



A short guide to technology development in cell biology

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New technologies drive progress in many research fields, including cell biology. Much of technological innovation comes from “bottom-up” efforts by individual students and postdocs. However, technology development can be challenging, and a successful outcome depends on many factors. This article outlines some considerations that are important when embarking on a technology development project. Despite the challenges, developing a new technology can be extremely rewarding and could lead to a lasting impact in a given field.

As is true for many fields of research, cell biology has always been propelled forward by technological innovations (Botstein, 2010). Thanks to these advances we now have access to microscopes and other equipment with exquisite resolution and sensitivity, a variety of methods to track and quantify biological molecules, and many ingenious tools to manipulate genes, molecules, organelles, and cells. In addition, we have hardware and software that enable us to analyze our data, and build models of cells and their components.

Naturally, even today’s technologies have limitations, and hence there is always need for improvements and for completely novel approaches that create new opportunities. Cell biology is one of the research areas with many chances for individual young scientists to invent and develop such new technologies. Numerous recent examples illustrate that such “bottom-up” efforts can be highly successful across all areas in cell biology; e.g., as a handy vector for RNA interference (Brummelkamp et al., 2002); as methods for visualization of protein–protein or protein–DNA interactions (Roux et al., 2012; Kind et al., 2013); as tools to study chromatin (van Steensel et al., 2001), ribonucleoprotein complexes (Ule et al., 2003), or translation (Ingolia et al., 2009); or as tags for sensitive protein detection (Tanenbaum et al., 2014), just to name a few examples.

As a student or postdoc, you may similarly conceive an idea for a new method or tool. Usually this idea is inspired by a biological question that you are trying to address in your

ongoing research project. You might then also realize that the new method, at least on paper, may have additional applications. Yet, the development of a new technique typically requires a substantial effort. Should you halt or delay your ongoing research and embark on the development of this new technique? And if so, what is the best strategy to minimize the risks and maximize the chance of success? How do you get the most out of the investment that it takes to develop the method? Here I will discuss some issues that students and postdocs might want to consider when venturing into the development of a new technique.

To develop or not to develop

Development of a new technique can take one to five years of full-time effort, and hence can be a risky endeavor for a young scientist. The decision to start such a project therefore requires careful weighing of the pros and cons (see text box). In essence, there are four main considerations.

First, conduct a thorough literature survey to ensure that the method has not been developed by others already, and to search for indications that the method may or may not work. The second consideration is the potential impact of the new technology. Impact is often difficult to predict, but it is linked to how broadly applicable the technology will be. Will the new technology only provide an answer to your specific biological question, or will it be more widely applicable? It may be helpful to ask: how many other scientists will be interested in using the technology, or at least will profit substantially from the resulting biological data or knowledge? If the answer is “about five,” then the impact will likely be low; if the answer is “possibly hundreds,” then it will certainly be worth the investment. This potential impact must be balanced against the third consideration, which is the estimated amount of time and effort it takes to develop the technology. The fourth major consideration is: What is the chance that my technique will actually work and what is the risk of failure? There is no general answer to this question, but below I will outline strategies to reduce the risk of failure and minimize the associated loss of time and effort. For this I will consider the common phases of technology development (Fig. 1).

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Points to consider before starting to develop a new technology.

- Literature search: Does a similar technology already exist? Is there published evidence for or against its feasibility?
- How much time and effort will it take?
- What is the chance of success?
- Are you in the right environment to develop the technology?
- Are simple assays available for testing and optimization?
- How important are the biological questions that can be addressed?
- How broadly applicable will the technology be?
- What are the advantages compared with existing methods?
- Is the timing right (will there be substantial interest in the technology)?
- Is there potential for future applications/modifications that will further enhance the technology?
- How easy will it be for other researchers to use the technology?

Quick proof-of-principle

An adage that is often heard in the biotechnology industry is “fail fast.” It is OK if a project turns out to be unsuccessful, as long as the failure becomes obvious soon after the start. This way the lost investment will be minimal. In an academic setting, it may also be good to prevent finding yourself empty-handed after years of work. As a rule of thumb, I suggest that one should aim to obtain a basic proof-of-principle within approximately four months of full-time work. If after this period there still is no indication that the method may eventually work, then it may be wise to terminate the project, because further efforts are then also likely to be too time-consuming. It is thus advisable to schedule a “continue/terminate” decision point about four months after the start of the project—and stick to it. Note that at this stage the proof-of-principle evidence may be rudimentary, but it is crucial that it is convincing enough to be a firm basis for the next step: optimization.

Optimization cycles

Obtaining the first proof-of-principle evidence is a reason to celebrate, but usually it is still a long way toward a robust, generally applicable method. Careful optimization is required, through iterations of systematic tuning of parameters and testing of the performance. This can be the most time-consuming phase of technology development. To keep the cycle time of the iterative optimizations short, it is essential that a quick, easy readout is chosen. This readout should be based on a simple assay that ideally requires no more than 1–2 d. It is important that the required equipment is readily accessible; for example, if for each iteration you have to wait for several weeks to get access to an overbooked shared FACS or sequencing machine, or if you depend on the goodwill of a distant collaborator who has many other things on his mind, then the optimization process will be slow and frustrating. If your technology consists of a lengthy protocol with multiple steps, try to optimize each step individually (separated from the rest of the protocol), and include good positive and negative controls.

