FUTUREWATCH

BIOTECHNOLOGIES TO 2025

MINISTRY OF RESEARCH, SCIENCE & TECHNOLOGY
TE MANATŪ PŪTAIAO

PREPARED FOR NEW ZEALAND GOVERNMENT AGENCIES BY
THE MINISTRY OF RESEARCH, SCIENCE AND TECHNOLOGY

IN ASSOCIATION WITH NAVIGATUS LTD, KATE DELANEY AND
ASSOCIATES, AND THE ROYAL SOCIETY OF NEW ZEALAND

JANUARY 2005

ACKNOWLEDGEMENTS This report was a collaborative effort and there are many we would like to acknowledge:

Dr John Butcher, Dr Wayne Cartwright of Navigatus Ltd and Shaun Killerby for their contributions to the chapters on the applications of biotechnology and its social context and for adapting their prior global scenario work for inclusion in this report.

Kate Delaney, Delaney & Associates Pty Ltd, for her expert guidance on our futurewatch programme and for her contributions on methodology.

Dr Steve Thompson and Dr Kathleen Logan of the Royal Society of New Zealand for convening a panel of scientists to contribute their knowledge and insights about emerging science.

The science panel themselves:
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Dr Kathleen Logan, Royal Society of New Zealand, Wellington (Panel Director)

And to the many people who peer reviewed this report and offered guidance during its development.

Thanks to you all from the Ministry of Research, Science and Technology Futurewatch Team:
Jane Cameron
Katherine Silvester
Karla Falloon
Robert Hickson
Richard Meylan

NOTE: This report has been prepared to describe broad trends in the development of biotechnologies. It draws on a wide range of information sources, which have been cited where relevant, but should not be regarded as comprehensive research on developments in biotechnology applications. Readers seeking more detailed or quantitative information on technology trends are advised to conduct further research.

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CHAPTER 1

INTRODUCTION

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FUTUREWATCH

Biotechnology rarely seems out of the headlines and is of interest to many agencies across government. Current issues include the development of gene patenting law, changes to the regulation of genetically modified organisms, support for the business development of biotechnology firms, new laws on human reproductive technologies and human tissues, support for closer biotechnology research links between Australia and New Zealand and public discussions on the cultural, ethical and spiritual dimensions of the use of animal organs for treating human diseases. But what lies beyond these immediate issues?

What might the future of biotechnology hold? How are biotechnologies being combined in novel ways, with information technologies for instance, or being developed for use in new applications? How is the global social and political context guiding these developments? And the most important questions. What might this all mean for New Zealand? How can we take advantage of biotechnology? How do we prepare?

This report is an overview of global trends in biotechnology. It focuses on developments in biotechnology for health, primary production, industrial, environmental, defence and security applications. These are presented with reference to their surrounding social and business context. The main tool used in gathering and understanding the information presented in this report is called "futurewatch" (see below).

The report is primarily for New Zealand government agencies – to help paint the big picture about how biotechnology may impact on our society in the future. It is intended to help provide early warning of upcoming developments and to stimulate thinking and discussion about the "so what for New Zealand" questions. We hope it provides a useful input into policy and operations – for illuminating issues, for framing policy questions and for analysis and decision making.

WHAT IS FUTUREWATCH?

Futurewatch can be thought of as a kind of "radar": a way of systematically scanning the external environment for signals. Scanning is most typically used at an organisational or sector level, but is increasingly being used by governments to inform perceptions and advice and to help make timely, quality decisions that help manage what will always be an uncertain future.

Futurewatch typically involves undirected or open information collection. This includes not only keeping in touch with overseas trends in science, business and society but monitoring events outside immediate areas of interest. A key aim of futurewatch is to identify new or different patterns or events that may be signals of important change. Futurewatch is particularly relevant in areas, like biotechnology, that have complex pathways of development and potentially transformational implications across the economy, environment and society.

The 2000–01 Royal Commission on Genetic Modification recommended that New Zealand develop a capability for what they called "biotechnology futurewatch". This was agreed by government through the New Zealand Biotechnology Strategy (May 2003) which notes that:

CHARTING CHANGES

A key aim of futurewatch is to provide early warnings of important change, or even lack of change. Studying the past to determine patterns of transformation that may play out in the future is a useful approach to detect patterns of change. This technique is derived from the way analysts develop understanding in macrohistory, archaeology and ecology. We have identified four types of change that we can identify with the history and future of biotechnology:

- **Innovations within a system.** These types of change occur through an advance or an acceleration within a particular system. Despite the hype about the radical nature of biotechnology, most change actually occurs through this process of incremental development. The doubling of genomic data every 18 months is an example of this.
- **Changes in paradigms.** Against this background we can also see occasional change that comes in the form of paradigm shifts. These tend to be transformational events. They don't necessarily occur rapidly but have widespread system effects and for that reason have particular importance for government. An example of a paradigm shift that has relevance to biotechnology may be the emergence of an environmental ethic, reflecting values in which humans are part of the environment rather than the centre of it.
- **Interruption of a system.** These changes involve a collapse, or interruption, or destruction of a system. Critical system elements are being interrupted or removed; nothing is added to the system. One example here may be the halting of GM crop development in Europe, driven in part by consumer and citizen concerns about adverse impacts.
- **Changes in interdependencies.** These changes represent a change in relationship between system elements. An example here may be the move towards testing of pharmaceutical drugs through chemical- and computer-based techniques, rather than animal and human trials. Like paradigm shifts, these types of change can have widespread implications for government.

"Futurewatch activities scan, analyse and disseminate information on emerging developments to provide early alerts of new opportunities and issues. There is a need to strengthen futurewatch capacity to enable better and earlier identification of emerging biotechnologies that should be discussed by New Zealanders. Enhanced biotechnology futurewatch capability, linked to the work of the Bioethics Council, will provide a source of information and analysis that can be linked to processes that involve New Zealanders in decision making on new biotechnologies. It will also provide the means to help improve the Government's capability to respond to new biotechnologies in the New Zealand context, including biotechnologies that link with other technological developments such as nanotechnology."

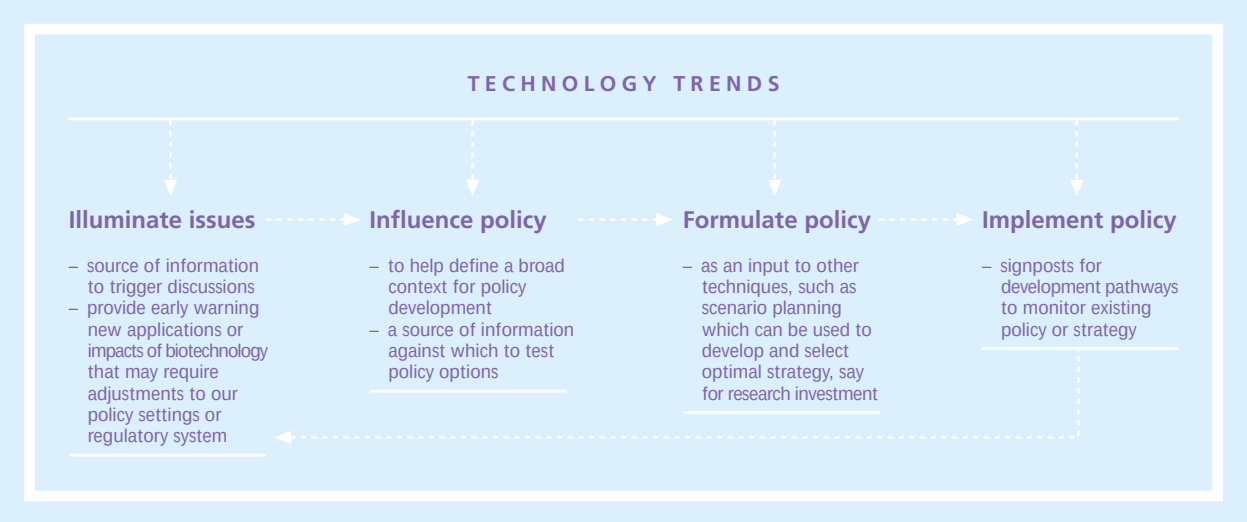
The Ministry of Research, Science and Technology (MoRST) was given responsibility, through the Biotechnology Strategy, to implement biotechnology futurewatch activities.[1] This report is our first substantive piece of work.

FUTUREWATCH IN BIOTECHNOLOGY

Assessing the external environment is already a core activity of many departments and organisations. So futurewatch isn't new in this sense. But scanning in biotechnology can present new challenges. First, it is a very broad field of technology that is developing rapidly. It is also an area that is surrounded by uncertainty (about events, the scale of change, when change may occur and the consequences of change), that is coloured by a range of different perspectives (about what is possible or desirable) and that can have high stakes (economic, social and environmental). Lastly, there is the challenge of making sense of the information – to use it to inform thinking and decisions, and to do this in the context of what matters to New Zealand.

HOW THIS REPORT CAN HELP

This report aims to help departments take biotechnology developments into consideration in policy development operations and implementation. Information about technology trends can be used at a number of steps in policy or strategy processes: to illuminate issues, to influence and formulate policy and to implement policy (see figure below). Trend information is particularly valuable for the construction of future scenarios, which can be used for the development of business or national strategy.



To fully make sense of any technology developments, and to draw out relevant implications, requires an understanding of the current landscape of the technology, trends and projected patterns of usage, and also the context which both shapes, and is shaped by, the technology. This report covers these areas, with a strong focus on the technology trends.

1 Further information about our role and work programme can be found on our website: www.morst.govt.nz. Type "futurewatch" into the search function.

Ultimately this work aims to help New Zealand make better and more timely decisions that relate to biotechnology. However, it is not our job here to say what these decisions should or could be. We believe this sort of consideration should be an interactive process, involving a wider range of knowledge and perspectives than we have drawn on to prepare this report. As with many future thinking exercises, the process, or means of getting the answer, is at least as important as the answer itself. This is work we plan to lead and stimulate through our ongoing work programme.

OUTLINE OF THE REPORT

The report includes the following chapters:

Chapter 2: Overview

For those wanting a quick read, this chapter provides a visual "helicopter" view of key technology trends. The poster in this chapter is also intended to help discussions about the implications of these trends and how changes in the global or New Zealand operating environment may affect the path of biotechnologies.

Chapter 3: Background

This chapter sketches the landscape of biotechnology – what it is, how the sector is developing and where New Zealand fits into the picture. It should be useful background for those not already familiar with biotechnology, and provide context against which to read the information about biotechnology trends that follows.

Chapter 4: Biotechnology and its Context

This chapter provides an introduction to some of the key trends occurring in the social, political and business context of biotechnology. It also provides an introduction to how to think about trends in the context of alternative futures.

Chapters 5–8: Application Scans

These are the main chapters in the report. They present current and likely future developments in applications of biotechnology up to 2025 related to:

- health and wellbeing;
- primary production;
- industry and environment; and
- security and defence.[2]

SPOTTING SIGNALS

The smart way to look for early signs of change is not to look exhaustively at all information, but to detect signals. These are the clues to change. Signals come in all sorts of guises but are often anomalies – things that don't quite fit the pattern. Sometimes they warrant immediate investigation; more often though they become things to keep a watch on. There is a range of signals that we've highlighted throughout this report, including:

- **Convergence** of science disciplines or areas of application often represent areas in which there is a rich mixing of ideas and consequently a harbinger of change. The convergence of biotechnology and nanotechnology is one example here.
- **Bottlenecks** or rate-limiting steps which, if and when released (eg by a technical breakthrough), could give rise to considerable new developments. An example here is the developments in tissue engineering that followed the successful culturing of human embryonic stem cells in 1998.
- **Uncertainties** are always useful to monitor as they can reflect crossroads for different future paths. Consumer acceptance or rejection of GM foods could be said to be a critical uncertainty. Weak signals are one type of uncertainty – these tend to be very uncertain, but also potentially very important.
- **Anomalies** are things that are unusual or do not fit the pattern. These could be cultural, technological, economic and political contradictions and opposites within a system. These opposites often point to emerging issues.

2 This framework is based on that used by New Zealand Trade and Enterprise and StatsNZ to categorise and measure the impacts of biotechnology: Biotechnology Growth Measurement Framework, NZTE, 2004.

In preparing these chapters we have gathered a wide range of up-to-date information about biotechnology developments. Each of these chapters includes a summary table that outlines key drivers of growth, technology trends and developments. As well, there is a selection of our observations around what may be things to keep a watch on: emerging paradigm shifts, bottlenecks and critical uncertainties. In doing this, we're not trying to predict the future; but what we do present here is a glimpse of what we gather the future may hold, based on current research directions and what can reasonably be factored into advice and decision making.

Our focus in these chapters is on the global[3] rather than the New Zealand picture, although a selection of New Zealand examples and case studies is provided throughout these chapters.

The information for these chapters was gathered by a small project team, drawing largely from review articles, sourced from expert literature. Key information sources are footnoted and referenced at the end of each chapter. A peer review process was used to check for overall coherence and technical accuracy.

Chapter 9: Science Discovery Scan

This chapter presents some of the newer discoveries in biological research that are shaping developments in biotechnology. It was prepared by an expert panel, convened by the Royal Society of New Zealand.

FUTUREWATCH IN ACTION

As this report goes to print, New Zealand's Human Assisted Reproduction Technology Act has just been passed. This legislation controls the use of assisted reproductive technologies and related research. It sets out requirements for things such as ethical review of the use of embryos in research, storage and handling of embryos created through fertility techniques, information keeping by clinics offering services and the disclosure of information about their biological parents to children born through assisted reproductive technologies.

An awareness of likely and possible technology developments has been important throughout the development of this legislation. New technologies will always emerge and can't always be foreseen. For this reason the legislation has a flexible approach: rather than prescribing requirements for all known technologies, it provides a generic framework that can accommodate future developments. The therapeutic use of embryo cloning (say, for future treatment of conditions such as Alzheimer's disease) is one example that, rather than being prohibited outright (as with reproductive cloning), may be subject to approvals under strict ethical review and oversight. Similarly, knowledge that somatic cells (ie body cells) may be used in reproductive procedures in the future led to careful definition of terms such as "reproductive research" and "gamete" so that the legislation could adequately capture this kind of procedure without the need for amendment.

3 We acknowledge that information has been drawn solely from English language sources and that it primarily represents developments occurring in North America, Europe and Australasia.

OVERVIEW

FUTUREWATCH

FUTUREWATCH

In this report we have identified trends and likely applications of biotechnologies in a time horizon to 2025. We have adopted a broad interpretation of biotechnology and divided our report into the following application areas: health and wellbeing, primary production, industry and environment, and security and defence. We have also included some emerging areas of science that are influencing the development of biotechnology.

This overview threads together some of the key findings of this report, together with examples of some implications for New Zealand and New Zealanders.

The overview is divided into the following sections:

1. Key findings, providing a comparative view across application areas and a snapshot of key emerging biotechnology and science trends and applications
2. Observations of relevance to public policy
3. A fold-out poster: a visual representation of forecast biotechnology developments to 2025.

KEY FINDINGS

A Comparative View

In today's world, most biotechnology research and related business is focused, ultimately, on health- and wellbeing-related knowledge and applications. Within the health sector, 90% of global value from biotechnology is currently derived from the biopharmaceuticals sector alone. This reflects the history of the industry, with the emergence of a distinct biotechnology industry in the late 1970s in the US which was focused in the first instance on health biotechnology applications.

Since the mid-1990s agricultural biotechnology applications have started to emerge more strongly, most notably on a global basis through the rapid growth in planting area of genetically modified (GM) crops. Although the growth has been rapid, 99% of GM crops are grown in only six countries (USA, Argentina, Brazil, China, South Africa and Canada). Consumer resistance in a number of key global markets (Europe and Japan) means that there is a degree of uncertainty over the future growth trajectory of this particular biotechnology. In New Zealand our biotechnology sector is quite unique, weighted far more heavily to primary production rather than health applications and not consisting fundamentally of GM crop technologies.

Industrial and environmental biotechnologies are often referred to as the "third wave" of biotechnology development. Industrial biotechnology today consists mainly of bioprocessing technologies (using micro-organisms and enzymes) for specialty products like detergents, nutraceuticals and some pharmaceuticals. Future projections envisage a growth in the production of renewable commodity products (like fuels and energy from woody biomass) supported by a growth in scale of production capacity and the emergence of biorefineries (analogous to today's petrochemical refineries).

As part of this report we have also investigated projected application developments in defence and security. Defence applications underpinned by biotechnology are

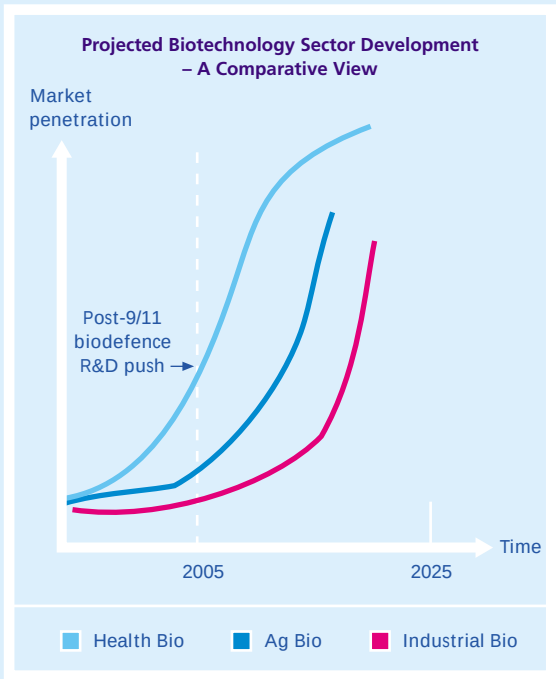
The report has been prepared primarily for New Zealand government departments and agencies to help inform advice and decisions related to biotechnology. It is, however, only one part of the picture. It focuses on biotechnologies and their possible development within a global context. It does not cover in depth the many factors that shape technology development, like ethical, cultural and spiritual factors or the impacts of markets and trade. Nor does it go as far as suggesting implications for New Zealand. We hope the report can, however, contribute usefully to fuller considerations of biotechnologies and how and why they may matter to New Zealand's future.

typically derived from developments in other biotechnology sectors. As such, in the post-September 11 environment national security investment in biotechnology can be viewed as more of a technology investment driver than a significant separate technology growth curve per se. Reminiscent of the history of much defence R&D, we can also anticipate spin-offs into civilian markets.

The graph at right depicts the predicted growth curves of the health and wellbeing, primary production and industrial biotechnology sectors during the course of this report's time frame. The growth of technology sectors over time typically takes the form of an "S curve": as shown, biotechnology is currently a relatively youthful technology platform.

Technology Trends

This section outlines what we consider to be some of the more significant technology trends, or in some cases paradigm shifts, towards new uses of biotechnology. (Further information about technology trends and key emergent applications are presented in the form of tables at the end of Chapters 5–8 of this report.)



(adapted from presentation given by Dr Rolf Bachman, McKinsey & Co at Bio2003)

General Trends	
CONVERGENCE	Biotechnology has a close relationship with developments in other technology sectors, like information technology and increasingly with developments in nanotechnology. Beyond increasing synergies between technology platforms, there are also growing convergences between biotechnology industry sectors (for example, the personalisation of treatment through genomic medicine is forecast to be mirrored in developments in the food and nutrition sector through advances in nutrigenomics).
DIAGNOSTICS – THE FIRST WAVE	Diagnostic technologies (eg DNA chips and biosensing devices) are developing rapidly. With applications across genomic medicine and nutrigenomics, food safety, environmental monitoring and biodefence, they are becoming significant general purpose technologies. Increased investment in biodefence technology development may drive adoption across industry sectors as the technology spills over to civilian markets.

Health and Wellbeing	
THE THREE Ps	Trends in genomic medicine are indicating that: ■ diagnostics will become more **predictive**; ■ therapeutic interventions will become more **preventive**; and ■ healthcare (including diet) will become more **personalised** and tailored to the individual. Developments in the diagnostics sector are outpacing those in the therapeutics sector.
FROM REPAIR TO REGENERATION	The development of regenerative medicine that is accompanying growing understanding of stem cells and the neurological system is signalling a shift from the emphasis on the replacement of tissues to a more biologically based method for the repair and regeneration of tissues.

Primary Production

FROM "HIGH-VOLUME, LOW-VALUE" TO "LOW-VOLUME, HIGH-VALUE" PRIMARY PRODUCTION

Primary industry products have traditionally been characterised by the production of high volumes for relatively low returns. Biotechnology is enabling a move towards more value added products being produced in the primary industries (for example, pharmaceutical proteins produced in livestock and plants).

Industry and Environment

FROM NON-RENEWABLE COMMODITY PRODUCTS TO RENEWABLES

The finite nature of fossil fuels, and oil shocks – coupled with advances in industrial biotechnology, both in the development of cost-effective technologies to convert biomass to its constituent parts and in the growth in scale of bioprocessing capability – are driving a trend towards the increased production of commodity products (biofuels and bioplastics) from renewable biomass, such as crops and trees.

Emerging Applications to Watch

The following is a small sample of some of the more significant emerging biotechnology applications identified in this report. Market forecasts have been drawn from global (and commonly US-based) market information and are not specific to New Zealand. For a more comprehensive breakdown of emerging applications, with identification (where possible) of forecasted market entry and technical bottlenecks to development, turn to Part 2 (at the end) of Chapters 5–8.

Health and Wellbeing

DNA CHIPS	DNA chips and genetic testing will become integrated into standard clinical practice as the genetic nature of more complex diseases is unravelled and diagnostic tools become cheaper. This has been forecast to occur in around 2012.
RNA INTERFERENCE (RNAi)	The therapeutic application of RNAi (or gene silencing) could theoretically be applied to any disease that is linked to an overactive gene or genes. The first filing of an investigational drug application based on RNAi technology occurred in August 2004. The earliest prediction for an RNAi drug to reach the market is around 2019.
STEM CELL THERAPIES	Stem cells are the cells "most likely" to enable forecasted tissue engineering applications due to their innate ability to differentiate into other forms of tissue. The emergence of stem cell-based therapies for the treatment of chronic diseases such as diabetes, Parkinson's and Alzheimer's and heart disease are forecast to emerge between 2015 and 2025.
NEUROPROSTHETICS	Neuroprosthetics use brain signals to operate devices like artificial limbs (wearers may also regain the sense of touch) or computer keyboards. Successes in the lab indicate they may be available on the market soon after 2010.
EMBRYO SCREENING FOR MULTIPLE GENETIC TRAITS	Recent improvements to DNA amplification techniques mean that doctors (potentially from as early as 2005) will be able to screen pre-implantation embryos for multiple genetic traits.

Primary Production	
GM CROPS – STACKED TRAITS	The ability to genetically modify plants with multiple genetic traits is known as trait "stacking". GM crops with multiple genetic improvements will enable, in the first instance, greater control over production traits, such as pest resistance. More complex transformations which target "output traits" in plants, like increased oils or glucose, will follow. Artificial chromosome technology and chloroplast transformation are the two most promising technologies for achieving controlled "stacked" transformations.
MARKER-ASSISTED SELECTION	Marker-assisted selection breeding technology for both plants and animals is likely to allow controlled, increasingly complex genetic traits in animal and plant reproduction, without the need for genetic modification.
BIOPHARMING	The production of high-value proteins (like pharmaceuticals), using plants or animals as bioreactors or "factories", is forecast to occur between 2007 and 2020. Biopharming using farm animals is forecast to occur before production in plants.

Industry and Environment	
BIOPROCESSING TECHNOLOGIES	Micro-organism and enzyme catalysed industrial processing is being transformed by emergent techniques like metabolic engineering, which manipulates microbial cells to bypass cell processes.
RENEWABLES – BIOPLASTICS	It is estimated that, by 2010, 10% of the global plastics market will be for renewables and, by 2020–25, this will have expanded to 20% of the market.

Security and Defence	
DIAGNOSTICS	National security needs (particularly in the United States) are driving the development of live-cell biosensing technologies and real-time lab-on-a-chip processing capability. These technologies are anticipated to have spin-offs into civilian markets.
ANTIVIRAL THERAPEUTICS	The development of antiviral therapeutics is being driven by biodefence purposes, as well as the emergence of diseases like SARS and Avian flu. Approaches include targeting the "commonalities" between different viruses and attempting to counter viral pathogens in a generic way.

Science Trends

Discoveries in the biological sciences are one of the key factors driving or slowing down developments in biotechnology. An expert panel convened by the Royal Society of New Zealand identified key science trends and areas to watch to contribute to this report. A selection of the panel's key findings is outlined here.

Trends in Biological Sciences	
COMPLEXITY	There is a move towards understanding multigene function and regulation rather than a focus on single genes. A key to 21st century biology will be understanding molecular regulation at a network level. As the wealth of genome sequence data has illustrated, large amounts of data are being rapidly produced. Making sense of this information is a key challenge.
CONVERGENCE OF DISCIPLINES	Convergence of, and linkage between, scientific disciplines will continue. This is not novel but a normal part of how science proceeds. Molecular biology, for example, resulted from a merging of physics and biology. Other new hybrid research areas include bioinformatics and nanotechnologies.

Areas to Watch	
SYSTEMS BIOLOGY	In response to the need to better understand complex biological systems, there is growing interest in systems biology. This is a new field in the context of biotechnology, and represents a convergence of existing and new scientific disciplines (for example, genomics, proteomics, metabolomics, mathematics, biological computing and engineering) aimed at integrating all types of biological information (DNA, RNA, proteins, networks, cells, tissues, etc).
EPIGENETICS	It is now being appreciated that there is more to inheritance and genetic information than just the DNA or RNA sequence. Epigenetics (sometimes called "genomic imprinting") is the study of heritable traits and characteristics that are not encoded in the sequences of DNA but by the interaction between DNA and other molecules, or by protein-protein interactions. An improved understanding of epigenetic processes will have practical applications. For example, several human diseases are due to incorrect imprinting, so knowledge of the process may lead to therapies.
CHEMICAL GENETICS	Chemical genetics is a new discipline emerging as a result of the Human Genome Project. It is a powerful technique that allows researchers to change and observe the function of proteins, to better understand their interaction with other proteins and their role in living systems.

OBSERVATIONS

Through taking a look at "the whole picture", as depicted in the poster to follow, it is possible to start thinking about how these emerging technologies may interact with each other, and how they may matter to New Zealand. The following are some initial observations that we have made in taking this approach. They are by no means exhaustive, and serve only to illustrate the types of observations that can be extrapolated from viewing technology trends comparatively. They are intended to stimulate discussion and we invite others to add to these observations with their own knowledge.

1. Intersections – a fork in the road?

Between 2008 and 2013, there are likely to be two key technological approaches for producing crop varieties with desirable, complex and controlled output traits, like enhanced nutritional value or drought resistance. These will be genetic modification and marker-assisted selection technologies (so-called "smart breeding"). With the known uncertainties of consumer acceptance of GM technologies, this presents the possibility of a "fork in the road", where

markets (say, by region or by sector) may choose one production path over the other. This could then have flow-on effects to the rate of development in other biotechnology market segments.

2. Interdependencies – synergy or clash?

Forecasts for the development of bioenergy, biofuels and commodity bio-based chemicals are dependent, to a large extent, on the assumption that forecasted future developments in GM crop applications will provide improved raw materials and crop yields to act as feedstock to fuel industry growth. If markets choose not to go down the GM road then there is a possibility that the large-scale development of bio-based industry may not occur as forecasted.

The possible development of a bioenergy sector based on GM crops will almost certainly raise some tensions between environmental values. On one hand, the development of a bioenergy sector contributing sustainable energy resources is environmentally desirable. On the other, if this outcome is dependent on the use of GM crop technologies to achieve increased crop yields and scale, then it may present difficulties for those who consider GM technologies to be in conflict with environmental outcomes.

3. Regulatory readiness – are we future-proofed?

The forecast of emergent biotechnologies reveals a number of technologies that New Zealand's legislative system may not yet adequately address. We have identified a number of areas that may warrant further exploration – for example:

- genetic testing, and developments in genomic medicine which raise issues related to ethics and privacy as well as particular cultural issues for Maori;
- neuroprosthetics (eg mind-controlled artificial limbs), which raises issues related to ethics and safety;
- bioprospecting, and the need to ensure adequate protection of our native flora and fauna while also enabling opportunities for innovation; and
- nanobiotechnology applications which may raise issues related to health, safety, ethics and privacy.

4. The emergence of a "possibility space" – from therapy to enhancement?

The convergence of technologies emerging from different market sectors can enable totally novel outcomes. We are calling these "possibility spaces".

For example, a possibility space may open up around 2020 if there are:

- incremental improvements in embryo screening and selection;
- significant advances in gene therapy applications; and
- meaningful results from the number of large-scale population-based national studies into the genetic and environmental determinants of disease.

The convergence of these three factors could enable a scenario whereby embryos could potentially be engineered to exhibit selected *desirable* genetic traits – so-called "designer babies".

5. Uncertainties – the need for flexibility

This work has highlighted many areas in which technological development is almost certain. We can see where research is currently focused, anticipate incremental developments in knowledge and application, and plan or prepare accordingly. But a more important aim of futures work is readying for uncertainty, not certainty. As well as highlighting areas of relative certainty, this work has brought into relief areas of uncertainty – for example:

- whether and how social values and views about biotechnology may change, and
- if and when New Zealand may experience a serious national-level bio-related incident, such as an influenza pandemic or a foot and mouth incursion.

These and other uncertainties reinforce the need to be alert to science and technology developments and their surprises, and to have the flexibility to adapt in order to manage issues and take advantage of opportunities.

CHAPTER 3

FUTUREWATCH

FUTUREWATCH

3 BACKGROUND

This chapter sketches the landscape of biotechnology – what it is, how the sector is developing and where New Zealand fits into the picture. It should be useful background for those not already familiar with biotechnology, and provide context for the information about biotechnology trends that follows.

WHAT IS **BIOTECHNOLOGY?**

Biotechnology is the technological use of living organisms to make or modify products, to improve plants or animals, to develop micro-organisms for specific uses or to provide goods and services.

If defined broadly, we can say that biotechnology has been around for centuries (for example, using yeast to make bread and beer, and using bacteria to make cultured dairy products such as cheese and yoghurt). Modern biotechnology came of age in the 1950s with the discovery of DNA. It includes genetic modification, but is far broader than this, including techniques for deciphering genetic codes (eg gene sequencing and genomics) and a wide range of cell technologies used for growing new tissue (eg plant cultivation and use of stem cells).

Throughout the world, biotechnology is used by:

- researchers, to understand living things and the mechanisms of human health and disease;
- developers, to create new products and services;
- health professionals, as part of many of the medical therapeutics and diagnostics (eg vaccines);
- firms, embodied in products and services, and commonly a source of intellectual property and hence commercial revenue;
- growers and farmers, embodied in new plant and animal varieties;
- resource managers, to control pests and manage waste; and
- consumers, through their consumption of some foods, medicines and industrial products.

When thinking about the future it is always useful to look into the past to obtain a sense of the pattern and rate of change. The timeline at right contrasts some significant historical science discoveries and successes in the lab with the emergence of actual biotechnology applications across the four application areas that we investigate in this report. This gives a sense of the time it takes to translate discovery to application, and also shows how the pace of that translation has picked up over time, in part driven by new tools and techniques like DNA sequencing. The historical timeline also gives a sense of the relative “maturity” of each market segment.

Historical Timeline

SCIENCE DISCOVERIES	HEALTH APPLICATIONS	PRIMARY PRODUCTION APPLICATIONS	INDUSTRIAL APPLICATIONS	SECURITY AND DEFENCE APPLICATIONS
1865 – Gregor Mendel discovers the laws of genetics				
1900 – Mendel's work rediscovered				
1928 – Alexander Fleming discovers germ-killing properties of the mould *Penicillium*				
1944 – First successful IVF of an immature egg	**1942** – Large-scale manufacture of penicillin achieved			
1952 – Cloning of frog embryonic cells by nuclear transfer results in the birth of tadpoles **1953** – Watson and Crick describe the double-helical structure of DNA		**1950** – Artificial insemination of livestock using frozen semen accomplished	**1950** – Enzymes used in manufacturing of detergents	
1960 – Messenger RNA is discovered				
1972 – Recombinant DNA molecules are first produced **1976–77** – DNA sequencing methods developed	**1976** – Genentech, the first commercial biotech company, founded **1978** – First recombinant DNA drug marketed: human insulin – Louise Brown, the first IVF (or "test-tube") baby, is born in the UK	**1970s** – R&D into breeding mussel sprat establishes aquaculture industry in NZ		
1985 – The polymerase chain reaction (PCR) is invented	**1980s** – Recombinant DNA human vaccines approved	**1984** – A sheep is cloned from early embryos = first verified cloning of a mammal by the process of nuclear transfer	**1980s** – Brazil implements large-scale production of cane sugar bioethanol	**1984** – DNA fingerprinting technique developed

continued over...

Historical Timeline continued...

SCIENCE DISCOVERIES	HEALTH APPLICATIONS	PRIMARY PRODUCTION APPLICATIONS	INDUSTRIAL APPLICATIONS	SECURITY AND DEFENCE APPLICATIONS
1986 – First automated DNA-sequencing instrument developed	**1989** – Pre-implantation genetic diagnosis (PGD) is performed for the first time to identify X-linked diseases	**1980s** – Recombinant DNA animal vaccines approved **1985–86** – Genetically engineered plants resistant to viruses, insects and bacteria are field-tested for the first time		
1990 – Human Genome Project launched **1998** – Human embryonic stem cells cultured in the lab **1999** – Sequence of first human chromosome (chromosome 22) completed	**1992** – Intracytoplasmic sperm injection (ICSI) developed to assist in cases of severe male infertility **1998** – Emergence of targeted gene-based therapeutics: Herceptin breast cancer drug approved by the FDA	**1994** – The FLAVRSVR tomato – the first genetically modified whole food on the market – ultimately rejected by consumers **1996** – Monsanto's first plant biotechnology products (Roundup Ready Soy and Canola and Bollgard Cotton) planted commercially **1996** – "Dolly" the sheep is the first successful clone from an adult mammalian cell conceived through the process of nuclear transfer	**1990s** – One-step fermentation production process for riboflavin engineered	
2000 – Draft version of the human genome sequence completed **2001** – RNA interference (RNAi) identified – First report of human embryos cloned from a body cell (developed to early six-cell stage) **2003** – Completed version of the human genome published – Virus genome synthesised from scratch	**2001** – Targeted gene-based therapeutic Gleevec approved by FDA for leukaemia treatment **2003** – First pharmacogenetic application on the market (gene chip test for drug metabolism enzyme) **1997–2004** – 16% of new drugs based on biotechnology	**2002** – Cattle cloned for commercial purposes	**2003** – Cargill Dow introduces 100% renewable bioplastic onto the market, produced in prototype biorefinery	**2001** – Biometric identification systems for airport security and border control

BIOTECHNOLOGY AS A SECTOR

As well as describing a class of technologies, the term "biotechnology" also describes a sector of the economy.

Biotechnology as a distinct sector was established in the United States in the mid-1970s and has since developed into a global industry. However, even on a global scale the biotechnology industry is still relatively small and remains at a nascent stage of development with regard to the translation of research and development into economic application.

The sector is composed of a large number of small usually R&D-intensive firms, and a small number of larger highly diversified companies (notably in the pharmaceuticals and agrifood industries). The small firms, where much of the early development work is done, often earn little if any revenue for long periods of time. This is because of the long lead-in time to commercial profit. Investors therefore tend to be larger companies which can sustain long-term investment.

The most significant global biotechnology market is the healthcare sector. Ninety per cent of global value from biotechnology is derived from biopharmaceuticals and the vast majority of biotechnology firms are working across this broad field. Fifteen per cent of all drugs are currently based on biotechnology and this is projected to grow to 40% by 2010.

Agricultural biotechnology is the second most significant global biotechnology sector and is characterised in many people's minds by GM crop production. GM crops entered the global marketplace in 1996 and the area covered by them has grown substantially from 2.8 million hectares in 1996 to 67.7 million hectares in 2003. However, 99% of GM crop production occurs in only six countries, with the United States alone being responsible for 63% of the global total.[4] Agricultural biotechnology is much more than GM crop production, however. It also covers traditional breeding techniques in both plants and animals and a range of genomic and cell-based technologies for enhancing productivity in the primary industries.

Industrial biotechnology is the smallest percentage of the global biotechnology sector. Here, biotechnology applications can already be seen in several industrial markets, including fine and specialty chemicals, paper, and textiles. There is growing activity in the energy sector as biotechnology offers alternatives to the use of fossil fuels.

