

ESSAY

How to succeed in science: a concise guide for young biomedical scientists. Part I: taking the plunge

Jonathan W. Yewdell

Abstract | Biomedical research has never been more intellectually exciting or practically important to society. Ironically, pursuing a career as a biomedical scientist has never been more difficult. Here I provide unvarnished advice for young biomedical scientists on the difficulties that lie ahead and on how to find the right laboratories for training in the skills that you will need to succeed. Although my advice is geared towards succeeding in the United States, many aspects apply to other countries.

If you are contemplating pursuing a career in the life sciences, or have already embarked on one, you need to give some thought to your career prospects. So, take a study break, grab a cup of coffee and read on.

Unfortunately, I need to begin with some depressing facts. First, only a small minority of Ph.D. students will ever have opportunities to become principal investigators (PI) in academic settings and direct their own independent research programmes (FIG. 1). Second, even if you are among this elite group, the odds are that you will be well down the path towards retirement by the time you receive your first research project grant (R01) (the average age is 43) from the National Institutes of Health (NIH), the principal source of funding for biomedical research in the United States. Third, for your entire career as a PI, you will put inordinate efforts into writing grants. If you should ever lose funding, you will be at the mercy of your institution for your continued employment. Fourth, if you do achieve the 'Holy Grail' of full professorship then you will not be poor, but you will be far worse off financially than nearly all of your peers who have similar levels of talent, energy and dedication, but who chose other careers.

Your professors might tell you that this is the way it has always been, but this simply isn't true. Twenty-five years ago the situation

was much rosier. Scientists gained independence a decade earlier and funding, although never easy, was more reliable and accessible. Universities were more humane institutions where accountants had less influence over institutional priorities and decisions. Our current lamentable situation is fixable, and will have to improve significantly if the United States is to maintain its position as a leader in science and technology. A positive outcome is not guaranteed, however, and fixing the current mess will require the concerted efforts of scientists, university presidents and politicians to save the biomedical goose that has laid golden eggs for US biotechnology and health care for the past 50 years.

Science rocks

But there is good news too. Society desperately needs your talents. The future health, wealth and even survival of *Homo sapiens* depend on a deeper understanding of the laws and mechanisms of nature and on using this information to develop new technologies and therapies. For rationally thinking people with an altruistic bent, life can be no more rewarding than when practising the scientific method for the benefit of all of the denizens of this fragile planet. As a budding scientist, you are trained to expertly use the scientific method. That is, you learn how to wield the body of techniques that are used to identify

and investigate natural phenomena by formulating and rigorously testing hypotheses. The origins of the scientific method date back at least 1,000 years, and it is arguably the most important invention of civilized man. Armed with the scientific method, we can explore and understand nature to the limits of our intelligence. As a high priest of 'Scientific Methodism', you will be equipped for success not only in science and its allied occupations, but in virtually any career that requires rational decision making (and in some, such as politics, that ought to).

More good news: for individuals with a hunger for knowledge and an insatiable curiosity about how things work, science offers a constant challenge and, best of all, the intense thrill of discovery. What can match being the first person who has ever lived to know something new about nature? And not just the big, infrequent, paradigm-making (or breaking) discoveries, but the small, incremental discoveries that occur on a daily or weekly basis too. If this doesn't give you goosebumps and if you are not in a rush to get to the laboratory in the morning to find the results of yesterday's experiment, then you should seriously consider a non-laboratory career. Making discoveries is the core reward for the myriad of difficulties you will face in your scientific career (see Part II, in which I discuss making discoveries¹). Although it is possible to succeed in science even if you lack this passion for discovery, you will almost certainly be miserable and make your colleagues, friends and family wretched too.

Science has other perks. Contemporary science is one of the most communal activities ever pursued by humanity, and is among the most international careers possible. You will probably be interacting on a daily basis with scientists from all over the world, both in your laboratory and over the internet. Once established in your career, you can fly to dozens of cities across the globe and be greeted by a colleague that you either know personally or through reading each other's publications. You might even train a generation of researchers in your laboratory who will disperse around the globe to pass the torch of the scientific method to the next generation of their nation.

