From the Board Room

BioTime's bid to end age-related disease: A look at CEO Michael West's Vision

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ABSTRACT

The regenerative medicine space is one that is set to explode with considerable innovation and profitability for shrewd biotechnologists. I had the opportunity to speak with Michael West, PhD., CEO of BioTime (BTX) and found a man passionate about regenerative medicine and of course passionate about his role in its future. In this conversation I learned of West's vision, which I think provides some powerful clues as to areas of future growth in the biotech sector. He points to three scientific advances that make this vision actualizable. First, sequencing technology that allows us to perform RNA sequencing for around 300 dollars or less, second the common and reversible molecular basis for age-related diseases, and finally industrial scaling of pure cell lines like the ones manufactured by BTX. Let's look at the three enabling technologies that West touched on and examine how they are being utilized to achieve West's vision within BTX and others involved in the anti-aging revolution.

Journal of Commercial Biotechnology (2015) 21(3), 42–44. doi: 10.5912/jcb706
Keywords: BioTime; corporate vision; anti-aging; longevity

Michael West's BioTime (BTX) is born of his initial passion for treating age-related disease that he feels companies like Geron lost; he was a founder of GRN and CEO at Advanced Cell Technology (ACTC) before BTX.[1] "It's going to be an exciting next 5 years," he says, speaking about his company, its growth potential and the field of regenerative medicine. For Dr. West, BTX is another company with the same aim as his first (Geron) which is a passion for restoring youth to the elderly by focusing on aging and age related disease. "My vision," West states, "was that there ought to be a company that focused uniquely on the challenges of age-related disease." Geron strayed from his vision, West claims, and it was one of the reasons he parted ways with the company he founded in 1990 after 8 years. "The vision is to find some of the most strategic areas that we can apply our modern understanding of aging and regenerative medicine and use it to repair chronic degenerative diseases for which medicines are ineffective." This vision is solidified in three biotechnological advances; low cost sequencing, molecular mechanism reversal and cell line scalability.

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LOW COST SEQUENCING AND BIG DATA

The cost of DNA and RNA sequencing has decreased dramatically in the past 20 years. "We used to sequence DNA using Maxam-Gilbert sequencing doing 300 base pairs at a time; taking a week or more," says West. Two advances, one by Sanger, whereby DNA could be determined via chain-terminating inhibitors,[2] and one by Allan Maxam and Walter Gilbert, via a chemical degradation of specific bases,[3] would allow the first DNA genome, of a virus, to be sequenced in 1977. "Can you imagine how many millennia it would take to sequence every RNA in a cell (using this method)?" he asks. In the next decade rapid advancements would allow for the first semi-automated DNA sequencing machines to be produced.[3] Further advances by Craig Venter at The Institute for Genomic Research, now the J. Craig Venter institute, lead to the first genome of a bacterium,[4,5] marking the first use of the shotgun sequencing approach that Venter and the Human Genome project would use to map the human genome. The revolutions in genome sequencing

led to the so-called 'next-generation' approaches that are now numbering in the dozens of proprietary methods; with names like massively parallel signature, Ion Torrent semiconductor and DNA nanoball sequencing, that have brought the price of sequencing down toward several hundred dollars in the past couple years.[6] From West's vantage, these are the powerful tools that "far surpass what was present 15 to 20 years ago," and make his vision of an anti-aging revolution defensible. In the early 1990s at GRN, West's bioinformatics team began looking for pan-cancer markers, and found telomerase, which became the poster technology for the company for over a decade and a half. "It's expressed abnormally in over 90% of human cancers," said West. And with BTX, using updated sequencing technology, he has been looking for more pan-cancer markers. "We had some of the same scientists on this bioinformatics team," West told me, "They found collagen 10 (collagen 10 alpha 1; CAL10A1). This is a small collagen variant that's involved in the transition of cartilage to bone." CAL10A1 is found in the growth plates; lines of hypertrophic cartilage at the end of long bones, and in the bone callus, "but its silent elsewhere in the body." Except that it is produced by the stromal tissue in a high percentage of cancer. "It is one of the markers in what we call PanC-Dx," says West, developed by BioTime and subsidiary Oncocyte for the detection of various human cancers. "I haven't calculated the percentage but its somewhere near 90% anyway." The use of sequencing technologies to aid in cancer diagnosis has facilitated rapid advancement for these technologies and regenerative medicine will ultimately capitalize on these advances to treat other age-related diseases as well. The wise investor might use this knowledge to seek out early stage and publicly traded companies investing in the growth of these technologies.

