COMMONWEALTH OF AUSTRALIA

Official Committee Hansard

HOUSE OF REPRESENTATIVES

STANDING COMMITTEE ON LEGAL AND CONSTITUTIONAL AFFAIRS

Reference: Human cloning

THURSDAY, 5 APRIL 2001

CANBERRA

BY AUTHORITY OF THE HOUSE OF REPRESENTATIVES

INTERNET

The Proof and Official Hansard transcripts of Senate committee hearings, some House of Representatives committee hearings and some joint committee hearings are available on the Internet. Some House of Representatives committees and some joint committees make available only Official Hansard transcripts.

The Internet address is: **http://www.aph.gov.au/hansard**

To search the parliamentary database, go to: **http://search.aph.gov.au**

HOUSE OF REPRESENTATIVES

STANDING COMMITTEE ON LEGAL AND CONSTITUTIONAL AFFAIRS

Thursday, 5 April 2001

Members: Mr Andrews *(Chair)*, Mr Billson, Ms Julie Bishop, Mr Cadman, Mr Griffin, Mr Kerr, Mr Murphy, Ms Roxon, Mr St Clair and Mrs Danna Vale

Members in attendance: Mr Andrews, Mr Billson, Ms Julie Bishop, Mr Cadman, Mr Murphy, Ms Roxon, Mr St Clair and Mrs Danna Vale

Terms of reference for the inquiry:

To review the the report of the Australian Health Ethics Committee of the National Health and Medical Research Council entitled *Scientific, Ethical and Regulatory Considerations Relevant to Cloning of Human Beings* dated 16 December 1998.

WITNESSES

Committee met at 11.56 a.m.

SMEATON, Dr John Richard, Chief Executive Officer and President, BresaGen Ltd and BresaGen Inc.

CHAIR—I declare open this public hearing of the House of Representatives Legal and Constitutional Affairs Committee inquiry into aspects of human cloning and I welcome Dr John Smeaton from BresaGen. Today we are interested in some of the scientific and commercial aspects of the research and we are pleased that Dr Smeaton has been able to join us.

Although the committee does not require you to give evidence under oath, the hearings today are legal proceedings of the parliament and warrant the same respect as proceedings of the houses themselves. The giving of false or misleading evidence is a serious matter and may be regarded as a contempt of parliament. We have received the submission from BresaGen and it has been authorised for publication by the committee. Would you like to make some opening comments?

Dr Smeaton—Thank you, Mr Chairman. I thought it would be useful to go over some of the background of how the technology we are trying to develop works. To that end, I have produced a handout of four diagrams, and perhaps it would be useful if I ran through it quickly. I hope I can explain to people what we are trying to do. BresaGen is involved in the conduct of a cell therapy program which is aimed at producing new types of cures for what have previously been intractable diseases which occur due to the failure of cells, which are the fundamental building blocks of our bodies.

I would first like to describe how we see a process of allogeneic cell therapy working. Allogeneic means that we would take a batch of cells and then put them into perhaps thousands of patients so there is no tissue match between the source of the cells and the recipients. The prime area where that sort of technology will work is in the central nervous system, where there is an immune privilege site, in that we see a much lower tendency of rejection response. Our feeling is that allogeneic cell therapy will have potentially major applications in the central nervous system. To do that, we will have to develop a source of cells and a very large bank of cells if we are going to treat larger numbers of patients from one cell bank. As the diagram shows, the original source of the cells that we are talking about using is non-implantable embryos from in vitro fertilisation clinics.

Perhaps I should expand a little on that. The clinics will develop a fairly large number of embryos, certainly in the tens, from a single patient. Those embryos are fertilised in an in vitro situation and then matured for several days. During that time these putative embryos are graded. They are fundamentally graded into two sorts: those developing embryos which are considered capable of implantation, and therefore going on to form a new human, and those which, judging by some years of experience, are very unlikely to do that. There is a separation at that point into prospective and non-prospective embryos. The first grade go on to be either implanted into the recipient prospective mother or frozen for later use. The others are discarded. It is this discarded tissue which I think should be thought about as tissue rather than a prospective new life. That tissue does contain what are potentially useful cells for the purposes that we are interested in.

We are now developing cell lines. This work is being carried out in the United States, in our subsidiary company there, because this type of work is not legal in South Australia. We take that tissue and are attempting now to develop cell lines, first of all, which go through a stage from the embryonic stem cell to what we call an EPL cell. That cell, in our mouse model, has been the subject of significant intellectual property filings by the company. The EPL cell is a very key branch point. It is also something that in our hands, in the mouse model, has proved to be expandable.

Ms ROXON—What does EPL stand for?

Dr Smeaton—It stands for primitive ectoderm like.

Ms ROXON—That does not really help me, but I just wondered what it was.

Dr Smeaton—It is from a particular type of cell that is present in the embryo. Peter Rathjen, in Adelaide, has been the prime identifier of this cell as being the important one in terms of development and in terms of the commercial potential for this technology. The EPL cell is able to form, essentially, all of the cells in the human body. I would add that neither the embryonic stem cell nor the EPL cell on their own are capable of forming a new human. To do that, you need a complete embryo that has the ability to form a placenta, which is one of the key other factors that is now missing.

We need to propagate cells to form a master cell bank. Then from that stage our technology is aimed at differentiating the process of change and of making the cells go down a particular pathway. In our case, we are interested principally in the ectoderm pathway, which leads to the central nervous system, tissue, skin and things like the eyes. We would then take these master cell banks, differentiate the whole population of cells in a synchronous manner—and this is a core part of our technology—and take them down to form a cell product of commercial interest. They are the cells shown in the diagram.

We have been able now, from our cell bank, to come up with potentially useful cells in a pure differentiated population. Those cells are then placed back into a patient or, in the case of allogeneic therapy, into perhaps thousands of patients. So that is the first approach, and that is the approach that we are using to try to come up with, firstly, a cure or certainly an advanced treatment for Parkinson's disease. We also see possibilities for other central nervous system complaints, such as Huntington's disease, possibly stroke, injury to the spinal cord and other aspects of disease in the central nervous system because of the immune privileged site.

