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ON THE
COVER**Regenerative Medicine Breakthroughs**

Will BioTime Reset the Clock of Aging?

By Julius Goepp, MD

Rapid advances in the field of stem cell therapeutics are bringing us closer to the elusive goal of harnessing the “immortal flame” that survives in all of us. Indeed, it has become clear that, in the words of internationally known gerontology researcher Dr. Michael West, “You and I are made from cells that have *no dead ancestors*.”

Life Extension interviewed Dr. West recently, to learn about his paradigm-shattering work, which has led to new techniques related to *induced pluripotent stem cells* (iPS) and *human embryonic progenitor cells* (hEP), both of which allow researchers to leap-frog over many previously existing barriers. Shortly after our interview, Harvard researchers announced that they had used the iPS technique to produce a **“robust new collection of disease-specific stem cell lines”** that hold immediate hope for advances in a host of diseases including Parkinson’s disease, type 1 diabetes, Huntington’s disease, Down’s syndrome, a form of combined immunodeficiency (“bubble boy disease”), two forms of muscular dystrophy, and others.¹



Based on our discussion with Dr. West, combined with the recent news from the Harvard researchers, it appears that we are truly poised at the threshold of an incredible new era in which scientists can unlock the inner workings of our cells and “mass produce” virtually any cell or tissue type in the human body in a youthful state.

The implications of these advances are enormous. They include readily accessible tissue and organ transplantation, the obliteration of genetic disorders, the end of chronic age-related diseases, and perhaps even physical immortality itself.

SOME BACKGROUND

“We’re seeing a congruence between some of mankind’s oldest aspirations and where modern science is heading,” West begins. “From ancient times, we’ve recognized that, although we as *individuals* age and die, the *species* does not. Amazing as it sounds, each of us is made of cells that have been proliferating since the dawn of life on Earth. And that, really, was the beginning of what we today seek to achieve through gerontology and regenerative medicine.”

The lineage of cells produced by the reproductive system has been known as “germ-line” cells since the work of 19th century German scientist August Weismann. West continues, “Weismann recognized that germ-line cells represent a *lineage of cells* that has continued unbroken since life began—*these cells obviously never aged or you and I would not be here*.”

Weismann was interested in this fundamental question: why is it that the non-germ-line cells in our bodies (the *somatic cells*) inevitably age and die on cue. As West asks, “Why are cells in our skin, our blood, our bones, and even our brains so reproducibly programmed to age in such a short period of time, while germ-line cells have been proliferating for billions of years?”

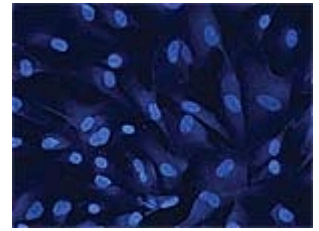
Intrigued, Weismann made an astonishing prediction in 1881, speculating that the reason individuals age is that *somatic cells* (what we are mostly made of) have somehow lost the capacity (still inherent in primitive single-celled creatures) for proliferating without limit. Restore that capability, Weismann claimed, and one would restore the cellular immortality still present in our germ-line cells.

A series of elegant and now classic experiments by the biologist Leonard Hayflick in the 1950s showed, in fact, that there is a limit to how many times human somatic cells can reproduce *in vitro* before they simply stop. Hayflick had discovered the existence of what amounts to a cellular “clock” that appears to run down after a relatively short number of generations of cell replication.

TELOMERES: CELLULAR FUSES

What is the actual physical nature of the mysterious “cellular clock” that limits the life span of human somatic cells?

At the time when Dr. West began his scientific career, he became convinced that this intrinsic clock of cellular aging was somehow connected with the chromosomes. He became intrigued by a little-known theory proposed in the early 1970s by Russian scientist Alexy Olovnikov.^{2,3} “Olovnikov’s idea was that repeating DNA sequences at the ends of each chromosome were like a burning fuse, which acted as a clock because every time the cell replicated, the segment (called a *telomere*) became shorter and shorter. When it ‘ran out,’ the cellular machinery signaled a fatal error in copying the vital genetic material, which would trigger the senescence of the somatic cell.” The full-length repeating telomere sequence was maintained in germ-line cells, Olovnikov suggested, by an “immortalizing enzyme” that continuously spun fresh telomere DNA, allowing germ-line cells to reproduce forever.⁴



Primitive embryonic cells that are stained to show the nuclei containing the DNA.

