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# Craig Venter discusses life after the Human Genome Project

Interviewed by Rebecca Lawrence

**Craig Venter,** President and CEO, Celera Genomics

***How do you see the elucidation of the human genome impacting on drug discovery in the future?***

I think it is going to have a huge impact on drug discovery – I think most of drug discovery in the future will be driven by the genome being completed. However, drug discovery will not change overnight. The pharmaceutical industry currently uses 400–500 targets and the human genome is in the order of 50,000 genes, over half of which are new to science and certainly new to the drug industry. This will lead to a holistic approach to biology and medicine. Until we had sequenced the genome, it has been a one-gene and one-protein at a time mentality, as this was all that was possible. With Celera completing the genome, we can start to look at biology in the way it actually happens, as we are not alive one gene at a time. Only by looking at the integration of all this complex information will we get a firm understanding of what the biological processes really are. Drug discovery is certainly not based on huge knowledge bases, but rather on trial and error.

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I think the elucidation of the genome is going to increase the number of potential targets exponentially. Instead of scientists designing ligands for seven-transmembrane receptors, we will have to contend with a whole set of receptors. We will be able to predict, just from doing simple assays, whether drugs will work, instead of by doing animal experiments. The science community for the most part cannot study the true unknown – if you cannot see it or measure it, it does not exist – that is why so many genes are new to science. But now that we have sequenced them and they do exist, it will change biology across the board. I think that the information that scientists in the pharmaceutical industry will have to work on will be growing more rapidly than probably in any other field.

***How do you think we should best tackle the problem of discovering the function of many of these genes?***

I think this is where there is a good role for both public and private efforts. I think when sequencing the genome is done in a dedicated-type facility, it needs to be validated by the current typical approach in academia in terms of people being focussed on a specific gene or a specific problem. All biology does not move to the industrial scale. As we really do need to understand the function of the individual genes and proteins and the links between them, I think there is an increased role for the academic community. The biotechnology and pharmaceutical industries have to learn how to interpret this information and how to decide what are the right targets to attack out of all of this new information. Just having the patents on a whole bunch of receptors has been satisfactory in the past, but maybe deep in the pathway beyond the receptor is actually the best site for intervention to cause a change in the pathophysiology.

***Where do you see the main bottlenecks in the discovery of new drugs from this information and how do you think we might best overcome them?***

I think the biggest bottleneck is the transition from preclinical to clinical stages, as we do not have good enough systems for making good decisions and so many compounds that go into the clinic never make it onto the market. If better preclinical decisions can be made (for example, Celera are trying to find markers and surrogate markers for drug actions in humans and other species), they will be used to monitor the efficacy of a drug. This will be based on knowledge not only from the human genome, but from the mouse, dog and even the chimpanzee genome at some stage, and we will therefore have models that will very accurately predict the success of a drug when it goes into the clinic. It varies between companies but my understanding is that 60–70% of the cost of producing a drug is after it goes into the clinic.

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Eventually, I think we will get to the point where we do not need to use animal models and will be able to go straight into humans. I think we can certainly begin to move in that way, although obviously new assays and new methods will have to be very well validated by regulatory bodies such as the FDA. A lot of animal models that are being used now do not make a lot of rational sense – they are just being used because that is what the FDA has had available to it – we should look forward to a future where we can restrict our use of animals for when we definitely need them.

***How do you think company strategies in R&D, development and registration should change to accommodate the pharmacogenomics era?***

I think that the larger pharmaceutical companies are going to be increasingly outsourcing more of their R&D because they cannot afford to do it in-house and it is too specialized. Databases are a great example of that. Some companies have been built with huge bioinformatics departments, spending $50–100 million a year trying to maintain those efforts. For example, to replicate our computer would be $100 million, but to subscribe to our database is only a tiny fraction of that, so they can get the combined efficiencies of companies like Celera in terms of the information side and can also get



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something similar on the laboratory side. We are also setting up proteomics on a scale that they cannot afford to do in a pharmaceutical company, so they will also want to outsource that effort. I think that overall, this will improve the efficiency and the cost-effectiveness of what they do.

***Where do you think drug discovery as a whole is going in this age of automation?***
Hopefully it is getting much more efficient. Obviously, developing the right assay for the high-throughput screen is still important, but if people really measure integration from all the information and use all the new data that we have produced, then it has to have a tremendous effect on moving discoveries forward faster. Most pharmaceutical companies will have to increase their drug discoveries about fourfold just to stay in business – it is a pretty tough effort as it is not easy to discover drugs – that is why I chose to do what I do!

***How important do you think elucidation of the other genomes are and what proportion of time and resources is spent on them at Celera?***
Well, when we finished the human genome, we said we were starting the mouse genome. If we just had the human genome alone, it would not be very useful. We will complete the mouse genome by the end of 2000. Even today, we can layer it on top of the human genome to interpret it. When we had the first genome in history, *Haemophilus*, it was only when we had another dozen or so genomes on top of it that genomics helped us to get much quicker answers concerning their roles and confirmation of their evolution. This has enabled us to make very quick decisions regarding target selection and understanding of their biology.

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We now need at least a third mammalian genome to help us interpret the human genome further, but we cannot have too many genomes in terms of this information because most of it is new and most of it is unknown. Only 3–5% of the actual human genome sequence is crucial in producing protein, so it will be a matter of sorting through all this information to be left with the right pieces. I think we will have to get orders of magnitude more efficient at sequencing genomes and I think we are decades away from ever saturating the value of the information. I think primary sequence information will be some of the most valuable information throughout this entire century.