If we turn to the next diagram, we are talking about autologous cell therapy, which has created quite a lot of interest recently. This is where material is sourced from the patients themselves. Here you are dealing with a population of one. You are talking about cells which come from the patient, are manipulated and then are put back. In this case, there has to be what we call cell reprogramming going on. A lot of this work is still highly theoretical at this stage, and there is a lot of fundamental research to be done before this approach, in our opinion, will become a commercially viable treatment. So a cell from a biopsy and maybe a skin cell or something like that is taken from the patient, and the nucleus is then transferred into an early stage cytoplast, which is essentially an enucleated cell. We have some very prospective technology in that area for developing those cytoplasts. Through a nuclear transfer process we

come up with a reprogrammed early stage cell which can be propagated and then differentiated in the same manner as the allogeneic application and then put back into the patient.

The difficulty we see here is that, because you are dealing with a single patient, there are aspects of time and of costs. In relation to cost, as it is a single patient, all of the appropriate quality control steps will have to be offset against a single treatment. Depending on how the regulatory agencies look at this, the indications at the moment are that if significant manipulations are involved—and we believe in this case there would be—there will be significant requirements for quality control of such cells. So there is a cost issue. The other issue is perhaps one of timing. As recently as in the last couple of days there have been reports, for example in the *New York Times,* on how stem cells may be used to restore heart muscle in heart attack patients. To do something like this requires some time. You would have to speculate as to whether it would be possible to isolate and derive the appropriate cells in the time frame that those sorts of patients have, which is generally of the order of three or four days. So autologous therapy is very attractive on the surface, but there is quite a long way to go before it becomes a practical reality, in our view, and certainly for it to be a practical and cost-effective reality.

Turning to the next diagram, this takes a little further the detail of what happens in the neural lineages of differentiation. It starts from tissue taken from our non-implantable, early stage embryo, going through an embryonic stem cell stage to the EPL cell, and differentiation then controlled into the ectoderm pathway so that all the cells are designated to become ectoderm. From there we can control, in our mouse model, differentiation into a number of very interesting cells. As I said, our focus is on the nervous system and Parkinson's disease, so we are interested in cells like neurones, dopaminergic neurones, perhaps neural crest cells and the neurectoderm cell. Because we have the ability to produce pure cultures of a wide range of these cells—all the cells along the pathway—we are in the unique position, I believe, to test these cells in a rat model of the disease to see which is the most appropriate cell to use. Having done that, as our human cell work starts to deliver the types of cells that are the parallel of the mouse model, we could then proceed to early clinical trials in human patients, following the path of one of our consultants, Dr Curt Freed, who has published work recently showing that cell therapy is a viable prospect for Parkinson's disease, even though his source of material, which was from aborted foetal tissue, was an uncontrolled tissue and also one that raises some difficult ethical and supply problems and so is not a practical source on a long-term basis.

The final diagram shows our conception of a Parkinson's disease product. Our product would consist of a dose of the appropriate cells. To put it in perspective, this would be in only microlitre quantities. They would be delivered to the appropriate part of the brain by a sophisticated catheter device, which also involves some MRI real time scanning for accurate placement of the cells in the appropriate part of the brain. The catheter has a very innovative microcoil device on the tip so that, through the use of the scanning MRI machine, you can see very clearly the area right around the tip of the catheter and you are able to make sophisticated measurements of the state of the metabolism in that part of the brain and to subsequently monitor what goes on after the cells have been deposited.

So we are looking at a very complete approach to the Parkinson's disease problem as our first rollout of a product in this type of technology. But bear in mind that even in the central nervous system the technology has potentially many more applications. As we move further down the

track and learn more about autologous therapies, there will perhaps be a very wide range of applications for this technology. That would conclude my statement. I hope it has been reasonably clear, given what I appreciate is quite a difficult subject for non-science people to get around.

CHAIR—Thank you. I have a couple of questions on the diagrams. There was a report a few weeks ago about some experiments in the US involving the injection of cells into the brains of patients suffering from Parkinson's disease, and in some proportion of those cases it actually seemed to make the patient's condition worse. I am relying on the newspaper reports—which we around the table know are not always accurate. Was that a similar procedure to this fourth diagram?

Dr Smeaton—That was the procedure that Dr Curt Freed carried out. He is one of our consultants. The work was widely reported, as a result of the *New York Times* article, which gave a somewhat distorted view of the result. In our view, it was clear that the reporter had not properly read and appreciated the article. I think it would be useful if members were to be referred to the *London Times*, which actually quoted and interviewed the patients who had had the side effects—dyskinesias, or uncontrolled movement, principally of one of their arms. They all said they would do it again. One of them had, essentially, no result; her result was about neutral. The other two had suffered the so-called severe side effects. They both said the side effects were a minor inconvenience compared with where they had been before. One gentleman, for example, was wheelchair bound, unable to speak and unable to feed himself. Following about nine or 12 months treatment, he was able to drive a car, go to restaurants with his family and was able to speak quite normally. He said that compared to where he had been, the uncontrolled movement of his left arm was a minor inconvenience.

CHAIR—How long did that last?

Dr Smeaton—He had subsequent surgery which fixed that. They implanted an electronic stimulation device in the brain for deep brain stimulation.

Mr BILLSON—So without that medical intervention the side effects would have continued?

Dr Smeaton—The side effects probably would have continued, but the side effects were something which is normally seen in quite a lot of Parkinson's patients anyway as a result of L-dopa treatment. If you look at the interviews with the patients, and if you look scientifically and analyse Freed's results, we think it is a very useful pioneering result which validates the general approach that is being taken here.

CHAIR—Could I come back to the allogeneic cell therapy? This seems to be based on a premise that having a master cell bank, which can be used in a whole range of patients, has potential. What is the evidence for that? I should say that other suggestions have been made to us that that is not going to be the path for the future and that, in fact, if this goes ahead it is going to be matching cells from a particular patient to reprogram, in a way, and to go back into that patient. What I am interested in is: how confident are you that this process is one which is going to lead anywhere in practical terms, leaving aside the research interests in doing it?