REVERSIBLE MOLECULAR MECHANISMS

West believes that diseases are biological processes that can be reversed or exacerbated by genetic changes. "Nature tells us that age-related degenerative diseases have reverse mechanisms behind it," he says, "as evidenced by diseases like Progeria and Werner's syndrome, where you have these single nucleotide changes leading to osteoporosis, grey hair, cataracts, type-2 diabetes, and coronary disease." These molecular changes, West believes, share a common molecular basis that if understood could be harnessed to reverse some of the signs and disease associated with aging or perhaps even prevent them from occurring. West believes that his company can be of practical utility is aiding healthy human aging through its recently acquired OpRegen Technology and another product, which is beginning clinical trials in Israel under the BTX subsidiary; Cell Cure Neurosciences, also funded by Israeli based Teva Pharmaceutical, to counteract both forms of acute macular degeneration (AMD) through reimplanting retinal pigment epithelial cells (RPE cells).[7] "When you lose the RPE cell you can't support the neuro retina," West says. This leads to a spreading plaque of neurodegeneration known as the dry form of AMD, "You can watch these patches grow like a grass fire," he says. His solution is to bring in new RPE cells derived from pure multipotent progenitors. The wet form of AMD is the only treatable form today, accounting for only 10% of AMD and it is treated via needle injections of angiogenic inhibitors to the eye. "They dry form," says West, "arguably would be a bigger market than the 5 to 7 billion dollar market for the wet form." By incorporating new RPE cells in the area of the neural retina, BTX is hoping to reverse the molecular mechanisms responsible for this age-related disease, increasing BTX profits but reducing the overall cost of aging. In general, companies focused on the reversible molecular mechanisms of disease will discover profitable new therapeutic.

SCALABLE STEM CELL LINES

The third component in West's assault against aging comes in the form of his so called PureStem technology, currently used by BTX subsidiaries Orthocyte and Recyte. "We've got over 200 distinct human cell types in a directly scalable clonally pure form in this PureStem template," West says. His subsidiaries are focused on bringing these products to market, with Orthocyte focused on reversing joint and skeleton degeneration, and Recyte focused on providing vasculature progenitors for ischemic disease. "The really blockbuster thing," West says is their scalable progenitors to brown fat. "It is dramatically lost with age. We can make that in scalable pure manner as well." With the baby boom and surge in aging in many developed countries, West thinks that regeneration of brown fat is "going to be the largest single opportunity in regenerative medicine." Researchers have determined that brown fat is the adipose tissue that burns other fat and West and his BTX team have described their clonally pure progenitors in recent meetings. Discovered in the last five years, brown fat has been shown to produce mitogens for the beta cell call betatrophin and other adipokines; cytokines produced by fat.[8,9] In a clinical trial underway in Europe, West hopes to establish that fat can be reincorporated into the elderly and show the utility of the BTX's Hystem matrix injection system,

paving the way for future injectable cell therapies meant to combat aging. He thinks that these off-the-shelf cell lines will become more and more useful in the treatment of age related disease. What is certain however, is that the mass production of cell lines focused on the production of factors necessary to treat age-related disease will play an increasingly important role in therapeutics.

Through BTX, West hopes to consolidate biotechnology under one company to defeat aging. "The vision," he says, "is to find some of the most strategic areas that we can apply our modern understanding of aging and regenerative medicine and use it to repair chronic degenerative diseases for which medicines are ineffective." Describing BTX's recently aggressive tactics in acquisitions West says, "we wanted a commanding position in intellectual property." To that end, BTX and its subsidiaries have accumulated over six hundred patents and patent applications worldwide, including all of GRN's stem cell assets, the licensing of assets from ACT, and Singapore's ES Cell International (ESI). And West suggests that in the next five to seven years BTX will be filing patents related to the 200 clonal progenitors represented by its PureStem technology. "The goal of the company," he says, "is to be the leading source of young healthy cells to replace cells like the degenerating RPE in the back of the retina." With technical advances in sequencing technology, leading to new molecular clues to the deleterious effects of aging, West and his team intend to target disease using injectable scaffolds of pure progenitor cells to correct these defects in the elderly and he is hoping that public investors in BTX will help him do it. Primarily West's focus is to build an umbrella company with investments in multiple scientific advancements. This 'de-risking' strategy will be advantageous in keeping his group of companies profitable.

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