Over the course of a year I attend 4 or 5 drug discovery conferences in the US and Europe. This gives me a good opportunity to visit exhibits, attend presentations and read posters. However, the best part of these meetings is the chance to discuss drug discovery with colleagues. The usual conversation at these meetings is: “See anything new?” And the response is most often: “No, nothing.” In 2009 the conversation often led to the state of innovation in drug discovery technology. I was surprised over the universal response that it had declined significantly. The comments were often much stronger than that, but the point was clear. It didn't matter if the conversation was with senior executives, bench scientists or technology developers involved in product R&D; they all believe that innovation has declined. This decline is not a recent phenomenon, but has been growing since the economic downturn of 2002 – a good part of a decade.

This is not an in-depth review of all that has occurred in drug discovery over the past 10 years. It is a personal view developed by first-hand experience and discussions with scientists in industry and academia.

Scope of drug discovery technologies
Before discussing innovation, the scope of drug discovery covered by this paper should be defined. The drug discovery process covers a broad range of disciplines from genomics and target discovery to pre-clinical testing. Within this space there are a variety of hardware, software and biological technologies. However, to keep this article to a manageable size, it will focus on developments primarily in assays and hardware used in target validation through screening and into profiling. This does not diminish the many important advances that have been made with RNAi, cell-based assays (especially the progress with stem cell), new biological approaches to target evaluation, data mining, image recognition software or other innovations.

What is innovation?
Innovation does not have a clear definition. This can lead to disagreement as to what is innovative. A certain amount of leeway is required. Common usage and dictionary definitions can range from definitions that are very loose as often used in a marketing context to very strict interpretations that would eliminate all but the most unique inventions. Probably the best definition to use is that an innovation must be at least a substantial improvement and not a small change over what is currently available. That still leaves room for a considerable difference of opinion so we should be flexible in what is considered innovation.
Examples of past innovation
There are two examples of past innovation in drug discovery that might help us define innovation as used here and then explore future innovations. The first is an example of innovation that would fit the looser definition of an improvement. Fluorescence Polarization (FP) is a technique with a theoretical basis going back to the 1920s and used in immunoassays until the 1960s. In spite of being used commercially as a diagnostic tool, it had limited success in drug discovery because it used a test tube format. When LJL Biosystems (later purchased by Molecular Devices, www.moleculardevices.com) launched the Analyst microplate reader for FP in the latter part of the 1990s, the method gained wide use and success in drug discovery. Some might not consider this innovative. While FP itself was not a new technique, developments in hardware combined to make it an innovative product. The number of publications in journals such as JBS (Journal of the Society of Biomolecular Sciences) attest to its wide use and popularity as do the large number of manufacturers that now offer FP capabilities in multi-mode plate readers.

An innovation that fits a stricter definition of something substantially new is the development of acoustic dispensing. The field of nanodispensing has developed over a number of years with a variety of methods to dispense picolitre to nanolitre volumes. The need was there, but the technologies (for example, piezo) could be temperamental. The introduction of acoustic dispensing (Echo systems, Labcyte, www.labcyte.com) stands as an important innovation. The Echo made nanodispensing much more robust and practicable for drug discovery from compound dispensing to assay assembly on automated systems.

Historical perspective
Innovation or a lack of it results from the closely linked relationship between technology availability and both market need and market conditions. It is a cycle that requires a market that is receptive to new technologies and vendors who take the risk of developing these technologies. Continuing innovation requires both and when the cycle is broken in any part, the process is disrupted. The growth and maturation of high throughput screening (HTS) is a good example of how need drives innovation.

Throughout the 1990s there was a technology need in HTS to meet very aggressive throughput goals. Screening 100,000 compounds a day became a widely accepted target. At the time this was a challenge, but it wasn’t the only goal. The throughput would not be sustainable unless it was combined with dramatically lower costs and high quality data. The willingness of pharmaceutical companies to work with vendors and gamble on a range of developing technologies gave vendors the incentive to take risks in researching, licensing and developing products. It was an exciting atmosphere of co-operation that resulted in a range of innovations that allowed the HTS goals to be met and exceeded. The advances, taken for granted today, include reliable automation (both for assays and compound storage/distribution), SBS standards for microplates, homogeneous assay technologies, multidetector readers, imaging hardware and software, liquid handling (both mL and nL), database and pattern recognition software and the development of skills in process control that brought throughput and quality to HTS. As more ‘hits’ were found, the equipment and skill moved to the next bottleneck: the downstream processes of profiling, lead optimisation and ADME. There has also been upstream migration of technology to target discovery, validation and robust assay development.

