How to succeed in science: a concise guide for young biomedical scientists. Part II: making discoveries [1]

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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 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. 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.

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 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 macro-behaviour 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 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.

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.

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