Interview

Commercial translation of cell-based therapies and regenerative medicine: learning by experience

Dr Haseltine speaks to Emily Culme-Seymour, Assistant Commissioning Editor

William A Haseltine, PhD has an active career in both Science and Business. He was a professor at Harvard Medical School and Harvard School of Public Health (MA, USA) from 1976 to 1993, where he was Founder and Chair of two academic research departments. He is well known for his pioneering work on cancer, HIV/AIDS and genomics. He has authored more than 200 manuscripts in peer-reviewed journals and is the author of several books. He is the founder of Human Genome Sciences, Inc. and served as the Chairman and CEO of the company until 2004. He is also the founder of several other successful biotechnology companies. William Haseltine is currently Chairman and President of ACCESS Health International, Inc., which supports access to affordable, high-quality health services in low, middle and high income countries, and Chairman of the Haseltine Foundation for Science and the Arts, which fosters a dialog between sciences and the arts. He is an Adjunct Professor at the Scripps Institute for Medical Research and the Institute of Chemical Engineering, the University of Mumbai, India. He is a member of the Advisory Board of the IE University, Madrid, the President's Council of the Cold Spring Harbor Laboratory, the Advisory Council for the Koch Institute of MIT, a member of the University Council Committee on technology transfer, Yale University, and is a Lifetime Governor of the New York Academy of Science (NY, USA). He is an honorary member of the Board of Trustees of the Brookings Institution, a member of the Board of Trustees of the Center for Emerging Markets of the Indian School of Business, a member of the Council on Foreign Relations, a member of the Board of AID for AIDS International, and a member of the Chairman's Circle of the Asia Society. He is a member of the Advisory Board of the Metropolitan Opera (NY, USA), the Chairman's Council of the Metropolitan Museum (NY, USA), the International Council of the Guggenheim Museum, the International Council of the Tate Modern, the Board of Directors of the Young Concert Artists, Inc. and the Youth Orchestra of the Americas.

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■ You were the Founder of Human Genome Sciences, Inc. in 1992. What was the concept behind the company?

To most people, genomics means the study of inherited traits – the study of why we are different from one another and how to make use of such knowledge to improve our health. There is another definition of genomics – the study of all genes. This is actually what the word means; gene plus omics (from omni). It is this second definition, the study of all human genes, what they are, and how they are used to build normal tissues, how they change in diseased cells and tissues that informed our work at Human Genome Sciences. We focused on the similarities between all human genes, not on their differences. It

is this second definition that has led to the successful development of new drugs and diagnostic tests from genomics.

The promises of genetic genomics have been largely unfilled. The hope that the technologies of genetic mapping and genomic knowledge would rapidly lead to a greater understanding of most inheritable genetic diseases has not yet been realized. Nowadays, it is believed that it may never be realized simply because evolution eliminates deleterious genes. Only about 5% of serious disease is attributed to inheritance.

The Human Genome Sciences approach is to treat genes as components of our micro-anatomy, the smallest determinants of the functions in our bodies. We created a complete catalog of human genes, a detailed map of our how genes are used and

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distributed in normal healthy bodies, and how they change in diseases. We believed that this information would allow us to develop drugs that act to restore normal functions. We did not distinguish between the genes of different human beings. We called this approach ‘anatomic genomics’ and thought of it as being very different from ‘genetic genomics’. Our motto was one drug for one disease for all people.

From the beginning, our plans were to develop protein and antibody drugs based on our discoveries. I was aware of the successes of the early biotechnology pioneers in developing protein and antibody drugs. This approach is what led to our recent success.

We also worked with established pharmaceutical companies to develop small-molecule drugs based on the information we provided. An enormous number of leads were found using the genomic tools we pioneered. Both the pharmaceutical and biotech industry proceeded to churn through leads that were found using anatomic genomics. There are several drugs now in the final stages of testing that were developed by our partners. The anatomic genomics approach is working.

■ How did the company go about identifying drug targets & developing these?

We started by looking through all the genes that had the potential to make proteins with a secretory tag on them; in other words, those proteins that might transit a cell membrane. We did this by sorting through all the genes. By 1995 we had at least one copy of 95% of all the human genes that make proteins. Using simple algorithms, we were able to identify these genes that encode secretory proteins. We then made small amounts of each of the proteins we selected. We focused on a subset of chemokines and growth-related proteins, as we thought they were likely to be major regulators of specific cell processes. That in itself was a purely genomic exercise; working with genes of unknown function, categorizing them as secreted proteins and asking which ones might be chemokines.

We found several hundred such candidate genes. At first, we did not know what the genes and the proteins they made did.

