

The focus of international and Australian scientific research

INTRODUCTION

4.1 The scientific advances with the birth of Dolly (1996)¹ and the isolation of human embryonic stem cells (1998)² focused immediate international attention on the scientific, medical, intellectual property and industrial opportunities now available. In the few years since, the field has expanded exponentially as demonstrated in the previous two chapters. This chapter summarises the status of the field at the time the report was written and indicates the balance required between basic and applied dimensions of the research. The examples provided below are a small selection illustrating work in progress.

United Kingdom

- 4.2 Cloning research in Britain is likely to increase dramatically since Parliament extended the purposes for which a licence to derive embryonic stem cells and to form embryos for cloning research and therapeutic technologies can be obtained.³
- 4.3 Some examples of work being carried out in the United Kingdom are given below:

1 Wilmut, I, *et al*, *Nature*, Volume 385, 27 February 1997, p.810

2 Thomson, J.A. *et al*, *Science*, Volume 282, 6 November 1998, pp.1145-1147

3 For more detail on the system of regulation in the UK see Chapter 10, from paragraph 10.73

- At the Roslin Institute in Scotland, Geron Bio-Med, a British subsidiary of Geron Inc (USA) was established to exploit research using cloning technology to create replacement tissues and organs for diseases such as Alzheimer's and Parkinson's.⁴
- PPL Therapeutics, has been given a licence to use the Roslin Institute's patented technology to create pharmaceuticals in the milk of animals. PPL announced in February 2001 that it has been able to demonstrate the possibility of producing multipotential stem cells without the need to go through an embryo stage. PPL's initial commercial target for its stem cell research is the production of insulin producing pancreatic islet cells.⁵
- At London's Imperial College School of Medicine researchers have recently shown that liver cells can be derived from human blood cells.⁶
- In other initiatives reported recently, British scientists are planning to inject stem cells into the brains of stroke patients. If this approach is successful, the technique will be used to treat Parkinson's disease and Alzheimer's. It is predicted there will be new therapies and drugs on the market within six years.⁷

United States of America

4.4 Funding and regulation of human embryo and embryonic stem cell research in the USA is discussed in Chapter 10.⁸ There are many privately and publicly funded laboratories working in stem cell biology in the USA. Examples of current work include:

- Dr James Thomson at the University of Wisconsin, the first investigator to isolate human embryonic stem cells, is focusing on the factors that promote ES cell renewal as well as the differentiation of primate ES cells to haematopoietic and neural cells. Human embryonic stem cells developed in Wisconsin have now been distributed to over 30 institutions in the USA and elsewhere.⁹

4 Roslin Institute, Annual Report 1998-99, p.15

5 PPL claims that they reverted fully differentiated bovine skin cells to stem cells first and then transformed these into a distinct population of heart cells. Their next challenge is to repeat the findings using human cells. Press release, 23 February 2001

6 *Nature*, Volume 406, 20 July 2000, p.257

7 House of Commons Research Paper 00/93, (UK) p.48

8 See paragraphs 10.44-10.71

9 Thomson, J.A. *et al.*, 1998, Neural differentiation of rhesus embryonic stem cells, *AMPHIS*, 106: 149-157; Kaufman *et al.* (2000) Transplantation therapies from human embryonic stem cells-circumventing immune rejection, *Regen. Med.* 1: 1-5; Odorico *et al.* (2001) Multilineage differentiation from human embryonic stem cell lines, *Stem Cells* 19: 193-204; Kaufman, D.S. *et*

