Kits and their unique role in molecular biology: a brief retrospective

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An innovation is one of those things that society looks at and says, if we make this part of the way we live and work, it will change the way we live and work.

—Dean Kamen

One of my primary objects is to form the tools so the tools themselves shall fashion the work and give to every part its just proportion.

—Eli Whitney

It’s what you learn after you know it all that counts.

—Harry S. Truman

Since their initial development nearly 20 years ago, molecular biology kits have evolved from simple protocols and reagents for cloning of DNA to the more recent complex reagent sets that enable whole genomic sequencing. Initially met with resistance by some who felt that using them deprived researchers of the basic knowledge of how to create reagents, molecular biology kits have taken on an important role in the biological sciences. In this article we describe kit development, why kits have succeeded in molecular biology, and how they have paved the way for the more recent widespread use of core facilities.

INTRODUCTION

Walk into any molecular biology laboratory and you will likely see shelves, refrigerators, and freezers filled not only with stand-alone reagents and biochemicals, but also with boxes and containers from reagent and instrumentation companies that include detailed instructions, helpful hints, and, most importantly, protocols for use (and for avoiding misuse!).

For BioTechniques’ 25th Anniversary we present a brief review of a phenomenon that appears to be unique to biology and that, for want of a better name, we call “kits.” When we first joined the BioTechniques Editorial Board (in the 1980s), kits were not common. What triggered this (r)evolution, and has it helped advance the field?

What Is a Kit?

In its simplest form, a kit consists of more than one component and a set of instructions. How do we define a kit in the molecular biology universe? We would propose that a kit be operationally defined as comprising: (i) a set of one or more reagents having variable input materials; (ii) instructions that guide the individual researcher to perform the same reaction on the input materials; (iii) transformation of the input materials; and (iv) the obtaining of identical end-results each time the input material is the same. Characteristics of a good kit include ease of use, clear instructions, a good troubleshooting guide, a rapid protocol, and, of course, reliability and reproducibility. A kit may be very complicated (for example, a complete genome sequencing kit), or as simple as a DNA ligation kit containing a few reagents and controls.

A kit for site-directed mutagenesis would be an obvious example of a complex kit. Less evidently, a buffer sold with a restriction enzyme could also be considered a kit, if it includes a set of instructions for using it. In the early days of molecular biology, many restriction enzymes were originally sold without their associated buffers. Researchers made their own buffers, a different solution for each enzyme (universal buffer and low-, medium-, and high-salt buffers are more recent inventions) (1). And if the researchers used good laboratory procedures, they needed to first test the buffers, enzymes, and DNA for proper digestion. Today, standardized buffers supplied with enzymes—and prepackaged reagent kits generally—have eliminated the need for users to control quality.

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Early Days

Today’s kit manufacturers were not among the advertisers in BioTechniques’ early years. In fact, most of the ads in the journal’s first two volumes offered medical and cell-fusion equipment, separations media, and specific chemicals. In 1983, several companies had put together kits—for M13 cloning (New England Biolabs, Bethesda Research Laboratories), exonuclease deletion (Stratagene Cloning Systems), and riboprobes (Promega)—but they promoted them mainly in their catalogs. Two years later, Promega advertisements in BioTechniques offered a system for making riboprobes using the company’s pGem vectors. (Another trend: after 1985, equipment advertisements were increasingly oriented to molecular biology—centrifuges, microscopes, DNA synthesizers, power supplies, etc.—which likely reflected this journal’s growing influence among biology lab researchers.)

In the early days, manufacturers often avoided using the word “kit.” Instead, we wrote and talked about “systems” for performing or developing certain applications. Today, by contrast, any recent issue of this journal carries many advertisements promoting the latest streamlined methods for performing complicated molecular biology protocols. Many are now even labeled kits.

Initial Opposition to Kits

Twenty-five years ago, academics actually debated whether kits represented the beginning of the decline of graduate education. Mentors felt that graduate students lost something when they performed experiments using store-bought kits instead of assembling their own materials and reagents. The teachers feared that students would lose the deeper understanding of the enzymology and basic nature of the work they simply followed the directions on the package insert.