However, we know how to look for potential medical applications of these newly discovered genes. For example, we looked for proteins that might make keratinocytes (skin cells) grow. We found several proteins that did exactly that. In other instances looked for proteins that might make B and T cells grow (important determinants of immunity), and others that specifically killed cancer cells.

One of the proteins we discovered turned out to stimulate the growth of one particular type of immune cell, B cells, which produce antibodies to help fight infections. We called this gene and protein B-lymphocyte stimulator (BLyS). We hoped that this protein could be used to treat people who do not make enough antibodies to protect themselves from infections. However, an inexpensive γ -globulin preparation also protects these patients. In the end, it turned out that the drug we developed was an antibody that inhibited this protein to quiet an overactive immune system.

Human Genome Sciences and our partners have had a number of successes using anatomic genomics for discovery. One of the first was an enzyme called PPLA-2, which is involved in vascular disease. The scientists at GlaxoSmithKline had characterized a fragment of the PPLA-2 protein, however, try as they might for many years, they had not able to find the corresponding gene. Within days of obtaining our gene sequence data they spotted the correct gene and had a working copy in their hands within several weeks. They went on to show that overexpression of the PPLA-2 protein poses a serious risk of cardiovascular disease. A drug to treat cardiovascular disease by inhibiting the PPLA-2 enzyme is now in advanced Phase III trials.

■ Human Genome Sciences, Inc. recently gained US FDA approval for a Lupus drug (belimumab). How was this drug developed?

We began with the idea that some autoimmune diseases might be caused by an overproduction of the BLyS protein. So we developed an assay to determine the level of BLyS in the blood. We measured BLyS levels in people with different types of autoimmune diseases and found that some people with Lupus had a very

high level. We followed this with a longitudinal study and found that just before the patients had a serious attack (Lupus is periodic), the levels of BLYS also spiked. We developed a fully human antibody that antagonized BLYS function. This is the drug, now called belimumab, that was recently approved by the US FDA for treatment of Lupus. I believe it is the first drug to be discovered based on pure genomic technologies. It may also be the first of another kind in biotechnology. Human Genome Sciences developed the discovery method (anatomic genomics), used the new method to discover the lead, developed and manufactured the drug and will now market the drug. The entire process took about 15 years to complete.

■ **How did you become involved in regenerative medicine?**

We discovered a protein that caused blood vessel-forming cells to grow, we named it EGF-2/VEGF-2. When we injected the *VEGF-2* gene into the muscle of an animal, a new vascular bed would form at the injection site. We then began to look for other proteins that could regenerate the cells and tissues of other organs.

■ **In Michael J Lysaght's 2008 paper, he references that you were one of the key founders of the term 'regenerative medicine' [1]. When did you first use the term?**

In 1999, I was asked to give a pre-dinner speech to a group of economists at a meeting on the shores of lake Como, Italy. I was looking for a friendly, understandable phrase to help them understand the medical potential of stem cell biology and tissue engineering. I came up with the phrase 'regenerative medicine'. Shortly thereafter, I became the Cofounder and President of the Society of Regenerative Medicine and the editor of a scientific journal with the same name.

Today, the term regenerative medicine refers mostly to work with stem cells. However, the concept as originally formulated is much broader. I regard regenerative medicine as any medical technique that restores to normal, healthy function of cells, tissues and organs, damaged by disease, injured by trauma or worn by time. Human genes, cells or proteins that

restore normal function fit the definition. So do mechanical prosthesis, including neuro-prosthetics.

■ **How do business models differ in regenerative medicine compared with Big Pharma?**

The pharmaceutical companies are very large nowadays, so unless a product is going to generate multibillion dollars of sales, then realistically the pharma companies are not going to pay attention to it. All things considered, most of the products that will come out within the regenerative medicine field are not going to look like billion-dollar products; they may eventually be billion- or multibillion-dollar products, but they are not going to start off looking like that. This leads us to a different business model and one that is inherently different from that of the pharmaceutical industry today. Pharmaceutical companies prefer to produce large quantities of an active ingredient of a drug inexpensively and in huge quantities. They formulate the drug as a pill or capsule and ship it out in bulk. Thereafter the work is done by the prescribing doctor, the pharmacist and the patient.

At its core, the pharmaceutical business is a bulk commodity business with a very high profit margin. There is virtually no labor by the manufacturer required once the product is made and shipped. Such will not be the case for regenerative medicine. Regenerative medicines, for the most part, will be used for one patient at a time; they will be either tissue or organs implanted in one patient at a time. The profit margins may not lie with the company that makes the substance of the product. It may be the doctor who makes the money or the hospital that has a new surgical unit in order to deliver the therapy.

