



## VCE BIOLOGY 2006–2009

### Introduction

There has been an ‘explosion’ of knowledge and understanding, and research in biology over the last 10 years. The successful completion of the Human Genome Project is one example of this rapid expansion where laboratory work and computer analysis operated in tandem to produce profound outcomes in a relatively short time span.

Contemporary studies in biology require students to develop an understanding of molecular biology including terms such as genome, proteome, bioinformatics and phenomics. Students should also be encouraged to consider the future possibilities of research, breakthroughs, and any associated community, social or ethical issues.

To assist teachers to implement the VCE Biology Study Design 2006–2009, the following expert paper has been prepared to provide up-to-date information and explanation of important terms and concepts, and is of relevance to Units 3 and 4.

## MOLECULAR BIOLOGY

By Stewart Jackel

Molecular Biology is one of the most rapidly growing areas of biology. It is concerned with the molecules of biological systems, namely of cells and viruses. Molecular biology involves the broad areas of biochemistry, cell biology, microbiology and genetics.

The techniques of molecular biology are based in the studies of biology and medicine and are applied to:

- Genetics: the science of heredity, the study of similarities and differences between individuals including cell biology, reproduction and population relationships
- evolutionary biology: the science of the relationships of populations over long periods of time including DNA sequencing, protein analysis, and electron microscopy
- bioinformatics including
  - micro-array data analysis: a new technology used to investigate the expression levels of thousands of genes simultaneously using statistics and computer science
  - statistical genetics: using statistical methods to localise genes that influence traits
  - biological sequence analysis: the extraction and use of information derived from the sequence of biological macromolecules such as DNA, RNA, and proteins
- biotechnology: the application of biological processes to the development of biological products and processes including wine making, cheese making, hormone and vaccine production, crop and animal breeding, development of insect-resistant crops, disease diagnosis and other medical applications
- genomics: the study of a genome, the total genetic material of an individual or a species
- proteomics: the study of an organism's total complement of proteins
- phenomics: science which integrates the genomics and proteomics of an organism into a survey of its phenotype.

### Bioinformatics

This is a new discipline that combines mathematics, computer science and biology. It allows the modelling of large amounts of data generated by research into sizeable studies such as The Human Genome Project. Information and Communication Technology (ICT) now enables rapid database design, construction of algorithms and design of artificial intelligence systems to manage, retrieve and cross-match data and carry out comparative analysis of entire genomes. This is often called Bio-IT.

The huge amount of data in the genome databases contain information about genetic predisposition to diseases, for example. Staff at The Walter and Eliza Hall Institute of

Medical Research (WEHI) and the Cooperative Research Centre for the Discovery of Genes for Common Human Diseases have produced a completed genotyping of the candidate regions in a large collection of individuals with multiple sclerosis. The link between a specific gene, *IL-12p40*, and type 1 diabetes has also recently been published.

## **Biotechnology**

Australians have played a significant role in the history of molecular biology. Researchers at Macquarie University were among the pioneers of proteomics and coined the term. WEHI has a major unit researching bioinformatics. The Australian Academy of Science was recently able to organise a ‘high flyers think tank’ of Australian scientists involved in the biotechnology of horticulture, crops production, new plant products (or pharming), livestock and aquaculture.

In its initial stages molecular biology focused on genetic engineering – transferring genes from one organism to another to enable a plant, animal or bacterium to manufacture substances it would not normally produce. The first gene-cloned product, the human protein insulin, appeared in 1982 to replace bovine (beef) and porcine (pig) extracted insulin. Bacteria can now be genetically engineered to produce other biologically active substances including human growth hormones and clot buster proteins for use in the treatment of heart attacks and strokes.

More recent techniques involve gene transfer to grow tomatoes that can be frozen and thawed, vegetables with higher nutrient value, and plants that are able to resist diseases, pests and herbicides. Bananas can now be genetically engineered to produce vaccines for diseases such as hepatitis. DNA matching is now a commonplace tool in forensic science and molecular biological techniques can be used in conservation biology to control feral animals and develop disease-resistant endangered species.

