Genomics and drug discovery

Stuart L Hazell
Faculty of Sciences
University of Southern Queensland
Toowoomba, QLD 4350
Tel: (07) 4631 2254
Fax: (07) 4631 2721
E-mail: S.Hazell@usq.edu.au

Introduction

Genomics represents a new tool in drug discovery. Microbial genomics have been at the forefront of a new era of whole cell molecular biology because genomic data provides a quantum leap in available genetic data. But while the tool is valuable and important, it is not the complete answer.

While releasing vast amounts of genetic code, the microbial genomes pose new questions, especially in terms of the large amounts of genetic information that cannot be categorised by function. Today we are beginning to undertake systematic studies of the network of interactions of genes and gene products that must be met if we are to increase our awareness of microbial physiology and pathogenesis and, ultimately, the management of disease.

How does genomics aid in drug discovery? This question can be answered in part by reference to technologies as diverse as bioinformatics, microarray technology, functional genomics, proteomics and high throughput screening. Specifically, we can look at the identification of novel therapeutic targets through a more complete understanding of the biochemistry and physiology of an organism. In addition we can seek to enhance our understanding of disease processes at the molecular level to reveal key determinants of virulence that may represent potential drug targets.

A major leap forward will be our capacity to undertake genome sequence comparisons (microbe-human or microbe-microbe) allowing identification of targets having the highest potential to minimise toxic side effects in the host or undesirable interactions (e.g. perturbation of the normal microbiota).

To achieve some of the above requires new approaches. A clear example is high throughput screening. Using technology such as microarrays and proteomics, whole genome expression profiles can be used to identify putative targets and so enhance the drug discovery process. This includes the potential to examine the interactions between genes and/or expressed proteins such as in signal transduction. Once a target has been identified it is hoped that new chemical entities can be developed that may avoid the resistance problems associated with 'natural' antibiotics. The design of novel chemical entities is being enhanced by the growing capacity to predict protein structures from genomic data ('structural genomics') and thereby accelerate drug design.

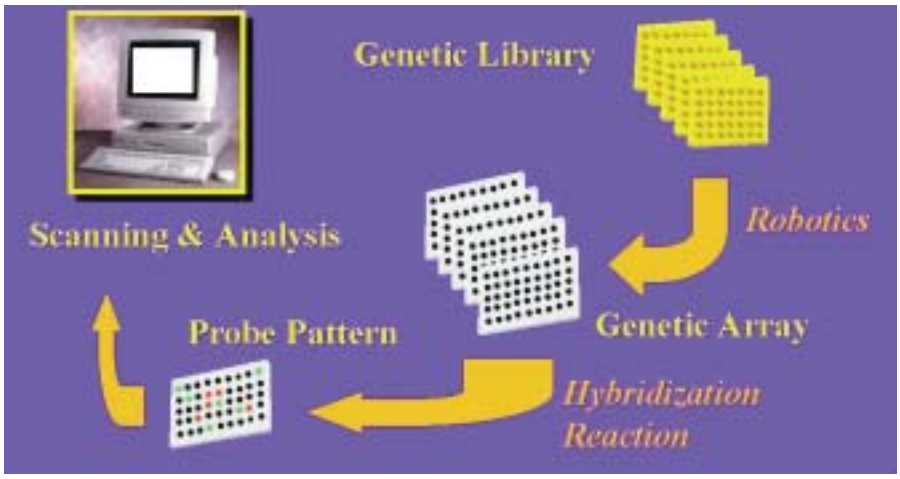
Yet genome comparisons represent only the first steps in the exploitation of genomic data for drug discovery [1]. Genes identified as being 'unique' and thus of interest need to be further interrogated looking for clues to function. Having identified a function for a potential drug target it is then necessary to establish that the target is essential prior to undertaking inhibitor synthesis. This in itself can be problematic as we are beginning to fully appreciate that a gene product that is not essential *in vitro* may be essential *in vivo*.

Microarrays

DNA microarray technology is one approach to gene function discovery. This is based on the simultaneous interrogation of a complete set of genes within a given organism. The genes of interest are arrayed on a suitable support and thus can be used as probes that may, for example, be used to explore gene expression within a prescribed set of circumstances [2]. One example of this approach has been the demonstration in *Mycobacterium tuberculosis* [3] that the antibiotic isoniazid induced genes encoding for proteins physiologically related to the mode of action of the drug.

To test their observations further, the authors tested the effect of ethionamide (which inhibits the same metabolic pathway) and noted that this drug induced the same genes as isoniazid. This research team also noted selected genes were not induced in isoniazid resistant isolates. Importantly, by using a microarray the authors discovered a number of genes induced by isoniazid

Representation of the generation, probing and analysis of a microarray.



that encoded proteins not known to be related to the mode of action of the drug. Thus potential new drug targets in isoniazid sensitive and resistant strains could be identified. Therefore one objective may be considered the removal of 'bottle necks' in the process of target identification [4, 5].

Structural genomics

As noted in a recent review in *Science* [6], structural biology has turned the corner. We are seeing today that modelling and high speed computing is allowing greater accuracy in the processes of predicting protein structure.

This approach has limitations, a classic example being the impact of molecular chaperones on the final conformation of a protein. However, it is not unreasonable to expect that advances in this field will facilitate the development of better computational systems.

We are approaching a time when biomedical science will have the tools that will allow both the identification of novel therapeutic targets and allow us to model drug-target interactions. That is, identify targets and design novel lead compounds *in silico*. Indeed, we may even be able to test for potential adverse effects and/or selective toxicity using the same technology.

References

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