

I'd like to introduce your first speaker, Ms. Natasha Pinol, in the Office of Public Programs at AAAS.

**Natasha Pinol**

Hello and good morning. I'm Natasha Pinol, Communications Officer for the journal *Science* in the AAAS Office of Public Programs. This embargo teleconference is being made possible today through the generosity of the American Association for the Advancement of Science or AAAS, the nonprofit, international Science Society that publishes the journal *Science*. I want to thank the panelists and the reporters for joining us this morning. An audio file of this teleconference will be posted on the *Science* press package website today.

Please note that the AAAS Office of Public Programs is lifting the embargo effective immediately on the article *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells* because of an embargo break. The article will be published online at the *Science* express website at noon today, 20 November.

On the line with me are Dr. James Thomson, professor of the University of Wisconsin, Dr. Junying Yu, from the Wisconsin National Primate Research Center at the University of Wisconsin, and Teri Debit, press officer with the University of Wisconsin. The authors will be our speakers today and will each offer about a 5 minute summary of their primary conclusions. Dr. Junying Yu is the lead author on the *Science* paper, and Dr. James Thomson, corresponding author on the paper who will speak first, then followed by Dr. Yu. The authors will then participate in a question and answer session following their remarks. Thank you for joining us. Dr. Thomson?

**Interviewee – James Thomson**

Hi, this is James Thomson. I should be a lot faster than 5 minutes because I know you have a lot of questions and have limited time. It's been about 10 years since we derived the first 2 embryonic stem cell lines, and at least this storm of controversy has lasted all the way up until today. And I believe that these new results, while they don't eliminate that controversy, it's probably the beginning of the end to that controversy because I think more and more labs will pursue a reprogramming task to get pluripotent cells rather than deriving them from embryos. This does not mean that it's the end of human embryonic stem cell research. If for no other reason we need a gold standard to which to compare these new cell lines. But I do believe that over time these new cells will be used by more and more labs and embryonic stem cells will be gradually used by fewer and fewer labs. (1:50-2:35)

Now that doesn't mean that human embryonic stem cells are not important. These new cell lines would definitely not have been derived if it had not been for the last decade or so of human embryonic stem cell research. We needed to understand what the cells are like, we needed to understand the culture conditions, and both our work and Dr. Yamanaka's would not have succeeded without that research. I do nonetheless think that the world has changed because of this new result. (2:36-2:59)

**Interviewee – Junying Yu**

So in this work we basically identified the 4 genes that can turn human skin cells into pluripotent stem cells. I would just like to point out that these 4 genes we identified among the 2 genes of 4 we found them to be essential for turning skin cells back into pluripotent stem cell state. The other 2, NANOG, and LIN28 are beneficial. That means that without these genes we can still get pluripotent stem cells from skin cells but at a very low efficiency. So I wouldn't be surprised if there will be other genes other than NANOG and LIN28, such as Oct3/4 and Klf4, from Yamanaka's work that go our work on deprogramming skin cells. (3:00-4:04)

**Natasha Pinol**

Thank you. Now we'll open a call for a question and answer session with the authors.

**Operator**

The first question comes from Maggie Fox from Reuters.

**Caller**

Good morning. I'm wondering Dr. Yu, you just touched on it that your team and the other team have 4 different genes that you're using to reprogram these cells. Is it going to be an optimal group of genes or is it going to be a moving target and what does this mean? (4:36-4:55)

**Interviewee – Junying Yu**

We don't know whether this is optimal genes, we just found these through subgenes that working, and from the genes that we screened, that's over 100 genes, these 4 genes give us the best result. And with the more workers try to understand how these genes actually can causes human skin cells to go back to a pluripotent state. I'm sure there will be additional genes for other treatments that can significantly improve the efficiency. (4:56-5:32)

**Caller**

Can I ask, did you try the other group's 4 genes since that had been published previously?

**Interviewee – Junying Yu**

Yes.

**Caller**

And what happened when you did?

**Interviewee – Junying Yu**

At that time we already found our own combination, so we didn't spend much time trying to figure out whether the mouse 4 genes work in humans. (5:46-5:56)

**Interviewee – James Thomson**

Basically we tried it kind of quickly and we couldn't get it to work, but it looks like the balance of the genes was really critical to getting it to work. We didn't spend that much time on it. (5:57-6:06)

**Operator**

The next question is from Malcolm Ritter of the Associated Press.

**Caller**

Hi. Two quick questions. One is I guess maybe for Dr. Thomson. You mentioned the strong controversy about embryonic stem cells. My boss actually wants me to ask, why did you seek this route, why did you seek this noncloning route, was it to avoid the ethical controversy of cloning. And secondly, would this method bring us closer to the cloning of humans – could you do that with these cells? (6:14-6:39)

**Interviewee – James Thomson**

So the first question is the reason we did this in the first place was Dolly. And prior to the cloning of Dolly development biologists really didn't think that things could go backwards like that. But it was clear that something in the egg was doing this. And one method of trying to figure out what's in the egg is people could vaccinate it and do biochemistry and do it that way. We just took a different approach where we took this commentarial screen and say can we find a set of genes that do it? So we weren't avoiding ethical controversy we just thought this was the more practical approach that would get there quicker, and it turned out because of the limited number of genes that this screen worked. If it turned out to be 100 genes this screen would never have worked in the first place. And remind me of your second question, I'm sorry. (6:40-7:19)

**Caller**

The second was whether these cells can be used to essentially clone a human?

