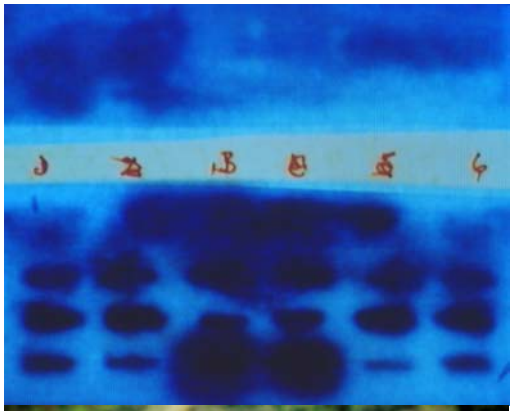

the ROYAL SOCIETY of NEW ZEALAND

BIOTECHNOLOGY SCIENCE SCAN

the ROYAL SOCIETY *of* NEW ZEALAND

2004 FUTUREWATCH

Photographs by Andy Wood, Courtney Lucas, David Straight, and Pip Brown for 'Revisioning Science', a project developed and produced by a team of Massey University photography students, scientists and researchers with funding from the Science and Technology Promotion Fund.

PREFACE

The Royal Society of New Zealand is the independent, informed and trans-disciplinary voice for New Zealand science, mathematics, social science and technology research and practice, established under its own Act of Parliament. The Royal Society is not a government agency. Our strength lies in our membership. We represent the applied, biological, earth, engineering, information, medical, physical and social sciences, mathematics, and technology in New Zealand and to the world.

We promote, invest in, and celebrate excellence in people and ideas in science and technology and put them to work as an example and inspiration to New Zealanders.

The Royal Society of New Zealand is contributing to New Zealand society by advancing science and technology education; promoting public awareness, knowledge, and understanding of science and technology; and providing expert advice on important public issues to the government and the community. We are also supporting New Zealand's science and technology community by encouraging, promoting, and recognising excellence in science and technology, providing support and a conduit for the professional needs and development of scientists and technologists, and establishing and administering for all members a code of professional standards and ethics in science and technology.

The Biotechnology Science Scan Panel

The panel, convened to undertake this science scan, was drawn from the Royal Society of New Zealand membership as well as the wider research community in biological sciences. The expertise of the panel included areas as diverse as biotechnology, animal biology, plant biology, genomics, bioinformatics, food technology, medicine and chemical engineering. Panellists came from many research sectors in New Zealand including universities, crown research institutes and industry. The aim of the panel was to provide unbiased, objective guidance and opinions in the service of New Zealand's government departments and public. In producing this report, there was spirited debate, but in the end the committee arrived at full consensus on what is included in this report. We were guided by the Ministry of Research, Science and Technology as to the nature of the report and the terms of reference. However, the content is attributable to the Panel and thanks are due to additional sources of information, named in the acknowledgments.

We hope that the information contained in this report will be educational and inspirational for its readership.

Kevin Marshall

Chair

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BIOTECHNOLOGY SCIENCE DISCOVERY – INITIAL BASELINE SCAN

A Report prepared by the Royal Society of New Zealand
for the Ministry of Research, Science and Technology, May 2004.

ABSTRACT

As part of a wider Ministry of Research Science and Technology project on biotechnology futurewatch, an initial baseline scan of biotechnological science for a government agency readership is presented. Both the historical and present contexts of biotechnological science are outlined. Key words that could form the basis of a biotechnological science scan are identified. As examples of futurewatch scanning, cell biology, systems biology, epigenetics, chemical genetics, reproduction and cloning, stem cells, transgenics, personalised medicine, and sensor biotechnology are discussed in more detail. Each section gives a description of the science, places the science in the innovation spectrum (discovery, development, application), discusses its potential application, including the level of uncertainty and what doors to alternative futures might be opened by the science, and outlines its potential relevance to New Zealand.

PANEL

The Panel, convened by the Royal Society of New Zealand, comprised:

- Dr Kevin Marshall, BE, MSc, PhD, Company Director (Panel Chair)
- Professor Paul Atkinson, PhD, FNZIAS, Chair of Chemical Genetics, Victoria University of Wellington
- Dr Rob Bower, PhD, Chief Scientist, Ovita Ltd, Dunedin
- Dr Phil Crosier, PhD, Department of Molecular Medicine & Pathology, University of Auckland
- Dr Stephen Goldson, CRSNZ, PhD, Leader of Biocontrol and Biosecurity Research Group, AgResearch Lincoln, and Professorial Fellow Lincoln University
- Professor Diana Hill, CNZM, FRSNZ, PhD, Chief Executive Officer, Global Technologies (NZ) Ltd, Dunedin
- Dr Zac Hanley, PhD, Biotechnologist, ViaLactia Biosciences, Auckland
- Dr Kathleen Logan, MRSNZ, PhD, Royal Society of New Zealand, Wellington (Panel Director)

Brief biographies are appended.

INTRODUCTION

Standing at a cross road in the forest,
Alice asked the Cheshire Cat, "Which path shall I take?"
"Where do you want to go?" he answered
"I don't know" said Alice.
"Then it doesn't really matter which path you take, does it?" replied the Cheshire Cat.

The future economic, social, cultural and environmental well-being of New Zealanders continues to be profoundly affected by developments in science and technology, both within New Zealand and in the rest of the world. New Zealand's government and people will be better able to foresee and cope with those developments, both desirable and undesirable, if systems are in place to forecast the developments and their potential impacts. Timely and quality actions can then be taken to benefit from opportunities or to mitigate disadvantages.

Background

The Royal Commission on Genetic Modification recommended that New Zealand develops a capability for biotechnology futurewatch '*to monitor and respond to emerging developments in biotechnology in terms of their implications in the New Zealand context*'. This was agreed by the Government in the Biotechnology Strategy. The Ministry of Research Science and Technology (MoRST) was assigned responsibility to: '*Implement biotechnology futurewatch activities, to be funded through Vote R, S &T'.*

The Biotechnology Strategy has a 'develop with care' approach to biotechnology and describes the Government's vision in this area as '*New Zealand responsibly develops and applies our world class biological knowledge, skills, innovation and technologies to benefit the wealth, health and environment of New Zealanders, now and in the future'.*

MoRST, as part of their responsibilities, contracted the Royal Society of New Zealand (RSNZ) to undertake a Biotechnological Science Discovery Scan to contribute to the early development of a biotechnology futurewatch capability. The science scan aimed to identify and record a range of emerging biotechnological discoveries and developments (both tools and knowledge) and possible future applications to inform policy making for a public sector readership.

The Biotechnology Science Discovery Scan project is to:

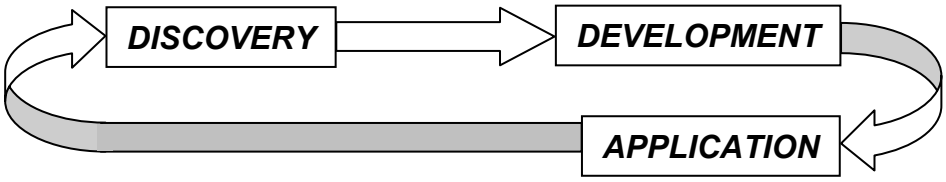
- Sit alongside a range of other initial pieces of work presenting some baseline scanning information. These pieces will include:
  - background to futurewatch/scanning
  - global trends information
  - scan of applications of biotechnology
  - social and environmental contexts.
- Be written for a central government agency audience (expected to be some 20 agencies including agriculture, bioethics, education, environment, health, science and technology, social, trade and enterprise, etc.) with the expectation that the agencies can then use the information for their own policy processes and work with their own sector.
- Focus on the global developments but also provide a sense of the relevance or implications of the developments for New Zealand science.

- Be regarded as part of a pilot exercise which will incorporate learning about the process, and need not provide a comprehensive picture of emerging science relevant to biotechnology.

The RSNZ assembled a panel to undertake this science scan over a period of five weeks. This paper is the report of that panel. This report is a baseline; it is not a complete picture and will be supplemented by further work. It is inevitably constrained by the expertise and experience of those on the Panel, and the report must therefore be construed as a living document to which other ideas will be added.

Process

The Panel agreed the following definition of its scope:



If the spectrum in innovation[1] *is seen as DISCOVERY > DEVELOPMENT > APPLICATION then the scope of this report is to suggest likely future significant opportunities in* ***biological discovery*** *pertaining to biotechnology, as distinct from development and commercial (or other) applications. Examples may be provided of outstanding developments and application problems needing innovation. Biological discovery could fall into one of three categories*:

- a paradigm shift,
- a change qualitatively different from what is being done now, or
- rate-limiting steps and/or barriers for which there is no obvious solution yet.

For the purposes of this work, a broad definition of biotechnology was adopted:

> *The application of biology to solve problems and make products – 'products via living systems'.*

The panel initially met for a day and used brainstorming to identify a large number of topics (see Appendix 1). This list of topics was edited to provide a framework relevant to the study.

A first draft of the report was prepared and critiqued by panel members, who subsequently met to agree on the material for the final report.

Historical Context

Futurewatch is not a prediction of the future, but rather 'informed guesses to the horizons of the possible'. The time-frame considered in this report is short (10-20 years) and yet, with hindsight, much can happen in such a short time. This is reflected in the exponential increase in analytical power and the plummeting costs of computers, and the emergence of the World-Wide-Web over the last 15 years. Few would have predicted the extent of those changes in 1989.

[1] Jordan, N. and Atkinson, P. 2003: Development of science discoveries in the New Zealand Crown Research Institutes. *NZ Science Review Vol 60 (2-3)*: p91-95.

Over the last 15 years, very important paradigm shifts have contributed to the rapid advances in the science underlying biotechnology. The flood of biomedical data and the overlapping and melding of traditional scientific disciplines have accelerated discovery. New, hybrid research areas such as molecular biology, bioinformatics, biophysics and nanotechnology have been in a creative ferment. Private companies have recognised the near-term value of biotechnology and, by entering the race and changing the way science is funded, brought advances, such as the rapid completion of the human genome.

