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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Box 1. Cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive inherited disorder that causes an abnormality in airway epithelia that prevents those affected clearing bacteria from their lungs and leaves them vulnerable to serious infections. The mutation, which is common and is carried by 1 in 22 Caucasians, causes a defect in the CF transmembrane conductance regulator (CFTR) involved in chloride ion excretion from airway epithelia. The defect closes the channel and prevents chloride ion excretion. This leads to a dramatic reduction in excretion of sodium ions and water. With little water in the airways, the mucus becomes thick and sticky and susceptible to colonization by *Pseudomonas aeruginosa*.

Current therapies for CF include physiotherapy to clear the airways, antibiotics to clear lung infections, treatments to improve sodium and chloride ion transport and reduce mucus viscosity, DNAse therapy to degrade the build up of DNA from dead inflammatory cells in the airways, and gene therapy to rectify the defective CFTR gene. The use of treatments has considerably expanded the lifespan of people with CF, but none of them is wholly effective.

to help them identify gene function. Of those used for comparison, *Escherichia coli* was the nearest relative, a fortunate discovery as a great deal is already known about the *E. coli* genome.

This technique enabled the researchers to predict the function of 54% of the *P. aeruginosa* genes. Apart from the expected array of 'housekeeping' genes required for motility, adhesion, DNA replication, protein synthesis, cell-wall biosynthesis, and biosynthesis of amino acids, nucleic acids and co-factors, the genome contains a surprisingly high proportion of genes that regulate transcription (341 genes) and genes that encode molecular transporters (408 genes).

The size and diversity of the *P. aeruginosa* genome, along with the high number of regulatory genes that enable the bacterium to switch genes on and off as the prevailing conditions dictate, helps explain the pathogen's ability to survive in many different conditions. Its remarkable ability to resist attack by antibiotics is also easy to explain now the genome has been sequenced: '*Pseudomonas aeruginosa* has many genes that allow the bacteria the capacity for exceptional adaptability. We now also know that it has quite a few pumps to extrude antibiotics before their intracellular concentrations reach a crucial threshold', says Christopher Penland, CFF Director of Research.

Availability of gene chips

The *P. aeruginosa* genome sequencing project was a prime example of the benefits of cooperation between scientists. In all, 61 *P. aeruginosa* experts were involved in interpreting the genome sequence alongside the central research team. The CFF plans to encourage further cooperation by making *P. aeruginosa* gene chips available at a discounted price to CF researchers. 'The gene chips are projected to be available in late 2000 or early 2001', says Penland.

In return for the cut-price gene chips, researchers will be expected to submit their data to a common database. 'Once data are submitted, researchers can examine data on an exclusive basis for 6 months. After the 6-month period has expired, the data will be accessible to all individuals who have submitted data', explains Penland. Researchers will also have access to a data mining utility software program known as Genomax that is licensed by the CFF from Informax, and that data will be available to be examined via the Internet 24 hours a day, 7 days a week.

Reference

1 Stover, C.K. *et al.* (2000) Complete genome sequence of *Pseudomonas aeruginosa* PA01, an opportunistic pathogen. *Nature* 406, 959–964

Higher-throughput automated systems for ion-channel screening

Kathryn Senior, freelance writer

Screening for drugs that target ion channels is currently difficult and slow. Recently, an Australian company based in the USA announced further testing of a prototype system they have developed to enable higher-throughput screening of compounds that bind to a whole spectrum of ion-channel proteins. Andy Blatz, Director of Cell-Based Screening Technology at Axon Instruments (Foster City, CA, USA) says that the prototype system will require 9–12 months of testing before the device is launched, probably next November.

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