**Interviewee – James Thomson**

Basically any cell in you body can do that, so I don't think that raises concerns that either the original database of the human embryonic stem cells raised originally or that cloning in Dolly had raised. So, in the Dolly it shows that theoretically any cell in your body can form a whole human being, and it's probably true of these cells if you manipulate them enough. If you simply put these cells into the body as they are, they would not form a human being. (7:25-7:47)

**Caller**

One last thing. You've talked about the prospect of some day directly reprogramming cells within a person's body from one adult type to another, not even going through a pluripotent state, what might that accomplish – can you talk about that? (7:48-8:01)

**Interviewee – James Thomson**

Yes, so this might be the first example of many. Dolly showed that you can go all the way back to this ground state and this is the first attempt at defining the factors that do that. But when you think about it, you don't really want to go back to the ground state,

you want to cause cells in your body that normally do not repair themselves to undergo a repair reaction. So if we understand what maintains a particular cell in its particular state, like the heart cell, we might be able to change it in another cell that could actually engage and repair in a way that they don't normally do, and because of Dolly, suddenly that all seems possible. So it's not a mistake or a coincidence that just disappears after the cloning of Dolly there's all those **transdifferentiation** papers, and a lot of that kind of faded away. But I think the idea of having cells become things that they don't normally become is very open and viable now, and this might be simply the first example of this, and there might be many to follow. (8:02-8:55)

**Caller**

But if you have a heart cell that's failing, you don't want to turn it into a liver cell.

**Interviewee – James Thomson**

No, but when you think about the heart, it normally undergoes a repair reaction that just gets fibrotic tissue. So if you can modulate that in a way that heart cells actually divide or repair more efficiently, that would be a very useful thing. And that is going back in development to the more modest way, but it seems more likely to happen though. It's not anytime soon, but I just think that in a robust regenerative medicine you're not talking about transplantation, you're talking about changing the face of cells in the body. (8:56-9:31)

**Operator**

The next question is from Erin Smith of CNN Money.

**Caller**

Hello there, thanks for your time. I was just wondering if we could just back up for a second and you could just explain in nonscientific language exactly what you discovered, this sort of cloning sidestepping method, and maybe go into a little bit of detail on its implications for stem cell research going forward. (9:39-9:59)

**Interviewee – James Thomson**

At a very basic level, embryonic stem cells are a cell that can divide forever, so they can make as many as you want. And they can form anything in the body. And there's never been good evidence for such a cell in the adult, but this new paper shows a method of making a cell into a state that's essentially identical to embryonic stem cells so they can divide forever and they can form anything in the body. So it's just a very powerful cell that can make individual cells from the human body either for basic research or for transplantation. And in some ways this changes everything because it really will change the ethical debate and the source of tissues, they're not from embryos anymore. But the same properties of embryonic stem cells apply to these so we're basically at the same ground state and all the challenges of using embryonic stem cells are pretty much intact for these cells. (10:00-10:43)

**Caller**

And you can use any kind of tissue to draw these cells from?

**Interviewee – James Thomson**

We don't know yet. We've tried skin fibroblast. It may be possible to do it from a variety of cells, but that's a very easily obtained cell type. (10:44-10:55)

**Caller**

Okay. And that's human skin tissue you used?

**Interviewee – James Thomson**

In this case, yes.

**Operator**

Does that conclude your questions?

**Caller**

Yes, thank you.

**Operator**

The next question is from Clyde Cookson from the Financial Times.

**Caller**

Thanks very much. I would like to ask what the patent position is here because the Wisconsin Patent became famous for human embryonic stem cell work. Are you planning to patent your discovery, you're combination of genes? What's the intellectual property composition here? (11:11-11:31)

**Interviewee – James Thomson**

In the United States, if you use federal funds you're required by law to assign the patent to your institution which, so I disclosed these findings to **work**. And what will be the patent position you should follow up with them because I suspect it will be very complicated. (11:32-11:44)

**Caller**

Okay, but this is being patented?

**Interviewee – James Thomson**

They will attempt to patent it, yes.

**Caller**

Okay, thank you.

**Operator**

The next question is from Rick Weiss of the Washington Post.

**Caller**

Hi, thank you. I wanted to know if any of you're experiments so far have shown evidence of tumor growth when these cells were put into, I don't know, either in vitro or put into mice, even though I know you don't have **the ischemic** genes in there, it seems like these are genes that lean towards proliferation. (11:57-12:17)

**Interviewee – James Thomson**

Yeah, so in the teratomas we made, so that is a tumor.

**Caller**

I guess I meant other than the teratoma that you're hoping to see.

**Interviewee – James Thomson**

So right now in a few of the clones, and this is a small number, there was a fairly undifferentiated population in that. If you look at the paper there's 4 different clones from the **fourth**. Two of them were less differentiated at 5 weeks than we would have anticipated. Now it wasn't consistent with a malignant growth, but it did suggest that the overexpression of the genes was changing the dynamics of differentiation in those growths. (12:20-12:52)

**Caller**

Were you able to see a difference in expression levels that correlated with that trend towards nondifferentiation?

**Interviewee – James Thomson**

Yeah, so in the 2 clones that did this, they didn't downregulate the NANOG and OCT4 very well during embryo body formation. And we suspect because they're not downregulating those genes they're partially inhibiting differentiation. (13:00-13:11)

**Caller**

So one last question – would alternative methods for getting these genes or gene products into a cell that did not involve retroviruses, would those kinds of methods inherently make it easier to make sure you got the downregulation or gene shutoff?

**Interviewee – James Thomson**

Yes, I think everybody is trying to do that right now. And given that Dr. Yamanaka had the cells for a couple of years in mouse, I guess he's pretty far along on that. There's no inherent reason why you can't use a nonintegrating vector to do the exact same thing, and we chose **lenti**virus just because it's what our lab uses all the time, but there's a variety of other vectors that don't integrate. (13:27-13:43)

**Caller**

And when they don't integrate you get downregulation easier?

