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Finding the Right Research Question: Quality Science Depends on Quality Careers

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Abstract

When making the transition from trainee to principal investigator, there are few steps more important than selecting the first independent research project. The project must synthesize the excitement and idealism of contributing to the well-being of humankind and the practical realities of an area of inquiry that is likely to lead to a successful career.

In the world of translational medicine the first question is particularly challenging, and clinical pharmacology is perhaps the quintessential translational science. It is challenging because our discipline covers the whole of medical therapeutics, including all areas of specialty, and because the need to apply the principles of therapeutics across all areas of translational research has never been greater. There is a huge need to exploit the many advances made in the basic sciences over the past 50 years and to cross the translational divide, and fulfilling it will require the sustained efforts of many.¹

There is a great and well-recognized need for clinical translational researchers. However, the recent increase in the number of clinician investigators who are beginning their research careers² and the inevitable competition for funding from the National Institutes of Health and other funding sources are making it increasingly difficult for young investigators to obtain sustained funding in the form of R-01 awards (which, the most recent data indicate, are awarded to researchers at the average age of 43 years; <http://grants1.nih.gov/grants/award/award.htm>). In other words, there are large numbers of young investigators who do not achieve either independent funding in an academic setting³ or an independent career in industry. It is therefore important to exploit every available means of sustaining these young careers. Progress to independence is a key marker of a significant contributor to clinical and scientific progress. The quality of scientific progress is therefore intimately linked to the number of independent careers fostered; quality science does depend on quality careers.

The pitfalls inherent in an interesting but nonfundable research project may be evident but are too often overlooked because of the needs of mentors, departments, and institutions. Although clinical translational research clearly has a huge potential to generate new findings that improve the diagnosis and treatment of human diseases, it will not be possible to do this in a sustained manner if a new generation of young researchers is not recruited and supported. This sustenance

will not come free and, ideally, should be based on the high quality and the importance of the science being carried out.

High-quality clinical translational science that will prove to be of value to many depends on the work of a large number of researchers with successful academic careers grounded in the principles of independence and peer-reviewed excellence. It follows that a key element in the process of career development is the identification of valuable research areas that not only can provide results in the short term but can sustain careers and survive the inevitable rigors of peer review, whether in the form of journal editors, study sections, or promotion and tenure committees.

For researchers embarking on the first stage of their careers, this is not a decision that should be taken lightly because, if addressed carefully, it can identify an area of research capable of sustaining a career that will be enjoyable and productive for many years. If the wrong decision is made at this stage, it can waste time and energy and generate years of frustration and lack of fulfillment. This makes the exercise of identifying one's research focus so important that it calls for hard work: a good amount of reading, the asking of penetrating questions, and much discussion with friends and colleagues. The worst scientific and career decisions are those that are not discussed and vetted at length. Bad mistakes happen when important decisions are made without data in the form of the opinions of informed mentors and colleagues whose motivations are both quality science and quality careers.

WHAT ARE THE CHARACTERISTICS OF A GOOD RESEARCH QUESTION?

First, the topic you choose must motivate you personally; it has to get you up in the morning. This is criterion number one, because you are the person doing the work and the research question has to be of sufficient importance to you—not your mentor or lab director but you. If this fundamental criterion is not satisfied, the project or question under consideration will not receive the full commitment of your heart and mind, and it will not work either for you or for your superiors. This fundamental truth has to empower you to enthuse about projects and questions that motivate you but also to say no to ones that do not. Saying no to an enthusiastic or charismatic mentor can be hard, but it is a must if you are not excited about a suggested project. There are ways of doing this while avoiding unnecessary conflict and preserving important relationships.⁴

Second, the topic must be one that poses a genuinely new question. This seems obvious, but it is always worth doing a very careful search of both the literature and relevant funding sources to check whether your question has actually already been answered or whether someone else is already funded to answer it. Information on funding by the National Institutes of Health can be easily accessed using keywords in the agency's Computer Retrieval of Information on Scientific Projects database: <http://crisp.cit.nih.gov/>. This is also a reasonable way to check whether a potential mentor is independently funded. A mentor's lack of funding from a peer-reviewed source should be a major red flag because it could compromise your own funding through the multiple mechanisms within the National Institutes of Health K-series and R-series awards aimed at young investigators.