- Dr Thomas B. Okarma, President and CEO of Geron Corporation, said that Geron uses cloning technology for purposes including regenerative medicine, predictive toxicology and drug discovery.¹⁰
- At the Johns Hopkins School of Medicine in Baltimore, Dr Gearhart has isolated human embryonic germ (EG) cells and demonstrated that they are pluritipotent.¹¹
- David Anderson and his colleagues at the Californian Institute of Technology claim to have identified many environmental triggers that stimulate the nervous system's stem cells to turn into neurons or supporting glial cells. According to a report in *Time* they have also isolated the genes responsible for the transformation.¹²
- At the University of California in San Francisco Dr Roger Pedersen has directed the differentiation of embryonic stem cells into cardiac muscle.¹³ He has announced recently that he will move to Cambridge University in the UK due to restrictions on embryonic stem cell research in the USA.
- Researchers in New Jersey claim they can produce an almost unlimited supply of nerve cells to repair patients' own bone marrow stem cells.¹⁴
- Massachusetts General Hospital reports a new technique for isolating human adult stem cells¹⁵ and has identified a key protein that appears to control the development and proliferation of haemopoietic stem cells.¹⁶
- The Jones Institute of Reproductive Medicine (private sector) in Norfolk, Virginia, announced that it has bought eggs from women volunteers and created human embryos for the sole purpose of harvesting ES cells.¹⁷

4.5 The size of the American science base, both public and private, together with its adaptability and speed allows hundreds of laboratories to work

al. Hematopoietic colony forming cells derived from human embryonic stem cells, *Proc. Natl. Acad. Sci. U.S.A.*, in press

10 The Committee on Energy and Commerce: Hearing on Issues Raised by Human Cloning Research (USA) March 2001, <http://www.house.gov/commerce/hearings/03282001-141/Okarma200.htm>

11 *Time*, 1 May 2000, p.55, <http://www.jhu.edu/~gazette/2001/jan0801/08stem.html>

12 *Time*, 1 May 2000, p.55; Stemple, D. L. and Anderson, D. J., 1992, 'Isolation of a stem cell for neurons and glia from the mammalian neural crest', *Cell* 71, 973-985

13 *Time*, 1 May 2000, p.54

14 *Journal of Neuroscience Research*, 15 August 2000

15 *New Scientist*, 19 August 2000, p.5 and p.16

16 *Science*, Volume 287, 10 March 2000, pp.1804-1808

17 *Nature*, Volume 412, 19 July 2001, p.255

on basic and clinical aspects of cloning and stem cell biology. The leading weekly journal, *Science*, seldom appears without new reports in this field.

Elsewhere

- 4.6 Other laboratories in many countries around the world are active in the field and are contributing significant new knowledge and approaches. For example:
- The Institute for Stem Cell research in Milan focuses its research program on adult stem cell differentiation.¹⁸
 - Hadassa University in Israel and the National University of Singapore have both derived embryonic stem cells from surplus IVF embryos and are building active research programs, including links with the Monash Institute for Reproduction and Development.¹⁹
 - At the Netherlands Institute of Developmental Biology in Utrecht researchers are working on aspects of embryonic stem cell differentiation particularly into cardiomyocytes (heart muscle cells).²⁰
 - In Japan, Amgen Ltd is carrying out research aimed at understanding self renewal and differentiation mechanisms of stem cells including haematopoietic stem cells, neural stem cells and embryonic stem cells. It is also developing methods to regulate functions of stem cells.²¹
 - A group of researchers at the Karolinska Institute in Stockholm, Sweden, including Jonas Frisen, is working with adult stem cells. Research demonstrated that adult mouse brain stem cells injected into early chick and mouse embryos gave rise to cells of various types and contributed to the generation of tissues and organs of all germ layers including heart, liver, intestine and nervous system.²²
- 4.7 However, the culture and maintenance of human embryonic and adult stem cells is still a difficult art, performed well in relatively few laboratories.

18 *House of Commons Research Paper* 00/93, p.24 (UK)

19 Pera, M.F (2001) *Human stem and precursor cells*, Cold Spring Harbor Laboratory Symposium

20 Mr Robert Klupacs, *Transcript*, p.179

21 <http://www.ims.u-tokyo.ac.jp/stem/>

22 *Science*, Volume 288, 2 June 2000, pp.1660-3

CURRENT AUSTRALIAN RESEARCH, ITS INTERNATIONAL STANDING AND FUTURE DIRECTIONS

4.8 Australian science has held a leading international role in assisted reproductive technologies from which the new fields of cloning and stem cell technologies have developed. Many scientists involved in cloning research consider that Australia has a leading role to play in these new technologies and that Australia stands to benefit from the ultimate commercial applications of new therapies arising from this research.²³ According to Associate Professor Pera:

Australia, as a whole, has a longstanding track record in reproductive biology, growth factor and stem cell research. Although the developmental biology community here is small, it is of very high quality and makes very significant contributions on the international scale.²⁴

4.9 Dr Tolstoshev²⁵ submitted:

There is a real chance that Australian organisations could take a leadership position in this field. It is also important to appreciate that the ultimate commercial impact of such new therapies could be very large.²⁶

4.10 Some examples of research in Australia include:

- At the University of Adelaide, Professor Peter Rathjen's group is studying embryonic stem cell differentiation in mouse and human stem cell model systems with a view to defining cell signals.²⁷
- At Monash University, Professor Alan Trounson's group has a comprehensive research program in stem cell biology including human and animal research. The Monash group has established four human embryonic stem cell lines, from cells extracted by colleagues in Singapore and derived in compliance with NIH guidelines.²⁸
- An Australian biotechnology company, BresaGen Ltd, is supporting and financing a program at the University of Adelaide whose main focus is to develop more effective cell-based treatments for Parkinson's

23 Professor Peter Rathjen, *Transcript*, p.65; Professor Alan Trounson, *Submissions*, p.S170. Similar views expressed by Dr Paul Tolstoshev, General Manager, Cell Reprogramming Division, BresaGen, *Submissions* p S822; Professor Peter Rathjen, *Submissions*, p. S767

24 Associate Professor Martin Pera, *Transcript*, p.6

25 Dr Paul Tolstoshev, General Manager, Cell Reprogramming Division, BresaGen Ltd

26 BresaGen Ltd, *Submissions*, pp. S822-823

27 Professor Peter Rathjen, *Transcript*, p.65

28 Professor Alan Trounson, *Transcript*, pp.4, 5

disease and other neurological disorders. Another area of interest is bone marrow replacement in cancer. BresaGen has combined with CytoGenesis Inc (USA), bringing together two researchers in cell therapeutics, Dr Steve Stice of the University of Georgia and Professor Peter Rathjen of the University of Adelaide and Scientific Director of BresaGen's Cell Therapy Program.²⁹

- A Melbourne-based company, Stem Cell Sciences is reported as having inserted human DNA into pig eggs to investigate whether a human nucleus will divide in a foreign cell. Dr Peter Mountford³⁰ is quoted as saying that embryos made this way developed to the 32 cell stage.³¹
- The Peter MacCallum Cancer Institute in Melbourne is focusing research on adult or somatic stem cells aimed at developing clinical applications.³²
- ES Cell International Pte Ltd, a joint venture company registered in Singapore but with management operations based in Melbourne, is funding research in a number of centres around the world. The focus of their research is embryonic stem cells for use in transplantation medicine and for discovery of genes and factors controlling the differentiation of embryonic stem cells.³³
- At the Walter and Eliza Hall Institute of Medical Research in Melbourne scientists have isolated adult neural stem cells from the brains of mice and directed their differentiation into muscle cells.³⁴

Funding Of Stem Cell Research In Australia

- 4.11 Major laboratories in Australia have a mixture of public and private sector support. Sources of funding include the host university, program and project grants from the National Health and Medical Research Council (NHMRC) and Australian Research Council (ARC), private funding from industry, venture capital and medical charities and overseas sources. In addition several laboratories have established close links with commercial companies, based in Australia and abroad.
- 4.12 At the centre of the funding issue is the protection of discovery through patenting strategies. Patented intellectual property gives value to the discovery and can be marketed to national or international companies

29 Press Release, 7 September 2000, BresaGen, *Submissions*, p.822 and *Exhibit 21*

30 Dr Peter Mountford, Chief Executive Officer, Stem Cell Sciences

31 *The Weekend Australian*, 17-18 March 2001, p.26

32 Peter MacCallum Cancer Institute, *Submissions*, p.891

33 Mr Robert Klupacs, *Transcript*, p.169

34 *Nature*, Volume 412, pp.736-739, *Sydney Morning Herald*, 16 August 2001, p.1

through licensing agreements. Although it is likely that much of the commercialisation of cloning and stem cell technologies will be developed abroad, a strong patent position for Australian 'inventors' will ensure the eventual return of some of the proceeds to Australia.

