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

bigger the company, the more they are affected by that problem. GSK is a significant part of the global healthcare system and therefore has to help move the system rather than be carried along by it. HTS is one of the key enabling technologies that will keep the industry delivering value for healthcare.

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

I think it will happen. Given the time span that it took for 384-well plates to become commonplace, it might take five years to get to 80% usage for the 1536-well plate. The reading technologies are now largely in place but a bit expensive, whereas the dispensing technologies are much more experimental. Some years ago when we thought we had screening with 384-well plates totally in place, there were still several components not really in place such as the sample handling. In the same way for 1536-well plates, companies will say they have the imaging and the detection technologies, but they do not have the sample handling sorted out. They say they have an integrated system but they do not really. Anyway, the technology is not cheap enough yet to make it generally applicable to the industry but this will happen eventually.

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

The answer depends on how good chemoinformatics predictive tools become. There has been an ongoing debate on whether to screen 'everything' or whether we should do it more intelligently and I suspect we will know the answer to that within the next five years. There will then be a realization that either the chemoinformatics is going to provide the novelty that is required to find the really innovative drugs or it is not.

If it is not, then the progress of miniaturization will roll on to try to capture more of chemical space. We might reach the point when the same global compound supply market is generally available to everyone. That might be a limiting factor for miniaturization but we are a long way from that. If someone produced a chemoinformatic package that was analytical, could produce novelty, and was so fast that we do not need to sample physical chemicals anymore then I think that would put a stop on further progression of miniaturization. Until then, I do not think there will be a voluntary stop – people will progress at the rate that suits them.

As technologies get cheaper, people will see that miniaturization is a way of getting whatever they used to do at a fraction of the price. In the end, the ultimate test will be whether the predictive software tools can do any better.

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

I am fairly on the side of 'screen everything' at the moment. To validate these chemoinformatic models, people need data. The type of discussions that are going on in industry at the moment tend to be in the absence of sufficient quantities of validating data to support their chemoinformatic hypotheses. Right now, there is no good reason for stopping testing everything. In reality, because you are looking for novelty, you are actually selling yourself short if you do not test everything you can access. The strategy used is, of course, driven by the resources you can attach to the problem: if you do not have sufficient resources, then you have to take a less comprehensive and less attractive strategy. I think that the companies that do not invest and do not compete on the scale of the large pharma companies will eventually fall back because of the fiercely competitive global environment.

Do you outsource any of your screening?

The hands-on screening work of drug discovery is generally always carried out internally. We tend to focus much more on licensing in key technologies as appropriate (bioassay techniques or automation or imaging technologies).

Keeping control of the samples, for IP reasons has been one reason for this. Another reason is the project management. In the past, we have found conflicting interests between the parties in collaborative screening deals. A major driver has also been cost, which we have considered to be extremely expensive compared with our in-house resources.

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

It provides us with a major challenge. My initial take is that the number of targets and genes means that the key distinction between humans and other eukaryotic organisms does not reside simply in the gene number. That is very good news for HTS as it means that each of those genes does a very different task compared with other organisms. Hence, aspects like modulation of activity or interactions between gene products mean that each of those gene products will have to be investigated for much more subtlety than perhaps had been anticipated. That means that the role of pharmacology – or the modification of biological properties using small molecules – becomes ever more significant. In terms of screening, it gives a whole new rationale to why screening and small-molecule drug discovery is necessary.

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

This process is definitely of major importance. If it fulfills the potential that many people believe it has, then it could change the whole face of screening. If it can achieve the hurdles of finding novel drug molecules for novel targets rather than just characterizing known families of

targets then it will make the whole process of screening almost irrelevant. It will enable you to go straight to the molecules that are of interest without the hard work in-between, but it still needs validating.

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 variety of tools to go through activity data and we put a lot of effort into the recursive partitioning technology to try to cluster activity and structure relationships. In terms of handling of data, we use IDBS ActivityBase, along with other packages. Spotfire is getting increasing good press as a visualization package.

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

HTS will either be a non-issue and everything will be done computationally or we could be in effectively the same position as now; supplying a pipeline of molecules to the rest of the drug discovery process, but conceivably 10–100-fold more efficiently. Another development could be, I think, the concept of personal HTS. The delivery of substantial screening power to an individual in a target-oriented environment is, to me, a very feasible new trend. In the same way as computing made the transfer from monolith to the desktop PC, so screening is getting smaller, cheaper and simpler and its target market will become much wider. The same trend has already happened with other analytical equipment.

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

In terms of miniaturization, Evotec has a lot of skill in readout technologies. For ultimate long-term gain, companies such as Caliper with the LapChip technology probably represent the new wave of technology but it requires a fair amount of work on their part to turn that into the reality of HTS screening. Aurora also has good readout technologies. Perkin-Ellmer has good imaging and readout technologies. The key direction in terms of HTS is certainly miniaturization, and good liquid-handling and detection technologies are vital to make progress. The Irori Nano-Kan system for library synthesis is also very elegant and clever technology.

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

Yes. Candidate drugs that had their origins in HTS are being progressed.

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?

In the early days of HTS, there was an ill-conceived view that HTS would deliver leads or even candidate drugs ready for development. This incorrect view has led to some dissatisfaction with the apparent 'success' of HTS. However, it is now recognised that HTS is only one part of the drug discovery process. HTS provides compounds that are active against targets of interest. The best active compounds must be selected and refined to produce leads that can then be optimized to give candidates for development as drugs. In this context, HTS complements activities such as structure-based design and traditional medicinal chemistry. When considered in its proper context, HTS can and does deliver value to drug discovery activities.

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

It is possible, even easy, to waste a huge amount of money on HTS and its associated technologies. If technologies are chosen and implemented wisely, then HTS will deliver in line with the level of financial investment. It needs teamwork, commitment and a non-parochial attitude or the likelihood of success is diminished.

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

Possibly. 384-well plates are now established as a commonly used format, although 96-well densities are still used. There are extra challenges in moving to 1536-well plates but they can be solved. The question really is related to whether moving to 1536-well plates is cost-effective and provides real benefit. I suspect there will be a fragmentation with different formats being used for different purposes so it might be that there will be no 'universal' format in the way that 96-well plates once were.

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

Possibly, but not in plates. I think that plates become increasingly troublesome as the well size gets smaller. Physics and chemistry will limit the degree of miniaturization that can be achieved in a robust, reliable and cost-effective manner in plates. Miniaturization will continue for certain applications but it is unlikely to be in plates with open wells.