THE UNIVERSITY OF MELBOURNE

25 October 2006

Dear Mr Humphery

Questions on notice for former members of the Lockhart Review

Professor Schofield, Associate Professor Kerridge and I respond to Senators' questions on notice as follows (Questions are in italics):

1. What percentage of submissions, regardless of form, received by the Review were opposed to changing the law to allow cloning for research and what percentage were in favour of such a change?

We do not have the calculations of the percentage of the 1035 submissions to indicate those that were for or against changing the law to allow cloning for research. Such a calculation would require the review of all submissions, which is not possible by 25 October. However, we can state that a clear majority of those who made written submissions (estimated at approximately 80%) said that they did not approve of human embryo or cloning research.

In addition, 9 form letters or petitions were received with a total of 898 (70%) individuals supporting a ban on cloning or embryo research and 378 (30%) supporting stem cell research.

However, as we stated when asked this question at the Senate Hearing, in our deliberations we were guided not by the raw number of submissions but by the substance and logic of arguments advanced for and against embryo research and human cloning, by evidence relating to technology, scientific potential and community standards (including but not limited to that presented to the Lockhart Review) and by moral reflection on the range of issues relevant to our terms of reference.

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2. In your report you state (p. xiv): "In framing the recommendations for these reviews, the Committee considered that the higher the potential benefits of an activity, the greater the need for ethical objections to be of a high level and widely accepted in order to prevent that activity. Conversely, where benefits are not yet established, or where there is widespread and deeply held community objection, then total prohibition through the legal system may be justified." In evidence to the Committee Professor Skene stated in regard to cloning "it will be our grandchildren by the time the research is done".

2.1 In the light of this admission, and of the exposure of the Hwang fraud, do you accept that, in relation to cloning "the benefits are not yet established"?

No. Professor Skene was emphasising that *cures* will not come from embryonic stem cell research in the immediate future, but rather will have potential impacts over a time frame of many years (i.e. 'for our grandchildren'). The discovery of new medicines and treatments typically takes years for discoveries to be made and proved, first in a laboratory, then in animal trials, then in human clinical trials. The development of the typical new drug takes on average 7-12 years from the time that the drug is shown to have effect in the laboratory.

However, we have also emphasised that long before any cures are developed, embryonic stem cell research is likely to produce knowledge that will assist in human health care, particularly in relation to disease aetiology and pathogenesis, pharmacogeneomics, cell biology, reproduction and organogenesis. There have already been several significant advances (see below) and scientists are learning more about the development of early embryos, including those that are impaired and not suitable for implantation. In time, that knowledge may be used in research on adult stem cells, and vice versa.

We do not accept the interpretation of the statement 'the benefits are not yet established' as this is a narrow interpretation of 'benefit' and misunderstands the process of scientific discovery and the generation of new knowledge. It is true that the clinical or therapeutic benefits have not yet been achieved as no SCNT derived human embryonic stem cell lines have been generated to date and no clinical trials using embryonic stem cells have yet taken place. But the terms of reference of our inquiry related to *potential* benefits of this research, and in our view there can be little scientific dispute that there are substantial potential benefits that may flow from ESC research and from SCNT, particularly as animal studies have clearly demonstrated proof of concept of this type of approach.

If embryonic stem cell research proves unproductive in the future and adult stem cell research were to show greater potential, scientists and biotechnology will naturally turn to the more promising type of research. That is not a reason to ban embryonic stem cell research from the outset. Almost all scientific proponents of both adult and embryonic stem cell research say that both should continue to be undertaken.

As stated in our testimony, the Lockhart Committee did not rely simply or solely on Dr Hwang's research (later shown to be fraudulent). As detailed in the Review, and supported by the independent analysis conducted in the Mathews Pegg Consulting report, there are a number of areas of both development and potential in the field of

somatic cell nuclear transfer. Further work has been published since the report was tabled in Parliament.

2.2 In the light of Critchley and Turner's[1] finding that "the majority [63%] of Australians were comfortable with the research using adult cells, but were not comfortable with scientists using cells created by cloning" would you accept that there is "widespread and deeply held community objection" to cloning?