- 4.13 In Australia, as for elsewhere in the world, the pace of research is such that future directions and results are impossible to specify. This pace, and the acquisition of intellectual property attached to new discoveries will depend on the continuing competitiveness of Australian research groups and their participation and collaboration with the global research enterprise.

Timeframe For Results

- 4.14 New avenues for improving the efficiency of cloning procedures, together with new discoveries of the underlying cell regulatory processes, suggest that progress will be rapid. It is difficult to predict time frames to results and clinical application other than in broad terms. Associate Professor Pera submitted that, subject to regulatory approvals:

...the first set of objectives, basic research on human development, is already happening. We are already using the cell lines to identify new genes expressed in early human development. I think within the next one to 10 years we will see the identification of factors active in tissue regeneration and repair. The *in vitro* models for drug discovery and toxicology will come on line perhaps in two to three years time, and I think transplantation is really the longest goal in terms of time frame and we will see that happening within perhaps five to 10 years before the beginning of clinical applications.³⁵

- 4.15 Dr John Smeaton indicated that treatment of patients with their own (genetically compatible) cells is still a long way off but some therapies using donor cells may begin clinical trials in 2-3 years.³⁶

- 4.16 Dr Robert Loblay of Central Sydney Area Health Service (RPAH Zone) made a five to ten year projection for results, assuming rapid progress in overcoming technical hurdles.

Consequently, I believe there will be an explosion of knowledge in cellular and molecular biology over the next few years. ... I expect that *in vitro* cloning of human cells and tissues will become rapidly

35 Associate Professor Martin Pera, *Transcript*, pp.5-6. See also Professor Roger Short, *Transcript*, p.7

36 Dr John Smeaton, *Transcript*, p.157. Dr Smeaton is Chief Executive Officer and President, BresaGen Ltd and BresaGen Inc.

feasible. My guess is that organs will be more difficult to produce in culture.³⁷

4.17 The Royal Society, in *Stem Cell Research—second update*³⁸ predicts:

...that time-scales for the use of stem cells may well be shorter than those anticipated³⁹ However, two points should be emphasised: (i) the occurrence of unexpected adverse reactions to stem cell transfer (eg tumour formation or the loss of cell function or control) would seriously delay the exploitation of these therapies; and (ii) that time-scales for realising medical advantages of stem cell therapy are likely to be different for different organs (eg brain repair therapies are likely to take longer to develop than islet cell replacement in the pancreas). Time-scales are always difficult to predict. Adult stem cells are already in routine use, in the form of bone marrow transplants and it is likely that the first clinical trials (probably in the USA) of both adult and embryonic stem cells will take place within the next 5, certainly 10 years.

Scientific Method And Animal Research

4.18 The AHEC report recommended the support of research in animals, including the establishment of a primate research facility for cloning and stem cell research in Australia.⁴⁰ The Committee noted the views of witnesses in oral evidence and in the submissions, arguing both sides of this issue.

4.19 The views ranged from support for a primate facility in order that normal scientific inquiry could be pursued with non-human primate embryos, to opposition to a facility, because adequate animal research has been completed and the research can now be done on humans.

4.20 Most of the scientists who made submissions to the inquiry considered that there is no benefit in the use of non-human primates in this research and that the establishment of a non-human primate facility is not the best way of using limited resources. Associate Professor Pera stated:

The proposed initiative for non-human primate ES cell and cloning research is not justified: funds should be committed to research on human cells. ...there is no benefit to the use of non-

37 Central Sydney Area Health Service (RPAH Zone), *Exhibit 8*

38 *Stem Cell Research - second update*, Policy document 9/01, June 2001, www.royalsoc.ac.uk

39 In *Therapeutic Cloning and Stem Cell Research and Therapeutic Cloning: an update*. Both documents are available at www.royalsoc.ac.uk. In *Stem Cell Research and Therapeutic Cloning: an update*, the Royal Society stated 'it might be several decades before we achieve a full understanding of how the specialised state of cells is achieved and maintained'

