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EDITORIAL

The Human Genome Project—A triumph (also) of structural chemistry: On Victor McElheny's new book, *Drawing the Map of Life*

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Abstract Structural chemistry greatly contributed to the feasibility of the Human Genome Project (HGP) by the discovery of the double helix structure of DNA. Victor McElheny's new book *Drawing the Map of Life* paints a panoramic picture of the story and the expected benefits of the HGP.

Keywords Double helix · DNA · Human Genome Project · James D. Watson · J. Craig Venter · Personalized medicine

The significance of the Human Genome Project (HGP) is difficult to overestimate and could be compared only to that of very few other grand projects such as harnessing nuclear energy, space exploration, interstate highway systems, transcontinental railroads, flood-control dike systems, and a few others. Its costs are lower but its long-range impact is greater than those of some of the others. For structural chemistry, the HGP is unique among these extraordinary projects because our domain of science has been part of the foundation of molecular biology through the discovery of the double helix structure of DNA.

Science journalist and biographer Victor McElheny has now published a book, *Drawing the Map of Life: Inside the Human Genome Project* (New York: Basic Books—A Merloyd Lawrence Book, 2010), which is worthy of close attention. The Sydney Brenner quote introducing it is surprising at first glance as it says that "progress in science depends on new techniques, new discoveries and new ideas, probably in that order." Intuitively one might assign preference to new ideas rather than to new techniques. However, closer scrutiny of various developments justifies Brenner's words. Thus, for example, one of the most crucial developments on the road to understanding the human genome—Frederick Sanger's discoveries of sequencing first proteins, then nucleic acids—clearly depended on new techniques in chromatography and elsewhere. Without them Sanger might have not even embarked on these tasks, but while working on his projects, Sanger himself became a great toolmaker.

Thus, at the start, McElheny justifiably focuses on the tools that eventually led to the HGP. These tools included enzymes, instruments, chemicals, and mathematical approaches, among them statistics. As molecular biology is in fact the conglomerate of all techniques used in modern biological research related to finding out about the molecular basis of life with genetics as a main focus, the bits and pieces communicated here come together as a rough history of this branch of science. And it is a highly personalized history: the discoveries and innovations are introduced along with some basic information about their principal protagonists.

At some point, there was a dilemma whether to wage a comprehensive attack in deciphering the human genome or continue to concentrate on various diseases in a piecemeal manner, one after the other and often by randomly looking for the genetic markers associated with their manifestations. It was soon recognized that everything could be done faster and more economically if the human DNA were deciphered in its totality at once. Crucial changes were taking place in the 1980s. This was not only in scientific techniques, but also in public awareness and, accordingly, in the political climate for considering the importance of

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what has come to be called "genomics." The involvement of politics was justified not only due to the expected benefits from the new science but also because new dangers—real or perceived—had to be handled as well.

When recombinant DNA initially became a possibility in the mid-1970s, the scientists themselves initiated policing (see, the famous Asilomar meeting), accompanied sometimes by hysterical reactions in the general public, but things eventually returned to normal. With the accumulating information from mapping the genes and from sequencing DNA, it was increasingly apparent that a larger-scale effort would be needed and that the ultimate goal should be the complete sequencing of the human genome. Some of the opponents of such a project hastened to point out that it would not be the final goal because knowledge of the complete sequence could not yet mean medical applications. However, it became clear that this was an unavoidable step.

The work had to take place on several fronts simultaneously. Information was to be collected about the sequence, but technology improvement was to be continued if sequencing was not to be considered a single project since it was realized that for true applications, i.e., discovering the genetic basis of diseases, numerous individual DNAs would have to be sequenced.

Questions such as the relationship between government-funded work and private enterprise came into the forefront just as it did between university research and commerce. The HGP was to be enormous with a price tag of an estimated 3 billion dollars. Other questions arose as well, such as whether DNA base sequences were patentable or not. And reality was moving rapidly without waiting for the outcome of lengthy deliberations.