By the early part of the 2000s, a large amount of time and money had been invested by technology providers and pharmaceutical companies in the development and implementation of innovative technologies. Vendors saw an immediate return and more and more companies were drawn to this lucrative market. Pharmaceutical (pharma) and biotech companies, however, did not see an immediate return. They could reduce the number of people in HTS labs as a result of automation and move more compounds into development, but the long timeframe of drug development precluded a rapid, quantifiable return on investment. In fact, there was little proof that the investment would lead to any improvement in the bottom line – more drugs on the market. Pharma management, faced with dwindling pipelines, difficult market conditions and economic downturns, reduced headcount and budgets. In the drug discovery area, management wanted proof that past investments were paying off before continuing to fund technology. The combination of decreased spending on new equipment and reduced personnel to manage technology assessment and implementation resulted in a much more critical look at new technology. Vendors, faced with reduced sales in a very competitive market, cut back as well. In difficult economic conditions it is a common reaction to focus on cost cutting and maximising sales of current products while reducing development investments. Why risk the development
cost of a new product unless there is more than a fair chance of it being successful?

There is one more important aspect of innovation that is exemplified by HTS. Does HTS, or any field in question, need that much more innovation? Most of the goals of HTS have been met to the point where the downstream processes (profiling, lead optimisation) cannot keep up. Some of the testing once done downstream, such as hit validation and optimisation, were taken up by HTS since they had the capacity and quality to do more. If there is already a backlog from HTS, why invest more to increase the backlog?

There is still a need for improvements in HTS, but there are more important places to focus. Approximately 50% of drug candidates fail in Phase I and II clinical trials because of toxicity or lack of efficacy. The development of physiologically relevant targets, assays (screening and ADMET) and cell-based models are more critical than incremental improvements in cost and efficiency in HTS. The needs of drug discovery are changing and so must the focus of investment. This is a critical change and will have a major impact on where technology developers apply their resources for the next wave of innovation.

**The current situation**

While there were signs of recovery after the economic downturn of the early 2000s, the atmosphere for new technology remained decidedly guarded. Pharmas were cautious about risk, vendor companies remained largely focused on incremental improvements and venture capital companies were very careful in what they funded and for how long. The severe worldwide economic downturn of 2008 and 2009 nipped any innovation recovery that may have been developing. Just as there is a long lag phase from drug discovery to an approved drug, there is also a lag between R&D and a commercial product. Until there are signs that customers are ready to invest in new products, vendors will delay their investments in R&D. There are investments being made, but most of these are in lower risk, short time-to-market products and not innovation. The cycle of innovation referred to earlier has been badly damaged and needs time to re-establish itself.

**There is still innovation**

While there is still concern about the uphill battle to develop and market innovative products, it has not ceased altogether. There are a number of examples that could be used, but let’s focus on two that cover a range of innovation discussed earlier.

As much as homogenous fluorescent methods (and similar assay technology innovations) have advanced drug discovery, they do not have universal applications and there is always the inherent danger that labels or conjugated molecules of any type will change the interactions being measured. For these reasons, along with the expense and labelling time, there has been considerable activity in the search for reproducible and inexpensive label-free technologies. There are few drug discovery conferences that do not include this topic. One of these promising technologies is back scattering interferometry (BSI). Interferometry as an optical measuring method has a long history of theoretical background and use in academic and industrial
settings. However, BSI is significantly different and innovative. The discovery of BSI is attributed to Dr Darryl Bornhop, Professor of Chemistry at Vanderbilt University (www.vanderbilt.edu) while he was studying for his doctorate. His presentation of this technology at a recent ELRIG meeting (Liverpool, September 2009) outlined the theory and potential for drug discovery (Figure 1). The method is based on measuring the shift in the interference fringe pattern that results from binding events on a CCD camera. It is now being developed for drug discovery in a microfluidic channel format by Molecular Sensing (www.molsense.com) where Dr Bornhop is a founder and Chief Technical Officer. Volumes as low as 1nL can be measured in solution without any components being immobilised. This could add an innovative label-free assay technology to advance the speed and relevance of measuring binding reactions.