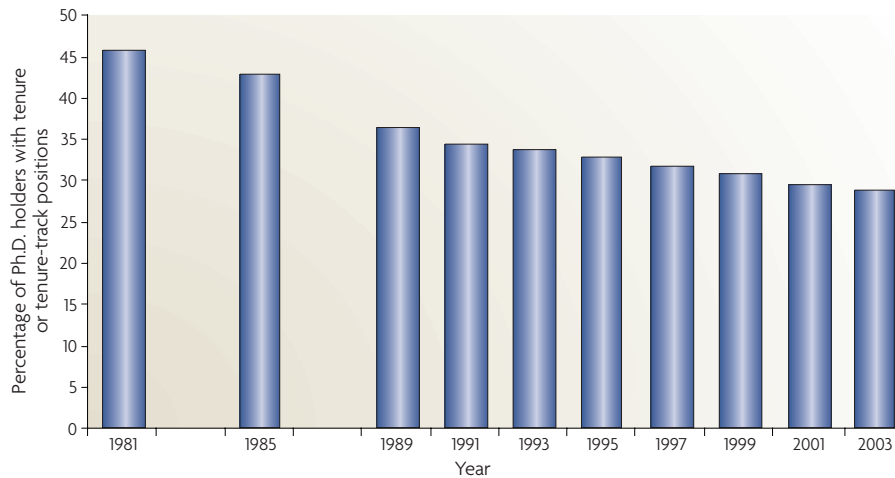


Figure 1 | The tenure track derails. The number of doctorate degrees awarded per year in the United States in the life sciences has increased more than threefold since 1966, whereas the number of tenured scientists has decreased slightly from a peak in 1981 (according to National Science Foundation data³). Consequently, in the past 25 years the fraction of Ph.D. holders with academic independent investigator positions has decreased steadily. The fraction of Ph.D. holders with tenure or tenure-track position is now ~30%. Graph reproduced from REF. 3 © (2007) FASEB.

This generational transfer of Scientific Methodism is, in fact, the most important and tangible achievement of a scientist. Discoveries are the joy and stock of our trade, but when your career is over (and probably well before this moment), few people will remember your brilliant papers. If you are successful (and lucky), you will have contributed a few lines to text books that future students will resent having to memorize. Through no fault of your own, and for reasons that you could not have anticipated, your discoveries might prove to be the artefacts that led your field in the completely wrong direction. You will be happiest in science if you are content with pursuing the truth to the best of your abilities and in passing the skills and insights you have developed to the next generation. Scientists who pursue fame are destined to be forgotten and forever dissatisfied with their achievements. In practical terms, peer recognition is needed only to maintain funding and to attract talented individuals to your laboratory who will make your daily laboratory life more productive and enjoyable. Beyond this, chasing fame is a waste of time that could be better spent on science itself, or on enjoying life outside the laboratory.

Getting started: graduate school

Choosing a graduate programme. Choosing a graduate school in which to pursue your Ph.D. should be largely based on the field that you would like to enter. Obviously, you should choose a programme that has a well-respected faculty. Size provides a

large number of advantages, including a larger number of potential mentors to choose from, more students and post-doctoral fellows who can become lifelong friends and colleagues, better chances for collaboration, greater access to reagents, techniques and specialist equipment, and a

more exciting intellectual environment. To minimize the insanely long ‘training’ period of your career, you should find a programme that takes pride in expeditiously awarding Ph.D. degrees. It should take 4 or 5 years for a decent student to finish a Ph.D., with an absolute upper limit of 6 years. Any longer than this and the student is either not suited for science or is being exploited by the mentor. Also, choose a department where the current Ph.D. students are treated as junior colleagues, with an eye towards their career development, and are not just exploited as inexpensive labour (small departments can be better in this respect).

Choosing a laboratory. Once you have chosen a school (or vice versa) to work in, your most important decision will be to choose a laboratory. The decision can be based either on the topic of research or on the mentor. I would strongly recommend the latter (BOX 1). Good scientists work on interesting and important topics, so a good mentor has this covered. Your goal as a graduate student is to become an expert in wielding the scientific method, and this can be achieved pursuing any project. The topic matters most in the types of experiments it entails. A good project will enable you to design, perform and analyse experiments on a routine basis,

Box 1 | On the innate superiority of rabbits over wolves

A rabbit is happily grazing one day when it is ambushed by a wolf.
 “Please don’t eat me Mr Wolf,” pleads the rabbit, “I haven’t completed my Ph.D.!”
 The wolf spits out the rabbit and laughs until he almost chokes.
 “Yeah right! A rabbit? Doing a Ph.D.? What about? Carrots? Duracell batteries? I just gotta hear this one!”
 The rabbit clears its throat and intones: “On the innate superiority of rabbits over wolves.”
 “That’s a crock for a start,” scoffs the wolf.
 “But I can prove it,” says the rabbit. “Come to my hole and I’ll show you my results, and if you still don’t believe me, then you can eat me. Deal?”
 “Sure. Can I have fries with that?” says the wolf, following the rabbit down the hole.
 But only the rabbit comes out.
 Months later the rabbit is grazing contentedly again when it meets another rabbit.
 “How’s tricks?” asks the friend.
 “Wonderful,” says our hero, “I’ve just submitted my Ph.D. dissertation.”
 “Congratulations! What’s it called?”
 “It’s called ‘On the innate superiority of rabbits over wolves.’”
 “Unbelievable — I mean, literally. Are you sure?”
 “Yes, I thought it was crazy at first too. But I’ve tested the model rigorously and that’s the result I get.”
 “Wow...”
 “Look, if you don’t believe me, why not come to my hole and I can show you the results?”
 “Of course, I’d love to!”
 So the two rabbits scurry down the burrow. In the first chamber is a workstation, covered with and surrounded by piles of books, papers, printouts and half-eaten carrots. In the second chamber are boxes and boxes of wolf bones, all catalogued and annotated. And in the final chamber, in a rocking chair, is a large and very satisfied looking bear.
 Moral: do your Ph.D. on any subject you like, provided you have a good supervisor.
 Posted on the [Nature Network](#).

