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.

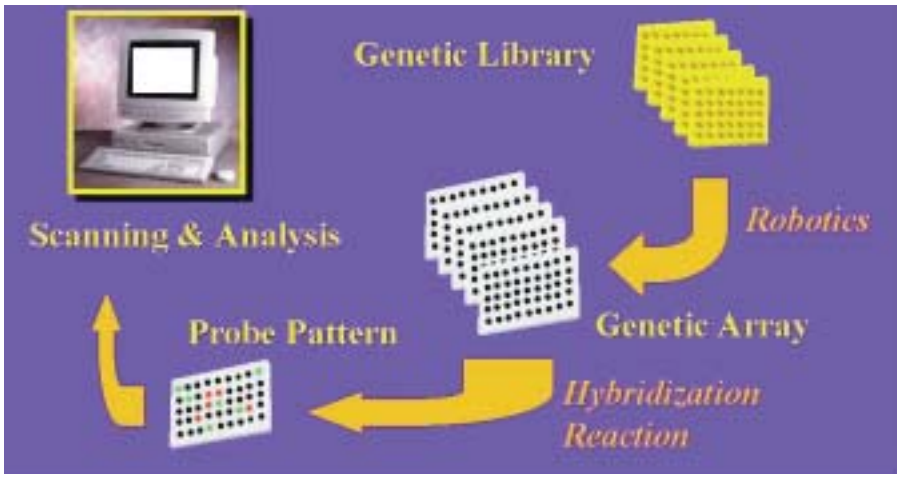
Yet genome comparisons represent only the first steps in the exploitation of genomic data for drug discovery [1]. Genes identified as being 'unique' and thus of interest need to be further interrogated looking for clues to function. Having identified a function for a potential drug target it is then 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

1 Moir DT, Shaw KJ, Hare RS & Vovis GF (1999). *Antimicrob Agents Chemother* 43:439-446.

2 Gingeras TR & Rosenow C (2000). *ASM News* 66:463-467.

3. Wilson M, DeRisi J, Kristensen H-H *et al* (2000). *PNAS* 96:12833-12838.

4. Rosamond J & Allsop A (2000). *Science* 287:1973-1976.

5. Cafrert S, Stewart FP, Swarna K & Wiseman JS (1999). *Current Opinion in Drug Discovery & Development* 2:234-238.

6. Service RF (2000). *Science* 287:1954-1956.

Old therapies, new science

Thomas V Riley
Department of Microbiology
The University of Western Australia
Division of Microbiology and Infectious Diseases
Western Australian Centre of Pathology and Medical Research
Queen Elizabeth II Medical Centre
Nedlands WA 6009
Tel: (08) 9346 3690
Fax: (08) 9346 2912
E-mail: Triley@cyllene.uwa.edu.au

With the emergence of antibiotic resistance as a major public health problem and the apparent decline in pharmaceutical company drive to produce new antimicrobials, there has been an increase in interest in revisiting remedies and agents once popular before the advent of the antibiotic era [1].

This makes sense – it is obvious that many of these therapies worked hundreds if not thousands of years ago, although the scientific basis of some is rather obscure. With others, however, good data exist on both *in vitro* and *in vivo* efficacy. Randomised clinical trials have been completed with good outcomes. Three compounds or groups of compounds used in traditional medicine – in which there has been a major resurgence of interest in the last 30 years to the extent that one has become an accepted therapy – are garlic, artesunate and essential oils.

Garlic

Garlic *(Allium sativum)* was once used by millions to ward off vampires and was first prescribed in 3000 BC by the Sumerians, a group who lived and still live in present day Iraq. Garlic has a wide spectrum of action and is considered to be antibacterial, antiviral, antifungal and antiprotozoal [2].

However, although garlic has been used for its medicinal properties for thousands of years, investigations into its mode of action have only occurred relatively recently. Early steps in identifying the active constituents of garlic were the discovery that the compound allicin (allyl 2-propene thiosulphinate) is formed when garlic is crushed and that its formation depends on the action of the enzyme allinase.

Methyl and allyl sulphide derivatives of allicin are formed by the steam distillation of crushed garlic [3]. The diallyl sulphide components of garlic oil are the most active and this activity is inversely proportional to the number of disulphide bonds, diallyl monosulphide having greatest activity. These diallyl sulphides inhibit various bacteria and fungi at concentrations similar to conventional antimicrobials [4].

Several recent studies have shown good activity of garlic materials against *Helicobacter pylori* [5] and clearly garlic has a long history of safe use. Epidemiological studies show a reciprocal relationship between gastric cancer, which is strongly correlated with *H. pylori* infection, and the consumption of *Allium* vegetables [6], suggesting the further investigation of garlic as an antimicrobial is warranted.

Artesunate

Traditional Chinese medicine has provided us with qinghaosu for the treatment of malaria. The isolation of artemisinin in 1972 by a Chinese scientist lead to the development of a number of derivatives and an impressive body of work relating to the understanding of the chemistry, pharmacological profiles, toxicology, metabolism and effects on the malaria parasite [7].