The emergence of DNA fingerprinting – the greatest advance in forensic science since the development of ordinary fingerprints in 1892 – is an example of the major changes that have occurred in biological science. DNA fingerprinting was first developed less than twenty years ago to discover the true parenthood in a contested immigration case. It seemed then an unwieldy, unreliable technology, requiring large quantities of DNA and producing questionable results. Within five years the process was much simpler, efficient and supported by extensive statistics, providing a degree of reliability unavailable to other forensic techniques. It is now a trivial task to produce a 'bar code' specific to an individual (or identical twin!) from miniscule amounts of biological material. Along with its use in forensics (including identifying individuals in mass graves and victims of disasters) and in human paternity testing, DNA profiling is now routinely used to identify infectious agents in medicine and animals as well as intercept biosecurity threats. It is also used to track parenthood in breeding schemes for important animal species such as cattle and racehorses, and may soon become an essential part of the registration of proprietary plants or animals (in patents and plant variety rights).

Other examples of dramatic changes in just fifteen years are given in Table 1.

However it also true that not all current predictions will be borne out. Success at cold fusion was reported in 1989 – this would have revolutionised power generation. Scientists around the world have tried in vain to repeat the experiment. In 1989, the mutation responsible for cystic fibrosis was identified. Within 5 years the first attempts at gene therapy were being tested in sufferers. To date, successful demonstration of improved lung function has occurred in only a handful of trials and no patients have been cured, though treatment of symptoms with alpha-1-antitrypsin continues to be a major palliative advance. There are many other examples.

Revisionism will also have an effect. In some cases, what we think we know today will eventually be superseded or corrected. A trivial example from genomics is the breakdown of the false equality ‘gene = function’. Similarly, there was perhaps initial naivety in the development of transgenic plants for pest management. The rate of acquisition of insect resistance to such plants has often been rapid, sometimes obviating their potential value, particularly in intensive applications. The management of such resistance is an example of where biotechnologists meet ecologists. Such changes are unpredictable today, and are where the future looks most different from the present.

Nevertheless, it is inevitable that change will continue to be at least as dramatic in the next 15 years as it has been in the past 15 years.

Table 1 Some examples of developments in biotechnology in the last 15 years

Development	1989 position	2004 position
Profiling gene expression	J Craig Venter's seminal paper on EST sequencing[2] was still 2 years away; and vital techniques such as SAGE and microarrays were still 6 years away.	Ubiquitous; trivial. Expression of oncogenes has vastly increased the medical management of cancers.
PCR and DNA sequencing	PCR Technology was 4 years old; use of thermostable polymerase was 1 year old. Automated sequencers were only 3 years old; low throughput.	High throughput sequencing of whole gene expression profiles at a time. Used in forensics and diagnostics, revolutionising these fields.
Analyzing epigenetic effects	Primitive; some concepts were in place; low throughput techniques.	Soon to be available in massively parallel assays; huge amount of research leading to a paradigm shift in our understanding of epigentics and cellular regulation.
Knowledge of whole genomes	Human genome project still in the planning phase.	20 important animal and plant genomes and more than 80 microbial genomes[3] are now available. Genomes (ORFs) are systematically being expressed and protein 3D-structure determined with huge implications for therapeutics. Protein therapeutics are now 30% of the total drugs on the market – and accelerating.
Crop plant transformation	First patents granted; first field tests ongoing	Many high-throughput functional genomics programs in monocots; Increasing proportion of food and commodity crops in the US and Asia is now transgenic.

Present Context

The following are components of the current environment which impact on the biotechnology science futurewatch.

People

Skilled, creative people will continue to be vital to advances in biotechnology. Trained individuals are required to translate biotechnological developments, occurring both here and overseas, into the New Zealand setting. New Zealand scientists must continue to strive for excellence and conduct science according to international norms; these drivers must be preserved.

[2] Adams MD, Kelley JM, Gocayne JD, Dubnick M, Polymeropoulos MH, Xiao H, Merril CR, Wu A, Olde B, Moreno RF, et al. 1991: Complementary DNA sequencing: Expressed sequence tags and human genome project. *Science vol 252 (5013)*: p1651-6

[3] http://www.er.doe.gov/production/ober/EPR/mig_cont.html

New Zealand scientists have comparative strengths in their ability to network and to run excellent biology projects at a programme scale. There is a strong complementarity between Crown Research Institutes, Research Associations, Universities and industry research teams.

But New Zealand science is also comparatively small and it is imperative that collaborations and partnerships with industry continue. The same applies to large scale and/or specialised overseas laboratories.

Continued awareness of the laws relating to intellectual property, patenting and freedom-to-operate will be an imperative.

Public Understanding

There is an increasing public awareness and, in some quarters, anxiety about biotechnology and the science that underpins it. Increasing globalisation and strengthening of the role of multinational organisations further heighten this anxiety. Proliferating regulations, codes of ethics, and ethical committees are attempts to address these issues. Early consideration of scientific ethics and acceptability of experiments is a key for today's scientists and this can be expected to increase in importance.

The proliferation of both public awareness (not necessarily informed by sound science), and disinformation, particularly via the Internet, may impact on the rate of acceptance of the outcomes of biotechnological science.

International

International science is characterised by the high mobility of people, capital and manufacturing. Outsourcing of services to cheaper providers will continue (e.g. information technology to India, apparel and electronics manufacture to Asia, biotechnological research to Asia and USA). In some parts of the world, there is a breakdown of the traditional peer review processes and increased political interference in scientific activities; such developments have the potential to be subverted for malicious intent.

Agricultural Base

New Zealand is an agriculturally based economy, and primary industries are likely to remain the mainstay of the economy for many years. Economic wealth depends on the continuing export of food, beverages and fibre, a two-sided story which needs to weigh national imperatives against international forces and trends. The 150-year knowledge base (including production systems, compliance, global politics and trading, as well as unique fauna and flora) is a significant, unique, asset that must be used as the springboard into the future. New Zealand must continue to develop excellence in agricultural biotechnology. Key requirements will be excellence in validating or certifying food, biosecurity, environmental sustainability and the capability to prevent, or respond quickly and effectively to potential disasters (e.g. BSE, foot and mouth disease, gypsy moth).

Because modern biology can underpin many applications there will almost certainly be opportunities to leverage from agricultural developments into medical biotechnology.

Trends in Biotechnological Science

The Longstanding Challenges

There are lots of puzzles in biology but there a number of big ones that have been around for longer than 15 years that may be explained in the next 15 years. They will certainly be solved in the next 50 years. They include:

- How does embryogenesis work in mammals (i.e. how an organism develops from a single fertilised egg to an entity made up of differentiated organs and billions of cells)?
- How does the brain work?
- How do gene and protein networks work?
- What is memory in the adaptive immune response?
- How does aging occur?

Simplistically, they have not been solved because we lack the tools to dissect the problems properly. Such tools are under development today. The knowledge derived from today's and tomorrow's genomics, epigenetics, mass transcript profiling, proteomics, and electromagnetic visualisation, etc. will lead to major advances in the next 15 years. We may see the following in that time:

- Non-destructive, in vivo imaging of subcellular components;
- Fine-grain neural imaging (magneto-electric status of individual neurons in living brains);
- Non-destructive sampling of subcellular components (or even functional molecules) from living subjects;
- Theoretical tools and concepts developed from model systems (*Drosophila melanogaster, Caenorhabditis elegans, Saccharomyces cerevisiae)*, and better understanding at the molecular level of the validity and shortcomings of such models.

Complexity

The biology of living organisms is staggeringly complex (see Info Box 1). The concepts of cellular function have been radically changing in recent years. Over the next 15 years we are going to understand just how complicated they really are. Genes are rarely the end-products of interest per se, it is the proteins and other products that are blueprinted by the genes which are becoming the focus. Proteins work in networks so complex that they are unlikely to be understood by purely reductionist, logical approaches. The unit of biological research is changing and, increasingly, studies will focus on a tissue or an organism as well as the components of a cell. A key to 21st century biology will be the understanding of biological molecular regulation at a network level. Systems biology, studying the whole organism, perhaps as a 'black box', will be an effective complement to reductionist research.

Convergence of Scientific Disciplines

Convergence of scientific disciplines will continue. Increasingly, biological science is becoming indistinguishable from chemistry and physics. Computing is an essential tool and enabler of biological science. The convergence of chemistry, physics and biology is leading to an exciting range of 'smart' biomaterials. Convergence of genomics, proteomics and nutrition is leading to the development of nutritional genomics (nutrigenomics).

Info Box 1 The Cell is Complex

For years we thought the cell was a bag of stuff and for a quarter of a century we have been amending that opinion in favour of it being an incredibly organised and dynamic, purposeful structure constantly rebuilding and retasking itself and its component parts, and controlled at dozens of levels. Consider the following: DNA sequence, DNA structure, ancillary chemical modification of DNA, DNA-associated RNAs or proteins, DNA editing, DNA repair, DNA interactions with RNA or proteins, DNA interactions with DNA, RNA processing, RNA structure, RNA modification, RNA fidelity checkpoints, RNA targeting, interactions within and between RNAs, RNA degradation, RNA interactions with DNA or protein, protein production, protein structure, protein modification, protein targeting, protein degradation, protein-protein interactions, protein-nucleic acid interactions, lipid production, lipid structure, lipid targeting, lipid modification, lipid interactions with other cellular components, organelle construction and maintenance, organelle replication and destruction, intra- and inter-organelle transport – every one of these processes and many others is either known or suspected to be a control point that has effects on cell behaviour. And over 15 years we are going to discover that every one of these processes and all the others are sometimes, rarely or always used as such control points. This does not take into account cell-to-cell interactions or cell-organ or cell-body interactions all the way up to pancreatic hormones causing mood disorders in brains.

When we thought the cell was a bag of stuff in which molecules floated around bumping fortuitously into each other we were very naïve: the cell is a multipurpose, self-repairing, micro-miniaturised engine for survival that bootstrapped itself into existence and spent 4 billion years taking out all the insurance options, backup plans and design decisions it could or would ever need in the face of constraints and situations of which we as yet understand little.

Fifteen years from now, we will know better but we still will not know much (relatively speaking). Consider this an argument for monitoring, and perhaps fostering, what some call blue skies research.