## **Genomics**

DNA is a cell’s information store and its means of transfer from one generation to the next. RNA acts as a temporary store of the information encoded in DNA and translates that information into proteins. The information in both these types of molecules is held in the linear sequence of the nucleotides of the nucleic acid.

The term genome refers to the complete genetic material of a cell or the entire genetic complement (all possible genes) of the individuals of a species. And genomics refers to the study of a species’ genome (the suffix -omics means study of).

Typically, research involving genomics also involves related fields of study. In Australia, for example, work on genes controlling adaptation to environmental stresses in wheat and barley also involves the stresses: salinity, drought, high and low temperatures, waterlogging, and mineral deficiencies. In another example, a cooperative venture between Australian and Indian interests is investigating genes in the malaria parasites *Plasmodium falciparum* (human) and *Plasmodium berghei* (rodent) and the role of the proteins they produce.

## **Proteomics**

DNA stores information and proteins form the basic structures and perform the basic functions of life systems. The biological functions of DNA, RNA and protein molecules are mostly encoded in the linear sequence of their basic units. Analysis of the unit sequences of DNA, RNA or proteins can reveal much about their function. It is now possible to make some reasonable predictions about the three dimensional structure and function of a protein from its primary structure and information based on the structure of the related gene. This is complicated by the fact that one gene may be responsible for the production of many proteins depending on the editing of the mRNA and the environment of the cell concerned.

## **Phenomics**

The genotype of an organism, the proteins it produces and the cellular environment, all of which contribute to the phenotype of the organism, are involved in the complex study termed phenomics.

Many human health problems, such as cancers, autoimmune diseases, allergies, cardiovascular disease and osteoporosis are brought about by a mismatch between our genetics and our environment. In some cases we know how to fix the mismatch but in many cases we are still confounded by the complexity of the pieces of the interacting jigsaws. Such is the emerging field of phenomics: the phenotype and its contributing imperatives.

## **Research**

An enormous amount of research is currently underway in Australia in all areas of molecular biology.

### *Potassium ion channels*

Potassium channels in the membrane of cells are critical for modulating action potentials in the central nervous system. A team at WEHI has investigated the three-dimensional structure of a potassium channel and the amino acid residues that form the “activation gate” of the channel. It is now possible to deduce how movement of these residues is coupled to the opening and closing of the pore.

### *Inter-cell communication*

Cells communicate with each other by means of cytokines – protein messengers. A cytokine binds to its cognate (chemically aware) receptor on the cell surface and releases a signal within the cell stimulating a specific action. Too big a response by the cell can be dangerous, so it is important that the signal does not last too long. Groundbreaking research in the Cancer and Haematology Division at WEHI led to the discovery of a family of proteins responsible for the moderation: the SOCS (suppressor of cytokine signalling) proteins. To define their physiological roles, mice have been engineered which lack expression of individual members of this family of molecules. Previous studies have revealed that SOCS-1 is critical for preventing inflammatory disease and that SOCS-2 is needed to prevent gigantism. The team

found that SOCS-3 controls not only the duration of response to the cytokine interleukin-6, it inhibits pathways activated by other cytokines.

#### *Tracking down susceptibility to multiple sclerosis*

Multiple Sclerosis (MS) is the most common neurological disease of young adults, with an overall incidence of 1 in 1000 individuals. Destruction of myelin in the central nervous system produces cumulative disability and only a proportion of patients benefit from current therapies. A team of clinicians, molecular biologists and statisticians from the Development and Neurobiology team and the Genetics and Bioinformatics team at WEHI have undertaken a major program to search for genes that predispose to MS. They have now completed a genome-wide scan of multiple sclerosis patients and unaffected families in Tasmania. Over a three year period, about 1 million genotypes have been assembled. Preliminary analysis has identified several patterns of inheritance that appear to be unique to MS patients. The study is now being extended to Victoria.

