

## The Thought Leader Interview: William Haseltine by Ann Graham

from **strategy+business** issue 54, Spring 2009

reprint number 09109



by Ann Graham

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hen most people think of the Human Genome Project — the scientific research that produced the first map of the genetic makeup of the human species — they think of it as a new knowledge base with the potential to transform modern medicine. And indeed, since the 1990s, the field of human genomics has helped biotechnology researchers identify life-threatening diseases, slow the aging process, and create more effective drugs. It is even possible today to construct human organs biologically to replace damaged ones. These organs are not artificial; they are made of a person's own cells. The implications for human health and well-being are immense. But what if the benefits of genomic research turned out to be much broader, with equally immense implications for the global economy and our natural environment?

Making that sweeping proposition seem credible has been a recent mission for William A. Haseltine, president and founder of the William A. Haseltine Foundation for Medical Sciences and the Arts. Haseltine has been at the vanguard

Photograph by Peter Gregoire

## William Haseltine: The Thought Leader Interview

A molecular biologist and entrepreneur sees green as the next wave of the genomic revolution.

## Ann Graham

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of discoveries in molecular biology and the commercialization of biotechnologies for more than three decades — as a medical school professor, entrepreneur, and health-care philanthropist.

In 1992, Haseltine founded Human Genome Sciences Inc. (HGSI), one of the first biopharmaceutical companies to patent human genomic sequences for medical use. He coined the term *regenerative medicine* to describe the use of natural human substances, such as genes, proteins, and stem cells, to regenerate diseased or damaged human tissue. As a professor at Harvard Medical School from 1976 to 1993, he was part of a team at the Dana-Farber Cancer Institute that led the race to discover how the human immunodeficiency virus (HIV) compromises, and ultimately destroys, the human immune system. His laboratory determined the genomic sequence of HIV, and Haseltine developed many of the tools that have led to successful combination chemotherapy for the treatment of AIDS.

After retiring as CEO of HGSI in 2004, Haseltine focused his attention further on developing life-saving drugs and medical devices

and making them accessible. Although he still believes genomics holds great promise for medicine, he questions the market potential of presymptomatic genetic testing and acknowledges that the commercialization of drugs has been more difficult than was expected. At the same time, Haseltine is a passionate advocate of “green” genomics. He foresees new applications of “synthetic biology” for healing the earth, for example, by using gene splicing and microbial cultivation in seawater to create a carbon-neutral source of energy from sunlight.

In October 2008, *strategy+business* sat down with Haseltine at the dining room table in his 86th-floor New York City apartment. Surrounded by floor-to-ceiling windows, with views both of Manhattan’s dense material labyrinth and the faraway Catskill Mountain greenery, we spoke of the changes that biotechnology will bring — and the uncertainties of our political, cultural, economic, and uniquely human responses.

**S+B:** Where are the most important advances in genomics emerging?

**HASELTINE:** The major benefit of genomic science thus far has been

for humans. But in the long run, it is not just *for* humans. It is *of* humans. Through the genomic revolution we are opening up all the genomes of life for our perusal, and few people have thought through the implications.

Medicine will still be important going forward; every week brings a few new genomes into our knowledge banks. But I don’t think medical applications will be the major use for investment dollars. The next revolution is going to be about energy, agriculture, and materials science. That, I think, is going to surprise people. Most of life on Earth is invisible. From the bottom of the sea at the hot sea vents, to the dirt under our city streets, there’s an enormous range of microorganisms that play fundamental roles in shaping the course of life everywhere. Now, genetic science allows researchers to intervene at that level.

If you think about the future of biotechnology, what’s old is becoming new again.

**S+B:** What do you mean by that?

**HASELTINE:** *Biotechnology* literally means technology applied to manipulate the living world. Humans have been at this a very long time.

It's one of the oldest technologies, and its greatest successes have been in agriculture, animal husbandry, and fermentation.

Now we are back in the same arenas, with a new set of emerging technologies. To give you an idea of the excitement around the use of biotechnology for energy: The Berkeley Center for Synthetic Biology received about US\$1 billion in grants in 2007. I'm the chairman of the board of trustees of this group. It was founded and is directed by Jay Keasling, a professor of bio- and chemical engineering at Berkeley and the director of Lawrence Berkeley National Laboratory's Physical Biosciences Division. About half the energy research money came from BP and the other half came from federal grants. This is only the beginning. Biotechnology will be the basis for a whole new petroleum-free carbon-based economy.