Dr Smeaton—We think this is actually the most prospective of the practical cost-effective therapies. That gets back to the fact that the costs of developing the cell bank and quality controlling it can be spread over perhaps thousands of patients. The evidence that this will work in the central nervous system comes, again, from Freed's experiments. He was able to autopsy patients as far as 10 years after implant and found no evidence of rejection, reflecting that the central nervous system is an immune privileged site. That gives us considerable comfort. There is other evidence also for the central nervous system there, but going into the central nervous system with the allogeneic cell therapy has great promise and is going to yield results rather sooner than the autologous therapy, which still has some significant technical hurdles in the reprogramming step.

Our company has spent quite a number of years in the animal cloning area. We have successfully cloned animals but we would have to report—and agree with other reports in the literature—and that involves essentially a reprogramming step. The hazards of that step have still quite a lot to be worked out. The number of healthy animals that you get from a cloning procedure is a relatively low percentage at this time. Until that step becomes a more reliable one, I think it is probably quite speculative to see that as the way to go immediately.

CHAIR—Does the allogeneic therapy rely upon a continual supply of embryos? For example, in the autologous therapy it seems to me that another limitation occurs unless you have a continual supply of excess embryos or specifically created embryos. To what extent does the allogeneic therapy rely on that? Or are you able to, in effect, replicate many EPL cells?

Dr Smeaton—In theory you need one embryo for all time. It will not be quite that way, but we think we will establish something like four or five or six different cell banks and, depending on the efficiency of our process, we think our process is really proving quite prospective at the moment. So a small number of embryos of the order of perhaps less than 10 will yield two or three cell banks. As long as that happens, and once we have the cell banks established, we do not need any embryos again.

Ms ROXON—From BresaGen's point of view, presumably the value in this process—and correct me if I am wrong—is that, once you can establish all of these things, you will basically have that cell product that you can sell.

Dr Smeaton—That is right.

Ms ROXON—So really the issue about whether or not the implantation is compatible or there are some difficulties is basically going to be somebody else's rather than BresaGen's. Do you understand the point I am making? There are people who are concerned about the use of embryos and those sorts of things, and obviously this process is favoured more by some people than others when you need to have a constant supply of embryos. If compatibility of the final cell product that you have is an issue, is that really one that affects your commercial interests or not?

Dr Smeaton—Our commercial interests really rely on delivering a useful, reliable and safe product for the treatment of various diseases. Parkinson's disease is our first target but certainly not the only target. So I guess from that point of view, yes, we are concerned that the product

will be safe and effective. It will not pass agencies like TGA and FDA unless we can convince them of that.

Ms ROXON—But it could be safe and still not compatible for all people, couldn't it?

Dr Smeaton—The evidence so far is that, as long as we are going into the central nervous system, that is unlikely to be the case. Freed was putting in much more immuno-hazardous material and much less defined material and did not run into any of those sorts of problems.

Ms ROXON—I guess I am probably not asking my question in a very clear way. Maybe the final diagram that you have given us shows that you still do have an interest, because some of your products are actually about how you then implant anyway.

Dr Smeaton—That is true.

Ms ROXON—I am just trying to understand how far your interest extends through this. Your group is one of the first we have talked to that has a commercial perspective on it, and we are interested to understand how that works. So do you follow it right through to the patient or not?

Dr Smeaton—Our objective at this stage—and of course we are always subject to the hazards of business, like takeovers and that sort of thing—is to take this product all the way to the clinic. We have scheduled a meeting with the FDA on 19 April, which is this month, to put before them our program as to how we see this becoming a product. Our product concept is summarised in that last diagram.

As a company we have already had a number of discussions with prominent neurosurgeons, both in Australia and in the United States, and we have determined that the population of neurosurgeons that we would be dealing with in the US, for example, is about 150 individuals. We think that, as a company, we are capable of developing the appropriate sales force—it will be a small sales force—to be able to take a product to that relatively small group of customers. That is our intention at this stage. We want to develop this product, take it to the marketplace and, as a company, reap all of the value added along that chain.

Ms ROXON—Rather than just sell products and—

Dr Smeaton—Rather than just licensing it out. A neurosurgeon will get two boxes: a box that contains frozen cells and a box that contains the necessary hardware. We will not actually be manufacturing the hardware; we are developing an OEM relationship for that. With both of the boxes will come a protocol as to how that should be dealt with. We are looking at a complete product concept.

Mr CADMAN—Can I just question that? You said protocol; I think you probably meant process.

Dr Smeaton—No, it is the protocol for how you would actually inject the cells.

Mr CADMAN—That is a process. A protocol means an ethical factor as well.

Dr Smeaton—I am not sure that I agree with that.

Mr CADMAN—I just needed to clarify the way you use the words. I am satisfied.

Dr Smeaton—It is the directions for use.

Mr CADMAN—Yes, directions for use.

Mr BILLSON—On the issue of the South Australian law and the way that has impacted on your company's work, I note in some of the material you have given us that it flags that it is unhelpful but that it does not necessarily knock off what you are doing. I suppose you can have the ideas in South Australia as long as you do not road test them there. Is that an issue you anticipate grappling with further as you develop the technologies—this jurisdictional inconsistency and uncertainty?

Dr Smeaton—Probably not. We have had experience of grappling with legal/parliamentary issues in the past when we were involved in the development of transgenic pigs, ultimately for food purposes. We spent 10 years wrestling with government to go about getting appropriate rules in place, and that eventually caught up with us. It did not happen in time and we abandoned that project. As a result of that experience, we are not really interested in taking on those sorts of tasks if we do not have to.

The South Australian law and the Victoria law—which I think are the same—at this stage are not actually an impediment to us, because we have been able to develop offshore and in other jurisdictions the cells that we are interested in. It is legal to bring those cells back into South Australia, so we can go ahead with further road testing of the process. Any impediment that has been present has been an inconvenience, and we are now past that.