Medical

The mapping of the human genome will lead to a paradigm shift in medicine as we increasingly understand the differences between individuals at the gene level, and the interactions between genes and the environment.

With increasing population we can expect the emergence of new diseases including diseases that will cross species barriers (recent examples are Ebola, AIDS, and SARS). Biotechnological science will anticipate and inform the management of such diseases. In New Zealand, with climate warming and high population mobility, we can expect new insects from abroad. Some may bring human viruses we have not hitherto worried about e.g. Nipah virus, Ross River virus and a variety of hepatitis viruses of the flavivirus family. The insect vectors will need far better mass screening diagnostics. Such mass screening diagnostics are also needed for such threats as BSE and scrapie disease.

Gene therapy may also emerge as significant for medical practice; there will be major ethical issues.

Platform Technologies

There are many platform technologies that will underpin biotechnological science (e.g. cloning, viral vectors in functional genomics and gene therapy, use of protein-only heritable material, high-throughput epigenetic analysis, chemical genetics, proteomics, transcript profiling, genetic marker acquisition, SNP analyses). All of these will become massively parallel, high-throughput, cheaper and often portable. Over the next 15 years they will enable other developments and become commodity services rather than paradigm-busters. We need to watch their development and use them appropriately as tools.

The developments in these platform technologies may not result in step changes but could possibly have major impacts. For example, Douglas Bennett in a recent discussion with MoRST staff mentioned work by NASA which may lead, in 10 to 15 years, to mapping of whole genomes in 4 hours using the tools of nanotechnology.

Traditional tools, such as mathematical genetics (both human and non-human), statistics, chemistry, physics, soil and plant science, taxonomy and all shades of engineering (including traditional biotechnology e.g. fermentation and separation and purification technologies), will also continue to be important and, in various combinations, could provide some seriously exciting and novel discoveries and tools!

Analytical Tools and Techniques

Over the next few years what might be called the 'array paradigm' will blossom. Analytical tools in biotechnology will be applied in extensive parallel, portable, surface-based motifs. What can be assayed slowly in specialist laboratories today will be analysable in bulk, in situ and in real time (e.g. epigenetic status; DNA fingerprints; microstructural features; disease status; intestinal, rumen, soil and water microflora; various pollutants and contaminants; species determination for biosecurity or medical diagnosis). High-throughput screening, robotics, automated microscopy, and large data-handling devices will be widely employed.

The main effect of this will be to accelerate data collection. The real advances will be made by those most proficient in deriving knowledge from the relevant data.

Information Technology

The accumulation of vast repositories of biological data and information (genomes, protein profiles, transcript profiles, epigenetic profiles, and most importantly the associated literature) means that developments in bioinformatics will be startling. Some of the greatest impact will be as a result of improved tools, e.g. algorithms, interfaces, methods of presenting data, integration across formats and across profile types. The specificity and selectivity of tools will improve to become broader and deeper in application than is currently available. These advances will lead to changes in information sharing and available research goals (both amenable to legislative control). The cross-compatibility of databases[4] and the subsequent increase in data movement will facilitate all this. Small players like New Zealand will need to encourage open access to data and publicly funded work, to tap in to the international effort – we cannot proceed by ourselves.

The internet has obvious enabling developments:

- New Zealand is more closely connected internationally than geography alone would dictate
- More data exists in accessible form; whether this discourages or encourages data sharing will be a matter of luck and legislation;
- More distributed effort (scientists, computing cycles, etc.) to bring to a particular problem.

[4] See W3.org for information on XML and the Semantic Web

SCIENCE FUTUREWATCH

Science futurewatch for biotechnology is extensive. Table 2 gives a list of potential keywords or phrases that could be used in a biotechnological science futurewatch database. These areas are showing particularly dramatic progress that may impact strongly on our future.

Table 2 Potential key words for database

Active packaging Amyloid structures as nanowires Animal breeding Aquaculture selective breeding cryopreservation hatchery technology polyploids Archaeal or uncultivatable diversity Array printing Artificial chromosomes Bacterial biodiversity (unique bacteria) Bioactives Biodefence Biodiversity genetics Bioinformatics and computational biology Biomaterials biomembranes biodegradable plastics, fuel, etc. from plants and microorganisms smart materials Biopesticides Bioremediation Biosensors C4 photosynthesis	Cancer Carbohydrate Cell biology Cellular immunology Chemical genetics Cloning, especially by nuclear transfer Comparative genomics Cross species pathogens DNA fingerprinting Electromagnetic visualisation Epigenetics Functional genomics Gene discovery Gene therapy Genetic markers Hydrogen cells Imaging, in vivo and fine grain neural Insect resistance Marker assisted selection Medical genetics Metagenomics Microarrays (genes, genomes, proteins) Microfluidics Miniaturisation Model systems (zebrafish, mice, rats, *C. elegans*, micro-algae cultivation, yeast, computer-based)	Nanotechnology Nutraceuticals Networks Nutrigenomics Personalised medicine Phylogenetics and evolution Plant breeding Pollution control Prion diseases Protein networks Proteomics Quantitative genetics Reproductive technologies Robotics Rumen microflora Sheep as a human disease model Small RNAs (non-translated) SNPs Stem cells Stereoselective organic synthesis for deracemisation Structural genomics Systems biology Transcript profiling Transgenics plants animals bacteria

As examples of what might be derived from such a futurewatch, the following sections provide detailed information around nine topics – cell biology, systems biology, epigenetics, chemical genetics, reproduction and cloning, stem cells, transgenics, personalised medicine, and sensor biotechnology. Each section gives a description of the science, places the science in the innovation spectrum (discovery, development, application), discusses its potential application, including the level of uncertainty and what doors to alternative futures might be opened by the science, and outlines its potential relevance to New Zealand. If relevant, the science is classified as a potential paradigm shift, or a means of clearing a bottleneck. Some key references are given so that those interested can find more information. It should be noted that the information is only an introduction to each topic and it is expected that further work will be undertaken in future to develop the information.

Cell Biology

Description

Cell biology is the academic discipline underpinning biotechnology. It is the study of '*the molecular mechanisms responsible for fundamental cell biological processes*'[5]. Cell biology seeks an understanding of the multitude of molecules in every cell and, most importantly, how they work together, separately, or in opposition, to create a living cell and ultimately a living organism. In order to use biology to solve problems and make products, we must understand what we are working with. How exactly does the multitude of single molecules work together or in opposition to create a living system like a cell? To answer this question, cell biologists study all of the following and more: macromolecular trafficking and sorting; cell adhesion and migration; signal transduction mechanisms by which cells perceive their surroundings; the controlled creation and destruction of cell components; the controlled creation and destruction of whole cells (i.e. cell cycle and apoptosis); the dynamic architecture of the cell and its components that contribute to shape, tension, movement and defence; developmental biology and growth; and the processes by which the cell blueprint, stored in the DNA and elsewhere, is read, interpreted, used, edited, maintained, copied and updated.

Innovation Spectrum

Some of the more prominent areas of today's biotechnological science, such as genetic modification, cloning and gene therapy, are based on the answers we now have to questions asked in the middle of the last century; questions like, how does DNA convey the blueprint that makes us? and, how is this blueprint read, interpreted, used, edited, maintained, copied and updated? Cell biology is arguably the greatest engine of discovery for biotechnology, and scientists today are asking more and harder questions the answers to which will be the foundation of future biotechnology.

Potential Application

Research in cell biology research underpins embryology, genetics, cloning, genetic modification, molecular breeding, biochemistry, microbiology, immunology, neuroscience and nutrition. It encompasses genomics, RNomics, proteomics and metabolomics. It develops or redeploys the tools of molecular biology, physics, genomics and chemistry (see section on Chemical Genetics). As such, it is the seed of many of the more significant opportunities that have been or will be developed into biotechnologies. Without it, none of the above fields, sub-disciplines, biotechnologies or opportunities can prosper or, in some cases, such as stem cells, even exist. Paradigm shifts and important breakthroughs in some of these fields, especially perhaps in embryology and neuroscience, will come from research in cellular biology.

Relevance to New Zealand

Research in cellular biology is an economic necessity for a biology-based economy like New Zealand. Agriculture treats the cell, indeed the organism, as a 'black box' of mysteries managed via inputs and outputs. Without a deep and practical understanding of the workings of the cell, it will be difficult or impossible for agriculture to produce the food necessary for the coming century in the face of an unpredictable environment. Cell biology in all its incarnations opens the box so that we can learn to do better with what we find inside.

[5] Definition from *Nature Cell Biology* – one of the flagship journals in the field: http://www.nature.com/ncb

Discoveries in cellular biology continue to provide new capabilities that are developed into biotechnologies, for example:

- the incredible promise of stem cells;
- significant advances in genetic modifications;
- understanding the ways in which cells recognise attackers has lead to therapeutics such as antibiotics and HIV triple therapy;
- understanding the ways in which cells make more cells and how this process is controlled has improved numerous cancer therapies;
- understanding how molecule-sized scaffolds and motors within cells work together is the only route to a nanotechnology age within the next half century.

The impacts on the availability, specificity and efficacy of both medical and agricultural interventions arising from cell biology will be felt by all New Zealanders.

Systems Biology

Description

Systems biology represents a convergence of existing and new scientific disciplines (for example, genomics, proteomics, metabolomics, nanotechnology, microfluidics, biological computing, and engineering) aimed at integrating all types of biological information (genes, DNA, RNA, protein, protein interactions, networks, cells, tissues etc.). Systems biology integrates this information in a way that is like dealing with 'subsystem modules' where the important factors become the interfaces between modules and how these interfaces are regulated. Though we do not know necessarily all the complexity of a subsystem module, we do know and can characterise some of its important outputs. This concept assists biology in its quest to make sense of high-complexity and a deluge of data. Special branches of mathematics such as graph theory and non-linear partial differentials are needed to work in this area.

Systems biology has been driven by new technological developments that have enabled researchers to collect high-throughput measurements and generate large, quantitative data sets about genes, proteins, cellular dynamics, and the response of organisms to changes that occur, for example, in reaction to disease or to the environment. All this information alone has not explained how an organism ticks. Because a system is not just an assembly of genes and proteins, its properties cannot be understood by simply drawing connections between all of the components, like a roadmap. The aim of systems biologists is to take up this challenge and use mathematics, statistics and computing to integrate data into a big picture on how biological networks function, from cells to whole organisms. In essence it represents multidimensional biology where models are built based on all levels of biology (genes, proteins, cells, organs and various model organisms).

