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

I think there is some truth to this in that HTS is not producing what people might have expected – we have not seen an overall increase in products produced by the drug discovery process, and there are probably a couple of reasons for that. First, the technologies have been built for a very large industrial process to discover hits and produce lead molecules, but that is, of course, a long way from a product. Second, the processes to characterize compounds and actually turn them into products have not really been made more efficient. So you have this very high-throughput process on the front end that is being fed into an extremely slow low-throughput process, so the overall benefit from the drug discovery effort is probably not as effective as one would have liked.

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

There might be some short-term value in further miniaturization but in the long-term, probably not. In the long-term, I think there will be a move toward actually reducing the number of experiments. I think more will be done on the computational side upfront, and experiments will be used either to build predictive models, to generate data for validation, or as confirmatory (rather than exploratory) tests that should naturally be rapid, but not necessarily high-density HTS.

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

State-of-the-art screening is not an area where we have a direct focus. However, what we are seeing is that people are moving away from screening huge numbers of compounds built around the same templates to using more templates and fewer numbers of compounds and being much more selective about how many compounds they screen and the nature of those compounds. They are moving away from trying to screen everything they can get hold of, as it is still cost-prohibitive, both financially and in terms of time.

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

For some companies it probably will be equal, but for the industry as a whole, it is a tough assessment to make. I think there are two things that can come from the current investments in HTS. Obviously, one is that if you screen compounds you hopefully end up with products just because of the odds of exposing so much chemistry to so many targets, even if this process is disappointingly slow. The other is the alternative uses for the data generated from HTS. You can imagine that as you build up information, either together with the chemistry that has been used to screen compounds or independently, that information can be used to make the whole process more efficient. Ultimately, therefore, the pay-off might be that HTS can generate enough data to create truly predictive tools and therefore reduce the need to continue to try to screen ever larger numbers of compounds.

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

It is hard to say 'essential'. Historically, approximately 500 targets have been the genesis of all drug products to date, but now there is anticipated to be upwards of 10,000 targets. One would therefore imagine that there is going to be a fundamental change to what we have done in the past, which is to identify a target and bombard it with as much chemistry as possible. We currently do not really use the information we gain from most screening efforts other than to identify hits. Much of the negative information is thrown aside and not used in any meaningful way. As we get more targets, one can imagine repeatedly screening the same chemistry against a large number of targets and effectively using both positive and negative information associated with that chemistry to produce a large experience within the library so that we can become more efficient in predicting activity against new targets.

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

Companies have an inherent desire not to send out what is going to be their core values – sending out early discovery compounds or having proprietary targets reside outside the company is an uncomfortable situation. I think screening might follow, in some ways, combinatorial chemistry, in that there was much interest in outsourcing chemistry, but then companies began to incorporate that technology internally. With screening, there will probably be certain things where it is more cost-efficient to do it outside (e.g. searching through libraries of compounds that are available externally), whereas if the screening is based on proprietary compounds, they might be more comfortable to do it internally.

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

I think there will be an immediate effort to make it faster and more miniaturized but then I think the pendulum will start to swing the other way. I think there will be many applications that will be carried out in

a lower throughput and that will be done in tandem with computational technologies. Hence, the process will be to generate some data, build a model and do a prediction to guide the experiments that need to be done, hopefully therefore becoming more time-efficient.

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

Most of what we do is still in 96-well plates.

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

Independent of internal large pharma efforts, certainly Aurora and Evotec come to the top of the list when you think of companies developing an industrialized scale screening technology.

Who do you think has most influenced your own career?

Other than my parents, of course, probably my major Professor (Joseph Robinson, University of Wisconsin) while I was a graduate student had a major impact on my career, from a technical aspect as well as for the work ethic and the importance of good science and where it fits into the industry in general.

Do you miss working at the bench?

Yes, there are some days when it would be a lot simpler to be at the bench – there is a certain aspect of proposing a theory, doing a number of experiments and proving it right or wrong and getting that fairly immediate gratification – I miss that part. But that is certainly an oversimplification of what actually happens. Those series of experiments can take a very long time and can be quite repetitive and tedious and I do not miss that part at all!

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

Probably two major things. I would like to have had some kind of positive impact, whether it be delivering a technology that helps the overall discovery process or whether it is involved in finding some therapeutic agent. I would also like to have some significant personal satisfaction, which would probably be in tandem with the level of contribution I had made.

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

HTS is the only drug discovery technique that has stood the test of time. You can go back to Alexander Fleming and the discovery of penicillin, or even before that to the discovery of the salicylates – these drugs were discovered by trying them and seeing if they worked – and that was screening. Two-thirds of new drugs in 1999 came from screening of one form or another.

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

I think that until the human genome is understood or characterized better, we will not have a good idea of the number of targets, and the number of drugable targets is going to be some subset of these. It really becomes a question of how much of a trade-off [between missing a drugable target and screening against a non-drugable target] you are willing to make. Even now, miniaturization of assays from 96- to 1536-well plates, and even from 12- to 96-well plates does not work all the time. It is a trade-off between the quantity of time you want to spend doing assay development and the amount of time you want to spend doing the assay.

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

The main bottleneck is assay development to get from genomic pseudotargets to an assay, so that you can apply each test without really limiting yourself to the easy-to-do targets such as genetic functional GPCRs or kinases.

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

I think the benefits are greater – you are talking about experimentation done more efficiently. I think that if you agree that the experiments have to be done, then obviously it is going to be cheapest to do it in the most efficient way possible.

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

Yes, absolutely.

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

I think there is still a level of skepticism that outsourcing can be used to hedge your bets or bring in more diversity. I think the fundamental problem with outsourcing is that