#### *Deciphering the molecular anatomy of the brain*

A consortium of scientists at WEHI and The University of Melbourne is undertaking an ambitious program known as the Melbourne Brain Genome Project. The first goal is to catalogue the gene expression profiles of different regions of the mouse brain. Much of the work is taking place in the Australian Genome Research Facility. They are using a Serial Analysis of Gene Expression (SAGE) technology. They have compared patterns in the hypothalamus – which regulates fundamental processes such as hunger, satiety, respiration, body temperature and water balance – and the neocortex, which is responsible for cognitive functions such as language, learning, memory and complex thought. Early reports suggest that gene expression in the neocortex is somewhat more complex than in the hypothalamus. The cortex showed higher levels of genes involved in higher order functions such as cell communication and neural development, whereas the hypothalamus expressed higher levels of genes associated with the homeostasis of calcium and metal ions, ribosome production and respiratory gas exchange.

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[http://www.wehi.edu.au/about/highlights/WEHI\\_Highlights\\_2003.pdf](http://www.wehi.edu.au/about/highlights/WEHI_Highlights_2003.pdf).

#### *Development of DNA microarrays*

The Australian company, Axon Instruments, was traditionally a supplier of electronic amplifiers and software for academic and pharmaceutical company researchers studying electrical mechanisms in the body that underlie essential functions such as memory, learning, pain and muscle control. The company had developed products to use fluorescence imaging to visualise calcium influx in neurons but had not worked out how to make those products commercially significant. They set up an internal technology task force of their own employees and an expert from Stanford University. They identified an opportunity to adapt their fluorescence imaging skills to genomics, a completely new market. The company is now the largest supplier, worldwide, of

laser scanners for DNA microarrays. A DNA microarray is a grid of DNA spots on a surface, such as a silicon chip, that is used to measure the expression of many genes.

### *Pathogen resistance in wheat*

The Genetic Manipulation (GM) is thought to be a superior solution for the problem of wheat rust. 'Pure' resistance genes can be cloned and non-essential genetic information removed. These can be stacked, several genes at a time and introduced into wheat through transgenic mechanisms. The stacked genes resist pathogen evolution so the resistance lasts much longer than that provided by a single rust-resistant gene. Because the stacked genes stay together on a single DNA molecule they essentially segregate as a unit.

### *Biodegradable plastics*

Polyhydroxy-alkanoates are linear polyesters produced naturally by soil-borne bacteria. The most common of these is poly-beta-hydroxybutyrate (PBH) produced using only three enzymes. It is produced by the fermentation of sugar or lipids. A range of different polymers can be produced from the basic molecule by varying the number of carbons in the side chain. The molecule is constructed from units which are present in plants. It is possible to take those three genes from the soil bacterium and localise them in the chloroplasts of *Arabidopsis*. (*Arabidopsis thaliana* is a member of the mustard Brassicaceae family.) Polyhydroxybutyrate accumulates in the cell without affecting the viability of the plant.

### *Silencing RNA – RNAi*

Long, double-stranded RNA molecules, dsRNAs, more than about 200 nucleotides in length have been observed to silence targeted genes, that is, genes they are homologous to. The process has been seen in a range of cell types of a range of organisms including worms, fruit flies, and plants.

RNA interference is a highly specific and very potent process that occurs naturally in cells. The process is not fully understood but we know that the machinery seeks out double-stranded RNA and cuts it into smaller strands and separates them and destroys the complementary strands.

Many viruses hold their genetic information as double-stranded RNA so RNA interference is a protection mechanism of cells against virus attack. The machinery can be used to artificially 'knockout' a specific gene in order to investigate its function, the protein it codes for and the role of the protein in the cell concerned. The production of an organism with a silenced gene – a knockout organism – is useful in the investigation of a gene that has been sequenced but whose function is not known.

Cells normally use the process to regulate the expression of its genes. mRNA is transcribed from DNA to code for proteins production and mRNA is generally long. MicroRNA – miRNA – has only about 20 to 25 nucleotides and it is not transcribed into protein; its function is regulatory. The miRNA folds back on itself like a hairpin. The RNA interference system detects these and destroys all mRNA that is complementary to the miRNA and preventing their translation. The result is that the production of double-stranded miRNA controls the expression of more than one gene.

Many allergens in foods, such as peanuts, can have disastrous consequences in susceptible humans. Some proteins and the genes that control them, which are responsible for the allergenic nature of the foods they are found in are being identified. Gene silencing can be used to inactivate the synthesis of allergenic proteins to reduce the allergenic nature of targeted grains and other foods.