ideally several per week, if not daily. This provides the best training and, importantly, is also the most fun. This will also develop your abilities to conceive the crucial controls that are needed to interpret the data in a meaningful way. 'Control creativity' is a central part of your scientific IQ; it comes only from the experience of designing and interpreting experiments. You should avoid projects that are largely based on using a single technique to develop a reagent or collect data (for example, generating a transgenic mouse).

Choosing a mentor. Although there is tremendous subjectivity in choosing a compatible mentor, there are a number of objective criteria (FIG. 2). Are the people in the laboratory happy and enthusiastic about their research? Have former students gone on to productive careers? Does the mentor treat students as junior colleagues and not as employees? Generally speaking, you should run from laboratories where a PI is referred to as Doctor X and not by his or her first name.

Frequently, you will have to choose between a small laboratory with a new investigator versus a large laboratory with a well-established scientist. Newly minted assistant professors will not have much of a track record as mentors; you might even be the first student they train. Still, you should seriously consider joining such a laboratory if the chemistry seems right. Although this has its obvious risks, you are a much more valuable commodity to a small laboratory, the survival of which could well depend on your personal success. Consequently, you will get more intense mentoring and will probably be working side-by-side with the PI. The best situation is to be the first Ph.D. student of a rising star, for you will be maximally productive, will generate well-developed ties to your field and will have an influential champion for years to come (although because academic 'star' formation is an inexact science, this often takes some luck).

Skills, not papers. Contrary to what you might have heard, it is not critical to have a spectacular publication record from your Ph.D. When the time comes to apply for a tenure-track job, the selection committee will focus on the productivity and promise you displayed during your postdoctoral fellowship. Furthermore, a solid Ph.D. with one good first-author paper that is based largely on your own work is all that is usually required to obtain the postdoctoral position of your dreams, particularly for citizens of



Figure 2 | **The nine types of principal investigator.** This cartoon was kindly provided by Alexander Dent, <http://dentcartoons.blogspot.com>.

the United States, who are in short supply at this level. Your focus as a graduate student should be to develop all of the skills you will need to be an independent scientist.

At some point as a graduate student you will need to take responsibility for all aspects of your career and develop the skills of an independent scientist. You need to develop confidence in your ability to make discoveries and learn new techniques, so that you will not be limited later in your career when your findings lead you to new and unexpected areas (see Part II (REF 1)). You need to do the background reading to place your results in their proper context and determine the next step in the project. You need to learn how to present a seminar in which you convey not only the data and conclusions, but also your depth of knowledge and enthusiasm for your field of research. Such public-speaking skills are critical for peer recognition of

the impact of your research, for recruiting students and fellows to your laboratory, and for effective teaching. Most importantly, you need to learn how to write concisely and lucidly², for without this skill, you will not be able to raise grant money or place your papers in high-impact journals.

Step two: postdoctoral fellowship

In many ways the most important decision on the PI career path is where you do your postdoctoral fellowship. It should be in a field in which you envisage starting your independent career, the success of which will be almost entirely dependent on your ability to attract funding. As a newly independent scientist, study sections will be loath to fund you to embark on a project that is not a direct continuation of your postdoctoral studies. This also means that you will need access to the reagents you developed as a postdoctoral

fellow. You will also need the blessings of your mentor and, optimally, your mentor should actively support your nascent career. So, in choosing your postdoctoral mentor, it is critical to determine whether a mentor enthusiastically supports, both materially and psychologically, the careers of their fledglings. This is easier to determine if the mentor is an established scientist with a pedigree. Established scientists will also be able to offer laboratories with a greater variety of expertise, reagents and greater financial resources, all of which will help you establish an independent line of research for you to parlay into an independent career.

