Landing a Successful R or K Grant: a Young Investigator's Journey

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There are many challenges that face young investigators in the field of medical toxicology who aspire to establish themselves as an independent investigator. The path to independency (often considered obtaining an R01 grant) can be long and arduous that is rarely a straight path. While a medical toxicology fellowship is a time to develop your clinical expertise in the care of poisoned patients, many also use this time to develop their niche which may include education, outreach, administration, or in this case, research. A successful research career is a careful and deliberate approach that includes a strong investigator (mentor/team), environment, training plan, and an innovative and thorough research focus. This, coincidentally, is also the same criteria that are used to gauge the potential success when budding young investigators apply for training grants. What is not directly stated, but equally important for success, is often time and money. While there are many research projects grants available, the three popular types of Research Projects (R) that many researchers consider are the R03, R21, and R01 available by the National Institutes of Health (NIH) [1]. An R01 is considered a mark of research independency and the goal of young investigators. While not the focus of this commentary, an R01 provides four or five years of independent support, funds, and time to complete a project and publish results to apply for another R01 (the circle of life).

While obtaining an R01 is the goal of any young investigator, most will likely apply for a career development award (CDA) which provides the time, training, preliminary data, and time to eventual apply for an R01. There are various CDAs available that include, but not limited to, the NIH Career Development (K) awards (K08 and K23 being the most common), foundation CDAs such as the Society of Academic Emergency Medicine (SAEM) Foundation Research Training Grant (which provides \$150,000 per year for 2 years), and the Harold Amos Medical Faculty Development Program. While they differ in small ways, many of these CDAs provide substantial salary support with a modest research budget to allow awardees to competitively compete for independent funding.

I will discuss other funding opportunities within the context of an NIH K award (or CDA equivalent). K awards provide anywhere from 3 to 5 years of 75% protected time with a modest research budget (25–50 k/year depending on the institute). Based on my own experience being on year 3 of my K award (K08HL136858), the reality of applying for an R01 is starting to sink in. My K currently provides 25 k/year for research supplies. At first glance that seems like a lot for a young investigator, but I quickly realized early on that I needed more money! Science is not cheap. I am quite fortunate in that I have an outstanding mentor and a lab with robust staffing as well as a very supportive department. I did not have to worry as much about hiring my own technician or preparing and buying common reagents, but there were project specific equipment and supplies I needed to be successful. That was going to require more money than what my CDA provided.

I do not think I'm the only young investigator in this situation, so I wanted to share my own experiences with some common funding mechanisms available within the NIH system that investigators on CDAs may want to consider leveraging to bolster both their funding to support projects and scientific credibility to be competitive for their first R01. The question about R03 and R21 grants comes up a lot among many junior investigators, so we hope this guide to provides some context for different grant mechanisms. My research focus is at the intersection of mitochondrial medicine, diagnostics, and

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therapeutics as it relates to critical care illnesses (obviously mostly toxicology) [2, 3]. Before moving further, it is worth noting a CDA is not a requisite for these grant opportunities nor are they needed to apply and obtain an R01. With that out of the way:

- The R03
 - Two-year award period
 - Provides a maximum of \$100,000 in direct costs over the two-year period
 - Often used for a small self-contained project or feasibility study
 - Shorter six-page Research Strategy (12 pages for an R01)
 - Not renewable

This is a popular funding mechanism. While very appealing for young investigators, a CDA should be the primary mechanism to garner salary support, as an R03 is not an effective way to obtain salary support. If one is early in their career with some support (institutional KL2 or T32 for example), then an R03 may be a consideration. Some NIH Institutes or Centers (ICs) will use the R03 mechanism for other purposes such as a mini career development award (NIA GEMSSTAR to promote aging-related research), or in my case to bolster funding for K awardees based on merit. Many ICs use the R03 mechanism specifically made available to only K awardees who are within the final two years of finishing their K awards or two years after their K award was completed.

NIH has recognized the challenges many young investigators face to obtain independency even with a K award. With this recognition, this specific R03 is used to better support K awardees with more funding to create compelling preliminary data to support an R01 submission, as well as more experience with grant writing. This K-specific R03 is like a normal R03 except that one is required to also submit a K progress report and how the R03 will be used to supplement current research progress. Reviewers will look for productivity on the K award (publications, data, and career advancement) and specifically how the R03 will help the K awardee obtain an R01. In my case, I proposed developing a large animal model of poisoning to study alteration in mitochondrial function to set-up work for a recent R01 submission. I specifically described how my current K has led to the R03 application, how I envisioned the R03 would support my R01 submission, and what data/papers I anticipated with the proposal (R03HL154232). The obvious metric for K awardees and this R03 is to convert to an R01, so a clear cogent plan on how an R03 will support this transition is critical. I also think another invaluable feature in general is the summary statement. The summary statement provides important feedback, not only for a resubmission

but also may provide insight into your overall research focus that may have not been apparent.

