Chapter 1
The Microarray Paradigm and Its Various Implementations

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1.1 The Beginnings

The essence of the microarray approach is its "highly parallel" nature, that is, the fact that information on a large number of entities is obtained in a single experiment, thanks to a regular arrangement of "probes" (whatever their molecular nature may be) on some kind of support and on assessment of signals detected after incubation with a sample (usually labelled). The origins of this technology can be traced to the widely practised method of "colony screening" that was used, once the cloning revolution had begun in the early 1970s, to identify a few bacterial or phage clones of interest among the many thousands present in a given library (Fig. 1.1). It is true that the arrangement of clones in such experiments was random and therefore unrepeatable, but it was only one step from there to "ordered libraries" in which individual genomic or cDNA clones had been picked from Petri dishes, then distributed into microtiter plates, and could subsequently be arrayed on a suitable support (usually a nylon or nitrocellulose membrane). The essential feature was that detection of a positive (radioactive) signal at a given position on the membrane immediately identified specific clone(s) that could then be recovered from storage and used for further experiments (Fig. 1.2). This scheme was largely pioneered by Hans Lehrach's group in Germany, who adapted or developed the necessary instruments to perform these sophisticated (for the time) manipulations (Michiels et al. 1987; Craig et al. 1990; Lennon and Lehrach 1991). It was just a further step from there to use such "high-density filters" to assess gene expression, using arrays of cDNA clones (or their DNA) and labelled cDNA prepared from total mRNA of a given cell line or tissue (Gress et al. 1992), as well as the newly appeared imaging plate systems (Amemiya and Miyahara 1988) that allowed quantification of the signals. This approach was used by several groups to perform studies measuring simultaneously the

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Fig. 1.1 A "colony filter" as used *circa* 1980 to find genes in clone libraries. Bacterial clones containing human DNA inserts are spread on nutrient agar in a Petri dish (ca 3,000 per dish). After growth of colonies, a nitrocellulose filter is placed on the plate, then removed and treated to lyse the bacteria and denature the DNA. The filter is then incubated with a radioactive probe corresponding to the gene of interest. After exposure to X-ray film, the "positive" clones can be seen and can be picked from the original Petri dish using the orientation marks drawn in radioactive ink

expression of hundreds or thousands of genes, an impressive feat at the time (Nguyen et al. 1995; Zhao et al. 1995) and, together with systematic tag sequencing of cDNA clones as pioneered by Craig Venter (Adams et al. 1991), gave the first general outlook on the human transcriptome as well as on that of a number of model organisms.

1.2 The Essential Miniaturisation Step

The detection system used in these experiments was radioactivity, that is, the cDNA prepared from the mRNA of the sample was labelled by incorporation of radioactive nucleotides containing 32P or 33P phosphate. Although this provided high sensitivity and a wide dynamic range, it severely limited the possible resolution and was also poorly adapted to many working environments. Thus, the first demonstration of an expression array using fluorescent labelling of the sample and detection with a confocal system (Schena et al. 1995; 1996) represented an important advance and is generally considered as the beginning of the microarray era. Meanwhile,

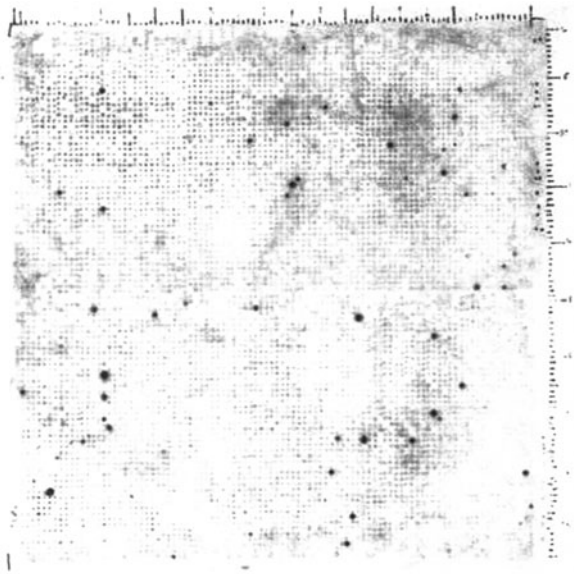

Fig. 1.2 A "high-density filter" used to access clone libraries (*circa* 1990). cDNA clones that have been picked from a library into microtiter plates are arrayed (100 × 100) on a large nylon filter. Hybridisation of this filter with a radioactive probe specific for the gene of interest detects several positive clones that can be directly recovered from storage for further study. Successive hybridisations of the same filter (or of replicas thereof) accumulate information on the 10,000 clones represented

the use, as probes, of oligonucleotides synthesised in situ had been described by Ed Southern as early as 1989 (see Fig. 1.3; Southern et al. 1992) and later by Steve Fodor (Pease et al. 1994). Rapid development followed, with commercial suppliers progressively taking over from research laboratories, and expression profiling using DNA arrays became a major approach in the late 1990s and early 2000s, with progressively more complex arrays that generally used oligonucleotides (pre-synthesised or synthesised in situ) as probes, and relied on fluorescent detection, although radioactivity kept some supporters and colorimetric methods were also implemented (Chen et al. 1998). By 2001, it had become possible to assess all (or most) of the human genes using a small set of commercial arrays, and by 2004, a single chip gave access of the whole human transcriptome.

1.3 Why Such Rapid Success?

The adoption of microarray technology (essentially for expression profiling in this first phase) was extremely rapid, both in terms of publications (hundreds in 2000, thousands in 2005) and of market size. It is clearly a technology that came at the right time: knowledge on genes and genomes had been accumulating for some time,

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