By 1986, West had read the work of biologist Howard Cook who found that telomeres shortened with each generation in white blood cells (which are somatic cells and have finite life spans), but maintained their length in germ-line cells like sperm.

Seeing these puzzle pieces fall into place was so convincing that West took a leave of absence from medical school to court venture capitalists, eventually starting a company called Geron to build on what West still refers to as the “telomere gamble.” “Forty million dollars later,” West recalls, “the gamble paid off.” West’s group had in fact produced Olovnikov’s mysterious enzyme, now known as *telomerase*, because of its ability to continuously spin out the vital strands of telomere DNA that keep germ cells immortal.

IMMORTALIZED CELLS: CAN THEY LENGTHEN INDIVIDUAL LIFE SPANS?

But would it work? Could Dr. West actually convert human somatic cells, destined to expire after a few score doublings in tissue culture, into immortal versions of themselves that could continue to grow normally? In a fitting tribute, West chose to collect actual skin cells from pioneer Leonard Hayflick and insert the telomerase gene into them. In a notebook headed “The Immortalization of Dr. Hayflick,” Dr. West recorded the astonishing findings: Hayflick’s untreated skin cells began to die off after about two months in culture, exactly as expected, but cells that had been infused with the telomerase gene continued to thrive in identical culture conditions! These “telomerized” human somatic cells had demonstrated scientists’ ability to “rewind” the clock of cellular aging.⁵

While the immortalization of cells was a giant leap forward, says Dr. West, it wasn’t clear what role the *telomere* and the *telomerase* enzyme played in aging at the level of a human individual.

There were several intriguing directions to go in at this point. It’s now known, for example, that telomere *length* is related to the risk of many chronic diseases.⁶⁻¹² What about simply finding a way to restore the telomerase gene to every somatic cell in the body, lengthening all the telomeres together—wouldn’t that result in a body with an essentially limitless supply of cells?

“That’s exactly how I was thinking back in the mid-90s,” West responds. “Why not just package the telomerase gene up in a virus? (Viruses provide a common laboratory method of introducing specific genes into cells.) Although gene therapy hadn’t come of age at that point, it seemed that if we took that approach and succeeded, it could have a profound impact on aging.

EMBRYONIC STEM CELLS AND CLONING

But gene transfer using viruses was a tricky business fraught with pitfalls, especially in the 1990s. In a dramatic conceptual leap, Dr. West suggested an alternative: why not go all the way back to embryonic stem cells, which are formed immediately after a sperm fertilizes an egg? For the first several cell division cycles, all cells are identical, and capable of differentiating into every cell type in the body (in fact, so-called “identical twins” are the result of a two-cell embryo splitting apart, producing an entirely new individual from each primitive embryonic stem cell).



BioTime scientist captures information on the molecular properties of new primitive cell types.

“If we could immortalize embryonic stem cells,” West says, “we could potentially repair the human heart, for example, after a heart attack, making young heart muscle by injecting these primitive cells into the heart to regenerate damaged tissue.” That was an astonishingly prescient vision because we’re already seeing clinical trials using this technique (*cardiomyoplasty*) in humans.¹³

In 1998, West reasoned that if an aged somatic cell were returned to the germ line, such as is used in cloning, it might be

possible to not only reprogram say a skin cell into embryonic stem cells, but also reset the clock of aging in the aged cell. In 1999, the team that cloned Dolly the sheep had reported that cloning did not in fact do this, that is, they reported that Dolly was born old because the egg cell could not reset telomere length.¹⁴ However, Dr. West's group later demonstrated that the Dolly team had it wrong, and that cloning could reset the clock of aging in animal cells after all.¹⁵

This suggested that there may actually be a way to use germ-line cells like the egg cell as a cellular time machine, resetting the clock of aging in human cells, turning a skin cell into the primitive embryonic stem cells we were originally developed from and creating young cells and tissues of any kind to repair the ravages of aging.

Of course, cloning and the use of human embryonic stem cells are highly controversial, to say the least. The situation has been made worse by extreme political posturing on the one hand,^{16,17} and instances of overt scientific fraud on the other.¹⁸⁻²¹ These procedures are also technically challenging.

