HTS personal perspectives: big pharma

Interviews by Rebecca N. Lawrence, Supplements Editor

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Has your company seen any success so far with leads generated from HTS programmes?

Yes, we have had success in Welwyn in identifying a number of good starting points for chemistry programmes. In the wider organization, compounds originally identified in HTS have progressed further. Our HTS activities have undergone fundamental, step-change improvements in investment, infrastructure and intensity within the past five years and we are seeing a steady increase in output quality and quantity. We feel that there is still considerable scope for increasing the contribution of HTS to the process of quality lead identification. It is important to emphasise that HTS is one of several complementary approaches to lead identification which can be carried out in parallel for a particular target.

Now that some drugs selected through HTS programmes have finally started to reach clinical trials, do you feel that HTS will eventually deliver all that was anticipated at the beginning?

Yes, I do, although we have always had a very balanced view of the relative delivery potential of HTS and its need to complement the many other arms of the drug discovery process.

At Roche, we are focusing on quality; the quality of every element and connectivity in the HTS process including target selection, assay format, compound libraries, hardware, informatics and cost control. In the past five years, advances in technology have meant that we can screen many more compounds and throughput is no longer the issue that it was in the mid-1990s.

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

In terms of our own operations, I think they will, but we have not yet had time to recoup the investment. The next two years will be the key period for assessment.

How do you see the future for miniaturization? Do you ever see the 1536-well plate becoming the most commonly used density?

I think they will be used commonly but not universally. With conventional *in vitro* assays, 384-well plate screens are attainable in most cases, although there are some cell-based assays that we have not been able to miniaturize. Constraints increase with progression down the miniaturization path and so some techniques are always left behind at each step.
At the moment, I don't think 1536-well plate technology is fully mature. Drivers for moving to 1536-well plates are not as strong as they were to 384-well plates because of the greater constraints. The reading technologies are up to the job now but I don't think liquid handling is quite there yet. At the end of the day, it comes back to quality and this is currently much more achievable in 384- than 1536-well plates. We will eventually get to routine use of 1536-well plates but cost-savings are sometimes overstated.

Do you think we should go towards further miniaturization, even past 3456-well plate densities?

I am not sure what the driver would be for density increases above 3456-well plates or how the cost–benefit ratio would figure out. With some specific technologies, different formats and high-density formats are quite valuable but I think 384-format provides for many of our current requirements. The Evotec and Aurora approaches have strong benefits in a narrower area. However, with both examples, the barrier to entry is quite high in terms of cost of investing.

Do you think companies are being selective enough about which compounds are being screened?

As technological capabilities have evolved, there has been a tendency to screen ever larger libraries increasingly rapidly and I do not think that is always appropriate. This approach might not be cost-effective and is often not the best route to the required result. I think we could make more use of a 'layered' approach to screening where, for example, computational approaches are used to identify subsets of priority compounds for sequential screening. We need to be more intelligent about what we screen for a given target and evaluate whether we want to go for a full screen in every case.

How do you think we should improve the screening process from the compound quality perspective?

We continue to make a large effort in library management within Roche globally and this is bearing fruit. With six global laboratories carrying out HTS, this is a

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major exercise. Great progress has been made in optimizing library diversity, purity, storage, growth and distribution. A key initiative is the elimination of compounds present for largely historical reasons that are no longer of interest. A major challenge is the logistical demand of supplying compounds for ultra-HTS; managing the compromises required in pre-preparing solution libraries and the impact of this on compound quality.

The increased difficulties of rigorously implementing selection criteria for very large numbers of compounds can also have consequences for library composition. In common with others, we dissolve our compounds in DMSO and we are focussed on protecting these solutions from hydrolysis arising from exposure to atmospheric moisture. We are also working to reduce compound freeze–thaw cycles for the samples we handle locally. When prioritizing hits from HTS, we have integrated physical methods to evaluate compound (hit) structure and purity data and this information is fed back to the global library management group with a view to eliminating unsuitable compounds.

Do you outsource any of your screening?

We tend to keep HTS in-house. This because it is a crucial activity, requiring close integration with many functions where timeliness, control and economies of scale are vitally important. The time required to manage external outsourcing is a considerable burden that should not be underestimated. We have invested heavily in HTS technology and our in-house capacity is not an issue. Another reason that I prefer to keep our activities in-house is that we compare and apply the lessons learnt over time across different targets and need to ensure data compatibility. It is not to say that we would not contract screening out; certainly, other sites have used outsourcing to access technologies we do not have internally.

What factors are necessary for successful outsourcing collaborations between pharma and biotech?

Clear objectives, clear timelines and a very strong interaction between the two companies. It is necessary to closely define and share responsibility between parties; both sides need to benefit, and there need to be clear objectives and structured ongoing management by both sides. Regular meetings of scientists are also very important to communicate the detail and complexity of targets for which we have considerable experience and understand intimately.

How do you think the human genome sequence information will impact HTS?

There is a real need for high-quality tractible ('drugable') targets and a greater understanding of the genes involved in different disease processes. The genome project gives us information but, as yet, comparatively little understanding, although it is still early days. We will not be tempted to screen because we can. Our standard target tractibility analysis will still apply. It will be inefficient and expensive if we start HTS work before we have developed a sufficiently strong scientific rationale for the target.

