

# Peeking into 'Human Genome Row'

I was asked to write a personal perspective on the publication of the human chromosome papers appearing in this special issue of *Nature*. The request was fortuitously timed, as I had just made the decision to resign from the United States Department of Energy (DOE) and join Synthetic Genomics Inc., and was understandably in a reflective mood about my many years with the DOE and its laboratories. That association dates back to 1973, when I was consulting at the Argonne National Laboratory while engaged in my Ph.D. work at Northwestern University, Illinois.

During my years with the DOE, the Fates have been kind to me in terms of offering me fascinating technical challenges across many disciplines, and I am privileged to have sampled several scientific fields. None has been as wonderful as my association with the Human Genome Project (HGP), which forms the subject of this brief perspective. Over the years, we never tired of reminding the world that the DOE started the HGP, and were often irked by our inability to persuade a large part of the community to acknowledge it. Perhaps I can now be dispassionate about that, and take a more balanced view of not only what the DOE has done for the HGP, but also what the HGP has done for the DOE.

Twenty years ago, Charles Delisi (one of my predecessors) proposed sequencing the human genome as a way to better understand how radiation affects human biology. The sequencing technologies were still relatively primitive, but it was expected that if such a programme was launched, the proper incentives would be created to advance these technologies, and to inspire the teaming of individuals and disciplines to complete the task. This approach, which was familiar to the physicists who have dominated the DOE, was alien to the world of biology, which was in the grip of hypothesis-driven research.

By now, several histories of the HGP have been written from different points of view and with various biases. In fact, any version is a great story about scientists, engineers,

politicians, federal managers and private citizens coming together to complete a task, the importance and attraction of which grew exponentially as the destination started emerging above the horizon. It has also been particularly gratifying to witness the expanding international participation in the HGP, as befitting a programme that affects all of humanity in such fundamental ways.

The DOE version of the HGP history naturally stresses the origins as well as the 'big science' approach that allowed its successful completion. Along the way, however, a major disconnect started to emerge. The human genome sequence was becoming a tool for better understanding human biology and for improving the practice of medicine. Apart from a modest role in radiation biology and a significant role in nuclear medicine, the DOE was not in the mainstream human health business, unlike the United States National Institutes of Health (NIH). Moreover, as the NIH budget embarked on its doubling trajectory, questions were raised about the role of the DOE after the completed human genome sequence was safely deposited in the public databases.

I remember those as days of mixed emotions: excitement about seeing the prize within our grasp coupled with anxiety about being the victims of our own success. However, while the attention was primarily riveted on the HGP another quiet revolution was taking place: the sequencing of microbes. In 1995, when Craig Venter sequenced the first microbial genome, that of *Haemophilus influenzae*, many considered the accomplishment to be mostly a test run for the HGP. In fact, microbial genome sequencing ushered in a new era of scientific innovation, and the DOE was first in line to fuel this new discovery engine. We now know that microbial genomics has been far more than just a stopping point on the way to deciphering the human genome code.

Microbial genomics has uncovered a great new world of wondrous complexity, teeming with incredible variety and unexpected potential. The tree (or, more accurately, the vine) of life is dominated by these invisible unicellular creatures, which, as individuals or as communities, are the virtuosos of the living world, having perfected most of the processes of life over billions of years. We have much to learn from these creatures, especially if we are to become better stewards of our planet and successfully harness natural resources to improve the lot of humanity.

The DOE seized the moment successfully and, with the help of a broad spectrum of scientific advisors, developed the Genomes to Life (GTL) programme as a successor to the HGP within the DOE. The GTL programme was designed with the same ambitious 'big science' vision of the DOE, but also focused on harnessing the capabilities of microbes and microbial communities to address the missions of the DOE in clean energy production, environmental bioremediation and carbon sequestration for climate change mitigation (<http://www.doe-genomes-to-life.org>).

We have come full circle. While we might have felt betrayed because the HGP that we launched was abandoning us for more attractive companions, perhaps this gave us a much worthier companion and a better partner in the GTL.

For the 13 April 2003 celebration of the HGP at the Smithsonian, I put my own lyrics to the Bob Dylan song, *Desolation Row*. The DOE was also celebrating its twenty-fifth anniversary, so I could not resist devoting a verse and a tease to the agency that has been my home for all these years:

*Now, DOE is looking out the window  
For her I feel so afraid  
On her twenty-fifth birthday  
She already is an old maid  
For her, nuclear waste is quite romantic  
She wears plutonium shrouds  
Her profession is nuclear weapons  
Her sins are her mushroom clouds  
And though her eyes are fixed upon  
Physics' great rainbow  
She spends her time peeking  
Into 'Human Genome Row'*

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