The drive toward greater sensitivity and miniaturisation has been a goal in drug discovery and diagnostics. Advances made in the broad field of nanotechnology are being applied to this application. I was fortunate enough to review an abstract on cantilever assays in biology for a presentation at MipTec (an annual drug discovery conference in Basel, Switzerland). The lead author, Manuel Vogtli, is a PhD candidate at the London Centre for Nanotechnology (LCN, a joint venture between the University College London and Imperial College London, www.london-nano.com). He presented his work on the application of nanotechnology to produce multiple arrays of cantilevers for biological assays. The method measures the deflection of the cantilever based on the binding of biomolecules. While his research is focused on understanding drug resistance in bacteria, the application for binding reactions is obvious. An important aspect of this technology is that the cantilever deflection (Figure 2) is not a function of mass so the measurement of small molecule binding is possible. Cantilevers are just one aspect of nanotechnology being researched at LCN. The field of nanotechnology covers everything from material science, consumer products, supercomputing, single atom manipulation and single molecule measurements on carbon nanotubes. It is a field worth watching for some groundbreaking advances.

Both BSI and cantilevers are highly miniaturised, label-free, sensitive and measure small volumes at physiological concentrations. They can be multiplexed in small systems for multiple simultaneous measurements. These attributes could make these

Figure 2
This graphic of an array of cantilevers demonstrates the deflection based on binding to a tethered molecule. Deflections as small as 10nM and up to 100s of nM can be reproducibly measured. Courtesy of Manuel Vogtli of the London Centre for Nanotechnology
innovations of significant benefit to drug discovery. It should be noted that both of these technologies come from funding academic research. The importance of academic research as a source of innovation for drug discovery cannot be overemphasised.

The mixed blessing of the microplate format

The microplate format has become the default standard for drug discovery. The infrastructure and investment built around this format is substantial and almost irreplaceable. The components of an automated HTS system can add up to millions of dollars. As expensive as these systems are, they are dwarfed by the cost of storage and distribution systems for millions of compounds in the corporate library. This kind of investment is not easy to displace or replace. If a technology is developed that does not integrate into the microplate format, what are the chances of it being widely accepted?

The example of FP was discussed earlier. It had little success in drug discovery until hardware was developed for the microplate. Back scattering interferometry and cantilever arrays were discussed earlier as examples of innovative technologies. Neither easily fits the microplate format. Will they find success in drug discovery? Whether they will have the attributes to displace the microplate will have to be left to the future. However, I believe they will find more immediate success downstream of HTS. There are numerous examples of technologies that do not fit HTS, but have been very successful in profiling and lead optimisation. HTS is very profitable for vendors, but not the only place in drug discovery where innovation can be successful. The dominance of the microplate infrastructure is an issue that many technology companies, start-ups and venture capitalists have to seriously evaluate in what they develop and fund.

Conclusion

Perhaps we have become spoiled with the constant advances in electronics such as faster and more powerful computers and more sophisticated cell phones, all with more capability at ever decreasing prices. Is it realistic to compare advances in consumer electronics to advances in technology for biological assays? It isn’t fair, but it doesn’t mean we won’t make those comparisons. We are also aware of the excitement and innovation in drug discovery of the past. Do we expect that to be the norm, or was it an exceptional period driven by a unique set of circumstances? It may be that these unconscious comparisons are partly why so many people see the decline in drug discovery innovation. I believe the decline is real, but is it as severe as generally believed? Whatever the fact or perception, innovation is a cycle and as such has its peaks and troughs. While this trough is particularly prolonged, it is not permanent. Innovation is still occurring, but perhaps at a slower pace than in past years and perhaps in different areas of drug discovery.

Advances in seemingly unrelated disciplines of academic research can find applications in unanticipated markets. Drug discovery has always drawn from advances from other fields and as long as there are entrepreneurs in large companies or start-ups, innovation will always be a part of drug discovery. It may be riskier than before, but it is still a rewarding and exciting adventure.

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