**Interviewee – James Thomson**

There's ways of getting rid of the vectors quite easily if they're not integrated. (13:47-13:49)

**Caller**

Okay, thanks.

**Operator**

The next question is from **Hurton Escavar of Esperado**.

**Caller**

Yes, good morning. How similar are these cells exactly to through embryonic stem cells. Like if you had this IDS cell right next to a true ES cell, could you tell the difference between them, and how could you differentiate between one and the other or are they pretty much exactly the same? (13:58-14:15)

**Interviewee – Junying Yu**

Pretty much most of the markers we know about embryonic stem cells they're expressed by these stem cells. At this point we really have no idea whether there's any significant difference between these cells and human embryonic stem cells. (14:16-14:36)

**Interviewee – James Thomson**

Basically they gave them to a researcher and didn't quite tell them where they came from. They **updated** embryonic stem cells. (14:37-14:44)

**Caller**

And just a followup on that. Based on these results, does it still make sense to continue to work with a nuclear transfer and the so called **cloning**, or do you see this as like the new frontier that everybody should be going in this direction now?

**Interviewee – Junying Yu**

Well, I would say no for the purpose of embryonic stem cell **anyway**. (15:00-15:06)

**Interviewee – James Thomson**

My feeling has always been that somatic cell nuclear transfer is a very good experimental technique that could lead to an understanding of reprogramming and it may still have a role in that. But it was so inefficient and expensive and difficult to do, so it'll probably never enjoy widespread therapeutic applications. I always felt that the technology would go around it. And I was a little surprised that it seemed to be going around it faster than I thought, but I really do think the path will be through direct reprogramming. (15:07-15:34)

**Caller**

Okay, thank you.

**Operator**

The next question is from Monia Baker from Nature.

**Caller**

Hi. I wanted to know what happened when you tried this with adult cells because you were using fetal skin and neonatal skin, right? (15:43-15:56)

**Interviewee – Junying Yu**

Yes, but we're currently testing with the adult skin cells for the 60-year-old female, and these skin cells actually come from epidermis and we already obtained the same pluripotent stem cells from them. (15:57-16:12)

**Caller**

And what's the efficiency?

**Interviewee – Junying Yu**

The efficiencies are lower than the fetal cells we have tried but it still is a reasonable efficiency. (16:15-16:24)

**Caller**

And I noticed that you said they'd been growing for 22 weeks at the time of the announcement. And I'm wondering if you have a, I don't know how long cells grow in culture that don't passage indefinitely – does that pass a particular barrier?

**Interviewee – Junying Yu**

In general I say the primary somatic cells will go under senescence after over 50 passages. And our cells definitely went past the limit. (16:45-16:55)

**Interviewee – James Thomson**

That's usually based on population doublings, and somatic cells usually go 50, 70 population doubling times, something like that. And ours are several fold higher than that already. (16:56-17:04)

**Caller**

And then one last question. It's really hard to assess the pluripotency of human cells, and I'm wondering 2 things. One is what additional experiments do you plan to do and there's a bill that's been proposed that would limit animal/human hybrids, and one test that was controversially tried, but it's controversial both scientifically and ethically was mixing human cells with a mouse embryo to see what would happen. And I'm wondering what you think of that and what other experiments you could try. (17:05-17:47)

**Interviewee – James Thomson**

So I think that certain kind of human/animal hybrids are frowned upon, but mouse models and other models are often used for transplantation recipients from human material. And I think these cells are no different in that regard. But it's very possible to

test a        function in such models. And also I think the primate model is going to come back now. It's the very first primate embryonic stem cells were derived in Rhesus cells prior to human embryonic stem cells. And embryonic stem cells from humans became very popular over the last decade, but when it comes to the practicality of showing the development potential and making transplantation models work, I think it's going to come back to that Rhesus model. And some of these issues are going to come down to reprogramming monkey material in a way that doesn't offend people as it would with human material. (17:48-18:32)

**Caller**

Thank you.

**Operator**

The next question is from John Faber of the Milwaukee Journal Sentinel.

**Caller**

Yes, could you go over again why you used fetal tissue and postnatal tissue, and I couldn't quite hear the answer on, I believe you said that there is an older adult that you've tried this with with some success although it's limited efficiency. Could you talk about why you chose fetal tissue as opposed to let's say a 50-year-old person who has Parkinson's or something like that? (18:40-19:09)

**Interviewee – Junying Yu**

Okay, so when you consider about the development of an individual, the cells coming from earlier stages like embryonic cells and fetal cells, they're closer to the pluripotent cells. These cells are much easier to be turned back into a pluripotent state compared to the cells coming from an individual, who's 50, 60 years old for example. So we basically tried to find out whether our gene combination works in the fetal cells, to confirm that. After we confirm that it worked for that, we tried more advanced stages of skin cells. (19:10-20:00)

**Interviewee – James Thomson**

The initial screen was actually for our group was done at embryonic materials derived from embryonic stem cells. And we discovered, Dr. Yu discovered that these based on that embryonic screen. And then we gradually pushed back what we thought would be more and more difficult cells. We didn't start with the most difficult we started with what we thought were the easiest ones, and it turned out that those 4 genes that she's found have worked for every cell we tested it so far. (20:01-10:26)

**Caller**

So are you confident that this can be done when it gets to the point of potential clinical applications that this can be done using the cells of someone who's 50 years old?

