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Cracking the Human Genome: A Look into How Competitive Forces Create and Reshape Collaborations

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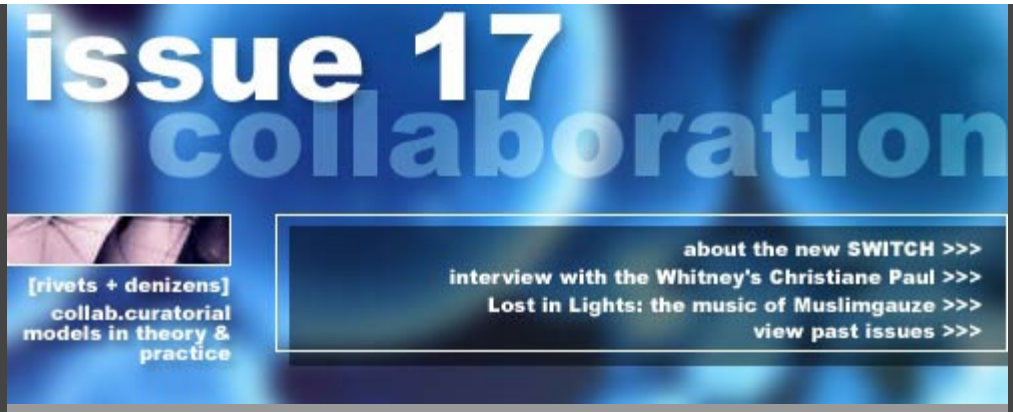

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Cracking the Human Genome: A Look into How Competitive Forces Create and Reshape Collaborations

Nora Raggio on Feb 11 2002 **issue 17**

This essay will outline two types of "takeovers" in collaborative projects. It first outlines the strategies taken by the U.S. to "takeover" credit for what was a truly multinational effort. Similar usurpations of credit emerge in other collaborations, whether they are scientific or artistic. The second part of this article deals with the strategies used by the corporate "takeover" of an essentially public collaboration.

"On Monday, June 26, 2000, President Clinton strode into the East Room of the White House, followed by two proud men: Craig Venter and Francis Collins. The hastily arranged occasion was to mark the joint announcement of the completion of the rough draft of the public Human Genome Project and Celera's "first assembly"…pride of place went to James Watson, who as a scientist and statesman was most responsible for instigating the Human Genome Project…Speaking via live satellite from London, British prime minister Tony Blair hailed the breakthrough as 'the first great technological triumph of the 21st century'."

Kevin Davies, Cracking the Genome (p236)

Interestingly, this is mainly an Americanized landscape (e.g. an American president celebrates the achievements of three Americans), even though the efforts to discover the rough draft of the human genome had involved hundreds of scientists from around the world, including many Nobel laureates, as well as massive investments in genetics and bioinformatics from a host of countries worldwide. In the ensuing days and weeks, media comparisons, likening this achievement to the first moon landing, further helped to create the illusion of this achievement as an American feat. The scene also hides the intense competition between the corporate and public initiatives to sequence the human genome.

Phase one of this essay/article looks into perceived international and domestic competitive threats and forces that led to the establishment of the U.S. led, collaborative, public Human Genome Project (HGP), officially formalized in October 1990.

Phase two of this essay/article will analyze how a competing, corporate, for-profit ideology clashed with the basic tenets of the "open source, free access" ideology underlying the public HGP—and how that collaborative effort was reshaped by the corporate assault.

Phase One: How the U.S. turned an internationally competitive landscape into a massive "collaborative" international project led by the U.S.

By the 1980s hundreds of labs around the world were focusing their efforts on genetics and genomics (the mapping and sequencing of genes) thanks to the invention of methodologies and equipment that could splice DNA and RNA, replicate it, sequence it, and map genetic sequences to specific segments of a chromosome. By the end of the

80s, however, not a single human chromosome had been sequenced and mapped entirely. Biology was still considered "small science"—not because of the significance of the discoveries and findings, but because most labs worked as small independent teams led by a key scientist. Thus, the landscape looked very much like small independent centers competing for fame yet sharing their data through publications or conferences. Throughout the 80's, however, national interests started to become involved in setting national genomic research policies, in what governments came to consider as a potential national resource, and a source of international prestige and economic competitiveness.