### Carbon-neutral Energy Farms

**S+B:** How would synthetic biology produce energy on a mass scale?

**HASELTINE:** *Synthetic biology* is not a name I like. I prefer to call this new discipline *constructive biology*, because this form of biology constructs new molecules.

But to answer your question: Plants have been fixing carbon from the atmosphere with the energy of sunlight, and converting it to fossil fuel, over the course of several hundred million years. This means that living systems have the power, of course, to make our fuel. The trick

is to do it much, much faster.

We already know how to effectively create biomass from plants. We grow forests for wood; we have agriculture. With a combination of modern biotechnology techniques we could remove carbon from the air, turn it into a fuel, use that fuel, and return the carbon to the atmosphere so the whole process is carbon-neutral with respect to the concentration of carbon dioxide in the atmosphere. Essentially, these techniques would allow us to farm energy, coupling the photosynthetic process with biochemical production of useful hydrocarbons.

Let me take you back in time to think about that for a minute. Before there was life on Earth, it was basically a wet, hot rock. When it cooled down, it was a rock with water. Living organisms arose (we're not quite sure how), and over the course of several billion years, they transformed rock and water into this beautiful Earth. That's enormous chemical power, and all of it is locked up in the genes of organisms that proliferate all over the world.

Now that we can directly read genomes, store them in computers, and analyze them, and splice genes from one organism to another, we can move hydrocarbons through almost any chemical pathway we want. Suppose you wanted to take yeast that normally makes ethanol and convert it to yeast that makes diesel fuel. You would write up the chemical path to show the normal process to ethanol, and then reroute the path to diesel fuel. In modern

organic chemistry, that would involve a series of eight or nine steps in a test tube using various catalysts. But now you can use genome database analysis to identify and isolate enzymes that can provide that pathway naturally. You can then modify those enzymes so they're more efficient. This is an example of constructive biology.

We know constructive biology works because these were the methods used to produce the antimalarial drug artemisinin in both bacteria and yeast. Plants use a very complicated and expensive process to make artemisinin. At the Center for Synthetic Biology, a project led by Jay Keasling (and funded by the Bill and Melinda Gates Foundation) recreated the entire pathway both in bacteria and in yeast. That breakthrough, which makes artemisinin cheaper to produce and therefore affordable to the world's poorest children, has made Keasling a leader in the field of constructive biology.

**S+B:** You mentioned energy farming. What does that look like?

**HASELTINE:** Many microorganisms grow in the sea, and there are a number of potential ways to use them for energy production. One is to place algae tanks far below the surface, but not so deep that they can't get sunlight piped down to them. Another is to create a series of saltwater-filled tubes on the surface of a large desert and place algae so that sunlight is absorbed as you pump the water through. There are a number of places in the world

where huge deserts are right next to the sea. You don't want to use arable land, and this gets us away from freshwater, too.

These farms could create a continual atmospheric carbon-neutral production cycle: algae taking sunlight, fixing carbon, and producing useful fuels. As I said earlier, what is old is new again. Humanity used to burn wood for energy. Less than 200 years ago, we started burning fossil fuels. Now we're returning to the older process, but it's more efficient with the modern advances of genomics, gene regulation, gene splicing, microbial cultivation, and massive ocean engineering.

**S+B:** Doesn't that suggest a reorientation for the energy industry?

**HASELTINE:** Some oil companies are already calling themselves energy companies. In the future, energy companies will be diversified. They will primarily use solar and wind energy to produce electricity and fuel; they will also provide some fossil fuel energy and atomic energy. The materials sector is also very important; it will be the next focus of synthetic biology and of chemistry. All the chemical companies are very interested in petroleum substitution and micro-materials, and the life sciences have enormous amounts to contribute to material manufacturing as well.

### Microbial Manufacturing

**S+B:** How will basic industrial manufacturing processes be changed?

**HASELTINE:** New manufacturing processes will not use the vats typical of a chemical plant. Instead, the manufacturing basis for materials will be microbial. Life sciences teach us that if you have one good organic

substance, it can reproduce itself endlessly and reproduce those products. All you have to do is keep feeding it. You don't have to keep making it again and again and again. We already know how to produce plastic precursors with yeast and bacteria or plants. So we can grow these materials as we manufacture them.