No. Most surveys of community views that were reviewed by the Lockhart committee have indicated broad support. The Lockhart Review was briefed on extensive research described in the report that was undertaken by Biotechnology Australia, an Australian government supported activity. Of 1067 people surveyed, nearly two-thirds approved or strongly approved in response to the question 'In relation to human stem cell issues, for each of the following situations, do you see them as being morally acceptable to society or not? Human stem cells being derived from embryos': Report p 83 (Table 1).

An opinion poll reported in the *Age* on 12 September 2006 undertaken by AC Nielson with 1415 respondents, asked the question, 'Do you support or oppose legislation with allows the cloning of stem cells for medical research?' It found 62% support, 12% oppose and 12% had no opinion [sic].

Conversely, a poll conducted by the Southern Cross Research Institute concluded that a majority of respondents to a survey it conducted did not approve of human embryo research. However in testimony to the Senate committee, Dr Pike admitted that the first 29 questions of this survey (which have not been presented to the Senate enquiry or to the public) were on the subject of abortion, which in itself may have contributed to the responses of those surveyed. Importantly, we believe that there are significant methodological flaws in this research and that the results must be interpreted with caution, particularly as the research instrument has not been published or subject to peer review. Our concerns were heightened by Dr Pike's testimony when he indicated in response to a question from Senator Webster that respondents who had no preference for adult or embryonic stem cell research were apparently reported as being against embryo research.

The survey of Critchley and Turner was not identified in our literature review or made available or drawn to the attention of the Lockhart Review by either the authors of the study, or by any individuals or groups who now choose to use this particular survey to support their own position. That gives us reason to caution against over-reliance upon this data. We would also caution against over-interpretation of survey data in general as the results may reflect systemic bias in the design of questions or the interpretation of data. The best means for avoiding such bias is through publication in peer-reviewed journals and through repetition in different populations and by different researchers. We believe that important research will continue to explore the attitudes of Australians to many of the issues raised by medicine and by research over the coming years.

In summary there are various surveys of community opinion, which vary in their methodological rigour and also in their conclusions. While there will no doubt be continuing debate about the extent to which Australians support ESC research and human cloning, it is clear that it is not possible to conclude that there is any evidence of a widespread and deeply held community objection to embryonic stem cell research and/or human cloning.

2.3 If this Committee concludes, on the basis of the scientific evidence, that the benefits of cloning are not yet established and, on the basis of the evidence regarding public opinion, that there is widespread and deeply held community objection to cloning would you agree that on the basis of the approach to resolving such questions expressed in your report the Committee should recommend that cloning for research should remain prohibited?

No. As is made clear in our report, we do not agree that there is widespread community objection to human cloning or that the potential benefits of this research are yet to be established. To the contrary, we found that there is evidence of support for this research, that there is substantial evidence of technological, medical and scientific advances and that there is (almost) uniform agreement regarding the considerable scientific and therapeutic potential of this research.

Evidence in support of our view is found in the answer to question 2.2 (above) and in the Matthews Pegg Consulting Report which stated that:

> the Committee noted that this is a very active field of research and that there have been a number of developments since 2002. Specific reference is made in the Committee's Report to:
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> • the first report of human cloning in 2002 when South Korean scientists claimed that they had cloned human embryos until the blastocyst stage to create ES cells. It was noted that in 2005, the same group of researchers applied the nuclear transfer methods to clone human embryos using somatic cell nuclei from patients who have various disease or injuries to derive 'tailor-made' stem cell lines; *[note that this research has been retracted on the basis of it being fraudulent]*
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> • research reported in the United Kingdom in 2005 that showed that nuclear transfer can be achieved in human oocytes using heterologous donor nuclei and surplus and donated oocytes;
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> • other researchers attempting to produce patient-matched ES cells by fusing the somatic cell nuclei from patients with ES cells. It was noted that one United States–based group has claimed to have achieved this (and called the resulting cells 'stembrids') but that the research has not yet been published in the peer reviewed literature; and
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> • research aimed at elucidating the genetic consequences of cloning is currently being conducted in a number of centres, and the results of this research are likely to be enormously significant to the entire field.