Although the U.S. led the pack in terms of number of publications and funding in the area of genetics, there was a certain uneasiness among some U.S. scientists that mapping and sequencing the human genome was not being given sufficient priority and attention, and that possibly Japan or a European nation might be able to win the race in "reading" the code (although technically there as many different genome codes as there are humans—yet all humans share more than 99% of the code) and profiting from that discovery.

When American researchers first began seriously considering the genome project, one of the goads to make the commitment was the fear that Japan would do it first. (Joel Davis, p178) Throughout the eighties, Japan pumped funding through a variety of government agencies into genomic efforts. Japan was considered one of the leaders in automated DNA sequencing technologies. Given that Japan was a major economic force to contend with in the eighties, and had won considerable market share from the U.S. in autos and consumer electronics, U.S. companies saw this incursion into genomics by Japan as a substantial threat. A project that had started in 1981, funded by Japan's Science and Technology Agency had a plan to convert genome sequencing into an "assembly line effort," with the goal of sequencing up to a million base pairs a day (more than had ever been sequenced by anyone in a year). This project had garnered the sponsorship of companies like Fuji, Hitachi, and Seiko—but by the end of the 80s this collaboration had failed to come up with a prototype to meet those high expectations. Some U.S. scientists grumbled in private that Japanese scientists were reluctant to share data that had not been already published. By 1985, Japan had come up with a proposal called the Human Frontiers Science Program (HFSP) in an effort to lead a collaborative international effort in basic biology and development of "key related" technologies, but this proposal was received with a lukewarm response by the international science community. Curiously, three years later, the U.S. was able to pull off HUGO (Human Genome Organization) led by the American Victor McKusick (but including directors from other key countries including Japan, U.K., France) to guide the collaborative international human genome project. Thus the U.S. usurped the international collaborative leadership from Japan.

In France, Nobel laureate Jean Dausset had created CEPH (Centre d'Etude du Polymorphisme Humain) by 1984—with both private funding and the support of the French government. A key goal of CEPH was to create a detailed map of genetic markers spanning all the chromosomes in the human genome. CEPH was indeed a very successful model of international collaboration. Dausset was culturing cell lines from 40 large multigenerational families, freely donated by researchers worldwide. Within a year of its founding, Dausset was collaborating with more than 15 labs worldwide, and by the 1990s that number had grown to several dozen. One of the key prerequisites for collaborations at CEPH was that researchers using DNA from the CEPH collection had to agree to refrain from using it for commercial purposes. (Joel Davis, p167). By 1988, Jacques Chirac was calling genomic research a national priority for France. This model posed another potential threat to American leadership of the genome project.

The U.K. had a long tradition of intellectual leadership in genetics. It was at the Cavendish Laboratories in Cambridge that Francis Crick and James Watson had discovered the helical nature of DNA back in the early 50s. In early 1988, the British government set up the Medical Research Council (MRC) in London to coordinate research to sequencing and mapping the human genome. The Imperial Research Cancer Fund (ICRF—a privately funded charity) and the MRC poured considerable funding into a "genome resource center"—which would coordinate mapping efforts in the U.K. The MRC also planned to establish a major computerized database that would store and distribute information about the structure and functions of the genome. The MRC would later become a key node coordinating centers in Europe for the genome project. The U.S. would clearly prefer the U.K. to be its ally rather than competitor.

Other countries including the then U.S.S.R. and Italy had vested interests in cracking the genome. It was in this landscape of competitive national interests that the U.S. Office of Technology Assessment (OTA) prepared a key report for Congress published in April 1988. Entitled Mapping Our Genes: Genome Projects, How Big, How Fast? the document was basically a SWOT (Strength, Weaknesses, Opportunities, Threats) analysis for U.S. Congress to consider. After analyzing the international genomic

research scene, it bluntly asked the question: "What would be the consequences if Japan or a European nation were to have the first complete set of ordered DNA clones representing all human chromosomes, or the first reference sequence of the human genome?" (OTA, p 174) This was clearly a potential threat for U.S. political prestige and U.S. economic and technological competitiveness.