***What were the main problems encountered in the Human Genome Project and how do you think these could be overcome for the more rapid elucidation of other genomes?***
The main problems were not so much from our side, but were rather from people in other aspects of the field catching up and understanding what Celera was doing and learning to adopt it. We thought we had proven what we were doing five years ago by sequencing the first three genomes in history. It is just hard to change some programs: people have built a program and are totally fixed on the directions they are going. It is like trying to steer a barge – you cannot steer it very well. I think that for a lot of science in general, it takes a while for very radical new approaches to be adopted.

***Do you think the Human Genome Project will have as significant an impact on drug discovery as was anticipated at the beginning of the project?***
I think having the human genome will have a much bigger impact – I think the early notions in terms of this discussion of molecular biology, even ten years ago, were rather naïve. I think that every modern successful pharmaceutical company that has done their own R&D has really started to incorporate molecular approaches. When I co-chaired our 2nd or 3rd genome sequencing conference ten years ago (called the *The Genome Project in the Pharmaceutical Industry*), most people in the pharmaceutical industry thought sequencing the genome would have no impact and did not think it would help them at all.

***Back in 1992, you left the NIH to set up TIGR. Do you have any regrets about leaving the NIH? Do you feel that you had no choice if you wanted to pursue your own ideas and ambitions?***
Well, it was a very risky move at the time – my team and I had permanent government positions and we could have stayed there and kept doing what we were doing. We left with no guarantees and no clear-cut future, but I have never looked back and never regretted it for a millisecond. It has changed by orders of magnitude what we can accomplish. That said, I think NIH programs are great places for researchers to get started and I think most young researchers should try to spend 5–10 years there if they could, but the system will have to change to enable that to happen.

In terms of accomplishing the science that I wanted to, it became very clear that I could not accomplish it in the government so, in that sense, I clearly had no choice but to leave. Also, most researchers would love to have had the opportunities I have had and would love to have their own research institute and to be able to determine their own fate, with all the risks and benefits that go with it, so I would not give that up for anything.

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***Do you feel it is ethical to patent human genetic information?***
I do not think it is a question of ethics at all. It is a question of what is legal and what is appropriate. Some companies have abused the system in terms of trying to patent tens of thousands of genes that they have no idea what they are, but that is not what patents were intended for. It is largely a European press issue about whether this is ethical or not, but it is part of the US Constitution to have patents. Patents are a reward to discoverers and inventors for releasing their findings to the public rather than keeping them as trade secrets. The exchange for a patent is that all the findings are published and made available to everybody else for making the next stage invention.

The pharmaceutical industry as we know it could not exist if there were no patents, and many human therapeutics would not exist, such as insulin, erythropoietin, GCSF – all of these compounds have probably saved tens of millions of lives to date. Hence, if there is a direct link between patents and new therapeutics, I guess if

anything, it seems unethical not to patent information if it moves treatments for human diseases forward.

I think the confusion comes because people, particularly in Europe, think patents are ownership of information or ownership of genes and the press has done a really bad job of trying to explain what they are. Genetech and Eli Lilly have their patent on the insulin gene, but they do not own your or my insulin genes – they have a commercial right to produce insulin as a therapeutic and that is all they have. This does not block research – in fact it promotes research because they have had to make all their information available.

***There have been reports that you may create a new form of life such as an artificial bacteria which could be used to clean up environmental spills or to create new drug delivery systems. Are you able to elaborate on how this might further research in the drug delivery field?***

Most of these reports were a lot of speculation based on the Human Genome Project and the research we had done to prove the biology associated with it. The hypothesis that came out of that research was that we would perhaps make a synthetic chromosome and people asked me to speculate on what other uses there might be for such a thing. It is not even clear if it is feasible to do that or if it would work. If it is pursued at all, it would be pursued at TIGR to answer fundamental questions about the basis of life – we are not trying to make any tools for the pharmaceutical industry nor for anyone else.

***Achievements made at Celera prompted discussion on how genetic information gained could be used. How do you feel that new genetic information should be used in employment?***

I have been urging the US Congress to pass bills that protect all of us from genetic discrimination so it should not be used for employment, by governments or by insurance companies for determining who gets healthcare. In the US and in other parts of the world, it is up to governments to ensure that people are protected. It is not something that is a consequence of sequencing the human genome – it was going on when we were discovering one gene at a time – the genome has just brought it to a head. I think government bills are a number-one requirement to prevent a GMO-type situation occurring with human healthcare. Recent human history has shown that many of our species will try to use whatever information they can get to try to discriminate against others.

***What lies on the horizon for genomic research over the next five years?***

I think it is going to be an exponentially growing field that not only will drive changes in the entire healthcare system but will be one of the biggest movers of the world economy.

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***What is your biggest concern about the current/future research?***

One is related to the misuse of genetic information. The other is that this notion of genetic determinism will be allowed to proliferate. My fear is that the public will believe that there is a genetic basis to everything and thus they are not responsible for anything because it has all been predetermined through their genes. I think this fallacy will be dispelled in the long-run, but in the short-term, it will not have positive outcomes for anybody if that is how it ends up. Scientist must help educate people that we are more than the sum total of our genes. We are products of our environments and our experiences, not simply a product of our genes.

***What would you like to have achieved by the end of your career?***

Probably coming up with some radical new approaches that have a huge impact on the pace of discovery research in the world by opening up genome sequencing with the first genomes in history. This work will be responsible for driving forward genes that are going to change human healthcare.

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