

COVER STORY

THERAPEUTIC CLONING UNDER FIRE
An Interview with Michael D. West, PhD

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A year and a half ago, Michael West, PhD, President and CEO of Advanced Cell Technology (ACT), revealed his plan to use "therapeutic cloning" to attack aging in humans (Life Extension magazine, June 2000, pg. 40). At that time, there was relatively little opposition to Dr. West's idea (see "The Media Befriend De-Aged Clones," LEM, August 2000, pg. 57). But when he announced recently that ACT had taken the first step towards human therapeutic cloning, he was suddenly criticized by everyone from President Bush to the Pope. Further, a bill outlawing human cloning (including therapeutic cloning) had already been passed by the U.S. House of Representatives, and President Bush urged the Senate to approve the bill as soon as possible. In the face of this criticism, Dr. West has patiently and calmly stood by his guns. He was interviewed by telephone on Dec. 2 by Gregory M. Fahy, PhD and Saul Kent of the Life Extension Foundation about the latest scientific advances made by ACT and the furor and controversy over cloning.

Life Extension Foundation (LEF): Can you explain the advances you've made at ACT towards therapeutic cloning for humans and why this is such an important area of research?

Michael West (MW): The dream of cell biologists is to be able to take a body cell from a patient of any age back in time to an embryonic state. Embryonic stem cells have the unique ability to make virtually any type of cell that the patient would need. So their use in medicine could be very broad. One immediately thinks of making pancreatic islet cells for diabetes, heart muscle cells for heart disease, neurons for Parkinson's disease or spinal cord injury and so on. I believe we have found the "time machine." It is somatic cell nuclear transfer, otherwise known as cloning. The idea is quite simple. We would take a somatic cell from a patient and transfer it into an egg cell whose DNA had been removed. The egg cell would then act as the "time machine" by taking the patient's cell back to an embryonic state. Since the embryonic cell would be made through cloning, it would be immunologically identical to the patient's own cells and could then be transplanted into the patient without risk of rejection. The great hope is to be able to make young cells, tissues and organs for the treatment of aging and degenerative disease.

Do we think that's actually possible? The answer is "yes." As you know, we published back in 2000 that, in the cow, nuclear transfer can restore cellular life span and rebuild the telomere, the clock of cellular aging. That work was later replicated in a mouse model by Teru Wakayama, who was the first scientist to clone a mouse (Nature 2000; 407:318-9).

In his experiment, Dr. Wakayama cloned a mouse, which he named Cumulina, after the cumulus cells that surround the egg. The donor nucleus had been taken from one of these cumulus cells. Then he cloned clones of Cumulina. And then clones of the clones of Cumulina. Every time he cloned these animals, the telomeres actually became slightly longer than they were originally. So Dr. Wakayama saw an effect on telomeres similar to what we saw in cows. (Editor's note: telomeres are regions of DNA at the ends of chromosomes that are partially lost when cells divide, which limits the number of times the cells can divide. They act as "clocks" of cellular aging.)

LEF: What did you publish in The Journal of Regenerative Medicine that caused all of the controversy (EBiomed: J. Regen. Med. 2001;2:25-31)?

MW: We published our initial experiments with human nuclear transfer for the purpose of therapeutic cloning. Now let me make something very clear at this point. We are building a technology to make cells for medical purposes, which we call "therapeutic cloning." We are not trying to clone humans, an application that is usually called "human reproductive cloning."

LEF: How does this differ from the results you reported a year and a half ago?

MW: This time we used human egg cells (oocytes), whereas in the past we were working with animal egg cells.

LEF: How far did you get in the work that was published?

MW: We made an encouraging first step. We saw the hallmark of what we call nuclear reprogramming, when a somatic (body) cell is taken back into an embryonic state. When the "time machine" works, the nucleus changes its morphology (its shape). It swells and takes on a particular appearance called a pronucleus.

When an egg is fertilized by a sperm, the sperm cell nucleus becomes a pronucleus. But if you effectively trick an egg into believing that a transplanted somatic cell nucleus is actually a sperm cell, then the nucleus will also become a pronucleus. What we saw was pronucleus formation after nuclear transfer, which in our experience is evidence that reprogramming is occurring within the nucleus.