It pointed out what it considered key weaknesses in U.S. genomic research policy. One of the weaknesses being a lack of clear, focused, national priority and international leadership in the HGP. The other being the competition between two key U.S. government agencies funding genomic research: the Department of Energy (DOE) and the National Institutes of Health (NIH). Although DOE had first proposed a first draft of the HGP in 1986, had the management skills to lead "Big Science" projects (e.g. the development of the atomic bomb), and was home to computational power and genetic databases such as Genbank, the NIH claimed that the biological and medical aspects of the genome project were clearly in their jurisdiction. The two agencies had been competing for genomic research funding from Congress and "informally" collaborating through ad hoc conferences. For a few years, this informal collaboration had been the status quo, until James Watson, in late 1987 made two points clear: "1. Bureaucrats must not be in charge of coordinating the genome project work done by the agencies involved. The coordination must be done by scientists. 2. It would not be possible to carry out such a major scientific and technical project without a lead agency. There's only one genome, Watson said, and we need one lead agency." (Joel Davis, p138). The OTA report seemed to further agree with Watson, on two points—that there should be only one lead agency and that the lead agency should be NIH.

The OTA report outlined the U.S.'s strength in genomics: in terms of the number of publications released, sequencing and mapping technology and equipment, and overall funding. The report also implied opportunities: that the U.S. use its strength in genomics to formalize a domestic as well as international HGP (led by the U.S.), that the NIH lead that effort, and that Congress increase funding to the tune of up to $200 million per year in order to complete the project by 2005 (roughly $1 per base pair for the approximately 3 billion bases in the human genome). The OTA recommendations soon became reality.

The NIH got the message. In early 1988, the NIH director invited James Watson to lead the newly created Office of Human Genome Research at NIH. By choosing one of the fathers of genetics as well as a seasoned diplomatic statesman, the NIH had become the de facto leader. The public HGP officially kicked off in October 1990, headed by Watson at NIH. Perhaps more significantly, the U.S. had designed the Human Genome Project to be a worldwide effort, "with about two-thirds of the work to be handled by university groups in the U.S., the remainder by the U.K., France, Germany, and Japan". (Kevin Davies, p30)

Thus, by the beginning of the 90s, the U.S. had essentially redefined the HGP game, transforming the competing national interests of the 80s—seen as a potential American threat--into a well-funded, massive international collaboration, headed by the U.S. This strategic, forceful collaboration, however, was poised to meet another competitive wave.

Phase Two: The ideological corporate competition/threat to the public HGP. Corporate ideologies clashing with the open-source, free-access approach to scientific inquiry.

This section deals mainly with the strategies used by Craig Venter and his company, Celera, to launch a corporate attack on the public HGP. Counterstrategies used by the international collaboration to stem the damage to their investment and reputation, as well as to secure free access to genomic sequences, are also discussed.

Before launching into the details of this highly publicized assault, however, I'd like to cover some precedents that already signaled changing attitudes in the scientific community regarding profiting from genomic data.

Prior to the formal creation of the public HGP in 1990, Nobel laureate Walter Gilbert had wanted to create his own company, the Genome Corporation, and hire hundreds of scientists to sequence the human genome. He suggested that his company would copyright the sequence and sell it for as much as the market might bear. He was unable to raise the funds to carry forth his dream. This proposal riled many scientists who believed that the human genetic sequence in itself should not be subject to profiteering.

Another brouhaha erupted around a proposed collaboration between CEPH and the American company Millennium Pharmaceuticals. Daniel Cohen, director of CEPH during the early 90s, was also a cofounder of Millennium. This was a rather interesting change in policy for CEPH: in the earlier years, its founder, Dausset, had clearly stated that

researchers using CEPH DNAshould refrain from using it for commercial purposes. At CEPH, Cohen had access to a priceless resource of blood from more than five thousand subjects from eight hundred families that had been collected by Phillipe Froguel for the purposes of studying genetic factors in diabetes. It just so happened that Millennium had been founded to discover the genetic source for complex disorders that included diabetes and obesity. In early 1994, Froguel and Cohen met with Millennium executives and lawyers to discuss the details of a possible collaboration. Froguel was unwilling to give away his patient samples to an American company, especially one in which Cohen owned considerable stock. In March of that same year, Froguel wrote to the French prime minister to seek his "urgent intervention to protect the national 'patrimony'," (Kevin Davies, p 78) and to save "French DNA" from being exploited. The scandal raged through France, with the French media depicting American biotech companies as seeking to profit from French donations of DNA.