(adapted from Ernst and Young – Global Biotechnology Report – 2003 & 2004)

4 ISAAA (2003), "Global Status of Commercialized Transgenic Crops: 2003".

The United States has by far the greatest share of global revenues from biotechnology (see figure p 19). Other nations are starting to develop more established biotechnology sectors. Canada and Germany, for example, are starting to exhibit signs of a more mature biotechnology industry, including growing revenues from biotechnology products and processes and a workforce composition that is no longer focused on R&D but also production and sales.[5] Countries like China, India and Singapore are also investing large amounts of public money in developing a strong biotechnology research base and infrastructure.

New Zealand Biotechnology

Ten years ago it would have been difficult to find or even define New Zealand's biotechnology sector. Although now still small, we recognise it as comprising some 350 organisations, 20 research centres and 42 core biotechnology companies, returning export value of around $250 million per annum.[6] This new sector hasn't come from nowhere – it has emerged from what has always been the very strong biological base to our economy and its strong underpinning of science and research. Part of the growth is through new firms and institutions, and part through a refocusing of what we've always done. New Zealand has, for example, a 150-year history in the genetic improvement of animals and plants for efficient primary production.[7] This tradition continues to be applied on farms throughout the country, remains a focus of ongoing research and development in research organisations such as AgResearch (www.agresearch.co.nz) and HortResearch (www.hortresearch.co.nz) and is supporting the development of commercial ventures such as Ovita, and its development of therapeutic diagnostic products related to sheep.

Reflecting this history, New Zealand's public purse has invested strongly in biotechnology research (and continues to do so). In 2004, New Zealand funded an estimated $170 million of biotechnology research through Vote RS&T.[8] This is around 15% of total government R&D

5 OECD (2004), "The Economic Impacts of Biotechnology – An introduction" – Working paper of National Experts on Science and Technology Indicators, DSTI/EAS/STP/NESTI(2004), p.9.

6 The Biotechnology Taskforce (2003), "Growing the Biotechnology Sector in New Zealand – A Framework for Action".

7 New Zealand Trade and Enterprise (2003), "Biotechnology in New Zealand".

8 MoRST (2004), unpublished data.

9 New Zealand Biotechnology Strategy: http://www.morst.govt.nz

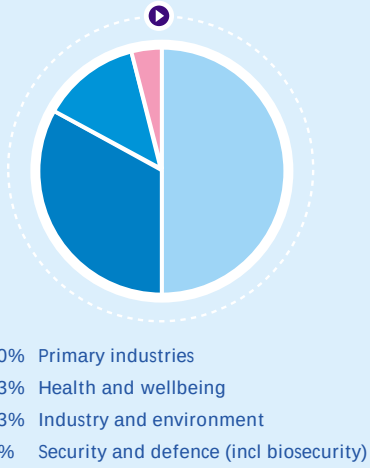
10 Ibid.

11 OECD (2004), op cit p.20.

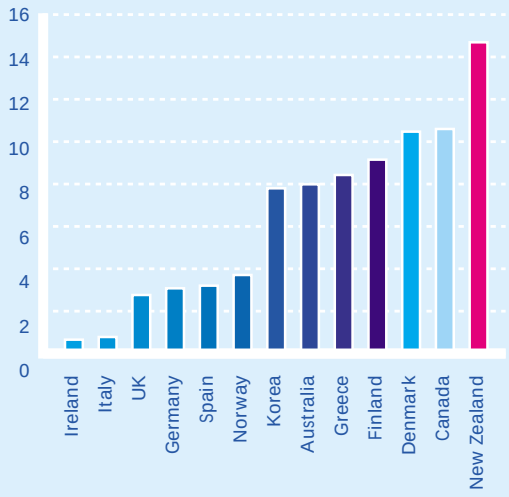
GOVERNMENT INTEREST

Government's interest in biotechnology in New Zealand extends beyond support for the research base. The New Zealand Biotechnology Strategy[9] was developed in 2002 and underpins government assistance for firms, for example through capability- and network-building and marketing assistance, maintenance and operation of the regulatory regime that controls the development and importation of biotechnology products, and support for education and public awareness about biotechnology.

Indicative distribution of public research in biotechnology in New Zealand directed towards, or broadly relevant to, the following sectors or applications[10]



Biotechnology R&D as a percentage of government R&D (2000)[11]



funding, a high proportion relative to other OECD countries (see figure at left). It is very difficult to assess the distribution of research across various sectors (because of the generic nature of much of the research), but as an indication around half of research is directed towards or broadly relevant to the primary sector and around one third to health and wellbeing outcomes, with the remainder spread between environmental and industrial applications.

In research, New Zealand's strengths in biotechnology lie in the following areas.[12]

1. **Large-animal-based biotechnologies**
   New Zealand's long history of large-animal farming (sheep, dairy, beef and more recently deer) has led to the development of world-class science and technologies. This includes genomics, reproductive and cloning technologies, large-animal models of human diseases, and using molecular approaches to solve animal health issues and to enhance human health. The convergence of agriculture and biomedicine is a defining and unique feature of the New Zealand biotechnology sector.

2. **Plant-based biotechnologies**
   We also have extensive knowledge of the biology of industrially significant plants, grasses, trees and crops (both arable and horticultural). Obvious examples are ryegrass and *Pinus radiata*. This includes access to some unique germ plasm and expanding genomic databases. For example, for nearly three decades, propagation of plants in culture from tiny tissue nodules has been a niche business in New Zealand.

3. **Biomedical science and drug discovery**
   Around one third of New Zealand's public research effort in biotechnology is in the area of health biotechnology. This is small compared with global research in this area, but includes research teams contributing to advances in areas such as neuroscience, cardiovascular disease, asthma, diabetes, cancer, osteoporosis and bone health.

4. **Bioprocessing technologies and biomanufacturing**
   New Zealand companies have been handling and processing biological material for over a century. This has led to expertise in the extraction of fine chemicals from meat and fish waste, as well as the retention of biological activity in unstable valuable compounds such as enzymes. As a consequence we are well placed to develop the bioprocessing technologies to manufacture and market high-value molecules. The development of Industrial Research Limited's (IRL) Biopharm[13] exemplifies how this expertise can be extended.

5. **Innovative foods and health**
   Food and beverage exports make up around 10% of New Zealand's GDP, with around half being value added rather than commodity products.[14] The New Zealand biotechnology sector is contributing through the identification of valuable bioactive compounds in food, enhancing their production and the design of extraction systems. Nutrigenomics (foods designed or matched to individuals' particular genetic make-up) is an emerging field in New Zealand, with the recent development of a research consortium.[15]

6. **Biocontrol, biosecurity and bioremediation**
   With an economy based on primary production, and a range of unique and sometimes endangered plants and animals, we are very vulnerable to biosecurity threats and environmental contamination. Biotechnology may help address these threats through a range of biocontrol and detection technologies, and reduce environmental damage through bioremediation (use of selected or modified bacteria or fungi to detoxify or degrade waste). We have a strong environmental research base and are beginning to use this in the development of innovative products.

12 NZ's biotechnology research strengths adapted from:
- Ministry of Research, Science and Technology (2004), "New Zealand Biotechnology Strengths"
- The Biotechnology Taskforce (2003), "Growing the Biotechnology Sector in New Zealand – A Framework for Action".

13 http://www.irlbiopharm.com/

14 Winger, R. (2004), "A study into the level of value-added products in New Zealand food and beverage exports", Massey University.

15 http://www.nutrigenomics.org.nz/

BIOTECHNOLOGY AND ITS CONTEXT

CHAPTER 4

FUTUREWATCH

FUTUREWATCH

4 BIOTECHNOLOGY AND ITS CONTEXT

No technology develops in isolation and biotechnology is notable for its rich connections with its societal environment. These connections are two-way: biotechnology both shapes, and is shaped by, a wide range of factors.

These factors can be grouped into two areas:

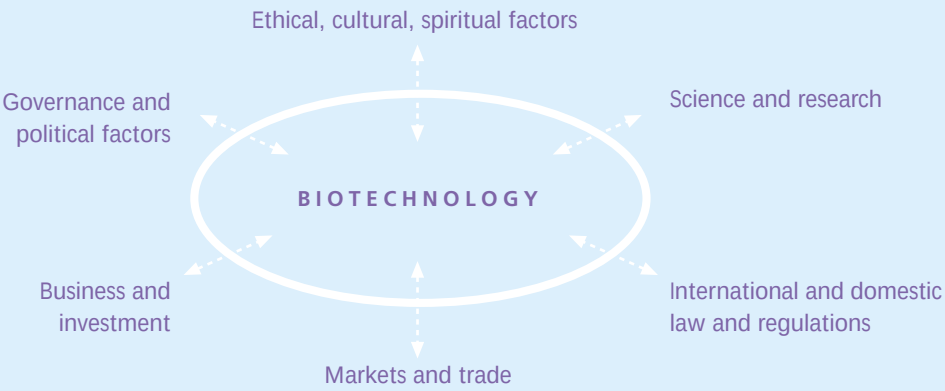
1. **global drivers** – important forces of change such as globalisation, demographic changes, environmental sustainability and unexpected high-impact events, like the emergence of the SARS virus; and
2. **the biotechnology "environment"** – things that are more specific to biotechnology, such as public attitudes to genetic modification, governance mechanisms for biotechnology and capital markets for biotechnology business.

Biotechnology is becoming an integral part of everyday life in contemporary society, increasingly used to help deliver healthcare, produce food and support the primary sector. But its social connection runs deeper than this. Because biotechnology deals with the basic processes of life and is such a potentially powerful set of tools it often touches on core values – such as what it means to be human, and what we think is best for the world and its people.

When thinking about the values and views that shape biotechnology, uppermost in many people's minds will be the various concerns expressed by consumers over recent years about genetic modification and its use in foods. There is, however, a richer picture. Values and beliefs are also expressed in the drive of scientists to discover new knowledge and of developers to solve problems and build businesses, the urge from patients for better healthcare, the desire to know (or not know) our genetic heritage and the sense of duty many have to protect the environment and the welfare of animals. This cluster of things – reflecting world views, values and beliefs – is a strong modulator of biotechnological development: sometimes an accelerator, other times a brake, and sometimes pointing to new roads.

This chapter outlines just some of the trends occurring in the social environment of biotechnology, to provide starting points for discussion. Further information on global drivers and factors in the environment for biotechnology are included in the overview (Chapter 2) and the application chapters that follow.

BIOTECHNOLOGY SHAPES, AND IS SHAPED BY, A WIDE RANGE OF FACTORS



GOVERNANCE AND POLITICAL FACTORS

Example trend: **More open styles of governance**

Governments with social democratic and centrist perspectives have moved towards more open styles of governance for biotechnology than has previously been the case around emerging science and technology. In this approach, government sees its role as fostering continual learning and adjustment that seek benefits and mitigate risks in an environment of uncertainty. An example is the Blair Government's "Third Way" approach. This has resulted in the formation of numerous panels, councils and debates that have been aimed at engaging with all stakeholders. Similar approaches are evident in Europe, Canada, Australia and New Zealand.

There are a number of drivers behind this trend. These include changing social attitudes, such as a decline in the authority given to science, far more conditional trust for government and regulators, and changing social and ethical stances. As well, there is recognition of the inherent uncertainty in biotechnology and newer approaches to dealing with risk and uncertainty, in part learnt from past experiences such as BSE. The rise of multinational NGOs and global media to lobby on the part of populations and the environment has also played a significant part.

A significant feature of this trend is that it is strongly aligned to nations and their particular social and political ideology. The divide between Europe and the US in their stance on GM crops and associated trade is one area where this difference is starkly expressed: the former advocating a more precautionary and inclusive approach to decision making, the latter supporting decisions based primarily on science.

ETHICAL, CULTURAL AND SPIRITUAL FACTORS

Example trend: Broadening sphere of ethics

10 to 15 years ago ethical concerns related to biotechnology tended to be restricted to issues around individuals: be they patients treated with biotechnology, animals and their welfare, or scientists and research ethics. These views were also held primarily by scientists and clinicians using biotechnology. Now, the ethics of biotechnology is something most people have a view on. The scope of concerns is becoming broader too, covering not only individual wellbeing and rights, but those of communities and of the environment.

In some ways the broadened scope of ethics has been a natural response to the movement of modern biotechnology from a largely contained laboratory-based tool to a more integral part of everyday products and services. It likely also reflects an actual change in ethical views in societies, either as an extension of current (human-centred) ethical principles or as a new environmentally centred ethical approach.

MARKETS AND TRADE

Example trend: Negative attitudes to GM hardening

Concern about health and the environmental impacts of genetic modification (and particularly GM foods) emerged strongly in Europe in the 1990s (paralleling the introduction of GM crops) and has since developed into a

NEW ZEALAND CASE STUDY

TOI TE TAIAO

Toi te Taiao, the Bioethics Council, was established in 2003 to advise government and foster dialogue in New Zealand on the cultural, ethical and spiritual aspects of biotechnology. Its establishment is a signal that the trend towards more open styles of governance (discussed at left) is evident, and actually quite advanced, in New Zealand. Another sign is reflected in our Hazardous Substances and New Organisms Act, which includes recognition of the need for "maintenance and enhancement of the capacity of people and communities to provide for their own economic, social, and cultural wellbeing and for the reasonably foreseeable needs of future generations".

view held in most developed nations. It is strongest in Europe and Japan and more moderate elsewhere, such as in the US.

Public views on non-GM biotechnologies are not as well studied but, in general, follow a similar pattern, with applications presenting human safety or ethical issues, such as xenotransplantation or cloning, similarly of concern. Recent reviews of US-based surveys of public opinion indicate that a slight majority believes that biotechnology will produce benefits in the future, but most also worry about the potential harmful effects of biotechnology.

BUSINESS AND INVESTMENT

Example trend: Fragile investment in biotechnology

Since the "biotech bubble" burst in 2000, private investment has been shying away from biotechnology. In Europe investment is available for only the best of companies. There are few specialised biotech investment funds in this region and competition for early-stage funding is particularly harsh. The European biotech industry is patchy, with many small firms that are not viable as businesses. This is not an environment that favours mergers and acquisitions to build strength – this usually involves one big, one small company. By contrast, the US has a variety of sources of capital and well-developed markets and there are some signs that investor confidence in biotechnology is beginning to pick up again.

Biotechnology firms are uniquely challenging for investors, as they may not be profitable for many years. At the time it is seeking investment, the firm's only substantial assets are likely to be its intellectual property (patents). The firm therefore can't be valued using traditional measures. Lack of investor expertise is a major problem in biotechnology globally, and drives the cycles of hype-boom/bust that make it hard for companies to find sustainable funding. In response to this, there is growing interest in the development of biotechnology-specific valuation techniques, which would factor in, for example, the level of risk at each stage of development.

NEW ZEALAND CASE STUDY

New Zealanders have opinions about biotechnology and its potential effects that differ from those in countries like Australia, the United Kingdom or the United States. Although lessons may be drawn from progress and process elsewhere, New Zealanders undoubtedly view biotechnology through a different lens.

A 2000 consultation found that New Zealanders link their views about biotechnologies with their identity as New Zealanders. "Certain characteristics, such as being close to nature and independent of outside influences, are seen as being part of our national identity and are a source of great pride. For some, aspects of biotechnology represent a threat to these attributes and hence to our sense of self as a country."[1]

There have been around 20 significant studies into various aspects of public awareness of, and attitudes towards, biotechnology and/or GM issues in New Zealand. Although a number have reported that GM or biotechnology is not usually a top-of-the-mind issue for most New Zealanders, when asked specifically, typically around half of respondents have concerns about eating GM products and are negative towards GM in food production. Respondents generally see more advantages in GM in medicines and medical research than in the use of GM in food, agriculture and horticulture.[2, 3]

1 Independent Biotechnology Advisory Council (2000), "Public Views on The Biotechnology Question" www.ibac.org.nz

2 Awareness and Attitudes Toward GMOs. ERMA NZ, 2002. http://www.ermanz.govt.nz/resources/publications/pdfs/ER-RE-01-2.pdf

3 Public Understandings of Biotechnology in New Zealand: Factors Affecting Acceptability Rankings of Five Selected Biotechnologies. Lesley M Hunt, John R Fairweather and Fiona J Coyle (2003). http://www.lincoln.ac.nz/aeru/publish/aeru266.htm

ALTERNATIVE FUTURES

The trends outlined above (and in the following chapters) are all things that are evident from the recent past and the current environment around biotechnology. What is less clear is whether and how these same trends will project into the future. Some we can be fairly certain will be ongoing; others undoubtedly will change and become less or more important than we thought.

One way of developing a fuller awareness of the different ways in which biotechnology may unfold is to consider a range of future scenarios, and project into these the trends related to biotechnology. The use of scenarios helps us recognise that the pathways of technology are highly dependent on other factors, many of which can be very uncertain. Thus, the trends we see now could shift considerably, depending on world events, presenting quite a different environment for biotechnology in terms of its priority, purpose and acceptability. This in turn underlines the need for flexibility with respect to technology-related policy.

Annex 1 sketches a set of scenarios that may be useful thinking tools to help interpret the trends presented in this report. These scenarios were developed by Navigatus Ltd (formed from Forest Research) in 2001/02 to help guide the development of its business strategy and have been adapted for a biotechnology context. The information is derived from a review of major global trends in the categories of social, technological, economic, environmental and political values and the interactions between them. The resulting global futures context is generally consistent with other published global foresight and scenarios. The annex also includes a table presenting some of the key trends identified throughout this report and an indication of how the trends may be different under alternative global scenarios.

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CHAPTER 5

FUTUREWATCH

FUTUREWATCH

5

HEALTH AND WELLBEING

This chapter outlines trends and likely future developments (up to 2025) in health and wellbeing applications for biotechnology. The healthcare sector is the biggest global biotechnology market. Ninety per cent of global value from biotechnology is derived from biopharmaceuticals, and the vast majority of biotechnology firms and research enterprises are working across this broad field.

Health biotechnology applications fall into two distinct categories:

1. applications involving the manipulation of cells, tissues, organs or whole organisms (eg assisted reproduction, tissue engineering and cloning); and
2. applications involving identifying the functioning at a molecular level of DNA, proteins and enzymes and their relationship to both disease onset and wellness (eg gene-based diagnostics and therapeutic interventions).

In this chapter we discuss the broad areas of genomic medicine, regenerative medicine, reproductive technologies, enhancement technologies and nutrition. The chapter is split into two parts. **Part 1** is a detailed analysis of trends in emergent health biotechnologies to 2025. **Part 2**, in the form of a table, provides an overview of the trends, grouped into drivers of growth, meta-trends, paradigm shifts, incremental growth trends, uncertainties and key emerging applications to 2025.

PART 1: EMERGENT HEALTH BIOTECHNOLOGIES TO 2025

GENOMIC MEDICINE

Genomics is the study of the functions and interactions of all genes within an organism. Genomic medicine seeks to identify the genes involved in the onset of diseases and to formulate therapeutic strategies based on this knowledge. This discipline is still in the early stages of development. When the draft mapping of the human genome was completed in 2000, forecasters quickly predicted the development of a large number of gene-based medical applications. That promise has not been realised to date. This is because the human genome map provides merely a "map of parts". There is still much more data to collect at both the cellular and population-based levels. And, crucially, there is much more data to interpret before we can begin to have an understanding of the complex genetic and environmental underpinnings of disease development.

Large-scale national gene-banking projects like the UK Biobank[16] and Iceland's deCode Genetics[17] will play an important role in helping us understand how diseases begin and progress, and how individuals respond to diseases and the drugs used to treat them. DeCode's project is one of the most advanced population-based genetics studies. Around 110,000 Icelanders, more than half of the adult population, have given samples of their DNA to deCode. The company is now at the initial stages of taking a drug to preclinical trial for heart disease.[18] However, it is believed that national initiatives like Biobank will require about ten years of data collection before any meaningful results can be derived from them.

Another key initiative is the International HapMap Project, which is aiming to create a catalogue of common genetic variants that occur in human beings. It will describe what these variants are, where they occur in our DNA, and how they are distributed among people within populations and among populations in different parts of the world. The project is designed to provide information that other researchers can use to link genetic variants to the risk for specific illnesses, which will hopefully lead to new methods of preventing, diagnosing and treating disease.

Despite the complexity of the task at hand, and the sheer volume of data that still needs to be collected and analysed, genomic medicine promises to transform the healthcare sector and drug development processes – albeit not as rapidly as was formerly envisaged.

The following sections will look at emerging technologies that are driving the development of genomic medicine. These include:

- emerging diagnostic tools;
- "personalised medicine" or pharmacogenetics; and
- emerging gene-based therapeutics.

Diagnostics – Gene Testing

Rapid diagnostic technologies make up the first significant "wave" of clinical applications in genomic medicine. It's possible to conceive of a future where gene-testing capabilities will be able to measure precisely tens, hundreds, thousands or even tens of thousands of messenger RNA, protein or small-molecule components in the blood. These components, or

16 www.ukbiobank.ac.uk

17 http://www.decode.com/

18 *MIT Technology Review*, September 2004, "Transplanting Iceland's Genes into Medicine".

"markers", differ for each type of disease, as well as for each stage of disease onset. It's anticipated that being able to precisely identify each marker will enable the right kind of treatment to be introduced at the most appropriate stage of the disease.[19]

Most current genetic testing is used for inherited disorders or singular disorders caused by a defect to a single gene or chromosome, which usually manifests itself as a specific medical condition or disorder (cystic fibrosis, Huntington's disease and haemophilia are all examples). However, the Human Genome Project (HGP) makes it easier to identify the wide array of genes that contribute to more complex multigene diseases like cancer, heart disease and diabetes. Using genetic testing, we can expect to see incremental growth in our understanding of more complicated genetic conditions. Genetic testing can also help us understand why certain people are susceptible to particular diseases, and can help us in developing tools to test for such diseases.

As the genetic nature of more complex diseases is unravelled – and if genetic testing and diagnostic tools become cheaper and more integrated in standard clinical practice – genetic testing will become a powerful and ubiquitous clinical tool. The Seventh Technology Foresight exercise undertaken by Japan's National Institute of Science and Technology Policy (NISTEP) forecasts that by 2012 it may be possible to "determine the entire base sequences of an individual including genetic structure and SNPs promptly and cheaply, leading to widespread use of such methods for diagnosis and tailor-made treatment".[20]

The Tools

The technologies that enable rapid testing of DNA include chips/microarrays, which can measure the expression levels of up to tens of thousands of genes in a single experiment on a small glass slide. Some of the first chip-based diagnostics are now commercially available for predicting cytochrome P450 metabolism (this is an enzyme responsible for the metabolism of many drugs).[21]

However, the currently available technology is expensive and those interpreting the results in a clinical environment need to be trained in molecular biology. This technology will only become mainstreamed when the price of the testing technology drops and there are adequate numbers of trained clinicians or software applications to interpret the data.

DNA chips are not the only emerging technology that will have an impact on diagnostics. The convergence of biotechnology and nanotechnology is expected to produce some powerful diagnostic tools. These will enable us to observe complex molecular interactions with a much greater degree of specificity. This specificity is needed because current technology isn't sensitive enough to work out how cells actually function; biological systems like cells work at the level of individual molecules.

Some of the earliest applications of nanobiotechnology may be in molecular diagnostics. Researchers believe that after DNA chips will come a generation of protein chips operating at the nanoscale. These chips will be able to assay multiple proteins or other protein- or DNA-binding molecules in a single diagnostic test. This capability will be crucial to effectively test for complex multigene diseases and, most importantly, assessing what stage of development the disease is at.[22]

So-called "protein pattern profiling" techniques are starting to identify the progression of some cancers. Drawing on algorithms from artificial intelligence theory, US researchers have begun to identify some cancer patterns from blood tests. A test for ovarian cancer based on protein profiling is currently under assessment for women in remission from the disease.[23]

Sensor technologies like nanowire sensors – an emerging application which appears to be 1000 times more sensitive than DNA tests and capable of producing results in minutes rather than days or weeks – could also pave the way for faster, more accurate medical diagnostic tests. These highly sensitive sensors represent the first example of direct electrical detection of DNA using nanotechnology.[24]

19 www.hapmap.org

20 National Institute of Science and Technology Policy (Japan), "The Seventh Technology Foresight – Future Technology in Japan toward the Year 2030 – Survey Results – Life Sciences", p.213.

21 Bell, John (2004), "Predicting disease using genomes", *Nature*, v429, 27 May, p.454.

22 Weston, A.D. & Hood, L. (2004), "Systems Biology, Proteomics, and the Future of Healthcare: Towards Predictive, Preventative, and Personalized Medicine", *Journal of Proteome Research* v3, p.190.

23 *MIT Technology Review* (2004), "Spotting Cancer Sooner", July/August.

24 *EurekaAlert*, 16 Dec 2003, "Tiny nanowire could be next big diagnostic tool for doctors".

Emerging imaging technologies also show particular promise for medical diagnostics. Imaging technologies, like magnetic resonance imaging, present a visual display of tissues, organ systems and their functions. It is believed that molecular imaging of gene expression in humans will be available within the next five years (the technology is already being used in animals). It has potential not only for diagnostics, but also for observing and assessing, in real time, the effects of many forms of pharmaceuticals and gene therapy applications.[25]

Nanoparticles, particularly quantum dots, look set to play an important role in the emerging area of imaging biomarker development. Quantum dots are crystalline structures which glow fluorescently under laser light. If coated correctly the dots can act as effective biological markers of disease, with the added advantage of being able to stand up to the rigours of biological processes without interfering with cellular function. Unlike commonly used organic dyes used for in vivo imaging fluorescence agents, which fade within minutes, quantum dots keep shining for weeks or longer, allowing researchers to watch cellular function unfold. They also allow researchers to use multiple colours simultaneously. Conceivably this could enable the viewer to watch the interaction of more than one molecule. Some experts believe that they may be a commonly used diagnostic tool by 2009.[26]

However, like all nanoparticles, quantum dots pose potential human health risks. For example, the dots are composed of metals such as selenium, lead and cadmium, and are likely to be toxic if released in the body. To lessen the chance of this happening, developers add coatings to ensure safety and stability. However, recent studies have demonstrated that the movement, retention and distribution of quantum dots vary greatly based on surface coatings. Therefore, before this technology can enter into human testing, researchers are going to have to develop coatings which are safe for the patient but which don't interfere with the dots working in an effective manner.[27]

Pharmacogenetics

The global vice-president of genetics at pharmaceutical giant GlaxoSmithKline was recently quoted as saying that 90% of today's drugs work in only 30–50% of the people that they are prescribed for.[28] This is because individuals vary in their response to the same medicine and is why pharmacogenetics – the study of genetic variation that affects an individual's response to medicines – is important. Some of this response is due to differences in genetic make-up. People with a particular genetic make-up may find some medicines ineffective, or may need higher or lower doses in order to achieve a therapeutic effect. This is because their body breaks down the substances either more or less rapidly. There are a large but finite number of systems our bodies can use to process medicines and, as our understanding of them advances, predictive genetic testing may be able to determine which medicines to prescribe and in what doses.

The first commercial pharmacogenetic application reached the market in 2003, in the form of a DNA chip which tests for two key enzymes responsible for drug metabolism. These enzymes are found in the human liver and are involved in the metabolism of around 45% of all medicines that are currently prescribed. About 7% of the Caucasian and 2% of the non-Caucasian population have a genetic variant which results in reduced activity of one of these enzymes.[29]

Pharmacogenetics applications may also become important in the drug development process, especially in clinical trials. Being able to screen precisely for individuals who are suitable for a trial beforehand may well have a large impact on how such trials are designed and managed as well as, potentially, reducing their cost.

It may also increase the flexibility in the process: a drug trial that would have been abandoned could potentially continue by excluding at-risk patients, coupled with a greater streamlining of the "standard" clinical trial process.[30]

A recent survey by the SNP Consortium found that most pharmaceutical companies believe that, by 2007, at least 50% of clinical trials will involve obtaining genetic data from participants.[31]

25 Institute for the Future (2003), "Healthcare 2010 – The Forecast – The Challenge", 2nd ed., p.115.

26 *Science* (2003), "Quantum Dots Get Wet", v300, p.80.

27 *The Scientist* (2004), "The Ups and Downs of Nanobiotech", August 30.

28 *The Guardian* – Dec 9, 2003, "The Great Drugs Lottery".

29 Nuffield Council on Bioethics (2003), "Pharmacogenetics – ethical issues" pp.13-15.

30 Boston Consulting Group (2001), "A Revolution in R&D: How Genomics and Genetics are Transforming the Biopharmaceutical Industry" pp.33-34.

31 Nuffield Council on Bioethics (2003), ibid pp.21-22.

Therapeutics

Over the past 10–12 years most pharmaceutical companies have struggled to maintain their shrinking drug pipelines. The initial iterations of the much hyped technologies of the 1990s – combinatorial chemistry and high-throughput screening which automated and sped up the process of drug discovery – produced many more targets. But with quantity did not come quality.

The sequencing of the human genome was expected to revolutionise the process of drug discovery. Despite the undeniable enormity of this achievement, the genome is no more than a "parts list" of genes whose connection with disease is still largely unknown. The flood of information has created a form of "paralysis" because, even though we have a parts list, researchers still do not know precisely which parts are related to which diseases. Without that knowledge, appropriate gene-based therapies cannot be developed. Consequently, the optimistic forecasts post-2000 of a rapid flood of gene-based therapeutics to market have now been tempered by a greater understanding of the true complexity of the task at hand.[32]

Despite the glut of data, we are nevertheless trending away from a drug development model based on "chemical-based blockbusters" towards "individualised biologicals". About 16% of new drugs since 1997 have been based on biotechnology. This share is forecast to rise by up to 40% by 2015 according to some industry observers. To add weight to this projection, more than 30% of drugs currently in development are biological.[33]

Only a handful of targeted gene-based drugs have reached the market. Two of the most well known are the breast cancer drug Herceptin® and the leukaemia drug Gleevec®. These drugs cater to specific genetic sub-populations. For example, Herceptin® is a monoclonal antibody which targets cancer cells that overexpress a hereditary protein called HER-2, or erb B2, which is found on the surface of some cancer cells. Only around 25–30% of breast cancer sufferers overexpress HER-2 and the drug is prescribed after genetic testing confirms susceptibility.

BIOLOGICAL DRUGS

We can broadly characterise biological drugs as substances "… made from a living organism or its products. Biologicals may be used to prevent, diagnose, treat or relieve symptoms of a disease. For example, antibodies, interleukins, insulin and vaccines are biologicals …"[34] The first biological drugs entered into clinical practice in the early 1980s (eg Genentech's recombinant human insulin).

Biological drugs are more complex products than chemical-based pharmaceuticals, to both administer and manufacture. Because biologics are based on molecules that are naturally found in the human body, they are larger than their small-moleculed chemical counterparts. As such, biological drugs are degraded by stomach acids and so cannot be taken orally. They need to be administered intravenously or by injection, typically by a health professional. A "drug delivery" sub-industry has subsequently emerged to try and find novel solutions for delivering biological material to the target site.

The first generation of biotechnology patents for biological drugs is now expiring. A significant emergent issue for the biotechnology industry and regulatory bodies is the imminent production of generic biologics (sometimes referred to as "follow-on biologics" or "bio-similars"). Biologics are difficult to manufacture and, because they are large molecules, they must be rigorously tested and monitored because they can potentially trigger immunogenic responses in patients.

Regulatory bodies like the FDA are currently in the process of examining the scientific issues surrounding the manufacture of generic biologics; at the same time, countries like South Korea and India are gearing up to manufacture them.

32 *Economist*, Mar 11th 2004, "Fixing the drugs pipeline".

33 OECD (2004), "The Economic Impacts of Biotechnology – An introduction" – Working paper of National Experts on Science and Technology Indicators, DSTI/EAS/STP/NESTI(2004), p.6.

34 http://www.cancer.gov/dictionary

However, in a recent development, researchers have discovered that, even with successful targeted therapeutics like Gleevec®, about 15–20% of leukaemia patients who take it are becoming resistant to the drug within three years. This is because the enzyme that it works on is becoming resistant.[35]

Experience based on the gene-based drugs already on the market signals a trend suggesting that genomic therapeutics are going to target, for the most part, sub-populations of disease. This appears to be the antithesis of the current pharmaceutical business model, which is largely predicated on a "one-size-fits-all" approach, and relies on the development of "blockbuster drugs" to remain profitable.

Taking a drug to market is currently very expensive and time consuming. Targeting sub-populations will not generate as much revenue for pharmaceutical companies if the costs of taking a drug to market remain the same. One hope is that being able to accurately identify target genetic populations early on in the clinical trial process may make the trials quicker and cheaper.

Gene Therapy

Gene therapy is "a therapeutic technique in which a functioning gene is inserted into targeted cells of a patient to correct an inborn error or to provide the cell with a new function".[36] The successful delivery of a functioning gene causes such cells to produce a therapeutic protein that supplements or replaces the defective gene or treats the effects of acquired diseases like cancer. Gene therapy applications promise the unique advantage of long-term production of therapeutic molecules in vivo.

Inherited genetic disorders were initially considered natural targets for such therapies. However, considerable difficulties have arisen in targeting delivery to specific cell types, making sure the cell expresses the right sort of therapeutic protein and discovering the appropriate vectors to deliver the therapeutic to the cell without causing a negative immune response. As a result, gene therapy hasn't yet achieved its projected potential.[37]

Most current gene therapy trials target cancer, and the Japanese "Technology Foresight" exercise forecasts that there will be widespread use of gene therapy for cancer by 2017.[38] To date, only one gene therapy product has been licensed globally for market use in China. The product, Gendicine, uses an adenoviral vector to carry the tumour suppressant P53 gene to tumour cells.[39]

RNA Interference

RNA interference (RNAi), or "gene silencing", is currently seen as a promising emergent technology by the research and commercial communities. A pivotal study[40] showed that some RNA molecules regulate or "silence" the expression of genes. This is one of the most important recent advances in biological science. From the onset RNAi has proven to be an extremely useful laboratory tool for validating drug targets. However, the therapeutic application of gene silencing could, in theory, be applied to treat any disease that is linked to an overactive gene or genes. It also potentially mitigates the risk of over-expression of the introduced genetic material – a problem which has previously resulted in tumour development.

The world RNAi market has been forecast to grow on average by 31.5% a year, reaching $328 million by 2010 (up from an estimated $48 million in 2003).[41] Most of this growth will likely come from using RNAi as a laboratory tool. However, in August 2004 the first filing of an investigational new drug application based on RNAi was made by a US-based company called Acuity Pharmaceuticals.[42]

35 *Wall Street Journal*, 10 September 2004, "Why targeted drugs to battle cancer fall short of promise".

36 Institute for the Future (2003), "Healthcare 2010 – The Forecast – The Challenge", 2nd ed., p.123.

37 Nabel, Gary J. (2004), "Genetic, cellular and immune approaches to disease therapy: past and future", *Nature Medicine*, v10, n2 p.137.

38 National Institute of Science and Technology Policy (Japan), "The Seventh Technology Foresight – Future Technology in Japan to the Year 2030 – Survey Results – Health and Medical Care", pp.250-251.

39 *China Daily*, 23 March 2004, "Chinese firm develops gene therapy injection".

40 Elbashir, S. et al. (2001), "Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells" *Nature*, v411, pp.494-498.

41 Pallarito, K. (2004), "Fueling the Fires of RNA Interference", *The Scientist*, v18, n17, Sept 13.

42 http://www.acuitypharma.com/

In spite of the advances that have occurred, analysts are predicting that it will be at least 15 years before an RNAi drug is approved.[43] And one of the major obstacles identified to date with developing therapeutic RNAi applications has been the "delivery issue".[44]

Delivery Technologies

Delivering therapeutic genes to the correct cells is one of the biggest technical barriers to developing gene therapy applications. There are a number of potential gene delivery vehicles and each is proving to have limitations and advantages, depending on the disease target.[45] Traditionally, disabled retroviruses have been used as vectors to deliver the therapeutic material. Scientists have tried to take advantage of the virus's natural ability to infect cells and transfer DNA. However, viruses have caused other problems such as toxicity, immune and inflammatory responses, and gene control and targeting issues.