Mr BILLSON—I guess I am trying to draw out a sense of how attractive/competitive our research environment is. I understand what you have done, and inconvenience is the sense I get of it as well. Yet, we have been grappling with not wanting to freeze out important biotechnological endeavours in our country by being heavy-handed. It has been put to us that a heavy regulatory regime would push that offshore.

Dr Smeaton—That is true. In our case, that regulatory regime has pushed some of our work offshore, as I have said. I think that the law as it stands now was actually framed in an earlier time, so the consequences of it in this area are perhaps unintended. As for this technology going forward, if the Australian parliament were to pass a law which was modelled on the recent British one, that would be quite forward looking and helpful in terms of the development of this technology. The British law goes a step further than the American one and allows the development of embryos specifically for research and development purposes.

Mr BILLSON—Looking at the process of your research and the vision for its application, is there an argument in your mind for having an encouraging research regime up to the point of the cell product development and then, when the cell product is being applied or inserted into a person, moving into more of a pharmaceutical type regulatory regime that does not seek to differentiate this kind of medical intervention from medicines?

Dr Smeaton—As I said, we are visiting the FDA this month. One of the reasons is that we believe they are in the forefront of world regulatory thought on this process and are perhaps going to lead and set the standard, so it is useful for us to interact with them. Our telephone interactions so far have been mutually beneficial, and there is quite a constructive dialogue going on between us and the agency. I think the TGA will ultimately move to perhaps get more involved in regulating this area. At the moment, it is not. Our anticipation is that regulatory agencies throughout the world will show an interest in this area and that appropriate guidelines will ultimately be laid down so that these products will be regulated in a parallel manner to pharmaceuticals.

Mr BILLSON—So the way in which they are developed may be different and challenging; but, at the end of the day, their application to repair tissue or some functionality deficiency is therapeutic and you would suggest that is the way to handle the regulation of their application?

Dr Smeaton—Yes, certainly. There will be regulation, just the same way as there is for other pharmaceuticals. These are just a new wave of pharmaceutical type products designed to treat disease. The regulators, along with the researchers, are all learning their way through this, identifying the potential hazards and the appropriate standards that need to be put into place. If you put in too early a cell, for example, you may well develop a tumour. Those sorts of safety issues have to be properly addressed.

Mrs VALE—I am sorry I came in late, so you have probably already explained this. You said that in the autologous cell the material was sourced from the patient. Does that mean you just take a body cell? From what part of the body is that cell taken?

Dr Smeaton—It could theoretically be any cell. We believe that once the whole process of differentiation is understood it should be possible to reverse pathways and perhaps back cells down a pathway into an earlier stage where you can multiply them and then take them down another path to generate the cell that you want. We are in the very early days of understanding this whole process.

Mrs VALE—So there was no particular part of the body you would derive a cell from?

Dr Smeaton—No. A skin fibroblast seems to be a popular cell to use for that.

Mrs VALE—You have not even started on this yet—this is still projecting into the future?

Dr Smeaton—This goes back to a question that was asked earlier as to how to overcome the need to use a new embryo each time. We have done some work and filed a patent on it, but we have not published it so I cannot go into the details. We believe we do have a prospective method for achieving that so that we would not need to use a new embryo every time for that process.

Mrs VALE—What does it mean when you say a non-implantable embryo of five days?

Dr Smeaton—The IVF clinics—certainly the ones we have worked with in the US—grade their embryos during the early stages of development into those which are considered viable and capable of implantation and those which are not. The ones which are either implanted or frozen

for later use, and those which are not are discarded. It is from tissue from those materials which are discarded that we are able to isolate prospective cells.

Mrs VALE—I see. In your allogeneic cell therapy, is that from the same non-implantable embryos?

Dr Smeaton—It is the same source.

Mrs VALE—You say the autologous cells are actually sourced from the patient. Where is the allogeneic cell sourced? Is that from the patient too?

Dr Smeaton—No. The allogeneic cell that is used is one which has come from an unrelated embryonic source.

Mrs VALE—I see. So it is one of the non-implantable ones.

Dr Smeaton—It is one of the non-implantable ones. So the genetic material is different from that of the patient. In the case of the autologous one, we are starting out with a cell from the patient. What we are actually interested in is the nucleus from that cell, and by reprogramming we take that nucleus back. So we are using—

Mrs VALE—So you still use the non-implantable embryo of five days, that particular tissue material, and you also take a cell from the patient himself.

Dr Smeaton—That is right.

Mrs VALE—So you are virtually working with two cells.

Dr Smeaton—You are working with two cells and your interests are in the non-nuclear content of one for the nucleus to be reprogrammed from the other.

Mrs VALE—Right. How far along is the research before you result in any clinical trials?

Dr Smeaton—As far as the autologous cell therapy is concerned, we are quite a long way away from that. That is not where our main focus is at the moment. We believe in the case of allogeneic. If some of our human cell work goes very well in terms of paralleling our mouse model, we could be ready to start clinical trials—and I am being very optimistic—in perhaps two years. But it will probably be more like three.

Mrs VALE—I have one last question. Apparently in March this year in the *Weekend Australian* there was actually an article that showed a United States report, where there were some Parkinson's patients who were injected with cells.

Dr Smeaton—That is right.

Mrs VALE—Some of them, about 15 per cent, had some rather alarming responses. Do you have any comments that you would like to make on that?

CHAIR—Dr Smeaton has actually answered that question before.

Mrs VALE—Has he? I am sorry. I must have been reading something else at the time and not paying attention.

Ms JULIE BISHOP—I would like to follow on from that and discuss the research environment in this country. From your experience, do you have any comment to make on the approach the Australian Taxation Office has taken with respect to syndicated research and development in relation to investors obviously seeking deductions? How has that sort of approach impacted upon the decisions that your company makes?