Remember that statistical analysis is your ally: it is a tool to distinguish probable signals from random noise and thus enables you to make rational decisions in the optimization process (did condition A really yield better results than condition B?). Assays with quantitative readouts are easier to analyze statistically and are therefore preferable.

Version 1.0: Reaping the first biological insights

During the optimization process it is helpful to define an endpoint that will result in “version 1.0” of the technology. Typically this is when the technology is ready to address its first interesting biological question. Once you have reached this point, it may be useful to temporarily refrain from further optimization of the technology, and focus on applying it to this biological question. This has two purposes. First, it subjects the technology to a real-life test that may expose some of its shortcomings, which then need to be addressed in further optimization cycles. Second, it may yield biological data that illustrates the usefulness of the technology, which may inspire other scientists to adopt the method. If you are based in a strictly technology-oriented laboratory, collaboration with a colleague who is an expert in the biological system at hand may expedite this phase and help to work out bugs in the methodology.

If version 1.0 performs well in this biological test, it may be time to publish the method. For senior postdocs, this may also be a good moment to start your own laboratory. A new technology is usually a perfect basis for such a step.

Disseminating and leveraging the technology

When, upon publication, other scientists adopt your new technology, they will often implement improvements and new applications, which makes the technology attractive to yet more scientists. This snowball effect is one of the hallmarks of a high-impact technology. An extreme example is the recently developed CRISPR–Cas9 technology (Doudna and Charpentier, 2014), for which improvements and new applications are currently reported almost on a weekly basis. What can you do to get such a snowball rolling?

First, it helps to publish the new technology in a widely read or Open Access journal, to present it at conferences, and to initiate collaborations in order to reach a broad group of potential users. Second, the threshold for others to use the new technology must be as low as possible. Thus, implementation of the technology must be simple, and users must have easy access to detailed protocols. A website with troubleshooting advice, answers to frequently asked questions, and (if applicable) software for download will also help. Depending on the complexity of the technology, it may be worth considering whether to organize hands-on training, perhaps in the form of a short course. This may seem like a big investment, but it can substantially contribute to the snowball effect.

Third, materials and software required for the technology should be readily available. Technology transfer offices of research institutes often insist on the signing of a material transfer agreement (MTA) before materials such as plasmids can be shared. But all too often this leads to a substantial administrative burden and delays of weeks or even months. Free “no-strings-attached” sharing of reagents is often the best way to promote your technology—and scientific progress in general.

Patents and the commercial route

Before publication of the technology, you may consider protecting the intellectual property by filing a patent application.

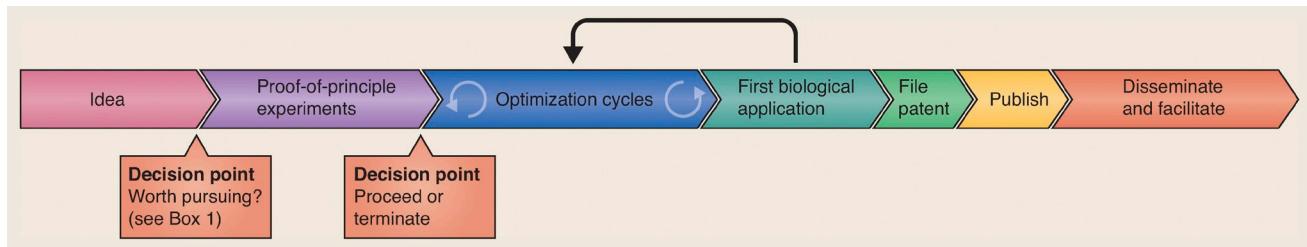


Figure 1. Flow diagram showing the typical phases of technology development.

Most academic institutes do this, but often the associated costs are high and the ultimate profits uncertain, in part because it can be difficult to enforce protection of a patented technology (how do you prove that your technology was used by someone else?). That said, some technologies or associated materials may be more effectively scaled up and disseminated through a commercial route than via purely academic channels. Specific companies may have distribution infrastructure or technical expertise that is hard to match in an academic laboratory. Founding your own company may also be a way to give the technology more leverage, as it provides access to funds not available in an academic setting. In these cases, timely filing of a patent application may be essential. Note that in certain countries one cannot apply for a patent once the technology has been publicly disclosed (e.g., at a conference).

Competing technologies

Often different technologies for the same purpose are invented independently and more or less simultaneously. It is therefore quite likely that sooner or later an alternative technology emerges in the literature, or appears on the commercial market. This is sometimes referred to as “competing technology,” but in an academic setting this is somewhat of a misnomer, as solid science requires multiple independent methods to cross-validate results. Moreover, it is extremely rare that two independent technologies cover exactly the same spectrum of applications. For example, one technology may have a higher resolution, but the other may be superior in sensitivity. The sudden emergence of a competing technology can however have strategic consequences, and it is important to carefully define the advantages of your technology and focus on these strengths.

A bright future for technology development

New technologies generally consist of a new combination of available technologies, or apply newly discovered fundamental principles. Because the pool of available knowledge and tools continues to expand, the opportunities to devise and test new methods will only improve. This is further facilitated by the increasing quality of basic methods and tools to build on. Thus, there is a bright future for technology development. With a carefully designed strategy, the risks associated with such efforts can be minimized and the overall impact maximized. In the end, it is extremely gratifying to apply a “home-grown” technology to exciting biological questions, and to see other laboratories use it.

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