**S+B:** What is the connection between nanotechnology and biotechnology?

**HASELTINE:** The fundamental architecture of matter is an atom and a molecule. Something as large as a forest is made of very tiny substances, hooked together. Life and materials sciences are teaching us that we can arrange atoms in precise locations, to self-assemble and form units in small to very large sizes — replicating the manufacturing processes of nature. The fact that forests grow and that bacteria proliferate shows you that nano-machines work, and can be very efficient. We can build materials that self-assemble, and this means we can reduce the amount of material used in our lives. For example, we don't have to carve objects out of great masses of metal (and discard the

waste), because we can have them assembled, at the molecular or multimolecular level, with every molecule used. Eventually we can make them intelligent so they'll assemble on command. The basic unit would be a very tiny, submicroscopic unit embodied with the information that says, "connect A, B, C, D." It will then, in effect, construct itself: We can make a chair, we can make a table, and we can build a house.

This type of construction will probably not be available until the end of this century or the beginning of the next century. Think of it as an intelligent Lego set that you could program so the pieces compose themselves. You could then create a program that says, "Make a candlestick, make a chair, and make a wall." Ray Kurzweil describes these types of technologies in his book *The Age of Intelligent Machines* (MIT Press, 1992).

**S+B:** What are the implications for food production?

**HASELTINE:** Earth's population is projected to rise to almost 10 billion by 2050. So the need for freshwater and land is acute; we must use our agricultural land more intensively.

# Constructive biology has the opportunity to produce fuels that are fully compatible with our existing infrastructure or system.

Genetically modified organisms can help with that. They can produce higher yields and more nutritious foods. They can obviate the need for plowing. Most people don't understand what plowing is for. It's really just a weed control technology. You plow over and under the previous year's crop. But if you have the right combinations of environment-friendly herbicides and the agricultural crops that are resistant to those herbicides, you don't need to plow. No-plow agriculture saves topsoil and energy. Once you don't need so much nitrogen fertilizer or complex pesticides, you can get to an agriculture that is much more energy efficient. You can also breed in drought resistance.

People will be healthier as a result. And it will allow us to restore many habitats, because we'll be using less land to grow food.

**S+B:** What about the fears about genetically modified foods?

**HASELTINE:** The technology is rapidly spreading, despite the European opposition. It's spreading in many parts of the world because of its obvious advantages. For example, meat is a highly inefficient source of protein; over the next 20 to 30

years, people will move from meat to plants as a source of protein. I've been in Chinese restaurants that serve something that looks like a fish with skin and scales, but it's entirely made out of soy protein, which is a plant product. You see a chicken that looks like a chicken, it's carved like a chicken, but it's not a chicken. You can make foods look and taste very attractive with manipulation, which, in this case, involves a process to spin soy proteins into fibers.

## Investment and Infrastructure

**S+B:** Do you think the bioenergy industry will move ahead faster than the pharmaceutical industry has in the last 20 years in its commercialization of genomic discoveries?

**HASELTINE:** The technology that might justify this amount of investment is finally emerging. Breakthroughs in the last few years have rapidly attracted large sums of investment capital. The Center for Synthetic Biology received its first half-billion-dollar grant less than a year and a half after showing proof of feasibility for the petroleum substitutes. Of course, that's not how it usually happens. People don't usu-

ally make huge breakthroughs and all of a sudden have a venture capitalist say, "OK, let's go." But the volatility of oil prices has made investors realize that this can be very important.

I guarantee you that there are similar programs in constructive biology (though they may not use that name) at all the major chemical and energy companies. They too are looking at making petroleum substitutes. This type of activity doesn't happen in isolation. When a group puts \$1 billion into research, it gets people's attention.

We also see the rise of very strong scientific communities in this field in other parts of the world. I have been working very closely with the leadership of the government of India. India's Council of Scientific and Industrial Research, which is one of its major funding agencies, has fostered an alliance between a large group of Indian scientists and our group at Berkeley. We're planning to [form similar alliances] with scientists in South America and China.

**S+B:** How challenging will it be to create the infrastructures for producing and distributing bioenergy?

**“It’s going to be possible to build a new pancreas for a person who’s a diabetic. We will be able to regrow an entire heart.”**

**HASELTINE:** Constructive biology has the opportunity to produce power and transportation fuels that are fully compatible with our existing infrastructure or system. We might not need as many refineries, but we will still need the tankers, pipelines, and transport system.

There are still some major engineering problems. If you’re going to use a marine microorganism as your photosynthetic source of energy, how do you engineer that to be environmentally safe and efficient? We can solve the biology problems pretty quickly. We can make the prototype organisms. But can we build the infrastructure at the large scale that will allow us to produce fuel from them?

I think the engineering problem is going to be solved, but there has to be a business motive to do that, and the motive will depend on the cost of energy and its environmental impacts.

### **Regenerative Medicine**

**S+B:** Most people, of course, still think of biotech as medical innovation. In that light, what is the significance of personalized medicine?