LEF: So you accomplished the first step.

MW: Yes. And we got the reconstructed embryos, as we call them, to begin dividing. In this experiment, we only got up to a total of six cells.

LEF: What happened afterwards?

MW: Further development was blocked, meaning that the embryos stopped dividing.

LEF: When that happened, was there any change you could detect, which might explain why they were blocked?

MW: In our experience, based on the other species we've worked with, cloning is largely trial and error, because we don't know how it works, ultimately. It's magic, it's a black box. And so what you do is fine tune this or that variable, the concentration of particular chemicals in the media, or the timing of events, until it works. However, you know you're getting close if you see pronucleus formation and some cell division. So the first few rounds of cell division we saw in our human experiments were encouraging.

LEF: Did you measure the telomere length in the human embryos you produced?

MW: No.



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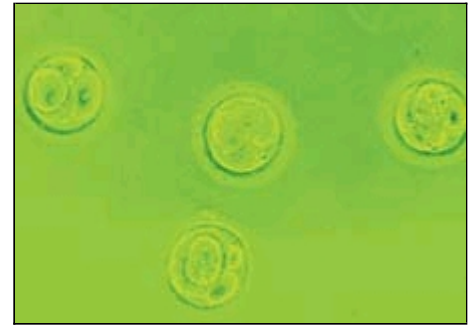


LEF: Critics have said that you didn't get very far at all because your embryos stopped dividing at the 6-cell stage.

MW: I don't understand the critics here. I think what this reflects, frankly, is that this is a very emotional area. It's a lot like the Wright brothers' first flight. When they got their plane to fly 120 feet, their critics said that the Wright Brother's plane had only managed to cover 120 feet, but the Wright brothers were thrilled that they had managed to fly at all.

LEF: Did you expect the extent of publicity you've gotten?

MW: No. We decided to publish our findings in The Journal of Regenerative Medicine because it's an Internet journal and we knew we could get it out there rapidly. U.S. News and World Report (Dec. 3, 2001, Vol.131, No. 23) was doing an in-depth story on us. They released their article within minutes of our publication in the journal, which took an obscure scientific publication and put it in an international spotlight.



Human cells dividing - 2 days old

LEF: Isn't it true that when you transferred nuclei from somatic human cells into cow eggs a couple of years ago, you created more developed embryos than you have with human eggs?

MW: It's true that we induced these embryos to develop to the blastocyst stage, but we've done thousands of inter-species nuclear transfers. It's a very inefficient process compared to using cells from the same species, but since we've done a lot more human-to-cow transfers, this explains our greater success with this procedure. It's important to point out that access to human oocytes is far more problematic than to cow eggs. It took us months to work out the right way to do this with human egg donors. Obviously, a lot needed to be done to protect these women who were doing such a great service for humanity in donating their cells. We needed to be sure that it was safe for them. We needed to work out a whole battery of physical and psychiatric exams and other procedures.



Bovine embryo from the tip of a hypo needle pictured next to a human hair. ACT's cloned human embryo is approximately the same size as this bovine embryo.

LEF: When you were first doing the human nucleus/cow egg experiments, did you get results similar to your initial human nucleus/human egg results in the early stages? And did you later overcome the problems to get more advanced development?

MW: As of today, our cross-species nuclear transfer procedure using a cow's egg cell and a human somatic cell is not yet efficient enough to meet our standards. We are still working on this and are hopeful for success. An alternative to human egg cells would make the therapies much less expensive.

LEF: Do you have greater efficiency with human-to-human transfers?

MW: It's too early to say. We're still fine-tuning, learning from our mistakes, and we're not even close yet to optimum conditions.

LEF: Could you identify the steps that need to be taken to develop therapeutic cloning and give us an estimate of how long it might take to achieve those steps?

MW: The first step will be to optimize the conditions for the cellular "time machine," according to the therapy we want to develop. We will then turn our attention to an animal model of disease and work to show we have a new therapy that is safe and effective. Once we've demonstrated the value of the therapy in animals, we will ask the FDA for permission to begin human clinical trials. All of this could take 7-10 years or longer, depending upon the disease.