**Interviewee – Junying Yu**

We've already got the cells that, the pluripotent stem cells from a 46-year-old female, so I'm pretty confident that it can be done with a person over 50. (20:38-20:51)

**Caller**

I had one last question if I could. One of the people that I had talked to had mentioned this discovery and the other one that took place in Japan may encourage a lot of people who are already doing work with embryonic stem cells to essentially abandon what they've been doing and in doing so may cause more delays in the ultimate delivery of potential therapies using these types of cells. Are you concerned at all that people will walk away from this field and walk away from potential therapies that are being developed now? (20:52-21:28)

**Interviewee – Junying Yu**

Personally I don't think it's a good idea to abandon research on the human embryonic stem cells. This new research is just the beginning. We had to understand how these cells work and how similar these cells are to embryonic stem cells. So I would think most of the people still want to do research on the human embryonic stem cells. (21:29-21:53)

**Interviewee – James Thomson**

I would be surprised if investigators already established in the human embryonic cell field would abandon those cells. If for no other reason you need a gold standard to compare these new cells to. So in our lab we have the same 5 cell lines from almost 10 years ago, we use them all the time and we'll continue to do so. (21:54-22:11)

**Operator**

The next question is from Andy Pollack from the New York Times.

**Caller**

Yes, thanks so much. You've touched on this in a variety of the questions, but could you just talk for a little bit about what impact will this discovery have on the ultimate goal of developing treatments and cures using stem cells based on the knowledge from stem cells, will this speed it up at all, slow it down? (22:19-22:41)

**Interviewee – James Thomson**

And it certainly will not slow it down, but we do have to put this new advance in context. And when you look at the challenges of using embryonic stem cells in transplantation therapy, the ones that I thought were the really big challenges are not solved by doing this. So immune rejection is probably solved by making these cell lines, and that is a big challenge, but for most of these there are pretty good immunosuppressive strategies out there – what is the major deal stopper. The thing that's hard is understanding the disease you're trying to cure, and putting cells in the body in a way that actually corrects the disease and allows function to be established. And these cells don't differ from embryonic stem cells in that basic problem. So even though we have this nice new source of cells, it doesn't solve all our downstream problems of getting them into the body in useful form. So, it does get around immune rejection, but I think that's one of many challenges facing us and we have a lot of work to do still. (22:42-23:36)

**Caller**

Thank you.

**Operator**

The next question is from Saben Russell from the San Francisco Chronicle.

**Caller**

Thank you. Given that Dr. Yamanaka has been able to clone mice from his cell lines that he developed, I was wondering if you could in very simple terms explain the difference between one of these treated somatic cells and an embryo. I think the distinction is a little hard for the lay, the lay press to understand at times, and I was wondering if you could just explain exactly how it's different from an embryo because it sounds like it "walks like a duck and quacks like a duck, why isn't it a duck"? (23:48-24:30)

**Interviewee – James Thomson**

So, Dolly showed that any cell in your body could potentially form a whole human being. Embryonic stem cells, if you simply place them back into the uterus, do not form an embryo. You can probably manipulate them, like by nuclear transfer to go through Dolly in a way that you could get a whole embryo, but the cells by themselves although they have this remarkable developmental potential, they don't have that structure in embryo and if you simply transfer them to a uterus they would not form a baby, it would not go to term. So they're very much similar to embryonic stem cells, and what Dr. Yamanaka showed in the previous paper was that like embryonic stem cells if you put them in chimeras with a normal embryo they contribute in a very dramatic way. But they don't form an embryo by themselves in and of themselves. (24:31-25:14)

**Caller**

You're describing the function. Physically what is the physical difference between one of these treated somatic cells and an embryo?

**Interviewee – James Thomson**

Well they're fairly equivalent to a part of an embryo partway through development. So in the mouse it's not entirely clear what these cells are equivalent to, but there's a stage which has something called primitive ectoderm we believe that's probably pretty close approximation of these cells. (25:25-25:41)

**Caller**

What's that term again?

**Interviewee – James Thomson**

It's primitive ectoderm. It's kind of a debate what these cells represent. In some ways they're   artifacts. But it represents part of an embryo, not an embryo as a whole. And unless you have an embryo that's whole, it's not the equivalent embryo. (25:42-25:54)

**Caller**

One other question if I can. What is the kind of magic of 4 elements? The 2 teams used different, somewhat different genes, and is there any reason to think that simply having a certain threshold number like 4 is what did the trick or is it what's in the genes themselves? (25:55-26:18)

**Interviewee – Junying Yu**

So I don't think 4 is a magic number. Like I already said at the beginning, basically we found 2 genes, OCT4, SOX2, to be essential, that means without either of genes you cannot get the pluripotent stem cells from skin cells. And the other 2, NANOG and LIN28, are beneficial. And that means without these genes you could get pluripotent stem cells at a very low efficiency. In our paper, we already presented the data and 2 out of the 8 cell lines we characterized only 3 genes. Our research basically suggests there are 4, the number can go down. (26:19-27:08)

**Caller**

Thank you.

**Operator**

The next question is from Peter Spotts of the Christian Science monitor.