Alternatives to using viruses as a delivery mechanism are being explored. For example, researchers are experimenting with directly introducing naked DNA into cells and using stem cells as vectors (this is the focus of about a third of gene therapy trials).[46] Experiments under way now use stem cells to treat diseases of the blood system. The aim is to introduce healthy genes into the blood, forming stem cells which can then develop into all types of blood cell and that can renew themselves.[47]

Human artificial chromosomes (HACs) are also seen as a technology with potential. Artificial chromosomes are claimed to be the ideal combined vector and gene expression agent for gene therapy application. Reasons for this claim include:

- they are removed from the host genome mitigating the risk of potential transgene mutation through inappropriate gene silencing or activation;
- they are not immunogenic (whereas disabled viruses can be); and
- they are large enough to potentially accommodate large inserts spanning multiple genes – which will be essential if complex disorders are to be treated by gene therapy.[48]

Much research effort over the past decade has been aimed at defining the structural requirements for artificial chromosomes in human cells. However, their development has been hampered by technical difficulties, partly due to the large size of chromosomes, and partly because it is difficult to produce molecules that are stable and fit-for-purpose. There have, however, been some successes in the lab with, for example, the stable integration and expression of human blood hormone into an artificial chromosome in mice. This technology, although promising, is still in its infancy, and the application of HAC technologies into clinical practice will not occur in the near term.[49]

Gene therapy technologies will continue to improve, albeit not as rapidly as once anticipated. Researchers are finding that different disease states require different gene delivery systems, so it seems reasonable to surmise that gene therapy applications will develop on a measured and disease-specific basis. Most recent forecasts place disease-specific gene therapy applications emerging between 2010 and 2020.

Vaccines

Historically, vaccines represent one of the most established and cost-effective procedures in medicine, with one of the greatest impacts on public health of any medical intervention.

The technology has been advanced by growing understanding of the nature of infectious microbes, but development also continues to be driven by a number of diseases that continue to challenge medical science, like AIDS, malaria and influenza. Recent emphasis on the potential threat of biological warfare has also pushed vaccine development back into the "strategic" limelight. The US Government, under Project Bioshield, has recently set aside US$5.6 billion for the

43 Pallarito, K. (2004), op cit.

44 Novina, C.D. & Sharp, P.A. (2004), "The RNAi revolution", *Nature*, July 8, v430 p.164.

45 Nabel, Gary J. (2004), ibid. p.138.

46 *New Scientist*, 19 June 2004, "Just add a chromosome".

47 European Commission (2003), "Report on Human Embryonic Stem Cell Research" p.21.

48 Grimes, B.R. et al. (2001), "Stable gene expression from a mammalian artificial chromosome", *EMBO Reports*, v2, n10, p.910.

49 *New Scientist*, 19 June 2004, "Just add a chromosome".

government to stockpile a medical arsenal against biological weapons. Over the next ten years, federal money will be used to buy drugs and vaccines to counter a wide range of pathogens.[50]

Since the 1980s many new and improved vaccines have been released, including the world's first genetically engineered varieties. These vaccines have been developed in the traditional way as a preventive measure against acute infectious diseases.

However, new therapeutic vaccines are emerging, designed for people who are already infected with a micro-organism, with the aim of boosting or expanding their immune response against it. Therapeutic vaccines have also been tested in clinical trials against non-infectious diseases, for example, to boost the immune response to certain types of cancer tumours. There are no therapeutic vaccines on the market as yet, but there are a number of applications in small-scale clinical trials. The most advanced of these are therapeutic vaccines for cancer, along with an increasing focus on HIV and the development of vaccine interventions to treat neurological diseases.[51]

There is also growing interest in the field of DNA vaccination, where "naked" DNA is used instead of protein to generate an immune response. DNA vaccines theoretically offer several advantages over other vaccines. For example, DNA vaccines work from the inside of cells; this generates a potentially stronger cell-mediated response, and there is hope that DNA vaccines may be able to outsmart continually mutating viruses like influenza. However, despite successes in animal models, early-stage human clinical trials have shown that DNA vaccines are not potent enough for human subjects. This has led to the exploration of using adjunct technologies like viral vectors as delivery mechanisms, and this is showing greater promise. A number of DNA vaccines are currently in clinical trials.[52]

The application of molecular biology to the identification of virulent genes has led to a new understanding of the pathogenesis of virulent microbes. This growing understanding, coupled with increasing knowledge about immune system response, has led some commentators to forecast that by 2010 DNA vaccines will be competing with biological and chemically based therapeutics for market share.[53]

REGENERATIVE MEDICINE

The emergence of regenerative medicine signals a paradigm shift from an emphasis on replacing tissues to an emphasis on repair and regeneration of diseased and aging tissues and failing organs through the use of biologically based methods. Cell-based regenerative therapies are forecast to enter into clinical practice as a way of treating disorders like Alzheimer's and Parkinson's diseases, diabetes and heart disease between now and 2025. In the much longer term the ultimate goal is to engineer entire organs.

Some of the key drivers accelerating research into regenerative medicine include the severe shortage of donor organs, blood and tissue, and the rapidly ageing population in developed countries.

Neurological technologies are also developing apace, and potential applications are emerging which will enable amputees and paralysis sufferers to use brain signals to operate artificial limbs (as well as external devices like wheelchairs, keyboards and so on). In the far term these technologies may even enable the reactivation of paralysed body parts.

This section of the report looks at the future development of the component parts of tissue engineering applications, including:

- cell derivation;
- biomaterials, biomolecules and scaffolding technology;
- biomanufacturing;
- bioartificial organ development; and
- forecast tissue engineering applications to 2025.

The final part of this section will discuss emerging neurotechnologies.

50 *The Washington Post*, July 26, 2004, "Bioshield too little for drug industry".

51 Nabel, Gary J. (2004), op cit. p.139.

52 Waldmann, T.A. (2003), "Immunotherapy: past, present and future", *Nature Medicine*, v9 n3 p.270.

53 Institute for the Future (2003), op cit pp.126-127.

Tissue Engineering

The large-scale generation of tissue-engineered products will require expertise in, and the integration of several areas of, research and development: medicine, materials science, biology and engineering. The required tasks involved in tissue engineering include:

- the procurement and expansion of cells or cell lines;
- the development of biomaterial scaffolds to support cell growth (which meet both in vivo and in vitro tissue growth needs);
- the expression and delivery of biomolecules that regulate growth and cell differentiation and vascular assembly;
- the solution of immunological rejection issues; and
- the creation of bioreactors and large-scale manufacturing and preservation systems that will enable cost-effective production.

Understandably, this is a very new area of biotechnology. It is also complex because the solutions to the tasks listed above are themselves at different stages of development. For example, the development of biomaterial applications is further advanced than our understanding of the proliferation and differentiation of cell types.

To date, a number of tissue-engineered products have reached the market. There are currently two dozen tissue-engineered skin substitutes on the market. There are also some rudimentary cartilage, bone, cornea and heart valve products available.[54]

The ability to apply tissue-engineered multicellular constructs has rarely been successful. In great part this is because of problems related to the host immune response and a limited knowledge of cell function regulation and maintenance. A number of science and technology bottlenecks remain to be addressed before the promise of tissue engineering is realised. Each important component in the process, including the bottlenecks to growth, are discussed below.

Cell Derivation

A significant issue in the development of tissue engineering is the procurement and expansion of cells and cell lines.

Cells and cell lines can be derived from a variety of sources. They can be derived from autologous sources (the host's own body), allogeneic sources (from a donor) and xenogeneic sources (from a different species). They can be derived from primary isolates (recently extracted cells with a finite lifespan) or cell lines – which require the establishment of sustainable cultivation in vitro. Within each source of cell derivation there can be further delineation into the different types of cell that can potentially be derived. The most promising of these are stem cells.

Stem cells are cells which have the ability to continuously divide and develop into various kinds of tissue, making them especially promising for medical science applications.

Embryonic stem cells (ESCs) are seen to have the most potential. However, the derivation of ESCs (from embryos, typically those remaining following in vitro fertility procedures) raises ethical issues. Different countries are divided in their regulatory approach to ESCs, and the development of ESC applications will very much depend on what regulatory approach is taken.

Adult stem cells present in organs (for example, liver stem cells, central nervous system cells and pancreas cells) are currently a strong research focus. Although adult stem cells do not have the same capacity to develop into many types of cell as do embryonic stem cells, it's possible they may participate in a regeneration process across organs. It has recently been observed, for example, that stem cells among bone marrow cells not only differentiate into red blood cells, but may also differentiate into liver cells if transplanted in the liver. Bone marrow also contains mesenchymal stem cells, which could potentially differentiate into bone, cartilage or cardiac muscle.[55]

54 Institute for Prospective Technological Studies (2003), op cit. pp.3-11.

55 National Institute of Science and Technology Policy (Japan) (2002), "The Seventh Technology Foresight – Future Technology in Japan toward the Year 2030 – Survey Results – Health and Medical Care", p.230.

Research into stem cell-based therapies is at a very early stage. A number of scientific and technical bottlenecks will need to be addressed before clinical application is achieved. These include:

- understanding the mechanisms regulating stem cell growth and differentiation into tissue;
- eliminating the risk of stem cell differentiation into cancer cells; and
- overcoming the risk of immune rejection which may arise when a patient is receiving stem cells from a donor – as would be the case with embryonic stem cell derivation.

Many countries – notably China, Singapore and the United Kingdom – are investing heavily in stem cell research. This is in direct contrast to the United States which, due to political, religious and ethical drivers, has had limits placed on the federal funding of embryonic stem cell research.

Cells derived from other species – xenocells – are discussed in Chapter 6, Primary Production.

NEW ZEALAND CASE STUDY

NEUROLOGICAL DISEASES AND STEM CELLS

Researchers at the University of Auckland are working towards using stem cells to treat neurological diseases. One of their aims is to speed up the regeneration of brain cells to combat cell death. Cell death is central to neurodegenerative diseases such as Huntington's disease, Parkinson's and Alzheimer's.

Adult stem cells that are naturally present in the human brain accelerate their cell proliferation activity in the face of these diseases. The researchers are working towards being able to accentuate this proliferative activity so that it happens sooner and intensely enough to compensate for the diseases' destruction.

Currently they are working to identify which chemicals and molecules act as cues to direct stem cell development. This could result in a treatment if the genes that produce the cues can be inserted into the affected regions of the brain using viral vectors. The inserted genes would guide and direct the patient's own stem cells to produce enhanced regenerative effects.

The market for effective treatments is large. In New Zealand alone, more than 40,000 New Zealanders have Alzheimer's disease and dementia, over 9000 have Parkinson's, and Huntington's affects 900. It is hoped that this research will provide innovative new developments to treat neurodegenerative diseases.

There is still considerable research to do to understand the biology and potential of adult stem cells for treating brain diseases. Ultimately it is hoped that this research will provide new treatments for validation in clinical trials. The research is funded by the University of Auckland, the Health Research Council, the Neurological Foundation and the Marsden Fund.

Biomaterials, Biomolecules and Scaffolding Technology

Biomaterials in tissue engineering applications are used to support and guide the growth of cells in specific two- or three-dimensional structures – commonly referred to as scaffolds. The ideal scaffold mimics the function of the extracellular matrix (ECM) – which naturally provides cells with a supportive structure of proteins, carbohydrates and signalling molecules.

Modern medical biomaterials have been developing since the 1960s. The table below marks the major advances in biomaterial technologies from the 1960s into the future.

MODERN MEDICAL BIOMATERIALS	TIMELINE	CHARACTERISTICS
	1st Generation 1960–70s	▪ Developed for use inside the human body with minimal toxic response and host rejection ▪ Biologically inert
	2nd Generation 1980–2000s	▪ Bioactive = components that could elicit a controlled action and reaction in the physiological environment ▪ Resorbable = exhibit clinically relevant controlled breakdown and resorption (eg biodegradable suture)
	3rd Generation – 2000s onwards	▪ Designed to stimulate specific cellular responses at the molecular level ▪ Convergence of bioactivity and resorbable abilities – integration of bioactive signal molecules into the biomaterial scaffold ▪ Activation of genes that stimulate regeneration of living tissues

(adapted from Third Generation Biomedical Materials – Science v295, 8 February 2002, pp.1014-1017)

Current research is now focusing on developing biomaterials with mechanical properties (eg weight-bearing and enhanced degradability). Of major interest is the integration of bioactive signal molecules (eg proteins with growth factor functions) into the biomaterial scaffold. Research into the delivery of biomolecules is being strongly influenced by the technological developments of gene therapy vectors. Incorporating bioactive molecules into scaffolds and the controlled release of physiologically appropriate growth factors is one of the next key steps in advancing the technology.[56]

The structural design aspects of the scaffold are of equal importance to the development of novel biomaterials. One promising technology development which may drive advances in this area is rapid prototyping or three-dimensional printing. Three-dimensional printing technology, in conjunction with technologies like CT scans and magnetic resonance imaging, enables exact anatomical models of organs and their blood vessel systems. Replicating the functioning of blood flow is one of the major technical hurdles in achieving organ and tissue regeneration. Three-dimensional printing technology, with its precise ability to model living systems, is seen as a particularly promising solution to help alleviate this bottleneck.[57]

Bionanotechnologies are also showing signs of helping to overcome the "blood flow" issue. For example, microfabrication techniques have allowed for the miniaturisation of tissue-engineered scaffolds, which could allow for the micro-level control of cellular surfaces more effectively mimicking the action of the blood vessels lining the walls of this type of tissue. Micro-machined biopolymers have also been engineered with capillary-sized channels and have shown promise as

56 Institute for Prospective Technological Studies (2003), op cit pp.14-16.

57 *The Economist*, 10 June 2004, "Press 'print' for body parts".

effective conduits to direct cells to adhere and form tubes though which blood could flow. One immediate and obvious use of these technologies is as replacements for failing cardiovascular tissues.[58]

Bioengineering and Manufacturing

Once the technical feasibility of tissue regeneration has been confirmed there are still several critical engineering design challenges to be overcome before large-scale manufacture is possible.

Tissue-engineered products grown outside the body will be dependent on the development of bioreactor technologies: these are crucial for the stable storage of cells and three-dimensional tissues before clinical use. A number of issues need to be addressed before the large-scale manufacture of tissues is possible, including:

- adapting existing bioreactor technology to enable large-scale cell expansion and three-dimensional tissue production;
- using bioreactors as organ support devices;
- developing strategies that support blood flow in engineered tissues; and
- developing bioreactors that apply shear and mechanical forces on developing tissue to mimic the physiological environment.

Whether the cells are grown in vitro or in situ has implications for future developments. There is much interest in the in situ growth of tissue from injected cells due to the advantages of not having to mimic the natural physiological environment artificially. If cells have to be engineered outside of the host into tissues for implantation then suitable cells must first be derived from the patient. If cells are derived from the host then a separate portable culture system could potentially be needed for each patient. This could pose extensive regulatory challenges as well as being extremely expensive.[59]

Bioartificial Organs

The development of bioartificial organs – essentially, bridging devices enabling patients to either fully recover or survive until there is a donor organ available for them – is relatively well progressed. Bioartificial organs take the plasma of a patient requiring a transplant and circulate these cells outside of the body in a bioreactor through healthy donor cells. This technology encompasses the middle ground between cell therapies and full organ regeneration. Two bioartificial liver devices with human liver cells and three devices using cells from pigs are already in clinical trial, or the company plans to start phase-one trials in the near future.[60]

Product Pipeline – What Tissue-engineered Products Could We Potentially See in Clinical Practice Before 2025?

Despite the plethora of technical challenges impeding the realisation of tissue engineering applications, experts are broadly forecasting a number of potential applications before 2025:

1ST WAVE 2004–10	■ Structural tissues (skin, bone and cartilage) dominate ■ Integration of biomolecular growth factors in engineered skin ■ Tissue-engineered cartilage for spinal disc replacement
2ND WAVE 2010–25	■ Xenocell therapies (such as brain and pancreatic islet cells) ■ Stem cell-based clinical therapies for the treatment of diabetes, heart disease, Parkinson's and Alzheimer's ■ Bioartificial organs ■ Stem cell-based clinical treatments for multiple sclerosis and the damaged nerves of paraplegics
3RD WAVE 2025→	■ Complete organ engineering

58 Bhushan ed. (2004), *Springer Handbook of Nanotechnology* p.310.

59 Senker, Jacqueline & Mahdi, Surya (2003), "Human tissue-engineered products – Today's markets and future prospects – Research activity and future developments of human tissue engineering in Europe and the US" p.15.

60 Institute for Prospective Technological Studies (2003), op cit, p.11.

Neurotechnology

Neurotechnology devices such as implanted deep-brain stimulation systems to treat diseases like Parkinson's – and, very recently, Tourette's syndrome – and spinal cord stimulation systems have already delivered a number of therapeutic advances to clinicians in neurological and neurosurgical specialties. These techniques, coupled with advances in knowledge about the central nervous system, neural signalling and the brain's motor cortex and sensorimotor system, are driving technical advances in this area. One particularly promising area is neuroprosthetics.

The study of neuroprosthetics explores the feasibility of using brain signals to operate artificial limbs or reactivated body parts, as well as external devices like wheelchairs, keyboards and so on. Neuroprosthetics could also enable people suffering from various types of paralysis to operate external devices using only their brain signals. Beyond that is the possibility of reactivating paralysed body parts. The potential for success in this area has already been demonstrated. The experiment involved a monkey in Brooklyn (whose brain signals were monitored by electrodes), who could control a three-dimensional robotic arm located in North Carolina as he watched it on the internet.[61]

The first wave of future applications will probably be artificial limbs on subjects who have the ability to sense or imagine manipulating the absent joints or body parts. Today's most advanced prosthetic forearms enable amputees to grasp and release objects at will by selectively flexing muscles in the remaining arm. However, what's missing from today's prosthetic forearms and hands is sensory feedback – in other words, the sense of touch. Recent developments are starting to bring researchers closer to achieving this aim through the decoding of neural signalling involved in sensation. A US-based research group connected electrodes to the peripheral nerves in a subject's forearms to both record and stimulate neural signals from a robotic arm. Patients were subsequently able to "feel" natural sensations through the device's fingers.[62]

Researchers at Duke University Medical Research Center in North Carolina are currently applying for federal approval to begin implanting experimental electrode arrays, long term, in quadriplegic patients. Such tests, planned to be conducted up until 2007–09, would involve implanting the arrays in specific regions, asking the patients to perform specific tasks and then exploring which tasks are best controlled by that region. If this research is carried out to plan, it will potentially underpin application development from 2009 onwards.[63]

REPRODUCTIVE TECHNOLOGIES

As of March 2004 just over half of all newborn babies in New Zealand have a mother aged over 30. This compares with four in ten women in 1994. This trend is consistent with other developed nations. As the conception age of mothers increases throughout the developed world, so too does the risk of an inability and/or difficulty in conceiving. This will be one of the key drivers of technical developments in this area.[64]

Research related to reproductive technologies covers two broad interrelated areas:

1. Discovery level science:
   - increasing understanding of how reproductive factors affect later adult health; and
   - increasing understanding of the relationship between genotype and phenotype.

2. Technological advancement:
   - increasing technical ability to control all aspects of the reproductive process; and
   - the ability to produce entirely novel reproductive outcomes.[65]

61 Craelius, William (2002), "The Bionic Man: Restoring Mobility", *Science*, v295, n.5557 p.1018.

62 *The Economist*, 10 June 2004, "Once again, with feeling".

63 Duke University Medical Center – Public release 23 March 2004, "Human studies show feasibility of brain-machine interfaces".

64 *NZ Herald*, 5 June 2004, "Most first time mothers now aged in their 30s".

65 MoRST Bioissues Forum – Reproduction in the Future, March 18, 2004.

NEW ZEALAND CASE STUDY

ASSISTED REPRODUCTIVE TECHNOLOGIES

Researchers at the University of Otago are trying to increase the success rates of assisted reproduction. They are working on ways to increase the percentage of pregnancies per cycle of IVF treatment, and tackling the tiny amount of tissue available on which to perform genetic diagnosis.

The survival rate for embryos transferred into infertile women is currently low, so multiple embryos are often introduced. Multiple transfers are becoming less common as recognition grows of the morbidity caused by the multiple births that sometimes result. The Otago researchers are developing diagnostic techniques to identify which eggs and pre-implantation embryos have the best chance of implanting and proceeding to term. This would increase the chances of single-embryo pregnancies being achievable on a consistent basis.

It is probable that the expression or inactivation of certain genes in pre-implantation embryos is associated with an enhanced chance of success. If gene markers could be identified, and each candidate embryo checked for them, IVF clinics would have a means of diagnosing the best embryos to introduce. To find potential markers, the Otago researchers are characterising the gene expression of mouse embryos, as this approach reduces the amount of human pre-implantation embryonic material needed. They will then identify corresponding human embryonic genes.

The team is also searching for follicle genes that are indicators of successful outcomes, doing so using human follicular material directly.

For any resulting diagnostic approach to be successful, it must be able to work with just one or two cells from an eight-cell embryo, as do current methods of pre-implantation genetic diagnosis. The team is developing novel methods of DNA and RNA amplification to achieve multiplex analysis of single cells. Resulting technology will be small, with instrumentation and software designed for sample-to-answer analysis at IVF clinics. Such technology would also be in high demand for disease-based pre-implantation genetic diagnosis, as well as other forms of DNA diagnostics. The multiple applications for the latter mean that its future market could potentially be very large.

The Otago researchers collaborate with scientists from Ottawa and Birmingham, and have external linkages with Otago Fertility Services Ltd, New Zealand Centre for Reproductive Medicine Ltd, IRL and Genesis Research and Development Corporation Ltd. The research is supported by the New Economy Research Fund (NERF).

The following discussion breaks down some of the emerging applications of reproductive technologies into two main areas:

- assisted human reproductive technologies; and
- testing – screening and selection.

Assisted Human Reproductive Technologies

The first successful birth (or “test-tube” baby) using in vitro fertilisation (IVF) technology occurred in the UK in 1978. Since then thousands of children have been born via IVF conception. IVF is still the most common form of artificial fertilisation. Both sperm and ova are extracted and cultured to maximise the probability of fertilisation, then combined and left undisturbed for 2–24 hours. At this point they are examined to see whether or not fertilisation has occurred.

Recent developments use more invasive techniques. In 1992 the first successful use of a technique known as intracytoplasmic sperm injection (ICSI) occurred. In this technique, fertilisation occurs not by chance, but by directly injecting a single sperm into the ovum. ICSI is particularly useful for cases of severe male infertility, and clinical application of this technique has been rising steadily.

Ooplasmic or cytoplasmic transfer is a controversial assisted reproductive technique which has been responsible for the birth of 30 children around the world to date.[66] This procedure, which has been performed on women whose fertilised ova do not develop normally due to a deficiency in their mitochondria, involves the patient's oocyte being injected with donor cytoplasm which contains healthy mitochondria. As a consequence of this the child is set to inherit the DNA of three individuals and the donor mitochondria could be passed on to future generations.

The development of fully artificial wombs is at a very early stage. Two research groups, one based at Cornell University's Center for Reproductive Medicine and Infertility and the other at Juntendo University in Tokyo, have been approaching the development of artificial wombs – with some success – from opposite directions.

The US group removed cells from the womb lining and grew them in the laboratory. They used hormones and growth factors, and used the technologies and approach of tissue engineering. Leftover embryos from IVF programmes have successfully been implanted into these artificial wombs for up to 14 days. The Japanese research team, by contrast, removed fetuses from goats and placed them in clear plastic tanks of amniotic fluid stabilised to body temperature – where they have been kept alive for up to ten days. The US research is aimed at those women with damaged wombs who have difficulty conceiving, whereas the Japanese research is designed to assist women who suffer from miscarriages or very premature births. Both teams believe that the technology may become available in the medium term.[67]

Further applications are possible if reproductive cloning technology is factored into the equation; artificial wombs raise the prospect of individuals giving "birth" to their own children completely removed from their own body.

Despite the claims of fringe groups like the Raelians, and "rogue" clinicians like US-based Panos Zavos and Antinori Severini (based in Italy), there is no genuine evidence that any cloned human embryos have ever been successfully implanted for reproductive purposes. Indeed, it was only in February 2004 that the first reported propagation of an embryonic human stem cell line derived from a cloned human blastocyst was achieved (by a South Korean research team).[68] The Korean success will have research implications for therapeutic cloning and biomedical research into such applications as tissue engineering. However, it is going to be a long time, if at all, before this technology moves into the human reproductive realm. Firstly, there are many technical implications to sort out. Secondly, this technology will be subject to much ethical debate.

Testing – Screening and Selection

Pre-implantation Genetic Diagnosis (PGD) is an in vitro technique whereby the early embryo is analysed by clinicians to check for certain genetic or chromosomal traits and markers, and selected accordingly for transfer into the patient. PGD was first performed in 1989 and is practised in around 50 clinics worldwide, mostly in the United States. There are no clinics practising PGD in New Zealand; the closest is in Australia.

The technology has been used over the past decade to avoid transfer of X-linked genetic diseases like haemophilia and Lesch Nyhan syndrome, chromosome abnormalities like Down's and Turner's syndromes and single-gene diseases like cystic fibrosis.

Before we can test confidently for complex disease traits, however, there is much discovery level science to be uncovered, surrounding such complex issues as the relationship between genotype and phenotype, environmental factors and the epigenetic bases of some diseases. PGD in this context also raises many difficult ethical issues.

For now, the capacity of the PGD technology to screen and select genetic traits has some technical limitations, including:

- technical limitations on the number of embryos that can be produced in a single PGD cycle; and
- the complexity of the relationship between single genes and phenotypic characteristics – which in turn complicates the development of genetic tests for many traits.[69]

PGD has also traditionally been limited by the small number of tests that can be performed on a single embryo; this has severely restricted clinicians from testing for multiple traits. However, a technique called DNA amplification could resolve

66 President's Council on Bioethics (2004), "Reproduction and Responsibility: The regulation of new biotechnologies".

67 *The Guardian*, 10 February 2002, "Men redundant? Now we don't need women either".

68 Hwang, Woo Suk et al. (2004), "Evidence of a Pluripotent Human Embryonic Stem Cell Line Derived from a Cloned Blastocyst", *Science*, v303, n5664, pp.1669-1674.

69 President's Council on Bioethics (2004), "Reproduction and Responsibility: The regulation of new biotechnologies".

this bottleneck. DNA amplification is not a new technology per se but one that has recently been improved upon. The improved version has subsequently been applied to embryo testing in the lab. At present only one or two cells can be taken from an early embryo without harming it; however, with DNA amplification techniques one can make duplicates of these cells which can subsequently be copied many times over. Previously, the technique has not been reliable enough to use in the PGD process; but refinements have enabled the accurate testing of up to 20 known traits without any degradation of the whole genome. A UK-based clinician is currently applying for permission to start using the technique in clinical practice.[70]

Tissue typing is a diagnostic test used to identify a group of genetic markers (HLA, or human leukocyte antigens) located on the surface of white blood cells. This information is always tested for before a patient receives a donor organ or tissues. Tissue typing was conducted on pre-implantation embryos in a Chicago clinic during 2002/03 for nine couples with other children suffering from a rare form of leukaemia. The screened embryos were intended to act as stem cell donors for their older brothers and sisters once they were born. Five HLA-matched children were born as a consequence. These are the first known cases of pre-implantation tissue typing – performed without PGD – for a causative gene.[71]

By the end of 2002, 331 babies had been born with the help of a technique known as "microsorting" or sperm selection. The separation of male and female sperm is based on the measurable difference in the quantity of genetic material (DNA) they contain. The sperm absorbs a dye, which attaches temporarily to the DNA, or genetic material, inside the individual sperm. When exposed to laser light, the dye fluoresces. Since the X chromosome is larger than the Y, there is more DNA for the dye to attach to; consequently, sperm with the X chromosomes fluoresce more brightly. Specialised equipment is able to pick up these differences in brightness and separate the sperm as they move through the machine, one at a time.

Currently, sperm sorting technology improves the odds of a female pregnancy to around 90% after sorting; for a male, the odds have improved to 75%. The technology is currently undergoing clinical trials and is likely to be used in clinical practice in the near term.[72]

[Germ line gene therapy and "designer babies" will be discussed in the Enhancement section.]

ENHANCEMENT

This section looks at how biotechnology can enhance non-medical traits. Advances in our understanding of more complex genetic traits and in the workings of the brain will drive the potential for applications in this area. Enhancement is already with us, with the increasing consumption of so-called "lifestyle drugs" in the developed world.

Lifestyle drugs are pharmaceuticals designed to improve wellbeing or appearance, not to treat illness. Among the trends underpinning lifestyle drug development are ageing populations, lengthening life expectancies and, importantly, changing cultural perceptions of ageing.[73] In today's world, many of the "symptoms" of ageing, once seen as normal, are now seen as inconveniences treatable by medication. The lifestyle drug sector is not only predicated on the pharmaceutical improvement of the perceived symptoms of ageing; it is also trending towards the production of performance-enhancing pharmaceuticals designed to sharpen physical and mental abilities. This market segment may also increasingly attract younger consumers in the future.[74]

Changing societal attitudes to the growing "medicalisation" of mood and performance traits may drive uptake for potential gene-based therapeutics. "Genetic enhancement" generally refers to the transfer of genetic material intended to modify non-pathological traits. Animal experiments to date have attempted to improve genetic traits like growth rate or muscle mass. Although this research is focused on developing ways of treating human diseases and conditions, it is well within the realm of possibility that there will be dual uses for these technologies to enhance traits as well as correcting deficiencies.[75]

70 *The New Scientist*, 24 July 2004, "Is a new era dawning for embryo screening?" p.7.

71 Verlinsky, Yury et al. (2004), "Preimplantation HLA Testing", *Journal of the American Medical Association*, v291, n17 p.2079.

72 Genetics and Public Policy Center – http://www.dnapolicy.org

73 Pallarito, K. (2004), "Fueling the Fires of RNA Interference", *The Scientist*, v18, n17 Sept 13.

74 Social Technologies – Technology Foresight Brief (2004), "Pharmaceutical Market – Run on Lifestyle Drugs Boosted by Demographic Trend", TF-2004-4.

75 Genetics and Public Policy Center – www.dnapolicy.org/genetics/enhancement.jhtml

The dual nature and potential of genetic therapeutic interventions raise some important ethical, regulatory and societal questions. For example, treatment for muscular dystrophy sufferers may also be used to enhance an athlete's muscularity; or, as scientists unravel the nature and causes of ageing and are able to treat the "symptoms", society will need to face the consequences of people staying healthier and living longer.

The following sections will investigate in greater depth some examples of potential technological advance in the following areas:

- arresting ageing;
- genetic enhancement – physical traits;
- genetic enhancement – "designer babies"; and
- cognitive enhancement – the memory.

Arresting Ageing

As mentioned before, the overarching trend driving this area of research is the ageing population. Considerable research effort is being invested in understanding the degenerative effects of ageing as well as the diseases and conditions of ageing (Alzheimer's, sarcopenia, stroke, etc). If this research does pay dividends, it could mitigate the upcoming crisis of exploding healthcare costs, brought about by an ageing population.

Not surprisingly, this is a high growth area of research. For example, the European Commission is now launching what will be the largest ever study of the extremely old. The Genetics of Healthy Ageing (GEHA) Project will gather genetic, health and lifestyle information on 2800 pairs of siblings who are more than 90 years old, who will be compared with the same number of younger controls with the aim of identifying the genetic basis of longevity.[76]

Key areas of research underpinning the potential development of age retardation technologies include:

- free radicals and mitochondrial dysfunction;
- calorific restriction (has restricted ageing in worms, mice and rats);
- bioactives (for example, enzymes such as resvestoral commonly found in red wine have been shown to slow the ageing process of human genes in the Petri dish);
- the genetics of ageing (for example, genes that govern low-level chronic inflammation – inflammatory cytokines (many conditions that afflict the elderly are associated with inflammatory response) – and genes that are involved in the metabolism of cholesterol are both subject to clinical trial);[77]
- telomere research; and
- regenerative medicine (see the section earlier in this chapter).

Experts forecast that we may see a true anti-ageing application on the market by 2014.[78]

Genetic Enhancement – Muscles

Research into the ageing processes of muscle and muscle-wasting diseases (like muscular dystrophy) is leading to a growing body of knowledge into how muscle mass is generated.

Muscular growth is regulated by specific protein growth factors – for example, primary insulin-like growth factor 1 (IGF-1) and a gene called mechano-growth factor (MGF). The genes for animal and human IGF-1 have been cloned and their DNA sequences determined. Gene expression vectors have been developed that permit the regulated production of the protein in model animals. In genetically modified mice – so-called "Schwarzenegger Mice" – enlargement of skeletal muscles was observed as early as ten days after birth. The skeletal muscle enlargement also persisted as the mice aged.

Current investigations are looking at whether this technology could be adapted for use in humans. The initial steps in applying muscular enhancement genetic therapy to humans will inevitably be performed to treat muscle-wasting diseases. For example, clinical trials involving muscular dystrophy sufferers may start within the next few years.[79]

76 Abbott, Alison (2004), "Growing old gracefully", Nature, v428 p.117.

77 Ibid, p.117.

78 *The San Francisco Chronicle*, 24 April 2004, "The Burden of Immortality – Slowing the aging process gives birth to ethical, sociological questions".

79 President's Council on Bioethics (2003), "Stronger, long-lasting skeletal muscles through biotech", Staff Working Paper.

If these trials prove to be successful the implications are immense. There would be potentially significant impacts on long-term human performance, and in arenas like sport this technology could potentially improve athletic performance – without it being detectable.

Genetic Enhancement – "Designer Babies"

Advances in gene therapy delivery techniques, together with our increased understanding of more complex genetic traits (both multigene disease traits and more cosmetic traits) and the relationship between genotype and phenotype, could lead to "designer babies" becoming a reality.

From a technical perspective, if advances in gene therapy are coupled with improvements in assisted human reproduction techniques and embryo selection capabilities, then a future where you could "design" your offspring seems distinctly plausible.

If gene therapy is performed on germ cells, as opposed to somatic cells, then the intervention will potentially be passed on to subsequent generations. Most commentators discussing developments in this area are touting artificial chromosomes as the most likely vector for delivering the additional genetic material to the embryo.[80]

Needless to say, there are many ethical issues that need to be debated before these technologies are permitted to move beyond the therapeutic to enhancement.

Cognitive Enhancement – the Memory

Advances in the neurosciences and our growing understanding of the functional workings of the brain will inevitably lead to drugs that will move, in many people's estimations, beyond therapy to enhancement.

For example, in the early 1990s, research on animals showed that the presence or absence of stress hormones like ephinephrine (adrenalin) in the brain during a period of memory consolidation affects the strength and durability of the memory. In small-scale clinical trials, beta blockers – drugs mainly used for preventing and treating heart disease and hypertension – have proven effective in nullifying the effects of a traumatic event (in the case of a 2002 clinical trial, car crash victims within six hours of the accident).[81]

However, before these techniques can become widely used, a number of ethical issues would need to be worked through. For example, not all individuals react to trauma in the same way. One thing about such treatments is that in order to be effective the drugs need to be administered immediately following the event. Consequently, a clinician has no real idea if a patient is being administered a preventive, or is having a memory blunted that could well have had a positive effect on some aspect of the patient's future life.

There are positives, though. Research into Alzheimer's disease and amnesia is increasing our understanding of the underlying biology of memory. For example, the discovery that cholinergic cells are the first to die in Alzheimer's patients has led to the development of a class of drugs that destroys the neurotransmitter that emits from these cells. In clinical trials, this class of drug helped to somewhat improve the memory of some patients, although it cannot reverse the disease's characteristic progressive destruction of the brain.[82]

80 Stock, Gregory (2002), "Redesigning Humans – Our inevitable genetic future", Houghton, New York.

81 President's Council on Bioethics (2003), "Beyond Therapy – Biotechnology and the Pursuit of Happiness".

82 President's Council on Bioethics (2003), "Better Memories? The Promise and Perils of Pharmacological Interventions", Staff Working Paper.

NUTRITION

The rising cost of healthcare, the ageing population, and lifestyle diseases (such as obesity and Type 2 diabetes) are among the overarching drivers of food and nutrition research. Coupled with this is a trend in the developed world towards self-diagnosis and preventive strategies utilising food and lifestyle to maintain health and manage illness.

The following broad areas of food research have been identified as having a significant impact on the future:

- designing foods and diets for weight loss;
- improving methods for identifying and evaluating components of functional foods that reduce chronic disease risk;
- improving nutrient levels through genetic modification and marker-assisted breeding of crops;
- evaluating the effects of processing, storage and genetic modification on the nutritional value of foods; and
- developing food components that improve blood lipid profiles and glycaemic responses.[83]

Functional Foods and Nutraceuticals

The terms "functional foods" and "nutraceuticals" are often used interchangeably. However, functional foods can be defined as those "whole, fortified, enriched or enhanced foods that provide health benefits beyond the provision of essential nutrients". Similarly, nutraceuticals can be defined as "any bioactive component that delivers a health benefit".

Well-known current examples of natural foods with strong evidence of functional compounds include Omega-3 fatty acids in oily fish like salmon and sardines, and fortified margarines that contain plant sterol and stanol esters that reduce cholesterol levels.[84]

The global functional foods market was estimated to be nearly $50 billion in 2002, up from around $30 billion in 1995. The US is the biggest market, followed by Europe and Japan.[85] This growth has been attributed to the "consumer self-care phenomenon" and the continued rapid growth in demand for health and wellness products.