It is essential to visit the laboratories that interest you to gauge the productivity, independence and happiness of the students and postdoctoral fellows. It is a good idea to contact scientists who have left the laboratory to obtain their honest opinion of their experience (in laboratories headed by evil mentors, this might be the only way to ascertain their pathology, as the current laboratory members may be too intimidated to express negative opinions). If the laboratory won't pay your travel expenses, then this does not augur well, as it indicates either limited financial resources or stinginess. All things being equal, it is advantageous to work at larger, wealthier institutions where there will be better access to expensive, state-of-the-art instruments and core facilities, greater overall intellectual ferment, more laboratories for collaboration and a better chance to impress other established scientists, who can write the crucial recommendation letters for getting your tenure-track application into the interview round. Sometimes, however, all things are not equal, and if the best mentor is at a smaller institution, this will do just fine.

What is it going to take?

Perspiration. Success in science will require a major commitment of your body and soul. As a graduate student, you should be spending a minimum of 40 hours per week actually designing, performing or interpreting experiments. As there are many other necessary things to do during the day (for example, reading the literature, attending seminars and journal club, talking to colleagues both formally and informally, and common laboratory jobs), this means you will be spending 60 or more hours per week in science-associated activities. The key to success and happiness is that most of this should not seem like work. If the laboratory is not the place you'd most like to be, then a career as a PI is probably not for you. At the postdoctoral level

you will have to work at least as hard, but your most intense effort will actually begin as a tenure-track faculty member, when you are expected to fund your research (and at least some of your salary too), teach undergraduates as well as graduate and professional students, serve on committees and run your laboratory, which itself entails learning an entirely new set of skills (such as accounting, diplomacy and psychology). Ironically, you will have more to learn as a fledgling professor than as a postdoctoral fellow. Until you are well into your career, there will be time in your life for just one additional significant activity (family, active social life with friends, a sport or a hobby), but probably not for much more than that.

Talent. Enthusiasm and effort are necessary but not sufficient for a successful scientific career. Talent is a key part of the equation, and at some point in your career (not necessarily as a graduate student), you will need to objectively assess your skills and potential relative to your peers. The inexorable weight of the scientific career pyramid squeezes out all but the most talented from getting the tenure-track job that will offer you the chance of establishing your own laboratory. Furthermore, the insanely competitive funding situation is making the previously safe transition between tenure-track and tenured professor a far dicier proposition. Scientific talent is not a single parameter, but a complex mix of innate and learned skills and abilities. Deficiencies in one area can be offset by strengths in another. Some scientists achieve success by their experimental skills or insights, others by their management or political skills. There is no one path to success and each successful scientist has unique combinations of strengths (and weaknesses).

If, for whatever reason, you decide that you are better suited for life outside the laboratory, there are numerous career alternatives. Neither you nor your mentor should consider this outcome a failure. It is unfair, and even irresponsible for mentors to expect trainees to emulate their own career paths. Each mentor has only to train a single replacement to maintain the PI population at equilibrium. Even with robust growth in NIH-funded biomedical research (which is unlikely in the foreseeable future), the current investigator-to-trainee ratio dictates that most trainees will pursue careers that differ fundamentally from those of their mentors.

Networking plays a key part in providing information about potential alternative careers and in landing such jobs. Alumni of the laboratories and departments you have

worked in are the most proximal source of networking partners. E-mail has opened a great portal into the academic community for initiating contacts that can be deepened by follow-up telephone conversations. It can be difficult to penetrate the corporate world by this path, but conferences provide ideal circumstances for meeting scientists out of the academic mainstream who can provide insight, advice and even job opportunities. It might be possible during your postdoctoral fellowship to develop your skills and attractiveness to potential employers by moonlighting or volunteering in the career path you are contemplating.

Final thoughts

So, your cup of coffee should be finished by now. Please don't be discouraged, but give some thought to your career path. If you are talented and passionate, you will have a good chance of becoming a PI; particularly in the United States, which still provides great opportunities for truly independent entry-level positions. If the trials and tribulations of being a PI aren't for you, there are many other ways to use your scientific training to make a decent living and a valuable contribution to society. Now get back to work.

Jonathan W. Yewdell is at the
Laboratory of Viral Diseases,
National Institute of Allergy and Infectious Diseases,
Bethesda, Maryland 20892, USA.
E-mail: JYEWDELL@niaid.nih.gov

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FURTHER INFORMATION

Jonathan W. Yewdell's homepage:
<http://www3.niaid.nih.gov/labs/aboutlabs/lvd/cellBiologyAndViralImmunologySection/BenninkYewdell.htm>
Graduate student resources on the web:
<http://www-personal.umich.edu/~danhorn/graduate.html>
Making the right moves: a practical guide to scientific management for postdocs and new faculty, second edition:
<http://www.hhmi.org/catalog/main?action=product&itemld=313>
Nature Network: <http://network.nature.com>
Resources for graduate students and post-docs: a compilation:
http://www.indiana.edu/~hallab/grad_resources.html
Richard Hamming: you and your research:
<http://www.paulgraham.com/hamming.html>
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ESSAY

How to succeed in science: a concise guide for young biomedical scientists. Part II: making discoveries

Jonathan W. Yewdell

Abstract | Making discoveries is the most important part of being a scientist, and also the most fun. Young scientists need to develop the experimental and mental skill sets that enable them to make discoveries, including how to recognize and exploit serendipity when it strikes. Here, I provide practical advice to young scientists on choosing a research topic, designing, performing and interpreting experiments and, last but not least, on maintaining your sanity in the process.

