companies with a great share of the market – maybe 5–10 companies controlling 70–80% of the market.

We see increasing interactions between different players in R&D such as academia, major companies, biotechs and the contract sector. What sort of dynamics will characterize the next five years?

JD: My expectation is for a continued increase in outsourcing – especially early in the process. We will continue to see a lot more strategic alliances between big pharmaceutical firms and biotechs and also between biotechs.

KK: The contract market is not close to being saturated at this point. To cut costs and improve efficiency there will be further reliance on outsourcing. The changes in the contract sector alone will be interesting to observe – i.e. the integration of the site management organizations (SMOs) and the CROs. Large full-service CROs are becoming more global as they move into China and developing countries, but there will always also exist the niche provider CROs, specializing in, say, pediatric trials or Phase IV trials.

How would you summarize the challenges and opportunities for the industry?

KK: The major challenge is to take advantage of the current environment worldwide (but particularly in the USA) where there exists a spirit of cooperation between regulatory authorities and the industry. There is no reason to assume that this level of cooperation will last forever, and there is currently a unique opportunity for the industry to work as a partner with the FDA. For example, it should be possible to improve the process of drug development – making it more efficient and obtaining more feedback earlier in the process on clinical development and trial design. A major challenge is for companies to operate effectively on a truly global basis. However, global initiatives such as ICH provide more direction and assistance to the industry to market products in this changing environment. It is definitely a time of change for the industry but also a time of opportunity.

JD: An important challenge in the current environment is for firms to discover more breakthrough products than they have in the past. Alongside that is the opportunity to take advantage of exciting scientific opportunities, which requires improved networking with academic research in the drug discovery area.

Information about research programmes, publications, workshops and other issues associated with the Tufts Center for the Study of Drug Development can be found on the Center's website (http://www.tufts.edu/med/research/csdd).

David Hughes

Natural extracts – a new perspective on assessing diversity

A revolutionary new technique for assessing molecular diversity in natural extracts has been developed by scientists at Eli Lilly's research laboratories in Indianapolis, IN, USA. The algorithmic technique based on chromatography and mass spectrometry assesses natural extracts using relevant information directly related to the drug-like compounds being searched for, rather than to any biological classifications of the source. The method will help researchers decide whether to pursue particular leads in different extracts without having to carry out isolation and assaying of individual compounds that could be dead-ends.

High-throughput screening is an everyday technique for screening huge libraries of known compounds, often generated by combinatorial techniques. Drug researchers, however, are still in hot pursuit of novel molecules in natural products that might display interesting biological activity.

Comparing extract diversity

Randall K. Julian Jr of Lilly's Natural Products R&D and his colleagues believe that it is possible to reduce the technical demands of natural extract screening. 'If two extracts are overly similar, the likelihood of them containing the same compounds is high,' says Julian. It would be like reinventing the wheel to isolate and screen such extracts, but assessing similarity is not trivial. Julian's technique allows the team to assess molecular diversity among paired extracts in a simple way without recourse to taxonomy, which acts only as an indirect predictor of chemical diversity. They can then decide in which extracts to invest limited resources. 'This investment takes the form of

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identifying and isolating the specific compound responsible for the activity – a time-consuming and expensive exercise,' adds Julian.

Julian's idea is based on using HPLC coupled to electrospray mass spectrometry. The HPLC separates the components of an extract and the ESI-MS then classifies each according to its major molecular ion. This effectively labels each sample 'tapped off' from the HPLC with a mass to charge ratio (m/z).

The team then uses a computerized image-analysis system to reduce the data from the HPLC and EIMS to a list of m/z values and chromatographic retention times. A computer algorithm then compares the lists in pairs and calculates a similarity index between samples. The index, explains Julian, is based on the number of ions common to both and scaled from 0 to 1.

Mining biodiversity

With the number of estimated species standing at several million, there are plenty of potential extracts to assess. Julian and his team have decided to test their technique on microbial fungi – an area of biology that pharmaceutical companies are tapping more and more.

They analysed 88 unknown fungal extracts isolated from soils and analysed the compounds in each with their HPLC-MS technique. An extract from an actinomycete broth known to produce tylosin factors was interspersed into the fungal samples to act as a control, giving information about HPLC column stability during the overall testing as well as an indication of sensitivity.

Using HPLC provides a compromise between speed and resolution of separation, while the very sensitive ESI-MS produces spectra free of fragment ions, which allows a single m/z to be obtained for each sample in the extract. They observed similarities ranging from 0.8 (replicates) to 0.1 (very dissimilar). 'This information can be used to judge the chemical diversity of natural extract samples,' explains Julian.

Julian and colleagues describe their HPLC-MS technique in *Analytical Chemistry* (1998) 70, 3249–3254.

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In short…

Myriad Genetics (Salt Lake City, UT, USA) has been awarded a US patent entitled *Island Hopping – a Method to Sequence Rapidly Very Large Fragments of DNA* (US-A-5807679). The patent covers a method of dramatically accelerating the sequencing of large fragments of DNA, and thus, the method will offer great potential for the swift discovery of disease-related genes and sequencing complete genomes of various species.

The method is called 'Island Hopping' after the set of single bands of DNA, or 'islands', that are selected for initiation of the sequencing process. Using parallel processing of samples and automatic ordering of DNA fragments, this method reduces the volume of sequencing and increases the speed of the overall process. Peter Meldrum, President and CEO of Myriad Genetics, believes that Myriad's technology is the most efficient high-speed method for full-length sequencing of disease genes.

Through this new high-speed, automated DNA-sequencing technology, Myriad now has the ability to process large volumes of sequence data, which is an essential element in both positional cloning of disease genes and drug discovery through Myriad's ProNet™ protein-interaction technology. Proteins with putative therapeutic value are identified through ProNet™, and the gene responsible for their production can then be isolated and sequenced for potential application in gene therapy.