Some commentators do voice concerns about the lack of a sufficiently strong scientific evidence base to underpin many of the claims made about the efficacy of functional foods, and the lack of regulatory structures in place to police these claims. Rigorous safety and testing regimes will be an important aspect for credible future development of this market sector.

Extensive research is currently being undertaken globally towards increasing our understanding of how functional foods and ingredients can optimise health and assist in disease prevention. Future market projections show little sign of abatement.

Nutrigenomics

The second wave of "personalised medicine", after pharmacogenomics, is forecast to be nutrigenomics. The premise of nutrigenomics is simple: diet is a large contributing factor in chronic disease, and an individual's genetic make-up is an important part of this interplay. Differences in gene expression between people can be seen, for example, in the activity of certain liver enzymes which affect the way in which dietary components or metabolic by-products are processed by the body and hence have a role in health and disease. This area will have considerable impact on the development of the functional food market.

The synergies between pharmacogenomics and nutrigenomics are evident. The goals of these areas are similar: "[the] customisation of therapy, prevention and management of disease, and market segmentation based on personalised criteria". The key element that distinguishes nutrigenomics from nutrition research is that the "observable response to diet, or phenotype, is analysed or compared in different individuals (or genotypes)".[86]

For consumers, their initial introduction to the practical application of nutrigenomics is likely to be through diagnostics, coupled with "treatment" in the form of functional food products or nutraceutical supplements, possibly also followed by the diagnostic monitoring of biomarkers. Currently, biomarker diagnostics like cholesterol levels are available and familiar

83 Social Technologies – Technology Foresight Brief (2003), "Food Research Trends: 2003 and beyond", TF-2003-4.

84 American Society for Nutritional Sciences (2002), "Functional Foods: Benefits, Concerns and Challenges" pp.3372-3374.

85 Sloan, A.E. (2002), "The 10 Functional Food Trends: The next generation", *Food Technology*, April v56, n4 p.32.

86 Fogg-Johnson, Nancy & Kaput, Jim (2003), "Nutrigenomics: An emerging scientific discipline", *Food Technology*, April v57, n4.

NEW ZEALAND CASE STUDY

PERSONALISED DIETS

The move towards personalising diet to genotype is being led in this country by the New Zealand Nutrigenomics Centre of Excellence. It is a collaboration between the University of Auckland, Crop & Food Research, AgResearch and HortResearch, and is funded by the Foundation for Research, Science and Technology.

The Centre aims to match individual human genotypes to foods that benefit the health of those individuals and enhance normal physiological processes.

The early-stage research is initially focusing on Crohn's disease as an example. Crohn's, like many other diseases, stems partly from genetic differences but is influenced by environment and diet. People with Crohn's disease respond inappropriately to bacteria in their colon, so an initial target is food that might modify colonic bacterial composition.

The Centre's methods involve screening patients' cells to isolate their genetic differences compared to healthy people. The cells are then combined with fractions of potentially beneficial foods in a laboratory setting, and examined for a response that indicates an improvement in the condition. Another important step is feeding the promising foods to animals with conditions that are comparable to the human disease. Furthermore, patients and healthy people are genotyped and complete a questionnaire to assess their response to food.

The final step will be a clinical trial to establish whether the promising foods cause measurable improvements in patients.

Once the concept is proven for Crohn's disease, the research will apply this approach to develop new foods for other health states and diseases. If a scientifically validated genetic test were available for the genes involved, a doctor or nutrition expert could use the information to recommend that patients increase or decrease intake of a specific food.

Also under development is POSIFoods, or "point-of-sale individualised foods". Food tailored to specific health requirements will be delivered from state-of-the-art vending machines. Snacks on offer will meet particular health needs such as low fat for calorie management, low cholesterol for heart health, high calcium for osteoporosis or low sugar for diabetes. Nutritional scientists, food engineers and food technologists will use the latest knowledge about nutrition, functional foods and nutraceuticals to develop the products.

POSIFoods research and development is being carried out by the Riddet Centre, which brings together scientists from Auckland, Otago and Massey Universities. It is funded by Fonterra, German-based multinational BASF and the Foundation for Research, Science and Technology, with the former two partners also contributing scientific expertise.

to consumers. Genetic testing is becoming available for the population, but the number of genetic markers which have been validated for dietary effects on phenotype is currently limited.

The most immediate application of gene testing and nutrigenomics will likely not be for a complex phenotype, like diabetes or obesity, but may be for "sub-phenotypes" such as insulin levels or glucose intolerance.[87]

It is important to be mindful that, at present, a vast amount of underpinning biology remains to be discovered and future markets will undoubtedly be made up of consumer sub-populations. Therefore, future uptake will invariably be gradual and piecemeal.

87 Ibid, p.65.

Food Safety

The development of the diagnostics market will also have a large role to play in the food safety arena. Smaller, more portable devices will enable handheld pathogen, spore and food spoilage sensors for food safety workers. Food science is anticipated to reach a point at which most food pathogens have been identified and their behaviours understood. Research investment to combat threats of bioterror are also poised to speed up our understanding and have positive spin-offs for the food technology industry.[88] (See Chapter 8, Security and Defence, for a more in-depth analysis.)

Biosensing diagnostic technologies underpin developments in this area. One of the more promising emerging applications in this area is a new nanoparticle test for E. coli bacteria. This test is so sensitive that it can detect a single bacteria cell within minutes. Current tests require a higher number of bacteria to be present before they can detect it and can take up to 48 hours to process.[89]

Biosensors are also starting to be equipped with radio frequency identification (RFID) tags. This means that food will conceivably be able to be tracked and monitored throughout the length of the food supply chain.[90]

PUBLIC OPINION ON HEALTH BIOTECHNOLOGIES

Public opinion about the use of biotechnology for human health and wellbeing applications is notably broad in scope, characterised by some extreme viewpoints and a wide range of perspectives. Extreme views can be seen in organisations which advocate "new eugenics", "transhumanism'' and "post-humanism", some to the point of funding genetic enhancement research.

Groups with a wide variety of other perspectives are also engaged in the debate, including human rights advocates; indigenous peoples and ethnic groups; religious groups; advocates for women, children, and family; gender groups; and scientists and health professionals. Scientists and health professionals are especially influential, and their viewpoints are varied. Opposition to reproductive cloning is strong, but largely on grounds of safety rather than broader consequences. Most scientists apparently oppose inheritable genetic modifications, but more mutedly, while some advocate its development.

Among the general public, reproductive cloning has always been consistently rejected by large majorities. Research cloning also tends to be rejected, but with less strength; and support rises for health-enhancing research. Opinions about inheritable genetic modification are mixed and highly dependent on introduction of specific possibilities and issues.

88 Social Technologies – Technology Foresight Brief (2003), "Food Research Trends: 2003 and beyond", TF-2003-4.

89 *New Scientist*, 11 October 2004, "Harmful bacteria shown up by nanoparticles".

90 *Wired News*, 26 August 2003, "RFID gussied up with biosensors".

PART 2: CHAPTER OVERVIEW: HEALTH AND WELLBEING

The following tables summarise the key trends and drivers that we have identified in this chapter.

Overarching Drivers of Growth	
DEMOGRAPHIC DRIVERS	There are several demographic trends which are driving technological advances in healthcare. Three key ones are: ■ longer life expectancy (particularly in developed countries); ■ increasing proportion of older people in the population; and ■ decreased fertility and delayed reproduction.
SCIENCE & TECHNOLOGY DRIVERS	Three important science and technology drivers identified in this scan are: ■ improving tools for data collection; ■ improving methods for data analysis; and ■ convergence of science disciplines.
IMPROVING HEALTH OUTCOMES	Finding solutions for health-related issues is a very strong driver of advances in biotechnology. Some of the key factors in this area are seeking treatments for: ■ cancer and inherited disorders; ■ diseases associated with ageing (eg Alzheimer's); ■ infectious diseases (eg AIDS and SARS); and ■ "lifestyle" diseases (eg Type 2 diabetes and obesity).
CONSUMER TRENDS	A number of consumer trends are also driving the growth of some segments of the health biotechnology sector. These include: ■ self-diagnosis and self-care; and ■ the increase in lifestyle drugs market – the medical "treatment" of non-pathological "disorders".
ECONOMIC DRIVERS	There are large profits to be made in the health biotechnology sector if, for example: ■ a drug target is successfully commercialised.

Meta-trends	
THE THREE Ps	■ Diagnostics will become more **predictive**; ■ Therapeutic interventions will become more **preventive**; and ■ Healthcare will become more **personalised** and tailored to the individual.
CONVERGENCE	Biotechnology application development enjoys a symbiotic relationship with the ICT sector, with each driving the other forward in achieving new levels of scale and complexity in large-scale data management. More recently there is an emerging and increasing convergence between nanotechnology and biotechnology, which can be seen as natural partners for working at the cellular and molecular scale.

Paradigm Shifts

FROM REPLACEMENT OF TISSUES TO REPAIR AND REGENERATION

Emerging trends in the development of regenerative medicine are signalling a paradigm shift from the emphasis on the replacement of tissues towards a more biologically based method for the repair and regeneration of tissues. This trend also signals a move towards less invasive surgical interventions. Trends are also emerging in the development of regenerative neurotechnological devices like mind-controlled prosthetics for amputees and devices for easing an individual's suffering from paralysis. These developments are starting to blur the boundaries between "human" and "machine".

FROM CHEMICAL-BASED TO BIOTECHNOLOGY-BASED DRUG DEVELOPMENT

We are trending away from a drug development model based on a "one-size-fits-all blockbuster drug" paradigm towards "individualised biologics", which involves developing drugs for niche sectors (such as tailored treatments for particular genotypes associated with a specific disease). About 16% of new drugs since 1997 have been based on biotechnology; this share is anticipated to rise considerably – up to 40% by 2015 according to some industry observers. To add weight to this projection, more than 30% of drugs currently in development are protein-based (and therefore developed using biotechnological techniques) not chemically based.

"DUAL USE" – FROM THERAPY TO ENHANCEMENT

Over the past ten years we have seen a big growth in the consumer market for lifestyle drugs. Lifestyle drugs are pharmaceuticals designed to improve wellbeing or appearance, not to treat illness. Developments in this market sector are also seeing the emergence of "off-label" uses for drugs which have dual uses – both in treating the unwell and enhancing the well, with no discernible short-term side effects. Developments in gene-based treatments will conceivably have even more powerful dual uses. There appears to be a growing market for lifestyle drugs, but it remains to be seen if this consumer appetite crosses over to the potential development of dual-use, gene-based therapeutics.

Incremental Growth Trends

DIAGNOSTICS LEADING THE WAY

The tools for performing molecular diagnostics (DNA chips, imaging technologies and so on) are developing rapidly. Emergent trends in the development of biological therapeutics, pharmacogenetics and nutrigenomics are all firmly underpinned by genetic diagnostic technologies. It is anticipated that diagnostic technologies – integrated with, for example, targeted gene-based therapeutic interventions – will lead the first wave of commercial genomic medical applications.

EMERGENCE OF DRUG DELIVERY AS AN INDUSTRY SEGMENT

As biotechnology advances, new areas of technical complexity are emerging which are requiring solutions. This is leading to the emergence of new industry segments to support application growth. A good example of this is the growth of the drug delivery industry. The associated challenges of delivering biologically based therapeutics with large molecular structures in vivo are leading to the emergence of a sub-industry catering to the challenges of drug delivery.

EMBRYO SCREENING AND SELECTION

The range of tests that researchers have been able to perform on embryos, before they are implanted into the womb during procedures like pre-implantation genetic diagnosis, has historically been limited. Emergent technology trends are signalling that genetic tests for multiple, complex genetic traits (both desired and undesired) that can potentially be performed on a single embryo could soon become much more available.

Uncertainties

ETHICAL, MORAL, RELIGIOUS	Biotechnology applications (actual or potential) have raised a range of public concerns. In the healthcare sector the genesis of these is most often ethical, moral or religious and is most often associated with: ■ human reproductive technologies; ■ the use of embryos to procure stem cell lines; and ■ the potential for genetic therapeutics to be used for enhancement purposes.
COMPLEXITY	Discoveries in the biological sciences, while driving developments in biotechnology, are also an area of critical uncertainty. The more we discover about biological processes and systems, the more we realise that the less we know. There was much hype about how the Human Genome Project would result in wondrous advances in healthcare, but to date this has not occurred due to the lack of appropriate tools and ways of analysing the information, and not understanding how genes, genetic variation and the environment may interact.
SYSTEMIC UNREADINESS	The ability and resilience of systems – at the market (pharmaceutical industry), governance (regulatory) and healthcare system levels – to respond to the future opportunities and challenges that developments in biotechnology will serve up are an area of uncertainty that will inevitably impact upon the pace of development.

Key Emerging Applications

Diagnostics

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
DNA chips	First app 2003. Widespread use 2012 → Rapid market growth.		Systemic unreadiness: is the healthcare sector prepared for clinical uptake?
Emergence of nanobiotechnology diagnostics applications: ■ protein chips ■ nanowire sensors ■ quantum dots	2009–10 →	Risk of nanoparticles being toxic when ingested by humans needs to be mitigated	

Therapeutics

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
Genomic drug development (individualised therapeutics – targeting sub-populations)	1998 → Incremental – growth to date – slow despite optimistic earlier forecasts	Interpretation of genomic data	Systemic unreadiness. Market structures in opposition to technology trends. Technical complexity.
Gene therapy	2010–20 Disease-specific/incremental application development. Growth to date – slow.	Drug delivery. Controlling gene expression.	Technical complexity
Gene silencing RNA interference (RNAi)	Close to entering into clinical trial → Growth to date – rapid. Earliest forecast to market 2019–20.	Drug delivery	Technical complexity
Human artificial chromosomes (HACs)	Early stage – success in animal models	Current inability to express stable molecules in vivo. Large size of HACs. Drug delivery.	Technical complexity
DNA vaccines	→ 2010	Lack of potency due to molecule degradation. Drug delivery.	Technical complexity

Regenerative Medicine

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
Tissue engineering – stem cell therapies	Stem cell-based regenerative therapy for diseased and damaged tissues: 2012–20 →	Understanding the basic mechanisms involved in cell growth and differentiation into different types of tissue. Eliminating the risk of differentiation of stem cell types into cancer cells. Overcoming the risk of immune rejection of donor cells. Supply issues concerning the procurement and expansion of adequate numbers of cells and cell lines.	Ethical, moral and religious issues within some cultures regarding the procurement and use of embryonic stem cells and stem lines. Technical complexity.
Bioartificial organs	2010–20 → (Artificial liver currently in clinical trial)		
Complete organ regeneration	2030 →	Understanding the basic mechanisms involved in cell growth and differentiation into different types of tissue. Eliminating the risk of differentiation of stem cell types into cancer cells. Supply issues concerning the procurement and expansion of adequate numbers of cells and cell lines. Overcoming the risk of immune rejection of donor cells. Developing strategies that support blood flow. The need to develop bioreactors that apply shear and mechanical forces on developing tissue to mimic the physiological environment.	Ethical, moral and religious issues around the procurement and utilisation of embryonic stem cells. Technical complexity.
Neuroprosthetics – using brain signals to operate artificial limbs and devices	2010 →		Technical complexity

Reproductive Technologies

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
Embryo screening and selection: tissue typing	2004 →		Ethical, religious, regulatory
Embryo screening and selection: sperm sorting (separation of male- and female-producing sperm)	2002 →		Ethical, religious, regulatory
Embryo screening and selection: DNA amplification (enables screening for multiple traits)	2005 →		Ethical, religious, regulatory
Embryo screening and selection: "predictive" embryo screening for complex pathological late-onset disease traits		Technical limitation on the number of embryos that can be produced in a single PGD cycle. The complexity of the relationship between genes and phenotypic characteristics will complicate the development of genetic tests.	Ethical, moral and religious concerns. Regulatory. Technical complexity.
Assisted reproduction: ooplasmic/cytoplasmic transfer	2002 → 30 children born to date		Ethical, religious and regulatory. (The technology has been halted due to concerns about the children potentially having the DNA of three parents.)
Assisted reproduction: artificial wombs	2020		Ethical, moral and religious concerns. Regulatory. Technical complexity.
Assisted reproduction: reproductive cloning			Ethical, moral and religious concerns. Regulatory. Technical complexity.

Enhancement

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
Designer babies: modification of non-pathological traits		If germ line gene therapy utilised: drug delivery and targeting mechanisms; and controlling gene expression. Embryo screening and selection. Technical limitation on the number of embryos that can be produced in a single PGD cycle. The complexity of the relationship between genes and phenotypic characteristics will complicate the development of genetic tests.	Ethical, moral and religious concerns. Regulatory. Technical complexity.
"Anti-ageing" drug	2014 →		
Gene therapy to enhance non-pathological traits	2010–20	Drug delivery. Controlling gene expression.	Ethical, regulatory, technical

Nutrition

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
Functional foods and nutraceuticals	→ Incremental growth – convergence with nutrigenomics		
Nutrigenomics: foods for health, tailored to an individual's genetic make-up	Underpinned by developments in diagnostics		

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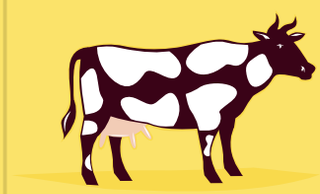

FUTUREWATCH

FUTUREWATCH

6 PRIMARY PRODUCTION

This chapter outlines trends and likely future developments (up to 2025) in primary production applications for biotechnology. It covers crop biotechnologies (including forestry) and animal biotechnologies (selective breeding, transgenic and cloning applications, animal health and companion animal developments).

Part 1 is a detailed analysis of emergent biotechnologies in the primary production sectors. **Part 2** provides, in table form, an overview of the trends, grouped into drivers of growth, technology trends, paradigm shifts, uncertainties and key emerging applications to 2025.

PART 1: EMERGENT BIOTECHNOLOGIES IN THE PRIMARY PRODUCTION SECTORS TO 2025

CROP BIOTECHNOLOGY – GENETIC MODIFICATION

Today, just six countries (United States, Canada, Argentina, China, Brazil and South Africa) account for 99% of the world's commercially grown "first wave" genetically modified (GM) crops. The rate of adoption in the principal growing countries has been rapid. From 1996 to 2001 the global area of GM crops increased over 30-fold from 1.7 million hectares to 52.6 million hectares. In 2003 alone, the total area of GM crops grew by 15%.[91]

The limited number of countries on the list above is telling. There is some polarity between nations in their attitudes to GM food and the environmental impacts of GM crops. On one hand, the United States is the world's leading GM nation, both in terms of area of cultivation and public acceptance of GM food. However, this enthusiasm is not shared to the same extent in countries like Japan and across much of Europe where there is strong consumer resistance to GM crops.

Even in the United States there are signals suggesting an increasing consumer reticence towards GM crops. Attitudes vary from resisting the implementation of certain GM crop applications to wanting an outright ban. In early 2004 Monsanto abandoned plans to introduce GM wheat onto the world market, despite proving that GM wheat increased yields by 5–15%. Pressure from US and Canadian farmers fearing a collapse in their billion dollar export markets to Europe and Japan led to the product being pulled off the market.[92] Similarly, Mendocino County in Northern California became the first US county to ban GM crops and animals.

GM Crops – Future Technology Projections

Broadly, the first wave of GM crops (which are already in commercial use) addresses production traits (sometimes referred to as agronomic input traits). The second wave, mostly lab-based research, addresses quality and/or nutritional traits (output traits). The third wave addresses complex environmental stress-related traits (such as drought or salt tolerance) and the production of novel products (biopharmaceuticals or plastics).

It is anticipated that second and third generation GM crops will comprise new products aimed to meet consumer needs or requirements, and therefore encourage greater acceptance. To reach this aim, scientists are increasingly seeking to use biotechnology to improve food quality, to deliver new medicines (production of pharmaceutical proteins), to contribute to disease prevention (edible vaccines) and to reduce health risks (altered nutritional composition). It will not be that easy, however. These traits, in contrast to the more rudimentary GM transformations of the first generation of GM crops, are controlled by multiple genes and complex biochemical reactions.

The table at right is adapted from a 2003 analysis of research occurring from the lab bench through to field trial and commercial release in Europe and North America. It is premised on the assumption that it takes about 8–12 years to develop a new crop variety. Some forecasted times to market are offered.

91 James, Clive (2003), "Global Status of Commercialized Transgenic Crops: 2003" International Services for the Acquisition of Agri-Biotech Applications (ISAAA).

92 *The Guardian*, 11 May 2004, "Monsanto abandons worldwide wheat project".

GM Plant Applications – Technology Forecasts

MARKET ENTRY PROJECTION DATES	FUTURE APPLICATIONS
1996 → 2011 1st Generation – production enhancement traits	■ Stacked input traits – eg herbicide and insect resistance in cotton ■ Disease- and virus-resistant GM plants
2007 → 2015 2nd Generation – output enhancement traits	■ Hypoallergenic crops ■ Enhanced functional ingredients ■ Modified starch, protein and fatty acid content ■ Modified fruit ripening
2013 → 2020s 3rd Generation – abiotic stress resistance and novel product development	■ Therapeutic food ■ Salt- and drought-resistant plants ■ Molecular pharming

(Key Source – IPTS – Review of GMOs under research and development and in the pipeline in Europe, 2003, p.28)

Europe and North America are not the only global centres for plant biotechnology. Countries like China, India and Brazil are also investing heavily in agricultural biotechnology. China is developing the largest plant biotechnology capacity outside of North America. China is also rapidly differentiating its largely public sector research investment in this area. The list of GM crops under intensive field trial in China differs from those being worked on in other parts of the world (with a list that includes staple food crops like rice, wheat, potatoes and peanuts). As at 2002, "in industrialised countries, 45% of field trials [were] for herbicide tolerance and improving product quality, only 19% for insect resistance. In China more than 90% of field trials target insect and disease resistance". Couple this with a growing low-cost workforce and infrastructure and we may see China emerge in this area over the medium term.[93]

Gene Delivery Technologies

One of the greatest technical challenges to overcome before more complex multigene modifications can be made successfully to crops is the effective delivery and subsequent reliable expression of the desired novel traits. The delivery of more than one novel trait to a plant is known as "trait stacking".

Historically, combining several genes together required many years of cross-breeding. The discovery of delivery methods to genetically engineer plants from the 1980s onwards sped up this process. Delivery methods include the bacterial vector *Agrobacterium tumefaciens*, protoplast fusion, microinjection and bioballistics. These technologies are relatively blunt instruments though, and so far haven't been widely used to reliably engineer plant tissue to stably express complex multigene traits. However, the development of "golden rice", which contains three genes to produce provitamin A, illustrates that multigene modifications are already achievable.

One of the more promising trait stacking technologies currently under development is artificial chromosome technology. Developed at the University of Chicago, so-called "mini-chromosome" technology promises to enable the stacking of multiple genes in a single event that – crucially – does not disrupt the plant's genome. The extra chromosome has been readily accepted by plants in the lab and has provided a stable platform from which designer-engineered genes can manufacture proteins that affect the plant's characteristics. The Chicago team has created artificial chromosomes for canola, rape, cabbage, soybeans, tomatoes and corn. The technology is currently undergoing field trials.[94]

Another leading-edge technology is chloroplast transformation. Chloroplast transformation is a technology in which introduced genes function only inside the chloroplast (the chloroplast is where photosynthesis occurs in plants). This technology is seen to have a number of advantages, including:

93 Huang, J. et al. (2002), "Plant Biotechnology in China", Science, v295 p.675.

94 *The Chicago Tribune*, 3 February 2004, "Easing process of gene-altering seeds; Chromosome firm looks for partners".

- From an environmental perspective, in some species, chloroplasts are only inherited maternally; therefore, they are not present in pollen and cannot be transferred to conventional crops or sexually compatible plants. So chloroplast transformation may provide a means of controlling the spread of GM material.
- Chloroplast transformation also enhances protein production in a cell; as such, the technology has potential for biopharming applications in plants.[95]

Chloroplast transformation field trials currently focus on producing pharmaceuticals in tobacco. Potentially, the technology may be used to develop biotech crops that are prone to pollen drift to mitigate the risks of cross-pollination. However, since there are many chloroplasts in each cell, work is required to improve transformation efficiency.

BEYOND GENETIC MODIFICATION

"Smart Breeding"

Not all developments in plant biotechnology are concerned with genetic modification. Advances in understanding of the precise genetics of plant traits may mean that traits like drought resistance or an increase in nutritional value can be achieved without genetic modification.

Over the past decade scientists have discovered that crops are full of dormant characteristics. In practice, this means that, rather than inserting a bacteria gene into a plant to ward off pests, it may be possible often to simply turn on a plant's own innate ability. Consumer resistance to GM food crops may also mean that smart breeding will have an important future role to play in crop development.

Developments in smart breeding are being technologically underpinned by:

- advances in plant genomics, bioinformatics and gene banking;
- DNA marker-assisted breeding techniques; and
- forms of culturing, like embryo rescue which enables breeders to cross distant relatives (domestic and wild species) with desirable, rare traits that normally wouldn't produce a viable offspring.[96]

Depending on the crop-specific generation time, it is forecast that marker-assisted selection breeding strategies could lead to the production of superior varieties with controlled complex traits within 5–10 years.[97]

Apomixis

Apomixis is a form of asexual reproduction. Several common plants, including dandelion, citrus, blackberry and certain forage grasses, reproduce this way. Over the past few years, researchers have identified a variety of genes that may determine whether plants reproduce sexually or asexually by apomixis. A few institutions around the world are working on apomixis, trying to find the molecular switches to turn on the trait, which may be lying dormant in some plants.

Technology development based on apomixis has a number of advantages, including:

- avoiding the degeneration of some vegetatively propagated plants, such as potato and cassava, which accumulate pathogens through repeated use; and
- if staple crops such as maize could be coaxed to become apomictic, this could help farmers in developing nations – who save seed each year for planting the next, and who consequently watch the vigour of their crops diminish annually.

Widespread use of apomixis, particularly if one company held the IP and had exclusive control of any future technological development, would be of great concern to seed companies as it could have a big impact on their profits.[98]

Some commentators forecast that apomictic technology may be available in the next 10–12 years.

95 http://www.chlorogen.com

96 Manning, Richard (2004), "Super Organics", *Wired*, n5 pp.178-179.

97 Peleman, J.D. & Rouppe van der Voort, J. (2003), "Breeding by Design", Trends in Plant Science, v8, n7 p.330.

98 Agriculture and Environment Biotechnology Commission (AEBC) (2002), "Looking ahead – An AEBC Horizon Scan" p.41.

NEW ZEALAND CASE STUDY

RYEGRASS GENETICS

Ryegrass is the main forage plant in New Zealand's pastoral agriculture. AgResearch has generated a sequence database containing about half of the predicted ryegrass genes. The sequence database has been used to develop a genetic map that is being used to create improved cultivars. GM solutions hold the greatest promise, but acceptance problems mean that marker-assisted breeding is also being used to move towards the goals.

Ryegrass is relatively low in carbohydrate and high in protein. Therefore, grazing animals have lower production and produce high levels of polluting methane and nitrogenous waste compared to grain-fed animals. AgResearch scientists have been able to increase the energy each plant provides by increasing leaf fat content. This has the potential to provide large economic benefits to farmers, who will be able to feed more animals per hectare. Methane and nitrogen emissions are expected to be lower, and meat and milk from animals fed on this diet are predicted to have a healthier fatty acid profile.

Another focus is to investigate the feasibility of producing condensed tannins in ryegrass in order to control bloat and internal parasites – two major animal health problems – and also improve the fatty acid profile of the meat and milk.

When ryegrass flowers, nutritional quality is compromised. Marker-assisted selection has the potential to produce a ryegrass cultivar with delayed flowering, and genetic modification could produce cultivars that never flower except in response to a farmer-controlled signal. Capitalising on international research on the genes that control plant flowering, AgResearch is working on a plant model that flowers only when it receives a signal, such as being sprayed with a beneficial or benign substance. This technology may also provide a way of containing GM crops.

Ryegrass in New Zealand grows symbiotically with an endemic fungus. The fungus makes compounds that provide insecticidal protection to the ryegrass, but some of its compounds have been associated with negative health effects in grazing animals (ryegrass staggers). AgResearch has developed and commercialised a fungus, AR1, that produces only the beneficial compounds. Building on this knowledge, it is working on using the fungal insecticidal genes in commercial crop plants.

Products resulting from this research are commercialised through Grasslanz, a subsidiary of AgResearch. The research and development is funded by the Foundation for Research, Science and Technology, commercial clients and reinvestment from royalties.

Forestry

Forestry biotechnology is less developed than in other plant crops. One of the fundamental reasons for this is the basic biology of trees. There are some specific technical challenges relating to this basic biology that need to be addressed before bioengineered trees could become a commercially viable and environmentally sound proposition:

- researchers have been unable to propagate most trees clonally (except the poplar genus and *Pinus radiata*);
- trees have a much longer life cycle and so it takes years to evaluate the effects of genetic transformation and identify suitable GM lines; and
- some trees are able to cross-hybridise within the same genus, complicating the patterns of gene flow and heightening the risk of cross-pollination and "escape" of the GM tree.[99]

Despite these difficulties there is some research in the pipeline. GM fungus- and virus-resistant fruit trees will probably come onto the market during 2007–11. GM trees with reduced lignin content are forecast to be commercialised after

99 Pew Initiative on Food and Biotechnology (2001), "Harvest on the Horizon: Future Uses of Agricultural Biotechnology" p.45.

2011.[100] (Lignin is the compound that makes trees stiff and is desirable for lumber but not paper; and removing it costs the global pulp and paper industry upwards of $20 billion annually and adds to environmental waste.)[101]

ANIMAL BIOTECHNOLOGY

Selective Breeding and Productivity Enhancement

Traditional practices for within-breed livestock improvement are based on mass selection, where individuals with outstanding phenotypes (eg live weights, wool weights and muscle mass) were selected and used as parents. The success of such strategies varies markedly according to the heritability of the trait and the nature of non-genetic influences.

As a consequence, however, farm animal populations contain rich collections of mutations with phenotypic effects that have been purposefully enriched by selective breeding. The mapping of livestock genomes, coupled with our nascent understanding of gene function, will enable breeders to obtain a far greater understanding of the genetic underpinnings of these traits. In the future this will result in farmers having greater control and certainty over the introduction of heritable desired traits.

One of the initial applications of modern biotechnology to livestock production is the use of genomics in animal breeding. Increasingly, marker-assisted selection using genetic markers is being used to determine the selection of desirable and ever more complex breeding traits, and for preserving genetic herd diversity.

Several genes causing desired traits (eg enhanced musculature and fecundity) have already been identified. Diagnostic DNA tests for some of these traits are currently used in practical animal breeding.

Theoretically, farm animals could be genetically engineered to exhibit traits which would enhance productivity. This is because genetic modification provides a method to *rapidly* introduce "new" genes into the germ line of farm livestock without having to wait for more time consuming cross-breeding. But there are many technical, ethical, food safety and animal welfare issues to resolve before GM technologies have an impact on mainstream agricultural production practices.

Transgenic (or GM) and Cloned Livestock

Transgenic (or GM) animals are produced by introducing "foreign" DNA into pre-implantation embryos. The introduced DNA is inserted into the genetic material and may be expressed in the tissues of the resulting offspring.

Two relatively recent technological developments will have the greatest impact on the future uses of transgenic reproductive technologies in livestock. These developments are the ability to:

- isolate and maintain embryonic and somatic cells directly from embryos, fetuses and adults in vitro; and
- use embryonic and somatic cells as nuclei donors in nuclear transfer (NT) cloning strategies.[102]

NT cloning technologies have resulted in high-performing bulls in Australia, New Zealand and the United States being cloned. Due to the expense of the cloning process, production has been limited to very high-value individuals. Australian-based company Clone International (in which Crown Research Institute AgResearch has a 25% stake) cloned Donor – Australia's number one ranked dairy bull – resulting in two cloned calves, Alpha Donor and Beta Donor. These calves have been sold to breeders in China who want to breed the calves to boost the quality of the national dairy herd. As a consequence, China may be the first nation to allow cloned farm animals to enter the food chain.[103] In October 2003 the FDA pronounced that there's no scientific evidence that meat or milk derived from healthy cloned farm animals can harm people. However, the FDA wants public reaction to this assessment before it decides if cloned farm animals will require government approval before being sold as food. This decision is expected to be announced in 2005.[104]

100 Institute for Prospective Technological Studies (2003), "Review of GMOs under Research and Development in Europe" p.28.

101 Mann, C.C. & Plummer, M.L. (2002), "Forest Biotech Edges Out of the Lab", *Science*, v295, n5560 p.1626.

102 Wheeler, M.B. (2003), "Transgenic animals in biomedicine and agriculture: outlook for the future", *Animal Reproduction Science*, n79 p.266.

103 *The Australian*, 5 February 2002, "For sale, two copy cattle".

104 www.fda.gov

NEW ZEALAND CASE STUDY

CLONING

AgResearch has one of the world's strongest cloning research programmes. Its primary emphasis is on cattle cloning, as the profitability of dairy farming provides an economic incentive. However, AgResearch has also created the world's largest population of sheep clones. Using the "Dolly" nuclear transfer technique, approximately 10% of AgResearch's cloned embryos result in viable offspring, which is high by most international standards.

Elite animals for agriculture

The production of genetically elite animals for agricultural purposes is a main focus of AgResearch's cloning programme. This has a commercial avenue in the form of Clone International, a company that holds an exclusive licence from the owner of the "Dolly" IP, Geron Corporation, to use nuclear transfer technology to commercially produce cloned cattle, sheep and horses in New Zealand and Australia. AgResearch provides scientific expertise to the venture. The services that Clone International offers are the cloning of existing animals now for breeding (eg high-quality bulls and rams) and the establishment of cell lines from existing animals so that the animal may be cloned at a later date.

Biopharming

AgResearch's other main cloning focus is the use of nuclear transfer to produce transgenic dairy herds for biopharming. It has produced transgenic herds that make proteins for biopharming, one of which has offspring that also produce the protein. New Zealand's farming industry is well suited to biopharming because of its lack of serious livestock diseases – we are arguably the "cleanest" country in the world in this sense. Strict regulatory processes and excellent veterinary care and husbandry systems combine with capable farmers and non-intensive outdoor farming systems to protect this advantage.

Future directions

Cloning has yet to be perfected. A major research thrust is to reduce the developmental problems that occur in some cloned animals, thought to happen because they develop from adult body cells rather than embryonic cells. This in turn will increase the cloning success rate, which will improve economic viability and animal welfare. The researchers are also trying to increase the precision of genetically modifying the donor cells used to produce transgenic farm animals.

Cloning remains a speculative area because of the regulatory and market challenges faced globally. In New Zealand, ERMA has approved developmental biopharming applications.

The genetic modification of farm animals used in conjunction with nuclear transfer is a technology combination that enables many potential biotechnological applications. These include the production of pharmaceutical therapeutic proteins; the production of animal organs/tissues suitable for transplantation into humans (xenotransplantation); the eradication of animal disease; the study of human diseases; and the genetic improvement of livestock.

The success rate of these techniques to date has been low. According to a 2002 UK report, overall only about 10% of farm animal embryos on which genetic modification is attempted survive to birth, and only about 10% of the offspring will be transgenic.[105]

Many of the technical pitfalls with transgenic animal production are related to the transgene itself, integration site, copy number and transgene expression. These include:

- unregulated expression of genes resulting in over- or under-production of gene products;
- possible side effects – growth hormone transgenic pigs had arthritis, altered skeletal growth, dermatitis, gastric ulcers and renal disease;
- insertional mutations which result in some essential biological processes being altered;

105 Agricultural and Environment Biotechnology Commission (2002), "Animals and Biotechnology – A report by the AEBC" p.10.

- mosaicism which results in transmission of the transgene to only some of the offspring; and
- transgene integration on the Y chromosome which results in only males carrying the transgene.[106]

Cloning is similarly inefficient, with a high proportion of clones resulting in stillborns, or difficult births and post-natal abnormalities. Many of the problems associated with cloning are attributed to "epigenetic effects", in which identical DNA can produce different outcomes. The consequences can be as harmless as unique colour patterns on an animal's coat or as damaging as placental failure and cardiovascular birth defects.[107]

Success rates are likely to improve due to considerable current research effort being directed at understanding the nature and cause of the problems (although it has to be noted that there has been no marked improvement in success rates in the 20 years since animals were first genetically modified or in the four years since cloning began).