Now, back to Craig Venter, a few years prior to his 1998 explicit challenge to the public HGP. In the early 90s, Venter, perhaps inadvertently, had given an early blow to public HGP. It happened while he was still working for NIH. Bernadine Healy, the NIH director at the time, was a strong advocate of a controversial NIH decision that sought patents for hundreds of gene fragments identified by Venter. She supported the move on the basis that she wanted to obtain clarification from the U.S. Patent Office on the legitimacy of patenting genes of unknown function. Watson, head of the public HGP at NIH at the time, was outraged with Healy's decision to move ahead with the patent application. Watson went public with his criticisms. Healy counterattacked by suggesting that Watson might have a conflict of interest in heading the HGP since he owned stock in biotechnology companies. Watson quit his position as HGP leader abruptly in April 1992, naming no successor. In August 1992, the patent office rejected the NIH application. It ruled that the claims failed to meet the three major criteria: novelty, utility, and non obviousness--because, they were "vague, indefinite, misdescriptive (sic), incomplete, inaccurate, and incomprehensible." (Kevin Davies, p64) It took the NIH about a year to find Francis Collins to lead the public HGP. Collins had brilliant credentials in the area of gene mapping—he had been one of the leaders in a team to be the first to discover and map the gene responsible for cystic fibrosis.

By 1998, Venter had left the NIH and was the head of TIGR (The Institute of Genomic Research) funded in large part by HGS (Human Genome Sciences). There were some rumblings in the scientific community that the HGP had only sequenced 4% of the genome. The claim was that the collaborative effort was focusing on mapping key genes and was waiting to sequence "junk DNA' (which is supposed to account for more than 90% of the human genome) when new automated sequencing equipment would make this more efficient and affordable.

In January 1998, Michael Hunkapiller, of Applied Biosystems Inc (ABI), called Venter to check out a new sequencing machine that he had just launched, the PRISM3700. It could automatically sequence up to a million nucleotide bases a day. Venter had been an early fan of ABI machines, testing them while he was still working at NIH (this type of arrangements between a private company and a government agency was very unusual at the time). Hunkapiller had ulterior motives in calling Venter. With his new machine, he was envisioning sequencing the entire human genome in record time, bypassing the public HGP altogether. But he acknowledged that ABI lacked skills in sequencing strategies—and he knew Venter was interested. Venter had just proven himself successful using a controversial "shotgun" sequencing technique for bacterial chromosomes. Venter was taken aback by this proposal, but by the end of a few days, he had done the numbers, and was convinced. PE Corporation, headed by Tony White, and parent company of ABI, would bankroll the idea—but it was up to Venter to create a new subsidiary to head this new venture.

On May 8, 1998, Venter and Hunkapiller met with Francis Collins, head of the public HGP at the United Red Carpet Club at Washington's Dulles Airport and broke the news of their genome sequencing enterprise. Venter proposed that his new company and the HGP share their data. Collins replied that he needed more time to consult the matter.

Now Venter was ready to wage the technological and infowar (as Paul Virilio might call it) on the HGP. Two days later, on May 10, 1998, Nicholas Wade, a veteran New York Times science reporter who had covered Venter's earlier successes, wrote a front page article on the Sunday Times. Venter's new company, as yet unnamed, would sequence the entire human genome by 2001, four years ahead of the HGP's scheduled goal. "If successful" Wade suggested…"the venture would outsrip and to some extent make redundant" the $3 billion public HGP. (Kevin Davies, p148) Contrary to the Bermuda agreement, a basic tenet of the public HGP, in which centers were to release DNA sequence data every twenty-four hours, Venter promised he would release his data for free every three months—but that pharmaceutical companies or other interested parties could gain access to his genome database for a license. Venter said he was

interested in patenting only a few hundred genes, less than 1% of the genome, but he was, perhaps intentionally, vague about the number. He was interested in building an information company, not a pharmaceutical company, he claimed.