**Caller**

Thank you very much for doing this. A couple of quick ones. First of all, bearing in mind your statement that the human embryonic stem cells are still the gold standard against which you'd like to compare these. Would you need as many lines of human embryonic stem cells to maintain that gold standard as points of comparison as this work progresses? (27:16-27:33)

**Interviewee – James Thomson**

I can only say for what my own lab plans to do, and we derived the 5 cell lines all those years ago. We derived a couple more in the meantime, and we did it because we had a new medium and wanted to make sure that there weren't funny selected pressures and whether the media worked. So for our own studies we might derive some in the future, but they'll likely be very limited in number. That being said, the broader scientific community very much would probably like to have access to a larger number of cell lines, and there's several hundred human embryonic stem cell lines in the world right now, and it would be nice if U.S. investigators could use them. (27:34-28:10)

**Caller**

I guess the other question I had was related to the future, and this sort of being the beginning of the end. What are some of the questions about perhaps the differences between the stem cells, stem cell like cells you've derived and the human embryonic stem cells? A couple of examples of the question so that at some point down the road you might be frankly feel a little more comfortable about pulling the plug on human embryonic stem cell work. (28:11-28:34)

**Interviewee – James Thomson**

Yes, I don't like the idea of "pulling the plug". I think you should allow them both to compete out there in the scientific universe, and little by little if scientists find these more useful to addressing the questions they want they'll just naturally migrate in that direction over time, things will drift. I think it's hard to define a set number of criteria they have to fit. They already fit the basic criteria for human embryonic stem cells we proposed in the *Science* article in 1998. The concerns now are multiple. So one is that the efficiencies for both Dr. Yamanaka of course and ours are relatively low, you're selecting a fairly rare cell out of that population with the initial starting cell, and that at least opens the possibility that you're selecting something abnormal. And over time we might find out that it's abnormal and it might be easier to get around that, it might be hard to get around that, we really don't know. So I wouldn't say that, you know, in 6 months we're going to know this, I think it'll take a couple of years for the scientific community to sort out, and in that time period people of course will want to keep doing human embryonic stem cell research. (28:35-29:34)

**Caller**

Thank you.

**Operator**

The next question is from Jerry Manier of Chicago Tribune.

**Caller**

Thanks very much and I apologize if you've already gone over this. Does adding, does inserting the genes make it potentially more difficult to use these, \_\_\_\_\_ cells in therapy and was there any particular kind of cell that you had most success with, ES cells, fibroblast cells, were any of them more efficient or produced better cells? You inserted the genes right, and when cells have been modified in that way, would that potentially pose a problem in therapy if you used those cells – are they abnormal in any way because they've been genetically modified? And in terms of the surface cells that you inserted the genes into, ES cells, fibroblasts, was there a specific cell type that was most successful? (29:41-30:34)

**Interviewee – Junying Yu**

To answer your first question. Because way is the approval \_\_\_\_\_ basically you develop an alternative which regulate the system, you turn the skin cells back into pluripotent stem cells. But you don't want the genes present in the induced stem cells. And there are many similar ways to do that. I think many other groups as well as ours will be working on this. To the second question, at the present we only tested the very limited types of cells. We needed cells with relatively good growth properties. So I wouldn't say these are the best cell types of but I think our genes will reprogram other cell types. The details have to be tested. (30:35-31:48)

**Caller**

You say that it will be a problem that we will still be working on as far as getting the genes out of the cells?

**Interviewee – Junying Yu**

Yes, this will be the second really important goal for other groups as well as ours. (31:58-32:06)

**Caller**

Thanks very much.

**Operator**

The next question is from Janet Babin of Marketplace.

**Caller**

Yes, hi. Thanks very much. Dr. Thomson, you've said people didn't know it would be this easy, and that thousands of labs in the U.S. can do this basically tomorrow. And I wonder if you guys can imagine that this breakthrough, that your breakthrough will save labs money and/or time in their research? (32:13-32:31)

**Interviewee – James Thomson**

No, I think a whole lot of money is going to be spent on this, and it's going to be well spent. But what will change is that if you're doing somatic cell nuclear transfer and you want to use human materials, it was very, very challenging to get those [redacted] and there's a very small number of labs that have the technical expertise to do it. And while I don't want to diminish the work we did in our lab, it's actually straightforward to repeat what we've done here by an average lab with molecular biology skills. And the cost of actually performing this procedure, it's not really that much, it's just kind of average everyday molecular biology. So I don't see it as a cost saving thing, but I think it will facilitate more and more labs getting into this field. (32:32-33:14)

**Caller**

Why?

**Interviewee – James Thomson**

Well, if for no other reason, there's been this strong stigma against human embryonic stem cell research, and scientists, most scientists anyway don't much like controversial things, and I think all the critical controversy over the last 10 years, I think the major impact is that scientists are very slow to get into the field. And I think that people are very excited about the field right now and it's already starting to exponentially blow, and I think this will just add to it. (33:18-33:41)

**Caller**

If I could just ask one more question. There is this, I've heard various things, like some scientists say that the ban on embryonic stem cell research, not the ban but the partial all the hurdles you have to jump, does force them out of the country to other places to do their research, and other people say it doesn't make a difference. What do you think? (33:42-34:00)

**Interviewee – James Thomson**

My feeling is that the political controversy set the field back about 4 – 5 years. And if you look at funding, from 1998 – 2001, there is no federal funding for this work in the United States. So there were 3 lost years where essentially nobody could do this work. And then the stigma associated with it, I really do think young investigators avoided getting into this field, and so talent just did not join the field. So from one positive point of view from the Bush decision, federal funding was allowed for this work starting in late 2001. It still represented very bad public policy as the primary concern, it did get the ball rolling. But I do believe because of the restrictions, and I do believe because of the political controversy the field is much slower taking off than it would have been otherwise. (34:01-34:49)

**Caller**

And so does your research then make it easier?

**Interviewee – James Thomson**

I certainly hope that it does. It remains to be seen if these cells do differ from embryonic stem cells in a significant way, so it's not the end of embryonic stem cell research. But I think more and more labs will get into it now. (34:50-35:06)

**Caller**

Thank you so much.

**Operator**

The next question is from Steve Conor of the Independent Newspaper.

