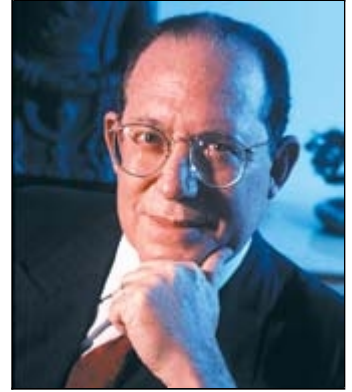


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REPORT

William Haseltine, Founder, Chairman of the Board and CEO, Human Genome Sciences

What would it take to be able to engineer an unlimited human life span? Although nobody knows for sure, being able to manipulate the complete "parts list" of all the molecular building blocks of the human body would be a nice resource to draw on. Human Genome Sciences claims to have something very close to that—a copy of almost every human gene in test tubes, and the ability to use them as drugs. Dr. William A. Haseltine is the Founder, Chairman of the Board and Chief Executive Officer (CEO) of Human Genome Sciences, a powerhouse biotechnology company that claims to have discovered over 90,000 human genes and to have filed patent applications on many of the most useful ones. Human Genome Sciences (ticker symbol, HGS) aims to create a new era in medicine, in which its gene-based products are used as specific, non-toxic, non-allergenic medicines that replace many drugs. Along these lines, Dr. Haseltine coined the term "regenerative medicine," and then a newer term, "rejuvenative medicine," to describe the expected medical revolution that, in his view, could lead to human immortality. Dr. Haseltine talked to us in an exclusive interview conducted by Gregory M. Fahy, Ph.D. on Sept. 10, 2001.



Dr. William Haseltine on
Regenerative Medicine,
Aging and Human
Immortality

Life Extension Foundation (LEF): Can you tell us how big Human Genome Sciences is?

William Haseltine (WH): We have about 1,000 employees. We have about 450,000 square feet, including about 350,000 square feet of manufacturing space. We have six products in clinical trials. Our income is about 25 million dollars a year from transactions. We have income from interest of about 100 million dollars per year. We have about 1.7 billion dollars in cash assets. We are very well capitalized.

LEF: How did you happen to become the founder of Human Genome Sciences?

WH: I was a professor at Harvard Medical School from 1975 until 1993. During that time I was, essentially, Chairman of two departments, both of which I founded: the Laboratory of Biochemical Pharmacology, which worked on cancer treatments; and the Division of Human Retrovirology, which conducted AIDS Research. From about 1980 on, I started creating biotechnology companies. The first was Cambridge Bioscience. I have now founded seven biotechnology companies, the most recent one being Human Genome Sciences. In addition, giving advice to HealthCare Ventures was instrumental in helping me create another 20 companies.

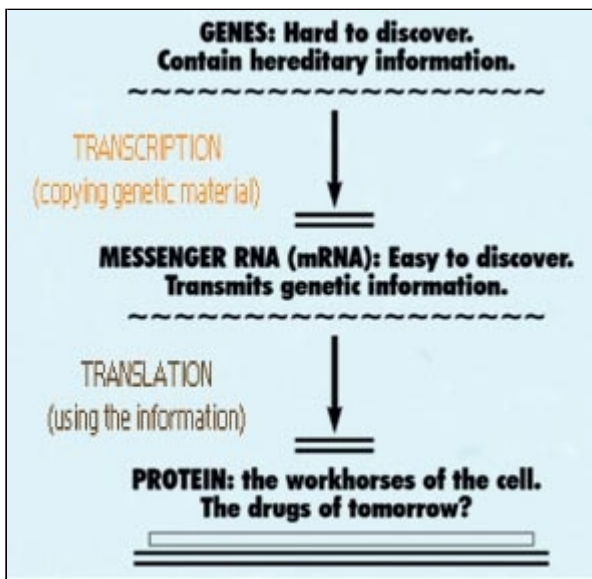
In 1992, I realized that the time was right to bring together technologies developed for the Human Genome Project that could generate a revolution in medical science. I realized that rather than completing the sequencing of the human genome in 10 to 15 years, one could obtain working copies of most human genes in useful form in two to three years. This could be done by focusing on messenger RNAs (mRNAs), the active products of genes, rather than on the genes themselves. Information about human mRNAs could be used to start a new pharmaceutical company based upon the use of human genes, proteins and antibodies as drugs. That is what we did with Human Genome Sciences.