**HASELTINE:** In my mind, medicine

has always been personal, if practiced properly. You are sick and a doctor interacts with you as an individual. This is one of the only times in your life when you have a professional response fully tailored to you as an individual. A good doctor wants to know about you and only you. Maybe he wants to know something about your family members, but that’s because of their relationship to you. If medicine isn’t personal, and isn’t therefore personalized, then it’s not really useful.

When people talk about personalized medicine they tend to focus on genetic inheritance, because it is fascinating to peer into your genetic past and present. But modern genetics, at best, is like looking at your future through a glass darkly. With very few exceptions, such as Huntington’s disease, you can’t say that if you have an inherited trait you’ll get the related disease. In most cases, you have a probability between 10 percent and 0.1 percent of getting the disease; you don’t know when or even if the disease will appear.

Ninety percent of breast cancer seems to have nothing to do with inherited genes. The same is true of prostate cancer in men. There is

some role for genetics in predictive medicine, but it’s a much smaller role than people think.

I believe the whole field of what’s called genetic medicine is not really ready for prime time, if it will ever be ready. If I seem negative, it isn’t because I think genetics is unimportant. It is just that genetic inheritance is a very minor aspect of genomics, whereas the applications that I’ve already outlined — energy, agriculture, and materials — are here and important now.

However, there is one tremendous breakthrough that I consider the ultimate personalization of medicine — using your cells to build new, healthier organs. Regenerative medicine involves developing your body’s own replacement organs and tissues if they are lopped off, damaged, broken, or diseased. Combine that with materials science and you begin to build organs. I just was visiting Dr. Anthony Atala at the Wake Forest Institute for Regenerative Medicine. He leads an organization that is building new human organs. These are not artificial organs; they are made of your own cells.

It’s going to be possible to build a new pancreas for a person who is a

diabetic. We will be able to regrow a retina, a heart muscle, and eventually even an entire heart. This is happening because, through genomics, we understand what a cell is doing, we can move genes in and out of cells, and now we have the ability to move genes around the body.

Another, more immediate benefit is differential diagnosis. Because we can define most of the things a cell does, we can define the characteristics of diseases much more precisely. For example, we used to look at leukemia as one type of white-cell disorder, but it turns out that there are perhaps 20 different leukemia diseases. Each will take a different course; each will require a different treatment.

Modern biology has also given doctors more techniques for understanding the disease you have in its current state. Your genes can tell you what you inherited, but they can't tell you how your cells are behaving now. If you think about a lot of cancer tests, they're not about what you inherited. They're about what your cancer is doing today.

**S+B:** What can you say about the progress of using genomics to create new drugs?

**HASELTINE:** There is no question that our knowledge has been helpful. But the problem also turned out to be much more complicated than anybody thought. People thought, for example, that maybe they would find a few extra genes that were involved in cancer. It turns out that almost every gene is involved in cancer at some level. And every cancer is genetically different. Even every cell in the cancer is different from every other cell. And maybe 20 or 30 major pathways are involved. Does gene research help us understand and solve cancer? Maybe it will give us some additional insights. But it isn't the answer to cancer.

### Pharmaceutical Productivity

**S+B:** Do you think advances in differential diagnosis will improve the pharmaceutical industry's return on R&D in terms of profits and human health benefits?

**HASELTINE:** R&D expenses in the pharmaceutical industry have gone up 20-fold in the last 20 years. That's even in adjusted dollars, per company and per industry. Meanwhile, productivity has decreased by about a factor of 10. This is probably the biggest productivity collapse the world has ever seen, and it affects the whole industry, biotechnology companies included. When you look at the number of new compounds that are approved, it's the sum of all the biotechnology, all the universities — the entire world trying to get approval for a new chemical.

So something is wrong, and I don't believe it is the science, which is moving forward at a pace beyond belief. It must be structural. I've been an advisor to many pharma-

ceutical companies, and I've set up several biotech companies, so I have a triangulated view. Size is at the root of a lot of problems. Research and innovation is done best in small groups, but we now have pharmaceutical companies with \$70 billion in sales, and they focus only on drugs that can have a broad impact. One product may be worth \$5 billion to \$7 billion in sales. If a company loses its bet on two or three of these, it's lost its business.

Typically, marketing people lead these companies. They look over the research results and analyze what might "make" a market. If a drug doesn't have a chance in the marketplace, they will demand changes to the testing to get a label on the drug to sell it. I call it the reverse Cinderella syndrome — taking a small foot and putting it into a big shoe. What's the consequence? Drug after drug fails to create a mass market, or a drug gets approved when it shouldn't and then gets withdrawn because of side effects.