LEF: Let's get to the opposition to your work and how that's led to the House bill which is going to be discussed in the Senate shortly.

MW: Well, what we have is, potentially, a solution to this age-old problem of transplantation, the ability to offer patients the cells they need, even biologically young cells, without the fear of rejection. Our opponents are objecting to this, I would argue, largely, out of fear of a brave new world scenario. A lot of people are afraid of the word "cloning." I can understand this. I mean, we've had a long stream of science fiction movies (including a new movie called "Attack of the Clones") which paint a very scary picture of cloning.

The second problem is that the pro-life community has picked up on this as a pro-life issue, which I think is unfortunate and short-sighted. Why? No serious ethicist or embryologist believes that a pre-implantation embryo is a human being. We are not talking about creating a pregnancy. We are talking about making a microscopic ball of cells with no body cells of any kind. These cells have not even individualized. They don't make a final decision as to whether they'll make one or two persons (identical twins) until

after they've been implanted in a uterus and passed the stage called "primitive streak." Because there are no body cells of any kind, and the cells have not yet individualized, they are not a person yet, by definition. Saying that a pre-implantation embryo is a human being and arguing that therapeutic cloning is, therefore, unethical is simply not based on fact.

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LEF: Isn't it true that the position of the Catholic Church is that, if you destroy the embryo after fertilization, you're destroying life?

MW: That's right. The Catholic Church takes the position (as do some others) that life begins at conception. I just don't know, nor do I think they know, how they came up with this. What happens is that the fertilized egg divides to form a little ball of cells, like a tiny lump of clay. If this little ball of cells doesn't implant in the uterus, it will die. It is estimated that up to 80% of these little balls of cells never attach to a uterus and consequently die. And for those that do attach, one, two or even three human beings, (identical twins) can be formed. We know that. And we can actually determine when individuation begins, which is about two weeks after development begins. So, it simply doesn't make sense to say "a human life begins at conception." Certainly cellular life is created at conception, but it's not yet a human life.

LEF: A cadaver with a beating heart and no brain function can be a source of organs for others, yet nobody worries about that.

MW: Yes, such a person has billions of living cells, even in the brain, but is considered a non-person, yet people argue that a microscopic ball of cells with no body cells of any kind, that you could balance on the point of a pin, should be considered a person with a right to life. I can draw an analogy to the World Trade Center attack. Our critics are in effect saying: "You attacked the World Trade Center buildings." But I argue that not only were there no people in the buildings, but the buildings hadn't even been constructed yet. In fact, the architect hadn't yet decided whether to have one tower or two. That's the stage of development we're talking about here. This microscopic ball of cells is a collection of the most blank cells you could ever find. A piece of dandruff is more human than these cells.

LEF: And this "blankness" is the whole attraction the cells have for therapeutic medicine. It is the reason they can be transformed into any types of body cells. When they did the first heart transplant, there was tremendous opposition. Then it became accepted. Today it is routine. The same thing is going to happen here. The problem is that if they pass a bill outlawing therapeutic cloning, it will be a major obstacle towards its acceptance.

MW: There is a long history here. I think the opposition is generated out of fear of the future and fear of the unknown. Anesthesia for childbirth was resoundingly condemned by the church on the basis of the Book of Genesis in the Bible, where God said women are supposed to have pain in childbirth because of Eve's sin in the Garden of Eden. Smallpox inoculations were objected to as an attempt to subvert God's will. More recently, there was in vitro fertilization (IVF). The Catholic Church called IVF immoral and illicit, and fought hard to try to get it struck down. There were bills debated that would have banned IVF or "test tube babies." But I think what shifted public opinion was seeing that Louise Brown, the first baby produced by IVF, was just like any other baby.

LEF: Too bad we can't show a smiling young man who used to be a frowning old man.