Castor beans contain castor oil and also ricin. Ricin is a protein that is poisonous to humans. It causes bleeding from stomach and intestines and multi-organ failure. Gene silencing can be used to silence the production of the ricin protein in castor crops making the plant safer to grow.

### *The Future*

The first wave of genetic engineering techniques involved the translocation of a gene from one organism into another to confer a desirable feature. This was sometimes said to involve 'input traits' – tolerance to a particular herbicide or resistance to insect attack. The second wave can be considered to involve 'quality traits' such as healthier edible oils that are low in saturated fats, the production of omega-3 compounds or allergen-free and vitamin-enriched grains. The third wave involves the production of industrial and pharmaceutical crops whereby plants are engineered to produce products they don't normally make. Poppy can be modified to produce reticuline, which could be the pre-cursor of a treatment for malaria rather than morphine. Other plants could be engineered to produce new industrial oils, biodegradable plastics and human pharmaceuticals.

There are many potential benefits from pharming such as the genetic profiling of organisms to inform breeding programs and genetic modification of organisms to produce proteins and other chemicals such as contraceptives, growth hormones, a blood clotting agent, blood clotting inhibitors, industrial enzymes, and vaccines that the organisms concerned do not naturally produce.

Plants are useful for producing GM products. They are low-cost systems that can be grown in very small to very large areas. Some plants, such as rice, are easily contained – they do not easily spread to other areas. Others, such as canola, are difficult to contain because they produce wind-borne pollen.

Animals are important systems for products that cannot be made in plants. For example, at present only animal cells can naturally glycosylate (add a sugar residue to) proteins. Animals have an advantage over plants as GM tools in that they can be reasonably well contained. It is a lot easier to restrain a GM cow or a GM abalone than to confine pollen to a paddock.

Microbes are easily scalable: test tube or large commercial fermenter. Brewing systems are already in place for scaling up the production of yeasts and bacteria.

Aquaculture for food production is a substantial growth sector both in Australia and worldwide. About 150 species are being developed in projects of varying sizes ranging from very small enterprises, such as yabbies, to industrial-scale production, such as salmon. Aquaculture is a field where fundamental old-fashioned biology and recent biotechnology are developing together. As well as increasing understanding of the biology of aquatic food species research is needed into the diagnostics of diseases

of the species involved, associated treatments, the production of environmentally sustainable nutritional products, and defining and improving genetic stocks.

Biopharming has the potential to improve the environment as well as improve food production. Bioremediation may involve the introduction of genes into micro-organisms so that they produce a protein, such as an enzyme, that can degrade herbicides in a paddock. The GM product could be purified and spread or the GM microbe could spread directly. Both possibilities have problems and advantages. As well, the development of biofuels may reduce our dependence on oil. It may be possible to develop bio-indicators – fish or plants that indicate environmental contamination. This could involve a GM plant that will change colour in the presence of, for example, heavy metal contamination.

Australia has large numbers of species of flora and fauna that could be used as a source of new genes to produce products which may have commercial applications. Australia also has diverse environments so it may be possible to develop products suitable to environments ranging from tropical to temperate that are saleable for growth in similar environments throughout the world.

Commercial issues involve:

- the cost of production compared to the value of the product
- the scalability of the process
- the cost of protection of the intellectual property to prevent unauthorized replication
- sources of funding for the research
- markets for the product
- global competitors
- ethical considerations
- public acceptance
- public consultation
- public and consumer benefit
- environmental and health risks.

At least seven Cooperative Research Centres (CRCs) have been set up in Australia. They have a significant role in research in livestock biotechnology. The largest single research effort in one organisation is probably in CSIRO Livestock Industries. The field of research is huge but the work is fragmented. The flood of genomic information is increasing through better capacity to acquire vast amounts of data. Keeping pace with 'genes of interest' and prioritising those that should be investigated in depth is an on-going problem. The results of research about humans, livestock and rodents tend to be kept isolated so that linkages are not identified. As well, it is no longer possible to understand biology without significant mathematical input.



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