There were also economic concerns: was it worth purchasing kits when the reagents could be made in-house? Modern researchers’ devotion to today’s kits suggests that they consider consistent reagents and tested protocols a good buy. Many of us who have spent at least part of our careers producing kits know that what we are really selling is quality control, reliability, and reproducibility. If a kit is well developed, users should be confident that, if they follow the directions, they will obtain the desired results. Because of these elements—quality control of the reagents, matching of components, labeling, and the provision of detailed manuals—kits routinely cost more than the individual components together. Early kit-users may not have understood how time- and labor-intensive these steps are. But in this case the added cost does indeed represent added value. In the early days, a reaction from a kit could cost anywhere from several dollars (for a simple restriction enzyme digestion) to tens of dollars (for a ligation or lambda-packaging reaction). Nowadays, researchers can purchase a next-generation DNA sequencing kit that may cost several thousands of dollars for a single use.

Troubleshooting and Controls

As inventors of kits, we have often tried to minimize the need for nonkit reagents, in order to reduce the potential impact of unknown, user-supplied reagents and materials. It is almost impossible to eliminate every potential problem, which is why kits are almost always supplied with control reagents; competent cells may come with plasmid DNA, for example. Using these supplied controls properly is a crucial part of troubleshooting problems when speaking with technical support.

In multistep kits, it is often important to include steps that are not time-dependent. In the early 1980s, some developers thought that no step in a procedure should be shorter than 15 min. Researchers, we reasoned, would take their own shortcuts: if we specified 15 min for a procedure, there was bound to be someone out there who would insist on doing the step in 5 min. It was sometimes a challenge to make sure that the truly critical incubation-time parameters were understood and followed.

Over the last 10 years, most kit developers have learned that “speed sells.” So we now have 10-min restriction enzyme digests, 5-min ligation kits, 10-min cell transformations, and 1-day procedures for complete genome sequencing, to name just a few.

Core Facilities: Going Beyond Kits

The ascendancy of core facilities in so many university and industrial settings in the early 1990s has further increased the distance between the researcher and the method. For example, 25 years ago, many researchers doing DNA sequencing prepared their own deoxyribonucleotide solutions and even their own polyacrylamide gels. Several companies soon began to package preassembled, pretested reagents for high-quality Sanger dideoxyribonucleotide sequencing. Researchers still needed to pour and run polyacrylamide gels to sequence their DNA samples, although there were attempts to provide these ready-made as well. The advent of early laboratory automation, limited as it was, made it more practical for many labs to outsource their sequencing. The core facilities arose. Today, procedures that require expensive or complicated equipment are almost always relegated to these core facilities, especially as the techniques become increasingly complex for beginners: DNA and protein sequencing, oligonucleotide and peptide synthesis, microarrays, enzyme kinetics, and certain types of imaging, for example.

Core facilities allow universities and industries to amortize costs over a wider base and perform analyses more cost effectively than individual labs or departments. Instrument-makers, for their part, see the core facilities as repositories of expertise for beta-testing new technology and as eager to adopt new instruments since they are already far up the learning curve. In a sense, the core facility is a kit writ large.

Kits and the Unique Role They Have Played in Biology

Why have kits played such an important role in molecular biology, and not in, say, physics and chemistry? Certainly, industrial chemists use kits. Water-quality testing kits are commonplace. Kits in the physical sciences have never caught on as they have in the
biological sciences. Today, we find kits not only in the lab, but everywhere from the medical practice to the home medicine cabinet. Over-the-counter home tests—descendants of lab kits of years gone by—include products for glucose testing, pregnancy testing, blood pressure testing, ovulation prediction, and urine testing. Ads for newer kits for testing your DNA are even now appearing online and will soon be available at your neighborhood drug store, if they are not there already.

Are Kits and Core Facilities Guiding Experimental Design in Science?