LEF: So the method involves extracting mRNAs from human cells and then translating them into proteins in the laboratory. Is that the basic idea?

WH: Yes. This approach offers a number of advantages. First, it is a way of reducing the complexity of finding genes by more than a hundred-fold. Only one one-hundredth of the genome gives rise to messenger RNAs.

Second, if a messenger RNA exists, it means the cell has transcribed the corresponding part of the genome [actually used a gene to make an active mRNA; see sidebar-Ed.] and is ready to use it to make a protein. In other words, there is no doubt that the information in the messenger RNA is relevant to the cell.

Third, because we can isolate messenger RNAs from specific tissues, we can gain some idea of where in the body and under what conditions those messenger RNAs are being used. That gives us a clue about the roles they may play in the body.



Fourth, we can copy a specific messenger RNA into DNA [thereby making "complementary DNA," or cDNA, which has the same information content as the mRNA being copied-Ed.], and then we can use that DNA to program a cell to make more copies of the original mRNA and therefore, more copies of the protein it normally produces.

One cannot do that from genomic information alone. We knew in 1992 that genomic information would not easily lead to whole genes, because the genes cannot be read from the genome in a direct way.

Between 1993 and 1995 we isolated at least one copy of what we believe to be more than 95% of all human genes. There is still a dispute over how many genes humans have. We think there are close to 100,000, and we have actually isolated 90,000 unique genes. About 60,000 genes remain to be found by others analyzing the human genome.

LEF: Have you isolated all those genes from adult tissues?

WH: We have also looked at fetal tissues, embryonic tissues, tumor tissues and other diseased tissues. We have looked at more than 1000 primary human tissues.

LEF: How sure can you be that the RNAs you've isolated are full-fledged RNAs and not just fragments or pieces of bigger mRNAs that are being recycled? You might translate meaningless fragments into proteins, but they might not be proteins that are actually made in cells.

WH: We have tested that possibility thousands of times. Typically, we look at the longest messenger RNA in our collection, then analyze it. In most of the cases we were able to make fully functional proteins, the same as those found in cells and tissues.

LEF: What about different alleles [variations of given genes, like brown and blue as variants of the eye color gene]? Is that a problem? Do you get all of these?

WH: For the most part, we ignore allelic variation. Alleles usually represent minor variations in function. We often have a choice of which alleles to take. We usually make proteins from the predominant allelic type.

LEF: If you were to give that dominant version of the protein as a therapeutic agent to a patient who did not make that version of the protein, is there a chance of an allergic response or an attack on the foreign protein?

WH: Generally, no. That is why insulin works for most people. That is why human growth hormone, g-CSF, gm-CSF [bone marrow related proteins] and many other proteins, work for most people. Humans tolerate proteins with non-self allelic variants. The moment we stop tolerating the alleles of others, we will no longer be members of the same species.

Even human antibodies can be used as drugs. Antibodies are created by individuals in response to a particular set of circumstances. Today those antibodies can be created in the test tube. They are extremely well tolerated when injected into the body. One might expect the body to make antibodies against the injected antibodies, but this does not appear to happen.

LEF: As you know, what we generally hear these days is that there are only 30,000 to 40,000 human genes, not 90,000 to 100,000.

WH: One of the first human genome publications said there were 26,000 genes. And another publication said there might be 30,000 genes. Then a paper (Genome Biology 2001 2(7): research 0025.1-0025.18) reported that most of the genes referred to in those publications were not the same. The new paper estimated that there are 65,000 to 75,000 human genes. So are we to believe there are 26,000 genes? Or 70,000 genes? The detection of different numbers of genes by different groups shows just how poor the methods of identifying genes from chromosomal DNA really are.

LEF: I've heard it said that there may be an average of three different splice variants of [different ways of using] each gene, and that might amplify the total effective number of genes.

WH: Such analyses fail to consider that almost all splice variants have the same function. That means it is still usually true that one gene corresponds to one function. Most of the time, for drugs based on human genes, the rule to remember is still one gene, one protein, one drug.

LEF: Are you personally responsible for the mission of Human Genome Sciences? Is the company fulfilling your dream?

WH: I am the one who shaped its formation and direction.

Our original mission was (and still is) to improve human health by bringing a wide variety of new products to patients and to treat diseases that could not previously be treated. Specifically, we seek to bring new protein and antibody drugs to market. Our goal is to become an independent global biopharmaceutical company. From the outset, we established four specific objectives.