Innovation Spectrum

The notion of system-level understanding in biological science has been a theme in existence for some time. It currently underpins much of the future discovery in biotechnological science. In September 2003, Harvard University recognised its importance by opening a new department, the first in its medical school for 20 years, to focus on systems biology. Many

other universities and organisations (including a joint initiative between Cambridge University and MIT[6]) have started systems biology institutes.

Potential Application and Relevance to New Zealand

Systems biology will catalyse fundamental changes in the future of healthcare and society in general. It will form the basis of predictive, preventative and personalised medicine. Systems biology will address urgent and severe bottlenecks in therapeutic discovery and development. These bottlenecks have arisen as a consequence of the fundamental difficulty in understanding and predicting how complex living systems operate. Left unsolved, the bottlenecks will have serious financial consequences for health authorities and for pharmaceutical and biotechnological industries. A dramatic change from the current 'one gene, one protein, one drug' approach is required if true advances are to be made.

It will also create and drive new opportunities in the agriculture and pastoral sciences.

The catalytic aspects of systems biology in the pharmaceutical, agricultural and other biotechnological industries will result in it having significant economic and ethical impacts in New Zealand.

Epigenetics

Description

Epigenetics is the study of heritable traits and characteristics that are not encoded in the sequences of DNA but in other macromolecules or cell structures. It operates both between generations of organisms and also within generations such as the heritable programming of somatic cells derived from stem cells. It has fundamental importance in biological development such as when an adult nucleus reprograms itself for an embryonic pattern of gene expression on transfer to an embryonic cellular environment (see nuclear transfer page 16). There are also unusual inheritance mechanisms such as prion phenomena that fall under the definition of epigenetics and there are views that some neuronal memory function could be prion-like behaviour.[7]

Epigenetic phenomena, in a similar manner to protein networks, demonstrate that biological function is not described by primary gene activity alone. Epigenetics can perhaps be likened to an orchestra playing a musical composition from a score, where the score represents the genome. The 'epigenetic' state of the orchestra is its physical arrangement, the acoustics of the room, the quality of individual instruments, the skills of individual musicians and, most importantly, who plays the solos. The effect of the score (the genome) is modulated by limitations and biases of the surrounding structure. The same composition will produce different results with different musicians or instruments and even on different days; in an analogous way the same genome can produce slightly different "identical" twins.

Innovation Spectrum

Epigenetics is at the discovery end of the spectrum because its effects are subtle, manifest and applicable to a wide range of uses. In gene expression, epigenetics is concerned with the distinct heritable patterns of methylation, described as genomic imprinting (i.e. patterns of methylation of both the histone proteins around which DNA is wound and of cytosine

[6] http://www.cambridge-mit.org/research

[7] Si K, Lindquist S, Kandel ER. 2003: A neuronal isoform of the aplysia CPEB has prion-like properties. *Cell. vol 115 (7)*: p879-91.

residues within certain short motifs of DNA sequences). It is likely that epigenetic inheritance and regulation will have to be understood within the framework of gene and protein networks such that, together, networks and epigenetics comprise perhaps *the* major challenge to modern biology.

Potential Application

The mammalian suppression maintenance protein Dnmt1 is involved in X-chromosome inactivation, parental imprinting and the silencing of retro-elements, all important to the correct development of an organism. While many of the specific roles are unknown of Dnmt1 (in the epigenetic regulation of developmental stage-specific and cell lineage-specific gene expression in vivo), it is thought to be critical to organ system homeostasis.

Stem cells are equipped to develop into many other cells types, whether brain cells, liver cells or muscle cells, because they carry the same 'score' as all other cells, but their epigenetic state is such that they can specialise in any direction.

T cell development is another excellent example of epigenetics affecting a critical biological function, i.e. immune surveillance[8]. Mammals produce about 10^{11} to 10^{12} T cell clones every few days, each expressing a different T cell receptor that matches most possible incoming foreign antigens. Those T cells with receptors that are appropriate to deal with an attack are rapidly multiplied in the 'adaptive immune response'. Others, not matching and not needed, undergo an equally regulated programmed cell death called apoptosis. These two processes are guided and driven by dynamic patterns of methylation, of timed gene activation and inactivation. Though epigenetic methylation is not responsible for the genetic re-arrangements that produce the enormous T-cell repertoire, the mechanism by which they are maintained is a prosaic but nonetheless critical epigenetic phenomenon.

The epigenetics of plant breeding is a developing field. Breeding schemes are rarely simple and this may be because the best parent plants are incompatible or result in progeny with complex, undesirable mixtures of traits. The problems can sometimes be due to epigenetic incompatibilities, when the imprinting of certain genes forbids certain combinations of parents or when uneven mixing of chromosomes is forced by non-DNA-encoded factors.

On a wider scale, much was made in the press of the apparently insufficient number of genes in the human genome, compared to other less cerebral, or 'lower' organisms. While some of this may be human arrogance and wishful thinking, the complexity of being human will rest also in the epigenetics of the human cell, in patterns of regulation and gene control, and in mechanisms of inheritance that pay scant heed to DNA.

Relevance to New Zealand

New Zealand has few epigenetics programmes that we are aware of, but the bovine transgenics program is one example in which there are objectives seeking to understand the epigenetics of nuclear reprogramming – the key step in mammalian transgenic technologies. What may emerge from the New Zealand programme are markers for nuclei in transgenesis that are more likely to undergo successful reprogramming (raising the efficiency of cloning and transgenesis) but also those that are likely to produce transgenic calves in the first (G0) transgenic generation with fewer physiological problems. It is worth noting that 'G0'

[8] Lee PP, Fitzpatrick DR, Beard C, Jessup HK, Lehar S, Makar KW, Perez-Melgosa M, Sweetser MT, Schlissel MS, Nguyen S, Cherry SR, Tsai JH, Tucker SM, Weaver WM, Kelso A, Jaenisch R, Wilson CB. 2001: A critical role for Dnmt1 and DNA methylation in T-cell development, function, and survival. *Immunity vol 15(5)*: p763-74.

problems in transgenic calves tend to disappear in the second transgenic generation and markers for this outcome are likely to be epigenetic as well. Epigenetic indicators may also prove to be economically useful markers to designate the best oocytes for cloning and IVF.

Chemical genetics

Description

Chemical genetics, in its most powerful form, generates, by advanced organic synthetic methods (diversity-orientated organic synthesis), large numbers of chemically diverse, natural product like-compounds. These can be directed as protein-binders of sufficiently high binding affinity (low K_ms) to become inhibitors of cellular processes in vivo[9]. The concept of 'one binding compound equals one protein affected' is fundamental to chemical genetics. Array technologies, backed by the appropriate informatics, allow simultaneous identification of the protein binding compounds and isolation of the proteins to which they bind. Binding compounds of interest can be resynthesised and used to assess effects in cell culture screens. This method can achieve 'gene-knockouts' having phenotypic effect akin to classical forward and reverse genetics. Unlike classical genetics, however, chemical genetics knockouts are reversible and quantifiable by varying the concentration of the compounds in the living cell environment. This bestows a critical advantage on chemical genetics for unravelling in situ gene function, especially in large animals where gene knockouts are ethically unacceptable and too expensive.

Innovation Spectrum

Chemical genetics sits very much in the discovery end of the spectrum. It provides the means for discovery of new and versatile biological probes. Upon identification of compounds with useful phenotypic effects, the approach should provide rapid transit across the rest of the discovery – development – application pathway.

Potential Application

Chemical genetics is a key next step in modern molecular biology. The latter now finds itself stymied by its own success in the cloning (i.e. isolation) and manipulation of genes with an overload of accessible genes as reagents but of unknown function. As an example, one New Zealand Crown Research Institute has the most comprehensive bovine gene-discovery potential in the world, in the form of an 'EST-database' in which some 21,000 of around 30,000 total bovine genes are represented. However, only 7,000 are of known function. The utility of such a database is limited by the dearth of methodologies for rapid screening for function. Chemical genetics fills this void.

In cells, proteins work in networks, that is to say one protein can affect the function of a number of others in feedback and other logical loops, generating an impenetrable complexity unlikely to be understood solely by reductionist approaches. Complexity is exacerbated in that the complement of all proteins is likely to be orders of magnitude more than gene coding sequences and further complicated by 'epigenetics'. A key attribute of chemical genetics is the ability to perturb 'modules' or networks10 with an observable outcome directly related to a particular protein.

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[9] Tan D.S. 2002: Sweet surrender to chemical genetics. *Nature Biotechnology vol 20(6)*: p561-3.

[10] Kitano H 2002: Systems biology: a brief overview. *Science*; *vol 295(5560)*: p1662-4 special focus *Science* edition March 2002

It has not escaped the attention of biology departments all over the world that Harvard and MIT for the first time in their history have formed a combined institute (The Broad Institute) to study chemical genetics – a US$300M operation at its outset.

Relevance to New Zealand

The Protein Structure Initiative (PSI; paid for by the USPHS NIH[11]) is systematically expressing proteins from genomes as they are sequenced for purposes of structure determination. Many of these proteins are of unknown function. Even when one function is discovered biochemically in vitro or classified to a family of functions by 3D-structure, the real function in situ may differ qualitatively or quantitatively in a network context in a living cell. It is likely there will be available very large numbers of expressed proteins from the PSI, many of which will not have an assigned function and will be amenable to chemical genetics probes. New Zealand has a crucial connection (in *Mycobacteria*), to this major international effort, based at the University of Auckland

New Zealand is a world-class participant in mammalian reproductive follicular development, having identified a key regulator in the form of a ligand for the TGF-beta Type II receptor by way of the sheep Inverdale mutation[12]. The Inverdale mutation, in a protein called 'BMP15', causes twinning in sheep as a heterozygote or infertility as a homozygote. Sheep are 'mono-ovulators', whereas rats are multi-ovulators (viz litter sizes) and the same protein mutated in rats has no effect. BMP15 acts through a cascade of other proteins (called the SMAD pathway) which are responsible for a huge diversity of cellular behaviour, leaving unexplained how the specificity and diversity are generated in transcription.[13] In the SMAD pathway there are a number of activating events caused by competing protein interactions as well as numerous co-activators and co-repressors. Probing such networks by chemical genetics to mimic Inverdale in sheep but not rats should provide an incisive way to solve the puzzles of such intracellular signalling pathways.