The first explicit calls for a project to sequence the human genome emerged as early as the mid-1980s. It was to become the task of a new generation, because the scientist most noted for his discoveries in sequencing, Frederick Sanger, retired in 1983, and the first big meeting about the HGP took place in 1985. When Sanger was asked at the time whether such sequencing should be done, he unequivocally supported such a project.

Everything seemed to be moving toward the HGP. Small organisms but of ever increasing complexity became subjected to complete sequencing and the best scientists were vocal in advocating the need for such a project and in actually participating themselves. This included people like Sydney Brenner, who had been one of the pioneers in establishing the genetic code, and Renato Dulbecco.

There were also opponents, to be sure. They were apprehensive about big science entering the traditionally small science arena of biology, but it was recognized that the scale of a possible HGP would truly have to be big science. On the other hand, there was no real danger of concentrating all the HGP in one huge center; rather, it was anticipated that big science in this case would mean a well-coordinated assembly of little science projects. Initially, there was a gap between the older scientists who supported the big project and the young ones who saw it not only as an infringement on their toiling ground but as a sponge absorbing the support that could have gone to more diverse projects. There was the promise that rather than depleting ongoing projects in biology, the HGP would be subsidized with additional funds.

One of the moving forces was another promise implicit in all the plans for the HGP and that was its potential in fighting cancer. Another was the benefits expected from the technological innovations for all biological science. Still another driving force—more influential than anybody else—was James D. Watson. Initially, in the mid-1980s, he was lukewarm toward such a project, however, he quickly warmed toward it, and he had excellent resources to back up his efforts. He had the Cold Spring Harbor Laboratory behind him and he had his ways to influence the general public and, in particular, the media as well as his fellow scientists. In addition, the presumably genetically based illness of one of his sons became publicized and added a personal touch to his involvement, and generated additional trust and sympathy toward what he advocated.

At one point, it was no longer a question of whether the HGP should be set up but rather at which institutions, with what framework, and under whose leadership it should operate. The Howard Hughes Foundation—the largest private organization of its kind—quickly bowed out. The U.S. Department of Energy (DOE) with its vast experience in big projects, such as those at Los Alamos and Livermore, was willing and interested. The DOE was not without prior involvement in biological research either. Nonetheless, the most logical choice seemed to be NIH due to its enormous funding of biomedical research and its responsibility for advances in human medicine where the HGP was expected to bring most of its benefits. Ruth Kirschstein, in charge of the National Institute of General Medical Sciences, was made responsible for studying the possibilities of the HGP on NIH's part. It was realized that the HGP would be much less expensive than the space program and probably more directly benefiting human life.

One of the preconditions for a meaningful HGP was the recognition of the universality of the genetic code, which by this time had been established. This is something we take for granted but initially it could not have been. The universality of the genetic code itself was something that had to be established. It impressed me when Marshall Nirenberg, who had accomplished the first step in cracking the genetic code, told me that it was a profound moment when he realized this universality. It had an almost

religious significance on the non-religious Nirenberg. He considered it an expression of the unity of Nature.

The preparations for the HGP involved U.S. legislation and Watson along with a few others got involved in informing members of Congress. Watson was such an important component that he appeared even to have a say in which of the two principal contending agencies should be involved, DOE or NIH, in administering the project. It was then also almost inevitable that he was chosen to initially direct the efforts with an appropriate title in the NIH administration. McElheny thoughtfully enumerates Watson's traits, both favorable and not so favorable, as a leader of the HGP. Although it could be doubted from the start whether Watson would have the stamina to carry on this function for long, it had great significance that he was at its helm at its very inception.

Watson's assuming the leader's role of HGP was advantageous because his fame added visibility to the project and generated additional trust. Now there was someone—someone well known, that is—who appeared to take responsibility for this great excursion into the unknown. Watson himself considered it important to have someone at the helm of the project who could take the blame in case of failure. An additional benefit was his authority among scientists who could be induced to join the project answering his call. He knew that success or failure depended to a large extent on the quality of cadres he would be able to attract. It was characteristic that a leading scientist suggested that offering sufficient cash would be attractive enough to recruit the right people. In contrast, Watson warned that such an incentive would attract the wrong people. He wanted to have people who were too busy to join, who had a lot of things going for them, and for whom merely a lot of money would not be decisive in making a career move. Watson's dedication to the HGP could not be demonstrated better than by pointing out that he continued his lobbying for it even after he had been "fired." One of his most telling personal imprints on the project was the allocation of a percentage of the HGP budget to studying its ethical, social, and moral issues. There was a lot of relevance to these questions and the emphasis on their studies from early on enhanced public trust in the project.