First, to be the first in finding most human genes in useful (that is, in cDNA) form. We accomplished that objective in mid-1995.

Second, to create systematic means to turn knowledge of new genes into medical uses. We wish to do that both for ourselves, so we can create new human protein and antibody drugs, and for our partners, so we can enable them to create new small-molecule drugs.

Third, to share our newfound knowledge with large pharmaceutical partners, which we have done.

We had a seven-year relationship with a group of pharmaceutical companies led by Glaxo-SmithKline. During that period, our partners used our technology to initiate about 460 different drug discovery programs. The most advanced of these is the first small-molecule drug developed through genomics to enter human trials, a drug that Glaxo-SmithKline is using to attempt to treat heart disease. The drug inhibits an enzyme called PLA2 that creates inflammatory reactions in blood vessels.

Part of the third objective was to obtain substantial payments from pharmaceutical companies to support our own research, as well as to participate in the sale of products after they are developed. Human Genome Sciences is entitled to a substantial portion of the sales of drugs developed by our partners.

The final objective was to build the infrastructure necessary to discover and bring to market our own human therapeutic protein and antibody drugs. We are well along on that path. So we have executed plans to accomplish all our original objectives.

LEF: I understand that you have singled out a subset of genes that you consider to be particularly interesting for patenting.

WH: We are focusing on genes that control external signaling pathways. Those pathways instruct our cells, from the outside, to perform one or more of several simple actions.

The signaling proteins can be on the surface of cells or can leave the cell surface and circulate. Such proteins generally are exported from cells by a common pathway, which involves the use of "signal sequences." We have used that common pathway to isolate (in cDNA form) about 10,000 human messenger RNAs that have the ability to make proteins with a signal sequence. We believe that these 10,000 human proteins comprise most of the proteins that will be useful as drugs.

These proteins signal the cell to grow or to remain static, to differentiate or to remain unspecialized, to live or to die, to stay stationary or to move. Those are the basic functions that cells perform.

This set of proteins also includes the targets of most antibody drugs. Antibodies work on the outside of cells, not on the inside, and therefore must recognize structures that are either in the blood or other body fluids, or on the surface of cells. Proteins that can be targets of antibodies almost all have signal sequences.

That's why we have focused on this subset of about 10,000 genes. In their cDNA form they are stable, and we can use them to make proteins. We are systematically analyzing their functions through biological experimentation.

LEF: One of the things I understand you've done is to use a sort of robotic system to proceed from simply finding the original proteins to getting information about what their functions are. How can you do this when there are so many possible functions?



We are focusing on genes that control external signaling pathways. Those pathways instruct our cells, from the outside, to perform one or more of several simple actions.

WH: We do analyses for one disease at a time. In one case, we were interested in diseases that could be treated by stimulating the immune system-either cell-mediated or antibody immune responses. We examined the ability of our set of 10,000 proteins to influence those processes. We have found several proteins that influence immune system function, which then became candidate drugs. One example is a drug we call B-Lymphocyte Stimulator, which stimulates cells that make antibodies. We have initiated two safety trials in patients with serious immunological disorders that leave them susceptible to a variety of infections. One group suffers from Severe Combined Immunodeficiency Disease; another group has Immunoglobulin A deficiency. B-Lymphocyte Stimulator might boost the immune system in ways that are beneficial in patients with AIDS. We believe that this protein has the ability both to boost the immune system's ability to fight ongoing infections and to potentiate vaccine activity. It seems to be the most potent stimulator of antibody production the body has.

LEF: So you simply search through the proteins until you find the best ones for accomplishing various predetermined tasks?

WH: Yes. We concentrate on substances with activities that fit a medical need.

LEF: In the past you've also talked about using genes as drugs. How do you make a gene into a therapeutic product?

WH: We view genes as specialized delivery vehicles for proteins. Genes, when injected into cells, can induce those cells to produce proteins. If one wishes a protein to persist for a longer period, one might inject a gene for that protein into a tissue. To date, the only tissue that works is muscle. Typically, a muscle cell will produce the protein for several weeks. Eventually, the injected gene will be degraded or otherwise inactivated, and production of the protein will stop.

We licensed one such gene to a company called Vascular Genetics, Inc. The company has attempted to create micro-vasculature in heart muscle by direct injection of DNA into that muscle. In preliminary experiments, the gene seems to have had some beneficial effect on cardiovascular disease in about 100 patients. There do not seem to be serious side effects associated with the use of this drug.