40 AHEC report, Chapter 1, paragraphs 1.23 and 1.24

human primates for such research. Many potential benefits of human ES research will stem from *in vitro* studies which carry no risks whatsoever to patients. The safety of human ES cells in transplantation applications will be addressed chiefly by *in vivo* studies in immunocompromised hosts such as SCID or nude mice, where for instance the potential for tumour formation, and the ability to engraft correctly, may be evaluated. Only very limited preclinical study in primates will be necessary or desirable. The highest priority for commitment of funds for research in this area should be for studies based on human cells: non-human primate ES cell research should be at best a minor adjunct to such a program.⁴¹

- 4.21 Professor Julian Savulescu considered ‘This proposal would set back research in this field by years’,⁴² and Professor Roger Short stated:

To set up a primate colony and try and do embryonic stem cell research would be ducking the issue and diverting scarce resources from the real core of the question, which is to study human embryonic stem cells, particularly those produced by cloning.⁴³

- 4.22 Professor Marilyn Monk said that ‘a limited amount of direct analysis on human embryos is essential. Research on animals other than the human is not sufficient and maybe misleading’ and it is ‘essential to work on human material that is as normal as possible’.⁴⁴

- 4.23 Professor Robert Norman was inclined to support research in non-human primates:

I think, in terms of embryonic stem cell technology, it would be wise to have primate research going on, but there should be the potential to move through into human work once adequate, safe experimental work has occurred in subhuman primates.⁴⁵

- 4.24 Dr Peter McCullagh argued for the establishment of an Australian primate facility for cloning and stem cell biology. He emphasised rigorous

41 Associate Professor Martin Pera, *Submissions*, p.S172. The establishment of a primate research facility also opposed by Dr Eloise Piercy, *Submissions*, p.S584. The view that the establishment of a non-human primate facility is not the best way of using limited resources was also expressed by Professor Robert Williamson, *Transcript*, p.26 and *Submissions*, p.S347; *Primates for Primates*, *Submissions*, p.S831; and Dr Oliver Mayo, *Transcript*, p.73

42 Professor Julian Savulescu, *Submissions*, p.S650. Similar views were expressed by Dr David Gawler, *Submissions*, p.S625

43 Professor Roger Short, *Transcript*, p.8

44 Professor Marilyn Monk, *Submissions*, p.S806

45 Professor Robert Norman, *Transcript*, p.73

scientific method together with the need for animal research including that on primates, to provide the basis for human applications.

It is axiomatic that, when assessing any research proposal involving human participants, as much information as possible should be derived from previous studies using animals. There are some types of human research for which animal analogues may not be attainable or appropriate (eg research on psychiatric conditions). However, in relation to cloning several mammalian species have been found to be suitable for research.... Certainly, non-human primate species are likely to be highly relevant to studies with human embryonic stem cells.⁴⁶

- 4.25 Concerns have been raised in relation to the introduction of embryonic stem cell technology into human trials without adequate testing in suitable animal models. Dr Bernadette Tobin summarised the reasons given by scientists for rejecting the recommendation of the AHEC report that research be done in non-human primates first as:

...even if we do research on non-human tissue or organs, we will have to revalidate that research in humans. A second reason was the resource allocation problem: there are better ways to spend the limited dollar that goes on medical research. A third reason is that it would be silly or unwise not to capitalise on the information that has been generated by the human genome project. A fourth reason was that we ought to use the primate facilities in neighbouring countries and not reduplicate what already exists. A very interesting one was the fifth reason: that was an unease about conducting research on primates.⁴⁷

- 4.26 Mr Peter Eddington extended the emphasis on rigorous scientific method to include a model that incorporates scientific and societal consultation.⁴⁸
- 4.27 The arguments put to the Committee for direct research on human material were both scientific, concerning the appropriateness and availability of model systems; and related to the scarce research resources available in Australia compared to many of our international scientific and industrial competitors. Australian scientists argued that collaborative arrangements could be made with established primate research centres in the USA, Indonesia and elsewhere.⁴⁹ In the USA research on cloning and