Reproductive technologies and cloning

Description

Reproductive technologies encompass several scientific areas, including: selective breeding, embryology, non-human cloning and transgenics (see page 18); and these all apply across phyla, being relevant to plants and animals.

Selective breeding is the use of gradual genetic modifications to develop desired traits in animals or plants, by crossing parents with the desired genes.

Embryology is the study of how sex cells are fertilised and develop into live offspring.

Reproductive cloning is the production of genetically identical offspring. In plants, this is usually done by cuttings and/or cell culture to produce numerous identical offspring from the same parent. In (non-human) animals, reproductive cloning is done by removing the nucleus of an egg cell just after fertilisation (i.e. a zygote), and replacing it with the nucleus of another cell, (usually obtained from tissue culture, for example a stem cell). The zygote is then cultured to embryo stage and grown in vitro or in vivo depending on the animal.

[11] http://www.nigms.nih.gov/psi/

[12] Montgomery G.W, Galloway S.M, Davis G.H and McNatty K.P. 2001: Genes controlling ovulation rate in sheep. *Reproduction vol 121*: p843-52

[13] ten Dijke P, Smith C.S. 2004: New insights into TGF-beta-Smad signalling. *Trends in Biochemical Sciences vol 29*: p265-73.

Innovation Spectrum

These technologies already operate over the complete innovation spectrum (for example *Pinus radiata* grown commercially in New Zealand is largely of one clone type, and cloned sheep, goats and cattle have been produced on an experimental scale). Much of the research could be described as qualitatively improving the status quo.

Potential Application

Cloning enables the production of many offspring with traits obtained from one parent. For example, in the dairy industry, it may enable the production of multiple offspring from one highly-producing female parent, rather than relying on the traits being transferred through the male line. It also enables production of transgenics from cells grown in culture. However, in mammals, there have been problems resulting in 'cloned offspring syndrome' including abnormal placentation, foetal loss and/or high birth weights. These are due in part to the embryo culture methods (which are rapidly improving[14]), and probably due in part to the epigenetic effects of nuclear transfer. Current research into epigenetic effects will answer the problems that prevent commercial use of this technology.

Relevance to New Zealand

All these techniques have relevance to New Zealand's agriculture, aquaculture, forestry and horticulture industries.

In particular the adaptation of already well established agricultural breeding techniques to aquaculture species will require new discoveries in embryology, such as embryo biochemistry, culture and cryopreservation of gametes, and ploidy manipulation.

In aquaculture, as in agriculture, the use of 'marker assisted selection', which uses DNA sequences of desired genes, will improve the traits of animal and plant products, including breeding-in disease resistance, breeding-out biotoxins from shell fish, breeding low-temperature tolerance into fish and drought tolerance into plants.

Stem cells

Description

Stem cells[15] are the foundation cells for every organ and tissue in the body. They have the fundamental property of either being able to divide indefinitely, (i.e. be self-sustaining and produce more stem cells), or alternatively giving rise to a myriad of different specialised cells in the body. For example, bone marrow haematopoietic stem cells are the cells that give rise to all the specialised blood cells and are currently the only stem cell used in therapy. Another type of stem cell, termed embryonic stem cells, makes up a specialised area called the inner cell mass of the blastocyst which forms approximately five days after an egg is fertilised. Embryonic stem cells can go on to form all the cell types in an adult animal and are often

[14] Cross JC. 2001: Factors affecting the developmental potential of cloned mammalian embryos. *Proc Natl Acad Sci U S A. vol 98(11)*: p5949-51

[15] * The ISSCR Web site, http://www.isscr.org, has valuable information and publishes a newsletter with important information for scientists working in the field.
* The National Institutes of Health Web site has information on stem cells for the public, for scientists and on federal policies.
* The Coalition for the Advancement of Medical Research (CAMR) Web site has information on advocacy in the areas of stem cell research and therapeutic cloning.
* A Web site of clinical studies conducted in the stem cell area can be found at http://www.clinicaltrials.gov

referred to as pluripotent stem cells. Until recently it was thought stem cells were present only in embryonic stages of development, but it is now known that there are also stem cells in adult tissues such as muscle and brain, opening a new way of thinking about aging.

Innovation Spectrum

Stem cell research is strongly at the discovery end of the spectrum, although some bone marrow cells are in use in developing therapies. Ongoing discoveries will inform much of biotechnological science. Over the next fifteen years this is the area in this futurewatch that will reliably move furthest along the innovation spectrum thanks to the strength of current research funding worldwide.

Potential Application

When cells in the body are seriously damaged or diseased they cannot generally be replaced by natural healing processes. This is in contrast to amphibians that grow new limbs following loss or damage. A challenge arising from the increasing knowledge of stem cell function is whether these cells can be harnessed or guided for tissue repair in human disease. Any disease resulting from tissue degeneration could be a candidate for stem cell therapies. Researchers are investigating the use of stem cells as a resource for various specialised cell types, such as nerve cells, muscle cells, blood cells and skin cells that can be used to treat various diseases. Do the unique properties of stem cells make them promising in the quest to treat diseases as diverse as Alzheimer's, Parkinson's, cancer, type-1 diabetes, spinal injury, stroke, osteoarthritis and rheumatoid arthritis? Other potential applications include: repairing damaged eyes resulting from retinal degeneration; reversing baldness by transplanting hair stem cells; and repairing damaged liver function using liver stem cells.

There are scientific questions to be answered if stem cell therapy is to become a clinical practice reality; for example, being able to accurately identify stem cell types, learning how to grow these cells, understanding how to guide stem cells towards developing into the specialised cell type required, and understanding whether such cells will be rejected following transplantation.

Associated with this are bioethical and religious questions surrounding the use of human embryonic tissue for deriving new embryonic stem cells.

Despite these research challenges the field of regenerative medicine mediated by the use of various stem cells, or their derivatives, has evoked considerable interest and hope. The great promise of stem cells is their ability to be modified into different functional adult cell types and serve as replacement cells to treat a range of diseases.

Relevance to New Zealand

Stem cell science has a clear application in many areas of biological science in New Zealand including medical, agricultural and aquacultural research.

Transgenics

Description

Transgenics are organisms with artificially altered genes; they are "genetically engineered". This is usually done by gene-splicing into the genomic DNA contained in the nucleus of the newly-fertilised egg cell. Transgenic cell lines can also be used to make transgenic organisms by nuclear transfer of transgenic cells into zygotes (see earlier section on cloning page 16).

Transgenics are not just a convenient way of speeding conventional plant and animal breeding. It is also of academic interest to understand the nature of evolution by studying heritability, stability and long term effects of genes (e.g. genes from different species or even phyla). Studying the effects over time of specific recombinations of genes will also inform on biosecurity and ethical issues of transgenesis and answer questions like 'is nuclear transfer necessary or will chromosome transfer do?'

Innovation Spectrum

Transgenics covers the full innovation spectrum. Genetics research for at least 30 years has been greatly assisted by the production of transgenics which became animal or plant 'models' to elucidate a specific genetic function. Transgenic models will continue to inform medical research into human diseases and other science areas in the future. An alternative, very new, technology called RNA interference is also becoming useful for elucidating gene function, and this may replace transgenic animal models in some instances. RNA interference uses small pieces of RNA in cultured cells to 'knock out' a genetic function, so that effects can be studied at the cellular level. This discovery has been ground-breaking and may enable hitherto unknown methods for cell biology research.

Potential Application and Relevance to New Zealand

In future, there will be better targeting and integration of transgenes, stacking of traits, use of artificial chromosomes, and the building of whole pathways. In addition to research, such techniques will be used in commodity organisms like crops and livestock. For example, targeting genes to mammalian mammary tissue for production of human proteins in milk is increasingly suggested as a method for biological pharmaceutical production. Current research into the genetics of marine organisms (e.g. genomics, proteomics) will lead to more sophisticated exploitation of the genetic potential of these organisms through aquaculture, and will form an important basis for genetic manipulation, e.g. of fish, should this become necessary and acceptable in the future. Transgenics and/or RNA interference may also assist in discoveries of genetic and cellular functions as we elucidate the effects of health bioactives (obtained from aquatic or terrestrial species) that may have anti-microbial, anti-cancer and/or nutritive value.

Today's up-and-coming plant genetic modifications attempt to address the issues associated with human exploitation of the world's ecological services, such as genes conferring tolerance traits for drought, salinity and temperature extremes. The effects of climate change may render many formerly productive regions agriculturally incompetent and transgenic biotechnology will be among the technologies used either to restore competency or to increase productivity. To this end, technologies such as the cloning of agricultural animals, the rapid production of quality plant seed via apomixis, and increases in photosynthetic efficiency via the activation/importation of C4 photosynthesis into ostensibly C3 plants, are potential routes to success that will be explored. Whether or not New Zealand chooses to grow such transgenic foods, we should be aware of developments in transgenics so we can capture future opportunities.

Predictive or Personalised Medicine and Nutrition

Description

The completion of the human genome provides the means to understand better human biology and the mechanisms of disease, and provides the opportunity to develop significant new

approaches to improve human health. Personalised medicine,[16] or pharmacogenetics, refers to the use of individual genetic profiles to identify and tailor lifestyle or drug therapies best suited to preventing and treating disease. The aim is to develop more directed, effective and safer therapies. Similar approaches apply to diet (nutritional genomics or nutrigenomics[17]).

Innovation Spectrum

Personalised medicine and nutrition are at the discovery phase, although major developmental programmes are underway in various institutions, including some in New Zealand.

Potential Application and Relevance to New Zealand

Studies of the genetic makeup of individuals have identified DNA changes in chromosomal regions implicated with cancer, arthritis, cardiovascular disease, etc. and have quantified that individuals react differently to the same medical treatment or diet. As the knowledge of the genetic basis of a drug/diet response is understood, genetic profiles will be used to inform the nature of treatment, instead of a trial-and-error approach. This will remove uncertainty and help eliminate adverse effects (adverse drug reactions cause some 150,000 deaths each year, world wide). Such information has the potential to help predict which individuals are at risk and identify what drugs or lifestyle changes will be most effective.