LEF: Are you using temporary rather than permanent gene transfer just in case something goes wrong?

WH: No. One does not necessarily need a protein to persist for a long time. Once new microvasculature has formed, the purpose of having the protein there disappears. Our blood vessels seem to maintain themselves for as long as they are needed.

LEF: Are you also working on permanent insertion of genes?

WH: We are not pursuing that strategy. We think that for a variety of reasons, our purposes are best served by focusing on proteins and antibodies as drugs. The technologies and methodologies for gene therapy have not yet been adequately developed, in my opinion.

LEF: Even limiting yourself to therapeutic proteins, can 10,000 proteins really be exploited within the 20-year life of a patent?

WH: That number is not achievable even by the entire pharmaceutical and biotechnology industry working in concert. But we already have partners who are developing 460 drugs based on genes, and typical drug sales today for large pharmaceutical companies are \$500 to \$700 million per year.

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REPORT



LEF: Did you coin the term "regenerative medicine?"

WH: I did. I meant it to describe an exciting and emerging field. Phase One of regenerative medicine is the use of natural human substances such as proteins and antibodies as drugs. Medicine has in the past been dependent upon plants. More recently, synthetic chemicals have become important. We now have in our hands the information and the genes to change medicine again. In the future, many new medicines will be human substances. Those substances, as I mentioned previously, are mostly interchangeable among the members of our species. We can take one gene, make one protein, then distribute it as a drug.

Human substances used as drugs have the ability to repair, rebuild and restore injured, diseased or worn-out tissues. It is conceivable that over time we will gain enough information to control the behavior of every cell in our bodies. Once we have achieved such mastery, we will be able to heal any disease. We will be able to cause tissues to rebuild themselves. On the other hand, when our natural tissues run amok—for example, when they produce too much of a growth factor or of a necrosis factor—we will short-circuit the destruction process.

Growth hormone is an interesting example of a human protein used as a drug. Too little is not healthy, nor is too much. A deficit can be overcome by injection of recombinant protein. A surfeit can be amended with antibodies against growth hormone.

Another such example is the B-Lymphocyte Stimulator referred to earlier. Too little results in patients developing immune deficiencies. This may be corrected by supplying the protein. Too much induces patients to develop autoimmune diseases, such as systemic lupus erythematosus and some forms of rheumatoid arthritis. We have begun trials of an antibody drug based on this work.

In summary, we are attempting to create a new type of medicine in which our organs and tissues are restored to normal function with exogenous but natural factors.

LEF: If you want to lower levels of TNF (Tumor Necrosis Factor) or growth hormone, don't you think the best way to do it would be to reduce transcription [conversion to the mRNA form] of the offending gene, rather than to try to clean it up with antibodies?

WH: Yes, but we cannot do that yet. I am not a fan of drugs that perturb regulation of transcription [control of the process whereby mRNA forms of genes are produced]. Signal transduction [transfer of a signal from the outside of a cell to the interior of a cell] and transcription initiation are typically mediated by a combination of proteins acting in concert, not

by one protein with unique specificity. It is much harder to disrupt such multi-protein (combinatorial) systems than it is to disrupt one-to-one cause-and-effect systems, such as signals on the outside of cells.

LEF: There is a company called Sangamo (ticker symbol: SGMO) that claims it can turn on or turn off genes. Do you disagree with their approach?

WH: It is possible to achieve some degree of control. There will always be exceptions. In general I think that route is much harder than ours.

LEF: You said signaling proteins can tell cells to live or to die. Can you discuss this aspect of regenerative medicine?

WH: In addition to stimulating repair and growth, regenerative medicine may also be used to bring about the regression of unwanted cells, or in some cases, their death. One might want to kill cells that are growing inappropriately. Some of our drugs stop cells from growing. Others are monoclonal antibodies that inhibit specific disease-causing activities.

LEF: So, for example, instead of using tamoxifen to kill breast cancer cells, you might use an antibody to the estrogen receptors in the breast?



WH: Herceptin is such an antibody. It can be used in addition to tamoxifen. One great advantage of drugs that are natural substances is that they seem to have additive anticancer effects without additive toxicities.

LEF: Very good.