**Caller**

Hi. You partially answered this in previous questions but I just wondered if you could elaborate a little bit more. What would it take to turn these cells into embryos and how would you know when you're actually at that stage? And do you think it would ever be possible to show that these embryos are viable in the sense of producing full term pregnancies? I know these are somewhat hypothetical questions, but I just wondered if that is something which you've thought about. (35:15-35:45)

**Interviewee – James Thomson**

I guess I'll answer that. No, I don't think these cells are qualitatively different from embryonic stem cells in that regard, if anything embryonic stem cells would be better at doing that. And the answer is it's not known. You would at least have to piece them together with other components and create some kind of structure so that you can plant and carry out their normal functions. So it would take some highly directed manipulation rather than just replacing them in the uterus. Certainly if you took a nucleus out of one of these cells, and you did somatic cell nuclear transfer, there's reason to believe that that would form a clone that would be viable, but that's true of other somatic cells also. (35:46-36:19)

**Caller**

But do you think you would need an egg cell to make these into viable embryos?

**Interviewee – James Thomson**

At least for somatic cell nuclear transfer you'd have to do that. Otherwise you'd have to do some other kind of manipulation. It's not something you'd expect to spontaneously happen. (36:20-36:31)

**Caller**

Thank you.

**Operator**

The next question is from Matt Herper from Forbes.

**Caller**

So, is there any intellectual property around the use of these genes? And will there be any restrictions on who can use them for commercial applications? And how do you think, what do you think the impact of these cells in drug discovery and toxicology will be? (36:39-36:57)

**Interviewee – James Thomson**

For the first one about intellectual property, I would suggest if you're going to write about that you followup with and followup with and just ask about who's filed what. My guess is that there's going to be a very complicated intellectual property for both of the groups, not just the 2 papers today, but I haven't looked myself. I think these are going to be very powerful in drug screening, and they're not qualitatively different from embryonic stem cells except you can prospectively get the genetics you want ahead of time. So embryonic stem cells come from IVF clinics and if you made enough of them you could match the genetic diversity of the United States. But people that undergo IVF in the United States are ethnically skewed because the economics of IVF. Whereas these cells, you can actually perspective go out and get cell lines that have a good representation of all the genetic ethnic backgrounds in the United States. Now if you did drug testing in animal cell lines, it should much better match drug responses which differ ethnically. So I think there's a tremendous potential in drug screening, even though they're basically embryonic stem cells. And of course if there's a specific disease that had the genetic predisposition and you identify a person with that disease, you can make accurate models by asking that person. (36:58-38:05)

**Operator**

The next question is from Marian Solko of CNN Medical News.

**Caller**

Hi. Thanks for taking these questions, it's nice to speak with you. It's been something for a while. I have 2 questions for you. Number one, when your research came out and when the whole funding issue popped up in 2001, everyone was talking about personalized medicine. Is this still the path to personalized medicine, or is this more a

path to understanding illness and as you mentioned just now, drug screening, etc. And then my second question is we've heard about adult stem cell research parallel to all the human embryonic stem cell research that has been attempted over the years. And they also claim this is less controversial, and they've also were able to turn certain cells into certain things. In simple layman's terms how is this different, how is this the much bigger step forward in adult stem cell research versus the previous adult stem cell research we've heard about? (38:18-39:17)

**Interviewee – James Thomson**

There's very clinically useful adult stem cells. The question has always been is there an equivalent to an embryonic stem cell in the adult, and there's still no evidence for that. There are populations of stem cells that give rise to a variety of clinically useful things, but not everything. These really do appear to be cells that can give rise to everything. And now whether you want to use these clinically or one of the adult stem cells, time will tell. It will be very disease specific. So for example, the **parenchymal** already can be expanded and already are in clinical trials, and embryonic stem cells can make **parenchymal** cells but maybe you don't bother doing that because you can get those directly out of the body. But other cells that don't directly grow that well, these cells are likely to be a better source. (39:18-40:02)

**Interviewee – James Thomson**

So I think that although these are just more or less embryonic stem cells and we have all the challenges of embryonic stem cells, it does allow you to create a completely genetically matched cell line to an individual, and I think over time they could probably be done pretty cost effectively. And if you do want to do a transplantation therapy, it makes all the sense in the world not to use immunosuppressive drugs. And I think these do have wide potential clinical applications because of that. But it doesn't solve all the problems in transplantation. I think it's still going to be challenging to get these cells in the body. (40:11-40:42)

**Caller**

What would be the most important message you think people should get out of these announcements, both your study and the other one out of Japan?

**Interviewee – James Thomson**

I think it's kind of a dual message, it's that this changes everything and nothing and caution is warranted. It changes everything because these are not from embryos, and it changes nothing because we're back to the same ground state stem cells, but the caution is warranted because we're not entirely sure that this is same as embryonic stem cells yet. And it's probably going to take a couple of years to work that out. And it's not the time to abandon embryonic stem cell research. (40:53-41:16)

**Operator**

The next question is from Malcom Ritter of the Associated Press.

**Caller**

Hi, thanks again for taking another question from me. I just would like simple explanation, Dr. Thomson, in layman's terms about sort of the cancer risk involved in using viruses that integrate into the genome and why it's so important to get rid of those viruses. (41:26-41:43)

**Interviewee – James Thomson**

Yes, I don't think anybody thinks that we're going to have those kind of vectors even a year from now, but it might prove more challenging than I think. We chose those simply because they're easy ways to get these genes into cells. When anything integrates in the genome, this is true of gene therapy, so the vectors that we're using are vectors that have been proposed for gene therapy. You potentially create a mutation in the gene where it integrates, which is more or less random, and if you get a really important gene it can change the function of a cell. And one of the things you really worry about is changing the function in a way that turns into a cancer cell. So, if you clinically derive some cell type and it had these integrations in there and it predisposed that individual to cancer, you certainly want to avoid that. So it would be much better to do this in a way that you don't create those mutations, and I think people will find those ways pretty rapidly, but time will tell. (41:44-42:33)

**Caller**

Thank you very much.