Therefore, even aside from the potential barrier of public acceptability, the practical entry of GM livestock into mainstream production is currently fraught with obstacles. These include the expense of the process, due to the small proportion of surviving value added embryos; incomplete knowledge of farm animal genomes; and the longer breeding cycles of these animals, limiting the pace at which research can advance.

There is currently no global market for products from transgenic animal sources. However, the production of biopharmaceuticals from transgenic farm animals will potentially be among the first wave of applications. In great part this is because of the significant reduction in production costs (estimated to be 1/1000th the cost of conventional methods) afforded by using farm animals as bioreactors.[108]

106 Wheeler, M.B. et al. (2003), ibid. p.281.

107 Pew Initiative on Food and Biotechnology (2003), "Animal Cloning and the Production of Food Products: Perspectives from the food chain".

108 Kues, W.A. & Niemann, H. (2004), "The contribution of farm animals to human health", *Trends in Biotechnology*, v22, n6 p.287.

NEW ZEALAND CASE STUDY

LOW BIRTH WEIGHT STUDIES IN SHEEP

Approximately 6000 babies are born small in New Zealand every year, due to either premature birth or poor growth in the womb. This can cause problems, including death, brain damage and developmental problems. Low birth weight is also associated with adult health problems including heart disease, stroke and Type 2 diabetes.

The University of Auckland's Liggins Institute is exploring the mechanisms involved in poor fetal growth and prematurity and examining how these can be prevented or treated. The Institute is combining these studies with its partners around New Zealand in the National Centre of Growth and Development.

Sheep form a useful model for these studies because they have a long gestation (five months) and the lamb is of similar size to a human newborn. The fetus can be manipulated during the pregnancy, allowing controlled studies of conditions such as intrauterine growth restriction.

Sheep were used in the landmark study that showed that modestly reducing the food intake of ewes around the time of conception led to reduced growth of the fetus and increased rates of premature delivery. This was a joint project between the Institute, the University of Toronto and Monash University.

If these findings are applicable to human pregnancies then they could have significant implications in preventing preterm birth. Currently about half of all preterm deliveries have no known cause.

This work is being continued in a new large-scale research facility that allows large numbers of ewes to be individually fed. The growth, metabolism and long-term health indicators of lambs from food-restricted ewes will be monitored, with the aim of eventually applying the results to humans.

Another research focus is the in utero treatment of fetuses that are growing poorly. Currently these babies are delivered early and exposed to all the risks of prematurity. Scientists are working on developing a treatment that could be added to the amniotic fluid, which fetuses swallow. The treatment is likely to contain growth factors or nutrients. Sheep with growth-restricted fetuses are being used to test the treatments.

How Farm Animals Could Contribute to Human Health

Farm animals will potentially contribute to human health in the following ways:

- production of therapeutic proteins;
- supply of cells, tissues and organs to patients requiring transplants; and
- production of antimicrobial peptides.

Biopharming

The production of rare human therapeutic proteins in transgenic animals is known as biopharming. Recently, the biotechnology industry has experienced an extreme shortage of manufacturing capacity for rare therapeutic proteins: conventional production from blood or tissue extracts is proving to be inefficient and capital-intensive, and the market for individual products is very small. Because transgenic animals can efficiently produce these proteins a lot of attention has been drawn to this research area. Using farm animals like cattle, sheep, goats and pigs as bioreactors has several production advantages, including the potential for scalable production, low running costs and higher expression stability. The most promising site for recombinant protein production is the mammary gland (since it produces lots of protein, and the protein is relatively easy to recover). Other body fluids, including blood, urine and seminal fluid, are also being explored.

There are currently a number of animal biopharmed products in various stages of the clinical trial process. If these therapeutic protein products progress successfully through clinical trials, they could reach the market in a few years and be applied in the following ways:

THERAPEUTIC APPLICATION	PRODUCTION SPECIES	POTENTIAL DATE TO MARKET
Genetic anticoagulant resistance	Goat	2006 →
Dissolving coronary clots	Goat	2006 →
Lung emphysema	Goat and/or sheep	2007 →
Haemophilia A	Sheep	2008 →
Blood substitute	Cattle	2008 →

(adapted from The Contribution of farm animals to human health – Trends in Biotechnology, June 2004, p.288)

Transchromosomal cattle were successfully developed in 2002. A human artificial chromosome containing the entire sequence of human immunoglobin was introduced into cattle. The resulting transchromosomal offspring expressed human immunoglobin in their blood. This system could be a significant step towards the production of human therapeutic polyclonal antibodies. Further studies are needed to prove whether the additional chromosome will continue to be inherited and its genes expressed in a stable fashion over subsequent generations.[109]

109 Kues, W.A. & Niemann, H. (2004), ibid p.288.

New Classes of Antibiotics

Antimicrobial peptides (AMPs) could provide an interesting natural antibiotic alternative to conventional chemical antibiotics. One of the key drivers advancing this work is the increasing antibiotic resistance in bacterial species and the subsequent need to develop new classes of antimicrobial treatments. AMPs are an important mechanism of innate immunity in plants and animals. They work by attacking the bacterial cell membrane, in a process called cell lysis. The following quote explains more about how it works and why it has potential:

"… most other antibiotics attack bacteria by attacking specific molecules that are part of the bacterial cellular machinery, against which bacteria can develop resistance. Yet bacteria have not been able to develop a resistance to AMPs that have existed for millennia …" [110]

Unfortunately, many naturally occurring AMPs are toxic. However, those derived from farm animals have the least harmful effects on human health. There are currently a few AMPs derived from farm animals in advanced clinical trial. These peptides are encoded by small genes that make their cloning easy. This should allow for easy expression and large-scale purification if they are proven to be clinically effective.[111]

Xenotransplantation

Xenotransplantation is the transplantation of organs, tissues or cells from one species to another. The key driver pushing its development is the considerable shortfall of donor organs and the associated healthcare system costs facing many nations. Farm animals, especially pigs, are seen to be the most potentially compatible animals, both in terms of structure and function, to serve as donor species to human patients.

Historically, however, there has been very little success in trans-species tissue and organ transplantation. The animal tissues and organs have proven to be structurally and functionally incompatible to humans. In many cases transplants have also resulted in a rapid immune rejection response.

Recently, though, interest in xenotransplantation has been rekindled. This has been driven, in great part, by some successes in genetically modifying pigs to negate the risk of adverse immune response in humans. There is one animal-to-human transplant regularly performed globally: non-modified pig heart valves. Because the valves are chemically treated to kill living cells, most nations do not regulate their use as xenotransplants.

A few clinical trials focusing on external therapies are currently taking place in the US and Europe. The most successful case in point is the use of external machines containing animal liver cells to treat acute liver failure. This method has shown some success in clinical trials, as a means of buying time for patients awaiting a liver transplant.

Researchers are predicting that between 2007 and 2014 animal cell therapies (such as brain and pancreatic islet cells), and external therapies like the liver cell treatment, could establish themselves clinically – due to the lessened risk of immune rejection.[112]

Immune rejection is still one of the key barriers to the growth of xenotransplantation. Coupled with that is the fear that xenotransplantation could transmit viruses that are harmless to pigs but deadly to humans. For example, all pigs carry porcine endogenous retrovirus; its potential effects on humans, although seen as a relatively slight risk, are as yet unknown.

Different countries have developed various different levels of regulation in response to these perceived risks. Regulatory oversight ranges from outright bans to moratoria to no government oversight at all. We can probably expect to see some of the most rapid developments in South Korea, which announced on 1 June 2004 a ten-year plan, backed up with a AU$72.66 million investment, to mass-produce genetically altered pig organs for human transplants.[113]

110 http://access.ncsa.uiuc.edu/Stories/cathelicidins/index1

111 Marshall, S.H. (2003), "Antimicrobial Peptides: A natural alternative to chemical antibiotics and potential for applied biotechnology", *Electronic Journal of Biotechnology*, v6, n2 p.276.

112 National Health and Medical Research Council (Australia) (2003), "Animal-to-human transplantation research – A guide for the community".

113 *Sydney Morning Herald*, 1 June 2004, "Korea to mass-produce pig organs for human transplants".

Animal Health Applications

Like the human health market, advances in modern biotechnology are affording many new opportunities to the development of animal health products. However, the animal health market is considerably smaller than that for human health (the human health market is 35 times the size of the animal health market). The consequences of this are twofold. On one hand, the animal health segment has benefited from developments in human health, with biotechnology companies working on animal health products as an extension of their human health pipeline. On the other, however, the relatively small size of the animal health market makes it a less venture-investment-friendly proposition. As in the pharmaceutical industry, small biotech companies in this market niche are trending towards partnering with the more established players in the animal health industry.[114]

Diagnostics and Therapeutics

Alongside genetic testing to identify desirable animal traits to guide livestock breeding and production management decisions, gene testing for diseases will become a powerful animal health tool. The growing number of commercialised gene tests is one of the immediate benefits of our increasing body of knowledge of animal genomes and disease pathology. As yet, only a limited number of genetic tests have been made into commercial diagnostic kits; however, it is estimated that by 2009–10 there will be widespread use of rapid diagnostic systems for livestock and fish diseases based on genetic testing.[115]

Vaccination of livestock has been practised for many years and has proven to be the most effective method to prevent infectious diseases and reduce economic losses due to infectious diseases. In addition, vaccination has been used to improve productivity by altering hormones that influence growth. For example, double muscling in certain types of cattle has been linked to a mutation in the myostatin gene. On this basis immunisation strategies have been developed to increase muscle mass in animals.[116]

DNA vaccines are seen as one of the most promising emerging applications to ensure herd health. Animals are vaccinated not with the protein that induces an immune response but instead with a piece of DNA that encodes such a protein. This has the potential advantage of being simpler to produce, and prolonging exposure of the animal's immune system to the immunogen induces more effective immunity. Importantly, the foreign DNA does not seem to integrate with the host's genome and so the vaccinated animal is not considered to be genetically modified.[117] The fact that the vaccinated animal does not have GM status means the DNA vaccine applications will be more loosely regulated and may subsequently reach the market more swiftly.

As yet, no DNA vaccines have made it to the marketplace. This is due in great part to their as yet relatively low efficacy in target species. However, several strategies are being investigated to overcome this bottleneck. These strategies include the use of mechanical devices (eg gene guns), addition of chemical adjuvants and vaccine formulation in microparticles or liposomes.[118]

Bacteriophage-based therapeutics is also a future growth area in animal health applications. Like humans, animals have developed some resistance to antibiotics. Bacterial infections can be a major problem on farms, causing loss in livestock, pollution of the environment (soil and water) and food contamination.

Bacteriophages are naturally occurring bacterial viruses that specifically attack and kill bacteria. Because bacteriophages grow exponentially, a single dose is often sufficient to treat an infection. A very important feature of phage therapy is that bacteriophages do not infect human or animal cells. The potential use of phages in the development of novel and unique therapies for disease-causing bacteria is potentially limitless. Several companies are attempting to commercialise bacteriophage-based therapeutics for animal health applications.[119]

114 Animal Pharm Reports (2004), "Biotechnology, Cloning and Genetics: A revolution in the animal health industry?" (executive summary).

115 National Institute of Science and Technology Policy (Japan) (2002), "The Seventh Technology Foresight – Future Technology in Japan toward the Year 2030 – Survey Results – Agriculture, forestry, fisheries and food", p.228.

116 Van Drunen Little-van den Hurk, S. et al. (2004), "Strategies for improved formulation and delivery of DNA vaccines to veterinary target species", *Immunological Reviews* v199, p.113.

117 Agricultural and Environment Biotechnology Commission (2002), "Animals and Biotechnology – A report by the AEBC" p.13.

118 Van Drunen Little-van den Hurk, S et al. (2004), op cit., p.114.

119 Martin, R. (2003), "How ravenous soviet viruses will save the world", *Wired*, n10.

Companion Animals

Products for use in companion animals (such as cats, dogs and horses) have been the main driver of growth in the market for veterinary medicines over the past decade. Viral, bacterial and parasitic infections are among the most common health challenges faced by companion animals. However, their increasing longevity isn't helping either. Chronic, often age-related, conditions such as cardiovascular disease and cancer are increasingly prevalent in dogs and cats. Cancer is now the leading disease-related cause of mortality in the US canine population. Veterinary cancer drugs are expected to be among developments occurring in the next ten years.[120]

Other emerging technological developments in companion animals relate to gene therapy and DNA vaccine trials for cancer. In 2002 the Faculty of Veterinary Medicine at Glasgow University embarked upon a gene therapy clinical trial on several hundred cats and dogs with tumours. This work may also have applications for human cancers.[121]

Much has been made of recent developments which could indicate the start of a trend towards the production of genetically enhanced "designer pets". The first GM pet, the GloFish® (a zebra fish that glows under fluorescent light), was originally developed in Singapore as a means to monitor water pollution. The fish were ill-equipped to monitor water due to the fact that once they started to glow they didn't stop.[122]

Another development (albeit somewhat controversial) is the Missiplicity Project. This project aims to move towards the commercial cloning of pets. It has been bankrolled in great part by a wealthy American benefactor who wants his dog, Missy, to be the first cloned dog. To date, a dog has not been cloned. The first kitten cloned from the cells of an adult cat, CC, was cloned in early 2002. This feat has not been repeated, but a handful of commercial enterprises are offering pet owners gene banking services to hold onto the DNA of their pets until the technology is able to reliably clone companion animals.[123]

Aquaculture

The global demand for seafood is not sustainable given the depletion of the natural fish stocks available to us in the world's oceans. To address this gap, aquaculture – or fish farming – is one of the world's fastest growing industries.

To date, aquaculture biotechnology developments have been concerned with enhancing the production capabilities of enterprises. The research and development of transgenic fish have focused initially on obtaining significant increases in growth rates – from two to 11 times faster than normal – by using growth hormone genes. Scientists have produced faster growing GM lines of many fish important to global aquaculture.

A 2003 analysis of GM fish research and development in the pipeline by the Pew Initiative on Food and Biotechnology[124] reveals that regulatory approval is currently being sought from the FDA for a strain of Atlantic salmon. This strain of salmon has been modified for increased growth rate and food conversion efficiency factors. If this is approved – and there is some uncertainty surrounding the timing of this eventuality due to consumer and environmental concerns – then fish will be the first GM animal to enter the human food chain.

Research still in the lab is concentrating on improving disease resistance, increasing cold tolerance in goldfish (with the insertion of an antifreeze protein gene) and investigating improved growth rate potential for prawns and other crustaceans.[125]

120 Animal Pharm Reports (2004), "Companion Animal Products: Prospects for Market Growth" (executive summary).

121 BBC News, 5 September 2001, "Pet cancer trials planned".

122 *AgBio Buzz* (2004), "From GloFish to Purple Carnations", v4 n2.

123 Genetic Savings and Clone – http://savingsandclone.com/

124 Pew Initiative on Food and Biotechnology (2003), "Future Fish".

125 Ibid.

PUBLIC OPINION ON PRIMARY PRODUCTION BIOTECHNOLOGIES

Public opinion has been a notably strong shaper of the business and technological development of biotechnology in the primary sector, particularly for plant-based agricultural biotechnology.

Agricultural biotechnology first focused on improving on-farm productivity and profitability for farmers and for biotechnology corporations. Unexpected resistance from consumers severely affected the profitability of this business model, which is now in the course of being substantially modified. The focus is now on benefits to all stakeholders in the value chain, and greater attention is being paid to safety aspects of agricultural products, especially those destined for the food chain. The uncertainties of wider environmental impacts from agricultural GMOs have also been a focus of significant public concern, and have driven a far greater attention to ecological studies.

Social pressure is also a factor in the greater attention being paid to introducing GM food crops into poor countries, concentrating on both nutritional enhancements and productivity enhancement within traditional farming practices, for potatoes, cassava, rice, wheat and millet, especially through resistance to drought and insects.

Compared with developments in agricultural plant biotechnology, public debate about animal biotechnology is more muted. Animal cloning developments result in public unease for two major reasons: transgression of natural processes, and evidence that some cloned animals have undesirable health difficulties and reduced longevity. The prospect of animal transgenics raises more concern, particularly about tangible evidence of species boundaries being breached.

As with GM food crops, there is concern about the safety of food derived from animals that have been genetically modified, such as meat and milk. This concern also stems, it has to be said, from a lack of scientific attention to this issue.

NEW ZEALAND CASE STUDY

ROYAL COMMISSION ON GENETIC MODIFICATION

New Zealand's Royal Commission on Genetic Modification found a notably high level of concern about the potential environmental impact of GM among New Zealanders. The view expressed by one of the public submitters appeared to be shared by many:

"... humans are messing with something very unique and ... doing so may cause irreversible harm to the ecosystem."

Recognising the considerable uncertainties in this area, the Commission recommended further research into the ecological impacts of GM. New Zealand research into the social and environmental aspects of biotechnology was extended and now makes up $8 million per annum (out of a total of around $135 million per annum for all biotechnology-related research).

PART 2: CHAPTER OVERVIEW: PRIMARY PRODUCTION

The following tables summarise the key trends and drivers that we have identified in this chapter.

Overarching Drivers of Growth

SCIENCE AND TECHNOLOGY DRIVERS	■ Improving tools for data collection ■ Improving methods for data analysis ■ Convergence of science disciplines
ECONOMIC DRIVERS	■ Productivity enhancement through increased yields ■ Extraction of higher value products from commodities ■ Market convergence with the human health sector

Technology Trends

GM CROPS – FROM "INPUT" TO "OUTPUT"

The current generation of GM crop technologies has been bred to exhibit "input traits" (eg herbicide and insect resistance) designed to enhance productivity for the farmer. Recent analyses of the prospective product pipeline have indicated a growing trend towards the development of GM crops exhibiting "output traits". In practice, this means crops with enhanced functional ingredients (eg modified starch, protein and fatty acid content) or plants with therapeutic properties.

SMART BREEDING

Marker-assisted selection using genetic markers is being used increasingly to determine the selection of desirable, and ever more complex, breeding traits for both crops and animals. Improvements will continue in an incremental fashion.

DIAGNOSTICS

Genetic diagnostic technologies are underpinning advances in both animal production and animal health.

LIVESTOCK CLONING

A number of farm animal species have successfully been cloned. However, cloning technologies are currently technically difficult, making them unviable for large-scale production. Emergent trends in the application of farm animal cloning appear to indicate that the technology is going to be used, at least in the nearer term, to clone high-value individuals. Many of the technical challenges are likely to be overcome through continued scientific research.

GM ANIMALS

Technical difficulties regarding the genetic modification of large mammals, coupled with consumer resistance to GM products, make the large-scale modification of farm animals for production purposes commercially untenable in the near term. However, the production of GM animals as bioreactors to produce high-value pharmaceutical proteins is anticipated to be much closer to commercial production. Trends signalling the future development of an emergent market for GM farm animals appear to be closely aligned to products for the health and pharmaceutical sector.

Paradigm Shifts

From "low-value, high-volume" production to "high-value, low-volume" production.

Uncertainties	
ETHICAL CONCERNS	Animal welfare, playing God
ENVIRONMENTAL IMPACTS	Strong environmental concerns and protests have accompanied the development and deployment of GM crop technologies
CONSUMER PREFERENCE	Consumers in many countries have overwhelmingly rejected GM crops
COMPLEXITY	The more we discover about biological systems and processes, the more we realise that the less we know

Key Emerging Applications

GM Crops

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
Stacked traits – artificial chromosome technology	→ 2010–11 currently in field trials	Achieving appropriate control of multigene traits	GM – consumer rejection. Environmental concerns.
Stacked traits – chloroplast transformation	→ 2010–11 currently in field trials	Increasing chloroplast transformation efficiency	GM – consumer rejection. Environmental concerns.
Modified starch, protein and fatty acid content	2007–11	Identifying the appropriate genetic pathways	GM – consumer rejection. Environmental concerns.
Salt- and drought-resistant plants	2013–20s	Identifying and controlling the appropriate genetic pathways	GM – consumer rejection. Environmental concerns.
Molecular pharming	2013–20s	Efficient production of pharmacologically active products. Effective control of dose if plant product is to be directly consumed. Development of appropriate extraction methodology for processed crops.	GM – consumer rejection. Environmental concerns.

Non-GM Methods of Crop Production

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
Production of plants with controlled complex genetic traits using marker-assisted breeding	2009–14	Overcoming reproductive barriers. Tools to dissect genetic and environmental influences.	Public acceptance – consumer rejection of other forms of biotechnology in food production
Apomictic technology (asexual reproduction)	2014–16	Understanding and ability to manipulate reproductive pathways	Public acceptance – control of the technology

Animal Production

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
Identification of productivity traits by marker-assisted selection	→ continued incremental growth	Tools to interpret glut of genomic data	
Genetic diagnostic technologies	→ continued incremental growth	Tools to dissect genetic and environmental influences	
Cloning	2001 → incremental growth (slow)	Success rates low (1–3%). High proportion of stillborns, difficult births (larger than usual fetuses) and post-natal abnormalities	Animal welfare. Technical complexity.

Farm Animals and Human Health

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
Biopharming – using transgenic animals as bioreactors for therapeutic protein development	2006–08 →	Technical difficulties with transgenic farm animal production (eg post-natal abnormalities, renal diseases, early-onset arthritis). Mosaicism. Insertional mutations.	Animal welfare. Technical complexity.
Xenotransplantation – trans-species tissue and organ transplantation	2007–14 → Cell therapies with liver and pancreatic islet cells	Immune rejection. Structural and functional incompatibility.	Animal welfare. Technical complexity. Ethical and cultural acceptability.

Animal Health Applications

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
DNA diagnostics	2009–10 – widespread use of rapid diagnostic systems for animal diseases	Tools to dissect genetic and environmental influences	
Vaccines		Identifying appropriate targets for vaccines	GM – consumer rejection

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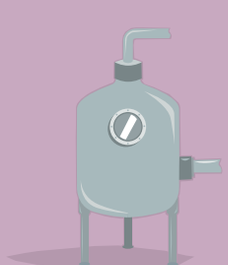
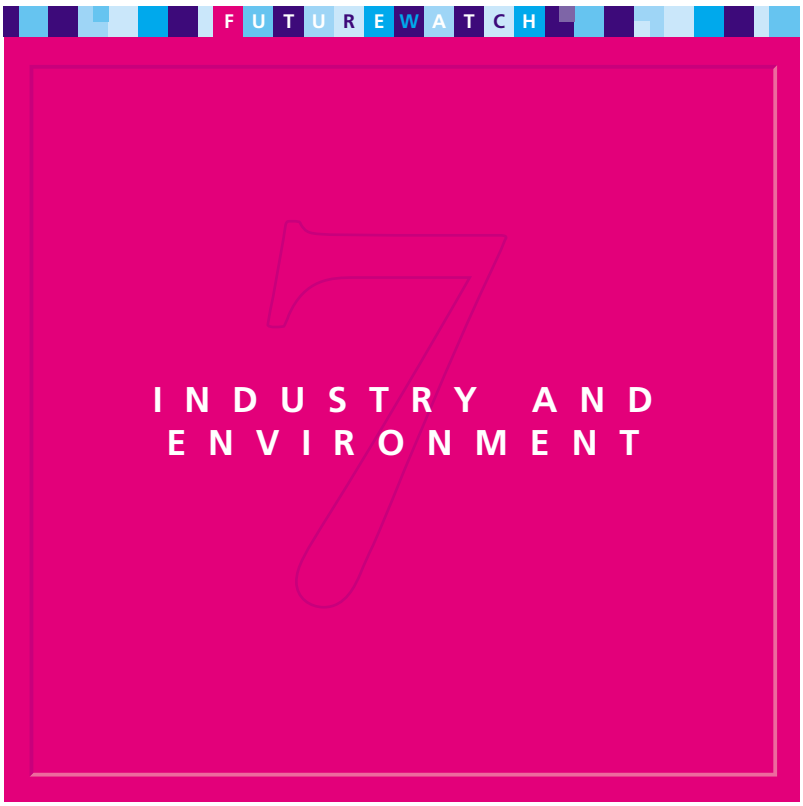
INDUSTRY AND ENVIRONMENT



FUTUREWATCH

CHAPTER 7



This chapter outlines trends and likely future developments (up to 2025) in industrial and environmental applications for biotechnology. Industrial applications for biotechnology span a very wide spectrum. They range from the use of simple fermentation technology in industrial processes to using transgenic plants and animals for many different purposes. This chapter is divided into two sections. **Part 1** is a detailed analysis of emerging industrial and environmental applications to 2025, including biomass feedstock sources, bioprocessing technologies, bio-based products and environmental applications. **Part 2** is a chapter overview, in a table format, incorporating drivers of growth, technology trends, paradigm shifts, uncertainties and key emerging applications to 2025.

PART 1: EMERGING INDUSTRIAL AND ENVIRONMENTAL APPLICATIONS TO 2025

For thousands of years, biological resources have been used for a multitude of (non-food) uses. They have provided energy, shelter, clothing and textiles, vehicles for transportation, and many of the basic tools and necessities of life. Plants have also been widely used for the production of chemicals and medicinal products.

Over the past two centuries, the widespread use of biological resources as a source of materials declined as they were replaced by non-renewable mineral and hydrocarbon resources. However, the fossil fuels powering this incarnation of the global industrial complex are a finite resource, with some pundits suggesting they may run out by 2070.[126]

In North America, Europe and many other countries, major initiatives are under way using bio-based resources. These initiatives – ranging from those undertaken by government in partnership with some large private sector companies to grassroots local initiatives – aim to produce power, fuel, chemicals (basic commodities to specialty products) and industrial fibre from renewable bio-based resources. Renewable materials will be a fertile area for uptake of biotechnology advances, particularly in industrial biotechnology applications where there is a relatively fast track to markets (at least when compared with food and healthcare applications).

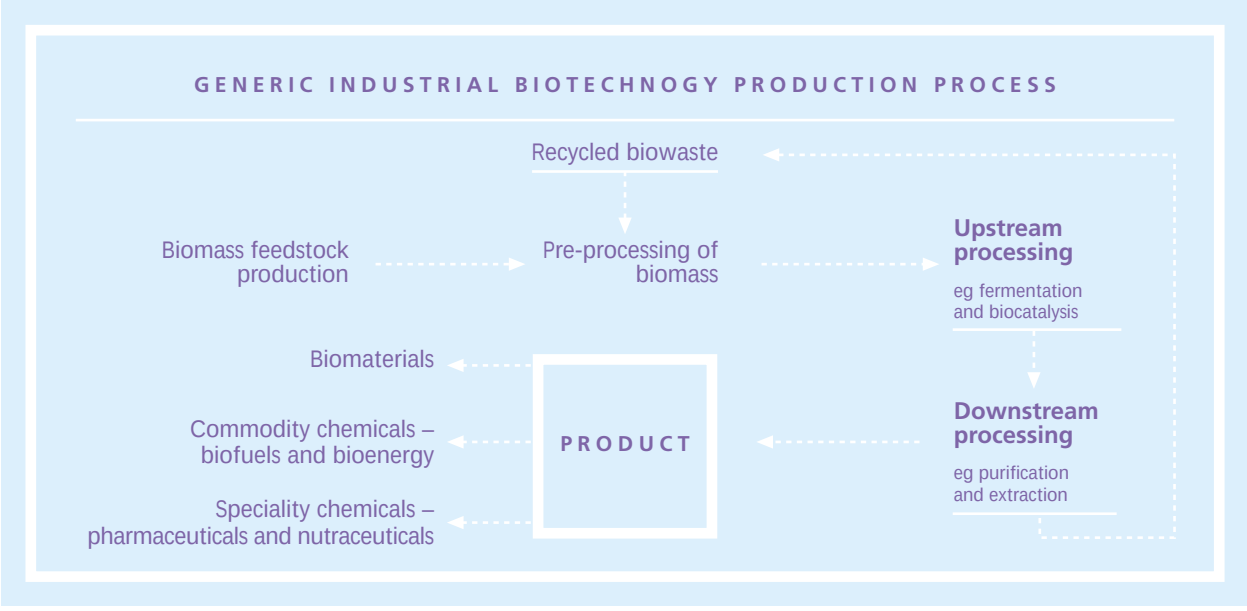
The OECD says that applications of industrial biotechnology fall into two groups:

1. the replacement of fossil fuel raw materials by renewable (biomass) raw materials; and
2. the replacement of a conventional, non-biological industrial process by one based on biological systems, such as whole cells or enzymes used as reagents or catalysts.[127]

Both groups are by no means mutually exclusive, with the conversion of biomass to a bio-based product very often being reliant on biological industrial processes.

The figure below represents an overview of a generic production cycle for a renewable industrial bio-based product: from biomass production to bioprocessing to product. Each stage of development is underpinned by a different suite of technologies and future issues. Hence this chapter is divided, by development stage, into the following sections:

- biomass feedstock production;
- bioprocessing technologies; and
- bio-based products (biomaterials, biofuels and bioenergy, bulk and fine chemicals, new materials and novel products, pharmaceuticals and novel proteins, and so on).



126 National Institute of Science and Technology Policy (NISTEP – Japan) (2002), "The Seventh Technology Foresight – Future Technology in Japan toward the Year 2030 – Survey Results – Materials and Processes", p.394.

127 OECD (2001), "The Application of Biotechnology to Industrial Sustainability", p.17.

BIOMASS FEEDSTOCK PRODUCTION

Biomass feedstocks are the raw materials that form the basis of bio-based industrial products. "Biomass" encompasses agricultural crops, wood, animal wastes, aquatic plants and the organic portion of municipal and relevant industrial wastes. The total annual biomass production on our planet is estimated at 170 billion tons, and consists of around 75% carbohydrates (sugars), 20% lignins and 5% other substances such as oils, fats, proteins and alkaloids. Of this total biomass production, only 3.5% is thought to be used for human needs. The renewable raw materials discussed here are almost all provided by agriculture and forestry. The animal breeding and fisheries sectors contribute (predominantly in the form of animal fats) but are considerably less significant than plant biomass.[128]

The following industrial sectors supply the most useful renewable raw materials:

- the sugar and starch sector: producing carbohydrates such as sugar, glucose starch and molasses from raw biomass such as sugar beet, corn and potatoes;
- the oil and fat processing sector: producing a number of fatty acids and alcohols, and glycerol, from biomass such as rape seeds, palm oil and soybeans; and
- the wood processing sector: with particular emphasis on cellulose and the paper industry.[129]

It's logical, therefore, that advances in feedstock production will have major impacts on final product development. The US Biomass Research and Development Technical Advisory Committee has identified a number of research challenges in feedstock production that will need to be overcome before we see the widespread adoption of industrial biotechnological applications and bio-based product development. These include:

- a better understanding of underpinning plant genomics, biochemistry and metabolism;
- scientific methods to produce and prepare plants and residues so that they meet specifications for end-use applications; and
- that agronomic practices and technologies must be improved to increase yield, crop sustainability, efficiency and reduction in the costs of production and delivery.[130]

The ability to produce high-value, economically viable bio-based fuels, power and products will require lower-cost feedstocks with enhanced desirable characteristics like high energy content, increased yield, fast growth and the ability to withstand drought and other environmental stresses. As we have seen in Chapter 6 (Primary Production), applications of GM technologies are forecast to deliver a number of these outcomes within our time frame to 2025. To recap:

GM Plant Applications with Implications for Industrial Biotechnology Development – Technology Forecasts

MARKET ENTRY PROJECTION DATES	FUTURE APPLICATIONS
2003 → 2011 1st Generation – production enhancement traits	■ Stacked input traits – eg herbicide and insect resistance ■ Disease- and virus-resistant GM plants
2007 → 2015 2nd Generation – output enhancement traits	■ Enhanced functional ingredients ■ Modified starch, protein and fatty acid content in soybeans, oilseed, rape, maize and potatoes
2013 → 2020s 3rd Generation – abiotic stress resistance and novel product development	■ Salt- and drought-resistant plants ■ GM plants with enhanced yield (all plants) ■ GM trees with modified lignin content

(Key Source – IPTS – Review of GMOs under research and development and in the pipeline in Europe, 2003, p.28)

In the near term it is anticipated that most raw biomass sources for industrial products will be converted from processed agricultural crop components, fermentable sugars from starch crops like corn, and from biomass wastes. Sources will come to include lignocellulosic materials from grasses, trees, shrubs and crop residues – when the technology and infrastructure

128 Royal Belgian Academy Council of Applied Science (2004), "Industrial Biotechnology and Sustainable Chemistry", p.10.

129 Ibid, p.10.

130 US Biomass Research and Development Technical Advisory Committee (2002), "Roadmap for Biomass Technologies in the United States", p.5.

exist to extract and process the useful component parts of these plant types.[131] New fibre crops for industrial uses are predicted to become mainstream after 2010, including modified hemp, flax and tree species.

Improvements in biomass pre-treatment will have a big impact on the development of future markets. For example, large increases in glucose reserves are potentially available from the lignocellulosic substances in trees and to a lesser extent other plants and waste paper. Cellulose can be hydrolysed by acid but most of the glucose is destroyed in the process. Pre-treatment by cellulase and hemicellulase enzymes can effectively cleave the cellulose molecules into their constituent sugars. However, these enzymes are currently too expensive to use in converting large amounts of lignocellulosic materials.[132]

BIOPROCESSING TECHNOLOGIES

The processing of raw biomass into useful products encompasses two stages of development: "upstream" and "downstream" processing. Upstream processing encompasses "any technology that leads to the synthesis of a product as well as the fundamental science and engineering needed to understand product formation". Downstream processing is "the cost-effective separation and purification of bioproducts, as well as biorefining".[133]

Upstream Processing

Biocatalysis

In industrial bioprocessing, a biocatalyst has traditionally been thought of as an enzyme, cell or micro-organism that activates or speeds up a biochemical reaction. Microbial fermentation, whole cell catalysis and isolated enzyme-based biocatalysis are the most commonly used industrial bioprocessing methods. These processes are contained within a bioreactor or fermenter. However, as discussed in Chapter 6 (Primary Production), transgenic farm animals and plants will also potentially be used as "factories" to produce valuable proteins and biochemicals. In this chapter we will focus on contained biocatalysis and the technologies that are emerging for enhancing microbial and enzymatic function. Methods of biodiscovery for new and robust enzymes and microbes, referred to as bioprospecting, will also be discussed.

Fermentation

Today's industrial biotechnology produces a wide variety of bulk and fine chemicals. Industrial fermentation is the most common technology used in most of these transformations. In this process, specially cultivated micro-organisms (bacteria, yeast and fungi) efficiently convert sugars into useful products. The range of products varies from inexpensive bulk products to very expensive fine chemicals like pharmaceuticals. The list of fermentation products below illustrates the economies of scale between market sectors:

Industrial Biotechnology Products Manufactured via Fermentation

PRODUCT	WORLD PRODUCTION (TON/YEAR)	WORLD MARKET PRICE (/KG)
Bioethanol	26,000,000	0.40
Citric acid	1,000,000	1.50
Vitamin C	80,000	8
Antibiotics (bulk products)	30,000	150
Antibiotics (specialties)	5000	1500
Vitamin B12	10	25,000

(adapted from Royal Belgian Academy Council of Applied Science (2004), "Industrial Biotechnology and Sustainable Chemistry", p.12)

131 Lignocellulosic biomass is the parts of plants (in particular, tree trunks and branches, stalks of plants and so on) made up of lignin, cellulose and hemicellulose compounds, which comprise the essential part of woody cell walls.

132 National Academy of Sciences (2004), "Bio-based Industrial Products – Priorities for Research and Commercialisation" p.39.

133 The US Biotechnology Research Subcommittee (1995), "Biotechnology for the 21st Century: New Horizons" http://www.nal.usda.gov/bic/bio21/

Genetic modification technologies have enabled researchers to make changes to the genetic material of these micro-organisms. For example, their performance during fermentation has been enhanced by two GM techniques: micro-organisms can be metabolically modified via a technique called metabolic pathway engineering, and through the insertion of genes from another species (micro-organism or higher organisms).

Metabolic Pathway Engineering

The field of metabolic pathway engineering manipulates microbial cells to bypass processes that will be redundant to the industrial task at hand. In technical terms, pathway engineering encompasses the directed modification of cellular physiology though the introduction, deletion and/or modification of metabolic pathways or regulatory functions of a cell.[134] In practice, this means that micro-organisms can be designed to undertake complex chemical synthesis in a single fermentation step.

An oft-cited example of this is the one-step biological production of vitamin B12, replacing the previous six- to eight-step chemical process (along with a 40–50% reduction in cost).[135] Genencor and Eastman Chemical are currently in the process of commercialising a metabolically engineered one-step production pathway to ascorbic acid (vitamin C).[136] The production of vitamin C has traditionally required one fermentation step and five chemical steps. The implications of technological breakthroughs of this nature go far beyond this one particular product; other enzymes can also be added to divert synthesis towards other end products.