WH: Phase Two of regenerative medicine is tissue engineering. When an organ cannot be restored to normal health through the use of natural substances, it must be replaced. Currently, the only means to replace an organ is by transplantation. A new field is now developing in which organs are grown for implantation. This field is an outgrowth of reconstructive surgery. It is now possible to build new bladder and to grow cartilage and bone for implantation. Blood vessels, heart valves and trachea are on the way. I recently wrote an introduction for a new book in the field (Methods of Tissue Engineering, 2nd Ed., Ed. by Anthony Atala and Robert Lanza, Academic Press, 2001). It is a fascinating compendium of what can be achieved today with tissue engineering.

The early development of tissue engineering is being conducted with adult cells harvested from the patient. The field holds great promise. The difficulty is that, unlike human proteins and antibodies, human cells are individual-specific, and are likely to remain so for many years. That means that tissue engineering is likely to be performed at the hospitals where the patients are. Tissue samples will be harvested from patients and worked on by technicians at a regional hospital. That is a different kind of business from ours.

LEF: Tissue engineering is really the only way to fill in the gap between the supply of the cells, tissues and organs we need for transplant today, and the demand.

WH: That is true. We are still in the early days. When we are able to combine advances in materials science, cell biology, and our knowledge of cell growth and differentiation, the result will be a very exciting area.

LEF: Do you have some direct initiatives in this area?

WH: Human Genome Sciences does not, but I am personally very involved in this field. I am President of the Society for Regenerative Medicine. Anthony Atala, a leading practitioner of tissue engineering, is Vice-President. I am also Editor-in-Chief of a journal called e-Biomed: The Journal of Regenerative Medicine. We hold an annual meeting in Washington, D.C.

LEF: What about the company that's building an artificial heart?

WH: I am also involved in that program. So far, it is more moral encouragement than anything real. Should the organizers need growth factors, however, we are in a position to help them.

LEF: Okay. Let's talk about the third stage of regenerative medicine.

WH: Phase Three of regenerative medicine involves the use of stem cells. This takes us from strictly regenerative to rejuvenative medicine.

Rejuvenative medicine can be done in two ways.

The first is by building younger tissues or organs for implantation. We can replace older tissues and organs with younger versions made from a patient's own cells. That would involve regressing adult cells to an embryonic state, then progressing them to differentiated states suitable for organ regeneration.

Second, rejuvenative medicine can be done by direct implantation of lineage-specific stem cells, or of stem cells capable of becoming lineage-specific or organ-specific. We know this works with hematopoietic [blood-forming] stem cells. There is some preliminary evidence that it may work for brain stem cells as well.

There is a tremendous amount to be learned at a fundamental level before stem-cell-based medicine can become a practical reality. For that reason I think it is not appropriate for most companies to invest in such research. It is appropriate for governments and not-for-profit research foundations to support it. Such research will have its major effect 20 to 30 years from now. In that respect the field resembles the War on Cancer, which the government launched in 1971. For almost 15 years, it remained just a government program. The effects on the biotechnology industry were not felt until the 1980s. I think the same will be true of stem cell research. With a few exceptions, the field is not generally ready for clinical applications.



We do analyses for one disease at a time. In one case, we were interested in diseases that could be treated by stimulating the immune system-either cell-mediated or antibody immune responses. We examined the ability of our set of 10,000 proteins to influence those processes. We have found several proteins that influence immune system function, which then became candidate

drugs.

LEF: Given that perspective, are you disappointed with the Bush Administration's decision about stem cell research?

WH: I think the decision is unfortunate. Any policy that presupposes what is or is not worth pursuing, that limits the potential of research, is likely to be unwise. There are too many unknowns and too many directions that must be pursued. If we had decided in the early 1970s not to pursue the War on Cancer, we would not be enjoying many of the benefits of modern medicine. I hope the Administration's restrictive policy on stem cells will be reconsidered. It could haunt future generations.

The other consequence of the President's approach is that research in Europe, Japan and other countries may jump ahead of research here. That would be unfortunate. The United States has a strong research foundation and strong research leadership. A human tragedy might also result. Our best scientists are eager to work on stem cells. Those scientists might decide to work in some other, less productive field, or leave the United States altogether.

LEF: Do you have any in-house stem cell effort?

WH: No.

LEF: Your approach, as I understand it, is to attack one disease and one disability at a time. But many of these diseases and disabilities arise from the aging process. Larry Ellison, one of the world's richest men, seems very interested in attacking aging directly, and it seems to me that if he and others succeed in that regard, it might make some of the things that you're trying to do obsolete.