It is predicted that, within the next 10-15 years, predictive medicine will emerge, capable of determining a probabilistic, individualised future health profile[18]. In this timeframe, the relevant parts of an individual's genome will be sequenced for less than a $US1000 in a few hours and the variants of all genes analysed to allow a statement regarding disease likelihood.

Genomic testing using biomarkers constitutes a major shift from the current practice of population-based treatments ('one drug or diet suits all') towards individual therapy or diet. Genetic databases, medical records and new medical imaging technologies provide significant resources to identify correlations or patterns associated with disease, diagnostics and treatments. Individual differences can be explained by genetic differences which affect the way drugs/food are absorbed or metabolised. Associated developments in 'lab-on-a-chip' technology and biomarkers that detect genetic changes provide the means to rapidly screen and test how or if an individual will react to particular drugs and/or diets.

Some of the following bottlenecks can be predicted and may need to be overcome:

- Significant age, gender and ethnic differences have been identified. Some 10% of Caucasians and 20% of Asians are poor metabolisers of drugs, e.g. 20% of the population fails to respond to Prozac™; 25% do not respond to beta blockers for high blood pressure and in more difficult cases (Alzheimer's disease, cancer and schizophrenia) the non-response rate for the best available drugs is still well above 50%.
- Personalised diagnostics and therapy for optimal efficacy and reduced toxicity will require cooperation between drug developers, diagnostic companies and regulatory authorities.
- 5 million human genetic variations provide endless combinations that can affect an individual's health and response to treatment.
- Drug labelling could be restricted to patients with a certain genotype thus reducing markets for new products.

[16] See http://nihroadmap.nih.gov/buildingblocks/index.asp for major overview
[17] Muller, M & Kerston, S. 2003: Nutrigenomics: goals and strategies. *Nature Reviews Genetics vol 4:* p315
[18] Weston AD & Hood, L (2004): Systems biology, proteomics, and the future of health care: toward predictive, preventative, and personalized medicine. *J Proteome Res. vol 3(2):* p179-96

- Health care costs to individuals and society (a chip for the CYP450 genes associated with drug metabolism currently costs $US400 each)

Sensor Biotechnology

Description:

Sensors recognise substances using reactions that are converted into detectable signals indicative of the presence of the substance being sought and of its quantity. Sensors may be self-powered and self-organising. They often have biological components (termed biosensors) e.g. DNA, RNA, enzymes, antibodies, and are frequently very small, calling for technologies like microfluidics, miniaturised engineering and materials science (nanotechnology). Biosensors can provide recognition when inorganic recognition systems are not available.[19]

Innovation Spectrum

Sensor biotechnology is still mainly at the discovery end of the innovation spectrum and understanding is emerging on sensor-related processes such as:

- how bacteria transfer energy to electrodes (self-powered networks);
- how insects recognise pheromones at very low concentrations;
- how molecular interactions can be reported (diagnostics based on nucleic acid and protein micro-arrays);
- how substances get in and out of cells (drug screening and effectiveness);
- how to use lipid-bilayer membranes as supports for ion channels (sensors for toxins, bio-active discovery etc.);
- how to make artificial antibodies that are more stable than those from biological systems (molecular imprinting);
- how to use bilayer lipid membranes as anti-fouling coatings for implantable devices or as supports for drug delivery.

Research into the longevity and robustness of operating sensor systems underpins this technology. A perennial problem with 'wet' systems (e.g. insect electo-antennagrams) is that they last for less than an hour.

Potential Application and Relevance to New Zealand

Biosensors offer huge potential world-wide. However, in New Zealand they are turning out to be particularly useful in real-time monitoring of food quality systems, given that there is increasing international concern about food quality and safety. Improving sensor-based quality-assurance systems will continue to be built into all bio-industries, including the manufacture of nutraceuticals and drug development, as well as dairy and meat processing. In all areas, sensors have great potential to reduce risk and assuage concern. Similarly, biosensors offer emerging capability with which to detect contamination in stored food products (e.g. disease-causing fungi in grain).

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[19] Ananthaswamy, A. 2003: March of the motes. *New Scientist vol 179 (issue 2409)*: p26

*Cote, GL. et al. 2003: Emerging biomedical sensing technologies and their applications. *IEEE Sensors J. vol 3*: p251-66.

*Leonard, P. et al. 2003: Advances in biosensors for detection of pathogens in food and water. *Enzyme and Microbial Technology vol 32*: p3-13.

Likewise sensor-based methods are being developed to ensure border biosecurity, especially in containers; the cryptic and concealed nature of many pests in freight and mail makes visual searches very difficult and insufficient. In the same way, sensor technologies are likely to be used increasingly in national security systems particularly those that can immediately detect materials indicative of sinister intent, such as biological weapons, toxic substances (e.g. nerve gas), explosives, radiation and narcotics. More positively, sensor technologies are already offering great potential as tools for diagnosis of disease and other physiological states (e.g. oestrous in livestock). There are also numerous emerging environmental applications, such as the accurate real-time monitoring of air-quality, the detection of toxic fungi in houses, and water quality monitoring e.g. rivers, lakes, ballast water and assessment of streams containing effluent for associated biological oxygen debt.

DISCUSSION

Biotechnology is very important to the economic welfare of New Zealand. It is a rapidly changing technology and has had, and will continue to have, a major influence on the lives of all New Zealanders, impacting on all primary industries, on our health, our food, and the environment.

A key aspect of biotechnology is the science that underpins and drives the technology. That science is undergoing rapid and accelerating change and growth. In order to be prepared for the outcomes of that change, it is imperative that the science is monitored so that the government and people of New Zealand are as well prepared as possible to take advantages of the opportunities offered and to mitigate any disadvantages.

People are becoming more aware of biotechnological science, or at least its outcomes, and there is anxiety in some quarters. It is subject to a high degree of active opposition and raises many ethical issues.

The science deals with complex interactions in organisms which require integrated approaches to be understood. Many of the advances in biotechnological science are consequential upon the convergence of a number of other scientific disciplines – biology, chemistry, physics, mathematics, and computing. Resulting in part from this convergence, new approaches have arisen such as systems biology.

The history of biotechnology has been primarily concerned with identifying genes and assigning functions to them. Two key technical developments in genetic research were the development of PCR and automated sequencing machines. The former, in particular, made DNA-based studies available to any reasonably well-funded laboratory. There is now more focus on looking at interactions of genes and proteins. Future focus will be on increased understanding of the complex networks that occur in organisms.

Rapid advances are occurring with the advent of high speed, high-throughput array based analytical tools, coupled with large data collection and analysis devices. Making sense of the data is, and will continue to be, dependent on the use of bioinformatics and computer models to identify connections.

This report, part of a wider portfolio of biotechnology futurewatch, is an initial baseline scan of the future in scientific discovery. It is inevitably not a complete view, and the material included reflects the timeframe of the study and the experience of the Panel members who undertook the task. It is expected that the material will be added to in the future.

The report identifies potential keywords for a biotechnological science scan. It discusses in more detail, nine important topics (to serve as selected case studies) in biotechnological

science (cell biology, systems biology, epigenetics, chemical genetics, reproduction and cloning, stem cells, transgenics, personalised medicine, and sensor biotechnology). Neither the topics nor the detail in each discussion should be considered as complete but they illustrate a view of the future of biotechnological science with particular reference to New Zealand.

Future analyses of a biotechnology futurewatch should include, within the one project, all aspects of the topic, particularly the discovery > development > application spectrum (i.e. not just scientific discovery). The Panel, while realising that this study was only a part of a larger project, nevertheless found it inhibiting to attempt to consider the scientific discovery aspect only, in isolation from the applications, and relevant economic, ethical, environmental and welfare aspects.

The Panel was also conscious that the viewpoints being expressed were limited by their own experience. Future biotechnology futurewatch surveys could consider using the techniques employed by the Japanese in their surveys (approximately once every 5 years) in foresighting future technologies. A Delphi technique was used for the 7th survey in 2001[20], and 1065 topics in 14 technology fields were considered. One questionnaire was answered by 3809 correspondents. It would not be practical nor necessary to use so many people for a New Zealand study, but a wider coverage and more rigour would be possible than was practical in preparing this report.

ACKNOWLEDGEMENTS

This report was prepared by the panel listed on page 1. Brief biographies are given below. Further helpful discussions were held with Professor Lynnette Ferguson (University of Auckland), Dr Lance Searle (Sealords Group Ltd), Dr Henry Kaspar (Cawthron Institute), Dr Dennis Thomas (Massey University), Dr Steve Thompson (RSNZ), and Dr Graeme Jarvis (Meat and Wool Innovation Ltd).

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Additional, significant input and guidance were received from Katherine Silvester, Jane Cameron, Karla Falloon and Robert Hickson (MoRST).

The contract was managed by Dr Steve Thompson (Chief Executive, RSNZ).

Panel Biographies

Dr Kevin Marshall

Dr Kevin Marshall chaired the panel and wrote this report based on the input from panellists. He is a chemical engineer/biotechnologist, now retired after 40 years in the dairy industry. His most recent roles were as Group Director, Global Research and Development for the New Zealand Dairy Board, Managing Director of ViaLactia Biosciences Ltd, and Chief Executive of New Zealand Dairy Research Institute. He has a BEng (Hons) (Chemical) (University of Canterbury, NZ), MSc (Bio Eng) (Birmingham University, UK) and a PhD in biotechnology

[20] The Seventh Technology Forecast: Future Technology in Japan toward the Year 2030. http://www.nistep.go.jp/achiev/ftx/eng/rep071e/idx071e.html

(Massey University). He is presently a company director on the boards of Wool Equities Ltd, Ovita Ltd, and Zespri Innovation Co Ltd.