What do you think will be the impact of informatics and computational chemistry on the direction of screening in drug discovery?

They are having a massive impact. Virtual screening tools and *in silico* models are very valuable and are impacting the way in which screening input and output is marshalled. The ideas have been around for some time and we have seen some success locally. Certainly, when a molecule with interesting biological properties is identified by HTS, *in silico* work can add a lot of value to the hit and help convert it to a lead.

There is also a more mundane but no less valuable use of computational methods to track HTS performance. This enables identification of areas for improvement once information is distilled from the HTS output using statistical analyses. Locally, this is going very well and as we do more of this, we see more opportunities. Software such as Spotfire and ActivityBase is invaluable to us, radically transforming the way we monitor screens as we run them.

Advances in HTS and increased compound availability have resulted in the generation of huge amounts of data. Which data-mining methods do you think could prove to be a leader?

We use a whole range of methods, but favour Spotfire for the opportunity that it provides to visualize large data sets. This makes cross-comparison more manageable. Such visualization, rather than rigorous statistical analysis, is very informative, converting the output of a screen into a picture from which hypotheses can be formulated.

Ideas can then be tested using more precise numerical techniques. Additionally, historical HTS output from all sites is held in an integrated global database for the benefit of ongoing research programs.

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

Assay formats and automation will be considerably more productive, flexible, cheaper, faster, smaller and more accessible. Informatics will have changed beyond recognition. For HTS to survive in broadly the same format as it is now, it needs to be much more productive for the level of input/investment. I see it much more as a controlled process akin to a production line, with multiple controls and continuous online quality monitoring; this ethos will become universal. One

additional spin off is that automated approaches are increasingly being used by traditional research functions leveraging the experience of HTS and these areas will develop along such lines over this period.

I would hesitate to guess where it is going in terms of technology and miniaturization. At the moment, it is not immediately clear to me what we will gain by going the next step. We have not yet recouped current investment and would need to see significant advantage before further major expenditure in developing technology. What we have now is way ahead of what we had five years ago and we need to capitalize on how we use it, particularly in terms of the information gathering. I think assay development, biological formats and the readouts that we use will be transformed over the next 5–10 years and HTS will move downstream into secondary, higher-information content screening.

Who do you think has the most innovative products/ideas in the HTS field?

In terms of versatile, integrated, microtitre, plate-based screening systems, the Zeiss uHTS system is exceptional. The system uses a 96-lens optical reader and enables parallel movement of plates around a flexible modular architecture. We have been using this in Welwyn for about six months now and we're very excited as a group about its productivity. I think the Evotec FCS approach is quite exciting. The Cellomics cell-based high-content screening approach is also interesting; I am not sure where it will go yet but I think it will be one to watch. As the HTS community generate many more compounds with lead potential, we will require increases in capacity downstream to deal with them. I think these technologies look very strong in that area as they provide much more detailed information about the mode of interaction of compounds with biological targets.

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Has your company seen any success so far with leads generated from HTS programmes?

We are seeing molecules from HTS programmes going into lead optimization but, not surprisingly, we do not see as many going forward from lead identification into the full drug discovery process. The main problem is the timelines. What we are seeing in development now reflects the state of screening several years back. Currently our pipeline has molecules from a mix of sources – some of our compounds have been licensed or have come from chemical programmes and some from screening approaches.

Now that some drugs selected through HTS programmes have finally started to reach clinical trials, do you feel that HTS will eventually deliver all that was anticipated at the beginning?

Yes, I think it will. As a large pharma company, one of the onuses on us is to make a significant amount of the progression for targets across the industry. How that is currently seen in GSK is our franchise in new targets. For example, the genomics investment that the old SmithKline Beecham organization made means that we have access to a considerable number of new target sequences and many of those have intellectual property associated with this company. Those are the targets that we feel will fuel the new generation of new drug molecules because that is where the novelty comes from.

One of the problems with the whole industry is that it is amazingly slow. Trends in the whole industry take years to find their way through and that is an issue. Things that we think are influential now such as taking novel gene targets and identifying function and then putting them into a drug discovery process could maybe only ever see their final output in ten years' time.

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

Yes, I do. Because the time scale of the whole process is so slow, it does need sustained investment and input into that process. It is easy to miss the bigger picture by looking at a biotech or a small start-up company that has a specific component of technology. At the time, the technology looks very interesting and powerful but essentially their aim is to capitalize on their discovery and then move on. A large company needs a longer strategy fuelled by continuous investment across the spectrum of the process.

The hurdles are clearly getting higher for the industry. The success rate of the pharma industry in producing novel drugs is poor – it has only gone up a few tens of percent over the past twenty years whereas the global investment of these companies in R&D has gone up hugely: over tenfold. However, the world market for innovative healthcare is not going away and I can see that the world population will consider healthcare to be an increasing part of their priorities. In the short term, we are facing a global environment where it appears that the cost–benefit ratio of pharmaceuticals in healthcare is not fully appreciated. The