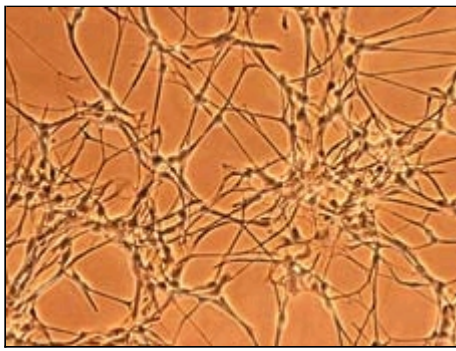
PARTHENOGENESIS AN ALTERNATIVE TO NUCLEAR TRANSFER

As Dr. West mentioned in his interview, his company (Advanced Cell Technology) is also working on methods of producing replacement cells, tissues and organs that do not involve standard cloning techniques. He spoke about the most unique of these alternative techniques in some detail at his presentation at the Regenerative Medicine meeting in Washington, D.C. in December 2001. The technique is parthenogenesis, or "virgin birth." With parthenogenesis, an egg cell can be activated and made to start dividing with no sperm cell or any new DNA added. Under the right conditions, a new offspring can arise from this process.

Dr. West reported that, when this process was started before monkey egg cells halved their nuclear DNA in preparation for merger with a sperm cell,



parthenogenic embryos were formed, from which embryonic stem cells were derived. When these stem cells were injected into nude mice, or grown in laboratory dishes, they formed intestine, skin, hair, cartilage, bone, beating heart muscle cells, at least two kinds of nerve cells (dopaminergic and serotonergic neurons), smooth muscle, liver and even a developing eye, depending on the growth conditions. While these tissues were not genetically identical to those of the egg's donor, they were made from a subset of the donor's DNA and, as a



Immature primate neurons

God.

LEF: Let's talk about the bill that is under consideration in the Senate.

MW: First there was the Weldon bill, which passed in the House. It not only bans the reproductive use of cloning, but the medical uses of cloning and the import of any products made from it. If this bill is enacted, and if you were able to have a new sinus node made for your heart in the U.K. using therapeutic cloning, you would then be banned from the U.S. because you'd be importing a product of therapeutic cloning.

LEF: So the big risk here is the fact that it might pass the Senate. I've seen the Senate version of the bill. It's almost identical to the House version.

MW: Yes. Senator Brownback, the sponsor of the Senate bill, is one of the leading proponents of the ban. I think our best hope here is that enough Senators recognize the gravity of the issue. We're talking about millions of human lives. The House pushed this through with only a twohour debate. The Senate, I'm certain, will spend more time on it. It's my hope that this is such a grave issue, involving human health and suffering, that they'll make the right decision. Imagine how their constituents will react when therapeutic cloning begins to save lives. Imagine that it's thirty years from now and Rep. Weldon is being interviewed by 60 Minutes. "Representative Weldon, in 2002, your bill banned therapeutic cloning. It was 15 years before the ban was lifted and, in those 15 years, we estimate that twenty-seven million people suffered needlessly and died because of your ban. What do you think about that?"

LEF: I hope we can put such concerns in enough Senators minds today, so that they won't have to be confronted with that kind of criticism later.

MW: Up to 80% of all pre-implantation embryos die, but I don't see our critics calling for a billion dollar crash program to try to save these embryos. I don't see them protesting against IVF clinics, which throw away thousands of pre-implantation embryos that are not wanted. The potential risk of getting this one wrong needs to be appreciated.

LEF: Did you testify on Capitol Hill before the House version of the bill was passed?

MW: Multiple times. I testified again on December 4, and I'll probably be testifying in the Senate when the bill is discussed there.

LEF: Apparently your testimony had no substantial effect. I mean, how many people voted against the ban in the House?

MW: The bill, called the "Human Cloning Prohibition Act," passed by a 265 to 162 margin. This is a tough one. The scientific community and patient groups really need to work hard on this. All Life Extension members need to start writing letters. We can't get this one wrong for two reasons. One, we have millions of people in the U.S. who need these therapies and two, we're a leader on this issue. The fact that the U.S. Congress is debating it means that it is being watched throughout the world.

LEF: I think the key to is get enough voters contacting the people in the Senate and indicating that there is strong support for this research. It looks as if they're trying to ban therapeutic cloning without much public debate.

MW: Yes, our opponents have tried real hard to do this in a lynch-mob type of way. They feel rushing it through gives them the highest chance of getting it passed because there won't be debate. And if there's debate, they're at risk of losing.

