The *Discussion Forum* provides a medium for airing your views on any issues related to the pharmaceutical industry and obtaining feedback and discussion on these views from others in the field. You can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. Publication of letters in this section is subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views provided are those of the authors and are not intended to represent the views of the companies they work for. Moreover, these views do not reflect those of Elsevier, *Drug Discovery Today* or its editorial team. Please submit all letters to Joanna Owens, News & Features Editor, *Drug Discovery Today*, e-mail: Joanna.Owens@elsevier.com

Probing the nature of microarray-based oligonucleotides ▼

Barrett and Kawasaki's recent review [1] of the three forms of probe (short oligonucleotides, long oligonucleotides and cDNAs) used on microarrays raised several points of discussion. None was more important than their assertion that the microarray field is in great need of standardization. Many would point to the nomenclature, annotation and sequence of array probes as being the prime example of this lack of standardization – and I agree. However, I always use the word 'probe' gingerly when referring to DNA arrays, and suggest that when standardization does finally occur we should clarify what to call those dots on the arrays. Historically, scientists labeled a defined oligonucleotide sequence, called it 'the probe' and hybridized it to a target population of nucleic acid. With microarrays, the process is reversed: the target population is labeled, and hybridized to a collection of defined oligonucleotide sequences. This inversion of the original procedures has confused many people regarding the definition of a probe. For example, does 'probe' refer to the defined gene sequence(s) under investigation or does it refer to the labeled component of the hybridization mix? Barrett and Kawasaki, like many others, use the word 'probe' to describe the labeled component. The *Henderson's Dictionary of Biological Terms* [2] defines 'probe' as a 'well-defined, labeled fragment of DNA or RNA used to find and identify corresponding sequences in nucleic acids by selectively hybridizing with them'. 'Well-defined' seems to be the key here, and suggests to me that the dots on the arrays, and not the labeled population, are the probes. Perhaps this indicates that the definition of a 'probe' in the context of molecular biology needs modernizing and/or redefining.

Undoubtedly there are those who think that this point is a disdainful lesson in semantics. Of more interest to them might be the authors' more pragmatic suggestion that the long oligonucleotide-based approach is a good candidate to replace cDNA arrays. This might well be the case for standard laboratory species whose genomic sequences have been characterized extensively. However, cDNA-based arrays might find a more enduring niche among those working on species whose genomes have not been so well characterized. For such species, cDNA-based arrays offer two advantages. (1) Commercially available arrays for human and standard laboratory species might be useful in cross-hybridization experiments. Such hybridizations are more likely to be successful with longer sequences because there is more opportunity for sufficiently similar sequences to exist and permit cross-hybridization. (2) For those wishing to generate their own species-specific arrays, it is relatively easy to generate a cDNA library from a target species, PCR the individual genes without prior knowledge of their sequences, array the PCR products, and then probe the array with RNA obtained from the developmental or chemical exposure models of choice.

An issue that will have some bearing on the standardization issue is how far and fast technology for the design and production of probes for two-dimensional DNA arrays will advance. Admittedly, there is work to be done in designing probes that demonstrate optimum specificity and hybridization characteristics. However, the recent development of nucleic acid analogs such as 'locked nucleic acids' (LNA [3–5]) might also play a significant role. LNAs are structurally similar to RNAs, and have several properties (e.g. increased thermal stability, high affinity for other nucleic acids, and nuclease resistance) that make them a good candidate to replace DNA-based probes on microarrays. Whether this will occur or not, only time and tide will tell.

References

1 Barrett, J.C. and Kawasaki, E.S. (2003) Microarrays: the use of oligonucleotides and cDNA for the analysis of gene expression. *Drug Discov. Today* 8, 134–141

2 Lawrence, E. (1990) *Henderson's Dictionary of Biological Terms*, Longman Scientific & Technical

3 Constans, A. (2002) Toward a 'one-chip-fits-all' array. *The Scientist* 16, 49

4 Elayadi, A.N. *et al.* (2002) Implications of high-affinity hybridization by locked nucleic acid oligomers for inhibition of human telomerase. *Biochemistry* 41, 9973–9981

5 Thacker, P.D. (2002) Locking down locked nucleic acids. *The Scientist* 16, 49

John C. Rockett

Reproductive Toxicology Division (MD-72)
National Health and Environmental Effects Research Laboratory
Office of Research and Development
US Environmental Protection Agency
Research Triangle Park
NC 27711, USA