Professor Diana Hill

Professor Hill (CNZM, FRSNZ) is the Chief Executive of Global Technologies Ltd (Dunedin). She gained her BSc and PhD from Otago University in Biochemistry and Molecular Biology. Professor Hill has an extensive research background notably including a post-doctoral fellowship with Noble Laureates Fred Sanger and John Walker at the Laboratory of Molecular Biology, Cambridge, UK. During her twenty years' research career at Otago University, Professor Hill founded the AgResearch /University of Otago Molecular Biology Unit, gained a personal Chair, and was seconded to Global Technologies to start up this commercial firm. Professor Hill is the Chair of the Marsden Fund Council (RSNZ), and was a member of the Ministerial Biotechnology Taskforce. Professor Hill has received numerous medals and distinctions including the Companion New Zealand Order of Merit (CNZM) for services to science.

Professor Paul Atkinson

Professor Atkinson (FNZIAS) gained a BSc (Hons; 1st class) from the University of Canterbury and a PhD in Cell Biology from the University of Auckland. He was Professor of Developmental Biology and Cancer at the Albert Einstein College of Medicine New York City from 1986 to 1991. On returning to New Zealand in 1992, he was Manager of Animal Health Research at Wallaceville Research Centre and then General Manager Science (Reproductive Technologies, Animal Genomics, and Food Sciences) from 1997 to 2004. Professor Atkinson is currently a Professorial Research Fellow in Chemical Genetics at the School of Biological Sciences, Victoria University of Wellington.

Dr Phil Crosier

Dr Phil Crosier is Associate Professor of Molecular Medicine and Principal Research Fellow in the School of Medical Sciences at the University of Auckland. He has been a member of a number of funding agency and review committees in New Zealand and Australia, served as Assistant Dean, Research in the Faculty of Medical and Health Sciences, and consulted for biotechnology companies in New Zealand and overseas. He has an MSc(Hons) from The University of Auckland, a PhD in Medicine from Otago University and has undertaken biomedical research at the Institut de Récherches sur les Mâladies du Sang in Paris, the Immunobiology Research Centre in Madison, USA and the biotechnology company, Genetics Institute in Cambridge, MA, USA.

Dr Stephen Goldson

Dr Stephen Goldson (CRSNZ) is the Science Leader of AgResearch's Biocontrol and Biosecurity Group as well as being a Professorial Fellow at Lincoln University and Deputy Director of the National Centre for Advanced Bio-Protection Technologies. Dr Goldson is an ecologist who has been working in the field of biological control for 30 years. Most recently, Dr Goldson has been working on the adaptation of sensor-based technologies to improve container biosecurity. Dr Goldson was elected a Fellow of the New Zealand Institute of Agricultural Science and the Royal Entomological Society of London. He has been a member of several national science policy advisory groups and in 1996-97 worked as the science adviser to the Minister of Science, Research and Technology, the Rt. Hon. Simon Upton. In 1999, he was appointed by Cabinet to the Independent Biotechnology Advisory Council.

Dr Kathleen Logan

Dr Kathleen Logan was, until recently, a reproductive physiologist working for AgResearch. She has a BSc. majoring in zoology (University of Canterbury, NZ) and a PhD in human reproductive physiology (University of Newcastle upon Tyne, UK). She has 11 years' laboratory research experience; including studies at Cambridge University investigating genomic imprinting and neuroscience, as well as in New Zealand studying embryology, transgenics and five years' post-doctoral experience studying ovarian physiology, genomics and bioinformatics. Now Dr Logan is at the Royal Society of New Zealand working as a policy analyst. In addition to scientific input to this report, and directing the panel on its production, she wrote the associated Process Analysis Report.

Dr Zac Hanley

Dr Zac Hanley is a biotechnologist working for ViaLactia Biosciences in Auckland. He gained a B.Sc. in Biotechnology and a Ph.D. for studies on molecular biology and plant secondary metabolism from the University of Sheffield (UK). He undertook post-doctoral work for five years at the University of Durham, studying lipid biochemistry and investigating the production of biodegradable plastics in plants. Since 2001 he has worked for ViaLactia as a senior scientist in forage genomics.

Dr Rob Bower

Dr Rob Bower is Chief Science Officer for Ovita Ltd, Dunedin, a company aimed at the application of biotechnology to developing products and intellectual property for on-farm and off-farm applications. His major roles are science program management and IP strategy management. Dr Bower gained his PhD from the University of Queensland in plant molecular biology and crop biotechnology. He was chief scientist for GrainBiotech Australia, a start-up commercial biotechnology company based in Perth which, in 2002, was one of 5 finalists in the World Technology Awards, Biotechnology.

APPENDIX 1 Biotechnology Keywords

This appendix assembles the results of a brainstorming session of areas which are currently undergoing new scientific advances and which are ripe for new discoveries. These key areas have been grouped under nine broad headings. Asterisks denote where a topic is related to more than one heading.

Analytical Tools
Atomic Force Microscopy
Biocontrol*
Bioimaging*
Bioinformatics
Biomathematics
Biomimetics
Clinical Research Orgs*
Comparative Genomics*
Data Integration (Systems Biology)
Engineering /Mech/Electronic/Bio
EST Databases (Expressed Sequence Tags)
Functional Genomics
Gene Discovery
Gene Maps
High Speed Data Access*
High Throughput Liquid Handling / Robotics
Information Technology
Mass Spectroscopy
Microarrays
Microfluidics
Model System Genetics
Nanogravimetrics
National Facilities /Infrastructure
NMR spectroscopy
Peptide Mass Fingerprinting
Phylogenetics /Taxonomy
Protein Networks
Proteomics
Rational Molecular Design*
Developing Technologies
Amyloid Structures as Nanowires*
Biomembranes*
Biopesticides*
Biosensors*

C4 Photosynthesis
Chemical Genetics
Chemical Racemer Resolution
Collapsing of Science Boundaries
DNA Computers
Electronic DNA Application
Epigenetics*
High Speed Data Access*
Hydrogen Cells
Industrial Substrates
Ionic Liquid
Miniaturisation
Modelling
Nano-DNA
Nanotechnology
Novel Forms of Life
Peptidomimetics*
Plants for Energy
Plants for pharmaceuticals*
Plants With Modified Properties
Responsive Biomaterials
Rumen Microflora
Small RNAs (Non-Translated)
Very Bright Light Sources e.g. Synchrotron
Economics
Aquaculture
Biodiversity*
Bioenergy
Energy
Fisheries Biodiversity
Food and Beverages
Forage
Water**

Environmental
Biodiversity*
Biopesticides*
Bioremediation*
Immunocontraception*
Water Bioindicators
Water Bioremediation
Medical/Veterinary/Health
Adaptive Immune Response
Ageing /Degenerative Disease
Animal /Plant /Human Welfare
Anthropology Discoveries
Antibody Replacements
Antibiotic Resistance
Antemortem Test*
Biodiscovery
Bioremediation*
Biotherapeutic Manufacturing
Cancer
Clinical Research Organisations*
Clinical Trials
Cloning*
Complex Genetic Traits*
Cross Species Pathogens*
Diseases /Human, Animal, Plant*
Drug Delivery (Across Membranes /New Methods)
Epigenetics*
Gene Therapy
Generic Medicines
Genetic Screening*
Immunocontraception*
Indigenous Medicine
Indigenous Species
Innate Immunity
New Drug Discovery
Novel Antibiotics
Novel Microorganisms
Nutraceuticals
Nutrigenomics /Diet
Obesity
Peptidomimetics*
Personalised Medicine
Plants Pharma*
Predictive Medicine
Prion Diseases*
Rational Molecular Design*
Regenerative Medicine
Reproductive Technologies
Stem Cells
Virus
Water**
Xenotransplantation
Transgenic Technologies
Cloning*
Transgenic Animals
Transgenic Plants
Genetic Selection/Breeding/Genetic Improvements/Population Genetics
Comparative Genomics*
Complex Genetic Traits*
Genetic Screening*
Genetics and Selection
Marker Assisted Selection
Quantitative Genetics
Biomaterials
Biomembranes*
Plant /Bacterial -Biodegradable Plastics, Biofuels
Smart Materials
Amyloid Structures as Nanowires*
Security
Antemortem Test*
Biocontrol*
Biodefence
Biohackers
Bioimaging*
Biosecurity
Biosensors*
Bioterrorism
Border Control
Cross Species Pathogens*
Diseases /Human, Animal, Plant*
Ecotoxicology
Forensics
Germplasm Storage
Market Access /Food Safety /Quality
Prion Diseases*
Water**

APPENDIX 2 – Further Information Boxes

In the course of this work, various Panel members developed discussions illustrating facets of science, including developments and applications. These items were subsequently considered to be inappropriate for the main body of the report. They are reproduced here to inform other parts of the biotechnology futurewatch.

Info Box 2 Sheep as human disease model

New Zealand has advanced understanding of all aspects of sheep rearing, with a high degree of natural variation in the national flock. Leveraging these advantages is leading to New Zealand becoming pre-eminent in the use of the sheep as a human disease model (spinabifida, congenital cataracts, hormonal systems, reproduction, ovarian cancer, etc.)

Info Box 3 Organisms as energy sources

In the next 50 years we can expect the fuel problem to become much more prominent (and many concerned parties are actively researching e.g. US Department of Energy). This will not be because the oil runs out (not yet) but because of the issues such as sustainability, pollution, and food-water-climate. The generation of power from biological sources is still the biggest energy provider in the world (we just do not tap into it much, except as oil). Modifications to plants to produce power (either electrical energy or chemical energy) should be entirely possible over the next decade and research should be monitored. As an example, it has been shown[21] that *Rhodoferax ferriducens* dug out of anaerobic sediment can completely oxidise glucose with 83% efficiency transferring electrons via an (undisclosed) membrane protein in the live bacterium to graphite electrodes, driving a battery that is dependant only on a supply of glucose and at voltages that are limited only by the area of graphite covered with live bacteria.

One could also be looking for organisms or proteins that could do the same thing photosynthetically and reinforces why New Zealand could do worse than to concentrate on its own unique bacterial biodiversity (soil and other).