LEF: What effect would this bill's passage have on Advanced Cell Technology?

MW: I think the debate is urgent. Even the critics admit these treatments could save millions of lives. Harold Varmus [the previous head of the National Institutes of Health] and others have spoken out. The National Academy of Sciences made a formal report recommending therapeutic cloning. So here we have the nation's best scientists and Harold Varmus, a Nobel laureate, all saying this is important, and the critics take their word for that. Okay, the critics say, so millions of lives could be saved, but even so, we want this stopped because we believe it is against the will of

result, it is thought that they might be close enough to avoid rejection when transplanted. Furthermore, it's known that cells made by parthenogenesis are likely to be healthy because there are healthy humans who are partly parthenogenic because they were created from the combination of a normal embryo and a parthenogenic embryo.

This is all very well and good if you're a woman, but what if you're a man? ACT scientists believe that a male parthenogenic embryo might be created by removing the nucleus from an egg cell and inserting two sperm heads into the cell. This experiment has yet to be done, but there are reasons to believe it might work.

-Dr. Gregory M. Fahy, PhD

MW: We have our feet firmly planted in U.S. soil. I was born in Michigan and can't imagine moving the company to another country. The point is that as a country we have to get this one right. We can make a wrong decision on raising or lowering taxes, but we should all cry if we get this one wrong. If nature hands us an important new medical strategy, it's unethical to ban scientific investigation and block medical progress.

At ACT, we're working on other techniques, but none of them is as promising as cloned embryonic stem cells. They include: standard nuclear transfer, nuclear transfer across species, parthenogenesis and cytoplasmic transfer, in which you add the cytoplasm of the egg cell to a somatic cell rather than the other way around.

LEF: When you were publishing that you had created embryos from the transfer of human somatic cell nuclei into cow eggs, there was less criticism than when you started doing it with human egg cells. Maybe in the mind of the legislators, it's only a human embryo if it comes from a human egg.

MW: I think they'll just add crossspecies cloning to their bills. I've debated these people many times. They never answer my rational argument that there are no differentiated body cells created by this process because they know it's true. So they use inflammatory language about "embryo farms," "brave new world," "Nazi experiments" and so forth. One effective slogan they use is "clone and kill." They are trying, in my opinion, to reduce this to another pro-life, pro-choice debate. But in scientific reality, the pro-life position here is to alleviate human suffering and potentially save the lives of millions. The fact is that they are trying to defend blank human cells at the cost of breathing, thinking human beings.

LEF: But abortion is legal, despite opposition to it. Why should therapeutic cloning be any different?

MW: I think we need to focus on the potential benefits for the sick and elderly. I think it will come down to patients who want a cure for heart failure, kidney failure and so forth. I would argue that "lack of cloning kills". You can see that I'm energized over this one, but frankly I'm furious that such a powerful means for good is actually at peril in our modern world.

LEF: What can members of the Life Extension Foundation who favor therapeutic cloning do to impress the Senators?

MW: Write to them. And call them (see "Don't Let The U.S. Government Ban Therapeutic Cloning" in this issue). Of course, the pro-life camp has their people doing the same thing and they have a very sophisticated means of communicating with the Congress. We have to have a grass roots effort to get people involved.

The people in Congress do look at letters, but I think we also need some additional actions. Such as a relentless stream of press releases in favor of therapeutic cloning by a succession of organizations. On our website (www.advancedcell.com), there are links to the National Academy of Sciences Report and the NIH Stem Cell Report. Both recommend the use of nuclear transfer. Nobel laureates such as Dr. Harold Varmus has stated: "There's not an area of medicine that this technology will not potentially impact." It's always helpful to explain that the nation's most prestigious scientists are in favor of our research. We need to put out a list of all the diseases that could be treated with therapeutic cloning.

We need to get out the message that this can affect someone you care for, using human cells derived from a microscopic dot smaller than the point of a pin. When people understand this, I think most of them will become enthusiastic about the technology.

LEF: Well, that's it then. Thanks a lot for talking with us. Good luck.

MW: I really appreciate your help here. Other projects we've worked together on have been fun, but this one really matters. Let's work hard on it.

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