Since the submission of the Lockhart Review no reports of the derivation of human

embryo clones by somatic cell nuclear transfer have been published. However, there are a number of publications that have shown significant advances in human and animal model stem cell research. These include:

1. Research reported in the United Kingdom in 2005 that showed that nuclear transfer can be achieved in human oocytes using heterologous donor nuclei and surplus and donated oocytes. This work was referenced in the Lockhart Committee's Report. This the first publication of the production of licensed human SCNT although we note that human embryonic stem cells were not isolated.
'Derivation of a human blastocyst after heterologous nuclear transfer to donated oocytes', by Miodrag Stojkovic, Petra Stojkovic, Christine Leary et al, Reproductive Biomedicine Online, vol. 11, no. 2, pp. 226-231.

2. Research reported from the US used the fusion of existing human ES cell lines that had been enucleated with adult cells to create cytoplasmic hybrid (cybrid) individual specific human ES cell lines. This research was also referenced in the Committee's Report but was published after the review:

'Reprogramming of human somatic cells by embryonic stem cell cytoplast', by Nick Strelchenko, Valeri Kukharenko, Artem Shkumatov et al, Reproductive Biomedicine Online, vol. 12, no. 1, pp. 107-111.

3. Research reported from the United States obtained human embryonic stem cell lines from single cells extracted from blastomeres. This suggests that embryonic stem cells might be derived from one cell removed from an eight-cell embryo:

'Human embryonic stem cell lines derived from single blastomeres', Irina Klimanskaya, Young Chung, Sandy Becker et al, Nature, letters published online 23 August 2006,

4. Research reported from Japan demonstrated that protein factors could be used to reprogram mouse fibroblast (skin) cell lines to become induced pluripotent stem cells that were demonstrated to contribute to embryonic development in mice.

'Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors', by Kazutoshi Takahashi and Shinya Yamanaka, Cell, vol. 126, pp. 1-14 and supplemental data.

5. Proof of concept studies in animal models in which a form of sickle cell anaemia was generated in mice and then corrected by treatment with embryonic stem cells.

We would note also that support for the validity and potential of ESC and Human Cloning research has come from the House of Lords; the majority of members of the US Senate; 80 US Nobel Laureates; the American Medical Association; the Canadian Medical Association; the Australian Academy of

Science; and many prominent Australian scientists including the Australian of the Year (Professor Ian Fraser) and Professor Gustav Nossal.

3. Where in your report do you provide a scientific rationale for the creation of human embryos using precursor cells from embryos or foetuses?

This procedure is considered only briefly in the Committee's report but the Committee took the view that embryos formed in this way are more in the category of an embryo formed by SCNT (which the Committee recommended should be permitted to be created and used in research under licence), than a 'sperm-egg embryo' such as those formed by a couple in a fertility program (which the Committee said should not could be created for research). For that reason, our arguments throughout the report cover this type of procedure.

4. Where in your report do you give consideration to community views on the creation of human embryos using precursor cells from embryos or foetuses?

Without reviewing all the submissions, we cannot recall submissions (if any) in which this was specifically discussed.

However, in many instances, submissions clearly identified an issue or entity of concern. For example, ART scientists and some medical researchers expressed a clear interest in mitochondrial DNA and the issues surrounding incorporation of genetic material from more than two individuals, and some IVF consumer research was concerned primarily with the creation of sperm-egg embryos (and the different cultural value attached to such entities). In other instances submissions were not specific either to a biological entity, a technique or a type of science, but reflected broad concerns or perspectives.

Consideration of these submissions and reflection on the issues they raised led us to our conclusions, including those relating to the creation of SCNT embryos. Importantly, further reflection led us to consider the implications of our thinking for other types of embryo research and other means of creating embryos (including means that are currently not possible but may become so in the future). Where these types of research seemed to us to be similar in terms of the ethical issues they raised or the legal/ regulatory responses they required, we drafted our recommendations in ways that, in our view, were logically and morally consistent.

5. Is your recommendation (26) that "creation of embryos using precursor cells from a human embryo or a human foetus should be permitted, under licence" intended to allow the creation of embryos by fertilisation using ova obtained from a foetus?