**Operator**

It's with **Hurton Escavar of Estado**.

**Caller**

Hi, thanks again. Just looking at the ethical debate from the embryos. When the first paper from the Yamanaka lab came out, there were several groups that are against embryonic stem cell research that used those results as kind of a scientific argument that you don't need to use embryos anymore because now we have this other technique that allows you to get embryonic stem cells without using the embryos. And the counterargument to that was that it was only done with mice and was not proven in humans and we still had a long way to go, etc. Does your paper give support to that kind of argument right now do you think? If anyone uses that argument would you support that, or how would you refute that? (42:49-43:31)

**Interviewee – James Thomson**

So certainly the argument is going to be made. I would say that again, caution is warranted because we don't know how similar these are to embryonic stem cells. But I think we should take a couple of steps back and kind of look at the broader issue here. In the United States there's something like 400,000 frozen human IVF embryos. And couples are given the choice of what to do with those embryos. Some donate them to other couples to have babies, some have them discarded, some donate them to research. I still think if there's even a chance that the embryos that are currently being discarded are

used in some way that can benefit people, that's a good ethical choice. I think that if you completely ban human embryonic stem cell research, it would simply mean that those embryos would be discarded, and I don't think that's a good outcome. So I think that over time reprogramming has a good chance of replacing embryonic stem cells derived from embryos. We're not at that point today, and human embryonic stem cell research might actually offer the clues of how to do that better. (43:32-44:31)

**Caller**

So the research should keep going?

**Interviewee – James Thomson**

Yes, so we're not abandoning the cell lines we have already, we don't plan to drive a whole lot of new cell lines right now, but again there might be challenges we don't anticipate **in these program results**. (44:32-44:45)

**Caller**

Okay, thank you.

**Operator**

The next question is from Mira Oberman with Agence France Presse.

**Caller**

Oh, hi. I think you might have answered this a little bit earlier, but I missed part of it. Can you elaborate on how these new stem cells will enhance the ability to design patient and disease specific stem cells? (44:58-45:11)

**Interviewee – Junying Yu [please check entire paragraph]**

With this technology we basically can derive pluripotent stem cells directly from patient that's genetically matches with an additional [redacted]. And so to validate itself as you mentioned earlier there's a lot of downstream work still we need to do. We are basically in the same situation as other stem cells. For the drug screening with this technology I can already derive **the right** stem cells from [redacted] for genetical background and that will [redacted] to identification of [redacted] with much less toxicity. (45:17-46:12)

**Caller**

All right. Thank you.

**Operator**

The next question is from Erin Smith from CNN Money.

**Caller**

Hi. Thanks for taking another question. I just wanted to ask the researchers about implanting these reprogrammed stem cells into other tissues, I believe you did this with heart tissue. And if so, could you explain what happened when you did that, and whether you tested it in any other organs and where this might go in the near future for the research? (46:20-46:42)

**Interviewee – James Thomson**

We have yet to do those experiments with these reprogrammed cells. A number of groups have done that with embryonic stem so we haven't used it in these cells yet. (46:43-46:49)

**Caller**

Okay, but what would be your first organ of choice, if you don't mind me asking?

**Interviewee – James Thomson**

There's a wide range of them, and on this campus cardiac or heart is one of the first choices because we have good expertise here. But neural differentiation to dopaminergic neurons is well worked out in human embryonic stem cells, and that will probably apply directly to those. Those 2 are the ones that are probably furtherest along because you can get the cells separated. (46:55-47:15)

**Caller**

So it's basically nerve cells and heart cells.

**Interviewee – James Thomson**

Yes, I'd say those are the first. There's high important targets like diabetes but people aren't terribly good at making the cells yet. (47:16-47:26)

**Caller**

And did you coordinate your research at all with Dr. Yamanaka's team?

**Interviewee – James Thomson**

No, it's actually an independent effort. He published one of course with the mouse, but we're doing these screens in humans. And what basically happened is he did all his primary screens on mouse material which is really fast, you can get experiments done in weeks that takes us months. We did all our primary screens in human materials, so it took us a lot longer. And then when he applied his 4 genes to the human he slowed down because he had to get the balance right and those conditions are different. And then our screens are done and we ended up in the same place. So it was independently done and he beat us very soundly with the proof of principal in animals, but we tried it on humans. (47:27-48:02)

**Caller**

Very good, thank you.

**Operator**

The next question is from John Faber of the Milwaukee General Sentinel.

**Caller**

Yeah, I believe you said that you have established 8 new stem cell like lines from these cells. Is one of them, the 46-year-old female and if not why wouldn't you have line for

that individual? And then secondly I believe the Yamanaka group had their cells differentiated into cardiac cells or neurons. Have you done any of that type of work, have you gotten your cells to become other types of cells such as pancreatic cells or brain cells or heart cells? (48:10-48:44)

**Interviewee – Junying Yu**

For the work that's coming out today we only presented for the fetal cells for postnatal skin cells. For this cell line we did differentiate it into other cells, and they basically became essentially embryonic stem cells. And for the adult skin cells, it currently being tested that we haven't characterized it in detail yet. (48:45-49:20)

**Caller**

So one of the 8 lines is not the 46-year-old female?

**Interviewee – Junying Yu**

No.

**Caller**

And the only differentiation your cells have made is into blood cells?

**Interviewee – Junying Yu**

The blood cells we also tested the neural differentiation and they basically behaved like embryonic stem cells. (49:30-49:37)

**Interviewee – James Thomson**

And recall that in the teratomas there's bone and cartilage and all the tissues you want, it just wasn't directed differentiation. (49:38-49:45)

**Caller**

Is that a difference between what your paper has found and the Yamanaka paper, that they actually have differentiated their cells into neurons and cardiomyocytes?