WHAT YOU NEED TO KNOW: REGENERATIVE MEDICINE BREAKTHROUGHS

- Stem cell therapy has tremendous potential for the development of medical applications to repair and regenerate diseased, injured, and aging organs and tissues. Stem cell therapy may even be able to turn back the clock of cellular aging and promote radical life extension.
- At the forefront of this exciting new field is gerontologist Dr. Michael West, CEO of BioTime, Inc.
- While somatic cells in the body age and die, germ-line cells have been proliferating for billions of years.
- The shortening of telomeres is linked with cellular aging, and telomere length is related to the risk of numerous diseases.
- Germ cells possess an enzyme called telomerase that allows them to maintain the length of their telomeres and reproduce forever. Introducing the telomerase gene into somatic cells increases their longevity.
- Dr. West has proposed that embryonic stem cells may offer tremendous therapeutic promise; however, the use of human embryonic stem cells derived from human embryos is highly controversial.
- Introducing transcription factors from egg cells to somatic cells can cause them to be transformed into embryonic stem cells that can be developed into every different cell type in the body.
- Studies show that induced pluripotent stem cells demonstrate an activated telomerase gene, which maintains the length of telomeres. This could be the first step in reversing cellular aging in humans.
- Embryonic progenitor cells are capable of developing into many cells of a particular tissue type, such as blood or nervous system cells. When injected into injured or aged tissue, they could develop into healthy appropriate cell types.
- Recent studies show that stem cell therapy holds promise in managing nervous system disorders, musculoskeletal conditions, ischemic stroke, brain tumors, and more.

BEYOND CLONING: AT THE THRESHOLD OF MODERN REGENERATIVE MEDICINE

"But the really good news," Dr. West says with obvious excitement, "is that a team at Kyoto University in Japan has now shown that it's possible to take some molecules, called *transcription factors*, out of the egg cell, and use them to act just like the egg cell itself in transforming an ordinary somatic cell, say from the skin, and taking it back in time to become an embryonic stem cell!"

No need for cloning and then deriving stem cells from the cloned embryo—or any of the challenging and controversial techniques that have preoccupied the media for the past decade. "*The new cells are called induced pluripotent stem cells (iPS)*," West explains. "They are equivalent in function to embryonic stem cells, but they don't come from an embryo—hence the name change. The idea is simple: take a skin cell, culture it in a dish, add in three or four of these transcription factors, and, over a couple of weeks, the skin cells are transformed back into colonies of stem cells that act



A microscopic view of neural crest cells that have the potential to make for the first time the cells of the human

exactly like embryonic stem cells.²²⁻²⁴ It's just spectacular, really."

face.

"And since numerous papers on iPS have now shown switching on the telomerase gene in these cells," continues Dr. West, "I believe that within the next 12 months, the scientific community will have documented, for the first time ever, ***the reversal of aging of a human cell.***"

ON THE COVER

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IPS: FROM VISION TO REALITY

Dr. West's exciting work at publicly traded BioTime, Inc. is aimed at making that vision a reality on the fast track. West's team is working on a "reprogramming matrix." BioTime recently licensed patents Dr. West had filed years before the publication of papers on human iPS cells that cover the use of the iPS genes in turning back the clock of human aging. "The goal is to use this material to permanently re-engineer old cells (say from a 100-year-old person), and bring them back to cells indistinguishable from those they were born with 100 years earlier.

"We're faced with a 'tsunami' of aging," West says, "and with the age wave of the baby boom generation, the timing is right for us as a nation to utilize these technologies to offer lower-cost therapies for crippling diseases like arthritis, for example. If we can rebuild the cartilage in your joints so you can walk to the store, the cost savings alone to this country would be just enormous. Many people have no idea that this emerging field of regenerative medicine was born of a desire to find a means to regenerate tissue function in the aged human and directly address this enormous human need.

"Now that we can turn back the arrow of time on human cells, the next question is how to learn how to make the cell types we need in a purified form and industrial scale for a host of age-related diseases. The good news here is that we've made some remarkable progress already."

The challenge Dr. West refers to is that scientists still don't understand just how stem cells "figure out" what kind of tissue they are destined to turn into. During natural embryonic development, there are specific genetic codes that seem to help cells "recognize" their environment, so that a cell developing at a location past the elbow joint turns into part of a wrist, a hand, or a finger—and never into an upper arm or a shoulder.²⁵⁻²⁷ "In some primitive animals," West points out, "an arm amputated above the elbow regenerates with a normal elbow and everything beyond it—but if the amputation is below the elbow, the limb grows back without producing a second elbow."