■ **How do you think stem cells will fit into the field?**

The field of stem cell biology is very exciting today. However, we have a very long way to go before the advances in our basic understanding of stem cells can be translated into clinical medicine. The hope is that we will be able to build our tissues and organs anew, from younger versions of our own cells. I believe that day will come, but not soon.

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■ How do you see regenerative medicine/biotech business models changing in the future?

I think the process of drug development will be inverted. Today, drugs and medical devices are initially developed for use in wealthy countries and then exported to poorer countries. In the new model, medical products will first be developed in poorer countries and eventually be used in wealthier countries. The cost of drug development is becoming prohibitive in richer countries. Much of the work is now exported. What has yet to be exported is the initial marketing. I believe that the discipline of competing in low margin countries will build very efficient companies that will eventually dominate the world markets, very much as has happened in the electronics industry.

I worked with CK Prahalad, who sadly passed away in April 2010. He wrote a book, *The Fortune at the Bottom of the Pyramid*, in which he pointed out how the business of the future, even a high-tech business, can be extraordinarily successful by focusing on the bottom of the pyramid. Take an example in the medical area, I spent time with Aravind, a network of not-for-profit eye hospitals in India, which he described in the book. This was a group working on a regenerative medicine product that replaced the lens in the eye during a cataract operation. You could use that surgical procedure to replace anything, whether it was a ligament, cornea or something else. Through understanding every piece of their process, and performing around 450,000 operations a year, this group has got the price down to about US\$25 per operation. This includes doctor's fees and hospitalization. Now, how did they do that? They developed a new nonproprietary, intraocular lens. By manufacturing it themselves, the group got the price down to about \$2 per lens. At that time, the price range on the market was \$200–2000 per lens. The group went on to do exactly the same thing for sutures. This company has now successfully transferred its methods to many countries in the developing world; they have a very forward-looking process and, importantly, they rationalized the surgical procedures.

Surgery is inevitably going to be a big part of what most regenerative medicine technologies will involve, so the question

of how one can do surgery at a reasonable cost is certainly one to consider. Looking at the whole field, delivering regenerative medicines can actually involve some of the highest priced labor in the world. Who has a greater labor cost than your doctor? This distinguishes the industry from a pharmaceutical business. The end user (i.e., the patient) is the one actually doing the handwork in the pharmaceutical business; they are the ones opening that bottle every day, reaching in and taking the pill. Equally, the pharmacist and the doctor are both engaged in the labor, so that is why the pharmaceutical industry is such a great business. This is not true amongst surgical businesses. I encourage people to think of what this approach could do for regenerative medicine businesses focused around implanting new tissues.

■ Considering your broad definition of regenerative medicine, is there a role for prosthetics & devices as a complement to biological methods of regeneration?

I think there is certainly a role for micro-devices, microelectronics and computer interfaces. There are remarkable things that you can now do with neural pick-ups in the brain. What one group of scientists decided to do was see if they could control a robotic arm directly from a monkey's brain. After a couple of weeks, the monkey learned to feed himself, and after a couple more weeks, he was as good with his mechanical arm as he was with his own arm. The prosthetic arm is controlled directly from the brain; there is no nerve connection there, just electrical signals coming out of his brain, into the motors that are moving this arm around. Most monkeys have better hand-eye coordination than humans, so if you ever try to play a video game with a monkey, you will lose; and he can beat you with a video game if he is in Vietnam and you are in London; it does not matter to him where the game is being played because it is transmitted. This is a sophistication that we can achieve now.

We should think in realistic terms about building truly artificial ears, retinas and maybe other 'telepathic' devices. The future of microelectronic interfaces should be looked at closely, not only for us to integrate with our organs, but also

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with our nervous system. This is a very big field, with a tremendous future that awaits us all.

■ Where do we go from here: are we talking about regeneration (i.e., restoring back to normal) or moving over the next few decades towards enhanced humans as a result of these technologies?

I think that most human beings would be happy to be normal and not enhanced. If you have a bad knee from a sports injury, even if they created an artificial knee for you it would never get back to the way it was. We have a long way to go before we even restore something even as 'basic' as a knee. Before we develop enhancements, we have a lot of work to do. The field of bioesthetics has been around forever. Whenever you mention the topic of regenerative medicine, the inevitable question comes "can I make myself look younger". There will always be a market for aesthetic

surgery. Regenerative medicine holds the solution to the problem of restoring normal, youthful function to most of our cells, tissues and organs. We should both be and look better.

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