WH: I would be delighted! I agree that many medical treatments might be made obsolete by some general and systematic solution to aging. Many of the conditions that we are working on are consequences of aging. Should the fundamental aging clock be stopped, or indeed reversed, the need for most of these medications would evaporate. That would be a happy day indeed.

LEF: Do you see the possibility that Human Genome Sciences will mount an attack on aging itself anytime soon?



WH: We will not pursue that goal directly for some time. We are engaged in, as you correctly pointed out, treating many of the symptoms of aging, with a series of very specific interventions. That is something real and tangible. Whether we, in our lifetimes, can stop or reverse the fundamental process of aging, other than through understanding the behavior of stem cells, is highly questionable. I am sure, however, that we will find many new drugs using the methods we have.

LEF: Have you heard of the gene chip experiments that are being done to study changes in gene expression during aging?

WH: Yes, I have.

LEF: I just interviewed Dr. Stephen Spindler of LSG Sciences. His recent paper in the Proceedings Of The National Academy Of Sciences ("Genomic Profiling of Short- and Long-Term Caloric Restriction: Effects in the Liver of Aging Mice" PNAS volume 98, pp. 10630-10635, 2001) showed that, as mice get older, only 46 genes change in expression in the liver, and most of those changes can be reversed with caloric restriction(CR).

WH: I am familiar with that work. The question, however, is, How long will those old mice live?

LEF: Well, we know that CR extends life span quite a bit, including maximum life span.

WH: It does so in mice.

LEF: Not only in mice, but also in rats, fleas, spiders and in all kinds of other creatures, too.

WH: But not necessarily in humans.

LEF: Well, two long-term CR studies in monkeys look as if the maximum life spans of the monkeys may be extended as well.

WH: People are very unlikely to restrict their caloric intake. A practical solution might be to find a gene whose expression, when modified, produces the same effects as caloric restriction. We recently discovered a gene that prevents pre-fat cells from developing

into fat cells.

Several years ago, working with Glaxo-SmithKline and their academic partners, we found a receptor involved in appetite called the orexin receptor, and orexin itself, a peptide hormone. Orexin and its receptor control pain and hunger.

LEF: We're very interested in your viewpoint about human immortality. Could you please tell us what your view is on this subject?

WH: In the past few years it has become possible for the first time to construct a scenario in which humans may become immortal: by the systematic replacement of stem cells.

Death is not an intrinsic property of life. Life is intrinsically immortal. Our germ cells are the decedents of a four-billion-year old, unbroken chain of cell divisions. The molecule that determines our structure and function, our DNA, has conveyed the basis of life continuously. There is no reason why DNA cannot continue to convey the basis of life for another four billion years. Nothing about life necessitates death.

One theory of aging is that the stem cells in an individual age and eventually fail to reproduce. If stem cell death is the predominant driver of aging, then the solution is to replace old stem cells with young. That hypothesis will be tested, first in animals, and if results are positive, in humans.

LEF: Are you familiar with research being done at Advanced Cell Technology?

WH: I am familiar with some of the work that company is doing.

LEF: Are you familiar with their demonstration that they can use therapeutic cloning to reverse the aging clock?

WH: They recently published a paper in the journal I edit showing that this does not yet work in the case of humans.

Development proceeds to a certain point-to about six cells-but not further. Until such time as it can be shown that the cloned embryo can develop past the 6-cell stage to the blastocyst stage, I think the jury is still out. It may be possible some day. That is one of the reasons we need many groups active in this area.

LEF: Going back to how stem cells might be used to eliminate aging, have you considered that there may be old cells around that are not dead, and therefore cannot simply be replaced, but are nevertheless misbehaving?

WH: That is possible. One way to address that possibility would be to introduce drug resistance markers into the new stem cells. Once those stem cells have displaced enough of the previous ones, the old cells could be killed.

LEF: Yes, that could be done.

WH: The strategy would depend on a very thorough and systematic replacement of the existing cells. However, we do not know enough about the fundamental processes of aging. The process of stem cell death may be only part of the answer.

LEF: Right.

WH: For the first time, though, it is conceptually possible to chart a path to human immortality. Whether that path will lead to success, nobody yet knows.

LEF: Has anyone criticized you for even thinking about things like that?

WH: I do not believe people should be criticized for thinking.

LEF: Very good. Thank you for a refreshing and forthright interview.

WH: Thank you.

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