**Interviewee – James Thomson**

It's not a substantial difference, they applied the conditions that people **worked** because they work. We didn't do that in the current paper, but there's no reason to believe they don't work fine. (50:00-50:12)

**Caller**

Thank you.

**Operator**

The next question is from Peter Spotts of the Christian Science Monitor.

**Caller**

Oh, thanks. I wonder, you mentioned earlier on, Dr. Thomson, the need for primate models for disease specific work that's undertaken. I wonder if you could kind of relate

this to the results that came out I guess it was last week on the somatic cell nuclear transfer cloning of a primate and is there a potential synergy here between that and the way you folks are deriving stem cells? (50:21-50:53)

**Interviewee – James Thomson**

Yes, there's actually a good synergy there because we can go to the same exact cell lines that they used for their somatic cell nuclear transfer, make IVF cell lines and then genetically compare them and say is either approach similar or different. And we have a number of recent embryonic stem cell lines already so we can make very direct comparisons the way we can't with human material. So I think there is quite a synergy there. But more broadly, I just think it's time to get back to animal models in a way that it'll bring transplantation things forward. And you need a long lived animal model that's not the mouse. Mouse embryonic stem cells are just different, and the lifespan of mice doesn't allow you to test for things like cancer and things in the same way that you can in a long model. I do think the field will now get back to the nitty gritty nuts and bolts of making transplantation therapies work in these cells now. And for the Rhesus monkey, it's hard to get genetically matched material when you do transplants with the heart transplant. You have to go, or say bone marrow or whatever. You usually have to use at least with a partial match. And because Rhesus monkeys are outbred in fairly small colonies it's hard to do that. If you have a genetically matched cell line, it just makes the procedures so much easier. (50:54-52:02)

**Caller**

So in other words I'm also thinking if-- we're using, what is it knockouts I guess to generate lines of monkeys that were predisposed to some particular disease, you could then use their tissue using this technique to try and perhaps experiment with therapies or something. (52:03-52:21)

**Interviewee – James Thomson**

Yes, that's actually a little hard, and certainly the somatic cell nuclear transfer might do that, but if you look at the efficiencies and the length of life of the Rhesus monkeys— sexual maturity is like 5 years, it's not the same thing as doing it in mice. So you might compare those 2 but I'm a little skeptical it will happen anytime soon. (52:22-52:37)

**Caller**

Okay, thanks.

**Operator**

The next question is from Emily Singer of Technology Review.

**Caller**

Hi. You mentioned previously the possibility now of creating disease specific stem cells. So I was wondering if you have or are planning to create lines of stem cells from someone with a complex genetic disorder like Parkinson's? (52:48-53:04)

**Interviewee – James Thomson**

Right now the number of people working on this lab is relatively limited and we have not had time to do that. But certainly in the future we're interested in doing that. (53:05-53:13)

**Caller**

Thanks.

**Operator**

The last question is from Marian Salco of CNN Medical News.

**Caller**

One more question, since you were just talking about organs, heart, etc. might be the first targets once you figure out better what these cells can and can't do. But in embryonic stem cell research, diabetes was one of the targets that was expected to render some good results first, and also was found to be one of the illnesses that was less likely to work from adult stem cells. Can you tell me if you know enough about these new pluripotent cells that you've created that might overcome that hurdle? (53:21-53:59)

**Interviewee – James Thomson**

So again these cells are essentially equivalent to embryonic stem cells, although we don't know if they're in detail equivalent. And it's proven pretty challenging to get the cell that's effective in diabetes, the Type I diabetes, the beta cell. But if people are      in getting those cells, then cells would be appropriate for that use. But the limitation there is really understanding the development of biology and getting the cells in sufficient numbers. As a transplantation tool, these cells really should work for diabetes, because it's a single cell, it's not physically integrated in the body in a really complicated structural way. And there's already transplantation therapy based on cadaver tissue. So I do think there's tremendous promise there, but it's going to take some time still. (54:00-54:45)

**Caller**

And for those who are wondering as they did when your research came out 10 years ago on human embryonic stem cells and then when the funding was approved, although very limited in 2001, people want to know when am I going to benefit from this? You said you still need 1 or 2 years to figure out if these are truly like embryonic stem cells, but for that question that we always get asked, when are we going to actually see cures, etc. from this? (54:46-55:10)

**Interviewee – James Thomson**

I just can't tell you a date. But I will say my personal barometer of optimism has gone up a lot. And in particular because I do think funding is finally going to go up because of this because it does remove the political debate. And as we engage more and more people in the United States and these problems, things will accelerate. At the time that Dolly was cloned I would not have predicted that only 3 or 4 genes would accomplish what Yamanaka's group and our group accomplished with these papers. And this went much faster than I anticipated. So I think if you engage more and more of the people in the

United States to do this research, the research will accelerate, but I can't give you a timeline on it. (55:11-55:50)

**Caller**

That's certainly several, several years away.

**Interviewee – James Thomson**

Well there's already people that are planning clinical trials with human ES cells, and I can't see why these cells would not be appropriate for the ones that are being planned already. (55:51-56:03)

**Caller**

Thank you very much.

**Natasha Pinol**

Again on behalf of *Science* and its publisher, AAAS, I want to thank the panelists and the reporters for joining us today. An audio file of this teleconference will be posted on the *Science* Press Package website. A summary of the article and a copy of the manuscript are available on the Scipack webpage. Again the embargo is being lifted so that reporters may freely publish their coverage now. If you have any further questions, please contact me or the *Science* press package team at 202-326-6440. Thank you.