Degrees of Freedom: Your Future in Biomedical Research

Biomedical research has never been so exciting, and opportunities for interdisciplinary and translational research are unprecedented. However, the percentages of PhD and MD-PhD scientists transitioning into sustained careers in academia is at an all-time low, and funding for basic research is uncertain. With these challenges facing us, how and by whom do we envision biomedical research being done in the future? What advice can we provide early career scientists as they set out to explore the increasing number of paths available to them? Two of us, one from the United States and one from Europe, provide our perspectives on the current and future state of the biomedical research enterprise and suggest how best to prepare oneself for an exhilarating but frequently challenging career in biomedical research.

During our careers we have witnessed dramatic technological and conceptual advances that have completely resculpted the biomedical research landscape. Scientific opportunities for trainees contemplating a career in basic and translational research are unprecedented. The ability to transcend disciplinary and geographic boundaries makes the adventure even more exciting for those who choose to pursue it. At the same time, however, data show that prospects for PhDs looking for faculty positions in the sciences are bleak, with estimates being that approximately 15% or less obtain academic positions as independent investigators in the United States, with much lower rates in some places in Europe, such as the United Kingdom at 3.5% (Powell, 2015). In the United States, the average age of obtaining a first National Institutes of Health (NIH) grant for investigators with PhDs is 42 years (NIH, 2012). Research-intensive medical schools in the United States are faced with financial pressures that could eventually limit the number of PhD scientist positions for which no "hard money" support is available were an individual to lose external sources of support. Prominent leaders in academia and research have suggested we are training too many PhDs in the United States, Europe, and Asia (Alberts et al., 2014; Cyranoski et al., 2011). However, doing research as an MD, with all of the associated competing responsibilities, presents its own challenges.

In light of these uncertainties, how does a person intent on biomedical research as a career decide on the best path for achieving this objective? What degree or degree combination provides the best opportunities? Will most biomedical research be done in the private sector, medical schools, institutes, or universities? In clinical or basic science departments? These questions are not easy to answer, because many unknown variables will factor into determining where, and by whom, research will be done in the next several decades. Changes in federal funding, possible reductions in the size of graduate programs, the willingness of clinical departments to hire PhDs, and even the future of tenure will all have an impact on the research profile of institutions. Similarly, there is not a single path to becoming a biomedical researcher. Indeed, the path is rapidly branching, but you may have more control over what that path looks like than you might think.

Before setting out on your journey, understand yourself

The primary driving force behind our decision to enter the world of academic research (decades ago) was the desire to figure out how stuff works. Today, the tools that are available for scientific exploration make the road to discovery an even more compelling and exciting one. The ability to translate these discoveries into clinically useful drugs and technologies that have impacts on human health is more possible today than ever before. However, the road can be challenging and sometimes treacherous. *Are you addicted to the rush that scientific exploration brings? Is your addiction strong enough to overcome the inevitable setbacks at the bench and beyond that, in the rat race of grant writing, mentoring, teaching, and administration?* If the answer is yes, read on for our tips on how to shape your own career path in research.

First, what sort of degree or degree combination is right for you?

Let's take the authors as an example. When we began our careers, neither of us thought about whether there would be a glass ceiling of sorts or a disadvantage to not seeing patients as PhD researchers. In part this is because neither of us envisioned ourselves so firmly entrenched at the

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interface of science and medicine, but here we find ourselves. So, if we could do it over again, what pros and cons would we see in getting that MD?[1]

Here are some considerations. First, having a combined degree gives one a skill set that is highly valued by clinical departments that engage in research, and the increasing emphasis on "translational" science makes MD-PhDs attractive as candidates for research positions, particularly in clinical departments. For some, the opportunity to be one of the pioneers who ushers in the golden age of translational research and a bridge between the sometimes disparate cultures of clinical and basic science is inspiring. In the United States in 2013, MD-PhDs fared better at obtaining highly prized NIH research program grants, with a 24.6% success rate for this group compared with 21.7% and 21.4% for single MD and PhD degrees, respectively NIH, 2014). Balancing the appeal of such a degree, the 8–9 years required to complete a typical Medical Scientist Training program poses a major disincentive for some. Then, once one has secured a faculty position, one must be sure to negotiate sufficient protected time to establish a robust and sustainable research program. In addition, there is a danger of being lured into clinical activities, with the resulting sense of accomplishment, at the expense of putting sufficient time into building a research program.