The Committee's recommendations envisaged that an embryo could be created for research in this way. The Committee considered this entity to be more in the category of an embryo formed by SCNT which it recommended should be permitted to be created and used in research under licence, than a 'sperm-egg embryo' such as those

formed by a couple in a fertility program, which should not could be created for research .

6. It is acknowledged that the Hwang South Korean Research was based on fraud and has been completely dismissed of levity. This research was the only peer review research relied upon by the Lockhart Committee to support its recommendation in favour of therapeutic cloning. Professor Skene has in two separate public forums agreed to forward to Senator Guy Barnett the further reports and evidence relied on by the Lockhart committee to support their recommendation in favour of therapeutic cloning. As at 23 October 2006 no such information has been forwarded. It is noted that your submission to the Senate Committee last (Friday 20 October 2006) made no reference to this research although it did include information and reports relating to embryo stem cell research.

Professor Skene included the references for some of the projects listed above in the handout of the slides that she used at the Scientific Panel in Canberra which Senator Barnett attended. Professor Skene did, however, tell Senator Barnett that she would send him some further information of recent developments, setting these out in lay terms. This information is set out in the next paragraph. We emphasise that the Lockhart Committee did not rely only on Dr Hwang's research that was later retracted. We have listed above the research publications on which we relied in the report, together with submissions we received from scientists, ART practitioners and others.

<u>Professor Skene's comments on recent developments for Senator Barnett</u>

I am not a scientist and I am therefore stating in lay terms what I understand has been achieved to date, based on scientific material I have read. As I have said throughout the Review, there are no *cures*, but progress is being made.

1. Processes have been established to grow human embryonic stem cells in large numbers. This will be necessary if they are ever to be used therapeutically.
2. Associated with this, a major UK group (under Professor John Burn) has recently been funded to build a special laboratory that will enable human embryonic stem cells to be produced in conditions that conform with Good Manufacturing Practice (GMP). Again, this is essential for the cells to be used in clinical trials and therapeutic applications.
3. Other scientists have recently been reported as producing embryonic stem cells without any animal material in them, to meet GMP practice.
4. A human blastocyst has been formed by SCNT by an English group, though embryonic stem cells were not derived from it (due to the conditions of the licence for that research).
5. Methods are being developed to differentiate human embryonic stem cells (which are totipotent) into specific types of human body cells – muscle, brain, pancreas etc.
6. The capacity of human embryonic stem cells to treat conditions in animals is starting to be demonstrated (proof of concept). For example, Chang, 2006: in experiments on mice, sickle cell anaemia was corrected by modifying a sickle cell genetic defect in mouse embryonic stem cells.

7. Research has been undertaken in five species of animals that have been bred with diseases that affect humans (animal models). These diseases include, for example, impaired heart function and spinal injury. Stem cells derived from human embryos have been transplanted into these animals and have produced an improvement in the conditions in some cases (see Dr Nick Gough' s paper, which has been sent to all federal parliamentarians, p 13).
8. Embryonic stem cells have been used in screening new drugs and in toxicology studies.
9. Above all, more is being discovered in the realm of pure science.

I am aware, of course, that these experiments do not involve human embryos that have been created by SCNT (that is not currently allowed in Australia but it is allowed in the UK and USA). However, if embryonic stem cells are proved to be effective in research such as that described above, then SCNT embryos will have the benefit that stem cells from them are much less likely to be rejected by a patient, because the stem cells will be matched to that person.

It is true that human embryonic stem cell therapies may not be effective even if they are developed. Embryonic stem cells do multiply rapidly and live for very long periods. They may cause cancers and may not differentiate as planned. However, scientists may be able to investigate and resolve these problems in vitro or in animal trials if they are permitted to do the research and, of course, no human trials would be permitted until these safety issues have been fully investigated and resolved.

It is true that the human embryo research that has been undertaken to date has not been done on SCNT embryos and our recommendations in that regard are based on the *potential* of such research, on which we were required by our Terms of Reference to report.

Yours sincerely

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Professor Ian Kerridge

Professor Peter Schofield