You're back for more advice, despite my best efforts in Part I (REF. 1) to paint the bleakest possible picture of career prospects in biomedical research? Well, I am delighted you haven't enlisted in the French Foreign Legion just yet. In fact, it's a great pleasure to welcome you as a fellow practitioner of 'Scientific Methodism'. Your mission now is to discover something completely unexpected about how cells or animals work. You might think that such surprises top nearly every scientist's 'to do' list, but this is not the case. The present culture in biomedical research favours conservative science, which essentially entails refining accepted models.

Swim against this current. Your mission as a scientist is to discover how current models are wrong, not right, and to create new paradigms. When you succeed, you will have to fight to publish and fund your research. However, if you persist (and are actually right) then the world will eventually come around to your point of view. At this point, your mission will be to expose the flaws in your new paradigm, and so on. The best part of your newly chosen career is that you will never have to worry about running out of things to discover.

Choosing a project

Experience counts. To make a discovery you'll first need to choose a research project. As a graduate student, it is wise for the principal

investigator (PI) to choose the initial project, or at least play a major part in choosing the project. You simply don't have the experience and judgment at this point to choose an interesting project with a significant chance of success. At a postdoctoral level, the decision is more conditional. If you are continuing in the field of your Ph.D. studies, you should be capable of choosing a good project. If it is a new field, however, your advisor will need to provide guidance as to what is feasible and interesting.

Make the most of your surroundings. In choosing a project, it is crucial to exploit the intellectual and physical resources of your immediate surroundings. This does not just mean that you should plough the same furrow that the laboratory has already seeded and harvested. Introducing new techniques and approaches to your laboratory provides many advantages. For example, you will gain confidence in your ability to follow up your findings wherever they lead. It is much easier, however, when you can learn from

“ The best part of your newly chosen career is that you will never have to worry about running out of things to discover. ”

the expertise of neighbouring laboratories. Imagine, for example, that your institution has a first-rate confocal microscope facility, but that confocal microscopy has never been applied to the major research interest of your own laboratory, even though it has a number of obvious applications. Should you take advantage of the situation? Of course! An extreme example to be sure, but many projects have foundered before they started because of the sheer impossibility of gaining access to the requisite technology or reagents.

Basic or applied research? There is an important dichotomy between applied and basic research. Funding agencies put a tremendous emphasis on applied research, which is clearly important, as it is the sole means of translating discoveries into therapies. However, applied research is based on the knowledge at hand, regardless of whether it is sufficiently sophisticated to have a reasonable chance of improving existing therapies. Furthermore, applied research is far less likely than basic research to lead to serendipitous findings that will provide novel insights into unexpected quarters. The nature of applied research is such that if a clinical trial does not work, the project is usually kaput. By contrast, biology is such a complex tapestry woven from a myriad of components and pathways that, with some patience, properly performed basic research will always lead to interesting discoveries. The problem is that translating these discoveries into therapies is often indirect, and invariably requires decades. This requires a level of patience from funding agencies that is difficult to maintain in the face of political pressure to provide immediate therapies and cures.

Big or little questions? Although it is a good idea to avoid following the herd, don't shy away from pursuing important questions, which by their very nature will attract the attention of other laboratories. It is usually no more difficult to work on something interesting and important than it is to work on something of limited interest that will be difficult to publish and fund. Ideally, you will be far ahead of the pack and won't have to worry about direct competition until you spill the beans about your great findings.



Figure 1 | **Another reason for small experiments.** This cartoon was kindly provided by Alexander Dent, <http://dentcartoons.blogspot.com>.

Having such a lead isn't always possible, but you should always aim to have a novel approach to your research question, even if your approach is a bit oblique.

Designing experiments

Ideas: they don't come from storks. Most graduate students have had minimal independent research experience and will depend heavily on their advisors (or on the postdoctoral fellows that they are teamed up with) to get a feel for designing experiments. Within their first year full time at the bench, however, students should be designing their own experiments. Experimental design encompasses many parameters. The most important, of course, is the hypothesis the experiment is designed to test. For this you need to have an original idea. But where do ideas come from?