Info Box 4 Smart materials

The advent of smart materials is of particular interest to New Zealand's primary industries. Smart materials result from the convergence of information technology, biotechnology, nanoscale manufacturing and materials, either traditional such as wool, cotton, leather, etc. or new materials from sustainable resources. Already, New Zealand has been involved in the manufacture of a woolen snowboard jacket with a built in MP3 player. Research is well advanced on materials that will respond to their environment, with potential uses for the military and health monitoring. A challenge is low-cost, miniature, light-weight power sources. Ongoing monitoring of the developments in smart materials could be valuable.

[21] Chaudhuri SK, Lovley DR. 2003: Electricity generation by direct oxidation of glucose in mediatorless microbial fuel cells. *Nature Biotechnology. vol 21(10)*: p1229-32

Info Box 5 Metagenomics

The rumen is a key to the conversion of pasture to the economically valuable products of meat, wool and milk. The rumen is a complex system to study. Metagenomics, the genomic analysis of uncultured microorganisms is one tool which may give significant insights into the ecosystem of the rumen, how it is altered by specific inputs and how it could be modified to target particular products. More generally, metagenomics can be used for two types of analysis of complex microbiological systems (e.g. rumen, soil, aquatic environments): a function-driven approach, in which metagenomic libraries are initially screened for an expressed trait; and a sequence-driven approach, in which libraries are initially screened for particular DNA sequences. New antibiotics and enzymes are among the early discoveries from metagenomics. Future refinement of methods that enrich for genes of particular function will accelerate the rate of discovery of useful molecules.

Info Box 6 Biosecurity

New Zealand's high level of dependence on agriculture, horticulture, forestry and fisheries for economic wealth means that monitoring of all aspects of biosecurity is mandatory. Research related to plant and animal diseases; cross species pathogens; germ plasma storage; and forensics related to market access, food safety and quality are all aspects that must be included in the monitoring.

Rapid screening systems are particularly useful for such things as prion diseases, foot and mouth disease and BSE, cross species pathogens, and plant and forest diseases. It would be beneficial if New Zealand developed techniques for bioimaging and tests which could detect such diseases as prions prior to slaughter of animals.

New Zealand is developing particular expertise in biosensors, particular small portable ones, for the detection of invading species e.g. in shipping containers and these should continue to be monitored. Nanotechnological approaches may be beneficial.

Bioterrorism is a specific aspect of biosecurity which requires monitoring so that New Zealand can have early alerts to potential activity.

Info Box 7 Aquaculture

Several areas of biotechnology research will benefit the further development of an aquacultural industry in New Zealand. The aim of current work in New Zealand is the 'total domestication' of aquaculture species for economic, conservation and environmental reasons – the ultimate objective is to farm the domesticated stock in the open marine system without interference between wild and farmed stocks. The application of agricultural breeding techniques to aquaculture species will require new technological systems. Selective breeding of marine species is central to the future of the aquacultural industry. Selective breeding will increase productivity, disease resistance and elimination of some food safety concerns (e.g. breeding biotoxins out of shell fish).

Current research in genomics and proteomics will lead to more sophisticated exploitation of the genetic potential of marine organisms e.g. marker-assisted selective breeding, parentage analysis with micro-satellites (for quality assurance in breeding and for forensics, disputes over stock origin), and better understanding of reproduction-related biochemistry from EST libraries. Stem cell and tissue culture techniques need to be developed to improve flexibility and efficiency in seed production and selective breeding. Current genetics research will also form an important basis for genetic manipulation of aquatic organisms should this become necessary and acceptable in the future.

Research into the preservation of gametes and embryos by cryopreservation will be a powerful tool to assist selective breeding – New Zealand is among the international leaders in this.

Research leading to methods of ploidy manipulation will lead to improved production rates and methods for complete uncoupling of cultivated stock from their wild cousins due to the infertility of some polyploids, an important biosafety consideration.

Developments in hatchery technology are a key. Bioreactor engineering principles developed for microbes will be adapted for the larger and complex organisms of aquaculture.

A potential limitation on aquaculture production in New Zealand is the relatively lower temperatures of our waters and breeding methods to address this could be important.

Some species will be commercially viable because they produce high-value, natural chemicals – bioactives. Biochemistry/chemistry research is required for this outcome. This is an area in which new discoveries could have step-wise changes, e.g. discovery of a bioactive that has strong anti-tumour, anti-bacterial, or immunological effects could engender a whole new aquaculture industry for pharma- or nutraceuticals or could provide the basic biological knowledge required to develop a synthetic medicine with the properties discovered in the bioactive.

Info Box 8 A new biological model?

Aquaculture research and development leads the field of micro-algae cultivation. Micro-algae have some of the characteristics that make bacteria easy to cultivate, but they are plants and they are eukaryotes. The biotechnology industry will be looking for such expression systems, particularly for the production of plant metabolites. Such a model organism would also have all the benefits of bacteria e.g. ease of growing, and yet not the disadvantages of a prokaryotic genetic system.

Info Box 9 Nutrigenomics

Nutritional genomics or nutrigenomics is the convergence of nutrition, food, health and lifestyle. Nutrigenomics seeks to

match foods to an individual human genotype to benefit the health of those individuals and enhance normal physiological processes, and
develop new foods for individualised health and nutritional benefit.

Nutrigenomics requires the application of high throughput genomics tools in nutrition research. It will promote an increased understanding of how nutrition influences metabolic pathways and homeostatic control; how this regulation is disturbed in the early phase of a diet-related disease and to what extent individual sensitizing genotypes contribute to such diseases. Ultimately, nutrigenomics will allow effective, targeted dietary-intervention strategies to prevent diet-related diseases.

Future research will allow the analysis of the response of whole systems to nutrients, from genes to organisms. In future, studying organism responses to particular dietary components at the metabolome, proteome and transcriptome levels will hopefully show valuable organ-specific patterns. An ambitious challenge for the next decade is to translate this type of nutrigenomics data into an accurate prediction of the beneficial or adverse health effects of dietary components.

Transgenic and knockout mouse models as well as in vitro experiments using tools such as inducible expression systems, transdominant negative adenoviral constructs and RNA interference (RNAi), remain the main investigative strategies. The use of laser-capture micro-dissection for single-cell gene-expression profiling should greatly improve the cell-specific information that is derived from nutrition experiments with intact organisms (in vivo). In addition, primary cells and cell lines are tools for studying the effects of nutrients on gene expression. Microarrays now make it possible to assess the effect of a specific diet or nutrient on the expression of a large proportion of the whole genome.

Nutrigenomics provides an important opportunity for New Zealand's biologically based economy. Many aspects of nutrition and food safety will be elucidated by nutrigenomics, leading to better design criteria for new foods and more informed and targeted guidelines for diet recommendations. The opportunity to identify an increasing range of bioactive compounds from New Zealand's unique flora, fauna, animals and fish (note than New Zealand's EEZ extends from the tropics to Antarctica) will be enhanced by the developments in nutrigenomics.

This convergence of food, health, nutrition and genomics applies equally to farm and marine animals, rumen organisms, and plants (food crops, forestry, forage).

Info Box 10 Packaging

Active Packaging is a technology that will have an impact on both New Zealand consumers and our export products. Active packaging seeks to do more than just act as a barrier that protects foods. For instance, they may soak up oxygen inside a wrapper to help prevent food spoilage or show when susceptible foods have been exposed to unsafe temperatures for significant times. Others may kill bacteria, indicate the food is deteriorating, or heat or cool the container when it is opened. While not new, many current techniques are expensive. We can expect considerably more food to be in active packaging over the next 20 years as new materials are developed.

Info Box 11 Nanotechnology

Nanotechnology is the science of the very small, involving manipulation of atoms and molecules, with applications in the areas of material sciences, medicine and biology. There is an increasing investment in this research internationally (US$3.8b from the US Government alone), and some strong research initiatives in New Zealand (MacDiarmid Institute). A commercial initiative is underway in Christchurch (Nano Cluster Devices – a unique way of clustering atoms to form nanowires for use in such niche products as hydrogen sensors and magnetic read heads). An estimate by the US National Science Foundation projects a US$1 trillion business by 2015.

Structural biology is a potentially powerful way of researching at the nanoscale. It is not possible to ignore that benzene ring pi-delocalisation of electrons can now be viewed directly in atomic force microscopy and that molecular motors can be visualised and manipulated. A recent paper in *Nature* from the Weizmann Institute reports on a biomolecular computer programmed to analyse biological information to detect and treat prostate cancer and a form of lung cancer in laboratory experiments. The microscopic computer is so minuscule a trillion could fit in a drop of water. Its input, output and software are made up of DNA molecules, which store and process encoded information about living organisms. Such devices could transform the future treatment of diseases.

Recent research in the field of nanometre-scale electronics has focused on the operating principles of small-scale devices and schemes to realize useful circuits. In contrast to established 'top-down' fabrication techniques, molecular self-assembly is emerging as a 'bottom-up' approach for fabricating nanostructured materials. Biological macromolecules, especially proteins, provide many valuable properties, but poor physical stability and poor electrical characteristics have prevented their direct use in electrical circuits. Recent work[22] describes the use of self-assembling amyloid protein fibres to construct nanowire elements. Self-assembly of a prion determinant from *Saccharomyces cerevisiae*, the N-terminal and middle region (NM) of Sup35p, produced 10-nm-wide protein fibres that were stable under a wide variety of harsh physical conditions. Their lengths could be roughly controlled by assembly conditions in the range of 60 nm to several hundred micrometers. A genetically modified NM variant that presents reactive, surface-accessible cysteine residues was used to covalently link NM fibres to colloidal gold particles. These fibres were placed across gold electrodes, and additional metal was deposited by highly specific chemical enhancement of the colloidal gold by reductive deposition of metallic silver and gold from salts. The resulting silver and gold wires were approximately 100 nm wide. These biotemplated metal wires demonstrated the conductive properties of a solid metal wire, such as low resistance and ohmic behaviour. With such materials it should be possible to harness the extraordinary diversity and specificity of protein functions to nanoscale electrical circuitry.

New Zealand has a respectable leadership in structural biology, atomic-force and electron microscopy, materials science, physics and chemistry and could develop a lasting niche in this technology.

[22] Scheibel T, Parthasarathy R, Sawicki G, Lin XM, Jaeger H, Lindquist SL. Department of Molecular Genetics and Cell Biology, University of Chicago, Chicago, IL 60637, USA