As the question of the scaling up of the genome project arose, various further considerations had to be addressed. They included multifaceted supports of the project, the dilemma between technological innovations and continuous use of more traditional methodology, and how the HGP functioned as a peculiar big science being constituted of numerous small-scale projects. Even though Watson's directorship did not last long, it appeared that it was crucial that he had had his imprint on it from the start. His scientific authority could not be questioned and his dedication was unconditional. Though he might have been forced out for reckless statements, it was his interest in some biotech companies that was used as a pretext to cause him embarrassment. Still, one has the impression that he might have been grateful for it is difficult to imagine him lasting too much longer in a bureaucrat's role. Amid bickering among various governmental branches, science kept going on, producing complete mappings and even sequences of organisms of ever increasing complexity.

Patenting appeared to be a crucial question, that is, whether the human genome and its portions could be patented at all. Curiously, there was not a clear-cut divide between those who supported patenting and those who did not. One might have expected the big pharmaceutical companies to prefer patenting, but they recognized its dangers and opted instead for the public domain approach. In contrast, I remember how dedicated Walter Gilbert appeared to me, during a personal encounter at a meeting "Frontiers in Biomedical Research" in Indian Wells, California, on February 2, 1998, to seeing his company earn money from genetic tests based on such patenting. I remember it because I had been on a low-salt diet from my youth due to my tendency toward elevated blood pressure. The test would determine whether people inclined to have such a condition would or would not benefit from a low-salt diet. When Gilbert told me about it the test had been on the market for just a few weeks.

An obvious player in scaling up was Craig Venter who had started at NIH, but moved out, and became the most conspicuous player in the private enterprise sector of the human genome race. At some point, Francis Collins succeeded Watson at the helm of the HGP. Even though Watson no longer occupied any formal position in the project, he continued his role behind the scenes and utilized his enormous authority for gathering support in Congress and elsewhere for the project. As Venter aggressively pursued his goals, he mobilized tremendous funds from the private sector for the project. It meant not only more monies but also more competition. The situation resembled the stimulating effects of excellent private universities on the state universities.

There were reasons for alarm as well. Venter's private sequencing company would release sequence data at 3-month intervals; thus, the private company would have considerable advantage in developing diagnostic tests and eventually drugs, and they would even patent genes and important functions. The British were especially vigilant in not letting patenting become a barrier to public access to the benefits of the HGP. Their efforts were financed by the Wellcome Trust, a private foundation.

It was realized from the start that deciphering the human genome would only be the beginning in revolutionizing the medical sciences. Various aspects were coming into the

A few of the principal players on the road to the Human Genome (all photos by and © of István Hargittai). From the top row, left, and in each subsequent row, from the left, Werner Arber, 2005; David Baltimore, 2004; Seymour Benzer, 2004; Paul Berg, 1999; Elizabeth Blackburn, 2003; Sydney Brenner, 2003; Erwin Chargaff, 1994; Francis Crick, 2004; Walter Gilbert, 1998; François Jacob, 2000; Ruth Kirschstein, 2000; Arthur Kornberg, 2001; Joshua Lederberg, 1999; Maclyn McCarty, 1997; Matthew Meselson, 2004; Kary Mullis, 1997; Daniel Nathans, 1999; Marshall Nirenberg, 1999; Richard Roberts, 2003; Frederick Sanger, 2001; Phillip Sharp, 2001; Maxine Singer, 2000; Hamilton Smith, 2001; Gunther Stent, 2003; John Sulston, 2003; Harold Varmus, 2002; Craig Venter, 2007; Robert Waterston, 2003; James Watson, 2000; Charles Yanofsky, 2006