Third, the project must have substance or "legs" of its own. This means it cannot be merely a cool experiment you're interested in doing. It has to be a series of experiments, and you have to be able to see what at least some of those experiments might be in the first year or so of your work. Having legs also means that you can envision yourself learning enough about this area to be a real expert in a few years. A good way to think about a question with substance is to read major journals such as this one, the *New England Journal of Medicine*, or *JAMA* and figure out what hypotheses the investigators tested or what questions their articles address. If you

cannot eventually envision articles such as those coming out of your work, then the question you are thinking of taking up is too small.

Fourth, your project or topic should identify you. Ideally, you should be able to occupy a niche in your department or school, and people should be able to say, a few years down the line: “Yes, that person is an expert in X.” This “X” may be something within the broad area of interest of your mentor, provided it is able to occupy a discrete niche. This can be difficult to achieve, but it is critically important and worth careful and open discussion. What will your seminars and presentations at national meetings be about? Why should people come to hear you talk?

Fifth, your question must be practical in the environment you are in. If the question you’re most motivated about has no local experts at all, you should probably pause, reconsider, and come up with a different idea or else actually go to a place where expertise in your area of interest is available. In fact, in this case, it would be reasonable to do some homework to determine the best location for pursuing this project. This process of exploration can help you to identify people who may well be your future competition, your future collaborators, or your future colleagues. By choosing an important research question, you are often choosing a community of friends and colleagues for a lifetime. If making a geographic move is necessary to pursue your research question, consider that it is a lot easier to move when you are young and at an early stage of your career.

This leads to the question of whether to choose a busy research area—that is, in an area such as treatment of hepatitis or breast cancer, in which thousands of researchers around the world are working hard to generate new treatments—or to opt for a less crowded area of investigation. If you have enthusiasm and the project appears to have a future, then either option is reasonable, but your geographic location does matter. If you want to work in a very busy field, it is really difficult unless you are located among people with the relevant expertise and who are “in the loop” and familiar with the latest developments, techniques, and discoveries. Outside of a big group it is extremely hard to keep up with a very busy field. In research areas such as these, it is a great challenge to be competitive if you are isolated. On the other hand, if you have the good fortune to be at an institution where there is broad expertise in such an area, then you are in a good position to be well informed, to be in the loop, and to find a discrete aspect of the larger picture where you can contribute.

Protection is also key to this process. It is important to choose and then insist on a research environment that allows you time to do research. Heavy clinical, teaching, or administrative burdens are common causes of academic failure, and you should be wary of any environment in which this is common. Red flags that signal such environments include the frequent moving of junior faculty to cover senior faculty’s clinical or teaching schedules and the placement of junior faculty in administrative positions as course directors, heads of training programs, or clinics. Perhaps the most common and egregious of these red flags is the frequent use of junior faculty to coauthor review articles, an activity widely looked down on by national research study sections and by all promotion and tenure committees but still widely practiced by senior faculty to generate reviews on their subjects of interest. These articles eat insidiously into protected time, rarely generate new scientific knowledge, and contribute much more to the reputation of senior investigators than to the careers of the junior faculty they purport to mentor. Academic environments in which this is common are not conducive to the generation of successful, independent investigators.

Lastly, a word about barriers. They will be put in front of you many times. One of the most common is the discovery that you don’t have the technique, expertise, toy (i.e., equipment), or skill necessary to answer a key question that logically follows from your work. This part is

about courage, gumption, or sheerchutzpah. You have to obtain that missing element. It can be got first by reading intensively and then by collaborating with the best possible people who have the missing skill, applying for a grant to fund it, or taking time to go to the appropriate place to learn about it. In this context, it is helpful to identify the person who knows most about and who is most skilled in the area in the world. Clinical science is truly more than just national; it is international, and it can be tremendously invigorating to be talking to the best people in the world about your area of research.

In conclusion, there are some key issues that need serious attention when you are setting out on a career in clinical research: your motivation, the novelty of your chosen field, its substance, its ability to provide you a niche, its practicality, and its conduct in a genuinely supportive environment. These issues hold the key to a quality career, one that generates exciting, novel, and effective therapies that can change lives.

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