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

if you can do something yourself, why let someone do it for you? The key thing is developing a trust and an understanding between organizations of the value that each one brings to the table. Obviously, right now, there are more targets and more leads to be developed than ever before, but we are still not making drugs faster, so I think outsourcing is a crucial approach. If you look at the auto industry now, they outsource everything (parts, manufacture, etc.) – the only thing they do is design. If pharma is going to go along the same path, they will have to outsource everything, and they are going to have to develop a level of trust with their suppliers.

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

With the accelerating pace that we are seeing, I think that HTS will be in the same boat that sequencing is today: 'What do you do with the information?' I think the function of HTS is going to ultimately change from lead identification to identifying tools for research or being able to characterize how small molecules interact with biological molecules.

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

We mostly use 384-well plates.

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

Probably Applied Biosystems – they have some bright engineers, they have the reagents and where they have identified weakness, they have gone out and bought the technologies to fill those gaps so I think they are putting together quite a powerhouse.

Who do you think has most influenced your own career?

My PhD supervisor (Jeremy Knowles, Harvard) – he has always had an interest in science and how science (in particular chemistry), medicine and biochemistry interact. He also has the ability to take ideas from different areas and to synthesize completely new fields of endeavor, and that is something I have learnt from him and which has been essential in HTS.

Do you miss working at the bench?

Yes, every 3rd or 4th day. I miss the short length of time between an idea and action – in the lab, if you have an idea, you try it and sometimes it works and sometimes it does not. It is probably the instant gratification that I miss.

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

I would like to see that an innovation, big or small, that I have had a part in actually changes the way people live.

See the next HTS supplement in June 2001 for the HTS personal perspectives from big pharma companies.

Pseudomonas gene chips – a new research tool for cystic fibrosis

Sharon Dorrell, freelance writer

Gene chips based on the newly sequenced *Pseudomonas aeruginosa* genome[1] will enable researchers to identify ways of fighting this highly antibiotic-resistant pathogen. The gene chips will be developed by Affymetrix (Santa Clara, CA, USA) in collaboration with the Cystic Fibrosis Foundation (CFF; Bethesda, MD, USA) and will be available to cystic fibrosis (CF) researchers via the CFF.

While *P. aeruginosa* rarely causes problems in healthy people, it has dire consequences for people with CF, whose mucus-filled lungs provide an ideal breeding ground for the bacterium (see Box 1). Once established in the lungs, the organism causes progressive tissue damage that eventually leads to death. These problems are compounded by the pathogen's resistance to treatment with antibiotics.

Genome sequence

The *P. aeruginosa* genome was recently sequenced by Stover and colleagues in close collaboration with the CFF (Ref. 1; http://www.pseudomonas.com). They discovered that the genome, at 6.3 million base pairs, is remarkably large and bigger than any of the bacterial genomes sequenced so far. Moreover, with 5570 predicted open reading frames (ORFs), *P. aeruginosa* is as genetically diverse as the simple eukaryote, *Saccharomyces cerevisiae*, whose genome encodes 6200 proteins, and has over one-third as many genes as the fruitfly *Drosophila melanogaster*.

Stover and colleagues used bioinformatics techniques to compare the *P. aeruginosa* genome with those of other bacteria

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