HTS personal perspectives: small companies

Interviews by Rebecca Lawrence

Paul England, Senior Scientific Fellow,
Aurora Biosciences Corporation,
11010 Torreyana Road, San Diego,
CA 92121, USA.
tel: +1 858 404 6650, fax: +1 858 404 6787,
e-mail: EnglandP@aurorabio.com

How would you respond to the claim that 'HTS is a waste of time as no successful leads have yet been produced'?

From my own experience when I was doing drug discovery at SmithKline Beecham (SB), a lot of the hits from screening went on to drive medicinal chemistry programs, and I believe that the same success rate has continued, if not improved, since I left. I also know from customers of Aurora that they are finding plenty of quality leads from screening that are then moving forward into chemistry. In terms of getting clinical candidates, it tends to take 2–3 years after finishing the screening to optimize drug candidates, and then an additional 1–2 years for pre-clinical safety assessment. As HTS has only been going for 5–8 years in most companies, there are clearly many leads from HTS that have only just started to make it into the clinic.

Do you think further miniaturization is the way to go in the future?

Beyond 384-well plates, definitely yes, but beyond 1–3 μl per well, probably not. There are enough problems with liquid handling with these smaller volumes that make it technically challenging to go beyond this. Also, by reducing assays volumes to 1–3 μl, you have made very large savings in reagents, which is one of the real benefits of miniaturization. Hence, miniaturization probably has a bigger impact on reducing cost than for increasing throughput.

What do you think is the main problem with HTS at the moment and how would you resolve it?

One of the greatest challenges is how to handle very large numbers of compounds and transfer them into assays reliably and relatively accurately at the sort of throughput levels at which one can run assays. Although there are plenty of solutions for compound storage, the actual transfer of compounds from storage formats into miniaturized assay formats is still a major problem. Aurora has developed a piezo system that will dispense down to about a nanoliter and will transfer 100,000–300,000 compounds a day into a miniaturized assay format, while other companies are working on this problem by running their transfer systems in parallel.

Do you think the benefits of HTS equal the level of financial input required?

I think there are a large number of targets that are relatively intractable to finding lead compounds in any way other than by using HTS. For example, there is not enough structural information or knowledge of the ligands for new drug targets that have come from the genome database [e.g. orphan G-protein-coupled receptors (GPCRs) and orphan kinases], and hence we have no rational idea of where to start with medicinal chemistry. The only way to generate leads is by using HTS to find compounds from your collection that will interact with these targets.

Do you feel HTS is essential to advance fields such as genomics?

Given the very large level of investment in genomics and the large number of targets being produced from the genome database, there is no other way of realizing your investment in genomics and target validation if you do not use HTS.

Do you think outsourcing of HTS is an essential part of pharma strategy or should it all be kept in-house?

I think you can do it either way. Outsourcing for equipment is standard. Generally, big pharma does not have the expertise or the will, nor is it really practical for them to develop their own equipment, so this will always be outsourced. As for outsourcing of screening, I think that companies will do this in a limited number of cases when the supplier companies have something special such as a large range of compounds, a specialized technology that is not worth bringing in-house, or a need for specific expertise. My general experience of big pharma companies is that they want to do it themselves in their own way, and they want to maintain a high level of control of the work. Many companies have made small initial investments in screening that are not too expensive. Hence, when it comes to outsourcing, they have already made an internal commitment that reduces the incentive to outsource. There is also the

1359-6446/00/$ – see front matter PII: S1471-1931(00)00112-9

logistical problem of supplying compounds to external collaborators, as it is, in practice, a lot of work.

Where do you think HTS will be in ten years time?

I think we will have probably solved the compound handling problems, but whether we will have solved it by retaining open-well microtiter formats or whether we will have gone to chips, I do not know. Chip-based systems are relatively new and, at the moment, are relatively limited in take-up. Although groups like Caliper Technologies have made big strides in this field, I cannot predict whether the closed architecture will be a common feature in ten years time. I think we will have certainly screened all the obvious families of targets (such as GPCRs, kinases and proteases), but I am not sure whether we will have leads or therapeutic utilities for all of these. We will then be looking to solve more intractable targets such as protein–protein interactions, which will offer a whole new range of pharmaceutical targets with their own problems in assay configuration and lead identification.

At your company, which well-plate size do you currently use the most?

Obviously we produce the 3456-well plate but we also do assays in 96- and 384-well plates for ion-channel work. However, we try to make all our assays suitable for the 3456-well plate format.

Who do you think has the most innovative products/ideas in the HTS field (other than your own company!)?

I think Scintillation Proximity Assays has changed the way a lot of radioactivity assays are being done. Also, the move to cell-based functional assays has had a large impact (e.g. FLIPR and reporter gene assays), as has the imaging of whole plates, various high-sensitivity detection systems, the use of fluorescence, and the ability to miniaturize.

Who do you think has most influenced your own career?

My post-doctoral supervisor, Ed Krebs (at the time at the University of California, CA, USA), was influential in my career as he introduced me to the areas of signal transduction and protein phosphorylation, which influenced what I did in academia and, to some extent, in industry. What probably influenced me most in terms of moving into screening was the signing of the deal between SB and Human Genome Sciences when I was at SB. This alerted SB to the need to have HTS as a centralized function rather than a small number of disparate groups working on their own separate targets. It also prompted the recognition that, with all the new targets, the only way to get leads was by having an HTS group.

Do you miss working at the bench?

I used to miss working at the bench very much as I did benchwork until my early 40s when I was in academia. Once I came into industry, I started to do less until, after three years, I did not have the time. However, I have always been very close to the science and have always looked at data and technologies and helped plan the research projects. I do not think I could go back to the bench now and run a research project as the techniques and the lab practices haved moved on too much. However, I have always tried very hard to see my job as a scientific manager rather than just a manager.

What would you like to have achieved by the end of your career?

I would like to have developed the careers of a lot of people by mentoring them and guiding them. I would also like to have contributed successfully to drug discovery, not just in screening but in general.

Lev Leytes, Member of Board of Directors,
c/o Kathleen Vargas,
Molecular Devices Corporation,
1311 Orleans Drive,
Sunnyvale, CA 94089, USA.

How would you respond to the claim that 'HTS is a waste of time as no successful leads have yet been produced'?

I think they need to talk to people who have produced successful leads. Several talks at the industry conferences reported leads produced by HTS, in fact faster than without HTS. So I cannot imagine how it can be a waste of time when you can get your lead faster and in a more cost-efficient way.

Do you think further miniaturization is the way to go in the future?

I think that miniaturization at 3–8 μl per data point is probably a very significant enabling step and this is a step I believe will be broadly applicable – there should not be any biological limitations that will prevent you from running an assay at this level. If you go beyond that into the nanoscale, you start coming across limitations. However, that is not to say that there could not be good applications