Although really good ideas seem to come from nowhere (at the same time, they also seem obvious after the discovery), they are seeded by information from external sources. The key concept is cross-pollination. Talk to your fellow students and more senior scientists in your department and at meetings. Discuss your (and their) research. Commonly, ideas and techniques that are standard in one field are novel in another, and their application can lead to breakthroughs. Read widely, but not necessarily deeply. Scan the major journals; if the title is interesting then read the abstract. Still intrigued? Read

the discussion. Only if the paper seems relevant should you actually look at the data and then carefully read all of the sections. While on this topic, reading the methods sections of irrelevant papers can give you good ideas about how to improve your experimental protocols or can suggest novel strategies to attack your problem. You should also attend seminars in other disciplines, but sit near the back and beat a strategic retreat if the talk turns out to be of little interest.

Box 1 | On fraud

Science always has been, and always will be, tarnished by fraud. Scientific fraud is ultimately self-correcting, but it wastes precious human and material resources. Fraud harms or even kills people when it involves clinical research. Fraud undermines society's faith in the integrity of science, and threatens public support of science and the scientific method.

Extreme competition for funding brings out the worst in human nature. When scientists' careers are on the chopping block with each paper or grant rejection, even good people can succumb to temptation. Fraud encompasses much more than pure black-and-white fabrication: it includes fudging data and cherry picking experiments to support the most convenient conclusion (this topic is treated wonderfully in the novel *Intuition*, by Allegra Goodman³).

Sooner or later in your career, you will suspect the legitimacy of a colleague's data. You are obliged to expose fraudulent activities, but you must do so in a careful, considered and deliberate manner. Being unable to reproduce the findings of others does not necessarily mean that the findings are fraudulent. Some experimental systems are exquisitely finicky. Some scientists are more skilled than others.

If you are convinced that fraudulent activity has occurred in your laboratory or in another laboratory, the first step is raise the matter with your principal investigator (PI). If you are not satisfied with the response of your PI, you should approach a different, sympathetic PI in your department, and ultimately the Chair. Still not satisfied? Contact the Office of Scientific Integrity or the responsible Dean or administrator.

You should be aware that with each step of the process, the stakes for everyone involved (including you, the whistle-blower) are magnified, and scientific careers can be destroyed.

Growing your wings. There is nothing like enthusiastic naiveté to seed a discovery. Knowing too much about a topic can actually be a barrier to discovery. Experiments that experts know won't work sometimes do, because either the experts' assumptions are wrong, or new reagents or technologies became available that allow nature to be queried in a new way. Imagine you have just read the latest issue of *Nature Reviews Molecular Cell Biology* and are struck with a stupendous idea. You excitedly barge into the office of your PI and propose your killer experiment. She spends the next 30 minutes explaining in excruciating detail, with impeccable logic, why the experiment not only can't possibly work, but will be uninterpretable if it does. Dejected, you stumble from the office in a haze of self-recrimination and doubt. But then, while cycling home, you regain your bravura and decide that you are going to do the experiment anyway.

This is exactly the right attitude that you should have. It is crucial during your training that you develop confidence in your insight and learn to think independently of your mentor (in the wise words of my first mentor, "the outcome of the perfect training experience is that you leave the laboratory thinking that your mentor is a good person, but a bit dumb"). So you do the experiment, and 95 times out of 100 the experiment doesn't work. Don't freak out. Here's a secret from the PI world: if you don't tell us, we won't know that you even did the experiment. When I walk through my laboratory, I have no idea what the postdoctoral

Box 2 | Conclusions are conditional

A mathematician, a biologist and a physicist are sitting in a street café watching people going in and coming out of the house on the other side of the street.

First they see two people going into the house. Time passes. After a while, they notice three people coming out of the house.

"The measurement wasn't accurate," says the physicist.

"No, no," says the biologist, "they have reproduced."

"I don't think so," says the mathematician. "If exactly one person now enters the house, then it will be empty again."

This joke was posted on [Profession jokes](#).

fellows are doing. I know what experiments they've done recently, and what we discussed they should probably do next (it's their decision), but on a day-to-day basis, I really don't know. Just watching them pipetting something or looking into a microscope, whatever the purpose, puts a smile on my face — they might discover something today!

So when the experiment doesn't work, put the data in your notebook (the failure will probably be useful down the road) and don't tell your PI. On the rare occasion when the experiment gives you a glorious result, you will have the great pleasure of strolling into the PI's office with a broad grin on your face and asking (magnanimously, of course) whether they would care to see the data from the 'experiment that would never work'. Only a control freak PI (see figure 2 in Part I (REF. 1)) could fail to share your joy and excitement. In fact, when you are a PI yourself be careful when discouraging your mentees from performing experiments, no matter how spectacularly flawed they might seem. There is simply no substitute for enthusiasm in science, and you douse it both at your own peril and at the peril of those whose careers are your responsibility.