The NIH leaders tentatively agreed to Venter's proposal, but were rather skeptical of Venter's shotgun sequencing strategy and declared that it would be premature to change the direction of the HGP. Venter counteracted in a Times piece by Wade: "It may not be immediately clear to members of Congress that having forfeited the grand prize of human-genome sequence, they should be now equally happy with the glory of paying for similar research on mice." (Kevin Davies, p150)

The public HGP leaders then met to find a way to counteract the corporate incursion. It took them a few months to reshape their strategy and the nature of the worldwide collaboration. Of all the issues raised by Venter's attack—the threat to the established collaborative genome centers worldwide, the HGP's strategy to focus on mapping rather than sequencing--the most vital concern was that of gene patenting. Watson compared Venter's attack on the HGP to Hitler's annexation of Poland and was wondering whether Collins would act as Churchill or Chamberlain. Collins decided to proceed with the project, and was adamant about publishing the gene sequences every day, so that they could not be patented, even if that meant giving data to the "enemy". He also reprioritized the HGP's goals to focus on a "rough draft" sequence of the entire genome by the year 2000: he reorganized the HGP operations and streamlined the organization so that NIH funds for this project would be redirected to only three centers in the U.S. Together with the DOE's Joint Genome Initiative and the Sanger Centre in Britain, the centers were dubbed G-5.The Wellcome Trust in Britain stepped up its funding of the Sanger Centre to $350 million and said it would challenge any patent applications on DNA that it considered without merit.

Ironically, these centers decided to "stock up" on automated sequencing machines and ordered hundreds of ABI 3700 PRISM machines. White, president of the parent company PE Corporation, commented: "we set off an arms race, and we were in the arms business. Everyone, including the government, had to retool and that meant buying our equipment." (Kevin Davies, p167) The "takeover" was more than simply ideological.

Many in Europe were angered by Celera's plan to patent gene sequences. A leading French geneticist, Alex Kahn declared his views on this process: "I compare this information to the discovery of celestial galaxies. I would patent the moon!" (Kevin Davies, p62). European genome centers were riled that they had not been consulted on the radical change in strategy of the HGP. However, by mid 1999, parties in Europe and Japan had signed on to these drastic changes.

By November 1999, the public HGP had sequenced one billion bases, or one third of the human genome. By December 1999, the public HGP had claimed the first human chromosome sequence, which it published in Nature. It was the work of one of the largest international collaborations to date. More than two hundred researchers working at the Sanger Centre in Britain, together with genome centers in the U.S. and Keio University in Japan, described most of the entire sequence of chromosome 22.

Celera, Venter's company, was also claiming to make progress at an amazing pace, and in the media they were seen as the likely winners. In January 2000, Celera claimed it had sequenced 90% of the human genome. Celera was working with Eugene Myers, its computer whiz, whose role was to "piece" together these massive sequences—since the shotgun approach was more like reading the scattered, torn pages of an encyclopedia, which then needed to be ordered.

By March 2000, negotiations between Celera and the public HGP became even more tense, with Collins concluding that "there is no real interest on the part of Celera in continuing to pursue this particular collaborative model" (Kevin Davies, p204). In that same month, the public HGP deposited its 2 billionth letter of DNA. A statement on March 14, 2000 by President Clinton and Prime Minister Tony Blair declaring "human DNA sequence and its variations, should be made freely available to scientists everywhere" shot the U.S. market bubble, and started its precipitous decline. Venter found the joint statement a crushing blow to corporate "accelerated" model.

On June 26, 2000, President Clinton and Prime Minster Blair decided to call it a tie for Venter and Collins re: the "rough draft" of the human genome sequence. Thus we come back to the beginning of our story. "The whole finish-line mentality is silly" said Eric Lander, one of the key figures in the public HGP. (Kevin Davies, p215) Celera would naturally have the advantage because it could access publicly available data deposited in Genbank.

The celebration could be interpreted as Americans winning on two ideological fronts: they had claimed leadership to the international public collaboration and had proven

that American corporate enterprise could speed up not only the rate of discovery, but also the rate of "technology transfer" (e.g. the commercialization of certain genomic sequences). California congressman Ken Calvert declared: "Dr. Venter and others are responsible for speeding up the sequencing of the human genome by five years. For this reason at least, I would rather have the problems of private-sector involvement in the human genome field than not. Some problems are good to have, and I think this is one of them."

Not everyone feels as smug about corporate incursions into the very fabric of science as does Calvert. Especially when these hybrid public/private models make use of a significant percentage of resources paid by taxpayers' money—and then deny free access to discoveries made.

Sources:

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