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Lecture Notes for Micro607: Bacterial Genetics
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The human context of grant proposals.

Imagine you're 50 years old - now I realize that at your age I might as well suggest that you imagine that you're rabbits, but make the effort.

You have been doing science and reading papers for 30 years and reviewing grants for 20. You are a faculty member at a research university and you have a grant of your own due in 6 months and you need to get some papers out, and you're teaching and you have some papers to review. And of course your furnace needs to be replaced and your daughter isn't sure if she wants to stay in college and your dog is sick and your parents are old.... the point is that you have a number of issues and distractions in your life, but you agreed to be on a grant panel, back when the date of that was long in the future. Then one day a box arrives by FedEx with 10-20 grants, depending on the agency and you have about a month to read them and write reviews, but you have to get papers out and a students need a letter of recommendation that they forgot to ask for and a number of other timely but not critical issues arise and are taken care of....but not the grants. So now there is a week to go until someone expects to get your reviews by email and so you finally throw yourself into them, mostly at night, because you still have the day job with its interruptions.

You know before you start reading that only 10-25% are going to get funded, depending on the agency and the federal budget. That is to say that only 1 in 4 to 1 in 10 will be funded on average, though your set might be a bit higher or lower. So while you read them carefully, noting what you like and don't like about each, you are really looking for those few that really must be funded. Even if they are all good, you will only really be able to argue that "this is grant has to be funded" a couple of times.

So what do you really look at? Certainly you DO look at the details and the previous productivity and the creativity. But, odd as it may sound, you look for a grant that gets you excited. You look for a grant for which you can say, "this one is highly likely to tell us something of scientific importance."

The problem is that you don't know the fields for all the grants you are reviewing. In fact, it is possible you don't know ANY of the fields in the sort of intimate detail you would like. Certainly you'll note errors in logic and if someone proposes to solve a certain problem with a method that you have used, you will certainly feel comfortable in deciding if that makes sense or not. But in fact you will be adrift with the details of many of the methods and you will also not have a good idea much of the time if the successful accomplishment of the project will be important to a larger community or not. So, for you to get excited about a grant, you need to be told, in a clear and orderly fashion, what is known in the field and why the problem is important. Then you need to be told why a certain set of experiments will make sense and are highly likely to make important progress on the biological problem that has been laid out. You will not take the time, largely because you do not have the time, to go back and read some of the papers by the PI or their competitors in order to understand some things alluded to in the grant. You will not take the time to read up on a novel method that the PI proposes to use to answer a question that, to you, seems really hard to address. You also are going to be tired when you read these, so you don't very badly want to read more than you have to. Frankly, your heart sinks when you pick up the next grant proposal and you see the PI has squeezed the margins and has no blank lines between sections, presumably because they have so many important things to tell the reviewer. You also get very tired of a proposal where every term is abbreviated, again to save space, because that makes you have to pause

and think repeatedly about what is referred to. You don't very badly want to spend another 30 minutes figuring out a detailed figure of complex data, though you are always grateful for a figure that provides some overview of an experiment or an entire section of the proposal. You very much like a clear statement in the start of each Aim about where that aim is going, as well as a conclusion about what is really important and likely to be gained from that aim, because you were also trying to figure out the details as you were reading.

So the first rule of writing a grant is "Don't piss off the reviewer." That is, produce as document that is not too dense to read in terms of detail and figures and text and for which it is not a puzzle to get at the key points and possible conclusions. And the second rule is "Be clear and organized." Tell the reader what they need to know about why this is interesting and important and why your proposed experiments are highly likely to give us results that will support valuable conclusions. Within the second rule, you must recognize that your reader is likely to be intelligent but ignorant, both of the biological question and of some of the methods. You must lay these out in sufficient detail to convince the reader that the question is important and the methods appropriate, but not more detail than that. Again, they must get excited by what they read.

Remember that humans think in stories, which are notions that have a single theme, yet are composed of different parts that tie together. As a technical detail, it is probably a mistake to expect that the grant will be read straight through without significant interruption. The phone will ring, that dog will chase the cat, it'll be time to eat or cook. That means that the Introduction, in which you tell them what the problem is and what is currently known, might not be read at the same time as the Progress Report, where you tell them what you have accomplished lately on those important issues or the Experimental designs, where you lay out the plan. For this reason, it is again useful to tell them where you are going. In the Intro, after laying out a specific issue, it is smart to say that "we have recently made progress on this issue by showing X, as described in the progress report and we will address this specific issue in the next grant period, as described in Aim 2." Then in Progress, you should remind than, "as mentioned in the Introduction, the nature of Y was unknown at the start of the previous grant period. We have made important progress on that as described below and will complete the analysis as described in Aim 2." Finally, in the Experimental Designs, remind that them you are following up the progress you have made recently on the important problem of xxx."