Dr Smeaton—It is an interesting question. We have had two syndicates in the past. The earliest one is the subject of one that the ATO is attacking, I guess. I think that currently the likelihood is that that case will go the Federal Court.

Ms JULIE BISHOP—Can you just give me an understanding of what the issue is in relation to the tax office's stand?

Dr Smeaton—It principally revolves around an issue of valuation of core technology, which I understand from a discussion with the tax office is a problem that they believe they have with quite a large number of syndicates. I think they are treading on fairly shaky ground here because, as we have seen perhaps in the recent gyrations of the stock market on a fairly gross level, the valuation of technology is very much a point in time thing.

So the tax office has some difficulty with my view on it, which is that there is a change in the approach. Basically the rules were changed after the game had been played. We entered into syndication in good faith. It was a previous government of course at the time and that program was being heavily promoted by the government as a way to encourage research and development. We went into it with perhaps a fairly large amount of legal advice and felt we were on sure ground, and that has proved not to be the case.

I guess the revisiting of technology valuations by the tax office in our case is proving to be a huge distraction of time. If it does go to the Federal Court I would speculate that that probably will not be an overall good for the health of the company, so we will be keen to insulate ourselves from that as much as possible, even though the company's actual downside has been capped at $1 million as described in our prospectus. More than half of the investment of original shareholders in the company is at considerable risk should we not prevail in the court—if it gets that far.

Ms JULIE BISHOP—In other words, the syndicate had rulings at the time but not in relation to the value of the core technology, although you would have known the figure at the time.

Dr Smeaton—We, as in all the other syndicates. There was a tax ruling and an IR&D board ruling and the valuation was all part of that. So we are not very happy with the current state of events even though we would be very confident that, if this did go to the Federal Court, we have a very strong case in defence. There is no doubt that the research was done. That is not an issue. The research was also prospectively successful. One of the principal aims was to bring a

Transgenic-based pig to the table. That was stopped by government inaction in terms of not having appropriate rules in place. Then the whole GMO debate caught up with it subsequently. So that would probably not have been a prospective thing but, if the timing had been right, that could have changed that whole debate. I can report that, as of yesterday, we have signed an agreement in principle with a large pig company to take that technology forward. So the notion that this technology was valueless, as the tax office contended at the time, I think is just plain wrong.

Ms JULIE BISHOP—In other words, when we are talking about a regulatory framework there is also the taxation regime that must be taken into account.

Dr Smeaton—That is certainly true, but we need surety in terms of government incentives—and I feel the R&D scheme was a government incentive; it was certainly sanctioned by the then government—and need to know that we are not going to have the rules changed down the track. If this all goes forward and one or two test cases are lost, that is going to send a very bad signal to the investment community. On the other hand, if we win, it will probably cost us $5 million for legal fees to take one of these cases to court. It just seems like a very unproductive use of time, and the loss will trigger a cascade of further legal cases through the system as perhaps investors sue packages, et cetera. A very ugly scene could evolve and be very distracting to Australian research going forward.

Mr MURPHY—I am interested in gaining a better understanding of Parkinson's disease, the aetiology of that disease, the impact on a patient and the central nervous system, and also your hypothesis arising from these two varieties of cell therapies that your company is developing. Could you explain to me briefly what happens to the body when one gets Parkinson's disease and how you believe these two varieties of cell therapies that actually implant cells into a patient could ultimately cure Parkinson's disease?

Dr Smeaton—Parkinson's disease is due to a small group of cells in the Substantia nigra which produce the signalling compound Dopamine. That group of cells dies and over a period of time—and it can be as long as 10 years for the initial symptoms to get worse and the disease may progress over 30 or 40 years in some cases and can be faster—the patient gradually loses the ability to move through stiffness of joints in the early stages. The end point is always death, but the patients become highly crippled along the way. They lose movement and speech. They sometimes develop Dyskinesias where they get uncontrolled movements. Shaking in the limbs is one of the early symptoms of the disease. So it is a progressive disease.

Our hypothesis, and it is somewhat validated by Freed's work, is that if you can replace those dying cells—and we do not know why they die—then there seems to be good reasons to believe that neurones placed in the right place will start to form the connections that have been lost and produce the Dopamine in the right areas. You can treat with L-dopa for a period of five to 10 years, depending on the patient, and get the some results, but the disease inevitably progresses.

Mr MURPHY—What reasonable hope would Parkinson's disease sufferers have with regard to a potential cure in our lifetime?

Dr Smeaton—I think we will be able to start clinical trials in the two-to three-year time frame if our work with the mouse is validated in human cells. Then clinical trials will take in the

order of two to five years, but we would perhaps start to see results in as early as one year. Given that very uncontrolled—that is, not measured or characterised or standardised—cellular implants have produced benefit in a small group of patients, that would give us great hope that, especially applied to younger patients—those under the age of 60 or 65—there is a good prospect for at least stopping the further progress of the disease and perhaps even curing it. We do not want to hold out false hopes to patients but this sort of therapy is going to produce results which we have not been able to see before.

Mr St CLAIR—You said you do not know why cells die. Is it that the cell would have a defect in it, or is it that it is an external influence upon the cell and therefore if you replace it—

Dr Smeaton—It may die too?

Mr St CLAIR—Yes.

Dr Smeaton—That is one of the concerns. It is also why we are interested in the catheter technology and the ability to measure the environment where we are placing the cells and to monitor it subsequently so that we may gain information and perhaps have to put in growth factors and things like that to nurture the new cells.

Mr CADMAN—Earlier, you described the process of discarded embryos and said that those are the ones you would want to use. How do you ascertain whether or not there are any genetic or metabolic disorders in those cells? You say that they are not suitable for implantation, so therefore there is something wrong with them and maybe there are more than a couple of things wrong with them. How do you verify that?

Dr Smeaton—That is a good question. How we would address that is by producing large cultures of these cells—we would be able to multiple them up essentially infinitely so we have a source of cells on which we can do quite extensive and very searching quality control procedures to determine, for instance, that the chromosome numbers are right and that sort of thing. We would be able to do a lot of evaluation on those cells to determine—

Mr CADMAN—Can you just stop there so I can make sure I have got this right. You have a large number of single cell embryos and you are unsure of the quality of them. What happens next?

