simple normalization procedures will not be adequate for large gene expression studies.

An attempt was made to discern from literature the genes that are the most relevant for the application. This approach is a completely closed system that will only provide results on strictly predetermined genes, which may already be well characterized. This microarray will not be representative of the entire genome. The advantage of smaller size and reduced complexity is that it facilitates the task of making a high specificity, high quality microarray for quantitative use. This is useful for focusing on mechanisms of action, when they are known. Other advantages of using such a hypothesis-driven microarray include costs, manpower, ease of use, and ease of data interpretation. However, the major disadvantage is the limited number of genes chosen. No amount of forethought can really predict all the important gene expression changes that may occur. In addition, the rat genome has yet to be completely sequenced and, as a consequence, annotation is difficult. At the moment, one of the most advanced rat array systems available is that from Affymetrix (A chip has 15,000 annotated genes and the B chip a further 13,000 ESTs).

6. TURNING DATA INTO KNOWLEDGE

It is well established that the expression of certain genes in intoxicated or diseased tissue is altered (over-expressed or suppressed). Continued elucidation of the genetic changes that drive toxicity and/or cancer progression is yielding new and mechanistically based information (Fig. 6). Nucleic acid based expression patterns are proven valuable tools for an early detection of toxicity and disease, for the confirmation or exclusion of a cancer diagnosis based on suspicious and nondiagnostic material, and for an assessment of the tumor burden and of the response to preventive approaches. Toxicity is a heterogeneous event driven by a complex array of genetic changes that may lead to an uncontrolled growth and potentially metastatic spread. The changes in gene expression profiles can be used as molecular fingerprints and for the early detection of metabolic deregulation. Based on our emerging knowledge of the gene expression profiles, various databases to provide novel information on drug profiling studies and to predict organ- and tissue-specific toxicity are being developed. Hence, the determination of patterns of altered gene expression will provide a rational basis for drug development decisions in a cost-effective and timely fashion. In general, toxicogenomic research will provide fundamental information on the mechanism of action of chemicals at the transcriptional level; and modulation of gene expression may predict toxicities not otherwise observed in preclinical or clinical drug studies.

In conclusion, microarrays are the tools for molecular and evidence-based medicine and hold promise to greatly impact the drug discovery