Writing a good proposal

(a) **What is the study section looking for?** They want to get excited - all the grants are good, but... You want them to say "this was my favorite grant," and that will be because you convinced them that it was an exciting topic and that you were going to really get something done. However, it is also because they could see the big exciting picture because you made it easy for them to do so. I believe the second rule of writing is to be clear and organized, but the first rule is "don't piss off the reviewer." I'll talk about the second below, but on the first: don't squeeze the margins, don't squeeze the text, don't try to pack in as much information as you can. Avoid excessive abbreviations and complicated data. DO provide explanatory figures. Do provide rationales of were you are going and summaries of what you have just covered.

(b) **Remember who you are writing for -** every on the panel is smart and knowledgeable about many things, but it is highly unlikely they will be knowledgeable about what you are working on. As a consequence, they will probably understand the methods and many of the pitfalls, but where they might really fall short is in knowing what others are doing and why you stuff is, or is not, novel and important. In other words, the biological importance of the area and of the expected results must be clearly laid out. Now it is true that many of the outside reviewers will understand this rather better, and might well comment on it, but they are not the ones in the room making the decision. You need to make this case succinctly, but very clearly.

(c) **Role of preliminary data -** there are two general issues here. First is just "general credibility." you wan to show that you have the ability to do most all of the experiments proposed, even if they have been published many times elsewhere by other people. For example, a biochemist who has never done any cloning in his or her life cannot get away with just saying, "so we'll clone it." The very best way of addressing this issue is to have published, so you can say "as we have done before ()." The next best way is to have a bit of preliminary data that shows you can pull it off. The next best is to have a lucid description of the method, showing that you know what to worry about. Finally, and not all bad, is a letter of support from a colleague - hopefully near by - saying "we do this all the time and are happy to help out with experimentation and analysis." Note that we tend to go overboard is defending those things that we are actually not so comfortable with and sometimes this can be a flag.

The other place where some preliminary data is important is where you have an absolutely critical result or approach proposed - essentially you are dead if you can't get this step done. Some data showing that you are highly likely to get this solved is critical.

However, remember that everyone reading these things is busy - and they probably put it all off to the last week etc etc. They have a lot to read and they do NOT want to spend a long time deciphering a complex set of data, so keep the results simple! Make the critical point and no more. Do NOT show them a bunch of data that they do not need to see. It is tiring, and a tired reviewer is not an excited one.

(d) **Key elements of a good proposal.** Humans think in stories, which are things that have a single theme, and link the various parts together in a coherent whole. Your proposal should have a single, simple theme and all parts of the proposal should be consistent with that. You should end up with 2-4 specific aims, each of which should have a biological goal and be internally consistent, but also should fall under the larger theme of the proposal. Related to this you should not assume that you have the reader's undivided attention - that the grant will be read in one fell swoop. In the Intro and Background, you need to say what is known, but it is nice to note where your recent progress has been important there and also where you will follow up on that point in the Experimental design. In the Progress, you cannot assume the reader has just read the Intro, so remind them in a sentence why the results are important and also tell them that this will be pursued in SA #X. Finally, in the ED, remind them briefly of the background and progress before launching into detail. Anytime the readers ask themselves "should I know this?" you have a problem, so too if they ask, "why are they doing this."

(e) **When should you write a proposal**? When you have a good story to tell. I see little reason to write a proposal that will not be funded and a poor proposal will hurt your future credibility a little bit.

(f) **How much time to spend on writing a proposal?** This is a toughie because it depends on the individual. However, I think it is important to start the process at least 6-8 months in advance for the following reason. If you decide that you want to tackle some new issue, then it will be important for you to have time to produce a bit of preliminary data for credibility and you can't get this done if you are writing two weeks before the due date. What you really want 6 months early is a title, the specific aims, and a rough set of the approaches and themes under each aim. The details of these can change without affecting the big picture much, but this at least allows you to decide what preliminary work is necessary and to spot potential weaknesses in the overall proposal structure.

Having said that, it is tough to start early and it is also true that most people can continue to tinker with a proposal ad nauseam. I posit that most of this is silly - we tend to primarily focus on technical details that are going to be beyond most readers. The critical issues should be the overall organization and clarity and we tend not to "tinker" with this. Indeed, by grinding through the details to an excruciating degree, we can often obscure the organization and clarity.

The other reason to get a draft done early is so someone else can read it and so you can be away from it for a while. On the latter point, when you write the first draft and then edit it a bit, you become too close to the arguments and have almost no ability to ask if the overall structure works. However, if you can let it sit for a couple of weeks and then return to it, you will probably have a better view.