Dr Smeaton—We would start with a single embryo which was going to be discarded. From that, we would grow out a culture, which probably starts from perhaps a single cell within that embryo. That cell we can then multiple up indefinitely, as an embryonic stem cell, to trillions of cells, if that is a requirement. We then have that cell culture where we have a lot of material available and it is genetically homogeneous.

Mr CADMAN—I understand what you are saying. How many cells of this type would you want to advance, as a reasonable sample, to be sure that you have covered the prospects of any metabolic or genetic problem?

Dr Smeaton—We would make the measurement on samples from that cell bank before and after the differentiation process.

Mr CADMAN—You are not answering the question, with respect—not in a way that I understand it, anyway. How many cells would you want to take to make sure that you covered any prospect of there being deviations that you did not accept?

Dr Smeaton—All the cells are the same, so it would be a sampling procedure.

Mr CADMAN—I am sorry, how many embryos would you need to make sure of that, because they are reject embryos?

Dr Smeaton—They are reject embryos. Each individual embryo was leading to a large culture, so the cultures are discrete and separate, and while genetically identical in themselves will be different to each other.

Mr CADMAN—So you would only need one cell from each embryo?

Dr Smeaton—You only need one cell from each embryo, in theory, to multiply up your culture. Then, having got that large culture, you can do the appropriate quality control tests on it.

Mr CADMAN—At what point would that be done?

Dr Smeaton—That could be done right at the beginning, once you have multiplied the cells up and have the cell bank. You would want to do that to make sure you had a high quality cell bank before going to further steps.

Mr CADMAN—At what point would you be able to assess the chromosome profile?

Dr Smeaton—You can do that right away.

Mr CADMAN—I am not sure that I completely understand the way in which you intend to do things. Let me think about that, and I will drop you a line if I need further information.

Dr Smeaton—Okay.

Mr CADMAN—It seems to me that a lot of the people we have heard from have obvious regulators in Australia. What are the regulators that you have to confront?

Dr Smeaton—We believe we will be discussing this technology with the TGA, although at the moment my understanding is that if you wanted to take something like this into a clinical trial you would only have to satisfy the ethics committee at the hospital at which you are going to do that work.

Mr CADMAN—Why would you need to even confront a hospital ethics committee?

Dr Smeaton—I think that would seem to be a prudent thing to do.

Mr CADMAN—But there would be no legal requirement, would there?

Dr Smeaton—I think there is.

Mr CADMAN—But aren't you outside that process?

Dr Smeaton—As the law stands, we believe we are outside the TGA process—which does not mean that we are not consulting with them—but I understand that, for this sort of therapy, we would be bound to talk to a hospital ethics committee. This is really a transplant type procedure.

Mr CADMAN—Yes. As a private organisation, I just do not know how you relate to that hospital environment. I do not see what role they would have to either supervise you or to advise you. You would set your own agenda, and they would only be interested in the end product.

Dr Smeaton—We have been working with hospital ethics committees even at this stage for some of the early work.

Mr CADMAN—Which ones?

Dr Smeaton—With the Royal Adelaide Hospital and also in work through the South Australian Health Commission.

CHAIR—Just so that I am clear: because the derivation of cells involves clinical procedures and is undertaken, presumably, in hospitals or in hospital related institutions, you work through the ethics committee?

Dr Smeaton—I think we are really looking ahead in making them aware of where we are trying to go and in getting a feel for what the ethical requirements may be. We are doing the actual isolation of the cells and the manipulation of the embryos in Atlanta. Similarly, we are working with an ethics committee there that, in this case, is an outside body set up for that purpose. The other thing is that we are following the NIH guidelines in terms of consent and that part of it. There is an issue there in using non-frozen material that we are now starting to discuss with FDA—and ultimately with NIH—as far as those guidelines are concerned.

CHAIR—When you said 'an outside body', I did not quite understand what you meant.

Dr Smeaton—I cannot remember what they are called, but it is like a board that monitors these sorts of things, an outside institution. It is not a government body, as I understand it, but it looks at these sorts of procedures.

CHAIR—Can I just follow that up further in terms of the American system? Some suggestions have been made that the new administration in America might have a more restrictive outlook. Do you have any comments about that?

Dr Smeaton—We are certainly following those developments with interest, but I think the main issue there is whether, through the National Institutes of Health, which is a publicly

funded body, public or taxpayers' funds are going to be used to carry out some of this research. The issue certainly has not been raised as to whether private funds will be in any way affected.

CHAIR—Are you saying that there may well be some constraints imposed through the National Institutes of Health on public funding but that if it is entirely privately funded you expect it will fall outside any such parameters?

Dr Smeaton—At the moment privately funded work is certainly permitted. NIH has been studying a liberalisation of the guidelines and procedures, because certainly there are a significant number of NIH supported scientists who want to work in this field with those funds. Until there was a change in administration there, it was certain that NIH was going to start funding this work. While the Bush administration have said that they want to take a look at it, I think the momentum is now coming back to NIH actually starting to get public funding going into this area.

Mr CADMAN—If you wanted to import these cells that you have derived from embryos in the United States, would there be any limitation? You would not have to pass any inspection criterion; you could just bring them in and start working on them?

Dr Smeaton—We did licence a cell line from a WiCell, which is associated with the University of Wisconsin, and we were able to bring that cell line in without any restrictions. AQIS were involved. Similarly, I believe, Alan Trounson has brought in a cell line from Singapore.

Mr CADMAN—Yes. That would be exactly the same process. However, I understand, because of the set up, he would have an ethics committee or a procedure anyway because of the public funding situation. He would have somewhat stricter controls or limitations. He would have to watch somebody watching him more carefully than you would. I do not mean that you would be careless—I do not want to imply that. The compliance factors that he has to deal with would be more significant than yours, wouldn't they?

