In this last of this series of genome anniversary vignettes, you will continue to find provocative thoughts—ranging from the impacts of this “big science” project on the rest of the research community to the commonalities between art and science. Exciting as all of the vignettes have been, our space is finite, and we know that there are many more opinions waiting to be expressed. We challenge you to reflect on the implications of this landmark event and look forward to your letters and e-letters!

—Barbara R. Jasny and Laura M. Zahn

The Accelerator

Eric S. Lander

President, Broad Institute of Harvard and MIT, Cambridge, MA, USA, and Cochair, President’s Council of Advisors on Science and Technology

When the Human Genome Project (HGP) was proposed some 25 years ago, the notion was so foreign to biology that commentators had to resort to metaphors from physics. The HGP was biology’s Manhattan Project, biology’s Moon Shot, biology’s Superconducting Supercollider particle accelerator.

To some, the project seemed like mindless drudgework aimed at a dubious goal. (Sydney Brenner waggishly suggested that the HGP be conducted in penal institutions, by “inmates sentenced to 20 megabases—with time off for accuracy.”) In reality, of course, it was the human genetics research of that early era that was marked by tedium (10 years to clone the gene for Huntington’s disease!). What smart young student would want to be an ant in an army scaling a linkage peak?

Ultimately, the HGP yielded discoveries as remarkable as any atom smasher or deep-space telescope. It revealed that the spectrum of protein-coding genes is far smaller than imagined, that physiology depends on a vast universe of regulatory controls and noncoding RNAs, that diseases arise from many unsuspected genes and pathways, that so-called junk DNA may be the mother of much invention.

In the end, though, the HGP might indeed best be viewed as a “high-energy accelerator”—not of particles, but of scientific work and scientific imagination. Individual investigators, the drivers of biomedical progress, can today carry out projects that once required legions: They can readily assay thousands of genes, millions of genetic markers, billions of nucleotides; they can interpret their findings in the context of public data sets representing tens of thousands of experiments worldwide and billions of years of evolutionary information. These capabilities have liberated them to think creatively and boldly about important biomedical challenges. Once seen as “big science,” the HGP has proved to be the most powerful enabler of “small science.”

Robert F. Kennedy famously said, “Some men see things as they are and say ‘Why?’ I dream things that never were and say ‘Why not?’” Increasingly, young biomedical scientists are bringing this same attitude to their work. They are impatient with technological limits that stand in the way of knowledge. They transcend disciplinary boundaries, fusing experimental, computational, and clinical science into a new biology. They roll up their sleeves to create vast data sets, comprehensive reagent collections, and powerful new methods—and they share them freely. They are not afraid to work in teams, if by working together they can change the world.

In the past week, I have attended three scientific meetings, where I heard young scientists brimming with vision about predicting all the ways in which tumors can become resistant to a therapy, unraveling the molecular basis of psychiatric diseases, characterizing the entire human immune response to stimuli, mapping the complete genomic landscape of all transcription factors through development, creating a comprehensive catalog of all cellular circuitry, and devising general methods to speed the development of new therapeutics.

If I had been asked to pick out a present to celebrate the 10th anniversary of the HGP, I could not have chosen better.

Making Sense of the Data

Peter Donnelly

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There is an old aphorism that you wait forever for a London bus, and then two come along together. After the huge international efforts to sequence the human genome, the past 10 years have seen an explosion of data documenting human genetic variation, and we are at the tipping point for what will be an avalanche of high-quality human genomes. Within a few years, tens of thousands of human genomes will have been sequenced.

A major strand in research since the human genome sequence has been the systematic attempt to identify, annotate, and understand the functional elements in the genome. For much of this time, the collection and analysis of human variation data might have seemed to be running in parallel to the functional work, with no direct connection. But that is illusory: Data on human genetic diversity have proved to be a valuable tool in the quest to understand human biology. One example is recombination. We have learned a great deal recently about this fundamental biological process through the study of humans and, in particular, of human variation. Another is population genetics—as others have noted, human variation data offer an unparalleled opportunity to understand the forces shaping patterns of genetic diversity and to identify genomic elements under selection. But perhaps most significantly, the identification of DNA sequence variation associated with phenotypes of interest, particularly with human disease, provides the starting point...
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