forefront that would show the way to utilization of the information from the HGP in human medicine. One of them was the determination of disease-causing variation—the change of a single nucleotide for another, called also the single-nucleotide polymorphism or SNP. A whole new area of biomedicine, "pharmacogenetics," was emerging. In the meantime, private companies flourished on NASDAQ due to the promise of personalized medicine with the yet more attractive goal of preventive medicine appearing close to reality in the not so distant future. On March 14, 2000, President Bill Clinton and Prime Minister Tony Blair took a strong stand against patenting, and, as a consequence, the shares of private companies dropped and the NASDAQ index slashed considerably, after they had, previously, skyrocketed.

Various analogies have been introduced to stress the importance of deciphering the human genome. A parallel was drawn between the periodic table of the 100 chemical elements as the guiding principle in twentieth century chemistry and the knowledge of the tens of thousands of genes of the human body in the biomedical sciences of the twenty-first century. There seemed to be a competition of superlatives in characterizing the importance of the human genome in which Watson appeared to be among the most restrained when he declared "…it's the script of life. It's the information for the play of life" (p. 161). Watson's preeminence in the project was acknowledged by President Clinton when he turned to Watson saying, "Thank you, sir" (p. 165). The occasion was a joint, electronically linked White House–10 Downing Street event on June 26, 2000, declaring the next triumph of the HGP.

The flood of information from the HGP gave hope for attacking numerous diseases, but the data had broader implications as well. It was established that well over 99.9% of the genome is the same in all humans and in this light the concept of "race" was fast losing importance. At the same time, the 0.1% still represented the possibility of 3 million differences among the 3 billion nucleotides. The possibilities of utilization were enormous, ranging from diagnostic tools to drug development, to genetic screening, forensic applications, and coming to decisive information in paternity disputes. One of the goals was the mapping of genes associated with every inheritable disease. Parallel to the virtually limitless potentials of the benefits of the HGP, possible dangers were also emerging. The information might make genetic discrimination possible in employment, insurance, and elsewhere. It might be that skin color and gender would not be the most decisive factors in discrimination, but it could become the variations in a person's DNA. So far, seven diseases have been identified as linkable to DNA mutations that included manic depression (bipolar disorder); coronary artery disease; irritable bowel syndrome (Crohn's disease); hypertension; rheumatic arthritis; type I diabetes; and type II diabetes. This is in addition to the susceptibility genes already known for breast/ovarian cancer, colon cancer, and Alzheimer's disease that were found using the targeted disease-based approach.

It was an event announced with big fanfare when in 2007 Watson and Venter posted, simultaneously, their own full DNA sequences on the Internet. Their purpose was to combat the fear on peoples' minds when they thought about the genome project. This reality was also demonstrated by Watson. He said that he was glad he had sons rather than daughters because his genome showed familial tendency for breast cancer. Even more to the point, he held back one section of his DNA that might have revealed information to him about his chances for Alzheimer's. He declined to learn about his chances for developing this awful condition. Venter wrote a whole book in connection of the publication of his DNA, *A Life Decoded*. He called it his genomic autobiography.

Of course, for developing personalized medicine the DNAs of thousands of others will have to be sequenced. However, this appears increasingly realistic. Sequencing the first human genome cost 3 billion dollars, Watson's price tag was a mere 1 million—a drastic decrease within only a decade and a half. The most immediate goals of reaping the benefits of the HGP would be pinning down the causes of mental illness and autism. The next would be establishing diagnostic tools for various cancers and finding their treatments. Tall orders to be sure, but considering the pace of progress in recent biomedicine there is justified optimism about reaching these goals.

McElheny's book is a great service for a broad audience in disseminating reliable knowledge in an accessible way. His background eminently qualified him for producing such a book. He was a science journalist during the decades that led to the HGP and during its initial periods. He worked for years at the Cold Spring Harbor Laboratory. He wrote an excellent biography of James D. Watson, *Watson and DNA*. It appears, the importance of the topic and the preparedness of the author made a perfect match and the result is an informative and readable account of the most important scientific project of our time (the photo collage shows some of the principal players on the road to the Human Genome).

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