Enzymatic Processes

Enzymes are produced from industrial fermentation processes and can subsequently be used as industrial biocatalysts in their own right. The use of enzymes in industry is by no means a new technology. They have been used in products like detergents since the 1950s. McKinsey and Co estimates that the total value created – in efficiency gains, enzyme sales and profits generated by products made by using industrial biocatalysis – could double to US$12 billion a year by 2010 in the US alone.[137]

Enzyme-catalysed industrial processes have always been a more efficient way of making molecules than traditional chemistry. This is because they often contain fewer synthetic steps, and the yield of each of those steps is almost always close to 100%. In contrast, the cumulative losses that arise from completing the process using complicated traditional chemical synthesis meant that the yield often ended up below 10%.[138]

However, the traditional problem with biological enzymes has been that they are "fussy molecules": exposure to the wrong temperature, acidity or pressure and they stop working.[139] Because of this, enzyme biocatalysts have traditionally been confined to the production of high-value products like pharmaceuticals and nutraceuticals. Advances in both the sourcing of robust enzymes (discussed in the bioprospecting section later in this chapter) and the manner in which they can be produced are starting to expunge many of these difficulties. In addition, emerging technological fields like directed evolution are beginning to produce a breed of customised, fit-for-purpose "super-enzymes" which we may begin to see penetrating the industrial landscape.

Directed Evolution

Directed evolution seeks to engineer enzymes to perform with improved performance under specific conditions from the ground up. In essence, researchers making enzymes via directed evolution are creating new micro-organisms which produce "super-enzymes". Using high-speed screening technologies and a technique known as gene shuffling,[140] researchers mix and match DNA from different organisms to achieve the right combination of catalytic properties. In some instances, these pathways are inserted into a bacterium like E. coli, and then performance tested in a variety of conditions (temperature, acidity and so on).

134 Sanford, K. et al. (2004), "Bioprocessing – Pathway Engineering through Rational Design", *Genetic Engineering News*, v24, n2, January 15.

135 OECD (2001), "The Application of Biotechnology to Industrial Sustainability", p.51.

136 http://www.genencor.com/wt/gcor/ascorbin

137 *Business Week*, 2 August 2004, "Biotech heads for the factory floor".

138 *The Economist*, 27 March 2003, "Reinventing Yesterday".

139 Ibid.

140 Gene shuffling mimics, yet accelerates, evolutionary microbial processes and allows the breeding and improvement of individual genes and subgenomic DNA fragments.

Currently, this technique is used mostly for producing fine chemicals. One of the ultimate goals of industrial biotechnology is to create organisms which can produce scalable quantities of these super-enzymes, which can be dropped into existing industries (some of which have not adopted biotechnological production methods) without manufacturers having to redesign their production lines.[141]

One of the key barriers to industry uptake of bioprocessing technologies has also been the time researchers take to develop appropriate catalysts fit for different industry processes, as well as the costs of this time lag. Techniques like directed evolution that use advanced biotechnological methods are speeding up the development process to the point where it may soon be cost-effective for bioprocessing technologies to start making inroads into industry sectors like the production of commodity chemicals.

Currently, however, these designer enzymes do not come cheap, and it will take time before the price is lowered sufficiently to enable integration into the commodity-product development process.

Bioprospecting

Bioprospecting is the search for new chemicals (in plants, animals and microbes) that can potentially be synthesised for some medical or commercial use. Already, the properties of many plants which have been used by indigenous peoples for centuries have been adapted by the pharmaceutical industry into successful drugs and medicines.

Big industry players like Craig Venter have begun to invest in bioprospecting activities. Venter, via his Institute for Biological Energy Alternatives, sampled for microbial life in the Sargasso Sea. Using an emergent technique called "metagenomics" (which sequences the DNA of an entire environment), about 1.2 million new genes turned up from an estimated 1800 hitherto unknown species of microbe.[142]

Of particular interest to industrial applications are a robust group of micro-organisms called extremophiles. Extremophiles thrive in extreme environments where no other micro-organisms are found, including high temperature, pH, pressure and salt concentration or low temperature, pH and nutrient concentration or low water availability. Some extremophiles can tolerate extremely high levels of radiation or toxic compounds. Once isolated from their environments they can be analysed by enzyme companies for protein expression. Some of these proteins may be useful starting points for developing industrial bioprocesses by techniques like metabolic engineering and directed evolution.

Downstream Processing

Downstream processing can be likened to the product recovery phase, and it can be a technically difficult and expensive procedure. Downstream processing following fermentation, for example, is mostly about the initial separation of the medium into a liquid phase and a solid phase, and subsequent separation, concentration and purification of the product. Downstream processing costs in this instance can be as high as 60–70% of the selling price of the product.[143]

The need to invest in R&D to improve downstream processing has been identified by a number of commentators[144] as a crucial step before industrial biotechnology processes can supplant conventional chemical processes, particularly in the production of chemical commodity products like biofuels. It is envisaged that the emergent techniques for the upstream pre-treatment of biomass feedstocks will start to drive down the costs of downstream processing.

Process Control

New methods of process monitoring and control in all aspects of the product development cycle will also play an important role in enabling industrial biotechnology to increase market penetration and scale up levels of production. The US National Academy of Sciences has identified the following areas where future research and development will need to occur to advance bioprocess control:

141 *Business Week*, 2 August 2004, "Biotech heads for the factory floor".

142 *The Economist*, 29 April 2004, "Sea of Dreams".

143 University of British Columbia http://www.bioteach.ubc.ca/index.htm

144 Cargill Dow (2003), "Fostering the Bio-Industrial Revolution", Presentation at the Bio 2003 Conference.

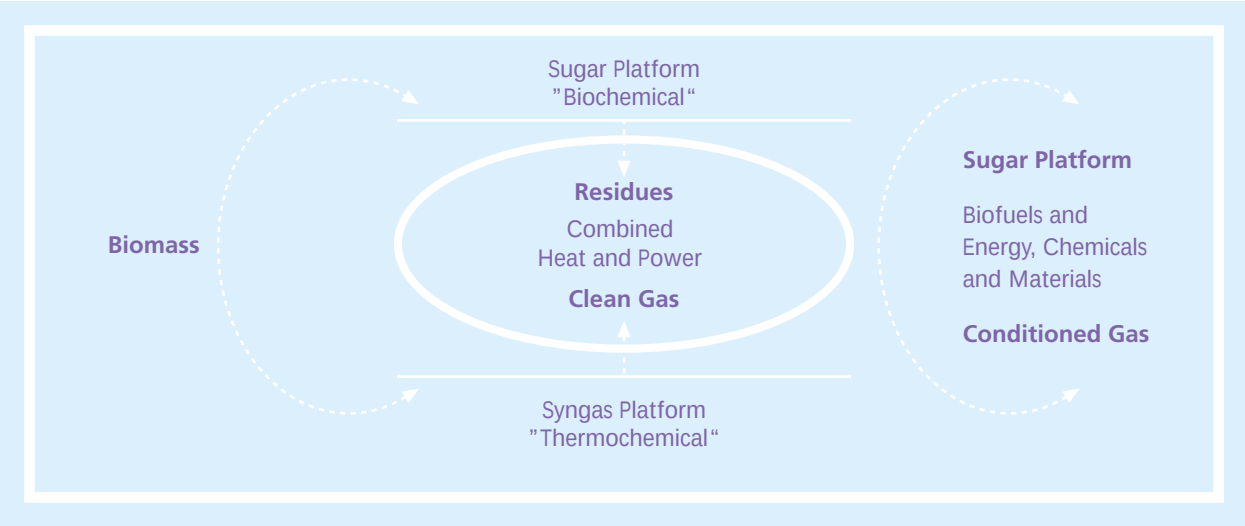
- cutting down production steps;
- developing new methods for monitoring biological processes (eg via biosensors and the real-time monitoring of bioreactors using digital imaging); and
- developing new concepts in process control (eg by using expert systems, artificial intelligence and neural networks).[145]

Achieving Scale – the Biorefinery Concept

To enable industrial biotechnology to penetrate the commodity chemical market, or to enable the effective use of biomass for bioenergy production, the processing base will need to be scaled up and costs reduced. The biorefinery concept is seen as the most likely route to achieve this goal.

A biorefinery is a facility that integrates biomass conversion processes and equipment to produce fuels, power and chemicals from biomass. It is analogous to today's petroleum refineries, which produce multiple fuels and products from petroleum. Industrial biorefineries are seen as one of the most promising routes to creating a new bio-based industry. Today's pulp and paper mills and corn wet mills can be thought of as prototype biorefineries, with elements of the requisite infrastructure in place. The difference between these prototype facilities and the imagined biorefinery of the future is a combination of scale, platform capabilities and the number of product lines produced from the raw feedstock.

The US National Renewable Energy Laboratory conceptualises the biorefinery of the future as follows, utilising a combination of technology platforms to achieve critical mass:



(adapted from the National Renewable Energy Laboratory website – http://www.nrel.gov/biomass/biorefinery.html)

145 National Academy of Sciences (2004), "Bio-based Industrial Products – Priorities for Research and Commercialisation" p.96.

Different conversion platforms are appropriate for different product streams. The two overarching biomass conversion platforms are thermochemical conversion and bioconversion. Underneath each platform are a number of different technological processes that produce different product lines. The table below illustrates the interdependencies between the development of these platforms and their underpinning technological processes, and the impacts these developments will have on future selected product lines (L = low impact, M = medium impact, H = high impact):

TECHNOLOGY PLATFORMS	BIOFUELS IMPACT	BIOPOWER IMPACT	BIOPRODUCTS IMPACT
Thermochemical – gasification	L	H	L
Thermochemical – direct combustion	L	H	L
Thermochemical – anaerobic fermentations	L	H	L
Bioconversion – fermentation and hydrolysis	H	M	H
Bioconversion – biocatalysis	H	M	H
Bioconversion – separation and purification	H	M	H

(adapted from US Biomass Research and Development Technical Advisory Committee (2002), "Roadmap for Biomass Technologies in the United States" p.13)

Governments are seen to be one of the key drivers in the achievement of a bio-based industry and scaling up biorefinery development to commercial levels of production. Of particular note are recent directives from the US Government and the European Commission (EU).

The United States recently published draft rules to encourage federal purchasing of bio-based industrial products in 11 categories, from lubricants to fibres, plastic and paints.[146] The US Department of Energy (DOE) is one of the key investors in biorefinery platform development. The development of an alternative platform for both fuel and energy production is seen as an area of national security for the United States. The volatility of the Middle East (the world's primary producer of oil), coupled with the finite nature of the earth's fossil fuel resources, is among the drivers pushing biorefinery development in the US. The DOE is subsidising the development of the bioethanol industry in the US.

To meet EU targets set by the Kyoto Protocol, around 9.3 million tons of ethanol will need to be produced annually in Europe by 2010. The EU has also adopted guidelines and production targets to expand the use of biofuels derived from agricultural, forestry and organic waste products. The biofuels target for 2005 is 2% of vehicle fuel, rising to nearly 6% by 2010.[147]

A number of big industry players are also driving the development of the biorefinery concept. Of note are the Cargill Dow joint venture in Nebraska and the Royal Dutch Shell and Iogen ethanol refinery in Canada. The Cargill Dow biorefinery (discussed in more depth later in this chapter) produces plastic packaging and textile fibres from maize (including biomass waste of stalks and crop leftovers) and bacteria. Royal Dutch Shell and Iogen are building an ethanol refinery that is converting biomass waste. The product EcoEthanol is made from the non-food portion of renewable feedstocks using a proprietary enzyme developed by Iogen to break down the biomass waste.[148]

The establishment of biorefineries is dependent on a number of elements. Not least is getting feedstocks of satisfactory price, quality and quantity, as well as economical and effective processes for converting raw materials into value added products.

146 http://www.biobased.oce.usda.gov/public/index.cfm

147 http://europa.eu.int/comm/energy/res/legislation/biofuels_en.htm

148 McMeekin, A. et al. (2004), "Prospecting Bioscience for the Future of Non-Food Uses of Crops" p.45.

NEW ZEALAND CASE STUDY

BIOTECHNOLOGY IN INDUSTRY

IRL-BioPharm is a company that was created as a subsidiary of Industrial Research Ltd. It uses fermentation processes to produce high-value pharmaceuticals for export.

A main product is new generation anti-cancer agents that promise to avoid the side effects of traditional chemotherapy, because they have a greatly reduced effect on normal cells. Only when they find and attach to cancerous cells do they release a highly cytotoxic compound that destroys the cell. This reduces the treatment dose required.

This feat is accomplished by chemically conjugating toxic compounds with antibodies. The antibodies – each of which is specific to a particular kind of cancer – hold onto the toxic substance until they find their cancer target. The antibody-drug conjugates form the key part of cancer medications called tumour-activated prodrug (TAP) therapy. This has the potential to change the face of cancer therapy.

IRL-BioPharm's clients are largely US- and UK-based biotech companies who are developing and trialling these drugs. They range from pharmaceutical multinationals like GlaxoSmithKline through to small-molecule anti-cancer drug innovators such as ImmunoGen in the USA.

Under contract to these companies, IRL uses advanced facilities to produce the cytotoxic drugs. (The company anticipates also chemically modifying the cytotoxins and performing the conjugation in future if required.) The process uses specific soil micro-organisms that produce the toxic compounds. A large population of these is grown in a fermenter, with all aspects of the growing environment and fermentation media being highly controlled. The potent cytotoxins that accumulate in the broth are extracted with solvents and then purified. The final quantities are small but valuable – in excess of $1000 per gram.

The company uses the same process to produce other drugs such as immune suppressors.

International companies use IRL-BioPharm for several reasons. Their production follows international regulations for current good manufacturing process (cGMP), which ensures product quality and protects human health and the environment. There are very few ventures in existence that have IRL-BioPharm's combination of expertise and facilities in fermentation, solvent extraction and potent molecule handling. They have a long history of isolating and recovering metabolites from micro-organisms and plant materials, and developing processes for these activities.

Future directions for IRL-BioPharm include using in-house expertise to develop new drugs, and the chemical modification of fermentation-derived metabolites. There are plans to implement facilities capable of producing greater quantities of the toxins when the drugs pass the required trials and reach the market.

PRODUCTS AND MARKETS

The products that are created either partially or completely by industrial biotechnological processes can be divided into the following:

- specialty chemicals (pharmaceuticals, nutraceuticals, animal feed, enzymes and so on);
- commodity chemicals (biofuels and bioenergy); and
- biomaterials (bioplastics, biopolymers, medical materials for tissue engineering and so on).

Each market group is at a different stage of development, each with different drivers, interdependencies, infrastructure development needs and value propositions. It is useful to compare them in order to give a clear picture of the future trajectory of industrial biotechnology. In this report we look more closely at:

- pharmaceuticals;
- bioplastics;
- biofuels; and
- bioenergy – hydrogen production.

Pharmaceutical Manufacturing

Currently, industrial biotechnology has the greatest degree of penetration in the pharmaceutical sectors, with 20–30% of the industry employing fermentation or enzyme

catalysis in the manufacturing process.[149] This industry segment is projected to grow in both the short and longer terms for a number of reasons.

In the short term, in the face of relatively empty drug pipelines and the threat of generic companies reaping benefits as blockbuster drugs come off patent, pharmaceutical companies are paying more careful attention to how they produce their existing products. Improved purity can serve to raise the bar for generic manufacturers attempting to copy a pharmaceutical company's drug.

From a productivity perspective, improved micro-organisms and enzymes will also serve to reduce the unit cost of drug manufacturing. This may also enable more effective use of existing manufacturing capability, and allow companies to put off capital expenditure on new capacity.[150]

We have already observed, in Chapter 5 of this report, the future growth trajectory of drugs based on biotechnology as opposed to chemicals. To recap: about 16% of new drugs since 1997 have been based on biotechnology; this share is anticipated to rise considerably – up to 40% by 2015. To add weight to this projection, more than 30% of drugs currently in development are biological. Biological drugs require biological manufacturing processes so it seems logical to surmise that manufacturing capability will be comparably scaled as well.

Trends in the composition of small-molecule chemical drugs are also signalling a growing dependence on industrial biotechnology to optimise the manufacturing process. For example, the increased use of chiral chemistry techniques in drug development lends itself to biological manufacturing. Chirality means that a chemical substance exists in two forms. This is most easily conceptualised as the forms being left- or right-handed, but identical in all other respects. The biological world is fundamentally chiral (for example, most carbohydrates are "right-handed", whereas amino acids are "left-handed"). Chirally pure compounds can halve the amount needed and increase the efficacy of drugs. Chemical catalysts cannot recognise chirality but enzymes can; so they are more effective in the manufacturing process of chiral drugs.[151]

The use of industrial biotechnology in the pharmaceutical sector will continue growing. This can be said of the specialty chemicals sector in general: products that are low in volume and high in value, with more modest manufacturing infrastructure requirements.

Bioplastics

Over the past couple of years, there have been a number of technological breakthroughs in the production of renewable bioplastics. In fact, bioplastics are regarded as the biopolymer most likely to enjoy significant penetration into the traditional petrochemical market in the near to medium term.

Currently, the two most advanced plastics projects are those of Dupont and Cargill Dow (a joint venture between the agricultural and chemical firms of those names). Dupont's product, Sorona,[152] was developed in collaboration with Genencor. Sorona is made from glucose syrup, which is made from maize starch and fermented through a bacterium which has been engineered with the biochemical pathways of three micro-organisms. The fermentation process produces a molecule called 1,3 propandiol. Sorona is not an entirely renewable fabric, however, as it is combined with a monomer called terephthalate, made from oil.

Cargill Dow's product, Nature Works,[153] on the other hand, is 100% renewable. Nature Works packaging is made from lactic acid, which is made from glucose. Traditional chemistry-based techniques are used only for the polymerisation of the lactic acid. Nature Works entered the market last year and, although more expensive than its petrochemical rivals, the product is marketed as a premium, environmentally friendly product.[154] Cargill Dow has invested significantly in the infrastructure to manufacture this product, with plans downstream for diversification into other products. If it works as it is supposed to, it will be an early realisation of the biorefinery concept.

149 McCoy, M. (2003), "Breeding Profits", *Chemical and Engineering News*, v81 n33.

150 Ibid.

151 Lewis, R. (1997), "Chiral chemistry enables firms to try old twists on new drugs", *The Scientist*, v11, n13, June 23.

152 http://www.dupont.com/sorona/home1.html

153 http://www.cargilldow.com/corporate/nw_pack_home.asp

154 *The Economist*, 27 March 2003, "Reinventing Yesterday".

McKinsey forecasts that, by 2010, 10% of polymers could involve biotechnology in some form. They also estimate that, by 2010, up to 20% of global value from the entire chemical industry will potentially come from biotechnology (it is currently estimated to be around 5%).[155] Other forecasts predict that biodegradable plastics will have cornered 30% of the market in around 2015–17.[156]

However, a number of technological roadblocks need to be overcome before either the feedstock or finished product is cheap enough to make this a reality. The key breakthrough needed to unlock the industry is the cheap production of glucose. The main source of industrial glucose globally is maize starch. Most of the dry weight of maize is composed of cellulose. Cellulose, like starch, is a polymer of glucose. Unlike starch, however, it is tough and difficult to break down. The race is on to develop the enzymes to turn the conversion of cellulose into a commercially viable industrial product.[157]

Biofuels

The technical feasibility of producing transport fuel from biomass has been firmly established. Bioethanol production using sugar cane fermentation has been commercially undertaken in Brazil since the 1980s, and produced from maize and other cereal crops in several US states for the past decade.[158] Animal by-products such as whey can also be a starting point for ethanol production. Fonterra recently announced a trial using whey (a waste product of casein production) to produce bioethanol as transport fuel for cars.[159]

The cost of producing biofuels from crops usually far exceeds the current price of diesel or petrol, mainly due to the higher costs of growing and converting biomass. The future use of the lignocellulosic material from trees and crop waste residues (stalks) is seen as a solution to this current bottleneck. Lignocellulosic biomass has been used for bioethanol production, but the material is more difficult to break down as it requires the removal of lignin, and then conversion of cellulose to sugars, before ethanol can be produced by fermentation. In 2003, Genencor International, funded by the US Department of Energy, announced the development of an economically viable enzymatic process for converting lignocellulosic material

155 *Business Week*, 2 August 2004, "Biotech heads for the factory floor".

156 National Institute of Science and Technology Policy (Japan) (2002), "The Seventh Technology Foresight – Future Technology in Japan toward the Year 2030 – Survey Results – Materials and Processes", p.408.

157 *The Economist*, 29 April 2004, "Sea of Dreams".

158 OECD (2004), "Biomass and Agriculture – Sustainability, Markets and Policies", p.48.

159 NZPA, 3 September 2004, "Fonterra looks at using milk waste as 'biofuel' for cars".

NEW ZEALAND CASE STUDY

BIOPOLYMER NETWORK

In anticipation of a strong future for biopolymers, a "virtual institute" called the Biopolymer Network has been formed and recently funded. Forest Research, Crop & Food Research and Canesis Network Limited have combined their natural polymer expertise, drawn from their history with wood, arable crops and wool, and linked up with chemistry and engineering expertise at the University of Auckland.

The network aims to develop technologies to deliver new higher value and knowledge-intensive products from renewable natural products. The technologies will initially build on existing polymers such as cellulose, proteins and starches, all of which are grown in abundance in New Zealand. These will be modified and transformed into a wide range of products that could include adhesives, fuel, lubricants, plastics, surfactants, packaging and construction materials. Natural fibres are low cost compared to petroleum products, and can exhibit good specific mechanical and physical properties.

Tunable degrees of flexibility or rigidity, strength, density or moisture resistance are achievable. Combining wood or wood fibres with polymers can improve the variability and stability while retaining the biodegradability. There is particular scope for environmentally friendly, biodegradable materials, for which natural fibres are ideal.

In some cases, the biopolymers will be based on by-products. An example of this is the tannins in bark. Traditionally used for tanning leather, tannin is now being developed for a host of new applications including high-performance adhesives and resins. Forest Research has developed formulations of resin that are resistant to chemicals, do not conduct electricity and do not soften with heat. These properties will enable them to replace high-performance synthetics, while being produced from a renewable resource.

The current scope for the network does not include pharmaceutical, nutraceutical or food targets, or the development of new species or cultivars.

The Biopolymer Network is funded by the Foundation for Research, Science and Technology, with additional investment from all the founding partners.

to ethanol. The company claims that this process enables a tenfold improvement in the economics of using biomass residues. It is currently in the process of looking for commercial partners to take this process to biorefinery scale.[160]

As bioethanol brings a renewable energy source to the petrol or gasoline market, biodiesel is the renewable energy emerging in the diesel market. Biodiesel is typically produced from fats and vegetable oils like oilseed rape and soybean oil. Glycerine is a by-product of production and is used in many industrial applications. Establishing new uses for glycerine is seen as a key requirement driving future economics.

Biodiesel is receiving considerable interest in both the EU (particularly Germany) and the US. It can readily be used in diesel engines and produces far lower emissions. In the United States alone the consumption of biodiesel grew from 15 million gallons in 2002 to 25 million gallons in 2003. Buses and trucks use the majority of biodiesel produced in the US.[161] Europe, however, is leading the charge with a 30% biodiesel blend available in France, and in Germany and Austria pure biodiesel is already on the market.[162]

Biodiesel production is also getting backing from some big players in the automotive industry. In Europe, DaimlerChrysler recently took steps to seed consumer interest in biodiesel by unveiling a new product line which is designed to use a biodiesel blend. The company has also joined with competitor Volkswagen and fuel developer Chloren Industries to produce SunDiesel, a biodiesel blend. The first batch of SunDiesel was produced in 2003 and can be used in any diesel engine without modification.[163]

Like other industrial biotechnologies, the uptake of biofuels into the marketplace has interdependencies with the development of other infrastructures and technologies: in this instance, the fuel distribution infrastructure and internal combustion engine technologies. The most commonly cited forecast sees biofuels in the near and medium term (2005–20) infiltrating global markets as blends with traditional fuel sources, followed by a more radical infrastructure redevelopment and the introduction of fuel sources like biohydrogen fuel cells post-2020.[164]

Bioenergy – Hydrogen Production

Although fossil fuels will continue dominating energy generation and energy products to 2025 and beyond, there is an increasing realisation that energy must eventually be produced from renewable resources. Hydrogen generation from biomass may become an important component of the so-called "hydrogen economy".

Currently at R&D stage, and forecast to start emerging onto the marketplace at the end of this report's timeline, is the production of hydrogen from biomass. If this forecast eventuates then hydrogen production will feed into the developing fuel cell market for the transport sector, and ultimately to develop an energy economy based on non-pollutant, renewable hydrogen. These technological developments are predicted from 2020 onwards.[165]

Several different technological approaches are under investigation for the production of biohydrogen. One examines hydrogen production by the anaerobic fermentation of carbohydrates using direct photosynthesis and cycling between sulphur and non-sulphur fermentation conditions. Another, showing promise, involves a three-step bioreactor process – carbohydrate production via photosynthesis using a green alga, followed by conversion of the carbohydrate to lactic acid by bacterial fermentation, and finally the production of hydrogen from lactic acid by purple bacteria. The most challenging route is direct photosynthetic conversion to hydrogen using cyanobacteria. All of these processes are dependent on techniques like metabolic engineering.[166]

Storage of hydrogen is seen as the pre-eminent technical barrier for large-scale commercial use. It is presently being pursued using metal/alloy systems, and carbon nanotubes are also looking like a promising storage technology.

Biological sources and processes for production of energy are predicted to play an increasing role over future years as hydrocarbon sources decline in use. In the short term, biomass for energy is likely to be used in distributed energy systems.

160 Genencor International, Press Release 29 April 2003, "Genencor exceeds research goal in effort to convert biomass to ethanol".

161 *Wired News*, 23 September 2004, "Automakers give biodiesel a boost".

162 Belgian Academy Council of Applied Science (2004), op cit., p.29.

163 Ibid.

164 Institute for Innovation Research (University of Manchester) (2004), "Prospecting Bioscience for the Future of Non-Food Uses of Crops", pp.43-44.

165 Institute for Prospective Studies (2003), "Potential for Hydrogen as a Fuel for Transport in the Long Term (2020–2030)", p.26.

166 Smith, Hamilton O. et al. (2003), "Biological Solutions to Renewable Energy", *The Bridge*, Summer.

ENVIRONMENTAL BIOTECHNOLOGY

At its core, environmental biotechnology is concerned with making industrial processes work more efficiently and create less pollution, as well as using biotechnology as an environmental management tool to more accurately gauge and manage the health of ecosystems.

There are clear synergies between industrial and environmental biotechnology:

- industrial biotechnology has the potential to create more environmentally friendly industries via the development of renewable biodegradable materials; and
- like the applications of industrial biotechnology products, many of the applications of environmental biotechnology are closely linked with understanding microbial systems and enzymes.

There are three main areas of application for environmental biotechnology: bioremediation, environmental monitoring and biological control.

Bioremediation

Bioremediation is a technology that can be used to reduce, eliminate or contain hazardous wastes. The waste is either transformed or degraded by micro-organisms or enzymes. Bioremediation occurs in the contaminated site (in situ) or the waste is removed from the site and treated in a bioreactor (ex situ). Bioremediation is by no means a "new technology"; both the composting of agricultural material and sewerage treatment of household wastes are based on the use of micro-organisms to catalyse chemical transformation. It is only the term "bioremediation" which is a modern construct (it first appeared in a peer-reviewed journal in 1987) – the use of compost piles by humans dates back to 6000BC.

Advances in our understanding of the biology and functioning of micro-organisms are making bioremediation technologies far more precise. That is because efficient bioremediation is dependent on the presence of appropriate micro-organisms in the correct amounts and combinations and in the right environmental conditions.

Bioremediation technologies are used in industrial and urban waste management and control. Such processes are mostly based on natural bacterial consortia, where the focus is on remediating waste streams that enter the natural environment. Increasingly, focus is shifting to exploiting biological waste streams and, through bioconversion processes, converting them into valuable products. In such instances selected, and often GM,

NEW ZEALAND CASE STUDY

BIOREMEDIATION

A New Zealand and American collaboration, called BioRemedi, is using the enzymes produced by fungi or bacteria to break down organopollutants such as PCPs and dioxin. This helps clean up contaminated soils left behind by industries such as mills, mines and factories that used contaminating chemicals.

BioRemedi identifies the contaminants and then finds an organism that can degrade them. A suitable organism is often already naturally present in the soil, but at a concentration too low to have any significant effect. Only organisms already present in the country in question are used.

Naturally occurring white rot fungi or other groups of fungi are used. These organisms excrete enzymes to digest the lignin in the wood on which they grow. The structures of the organopollutants are similar to lignin, so the enzymes break them down also.

After carrying out laboratory and pilot scale trials to test the efficacy of the decontamination, the organisms are grown on a large scale on a bulking agent such as wood chips. Contaminated soil is then mixed in to form a "biopile". The biopile is monitored for moisture and temperature to maintain optimum conditions for the organism to produce the enzymes to break down the contaminant.

The process then takes between one and six months, and involves monitoring the contaminant's degradation as well as any by-products from the contaminant that may form during the process.

Independent laboratories use analytical techniques to assess the remaining levels of organopollutant contamination. In some cases other contaminants such as boron may remain.

BioRemedi is a joint collaboration between the University of Waikato and Earthfax Development Corporation, a specialist engineering and research and development company based in Utah in the United States. The research was funded in part by Carter Holt Harvey.

NEW ZEALAND CASE STUDY

ENVIRONMENTAL MANAGEMENT

Genomic techniques are helping Landcare Research conserve New Zealand's threatened and endangered species.

A key focus is to document genetic diversity within species in order to identify those at risk of extinction due to genetic factors. This research aims to identify groups that are threatened due to genetic processes, determine the relevant genetic diversity needed to prevent species loss and incorporate this information into recovery planning and ecosystem restoration projects.

For example, the use of DNA sequence information has revealed vital clues to the dispersal patterns of endangered skinks and how to best manage their habitat. The grand skink lives in small groups on rocky outcrops that are separated by either native tussock grass or pasture. Genetic data showed that skinks in pasture disperse less and were less genetically varied. They are therefore less abundant and more extinction-prone than populations in tussock. This knowledge will help land managers minimise impacts on skinks without necessarily excluding agriculture.

Genetic approaches to measuring dispersal are potentially faster and less expensive than traditional methods, which usually involve ongoing observation.

DNA sequencing has also revealed groups of freshwater fish, shore birds, dolphins and reptiles that are genetically unique and therefore need special protection.

Advances in forensic DNA methods are being used to help manage pest animals, particularly to obtain accurate information about pest numbers. This is particularly important when assessing how many survive control operations. Traditional estimates are based on the number of pest animals caught in traps. Researchers can now use genetic "fingerprints" to identify individual stoats from hair samples, and possums from droppings. These methods have provided the first ever direct estimate of stoat population density in New Zealand, and have shown that traditional methods of assessing possum density can vastly underestimate possums left in an area after control.

Forensic techniques can also be used to identify predators (for example, saliva swabbed from kiwi carcasses can reveal the bird's killer), and the origin of timber suspected to have been poached from protected areas can be identified.

Functional genomics holds promise for the future. International databases provide increasing information on functional properties of genes. Applying this knowledge to our native species will assist in identifying genes involved in maintaining population viability, such as those associated with disease resistance and reproductive performance. Ultimately this will help assess which species are most likely to become extinct, and therefore set priorities for conservation efforts.

micro-organisms are used. These industrial applications lead to closed-loop industrial processing where the waste stream of one process is the feedstock for another.

Due to consumer attitudes there has been a marked reluctance to exploit the technological breakthroughs made in industrial biotechnology via the genetic modification of microbes. This is particularly true of in situ remediation methods.

Bioremediation is used to remediate soils contaminated with both metals (eg arsenic and mercury) and organic compounds (eg PCPs and PCBs). Higher plants (phytoremediation) can also be used to decontaminate soils and also to colonise toxic wastelands. GM plants are targeted to bring deserts (drought-resistant plants) and salinated lands (salt-resistant plants) back to fertility. Currently, though, there is strong opposition to such use from some environmental groups and governments, and the lack of "proof of concept" trials means that the feasibility of such applications is uncertain.

In the future we will most likely see a continued incremental growth in the adoption of bioremediation technologies. This will be driven by advances in our understanding of microbial life and the discovery of ever more efficient and robust microbes and enzymes to undertake this work via methods like bioprospecting (detailed earlier in this chapter).

Environmental Monitoring

There is a growing interest in using biosensor technologies to develop techniques for rapid, accurate monitoring of environments. There are applications in this area for biosecurity, public health and environmental management.

Genetic techniques have been used for many years now to identify and classify species, and to assess genetic diversity and relationships within and between populations. Such applications are expected to continue, with the development of new genetic markers and DNA amplification and sequencing technologies making the techniques much more easily applied. In addition, new techniques for culturing and isolating large genomic fragments from currently unculturable microbes are likely to make accessible a much greater proportion of the biological world for further study. As noted in Chapter 9 (Science Discovery Scan), application of array technologies could be applied to micro-organisms to find suitable conditions for culturing them. Large-scale sequencing of genomes from environmental samples is already under way, and refined techniques for copying large pieces of DNA from very small samples are also being used on bacteria, opening up research into large numbers of unknown microbes.

Perhaps the most likely early uptake of genetic diagnostics will be by border control and health agencies for biosecurity purposes to help identify pest species. Closely related species, or even subspecies, can have quite different health or environmental impacts, so improved means of identifying suspected pest species can enable more efficient and effective management of pests.

A greater understanding of insect sensory systems, particularly studies of their sense of smell using electrophysiological techniques, holds promise for development of remote sensing and control applications for certain insect species (such as orchard moth pests). Other developments for sensing and characterising volatile substances from organisms and inanimate materials are also moving into "proof of concept" stages for remote detection of pests and disease agents. The United States Government is investing significant funding into technologies to detect both toxic chemicals and pathogens, but there is uncertainty over how reliable existing methods are when applied outside of the lab.[167] Such applications, if reliable, would greatly facilitate detection and control of pests before and after they arrive in a country.

For environmental monitoring purposes, genetic data will need to be closely linked with ecological and taxonomic skills and understanding so that the significance of the results can be reliably interpreted. Research is already under way to investigate whether genetic diversity (and changes in such diversity) in some complex communities (such as a lake bottom) can be used as a quicker and more reliable method of inferring the health of the community. Successful application of such genetic monitoring could significantly improve the scale and sensitivity of environmental monitoring methods.

However, a key uncertainty associated with this application is the extent to which the results are or can be taken up by management agencies (such as health, conservation and agricultural agencies). With increasing data, making sense of it from a scientific and management perspective will be a significant bottleneck. In addition, limited funds and priority setting in such agencies may mean that such biotechnology applications are not able to be fully utilised.

Biological Control Agents

Biotechnology is now playing a major role in controlling or eliminating noxious animals such as flies, mice, possums, rabbits and foxes. Sterile insect technique (SIT) has been successfully used for many years for controlling or even eradicating certain species of pest flies (such as screw worm and Mediterranean fruit fly). This technique involves the mass rearing of males of the target species, irradiating them to make them sterile and then releasing them in huge numbers (millions of flies per day or week) to overwhelm the wild male population and mate with females. This technique only works for a limited number of species, and the mass rearing, irradiation and distribution methods can be lengthy and very expensive.

Research is already under way to develop immunocontraceptives that can be introduced into wild mammalian populations (via baits, bacteria, viruses or nematodes) and render males or females of the target species sterile. A similar approach is being considered for the control of possums in New Zealand. Thought is also being given to using genetic sterilising techniques on insects such as malaria-carrying mosquitoes,[168] which have so far not been able to be controlled using SIT, as well as the malarial parasites themselves. In New Zealand, genetic modification of sheep blowflies as a method of control is also being considered by researchers.

167 Brown, Kathryn (2004), "Up in the Air", *Science*, v305, 27 August, pp.1228-1229.

168 Ito, J. et al. (2002), "Transgenic anopheline mosquitoes impaired in transmission of a malaria parasite" *Nature* v.417, pp.452-455.

Genetic modification of bacteria and fungi to control plant diseases is also a topic of scientific enquiry. Use of GM technologies in these applications may be seen to bring significant environmental benefit, given the damage done by these types of pest to human health, natural ecosystems and agriculture, and the growing public antipathy towards use of poison baits and sprays. However, current public attitudes towards genetic modification make development and application of GM technologies for pest control very uncertain, even with obvious perceived benefits of reduced pesticide use and more effective pest control. There will also be scientific uncertainty over the success of such techniques because, to be effective, high levels of sterility or other control will need to be achieved, and there is the potential for immunity or evolution to quickly circumvent the contraceptive or other method of genetic control.