(g) **Who should read your draft proposal?** It is OK having a collaborator read it, and indeed they might help a bit on some technical matters, but this is NOT the best reader. They already understand why its important and they already believe this is the right approach, so they don't notice when you fail to make those arguments. They also understand the details, so they don't get confused where a reviewer might. Instead, you really want a person rather like those who will be on the study section - smart and critical, but largely ignorant of the field. Obviously you should give such people a week or so to do the reading and then you'll need some time to address those concerns. When you sit down with that person, don't debate them over their concerns. I argue that "all readers' concerns are valid even if they are completely wrong" - that is, if you said "X is Y" and the reader missed it, you must not have emphasized it sufficiently.

Other issues

(a) **Competitive vs non-competitive renewals** - non-competitive renewals are just a few pages to show them that you are alive. I think it is very hard to mess this up enough to terminate funding prematurely. Competitive renewals are compared with brad new grants. You do get a few brownie points for being "ongoing", but there is a significant emphasis on productivity in the previous period. Brand new PIs are cut a bit of slack in their first renewal, since it is recognized that it takes a while to get a lab up and running.

(b) **Budgets** - depends on NIH vs others. For all agencies, you need to justify the amount you are asking for, though you don't need to account for supplies very specifically, as long as they are $5-8K per scientist. However, no matter what you justify for USDA, and it is nearly the case also for NSF and DOE, you will simply get the "standard grant." Now presumably you knew that and wrote an appropriately sized proposal, but, if funded for less than you requested, you have the opportunity to modify (shorten) your aims. Normally, this doesn't really matter - it's not a contract after all. It might matter, however, if

you wanted to try to split off a portion and seek other funding. For NIH, the question is actually how much money you need to get this done - and money is measured primarily in terms of the number of type of individuals proposed to be funded. It is therefore generally important to build a case for the role of each individual in the proposal, to avoid having a person or two cut from the grant.

For competitive renewals at most agencies, there is no discussion of the previous level of funding because that will typically be a given. However, while there SHOULD be such a discussion at NIH (where grant can range from $60K-$400K per year), I think insufficient scrutiny is given to productivity per dollar.

(c) **New applications vs renewals.** AND Beginning investigators vs more established investigators New applications from new PIs are given special consideration. Some agencies have special pots of money - NIH did for some time, but I don't know if they still do. However, even without this, the panel judges these appropriately. A new PI is held up for little scrutiny on previous results (though critical previous results will always be important, as will evidence of decent productivity as a post-doc) and is certainly cut a bit of slack in terms of how much is proposed etc. A competitive renewal will have an advantage if the PI has really gotten a lot done, but will be appropriately penalized if they have not - there is little enthusiasm for throwing money at someone who does not get science done - as judged by publications. Now the very first competitive renewal of a new PI is given a bit of leeway as well, in part because everyone recognizes that it takes a while to get a lab up and running.

(d) **What agency to apply to**. You want to look around and see what agencies have a mandate to fund the sort of research you want to do. You absolutely must justify your work in that context. Now there is certainly a bit of wiggle room here, but the more of a struggle you have to go to in order to justify why they should consider this proposal, the less excited the reviewer is going to be. You should therefore read the agency guidelines, which tends to be rather specific about the appropriate areas.

Now there was someone in the 1930's who was asked why he robbed banks, to which he replied, "because that's where the money is." Right now, the money is in NIH, so if you can justify the work for medical - or basic science reasons, certainly go to NIH. You will get more money if funded and the pay line is almost always better.

Where does the money go?

(a) **Overhead**. Every university cuts a deal with the major funding agency at that university (NIH here) as to the appropriate overhead rate and with one exception, this is applied to all grants irrespective of agency. That exception is USDA, which gives out such piddling grant, that a 40-60% overhead cut would nearly eliminate them, so they mandated a lower "take it or leave it" and universities have generally taken it. The overhead here is ~(*out-of-date*)% of direct costs (which is the money you can actually spend). Officially it goes to libraries, lab support, administration, etc etc and this is doubtless true, but most PIs firmly believe that much of it gets co-mingled with other funds and helps support other parts of the university.

(b) **Salaries**. Salaries must also include fringe benefits, which can be over 30% of "salary", so a technician earning only $25 K/year costs ~$35K in direct costs and costs most funding agencies ~$50K in total costs, though this doesn't matter so much to the PI.

(c) **Time period for expenditure**. Grants come for 1-5 years, with 3-4 being most common. A two-year grant means that you need to start writing the competitive renewal after less than one year, because there needs to be time for review and then decision prior to the termination of the preceding grant. Even a 4-year grant requires a renewal after only about 3 years.

Typically, when a grant is funded, there is a start date (which would typically be 7-10 months after the initial proposal was due) when one can start spending the money. Even though most agencies provide funds "by year", one really doesn't need to come very close in spending it that way, but budgeting should come out about even by the end of the grant.