaches or research questions are not likely to be funded. Nagele knows this. After a discovery that the anaesthetic gas nitrous oxide could act as an antidepressant, he and his collaborators wanted to submit an R01 application for a clinical trial of that idea. A discussion with a programme officer at the National Institute of Mental Health revealed that the institute does not fund clinical trials unless the intervention works on a specific biological target in the brain; the mechanism was unknown for nitrous oxide.

"Had we prepared that R01, after several weeks or months of work, it would have been dead on arrival," says Nagele. Instead, he applied for and won an R21 to investigate where nitrous oxide acts in the brain.

Another time to seek advice is on receipt of a review-summary statement after the study-section meeting. If an application's score falls well outside the probable payline, a programme officer can tell investigators which criticisms carried the most weight during review and should therefore be given priority when the application is revised for resubmission. The programme officer can also offer guidance if an application's score is close to what might be funded; paylines can shift for various reasons.

Ainsztein often advises investigators in this "doughnut hole" range to resubmit an application before funding decisions are made because, as experiments continue, they usually have updates. And a resubmission does not prevent the first attempt from being successful. "It is more work," Ainsztein says, "But there are no guarantees until the award notice goes out."

Programme officers ask that researchers be respectful of their time, however — waiting until three days before a deadline to seek help with a grant is ill-advised.

Ainsztein also encourages researchers to get involved in the review process itself. Young scientists, she says, should apply to the Early Career Reviewer programme at the NIH, which allows them to serve as grant reviewers in a limited capacity. Learning the process from the inside can be invaluable (see 'Grant guidance'). Piccolo did this and says that the experience bolstered his confidence. After seeing other people's proposals, he says, "I thought, 'I can do this. If I put the effort in, I can be successful.'"

But optimism is not in vast supply these days. Dara Ghahremani, an addiction researcher at the University of California, Los Angeles, says he feels as if he is on a grant-writing treadmill and someone keeps turning up the speed. Ghahremani earned an R21 early in his associate research-faculty position, but has since failed in seven attempts to obtain R21s and other grants. He has resorted to applying as a co-investigator on other people's grant applications to cover his salary. With his time spread thinly, he has not been able to publish his own work in a timely manner, making it harder to apply for independent funding.

And the treadmill doesn't stop after that first R01 is secured. Lorsch and his NIH colleagues are very much aware that renewing an R01 grant is also a daunting task. The success rate for first-time renewals has dropped dramatically over the past decade, from about 53% to 32%.

"We don't want to bring a whole bunch of ESIs into the system if there's not much for them downstream," says Lorsch. He has some simple advice for those investigators who have earned their first R01: "Focus on the work you are doing for that grant." That means ignoring the temptation to immediately try to win a second major grant, he says. The number one reason that investigators fail to renew a grant is that they have not shown enough productivity or progress, Lorsch says.

For the many young investigators whose first R01 attempts are triaged without being scored, Friedman-Hill offers encouragement: "Fifty per cent of the applications didn't get discussed. They have good company." Those applications come from a mix of new, experienced and very senior investigators, she says. "The difference is that experienced investigators will just keep trying." ■

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