For those with a desire to focus on basic research without the distractions of clinical responsibilities, a classic PhD program holds a lot of appeal. This is the path we chose. These days it may be considered risky to have a single PhD degree in the academic setting of a medical school, with very little in the way of a safety net for those who do not have clinical credentials. However, in our opinion, the best PhD scientists have excellent career opportunities, including academic ones, if they plan smartly, are networked, and remain open to possibilities. Bipartisan support in the United States for programs such as Precision Medicine and the "Moon Shot" to cure cancer, highlighted in President Obama's January 2016 State of the Union address, signal renewed recognition of the importance of basic research as an investment in our efforts to ameliorate disease (State of the Union Address, 2016).

For those choosing the PhD-only path, being savvy increases the chances of a smooth ride

This begins with shaping a research program with the objective of defining a clear niche for oneself in an area that attracts sustainable funding. As an example, neither one of us came into our careers with any idea we would end up working in the area of skin biology. We both think of ourselves foremost as cell biologists trying to figure out how cells function within a tissue. However, it turns out that the skin offers us an outstanding opportunity to address fundamental questions in cell biology that are also disease relevant. And working in an organ system while keeping one's feet firmly planted in a basic discipline such as cell biology can be an incredibly exciting way to do science and a good career strategy as well. Keeping a toehold in both worlds by maintaining memberships in general (e.g., the American Society for Cell biology) and organ-specific (e.g., the Society for Investigative Dermatology) societies provides one with insights into both worlds that can be critically important in establishing transdisciplinary collaborations.

Being both a generalist and a specialist also opens up additional funding opportunities and a broader scope of committees in which research projects can be reviewed

As an example, in the United States, NIH applications are reviewed by one of a large number of study sections (committees) within the Center for Scientific Review, whose areas of expertise range from basic mechanisms of cell function to higher levels of human disease pathophysiology. If one studies keratinocyte functions in vitro, the investigation may be reviewed by one of a very few, highly competitive, cell biology study sections. However, studies of keratinocytes within their native environment, the skin, may be reviewed by the Arthritis, Connective Tissue and Skin section or, depending on the research question, one of several cancer-related study sections.

On the other hand, the issue of where best to target our research project applications can be a struggle for us as basic cell biologists, because we are driven to understand pathways and mechanisms, which means we are not necessarily wed to the skin. In fact, studying pathways in multiple tissues, and comparing and contrasting how these pathways are manifested in disease, can be revealing. One example comes from cardiocutaneous diseases caused by mutations in desmosome molecules that give rise to arrhythmogenic cardiomyopathy and a range of skin disorders. A recent study in the Green lab (Northwestern University) found that loss of function of one desmosome model in cardiac myocytes triggered the initiation of a fibrotic program in this cell type (Dubash et al., 2016). Although the pathway was intact in keratinocytes, the fibrotic program was not initiated because of a difference in degradation of a key junctional protein in one cell type versus the other. As cell biologists we are lured into looking at multiple models, which can lead to important insights but also comes with its own challenges. These include the increased cost of doing business and difficulty in finding a home institute (or even study section), because many institutes focus on specific organs. This is a challenge associated with the NIH extramural funding system and limits the insights that could be gained by looking at multiple organ systems.

For those at the interface of basic science and medicine, is it a handicap not to have direct clinical involvement with diseases relevant to one's research focus?

For us, the answer to this question is *no*. There are ample opportunities for PhDs to actively participate in bench-to-bedside sessions and translational activities. Training programs for PhDs are becoming increasingly tailored for introducing trainees to translational research and

[1] Note that we will not discuss the single MD degree in this piece. Although it is possible to have a research-intensive career with a single MD degree, in our opinion this route works for a small group of individuals who obtain extensive research training in other ways, and we do not advise it for most individuals desiring to do research heavily focused on basic science. We refer the reader to other reviews that provide guidance to this group of individuals (Payne and Brass, 2013).