PUBLIC OPINION ON INDUSTRIAL AND ENVIRONMENTAL BIOTECHNOLOGIES

So far, there has been relatively limited public awareness or discussion about the use of biotechnology for industrial and environmental applications. This may reflect the fact that most current applications in commercial use are contained and in very early-stage development, and many also use micro-organisms, which may raise fewer ethical concerns than genetic modification of plants or animals.

It is, however, significant to note that many of the potential applications discussed earlier in this chapter will require extensive environmental release of genetically modified or otherwise manipulated organisms. One example would be to use bioengineered plants to produce biofuels. If the current trajectory of technological development continues, it is reasonable to foresee the same sort of safety, ethical and environmental issues that followed the release of GM crops to be mirrored in industrial and environmental applications. A key uncertainty that arises is whether public discussions will be fostered ahead of developments, and hence be able to shape the course of development in this area.

PART 2: CHAPTER OVERVIEW: INDUSTRY AND ENVIRONMENT

The following tables summarise the key trends and drivers that we have identified in this chapter.

Overarching Drivers of Growth	
ECONOMIC DRIVERS	■ Productivity enhancement ■ Fossil fuel replacement ■ Petrochemical giants' investment push ■ Energy security ■ Primary sector development
ENVIRONMENTAL DRIVERS	■ Sustainable industrial development ■ Affluent consumers prepared to pay premium for renewable products ■ Kyoto Protocol ratification
GOVERNMENTAL DRIVERS	Government intervention and investment driving uptake of renewable energy sources and products: ■ European Commission directive on the use of biofuels; and ■ US Dept of Energy investment in biofuel and bioenergy research and infrastructure development.
SCIENCE AND TECHNOLOGY DRIVERS	Three important science and technology drivers identified in this scan are: ■ improving tools for data collection; ■ improving methods for data analysis; and ■ convergence of science disciplines.

Technology Trends

BIOMASS

Most biomass used for industrial product development is currently derived from agricultural sources (maize, canola and so on). The advent of enzymatic pre-treatment technologies will increasingly make forestry and biomass waste products suitable (and cost-effective) for the purpose of extracting high-value sugars and cellulose to act as product feedstocks.

GENETIC MODIFICATION OF CROPS AND TREES

Forecasted trends in the development of GM agricultural crops and trees suggest that the starch, oil and lignin content of plants and trees is going to be enhanced, thereby increasing the yield of industrially valuable plant components.

SUPER-ENZYMES

Emerging enzyme-engineering techniques like "directed evolution" are starting to produce "super-enzymes" which are capable of far greater productivity, longevity and robustness to environmental extremes.

METABOLICALLY ENGINEERED MICRO-ORGANISMS

By genetically modifying micro-organisms researchers are increasingly able to knock out biochemical pathways that are irrelevant to the manufacture of the product at hand. Some products have now been reduced to a one-step synthesis.

BIOPROSPECTING

Micro-organisms to be adapted for industrial purposes are increasingly being sourced from inhospitable environments like geothermal vents. The organisms that live in these harsh environments are known as extremophiles, and they produce far more robust enzymes than other living organisms. They are increasingly being studied and adapted for industrial use.

BIOSENSORS AND DNA DIAGNOSTICS FOR ENVIRONMENTAL MANAGEMENT

There is growing interest in developing techniques for rapid and accurate monitoring of environments using smart sensor technologies. There are applications in this area for biosecurity, public health and environmental management.

Paradigm Shifts

Move towards using renewable products and materials – replacing petrochemical products

Closed loop manufacturing processes

Uncertainties

SYSTEMIC READINESS

The widespread future development of renewable products and energy sources is largely dependent on the favourable alignment of a number of systemic elements: for example, the price (availability, quality, quantity) of renewable as compared to petrochemical feedstocks; infrastructure development and the degree of government intervention into that development; and technology diffusion and uptake by the smaller players in the chemicals industry.

CONSUMER RESISTANCE TO GM CROPS

Attitudes of consumers are hardening to GM crop production in many parts of the world. Much of the forecasted development of biomass-derived commodity products (biofuels and bioenergy) is predicted of future development in GM crop technologies.

Key Emerging Applications

Biomass

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
Enzymatic pre-treatment of lignocellulosic feedstocks with cellulase and hemicellulase	Currently on the market		Expense – currently too expensive to be cost-effective
GM trees with modified lignin composition	2011–15		Environmental concerns
GM crops with enhanced starch and oil content	2007–15		Environmental concerns

Bioprocessing Technologies

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
Biorefineries	Prototypes emerging 2002 → – forecast to be wider spread by 2010		Systemic readiness

Emerging Industrial Bioproducts

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
Bioplastics	2010 = 10% of the global market. 2020–25 = 20% of the global market.		Systemic readiness
Petrol bioethanol blends	2005–10 → incremental growth (rapid)		
Biodiesel	2005–10 → incremental growth (rapid)		
Methane production from biomass waste and landfill	2014–20 →		Systemic readiness
Hydrogen fuel cells	2020 →	Hydrogen storage technologies	Systemic readiness

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FUTUREWATCH

FUTUREWATCH

8 SECURITY AND DEFENCE

This chapter outlines trends and likely future developments (up to 2025) in security and defence applications for biotechnology. Security and defence issues have been thrown into high relief globally over the past few years following on from the September 11, 2001 attacks on the United States and subsequent attacks on places like Bali and Saudi Arabia. As part of this heightened concern, attention has been given to the threat of biological attacks. In this chapter we take a broad interpretation of security and defence, investigating emerging biotechnologies underpinning biodefence efforts, military applications and border control, as well as looking at DNA forensics and crime-fighting applications.

The chapter is split into two parts. **Part 1** is a detailed analysis of trends in emergent defence and security biotechnologies to 2025. It is divided into the following sections: countering bioterrorism (including biological detection agents and health applications); advanced biological warfare agents; border control; forensic applications; and military applications. **Part 2**, in the form of a table, provides an overview of the trends, grouped into drivers of growth, technology trends, uncertainties and key emerging applications to 2025.

PART 1: EMERGING SECURITY AND DEFENCE APPLICATIONS TO 2025

COUNTERING BIOTERRORISM

In the wake of events like the September 11, 2001 attacks on the US and the subsequent letters containing weaponised anthrax which turned up via the US postal service, many nations have reviewed and updated their strategies to counter bioterrorism. These updated "biodefence" strategies and suggested surveillance requirements are strongly underpinned by the development of several biotechnology-based countermeasures.

Biodefence can be most simply defined as the procedures involved in taking defensive measures against attacks using biological agents. Biodefensive action can be taken against the threat of bioterrorism and threats on human health or (as we will discuss later in this chapter) against accidental or deliberate introduction of biological threats into indigeonous ecosystems or primary production systems. In this section we will concentrate on the threat of bioterrorism and the types of responses that are emerging to counter it.

Unsurprisingly, it is the US that has implemented the most comprehensive biodefence strategy to date.

The UK Royal Society aptly observes that investment in this type of area is invariably related to the level of risk, or at least "the perceived level of risk". The US response after the attacks of September 11, 2001 reflects the impact that the attacks have had on US society and politics.[169]

By necessity, parts of this chapter are heavily influenced by developments in the US. This is in great part due to the fact that the US is leading the charge with investment and R&D into biodefence and military applications to counter terrorism. The US federal civilian biodefence budget from 2001 onwards provides a useful indicator to observe how dramatically spending has increased in this area.

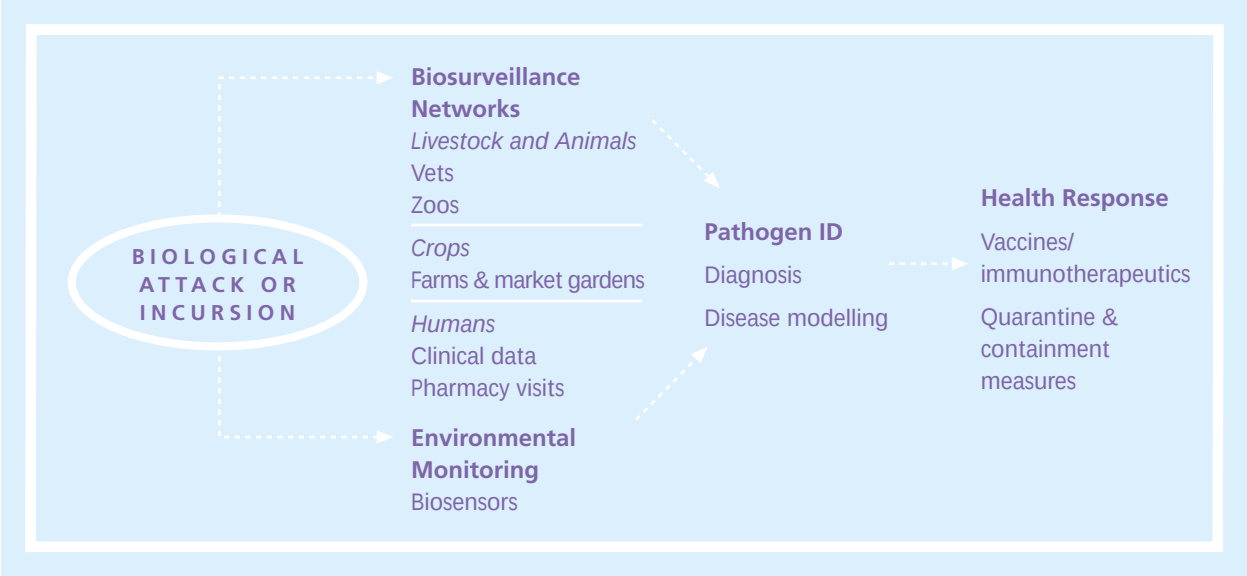
US Govt Civilian Biodefense Funding, FY2001–FY2005 (in US$ millions)

	FY2001	FY2002	FY2003	FY2004	FY2005	TOTAL
Dept of Health and Human Services	271.0	2940.0	3986.0	3500.0	4005.0	14,702.0
Dept of Homeland Security (created 2003)	n/a	n/a	412.0	1622.0	2938.0	4972.0
Dept of Defense	123.0	509.0	107.0	207.0	195.0	1141.0
Dept of Agriculture	0.0	0.0	204.0	78.0	381.0	663.0
Environmental Protection Agency	20.0	184.72	132.9	118.7	91.6	547.92
National Science Foundation	0.0	9.0	31.3	32.0	32.0	104.3
Dept of State	0.0	0.0	0.0	1.2	0.0	1.2
Total Civilian Biodefense Budget	414.0	3642.72	4873.2	5558.9	7642.6	22,131.42

(adapted from: Schuler, Ari (2004), "Billions for Biodefense: Federal Agency Biodefense Funding, FY2001–FY2005"), Biosecurity and Bioterrorism: Biodefense Strategy, Practice and Science, v2, n2, 2004, p.86)

169 The Royal Society (2004), "Making the UK safer" p.12.

Taking a systemic approach, a generic model for a biodefence surveillance and response system looks like this:



You can see from the above figure that a number of the countermeasure steps in this process will potentially be informed by biotechnological applications. The following section discusses emergent applications (most informed by sectors that we have already investigated in this report) that will potentially underpin countermeasures to a biological attack.

Biotechnologies underpinning biodefence systems fall under the following response categories:

- early warning through biological detection technologies; and
- advanced vaccines, diagnostics and therapeutics.[170]

Biological Detection Agents

Biological sensors, or biosensors, are "devices that probe the environment for specific molecules or entities through chemical, biochemical, or biological assays".[171] Their targets can be airborne, in liquids or in solid materials. Biosensor components may have microscale features (and emerging applications have nanoscale features), but may not necessarily be microscale themselves. A small sensor can, however, perform all the functions normally carried out at the lab bench; hence, they are often referred to as a "lab-on-a-chip".

Research into devices to identify potentially deadly pathogens has been undertaken by researchers for some time. Despite this, currently deployed biosensing network technologies are generally not adequate for quickly identifying a biological threat. For example, the network of biosensors the US Department of Homeland Security uses in its BioWatch Program[172] are little more sophisticated than a vacuum cleaner. The sensors suck in air and deposit samples onto special filters. The samples are then collected and taken to a lab for testing. The network currently costs around $2 million per city, per year – mostly for the labour involved in maintaining the system.[173]

Technologies like protein detection kits can identify whether biological material is present in a suspicious sample, but the material can only be identified by being sent to a laboratory for testing. Likewise, immunoassay kits, which provide simple rapid tests for specific agents like anthrax, are not renowned for their accuracy. This means any positive results need to be double-checked in the lab.[174]

170 Potomac Institute for Policy Studies (2003), "Technologically-Based Biodefense", p.4.

171 National Academy Press (2003), "Opportunities in Biotechnology for Future Army Applications" p.16.

172 The BioWatch initiative has deployed a network of biosensors to analyse the air in more than 30 US cities for biological threats.

173 *Business Week Online*, 25 May 2004, "A Sharper Nose for Danger".

174 The Royal Society (2004), op cit., p.17.

We are, however, on the brink of change. In the wake of September 11 there has been a considerable amount of expenditure and research effort put into developing biosensing applications that will have the requisite sensitivity, accuracy, portability and cost-effectiveness. In late 2004, for example, the US Department of Homeland Security is scheduled to upgrade its biodetection network with a new breed of biosensors that not only collect samples but also conduct tests on location before sending the results to the lab wirelessly.[175]

The emerging generation of biosensors are smaller, reusable and capable of testing for a wider range of biological agents. Emerging applications have cell-based systems as recognition elements, and nanoparticle and lab-on-a-chip technologies functioning as processing technologies. Cell-based biosensors offer unique potential for agent detection coupled with the ability to relate the data the machine collects to human physiology, toxicity and pathology. Lab-on-a-chip technologies are enabling portable handheld technologies, which are at the micro- or nanoscale, to run parallel or simultaneous pathogen recognition systems.[176]

An example of an emerging biosensing device with biodefence applicability is the Cellular Analysis and Notification of Antigen Risks and Yields (CANARY). The CANARY project was started in 1997 by researchers at MIT's Lincoln Laboratories. It involves the use of B-lymphocytes, a type of white blood cell that our bodies use against bacterial and viral pathogens. These cells have been genetically engineered with a jellyfish luminescence gene to glow in the presence of specific contaminants. It is a much faster, sensitive and more specific device than anything before it.[177]

From a process innovation perspective, scientists at the Naval Research Laboratory in Washington DC have developed a shoebox-sized biodetector which could eventually screen simultaneously for 12 times as many pathogens as today's devices. Microarray technology, using laser light, illuminates the samples. The technology then interprets the fluorescent patterns generated by the sample, enabling any specific pathogens or toxic proteins to be identified. In addition, bacterial samples are not destroyed in the process, leaving them available for further testing to determine, for example, whether they are resistant to antibiotics.[178]

As military and security biosensor development continues, and their purchase and operating costs decline, their use will inevitably expand into other sectors. Food safety, medical diagnostics, pharmaceutical manufacture and environmental monitoring are particular areas that will benefit from the ability to screen for pathogens and toxins.

Health Applications

Both the health and research sectors play key roles in responding to biological threats, via public health surveillance methods and networks and biomedical research capability and infrastructure.

Basic and applied biomedical research into preventing, diagnosing and treating immune-mediated and infectious diseases will underpin responses to bioterrorism. A number of different pathogenic microbes (established, emergent or re-emergent) have been identified as key threats to civilian populations. Those selected for special attention share the following common characteristics:

- high morbidity and mortality;
- potential for person-to-person transmission and low infective doses and high infectivity by aerosol;
- ability to contaminate food and water supplies; and
- lack of specific diagnostic tests or effective vaccines or therapeutic agents.[179]

On the "Category A" list are anthrax, smallpox, plague, botulism, tularaemia and viral haemorrhagic fevers like Ebola. The lion's share of the biodefence research effort is currently going into understanding the underlying biology and genomics of these pathogens, and developing vaccines and/or immunotherapeutic treatments for them. US citizens in some areas of the country have been resistant to the construction of biocontainment labs housing dangerous pathogens

175 *Business Week Online*, 25 May 2004, "A Sharper Nose for Danger".

176 The Royal Society (2004), op cit p.19.

177 Rider, T.H. et al. (2003), "A B Cell-Based Sensor for Rapid Identification of Pathogens", *Science*, v301 pp.213-215.

178 Armstrong, Robert et al. (2004), "Looking for Trouble: A Policy-Maker's Guide to Biosensing", Centre for Technology and National Security Policy – National Defense University p.20.

179 National Institutes of Allergy and Infective Diseases (2002), "NIAID Strategic Plan for Biodefense Research" p.3.

near to towns. Some have even sued in an attempt to block construction.[180] This may prove a barrier to undertaking research in some areas.

The US president signed Operation BioShield into law in July 2004. BioShield aims to ensure that resources will be available in the US to pay for "next-generation" medical countermeasures. It provides incentives for biotech companies to develop treatments against agents of attack, such as anthrax and smallpox, with the government investing $5.6 billion over ten years, largely to procure improved vaccines or drugs. This pool of money is by no means limited to US-based companies. In addition to allocating money, the legislation also allows waivers in emergencies to allow companies to bypass the FDA's lengthy clinical trial processes.[181]

BioShield has, according to some commentators, received only a lukewarm response from the companies. It was designed to lower the bar for biotechnology companies working in these areas but, for example, it does not offer complete liability protection should a drug have adverse effects on patients or fail to protect them from a virulent pathogen – which could lead to lawsuits in a litigious country like the US.[182]

Pharmaceutical companies invest 10–20 times less in vaccine development than they do in therapeutics. Among the reasons for this is a lower return on investment for the companies. Therapeutics for diseases like cancer or heart disease which affect large populations, need to be taken continually over time, are considerably more lucrative to pharmaceutical and biotechnology companies than vaccines – which are administered only once or a few times.

Vaccines

Vaccines have shown themselves to be the most cost-effective way to protect populations against viral and bacterial pathogens, and prevention is much cheaper than treatment. However, in considering a biological attack, it is not possible or indeed advisable to inoculate every potential victim against all the possible pathogens of interest to terrorists. For starters, vaccination usually needs to be undertaken weeks or months before an attack in order to build up immunity (smallpox is an exception). There is a physical limit to the number of vaccinations an individual can withstand before an adverse reaction would occur, particularly considering the number of pathogens which could pose a threat (estimates of known threats range between 19 and 50).[183]

On top of this the time scale for developing a bioweapon on an industrial scale is 3–5 years, while it takes 12–15 years to develop a vaccine.[184] Of the 13 infective Category A agents only two currently have available vaccines. But despite the inherent difficulties, in the US at least, a considerable amount of funding is available for and already allocated to biotechnology companies to develop vaccines (in the first instance for Category A pathogens).

The Battelle Memorial Institute convened a panel (US science, technology and defence experts) in 2003 to forecast the top ten national security and defence innovations by 2012.[185] Among their list is the emergence of a "universal inoculation" by 2012. The panel envisages people being protected from potential pathogen threats by mass inoculations. An analysis of this report by futures consultancy Social Technologies questions this assertion, pointing out that the authors may underestimate the wariness of the public to such mass inoculations. Even in the US military some personnel have opposed anthrax inoculations, and speculation continues about the role of experimental inoculations in the emergence of the "Gulf War Syndrome".[186]

The push to produce and stockpile vaccines and therapeutics as biodefence countermeasures means that the capability of the production and manufacturing infrastructure needs to be appropriately scaled to match demand. Therefore, gearing up the bioprocessing infrastructure is seen as an important facet of developing an effective countermeasure system. The push to drive growth in this area will also have spin-offs for the development of the industrial biotechnology sector, not least due to the limited shelf life and storage difficulties inherent in biologically active vaccines.

180 Kaiser, Jocelyn (2004), "Citizens sue to block Montana biodefense lab", *Science*, v.305, p.1088.

181 http://rpc.senate.gov/_files/L67BioShieldDM.pdf

182 *The Washington Post*, 26 July 2004, "BioShield Too Little for Drug Industry".

183 Potomac Institute for Policy Studies (2003), ibid. p.9.

184 House of Commons Science and Technology Committee (2002–2003), "The Scientific Response to Terrorism – Eighth report of Session 2002-03, Vol 1" p.24.

185 Battelle Science and Technology International (2003), "Top Ten Innovations on Security and Defense by 2012" http://www.battelle.org/forecasts/defense.stm

186 Social Technologies (2003), "Top Ten National Security and Defense Innovations by 2012", *Technology Foresight*, Fall 2003/TF-2003-3.

The current fragility of some of these production systems was aptly demonstrated by the recent meltdown of biotechnology company Chiron's UK-based influenza vaccine production capability. As a consequence of the manufacturer being shut down for not meeting current Good Manufacturing Practice (cGMP) standards, the US has suffered an almost 50% shortfall of ordered doses for the winter of 2004–05.[187]

Viral Therapeutics

Antiviral drugs initially emerged in the 1980s. Unlike vaccines, which are taken before exposure to a disease, antiviral drugs are taken after exposure. The development of antiviral drugs has been driven in recent times by diseases like HIV and AIDS, as a means of staving off their worst ravages. Likewise, the emergence of novel viral zoonotic diseases like SARS and Avian flu is providing a further catalyst for honing antiviral development capability. For the most part, antiviral biological drugs are developed in conjunction with unravelling the biological structure and functioning of the virus in question – to provide drug targets for developing a biopharmaceutical response.

The research effort that is being put into understanding the biology of, in the first instance, Category A pathogens will invariably lead to the emergence of new antiviral therapeutics.

Another approach is looking for methods to counter the chemistry and mechanics of viral infections and to look for "commonalities" in the way that different agents wreak havoc. The aim is to develop ways of countering pathogen attack in a generic way. Both the Defense Advanced Research Projects Agency (DARPA) and the Department of Energy have research programmes in place in the field of microbiology, and work actively in these areas of research.[188]

Antibiotics

The production of new antibiotics has suffered from a similar lack of enthusiasm from pharmaceutical companies to vaccine development. This is again due to the fact that there is less commercial incentive to develop medication that "cures", instead concentrating on more lucrative areas like chronic illness and mood disorders that require ongoing dosage. In parallel to this, antimicrobial resistance to antibiotics is threatening to turn the clock back to a time when bacterial infections were considered life-threatening. This may have major implications for biodefence.

The current iteration of Project BioShield does nothing to protect the US public against the demise of antibiotics. A second iteration, Project BioShield II, is planned to be introduced into Congress in late 2004. BioShield II would seek to offer incentives to develop new antibiotics. That said, there are a number of scientific bottlenecks to be cleared before this occurs. For example, nearly all existing classes of antibiotics are over half a century old.[189] To solve the problem of resistance, new classes will need to be developed. Biotechnology may provide some of the answers. As discussed in Chapter 6 (Primary Production), emergent work in developing treatments from antimicrobial peptides and bacteriophages may offer elements of solutions to address these problems.

ADVANCED BIOLOGICAL WARFARE AGENTS

The current development of biodefence countermeasures so far described is in response to "known risks" – in other words, naturally occurring pathogens that are physiologically suitable for "weaponisation".

Models for future biological warfare agents could be derived from the growing banks of genomic and proteomic (protein) data of viruses and bacteria. Using this ever increasing information base, advanced biological warfare agents of the future will potentially be designed to target specific biological systems – for example, the cardiovascular or neurological systems.[190] Examples of potential modifications to known risks could include "antibiotic resistance, increased aerosol stability, or heightened pathogenesis. Importantly, genetic modifications may alter … sequences used for detection and diagnostics, necessitating that multiple points of reference be incorporated into these systems and highlighting the need for security".[191]

Moving beyond merely genetically re-engineering existing micro-organisms, recent developments in the field of synthetic biology suggest that we are on the cusp of being able to rapidly synthesise genomes, altering the genetic code and

187 *New York Times*, 13 October 2004, "US begins investigation of vaccine supplier".

188 National Science Foundation (2002), "Converging Technologies for Improving Human Performance – Nanotechnology, Biotechnology, Information Technology and Cognitive Science", p.347.

189 Leeb, Martin (2004), "A shot in the arm", *Nature*, v431, 21 October, pp.892-893.

190 Ibid, p.162.

191 Petro, James B. et al. (2003), "Biotechnology: Impact on Biological Warfare and Biodefense", *Biosecurity and Bioterrorism: Biodefense Strategy, Practice and Science*, vol.1, no.3 p.162.

designing completely novel life forms. The synthesis of a bacteriophage virus from scratch in three weeks by Craig Venter's team at the Institute for Biological Energy Alternatives in late 2003[192] aptly demonstrated that the capability to do this type of assembly is already with us. That said, however, the technique has not been perfected. The virus produced had mutations, so the current technique will have to be coupled with others designed to correct those errors.[193]

The expanding toolbox of ways to re-engineer microbes and even construct new ones has opened up significant possibilities for biomedical discovery and environmental engineering. However, it also carries potential dangers: abuse of these techniques is a distinct possibility. The ease with which a US virologist constructed a live polio virus from scratch in 2002 is a case in point. The segments of DNA used in the synthesis of the virus were sourced via mail order and the viral genomic map was sourced from the internet.[194]

Beyond microbe engineering, research into converging areas of technology – like the use of nanoparticles in storage and delivery of pharmaceuticals and vaccines – could yield findings with potential application for the improved weaponisation and storage of biological warfare agents. As it stands, current microencapsulation technology is focused on developing processes to encapsulate biologically active organisms and proteins within a nanoparticle coating substance.[195]

It is worthwhile noting that, despite what could be, a biological attack does not need to be novel or technologically sophisticated to have the desired effect of destabilising a population or economy. As we have witnessed in the past, a single case of foot and mouth disease or a letter containing anthrax can have considerable follow-on effects.

BORDER CONTROL

The threat of terrorism has also resulted in heightened vigilance in managing the flow of people between nations at airports, ports and overland border crossings. This can be coupled with the environmental and economic concerns of a biological incursion into primary industries or native flora and fauna à la foot and mouth or, as we have experienced in New Zealand, the deliberate introduction of the RCD virus into Otago to control rabbits.

"DUAL USE" TECHNOLOGIES

"Dual use" technologies is the term given to any technological development that can be used for productive purposes as well as to cause harm. In the case of the biological sciences, the same techniques used to gain insight into the fundamental processes of life for application into sectors like healthcare could also be subverted by a "hostile" government or individuals to create a new generation of biological weapons.

Governments and regulators are currently grappling with the implications of dual use technologies in the biosciences and are endeavouring to achieve a balanced approach that both mitigates risks and ensures scientific freedom.

Further reading: National Academies of Science (2004), "Biotechnology Research in an Age of Terrorism"

192 http://www.venterinstitute.org/

193 *The New Scientist*, 14 November 2003, "Virus synthesised in a fortnight".

194 Ball, Philip (2004), "Starting from Scratch", *Nature*, v431, p.624.

195 Petro, James B. et al. (2003), p.164.

NEW ZEALAND CASE STUDY

SNIFFERTECH AND VOICE100

Two electronic devices are being used in unison to develop a highly sensitive sensor system capable of picking up border threats. Sniffertech has been developed by AgResearch and Voice100 by Syft Technologies Limited.

Sniffertech is a device the size of a mobile phone that can be placed inside sea freight containers. It repeatedly samples the air (for example, during container transit) to preconcentrate low levels of volatile organic compounds that are emitted by everything from wood and snakes to explosives and humans. The sampling is automated and controlled so no sampling occurs after the container has been opened, when compounds entering from outside air would confuse results.

Improved sea freight container screening has been recognised as a high priority by the Biosecurity Council due to the large numbers of containers that arrive every year. Preconcentration makes the device powerful enough to detect a matchbox-sized piece of wood inside a freight container, for example. Wood packaging is a perennial concern because it can harbour insects and diseases that potentially threaten New Zealand's biosecurity.

At the wharf, the Sniffertech device is loaded onto a docking station developed by Syft Technologies. The docking station provides an interface to the Voice100 machine, which releases, identifies and quantifies Sniffertech's stored volatiles within seconds by matching them with its library of "fingerprint" compounds. It can identify compounds at concentrations as low as parts per trillion.

The Voice100 system relies on selected ion flow tube mass spectrometry (SIFT-MS). Mass spectrometry is the traditional way to detect and identify volatile organic compounds, but other mass spectrometry analyses are much slower than SIFT because samples need extensive preparation and require laboratory processing by trained experts. Syft's technology is uniquely fast, user-friendly and relatively portable.

The technologies have other applications. SIFT-MS has been successfully commercialised by Syft Technologies and is being used or trialled in industrial process control, non-invasive medical diagnostics, biosecurity, national security and environmental monitoring. Sniffertech is still under development but a range of applications are possible: it can sample any stable air mass, so packages at customs could be non-invasively checked for explosives, drugs or food, for example.

Both devices are unique in the world and are attracting considerable international interest. The development of Sniffertech was funded by the Ministry of Agriculture and Fisheries, the Foundation for Research, Science and Technology, and AgResearch itself. Syft Technologies is a joint venture between Breathe Technology and the University of Canterbury.

Biometrics

Biometrics is the science of using a person's "unique physiological characteristics to verify their identity".[196] Biometric technologies include iris scanning techniques, fingerprint and palm-print scanning, voice and face recognition technologies and even personal odour. Different systems currently have different levels of accuracy. For example, while iris recognition can achieve rates just tenths of a percentage short of perfection, rates for facial recognition software fail in more than 10% of cases.[197]

The ability to capture and store information about a person's unique characteristics offers the prospect of ensuring that travellers are who they claim to be. Since September 11, a number of countries have put in place various biometric

196 *CBS News Online*, 23 January 2004, "Biometrics: The future of security".

197 Harvey, Fiona (2004), "Does the new security work?", *Financial Times*, 22 January.

identification systems at their borders. This has been driven in part by the US flagging, in October 2003, that countries with a visa waiver arrangement with the US must start issuing passports that include biometric information. The plans being prepared as a result of the US's actions signal the largest trial of biometric technologies ever undertaken. While it has been used in business and for security reasons for a number of years, the technology has never been used on millions of people.

An important privacy issue exists with biometrics around how the information will be stored and subsequently used or shared.

Biosecurity

The meaning of "biosecurity" in New Zealand differs substantially from the emerging use of the term internationally. To New Zealanders our biosecurity has traditionally referred to keeping our borders and environment free of pests and diseases which would have a detrimental effect on either our primary industries or indigenous biodiversity. With the global context being as it now is, the term "biosecurity" is increasingly being used to describe responses to biowarfare threats. Globally, the threat of bioterror is being considered in increasingly broad terms to encompass the threat of biological attack, like foot and mouth or BSE on primary industries, and the subsequent economic implications of an event of this nature.

For this section of the report we will be discussing biosecurity as per the New Zealand definition.

Growing international trade, greater mobility and climate change are making borders increasingly vulnerable to new pests and diseases. The New Zealand Biosecurity Strategy[198] usefully breaks down the different activities involved in biosecurity as follows:

- **prevention and exclusion:** preventing the entry and establishment of pests and unwanted organisms;
- **surveillance and response:** early detection, identification and assessment of pests and unwanted organisms; and
- **pest management:** effective management (including eradication, containment and control, of established pests and unwanted organisms.[199]

Biotechnology applications assist in maintaining biosecurity via biosensing systems, rapid multi-species DNA-based identification methods and the biological control of pest species. Once again, advances in the diagnostic technologies that we have discussed at some length both in Chapter 5 (Health and Wellbeing) and earlier in this chapter (DNA and protein chips, biosensing devices) will play a significant part in protecting our borders.

Once a pest species has made it into a country, biotechnology is also offering up some solutions to the pest management aspect of biosecurity. For example, as we have discussed in Chapter 7 (Industry and Environment), New Zealand's Landcare Research has a possum immunocontraceptive under development.[200]

FIGHTING CRIME – FORENSIC APPLICATIONS

The use of DNA as a crime-fighting tool has become rapidly entrenched since the emergence of DNA fingerprinting in the mid-1980s. Beyond this, DNA forensics has also become a popular cultural phenomenon or genre, with any number of novels, television shows and films being produced on this topic. This section investigates emerging applications in this field.

Human Identity Testing

Over the past 20 years the analysis of DNA by DNA fingerprinting and profiling technologies has revolutionised human identity testing and forensic science. DNA analysis has become an indispensable and routine part of modern forensic casework. Sensitive PCR-based techniques are used to analyse all manner of biological material. Now only minute traces of DNA are required to link a suspect to a crime scene. Human identity testing is used in more instances than simply matching a suspect with evidence – for example, it is used in paternity testing and identifying victims of mass disasters.

198 The New Zealand Biosecurity Strategy (2003), http://www.maf.govt.nz/biosecurity/bio-strategy/index.htm

199 Ibid., p.10.

200 http://www.landcareresearch.co.nz/research/biosecurity/biocontrolpossums/

NEW ZEALAND CASE STUDY

FORENSICS: Y CHROMOSOME ANALYSIS

ESR uses DNA to help identify criminals and missing persons. Its standard method is to analyse autosomal nuclear DNA in biological material from a corpse, crime scene or investigation using short tandem repeats. The DNA profiles are then tested for a link to samples from known missing persons, crime suspects or the National DNA Databank. The latter is a collation of DNA profiles from convicted offenders and volunteers. Such DNA links are often used to convict criminals.

Several new techniques are being developed to further refine the information that can be gleaned from DNA. ESR has recently begun Y chromosome analysis, which involves analysing short tandem repeats on the Y chromosome only. Because the Y chromosome is unique to males it can be used to isolate small amounts of male DNA – as little as one or two sperm – from a sample that contains much larger amounts of female DNA. It can also reveal whether a sample is from more than one male.

The Y chromosome is passed almost unchanged from father to son, which means it is useful for tracking family relationships. But there are distinctly different types of "Y". Polynesians, for example, have fewer and different forms of Y chromosome than do European males. Analysing the "Y" can therefore predict the ethnicity of its owner. However, because it is possible for a male with a European Y chromosome to look very Polynesian or vice versa, the prediction can never be absolute.

Therefore, like most forensic techniques, Y chromosome analysis has had to be validated with samples from the New Zealand population. Systems developed abroad are not suitable because of the characteristic genes in New Zealand's ethnic mix.

ESR is also poised to introduce a novel real-time PCR method it has developed to measure the amount of DNA in a sample. When very small amounts are present they can be amplified using "low copy number analysis" which increases sensitivity by using a greater number of cycles. Knowing the original amount is desirable in order to avoid the problem of overamplification during this process, and to minimise the common problem of contamination. Existing methods of quantifying DNA are not sensitive enough for this purpose.

Y-SNP analysis is also being investigated as a method for enhanced analysis of the Y chromosome and as a stepping stone to more extensive use of SNPs in the future. This technique is ideal for specialised casework involving degraded DNA, because SNP systems can be specifically designed for the relevant population and also for short DNA fragments. It is amenable to automation and is likely to be an important forensic tool in the future.

The technological breakthrough that has fuelled this revolution occurred in 1985 when a new type of genetic marker, VNTRs (variable number of tandem repeats) showed much greater reliable variability among people than previous systems. VNTRs were soon superseded by STRs (short tandem repeats) in which a short gene sequence is repeated in tandem 100 or more times. STRs have a number of advantages over VNTRs, not least the ease with which their DNA can be amplified by PCR. STRs became the standard genetic marker for forensics work throughout the 1990s, with most countries using between 10 and 13 core STR loci as their forensic testing standard.[201]

Other supplementary genetic marker systems have also been established. Y chromosome and mitochondrial DNA (mtDNA) are establishing themselves as useful systems in different circumstances. Y chromosome testing, as the name suggests, is confined to the male population only. The testing has proven useful in scenarios where scientists are testing samples where there is DNA from more than one contributor – for example, in cases of sexual assault. mtDNA is inherited

201 National Institute of Justice (2000), "The Future of Forensic DNA testing – Predictions of the Research and Development Working Group", pp.1-2.

down the maternal line and can be recovered from samples such as hair shafts and degraded human remains when bodies are too badly decomposed for other means of identification.

"Trace DNA" and the ability to test for it has been the real boundary pusher over the past couple of years. Where once DNA required a sample the size of a 20 cent coin, now a profile can be obtained from a nose-print on a window or a licked envelope seal. The UK Forensic Science Service has developed a technique called DNA Low Copy Number (DNA LCN) which enables scientists to produce DNA profiles from very few cells, even if they are too small to be visible to the naked eye. The main application of this technique has been where it is believed that an offender may have transferred DNA through touch. Another example of DNA LCN yielding results is in "cold cases", crimes from the past where the technology of the time failed to yield a usable DNA profile due to sample size.[202]

Two emerging developments are likely to have the biggest impact on forensic science in the next 5–10 years. Firstly, the tools to test and analyse DNA data in the field will enable instant processing of trace DNA in real time. DNA chips will enable the generation of a DNA profile and these profiles will be able to be instantly processed via a secure modem and dialling into a secure databank. Secondly, genetic marker systems will continue to be developed to supplement the core STR system, the most important of these being single nucleotide polymorphisms (SNPs) (pronounced "snips").