Size matters. Having a good idea (or even a bad idea, sometimes any idea will do, as they can all lead to serendipity) is only the start. Designing experiments is an art that you will continue to improve for as long as you work at the bench or supervise those who do. The size of the experiment is crucial (FIG. 1). It should be just large enough to have a sufficient number of repeat samples and positive and negative controls for you to interpret the results with confidence. Small experiments are much more likely to work than big ones, as there is less to go wrong. Furthermore, no matter how much thought you give to the experiment, the crucial controls will occur to you after doing the experiment, typically only after many repetitions, if at all. Rare is the scientist who has not been confronted with an essential control when the work is presented in a seminar or for publication. By doing a series of small experiments with constant modifications based on each preceding experiment, you will progress much more rapidly than by performing larger experiments that try to anticipate all of the problems and possible outcomes. An important psychological advantage of small, rapid experiments is that failure (the typical fate of new experiments) is much less depressing than after spending huge amounts of time and energy in a much larger but equally unsuccessful effort.

Doing experiments

Golden eyes. Every well-established laboratory has a 'Hall of Fame' of legendary alumni with 'golden hands'. Golden hands? Golden eyes is closer to the mark. Experimental science does not demand the dexterity of neurosurgery, but it does demand the neurosurgeon's focus on the task at hand. The key to being a good experimentalist is obsessive attention to detail. They are constantly thinking about the matter at hand (and not about dinner, their next work-out or the cute student in the next laboratory). They constantly use their eyes to monitor every relevant detail. For example, is the water bath too hot? Is the CO₂ setting in the incubator correct? Is the buffer cloudy or off-colour? In cell-based experiments, the golden eyed pay close attention to the cells. They have a feel for how cultured cells look when they are thriving and for how to keep cells in tip-top shape for each experiment. They are constantly scrutinizing the cells during the experiment, even using the microscope when convenient to monitor cell happiness (and to make the odd discovery based on the macrobehaviour of cells). They notice the size, colour and texture of the cell pellets and how they disperse. Details, details, details!

Good experimenters understand every part of an experiment (including buffer and detergent selection) and quickly learn to recognize which are the most important aspects of an experiment and which steps can be shortened or even discarded. While doing the experiment they are already planning how each step could be improved or done more efficiently (doing things more quickly allows more samples to be included or more experiments to be performed, and can be crucial for making discoveries).

Although the repetition of experiments is an essential step to gain confidence in a finding, it is a poor experimenter who does not frequently make at least minor changes to their protocol. In fact, making the same finding after modifying an experiment bolsters the validity of the finding. Above all, as an experimental scientist, you must be certain that your observations are reproducible (BOX 1).

Laboratory notebook: the scientist's best friend. An essential part of each experiment is to record accurate and appropriately detailed notes. Start each experiment entry with a statement regarding the hypothesis you are testing. In describing your actions, make sure you include all of the unique details of the experiment that you will need in order to repeat it. Those who don't heed

this advice are fated to make an incredibly exciting finding that they will never be able to repeat. Believe me, this really hurts.

Record the important events that occurred that will help you interpret your findings (such as when the centrifuge tube cap flew off in the centrifuge and (Argh!) weird material collected in your cell pellet). Neatly write or tape data into your notebook. After careful thought, force yourself to write a conclusion: what went right, what went wrong, how does your hypothesis look now and what is the next step. Writing the conclusion is important — it is all too easy to fall into the trap of working hard without thinking hard. If you are going to be an independent scientist, you must do both.

There is an element of luck behind most great discoveries. Your luck will be proportional, however, to the number of well-conceived and expertly performed experiments that you execute and on how prepared your mind is to process unexpected findings. As famously attributed to Louis Pasteur, one of the greatest experimentalists of all time, "Dans les champs de l'observation, le hasard ne favorise que les esprits préparés" (in the fields of observation, chance favours only the prepared mind).

Interpreting experiments

Think big. Discoveries are not physical entities, but the products of cogitation. Making discoveries is the best part of science: it hooks you as a student and never lets you go. Some discoveries hit you like a frying pan and don't require a huge amount of thought. These are a real kick, so enjoy the initial glow because sooner or later doubts will tarnish your bright, shiny, discovery as you carefully consider its implications. Other discoveries are more subtle, at least given our mindset, which is hobbled by existing paradigms. To break