So today's stem cell researchers must "decode" the cells' intricate and complex position-finding mechanism—a daunting task considering the thousands of cell types and subtypes in the body, which not only have to form properly, but then must work together correctly. Or is that arduous decoding actually necessary? According to West, *absolutely not*.

Using a bold new approach, West's lab simply exposes stem cells to a "shotgun" mix of conditions, and then uses modern genetic techniques to figure out what they've produced. "Instead of looking up at the apple tree and saying, 'we want to pick that particular apple right there,' West says, "we just lay out a tarp on the ground and shake the tree. It's a random approach, but it is turning out to be very powerful—we produced 140 different cell types in just our first experiment alone." Each of those 140 types is known as an *embryonic progenitor cell*—more advanced than a stem cell, but still capable of developing into many cells of a particular tissue type—say cells in the musculoskeletal system, or blood cells, or even nervous system tissue.²⁸ These cells may have the capacity to "recognize" their environment when injected into injured or aged tissue, and proceed to develop into appropriate cell types and even organize themselves into functioning tissue based on the environment in which they find themselves.

"The bottom line," Dr. West says, "is that for the first time, medicine has an all-powerful stem cell to make everything in the human body, and young cells of any kind can be generated that are genetic matches to the patient who needs them. The hope—I would even say the anticipation—is that we'll be able to fulfill the vision of regenerative medicine, which is to make cells for an old person just like those they were born from decades earlier. They can be used to regenerate at least some aspects of the human body's function, whether it be the heart or the hair cell of the inner ear to restore hearing, and so on."

Pathways to Developing Rejuvenating Stem Cell Therapies

EMBRYONIC STEM CELLS DERIVED FROM HUMAN EMBRYOS

Illustration of the steps (counterclockwise from upper left) involved in developing embryonic stem cell therapy.



1: An egg cell is fertilized by a sperm cell.

2-4: The resulting embryo divides three times over the next three days.

5: By around day five, the blastocyst embryo has developed and consists of an inner cell mass of stem cells and an outer layer that will form the placenta. The stem cells would differentiate into the various tissues of a fetus.

6: Here, the stem cells are removed and cultured.

7: Different tissue types may be grown, including bone marrow and skin.

8: Youthful stem cells are developed into therapies, which are injected into the body to regenerate tissues and treat disease.

INDUCED PLURIPOTENT STEM CELLS TRANSFORMED FROM ADULT SKIN CELLS

Skin cells removed from a patient are transformed by genes in a Petri dish into rejuvenated immortal cells, which are then developed into biocompatible therapies that are administered to the patient to regenerate tissues and treat disease.



THE BRIGHT FUTURE OF STEM CELL THERAPY

In wrapping up, we ask Dr. West to speculate cautiously which of the major age-related diseases might be addressed with the new technology within the lifetime of people reading this article.

“First I think it’s important to understand that we’re very early in the dawn of this phase of medicine. The Bush administration’s highly ill-advised restrictions on funding in this area continue to hamper progress, though California has stepped up to the plate with three billion dollars to advance the field. But with those caveats, I’m still terribly excited about how we can potentially affect some of the largest aspects of aging.”

“There’s an old adage in gerontology,” West continues, “that ‘you’re only as old as your arteries.’ In fact, children afflicted with catastrophic premature aging diseases such as progeria and Werner’s syndrome have the identical, short-telomere-induced cardiovascular changes as people literally 10 times their age.²⁹ “We can actually see vascular *endothelial* cells getting old by measuring their telomeres—the cells “know” in a sense that there’s something terribly wrong, and then send out signals that arrest normal blood flow, accelerate clotting, and produce inflammatory signals that cause immune cells to invade the vessel wall—that’s what produces cardiovascular disease.”

“Well, could we fix that? At my previous company, we showed that it is possible to make young circulating precursors that can become either blood vessel cells or actual blood cells. We could actually label those cells and watch them traffic through the blood and see them land in damaged vessels and patch the damage. So we believe that if you could infuse the aged human with these cells, we could not only give older people a younger immune system, but we could potentially repair their vasculature as well.” In fact, human studies now bear out these cells’ potential for stimulating vessel growth in ischemic tissues.^{30,31}

WHAT ABOUT THE RISK OF CANCER?

You may be wondering whether the telomere “clock” helps cells “know” when to die, and prevents them from out-of-control growth. “There’s no evidence that switching on telomerase, the enzyme that keeps germ cells immortal, interferes with normal developmental pathways or cell control mechanisms,” Dr. West says. “Telomerase doesn’t force a cell to keep reproducing, it just allows it to reproduce if and when it’s called upon to do so.”