Dr Smeaton—I suspect we are actually treating it in very similar ways in terms of how we are involving ethics people.

Ms ROXON—Let me ask a question on a separate issue—and if you have already answered it, please let me know. One of the reasons that we are being encouraged to make sure that we do not do anything that restricts this type of research unnecessarily in Australia is the potential benefit to Australia of being able to commercialise as a result of the research being done here. But you said in passing that anyone who is using these products will get sent two boxes: one with the cells and one with the hardware, which you are not going to be making. What actual benefits will there be to Australia? What will be commercialised here under the way your company is operating? With respect to the people who are urging us to make this decision on the research, could you give us an example of how that would develop and deliver some benefit to the country if we were to do that or to continue to allow it?

Dr Smeaton—The benefits flow potentially in two ways. There is a reasonably obvious benefit to patients if the technology proves to work. From the company point of view, because we would be trying to sell this technology as widely as possible, we have already taken steps to

internationalise our operations. We collaborate with a group in the UK on another product and we have our operation in Georgia in the United States. So we are trying to have a footprint in different parts of the world to interact with the regulators and to be involved in the markets. Just from a population point of view, the major markets for this technology will be in the United States, other parts of North America, Europe and Japan and, increasingly, in places like the Middle East where there is a rising population that is able to afford this type of advanced medical technology. We certainly intend to sell our technology on a world basis, and the benefits of that will, of course, ultimately come back to our shareholders. At the moment the shareholder base is about 80 per cent Australian. In that way, Australia will benefit from the work.

Ms ROXON—But not from any larger scale production here and then exporting of the catheter and micro-coils, or whatever particular things you might then sell?

Dr Smeaton—I think perhaps the real benefits in this come from the commercialisation of intellectual property as opposed to what you might call widget manufacturing. While there would be a profit associated with making the actual catheters, the real benefits will come in the intellectual property which is going to be reflected in the price of the product as opposed to the overall price of production. In terms of production of the cells, our current belief is that it will be necessary to manufacture those reasonably close to the market for logistical issues so we would anticipate making cells in a number of places around the world from standardised cell banks.

CHAIR—On intellectual properties, I understand that Geron Inc. has claims to ownership over a lot of the intellectual property in this area generally. Do you have licensing arrangements with Geron in relation to what property it claims to own?

Dr Smeaton—No, we do not. Similarly, Geron does not have licences to the intellectual property that we claim to own. We have perhaps a different opinion to Geron on the potential value of its intellectual property. While I cannot go into details for commercial reasons, we believe that we may be able to find ways that its intellectual property is not actually required to practise our art.

CHAIR—But if you cannot one would presume, given Geron's size and interest, that Geron would be pressing its claims.

Dr Smeaton—Likewise if they were transgressing on our intellectual property, we would have similar claims. While they may have claims to the basic embryonic stem cell technology, we have claims which relate to how you may use that technology. The normal commercial course here is that some sort of cross-licensing arrangement is perhaps entered into, and Geron are not that much larger than we are in terms of the number of people employed.

Ms ROXON—I understand the commercial interest between the different companies, but what about if we, as politicians, are concerned about the public interest and we are worried about benefits that can ultimately be delivered to the patients? Why is it in the patients' or consumers' interests for us to set up a system which allows you to protect rather than share the different types of areas and intellectual property that you have that might, through working

together, deliver a better benefit to the patients who are ultimately going to use your technology?

Dr Smeaton—When you say 'working together', do you mean the companies working together?

Ms ROXON—If the companies are asserting the intellectual property interests, which presumably they are, and you are seeking to protect your own interests by restricting who else can use it, don't we lose some of the benefits of cooperative research or of what should be in the public domain?

Dr Smeaton—No, I do not really think so at all. If there were not the ability to protect the intellectual property, there would be no incentive for the work to be done in the first place. So it simply would not happen with private funding. Given that a number of companies are involved in this, and there are several mining claims being staked out, you will probably see that it will be some sort of coalescence of the different claimants to form a very large mine perhaps at the end. That is the normal course of these things. There will be a lot of companies involved at this stage, and there are new ones forming quite rapidly with different angles in this area.

Ms ROXON—It will be survival of the fittest.

Dr Smeaton—Yes, it will be survival of the fittest. It will all come together, but the driving force is to put products out into the marketplace for the benefit of patients.

Mr BILLSON—On the widget manufacturing not being terribly high value and arguably the cell production not being of great wealth creating value either, your art, as you described it, obviously is where the key value is in what you are doing. How would you envisage your research feeding into the practice of your art delivering benefits for Australia so as to warrant a world competitive, attractive research environment? I guess the corollary of that is if, at the end of the day, you are practising your art at corners around the globe—and all we are going to get are a few high-powered medicos earning some decent bucks in Oz, paying their taxes—then the public pain of arguing vigorously for a favourable research environment might be less attractive than it would if we could show a broader benefit to the economy.

Dr Smeaton—Surely there is a broad benefit to the economy if it is Australian based shareholders who are capturing that intellectual property value.

Ms ROXON—But there is nothing to control it so that your company will continue to have Australian based shareholders. There is nothing to restrict that, is there?

Dr Smeaton—That is the same with any company. Shareholders are able to buy and sell their shares as they see fit.

Mr BILLSON—Can I put the question another way: one of my strong contentions is that there is broader good in an attractive research environment, and your eloquent presentation has basically shot a lot of holes in that argument—thank you for that—because of the factors that are at play there. I am hoping you will rearticulate the virtue of a conducive research environment in Australia to reassemble some of my argument, please.

CHAIR—If we were in a court of law, I would be objecting most strenuously now.

Mr BILLSON—I am heavily leading the witness. One of the issues is that there is a broader public, economic and social good in having this leading-edge international research done here and not somewhere else, but it is very easy for people to say, 'This is horrendous. The world is going to come to an end. Regulate the life out of it and send it somewhere else.' I do not think that is terribly clever. Some of the arguments for bouncing that sort of argument involve the return to our nation.

