the principles used successfully in managing scientists in smaller companies should not be abandoned, because not developing and harnessing the full creative potential of your scientists is an unaffordable extravagance. After all, size isn't everything.

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Optimizing screening technology: how much to invest?

The foundation for long-term growth of a pharmaceutical company lies in the development and implementation of new technologies for drug discovery. Unfortunately, new technologies do not always meet expectations. In the past several years, we have seen vast improvements in the instrumentation associated with the screening of large chemical libraries for drug leads. Yet making rational decisions concerning investments in screening technologies is often very difficult. With finite resources it seems unreasonable and impractical to continually upgrade and instigate new technologies that might not offer what they promise, and that require much testing to determine their true value.

The trends in HTS have been towards testing compounds in cell-based and biochemical assays at increasing rates and in smaller volumes. The proposed advantages are that more leads will be found in less time and with less reagent use and that larger libraries can be screened, thus increasing the information content of the screen and increasing the odds of finding good leads. However, alternative screening paradigms suggest that there are limits to the diversity space of large libraries and that smaller, more carefully designed libraries are adequate, especially in conjunction with the medicinal chemistry effort required for optimizing a lead.

There is a point where screening rates and lead discovery rates no longer present a bottleneck in the drug pipeline and therefore a point at which further investments in screening technologies are no longer worth the benefits they provide. Thus, when planning improvements in core screening facilities, one has to ask whether efforts toward implementing new screening technologies are worth the expenditure and what screening rates are necessary to keep a competitive pipeline.

In the past few years significant improvements in two areas of routine screening have been made:

- A switch from 96 to 384-well liquid handling in 20–30 μl volumes.
- A variety of mix-and-read, cell-based and binding assay methodologies, for example, luciferase reporter assays, time-resolved fluorescence resonance energy transfer, fluorescence correlation, fluorescence polarization, scintillation proximity, and luminescent oxygen channeling.

Although it is difficult to quantify the overall contribution of these improvements to drug discovery, one can safely say that, given a choice to run an assay in 96 or 384-well formats, one would always choose 384. Furthermore, given the choice between plate washing or mix-and-read, one would choose mix-and-read. The benefits of 384-well, mix-and-read formats are that one can process twice as many assays per person per dollar with 30–40% of the reagent usage. The technology that is commercially available is easy to use, reliable and cost-effective.

We will probably find the same to be true with 1536-well screening in 5–9 μl volumes. The optical readers, imagers and dispensers that are becoming available are relatively good. Although in many cases, considerable effort must be put into reformatting libraries, by analogy, we would expect to see the same dramatic improvements in screening efficiency as we have observed with 384-well screening.

However, contrary to what some technology advocates would have us believe, many of the novel screening technologies that promise greater levels of miniaturization are of questionable practical value in drug discovery. The production of assay reagents is no longer a limiting factor with the currently available levels of miniaturization. One can test 50,000 targets (every protein in a cell) with a few milligrams of compound. With modern gene-expression technology, producing a few milligrams of protein reagents per screen is not a limitation. Furthermore, novel ways to measure compound-induced biomolecular changes are desirable only to the extent that they can measure formerly intractable 'prize' targets. Such screening-unfriendly targets include enzymes involved in sugar and lipid metabolism, for which we have seen little improvement in screening methods.

Many of the more 'academic' technologies are tested with unrealistic proof-of-principle experiments. Development of these technologies will require a new generation of liquid handling systems, compound handling systems, chemical synthetic procedures, plate materials, optical technologies, automation and bioengineered cell lines, which come at a large expense. In routine screening of compound libraries, the speed and efficiency that 1536-well screening affords with the battery of assays now available is more than adequate to meet lead discovery needs. With appropriate automation and organization, libraries of one million or more compounds can be screened in a week or less. If one wants to increase the screening throughput, one can increase

the level of parallel processing, an approach that is considerably less expensive than investing too early in visionary new technologies.

Although continuing efforts at maximizing the efficiency of HTS are worthwhile, we must keep in mind the law of diminishing returns. If we abide by this law, we will be free to invest our efforts in the more compelling problems of drug discovery, for example, validating targets, improving times for lead optimization, increasing the rate of *in vivo* testing of optimized leads, and developing better experimental predictors of clinical safety and efficacy.

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Whither solid-phase chemistry? – Reply ▲

Initial letter: Terrett, N. (2000) *Drug Discovery Today* 6, 16

Response from Tony Baxter

I agree with much of the detail of Dr Terrett's letter. Certainly, preparing and screening mixtures of compounds is now seen as largely an outmoded concept. Improvements in synthetic methodology and, in particular, analytical techniques have ensured that the quality of single compound libraries has significantly increased and this, coupled with improvements in HTS techniques, has meant that screening mixtures is now largely redundant.

With regard to the use of solid-phase chemistry, I am not totally in agreement with Dr Terrett. Whilst solution-phase techniques have been more widely embraced within the library synthesis community (certainly at Oxford Asymmetry International, >50% of compounds are produced using solely solution-phase methods), it is still true to say that solid-phase chemistry plays a valuable role in the production of larger 'lead discovery' libraries and can have a significant impact on the speed in which certain lead optimization programmes can proceed.

The main issue with solid-phase chemistry is that it takes significant resources, training and time to build up a critical mass of knowledge and skills that can then be applied to various projects. The pharmaceutical industry, typically, does not have the time or resources available to dedicate to producing such a skill base and I suspect that it will be the larger service-based companies that will be the main users and beneficiaries of such technologies in the future. It should also be stated that solid-phase chemistry should not be seen in a competition context with solution-phase methods but more realistically as a complementary methodology in which both techniques have their place in the synthetic armoury of today's medicinal chemist.

We very much support the efforts of the academic community who are further developing new solid-phase methodologies that can be applied to industry-based synthetic problems. There is a view that such new methods and technologies represent new and better tools that can be added to the technical 'toolbox' and applied to an ever-increasing range of given problems.

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