Finally, because some things have become so easy to do, we now find we must do them. As new techniques and technologies become popular, they drive the market to produce kits to make these methods readily available to researchers. In the early days of molecular biology, there were two popular methods of DNA sequencing: Maxam-Gilbert chemical cleavage and Sanger dideoxyribonucleotide chain termination. But today, almost all (non-next-generation) sequencing is performed by a dye-labeled method based on Sanger-type sequencing. Could this be a result of the availability of early kits for dideoxy sequencing? Or is it due to other factors (3)? More recently, RNA interference (RNAi) has emerged as a super-charged technique, and using it for target validation has increased our knowledge of some very basic biological processes. The first RNAi kits for routine lab use emerged soon after the method’s discovery. Today, most researchers doing RNAi work probably use some kind of kit. More kits are being released every year. Kits based on Nobel Prize–winning technology now appear before the prize itself is awarded.

So, are kits driving scientific experimental design? When it is so convenient to purchase a kit to perform a molecular biology procedure, does performing that procedure become a requirement? Does having a kit easily available bias the content and direction of the research that is being pursued? Has, for example, the availability of kits for quantitative PCR or nonradioactive labeling helped drive gene-expression experimentation faster than if the kits were not available? Likely, yes. Did these kits change the direction of science? Likely not.

“Buying In”: The Baking Lesson

Does every home baker really need to have all of the raw ingredients and an understanding of baking chemistry to make a batch of brownies with nuts and chocolate chips? Or will a prepackaged mix produce sufficient results? Like cake mixes, the use of kits liberated researchers from the mundane tasks of mixing reagents and ensuring their quality, freeing them up for the more significant task of understanding the biology. To those of us producing the kits, the late-1980s arguments for and against using kits sounded similar to the early-1990s arguments about using calculators in high school math classes.

Why Do Kits Sell?

Users like to adopt a method, modify it, and hone it for their own purposes. Kits catch on, in part, when users can “appropriate” them in this way. Research by General Mills (described by Vance Packard in The Hidden Persuaders (2)) showed that cooks who purchased the company’s cake mixes insisted on adding milk . . . even though the instructions explicitly called for water. The substitution invariably made the cakes fail. Despite this, consumer research showed, the cooks were happier with the end product if they felt they played a part in the baking process. General Mills changed its mix to require milk, and the product’s popularity soared (2).

Similarly, researchers who use molecular biology kits are inherently required to appropriate them (in our special sense). A kit for site-directed mutagenesis requires the researcher to use her own vector and oligonucleotides; a kit for a plasmid preparation requires growing the plasmid to a particular concentration; ligations require a determination of vector and insert ratios. The kit is a shortcut to results, not a substitute for technical knowledge. Successful labs tended to use kits more frequently to get faster results. Other labs saw this success and followed the trend.

The Future

Whenever a new procedure becomes important or popular, molecular biology manufacturers are generally quick to respond, sensing the market and researchers’ desire for a way to use the tool easily. Kits that speed up research or make lab life easier are also in high demand: RNAi, quantitative PCR, fast PCR, long-range PCR, genotyping, etc. Kits are now integral parts of much biological instrumentation (consider, for example, how many PCR and sequencing instrument companies now also sell associated reagents). Kits are now fully ingrained into the molecular biology lexicon. As science moves faster and becomes more complex, as mentors have less time to train staff and students, as time-pressed teaching labs need experiments to work consistently and repeatedly, kits play an essential role in the molecular biology laboratory and in learning.

Because we are scientists who have used kits in our own research and who have helped conceive, make, and market them, we have followed these trends with intense interest. We now need to ask: has molecular biology lost anything in the kit revolution? Purists might say that it has: the knowledge for making the basic tools of research has moved from students and teachers to manufacturers. In many cases, in fact, the exact components of kits are never revealed, but guarded to protect future patent rights or preserve trade secrets. Pragmatists, however, might counter that kits have greatly accelerated scientific advancement. Biotechnology companies have used kits to both increase sales and keep themselves at the forefront of their science. Instructors have been able to focus on teaching the methods, not on...
making the reagents. All in all, kits appear to have provided a selective advantage to the molecular biology field. And this they will continue to do.

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COMPETING INTERESTS STATEMENT

Both authors are involved in the development of molecular biology reagents and head their own independent research laboratories.

REFERENCES


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