Dr Smeaton—I think having a conducive research environment will ensure that major intellectual property is developed here so that the ownership of that intellectual property rests here. We will just have to hope that Australian investors increasingly come to recognise that. At the moment it is probably fair to say that they place a lower value on it than some of the overseas investors. In some of the dot.com areas, they might have been very wise.

If the research is done here, you will see the generation of companies like ours. We are not a large company at this stage, but we are certainly significantly larger than we were three or four years ago and we are growing. While we are growing here and we are also growing in the United States, the fact is that we are growing here and that we will have a growing presence. That all depends upon having a conducive research environment and the ability to patent inventions and to ultimately obtain that benefit. There is a lot of value added when you have a unique proprietary product.

Mr BILLSON—Thank you for the CPR for my thinking. I appreciate that.

CHAIR—Just to follow up on Ms Roxon's question, I seem to recall that at one stage you announced that were going to seek listing on Nasdaq.

Dr Smeaton—We actually have a level 1 Nasdaq listing at this stage, which means that ADRs, American depository receipts, can be traded by investors in the United States who wish to participate in our growth. We want to move to a level 2 Nasdaq listing later on this year, which means that the stock will be listed on the over-the-counter market. Our interest there is ultimately to have a platform in recognition of our achievements and our intellectual property in what is a larger and perhaps more sophisticated market in the evaluation of these technologies. We hope that will flow through to be reflected in the overall value of the company.

Certainly, the markets are rather difficult at the moment compared to how they have been, but that will change. Getting a larger valuation, a greater appreciation of our intellectual property, will enable us to perhaps raise the next funds that will be necessary to carry this through to a completed product to put before patients at a much lower dilution to our existing shareholders. While we will welcome continuing participation by Australian shareholders, we think we can perhaps do them a great favour by having a valuation that is higher and is put on by world markets rather than by Australian ones.

CHAIR—Do you foresee any limiting factors in the US?

Dr Smeaton—The regulatory issue is always one, but that is one we all have to face. I think getting past that one will be important, expensive and time consuming, but nevertheless it is

something that has to be done. Part of our thinking in being involved in the US on a physical basis is that we are now sitting behind what, in my view anyway, is a non-tariff trade barrier. The FDA, while it is a regulatory agency, certainly favours domestic companies and, by being behind that, I think we overcome that problem.

Mr CADMAN—Do you think scientists would leave Australia if regulations were more restrictive in Australia?

Dr Smeaton—That would be a risk, but I do not think scientists are against sensible regulation. We recognise the need especially for product safety to be monitored by an outside body to give consumers ultimately the confidence that they require to utilise these advanced products. There is probably more an issue of being able to pursue areas of science which people are interested in and perhaps of the personal award system. We have still got a long way to go to have a competitive tax system for more entrepreneurial people here.

CHAIR—Have you looked at the impact of the new Gene Technology Act?

Dr Smeaton—Not specifically in terms of this. It basically follows the GMAC guidelines and puts those into law. My personal view is that GMAC was one of the better examples around the world of how that area of endeavour was regulated, if that is the right word. From what I could see, the voluntary compliance worked very well, and I think it is a pity that that had to be replaced by something which is much more expensive and clumsy for the taxpayers to run. That was unfortunate, but that has happened. In terms of this work we are doing now, we are not contemplating gene modification in our first product endeavours so we do not actually run up against those requirements.

Mr BILLSON—Plus you do not cross over the containment ethos in the GTA until you start wanting to do something with what you have mucked around with, and you are not quite there yet.

CHAIR—I only asked that because there is some debate about what certain definitions in that act actually mean. I take it you have not looked at that.

Dr Smeaton—I have not had the need to look at it carefully. Since we got out of making transgenic pigs, we have been doing very minor stuff in that, using modified bacteria to make proteins.

CHAIR—You said that the UK law would be helpful. I take it that you would be happy with the provisions of the UK legislation—for example, seeking specific licences for specific projects, which you require under the Human Embryology and Fertility Act; and the consent provisions, such as that persons must give consent to the use of an embryo produced from their gametes, specifying the purpose or purposes for which it may be used.

Dr Smeaton—We are already complying with equivalent provisions in terms of how we are operating in the US, using basically the NIH guidelines. We have two stages of consent: first of all, to use the embryos at all and then, subsequently, at a time point which is removed, to gain a further consent to use them for commercial purposes.

CHAIR—What about the first part that I asked you about, namely the research licences?

Dr Smeaton—I would probably prefer not to have those sorts of restrictions, but that would be something that probably would not be too big a barrier.

CHAIR—John, you wanted to ask something.

Scientific Adviser—Yes. Dr Smeaton, I wondered if you were proposing to carry out studies on adult stem cells, or ways to avoid an embryo stage of development?

Dr Smeaton—We had a program as a result of an acquisition in the US—we acquired a company there and inherited a program which was looking at stem cells isolated from cadavers, from recently dead people. We have chosen to discontinue that program because, while there were some interesting cells being produced, we felt that that type of approach had risks in terms of CJ disease, which has been a problem from that sort of material in the past. We also feel that the quality of the cells that we are able to make from embryonic stem cells—and this is very subjective, looking at other people's data—appears to be higher, which is an advantage. We are following what is a natural pathway and we think we know a lot more about the material. So while we would not totally discount the ultimate use of intermediate stem cells, particularly when it comes to autologous types of therapy, that is not really one of our current interests. The other thing is that there is an intellectual property minefield in that area which we do not really have a position in.

CHAIR—Dr Smeaton, thank you for coming today and discussing this with us. It has been most interesting and, hopefully, useful for us in our deliberations. We appreciate your time.

Dr Smeaton—Thanks for the opportunity to come and talk.

CHAIR—I thank everyone for their attendance and thank those recording the evidence.

Resolved (on motion by **Mr Billson**):

That this committee authorises publication of the evidence given before it at public hearing this day.

Committee adjourned at 11.10 a.m.