- The R21
 - Two-year award period
 - Provides a maximum of \$275,000 in direct costs over the two-year period
 - Often used for exploratory and high-risk research
 - Shorter six-page Research Strategy (12 pages for an R01)
 - Not renewable

While a two-year grant seems “easier” to get, NIH data clearly shows these are as difficult, if not more difficult, to obtain than an R01. At least half of those obtaining an R21 are established investigators. Because of this, many mentors advise younger investigators to “just go for the R01” because (a) R21s are not renewable, (b) they can be as competitive as R01s, and (c) the time to write an R01 may not be substantially different from an R21. In my own experience, my early K work was focused on treatment of mitochondrial dysfunction with a succinate prodrug using *in vitro* poisoning models. We saw some very exciting preliminary results, so I submitted an R21 to explore the use of this drug in a murine model of poisoning that was well-received (R21ES031243). While one does not get any special consideration for being an early stage investigator (ESI) with this mechanism, there were a few comments from reviewers that noted this R21 would help me apply for an R01 which is nice for study section members to recognize. I also applied for this R21 with my mentor as a Co-I and did not ever refer to him as a “mentor” in the application. I discussed his role as a Co-I and what skills he would bring to the project which I think is important for those who want to involve their mentor as a Co-I. As a general rule for those on a CDA, this is an important time to establish your area of expertise. It must be clear that it is different from your mentor, especially if you intend to apply for future funding with your mentor. At the time of the application, we did not even have a paper together so do not let that be a barrier if you are early in your CDA with your mentor.

I do think there are a few caveats for those interested in this funding mechanism (whether you have a CDA or not). For a young investigator who is looking for funding to support a significant amount of time, the R21 is not the way to go. An R21 will likely only support 10–15% of your effort. It is way more fruitful to apply for a CDA that will support a much higher percentage. Another myth about an R21: while the grant instructions state that preliminary data is not required, virtually all funded R21s include some form of preliminary data. Obviously, the definition of what constitutes “preliminary” data is in the eye of the beholder. As a rule, the most important thing to do (as with all grants) is to talk to the Program Officer (PO). I discussed my research idea early in

the process and was in close contact after my first submission and re-submission. The last point is that not all NIH ICs offer the R21 mechanism. Again, reach out to the PO so you do not waste time crafting an application that cannot even go to the appropriate IC. My K's home IC (NHLBI) did not offer the R21, so I reached out to another IC (NIEHS) where my toxicology work seemed to fit. For those within the NIH system, going through different ICs is a good way to expand your work and portfolio to remain agile in terms of future funding.

Timeline It is worth mentioning that from the time of submission to funding can be close to a year and well over a year with re-submission, so this is important to consider in your overall timeline. For the R21, my first submission was 2/2019 and while close to the pay line was not funded, re-submitted in the fall cycle of the same year. The re-submission was funded, totaling about 1.5 years from initial submission. The R03 was submitted around 11/2019 (slightly different submission cycle), and while funded on the first submission (7/2020), was still a 9 to 10-month process. Another important consideration in one's overall timeline in the quest for independency is to avoid applying for these smaller grants if this means missing out on applying for your first R01 as an ESI. As long as one applies for their first major grant (R01) within ten years of their terminal degree (MD or PhD) or clinical fellowship (would most likely be our medical toxicology fellowship) you will be reviewed as an ESI. As an ESI you will be compared among other ESIs, many ICs often will have better paylines for ESIs, and the budget is often not cut so trying to submit your R01 as an ESI is a major advantage.

Mentorship I do want to make special mention of mentorship: any successful established researcher will most likely state that while hard work and all that was a factor in their success, perhaps the most critical factor is getting the appropriate mentorship. With an excellent mentor (or mentorship team), all good things happen. A great mentor is someone who provides support (ranging from lab to conduct experiments, opportunity to expand one's skillset, and maybe a pat on the back) to be successful. Many young trainees often have mentors outside their respective field which provides a different and important perspective. In my case, Dr. Todd Kilbaugh is considered an international expert in the field of large animal models of pediatric TBI and cardiac arrest [4, 5]. My K training has focused on in vitro models of poisoning and mitochondrial medicine which I have implemented his expertise to my future work. This has led to collaborative papers and grants where my work has benefited tremendously from his expertise [6, 7]. It does go without saying that your expertise can be different from your mentors; a good mentor will guide you in the right direction.

In summary, it is important for any investigator to understand the differences among these various funding pathways

to be successful. The primary purpose of any CDA is to obtain the skills, papers, and data to submit a competitive R01. Depending on where one is in their development, consider applying for a smaller R (R03 or R21) if you find it fits within the greater plan for an R01 as opposed to applying for the sake of applying. Finally, I want to make readers aware of the Research Concepts Section in JMT. This is an amazing mechanism many toxicology investigators have leveraged to publish their early collaborative manuscripts which were used to support successful grant applications [8].

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Compliance with Ethical Standards

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