46 Dr Peter McCullagh, *Submissions*, p.S313. The Executive Council of Australian Jewry also called for increased budget allocation to establish a primate research facility for approved research relating to cloning technologies, *Submissions*, p.S728

47 Dr Bernadette Tobin, *Transcript*, p.29

48 Mr Peter Eddington, *Submissions*, p.S96

49 Professor Robert Williamson, *Transcript*, p.27; Professor Alan Trounson, *Transcript*, p.26; Dr Oliver Mayo, *Transcript*, p.73

stem cell biology in animal model systems is being promoted and supported strongly by the NIH.⁵⁰

- 4.28 While the Committee supports the need for more basic research including that in animals, current priorities are to focus on human cell differentiation. The Committee was not presented with sufficient evidence supporting the need for the establishment of primate facility for cloning and stem cell research in Australia.

Alternative Technologies And Limited Health Resources

- 4.29 Concerns were expressed in a number of submissions that therapeutic cloning technologies may have significant potential for medicine, but other more cost-effective approaches may deliver benefits for a greater number of people. Some submissions also suggested that alternative cloning and transplantation technologies such as xenotransplantation, the use of foetal tissue and organs derived from transgenic animals might provide new options. The Committee notes these concerns but in this inquiry is not involved in determining priorities for research funding.

- 4.30 The Consumers Health Forum (CHF) submitted that:

... in an environment of limited resources, it is not only the absolute merit of particular projects which needs to be considered, but also their relative potential for promoting improved health outcomes for all Australians.⁵¹

- 4.31 CHF also expressed concern

...about poor utilisation of medical research findings and that too little weight is given to “low-tech” research which can significantly improve quality of life. CHF concluded that more work should be done to ensure positive research findings actually result in positive health outcomes through the development and implementation of best practice guidelines.

...research into the use of therapeutic cloning procedures is very much “state of the art” medical research. Whilst this research may have significant potential, it is important it is not undertaken at the expense of lower technology (and significantly cheaper) research,

50 <http://www.nih.gov/grants/guide/pa-files/PA-99-086.html>

51 Consumers Health Forum, *Submissions*, p.S793. See also Dr Eloise Piercy, *Submissions*, p.S583; Drs Chris Ireland and Sally Pittman, *Submissions*, p.S181; Ms Maryke Vaartjes, *Submissions*, p.S129; Frances Murrell, *Submissions*, pp.S42-43

simply *because* it is cutting edge—it is certainly no panacea for all the ills of the world.⁵²

4.32 Drs Fleming and Pike of the Southern Cross Bioethics Institute commented:

Perhaps the seemingly obvious outcomes of ES cell research could be supplanted by more effective and morally acceptable research using adult stem cells. In the serendipitous world of scientific research, it would not be the first time that less conspicuous research turns out to be the most fruitful approach for medical therapeutic application.⁵³

SUMMARY

- 4.33 The Committee noted the current contribution of Australian science and scientists in cloning and stem cell biology, and the opportunities presented for Australian intellectual property in biosciences, biomedicine and biotechnology. The longer term applications in agriculture and food, medicine and health and perhaps in environment and conservation could be revolutionary.
- 4.34 The recommendation in the AHEC report that a primate research facility be established for cloning and stem cell research in Australia was not thought to be the best use of limited resources by the majority of scientists who submitted evidence.
- 4.35 In considering initiatives in cloning and stem cell technologies, the Committee noted the views of those supporting other research approaches. The emphasis on basic and strategic research, rather than on clinical applications at this time, was a feature of much of the evidence.

52 Consumers Health Forum, *Submissions*, pp.S794. The National Caucus of Disability Consumer Organisations submitted that ‘Even a small proportion of the budgets devoted to genetic and cloning research could produce important outcomes for people already condemned by our society to live low quality lives because disability care is not the ‘sexy’ issue that cloning and genetics is’, *Submissions*, p.S775

53 Drs Fleming and Pike, *Submissions*, p.S563. A similar view was expressed by Dr Peter McCullagh and the suggestion that xenotransplantation is another alternative, *Submissions*, p.S315