Box 3 | **Staying happy and sane in the laboratory**

- Your default opinion of others should be that they, like you, are sincere, well meaning individuals. Assume that dust-ups stem from an easily resolved misunderstanding. Wait before confronting. Most problems solve themselves in a few days. If not, patiently plan a conservative course of action. For advice, consult senior members of the laboratory or department. Involve your principal investigator (PI) only when absolutely necessary. Why? Whatever the issue, it will probably not reflect well on you, regardless of your innocence. Having the PI intervene will permanently mar your relationship with the other laboratory member and negatively affect laboratory esprit.
- Never write an emotional e-mail: have your confrontations on the phone or, better still, in person, as you will have the benefit of visual clues that will allow you to determine the effect of your words on your antagonist. Because of the imperfection of memory, spoken words (unlike written words) remain shrouded in the mists of uncertainty.
- Your career will be much easier if you develop a thick skin. You should embrace valid criticism, because it can improve your science and qualities as a scientist and a person. Of course, not all criticism is valid. With time you will develop a sense for legitimate criticism that needs to be addressed, and other criticism that should be ignored (with no malice to the source).
- If possible, avoid intra-laboratory romances, which typically lead to awkward break ups. Yes, only another scientist will truly understand you, but try to find your soul mate in another laboratory!
- Daily exercise will enhance your energy levels and improve your mood. No matter how brief or easy the workout, it is better than no workout at all. Vacations are essential to maintain your mental health and enthusiasm for science. Get as far away from laboratory life as possible and stay away from your e-mail!

the shackles of convention, the first thing you should do with fresh data is to come up with the most interesting possible interpretation of the results. This has several benefits. First, occasionally, you will actually be right. A surprising number of great discoveries were missed by previous investigators who made the same findings but never made the intellectual leap. Go to enough meetings and you will hear somebody lament “Oh, we saw that too, but didn’t make anything of it”. Second, even when the most interesting interpretation is wrong, thinking creatively will help you to place your findings in their proper context and will pay large dividends in designing and interpreting future experiments. Third, it is fun, particularly if it leads to brain storming with your mentor and other members of the research team.

Repetition trumps p values. Experiments have two general outcomes. Either they are interesting or they aren’t. If they are interesting, you need to repeat them to the point where you are sure they are correct. It is far better to repeat a given phenomenon in a series of slightly imperfect experiments than to rely on a single experiment with perfect replicates that yield impeccable p values. Although statistics are important, don’t be blinded by them — they are only as good as the assumptions they are based on. Statistically significant differences between samples only mean that something was different between the samples. The something might be the thing you were testing, or

it might be something you didn’t consider, like the temporal or spatial order in which you set up the samples.

Yes you can! You’ve done a superb experiment and your brilliant and subtle interpretation has led to an important discovery. This step actually trips up many young scientists, who lack the confidence to believe that their own two hands and brain could achieve such a thing. You need to get over this attitude immediately. Although oversized egos are as big a problem in science as in any profession, you need a healthy ego to be successful in science. You have got to believe that you have good ideas and can make an important contribution to your field (and don’t fret, it’s really true).

Embrace serendipity. What if your great discovery is not on the list of specific aims? Frequently, the best discoveries are serendipitous. Serendipity is easiest to embrace if it provides insight into your question of interest, but it often leads you into other fields. You should seriously consider pursuing these leads, but the final decision will have to be made by your PI. After all, it is your PI who is paying the bills. When you are a PI, these will be some of your more difficult scientific decisions. When you are in this position, remember that an excursion into a new field need not be permanent, but can be an exploratory expedition that may or may not lead to a permanent shift in direction.

Avoid the P-word. Without going off the philosophical deep end, it is useful to occasionally step away from the trenches of day-to-day research and contemplate the nature of discoveries. Observations are statistical phenomena that can be verified beyond a shadow of doubt. For example, a dead mouse is really and truly dead. By contrast, conclusions are the product of human thought based on an existing theoretical framework that is imposed on a system (that is, nature) that is inchoate and therefore essentially unknowable — for inspiration, see Huxley’s translation of Goethe’s view of nature (the system), which is the opening essay in the very first issue of *Nature* (the journal)². Conclusions, therefore, are conditional; they are always wrong or incomplete in some manner, it’s just a question of the degree to which they are incomplete (BOX 2). Do not fall into the all too common habit of stating that your findings ‘prove’ a given conclusion. They don’t, and thinking this way closes your mind to alternative explanations and future discoveries.

Remember — science should be fun

Well, that’s about it. Here’s one last bit of advice — science is much more enjoyable and productive when it’s fun (BOX 3). Maintain your sense of humour, particularly about yourself. Above all, pass on the joy of science to the next generation.

Now go and discover something that shocks everybody and makes your mother proud.

Jonathan W. Yewdell is at the Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland 20892, USA. E-mail: JYEWDELL@niaid.nih.gov

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FURTHER INFORMATION

Jonathan W. Yewdell’s homepage:
<http://www3.niaid.nih.gov/labs/aboutlabs/lvd/cellBiologyAndVirallmmunologySection/BenninkYewdell.htm>
Profession Jokes:
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