“Think about it,” he continues. “When you’re young and have a whole lifetime of telomere length in your cells, they don’t flip right out of control just because they have great proliferative reserves. And so resetting the telomere clock would not be predicted to have impact on normal development—skin cells would still slough off on cue and so on, just as they did when you were young. It’s just that the cells that produce them remain young themselves—they just don’t run out of time.”

So is the implication that one can not only stop further aging with this technology, but perhaps actually reverse some existing changes? “There are animal data to suggest that,” Dr. West responds. In fact, a quick search of the medical literature for 2008 alone reveals the following astonishing discoveries:

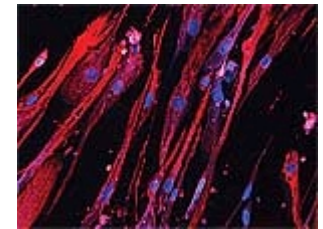
iPS cells from patients with the crippling paralytic disease, *amyotrophic lateral sclerosis* (ALS, or Lou Gehrig’s disease), can be directed to develop into functioning motor nerve cells;³² injection of stem cells into humans has already been shown to be safe and effective at slowing ALS disease progression.³³

Laboratory and animal studies have shown that musculoskeletal stem cells can be directed to develop into functional bone and cartilage cells with physical characteristics similar to young healthy bones and joints.³⁴⁻³⁷

Neural-derived stem cells have improved status of mice with Huntington’s disease, promoted recovery in rats with ischemic stroke, and are being explored as potential therapy for patients with brain tumors.³⁸⁻⁴⁰

SUMMARY

“We are always accused of hyping all this,” Dr. West says wryly as we end our conversation. “I believe that with time, people will begin to understand the basis of our excitement. The problem is that so many people still believe that aging is inevitable—what they don’t understand is the immortality of the species. I know this defies common wisdom, but common wisdom is perhaps wrong: the reality is that *we’re born from cells that have been proliferating since the dawn of life on Earth*. That’s just the way it is.”



“As scientists, we’ve got this duty to find ways to clarify truth and dispel myth. We have to explain that aside from the innumerable circus shows, snake oil salesmen, and all that, there’s really serious gerontology at work. Molecular biology today is able to do experiments a thousand times faster and better than it could even 10 years ago, and it’s leading to some really dramatic breakthroughs. Our tools are just so powerful these days. I conceive of the day when we can engineer embryonic stem cells at a molecular level and create new kinds of cells that never existed even in nature.”

Dr. West readily acknowledges that it’s impossible to tell just how far this technology can take us. But with more than 6,000 studies on stem cells published in 2008 alone, it’s clear we are privileged witnesses to a genuine scientific revolution. Will BioTime succeed in reversing the aging of human cells? Must we continue to succumb to aging-related disease and death? Or can we harness the power of our undying cell lineages to achieve a taste of immortality? Only time will tell.

GLOSSARY OF TERMS

Embryonic stem cells: Cells derived from embryos developed from eggs fertilized in a laboratory that are capable of differentiating into all cell types in the body.

Germ-line cell: Cells containing genetic material that can be passed on from generation to generation.

Induced pluripotent stem cells (iPS): Cells that can differentiate into numerous cell types; typically derived from differentiated adult somatic cells in the laboratory via exposure to certain genes. Although they are functionally equivalent to embryonic stem cells, they are not derived from an embryo.

Human embryonic progenitor cells (hEP): Human cells derived from induced pluri-potent stem cells (iPS) that have the capacity to differentiate into specific types of differentiated somatic cells.

Somatic cell: Differentiated cells within the body of an organism, aside from gametes (eggs and sperm). Somatic cells have a

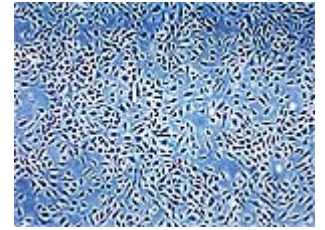
finite life span.

Telomere: Repetitive DNA sequences at the ends of chromosomes that protect the chromosomes from destruction. Shortening of telomere length leads to reduction of cell replication.

Telomerase: The enzyme that elongates telomeres, which are typically shortened after each cycle of cell replication.

In the meantime, the Life Extension Foundation continues to contribute funding to Dr. West's pioneering research.

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If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

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