Differences in individual bases are by far the most common type of genetic variation. These genetic differences are known as SNPs. About 10 million SNPs are estimated to occur commonly in the human genome. SNPs can be used to detect changes in single DNA bases. The practical advantage of SNP typing is that DNA template size can be considerably smaller than the number of DNA base pairs needed in STR profiling. This makes SNPs of particular interest in identifying severely degraded material. Technical development of a SNP marker system was driven by the efforts in identifying the victims of September 11.[203]

The development of DNA population databases was pioneered in 1995 by the UK Forensic Science Service's establishment of the first DNA databank to store the DNA samples collected by law enforcement agents. The UK Forensic Science Unit now has the largest DNA database in the world, with DNA samples from more than three million people. New Zealand was the second country in the world to set up a DNA databank and we can now boast (perhaps by dint of population) the world's highest databank hit rate – 52% of samples produce positive identifications.[204]

Not all DNA samples are matched to individuals on national DNA databanks. In these instances, DNA samples often allow a scientist to gain an approximation of the ethnicity of a victim or perpetrator and, at present, a very limited number of phenotypic characteristics. Genetic variation is found within different human populations, and individuals from any ethnic population are on average slightly different from individuals from other ethnic populations. This allows sets of markers to be developed to predict population of origin. However, these markers – although at times accurate – are by no means foolproof. The only relevant phenotypic trait that has undergone any serious investigation is pigmentation and only a minority of genes appear to influence "normal" variation. The best studied is the melacortin 1 receptor (MC1R). The MC1R gene has more than 30 known variants, one of which is strongly associated with red hair and freckles. The test detects about 84% of redheads.[205]

It is anticipated that future breakthroughs will enable the identification of genes that encode further human physical characteristics such as eye and skin colour and facial structure. However, the complexity of these traits, coupled with the variability introduced by environmental and nutritional differences, means that even if the genes influencing phenotypic characteristics were identified there is no guarantee that simple "deterministic" tests will emerge.[206] That said, the needs of law enforcement agencies and forensic scientists may act as a driver to try to uncover links between appearance and genetics.

202 The Forensic Science Service (2004), "Factsheet – DNA Low Copy Number" http://www.forensic.gov.uk/forensic_t/inside/news/docs/DNA_LCN.doc

203 Jobling, Mark & Gill, Peter (2004), "Encoded Evidence: DNA in Forensic Analysis", *Nature Genetics*, v5, p.748.

204 *Weekend Herald (Canvas)*, 25-26 September 2004, "Crimebusters", p.14.

205 The Forensic Science Service (2004), "Factsheet – Commonplace Characteristics" http://www.forensic.gov.uk/forensic_t/inside/news/docs/Commonplace.doc

206 Jobling, Mark & Gill, Peter (2004), ibid., pp.747-748.

Non-human Genomes in Forensics

Beyond human DNA analysis each individual carries a unique assortment of viruses, bacteria and other parasites. In future, micro-organisms may also play an important role in identifying humans and supplementing or supplanting chromosomal DNA. Likewise, a crime scene is made up of material from micro-organisms, plants and animals, and future DNA forensics are likely to exploit genetic information from them as we learn more about their structural genomics.

OPERATIONAL MILITARY APPLICATIONS

Traditionally, military research has sat at the cutting edge of technological development. Many technologies have been adapted from military applications to everyday civilian uses. One example that we have already touched upon in this chapter is the fact that sensing technology development (driven by biodefence needs and funding) will have logical spin-offs for both the environmental management and food safety monitoring industries.

From an operational perspective, a growing proportion of military research involves developing biotechnology applications. These are targeted at developing applications that will enhance the physical performance of soldiers, as well as improving battlefield efficiency and risk detection capabilities.

As has been the case with much of this chapter, this section will rely heavily on applications that are emerging from the US and the advanced research arms of organisations like the Pentagon and the US Department of Defense. There is no country in the world that can rival the US on military R&D spending, and, as such, some of the most future-focused application development emerges from there. One of the key players in this area is the Defense Advanced Research Projects Agency (DARPA). DARPA pursues research for the Department of Defense "where risk and pay-off are both very high and where success may provide dramatic advances for traditional military roles and missions".[207]

A selection of DARPA's work areas aptly demonstrates some of the most "out there" and boundary-pushing of all biotechnology research.

Optimising Soldier Performance – "Metabolic Dominance" and "Persistence in Combat"

Warfare and the battlefield environment put severe physical stresses and strains, both physical and psychological, on humans. The drive to improve the physiological performance of army personnel to perform at peak fitness and health provides a powerful driving force for military research.

DARPA's "Metabolic Dominance" research programme is working on the fundamental question "Are there temporary biochemical approaches we can use to squeeze the last ounce of performance out of soldiers when they're already worked to exhaustion?"[208]

Strategies for achieving this include:

- cocktails of nutraceuticals;
- lowering soldiers' core body temperature by studying the thermodynamics of the human body to keep them from overheating; and
- at a molecular level, boosting the performance of mitochondria (the body's energy suppliers).[209]

Many commentators question whether this is achievable.

The "Persistence in Combat" research programme investigates "self-healthcare" and the ability of soldiers to heal themselves when wounded while on military missions. For example, DARPA has co-funded the development of a "pain vaccine" developed by a company called Rinat Neuroscience, a spin-off of Genentech based in Palo Alto, California. The drug, which is known as RI 624, uses an antibody to keep in check a neuropeptide that helps transmit pain sensations from the tissues to the nerves. The drug entered into human trials in June 2004.[210]

207 http://www.darpa.mil/

208 *Wired News*, 17 February 2004, "DARPA offers no food for thought".

209 Ibid.

210 http://www.rinatneuro.com/

Biomimetics

DARPA has an established biomimetics research programme. Biomimetics is the development of synthetic systems based on information from biological systems. Examples from nature suggest that soldier load-carrying capacity and efficiency can be increased. For example, an ant can lift 50 times its own weight and pull 30 times its own weight. If this phenomenon were understood, perhaps mimicking the ant might lead to solutions that would help soldiers carry heavier loads. DARPA has investigated the behaviour of insects and other animals on contract to the US Defense Department in areas like the development of load-bearing exoskeletons.[211]

Beyond the futuristic work of agencies like DARPA there is prospective military applicability in biotechnology areas like:

- biosensors and biosensing networks to identify chemical, biological and environmental threats;
- biomaterials to provide camouflage and concealment; and
- renewable, portable energy sources in remote locations using technologies like biological photovoltaics and cell-based energy systems.[212]

Defence R&D, particularly in the US, is a significant driver and priority investment area. Beyond the concept of dual use technologies as we have discussed it in this chapter, many applications developed for military and defence purposes have clear spin-offs as civilian technologies. An obvious example on the near-term horizon is the use of sensing technologies developed for biodefence purposes being used for environmental management purposes.

PART 2: CHAPTER OVERVIEW: SECURITY AND DEFENCE

The following tables summarise the key trends and drivers that we have identified in this chapter.

Overarching Drivers of Growth
NATIONAL SECURITY The post-September 11 global environment, with its emphasis on the threats of terrorism and bioterrorism, is driving government investment and developments (particularly in the US) in security and defence biotechnologies.

Technology Trends
DUAL USE TECHNOLOGIES The pervasive technology trend that can be linked to security and defence applications is the potential for biotechnologies to be misused with malicious intent.
DIAGNOSTICS IN REAL TIME The need to detect biological threats (both to human health and the environment) is driving development of portable lab-on-a-chip, or biosensing, devices which are able to process samples in real time. While defence and security needs are driving research in this area, there may well be civilian spin-off uses in medical diagnostics, food safety systems or environmental monitoring applications.

Uncertainties
By their very nature, bioterrorism attacks are incidents of high uncertainty (both in time of occurrence and nature of the threat), and countermeasure and response preparations are linked to perceptions of risk – real or imagined.

211 National Academies of Science (2003), "Opportunities in Biotechnology for Future Army Applications" pp.14-15.

212 Ibid., p.2.

Key Emerging Applications

APPLICATION	FORECASTED MARKET ENTRY AND/OR GROWTH TRAJECTORY	TECHNICAL BOTTLENECKS	UNCERTAINTIES
Cell-based biosensors operating in real time	2005–10		
Emergence of vaccines and antiviral treatments for identified high-risk pathogens like anthrax, smallpox and Ebola	2005–10 →		
Biometric (eg iris scanning) technologies at borders	2005 → Widespread implementation		
Forensic DNA testing and result processing in real time	2005–10		

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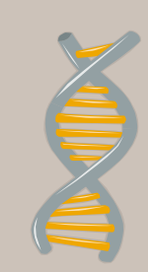
SCIENCE DISCOVERY SCAN



FUTUREWATCH

FUTUREWATCH

9 SCIENCE DISCOVERY SCAN

This chapter highlights some key scientific areas and future trends that are likely to have significant relevance to biotechnology. Providing first a brief historical context, the chapter outlines some general trends in biological science and then a selection of "areas to watch". This chapter will be of interest to those wanting to better understand the science of biotechnology and where it may be heading over the next 20 years.

Most of the biological sciences now have at least some connection to biotechnology. Similarly, scientific developments in fields not normally considered to be biotechnology will have important influences on biotechnology applications. Consequently, many areas of science need to be followed to determine trends in biotechnology.

This chapter highlights some key scientific areas and future trends that are likely to have significant relevance to biotechnology. It largely draws on the Biotechnology Science Scan undertaken by the Royal Society of New Zealand (RSNZ) as part of the process of developing this report. The original RSNZ scan is available on the Royal Society website (http://www.rsnz.org). Although this science scan is not a comprehensive assessment of science trends, it does illustrate some important areas of emerging research.

HISTORICAL CONTEXT

One of the biggest areas of biological research in the first half of last century was focused on understanding the biological basis of inheritance. Once DNA was demonstrated to be the heritable material, much research effort was then put into dissecting this process and understanding how genetic information is converted into proteins, and how cells and organisms function at the molecular level. This is still the case, and will continue to be a part of the discovery process over the coming decades. More recently, private companies have recognised the near-term value of biotechnology and have had a big influence on the way some science is conducted and funded. This has been most dramatically illustrated by the rapid completion of sequencing the human genome.

The Human Genome and similar projects have led to a flood of genetic data, the merging of traditional scientific disciplines and the development of new techniques and technologies. These have accelerated discovery, but have also created problems regarding how to effectively analyse and interpret all this information.

Drivers

A key driver in science is the people undertaking the research. They are motivated by a variety of factors, but most share a desire to understand how nature works by asking challenging questions and/or devising ways of answering those questions. The types of questions and how people go about answering them shape the discovery process.

Molecular biology has traditionally adopted a reductionist approach – identifying the fundamental biological components of cells and then building on that. This has provided great insights, but has also highlighted large gaps in our understanding, such as not knowing how many of the components interact with each other. Recent technological developments have enabled researchers to rapidly collect large amounts of information on genes, proteins, cellular dynamics, etc. Considerable thought and effort is now being directed to how best to integrate all this data and make sense of it.

FUTURE FOCUS

It appears to be generally accepted that current trends in underpinning technology will further accelerate data collection. Analytical tools in biotechnology will increasingly be applied in parallel and portable devices. What can be assayed slowly in specialist laboratories today will be analysable in bulk, in situ and in real time (eg DNA fingerprints, disease status of individuals, epigenetic status, the microflora of diverse environments (animal digestive systems, soils and water sources), various pollutants and contaminants). High-throughput screening, robotics, automated microscopy, other imaging technologies and large data-handling devices will be widely employed. Such tools are essential for unlocking how cells and bodies function. The RSNZ science scan calls this the "array paradigm".

This technological approach is already being adopted in other areas, such as in the development of DNA or gene chips and in protein crystallography, resulting in quicker and cheaper ways of doing repetitive science. It is likely that this approach will be adopted in other fields, such as combining existing drugs to find better treatments for specific disorders,[213] and finding suitable growth conditions for currently unculturable bacteria.

213 Mooney, C. (2004), Cocktail hour "*Wired*", July, pp.111-113.

The real advances in understanding will be made by those most proficient in deriving knowledge from the relevant data. Science is synergistic, and developments in other areas of science will continue to play an important role in biotechnology and vice versa. Good examples of these synergies are how mathematics and statistics have been applied to analysing genetic information, and how genetic markers and gene sequencing have been applied to studying disease outbreaks.

Future Challenges

This future focus will inevitably raise challenges. A consequence of the "array paradigm" is the potential for an "array problem". Biotechnology can be very quick to adopt new tools and technologies to generate or analyse information, but the limits and assumptions of these techniques need to be recognised by the users, otherwise they can impede real advances in research and development. An illustration of this is that some early results using arrays have not been repeatable, or it is very difficult to interpret the information. A consortium of researchers is now developing standard procedures to provide guidelines for the proper design of experiments and interpretation of data from arrays. Similar cautions will need to be applied to other technological developments.

The RSNZ science scan notes that there are lots of puzzles in biology, but some significant ones that have been around for a while may be explained (at least in part) in the next 15 years. They include:

- How does the human brain work? This is regarded as the major challenge for biologists in this century. Given the human brain's complexity this question will not be solved in the next 15 years, but major advances in our understanding are anticipated.
- How does an adult mammal, containing billions of cells, develop from a fertilised egg? Despite being an area of study for over 100 years there are still large gaps in understanding this developmental process.
- How does ageing occur? Considerable molecular and environmental research is currently under way in this area.
- How do gene and protein networks work? Genes and proteins don't work in isolation, but we have limited understanding of how they really work in concert.
- How does the immune system remember infections? The body can "remember" a past infection and quickly mount another defence against it many years later. Many medical conditions involve the immune system, so an understanding of it is central to medical research and improved patient care.

These puzzles have not been solved, primarily because we lack the tools (both technical and conceptual) to precisely define the problem (which may mean, for example, needing to ask questions about individual molecules). Such tools are under development today. The knowledge derived from today's and tomorrow's scientific research will lead to major advances in the next 15 years.

MAJOR BIOLOGICAL SCIENCE TRENDS

Three major trends identified in the RSNZ scan, and echoed in other chapters of this report, are:

- the increasing complexity of science in general, and biological sciences in particular;
- the convergence of, or increased interaction between, different scientific disciplines; and
- the growing need for identification and diagnostic methods across the range of biotechnology applications.

Complexity

The biology of living organisms is complex. It is expected that molecular and cellular biology will follow a course analogous to the development of botany and zoology in the last century. These fields moved from simply identifying and describing species to ecological approaches involving studying the interactions of species with each other and their environment. Such an approach will no doubt show us how complicated cellular function really is. As with ecology, the molecular systems approach will answer some questions but lead to many more. It should also, though, help develop or improve upon biotechnology applications.

A key to 21st century biology will be understanding molecular regulation at a network level. As the wealth of genome sequence data has illustrated, large amounts of data are being rapidly produced. Making sense of all this type of information is the major issue, though. Genes are rarely the end products of biotechnology 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. Systems biology (discussed later in this chapter) will be an effective complement (rather than a replacement) to reductionist research.

The unit of biological research is changing as well; increasingly, studies will focus on a tissue or an organism as well as the components of a cell. The US National Science Foundation has launched a large funding initiative called "biocomplexity" that encourages more interdisciplinary research to tackle investigations into biological complexity; this is likely to influence some biotechnology-related research.

Addressing cellular complexity will involve developing new tools and techniques for dissecting genetic and cellular pathways, as well as new ways for synthesising that information.

Convergence of Scientific Disciplines

Convergence of, and linkage between, scientific disciplines will continue. This is not novel but a normal part of how science proceeds. Molecular biology, for example, resulted from a merging of physics and biology. Other new hybrid research areas such as bioinformatics and nanotechnologies are also resulting in creative ferments. Many national and international science funding schemes now promote collaboration across disciplines to encourage development of new applications for science. (Many of the other chapters in this report contain examples of these sorts of convergence.)

It is important to note, though, that convergence and collaboration don't necessarily mean that only large, well-funded interdisciplinary groups will make the breakthroughs. As the history of science shows, small research groups that design and conduct elegant experiments, or develop new theories, can be as influential as large teams.

Diagnostics

There is a growing demand for tools and techniques for identifying specific genetic linkages for traits, cell types, cell or tissue activity, pathogens, species diversity, etc. There is also a similar demand for methods to diagnose and monitor physiological or environmental conditions, or to detect specific substances. Such diagnostics are already widely used, but there is a large gap between supply and demand. This is likely to be accentuated by the accumulation of genome data (with diagnostics providing a way to filter the information) and the increasing awareness of the importance that genetic variation may have in some disease states and some pest populations. However, there are complexities that need to be factored in. For example, the development of accurate diagnostic markers (particularly in the area of medical applications) may require integration of molecular data with knowledge of environmental factors that modulate the genetic effect (such as diet or other lifestyle factors).

Development of genetic markers for microbial (and other) species is also becoming an important aspect of environmental monitoring. With increasing human population growth, and changes in the climate and environment, we can expect the spread of existing diseases as well as the emergence of new diseases – including diseases that cross species barriers (recent examples are Ebola, AIDS and SARS). To detect and identify these diseases we will need far better mass-screening diagnostics than we have currently, as well as taxonomic and ecological research that assists in the capture and identification of the diseases and the species that transmit them. Such mass-screening diagnostics are also needed for such agricultural threats as BSE and scrapie.

SOME SCIENTIFIC AREAS TO WATCH

The RSNZ science scan noted a range of science areas that underpin biotechnology or are areas of research that are likely to play prominent roles in biotechnology. This is not a comprehensive survey, but it does highlight some current limitations and how they are being overcome. We summarise some of these areas below. Further information is available in the RSNZ's report.

Cell Biology

A strong theme from the RSNZ science scan was that cell biology will continue to underpin biotechnology. Cell biology is about investigating what molecules do in a cell; how they move within, into and out of cells; how cells move and interact with other cells; how cells perceive and react to messages from their environment; and how cells and their components are formed and destroyed.

We understand some cell structures and biochemical pathways but there are many more that we don't. There is a wealth of information on cell components and some on their organisation;[214] but, despite over 100 years of research, we don't have a detailed understanding of how cells work as a whole, even for "simple" bacteria. Improving our understanding of how cells work is going to be essential for developing new biotechnologies or more refined applications.

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

- understanding the ways in which cells recognise attackers has led 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 what controls the growth and differentiation of stem cells may lead to important therapeutic uses;
- understanding how genes and biochemical pathways are regulated is leading to more advanced genetic modification techniques;
- understanding how cells sense their environment, and how these processes can be used to develop biosensors for a broad range of applications; and
- understanding how molecule-sized scaffolds and motors within cells work together will likely underpin biological applications of nanotechnology in the next half-century.

Research in cellular biology is an economic necessity for a biology-based economy like New Zealand. Primary production industries often treat 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 – perhaps impossible – for agriculture, horticulture, etc to produce the food and other products necessary for the coming century in the face of a possibly increasingly unpredictable environment. Cell biology in all its incarnations opens the "box" so that we can learn to do better with what we find inside.

An often underappreciated aspect of research in this area is the identification of materials and conditions for growing specific cells in culture – being vital, for instance, for stem cell and reproductive research. As illustrated by traditional fermentation, being able to grow cells and control their development in vitro, as well as in vivo, will be necessary precursors to biotechnology advancements. We do not yet have this understanding for many cell types.

The RSNZ illustrated the importance of cell biology by reference to epigenetics and discussions of stem cells and cloning.

Epigenetics

Initially, it was thought that knowing the DNA sequence would explain everything about inheritance. However, it has been realised that there's more to inheritance and genetic information than just the DNA or RNA sequence. Epigenetics (sometimes called "genomic imprinting") is the study of heritable traits and characteristics that are not encoded in the sequences of DNA but by the interaction between DNA and other molecules, or by protein-protein interactions. It is often considered to represent a special form of "Lamarckian inheritance" (otherwise known as the "inheritance of acquired characteristics"). It has fundamental importance in biological development such as the formation of reproductive cells. There are also unusual inheritance mechanisms such as prion phenomena that fall under the definition of epigenetics and there is a belief that some neuronal memory function could be prion-like behaviour.[215]

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.

214 Alberts, B. et al. (2002), *Molecular Biology of the Cell*, fourth edition, Garland Science.

215 Si, K., Lindquist, S. & Kandel, E.R. (2003), "A neuronal isoform of the aplysia CPEB has prion-like properties", Cell, v115(7), pp.879-891.

Potential Applications of Epigenetics

An improved understanding of epigenetic processes will have practical applications. Several human diseases are due to incorrect imprinting, so knowledge of the process may lead to therapies. The therapeutic use of stem cells and efficient production of cloned animals is currently limited, in part, by lack of understanding and/or control of epigenetics. A greater understanding of epigenetics is therefore likely to lead to greater control of the process and/or the development of markers to enable selection of cells that are in the desired epigenetic state.

Systems Biology

Another research field noted by the RSNZ was "systems biology". Systems biology is a new emerging discipline for biotechnology that is expected to grow over the coming decade. As discussed earlier, there is a growing complexity and convergence of science disciplines. We already have a wealth of data, but making sense of it is now the problem and is perceived as a key limitation for developing applications from biological knowledge. In response, there is now a growing movement in areas of molecular science to take a "top-down" systems approach to studying cells and organisms. This is being called "systems biology".

The notion of system-level understanding in biological science has been a theme in existence for some time – ecology and epidemiology utilise this approach – but "systems biology" is a new development for molecular and cellular research. It represents a convergence of existing and new scientific disciplines (for example, genomics, proteomics, metabolomics, mathematics, biological computing and engineering) aimed at integrating all types of biological information (DNA, RNA, proteins, 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 communicate with each other.

A superficial analogy is the healthcare system. To understand how the healthcare system works it is essential to identify and understand what the key components are (such as hospitals, doctors, nurses, patients, boards, government) and how they function and interact with each other.

The shift towards systems biology does not mean that biotechnology science will abandon test tubes and Petri dishes in favour of computer models. Systems biology is not an end in itself but a means of synthesising information and generating hypotheses of how cell processes work. Hypotheses developed through a systems approach will still need experimental testing. Systems biology should result, however, in more mathematically literate biologists and more biologically literate mathematicians working collaboratively (as seen in the field of molecular phylogenetics). Such a collaboration and interaction is essential so that the assumptions and limitations of mathematical models are recognised by the biologists. As a consequence, "biological realties" will (hopefully) be more readily incorporated into mathematical models.

In 2003 Harvard University recognised the importance of a systems approach 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 the Institute for Systems Biology[216] and a joint initiative between Cambridge University and MIT)[217] have started systems biology institutes.

Potential Applications of Systems Biology

Systems biology is anticipated to catalyse fundamental changes in the future of healthcare and other areas of biology, by helping make sense of complex biological information. It is likely to form the basis of predictive, preventive and personalised medicine. Systems biology is likely to facilitate passing through severe bottlenecks in therapeutic discovery and development by helping identify key cellular processes. Left unsolved, the bottlenecks will have serious financial consequences for health authorities and for pharmaceutical and biotechnological industries.

It will also create and drive new opportunities in the agriculture and pastoral sciences by improving our understanding of how cells, organisms and their environment interact. (In such cases it should be noted that a detailed understanding of ecology as well as cell and molecular biology is required.)

216 http://www.systemsbiology.org/

217 http://www.cambridge-mit.org/research

This catalytic effect of systems biology in the pharmaceutical, agricultural and other biotechnological industries is likely to mean it will have significant economic and ethical impacts in New Zealand and elsewhere.

Platform Technologies

Platform technologies are tools or techniques that underpin a broad range of applications. The RSNZ science scan discussed some key tools for assisting the study of gene function and the production of novel products, processes or services. Two important ones are:

- transgenics; and
- chemical genetics.

Transgenics

Transgenics are organisms with artificially altered genes (usually containing genes from other species). They are often also referred to as "genetically engineered" or "genetically modified". 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.

Transgenics are not just a convenient way of speeding up conventional plant and animal breeding. They are also an important component of medical research, where the nature of human diseases is investigated by mimicking the genetic defects in mice and rats. Genetics research for at least 30 years has been greatly assisted by the production of transgenics which became animal or plant "models" for elucidating a specific human genetic function. Transgenics are thus a key enabling technology for biotechnology.

Key components of transgenic technology are:

- the vector that contains the foreign genetic material;
- the delivery method for the vector; and
- control of expression of the foreign genetic material.

Choices made for all of these components depend on the target organism and the nature of the modification; obviously, these choices can also influence the success of the modification. Current genetic modifications are usually not efficient, controlled or precise, and may result in unanticipated disruptions to other genes or the transgenes. Research is refining how to more efficiently, precisely, safely and stably introduce genetic modifications into target cells and cell structures (chloroplasts and mitochondria), and how to introduce gene complexes rather than single genes. It is anticipated that technologies for introducing and controlling the expression of foreign genetic material will soon improve.

The ability to introduce gene complexes would open the way for inserting novel biochemical pathways rather than a single gene trait into organisms. This would dramatically increase the range of achievable applications, since many traits of agronomic or medical interest are due to multiple genes.

The development of "golden rice" (which contains genes from three species to produce vitamin A) is perhaps a very simple example of what may be able to be achieved in the future using transgenic techniques. The use of multi-component vector systems and artificial chromosomes is also being investigated for introducing gene complexes into cells. Small chromosomes containing several genes have already been introduced into mice. In addition to being able to introduce more genetic material, artificial chromosomes would avoid genetic disruptions caused by insertion of transgenes into other genes. However, the stability and inheritance of such chromosomes require further study.

An emerging area of research related to transgenics is called RNA interference (or RNAi). This involves using small pieces of RNA that "knock out" the function or decrease the level of expression of specific genes. RNAi can allow genes to be disrupted more quickly and cheaply than classical gene knockouts, and is amenable to high-throughput applications so can enable the analysis of gene networks.[218]

218 * Couzin, J. (2002), "Small RNAs make big splash", *Science* 298, pp.2296-2297.
* Novina, C.D., Sharp, P.A. (2004), "The RNAi revolution", *Nature* 430, pp.161-164.

RNAi also illustrates a paradigm shift. Just a few years ago RNA was thought to have no involvement in gene regulation, but now RNAi is being extensively used to study gene regulation, and therapeutic or other applications may use this method in the future.

As with other areas of biotechnology research, transgenics are attracting considerable attention and concern from governments and communities, and such attention is likely to be influential in determining future applications. Some of the applications of transgenics are discussed in other chapters.

Chemical Genetics

Chemical genetics involves the production of large numbers of chemicals that may bind to proteins; in doing so they inhibit the protein's function.[219] This is a new discipline that is emerging as a result of the Human Genome Project. The intention of chemical genetics is to produce compounds that bind to only a single protein and to use these to "knock out" a protein (that is, to disrupt its function) and observe the effect. Unlike gene knockouts (which physically and permanently remove or inactivate the gene), chemical genetic knockouts are reversible and the strength of binding is quantifiable. This means that the observable effect can be quickly reversed and more information is obtained about the nature of the interaction. Such reversible effects signal an important advance for studying gene and protein function in whole organisms. This is likely to be especially important in large animals, where gene knockouts are ethically unacceptable and too expensive.

In cells, proteins work in networks. That is to say, one protein can affect the function of a number of others in a variety of ways. This can generate an almost impenetrable complexity that's unlikely to be understood solely by reductionist approaches. Adding to the complexity is the fact that there are many more proteins than genes, and that epigenetic factors (see above) can further influence gene activity. A key attribute of chemical genetics is the ability to perturb "modules" or networks[220] with an observable outcome directly related to a particular protein.

As noted earlier, it is now relatively easy to identify genes but understanding what function(s) they have is still difficult. Chemical genetics 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 Applications of Chemical Genetics

Chemical genetics is a key next step in modern molecular biology. Molecular biology now finds itself stymied by its own success in identification of genes, with methods for determining the functions of these genes lagging far behind. As an example, one New Zealand Crown Research Institute has the most comprehensive database of cow genes in the world, with some 21,000 of around 30,000 total cow genes represented. However, only 7000 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 and so helps link genetic information with functional information. Other such gene sequence or protein databases will be amenable to chemical genetics probes.

Chemical genetics could also be used to probe protein networks. As an example, the RSNZ science scan notes potential application of chemical genetics to solve the cell signalling pathways associated with sheep fertility (such as the Inverdale mutation).

The infrastructure for studying chemical genetics is starting to be put in place. One notable development is that Harvard and MIT have, for the first time in their history, formed a combined institute (the Broad Institute) to study chemical genetics – a US$300 million operation at its outset.

219 Tan, D.S. (2002), "Sweet surrender to chemical genetics", *Nature Biotechnology,* vol 20(6), pp.561-563.

220 Kitano, H. (2002), "Systems biology: a brief overview", *Science*, vol 295(5560), pp.1662-1664, special focus, Science edition March 2002.

CONCLUSIONS

By the 1970s many of the original molecular biologists were declaring the end of the golden age of molecular biology. In their view the major problems had been solved and future scientists would just be filling in the details. This has not proven to be the case. Significant questions about molecular and cellular biology remain to be answered, and the potential for this knowledge to be applied in the areas of human health, primary production, environmental management and industrial processes is growing.

Scientists appreciate that many significant scientific discoveries are often serendipitous. They aren't planned, but they are also not just "dumb luck". Scientific luck favours the prepared mind. There are many examples of chance discoveries that have created new research fields or had a major impact on existing research. Vaccination was developed after Edward Jenner realised that some milkmaids were protected from smallpox by catching cowpox. Alexander Fleming, and others, followed up on a curious result when a plate of bacteria became infested with mould. This led to the discovery of antibiotics. Viagra was initially developed to treat angina. It wasn't so good for that, but some of its side effects proved very interesting.

So we can't predict where science will lead us. There are, however, clear gaps in understanding and other problems that science is seeking to fill or solve. Some of these have been highlighted here or in the RSNZ's science scan. The future directions of biotechnology will rely both on our understanding of biological processes and on the tools we develop to further dissect these processes.

Further developments in thinking and techniques in other scientific areas are likely to be just as influential to biotechnology as developments within what we currently consider to be biotechnology. We shouldn't, but no doubt will, be surprised when such research shows us new ways of seeing the world, and new ways of applying such knowledge.

CHAPTER OVERVIEW: SCIENCE DISCOVERY SCAN

The following tables summarise the trends and drivers that we have identified in this chapter.

Drivers	
THE SCIENTISTS	The types of questions asked and how scientists go about answering them shape the discovery process.
INTEGRATION OF GENETIC AND OTHER DATA	There is a lot of biological information available but making sense of it is now a significant barrier to advancing understanding. Improving data collection and analysis methods will contribute greatly to enhancing our understanding.

Meta-trends	
INCREASING COMPLEXITY OF INFORMATION	The focus is moving from collecting information on single genes to understanding gene and protein networks.
CONVERGENCE OF DISCIPLINES	This is a continuation of an existing trend, but funding providers are encouraging greater interdisciplinary research.
IDENTIFICATION & DIAGNOSTICS	Development of new tools and markers to identify, detect and diagnose a whole range of molecules, cell types, medical conditions and species. Application of mass-screening data collection and diagnostics in many areas (health, agriculture and environment) is likely to be seen over the coming years.

Areas to Watch

CELL BIOLOGY	A more detailed understanding of how cells function, grow and divide is necessary for developing biotechnology applications.
EPIGENETICS	There is a recognition that some key developmental and regulatory processes are influenced by factors other than the DNA sequence. A better understanding of these epigenetic factors will facilitate applications involving disease treatments, stem cell uses, cloning and reproductive biology.
SYSTEMS BIOLOGY	A rapidly growing field that seeks to describe molecular and cellular networks and interactions, and make sense of the wealth of molecular data being collected.
TRANSGENICS	A platform technology where advances in vector constructs, vector delivery and control of gene expression will have a significant influence on types of biotechnology applications.
CHEMICAL GENETICS	An emerging discipline that seeks to improve the rate of determining protein function.

Uncertainties

COMPLEXITY	The more that is discovered, the more we realise that the less we understand. There is an ever increasing amount of molecular and cellular information being collected, and we have yet to develop tools and techniques for making sense of this information.
SERENDIPITY	This plays a major role in science, and it is difficult to know what new discoveries or insights could radically affect how we perceive or use organisms.

ANNEX 1: GLOBAL FUTURES CONTEXT

One way of developing a fuller awareness of the different ways in which biotechnology may unfold is to consider a range of future scenarios. Scenarios can be used to make sense of complex, unformed futures by making explicit a variety of risks and opportunities that would otherwise tend to remain "hidden" or at least unexplored. Scenarios work by bringing together clusters of uncertainty about the future. Once these clusters have been identified it is possible to reason through and debate the separate images or "worlds" of the future.

Scenarios stop us assuming that the future will be a minor variation of today. They are useful for creative planning because they can alert decision makers to alternative outcomes and can direct attention to how different possibilities may emerge. Scenario planning also enables a wide group of people to engage in a broad discussion with shared frames of reference, using several common stories about the future.

The trends, patterns, certainties and uncertainties identified through scanning (or what we call "futurewatch") provide a valuable information base for the development of scenarios. While this current project has not developed scenarios, we did examine pre-existing scenarios as part of the research and in particular to help shape ideas about the context for biotechnology and about how the trends we see now may change with time. The scenarios we used were developed by Navigatus Ltd in 2001/02[221] to inform the business strategy of Forest Research (a New Zealand Crown Research Institute).

The scenarios are titled "Globalisation and Security", "Conflicted World" and "Sustainability Emerges" (outlined below). The scenarios were derived from a review of major global trends in the categories of social, technological, economic, environmental and political values and the interactions between them. While these scenarios were not focused on biotechnology, science and technological change were important features and focuses of interest. For our purposes they were updated and adapted for a biotechnology context.

OUTLINE OF THREE GLOBAL SCENARIOS

"Globalisation and Security"

In this scenario, globalisation is a key driver, constrained and moderated by increasing anxiety, conflict, security measures and strengthened national borders. Geopolitics retains elements of multilateralism, but is increasingly bloc-orientated and bilateral. The environment for science and technology in this scenario is characterised by support for world-class science, strategic partnering and collaboration in blocs, yet reducing information flows. In simple terms, this is a "biotechnology for profit" scenario. This is the scenario that is most likely to be prominent in the future, with events unfolding further along the trends established since 2000.

"Conflicted World"

This scenario extends the "Globalisation and Security" scenario, envisioning further decline and eventual breakdown of international and multilateral trust, agreements and institutions, brought about by more intense conflicts and unilateral responses. Nationalism rises and self-sufficiency substitutes for substantial international trade, leading to severe recession. The environment for science and technology in this scenario is characterised by science for national needs, restricted collaboration and information flows, and technology duplication. This is a "biotechnology for basics" scenario.

"Sustainability Emerges"

This scenario is based on an emergent grass roots social belief that the dominant globalisation/security economic model is not environmentally sustainable in the medium (or even short) term. In this scenario, ecological values dominate, and economic activity is incentivised and regulated with environmental imperatives. Multilateral agreements shift from trade and security to sustainability. The environment for science and technology in this scenario is characterised by world-class science, open collaboration and information flows, technology sharing and world collegiality. This is a "biotechnology for life" scenario.

221 Future Insight Development, Global Scenarios, Forest Research, 2002.

For our purposes, examining these pre-existing scenarios highlighted the way in which trends may be different depending on the global futures context and reinforced the need to maintain an awareness of this context. The table below shows a selection of the biotechnology developments or trends identified throughout the report and an indication of their strength or significance under each of the three scenarios.

Projected Biotechnology Trends to 2025 Within Three Future Scenarios

	GLOBALISATION AND SECURITY (BIOTECHNOLOGY FOR PROFIT)	CONFLICTED WORLD (BIOTECHNOLOGY FOR BASICS)	SUSTAINABILITY EMERGES (BIOTECHNOLOGY FOR LIFE)
Biotechnology application			
Gene-based personalised healthcare	↑↑	↓	↑
Molecular farming	↑	↓	↑ (crops) ↓ (animals)
Human genetic enhancements	↑	↓ (except for security needs)	↓↓
Organics	↑ niche	↓	↑↑ mainstream
Livestock cloning	↑	↓	↓
Biofuels	↑	↑↑ (for non-oil-producing countries)	↑↑
Bioplastics	↑	↓	↑↑
Biotechnology environment trends[222]			
More open styles of governance	↑	↓	↑
Broadening sphere of ethics	↑	↓	↑↑
Investment in biotechnology	↑ (health and primary industries)	↓	↑ (industrial and environmental)

222 Identified in Chapter 4.