One solution would be to create "virtual" pharmaceutical company structures, where you have many small companies with access to capital and scientists who understand the medical needs. Expenses would be kept minimal through outsourcing. Expertise would be consolidated so it isn't redundant. Companies would aim their products at smaller markets. It may be a \$50 million or \$300 million market, but if they don't invest much, they would make a lot of money.

Some of those drugs will be blockbusters, although you can't predict which ones. Those drugs will go into the mass market, but you will have drugs selling at a much lower margin. It will be more

like cosmetics companies, which aren't bad businesses. To be an Estée Lauder, you need 4,000 products and 2,000 changes every year.

It's not going to be easy, but it can be done. A new generation of pharmaceutical executives is rising in the industry, although it will be the next CEO cycle before we see significant change. I predicted that the pharmaceutical price-to-earnings ratio would change from about the mid-20s to the low teens, and [now] I think it's going to go to the single digits. When it does, people are going to reevaluate how they do research. There will be tremendous opportunities to do things differently and better.

### Benefits for the World's Poorest

**S+B:** You mentioned the breakthrough in creating an antimalarial drug that will be affordable to populations who need it most. Can we expect the next wave of medical and green genomics to reach more of the two-thirds of the world's people who live at the "bottom of the pyramid," in lower-income countries?

**HASELTINE:** When the Soviet Union fell and the Cold War ended, the Russians, the Chinese, and the Indians all joined the global economy. C.K. Prahalad's *The Fortune at the Bottom of the Pyramid: Eradicating Poverty through Profits* [Wharton School Publishing, 2004] was one of the first books to recognize this. It is a profound work that is now changing the thinking of a new generation of leaders. What is about to happen, and is already happening in India, is a reorientation of business toward the 2 billion people worldwide who are emerging from poverty. This is a fundamental transformation.

**S+B:** And it's not just about selling consumer goods to them.

**HASELTINE:** Absolutely not. The rest of the world is going to want energy, more food and better food, and good medicine. The structures that we currently have in place cannot deliver all of those things to so many people without destroying our world.

That's why we have to get away from petroleum-based energy. Agriculture needs to be much more efficient. We need to feed more people and to feed them well. Many solutions lie in biotechnology. It takes twice as much water, and I think about five times as much energy, to feed a meat eater as it does to feed a vegetarian. There is a tremendous savings to be had in promoting a vegetarian diet, and I think the world will move in that direction.

I am working in India now through a foundation I've created to deliver high-quality, cost-efficient health care. I believe it's possible to get equal quality at a cost between 10 and 20 percent below current costs. (See "The Innovation Sandbox," by C.K. Prahalad, *s+b*, Autumn 2006.) There are a number of experimental enterprises using technology to create high-quality, affordable, low-cost health care for the Indian middle and lower-middle classes. These are self-sustaining, profitable organizations. There is a tremendous amount of experimentation. The common theme is, How do you solve the problems of getting high-quality health care at very low cost to very large numbers of people?

That is not just a problem for health; it's a problem for the whole economy. How do you provide efficient energy, health care, food, and services to very large numbers of

people? India is a great laboratory, because of its demographics and mix of high-tech wealth and poverty. And hopefully those solutions then get translated to another 2 billion people globally.

**S+B:** Are you saying that the innovations spawned by biotechnologies can help eliminate the "have" and "have-not" economic extremes?

**HASELTINE:** You'll never see an end to economic disparity, but you will see unprecedented upward mobility in the developing world. We are already seeing something like 35 million to 40 million people a year moving into India's and China's middle classes. Think of it as a quarter of the United States' total population joining the middle class each year. Remember, it was middle-to-lower-middle-income Americans, not the upper class, that drove the world economy until very recently.

Mass markets are very powerful, even when the price points are low. So we're seeing these huge transformations take place, and I think that they can continue, but we need to solve the production problems in order to make these lifestyles sustainable on our planet.

**S+B:** Can industrial society be sustainable when there are nearly 10 billion people on the planet?

**HASELTINE:** Yes, if we replace our current generation of wasteful technologies. Biotechnologies will have a significant role in that change. If you look at the full range of what we've talked about, we have gone from burning wood to regrowing arteries. That's a pretty broad span of life sciences, and it's tremendously exciting. +

Reprint No. 09109

*strategy+business* magazine  
is published by Booz & Company Inc.  
To subscribe, visit [www.strategy-business.com](http://www.strategy-business.com)  
or call 1-877-829-9108.

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